UNIVERSIDADE DA BEIRA INTERIOR
Ciências da Saúde

Desenvolvimento e avaliação de estratégias para aumentar a adesão à terapêutica farmacológica anti-hipertensora

Estudo da intervenção do farmacêutico hospitalar no controlo da pressão arterial

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Tese para obtenção do Grau de Doutor em
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Dedicatória

À minha Mulher pelo apoio e colaboração inestimáveis.

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Resumo

Introdução: A hipertensão arterial (HTA) é uma doença com elevada prevalência na população adulta, constituindo um importante problema de saúde pública devido às complicações cardiovasculares graves que origina. Apesar do vasto leque de opções terapêuticas disponíveis com eficácia comprovada em ensaios clínicos controlados e aleatorizados, a proporção de hipertensos cuja tensão arterial (TA) se encontra controlada é, ainda, muito baixa, tornando primordial a criação de linhas de investigação e o desenvolvimento de estratégias de intervenção nesta área.

Objectivos: Numa primeira fase, determinar a percentagem de doentes hipertensos, da zona de influência do Centro Hospitalar Cova da Beira, E.P.E. (CHCB), com a TA controlada e estudar os factores preditores de TA não controlada. Numa segunda fase, desenvolver, implementar e avaliar uma intervenção farmacêutica hospitalar que permita aumentar o controlo eficaz da HTA.

População e Métodos: Para o desenvolvimento da primeira parte do projecto, realizou-se um estudo observacional transversal em doentes adultos com diagnóstico de HTA que acorreram, de Julho a Setembro de 2009, à consulta de hipertensão / dislipidémia de do CHCB. Foi realizada uma entrevista estruturada tendo em vista a recolha de dados sobre: características sócio-demográficas, adesão à medicação anti-hipertensora, conhecimentos sobre a HTA e presença de reacções adversas medicamentosas (RAMs). Os dados antropométricos, fisiológicos e clínicos para a realização do estudo foram prospectivamente obtidos através dos processos clínicos. Para a definição de controlo da HTA, foram seguidos os critérios da Direcção-Geral da Saúde e do "Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure"(JNC 7). A determinação das variáveis independentes com influência significativa no controlo da TA foi efectuada por regressão logística. Para o desenvolvimento da segunda parte do projecto, realizou-se um ensaio clínico, controlado e aleatorizado tendo em vista o estudo do efeito da intervenção do farmacêutico hospitalar na adesão à terapêutica anti-hipertensora e no controlo da TA. Este ensaio decorreu de Julho de 2009 a Junho de 2010, tendo participado os mesmos doentes com diagnóstico de HTA que foram incluídos no estudo realizado na primeira fase do projecto.

Resultados: Foram incluídos no estudo um total de 197 doentes hipertensos, os quais satisfizeram os critérios de inclusão e consentiram participar. Apenas 33,0% dos doentes tinham a TA controlada, sendo a taxa de adesão à terapêutica anti-hipertensora de 48,2%. A análise de regressão logística revelou a existência de três covariáveis com influência significativa no controlo da TA: adesão à medicação (OR = 4,8; IC 95%: 2,4-9,5; P < 0,001),

estado marital (OR = 5,3; IC 95%: 1,7-16,4; P < 0,004) e diabetes (OR = 4,4; IC 95%: 1,4-13,5; P < 0,011). A mesma análise revelou, ainda, que as seguintes variáveis independentes influenciam significativamente a adesão à terapêutica: conhecimento dos valores alvo de TA (OR = 3,7; IC 95%: 1,9-7,4; P < 0,001), reacções adversas atribuídas à medicação anti-hipertensora (OR = 3,7; IC 95%: 1,6-8,3; P < 0,002), monitorização regular da TA (OR = 2,5; IC 95%: 1,2-5,2; P < 0,015), conhecimento da indicação dos medicamentos (OR = 2,4; IC 95%: 1,1-5,2; P < 0,021) e conhecimento dos riscos da HTA (OR = 2,1; IC 95%: 1,1-4,2; P < 0,026).

Embora no início do ensaio clínico não existissem diferenças significativas em ambos os grupos do estudo (controlo e intervenção) no que respeita a todos os parâmetros relevantes analisados, no final da intervenção farmacêutica, a percentagem de doentes com a TA controlada era significativamente maior no grupo de intervenção (OR = 2,2; IC 95%: 1,3-4,0; P = 0,005). Foram, igualmente, observados, no final do estudo, valores significativamente mais baixos de TA sistólica (-6,8 mm Hg, P = 0,006) e de TA diastólica (-2,9 mm Hg, P = 0,020) no grupo de intervenção. No final do ensaio clínico observou-se, ainda, que a adesão à medicação era mais elevada no grupo de intervenção (74,5% vs 57,6%, P = 0,012).

Conclusões: Uma percentagem significativa de doentes hipertensos a quem foram prescritos medicamentos anti-hipertensores não apresenta a TA controlada, sendo a taxa de adesão a estes medicamentos muito inferior à que seria desejável. A baixa adesão à terapêutica, o desconhecimento, por parte do doente, dos valores alvo de TA, dos riscos da HTA não controlada e das indicações dos medicamentos, bem como a ocorrência de RAMs e a falta de monitorização regular da TA devem ser estudados como possíveis causas de TA não controlada e devem ser considerados em qualquer intervenção que tenha como objectivo aumentar o controlo da TA. A intervenção farmacêutica pode modificar os factores que influenciam a adesão à terapêutica e aumentá-la significativamente, conduzindo, deste modo, a um aumento do controlo da TA em doentes tratados com anti-hipertensores. A inclusão do farmacêutico hospitalar na equipa multidisciplinar de saúde, responsável pelo tratamento dos doentes com HTA, constitui uma estratégia vantajosa para combater este importante problema de saúde pública.

Palavras-chave

Adesão à medicação, anti-hipertensores, estatinas, farmacêutico hospitalar, hipertensão, intervenção farmacêutica, Portugal, tensão arterial.

Abstract

Introduction: Arterial hypertension (AHT) is a disease with high prevalence among adults, being a major risk factor for cardiovascular disease and an important public health problem. Despite pharmacological advances in the treatment of this disease, with efficacy demonstrated in randomized clinical trials, AHT control rates continue to be suboptimal, making it essential to create lines of research and to develop intervention strategies in this area.

Objectives: The initial aim of the present study was to evaluate the percentage of hypertensive patients, attending the hypertension / dyslipidemia clinic at the university teaching hospital of Cova da Beira Hospital Centre, Covilhã, Portugal, with controlled blood pressure (BP) and to study the covariates associated with poor BP control. The following stage aimed to develop, implement and evaluate a hospital pharmacist intervention to increase BP control.

Population and Methods: A cross-sectional observational study was conducted in adult (aged 18 or over) hypertensive patients attending the aforementioned clinic from July to September 2009. Patients were asked to participate in a structured interview which included socio-demographic characteristics, medication adherence, knowledge about AHT and existence of adverse drug reactions. Detailed anthropometric and clinical information was prospectively obtained from medical records. According to the Directorate-General for Health and the "Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" (JNC 7), hypertensive patients without diabetes and chronic kidney disease (CKD) with BP < 140/90 mm Hg were considered to have their BP controlled. For hypertensive patients with diabetes or CKD, BP control was defined as BP measurements < 130/80 mm Hg. Logistic regression was used to determine significant independent predictors of poor BP control. A randomized controlled trial (RCT) was also undertaken, from July 2009 to June 2010, to evaluate the hospital pharmacist's interventions aimed to improve antihypertensive medication adherence and BP control in the abovementioned hypertensive population.

Results: A total of 197 hypertensive patients meeting the inclusion criteria and consenting to participate were included in the study. Of these, only 33.0% had their BP controlled, the antihypertensive medication adherence rate reaching 48.2%. Logistic regression revealed that the covariates medication adherence (OR = 4.8; 95% IC: 2.4-9.5; P < 0.001), marital status (OR = 5.3; IC 95%: 1.7-16.4; P < 0.004) and diabetes (OR = 4.4; IC 95%: 1.4-13.5; P < 0.011) were the independent variables that significantly influenced BP control. Logistic regression also revealed that knowledge of target BP (OR = 3.7; 95% CI: 1.9–7.4; P < 0.001), reporting of drug

side effects (OR = 3.7; 95% CI: 1.6–8.3; P < 0.002), measuring BP regularly (OR = 2.5; 95% CI; 1.2–5.2; P < 0.015), knowledge of drug indications (OR = 2.4; 95% CI; 1.1–5.2; P < 0.021), and knowledge of hypertension risks (OR = 2.1; 95% CI; 1.1–4.2; P < 0.026) were the independent variables that significantly influence medication adherence.

Although at the beginning of the RCT there were no significant differences in both groups (control and intervention) concerning mean age, gender, body mass index, and antihypertensive pharmacotherapy, BP control was higher in the intervention group (OR = 2.2; 95% IC: 1.3-4.0; P = 0.005) at the end of the study. Significantly lower systolic BP (-6.8 mmHg, P = 0.006) and diastolic BP (-2.9 mmHg, P = 0.020) levels were observed in the intervention group. Medication adherence was also significantly higher in the intervention group at the end of the study (74.5% vs 57.6%, P = 0.012).

Conclusions: A significant percentage of hypertensive patients prescribed with antihypertensive medication do not have their BP controlled. The medication adherence rate falls well below the desired value. Poor medication adherence and patient unawareness about target BP values, hypertension risks and antihypertensive drug indications, as well as the presence of drug side effects and lack of regular BP monitoring should be considered as possible underlying causes of inadequately controlled BP and must be addressed in any intervention aimed to improve BP control. Pharmacist intervention can modify factors affecting medication adherence, improve adherence and reduce BP levels in patients treated with antihypertensive agents. This study suggests that one effective method of improving BP control is for pharmacists to recognize inadequate hypertension knowledge and medication adherence and develop strategies that enlist the patient as a participant in the management of his/her health. Thereby, this report also reinforces the pharmacists' role in improving the health care system, leading to superior outcomes in what concerns hypertensive patients.

Keywords

Antihypertensives, blood pressure, hospital pharmacist, hypertension, medication adherence, pharmacist intervention, Portugal, statins.

Índice

Lista de Figuras

Lista de Tabelas

…

xx

Lista de Acrónimos

AHT	*Arterial hypertension*
ANTALDs	Antagonistas da aldoesterona
ARAs	Antagonistas dos receptores da angiotensina
AVC	Acidente vascular cerebral
BB	Bloqueadore beta
BEC	Bloqueador da entrada do cálcio
BP	*Blood pressure*
CDV	Cardiovascular
CHCB	Centro Hospitalar Cova da Beira, E.P.E.
CI	*Confidence interval*
CKD	*Chronic kidney disease*
CT	Colesterol total
DASH	*Dietary approaches to stop hypertension*
DBP	*Diastolic blood pressure*
DGS	Direcção-Geral da Saúde
DIURs	Diuréticos
DP	Desvio padrão
DPOC	Doença pulmonar obstrutiva crónica
ECG	Electrocardiograma
HCTZ	Hidroclorotiazida
HTA	Hipertensão arterial
IC	Intervalo de confiança
IECA	Inibidor da enzima de conversão da angiotensina
IIQ	Intervalo interquartil
IMAOs	Inibidores da monoaminoxidase
IMC	Índice de massa corporal
ITT	*Intent-to-treat*
JNC 7	*Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*
MAPA	Monitorização ambulatória da pressão arterial
MEMS	*Medication event monitoring system*
n	Frequência
OMS	Organização Mundial da Saúde
OR	*Odds ratio*
PTH	Hormona da paratiróide ou paratormona
RAMs	Reacções adversas medicamentosas
RCT	*Randomized controlled trial*
ROC	*Receiver Operating Characteristic*
SBP	*Systolic blood pressure*
SCORE	*Systematic coronary risk evaluation*
TA	Tensão arterial
TAC	Tomografia axial computorizada
TAD	Tensão arterial diastólica
TAS	Tensão arterial sistólica
TG	Triglicéridos

TSH	Hormona estimuladora da tiróide

Capítulo 1

Introdução

"*Drugs don't work in patients who don't take them.*"
C. Everett Koop, MD, US Surgeon General, 1982-1989

A hipertensão arterial (HTA) é o factor de risco mais comum de morbilidade e mortalidade cardiovascular. De acordo com estimativas da Organização Mundial da Saúde (OMS), a HTA é responsável, a nível mundial, por 7,1 milhões de mortes prematuras e por 4,5% do custo total das doenças [64 milhões *disability-adjusted life years* (DALYs)] (Whitworth 2003). Estima-se que existam actualmente cerca de 1 bilião de pessoas no mundo com HTA (333 milhões nos países economicamente desenvolvidos e 639 milhões nos países em vias de desenvolvimento económico) e a sua incidência tem aumentado devido ao envelhecimento da população e ao excesso de peso/obesidade que se verifica nos jovens e adultos (Chockalingam et al. 2006; Chobanian 2008). Prevê-se que o número de adultos com HTA em 2025 aumente cerca de 60%, para um total de 1,56 (1,54 – 1,58 biliões) (Kearney et al. 2005).

A HTA é o problema de saúde pública mais importante em Portugal, sendo responsável por um elevado número de complicações cardiovasculares e constituindo a principal causa de morte e de incapacidade no nosso País (Silva et al. 2009). Estima-se que a prevalência de HTA na população adulta portuguesa seja de 42,1%, o que significa que mais de três milhões de portugueses adultos sofrem desta doença, embora apenas cerca de metade (46,1%) tenha conhecimento de que tem a tensão arterial (TA) elevada (De Macedo et al. 2007). Ainda no nosso País, apenas 39,0% do total de hipertensos adultos está medicado com fármacos anti-hipertensores, mas estima-se que uma percentagem significativa daquele total (cerca de 88,8%) não tem a HTA controlada (De Macedo et al. 2007). A região Centro é, a seguir ao Alentejo, a região de Portugal onde a percentagem de doentes hipertensos adultos controlados é mais baixa (9,7%) (De Macedo et al. 2007).

A HTA é um reconhecido factor de risco cardiovascular, contribuindo para o desenvolvimento de doença cerebrovascular, doença cardíaca isquémica, insuficiência cardíaca e insuficiência renal. O tratamento da HTA está associado a uma redução de cerca de 35-40% do risco de acidente vascular cerebral, de cerca de 20-25% do risco de enfarte do miocárdio e de mais de 50% do risco de insuficiência cardíaca (Collins et al. 1990; Chobanian et al. 2003).

A adopção de um estilo de vida saudável proporciona geralmente uma descida significativa da TA (Chobanian et al. 2003; Direcção-Geral da Saúde 2004). Entre os hábitos de vida saudável sublinha-se a importância de: 1 - redução da ingestão de sal; 2 - a preferência por uma dieta rica em frutos, vegetais e com baixo teor de gorduras saturadas; 3 – prática regular de exercício físico; 4 – consumo moderado de álcool; 5 – cessação dos hábitos tabágicos; 6 – redução de peso no caso dos indivíduos obesos (Chobanian et al. 2003; Direcção-Geral da Saúde 2004).

Nas situações de HTA em que as medidas não farmacológicas, isoladamente, sejam consideradas insuficientes, será necessário de, a estas, adicionar medidas farmacológicas, nomeadamente, através da administração de fármacos anti-hipertensores. No entanto, há que ter presente que estes fármacos não constituem um tratamento etiológico da HTA, destinando-se apenas a controlá-la. De facto, após a sua administração, estes fármacos, através de diversos mecanismos de acção, consoante a classe farmacoterapêutica a que pertençam, possibilitam uma descida da TA para valores normais, a qual, de um modo geral, regressa aos valores anteriores após a eliminação do fármaco do organismo. Deste modo, uma vez iniciado, o tratamento anti-hipertensor deverá, em princípio, ser continuado e mantido por toda a vida. Os objectivos da terapêutica farmacológica deverão ser controlar a TA com o menor número e a menor dose de fármacos. Menos medicamentos significa menos reacções adversas medicamentosas (RAMs) e menos custos para o doente.

Na população hipertensa em geral, o objectivo será a redução da TA para valores inferiores a 140/90 mm Hg (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Polonia et al. 2006; Mancia et al. 2007). Nos doentes hipertensos diabéticos ou com doença renal crónica, o objectivo será a redução da TA para valores inferiores a 130/80 mm Hg (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Polonia et al. 2006; Mancia et al. 2007). Em doentes com insuficiência renal e proteinúria > 1g/dia o objectivo será a redução da TA para valores inferiores a 125/75 mm Hg (Direcção-Geral da Saúde 2004; Polonia et al. 2006).

Embora diversos ensaios clínicos tenham demonstrado a eficácia do tratamento farmacológico no controlo da HTA e na prevenção da doença cardiovascular, a proporção de doentes hipertensos cuja TA se encontra controlada é ainda muito baixa (De Macedo et al. 2007; Morgado et al. 2010; Morgado et al. 2010).

Um estudo efectuado na população adulta portuguesa revelou que apenas 28,9% dos hipertensos a tomar medicação anti-hipertensora tinha os valores da TA inferiores a 140/90 mm Hg (De Macedo et al. 2007). Novamente, a região Centro é, a seguir ao Alentejo, a região de Portugal onde a taxa de controlo (TA < 140/90 mm Hg) dos doentes hipertensos tratados com medicação anti-hipertensora é mais baixa (26,1%) (De Macedo et al. 2007).

Um dos principais obstáculos ao controlo eficaz da HTA está relacionado com a falta de adesão do doente ao tratamento com fármacos anti-hipertensores (Godley et al. 2001; Whitworth 2003; Schroeder et al. 2004). De facto, é hoje consensual que uma percentagem considerável de doentes hipertensos não toma a medicação prescrita de acordo com as indicações do médico, existindo diversos factores que influenciam a adesão à terapêutica com anti-hipertensores (Flack et al. 1996; Burke et al. 1997; De Macedo et al. 2007). A este respeito é importante destacar o facto de a HTA ser considerada uma patologia silenciosa, que não apresenta sintomas, não facilitando, assim, uma adesão do doente a um tratamento não "sentido" como necessário. Por outro lado, num tratamento a longo prazo, muitas vezes para o resto da vida, é importante ter em conta a comodidade da toma dos medicamentos, assim como a tolerabilidade dos mesmos (Chobanian et al. 2003; Direcção-Geral da Saúde 2004). É hoje consensualmente aceite que um anti-hipertensor só é eficaz se for tomado regularmente devendo, no entanto, apresentar um esquema posológico cómodo e ser bem tolerado para que tal suceda. De facto, as taxas de abandono ao tratamento verificadas em algumas classes terapêuticas de anti-hipertensores reflectem a elevada incidência de RAMs (p. ex., tosse, cefaleias, edemas maleolares) associadas a alguns medicamentos. Outros factores que podem influenciar a adesão à terapêutica com anti-hipertensores são: custos elevados dos medicamentos, idade, falta de clareza nas instruções relativas ao tratamento ou dificuldade na compreensão das mesmas, falta de conhecimento acerca da HTA e das suas possíveis complicações (Flack et al. 1996).

Num relatório da OMS, de 2003, intitulado "Adherence to Long-Term Therapies - Evidence for Action" (Sabaté 2003), é referido o seguinte:

"Studies consistently find significant cost-savings and increases in the effectiveness of health interventions that are attributable to low-cost interventions for improving adherence. Without a system that addresses the determinants of adherence, advances in biomedical technology will fail to realize their potential to reduce the burden of chronic illness. Access to medications is necessary but insufficient in itself for the successful treatment of disease" (Sabaté 2003).

Por outro lado, Haynes et al., numa revisão sistemática da *Cochrane Database Systematic Reviews* (Haynes et al. 2000), citada no referido relatório da OMS, expõem:

"Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments" (Haynes et al. 2000).

A avaliação da adesão à terapêutica com anti-hipertensores e o conhecimento dos diversos factores que a influenciam são determinantes para o desenvolvimento de estratégias, por

parte dos diversos profissionais de saúde, tendo em vista aumentar essa mesma adesão, fundamental para o controlo eficaz da HTA e para a prevenção das complicações cardiovasculares graves que lhe estão associadas.

Capítulo 2

Revisão da Literatura

2.1 Definição e classificação de hipertensão arterial

A pressão arterial é a força exercida pelo sangue contra a superfície interna das artérias. Esta força é gerada pelo batimento cardíaco na sua função de bombear o sangue e pode ser modificada por diversos factores, que conduzem a uma subida ou descida da tensão arterial.

Hipertensão arterial significa excesso de pressão arterial ou, mais correctamente, de tensão arterial. Uma comissão de peritos da OMS definiu há mais de cinquenta anos a HTA como a elevação persistente da TA sistólica (TAS) ou da TA diastólica (TAD), ou de ambas, simultaneamente, acima dos valores considerados normais (Tovar 2009). É importante sublinhar, nesta definição, a condição de persistente, indicando que elevações transitórias ou circunstanciais da TA não pressupõem a existência de HTA.

Esta definição poderia, à primeira vista, parecer clara e simples, mas a realidade é um pouco mais complicada e isso deve-se à dificuldade de definir qual a TA normal. De facto, há mais de 100 anos que se discute a partir de que valores de TA se deve falar de HTA (Tovar 2009), o que indica que não existe uma linha divisória clara que permita separar os valores considerados normais dos considerados HTA. De acordo com a Direcção-Geral da Saúde (DGS), o limiar para a HTA deve ser considerado flexível, sendo mais ou menos elevado, dependendo do perfil de risco cardiovascular global de cada indivíduo (Direcção-Geral da Saúde 2004).

Outra forma de entender o conceito de HTA é através das suas consequências, atendendo a que os doentes hipertensos estão mais expostos a sofrer de doenças cérebro e cardiovasculares e vivem, em média, menos anos do que os indivíduos sem HTA. Desta última consequência da HTA estiveram sempre bem conscientes as companhias de seguros e o facto ficou patente numa publicação de 1950 da Sociedade dos Actuários de Chicago, onde ficou registado que a TA elevada se associava a um aumento da taxa de mortalidade e, pelo contrário, a mortalidade era menor em indivíduos com valores mais baixos de TA (Tovar 2009).

As doenças cérebro e cardiovasculares e a morbilidade e mortalidade associadas constituem, pois, consequências que se encontram relacionadas com a HTA e, neste sentido, pode dizer-se que a HTA é fundamentalmente um factor de risco cérebro e cardiovascular, ou seja, uma situação que favorece o aparecimento de complicações que afectam a integridade e o

funcionamento de determinados órgãos, sobretudo o coração, o cérebro, os rins e, logicamente, também as próprias artérias, que sofrem os efeitos da tensão elevada. A HTA constitui o factor de risco quantitativamente mais influente no desenvolvimento da doença vascular cerebral e coronária e da insuficiência cardíaca (Polonia et al. 2006).

Existe uma correlação directa entre a progressão dos valores de TAS e de TAD e o aumento de risco de doença cardiovascular e isto acontece de forma contínua a partir de 110-115/70-75 mm Hg (Figuras 1 e 2) (MacMahon et al. 1990; Lewington et al. 2002; Kaplan 2006). Este facto torna arbitrária qualquer definição e classificação numérica de HTA (Direcção-Geral da Saúde 2004; Polonia et al. 2006; Mancia et al. 2007).

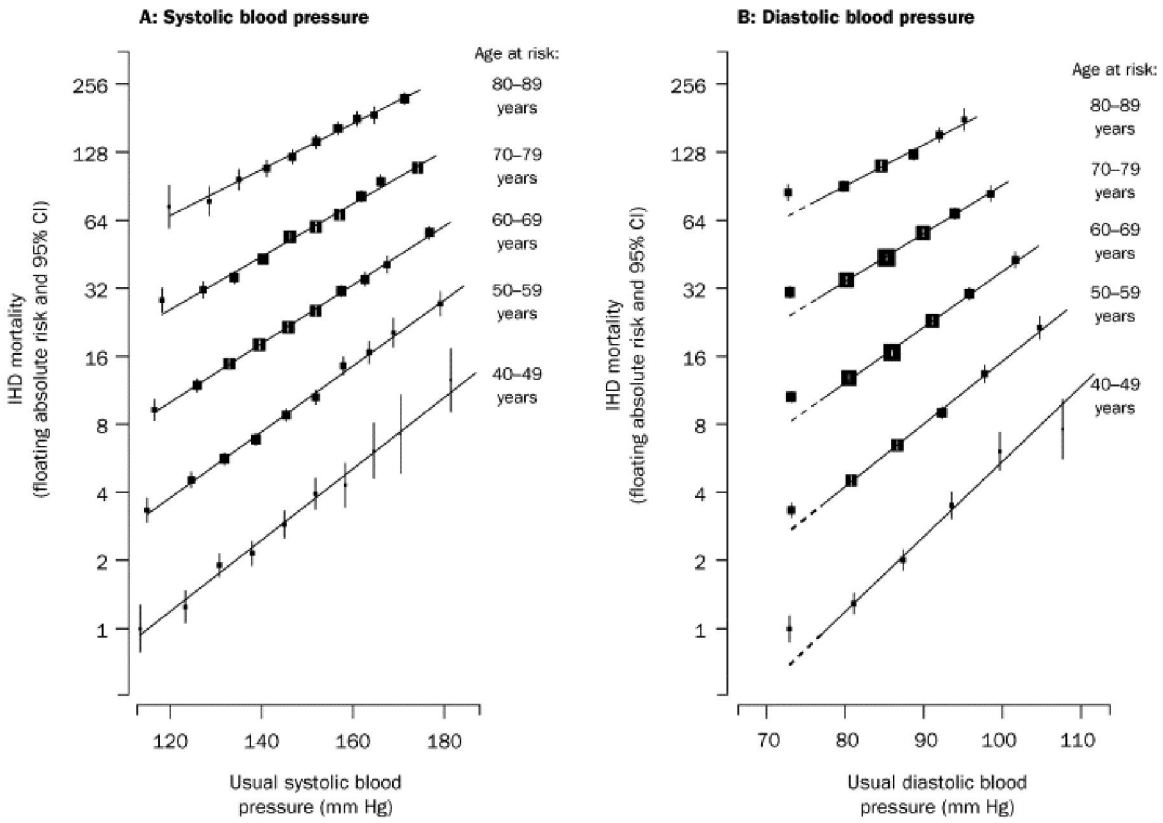


Figura 1 – Taxa de mortalidade por doença cardíaca isquémica em cada década de idade versus tensão arterial habitual no começo de cada década (Lewington et al. 2002). CI – intervalo de confiança; IHD – doença cardíaca isquémica.

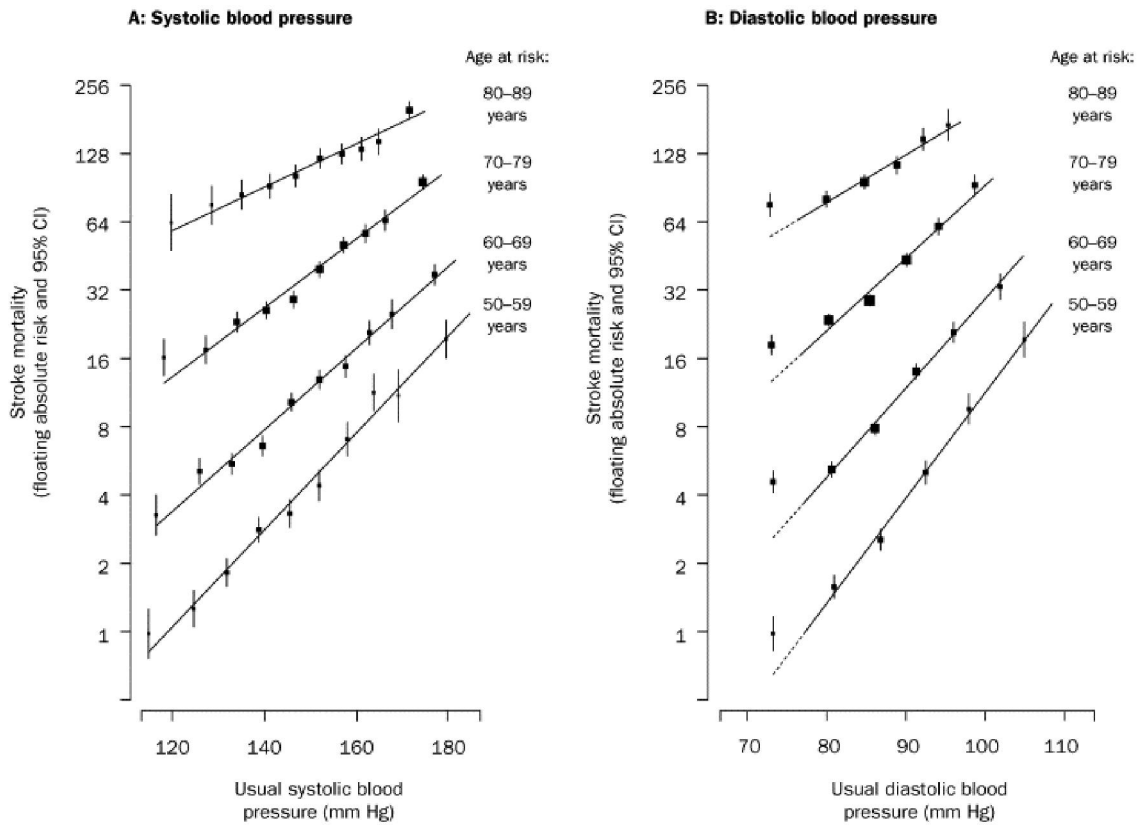


Figura 2 - Taxa de mortalidade por acidente vascular cerebral em cada década de idade versus tensão arterial habitual no começo de cada década (Lewington et al. 2002). CI – intervalo de confiança.

Contudo, uma definição de HTA baseada no risco cardiovascular permanente associado aos valores de TA é de pouca utilidade quando é preciso estabelecer um diagnóstico e um tratamento na prática clínica diária. Daí a necessidade de escalonar um risco contínuo, tendo em vista a homogeneização de grupos em avaliação e a hierarquização em estratos desse risco e das atitudes terapêuticas nesses grupos (Polonia et al. 2006; Mancia et al. 2007).

À medida que se foram realizando estudos que permitiram relacionar os valores da TA com o aparecimento de complicações cardio-cérebrovasculares, foram-se estabelecendo diferentes classificações dos registos da TA que permitiram definir a partir de que valores se deve falar de HTA e, também, estabelecer a partir de que valores se deve instituir um tratamento.

A classificação actualmente reconhecida pela maioria das sociedades científicas e organizações de saúde é a que estabelece que a HTA se define nas pessoas adultas (≥ 18 anos) a partir de valores iguais ou superiores a 140 mm Hg para a TAS e/ou a 90 mm Hg para a TAD (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Polonia et al. 2006; Mancia et al. 2007).

Embora existam diversas *guidelines*, de mérito internacionalmente reconhecido, para a prevenção, o diagnóstico e o tratamento da HTA (Chobanian et al. 2003; Whitworth 2003; Mancia et al. 2007), em Portugal, o documento que vigora sobre o *Diagnóstico, Tratamento e Controlo da HTA* é a Circular Normativa Nº 2/DGCG de 31/03/2004 da DGS (Direcção-Geral da Saúde 2004). Este documento adopta a seguinte classificação de HTA:

Tabela 1 - Classificação dos grupos tensionais (Direcção-Geral da Saúde 2004; Polonia et al. 2006).

Categoria	**Tensão Arterial Sistólica, mm Hg**		**Tensão Arterial Diastólica, mm Hg**
Normal	120 – 129	e	80 - 84
Normal alto	130 – 139	ou	85 - 89
Hipertensão Estádio 1	140 – 159	ou	90 - 99
Hipertensão Estádio 2	≥ 160	ou	≥ 100

Pela sua relevância internacional, importa considerar, ainda, as classificações adoptadas pela *European Society of Hypertension* e *European Society of Cardiology* (Mancia et al. 2007) (Tabela 2) e pelo *Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC 7) (Chobanian et al. 2003) (Tabela 3).

Tabela 2 - Classificação dos valores de tensão arterial de acordo com a *European Society of Hypertension* e *European Society of Cardiology* (Mancia et al. 2007).

Categoria	**Tensão Arterial Sistólica, mm Hg**		**Tensão Arterial Diastólica, mm Hg**
Ideal	< 120	e	< 80
Normal	120 - 129	e/ou	80 - 84
Normal alto	130 - 139	e/ou	85 - 89
Hipertensão Grau 1	140 - 159	e/ou	90 – 99
Hipertensão Grau 2	160 - 179	e/ou	100 - 109
Hipertensão Grau 3	≥ 180	e/ou	≥ 110
Hipertensão sistólica isolada	≥ 140	e	< 90

A hipertensão sistólica isolada deve também ser classificada num determinado grau (1, 2 ou 3) de acordo com os intervalos de tensão arterial sistólica indicados.

Tabela 3 - Classificação dos valores de tensão arterial de acordo com o *Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC 7) (Chobanian et al. 2003).

Categoria	**Tensão Arterial Sistólica, mm Hg**		**Tensão Arterial Diastólica, mm Hg**
Normal	< 120	e	< 80
Pré-hipertensão	120 - 139	ou	80 - 89
Hipertensão Estádio 1	140 - 159	ou	90 - 99
Hipertensão Estádio 2	≥ 160	ou	≥ 100

De notar que, em qualquer das normas de orientação mencionadas, quando a TAS e a TAD estão em categorias diferentes, para a classificação de HTA prevalece a mais elevada.

Como principais diferenças entre estas três normas de orientação há a referir o seguinte:

- O JNC 7 considera uma nova entidade (não presente no JNC 6), a pré-hipertensão arterial (120-139/80-89 mm Hg), em vez da HTA normal alta (130-139/85-89 mm Hg) considerada pela Circular Normativa da DGS e pelas *guidelines* Europeias;
- As *guidelines* Europeias apresentam o conceito de HTA de grau 3 (≥ 180/110 mm Hg), que foi enquadrado na HTA de estádio 2 (≥ 160/100 mm Hg) da Circular Normativa da DGS e das *guidelines* do JNC 7.

A unificação, pelas *guidelines* do JNC 7, das categorias "normal" (120–129/80-84 mm Hg) e "*borderline*" (130–139/85-89 mm Hg) (presentes nas *guidelines* do JNC6) numa única entidade designada "pré-hipertensão" (120–139/80–89 mm Hg) baseou-se nos resultados do estudo de Framingham (Vasan et al. 2001; Vasan et al. 2002), em que se verificou que a probabilidade daqueles indivíduos de desenvolverem HTA é maior do que a dos indivíduos com uma TA < 120/80 mm Hg (classificada, nas últimas *guidelines*, como "normal"). A HTA de estádio 3 (≥ 180/110 mm Hg) estava também presente nas *guidelines* do JNC 6, mas foi combinada, nas *guidelines* do JNC 7, com a HTA de estádio 2 (160-179/100-109 mm Hg), dando origem a uma única categoria designada HTA de estádio 2 (≥ 160/100 mm Hg). Esta alteração foi justificada com o facto de o tratamento e a monitorização daqueles dois estádios serem semelhantes (Chobanian et al. 2003).

Diversos estudos populacionais revelaram que os valores de TA medidos no consultório ou clínica, pelo médico ou enfermeiro, são geralmente mais elevados do que os obtidos quando a determinação é efectuada em casa, pelo próprio indivíduo ou familiar, ou em regime de ambulatório, de forma automática, por um período de 24 horas (MAPA, Monitorização

Ambulatória da Pressão Arterial) (Staessen et al. 1991; Mancia et al. 1995; Ohkubo et al. 1998). Consequentemente, diversas sociedades científicas e organizações de saúde estabeleceram diferentes limites de TA para a definição de HTA, em função dos métodos usados na medição da TA (consultório / clínica, automedição em casa ou MAPA) (Direcção-Geral da Saúde 2004; Polonia et al. 2006; Mancia et al. 2007). Os limites adoptados pela DGS e pela Sociedade Portuguesa de Hipertensão estão representados na Tabela 4 (Direcção-Geral da Saúde 2004; Polonia et al. 2006).

A detecção precoce da HTA, particularmente nos indivíduos com risco cardiovascular acrescido (p. ex. diabéticos, insuficientes renais, doentes com dislipidémia, obesos, fumadores) e a prossecução dos objectivos de controlo tensional ao longo dos anos deverão constituir prioridades de intervenção dos serviços prestadores de cuidados de saúde (Direcção-Geral da Saúde 2004; Polonia et al. 2006).

Tabela 4 - Limites de TA adoptados pela Direcção-Geral da Saúde e pela Sociedade Portuguesa de Hipertensão para a definição de HTA em função do método usado na medição da TA (Portuguese Department of Health 2004. Available at http://www.dgs.pt/. Accessed on 07/15/2010; Polonia et al. 2006).

Método	Limites (mm Hg) para definição de hipertensão arterial	Comentários
TA de consultório	TAS ≥ 140 e/ou TAD ≥ 90 mm Hg	Dois registos, doente sentado, intervalo de 5 minutos. Confirmar TA no braço contralateral.
Monitorização ambulatória da tensão arterial de 24 horas	TAS 24h ≥ 125 e/ou TAD 24h ≥ 80 mm Hg e/ou TAS diurna ≥ 135 e/ou TAD diurna ≥ 85 mm Hg	Indicada na avaliação de: “hipertensão da bata branca”, “hipertensão mascarada”, hipertensão nocturna”, “hipertensão resistente” e “hipertensão da grávida”. Descida da TA nocturna < 10% pode indicar maior risco cardiovascular.
Automedição da TA	TAS ≥ 135 e/ou TAD ≥ 85 mm Hg	Informa sobre resposta à terapêutica. Pode contribuir para aumentar a adesão à terapêutica e para o diagnóstico da “hipertensão da bata branca”.

2.2 Avaliação da tensão arterial

A TA sofre variações circadianas consideráveis, variando igualmente ao longo dos dias, dos meses e das estações (Mancia et al. 1983; Sega et al. 1998; Modesti et al. 2006). Desta forma, o diagnóstico de HTA deve ser feito com base em diversas medições da TA, efectuadas em diferentes ocasiões ao longo de um período de tempo (dias, semanas ou meses). Se a TA está

apenas ligeiramente elevada, devem ser efectuadas determinações adicionais ao longo de um período de vários meses para determinar a TA "habitual" de forma o mais precisa possível (Mancia et al. 2007). Pelo contrário, se o doente apresenta uma elevação mais acentuada da TA, evidência de lesão de órgãos relacionada com a HTA ou um risco cardiovascular elevado, devem ser efectuadas medições adicionais da TA ao longo de períodos de tempo mais curtos (dias ou semanas) (Mancia et al. 2007). De um modo geral, o diagnóstico de HTA deve ser feito com base em, pelo menos, duas medições da TA por consulta e em, pelo menos, 2 a 3 consultas, embora, nas formas mais severas de HTA, o diagnóstico possa ser feito na primeira consulta (Mancia et al. 2007).

A TA deve ser avaliada com o indivíduo sentado, em ambiente calmo, homeotérmico, sem agressão por poluição sonora ou luminosa e sem ingestão ou inalação de produtos excitantes (bebidas com cafeína, álcool, tabaco, etc.) no período imediatamente antecedente (15 - 30 minutos) (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Polonia et al. 2006). Devem ser utilizados aparelhos aferidos e validados que avaliam a TA na artéria umeral, usando uma braçadeira em que a câmara insuflável ocupe entre metade e 80% do diâmetro do braço (ideal de 75% a 80%) (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Polonia et al. 2006); a braçadeira deve ficar ao nível do coração, qualquer que seja a posição do indivíduo (Chobanian et al. 2003; Mancia et al. 2007). O doente deve descansar, sentado numa cadeira com apoio para a coluna e com os pés bem assentes no chão, pelo menos 5 minutos, antes de medir a TA (Chobanian et al. 2003). Na primeira determinação da TA, a medição deve ser efectuada em ambos os braços; as medições posteriores devem ser feitas no braço em que se registou o valor mais elevado (Mancia et al. 2009). Devem ser efectuadas, pelo menos, 2 medições da TA com um intervalo de 1 – 5 minutos e registada a média dos valores obtidos (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Polonia et al. 2006; Mancia et al. 2009); devem ser realizadas medições adicionais se existir uma diferença considerável entre as duas primeiras medições efectuadas (Mancia et al. 2009). No caso de doentes idosos, diabéticos ou em outras situações em que se suspeite de hipotensão ortostática a medição deve ser efectuada com o doente sentado e em pé (no primeiro e quinto minuto após o ortostatismo) (Chobanian et al. 2003; Polonia et al. 2006; Mancia et al. 2007). Nos métodos auscultatórios de medição da TA devem utilizar-se as fases I e V de Korotkow para a definição da TAS e da TAD, respectivamente (Chobanian et al. 2003; Polonia et al. 2006; Mancia et al. 2007).

2.3 Hipertensão da bata branca

A hipertensão da bata branca consiste na TA persistentemente elevada em ambiente de consultório ou hospitalar (> 140/90 mm Hg em, pelo menos, três consultas), enquanto que fora destes locais os valores são normais. Nestes doentes a monitorização ambulatória da TA de 24 horas revela valores normais (< 125/80 mm Hg), bem com a TA diurna (< 135/85 mm Hg) e a automedição da TA realizada em casa (< 135/85 mm Hg) (Mancia et al. 2007).

Estima-se que a hipertensão da bata branca esteja presente em cerca de 15% da população em geral, tendo sido reconhecida a sua influência no diagnóstico e controlo da HTA, podendo contribuir para uma fracção considerável (um terço ou mais) dos indivíduos diagnosticados com HTA (Ohkubo et al. 2005; Hansen et al. 2006; Mancia et al. 2006). A monitorização ambulatória da TA de 24 horas bem como a medição da TA realizada em casa são, pois, de grande importância no diagnóstico da hipertensão da bata branca (Polonia et al. 2006).

Parece haver evidências que os indivíduos com esta condição apresentam um risco cardiovascular intermédio entre os doentes hipertensos e os normotensos (Mancia et al. 2006). O doente com hipertensão da bata branca (TA consultório ≥ 140 e/ou 90 mm Hg após, pelo menos, três consultas e TA de 24 horas < 125/80 mm Hg) e sem lesão dos órgãos alvo, necessita de vigilância e de alteração dos estilos de vida, mas pode dispensar a terapêutica farmacológica (Polonia et al. 2006; Mancia et al. 2007). Contudo, se existir lesão dos órgãos alvo ou um risco cardiovascular elevado, deverá ser instituída a terapêutica farmacológica (Mancia et al. 2007).

Os idosos apresentam uma maior variabilidade na TA e uma maior tendência para a hipertensão da bata branca, com uma prevalência de 17% (Ommen and Lipkowitz 2007). É também mais frequente em mulheres diagnosticadas com HTA de estádio 1, em não fumadores, nos hipertensos recentemente diagnosticados e quando existe um número limitado de medições da TA no consultório (O'Brien et al. 2003). A massa ventricular esquerda determinada por ecocardiografia é frequentemente normal nos indivíduos com hipertensão da bata branca (Verdecchia et al. 2003).

2.4 Hipertensão mascarada

A hipertensão mascarada é considerada o fenómeno inverso da hipertensão da bata branca, no sentido em que consiste na TA de consultório normal (< 140 / 90 mm Hg) enquanto que a TA ambulatória (MAPA ou TA em casa) se encontra elevada (Bobrie et al. 2004; Fagard et al. 2005; Ohkubo et al. 2005; Hansen et al. 2006; Mancia et al. 2006; Pickering et al. 2006).

Estima-se que a sua prevalência seja aproximadamente semelhante à da hipertensão da bata branca (Bjorklund et al. 2003; Ohkubo et al. 2005; Hansen et al. 2006; Mancia et al. 2006), calculando-se que 1 em cada 7 ou 8 indivíduos com a TA de consultório normal tenha hipertensão mascarada (Mancia et al. 2006). É mais frequente nos grupos etários mais jovens, sendo difícil de detectar (Pickering et al. 2002). Suspeita-se, também, que seja mais frequente em indivíduos com hábitos tabágicos, com sedentarismo, com diabetes, em doentes com múltiplos factores de risco cardiovascular e nos que têm antecedentes familiares de HTA nos dois pais (O'Brien 2003). A monitorização ambulatória da TA de 24 horas é de grande

importância no diagnóstico da hipertensão mascarada, tendo contribuído decisivamente para o reconhecimento deste fenómeno (Pickering et al. 2002; Ommen and Lipkowitz 2007).

Alguns estudos apontam para a existência de maior número de lesões dos órgãos alvo e de eventos cardiovasculares neste grupo de doentes, quando comparados com os normotensos e lesões semelhantes quando comparados com os do grupo de hipertensos com hipertensão dentro e fora do consultório (Fagard et al. 2005; Ohkubo et al. 2005; Hansen et al. 2006; Mancia et al. 2006; Ommen and Lipkowitz 2007). Por este motivo, se a hipertensão mascarada se mantiver persistente, é importante instituir a terapêutica farmacológica anti-hipertensora, pois os indivíduos que a apresentam têm um risco 2,5 vezes superior de morte cardiovascular ou de acidente vascular cerebral do que os normotensos (Lurbe et al. 2005; Ommen and Lipkowitz 2007).

A TA ambulatória (MAPA ou auto medição da TA no domicílio) é melhor factor preditivo dos eventos cardiovasculares (Bobrie et al. 2004) e da mortalidade (Ohkubo et al. 1998; Bobrie et al. 2004) do que a TA avaliada no consultório, tanto na população em geral como nos grupos de alto risco (Verdecchia et al. 2004; Mancia et al. 2007). Da mesma forma, existe uma melhor correlação da TA ambulatória relativamente à TA no consultório no que se refere ao atingimento dos órgãos alvo, particularmente, hipertrofia ventricular esquerda, proteinúria, retinopatia e espessamento da parede carotídea (Kamoi et al. 2002; Mule et al. 2002; Tsunoda et al. 2002; Verberk et al. 2005).

2.5 Pseudohipertensão

A pseudohipertensão é uma condição em que os valores de TA obtidos por esfigmomanometria são inapropriadamente altos quando comparados com as verdadeiras pressões intra-arteriais e devem-se à incapacidade da braçadeira do aparelho de medição de comprimir uma artéria braquial endurecida, espessada ou calcificada (Chobanian et al. 2003; Mancia et al. 2007). É ocasionalmente encontrada em pessoas idosas com aterosclerose generalizada (Chobanian et al. 2003; Paiva 2005). Deve suspeitar-se da presença de pseudohipertensão quando existem sintomas de hipotensão atribuídos à medicação anti-hipertensora (p. ex., tonturas, astenia), na ausência de uma excessiva redução da TA (Spence et al. 1978). Para além destes sintomas, existem alguns sinais que podem levar à suspeita de pseudohipertensão: HTA severa sem grande repercussão nos órgãos alvo; evidências radiológicas de calcificação da artéria braquial; valores de TA mais elevados na artéria braquial que nas extremidades inferiores; hipertensão sistólica isolada severa (Paiva 2005).

O diagnóstico definitivo de pseudohipertensão requer a medição directa da pressão intra-arterial, que apresenta o inconveniente de ser um procedimento invasivo (punção arterial directa). Uma alternativa consiste na determinação da TA utilizando um aparelho infrasónico automático ou pletismógrafo (Oparil and Calhoun 1998; Vidt 2000).

2.6 Causas identificáveis de hipertensão arterial

Em cerca de 95% dos doentes hipertensos a etiologia da HTA não pode ser identificada (HTA primária ou essencial) (Carretero and Oparil 2000), definindo-se como HTA secundária aquela cuja origem é conhecida (Tabela 5).

Tabela 5 - Causas identificáveis de hipertensão arterial e respectivos testes de diagnóstico (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Polonia et al. 2006).

Causas identificáveis de HTA	Teste de diagnóstico
Apneia do sono	Estudo do sono com avaliação da saturação de O_2 no sangue arterial
Induzida por fármacos (contraceptivos orais, corticosteróides, anti-inflamatórios não esteróides, simpaticomiméticos (descongestionantes, anorécticos), hormonas da tiróide, IMAOs, esteróides anabolizantes, eritropoetina)	História clínica; pesquisa de substâncias activas nos fluidos biológicos
Doença renal crónica	Taxa de filtração glomerular estimada
Hiperaldosteronismo primário e outros excessos de mineralocorticóides	Concentração de aldosterona ou determinações específicas de outros mineralocorticóides na urina de 24 horas
Hipertensão renovascular	Ecografia Doppler das artérias renais para estudo do fluxo; angiografia por ressonância magnética nuclear
Síndrome de Cushing ou terapêutica esteróide	História clínica; teste de supressão pela dexametasona
Feocromocitoma	Metanefrina e normetanefrina na urina de 24 horas
Coarctação da aorta	Angiografia por tomografia computorizada
Doença tiroideia e paratiroidea	TSH; PTH sérica

IMAOs – Inibidores da monoaminoxidase; TSH - hormona estimuladora da tiróide; PTH - hormona da paratiróide ou paratormona.

Deverá suspeitar-se de uma causa identificável de HTA nos doentes (Chobanian et al. 2003; Mancia et al. 2007):

1) cuja idade, história clínica, exame físico, gravidade da hipertensão ou valores laboratoriais sugiram causas identificáveis;

2) que não respondam ou respondam de forma insatisfatória à terapêutica farmacológica;

3) que tendo a TA controlada iniciem uma descompensação por motivos incertos;

4) apresentem valores de TAS ≥ 180 mm Hg e/ou TAD ≥ 110 mm Hg;

5) com aparecimento súbito de HTA.

A Tabela 6 sumaria os sintomas e sinais frequentemente associados a algumas causas de hipertensão secundária, que podem orientar na realização dos exames diagnósticos necessários em cada caso (Paiva 2005).

Tabela 6 - Sinais e sintomas indicativos de hipertensão arterial secundária (Paiva 2005).

Doença parenquimatosa renal	**Hiperaldosteronismo primário**
• Elevação da creatinina plasmática	• Hipocaliemia espontânea ou provocada
• Sedimento urinário patológico: proteinúria, hematúria, cilindros celulares	• Cãibras musculares, debilidade
• Diminuição do tamanho da silhueta renal	• Poliúria, ocasionalmente polidipsia
	Coarctação da aorta
Doença vascular renal	• Diminuição dos pulsos femorais
• HTA de aparecimento brusco, antes dos 30 anos ou depois dos 50	• Gradiente de pressão entre os membros superiores e inferiores
• HTA estádio 2 (TA ≥ 160/100 mm Hg)	• Sopro sistólico
• Insuficiência renal aguda após toma de IECA	• Sopro contínuo sobre as artérias intercostais
Sopro abdominal ou sopro epigástrico contínuo	
• HTA de aparecimento recente em idoso com doença vascular difusa	**Patologia tiroidea**
• Assimetria do tamanho renal	• Aumento nodular difuso da glândula
	• Hipertiroidismo: ansiedade, tremor, transtornos do sono, perda de peso, debilidade de grupos musculares proximais, amenorreia; dispneia, palpitações, taquicardia, pressão de pulso elevada
Feocromocitoma	
• Crises paroxísticas	
• Cefaleias, palpitações, sudação difusa	
• Grande variabilidade dos valores de TA	• Hipotiroidismo: letargia, depressão; intolerância ao frio, síndrome do túnel cárpico aumento de peso; rouquidão, afonia; parkinsonismo
• HTA estádio 2 (TA ≥160/100 mm Hg)	
• Resposta hipertensiva a fármacos anti-hipertensores ou anestésicos	
• Massa abdominal	
Síndrome de Cushing	
• Obesidade troncular, cara de lua-cheia, hirsutismo	
• Estrias cutâneas	
• Debilidade muscular	
• Transtornos emocionais	
• Amenorreia, diminuição da libido	
• Fracturas ósseas espontâneas	

HTA – hipertensão arterial; IECA – inibidor da enzima de conversão da angiotensina; TA – tensão arterial.

Por exemplo, deve suspeitar-se de feocromocitoma nos doentes com hipertensão lábil ou paroxismos de hipertensão, acompanhados de cefaleias, palpitações, palidez e sudorese (Lo et al. 2000; Manger and Gifford 2002). Sopros abdominais, particularmente aqueles que lateralizam para áreas renais ou têm componente diastólica, sugerem doença renovascular;

massas abdominais ou nos flancos sugerem rins policísticos; ausência ou demora do pulso da artéria femoral e níveis pressóricos diminuídos nas extremidades inferiores podem indicar coarctação da aorta; obesidade troncular, intolerância à glucose e estrias cutâneas de cor avermelhada e violeta sugerem síndrome de Cushing. Exemplos de pistas sugeridas por testes laboratoriais incluem hipocaliemia não provocada (aldosteronismo primário), hipercalcemia (hiperparatireoidismo) e creatinina elevada ou exame de urina anormal (doença parenquimatosa renal). Investigações apropriadas devem ser conduzidas quando houver alto índice de suspeita de causa identificável de HTA (Tabela 5), dada a sua potencial cura ou tratamento específico.

2.7 Hipertensão arterial primária ou essencial

Na grande maioria dos doentes com HTA desconhece-se a sua etiologia, não querendo isto dizer que a hipertensão não tem uma (ou várias) causa(s), mas, de momento, esta(s) não é(são) conhecida(s); esta forma de TA elevada denomina-se hipertensão essencial, primária ou idiopática. Possivelmente, é a conjugação de diversas variações genéticas com diversos factores ambientais / comportamentais, como determinados estilos de vida e hábitos alimentares, que cria as condições necessárias para que a HTA se desenvolva (Figura 3) (Carretero and Oparil 2000; Kunes and Zicha 2009).

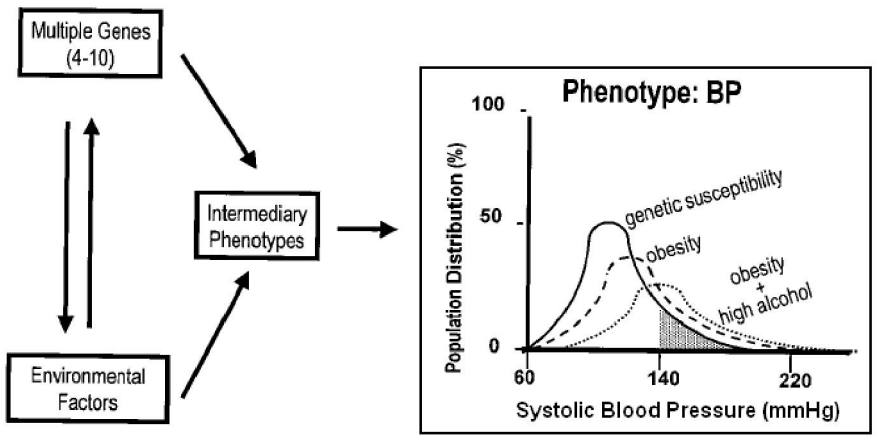


Figura 3 - Interacção entre factores genéticos e ambientais no desenvolvimento da HTA. O lado esquerdo da figura pretende ilustrar que os factores ambientais e diversos genes responsáveis pela TA elevada podem interagir e influenciar fenótipos intermediários. O resultado destes fenótipos intermediários é uma distribuição normal, com um desvio para a direita, da TA. A linha contínua indica a distribuição teórica da TA numa população não afectada for factores hipertensinogénicos; a área a sombreado indica a TAS no intervalo da HTA (≥ 140 mm Hg). As linhas a tracejado e a pontilhado indicam, respectivamente, populações com 1 (obesidade) ou 2 (obesidade e ingestão excessiva de álcool) factores hipertensinogénicos. Nestas duas populações as curvas de distribuição estão desviadas para a direita (TA mais elevada) e o número de indivíduos hipertensos aumenta significativamente com a introdução de factores hipertensinogénicos (Carretero and Oparil 2000). BP – blood pressure.

De referir que existem doenças genéticas raras responsáveis por formas mendelianas de hipertensão, em que a mutação de um único gene é responsável por elevações acentuadas da TA (p. ex., aldosteronismo remediável por glicocorticóides, deficiências de 11beta-hidroxilase e 17alfa-hidroxilase, síndrome de Liddle, síndrome do excesso aparente de mineralocorticóides, pseudohipoaldosteronismo do tipo II) (Carretero and Oparil 2000; Lifton et al. 2001). Nestas formas monogénicas de hipertensão, o diagnóstico da mutação genética envolvida facilita a terapêutica direccionada e o rastreio de familiares portadores da mesma patologia. A contribuição destas mutações genéticas para os níveis de TA da população em geral é, contudo, muito reduzida (Chobanian et al. 2003).

Contrariamente às doenças monogénicas referidas, a hipertensão primária é considerada uma patologia complexa, multifactorial, em que estão envolvidos múltiplos alelos génicos (poligénica) e múltiplas interacções destes genes com diversos factores ambientais, como a obesidade, o tabagismo, a ingestão de sal e de álcool, a actividade física, o stress, etc. (Carretero and Oparil 2000; Kunes and Zicha 2009).

As variações genéticas associadas à hipertensão primária permanecem desconhecidas na sua grande maioria (Luft 1998; Gong and Hubner 2006). Diversos polimorfismos e mutações em diversos genes foram associados ao desenvolvimento da HTA (p. ex., angiotensinogénio, enzima conversora da angiotensina, receptor adrenérgico beta-2, alfa-aducina, angiotensinase C, proteína de ligação à renina, subunidade beta-3 da proteína G, factor natriurético auricular, receptor da insulina); contudo, na maioria dos estudos, a associação observada foi fraca, além de que se estima que a contribuição destas variações genéticas já estudadas, isoladamente ou em combinação, para os níveis de TA da população em geral é muito pequena (Carretero and Oparil 2000; Chobanian et al. 2003). Gong e Hubner (Gong and Hubner 2006) efectuaram uma excelente revisão das variações genéticas associadas à HTA.

Carretero e Oparil (Carretero and Oparil 2000) designaram por “TA hereditária” os valores da TA que são geneticamente determinados, embora não sejam conhecidos a grande maioria dos genes que fazem a TA variar; estudos realizados em familiares do primeiro grau revelam que a “TA hereditária” pode variar desde a categoria “normal” até à “hipertensão de estádio 2”. Os factores ambientais / comportamentais que conduzem a um aumento da TA, tais como a obesidade, o tabagismo, a ingestão elevada de sal e de álcool, são designados por “factores hipertensinogénicos” (Carretero and Oparil 2000). A “TA hereditária” é, então, considerada a “TA *core*” e os “factores hipertensinogénicos” contribuem para o aumento da TA para além do valor “core” geneticamente determinado, originando, assim, as 4 principais possibilidades seguintes (Carretero and Oparil 2000): (1) indivíduos que têm uma “TA hereditária” na categoria ideal (<120/<80 mm Hg); se forem adicionados 1 ou mais “factores hipertensinogénicos”, a TA aumentará até <130/<85 mm Hg (normal) ou mesmo até 130-139/85-89 (normal alto); (2) indivíduos que têm uma “TA hereditária” no intervalo 120-

129/80-84 mm Hg (normal); se forem adicionados 1 ou mais "factores hipertensinogénicos", a TA aumentará até 130-139/85-89 mm Hg (normal alto) ou mesmo até 140-159/90-99 mm Hg (hipertensão de estádio 1); (3) indivíduos que têm uma "TA hereditária" na categoria 130-139/85-89 mm Hg (normal alto); se forem adicionados 1 ou mais "factores hipertensinogénicos", a TA aumentará até 140-159/90-99 mm Hg (hipertensão de estádio 1) ou mesmo até ≥160/≥100 mm Hg (hipertensão de estádio 2); e (4) indivíduos que têm uma "TA hereditária" na categoria 140-159/90-99 mm Hg (hipertensão de estádio 1); se forem adicionados 1 ou mais "factores hipertensinogénicos", a TA aumentará até ≥160/≥100 mm Hg (hipertensão de estádio 2).

Daqui resulta que o conhecimento dos factores hipertensinogénicos é extremamente importante tendo em vista a prevenção e o tratamento da HTA. Importa, no entanto, referir que alguns factores hipertensinogénicos, tais como a obesidade, a resistência à insulina e o consumo elevado de álcool, podem também ter uma componente genética significativa.

2.8 Factores que podem contribuir para a hipertensão arterial

Na maioria das pessoas que sofre de HTA é habitual verificar-se a concorrência de factores favorecedores hereditários, de estilos de vida e hábitos alimentares.

Existem diversos factores que podem contribuir para a elevação da TA em indivíduos geneticamente susceptíveis: excesso de peso, resistência à insulina, dislipidémia, consumo excessivo de álcool, consumo de sal, baixa ingestão de potássio, tabagismo, sedentarismo, stress e idade. Além disso, muitos destes factores revelam um efeito aditivo.

2.8.1 Obesidade

A obesidade (avaliada pelo índice de massa corporal, Kg/m^2) e a hiperinsulinemia estão associadas com o aumento da TA e diminuição da resposta à terapêutica (Carretero and Oparil 2000). Nem todas as pessoas obesas são hipertensas, do mesmo modo que os indivíduos sem excesso de peso também podem desenvolver HTA. No entanto, a obesidade, especialmente a obesidade abdominal, está frequentemente associada à HTA e a perda de peso é uma forma eficaz de reduzir a TA (Carretero and Oparil 2000; Carretero and Oparil 2000). A relação entre o índice de massa corporal e a TA existe tanto para a TAS como para a TAD, verifica-se em homens e mulheres e aumenta com a idade (Neter et al. 2003; Kaplan 2006; Tovar 2009).

A obesidade, particularmente a obesidade abdominal, é o principal factor hipertensinogénico. O estudo de Framingham revelou que cada aumento de 10% de peso corporal está associado a um aumento de 6,5 mm Hg da TAS (Ashley and Kannel 1974). Estudos observacionais revelaram que a TA está directamente associada ao índice de massa corporal (Kg/m^2) (Daniels

et al. 1996; Field et al. 2001) e que o excesso de massa adiposa constitui um factor que contribui para o aumento da TA e para o desenvolvimento da HTA (Stamler 1991).

A obesidade constitui um importante factor de risco cardiovascular. A obesidade é também uma causa de resistência à insulina, dislipidémia, diabetes mellitus tipo II, hipertrofia ventricular esquerda e doença aterosclerótica. A sua incidência e prevalência têm aumentado na maioria dos países industrializados e nos Estados Unidos da América atingiu mesmo proporções epidémicas. Um índice de massa corporal de 26 – 28 Kg/m^2, quando comparado com um inferior a 23 Kg/m^2, aumenta o risco de HTA em cerca de 180% e o risco de resistência à insulina de cerca de > 1000% (Carretero and Oparil 2000). A resistência à insulina e a consequente hiperinsulinemia estão, desta forma, presentes em muitos doentes com obesidade e HTA. No entanto, dependendo das populações estudadas e dos métodos usados para definir a resistência à insulina, esta está também presente em 25% - 40% dos hipertensos não obesos e não diabéticos (Lind et al. 1995).

Os mecanismos pelos quais a obesidade aumenta a TA não estão completamente esclarecidos, mas o aumento do índice de massa corporal está associado a um aumento do volume plasmático e do débito cardíaco; estes dois parâmetros, bem como a TA, podem ser diminuídos através da perda de peso, tanto em indivíduos normotensos como em hipertensos (Rocchini et al. 1989), mesmo quando a ingestão de sódio é mantida constante (Reisin et al. 1978). Diversos estudos revelam, contudo, que as diferentes estratégias que visam a redução de peso têm uma taxa de sucesso reduzida (excepção feita para as cirurgias gástricas), particularmente a longo prazo (Moore et al. 2003) (Kaplan 2006).

2.8.2 Resistência à insulina

A resistência à insulina está também associada à HTA, conforme demonstrado em diversos estudos laboratoriais e clínicos (Ferrannini et al. 1987; Ferrari and Weidmann 1990). Foram propostos diversos mecanismos para explicar o aumento da TA causado pela resistência à insulina, sendo de salientar o aumento da actividade do sistema nervoso simpático, a retenção de sódio e de água, e a hipertrofia do músculo liso dos vasos de resistência, induzidas pela insulina (Figura 4) (Kotchen 1999).

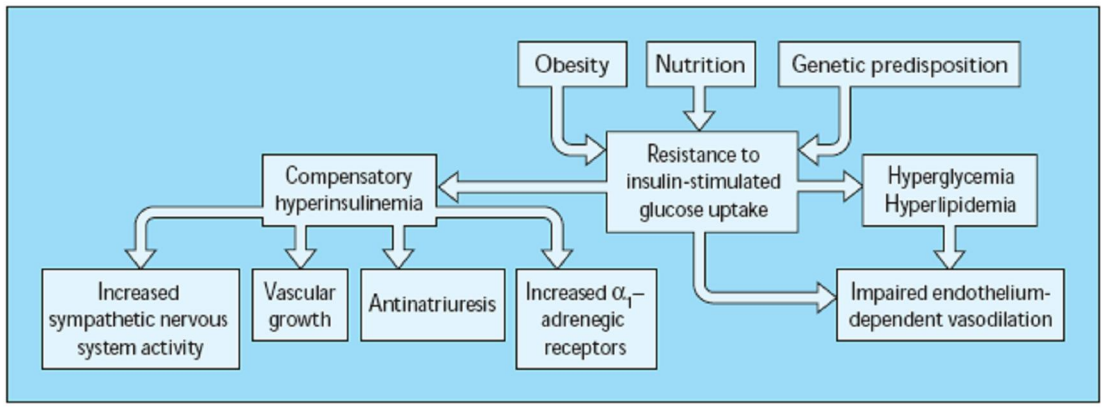


Figura 4 - Hipertensão associada à resistência à insulina. Potenciais mecanismos pelos quais a hiperinsulinemia associada à resistência à insulina origina a hipertensão (Kotchen 1999).

De notar que existem diversos factores genéticos e nutricionais que contribuem para o desenvolvimento de resistência à insulina e que a obesidade, a diabetes mellitus tipo II e a dislipidémia, para além da HTA, aparecem muitas vezes associados à hiperinsulinemia.

2.8.3 Dislipidémia

A dislipidémia constitui outro factor de risco cardiovascular que aparece muitas vezes associado ao desenvolvimento de HTA (Hunt et al. 1991; Haffner et al. 1996; Halperin et al. 2006; Laaksonen et al. 2008). Vários estudos avaliaram prospectivamente a relação existente entre os lípidos plasmáticos e o futuro desenvolvimento de HTA, tendo verificado que existe uma associação entre a dislipidémia e o desenvolvimento de HTA em indivíduos inicialmente não hipertensos (Hunt et al. 1991; Haffner et al. 1996; Halperin et al. 2006; Laaksonen et al. 2008). Desta forma, diversos autores sugeriram que a detecção de dislipidémia pode ser útil na identificação de indivíduos em risco de desenvolver HTA (Halperin et al. 2006; Laaksonen et al. 2008). Adicionalmente, verificou-se que o tratamento da dislipidémia, tendo em vista a diminuição do colesterol plasmático total, conduziu a uma diminuição significativa da TAS e da TAD (Glorioso et al. 1999; Ferrier et al. 2002; Borghi et al. 2004), tendo esta diminuição sido mais acentuada nos indivíduos tratados com estatinas (Borghi et al. 2004). Os mecanismos biológicos pelos quais os lípidos aterogénicos conduzem, de forma independente da resistência à insulina, ao desenvolvimento de HTA permanecem pouco esclarecidos, estando, contudo, claramente estabelecido que as anormalidades lípidicas conduzem a uma disfunção endotelial (Oparil et al. 2003), possivelmente através da interferência com a produção e a actividade do óxido nítrico, bem como de alterações na expressão de endotelina-1, endotelina A e receptor B (Nohria et al. 2003). Foi, então, sugerido que estas alterações endoteliais conduziriam a uma vasodesregulação, traduzida por uma incapacidade ou diminuição do processo de vasodilatação em resposta aos estímulos apropriados (Halperin et al. 2006). Nickenig e Harrison (Nickenig and Harrison 2002; Nickenig and Harrison 2002) relacionaram os lípidos aterogénicos e a HTA através de um mecanismo envolvendo a sobreexpressão de angiotensina I. Tal como a resistência à insulina, também a dislipidémia foi

associada a uma hiperfunção simpática, a qual pode contribuir para o desenvolvimento de HTA (Egan 2003).

2.8.4 Consumo de álcool

A ingestão de álcool conduz a uma elevação aguda e crónica da TA. Estudos observacionais, transversais e prospectivos, efectuados em diversas populações revelaram que existe uma relação linear e consistente entre o consumo de álcool, os níveis de TA e a prevalência de HTA (Puddey et al. 1997). O mecanismo pelo qual o álcool aumenta a TA não se encontra esclarecido. Este efeito aumenta com a idade, é independente do tipo de bebida alcoólica e é aditivo, mas independente, dos efeitos da obesidade, dos contraceptivos orais e do consumo elevado de sal (Arkwright et al. 1982). Estudos clínicos revelaram que a TA diminui 4 a 5 mm Hg dentro de alguns dias ou de algumas semanas após a suspensão da ingestão de álcool (Beilin et al. 1996; Dickinson et al. 2006). Além disso, o álcool diminui reversivelmente a eficácia da terapêutica farmacológica anti-hipertensora, pelo que a HTA se torna mais fácil de controlar quando cessa o seu consumo (Puddey et al. 1987). Os homens hipertensos que bebem bebidas alcoólicas devem limitar o seu consumo até um máximo de 20 – 30 g de etanol por dia, e as mulheres hipertensas até um máximo de 10 -20 g de etanol por dia (Mancia et al. 2007). Devem, além disso, ser avisados para o risco aumentado de acidente vascular cerebral no caso de ingestão excessiva de álcool (Wannamethee and Shaper 1996; Mancia et al. 2007). Estudos realizados nos Estados Unidos da América e na Austrália revelaram que a contribuição do consumo elevado de álcool para a prevalência da HTA é de 5% – 7%; essa contribuição foi maior nos homens (11%) devido ao maior consumo de álcool por estes quando comparados com as mulheres (MacMahon 1987). Nos consumidores de quantidades elevadas de álcool, não obesos, a TAS foi cerca de 4 a 5 mm Hg mais elevada do que nos não consumidores (Arkwright et al. 1982).

2.8.5 Ingestão de sal

Estudos epidemiológicos sugerem que o sal da dieta é um factor que contribui para a elevação da TA e para a prevalência da HTA (Law 1997). Ensaios clínicos controlados revelaram que a redução da ingestão de sódio de 80 – 100 mmol (4,7 – 5,8 g de cloreto de sódio) por dia, em doentes hipertensos que ingeriam inicialmente cerca de 180 mmol (10,5 g de cloreto de sódio) por dia, conduziu a uma redução da TA de cerca de 4 – 6 mm Hg, embora com uma variabilidade inter-individual considerável (Cutler et al. 1997; Graudal et al. 1998; He and MacGregor 2003; Robertson 2003). O efeito da redução do sal da dieta na TA é maior nos indivíduos de raça negra, nos de meia-idade e nos idosos, bem como nos indivíduos com HTA, diabetes ou doença renal crónica, i. e., grupos com um sistema renina-angiotensina-aldosterona menos responsivo (He et al. 2001), cuja activação, conjuntamente com uma activação do sistema nervoso simpático (Grassi et al. 1997; Grassi et al. 2002), pode contrariar o efeito da redução da TA provocado pela restrição sódica. Um consumo excessivo de sal é também uma causa frequente de hipertensão refractária em doentes que cumprem

com a toma da medicação anti-hipertensora (Paiva 2005; Calhoun et al. 2008). A restrição sódica pode ter um maior efeito anti-hipertensor se combinado com outras medidas dietéticas [p. ex. dieta mediterrânica, dieta DASH (Dietary Approaches to Stop Hypertension) (Sacks et al. 2001)] e pode permitir a redução do número e das doses de medicamentos anti-hipertensores usados para controlar a TA (Mancia et al. 2007). Desta forma, os doentes hipertensos devem ser aconselhados a reduzir a ingestão de sal (< 5 g de cloreto de sódio por dia) e de gorduras saturadas e a efectuar um consumo adequado de frutos e vegetais ricos em potássio (Paiva 2005; Appel et al. 2006; Mancia et al. 2007).

Uma ingestão adequada de potássio (> 100 mmol por dia), de preferência a partir de alimentos naturais, deve ser recomendada para os indivíduos com hipertensão e para aqueles com TA normal-alta (Carretero and Oparil 2000; Mancia et al. 2007). Uma dieta rica em frutos e vegetais (p. ex. dieta mediterrânica, dieta DASH (Sacks et al. 2001)) é preferível à toma de suplementos de potássio sob a forma de comprimidos, uma vez que aqueles alimentos naturais contêm outros nutrientes, como por exemplo, cálcio, magnésio e vitaminas, que também podem ter efeitos benéficos na TA. Além disso, os suplementos de potássio podem ter efeitos adversos graves em doentes com insuficiência renal, diabetes e nos doentes a tomar diuréticos poupadores de potássio, inibidores da enzima de conversão da angiotensina ou antagonistas dos receptores da angiotensina, pelo que deverão ser evitados ou utilizados com muita precaução e apenas sob vigilância médica nestes grupos de doentes (Appel et al. 1997; McCarron et al. 1997; Svetkey et al. 1999).

Como regra geral, os doentes com HTA devem ser aconselhados a comer frutos e vegetais, peixe rico em ácidos gordos poliinsaturados ómega-3, lacticínios magros (fonte de cálcio importante para a prevenção da osteoporose) e a reduzir a ingestão de sal, açúcar, gorduras saturadas e de colesterol (Mancia et al. 2007). Tanto a dieta mediterrânica como a dieta DASH (Sacks et al. 2001) incorporam estes princípios gerais de uma alimentação saudável, estando, portanto, recomendadas nos doentes hipertensos.

2.8.6 Tabagismo

A relação entre o consumo de tabaco e os valores de TA é algo paradoxal, na medida em que, por um lado, se sabe que o tabaco não aumenta os valores da TA (excepto nos primeiros 15 - 30 minutos após fumar um cigarro) (Seltzer 1974), mas por outro, os fumadores apresentam normalmente valores ambulatórios de TA mais elevados, conforme determinado pela monitorização ambulatória da TA (MAPA) (Mann et al. 1991; Verdecchia et al. 1995; Bang et al. 2000), sendo esta elevação mais acentuada nos grandes fumadores (Groppelli et al. 1992). Vários autores referiram que o hábito de fumar é um factor preditor da elevação da TAS (Mundal et al. 1997), mas não se encontrou um efeito crónico do tabagismo na TA que fosse independente de outros factores (p. ex., idade, índice de massa corporal, álcool, nível sócio-económico) (Primatesta et al. 2001) e a cessação tabágica não reduziu a TA (Omvik 1996).

Contudo, o tabagismo é um importantíssimo factor de risco cardiovascular (Doll et al. 1994), causando danos significativos no endotélio vascular e a cessação tabágica constitui, provavelmente, a medida isolada mais eficaz para prevenir a ocorrência de doenças cardiovasculares como o enfarte do miocárdio e o acidente vascular cerebral (Manson et al. 1992; Doll et al. 1994). Os doentes hipertensos devem, portanto, ser aconselhados a deixar de fumar, o que é importante, sobretudo, numa perspectiva de redução do risco cardiovascular global (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Mancia et al. 2007). É importante salientar, ainda, que, a par dos efeitos nocivos sobre o aparelho cardiovascular, o tabagismo possui, também, efeitos nocivos sobre o sistema nervoso central, o aparelho respiratório e o aparelho digestivo.

2.8.7 Sedentarismo

A falta de exercício físico é um forte preditor da mortalidade cardiovascular, independente da TA e de outros factores de risco cardiovascular (Sandvik et al. 1993). O exercício físico estabelece, porém, uma relação paradoxal com a HTA, na medida em que apesar de ajudar a controlar o excesso de peso e de ter um efeito benéfico, embora moderado, sobre os valores de TA nos indivíduos hipertensos (Cornelissen and Fagard 2005), não existe uma relação provada entre o exercício físico e uma menor frequência de aparecimento da HTA. Ou seja, as pessoas que não fazem exercício físico não se encontram mais expostas a sofrer de HTA mas de excesso de peso. Contudo, por outro lado, o exercício físico aeróbio regular é aconselhável nos doentes hipertensos porque ajuda a controlar a TA (Chobanian et al. 2003; Cornelissen and Fagard 2005). Uma meta-análise de ensaios clínicos controlados e aleatorizados concluiu que a actividade física aeróbia reduz a TAS e a TAD de 3,0/2,4 mm Hg, tendo esta redução sido mais pronunciada no grupo de indivíduos hipertensos (6,9/4,9 mm Hg) do que no dos normotensos (1,9/1,6 mm Hg) (Cornelissen and Fagard 2005). Esta actividade física também reduziu o índice de massa corporal, a gordura corporal e o perímetro abdominal e aumentou a sensibilidade à insulina e os níveis de colesterol-HDL (Cornelissen and Fagard 2005). Os indivíduos sedentários que não tenham impedimento médico devem, por isso, ser aconselhados a realizar uma actividade física aeróbia regular, como, por exemplo, caminhar apressadamente durante 30 minutos por dia, 5 – 7 dias por semana (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Mancia et al. 2007).

2.8.8 Factores psicossociais

Diversos estudos sugerem que existe uma relação entre os factores psicossociais e a HTA e que os indivíduos expostos a um stress psicogénico repetido podem desenvolver hipertensão com uma frequência maior do que indivíduos semelhantes não expostos a esse stress (Stamler et al. 1992; Markovitz et al. 1993; Kaufman et al. 1996; Diez Roux et al. 2002; Cesana et al. 2003; Steptoe and Willemsen 2004; Gerin et al. 2005). Por exemplo, alguns estudos conseguiram demonstrar uma maior prevalência de HTA em grupos populacionais de nível

sócio-económico baixo e com uma elevada percentagem de desestruturação social, embora factores como a alimentação, o álcool ou outros possam também estar envolvidos (Stamler et al. 1992; Diez Roux et al. 2002). Os níveis de stress associados a determinadas actividades profissionais parecem também estar relacionados com a elevação da TA observada em alguns trabalhadores (Cobb and Rose 1973; Cesana et al. 2003; Steptoe and Willemsen 2004). O stress psicogénico conduz a uma activação do sistema nervoso simpático, pelo que as catecolaminas são consideradas as principais responsáveis, quer pelo mecanismo vasoconstritor que desencadeia a elevação inicial da TA, quer pelas acções tróficas que mantêm a hipertensão através da hipertrofia vascular (Grassi and Mancia 2004; Kaplan 2006). É, contudo, possível que, na patogénese da hipertensão primária pelo stress, estejam envolvidos, adicionalmente, outros mecanismos (p. ex., estimulação da síntese das proteínas inflamatórias interleucina-6 e fibrinogénio) (Brydon and Steptoe 2005). Alguns estudos conseguiram demonstrar os efeitos favoráveis de intervenções psicofisiológicas na TA (p. ex., relaxação por *biofeedback*) (McGrady).

2.8.9 Idade

A idade é outro factor que contribui para o aparecimento da HTA. Estudos epidemiológicos revelaram que a TAS e a TAD variam com a idade. A TAS tende a aumentar progressivamente ao longo da vida, tanto nos homens como nas mulheres. Pelo contrário, a TAD aumenta até, aproximadamente, aos 50 anos, tendendo a estabilizar a partir desta idade e a manter-se constante ou mesmo a declinar com o evoluir dos anos (Figura 5) (Burt et al. 1995; Franklin et al. 1997)

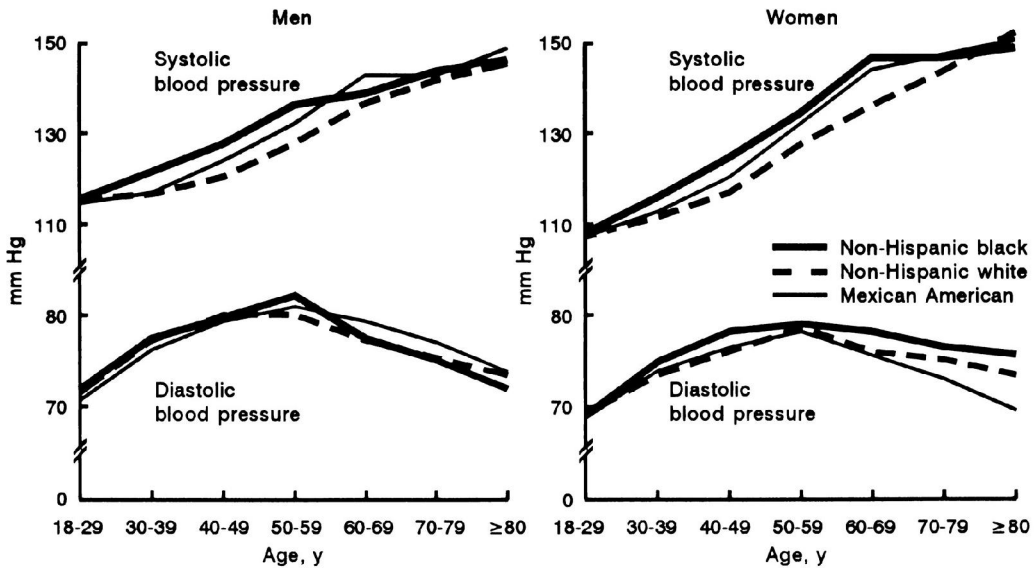


Figura 5 - Tensão arterial sistólica e diastólica médias em função da idade e raça/etnia para homens e mulheres (população dos EUA com idade ≥ 18 anos) (Burt et al. 1995).

Desta forma, a hipertensão diastólica predomina antes dos 50 anos, quer isoladamente, quer conjuntamente com a elevação da TAS. A prevalência da hipertensão sistólica aumenta progressivamente com a idade e acima dos 50 anos representa a forma mais comum de hipertensão. A TAD é um factor de risco cardiovascular mais potente que a TAS até cerca dos 50 anos; a partir dessa idade a TAS constitui um factor de risco cardiovascular mais importante (Figura 6) (Franklin et al. 2001).

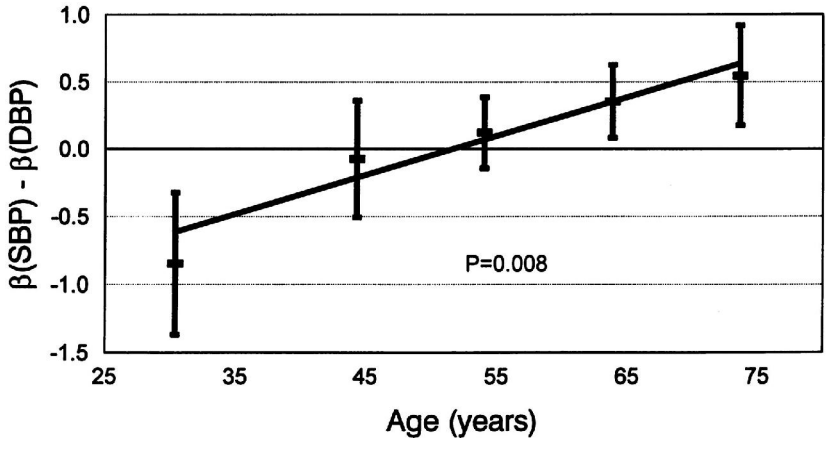


Figura 6 - Diferença da capacidade preditiva de doença cardíaca coronária da TAS e da TAD em função da idade. A diferença dos coeficientes ß da TAS e da TAD (modelo de riscos proporcionais de COX) em função da idade originou a seguinte equação de uma recta: ß(SBP) - ß(DBP) = -1.4948 + 0.0290 x age (*P*=0.008) (Franklin et al. 2001). DBP – tensão arterial diastólica; SBP – tensão arterial sistólica.

Diversos ensaios clínicos demonstraram que o controlo da hipertensão sistólica isolada reduz a mortalidade de causa cardiovascular e a ocorrência de acidentes vasculares cerebrais e de insuficiência cardíaca (SHEP Cooperative Research Group 1991; Kostis et al. 1997; Staessen et al. 1999). De referir que a baixa percentagem de controlo da TAS é, em grande parte, responsável pelas taxas de controlo inaceitavelmente baixas da HTA (Lloyd-Jones et al. 2000; Hyman and Pavlik 2001). Nos ensaios clínicos ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) e CONVINCE (Controlled Onset Verapamil Investigation of Cardiovascular End Points), as taxas de controlo da TAD excederam os 90%, mas as taxas de controlo da TAS foram consideravelmente menores (60% - 70%) (Black et al. 2001; Cushman et al. 2002).

2.9 Risco cardiovascular global

A avaliação e a terapêutica do doente hipertenso devem ser empreendidas numa perspectiva de redução do risco cardiovascular global (Polonia et al. 2006; Direcção-Geral da Saúde 2007; Mancia et al. 2007). O risco cardiovascular global define-se como a probabilidade de desenvolver uma doença ou um evento cardiovascular num período de tempo definido, normalmente calculado para 10 anos (Mancia et al. 2007).

Um factor de risco cardiovascular corresponde a uma característica biológica ou comportamental presente num indivíduo, que está relacionada, de forma independente, com o desenvolvimento posterior de doença/evento cardiovascular, aumentando a probabilidade da sua ocorrência. A identificação dos factores de risco *major* cardiovasculares (Tabela 7) é muito importante não só na avaliação clínica inicial do doente, mas também na avaliação da eficácia da terapêutica e da redução do risco.

Tabela 7 - Identificação de factores de risco *major* cardiovasculares (Polonia et al. 2006).

- Hipertensão arterial
- Diabetes mellitus
- Dislipidémia
- Obesidade (Índice de massa corporal ≥ 30 kg/m2
  e/ou Perímetro abdominal ≥ 102 cm nos homens e ≥ 88 cm nas mulheres)
- Sedentarismo
- Hábitos tabágicos
- Idade > 55 anos nos homens e > 65 anos nas mulheres
- História familiar de doença cardiovascular prematura
  (< 55 anos nos homens e < 65 anos nas mulheres)
- Taxa de filtração glomerular (TFG) estimada < 60 ml/min
- Microalbuminúria

Os factores de risco cardiovascular podem ser não modificáveis ou modificáveis. Nos primeiros temos, como exemplo, os antecedentes familiares de doença cardio-cérebrovascular prematura (homens com idade < 55 anos e mulheres com idade < 65 anos), a idade, o sexo, etc. Como exemplo de factores de risco cardiovascular modificáveis temos o tabagismo, o sedentarismo, os valores de tensão arterial, etc.

A determinação do risco cardiovascular global, baseada na identificação e avaliação dos factores de risco cardiovasculares, permite estratificar os doentes em grupos de risco tendo em vista a implementação das medidas de intervenção mais adequadas, que contribuam para a redução ou controlo do referido risco (Direcção-Geral da Saúde 2007).

Existem diversos métodos para estimar o risco cardiovascular global. Estes métodos baseiam-se em estudos epidemiológicos de *coortes*, onde a presença dos factores de risco foi relacionada com a incidência posterior de eventos cardio-cérebrovasculares (Direcção-Geral da Saúde 2007). Desta forma, foi possível calcular a probabilidade de ocorrência de um evento em função do número e da intensidade dos factores de risco presentes num indivíduo. Esta probabilidade é, normalmente, expressa numa percentagem, que indica a proporção de

doentes, com as mesmas características, em que é esperada a ocorrência de um evento cardiovascular, num determinado período de tempo.

Os métodos mais simples baseiam-se na identificação da presença ou ausência de factores de risco e definem como baixa (< 15%), moderada (≥ 15% e <20%), alta (≥ 20% e <30%) ou muito alta (≥ 30 %), a probabilidade do indivíduo vir a sofrer um evento cardiovascular nos próximos 10 anos. Esta classificação é recomendada pelas *guidelines* para o controlo da hipertensão das Sociedades Europeias de Cardiologia e Hipertensão (Mancia et al. 2007) (Figura 7) e baseia-se no esquema proposto pela OMS nas suas *guidelines* para o controlo da hipertensão (World Health Organization and International Society of Hypertension 1999). A linha a tracejado da Figura 7 ilustra como a avaliação do risco cardiovascular global influencia a definição de hipertensão, quando esta é adequadamente considerada como o valor de TA acima do qual o tratamento origina mais benefícios do que riscos (Evans and Rose 1971).

	Blood pressure (mmHg)				
Other risk factors, OD or Disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors, MS, OD or Diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

Figura 7 - Estratificação do risco cardiovascular em 4 categorias (Mancia et al. 2007). Refere-se a risco a 10 anos de evento cardiovascular fatal ou não fatal: "Low" <15%; "Moderate" ≥ 15% e <20%; "High" ≥ 20% e <30%; "Very high" ≥ 30 %. O termo "added" é usado para enfatizar um risco relativo superior ao risco médio. A linha a tracejado indica como o conceito de hipertensão controlada pode variar, dependendo do nível do risco cardiovascular global. A síndrome metabólica é definida por 3 dos seguintes 5 factores: obesidade abdominal; anomalia da glicemia em jejum; TA ≥ 130/85 mm Hg; C-HDL <40mg/dL nos homens e 46 mg/dL nas mulheres; TG ≥ 150 mg/dL. CV – cardiovascular; DBP – tensão arterial diastólica; HT – hipertensão; MS – síndrome metabólica; OD – lesão subclínica nos órgãos alvo; SBP – tensão arterial sistólica.

A estratificação do risco cardiovascular global naquelas quatro categorias, tem em conta os valores de TA (obtidos em, pelo menos, duas ocasiões diferentes) e a presença de (Tabela 8):

- Factores de risco de doença cardiovascular
- Lesão subclínica nos órgãos alvo
- Doenças clínicas associadas

Tabela 8 - Factores que influenciam o prognóstico (variáveis clínicas mais comuns que devem ser usadas para estratificar o risco cardiovascular global) (adaptado de Mancia et al. 2007).

Factores de risco	**Lesão subclínica nos órgãos alvo**
- Valores de TA - Valores de tensão de pulso (idosos)[1] - Idade (H > 55 anos; M > 65 anos) - Tabagismo - Glicémia em jejum 102-125 mg/dL - Tolerância à glicose diminuída - Dislipidémia (CT>190mg/dL ou C-LDL>115mg/dL ou C-HDL: H<40mg/dL, M<46mg/dL ou TG>150mg/dL) - História familiar de doença CDV prematura (H<55 anos; M<65 anos) - Obesidade (IMC ≥30 kg/m2 e/ou perímetro abdominal: H≥102 cm ou M≥88cm) - Sedentarismo	- Hipertrofia ventricular esquerda (por ECG, ecocardiograma) - Microalbuminúria (30-300mg/24h) - Ultra-som, evidência radiológica ou TAC indicando placa ateroesclerótica (carótida, artérias femoral e ilíaca, aorta, coronárias) - Índice de pressão tornozelo/braço < 0,9 - Aumento da creatinina plasmática (H: 1,3-1,5 mg/dL, M: 1,2-1,4 mg/dL) - Taxa de filtração glomerular estimada baixa (<60 mL/min/1,73m^2) ou clearance da creatinina[2] baixa (<60mL/min)
Diabetes mellitus	**Doença cardiovascular ou renal associada**
- Glicémia em jejum >126 mg/dL ou - Glicemia pós-prandial >198 mg/dL	- Doença cerebrovascular (AVC isquémico, hemorragia cerebral, acidente isquémico transitório) - Doença cardíaca (enfarte do miocárdio, angina, revascularização coronária, insuficiência cardíaca congestiva) - Doença renal (nefropatia diabética ou creatinina plasmática: H > 1,5 mg/dL, M > 1,4 mg/dL ou proteinúria > 300 mg/24h) - Doença arterial periférica - Retinopatia avançada (hemorragia ou exsudados, papiloedema)

[1]Diferença entre os valores das tensões sistólica e diastólica. [2]Fórmula de Cockroft-Gault; AVC – acidente vascular cerebral; CT – colesterol total; CDV – cardiovascular; ECG – electrocardiograma; H – homens; IMC – índice de massa corporal; M – mulheres; TA – tensão arterial; TAC – tomografia axial computorizada; TG – triglicéridos.

O risco cardiovascular aumenta continuamente à medida que os valores de TA aumentam. De referir que, para além dos factores de risco indicados na Tabela 8, existem outros não considerados para a estratificação do risco cardiovascular que influenciam negativamente o prognóstico, como o stress excessivo, os erros alimentares ou o consumo excessivo de álcool.

Outro método para avaliar o risco cardiovascular global é através das tabelas derivadas do projecto SCORE (Systematic Coronary Risk Evaluation). Este método é mais preciso que o anterior pois o valor do risco é obtido a partir de modelos matemáticos baseados em variáveis contínuas, em vez da classificação em categorias. A sua utilização foi determinada pela Direcção Geral de Saúde através da Circular Normativa Nº 06/DSPCS, de 18/04/07 (Direcção-Geral da Saúde 2007). É também o método recomendado pela Sociedade Europeia de Cardiologia nas suas *guidelines* para a prevenção da doença cardiovascular na prática clínica (Graham et al. 2007).

Para a determinação do risco cardiovascular global devem ser utilizadas as tabelas desenvolvidas por um conjunto de Sociedades Científicas congéneres Europeias, com o recurso à base de dados epidemiológica do projecto SCORE. Foram construídas duas tabelas diferentes, tendo em consideração as regiões da Europa de alto e baixo risco cardiovascular (Tabelas 9 e 10). O risco cardiovascular global pode ainda ser calculado através de um programa informático simples, que pode ser acedido gratuitamente através da Internet, no sítio da Sociedade Europeia de Cardiologia (www.escardio.org).

Neste método, a estimativa do risco cardiovascular global baseia-se no sexo, idade, tabagismo, tensão arterial sistólica, colesterol total ou rácio colesterol total/colesterol-HDL (Direcção-Geral da Saúde 2007). Este risco é classificado em sete categorias diferentes (desde < 1% a ≥ 15%), cada uma com uma cor correspondente (Direcção-Geral da Saúde 2007). Ao contrário do método anteriormente descrito, este considera apenas a probabilidade de eventos cardiovasculares fatais. Desta forma, com base no risco de morte cardiovascular nos próximos 10 anos, considera-se como categoria de alto risco, susceptível de medidas eficazes de prevenção farmacológica, um risco absoluto ≥ 5%.

Tabela 9 - Tabela SCORE para a determinação do risco a 10 anos de doença cardiovascular fatal em populações de alto risco (Albânia, Argélia, Arménia, Áustria, Bielorrússia, Bulgária, Croácia, República Checa, Dinamarca, Egipto, Estónia, Finlândia, Geórgia, Hungria, Islândia, Irlanda, Israel, Letónia, Líbano, Líbia, Lituânia, Antiga República Jugoslava da Macedónia, Moldávia, Marrocos, Noruega, Roménia, São Marino, Sérvia e Montenegro, Eslováquia, Eslovénia, Holanda, Tunísia, Turquia, Ucrânia, Reino Unido).

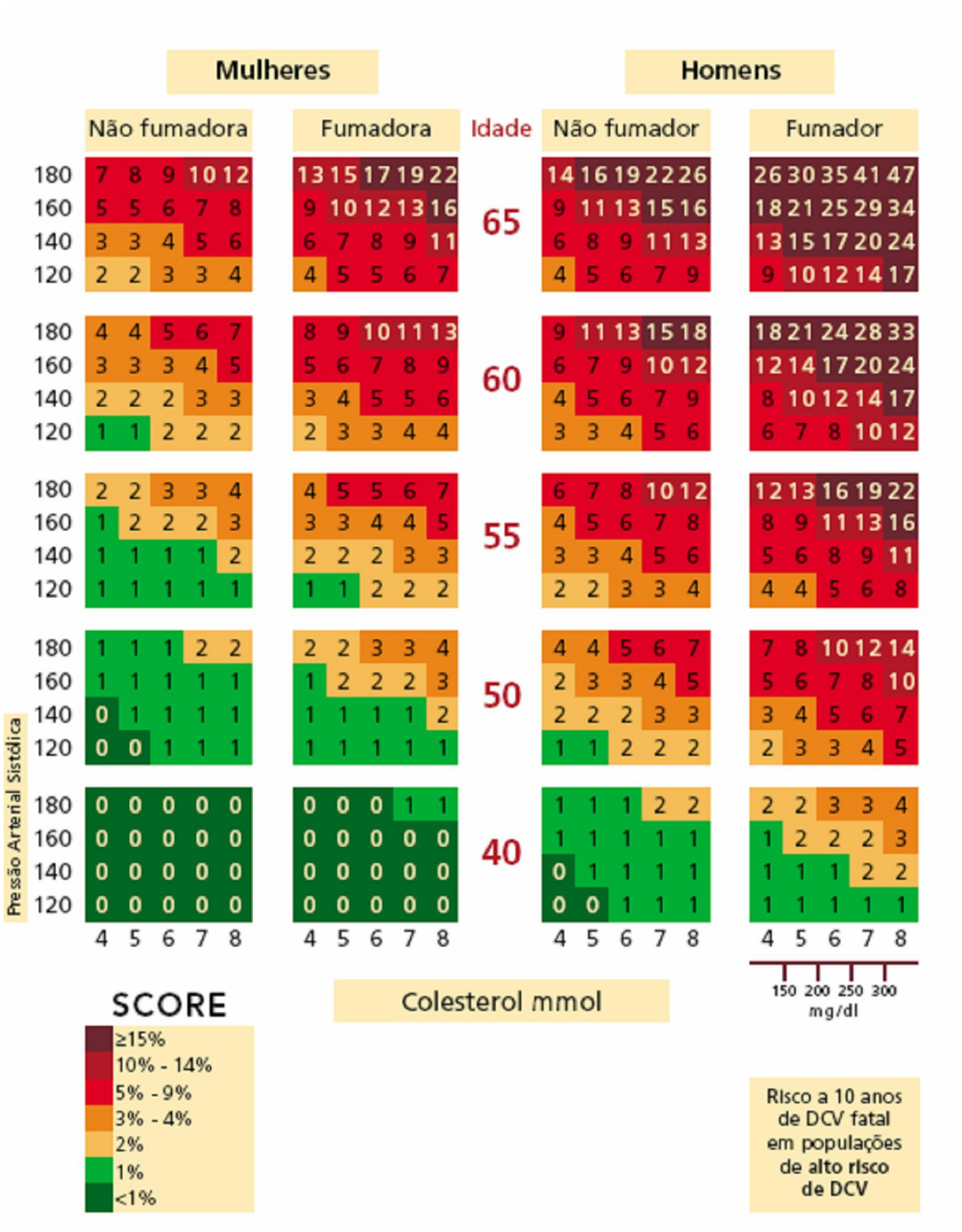
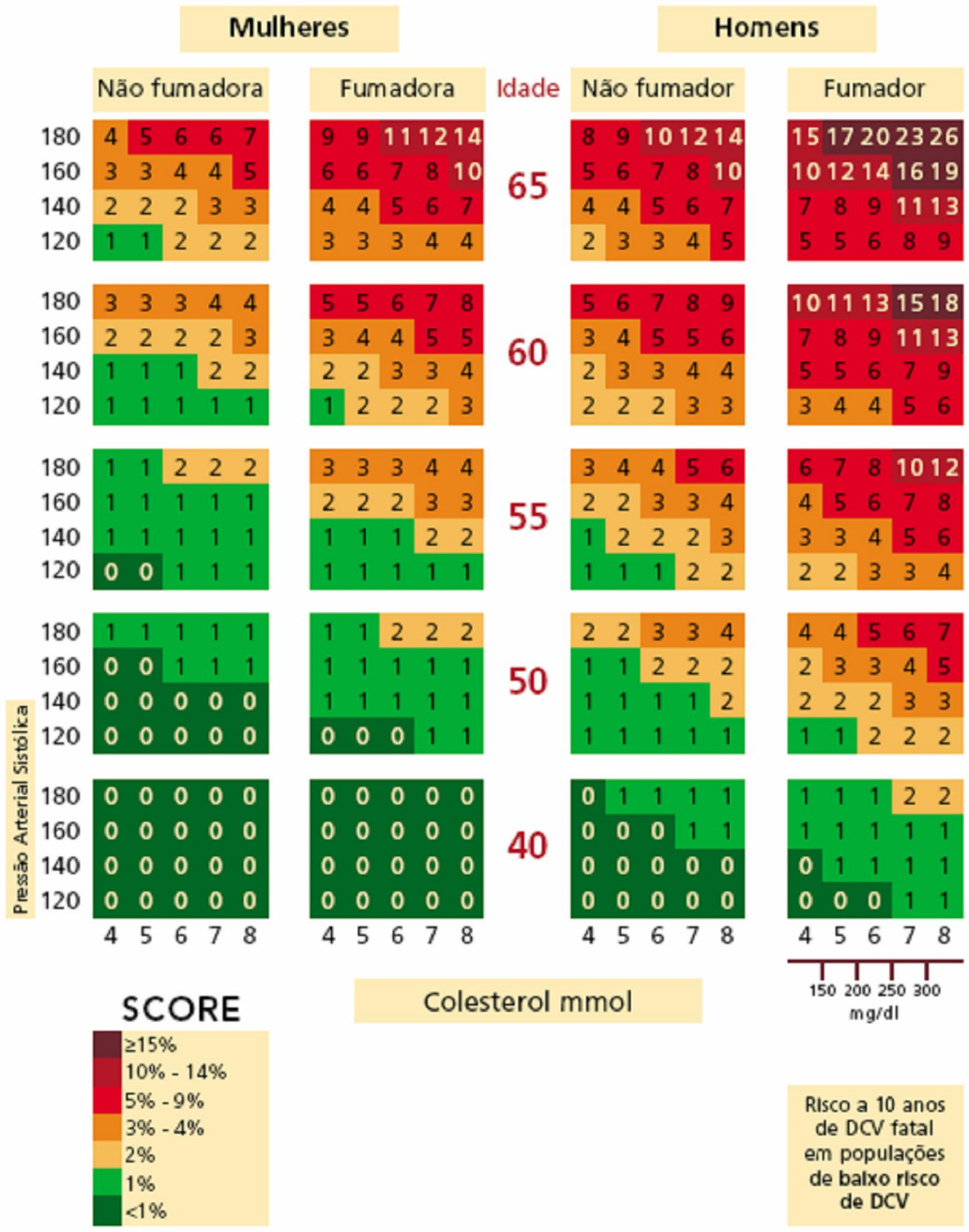


Tabela 10 - Tabela SCORE para a determinação do risco a 10 anos de doença cardiovascular fatal em populações de baixo risco (Bélgica, França, Itália, Luxemburgo, Suíça e Portugal).



É importante referir que as tabelas de estimativa de risco não são totalmente ajustáveis a doentes diabéticos, com doenças clínicas associadas (doença cerebrovascular, doença cardíaca, doença renal ou doença vascular periférica) ou com valores muito elevados de um dos factores individuais de risco. Estes doentes apresentam sempre um risco cardio-cérebrovascular alto, independentemente dos valores que apresentarem para outros factores de risco e necessitam de intervenção em todos os factores de risco (Graham et al. 2007; Mafra and Oliveira 2008). Nestes casos, o cálculo do risco cardiovascular global não é utilizado para avaliar o grau de risco, uma vez que esse já é conhecido, mas pode ser útil para avaliar

o benefício das intervenções terapêuticas usadas, ao permitir comparar um valor prévio de risco com um segundo, obtido após terapêutica (Mafra and Oliveira 2008).

2.10 Avaliação clínica inicial

De acordo com a DGS (Direcção-Geral da Saúde 2004) e a Sociedade Portuguesa de Hipertensão (Polonia et al. 2006) a avaliação clínica inicial do doente, no âmbito do diagnóstico, tratamento e controlo da hipertensão deve incluir:

- Avaliação da TA (determinação dos valores de TAS e TAD, mm Hg);
- Identificação dos factores de risco cardiovasculares (Tabela 7);
- Pesquisa de causas identificáveis de HTA;
- Avaliação de lesão dos órgãos alvo e doenças associadas;
- Colheita de história clínica e exame físico;
- Testes laboratoriais: urina tipo II (incluir sedimento), hemoglobina, hematócrito, glicemia, perfil lipídico e sódio, potássio, ácido úrico, creatinina e cálcio séricos. (Opcional: relação albumina/creatinina na primeira urina matinal);
- Electrocardiograma.

A lesão subclínica dos órgãos alvo deve ser investigada de acordo com as necessidades de cada situação. De aplicação a todos os casos deve ser a pesquisa de microalbuminúria e a avaliação da filtração glomerular da creatinina, que permite caracterizar a lesão renal, bem como a realização de um electrocardiograma, para avaliar a presença de hipertrofia ventricular esquerda (um dos mais significativos marcadores de risco na HTA), de isquémia do miocárdio ou de arritmias. O ecocardiograma poderá ser efectuado para uma melhor caracterização da hipertrofia ventricular esquerda e avaliação da disfunção diastólica. O estudo ecocardiográfico das carótidas poderá caracterizar situações de aterosclerose vascular. A velocidade da onda de pulso será útil na avaliação da distensibilidade das grandes artérias e o índice da pressão braço-perna caracterizará o estado das resistências periféricas. Em casos seleccionados terá interesse a avaliação cerebral através da tomografia axial computorizada (TAC) ou da ressonância magnética nuclear (RMN), bem como a fundoscopia nas situações de hipertensão grave.

Para além do interesse da sua avaliação inicial, a evolução da lesão subclínica dos órgãos alvo permite avaliar a eficácia da terapêutica anti-hipertensora e a redução do risco, constituindo um dado clínico importante.

2.11 Princípios e objectivos do tratamento anti-hipertensor

O principal objectivo do tratamento do doente hipertenso é obter a longo prazo a máxima redução da morbilidade e mortalidade cardiovascular e renal (Chobanian et al. 2003;

Direcção-Geral da Saúde 2004; Polonia et al. 2006; Mancia et al. 2007). Este propósito poderá ser conseguido pela redução dos valores elevados da TA e pelo tratamento dos factores de risco modificáveis e das doenças associadas (Direcção-Geral da Saúde 2004; Polonia et al. 2006).

A redução da TA deverá, desta forma, ser encarada num contexto de redução global do risco cardiovascular. Os valores a atingir devem ser considerados flexíveis, sendo mais ou menos elevados, consoante o perfil do risco cardiovascular global de cada indivíduo (Polonia et al. 2006). Na população hipertensa em geral, o objectivo será a redução da TA para valores inferiores a 140/90 mm Hg (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Polonia et al. 2006; Mancia et al. 2009). A redução da TAS e da TAD para valores inferiores a 140/90 mm Hg está claramente associada a uma diminuição das complicações cardio-cérebrovasculares (Collins et al. 1990; Hansson et al. 1998; Neal et al. 2000). Nos doentes hipertensos diabéticos ou com doença renal, o objectivo será a redução da TA para valores inferiores a 130/80 mm Hg (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Polonia et al. 2006). Em doentes com a TA na categoria normal – alta (TAS 130 - 139 mm Hg ou TAD 85 - 89 mm Hg) e três ou mais factores de risco *major* cardiovasculares, lesão dos órgãos alvo ou doença/eventos cardiovasculares, a TA deverá ser reduzida para valores inferiores a 130/80 mm Hg (Direcção-Geral da Saúde 2004; Polonia et al. 2006). Em doentes com insuficiência renal e proteinúria superior a 1 g/dia o objectivo será a redução da TA para valores inferiores a 125/75 mm Hg (Direcção-Geral da Saúde 2004; Polonia et al. 2006).

Deve ser verificada a exequibilidade de se alcançarem estes valores desejáveis, devendo, para tal, o esquema terapêutico ser adaptado a cada caso individual. A redução da TAS para valores inferiores a 140 mm Hg pode ser difícil de obter em alguns casos, especialmente em pessoas idosas (Direcção-Geral da Saúde 2004; Polonia et al. 2006).

Uma vez que a maioria dos doentes com HTA, particularmente aqueles com idade superior a 50 anos, atingem a TAD desejável uma vez que a TAS desejável seja atingida, o objectivo principal deverá ser atingir a TAS alvo (Chobanian et al. 2003). Estima-se que em doentes com HTA de estádio 1 (TAS 140 - 159 mm Hg e/ou TAD 90 – 99 mm Hg) e factores de risco cardiovasculares adicionais, uma redução sustentada da TAS de 12 mm Hg durante cerca de 10 anos é capaz de prevenir uma morte por cada 11 doentes tratados (Ogden et al. 2000). Na presença de doença cardiovascular ou lesão dos órgãos alvo, apenas 9 doentes necessitarão daquela redução da TAS para prevenir uma morte (Ogden et al. 2000).

Os objectivos tensionais mencionados deverão ser alcançados através da instituição de medidas terapêuticas, farmacológicas e não farmacológicas, de um plano de vigilância (consultas de *follow-up*) e de um programa de educação do doente.

É importante referir que a Sociedade Europeia de Hipertensão reavaliou, em 2009, as *guidelines* Europeias de 2007 sobre o controlo da HTA, com base nos resultados entretanto obtidos em importantes ensaios clínicos (Mancia et al. 2009). Nesta reavaliação foram extraídas algumas conclusões importantes (Mancia et al. 2009):

1) Em doentes com TA normal alta (TAS 130 - 139 mm Hg ou TAD 85 - 89 mm Hg) sem diabetes nem eventos cardiovasculares prévios, não existe evidência do benefício do tratamento medicamentoso anti-hipertensor, a não ser um atraso no aparecimento da HTA (≥ 140/90 mm Hg);

2) Não existe evidência do benefício de iniciar o tratamento medicamentoso anti-hipertensor em diabéticos com TA normal alta. Contudo, por enquanto, considera-se prudente iniciar o tratamento nestes doentes se existir lesão subclínica de órgãos alvo (particularmente microalbuminúria ou proteinúria).

3) A evidência existente no que respeita ao tratamento com anti-hipertensores de doentes com eventos cardiovasculares prévios na ausência de HTA (≥ 140/90 mm Hg) é controversa, sendo necessários mais estudos para a elaboração de recomendações mais robustas.

4) De um modo geral, existe evidência para baixar a TA para valores < 140/90 mm Hg em todos os doentes hipertensos (risco baixo, moderado ou elevado). Falta apenas evidência do benefício em baixar a TAS para valores < 140 mm Hg em hipertensos idosos (> 65 anos), uma vez que nunca foram realizados ensaios clínicos aleatorizados que o demonstrassem (embora os mesmos autores recomendem que a TAS seja reduzida para < 140 mm Hg nestes doentes).

5) A recomendação de reduzir a TAS para < 130 mm Hg em diabéticos e doentes com risco cardiovascular muito elevado (com eventos cardiovasculares prévios) é considerada prudente, embora não exista evidência consistente do benefício proveniente de ensaios clínicos.

6) Com base na evidência disponível actualmente, considera-se prudente recomendar a redução da TAS/TAD para valores nos intervalos 130-139/80-85 mm Hg, e possivelmente para valores mais próximos dos limites inferiores daqueles intervalos, em todos os doentes com HTA. Contudo, é desejável a obtenção de evidência adicional proveniente de ensaios clínicos aleatorizados.

2.11.1 Modificação dos estilos de vida

A adopção de estilos de vida saudáveis constitui uma componente indispensável da terapêutica de todas as pessoas com HTA. Os estilos de vida saudáveis estão igualmente recomendados em indivíduos com TA normal – alta e em indivíduos com a TA normal susceptíveis de vir a sofrer de HTA, sobretudo naqueles com factores de risco *major*

cardiovasculares, podendo, nestas situações, contribuir para a prevenção ou o retardamento da sua ocorrência (Whelton et al. 2002). Estas medidas não farmacológicas, se suficientemente duradouras, poderão permitir, consoante os indivíduos, reduções da TA de 2 a 20 mm Hg e a redução do risco cardiovascular global (The Trials of Hypertension Prevention Collaborative Research Group 1997; He et al. 2000; Xin et al. 2001; Whelton et al. 2002; Chobanian et al. 2003). Além disso, contribuem, também, para o aumento da eficácia dos medicamentos anti-hipertensores em indivíduos hipertensos, possibilitando uma redução das doses e/ou do número destes medicamentos (Chobanian et al. 2003; Mancia et al. 2007).

Os estilos de vida amplamente reconhecidos como capazes de contribuir para a redução da TA e do risco cardiovascular global são (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Polonia et al. 2006; Mancia et al. 2007):

- redução do peso em indivíduos obesos ou com excesso ponderal, idealmente para valores de índice de massa corporal de 18,5 a 24,9 Kg/m^2;
- adopção de uma dieta rica em frutos e vegetais (ricos em potássio), lacticínios magros (fonte importante de cálcio) e com baixo teor de gorduras saturadas e colesterol (p. ex., dieta mediterrânica, dieta DASH);
- redução da ingestão de sal (não mais do que 2,4 g de sódio ou 6 g de cloreto de sódio por dia);
- actividade física, por exemplo, exercício aeróbio, como caminhar 30 minutos por dia, 5 a 7 dias por semana;
- ingestão de álcool apenas com moderação (um máximo de 30 ml de etanol por dia nos homens e 15 ml por dia nas mulheres e homens com baixo peso);
- cessação dos hábitos tabágicos (no caso dos fumadores), que é sobretudo importante numa perspectiva de redução do rico global cardiovascular.

Os efeitos benéficos resultantes da implementação destes estilos de vida são dose- e tempo-dependentes, podendo ser maiores para alguns indivíduos do que para outros (Chobanian et al. 2003). Por exemplo, nalguns indivíduos, um plano dietético DASH com 1,6 g de sódio por dia pode ter efeitos na redução da TA semelhantes ao da terapêutica farmacológica anti-hipertensora em regime de monoterapia (Sacks et al. 2001). A adopção de dois (ou mais) daqueles estilos de vida saudáveis pode conduzir a resultados ainda melhores (Appel et al. 2003).

A informação verbal relativa às recomendações dos estilos de vida saudáveis, deverá, sempre que possível, ser complementada com informação escrita. Além disso, aquelas recomendações deverão ser implementadas com o apoio de profissionais de saúde especializados, que conduzam à adopção de hábitos alimentares e medidas comportamentais

adequados (Mancia et al. 2007). É igualmente importante que estas recomendações acerca dos estilos de vida saudáveis sejam reforçadas periodicamente (Mancia et al. 2007).

Atendendo a que a adesão, a longo prazo, aos estilos de vida saudáveis é notoriamente baixa (Haynes et al. 2002) e que existe uma grande variabilidade na redução da TA desencadeada por aqueles estilos de vida, os doentes sob tratamento não farmacológico devem ser avaliados frequentemente, para que, caso seja necessário, a terapêutica farmacológica seja oportunamente iniciada (Mancia et al. 2007).

2.11.2 Tratamento farmacológico

O principal objectivo da terapêutica farmacológica anti-hipertensora é a prevenção da ocorrência de eventos cardiovasculares e renais e do seu agravamento ou recorrência (Direcção-Geral da Saúde 2004; Polonia et al. 2006). Este objectivo é atingido através da redução da TA para os valores alvo recomendados, com o mínimo de reacções adversas de forma a conservar o melhor possível a qualidade de vida (Direcção-Geral da Saúde 2004; Polonia et al. 2006).

A decisão de iniciar o tratamento farmacológico anti-hipertensor deve basear-se, essencialmente, em dois critérios fundamentais (Direcção-Geral da Saúde 2004; Polonia et al. 2006; Mancia et al. 2007):

1) O valor da TAS e da TAD, como classificado na Tabela 1;
2) O risco cardiovascular global.

Nos indivíduos com TA normal-alta (TAS 130-139 mm Hg ou TAD 85-89 mm Hg) somente se deverá aplicar a recomendação de iniciar a terapêutica anti-hipertensora nas situações de risco global elevado e muito elevado (três ou mais factores de risco *major*, lesão dos órgãos alvo ou doença/eventos cardiovasculares) (Direcção-Geral da Saúde 2004; Polonia et al. 2006). Nos restantes indivíduos, com risco moderado ou baixo, recomendam-se a adopção de atitudes e estilos de vida saudáveis, a monitorização periódica da TA e a correcção de outros factores de risco modificáveis (Mancia et al. 2007); de facto, não existe evidência científica que demonstre a existência de benefícios clínicos neste subgrupo de indivíduos, a não ser um possível retardamento no aparecimento de HTA (valores de TA acima do *cutoff* 140/90 mm Hg) (Julius et al. 2006; Mancia et al. 2009).

Nos indivíduos com HTA de estádio 1 (TAS 140-159 mm Hg ou TAD 90-99 mm Hg) com risco cardiovascular moderado ou baixo, quando as medidas não farmacológicas implementadas durante um período de três a seis meses não são suficientes para normalizar os valores de TA, impõe-se o tratamento com medicamentos anti-hipertensores (Mancia et al. 2007; Mancia et al. 2009). Nos indivíduos com HTA de estádio 1 com risco global elevado e muito elevado as

atitudes e comportamentos de vida saudável e o tratamento farmacológico devem ser, de imediato, iniciados simultaneamente. Este último deve ser iniciado, de preferência, em regime de monoterapia com doses baixas de um diurético tiazídico (sempre que possível) ou de um fármaco das outras quatro principais classes de anti-hipertensores [inibidores da enzima de conversão da angiotensina (IECAs), antagonistas dos receptores da angiotensina (ARAs, vulgarmente designados por "sartans"), bloqueadores da entrada do cálcio (BECs) ou bloqueadores beta (BBs)] (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Polonia et al. 2006); caso seja clinicamente justificável, o tratamento farmacológico pode, ainda, realizar-se em regime de associação, em dose fixa ou não, neste caso, incluindo preferencialmente, um diurético em doses baixas (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Polonia et al. 2006).

Nos indivíduos com HTA de estádio 2 (TAS ≥ 160 mm Hg ou TAD ≥ 100 mm Hg) a terapêutica deverá ser iniciada com associação de dois anti-hipertensores, em dose fixa ou não, incluindo, preferencialmente, um diurético tiazídico em doses baixas e, simultaneamente, a adopção de estilos de vida saudáveis (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Polonia et al. 2006; Mancia et al. 2007). A identificação de outros factores de risco, lesão de órgãos alvo ou de doença associada, poderá processar-se após a introdução da terapêutica farmacológica (Direcção-Geral da Saúde 2004; Polonia et al. 2006). De facto, diversos ensaios clínicos demonstraram que, em doentes com HTA de estádio 2, a redução da TA diminui a incidência de morbilidade e mortalidade cardiovascular, independentemente do seu risco cardiovascular global (Collins et al. 1990; Collins and MacMahon 1994; Staessen et al. 2000; Turnbull 2003).

2.11.2.1 Algoritmo para o tratamento da hipertensão arterial

Estima-se que cerca de 2/3 dos doentes hipertensos não conseguem controlar a TA com um único anti-hipertensor, necessitando de dois ou mais medicamentos anti-hipertensores de diferentes classes terapêuticas para controlar a HTA (Hansson et al. 1998; Cushman et al. 2002; Dahlof et al. 2002; Black et al. 2003). Nos doentes hipertensos com valores alvo de TA mais baixos (diabéticos, insuficientes renais) ou com valores de TA mais elevados (HTA de estádio 2) podem mesmo ser necessários três ou mais anti-hipertensores para controlar a HTA (Chobanian et al. 2003).

A associação de um segundo fármaco anti-hipertensor, de diferente classe terapêutica, deverá ter lugar quando não se consegue obter o desejável controlo da TA com as doses adequadas (função da dose máxima autorizada e/ou dos efeitos adversos experimentados pelo doente) de um único fármaco. A associação de dois anti-hipertensores deverá, inclusivamente, ser considerada como a primeira escolha terapêutica quando a TAS ou a TAD se encontram, respectivamente, 20 mm Hg ou 10 mm Hg acima do valor desejável (p. ex., HTA de estádio 2, diabetes, insuficiência renal) (Direcção-Geral da Saúde 2004; Polonia et al. 2006; Mancia et al. 2007); nestas situações existe a necessidade de obter maiores

reduções da TA, o que é difícil de conseguir através de um regime de monoterapia (Figura 8) (Mancia et al. 2007).

Diversos autores recomendam a utilização de um diurético tiazídico como terapêutica inicial na maioria dos doentes, quer isoladamente, quer em associação com um anti-hipertensor de outra classe terapêutica (IECAs, ARAs, BECs, BBs) (Chobanian et al. 2003). A selecção de um destes últimos anti-hipertensores como terapêutica de primeira linha está recomendada quando um diurético está contra-indicado (p. ex., gota) ou quando existe uma indicação preferencial de determinados grupos terapêuticos de anti-hipertensores (p. ex., IECAs ou ARAs na microalbuminúria) (Chobanian et al. 2003).

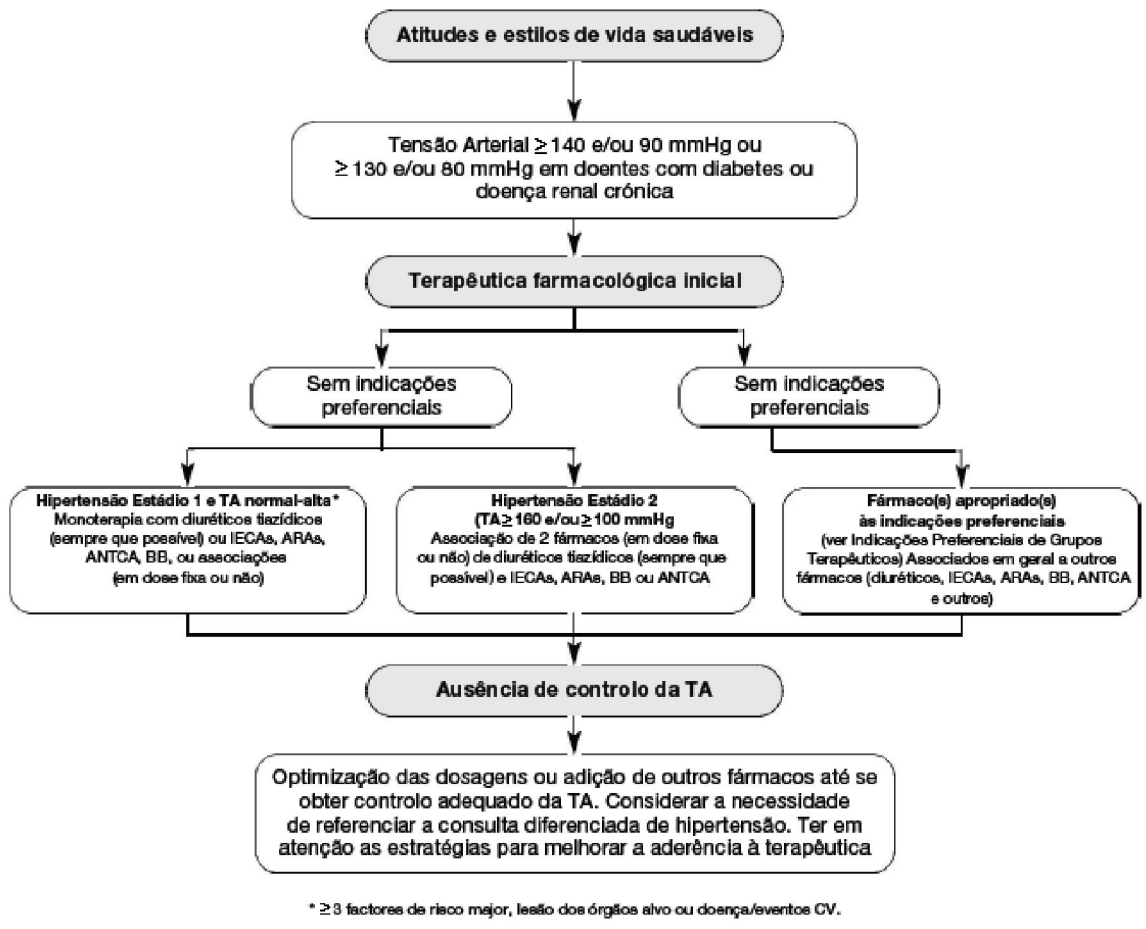


Figura 8 - Algoritmo de tratamento da HTA e escolha do primeiro fármaco (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Polonia et al. 2006). ANTCA – bloqueadores da entrada do cálcio; ARAs – antagonistas dos receptores da angiotensina; BB – bloqueadores beta; CV – cardiovasculares; IECAs – inibidores da enzima de conversão da angiotensina; TA – tensão arterial.

Uma desvantagem óbvia de iniciar o tratamento com dois anti-hipertensores reside na possibilidade de estar a expor alguns doentes a um fármaco potencialmente desnecessário.

Existem, contudo, diversas vantagens (Chobanian et al. 2003; Mancia et al. 2007): 1) uma associação de dois anti-hipertensores possibilita a utilização de doses mais baixas dos fármacos em causa do que a utilização dos mesmos fármacos em regime de monoterapia, com a consequente diminuição dos efeitos adversos; 2) em doentes com HTA de estádio 2 ou com lesão dos órgãos alvo, evitam-se os inconvenientes e a decepção de, repetidamente e infrutiferamente, experimentar regimes monoterapêuticos ineficazes; 3) iniciar a terapêutica com uma associação de dois anti-hipertensores possibilita que os valores alvo de TA sejam atingidos mais rapidamente.

No sentido de facilitar a adesão à terapêutica medicamentosa e de obter um controlo adequado da TA ao longo das 24 horas, é preferível optar, sempre que possível, por preparações farmacêuticas que, em toma única diária, assegurem uma duração de acção anti-hipertensora de cerca de 24 horas.

A utilização de associações de anti-hipertensores, embora aumente probabilidade de se obter o desejável controlo da TA, deve ser acompanhada de determinadas precauções, sobretudo no início da terapêutica, em doentes com disfunção autonómica, diabetes ou pessoas idosas, com propensão para a hipotensão ortostática (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Polonia et al. 2006).

Anti-hipertensores de diferentes classes poderão ser associados se (Mancia et al. 2007): 1) tiverem mecanismos de acção diferentes e complementares, 2) existir evidência de que o efeito anti-hipertensor da associação é significativamente maior do que o de cada componente isoladamente, 3) a associação tiver um perfil de tolerância favorável, tornando possível a redução da TA com menor incidência de RAMs.

A Figura 9 representa esquematicamente as associações de dois anti-hipertensores preconizadas pelas *guidelines* de 2007 da Sociedade Europeia de Hipertensão e da Sociedade Europeia de Cardiologia, consideradas eficazes, bem toleradas e que apresentaram resultados favoráveis em ensaios clínicos (Mancia et al. 2007).

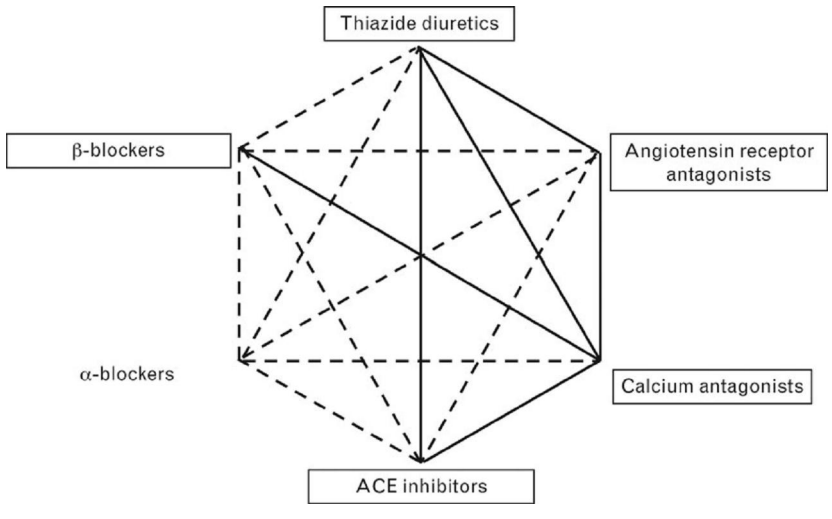


Figura 9 - Combinações possíveis entre as várias classes de fármacos anti-hipertensores. As linhas a cheio indicam as associações preconizadas. Os rectângulos indicam as classes de anti-hipertensores que demonstraram ser eficazes em ensaios clínicos (Mancia et al. 2007). ACE – enzima de conversão da angiotensina.

Na reavaliação daquelas *guidelines*, efectuada em 2009 (Mancia et al. 2009), foram, contudo, consideradas de utilização prioritária as seguintes combinações:

- Diurético e IECA
- Diurético e ARA
- Diurético e BEC
- IECA e BEC
- ARA e BEC

Apesar da associação bloqueador beta/diurético ter demonstrado, em ensaios clínicos, ser eficaz na redução da TA, favorece o aparecimento de diabetes, pelo que deve ser evitada em doentes susceptíveis de desenvolverem esta patologia (Mancia et al. 2006; Mancia et al. 2009). A associação IECA/ARA, composta por fármacos que interferem, embora a diferentes níveis, com o mesmo mecanismo fisiológico (sistema renina-angiotensina), apresenta uma potenciação duvidosa dos benefícios com um aumento consistente dos efeitos adversos (hipercaliemia e aumento da creatinina sérica) (Mancia et al. 2009). Os potenciais efeitos benefícios desta associação em doentes com nefropatia (conseguidos através de um efeito antiproteinúrico superior) (Nakao et al. 2003), bem como em doentes com disfunção ventricular esquerda ou insuficiência cardíaca (McMurray et al. 2003), foram questionados (Pfeffer et al. 2003; Vogt et al. 2003; Kunz et al. 2008) e carecem de confirmação (Mancia et al. 2009).

Mais recentemente foi introduzido no mercado farmacêutico um novo bloqueador do sistema renina-angiotensina, o aliscireno, tendo sido autorizado pela US Food and Drug Administration

(FDA, em 5 de Março de 2007) e pela European Medicines Agency (EMEA, em 22 de Agosto de 2007) para o tratamento da HTA essencial (Mancia et al. 2009). O aliscireno, um anti-hipertensor activo por via oral, é um inibidor directo da renina, a enzima limitante da taxa de produção da angiotensina II. Esta constitui o produto final da cascata de reacções do sistema renina-angiotensina, sendo um peptídeo vasoactivo potente. O aliscireno é um anti-hipertensor de longa duração de acção (tempo de meia-vida ≈ 40 horas) e, em diversos ensaios clínicos, revelou-se eficaz na redução da TA, seguro e bem tolerado em tomas únicas diárias de 150 mg e 300 mg (Gradman et al. 2005; Kushiro et al. 2006; Oh et al. 2007; Oparil et al. 2007; Pool et al. 2007; Villamil et al. 2007). O principal efeito secundário consiste num aumento da incidência de diarreia (≥ 1/100, < 1/10) (O'Brien et al. 2007; Novartis Europharm Limited 2009. Available at www.ema.europa.eu/docs/pt_PT/document_ library/EPAR_-_ Product_Information/human/000964/WC500047220.pdf. Accessed on 7th November 2010). Numa revisão sistemática e meta-análise recentemente publicada, envolvendo seis ensaios clínicos aleatorizados com dupla ocultação e tendo como objectivo quantificar a eficácia anti-hipertensora do aliscireno em adultos com HTA essencial, obtiveram-se as seguintes reduções médias ponderadas [com intervalo de confiança de 95% (IC 95%)] das TAS/TAD: aliscireno 150 mg, -5,5 (-6,5, - 4,4) / - 3.0 (-3.7, -2.3) mm Hg; aliscireno 300 mg, -8.7 (-9.7, -7.6) / -5.0 (-5.6, -4.3) mm Hg (Musini et al. 2009). Em ensaios clínicos aleatorizados com dupla ocultação de 8 semanas de duração, a associação aliscireno/hidroclorotiazida (HCTZ) reduziu as TAS/TAD de forma mais significativa que o placebo, aliscireno em monoterapia e HCTZ em monoterapia (Chrysant 2008; Baldwin and Plosker 2009). As associações de doses fixas de aliscireno/HCTZ (150/12.5 mg, 150/25 mg, 300/12.5 mg, 300/25 mg) foram recentemente autorizadas pela US FDA (18 de Janeiro de 2008) e pela EMEA (16 de Janeiro de 2009) para o tratamento de adultos com HTA essencial, cuja TA não esteja adequadamente controlada com o aliscireno ou HCTZ em monoterapia e como terapêutica de substituição em doentes adequadamente controlados com aliscireno e hidroclorotiazida, administrados em simultâneo, com o mesmo nível de dose da associação (Novartis Europharm Limited 2009. Available at www.ema.europa.eu/docs/pt PT/document library/EPAR - Product Information/human/000964/WC500047220.pdf. Accessed on 7th November 2010). Morgado et al. fizeram recentemente uma revisão sistemática e análise meta-analítica da associação aliscireno/HCTZ (Morgado et al. 2010; Morgado et al. 2011).

Estima-se que, pelo menos, 15% - 20% dos doentes hipertensos não conseguem controlar a TA com uma associação de dois anti-hipertensores, podendo ser necessário uma associação de três ou quatro fármacos, particularmente nos doentes com diabetes ou doença renal (Mancia et al. 2007; Mancia et al. 2009). A associação inibidor do sistema renina-angiotensina/BEC/diurético tiazídico pode constituir uma associação tripla racional, embora outros anti-hipertensores, como um bloqueador beta ou um bloqueador alfa, possam ser incluídos nestas associações múltiplas, dependendo das circunstâncias clínicas (Mancia et al. 2009).

Existem diversos modelos propostos para a sequência de etapas do tratamento farmacoterapêutico da HTA, sendo de destacar, pela sua importância na prática clínica portuguesa, o modelo adoptado pela DGS e pela Sociedade Portuguesa de Hipertensão, o qual se baseia na progressão por passos, perante a ausência de obtenção do controlo desejável da TA (Direcção-Geral da Saúde 2004; Polonia et al. 2006):

I) Indivíduos com TA normal-alta (TAS 130-139 mm Hg ou TAD 85-89 mm Hg), com três ou mais factores de risco *major*, lesão dos órgãos alvo ou doenças/eventos cardiovasculares e doentes com HTA de estádio 1 (TAS 140-159 mm Hg ou TAD 90-99 mm Hg):

1º) Monoterapia em doses baixas;
2º) Substituição por outro fármaco em monoterapia em doses baixas;
3º) Associação de dois fármacos em doses baixas;
4º) Associação de dois fármacos em doses máximas;
5º) Adição de terceiro fármaco;
6º) Adição de quarto fármaco.
Em cada etapa: optimização das doses dos fármacos escolhidos.

II) Doentes com HTA de estádio 2 (TAS ≥ 160 mm Hg ou TAD ≥ 100 mm Hg)

1º) Associação de dois fármacos em doses baixas;
2º) Associação de dois fármacos em doses máximas;
3º) Adição de terceiro fármaco;
4º) Adição de quarto fármaco.
Em cada etapa: optimização das doses dos fármacos escolhidos.

Deverá ser dada preferência às preparações farmacêuticas capazes de assegurar um efeito anti-hipertensor durante 24 horas com uma toma única diária, pois a simplificação do regime posológico favorece a adesão à terapêutica (Chobanian et al. 2003). Deverá, igualmente, ser dada uma grande atenção à presença de efeitos adversos dos anti-hipertensores, uma vez que constituem uma das principais causas de não adesão à terapêutica, sendo de salientar que os efeitos adversos diferem de fármaco para fármaco e de doente para doente (Chobanian et al. 2003).

2.11.2.2 Seguimento (*follow-up*) dos doentes com hipertensão arterial

Uma vez iniciada a terapêutica anti-hipertensora, os doentes deverão ser reavaliados a cada 2 – 4 semanas para proceder à titulação dos fármacos, até se obter o desejável controlo da TA (Perdigão 2010). Poderão ser necessárias consultas mais frequentes em doentes com HTA de estádio 2 ou com doenças associadas/co-morbilidades (p. ex., diabetes, insuficiência

cardíaca) (Chobanian et al. 2003). Após a estabilização da TA nos valores desejáveis, a periodicidade das consultas de "follow-up" deverá processar-se com intervalos de 3 a 6 meses, de acordo com a adesão à terapêutica percepcionada e a presença de outros factores de risco cardiovascular, doenças associadas ou alterações analíticas relevantes (Chobanian et al. 2003; Perdigão 2010).

Devem ser implementadas atitudes e comportamentos com o objectivo de controlo dos outros factores de risco cardiovascular (p. ex., redução de peso em indivíduos obesos ou com excesso ponderal, cessação tabágica, actividade física, etc.). Sempre que possível deve ser incentivada a colaboração de outros profissionais de saúde (p. ex., enfermeiros, farmacêuticos, fisioterapeutas, nutricionistas, pneumologistas) no seguimento do doente hipertenso (Chobanian et al. 2003). A monitorização da TA pelo doente deve também ser recomendada, não só porque, nos contextos apropriados, os registos feitos em casa ou na farmácia comunitária encerram informação adicional importante relativamente ao objectivo de um controlo mais adequado da TA, mas porque contribui, ainda, para aumentar a adesão do doente ao tratamento (Zarnke et al. 1997; Ogedegbe and Schoenthaler 2006; Mancia et al. 2007).

A creatininémia e a caliémia e, eventualmente, outros parâmetros analíticos, deverão ser avaliados, pelo menos, 1-2 vezes por ano (Chobanian et al. 2003). A coexistência de doenças associadas, como insuficiência cardíaca, diabetes, doença renal, ou alterações analíticas relevantes (p. ex., no perfil lipídico), poderá exigir consultas mais frequentes e exames complementares específicos (p. ex., electrocardiograma, fundoscopia, pesquisa de microalbuminúria) (Polonia et al. 2006; Perdigão 2010).

A presença de outros factores de risco cardiovascular e/ou doenças associadas poderá exigir a associação à terapêutica anti-hipertensora de outros medicamentos com benefício provado na redução do risco cardiovascular global (estatinas e outros antidislipidémicos, antidiabéticos, antiagregantes plaquetários, anticoagulantes, etc.) (Polonia et al. 2006; Mancia et al. 2009). As *guidelines* da Sociedade Europeia de Hipertensão e da Sociedade Europeia de Cardiologia recomendam que se considere a terapêutica com estatinas em hipertensos com menos de 80 anos que tenham um risco de doença/evento cardiovascular (estimado para um período de 10 anos) ≥ 20% ou um risco de morte cardiovascular (estimado pelo SCORE) de ≥ 5% (Mancia et al. 2007; Mancia et al. 2009). Alguns estudos indicam que a administração de estatinas a doentes hipertensos e hipercolesterolémicos pode também contribuir para alguma redução da TA (Glorioso et al. 1999; Ferrier et al. 2002; Borghi et al. 2004; Strazzullo et al. 2007; Morgado et al. 2010; Morgado et al. 2011), embora existam outros estudos em que esta redução não foi observada (Tonelli et al. 2006; Williams et al. 2009; Mancia et al. 2010). Os valores alvo recomendados relativamente ao colesterol total e colesterol-LDL séricos são, respectivamente, < 5 mmol/L (190mg/dL) e < 3 mmol/L (115mg/dL) (Mancia et al. 2007). A

maioria dos doentes consegue atingir estes valores alvo através da toma de uma estatina em doses adequadas conjuntamente com a adopção medidas não farmacológicas (Mancia et al. 2007). Os antiagregantes plaquetários (p. ex., ácido acetilsalicílico em baixas doses) só deverão ser administrados a hipertensos que tenham a TA adequadamente controlada, devido ao risco aumentado de hemorragia cerebral em doentes com HTA não controlada (Chobanian et al. 2003).

2.11.2.3 Situações especiais no tratamento da hipertensão arterial

Diversas *guidelines* (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Polonia et al. 2006; Mancia et al. 2009) preconizam uma abordagem específica nas opções terapêuticas e no seguimento de doentes com HTA e determinadas co-morbilidades, fundamentando-se em ensaios clínicos controlados e aleatorizados.

A Tabela 11, adoptada pela Direcção Geral de Saúde (Direcção-Geral da Saúde 2004) e pela Sociedade Portuguesa de Hipertensão (Polonia et al. 2006) e claramente alinhada com as mais importantes *guidelines* internacionais (Chobanian et al. 2003; Mancia et al. 2007; Mancia et al. 2009), resume as "indicações preferenciais" de determinados grupos/subgrupos de anti-hipertensores em doentes de risco elevado.

Tabela 11 – Indicações preferenciais dos diversos grupos de anti-hipertensores (adaptado de Direcção-Geral da Saúde 2004 e de Polonia et al. 2006).

Indicações Preferenciais	**Opções Terapêuticas Recomendadas**
Insuficiência cardíaca	DIURs, BBs, IECAs, ARAs, ANTALDs
Após enfarte do miocárdio	BBs, IECAs, ARAs, ANTALDs
Risco elevado de doença coronária	DIURs, BBs, IECAs, ARAs, BBEs
Diabetes	DIURs, BBs, IECAs, ARAs, BECs
Doença renal crónica	DIURs, IECAs, ARAs
Prevenção da recorrência de AVC	DIURs, IECAs, ARAs
Hipertrofia ventricular esquerda	IECAs, ARAs, BECs, DIURs
Microalbuminúria	IECAs, ARAs

Abreviaturas: ANTALDs – antagonistas da aldoesterona; ARAs – antagonistas dos receptores da angiotensina; AVC – acidente vascular cerebral; BBs – bloqueadores beta; BECs – bloqueadores da entrada do cálcio; DIURs - diuréticos; IECAs – inibidores da enzima de conversão da angiotensina.

As "indicações preferenciais" para um determinado grupo/subgrupo anti-hipertensor incluem condições de risco elevado que podem ser sequelas directas da HTA (insuficiência cardíaca, enfarte do miocárdio, doença renal crónica, acidente vascular cerebral, hipertrofia ventricular esquerda, microalbuminúria) ou condições frequentemente associadas à HTA (diabetes, doença coronária) (Chobanian et al. 2003). Na maioria das situações será necessário recorrer a associações de anti-hipertensores de diferentes grupos terapêuticos. Os

esquemas terapêuticos deverão ser seleccionados tendo em vista, quer a diminuição da TA para os valores alvo, quer os benefícios demonstrados na evolução natural da condição associada (Chobanian et al. 2003; Polonia et al. 2006). Para além das indicações preferenciais (Tabela 11) é, também, importante ter em consideração que há determinadas situações patológicas (p. ex., osteoporose, hipertiroidismo, hipertensão secundária à utilização de ciclosporina em transplantados renais) ou fisiológicas (p. ex., faixa etária, gravidez, etnia) em que determinados anti-hipertensores poderão ser mais úteis (Tabela 12).

Tabela 12 - Condições que favorecem o uso de determinadas classes terapêuticas de anti-hipertensores (adaptado de Mancia et al. 2007).

Classe de anti-hipertensor	**Indicações principais / possíveis**
Diuréticos tiazídicos	Hipertensão sistólica isolada (idosos); insuficiência cardíaca; hipertensão na raça negra; osteoporose; litíase renal cálcica.
Bloqueadores beta	Angina de peito; pós-enfarte do miocárdio; insuficiência cardíaca[1]; taquiarritmias; glaucoma; gravidez; hipertiroidismo; enxaqueca[2]; tremor essencial[2].
Antagonistas do cálcio (dihidropiridinas)	Hipertensão sistólica isolada (idosos); angina de peito; hipertrofia ventricular esquerda; aterosclerose coronária / carotídea; gravidez; hipertensão 2ária à utilização de ciclosporina / tacrolimus[3].
Antagonistas do cálcio (verapamil, diltiazem)	Angina de peito; aterosclerose carotídea; taquicardia supraventricular; enxaqueca; hipertensão secundária à utilização de ciclosporina / tacrolimus[3].
IECAs	Insuficiência cardíaca; disfunção ventricular esquerda; pós-enfarte do miocárdio; nefropatia diabética; nefropatia não-diabética; hipertrofia ventricular esquerda; aterosclerose carotídea; proteinúria / microalbuminúria; fibrilhação auricular; síndrome metabólica.
ARAs	Insuficiência cardíaca; pós-enfarte do miocárdio; nefropatia diabética; proteinúria / microalbuminúria; hipertrofia ventricular esquerda; fibrilhação auricular; síndrome metabólica; tosse com IECAs.
Diuréticos (anti-aldosterona)	Insuficiência cardíaca; pós-enfarte do miocárdio.
Diuréticos da ansa	Insuficiência renal; insuficiência cardíaca.

[1]Carvedilol (bloqueador alfa e beta), atenolol, bisoprolol, metoprolol, nebivolol (selectivos cardíacos).

[2]Bloqueadores beta não selectivos.

[3]Deve ser dada atenção aos níveis plasmáticos de ciclosporina / tacrolimus pois poderão subir.

ARAs - antagonistas dos receptores da angiotensina; IECAs - inibidores da enzima de conversão da angiotensina.

A presença de outras patologias que possam constituir contra-indicação para a utilização de determinadas classes de anti-hipertensores (Tabela 13), a ocorrência de RAMs, a possibilidade de interacção com outros medicamentos prescritos e os custos dos medicamentos constituem outros factores que deverão, igualmente, ser tidos em consideração na selecção do esquema terapêutico anti-hipertensor (Mancia et al. 2007).

Tabela 13 - Contra-indicações principais e possíveis dos anti-hipertensores (Mancia et al. 2007).

Classe de anti-hipertensor	Contra-indicações principais	Contra-indicações possíveis
Diuréticos tiazídicos	Gota	Síndrome metabólica Intolerância à glicose Gravidez
Bloqueadores beta	Asma Bloqueio auriculoventricular do 2º - 3º graus	Doença arterial periférica Síndrome metabólica Intolerância à glicose Desportistas / actividade física DPOC
Antagonistas do cálcio (dihidropiridinas)		Taquiarritmias Insuficiência cardíaca
Antagonistas do cálcio (verapamil, diltiazem)	Bloqueio auriculoventricular do 2º - 3º graus Insuficiência cardíaca	
IECA	Gravidez Edema angioneurótico por IECA Hipercaliemia Estenose bilateral das artérias renais	
ARA	Gravidez Hipercaliemia Estenose bilateral das artérias renais	
Diuréticos (anti-aldosterona)	Insuficiência renal Hipercaliemia	

ARAs - antagonistas dos receptores da angiotensina; DPOC – doença pulmonar obstrutiva crónica; IECAs - inibidores da enzima de conversão da angiotensina.

Diversas *guidelines* nacionais (Direcção-Geral da Saúde 2004; Williams et al. 2004; Halimi 2006; Polonia et al. 2006) e internacionais (Chobanian et al. 2003; Mancia et al. 2007; Mancia et al. 2009) revisaram detalhadamente a abordagem terapêutica anti-hipertensora e evidência científica associada nas seguintes situações particulares: diabetes, doença cerebrovascular (acidente vascular cerebral e acidente isquémico transitório), doença coronária, insuficiência cardíaca, hipertrofia ventricular esquerda, fibrilhação auricular, insuficiência renal crónica, síndrome metabólica, disfunção eréctil, idosos, mulheres, gravidez, crianças e adolescentes, grupos étnicos (caucasianos / raça negra / asiáticos) e urgências / emergências hipertensivas.

2.12 Hipertensão resistente

A HTA é geralmente considerada resistente ou refractária se os valores de TA alvo não são atingidos em doentes que recebem tratamento anti-hipertensor constituído por doses máximas de, pelo menos, três fármacos de diferentes grupos, incluindo um diurético (da ansa

se houver insuficiência renal) (Chobanian et al. 2003; Direcção-Geral da Saúde 2004; Paiva 2005; Polonia et al. 2006). A prevalência de hipertensão resistente varia entre 3 e 29%, dependendo dos estudos (Vidt 2000; ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2002; Mancia et al. 2007), existindo diversos factores que podem contribuir para a sua ocorrência, de entre os quais de destacam a falta de adesão ao tratamento, o tratamento anti-hipertensor inadequado (p. ex., associações inadequadas), as interacções farmacológicas (p. ex., anti-inflamatórios não esteróides, corticosteróides, alguns estimulantes centrais e inibidores do apetite, simpaticomiméticos, contraceptivos orais, ciclosporina, eritropoetina, alguns suplementos de origem vegetal, etc.), a terapêutica diurética inadequada, a adopção de estilos de vida pouco saudáveis (p. ex., excesso de ingestão de sal e/ou álcool), a obesidade / hiperinsulinemia, a síndrome da apneia do sono, a hipertensão secundária e a pseudoresistência (p. ex., pseudohipertensão, hipertensão da bata branca, utilização de braçadeira de dimensões reduzidas para o braço do doente) (Paiva 2005; Polonia et al. 2006; Mancia et al. 2007). Uma abordagem adequada de cada doente, que requer, por vezes, a referência a consultas especializadas, pode permitir a identificação adequada destes factores, reduzindo significativamente a proporção de hipertensos resistentes ao tratamento.

De referir que, da forma como está definida, a hipertensão resistente inclui os doentes cuja TA se encontra controlada com a utilização de mais do que três anti-hipertensores. De notar, ainda, que diversos autores são peremptoriamente mais restritivos na definição de hipertensão resistente, não incluindo as situações em que a TA alvo não é atingida por falta de adesão ao tratamento e/ou utilização de um regime terapêutico inadequado (Calhoun et al. 2008).

2.13 Adesão à terapêutica medicamentosa

Um dos principais obstáculos ao controlo eficaz da HTA está relacionado com a falta de adesão do doente ao tratamento com fármacos anti-hipertensores (Flack et al. 1996; Burnier et al. 2001; Whitworth 2003; Krousel-Wood et al. 2004; Yiannakopoulou et al. 2005; Bramley et al. 2006; Munger et al. 2007). De facto, a falta de adesão à medicação foi implicada em cerca de 30% - 50% dos casos de hipertensão refractária (Oparil and Calhoun 1998; Burnier et al. 2001; Paiva 2005). Estima-se que as taxas de adesão à medicação anti-hipertensora sejam de cerca de 50% (Puigventos Latorre et al. 1997; Haynes et al. 2002), embora exista uma variabilidade considerável entre os vários estudos, atribuível, em parte, a diferenças de natureza metodológica na avaliação da adesão (Hamilton 2003; Prado et al. 2007; Bloch et al. 2008). Estudos retrospectivos indicam que cerca de 40% dos doentes recentemente diagnosticados com HTA, descontinuam a medicação anti-hipertensora durante o primeiro ano de tratamento (Caro et al. 1999; Mazzaglia et al. 2005). Após 5 – 10 anos de tratamento, menos de 40% dos hipertensos persistem com a toma adequada dos anti-hipertensores prescritos (Caro et al. 1999; Van Wijk et al. 2005). No estudo AMALIA (Drugs Innovation

Impact in Cardio and Cerebrovascular Diseases in Portugal) cerca de 1/3 dos doentes hipertensos tratados referiu ter-se esquecido de tomar os medicamentos mais do que uma vez na última semana (Macedo et al. 2008; Perdigão 2010). Noutro estudo realizado em Portugal, Ramalhinho e Cabrita avaliaram a adesão à medicação anti-hipertensora em 95 doentes, tendo obtido uma taxa de adesão de 46,3% pelo método da contagem dos medicamentos (Ramalhinho and Cabrita 1998). A falta de adesão à terapêutica deve, pois, ser uma consideração primária na avaliação de doentes com HTA difícil de controlar.

A adesão à terapêutica pode ser definida como a decisão do doente de aceitar e seguir as instruções de um profissional de saúde relativas à toma da medicação. Este cumprimento pressupõe aderir às instruções relativas à dose, à frequência, ao intervalo interdose e à duração da terapêutica medicamentosa prescrita. Sempre que existam alterações significativas de qualquer destes parâmetros, o doente é classificado como não aderente, quer seja por excesso, quer por defeito. A adesão à terapêutica é frequentemente expressa através de uma taxa que indica a proporção de doses tomadas face ao número total de doses prescritas, considerando-se que o doente é aderente se a sua taxa de adesão se situa entre 80% e 120%. De referir que este critério utilizado para classificar os doentes como aderentes ou como não aderentes não é consensual, existindo outros métodos de avaliação de adesão à terapêutica, em que os resultados são expressos de maneira diversa, devendo este aspecto ser claramente apresentado na metodologia. Contudo, é importante referir que, no caso concreto da HTA, há autores que defendem que uma adesão de 80% é considerada suficiente para obter os resultados clínicos desejados de normalização da TA (Luscher et al. 1985).

A avaliação da adesão à terapêutica com anti-hipertensores e o conhecimento dos diversos factores que a influenciam são determinantes para o desenvolvimento de estratégias, por parte dos diversos profissionais de saúde, tendo em vista aumentar essa mesma adesão, fundamental para o controlo eficaz da HTA e para a prevenção das complicações cardiovasculares graves que lhe estão associadas.

2.13.1 Avaliação da adesão à terapêutica medicamentosa

Não existe um método universalmente eleito (“gold standard”) para avaliar a adesão à terapêutica medicamentosa em todas as diferentes situações clínicas, sendo um facto que todos apresentam vantagens e desvantagens (Osterberg and Blaschke 2005). De uma forma geral, os métodos para avaliar a adesão à terapêutica medicamentosa classificam-se em directos e indirectos, encontrando-se os mais utilizados referidos na Tabela 14.

Tabela 14 - Métodos de avaliação da adesão à terapêutica (adaptado de Osterberg and Blaschke 2005).

Classificação	Vantagens	Desvantagens
Métodos directos		
Terapêutica observada directamente.	Mais preciso.	Os doentes podem esconder os comprimidos na boca e rejeitá-los posteriormente; impraticável para uso rotineiro.
Determinação quantitativa do fármaco ou metabolitos nos fluidos biológicos.	Objectivo.	Variações farmacocinéticas inter e intra-individuais; o facto do doente voltar a tomar a medicação em dias anteriores à consulta médica pode resultar numa falsa impressão de adesão; dispendioso; exige recolha de fluidos biológicos.
Avaliação de marcadores biológicos no sangue.	Objectivo; em ensaios clínicos pode também ser usado para medir a adesão ao placebo.	Ensaios quantitativos dispendiosos e exige recolha de fluidos biológicos.
Métodos indirectos		
Relatos de doentes, questionários / entrevista estruturada a doentes	Simples; baixo custo; é o método mais útil na prática clínica.	Os resultados podem ser distorcidos pelo doente; questionários extensos podem ser pouco exequíveis na prática.
Contagem dos comprimidos/cápsulas (*pill count*).	Objectivo; método quantitativo fácil de executar.	Os dados são fáceis de alterar pelo doente (p. ex., *pill dumping*); Não fornece indicação sobre o intervalo interdose nem sobre a duplicação na terapêutica (p. ex. tomar 2 comprimidos na toma seguinte quando se esqueceu de uma toma). Pouco exequível em ambiente hospitalar se os medicamentos são adquiridos nas farmácias comunitárias.
Taxa de aviamento das prescrições médicas nas farmácias.	Objectivo; fácil obtenção de dados (armazenados informaticamente).	O aviamento do receituário não equivale à toma da medicação. Método mais eficaz em sistemas de saúde fechados (p. ex., HMO).
Avaliação da resposta clínica.	Simples; geralmente fácil de aplicar.	Outros factores para além da adesão à medicação podem influenciar a resposta clínica.
Dispositivos electrónicos de dispensa da medicação (p. ex. MEMS®).	Preciso; resultados facilmente quantificáveis; permite rastrear os padrões de toma da medicação, com informação completa sobre o intervalo interdose e duplicação na terapêutica.	Dispendioso; requer visitas continuadas à farmácia para que os dados sejam descarregados dos frascos para o computador.
Avaliação de marcadores fisiológicos (p. ex., frequência cardíaca em doentes que tomam bloqueadores beta).	Muitas vezes são fáceis de aplicar.	Os marcadores podem estar ausentes por outras razões (p. ex., aumento do metabolismo, baixa absorção, ausência de resposta).
Registo diário feito pelo doente.	Auxiliar de memória.	Fáceis de alterar pelo doente.

HMO – Health Maintenance Organization; MEMS® - Medication Event Monitoring System.

Os métodos directos de avaliação da adesão à terapêutica anti-hipertensora, tal como o nome indica, permitem verificar *in loco* se o medicamento foi tomado ou não pelo doente e incluem: observação directa da toma do medicamento; a determinação do princípio activo ou dos seus metabolitos nos fluidos biológicos (p. ex., sangue, urina); utilização de marcadores biológicos (p. ex., brometo de potássio) que podem ser adicionados ao medicamento (p. ex., incorporação nas cápsulas) e doseados no sangue (Braam et al. 2008). O primeiro método mencionado é mais preciso, embora seja inexequível na prática clínica para doentes em regime de ambulatório. Os outros métodos directos, embora objectivos, têm como principais inconvenientes o facto de serem dispendiosos e de os resultados poderem ser influenciados por variações farmacocinéticas inter- e intra-individuais.

Os métodos indirectos de avaliação da adesão à terapêutica anti-hipertensora incluem: auto-relato do doente quando lhe é pedido oralmente para explicar como é que toma a medicação (método mais simples de avaliar a adesão ao regime posológico prescrito); questionários escritos / entrevistas estruturadas relacionados com a toma da medicação (Pineiro et al. 1997; Hamilton 2003) (p. ex., questionário de Batalla (Batalla et al. 1984), questionário de Haynes-Sackett (Sackett et al. 1975), questionário de Morisky (Morisky et al. 1986), etc.); contagem dos comprimidos / cápsulas remanescentes para determinação dos que foram tomados (comprimidos / cápsulas adquiridos – comprimidos / cápsulas remanescentes); verificação das receitas aviadas nas farmácias comunitárias (de notar que a dispensa de medicamentos anti-hipertensores pelas farmácias hospitalares não se encontra abrangida pela legislação portuguesa em vigor); grau de controlo da tensão arterial (valores de tensão arterial no consultório de < 140/90 mm Hg para a população em geral e < 130/80 mm Hg para diabéticos e doentes renais); dispositivos electrónicos para monitorização da adesão (p. ex. MEMS® - Medication Event Monitoring Systems), os quais são utilizados não apenas para avaliar a adesão à terapêutica medicamentosa, mas também como estratégia para aumentar essa mesma adesão (Brunenberg et al. 2007).

Os métodos indirectos para a determinação da adesão à terapêutica são, indiscutivelmente, os mais utilizados na investigação clínica em doentes com HTA, em particular as medidas psicométricas de adesão, sendo de salientar, de entre estas, o questionário de Morisky et al. (Morisky et al. 1983; Morisky et al. 1986), validado para doentes hipertensos e seguramente o mais utilizado nas duas últimas décadas no estudo de populações hipertensas. O teste de Morisky et al. é constituído por 4 questões relacionadas com a toma da medicação, cuja resposta deve ser dada na forma dicotómica sim/não, sendo considerado simples e rápido de aplicar em entrevistas estruturadas (Shalansky et al. 2004). No estudo com 290 hipertensos, realizado por Morisky et al., com a finalidade de validar esta medida de adesão aos tratamentos, os 4 itens da mesma apresentaram uma consistência interna razoável (alfa de Cronbach de 0,61) (Morisky et al. 1986).

Uma versão melhorada da medida de adesão de Morisky et al. (Morisky et al. 1986) foi elaborada por Shea et al. (Shea et al. 1992), a qual é actualmente muito utilizada no estudo da adesão à medicação em populações hipertensas (Ramalhinho 1994; Elliott 2010. Available at www.ash-us.org/annual_meeting/index.htm. Accessed on 7th November 2010). O questionário de Shea et al. (Shea et al. 1992) é constituído por 5 questões, com resposta aos respectivos itens também na forma dicotómica sim/não, tendo apresentado um alfa de Cronbach mais elevado (0,71) do que o questionário de Morisky et al. (Morisky et al. 1986) no estudo da adesão à terapêutica em doentes com HTA (Shea et al. 1992).

2.13.2 Estratégias para aumentar a adesão à terapêutica medicamentosa

Uma percentagem considerável de doentes hipertensos não toma a medicação prescrita de acordo com as indicações do médico, existindo diversos factores que influenciam a adesão à terapêutica com anti-hipertensores (Flack et al. 1996; Burke et al. 1997; De Macedo et al. 2007; Morgado et al. 2010). A este respeito é importante destacar o facto de a HTA ser considerada uma patologia silenciosa, que não apresenta sintomas, não facilitando, assim, uma adesão do doente a um tratamento não "sentido" como necessário.

Por outro lado, num tratamento a longo prazo, muitas vezes para o resto da vida, é importante ter em conta a comodidade da toma dos medicamentos, assim como a tolerabilidade dos mesmos (Chobanian et al. 2003; Direcção-Geral da Saúde 2004). É hoje consensualmente aceite que um anti-hipertensor só é eficaz se for tomado regularmente devendo, no entanto, apresentar um esquema posológico cómodo (administração única diária) e ser bem tolerado para que tal suceda (ausência de efeitos secundários significativos). De facto, as taxas de abandono ao tratamento verificadas com algumas classes terapêuticas de anti-hipertensores reflectem a elevada incidência de RAMs (p. ex., tosse, cefaleias, edemas maleolares, disfunção eréctil, obstipação) associadas a alguns medicamentos. Outros factores que podem influenciar negativamente a adesão à terapêutica com anti-hipertensores são: esquecimento da toma da medicação, interferência da terapêutica com o estilo de vida do doente, percepção da falta de efectividade do medicamento, desvalorização da doença, falta de clareza nas instruções relativas ao tratamento ou dificuldade na compreensão das mesmas, falta de conhecimento acerca da HTA e das suas possíveis complicações, dificuldade em compreender a necessidade da terapêutica, depressão ou outras perturbações psiquiátricas, perturbações cognitivas, ingestão excessiva de álcool, estabelecimento de uma relação não concordante entre o doente e o médico e a falta de acesso ao medicamento (por questões geográficas, económicas, burocráticas ou outras) (Flack et al. 1996; Krousel-Wood et al. 2004; Borzecki et al. 2005; Osterberg and Blaschke 2005).

Estão descritas diversas estratégias para aumentar a adesão dos doentes à terapêutica anti-hipertensora. Uma das estratégias mais eficazes consiste na prescrição de esquemas terapêuticos simples, recorrendo, sempre que possível, a medicamentos que assegurem um

efeito anti-hipertensor durante 24 horas com uma administração única diária (p. ex., utilização de formas farmacêuticas de libertação prolongada ou de princípios activos com maior tempo de semi-vida). A utilização de associações de doses fixas de anti-hipertensores contribui também para a simplificação da terapêutica, na medida em que diminui o número de medicamentos que o doente tem de tomar. Outro aspecto muito importante diz respeito às RAMs, devendo ser encorajada a discussão deste assunto com o doente, tendo em vista a selecção de um esquema terapêutico que seja bem tolerado pelo doente (ausência de efeitos secundários significativos) (Chobanian et al. 2003). O esquema terapêutico deve ser incorporado nas rotinas diárias do doente, não devendo o horário da toma da medicação ser inconveniente para o doente. Daqui resulta que é extremamente importante incluir o doente no processo de selecção do esquema terapêutico, o qual deve ser individualizado atendendo às suas características particulares. O encorajamento da medição e registo da TA em casa é outra estratégia que se revelou eficaz para aumentar a adesão à terapêutica medicamentosa, devendo o doente ser informado dos seus valores alvo de TA (Ogedegbe and Schoenthaler 2006; Pickering 2008). Deve procurar-se, tanto quanto possível, minimizar o custo da terapêutica sem, contudo, comprometer a sua eficácia e segurança.

Simultaneamente, são também muito importantes as intervenções educacionais tendo em vista a educação do doente acerca da HTA e da importância do esquema terapêutico prescrito, alertando para os riscos da TA não controlada. É fundamental a educação para a toma correcta da medicação, devendo ser dispensada informação oral e escrita acerca da terapêutica instituída e ser sempre confirmado que o doente compreendeu claramente as instruções a este respeito. Deve igualmente ser enfatizado que o controlo da TA não significa a cura da HTA, havendo necessidade de continuar o tratamento (farmacológico e não farmacológico) mesmo que os valores alvo de TA tenham sido atingidos. Deve também ser salientada a natureza silenciosa da HTA pelo que a TA deve ser medida regularmente. O doente deve também ser informado acerca dos estilos de vida saudáveis e incentivado a aderir aos mesmos. A adesão à terapêutica deve ser um tema a abordar em todas as visitas clínicas, devendo o doente ter conhecimento deste facto logo à partida. Os comportamentos adequados e os bons resultados devem ser reforçados (Osterberg and Blaschke 2005). Caso seja necessário, os familiares ou cuidadores devem ser envolvidos no acompanhamento da doença e no tratamento do doente.

Para além da decisão do médico partilhada com o doente e das estratégias comportamentais e educacionais já mencionadas, é evidente que a melhoria da adesão à terapêutica e do controlo da TA só pode ser conseguida com estratégias organizacionais que permitam um *follow-up* regular dos hipertensos (Glynn et al.; Rocha 2008).

Devem ser avaliadas, para cada caso individual, as razões subjacentes à não adesão à terapêutica, com o objectivo de seleccionar, com a colaboração do doente, as intervenções

mais adequadas. Por exemplo, nos doentes que se esquecem frequentemente do horário da toma da medicação poderá ser útil recorrer a dispositivos de dispensa da medicação com sistema de alarme ou a memorandos para exposição em locais bem visíveis (Haynes et al. 2002). Num doente que se queixe de disfunção eréctil associada à toma dos anti-hipertensores poderá ser prescrito um inibidor selectivo da fosfodiesterase 5, activo por via oral (p. ex., sildenafil, tadalafil, vardenafil).

Diversos modelos comportamentais indicam que outra estratégia para estimular a adesão à terapêutica consiste na adopção de técnicas motivacionais que conduzem o doente a seguir com vontade a prescrição que lhe foi proposta (Possidente et al. 2005). A motivação está muito associada à comunicação, empatia e confiança na equipa dos cuidados de saúde (Barrier et al. 2003; Possidente et al. 2005).

As estratégias que se revelaram mais eficazes para aumentar a adesão à terapêutica e o controlo da TA em populações hipertensas são complexas e trabalhosas, envolvendo múltiplas intervenções e diversos profissionais de saúde (Haynes et al. 2002; Morgado et al. 2010). Diversos estudos revelaram que a integração de enfermeiros e de farmacêuticos na equipa multidisciplinar de saúde envolvida no tratamento de doentes hipertensos conduziu a um aumento da adesão à terapêutica e do controlo da TA (Glynn et al.; Hill and Miller 1996; Carter et al. 2009; Carter et al. 2009).

2.14 Papel do farmacêutico na adesão à terapêutica e no controlo da tensão arterial

De acordo com o JNC 7, diversos profissionais de saúde (p. ex. enfermeiros, farmacêuticos, nutricionistas) devem colaborar com o médico no tratamento dos doentes hipertensos, reforçando a informação acerca dos riscos da HTA e da importância de adoptar estilos de vida saudáveis, de medir regularmente a TA, de aderir à terapêutica medicamentosa e de atingir os valores de TA alvo (Chobanian et al. 2003).

Diversos estudos (ensaios clínicos controlados e ensaios clínicos não controlados) revelaram que a inclusão do farmacêutico na equipa multidisciplinar de saúde envolvida no tratamento de doentes hipertensos conduziu a um aumento estatisticamente significativo da adesão à terapêutica e do controlo da TA (Blenkinsopp 2000; Brouker et al. 2000; Chabot et al. 2003; Sookaneknun et al. 2004; Zillich et al. 2005; de Souza et al. 2007; Aguwa et al. 2008). Em todos estes estudos, a intervenção farmacêutica foi complexa, multifactorial, incluindo acções quer junto dos médicos, quer junto dos doentes hipertensos (Morgado et al. 2010; Morgado et al. 2011).

A colaboração estreita com os prescritores é fundamental para o farmacêutico propor esquemas farmacoterapêuticos mais eficazes (p. ex., através da intensificação da terapêutica quando a TA permanece não controlada, não obstante uma comprovada adesão à terapêutica medicamentosa, combatendo, desta forma, a inércia clínica), mais simples (p. ex., através do recurso a medicamentos de toma única diária e/ou a associações de anti-hipertensores na mesma preparação farmacêutica), mais seguros (p. ex., através a selecção de alternativas terapêuticas menos susceptíveis de originarem determinados efeitos secundários ou de outros medicamentos capazes de contrariar os referidos efeitos secundários) e mais económicos.

A intervenção farmacêutica junto dos doentes hipertensos ou dos seus cuidadores tem como principais objectivos os seguintes: promover a toma correcta dos medicamentos; identificar problemas relacionados com a efectividade e a segurança na utilização de medicamentos; avaliar e promover a adesão à terapêutica; identificar as barreiras à adesão à terapêutica e propor, em coloração com o médico e o doente, estratégias para as ultrapassar; informar sobre a HTA e riscos associados, sobre a importância de adoptar estilos de vida saudáveis, sobre os valores alvo de TA e a importância de medir e registar regularmente a TA.

A informação ao doente deve ser dada sob a forma de comunicação verbal e reforçada com informação escrita sob a forma de folhetos informativos. Relativamente á informação sobre a forma correcta de utilizar os medicamentos, é importante descrever, numa linguagem simples e compreensível, os seguintes elementos informativos básicos: nome do medicamento, forma farmacêutica, dosagem, indicações e acções esperadas, via de administração, posologia, horário de administração e duração do tratamento, precauções a tomar durante a administração, efeitos secundários comuns que podem surgir, como evitá-los e como actuar se se apresentarem, contra-indicações terapêuticas, interacções potenciais com outros medicamentos ou com alimentos, que fazer em caso de esquecimento de uma toma e normas para a correcta conservação (Martins et al. 1999).

Embora, em Portugal, esta intervenção farmacêutica esteja descrita a nível das farmácias comunitárias (Garção and Cabrita 2002), não existem, tanto quanto é do nosso conhecimento, quaisquer estudos publicados relatando esta intervenção a nível hospitalar.

Estudos realizados noutros países revelaram que a inclusão do farmacêutico hospitalar na equipa profissional de saúde envolvida no tratamento de doentes hipertensos conduziu a uma diminuição da TAS e da TAD (Lee et al. 2006; Roumie et al. 2006; de Souza et al. 2007; Carter et al. 2008). Com efeito, em ambiente hospitalar, onde uma maior colaboração entre os diversos profissionais de saúde é possível, o farmacêutico hospitalar encontra-se numa posição privilegiada para influenciar favoravelmente a adesão à terapêutica anti-hipertensora e o controlo da HTA.

O presente trabalho pretende estudar a intervenção do farmacêutico hospitalar na adesão à terapêutica anti-hipertensora e no controlo da TA numa população hipertensa adulta em regime de ambulatório da zona de influência do Centro Hospitalar da Cova da Beira, E. P. E., Covilhã, Portugal.

Capítulo 3

Objectivos e Organização Geral da Dissertação

O objectivo principal da presente dissertação consiste em desenvolver, implementar e avaliar uma intervenção farmacêutica hospitalar que permita aumentar o controlo da TA numa população hipertensa da zona de influência do Centro Hospitalar Cova da Beira, E. P. E..

A consecução deste objectivo principal foi realizada através das seguintes etapas:

1) Realização de uma revisão bibliográfica tendo em vista a análise de todas as intervenções farmacêuticas desenvolvidas com o objectivo de aumentar a adesão à terapêutica anti-hipertensora e o controlo da TA. Desenvolvimento de uma revisão sistemática e meta-análise de todos os estudos relevantes publicados na última década (de 1999 a 2009).

2) Estudo retrospectivo da população hipertensa da zona de influência do Centro Hospitalar Cova da Beira, E. P. E. com o objectivo de avaliar o grau de controlo da TA e o padrão da terapêutica farmacológica anti-hipertensora. Este estudo envolveu a análise dos dados da referida população hipertensa de Janeiro de 2008 a Junho de 2009.

3) Revisão sistemática e análise meta-analítica de todos os ensaios clínicos controlados e aleatorizados envolvendo a associação aliscireno/HCTZ. Com este estudo pretendeu-se analisar a eficácia anti-hipertensora e o perfil de segurança desta associação recentemente introduzida no mercado farmacêutico europeu.

4) Estudo observacional transversal da percentagem de doentes hipertensos, da zona de influência do Centro Hospitalar Cova da Beira, E. P. E., com a TA controlada e estudo dos factores preditores de TA não controlada. Este estudo foi efectuado de Julho de 2010 a Setembro de 2010. Nesta fase estudou-se, igualmente, o grau de adesão à terapêutica anti-hipertensora e os factores envolvidos na não adesão à medicação, tendo em vista o desenvolvimento e a implementação de estratégias que permitam aumentar a adesão à terapêutica e o controlo eficaz da HTA. Foi, ainda, analisada a existência de uma possível associação entre a terapêutica com estatinas e o controlo da TA nos doentes com HTA de estádio 1 e hipercolesterolémia incluídos neste estudo observacional transversal.

5) Realização de um ensaio clínico controlado e aleatorizado com a finalidade de estudar o efeito da intervenção do farmacêutico hospitalar na adesão à terapêutica anti-hipertensora e no controlo da TA. Este ensaio clínico envolveu todos os doentes hipertensos incluídos no estudo observacional transversal da etapa 4). A intervenção do farmacêutico consistiu na

implementação de estratégias planeadas com base nos resultados obtidos nas etapas anteriores.

A metodologia utilizada para a consecução das três primeiras etapas encontra-se devidamente abordada nos respectivos artigos que cada uma daquelas etapas originou (Morgado et al. 2010; Morgado et al. 2011; Morgado et al. 2011). Contudo, para as restantes etapas da dissertação, não foi possível, por limitações de espaço, abordar, nos respectivos artigos produzidos (Morgado et al. 2010; Morgado et al. 2011; Morgado et al. 2011), a metodologia utilizada com o devido pormenor. Desta forma, é realizada, na secção seguinte, uma descrição pormenorizada da "População e Métodos" utilizados no desenvolvimento das duas últimas etapas mencionadas.

Capítulo 4

População e Métodos

A realização do estudo observacional transversal e do ensaio clínico mencionados no capítulo anterior tiveram o parecer positivo da Comissão de Ética para a Saúde e a autorização do Conselho de Administração do Centro Hospitalar Cova da Beira, E.P.E., tendo apenas sido incluídos no trabalho de investigação os doentes que deram o seu consentimento livre, informado e esclarecido para a participação no projecto, o qual foi dado por escrito antes do início dos estudos.

O desenvolvimento deste projecto (estudo observacional transversal e ensaio clínico) foi dividido em duas fases. Na 1ª fase, que decorreu de Julho a Setembro de 2009, procedeu-se à avaliação inicial de todos os doentes que acorreram à consulta de hipertensão / dislipidémia do Centro Hospitalar Cova da Beira, E.P.E. e à sua inclusão no estudo (feita em função do consentimento livre, informado e esclarecido e dos critérios de inclusão e de exclusão previamente definidos). Na 2ª fase, que decorreu de Julho de 2009 a Junho de 2010, procedeu-se à alocação aleatória dos doentes incluídos no estudo pelos grupos controlo e de intervenção do ensaio clínico. No período de Julho a Setembro de 2009 desenvolveram-se, portanto, simultaneamente, as duas partes do projecto, pois após a avaliação inicial e a inclusão no estudo, os doentes eram imediatamente alocados aleatoriamente para um dos grupos do ensaio clínico. No caso dos doentes do grupo de intervenção, ocorria, ainda, a primeira consulta com o farmacêutico hospitalar.

4.1 Primeira fase do projecto

A primeira fase do projecto envolveu os seguintes estudos: 1) Avaliação do grau de controlo da TA numa população hipertensa da zona de influência do Centro Hospitalar Cova da Beira, E.P.E.; 2) Determinação dos factores preditores de HTA não controlada e de não adesão à terapêutica anti-hipertensora; 3) Análise da existência de uma possível associação entre a terapêutica com estatinas e o controlo da TA nos doentes incluídos com HTA de estádio 1 e hipercolesterolémia.

Para o desenvolvimento desta primeira parte do projecto, realizou-se um estudo observacional transversal em doentes com diagnóstico de HTA que acorreram, de Julho a Setembro de 2009, à consulta de hipertensão / dislipidémia do Centro Hospitalar Cova da Beira, E.P.E.

A população em análise englobou doentes de ambos os sexos, com idade igual ou superior a 18 anos, que tenham dado o seu consentimento livre, informado e esclarecido para a participação no estudo, com diagnóstico de HTA e que estivessem a efectuar terapêutica farmacológica para esta patologia há, pelo menos, 6 meses. Foram excluídos os doentes com patologia mental incapacitante, grávidas e lactantes.

Foi solicitado a todos os doentes incluídos no estudo que respondessem a uma entrevista estruturada, tendo em vista o registo dos seguintes dados relativos a cada doente: características sócio-demográficas (sexo, idade, escolaridade, estado civil), hábitos tabágicos, duração da HTA, adesão à medicação anti-hipertensora, conhecimento dos valores alvo de TA, dos riscos da HTA não controlada e da indicação clínica dos anti-hipertensores prescritos, frequência da monitorização da TA e presença de RAMs atribuídas aos anti-hipertensores.

Para a análise da existência de uma possível associação entre a terapêutica com estatinas e o controlo da TA foram apenas incluídos os doentes com diagnóstico de HTA de estádio 1 (valores no consultório de TAS de 140-159 mm Hg e/ou de TAD de 90-99 mm Hg) e hipercolesterolémia (colesterol sérico total em jejum ≥200 mg/dL). Estes doentes hipertensos hipercolesterolémicos foram incluídos no grupo das estatinas (quando se encontravam a tomar uma estatina há, pelo menos, 6 meses) ou no grupo controlo (no caso de não se encontrarem prescritos com uma estatina), tendo-se procedido à análise dos valores médios de TA e da percentagem de controlo da mesma em ambos os grupos. Nesta análise, para além dos critérios de exclusão mencionados, foram ainda considerados os seguintes: HTA de estádio 2 (valores no consultório de TAS ≥ 160 e/ou de TAD ≥ 100 mm Hg) e prescrição de uma estatina há menos de 6 meses.

4.1.1 Medição da tensão arterial

A medição da TAS e TAD foi efectuada com o doente na posição sentada, em ambiente calmo, após um período de repouso de cerca de 5 minutos. A determinação foi efectuada por enfermeiras cegas-para-o-estudo (sem qualquer conhecimento dos doentes incluídos e excluídos do estudo) utilizando um esfingmomanómetro de coluna de mercúrio (Kamiya Tsusan Kaisha, Ltd., Japan) ou um aparelho medidor de TA automático (Omron M4-I) devidamente aferidos e tendo sido registada a média de duas medições consecutivas, realizadas com um espaçamento de 1-2 minutos. Foram realizadas medições adicionais da TA nas situações em que os resultados das duas primeiras medições foram consideravelmente diferentes. De acordo com as orientações definidas pela DGS (Direcção-Geral da Saúde 2004), pela Sociedade Portuguesa de Hipertensão (Polonia et al. 2006) e pelo JNC 7 (Chobanian et al. 2003), os doentes hipertensos sem diabetes nem doença renal crónica com valores de TA inferiores a 140/90 mm Hg foram considerados controlados. No caso dos doentes hipertensos diabéticos ou com doença renal crónica, a TA foi considerada controlada

apenas para valores inferiores a 130/80 mm Hg (Chobanian et al. 2003; Direcção-Geral da Saúde 2004).

4.1.2 Adesão à medicação anti-hipertensora, conhecimentos gerais sobre hipertensão arterial e sua monitorização

A avaliação da adesão à medicação anti-hipertensora foi efectuada utilizando o questionário desenvolvido por Morisky et al. (Morisky et al. 1983; Morisky et al. 1986) modificado por Shea et al. (Shea et al. 1992; Shea et al. 1992), amplamente utilizado na população hipertensa Norte-Americana e Europeia (Anexo I). Considerou-se como baixa ou elevada adesão à terapêutica medicamentosa a obtenção de uma classificação, respectivamente, ≥ 3 ou ≤ 2, na resposta à totalidade das 5 questões (Anexo I); os doentes que obtiveram aquelas classificações foram considerados, respectivamente, não aderentes ou aderentes à medicação. Foi também avaliado o conhecimento dos valores alvo da TA e dos riscos da HTA não controlada. Considerou-se que os doentes tinham conhecimento dos valores alvo da TA se referiam correctamente tanto a TAS e como a TAD a atingir (< 140/90 mm Hg no caso dos doentes sem diabetes nem doença renal crónica e < 130/80 mm Hg no caso dos doentes com pelo menos uma daquelas patologias). Considerou-se que tinham conhecimento dos riscos da HTA não controlada se referiam correctamente pelo menos duas das consequências negativas da TA não controlada (patologia cerebral, patologia cardíaca, patologia renal, patologia oftálmica). Considerou-se que os doentes monitorizavam regularmente a TA se efectuavam a sua medição e o seu registo pelo menos uma vez por mês.

4.1.3 Parâmetros antropométricos, fisiológicos e clínicos

Os dados antropométricos, fisiológicos e clínicos para a realização do estudo, incluindo peso, altura, valores de TA, medicação prescrita e patologias concomitantes foram prospectivamente obtidos através dos processos clínicos dos doentes no dia da consulta. Qualquer dúvida que eventualmente surgisse na recolha destes dados era de imediato esclarecida com os médicos e/ou enfermeiras envolvidos na consulta de hipertensão / dislipidémia.

4.1.4 Análise estatística

As variáveis demográficas e antropométricas, os valores de TA, o perfil lipídico e os dados clínicos, bem como os dados relativos à medicação anti-hipertensora e antidislipidémica prescrita, adesão à terapêutica anti-hipertensora, monitorização da TA, conhecimento dos doentes no que respeita à HTA e presença de RAMs, foram avaliados por análise estatística descritiva e expressos em termos de média ± DP (desvio padrão), frequência e percentagens. A comparação entre grupos, relativamente a variáveis contínuas, foi conduzida através do teste t-Student ou, no caso em que o pressuposto da normalidade não foi verificado, do teste não paramétrico de Mann-Whitney. Foram utilizados o teste do qui-quadrado e o teste exacto

de Fisher (nos casos em que se observaram células com frequências esperadas inferiores a 5) para a análise das variáveis categoriais. A determinação das variáveis independentes com influência significativa no controlo da TA e na adesão à terapêutica anti-hipertensora, bem como dos respectivos *odds ratios* (OR) e intervalos de confiança de 95% (IC 95%), foi efectuada recorrendo à regressão logística, utilizando o algoritmo de selecção de variáveis com poder preditor *forward likelihood ratio*. Todas as análises estatísticas foram efectuadas utilizando o programa informático SPSS para Windows, versão 17.0 (SPSS Inc., Chicago, IL), tendo sido considerada a existência de significância estatística a presença de um valor de $P < 0,05$.

4.2 Segunda fase do projecto

A segunda fase do projecto envolveu a realização de um ensaio clínico, controlado e aleatorizado tendo em vista o estudo do efeito da intervenção do farmacêutico hospitalar na adesão à terapêutica anti-hipertensora e no controlo da TA.

Para o desenvolvimento desta segunda fase do projecto, realizou-se um ensaio clínico, controlado e aleatorizado, de Julho de 2009 a Junho de 2010, em que participaram os mesmos doentes com diagnóstico de HTA que foram incluídos no estudo observacional transversal realizado na primeira fase do trabalho.

4.2.1 Procedimento de alocação

Os referidos doentes foram aleatoriamente alocados para um de dois grupos paralelos (*ratio* de alocação 1:1): grupo controlo (em que os doentes recebiam os cuidados habituais, sem qualquer intervenção do farmacêutico hospitalar) ou grupo de intervenção (em que os doentes recebiam adicionalmente cuidados farmacêuticos, através do acompanhamento, com uma periodicidade trimestral, por um farmacêutico hospitalar, durante o período de 9 meses).

Os doentes foram alocados aleatoriamente para cada um dos grupos por um processo de aleatorização simples (alocação igual e sem restrições), usando uma lista de números aleatórios gerada por computador. A sequência de alocação foi ocultada do farmacêutico hospitalar encarregue da avaliação inicial e inclusão dos doentes em envelopes sequencialmente numerados, opacos e selados. A produção por computador da sequência de números aleatórios e a preparação dos envelopes foi efectuada por um investigador sem qualquer envolvimento no ensaio clínico.

4.2.2 Intervenção farmacêutica

O acompanhamento farmacêutico prestado ao grupo de intervenção consistiu numa consulta individual inicial de cerca de 30 minutos e de consultas individuais *follow-up* com a duração

de cerca de 20 minutos e efectuadas ao 3º e 6º meses após a primeira consulta. O farmacêutico hospitalar podia ainda agendar consultas individuais adicionais sempre que o considerasse necessário.

Em cada consulta realizada individualmente com cada doente do grupo de intervenção, o farmacêutico hospitalar realizava uma entrevista tendo em vista a identificação de eventuais problemas que pudessem ser responsáveis pela falta de controlo adequado da TA, prestava informações tendo em vista a educação do doente na área da HTA (p. ex., definição de HTA, riscos da HTA não controlada, valores de TA alvo, importância das medidas não farmacológicas e farmacológicas para o controlo da TA) e dava recomendações tendo em vista a adopção de estilos de vida saudáveis e de comportamentos que contribuíssem para um melhor controlo da TA (p. ex., alimentação saudável, exercício físico, adesão à terapêutica farmacológica, procedimentos para evitar/controlar algumas RAMs, monitorização regular da TA). Paralelamente, o farmacêutico hospitalar, sempre que o considerasse necessário, elaborava propostas de alteração à terapêutica medicamentosa que eram apresentadas ao médico responsável.

As recomendações, relativas à adopção de estilos de vida saudáveis, efectuadas pelo farmacêutico hospitalar aos doentes do grupo de intervenção, tendo em vista o controlo da TA, estavam alinhadas com as recomendações da DGC (Direcção-Geral da Saúde 2004), da Sociedade Portuguesa de Hipertensão (Polonia et al. 2006), da Sociedade Europeia de Hipertensão/Sociedade Europeia de Cardiologia (Mancia et al. 2007) e da JNC 7 (Chobanian et al. 2003) e incluíam: (1) perda de peso nos doentes com excesso de peso, (2) redução da ingestão de sal, (3) exercício físico, (4) consumo de álcool apenas com moderação e (5) cessação dos hábitos tabágicos nos doentes fumadores. O farmacêutico forneceu também aos doentes do grupo de intervenção três folhetos informativos, elaborados numa linguagem simples e acessível, acerca da HTA, potenciais riscos quando não devidamente controlada e comportamentos adequados para o seu controlo eficaz (Anexos II, III e IV). Além disso, estes doentes foram incentivados a trazer para as consultas as embalagens vazias de medicamentos (cartonagem e blisteres) para reciclagem e verificação da adesão à terapêutica.

Os doentes do grupo controlo não tiveram qualquer intervenção do farmacêutico hospitalar, recebendo apenas o acompanhamento habitual por parte do pessoal médico e de enfermagem.

4.2.3 *Outcomes* primários e secundário

Os *outcomes* primários, no que respeita à determinação da eficiência da intervenção farmacêutica, foram a percentagem de doentes com a TA controlada e a redução da TAS e da TAD relativamente aos valores iniciais. A TA foi determinada como anteriormente descrito, por enfermeiras que desconheciam a que grupo (intervenção *vs* controlo) pertenciam os doentes. Foram adoptados os critérios já descritos anteriormente para classificar os doentes

em controlados e não controlados, no que respeita à HTA. Como *outcome* secundário considerou-se a adesão à terapêutica anti-hipertensora, a qual foi determinada como descrito anteriormente. Avaliou-se, ainda, o conhecimento dos doentes no que respeita aos riscos da HTA não controlada e aos valores alvo de TA, tal como descrito anteriormente.

4.2.4 Calendário da avaliação dos doentes

A determinação da TAS e da TAD, a avaliação do controlo da TA e da adesão à terapêutica e a avaliação do conhecimento dos doentes no que respeita aos riscos da HTA não controlada e aos valores alvo de TA foi avaliada, para ambos os grupos do estudo, na consulta inicial e após 9 meses. De referir que na consulta relativa a esta última avaliação (final do período de 9 meses) o grupo de intervenção não recebeu qualquer intervenção farmacêutica. Nos casos em que o doente não compareceu à consulta correspondente à avaliação final, utilizaram-se os últimos valores registados de TAS e de TAD para a realização da análise *intent-to-treat*.

4.2.5 Determinação do tamanho da amostra

Para a determinação do tamanho da amostra do ensaio clínico, considerou-se que para a detecção de uma redução na TAS de 8-10 mm Hg (DP 16-18 mm Hg), que está de acordo com diversos estudos (SHEP Cooperative Research Group 1991; Erickson et al. 1997; Vivian 2002; Carter et al. 2003), com um nível de significância de 5% e um poder estatístico de 80%, são necessários 90 doentes por grupo (um total de 180 doentes), assumindo uma taxa de desistências de 10%. Com base no historial do número de doentes atendidos na consulta de hipertensão / dislipidémia, estimou-se que para recrutar aquele número total de doentes seria necessário um período de recrutamento de 3 meses (Julho a Setembro de 2009).

4.2.6 Análise estatística

As variáveis demográficas e antropométricas, os valores de TA e os dados clínicos, bem como os dados relativos à medicação anti-hipertensora prescrita, adesão à terapêutica, monitorização da TA, conhecimento dos doentes no que respeita à HTA e presença de RAMs, foram avaliados por análise estatística descritiva e expressos em termos de média ± DP, frequência e percentagens. A comparação entre grupos, relativamente a variáveis contínuas, foi conduzida através do teste t-Student ou, no caso em que o pressuposto da normalidade não foi verificado, do teste não paramétrico de Mann-Whitney. O teste do qui-quadrado e o teste exacto de Fisher (nos casos em que se observaram células com frequências esperadas inferiores a 5) utilizaram-se para a comparação das variáveis categoriais. Tal como anteriormente descrito, todas as análises estatísticas foram efectuadas utilizando o programa informático SPSS para Windows, versão 17.0 (SPSS Inc., Chicago, IL), tendo sido considerada a existência de significância estatística a presença de um valor de $P < 0,05$.

Capítulo 5

Artigos Publicados

5.1 Artigo I

Morgado MP, Morgado SR, Mendes LC, Pereira LJ, Castelo-Branco M. **Pharmacist interventions to enhance blood pressure control and adherence to antihypertensive therapy: Review and meta-analysis.** Am J Health Syst Pharm 2011;68:241-253. DOI: 10.2146/ajhp090656. PMID: 21258029

5.2 Artigo II

Morgado MP, Rolo SA, Pereira L, Castelo-Branco M. **Blood pressure control and antihypertensive pharmacotherapy patterns in a hypertensive population of Eastern Central Region of Portugal.** BMC Health Serv Res 2010;10:349. PMID: 21192829

5.3 Artigo III

Morgado M, Morgado S, Pereira L, Castelo-Branco M. **Efficacy of Aliskiren/Hydrochlorothiazide Combination for the Treatment of Hypertension: A Meta-Analytical Approach.** Open Cardiovasc Med J 2011;5:6-14. DOI: 10.2174/1874192401105010006

5.4 Artigo IV

Morgado M, Rolo S, Macedo AF, Pereira L, Castelo-Branco M. **Predictors of uncontrolled hypertension and antihypertensive medication nonadherence.** J Cardiovasc Dis Res 2010;1:196-202. DOI: 10.4103/0975-3583.74263. PMID: 21264184

5.5 Artigo V

Morgado M, Rolo S, Macedo AF, Castelo-Branco M. **Association of statin therapy with blood pressure control in hypertensive hypercholesterolemic outpatients in clinical practice.** J Cardiovasc Dis Res 2011;2:44-49. DOI: 10.4103/0975-3583.78596

5.6 Artigo VI

Morgado M, Rolo S, Castelo-Branco M. **Pharmacist intervention program to enhance hypertension control: a randomised controlled trial.** Int J Clin Pharm 2011;33:132-140. DOI: 10.1007/s11096-010-9474-x. PMID: 21365405

66

5.1 Artigo I

“Pharmacist interventions to enhance blood pressure control and adherence to antihypertensive therapy : Review and meta-analysis”

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Pharmacist interventions to enhance blood pressure control and adherence to antihypertensive therapy: Review and meta-analysis

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Purpose. Pharmacist interventions to enhance blood pressure (BP) control and adherence to antihypertensive therapy in adults with essential hypertension were reviewed.

Methods. A literature search was conducted to identify relevant articles describing pharmacist interventions intended to improve adherence to antihypertensive medications. Studies were included if they described a pharmacist intervention to improve medication adherence and analyzed adherence to therapy and BP control as outcomes. A fixed-effects model was used to combine data from randomized controlled trials.

Results. A total of 15 studies were identified, testing 16 different interventions and containing data on 3280 enrolled patients. Although 87.5% of the interventions resulted in significant improvements in treatment outcomes, only 43.8% of the interventions were associated with significant increases in medication adherence. All interventions that increased antihypertensive medication adherence also significantly reduced BP. Almost all the interventions that were effective in increasing adherence to medication were complex, including combinations of different strategies. Meta-analysis of 2619 patients in 8 studies found that pharmacist interventions significantly reduced systolic blood pressure (SBP) ($p < 0.001$) and diastolic blood pressure (DBP) ($p = 0.002$) and that the meta-analytic differences in SBP and DBP changes from baseline to endpoint in intervention and control groups were −4.9 ± 0.9 mm Hg ($p < 0.001$) and −2.6 ± 0.9 mm Hg ($p < 0.001$), respectively.

Conclusion. A literature review and meta-analysis showed that pharmacist interventions can significantly improve medication adherence, SBP, DBP, and BP control in patients with essential hypertension. Interventions were complex and multifaceted and included medication management in all analyzed studies.

Index terms: Blood pressure; Compliance; Hypertension; Hypotensive agents; Interventions; Patients; Pharmacists

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Hypertension is a major risk factor for cardiovascular disease and an important public health problem worldwide. The risk of cardiovascular morbidity and mortality is particularly marked when there is insufficient hypertension control and prevention at the community level. Randomized controlled trials (RCTs) have demonstrated that treating high blood pressure (BP) with medication can substantially reduce the risk of stroke by 35–40% and myocardial infarction by 20–25%.[1,2] Although the treatment of hypertension has been shown to reduce the risk of cardiovascular disease and mortality, hypertension remains inadequately managed worldwide, with a lack of adherence to BP-lowering medication playing a major role in poor BP control.[3-7] Hypertensive patients may fail to take their medication because of the symptomless nature of the condition, the long duration of therapy, adverse effects of medi-

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69

cation, complicated drug regimens, the lack of understanding about hypertension management, costs of medication, and the challenge to individual patients' health beliefs.[8,9] Adherence rates to antihypertensive agents differ depending on the population studied, ranging between 50% and 70%.[5,10,11]

The importance of improving adherence to antihypertensive medication has been addressed by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, emphasizing the role of all health care professionals, including pharmacists, to improve adherence to treatment.[1] In the past two decades, pharmacists have been developing and implementing validated methods and services to improve adherence to antihypertensive medication and the clinical outcomes of this "silent" disease.[12]

One systematic review, which included studies from 1978 to 2006, assessed pharmacist interventions in hypertensive patients in order to enhance patients' adherence to medication and reduce systolic BP (SBP) and diastolic BP (DBP).[13] Since then, several important RCTs[14-17] and non-RCTs[18-20] have been conducted to assess the effect of pharmacist interventions on medication adherence and BP control in hypertensive patients.

While there is strong evidence supporting the benefits of antihypertensive drug therapy,[21] there is little clear evidence as to which types of pharmacist interventions for hypertensive patients are most effective for increasing medication adherence and improving hypertension control. We conducted a systematic review of published data on pharmacist interventions targeting antihypertensive medication adherence in adults with essential hypertension to evaluate the effect of pharmacist interventions on antihypertensive medication adherence and quantify the reductions in SBP and DBP resulting from those interventions.

Methods

A literature search to identify pharmacist interventions intended to improve adherence to antihypertensive medications and BP control was conducted. To be included in the systematic review, studies had to (1) have a population of adults with essential hypertension currently treated with BP-lowering drugs in a primary care, an outpatient, or a community setting, (2) clearly describe and evaluate an intervention delivered by a pharmacist to improve adherence with antihypertensive drugs and BP control, and (3) include both adherence to antihypertensive medication and mean SBP, mean DBP, or BP control as outcomes. Studies describing multidisciplinary interventions were included only if the pharmacist's role in patient care was clearly described. Articles describing different health conditions (e.g., cardiovascular diseases not involving essential hypertension) were excluded, as were studies assessing SBP and DBP or BP control but not antihypertensive medication adherence. The criteria used to assess adherence and treatment outcome were based on the observation that studies showing an increase in adherence without an improvement in clinical outcome provide no practical guidance for practice. Articles were also required to be written in English, French, Spanish, German, Portuguese, or Italian.

We searched the main electronic databases freely available in our research center: MEDLINE, The Cochrane Library, and ISI Web of Knowledge. Each database was independently searched by two reviewers for articles published from January 1999 through June 2009, using the terms *high blood pressure*, *hypertension*, *pharmaceutical services* or *pharmaceutical care or pharmacist*, and *patient outcomes* (i.e., *adherence*, *compliance*, *systolic blood pressure*, *diastolic blood pressure*, and *blood pressure control*). We also hand searched bibliographies of all retrieved articles to identify additional publications of pharmacist interventions on patient medication adherence.

Two authors independently selected articles by first reading titles, then abstracts, and, finally, full texts. The reviewers selected articles based on the predefined inclusion and exclusion criteria and then compared results. Any disagreements were resolved by consensus. The rationale for decisions was discussed until reviewers agreed on the final decision. A third author was called to resolve any remaining discrepancies concerning article eligibility.

Data extraction was also performed by two independent authors, and disagreements were resolved through the same consensus process used with article selection. The following data were obtained in duplicate and verified: year of publication, study design, use of a comparison group, type of pharmacist interventions, extent of follow-up, study setting, sample size of both intervention and control groups, patients lost to follow-up, methods used to measure medication adherence, and outcomes measured. The outcomes of particular interest were medication adherence, SBP, DBP, and BP control. During data extraction, we wrote to corresponding authors of studies to request missing data and clarify study details.

After data were extracted, we classified study outcomes as either sensitive or nonsensitive. Sensitive results were those that were influenced positively by the pharmacist intervention from a clinical point of view and that had statistical significance (i.e., p of ≤ 0.05 at the endpoint of the study). Pharmacist interventions aimed to increase adherence to BP-lowering medication and BP control were classified as (1) medication management (drug therapy monitoring and adjustments; simplification of anti-

hypertensive regimens; optimization of drug regimen in order to solve adverse drug reactions, drug–drug interactions, and food–drug interactions; generic substitution), (2) educational interventions directed at the patient (hypertension education, BP self-monitoring recommendation, lifestyle education and counseling, medication education and counseling), (3) self-monitoring and recording of BP, including education, encouragement, and validation of BP monitor, (4) medication reminders, including education and counseling tips (adherence aids), and appointment reminders (e.g., telephone or computer-based), (5) improved administration systems (e.g., Medication Event Monitoring System [Aardex Group Ltd., Slon, Valais, Switzerland]), and medications dispensed using an adherence aid (e.g., blister packs), (6) more-frequent follow-up appointments or contacts, (7) educational interventions and alerts directed at the health care professional (personal, telephone- or computer-based), and (8) pharmacist clinical visits in medical, university, hospital, and community-based clinics.

Two reviewers assessed the quality of accepted studies independently and in duplicate, using the quality scale of Downs and Black,[22] which was developed based on epidemiologic principles, reviews of study designs, and existing checklists for assessing RCTs. Disagreements regarding study quality were handled by consensus, and additional information about study design was requested from the authors if necessary. The method of Downs and Black[22] has been validated, and it allows for the scoring of quality of RCTs and observational studies. The instrument consists of a 28-item checklist that addresses a study's quality of reporting (10 items), external validity (3 items), internal validity or bias (7 items), confounding variables (6 items), power (1 item), and a global score (1 item assessing the rater's overall impression of the quality of a paper) and has a possible total score of 42 (corresponding to the maximum quality score of 100%). Scores below 50% were considered weak, those between 50% and 69% were considered fair, scores of 70–79% were good, and scores of 80–100% were very good. We used a Mann-Whitney *U* test to compare quality scores between sensitive and nonsensitive outcomes, because there may be a relationship between the methodological quality of the included studies and the success of their respective interventions.

Medication adherence was reported in the individual groups of the studies at baseline and end of study. Whenever feasible, the percentage of participants with controlled BP at the end of the study and the corresponding odds ratio were mentioned. In each study, BP was classified as controlled using the national or international guidelines applicable at the time of the study. Because of the substantial differences among selected studies in terms of the various methods that were used to measure adherence (e.g., prescription refill data, pill count, compliance questionnaire, plasma drug level), we believed that pooling of the medication adherence results was inappropriate. A fixed-effects meta-analytic model was used to combine SBP and DBP results. However, only studies with extractable data and that had a contemporary control group were included in the meta-analysis (i.e., subjects allocated to usual care [control group] were treated during the same time period [contemporary] as the intervention group) to ensure that the only difference between the groups was the pharmacist intervention under investigation.

We explored the potential for publication bias by using funnel plots and calculating the Begg–Mazumdar[23] statistic. We examined the heterogeneity of outcomes using the chi-square test.[24] All analyses were conducted with SPSS, version 17.0 (SPSS Institute, Chicago, IL) and Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ), and the a priori level of significance was 0.05.

Results

Initially, 225 potential articles were identified. After assessing their titles and excluding those not mentioning any information pertinent to hypertension, BP, or medication adherence studies, 130 remained and their abstracts read. Of the 47 articles retrieved for full-text review, 32 were excluded for the following reasons: not an interventional study,[25-27] studied participants with a different disease not relevant to review,[28-32] did not include pharmacists in the study interventions,[33] presented pharmaceutical interventions and outcomes investigating neither adherence nor BP,[34-37] presented pharmaceutical interventions and outcomes investigating BP but not adherence,[38-53] investigated medication adherence outcome in the intervention group only and baseline adherence was not measured,[54] and not studies but reviews.[13,55] A total of 15 articles were included as full-text in our systematic review.[14-20,56-63]

Table 1 details some characteristics of the included studies. One study tested different interventions in three distinct intervention groups.[16] In this study the authors attributed the simplest intervention (provider education) to the control group and the remaining interventions ("provider education and alert" and "provider education and alert and patient education") to two intervention groups. Another study included two pharmacist-intervention groups, designated as a high-intensity intervention and a low-intensity intervention. We considered the low-intensity group, in which the only pharmacist intervention was measurement of BP and

71

Table 1.
Characteristics of Studies Evaluating Pharmacists' Interventions in Hypertension Treatment[a]

Ref.	Study Design[b]	Setting (Country)	Pharmacist Intervention[c]	Frequency of Pharmacist–Patient Interaction in Intervention Group
14	RCT	Community-based primary care clinics (United States)	A, B, C	Mean, 7.2 times in 12 mo[d]
15	RCT	Army medical center (United States)	B, D	Every 2 mo[e]
16	Cluster RCT	Hospital-based clinics (United States) Community-based clinics (United States)	C A, C	>3 times in 6 mo[f]
17	Cluster RCT	University clinics (United States)	A, B, C, E, F, G	Mean ± S.D., 6.8 ± 1.6 times in 9 mo[g]
18	SGCT	Primary-care clinics and community pharmacies (United States)	A, B, C, E	5 times in 9 mo[h]
19	SGCT	Clinic in university teaching hospital (Brazil)	A, B, C, F	Mean, 10.5 times in 12 mo[h]
20	SGCT	Community pharmacy (Nigeria)	A, B, C, E	Monthly[h]
56	RCT	Community pharmacies (United Kingdom)	A, B	Every 2 mo[i]
57	SGCT	Aircraft carrier (United States)	A	Every 2 wk[h]
58	Non-RCT	Community pharmacies (Canada)	A, B, C, F	Mean, 5.8 times in 9 mo[j]
59	RCT	Medical clinic (Brazil)	A	Monthly[f]
60	RCT	Medical clinic (United States)	A, B, C, E	Monthly[j]
61	RCT	Community pharmacies (Thailand)	A, B	Monthly[i]
62	RCT	Medical clinic (United States)	A, B	Monthly[j]
63	RCT	Community pharmacies (United States)	A, B, C, E	4 times in 3 mo[k]

[a] Medication adherence and blood pressure were measured in all studies. Other measured outcomes included quality of life, self-measurement of blood pressure, alcohol moderation, exercise, salt restriction, smoking cessation, number of antihypertensive drugs, adverse drugs effects, hypertension-related knowledge, patient satisfaction, resource utilization, low-density-lipoprotein cholesterol concentration, and intensification of antihypertensive regimen.

[b] RCT = randomized clinical trial, SGCT = single-group clinical trial.

[c] In all studies, pharmacists' interventions included medication management (e.g., drug therapy monitoring or adjustment, simplification of antihypertensive regimens, resolution of adverse drug reactions). A = educational interventions directed to the patient (e.g., hypertension education, lifestyle education and counseling), B = scheduling more-frequent follow-up appointments or contacts, C = educational interventions and alerts directed to health care professionals, D = providing improved administration systems (e.g., medication event monitoring system, blister packs), E = instituting self-monitoring and recording of blood pressure, including education, encouragement, and validating blood pressure monitor, F = providing medication reminders, including education and counseling tips (adherence aid tools) and appointment reminders (e.g., telephone based, computer based), G = pharmacist clinical visit attendance.

[d] Interaction in the control group occurred a mean of 4.9 times in 12 months.

[e] Interaction in the control group occurred at baseline and at the midpoint and end of the study.

[f] Interaction in the control group occurred with the same frequency as in the intervention group.

[g] Interaction in the control group occurred a mean ± S.D. of 5.5 ± 1.3 times in 9 months.

[h] Patients at baseline served as their own controls.

[i] Interaction in the control group occurred at baseline and at the end of the study.

[j] Interaction in the control group occurred 4 times in 9 months.

[k] Interaction in the control group occurred 3 times in 3 months.

patient counseling to contact their physician whenever BP was above normal, as the control group.

Medication management, educational interventions directed to the patient, and more-frequent follow-up appointments or contacts were the most frequently used pharmacist interventions. The number of pharmacist interventions per study ranged from two to five. After BP values and medication adherence outcomes, which were evaluated in all tudies, patient quality of life was the most evaluated outcome, present in 6 of the 15 included studies.[14,18-20,60,62]

Table 1 also details the pharmacist–patient interaction in control and intervention groups of included studies. The most common frequency of pharmacist–patient interaction in the intervention group was between monthly and every two months, and the purpose of the interaction was to provide pharmacist interventions. The pharmacist–patient interaction in the control group involved mostly baseline, intermediate, and endpoint assessment of described outcomes.

Article quality scores, sample size, duration of follow-up, losses to follow-up, and outcomes sensitive to pharmacist interventions are shown in Table 2. The mean ± S.D. article quality score was 67.5% ± 10.6% (range, 50–76%), which was considered fair. The mean ± S.D. sample size was 218.7 ± 331.7 patients (median, 111 patients; range, 26–1341 patients). The follow-up period of the studies evaluated ranged from

72

two weeks to 12 months, with an average duration of 6.7 ± 10.6 months. Losses to follow-up ranged from 3.4% to 48.5% (mean ± S.D., 18.9% ± 15.3%). Article quality scores did not increase from 2000 to 2008 ($y = 596.848 - 0.264x$, $r^2 = 0.006$, $p = 0.790$, where y = article quality score and x = publication year). Sixty-one percent of the outcomes (28/46) were categorized as sensitive to the pharmacist interventions.

Effect on medication adherence and BP control. Adherence was measured in different ways, including self-report (through questionnaire or direct questioning), pill counts, analysis of prescription refill data, and plasma levels of hydrochlorothiazide. Various criteria for adherence were used in the studies, making a pooled analysis inappropriate (Table 3). Baseline medication adherence to antihypertensive drugs ranged from 35% to 88.6%, and medication adherence at study end ranged from 50% to 95.8%, which points to an increase in medication adherence due to pharmacist interventions. In fact, 7 of 16 intervention groups demonstrated a significant improvement in medication adherence when compared with the control groups. Differences in adherence rates at study end between pharmacist intervention groups and control groups varied from 8% to 58% in studies with positive sensitive outcomes. Although 5 studies revealed that pharmacist interventions had a negative effect on patients' treatment adherence compared with the control group, which ranged from –1% to –8%, these negative results were not significant. One study found an abnormally high increase in treatment adherence rate (increase of 58% from baseline); however, no comparison group was used in this study, and the follow-up period was only two weeks. The correlation between article quality scores and impact of pharmacist interventions was –0.680 ($p = 0.004$) for medication adherence. This ob-

Table 2.
Article Quality Scores, Sample Size, Duration of Follow-up, and Losses to Follow-Up of Selected Studies[a]

Ref.	Quality Score, %	*n*	Intervention Group	Control Group	Duration of Follow-up (mo)	No. (%) Pts Lost to Follow-up	Outcomes Sensitive to Pharmacist Interventions
14	76	463	230	233	12	191 (41.3)	SBP
15	69	159	83	76	6	13 (8.2)	Adherence, SBP
16	76	1341	1017	324	6	366 (27.3)	SBP[b]
17	67	179	101	78	9	19 (10.6)	SBP, DBP
18	50	103	103	…[c]	9	50 (48.5)	Adherence, SBP, DBP
19	57	48	48	…[c]	12	4 (8.3)	Adherence, SBP, DBP
20	52	40	40	…[c]	5	16 (40.0)	Adherence, SBP, DBP
56	67	282	167	115	6	102 (36.2)	Adherence, SBP
57	56	26	26	…[c]	0.5 (2 wk)	4 (15.4)	Adherence, SBP
58	74	111	41[d]	59[d]	9	11 (9.9)	SBP
59	82	71	34	37	6	7 (9.9)	None
60	67	41	20	21	6	5 (12.2)	DBP
61	82	235	118	117	6	8 (3.4)	Adherence, SBP, DBP
62	78	56	27	29	6	3 (5.4)	SBP, DBP
63	59	125	64	61	3	8 (6.4)	SBP, DBP

[a]SBP = systolic blood pressure, DBP = diastolic blood pressure.
[b]Provider education and alert and patient education intervention group.
[c]Patients served as their own controls.
[d]Patients at the end of the study (the article does not mention the number of patients enrolled in each group at the beginning of the study).

Table 3.
Medication Adherence Sensitivity to Pharmacist Interventions[a]

Ref.	Method of Measuring Adherence	Baseline Medication Adherence: % Adherence, Control Group	Baseline Medication Adherence: % Adherence, Intervention Group	Baseline Medication Adherence: *p*	Endpoint Medication Adherence: % Adherence, Control Group	Endpoint Medication Adherence: % Adherence, Intervention Group	Endpoint Medication Adherence: *p*	Endpoint Medication Adherence: % Difference Between Intervention and Control Groups	Endpoint Medication Adherence: *p*
14	SR[b]	NR	61	NR	69	67	0.52 (control), 0.08 (intervention)	–2	0.77
15	Pill count and PRD	61.1	61.4	0.88	69.1	95.5	NR	26.4	<0.001
16	PRD	86	85[c]	0.13	89	89	NS	0[c]	NS
			83[d]	0.13		88	NS	–1[d]	NS
17	Pill count	88.6	71.1	<0.001	92 (NS)	94 (NR)	NS (control), NR (intervention)	2	0.369
18	PRD	70.6	NA	NA	NA	95.8	NA	25.2	0.02
19	Pill count and SR	63.6	NA	NA	NA	95.5	NA	31.9	<0.05
20	PRD	66.3	NA	NA	NA	83.5	NA	17.2	0.001
56	SR[e]	51.0	52.3	NS	50.0	62.9	NS (control), <0.05 (intervention)	12.9	<0.05
57	SR[f]	35	NA	NA	NA	93	NA	58	0.0001
58	SR[b] and PRD	83 (SR), 93 (PRD)	68 (SR), 98 (PRD)	0.085 (SR), 0.643 (PRD)	80.4 (SR)	74.3 (SR)	NS for both	–6.1	NS
59	Plasma drug level and SR[g]	NR	NR	NR	80	77.8	NR	–2.2	0.904
60	PRD	NR	NR	NR	89	82	NR	7	0.29
61	Pill count	56.5	51.3	0.534	55.6	63.6	NS (control), NR (intervention)	8	0.014
62	PRD and SR[f]	NR	NR	>0.2	93	85	>0.07 (for control and intervention)	–8	>0.42
63	SR[b]	74.1	61.3	NS	84.2	87.7	0.07 (control), 0.004 (intervention)	3.5	0.38

[a]SR = self-report, NR = not reported, PRD = prescription refill data, NS = not significant, NA = not applicable.
[b]Morisky questionnaire.
[c]Provider education and alert intervention group.
[d]Provider education and alert and patient education intervention group.
[e]Horne's Medication Adherence Report Scale used in questionnaire and with direct questioning by pharmacist.
[f]Compliance questionnaire.
[g]Dáder method by means of a pharmacotherapy history and using pharmacist's direct questioning.

servation suggests that higher quality scores are associated with a lesser effect on medication adherence. All of the 4 single-group controlled trials evaluated (with no contemporary comparison control group) reported a significant increase in medication adherence. The remaining 3 studies, which were RCTs, that reported a significant increase in medication adherence had more-frequent follow-up with the intervention group. Six other studies also adopted more-frequent follow-up without a significant increase in medication adherence. In 5 of these 6 studies, the endpoint adherence rate was high (>80%) in the control group, possibly making it difficult to achieve a further increase in the intervention group. Indeed, all 7 studies with a high adherence rate at study endpoint (>80%) in the control group found that pharmacist interventions had a nonsignificant effect on medication adherence. All other studies but 1 revealed that pharmacist interventions had a positive effect on medication adherence, with a mean difference in adherence rates at endpoint between intervention and control groups of 22.2%.

Likewise, various criteria were used to report BP outcome, making it inappropriate to pool data from all included studies, though the range of results from individual studies are presented (Table 4). Of the 15 studies evaluated, 2 did not measure SBP or DBP, 7 studies described a significant improvement in both SBP and DBP, 4 described a significant improvement in SBP alone, and 1 study noted a significant improvement in DBP alone. Significant improvements in SBP and DBP ranged from –5.0 to –18.6 mm Hg and from –1.0 to –12.2 mm Hg, respectively.

Three of the included studies did not describe the percentage of participants with controlled BP at the end of the study. Seven studies found a significant increase in the percentage of participants with controlled BP at the end of the study when comparing intervention and control groups, which ranged from 17.5% to 51.0%. The authors of each study classified BP as controlled using the national or international guidelines applicable at the time of the study (in most studies, BP was considered controlled when SBP was < 140 mm Hg and DBP was < 90 mm Hg). In 11 studies, we were able to calculate the odds ratio for the rate of patients achieving controlled BP at endpoint in the intervention group compared with the control group, and a range

Table 4.
Effects of Pharmacist Interventions on Blood Pressure (BP) Control[a]

Ref.	Difference in BP in Intervention vs. Control Group, mm Hg (*p*)		% Pts With Controlled BP at End of Study		*p*	OR (95% CI)
	SBP	DBP	Control Group	Intervention Group		
14	5.0 (<0.001)	1.0 (0.235)	44.0	62.0	0.003	2.1 (1.4–3.0)
15	7.3 (0.001)	1.4 (0.216)	NR	NR	NR	NR
16	–0.3 (NS)[b] 6.0 (<0.001)[c]	1.3 (NS)[b] 3.3 (NS)[c]	42.0	59.5	0.003	2.0 (1.5–2.7)
17	11.6 (<0.001)	3.3 (0.005)	52.9	89.1	<0.001	7.2 (3.2–15.6)
18	16.7 (0.02)	12.2 (0.04)	NR	NR	NR	NR
19	18.6 (<0.05)	9.1 (<0.05)	0	41.0	<0.05	12.2 (4.6–32.5)
20	14.3 (<0.001)	10.8 (<0.001)	NR	NR	NR	NR
56	NR	NR	17.1	35.7	<0.05	2.7 (1.5–4.7)
57	NR	NR	42.0	73.0	0.02	3.7 (1.2–11.9)
58	HI: 8.3 (0.01) LI: –4.4 (NS)	HI: 2.5 (0.28) LI: –2.5 (NS)	HI: 42.0 LI: NS	HI: 69.0 LI: NS	0.073 0.895	3.1 (0.8–12.4) NS
59	5.0 (0.063)	2.0 (0.281)	NS	NS	NS	NS
60	10.1 (0.069)	6.7 (0.022)	22.0	44.0	>0.1	2.8 (0.7–10.8)
61	5.7 (0.001)	2.5 (0.029)	57.2	66.1	0.061	1.5 (0.9–2.5)
62	14.1 (<0.001)	14.8 (<0.001)	30.0 12.0 (diabetic pts)	81 91.0 (diabetic pts)	<0.001 <0.001	9.8 (2.8–34.1) 70.0 (5.6–882.2)
63	4.6 (0.041)	3.2 (0.014)	30.0	42.0	0.45	1.7 (0.8–3.5)

[a]SBP = systolic blood pressure, DBP = diastolic blood pressure, OR = odds ratio, CI = confidence interval, NR = not reported, HI = high income, LI = low income, NS = not significant.
[b]Provider education and alert intervention group.
[c]Provider education and alert and patient education intervention group.

75

of 1.46–12.18 was obtained, with a mean ± S.D. value of 4.43 ± 3.6.

Of the 7 studies that found a significant improvement in both SBP and DBP, 42.9% were single-group controlled trials (with no contemporary comparison control group). Thus, we analyzed the correlation between article quality scores and the impact of pharmacist interventions on SBP and DBP. This correlation was –0.599 ($p = 0.018$) for SBP and –0.659 ($p = 0.007$) for DBP. These observations suggest that higher quality studies are associated with a lesser effect on BP control.

A total of 8 controlled trials were included in the meta-analysis (Table 5). The remaining 7 studies were not included because the data were not extractable[56,58,60] and a comparison contemporary control group was not used.[18-20,57]

Effects on SBP. Sensitive outcomes were reported in 11 of 13 studies evaluating SBP. It was possible to include only 8 studies for the meta-analysis of SBP outcomes. A funnel plot (data not shown) did not rule out the possibility of publication bias; therefore, we applied the trim-and-fill method,[64] which increased the difference in SBP change between intervention and placebo from 4.9 to 5.6 mm Hg ($p < 0.001$). However, the Begg–Mazumdar[23] statistic was very small and nonsignificant ($t < 0.001$, $p = 1.0$). The Q statistic for heterogeneity of effects was not significant ($\chi^2 = 0.741$, $p = 0.99$); therefore, we considered the study results to be combinable.

The meta-analytic mean ± S.D. baseline and endpoint SBPs in the pharmacist intervention group were 153.0 ± 4.7 and 130.9 ± 4.6 mm Hg, respectively, producing a clinical and statistical weighted difference of –19.4 ± 3.5 mm Hg ($p < 0.001$). A significant difference was also observed in the mean ± S.D. SBP from baseline (151.3 ± 4.9 mm Hg) to endpoint (137.5 ± 6.4 mm Hg) in the control group, with a meta-analytic difference of –11.3 ± 4.2 ($p = 0.007$). Meta-analytic differences from baseline to endpoint of both groups were calculated and are presented in Figure 1. The meta-analytic mean ± S.D. difference in SBP from baseline to endpoint between intervention and control groups was –4.9 ± 0.9 mm Hg ($p < 0.001$).

Effects on DBP. Sensitive outcomes were reported in 8 of 13 studies evaluating DBP. It was possible to include only 7 studies for the meta-analysis of DBP evaluation. The funnel plot was similar to that for SBP (data not shown). Use of the trim-and-fill method increased the difference between intervention and placebo from 2.6 to 3.3 mm Hg ($p < 0.001$). However, the Begg–Mazumdar[23] statistic did not detect publication bias ($\tau = –0.09$, $p = 0.76$). The Q statistic found no heterogeneity of effects ($\chi^2 = 2.23$, $p = 0.90$), so the results were considered combinable.

The meta-analytic mean ± S.D. baseline and endpoint DBPs in the pharmacist intervention group were 82.6 ± 4.3 and 74.6 ± 3.8 mm Hg, respectively, producing a clinical and statistical weighted difference of –8.8 ± 2.9 mm Hg ($p = 0.002$). However, a nonsignificant difference was observed in DBP from baseline (81.7 ± 4.3 mm Hg) to endpoint (76.9 ± 4.2 mm Hg) in the control group, with a meta-analytic difference of –4.9 ± 3.0 mm Hg ($p = 0.103$). Meta-analytic differences from baseline to endpoint of both groups were calculated and are presented in Figure 1. Pharmacist intervention reduced the DBP of the intervention group an additional 2.6 ± 0.9 mm Hg when compared with the control group ($p < 0.001$).

Discussion

The majority of the studies included in our analysis were RCTs. Although the mean quality of these RCTs was considered good (quality score, 72.3%), the mean quality of all the studies evaluated was fair (quality score, 67.5%). It is not feasible to blind hypertensive patients in pharmaceutical intervention models, as this process of blinding is assessed in one item of the Downs and Black[22] quality checklist. By removing this item, the average quality of all articles included would increase to over 70%. However, 6 studies in which patients were not randomized to intervention groups, which are assessed by two items of the Downs and Black quality checklist, prevented a further increase of the overall quality score.

Although 88% of the interventions tested (14 of 16 in 15 studies) resulted in significant improvements in treatment outcomes (SBP, DBP, or percentage of participants with controlled BP at the end of the study), only 44% of the interventions (7 of 16 in 15 studies) were associated with significant increases in medication adherence. These results were higher than those obtained by Machado et al.,[13] who found that 76.6% and 38.5% of studies analyzed reported improvement in treatment outcomes and in medication adherence, respectively, though they did not address BP control specifically. Differences obtained in the systematic review of Machado et al.[13] and in our review reflect a trend toward improved medication adherence and treatment outcomes obtained with the most recent studies, which included more interventions involving physician–pharmacist collaboration.[14,16-20] In both systematic reviews, all studies that found a significant increase in medication adherence also demonstrated a significant improvement in treatment outcomes, revealing that medication adherence is a key factor (though not the only one) for achieving BP control.

Drug therapy adjustments may have contributed to improvements in BP control in studies where medication adherence rates did not significantly change. Some studies suggested that antihypertensive medications are frequently not intensified when BP remains uncontrolled (clinical in-

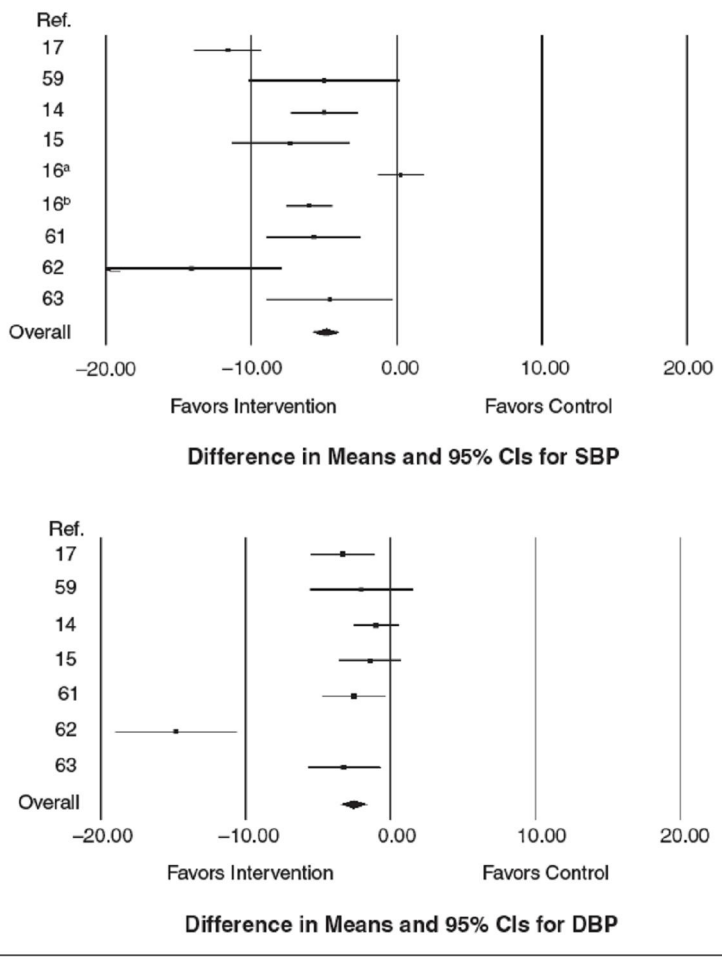
76

Table 5.
Meta-analytic Differences From Baseline to Endpoint of SBP and DBP in the Intervention and Control Groups[a]

Outcome and Ref.	Intervention Group				Control Group			
	n	Mean ± S.D. Baseline Value, mm Hg	Mean ± S.D. Endpoint Value, mm Hg	Mean ± S.D. Meta-Analytic Difference, mm Hg	*n*	Mean ± S.D. Baseline Value, mm Hg	Mean ± S.D. Endpoint Value, mm Hg	Mean ± S.D. Meta-Analytic Difference, mm Hg
SBP								
14	230	173.0 ± 15.0	142.0 ± 19.0	–31.0 ± 12.3	233	174 ± 15.0	148.0 ± 22.0	–26.0 ± 13.8
15	83	133.4 ± 17.6	124.4 ± 14.0	–9.0 ± 11.4	76	135.0 ± 20.3	133.3 ± 21.5	–1.7 ± 14.8
16[b]	547	158.0 ± 12.4	146.0 ± 19.0	–12.0 ± 11.8	324	157.3 ± 11.9	145.0 ± 19.0	–12.3 ± 11.8
16[c]	470	156.3 ± 11.4	138.0 ± 18.0	–18.3 ± 11.2	…	…	…	…
17	101	153.1 ± 10.0	124.2 ± 9.7	–28.9 ± 7.0	78	150.3 ± 9.0	133.0 ± 14.2	–17.3 ± 8.8
59	30	140.0 ± 18.0	134.0 ± 11.0	–6.0 ± 11.1	34	136 ± 14.0	135.0 ± 15.0	–1.0 ± 10.3
61	118	144.8 ± 19.7	121.5 ± 14.9	–23.3 ± 12.6	117	142.4 ± 19.8	124.8 ± 18.0	–17.6 ± 13.4
62	26	149.0 ± 15.3	130.5 ± 13.2	–18.5 ± 10.2	27	152.8 ± 14.3	148.4 ± 21.0	–4.4 ± 13.1
63	64	151.6 ± 18.6	138.1 ± 15.9	–13.5 ± 12.3	61	151.5 ± 17.1	142.6 ± 19.1	–8.9 ± 12.9
Overall	1669	153.0 ± 4.7	130.9 ± 4.6	–19.4 ± 3.5[d]	950	151.3 ± 4.9	137.5 ± 6.4	–11.3 ± 4.2[e]
DBP								
14	230	90.0 ± 14.0	77.0 ± 10.0	–13.0 ± 8.8	233	92.0 ± 14.0	80.0 ± 12.0	–12.0 ± 9.3
15	83	71.7 ± 9.1	67.5 ± 9.9	–4.2 ± 6.7	76	71.4 ± 10.6	68.6 ± 10.5	–2.8 ± 7.5
17	101	84.9 ± 12.0	74.7 ± 9.6	–10.2 ± 7.8	78	85.4 ± 11.0	78.5 ± 10.9	–6.9 ± 7.7
59	30	80.0 ± 11.0	77.0 ± 10.0	–3.0 ± 7.4	34	79.0 ± 10.0	78.0 ± 11.0	–1.0 ± 7.4
61	118	85.7 ± 13.6	71.6 ± 10.8	–14.2 ± 8.8	117	86.0 ± 12.9	74.2 ± 11.9	–11.7 ± 8.8
62	26	89.8 ± 10.9	77.5 ± 10.7	–12.3 ± 7.6	27	77.9 ± 11.9	80.4 ± 11.4	2.5 ± 8.2
63	64	85.3 ± 11.2	76.5 ± 9.5	–8.8 ± 7.4	61	85.3 ± 10.3	79.7 ± 10.2	–5.6 ± 7.2
Overall	652	82.6 ± 4.3	74.6 ± 3.8	–8.8 ± 2.9[f]	626	81.7 ± 4.3	76.9 ± 4.2	–4.9 ± 3.0[g]

[a]SBP = systolic blood pressure, DBP = diastolic blood pressure.
[b]Provider education and alert intervention group.
[c]Provider education and alert and patient education intervention group.
[d]Pairwise comparison, inverse variance method ($Z = -5.493$, $p < 0.001$).
[e]Pairwise comparison, inverse variance method ($Z = -2.698$, $p = 0.007$).
[f]Pairwise comparison, inverse variance method ($Z = -3.025$, $p = 0.002$).
[g]Pairwise comparison, inverse variance method ($Z = -1.632$, $p = 0.103$).

Figure 1. Meta-analytic differences in improvement of systolic blood pressure (SBP) and diastolic blood pressure (DBP) (mm Hg) between patients receiving a pharmacist intervention and patients in control groups. Negative estimates favor the intervention group over the control group in the reduction of SBP or DBP in hypertensive patients. The squares represent the difference in improvement between groups, with 95% confidence interval (CI).



[a]Provider education and alert intervention group.
[b]Provider education and alert and patient education intervention group.

ertia).[65,66] By addressing suboptimal medication regimens, pharmacists may have contributed to changing unsuccessful regimens, searching for those regimens that would be more likely to succeed. However, it is also possible that the several methods used to measure adherence, some of which were unreliable, may have contributed to the inconsistency in adherence-rate differences between control and intervention groups. Large high-quality trials that use reliable methods of measuring adherence are needed to investigate the relationship between adherence and BP reduction.

SBP and DBP were definitely sensitive to pharmacist interventions, as we found that baseline to endpoint reductions in these outcomes were significantly influenced in intervention groups compared with control groups. These results also differ from those obtained by Machado et al.,[13] whose review showed that only SBP was sensitive to pharmacist interventions.

Almost all the interventions that were effective for medication adherence or BP control improvements were complex, including combinations of medication management, educational programs directed at the patient, scheduling of more-frequent follow-up appointments, medication reminders, counseling, self-monitoring of BP, and other forms of additional supervision or attention. We were not able to find a pattern of types or numbers of interventions that predicted success. Methods for improving antihypertensive adherence and BP control were generally labor-intensive (and therefore expensive) and not predictably effective. However, many intervention programs did lead to improved adherence or treatment outcomes. In 10 studies, we were able to calculate the odds ratio for the rate of patients achieving targeted BP at endpoint in the intervention group when compared with the control group, and a range of 1.46–12.18 was obtained, with a mean ± S.D. value of 4.43 ± 3.6. These values imply that achieving controlled BP at the end of the study was more likely in the intervention group and are in accordance with the values obtained by Carter et al.[67] In addition, studies with the largest effect sizes (i.e., the largest reductions in SBP or DBP from baseline to endpoint) had higher mean baseline SBP and DBP values (Table 5). Thus, the clinical impact of pharmacist interventions in hypertensive patients is expected to be more pronounced in high-risk patients. Moreover, it is possible that some pharmacist intervention programs put more emphasis on better communication and empathetic reinforcement, as these actions build trust, are potent motivators, and tend

78

to improve outcomes.[1] Motivation improves when patients have positive experiences with and trust in their health care staff. More studies are needed to assess the role of communication and empathetic reinforcement skills of pharmacists and other health care personnel on patient motivation and outcomes improvement.

Our study had several limitations. Comparing the different studies included in this review was difficult due to marked heterogeneity in terms of research designs, interventions, duration of follow-up, methods to measure medication adherence, and reporting of clinical outcomes. Some studies demonstrated poor methodological quality, particularly with regard to the presence of a contemporary comparison control group, randomization, blinding of outcomes assessment, and losses to follow-up. In two studies, the duration of follow-up was too short (three months or less), which is considered inadequate to classify adherence rates accurately[25,68] and to demonstrate persistent positive clinical findings.[69]

Adherence was measured and calculated in various ways, which made a pooled analysis inappropriate. For example, in one study,[58] the baseline adherence measured by the Morisky et al.[70] questionnaire was 83% and 68% in the control and intervention groups, respectively. When using refill-data analysis, the baseline adherence of the same patients was 93% and 98% in the control and intervention groups, respectively. Medication adherence was usually assessed unblinded to allocation status, which constitutes a potential source of bias. Without an agreement on criteria to measure and define medication adherence, it is not surprising that the effect of most interventions on adherence and BP was variable, making it difficult to examine the relationship between medication adherence and subsequent BP control.

We were not able to include several studies in our meta-analysis of SBP and DBP in the intervention and control groups, because some studies either did not report these data or did not use a comparison or control group. One other limitation is based on the quality of pharmacist interventions made. It is possible that the same pharmacist intervention led to different results, depending on the empathetic reinforcement and motivation provided by the health care personnel that have contact with hypertensive patients. Therefore, some degree of variation of results is expected in clinical pharmacy practice. Another limitation is our literature search was conducted using the main electronic databases freely available in our research center, leaving out important databases like International Pharmaceutical Abstracts and EMBASE. We tried to circumvent this limitation by hand searching bibliographies of all retrieved articles to identify additional publications of pharmacist interventions on patient medication adherence. Finally, a chance of publication bias cannot be ruled out based on funnel plot analyses and the trim-and-fill method, though our search criteria were intended to capture all published articles evaluating pharmacist interventions on both antihypertensive medication adherence and BP control. Publication bias occurs when authors are more likely to submit, or editors accept, positive rather than null (negative or inconclusive) results. A search performed for unpublished data would have helped to minimize the occurrence of publication bias.

Conclusion

A literature review and meta-analysis showed that pharmacist interventions can significantly improve medication adherence, SBP, DBP, and BP control in patients with essential hypertension. Interventions were complex and multifaceted and included medication management in all analyzed studies.

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80

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5.2 Artigo II

“Blood pressure control and antihypertensive pharmacotherapy patterns in a hypertensive population of Eastern Central Region of Portugal”

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84

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RESEARCH ARTICLE Open Access

Blood pressure control and antihypertensive pharmacotherapy patterns in a hypertensive population of Eastern Central Region of Portugal

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Abstract

Background: Interventions to improve blood pressure control in hypertension have had limited success in clinical practice despite evidence of cardiovascular disease prevention in randomised controlled trials.
The objectives of this study were to evaluate blood pressure control and antihypertensive pharmacotherapy patterns in a population of Eastern Central Region of Portugal, attending a hospital outpatient clinic (ambulatory setting) for routine follow-up.

Methods: Medical data of all patients that attended at least two medical appointments of hypertension/dyslipidemia in a university hospital over a one and a half year period (from January 2008 to June 2009) were retrospectively analysed. Demographic variables, clinical data and blood pressure values of hypertensive patients included in the study, as well as prescribing metrics were examined on a descriptive basis and expressed as the mean ± SD, frequency and percentages. Student's test and Mann-Whitney rank sum test were used to compare continuous variables and χ^2 test and Fisher exact probability test were used to test for differences between categorical variables.

Results: In all, 37% of hypertensive patients (n = 76) had their blood pressure controlled according to international guidelines. About 45.5% of patients with a target blood pressure <140/90 mmHg (n = 156) were controlled, whereas in patients with diabetes or chronic kidney disease (n = 49) the corresponding figure was only 10.2% ($P < 0.001$). Among patients initiating hypertension/dyslipidemia consultation within the study period 32.1% had stage 2 hypertension in the first appointment, but this figure decreased to 3.6% in the last consultation ($P = 0.012$). Thiazide-type diuretics were the most prescribed antihypertensive drugs (67%) followed by angiotensin receptor blockers (60%) and beta-blockers (43%). About 95.9% patients with comorbid diabetes were treated with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.

Conclusions: Clinically important blood pressure decreases can be achieved soon after hypertension medical appointment initiation. However, many hypertensive patients prescribed with antihypertensive therapy fail to achieve blood pressure control in clinical practice, this control being worse among patients with diabetes or chronic kidney disease. As pharmacotherapy patterns seem to coincide with international guidelines, further research is needed to identify the causes of poor blood pressure control.

Background

Hypertension is a major risk factor in the development of cardiovascular disease, with myocardial infarction and stroke being one of the most important health problems in Portugal causing excess morbidity and mortality [1]. It is estimated that over three million Portuguese adults (about 30% of the Portuguese population) suffer from hypertension [2]. In a recently published survey [2], only 11.2% hypertensives had their blood pressure (BP) controlled (<140/90 mmHg). This figure is even lower for the Central Region of Portugal, where only 9.7% of the total number of hypertensives have their BP controlled [2]. Furthermore, of the total number of Portuguese hypertensives who were aware of having hypertension

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and reported taking their medication regularly, only 28.9% had their BP controlled. Again, this figure was lower in the Central Region of Portugal, where the rate of control was only 26.1%. The definition of controlled hypertension in this Portuguese survey was considered as mean systolic BP <140 mmHg and diastolic BP of <90 mmHg and did not take into account hypertensive patients with diabetes mellitus or chronic kidney disease (CKD). The seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) set a lower BP target (<130/80 mmHg) for hypertensive patients with diabetes or CKD [3].

The Eastern Central Region of Portugal possesses a university teaching hospital at Covilhã, named Cova da Beira Hospital Centre, with an important hypertension/dyslipidemia outpatient clinic, which serves a significant hypertensive population of the District of Castelo Branco. To better understand the unsatisfactory levels of BP control of this hypertensive population and focus efforts on improving them, it would be useful to know the extent to which hypertensive patients with different risk for vascular complications are not satisfactorily controlled.

Accordingly, a retrospective study was conducted to evaluate the level of BP control in hypertensive patients, attending the afore mentioned hypertension/dyslipidemia outpatient hospital clinic for routine follow-up, according to the JNC 7 guidelines (<140/90 mmHg for general hypertensive patients and <130/80 mmHg for hypertensive patients with diabetes or CKD).

Methods

Settings

This study was conducted in a hypertension/dyslipidemia clinic in the university teaching hospital of Cova da Beira Hospital Centre, Covilhã, District of Castelo Branco, located in the Eastern Central Region of Portugal. This outpatient clinic is one of the most important clinics of this region of Portugal in the field of hypertension/dyslipidemia and serves a significant hypertensive population of the Covilhã surrounding area, with a population of 35,000 inhabitants. It should be emphasized that due to a decreased supply of primary care practitioners in this Region of Portugal that has led to a shortage in primary care delivery, this outpatient clinic provides follow-up care to hypertensive patients. This is done by a health care team composed of internal medicine physicians and nurses. Virtually all hypertensive patients managed and monitored in this clinic have essential arterial hypertension.

Study population

The study population consisted of outpatients that attended the hypertension/dyslipidemia clinic in the university teaching hospital. All patients are adults aged 18 or over. They were included if they had an established diagnosis of arterial hypertension (BP measurements in the clinic of ≥140/90 mmHg) and had attended at least two medical appointments over a one and a half year period (from January 2008 to June 2009). Hypertensive patients without diabetes and/or CKD with BP <140/90 mmHg in their last appointment were considered to have their BP controlled. For hypertensive patients with diabetes or CKD, BP control was defined as BP measurements <130/80 mmHg in their last appointment. Study subjects were also analyzed based on whether they had selected "high-risk" conditions or characteristics listed by JNC 7 as "compelling indications" (i.e., cerebrovascular disease, CKD, heart failure, ischemic heart disease, diabetes) or "special situations" (i.e., obesity, hyperlipidemia, metabolic syndrome, advanced age) and by stage of hypertension (i.e., Stage 1, 140-159/90-99 mmHg; Stage 2, ≥160/100) [3]. Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the BP [3]. Patients with both compelling indications and special indications were classified into the "compelling indications" group. The presence of these conditions among study subjects was ascertained based on available diagnostic information, laboratory/exam values, and treatments/medications recorded anytime during the study period. BP was measured in a seated position after a five-minute rest period, using a mercury sphygmomanometer or semi-automatic device, the mean of two consecutive measurements being recorded.

Data extraction

Data for this study were retrospectively obtained from the hospital electronic medical records (HEMR) database. The HEMR database of Cova da Beira Hospital Centre is comprised of detailed patient-level clinical and administrative information from all patients that utilized, at least once, this hospital. Available information includes patient demographics, medical problems (including the date on which each medical problem was first diagnosed), various measures of physiological status and medications prescribed. Dates for each medical contact are also provided, allowing all data to be analysed in chronological order. This database is authorized by the Portugal Department of Health, the government department responsible for public health issues and it ensures patient data confidentiality. Since subjects cannot be identified and confidentiality was warranted, institutional review board approval for this study was neither needed nor sought.

Statistical analysis

Demographic variables, clinical data and BP values of hypertensive patients included in the study, as well as

86

prescribing metrics were examined on a descriptive basis and expressed as the mean ± SD, frequency and percentages. Student's test and Mann-Whitney rank sum test were used to compare continuous variables and χ^2 test and Fisher exact probability test were used to test for differences between categorical variables. For the comparison between results in the first and in the last appointment in the same hypertensive patients who initiated hypertension consultation within the study period, the Wilcoxon rank sum test for paired data was used. All statistical analyses were done using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL) and a *P*-value of less than 0.05 was considered to indicate statistical significance.

Results

Patient characteristics

Overall, 273 patients attended medical appointments at the hypertension/dyslipidemia clinic of Cova da Beira Hospital Centre for routine follow-up during the study period. Among these patients, evaluation of 25 patients was still under course and there wasn't an established diagnosis of arterial hypertension and/or dyslipidemia and 10 patients had a diagnosis of dyslipidemia but not arterial hypertension. Of the remaining 238 patients, with an established diagnosis of arterial hypertension, 33 were excluded from our study because they had only attended one medical appointment. Most of these patients (n = 27) are no longer followed by the hypertension/dyslipidemia clinic due to several reasons (e.g., referral to other hospital clinics, residency change to other region served by a different hospital, renouncement to medical appointments, death); the remaining 6 hypertensive patients had been admitted to the hypertension/dyslipidemia clinic very recently (May or June 2009) and their antihypertensive medication was probably not yet fully titrated. It should be noted that the first months of antihypertensive therapy may be a critical period for many patients, especially for those at the highest risk for adverse outcomes and several alterations of the therapeutic regimen are often required to control BP and adverse effects.

Altogether, 205 hypertensive patients satisfied our inclusion criteria and were included in our statistical analyses. The overall mean age of these patients was 60 ± 12 years, 40.5% being male and 59.5% female (Table 1). Among these patients, 156 (76%) had neither diabetes nor CKD and were considered to have a target BP of <140/90 mmHg, whereas the remaining 49 (24%) had either diabetes and/or CKD and were considered to be controlled with a BP of <130/80 mmHg. Mean ages were 58 ± 12 years for patients without diabetes and CKD, and 66 ± 10 years for patients with either or both these pathologies ($P < 0.001$). There were 37% (58/156) males in the first group and 51% (25/49) in the second group ($P = 0.085$). Most patients were long term hypertensives, with 65% of all patients having high BP for over five years. Only 8 patients have been diagnosed hypertensive for the first time within the last twelve months of the study period.

Table 1 Characteristics of hypertensive patients included in the study (n = 205)

Characteristics	n	Frequencies (%)
Age		
≥18 - <35 years	4	2.0
35 - 64 years	128	62.4
≥65 years	73	35.6
Gender		
Male/Female	83/122	40.5/59.5
Duration of hypertension		
<1 year	8	3.9
≥1year and <5 years	83	31.2
≥5 years and <10 years	80	41.5
≥10 years	34	23.4
Comorbid conditions		
Cerebrovascular disease	16	7.8
Chronic kidney disease	12	5.9
Diabetes	41	20.0
Heart failure	2	1.0
Ischemic heart disease	8	3.9
Dyslipidemia	122	59.5
Metabolic syndrome	4	2.0
Obesity (body mass index ≥30)	50	24.4
Peripheral arterial disease	5	2.4
Advanced age (≥65 years)	73	35.6
None of the above	35	17.1
Target BP values (JCN 7 guidelines)		
<140/90 mmHg	156	76.1
<130/80 mmHg	49	23.9

Thirty-one percent of the study population had a compelling indication and 52% had a special situation, as defined by JNC 7. The most common compelling indications were diabetes (20%), cerebrovascular disease (8%) and CKD (6%), whereas dyslipidemia (60%), advanced age (36%) and obesity (24%) were the most common special situations (Table 1).

The distribution of age-groups and target BP values in the hypertensive study population are shown in Table 2. It is worth mentioning that all patients in the age-group ≥18 - <35 years had a BP target value of <140/90 mmHg, and 59.2% patients in the higher cardiovascular risk group were ≥65 years.

Blood pressure control

Overall, the mean systolic BP of the 205 hypertensive patients included in our analysis was 140.1 ± 15.0

Table 2 Number of patients in each age group/target BP value combination that achieved BP control

	Target BP values	
Age	<140/90 mmHg	<130/80 mmHg
≥18 - <35 years	50% (2/4) patients	0 patients
35 - 64 years	54% (58/108) patients	10% (2/20) patients
≥65 years	25% (11/44) patients	10% (3/29) patients

mmHg and the mean diastolic BP was 81.5 ± 11.1 mmHg, with 44% (91/205) patients attaining BP <140/90 mmHg (Table 3). Among the remaining 56% (114/205) patients, with a BP equal or higher than 140/90 mmHg, 45% (92/205) patients had stage 1 hypertension and 11% (22/205) had stage 2 hypertension.

When we consider the target BP values defined by the JCN 7 guidelines, 45.5% (71/156) patients with neither diabetes nor CKD attained a BP <140/90 mmHg, whereas only 10.2% (5/49) patients with diabetes and/or CKD attained the target value of <130/80 mmHg (< 0.001). In the first group, 45.5% (71/156) patients had stage 1 hypertension and 9% (14/156) had stage 2 hypertension, according to the JNC 7 classification of BP for adults. In the second group, 31% (15/49) had their BP within 120-139/80-89, 43% (21/49) had stage 1 hypertension and 16% (8/49) had stage 2 hypertension. Overall, only 37% (76/205) of hypertensive patients had their BP controlled according to the JCN 7 guidelines. All 5 patients that achieved BP control in the second group were males, although a significant difference between sexes was not achieved (P = 0.050). Likewise, the proportion of males in the total of patients that achieved BP control in the first group (39%, 28/71) was not significantly different from the proportion of males in the total of patients that did not achieve BP control (35%, 30/85, P = 0.594). When considering obese hypertensive patients (body mass index ≥30), 36.4% (12/33) achieved BP control in the first group, which is arithmetically lower, although not significantly (P = 0.232), than the BP control obtained in nonobese patients (48.0%, 59/123). In the diabetes and CKD group there was also not a statistically significant difference (P = 1) in the BP control between obese (11.8%, 2/17) and nonobese patients (9.4%, 3/32); however, the number of obese hypertensive patients in this group was too small to extract accurate statistical conclusions.

Among patients initiating hypertension consultation within the study period, 32.1% (9/28) had stage 2 hypertension in the first appointment, but this figure decreased to 3.6% (1/28) in the last consultation (P = 0.012), and was not significantly different from the remainder overall population at the last appointment (11.9%, 21/177, P = 0.322). However, there was a significant higher percentage of patients with stage 2 hypertension in the first medical appointment at the hypertension/dyslipidemia clinic, when compared to the total study population at the last appointment (P = 0.009). Despite this improvement in BP measures in patients initiating hypertension consultation within the study period, there was not a statistically significant (P = 0.188) improvement in the percentage of patients with controlled BP, according to JNC 7 guidelines, between the first and the last appointments. However, in these patients, there was a significant decrease in the mean ± SD systolic BP from the first to the last appointment (149.4 ± 17.1 versus 138.1 ± 11.0, P < 0.001). Conversely, the decrease reported in the diastolic BP from the first to the last appointment was not statistically significant (87.3 ± 13.2 versus 83.7 ± 9.3, P = 0.072). The average interval time between the first and the last appointment was 6 months in this subgroup of patients, with an average of 4 medical appointments per patient.

The attainment of BP control per age-group and cardiovascular risk are represented in Table 2. Concerning

Table 3 Blood pressure control of hypertensive patients

BP	All patients (n = 205)	Patients with target BP <140/90 mmHg (n = 156)	Patients with target BP <130/80 mmHg (n = 49)	Patients initiating HT appointments within the study period (n = 28) - First appointment	Patients initiating HT appointments within the study period (n = 28) - Last appointment
Mean ± SD SBP/DBP (mmHg)	140.1 ± 15.0/81.5 ± 11.1	138.6 ± 14.4/81.9 ± 10.5	144.6 ± 16.2/80.4 ± 12.9	149.4 ± 17.1/87.3 ± 13.2	138.1 ± 11.0/83.7 ± 9.3
BP <140/90 (mmHg)	91 (44%)	71 (45.5%)	20 (41%)	6 (21%)	11 (39%)
BP ≥140/90 (mmHg)	114 (56%)	85 (54.5%)	29 (59%)	22 (79%)	17 (61%)
BP controlled (JCN 7 guidelines)	76 (37%)	71 (45.5%)	5 (10%)	6 (21.4%)	10 (35.7%)
BP not controlled					
120-139/80-89	15 (7%)	NA	15 (31%)	0	1 (3.6%)
Stage 1	92 (45%)	71 (45.5%)	21 (43%)	13 (46.4%)	16 (57.1%)
Stage 2	22 (11%)	14 (9%)	8 (16%)	9 (32.1%)	1 (3.6%)

DBP - Diastolic BP; HT - Hypertension; NA - Not applicable; SBP - Systolic BP.

the lower cardiovascular risk group, the percentage of patients achieving BP control was not significantly different (P = 1) in the age groups ≥18 - <35 years (50%) and 35-64 years (54%), but was significantly lower (P = 0.001) in the age group ≥65 years (25%). When considering the higher cardiovascular risk group, the percentage of patients achieving BP control was only 10% for both age groups involved.

Antihypertensive therapy

In all, 196 patients were prescribed with antihypertensive medication. The remaining 9 patients have only been counselled to adopt lifestyle modifications in order to control their BP, and 6 of these were already controlled without any antihypertensive medication. It is worth noting that these 9 patients were significantly younger than the average population, with an overall mean age of 44 ± 13 years (P < 0.001). The recommended lifestyle changes for BP control were in accordance with the JNC 7 guidelines and included: (1) weight loss in the overweight patients, (2) reduced sodium intake, (3) increased physical activity, and (4) limited alcohol consumption.

Overall, the patients took a mean ± SD of 2.7 ± 1.4 antihypertensives daily. Thiazide-type diuretics were the most frequently prescribed antihypertensive agents, with a total of 66.8% (137/205) patients being prescribed with this class of drugs, followed by angiotensin receptor blockers (ARBs) (60.1%, 123/205) and beta-blockers (42.6%, 87/205). These three classes of antihypertensives were the most prescribed (and in the same ranking order) both in patients without diabetes and/or CKD and in patients with these diseases (Table 4). However, the first group took 2.5 ± 1.3 antihypertensives daily, whereas in the second group this figure was 3.2 ± 1.3 (P = 0.005).

The number of antihypertensive drugs taken per patient ranged from 1 to 6 (Figure 1). The percentage of patients taking 1 or 2 antihypertensive drugs were higher in hypertensives with a target BP of <140/90 mmHg; on the contrary, the percentage of patients taking 3, 4, 5 or 6 antihypertensive drugs were higher in patients with a lower target BP (<130/80 mmHg).

As shown in Figure 2, the rate of BP normalization seemed to be inversely related to the intensity of the treatment: in patients prescribed with antihypertensives, the higher the number of drugs, the lower the rate of BP normalization, with a significant correlation between the two variables. In patients with target values of <140/90 mmHg the correlation between those variables was -0.916 (P = 0.010), and in patients with target values of <130/80 mmHg the correlation was -0.935 (P = 0.006). It should be noted that in the first group of patients BP control was not achieved only with a 6-drug combination regimen therapy, whereas in the second group it was not achieved with 4-, 5- or 6-drug combinations (Figures 1 and 2). Resistant hypertension must be strongly suspected at least in 4 patients in whom BP control was not achieved even with a 6-drug combination therapy.

For patients without compelling indications, beta-blockers were the most frequently prescribed antihypertensive agents as monotherapy; for those with compelling indications angiotensin-converting enzyme inhibitors (ACEIs) were the most frequently prescribed. In all, the most common 2-drug combinations were thiazide diuretic plus ARB (37% of all patients receiving 2 drugs) and thiazide diuretic plus ACEI (22% of all patients receiving 2 drugs). These 2-drug combinations were the most common both in patients without or with compelling indications.

Almost all patients with comorbid diabetes (95.9%) were treated with an ACEI or ARB, according to the best practice recommendations; also, according to best practice, the two reported hypertensive patients (100%) with comorbid congestive heart failure were treated with ACEI, ARB, or beta-blocker; however, only one patient (25%) with a history of myocardial infarction was treated with beta-blockers.

Discussion

The results presented in this study describe the demographic and clinical characteristics of hypertensive patients attending the medical consultation of hypertension/dyslipidemia in a university teaching hospital located in the Eastern Central Region of Portugal for routine follow-up, focusing on the level of hypertension control and antihypertensive therapy.

According to a survey conducted in 2003 [2], of the total number of hypertensives in the Central Region of Portugal who reported taking their medication regularly, only 26.1% had their BP measurements <140/90 mmHg, which is significantly smaller than the 44.4% obtained in our study (Table 3). This difference possibly points to an improved current care of the hypertensives included in our study when compared to those included in the above mentioned survey. Increased awareness of hypertension and the importance of lower BP may have prompted Portuguese providers and patients to more aggressively treat high BP, especially after the publication of the JNC 7 report in 2003. Till now there has been no data about the percentage of treated hypertensives in clinical practice, in this Portuguese region, with their BP controlled according to the JNC 7 guidelines. Our study revealed that 37.1% of hypertensive patients had their BP controlled according to those guidelines, with the percentage of patients without diabetes or CKD attaining BP control (45.5%) significantly higher

Table 4 Antihypertensive medication prescribed to hypertensive patients

Antihypertensive Drug	All patients (n = 205) (%)	Patients with target BP <140/90 mmHg (n = 156) (%)	Patients with target BP <130/80 mmHg (n = 49) (%)	*P* Value*
Loop diuretics	**13.2**	**11.5**	**18.4**	0.218
Furosemide	13.2	11.5	18.4	
Thiazide diuretics	**66.8**	**64.1**	**75.5**	0.139
Altizide	1.0	0.6	2.0	
Hydrochlorothiazide	50.7	46.8	63.3	
Indapamide	15.1	16.7	10.2	
Potassium-sparing diuretics	**3.9**	**1.3**	**12.3**	0.003
Spironolactone	2.9	1.3	8.2	
Triamterene	1.0	0.0	4.1	
Renin inhibitor	**2.0**	**1.9**	**2.0**	1
Aliskiren	2.0	1.9	2.0	
Angiotensin-converting enzyme inhibitors	**29.8**	**27.5**	**36.8**	0.221
Cilazapril	1.0	1.3	0.0	
Enalapril	11.7	7.7	24.5	
Imidapril	0.5	0.6	0.0	
Lisinopril	3.4	3.2	4.1	
Perindopril	6.8	9.0	0.0	
Ramipril	5.9	5.1	8.2	
Trandolapril	0.5	0.6	0.0	
Angiotensin II-receptor antagonists	**60.1**	**58.4**	**65.3**	0.383
Candesartan	6.3	7.7	2.0	
Eprosartan	2.0	1.3	4.1	
Irbesartan	8.8	8.3	10.2	
Losartan	12.2	13.5	8.2	
Olmesartan	2.0	2.6	0.0	
Telmisartan	15.1	13.5	20.4	
Valsartan	13.7	11.5	20.4	
Calcium channel blockers	**39.7**	**36.4**	**48.9**	0.121
Amlodipine	21.5	18.6	30.6	
Felodipine	2.0	1.9	2.0	
Lercanidipine	3.9	3.8	4.1	
Nifedipine	5.4	5.1	6.1	
Nimodipine	0.5	0.6	0.0	
Nitrendipine	1.0	1.3	0.0	
Diltiazem	5.4	5.1	6.1	
Beta-blockers	**42.6**	**41.6**	**45.0**	0.689
Atenolol	5.9	6.4	4.1	
Bisoprolol	5.9	6.4	4.1	
Metoprolol	0.5	0.6	0.0	
Nebivolol	23.9	21.2	32.7	
Propranolol	0.5	0.6	0.0	
Carvedilol	5.9	6.4	4.1	
Central alpha-2 agonists	**10.8**	**10.8**	**10.2**	0.888
Clonidine	0.5	0.6	0.0	
Methyldopa	0.5	0.6	0.0	
Rilmenidine	9.8	9.6	10.2	

*P values are for comparison between the two last columns.

90

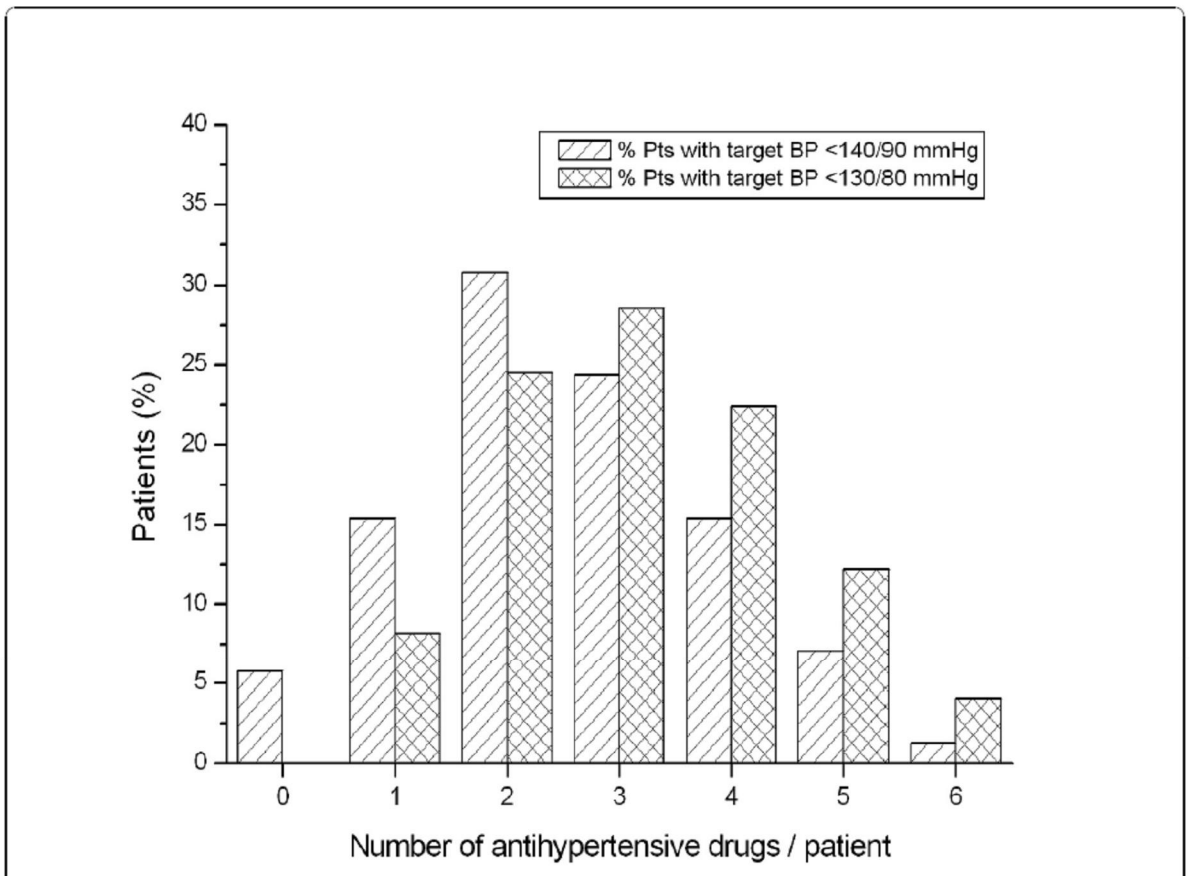

Figure 1 Number of antihypertensive medications per patient.

($P < 0.001$) than the percentage of hypertensive patients with diabetes or CKD (10.2%). It should be noted that the reported levels of BP control can vary greatly depending on the study population, methods and time frame [4,5]. For example, in one study based on data from the US National Health and Nutrition Examination Survey 2003-2004, the BP control rate (to <140/90 mmHg) was 56.6% in treated hypertensives, and 37.5% in treated hypertensive persons with diabetes mellitus (for whom the goal BP is <130/80 mmHg) [6]. In a regional survey performed in the middle-West of France and involving 1050 treated hypertensives, Ragot *et al.* reported that 39% of patients had BP figures <140/90 mmHg and only 13% of the diabetic population were normalized according to the international recommendations (<130/80 mmHg) [7]. In a more recent retrospective observational study conducted in the United States, Jackson *et al.* [5] reported a BP control of 49.3% in an after-JNC 7 cohort. In this cohort, a significantly higher percentage of nondiabetic patients achieved BP control compared with those with comorbid diabetes (60.9% versus 29.4%). Similarly, Andros *et al.* [8] conducted a retrospective observational study of BP control in an insured diabetic population, obtaining a BP control rate (defined by JNC 7) of 28%, similar to the 29.4% obtained by Jackson *et al.* [5]. The results obtained in our study are less optimistic, especially when considering the percentage of BP control attained by hypertensives with diabetes or CKD (10.2%) and seem to be similar to those obtained by Ragot *et al*. in a French population [7]. The percentage of patients taking a higher number of antihypertensive drugs were higher in patients with a lower target BP (<130/80 mmHg) (Figure 1), suggesting that an effort is being made to further lower BP in this hypertensive subgroup. However, our results insinuate that prescribers may not be fully following the JNC 7 recommended BP targets, especially those related to hypertensives with diabetes or CKD, because the above mentioned studies demonstrated that it is possible to obtain a higher BP control in this hypertensive

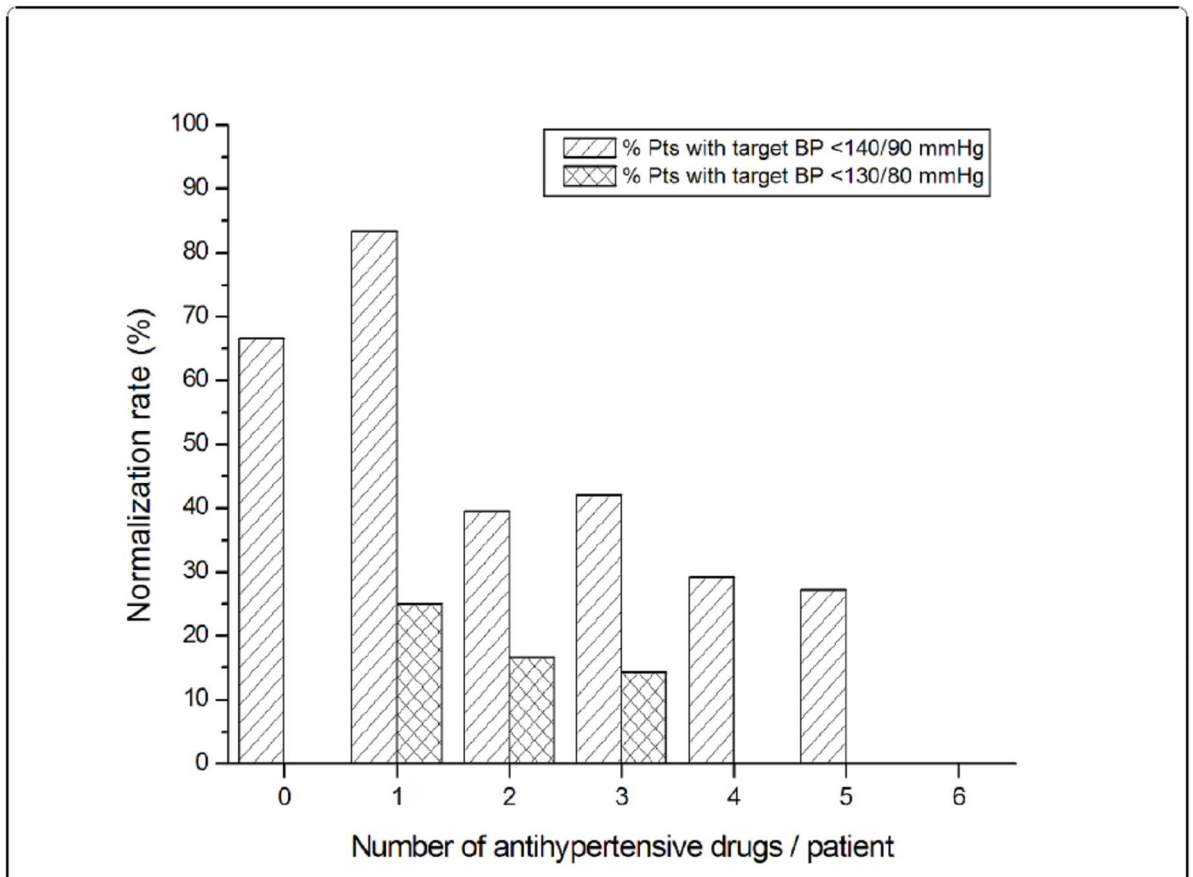

Figure 2 Blood pressure normalization according to the number of antihypertensive drugs.

subpopulation. In fact, there was no significantly difference in the percentage of hypertensives in each cohort that achieved a BP of <140/90 mmHg (45.5% versus 40.8%; $P = 0.564$). Thus, our findings indicate that patients who would benefit most from tighter control of BP, especially those with compelling indications, appeared to do worse than those with uncomplicated hypertension. Furthermore, it seems to us that stage 1 hypertension is not seen as a major problem because a rather significant percentage of hypertensive patients is maintained in this hypertension stage (Table 3). Other possible underlying causes of poor BP control are guidelines unawareness and therapeutic inertia on the part of providers and poor adherence and persistence with prescribed medications and lifestyle modifications by patients. Results of studies suggest that antihypertensive medications are frequently not intensified when BP remains uncontrolled, termed clinical inertia [9-11]. In the recent Harris Survey [12], more than 30% of hypertensive patients reported that their medication was not changed or increased despite the fact that their BP was still >140/90 mmHg. Antihypertensive medication nonadherence is another major factor that must be thought about when considering the possible reasons for the inadequate BP control. Indeed, there is a large proportion of patients in our study (65%) who had hypertension for over five years. It is known that patient persistence with prescribed therapy for any chronic disease typically declines over time, and hypertension is no exception [13-15].

Of particular note is that the BP control rate in patients with target values of <140/90 mmHg was significantly lower in older hypertensive individuals (25%; Table 2), which is in accordance with rates mentioned in the literature and are largely due to poor control of systolic BP [3,16]. Obesity is identified as one cause of resistant hypertension [17] and there was a trend, albeit not significant, toward higher BP control between nonobese hypertensive patients (40% vs 28%, 0.127). The nonsignificant difference in BP control rate between

obese and nonobese in our analysis could be because of the limited sample size, because >75% of the patients with diagnosed arterial hypertension were nonobese (body mass index <30).

The differences in rates of BP control between males and females were not significant in the <140/90 mmHg and in the <130/80 mmHg BP targeted population. Our results are in accordance with a recent study assessing gender difference in BP control that used the same cut points of uncontrolled BP defined by the JNC 7 [18].

Our results also indicate that there is a significantly higher percentage of patients with stage 2 hypertension in the first medical appointment at the hypertension/dyslipidemia clinic, when compared to the same patients and to the total study population at the last medical appointment. The decrease in stage 2 hypertension in patients attending the hypertension/dyslipidemia clinic for the first time was paralleled by a significant decrease in the systolic BP from the first to the last appointment (from 149.4 ± 17.1 to 138.1 ± 11.0, $P < 0.001$). These facts suggest that clinically important BP decreases can be achieved soon after hypertension medical appointment initiation.

Results from this study indicate that prescribers are following the JNC 7 drug therapy recommendations, including the use of thiazide-type diuretics as preferred initial agent in patients without compelling indications and those related to compelling indications. In fact, the use of ACEIs and ARBs in patients with diabetes and/or congestive heart failure coincides with JNC 7 recommendations. Data reported here do not, however, suggest that postmyocardial infarction patients are being mostly treated with beta-blockers.

The observed relationship between increased number of antihypertensive drugs and poorer BP control (Figure 2) could be explained by the fact that patients whose BP is more difficult to control are likely to be treated with multiple drugs. Thus, this measurement may be a consequence of poor BP control.

Several features of our study deserve further comment. First, the objective of this study was to describe levels of BP control in subgroups of hypertensive patients defined on the basis of important characteristics, and not to directly compare such levels across subgroups. For this motive, analyses adjusted for other characteristics were not conducted. Second, apart from patients initiating hypertension appointments within the study period, in which the BP measurements in the first appointment was also considered, BP control was determined based on the last available readings during the retrospective study period. These measurements may or may not be representative of the adequacy of control over the entire corresponding period. Third, drug information in the study database is confined to prescriptions written and not necessarily to those dispensed or used. Whether written prescriptions were filled by the patients and the level of medication adherence among patients who did fill the prescriptions is unknown. Finally, because of the retrospective design of the study, some data were not available or not able to be validated during the data collection process (Table 1). Although the missing data were quite reduced, the possibility exists that certain patient characteristics, conditions and risk factors were over- or under-represented.

Conclusions

The findings of this study indicate that many treated hypertensive patients fail to achieve BP control according to the JNC 7 guidelines. The most troublesome result, however, is the extremely low BP control rate attained by hypertensives with diabetes or CKD, i.e., BP control is worse among patients who are at high risk for adverse outcomes and may benefit the most from lower BP levels. The results obtained in this hypertensive subpopulation are significantly worse than those obtained by other authors. Even the BP control in hypertensives without diabetes or CKD can be improved if we compare our results with those obtained in clinical practice in other countries. Additional research is needed to identify the underlying causes of poor BP control, such as guidelines unawareness and therapeutic inertia on the part of providers and poor adherence and persistence with prescribed medications and lifestyle modifications by patients, so that team-based health care providers and patient interventions can be established that may address these causes.

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Authors' contributions

MM participated in the acquisition, analysis and interpretation of data and has been involved in drafting the manuscript. SR participated in the analysis and interpretation of data and has been involved in drafting the manuscript. LP participated in the design of the study and performed the statistical analysis. MCB conceived the study, participated in its design and coordination, helped to draft the manuscript and gave final approval to the version to be published. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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5.3 Artigo III

“Efficacy of Aliskiren/Hydrochlorothiazide Combination for the Treatment of Hypertension: A Meta-Analytical Approach”

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Open Access

Efficacy of Aliskiren/Hydrochlorothiazide Combination for the Treatment of Hypertension: A Meta-Analytical Approach

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Abstract: *Background:* Single-pill combinations of aliskiren/hydrochlorothiazide have recently been approved by the European Medicines Agency for the treatment of hypertension.

Objective: This study aimed to assess the antihypertensive efficacy of aliskiren/hydrochlorothiazide combination in reducing systolic and diastolic blood pressure in hypertensive patients.

Methods: A search in International Pharmaceutical Abstracts, MEDLINE, The Cochrane Library and ISI Web of Knowledge was performed from 2000 to November 2009, to identify randomized, double-blind, clinical trials using aliskiren/hydrochlorothiazide for the treatment of hypertension. Studies were included if they evaluated the antihypertensive efficacy of aliskiren/hydrochlorothiazide in patients with mild or moderate essential hypertension and age ≥ 18 years. The meta-analytical approach calculated the weighted average reductions of systolic and diastolic blood pressure for each daily dosage combination.

Results: We included 5 clinical trials testing several combinations of aliskiren/hydrochlorothiazide and containing data on 5448 patients. In all studies blood pressure was assessed at inclusion (baseline) and after 8 weeks of therapy. Blood pressure reductions and control rates were significantly ($p < 0.05$) higher with the aliskiren/hydrochlorothiazide combinations than with placebo and the same doses of aliskiren or hydrochlorothiazide alone. The weighted mean reductions (mm Hg) from baseline of systolic and diastolic blood pressure for each aliskiren/hydrochlorothiazide combination were: -15.8/-10.3 (150/25 mg); -15.9/-11.8 (300/12.5 mg); -16.9/-11.6 (300/25 mg). Blood pressure control rates (%) for the above combinations were, at least, respectively: 43.8, 50.1 and 51.9.

Conclusions: Aliskiren/hydrochlorothiazide provided clinically significant additional blood pressure reductions and improved blood pressure control rates over aliskiren or hydrochlorothiazide monotherapy.

Keywords: Aliskiren; aliskiren-hydrochlorothiazide; combination therapy; hypertension; blood pressure; antihypertensives.

INTRODUCTION

Hypertension is a major risk factor in the development of cardiovascular disease, heart attack and stroke and one of the most important public health problems worldwide due to its high prevalence and deleterious impact on the population in terms of excessive morbidity and mortality. Currently, hypertension is estimated to affect approximately 30% of the US and European population and 1 billion people worldwide and, as the population ages, this number is expected to increase even further. Moreover, despite advances in treatment of the condition, hypertension control rates continue to be suboptimal in both the US and Europe as only about one third have their blood pressure (BP) reduced to the recommended levels by the 7th Joint National Committee (JNC-7) to under 140/90 mm Hg for uncomplicated hypertension, and less than 130/80 mmHg for those with diabetes mellitus or renal disease [1]. Since monotherapy controls the BP of less than 50% of treated hypertensive patients [2, 3], combination therapy with two or more antihypertensive medications is often required to achieve BP control to recommended levels [1, 4]. At present, the most widely used antihypertensive combinations involve hydrochlorothiazide (HCTZ) and drugs that block the renin-angiotensin system (RAS), such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). Recently a new blocker of the RAS, aliskiren, has been developed and approved by the US Food and Drug Administration (FDA, on 5th March 2007) and by the European Medicines Agency (EMEA, on 22nd August 2007) for the treatment of essential hypertension. Aliskiren is an oral direct renin inhibitor, the rate-limiting enzyme in the production of the end product of the RAS cascade, angiotensin II, a potent vasoactive peptide. Aliskiren is a long-acting antihypertensive (half-life ≈ 40 hours) and has been shown in several clinical trials to be effective in lowering BP, safe and well tolerated in daily doses of 150 and 300 mg (approved once-daily doses) [5]. In a recent systematic review and meta-analysis of six double-

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blind randomized clinical trials to quantify the systolic and diastolic BP (SBP and DBP) lowering efficacy of aliskiren in the treatment of adults with essential hypertension, the obtained weighted mean differences with 95% CI were: aliskiren 150 mg, -5.5 (-6.5, -4.4)/-3.0 (-3.7, -2.3) mm Hg; aliskiren 300 mg, -8.7 (-9.7, -7.6)/-5.0 (-5.6, -4.3) mm Hg [5]. In double-blind randomized 8-week clinical trials, aliskiren/HCTZ combination therapy reduced SBP and DBP from baseline to a significantly greater extent than placebo, aliskiren monotherapy and HCTZ monotherapy [6, 7]. Aliskiren/HCTZ also produced significant additional SBP and DBP reductions in patients inadequately responsive to 4 weeks' prior treatment with aliskiren or HCTZ alone [6].

Single-pill combinations (SPCs) of aliskiren/HCTZ (150/12.5 mg, 150/25 mg, 300/12.5 mg, 300/25 mg) have recently been approved by the US FDA (18th January 2008) and by EMEA (16th January 2009) for the treatment of adults with essential hypertension whose BP is not adequately controlled with aliskiren or HCTZ alone, and as a substitution treatment in patients with hypertension adequately treated by the two individual drugs concomitantly at the equivalent fixed dosage. There have been several reviews published with a general scope of pharmacology, pharmacodynamic and pharmacokinetic profile and clinical studies of aliskiren/HCTZ combination. In this paper, we performed a systematic analysis of the literature and a meta-analytical approach to the available clinical trial data for the various combinations of aliskiren/HCTZ to assess their antihypertensive efficacy in the treatment of mild to moderate hypertension.

The aim of this review was to assess the antihypertensive efficacy and tolerability of the aliskiren/HCTZ combination therapy (as a combination of the individual components or as SPCs) in reducing SBP and DBP in patients with mild to moderate hypertension by using systematic analysis of the literature and meta-analytical approach to combine data from different randomized, double-blind, clinical trials.

MATERIALS AND METHODOLY

A literature search to identify clinical trials using aliskiren in combination with HCTZ for the treatment of hypertension was conducted on December 2009 to obtain all published study reports that met our inclusion criteria.

Inclusion and Exclusion Criteria

We included all articles in the literature written in any of the major languages. To be included in our review studies were required to be randomized, double-blind, clinical trials using aliskiren in combination with HCTZ (as a combination of the individual components or as SPCs) for the treatment of hypertension. Additionally, studies were included if they evaluated the antihypertensive efficacy (outcome measure) of aliskiren/HCTZ in patients with mild or moderate essential hypertension (SBP 140-179 mm Hg and/or DBP 90-109 mm Hg, as defined in current international guidelines [4]) and patient age ≥ 18 years. Articles were automatically excluded if their results were not reported or had been presented in forms such as abstracts, letters, or commentaries.

Literature Search Strategy

We searched the following electronic databases: International Pharmaceutical Abstracts, MEDLINE, The Cochrane Library and ISI Web of Knowledge. Each database was independently searched by 2 reviewers for articles published from 2000 to and including November 30, 2009, using the search terms *aliskiren*, *aliskiren/hydrochlorothiazide*, *aliskiren-hydrochlorothiazide*, *aliskiren in combination with hydrochlorothiazide, renin inhibitor*. The reviewers selected articles based on the predefined inclusion/exclusion criteria and results were matched. A consensus method was applied to judge any article selection divergences. The rationale for decisions was discussed until reviewers agreed on the final decision. A third author was called to resolve any remaining discrepancies concerning article eligibility.

Selected articles' references and reviews of the subject were hand searched for additional studies that were not obtained through our initial electronic search.

Data Extraction

The following information was gathered for each clinical trial: author names, year of publication, study design and duration, setting, characteristics of the patients enrolled, sizes of the treatment groups, daily treatment regimens and primary endpoint. Outcomes extracted from articles included mean and variation of SBP and DBP at baseline and final assessments for each group, responder rate (DBP < 90 mm Hg or ≥10 mm Hg reduction from baseline) and BP control rate (SBP < 140 mm Hg and DBP < 90 mm Hg). Changes from baseline in plasma renin activity (PRA) and plasma renin concentration (PRC) with aliskiren/HCTZ and with either component alone were also extracted whenever reported, as well as adverse events recorded during the trials. During the data extraction phase, we wrote to corresponding authors of studies to request missing data and clarify study details.

Quality Assessment

The quality of selected articles was assessed by the same principles used in article selection and data extraction (i.e., 2 independent reviewers), and was based on the Jadad *et al.* method to measure the risk of bias [8]. Their 3-item quality assessment checklist evaluates the following methodological parameters: controlled trial, random allocation of treatments, double-blind follow-up, dropout rate, intention-to-treat (ITT) analysis and absence of other biases. Quality scores were presented as proportions of the total possible score (i.e., 5) of the quality assessment scale (where 100% represents the maximum quality). The scores were categorized according to the following criteria: weak (<60%), fair (60%), good (80%), or very good (100%).

Analysis Method

For trials meeting the criteria for inclusion in the analysis, the efficacy of treatment was evaluated *via* measurements of SBP and DBP at the start of the trial (baseline) and after 8 weeks of therapy. The meta-analytical approach therefore compared the efficacy of each aliskiren/HCTZ dose combination in reducing SBP and DBP over this period of time. The analysis method used was based on calculation of

the mean BP reduction for a set of aliskiren/HCTZ dose combinations evaluated, by weighting the combined data for the trial size using the following formula: (BP reduction [trial 1] • number of patients [trial 1] +…+ BP reduction [trial n] • number of patients [trial n])/total number of patients (trial 1 +…+ trial n).

RESULTS

A completed QUOROM flow chart [9] of the literature search strategy applied and results found is depicted in Fig. (**1**). Initially, 46 potentially relevant RCTs were identified that appeared to meet the inclusion criteria and were screened for retrieval based on their titles and abstracts. Thirty of those articles were excluded for not evaluating aliskiren in combination with hydrochlorothiazide. The remaining 16 articles were retrieved for full-text review. Eleven of those articles were excluded for the following reasons: two had data that were not extractable [10, 11], three presented excluded study designs [12-14], one enrolled patients with severe hypertension [15], four appeared only in the abstract form [16-19] and one was indexed in MEDLINE in duplicate [20]. Therefore, after exclusion criteria were applied, a total of 5 studies involving a total of 5508 patients were included in this analysis [20-24].

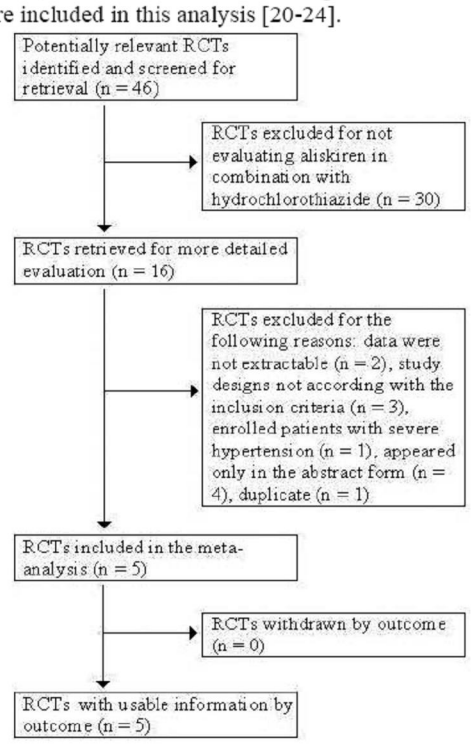

Fig. (1). Quorom flow chart of literature search strategy applied and results. Five double-blind randomized controlled trials met the inclusion criteria, using aliskiren in combination with HCTZ for the treatment of hypertension.

Table **1** presents the overall characteristics of the evaluated studies. The average sample size was 1102 ± 947 (mean ± SD), with a median of 722 and range from 489–2776 patients. All included studies were randomized, double-blind, multicenter clinical trials, proceeded by a single-blind, placebo [21] / active comparator [20, 22-24], run-in period of 2-4 weeks. Moreover, all five studies specified the change from baseline (start of double-blind treatment) in mean sitting DBP (msDBP) at 8 weeks as the primary endpoint. Secondary efficacy measures included the change in mean sitting SBP (msSBP) [20-24], the proportion of patients with successful response to treatment (defined as msDBP < 90 mmHg and/or a ≥ 10 mmHg reduction from baseline) [21, 22] and the proportion of patients attaining BP control (defined as msDBP < 90 mmHg and msSBP < 140 mm Hg) [20-24]. Two trials used the SPC [21, 22], and three combined the individual components [20, 23, 24], with aliskiren and HCTZ administered orally as single daily doses in all studies. One trial enrolled obese hypertensive patients only (obesity defined as body mass index of ≥ 30 kg/m^2) [22], although in the remaining four trials subgroups of patients with obesity were also present. In the five included clinical trials patient demographics and baseline characteristics were similar across treatment groups. Brief details of the characteristics of each individual trial and treatment group, including mean patient ages, sex ratios, body mass index / obesity and baseline SBP and DBP are provided in Appendix. The average quality score of study reporting was 84% ± 22% (range 60–100%), which could be categorized as very good. One study failed to report all information on data variability [21], which prevented the use of an approximation for standard error of the mean (SEM) or confidence interval (CI) estimation, when calculating some weighted average reductions in SBP and DBP. We contacted the corresponding author of this study by email to request missing data on SEM as well as on BP control rate at endpoint for each aliskiren/HCTZ, aliskiren and HCTZ daily doses tested, but no response was provided.

Table **2** details results from clinical trials on the efficacy of aliskiren/HCTZ in reducing BP. In the only placebo-controlled study (and also the largest of the RCTs), aliskiren/HCTZ combination reduced SBP and DBP from baseline to a significantly ($p \leq 0.0001$) greater extent than placebo in patients with mild to moderate hypertension [21], furthermore, aliskiren/HCTZ combination (at all but the 75/12.5 mg and 150/6.25 mg dosages, both of which are not commercially available) decreased SBP and DBP from baseline to a significantly ($p < 0.05$) greater extent than the component monotherapies [21]. In the other selected RCTs, all of which with an active comparator and a non-responder study design [20, 22-24], aliskiren/HCTZ combination was an effective treatment option, producing significantly additional reductions in SBP and DBP in patients with mild to moderate hypertension inadequately responsive to 4 weeks' prior treatment with aliskiren [20] or HCTZ [22-24] alone. In the five included RCTs, BP control rates were also significantly higher with all aliskiren/HCTZ combinations commercially available than with placebo, aliskiren alone and HCTZ alone. One of the included studies did not report the BP response rate [24], in the remaining four studies, BP response rates were also significantly higher with all aliskiren/HCTZ combinations commercially available than with placebo; however, only the three higher dosages of aliskiren/HCTZ combinations yielded significantly higher BP response rates than the component monotherapies [20-23]. Two studies also compared the efficacy of aliskiren/HCTZ 300/25 mg combination in reducing and controlling BP with other treatment

Table 1. Published Clinical Trials of Aliskiren/HCTZ for Treatment of Mild to Moderate Hypertension

Reference (Year)	Study Design, Duration, Setting, BP measurement, No of patients	Demographics and Baseline Characteristics[a]	Daily Treatment Regimens	Primary End Point	Quality Score[b]
Villamil (2007) [21]	Randomized, double-blind, placebo-controlled, multicenter; 8 wks; clinic; trough BP; n=2776	Age ≥ 18 yrs. Eligibility for single-blind phase: msDBP ≥95 and <110 mmHg (baseline). Eligibility for double-blind phase: msDBP ≥95 and <110 mmHg after 2 or 4 wks on placebo. Mean age 55 yrs; 55% men; 86% Caucasian.	Single-blind, placebo run-in period (2 wks or 4 wks): Placebo. Double-blind treatment (8 wks): Placebo; Aliskiren 75, 150, 300mg; HCTZ 6.25, 12.5, 25mg; Aliskiren/HCTZ 75/6.25, 75/12.5, 75/25, 150/6.25, 150/12.5, 150/25, 300/12.5, 300/25mg.	Change in msDBP from baseline (start of double-blind treatment) to wk 8 endpoint (aliskiren monotherapy vs placebo; combination therapy vs respective monotherapies)	60%[c]
Jordan (2007) [22]	Randomized, double-blind, multicenter; 12 wks; clinic; trough BP; n=489	Age ≥ 18 yrs. Eligibility for single-blind phase: msDBP ≥95 and <110 mmHg (baseline). Eligibility for double-blind phase: msDBP ≥90 and <110 mmHg. BMI ≥ 30 kg/m^2; Mean age 54 yrs; 44% men; 99.6% Caucasian.	Single-blind treatment (4 wks): HCTZ 25mg. Double-blind treatment (first 4 wks – next 8 wks): Placebo–HCTZ 25 – 25mg; Aliskiren/HCTZ 150/25 - 300/25mg; Irbesartan/HCTZ 150/25 – 300/25 mg; Amlodipine/HCTZ 5/25 – 10/25mg;	Change in msDBP from baseline (start of double-blind treatment) to wk 8 endpoint (aliskiren/HCTZ 300/25 mg vs placebo–HCTZ 25 mg)	100%
Nickenig (2008) [20]	Randomized, double-blind, multicenter; 8 wks; clinic; trough BP; n=880	Age ≥ 18 yrs. Eligibility for single-blind phase: msDBP ≥95 and <110 mmHg or msDBP ≥85 and <110 mmHg if treated for HT within the 4 wks prior to screening (baseline). Eligibility for double-blind phase: msDBP ≥90 and <110 mmHg after 4 wks of aliskiren 300 mg monotherapy. Mean age 55 yrs;55% men;83% Caucasian.	Single-blind treatment (4 wks): Aliskiren 300mg. Double-blind treatment (8 wks): Aliskiren 300mg; Aliskiren/HCTZ 300/12.5, 300/25mg.	Change in msDBP from baseline (start of double-blind treatment) to wk 8 endpoint (aliskiren monotherapy vs combination therapy)	100%
Blumenstein (2009) [23]	Randomized, double-blind, multicenter; 8 wks; clinic; trough BP; n=722	Age ≥ 18 yrs. Eligibility for single-blind phase: patients with HT, who were newly diagnosed, untreated or treated at the time of screening. Newly diagnosed pts or pts who had not been treated for HT in the 4 wks prior to screening had to have msDBP ≥95 and <110 mmHg at the time of the screening. Eligibility for double-blind phase: msDBP ≥90 and <110 mmHg after 4 wks of HCTZ 25 mg monotherapy. Mean age 54 yrs; 59% men;91% Caucasian.	Single-blind treatment (4 wks): HCTZ 25mg. Double-blind treatment (8 wks): HCTZ 25mg; Aliskiren/HCTZ 150/25, 300/25mg.	Change in msDBP from baseline (start of double-blind treatment) to wk 8 endpoint (HCTZ monotherapy vs combination therapy)	100%
Geiger (2009) [24]	Randomized, double-blind, multicenter; 8 wks; clinic; trough BP; n=641	Age ≥ 18 yrs. Eligibility for single-blind phase: pts with mild to moderate HT taking antihypertensive agents. Eligibility for double-blind phase: msDBP ≥95 and <110 mmHg after 4 wks of HCTZ monotherapy. Mean age 53 yrs; 57% men; 86% Caucasian.	Single-blind treatment (4 wks): HCTZ 12.5mg for 1 wk followed by HCTZ 25mg for 3 wks. Double-blind treatment (8 wks): HCTZ 25mg; Aliskiren/HCTZ 150/25mg for 4 wks followed by 300/25mg for another 4 wks; Valsartan/HCTZ 160/25mg for 4 wks followed by 320/25mg for another 4 wks; Aliskiren/Valsartan/HCTZ 150/160/25mg for 4 wks followed by 300/320/25mg for another 4 wks.	Change in msDBP from baseline (start of double-blind treatment) to wk 8 endpoint (aliskiren/HCTZ and valsartan/HCTZ vs aliskiren/valsartan/ HCTZ)	60%[d]

[a] In each published clinical trial, patient baseline and demographic characteristics were comparable for all treatment groups.
[b] The percentage of the total possible score (i.e., 5) of the quality assessment scale applied (100% represents the maximum quality).
[c] Method to generate the sequence of randomization and method of double blind were not described; additionally, some information on outcome variability was not provided.
[d] Method to generate the sequence of randomization and method of double blind were not described.
BP; blood pressure; HCTZ – hydrochlorothiazide; HT – hypertension; msDBP – mean sitting diastolic blood pressure; pts – patients; wk – week.

Table 2. Clinical Trial Data on the Efficacy of Aliskiren/HCTZ in Reducing BP

Reference	Patients, n (ITT)	Treatment and Daily Dose (mg)	Change in SBP from Baseline at Endpoint (mm Hg)	Change in DBP from Baseline at Endpoint (mm Hg)	Responder Rate (%)	BP Control Rate at Endpoint (%)
Villamil (2007) [21]	192	Placebo	-7.5	-6.9	45.8	28.1
	183	Aliskiren 75	-9.4	-8.7±0.59[a]	51.9	(29.0
	183	Aliskiren 150	-12.2[b]	-8.9±0.59[a]	51.9	to
	180	Aliskiren 300	-15.7[c]	-10.3±0.60[c]	63.9[b]	[c] 46.7)
	194	HCTZ 6.25	-11.0[a]	-9.1±0.58[a]	53.6	(32.5
	188	HCTZ 12.5	-13.9[c]	-10.1±0.59[c]	60.6[a]	to
	173	HCTZ 25	-14.3[c]	-9.4±0.61[a]	59.0[a]	37.8)
	187	Aliskiren/HCTZ 75/6.25	-14.3 ±0.93[c,d]	-10.8[c,d]	61.5[a]	[a]
	189	Aliskiren/HCTZ 75/12.5	-15.6[c]	-11.1[c]	63.5[b]	[a]
	186	Aliskiren/HCTZ 75/25	-17.3[c,d]	-11.5[c,d]	70.4[c,d]	[a,d] (37.4
	173	Aliskiren/HCTZ 150/6.25	-15.3[c]	-10.4±0.59[c]	58.4[a]	[a] to
	184	Aliskiren/HCTZ 150/12.5	-17.6[c,d]	-11.9[c,d]	69.6[c]	[a,d] 59.5)
	187	Aliskiren/HCTZ 150/25	-19.5[c,d]	-12.7[c,d]	71.1[c,d]	[a,d]
	180	Aliskiren/HCTZ 300/12.5	-19.8[c,d]	-13.9[c,d]	80.6[c,d]	[a,d]
	173	Aliskiren/HCTZ 300/25	-21.2±0.97[c,d]	-14.3±0.61[c,d]	76.9[c,d]	[a,d]
Jordan (2007) [22]	117	HCTZ 25	-8.6±1.00	-7.9±0.73	59.0	34.2
	113	Aliskiren/HCTZ 300/25	-15.8±1.01[e]	-11.9±0.74[e]	73.5[f]	56.6[g]
	117	Irbesartan/HCTZ 300/25	-15.4±1.00[h]	-11.3±0.72[h]	70.9[h]	54.7[h]
	122	Amlodipine/HCTZ 10/25	-13.6±0.98[h]	-10.3±0.71[h]	68.0[h]	45.1[i]
Nickenig (2008) [20]	296	Aliskiren 300	-8.0±0.9	-7.4±0.5	62.2	40.9
	292	Aliskiren/HCTZ 300/12.5	-13.5±0.9[j]	-10.5±0.5[j]	73.3[k]	57.9[j]
	284	Aliskiren/HCTZ 300/25	-15.9±0.9[j]	-11.0±0.6[j]	77.1[j]	60.2[j]
Blumenstein (2009) [23]	244	HCTZ 25 mg	-7.1±0.7	-4.8±0.4	47.1	25.8
	242	Aliskiren/HCTZ 150/25	-12.9±0.7[l]	-8.5±0.4[l]	67.4[l]	48.8[l]
	232	Aliskiren/HCTZ 300/25	-16.7±0.7[l,m]	-10.7±0.4[l,n]	78.5[l]	58.2[l,o]
Geiger (2009) [24]	151	HCTZ 25	-6±1.12	-6±0.70	NR	20.53
	164	Aliskiren/HCTZ 300/25	-15 ±1.08[l]	-11±0.67[l]	NR	40.85[l]
	154	Valsartan/HCTZ 320/25	-18 ±1.12[l]	-14±0.70[l]	NR	48.70[l]
	168	Aliskiren/Valsartan/HCTZ 300/320/25	-22±1.07[l,p,q]	-16±0.67[l,p,q]	NR	66.67[l,p,r]

Changes in blood pressure are presented as the least-squares mean changes (with ± SEM, whenever provided by the authors).
[a]$P < 0.05$, [b]$P < 0.001$, [c]$P \leq 0.0001$ vs placebo; [d]$P < 0.05$ vs each component monotherapy; [e]$P < 0.0001$ vs HCTZ 25 mg; [f]$P < 0.05$ vs HCTZ 25 mg; [g]$P = 0.0005$ vs HCTZ 25 mg; [h]$P > 0.05$ vs aliskiren/HCTZ 300/25 mg; [i]$P = 0.052$ vs aliskiren/HCTZ 300/25 mg; [j]$P < 0.001$ vs aliskiren 300 mg; [k]$P = 0.002$ vs aliskiren 300 mg; [l]$P < 0.001$ vs HCTZ 25 mg; [m]$P = 0.009$ vs aliskiren/HCTZ 150/25 mg; [n]$P < 0.001$ vs aliskiren/HCTZ 150/25 mg; [o]$P = 0.033$ vs aliskiren/HCTZ 150/25 mg; [p]$P < 0.001$ vs aliskiren/HCTZ 300/25 mg; [q]$P < 0.01$ vs valsartan/HCTZ 320/25 mg; [r]$P < 0.001$ vs valsartan/HCTZ 320/25 mg.
BP – Blood pressure; DBP – Diastolic blood pressure; HCTZ – Hydrochlorothiazide; ITT – Intention-to-treat analysis; NR – Not reported; SBP – Systolic blood pressure.

combinations (amlodipine/HCTZ 10/25 mg, irbesartan/HCTZ 300/25 mg, valsartan/HCTZ 320/25 mg and aliskiren/valsartan/HCTZ 300/320/25 mg) [22, 24]. Only the last combination yielded significantly greater decreases in SBP and DBP and higher BP control rates than the aliskiren/HCTZ 300/25 mg combination [24].

Table **3** presents the weighted mean reductions from baseline of SBP and DBP and BP control rate for each aliskiren/HCTZ combination commercially available. It should be noted that four RCTs were not placebo-controlled and, furthermore, the active comparator (aliskiren or HCTZ) differed in these studies [20, 22-24]. In these circumstances, appraisal of the change from baseline in SBP and DBP achieved by each aliskiren/HCTZ combination allows some appreciation of their antihypertensive efficacy since all data are derived from studies of similar design. Nevertheless, the higher BP reductions reported in the Villamil (2007) trial [21] with aliskiren/HCTZ (a fact also observed with aliskiren and HCTZ monotherapies) must be observed with some caution, as they clearly diverged upward from the results

Table 3. Weighted Average Reductions From Baseline of SBP and DBP and BP Control Rate for Each Aliskiren/HCTZ Combination Commercially Available

Aliskiren/HCTZ Combination Evaluated	Number of Clinical Trials	Total number of Patients	Change in SBP from Baseline at Endpoint (mm Hg)	Change in DBP from Baseline at Endpoint (mm Hg)	BP Control Rate (%)[a]
Aliskiren/HCTZ 150/12.5 mg	1	184	-17.6	-11.9	[37.4, 59. 5][a]
Aliskiren/HCTZ 150/25 mg	2	429	-15.8	-10.3	[43.8, 53. 5][a]
Aliskiren/HCTZ 300/12.5 mg	2	472	-15.9	-11.8	[50.1, 58. 5][a]
Aliskiren/HCTZ 300/25 mg	5	966	-16.9±0.4	-11.6±0.3	[51.9, 55. 9][a]

Changes in blood pressure are presented as the weighted least-squares mean changes ± SEM (not all variability information was provided in the trial of Villamil (2007) [21], preventing the use of an approximation for SEM or confidence intervals estimation for the first three aliskiren/HCTZ dose combinations).
[a]The range presented is due to the trial of Villamil (2007) [21], which presented the range of BP control rate for aliskiren/HCTZ combination, without specify the values for each dose combination.
BP – Blood pressure; DBP – Diastolic blood pressure; HCTZ – Hydrochlorothiazide; SBP – Systolic blood pressure.

obtained by other authors and yielded an unexpected higher effect of the lowest dose of aliskiren/HCTZ commercially available (150/12.5 mg).

Some authors also studied changes from pre-treatment [22] (start of single-blind treatment) or baseline [21, 24] (start of double-blind treatment) in PRA and PRC with aliskiren and HCTZ monotherapy and combination therapy. Aliskiren 75, 150 and 300 mg/day decreased (the geometric) PRA from baseline by 54.2%, 65.1% and 57.6%, respectively [21]. Conversely, HCTZ monotherapy significantly increased PRA at 12.5 and 25 mg/day dosages [21, 22]. When combined, aliskiren/HCTZ significantly reduced PRA from pretreatment (by 45%) [22] and baseline (by 40.5-62.3%) [21, 24], whereas combined treatment with amlodipine/HCTZ, irbesartan/HCTZ and valsartan/HCTZ significantly increased PRA [22, 24]. Aliskiren elevated PRC from baseline in a dose-dependent manner, with increases of 164%, 192% and 348% at dosages of 75, 150 and 300 mg/day, respectively [21]. HCTZ 25 mg/day increased PRC by 108%, whereas lower dosages did not cause alterations in PRC that significantly differed from placebo. All aliskiren/HCTZ combinations significantly increased PRC [21, 24], the magnitude of increases was related to the dosages of both components, with the most marked increase (1211% from baseline) occurring in the aliskiren/HCTZ 300/25 mg group [21]. Furthermore, increases in PRC in several combination groups were considerably greater than the sum of the increases seen with each component [21]. It should be noted that Geiger *et al.* measured the baseline PRA and PRC at the end of the 4-week single-blind HCTZ period [24]. Therefore, the effect of HCTZ on PRA and PRC might have been stabilized with this initial therapy and no further changes after the 8-week additional HCTZ treatment was observed [24].

Each published study also describes the most common adverse events reported in the clinical trials. Aliskiren/HCTZ, as a SPC or as a combination of the individual components concurrently administered, was generally well tolerated in the five clinical trials reviewed. The majority of adverse events were mild and transient in nature, with the most commonly reported events including nasopharyngitis [20-24], headache [20-24], dizziness [22, 23], back pain [23], vertigo [23] and hypercholesterolemia [20]. The proportion of patients experiencing hypokalaemia (defined as serum potassium levels <3.5 mmol/L) were numerically lower with aliskiren/HCTZ than with HCTZ alone [21, 23, 24]. The proportion of patients with hypokalemia was also lower in the aliskiren/HCTZ 300/12.5 mg group (0.4%) and aliskiren 300 mg monotherapy group (0.4%) than in the aliskiren/HCTZ 300/25 mg group (2.5%) [20]. In obese hypertensive patients, hypokalemia occurred in 4.9% patients of the aliskiren/HCTZ group versus 2.5%, 10.3% and 4.1% of patients treated with irbesartan/HCTZ, amlodipine/HCTZ or HCTZ alone, respectively [22].

DISCUSSION

SPCs of aliskiren/HCTZ has recently been introduced in European Union for the second-line treatment of adults with essential hypertension whose BP is not adequately controlled with either drug alone, or as a substitution treatment in patients with hypertension adequately treated by the two individual drugs concomitantly at the equivalent fixed dosage. To our knowledge, this study represents the first published meta-analytical approach to the efficacy of aliskiren/HCTZ in reducing BP in patients with mild to moderate hypertension. Although other reviews dealing with the same topic are available in the literature, no study has provided a synthesis of data from clinical trials.

The five studies included in this systematic review are short-term (8-12 weeks) randomized, double-blind, clinical trials with a similar design and comparable primary endpoints and secondary efficacy measures. All studies compared the change in SBP and DBP from baseline (start of double-blind treatment) to week 8 endpoint in each aliskiren/HCTZ combination group with that in placebo and/or aliskiren monotherapy and/or HCTZ monotherapy group. Patient demographics and baseline characteristics were also similar across treatment groups in all included studies, except that one study included obese patients only [22]. The average quality of the articles was considered to be very good.

In this study we chose to present the results by way of weighted average sums of BP reductions over 8 weeks, a period consistent with current clinical recommendations for

assessing the clinical efficacy and tolerability of antihypertensive drugs following their initiation [1, 4]. The weighted means method, which has been used in other meta-analyses [25-27], takes into account the different sizes of trials and provides results that are easy to interpret clinically.

In all clinical trials selected for analysis, commercially available aliskiren/HCTZ combinations (150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg) provided clinically significant additional SBP and DBP reductions and improved BP control rates over aliskiren or HCTZ monotherapy, which demonstrates that aliskiren/HCTZ SPCs are a effective treatment option for patients with mild to moderate hypertension who do not achieve BP control with aliskiren 300 mg or HCTZ 25 mg alone. A meta-analysis of 354 randomized clinical trials involving more than 40,000 treated patients with hypertension revealed that the additional reduction in BP achieved with antihypertensive combination therapy versus monotherapy provide a reduced risk of stroke and ischemic heart events [28]. In another meta-analysis, examining individual data from one million adults in 61 prospective studies, it was found that, at ages 40-69 years, each increase of 20 mm Hg usual SBP (or, approximately equivalently, 10 mm Hg usual DBP) is associated with more than a twofold difference in the stroke death rate, and with twofold differences in the death rates from ischaemic heart disease and from other vascular causes [29]. Thus, the additional mean BP reductions of up to 8.0/4.8 mmHg (versus HCTZ 25 mg) or 6.0/3.1 mmHg (versus aliskiren 300 mg) provided by aliskiren/HCTZ 300/25 mg in the present analysis might be expected to reduce the risk of cardiovascular mortality. However, long-term and large-scale studies analysing the effects of aliskiren/HCTZ combination therapy on clinical outcomes are required to confirm this hypothesis.

The capacity of aliskiren to enhance the antihypertensive efficacy of HCTZ reflects its complementary mode of action, targeting the RAS at its point of activation and thus suppressing PRA. HCTZ monotherapy increased PRA, as a result of stimulated renin release in response to reduced intravascular volume. The addition of aliskiren counteracted this effect, resulting in a significant ($p < 0.05$) overall decrease in PRA compared with HCTZ monotherapy [21, 22, 24]. Furthermore, aliskiren effectively inhibited the renin enzyme, despite marked elevation in PRC, to produce an overall reduction in PRA from baseline. This contrasts to agents that block the RAS at other points, such as ACEIs and ARBs, which induce increases in PRA in parallel with PRC [22, 24, 30].

Aliskiren/HCTZ was generally well tolerated in the clinical trials reviewed and not associated with a notably higher incidence of adverse events than treatment with either component alone. These results are consistent with a long-term open-label study in 1955 hypertensive patients showing that aliskiren/HCTZ free combinations were well tolerated over up to 12 months of treatment [16, 19]. In three included trials, when aliskiren and HCTZ were administered in combination, aliskiren opposed the adverse hypokalaemic effects of HCTZ [21, 23, 24]. The safety profile of an aliskiren/valsartan/HCTZ combination was also investigated in one clinical trial and was similar to the 2-drug combinations (aliskiren/HCTZ or valsartan/HCTZ), with a greater BP-lowering effect in patients not adequately responding to HCTZ monotherapy [24].

Most patients with hypertension will require combination treatment with two or more antihypertensive medications in order to achieve BP control to recommended levels [1, 4]. A meta-analysis of adherence studies showed that the use of SPC regimens reduced the rate of non-compliance by 24–26% compared with respective free combinations [31]. Aliskiren/HCTZ SPCs therefore offers the convenience of a single-tablet once daily treatment regimen, which may improve treatment compliance and subsequent BP control.

The limitations of this study should be noted. The intervention effect size as reported above (Tables **2** and **3**) could be an overestimate due to publication bias since the manufacturer (Novartis Pharmaceuticals Corporation) sponsored four [20, 22-24] of the included published studies and one author of the remaining study [21] is employee of Novartis Pharmaceuticals Corporation. It is possible that less optimistic studies have not been published and therefore not included in our analysis. In addition, because the BP lowering efficacy estimate is limited to 8 weeks, we cannot extrapolate our results to the longer term benefits of the treatments on cardiovascular morbidity and mortality. However, in this regard, the 2007 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines are pertinent, which state that the size of BP reduction is more important than the class used for cardiovascular event reduction [4]. One other limitation is based on the fact that there is only one clinical trial investigating the antihypertensive efficacy of the lowest dose of aliskiren/HCTZ commercially available (150/12.5 mg), which, additionally, lacks information on outcome variability (SEM or CI) [21]. This fact was responsible for an unexpected higher efficacy of aliskiren/HCTZ 150/12.5 mg in reducing SBP and DBP, when compared with higher combination dosages (Table **3**). Further studies are required to accurately evaluate the dose-related antihypertensive efficacy of the commercially available aliskiren/HCTZ combinations.

In conclusion, aliskiren/HCTZ combinations commercially available were effective and generally well tolerated in clinical trials evaluating its antihypertensive effects in adults with mild to moderate hypertension and in hypertensive patients with obesity, providing clinically significant additional BP reductions and improved BP control rates in patients who are inadequately controlled with aliskiren or HCTZ monotherapy. The aliskiren/HCTZ SPCs present the convenience of a once-daily single-tablet treatment regimen, which may improve treatment adherence and subsequent BP control. Further studies are required to evaluate the relative benefits of the aliskiren/HCTZ SPCs with generically available alternatives. Also, long-term trials evaluating the efficacy and tolerability of this combination therapy would be of interest to establish the ultimate effects of treatment on the cardiovascular morbidity and mortality of hypertension.

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APPENDIX

Main Patient Baseline and Demographic Characteristics by Treatment Group of the Included Clinical Trials (Randomized Population)

Reference	Pts., n	Treatment and Daily Dose (mg)	Patient Age (years)	Sex Ratio (M/F)	BMI (kg/m^2)	Obese (BMI ≥ 30 kg/m^2) (%)	SBP Baseline (mm Hg)	DBP Baseline (mm Hg)
Villamil (2007) [21]	195	Placebo	54.4	109/86	NR	40.5	152.7	99.3
	184	Aliskiren 75	55.0	103/81	NR	41.8	153.2	99.4
	185	Aliskiren 150	53.5	112/73	NR	32.4	153.4	98.8
	183	Aliskiren 300	54.2	99/84	NR	38.8	154.4	99.3
	194	HCTZ 6.25	55.2	109/85	NR	41.2	153.4	99.3
	188	HCTZ 12.5	55.4	103/85	NR	38.8	153.4	99.1
	176	HCTZ 25	55.1	92/84	NR	32.4	154.5	99.1
	188	Aliskiren/HCTZ 75/6.25	55.1	108/80	NR	37.8	154.5	98.9
	193	Aliskiren/HCTZ 75/12.5	54.4	101/92	NR	39.9	154.0	100.0
	186	Aliskiren/HCTZ 75/25	54.7	101/85	NR	38.7	152.9	99.0
	176	Aliskiren/HCTZ 150/6.25	53.9	96/80	NR	37.5	153.3	99.0
	186	Aliskiren/HCTZ 150/12.5	54.7	98/88	NR	35.5	154.1	99.1
	188	Aliskiren/HCTZ 150/25	53.7	104/84	NR	37.8	153.2	98.4
	181	Aliskiren/HCTZ 300/12.5	55.5	89/92	NR	42.0	153.2	99.5
	173	Aliskiren/HCTZ 300/25	54.8	98/75	NR	41.0	154.6	99.3
Jordan (2007) [22]	122	HCTZ 25	55.2±12.3	52/70	34.0±4.1	NR	149.5±11.3	97.2±4.6
	122	Aliskiren/HCTZ 300/25	53.1±11.9	60/62	34.8±5.2	NR	149.4±11.6	96.8±4.9
	119	Irbesartan/HCTZ 300/25	53.0±11.0	48/71	34.3±4.7	NR	149.1±13.4	96.6±4.4
	126	Amlodipine/HCTZ 10/25	55.2±11.9	53/73	34.5±4.1	NR	149.8±11.5	96.7±5.0
Nickenig (2008) [20]	298	Aliskiren 300	55.5±10.6	159/139	29.2±4.5	NR	149.8±12.6	95.5±4.4
	293	Aliskiren/HCTZ 300/12.5	54.9±10.5	155/138	29.2±4.9	NR	150.3±12.5	95.5±4.3
	289	Aliskiren/HCTZ 300/25	54.4±10.3	172/117	28.9±4.6	NR	150.8±12.8	95.8±4.7
Blumen-stein (2009) [23]	246	HCTZ 25 mg	52.9±11.5	143/103	29.7±5.0	NR	151.8±11.9	96.3±4.9
	244	Aliskiren/HCTZ 150/25	53.6±11.1	144/100	28.9±4.7	NR	151.2±12.7	96.1±4.9
	232	Aliskiren/HCTZ 300/25	54.1±9.5	140/92	29.9±5.0	NR	151.1±12.3	96.1±4.6
Geiger (2009) [24]	152	HCTZ 25	52.6±9.93	94/58	31.8±6.13	NR	154.1±12.61	99.9±4.33
	166	Aliskiren/HCTZ 300/25	52.3±10.90	92/74	31.3±6.28	NR	153.3±12.68	99.3±4.10
	155	Valsartan/HCTZ 320/25	55.0±11.40	88/67	31.3±5.85	NR	156.7±12.49	99.9±3.97
	168	Aliskiren/Valsartan/HCTZ 300/320/25	52.9±10.83	91/77	31.9±6.21	NR	152.7±11.64	99.2±3.70

Values are mean ±SD unless otherwise stated.
BMI – Body mass index; DBP – Diastolic blood pressure; F - Female; HCTZ – Hydrochlorothiazide; M – Male; NR – Not reported; Pts – Patients; SBP – Systolic blood pressure.

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5.4 Artigo IV

“Predictors of uncontrolled hypertension and antihypertensive medication nonadherence”

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Predictors of uncontrolled hypertension and antihypertensive medication nonadherence

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ABSTRACT

Background: Although hypertension is, in most cases, a controllable major risk factor in the development of cardiovascular disease, studies have demonstrated that hypertension remains poorly controlled in Portugal. Our aim was to evaluate the covariates associated with poor blood pressure (BP) control in a Portuguese hypertensive population. **Patients and Results:** We conducted a cross-sectional survey in a hospital hypertension outpatient clinic, located in the Eastern Central Region of Portugal. Patients attending the clinic from July to September 2009 were asked to participate in a structured interview including medication adherence and knowledge about hypertension. Eligible participants were all adults aged 18 or over with an established diagnosis of arterial hypertension and had been on antihypertensive drug treatment for at least 6 months. Exclusion criteria were dementia, pregnancy, and breastfeeding. Detailed clinical information was prospectively obtained from medical records. A total of 197 patients meeting the inclusion criteria and consenting to participate completed the interview. Of these, only 33.0% had their BP controlled according to the JNC 7 guidelines. Logistic regression analysis revealed three independent predictors of poor BP control: living alone (OR = 5.3, $P = 0.004$), medication nonadherence (OR = 4.8, $P < 0.001$), and diabetes (OR = 4.4, $P = 0.011$). Predictors of medication nonadherence were: unawareness of target BP values (OR = 3.7, $P < 0.001$), a report of drug side effects (OR = 3.7, $P = 0.002$), lack of BP monitoring (OR = 2.5, $P = 0.015$) and unawareness of medication indications (OR = 2.4, $P = 0.021$), and of hypertension risks (OR = 2.1, $P = 0.026$). **Conclusions:** Poor medication adherence, lack of information about hypertension, and side effects should be considered as possible underlying causes of uncontrolled BP and must be addressed in any intervention aimed to improve BP control.

Key words: Antihypertensives, blood pressure control, hypertension, medication adherence, Portugal

INTRODUCTION

Hypertension is a major risk factor in the development of cardiovascular disease and one of the most important public health problems in Portugal affecting over 3 million Portuguese adults (about 30% of the Portuguese population).[1] In well-conducted clinical trials, numerous drugs and combination therapies have demonstrated their ability to reduce blood pressure (BP), with rates of BP control ranging from 45% to 66%.[2, 3] However, in the clinical practice, control rates of high BP are expected to be lower than those observed in the high motivated, closely controlled, and monitored patient population of the clinical trials. In a recently published survey,[1] only 28.9% Portuguese treated hypertensives had their BP controlled (<140/90 mmHg). This figure is even lower in the Central

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Region of Portugal, where only 26.1% of the total number of treated hypertensives have their BP controlled.[1] One of the major drawbacks of this Portuguese survey relies on the definition of controlled hypertension, which was considered as the mean systolic BP <140 mmHg and diastolic BP of <90 mmHg. This definition does not take into account the seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), according to which for hypertensive patients who also have diabetes or chronic kidney disease (CKD) target levels of BP are even lower (<130/80 mmHg).

The Eastern Central Region of Portugal possesses a university teaching hospital at Covilhã, named Cova da Beira Hospital Centre, with an important secondary care hypertension/dyslipidemia outpatient clinic, which serves a significant hypertensive population of the District of Castelo Branco. To better understand the unsatisfactory levels of BP control of this hypertensive population and focus efforts on improving them, it would be useful to know the extent to which hypertensive patients with different risks for vascular complications are not satisfactorily controlled and to identify some possible factors that may be involved in inadequate BP control. Accordingly, we conducted a cross-sectional study to evaluate the level of BP control in hypertensive patients attending the mentioned hospital hypertension/dyslipidemia outpatient clinic and to recognize some factors that may underlie insufficient BP control and poor medication adherence.

PATIENTS AND METHODS

Settings and study design

In July–September 2009, we conducted a cross-sectional survey in a secondary care hypertension/dyslipidemia clinic in the university teaching hospital of Cova da Beira Hospital Centre, Covilhã, District of Castelo Branco, located in the Eastern Central Region of Portugal. This outpatient clinic is one of the most important clinics of this region in Portugal in the field of hypertension/dyslipidemia and serves a significant hypertensive population of Covilhã Area, with a population of 35 thousand inhabitants.

Study population

All hypertensive patients attending the medical clinic during that period were asked to complete the structured interview. Patients were asked to complete a structured questionnaire on demography, medication adherence, and knowledge about target BP values, hypertension risks, indications of antihypertensive medication, and the presence of drug side effects. Subjects were also asked whether they used a home BP monitoring device and/or whether they measure their BP regularly. The study was approved by the Institutional Ethics Committee for the use of humans in research, and written informed consent was obtained from all participants before their enrolment in the study.

Eligible participants were all adults aged 18 or over with an established medical diagnosis of arterial hypertension (BP measurements in the clinic of systolic BP (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥90 mm Hg). Furthermore, all included patients had been on established antihypertensive drug treatment for at least 6 months. Exclusion criteria were dementia, pregnancy, and breastfeeding.

Blood Pressure measurements

BP was measured in a seated position after a 5-min rest period, using a mercury sphygmomanometer or semi-automatic device, the mean of two consecutive measurements being recorded. According to the JNC 7 guidelines, hypertensive patients without diabetes and CKD with BP <140/90 mmHg were considered to have their BP controlled. For hypertensive patients with diabetes or CKD, BP control was defined as BP measurements <130/80 mmHg.

Medication adherence, hypertension knowledge, and management evaluation

Assessment of antihypertensive medication adherence was determined using the instrument validated by Morisky *et al.*[4, 5] Poor medication adherence was defined as answering yes to three or more of five questions. We also evaluated patient knowledge of target BP values and of the potential impact of hypertension on the morbidity and mortality associated with stroke, cardiac disease, and kidney disease. Patients were considered knowledgeable of target BP values if they knew both target BP figures (<140/90 mmHg for hypertensive patients without diabetes and CKD and <130/<80 mmHg for hypertensive patients with diabetes or CKD). They were considered knowledgeable of the negative impacts of hypertension to health if they mentioned at least two potential major negative consequences of uncontrolled hypertension. It was considered that BP was measured regularly if values were recorded at least once a month.

110

Clinical parameters

Clinical data for this study, including BP measures, medications prescribed, and medical problems, were prospectively obtained from the Hospital Electronic Medical Records (HEMR) database. The HEMR database of Cova da Beira Hospital Centre is comprised of detailed patient-level clinical and administrative information of all patients that have used this hospital at least once. Available information includes patient demographics, medical problems, various measures of physiological status, and medications prescribed. This database is authorized by the Portugal Department of Health, the government department responsible for public health issues, and patient data confidentiality was ensured.

Statistical analysis

Demographic variables, clinical data, and BP values of hypertensive patients included in the study, as well as prescribing metrics were examined on a descriptive basis and expressed as the mean ± SD, frequency, and percentages. To test for differences between categorical variables χ^2-test were used. Multivariate analyses were conducted using logistic regressions with the forward likelihood ratio (Forward:LR) selection algorithm. All statistical analyses were carried out using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL), and a *P*-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

A total of 222 patients attended the medical clinic during the recruitment period (from July 2009 to September 2009), and all were assessed for eligibility. Of these, 17 were excluded from the study because they did not meet the inclusion criteria, 1 was excluded because of breastfeeding, and 7 were excluded because they declined to participate (they did not sign the informed consent). Thus, a total of 197 (89%) hypertensive patients met the inclusion criteria and consented to participate [Figure 1].

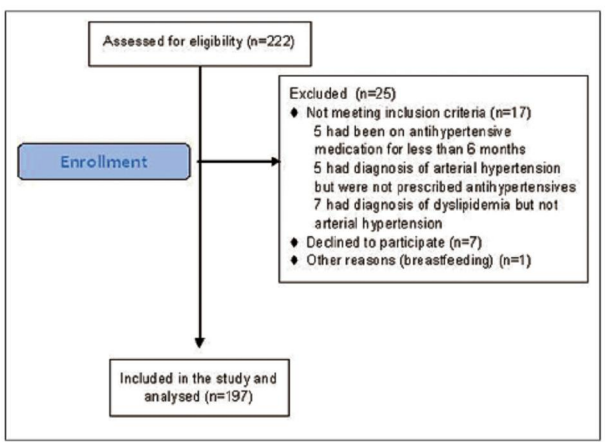

Figure 1: Diagram of patient enrollment.

The overall mean age of the included patients was 60 ± 12 years, 40.1% being male and 59.9% female [Table 1]. Among these patients, 153 (77.7%) had neither diabetes nor CKD and were considered to have a target BP of <140/90 mmHg, whereas the remaining 44 (22.3%) had either diabetes and/or CKD and were considered to be controlled with a BP of <130/80 mmHg. Most patients were long-term hypertensives, with 74.1% (146/197) of patients taking antihypertensive medications for at least 5 years. Only four patients have been prescribed hypertensive medication for the first time in the preceding 12 months. Overall, only 48.2% of patients were considered to be highly adherent to antihypertensive medication. Other demographic and clinical characteristics, as well as results obtained in the structured interview are represented in Table 1. All variables listed in Table 1 were covariates in the analyses.

Overall, the mean systolic BP of the 197 hypertensive patients included in our analysis was 141.8 ± 16.5 mmHg, and the mean diastolic BP was 85.8 ± 11.80 mmHg, with 33.0% (65/197) patients attaining controlled BP according to JNC 7 guidelines. Among patients with neither diabetes nor CKD, 39.2% had their BP controlled, whereas among patients with one or both of these pathologies this figure was 11.4% ($P = 0.009$). In all, 37.1% (73/197) patients attained BP values <140/90 mmHg.

Forward:LR logistic regression revealed that the covariates medication adherence (OR, 4.8; 95% CI, 2.4–9.5; $P < 0.001$), marital status (OR, 5.3; 95% CI, 1.7–16.4; $P < 0.004$), and diabetes (OR, 4.4; 95% CI, 1.4–13.5; $P < 0.011$) were the independent variables that significantly influenced BP control. Using the logistic regression coefficients (ln(OR)) for those covariates, the following significant logistic regression model (G^2 (3) = 46.054; $P < 0.001$; X^2_{HL} (4) = 4.152; $P = 0.386$; $R^2_{CS} = 0.208$; $R^2_N = 0.290$; $R^2_{MF} = 0.184$, where G^2 is the likelihood-ratio goodness-of-fit statistic, X^2_{HL} is the Hosmer and Lemeshow statistic, R^2_{CS} is the Cox and Snell *R* square, R^2_N is the Nagelkerke *R* square, and R^2_{MF} is the McFadden *R* square) was obtained:

$$Pb = \frac{e(-0.436+1.562ADH+1.670MS+1.472DIAB)}{1+e(-0.436+1.56ADH+1.670MS+1.472DIAB)}$$

Table 1: Patients demographics and clinical characteristics and data collected in the structured interview (n = 197)

Demographic/clinical characteristics	Values
Gender, n (%)	
Male	79 (40.1)
Female	118 (59.9)
Age, mean (SD)	59.5 (11.7)
Body mass index (kg/m2), mean (SD)	29.4 (4.8)
Married, n (%)	160 (81.2)
Education, n (%)	
Illiterate	10 (5.1)
Elementary schooling	156 (79.2)
High schooling	20 (10.2)
University education	11 (5.6)
Current smoker, n (%)	17 (8.6)
Comorbid conditions, n (%)	
Cerebrovascular disease	26 (13.2)
Chronic kidney disease	11 (5.6)
Diabetes	36 (18.3)
Heart failure	1 (0.5)
Ischemic heart disease	5 (2.5)
Myocardial infarction	3 (1.5)
Left ventricular hypertrophy	5 (2.5)
Dyslipidemia	148 (75.1)
Metabolic syndrome	4 (2.0)
Obesity (body mass index ≥ 30 kg/m2)	81 (41.1)
Number of years in antihypertensive drug treatment, mean (SD)	9.8 (7.7)
Low self-reported medication adherence, score ≥ 3, n (%)	102 (51.8)
Knowledge of target BP values, n (%)	117 (59.4)
Knowledge of hypertension risks, n (%)	108 (54.8)
Knowledge of drug indications, n (%)	139 (70.6)
Regular monitoring of BP, n (%)	139 (70.6)
Reported side effects, n (%)	45 (22.8)

Abbreviations: BP, Blood pressure; SD, standard deviation.

(1) where Pb is the probability of a given patient to have uncontrolled BP, ADH is medication adherence (0, adherent; 1, nonadherent), MS is marital status (0, married; 1, single, widowed, divorced, or separated), and DIAB is diabetes (0, without diabetes; 1, with diabetes).

This model has acceptable sensitivity (77.3%) and specificity (63.1%), as well as an acceptable discrimination power (area under ROC curve = 0.764; $P < 0.001$).

Of the three covariates figuring in Eq. (1), medication adherence is the independent variable more likely to be favorably influenced by a health care professional team in order to enhance BP control. Thus, we determined the covariates that significantly influence the dependent variable medication adherence. Forward:LR logistic regression revealed that knowledge of target BP (OR, 3.7; 95% CI, 1.9–7.4; $P < 0.001$), reporting of drug side effects (OR, 3.7; 95% CI, 1.6–8.3; $P < 0.002$), measuring BP regularly (OR, 2.5; 95% CI, 1.2–5.2; $P < 0.015$), knowledge of drug indications (OR, 2.4; 95% CI, 1.1–5.2; $P < 0.021$), and knowledge of hypertension risks (OR, 2.1; 95% CI, 1.1–4.2; $P < 0.026$) were the independent variables that significantly influences medication adherence. Using the logistic regression coefficients (ln(OR)) for those covariates, the following significant logistic regression model (G^2 (5) = 54.446; $P < 0.001$; X^2_{HL} (7) = 2.448; $P = 0.931$; R^2_{CS} = 0.241; $R^2_N = 0.322$; $R^2_{MF} = 0.200$) was obtained:

$$Pb=\frac{e(-1.546+1.307TBP+1.296SE+0.906BPR+0.89DI+0.759HTR)}{1+e(-1.546+1.307TBP+1.296SE+0.906BPR+0.89DI+0.759HTR)}$$

(2) where Pb is the probability of a given patient to be nonadherent to medication, TBP, knows target BP (0, yes; 1, no); SE, reports side effects (0, no; 1, yes); BPR, measures BP regularly (0, yes; 1, no); DI, knows drug indications (0, yes; 1, no); and HTR, knows hypertension risks (0, yes; 1, no).

This model also revealed to have acceptable sensitivity (71.6%) and specificity (72.6%), as well as an acceptable discrimination power (area under ROC curve = 0.788; $P < 0.001$).

All independent variables figuring in Eq. (2) are amenable to improvement by team-based health care professionals'

112

interventions in order to increase medication adherence and, thereby, BP control.

DISCUSSION

The results presented in this study describe some demographic and clinical characteristics of hypertensive patients attending the medical consultation of hypertension/dyslipidemia in a university teaching hospital located in the Eastern Central Region of Portugal, focusing on the level of hypertension control and antihypertensive medication adherence. According to a survey conducted in 2003,[1] of the total number of hypertensives in the Central Region of Portugal prescribed with antihypertensives, only 26.1% had their BP measurements <140/90 mmHg, which is significantly smaller than the 37.1% obtained in our study. This difference possibly points to an improved current care of the hypertensives included in our study when compared to those included in the abovementioned survey. Increased awareness of hypertension and the importance of lower BP may have prompted Portuguese providers and patients to treat high BP more aggressively, especially after the publication of the JNC 7 report in 2003. The issuing, in 03/31/2004, of the legal document "Guidelines to detect, treat and control arterial hypertension",[6] by the Department of Health of the Portuguese Government, definitely contributed to an evidence-based approach to the prevention, detection, evaluation, and treatment of high BP. These guidelines have many similarities with the JNC 7 report and were subsequently updated, in 2006, by the Portuguese Society of Hypertension.[7] Till now, there was no prospective data about the percentage of treated hypertensives in clinical practice, in this Portuguese region, with their BP controlled according to the JNC 7 guidelines. Our study revealed that 33.0% of hypertensive patients had their BP controlled according to those guidelines, and that there was a significantly greater BP control ($P = 0.009$) in patients without diabetes or CKD (39.2%) when compared to patients with diabetes and/or CKD (11.4%). To the best of our knowledge, this prospective study presents for the first time the percentage of treated and controlled hypertensives, according to the JNC 7 guidelines, in a Portuguese subpopulation. It should be noted that the reported levels of BP control can vary greatly depending on the study population, methods, and time frame.[8, 9] In one study, on the basis of data from the US National Health and Nutrition Examination Survey 2003–2004, the BP control rate (to <140/90 mmHg) was 56.6% in treated hypertensives, and 37.5% in treated hypertensive persons with diabetes mellitus (for whom the goal BP is <130/80 mmHg).[10] In a regional survey performed in the middle-West of France and involving 1050 treated hypertensives, Ragot *et al.*, reported that 39% of patients had BP figures <140/90 mmHg and only 13% of the diabetic population were normalized according to the international recommendations (<130/80 mmHg).[11] In a more recent retrospective observational study conducted in the United States, Jackson *et al.*[9] reported a BP control of 49.3% in an after-JNC 7 cohort. In this cohort, a significantly higher percentage of nondiabetic patients achieved BP control compared with those with comorbid diabetes (60.9% vs. 29.4%). Similarly, Andros *et al.*[12] conducted a retrospective observational study of BP control in an insured diabetic population, obtaining a BP control rate (defined by JNC 7) of 28%, similar to the 29.4% obtained by Jackson *et al.*[9] The results obtained in our study are similar to those reported by Ragot *et al.*, in a middle-West French treated hypertensive population, for both patients without diabetes and CKD and patients with these pathologies.

The logistic regression analyses of the study population revealed that the covariates medication adherence, marital status and diabetes significantly influence BP control, such that the probability of a nonadherent, unwed, diabetic patient to have uncontrolled hypertension is 98.6%. At the other end, the probability of an adherent, married, nondiabetic patient to have uncontrolled hypertension is only 39.3%. Surely, there are more unstudied independent variables that significantly influence BP control (e.g., prescribed antihypertensive medication). For example, the possible existence of clinical inertia and undertreatment must be analyzed in patients with diabetes or CKD. However, sensitivity, specificity, and ROC curve analysis revealed an acceptable model performance.

Of the three covariates significantly influencing BP control, the variable most likely to be favorably influenced by team-based health care professionals' interventions is medication adherence. In patients with hypertension, medication nonadherence is a significant, often unrecognized, risk factor that contributes to poor BP control, thereby contributing to the development of further vascular disorders such as heart failure, coronary heart disease, renal insufficiency, and stroke.[13] Antihypertensive medication adherence rates have differed widely depending on the population studied, and it is estimated to range between 50% and 70% in patients with treated hypertension.[14-16] Therefore, the percentage of antihypertensive medication adherence found in our study is largely within the range reported in the literature.[17, 18] The importance of improving adherence to antihypertensive medication has been addressed by JNC

7, and emphasis has been put on the role of all health care professionals, including pharmacists, to improve adherence to the treatment.[19]

Logistic regression revealed that knowledge of target BP values, the presence of drug side effects, measuring BP regularly, knowledge of drug indications, and knowledge of hypertension risks are the independent variables that significantly influence medication adherence. According to our logistic regression model (Eq. (2)), the probability of a hypertensive patient ignoring target BP values, drug indications and hypertension risks, reporting drug side effects and not monitoring BP regularly to be nonadherent is 97.4%. On the contrary, the probability of a hypertensive patient knowing the target BP values, drug indications and hypertension risks, not presenting drug side effects and monitoring BP regularly to be nonadherent is only 17.6%.

Although a significant percentage (70.6%) of patients reported to measure BP regularly, only ($P = 0.020$) 59.4% were aware of their target BP figures (systolic and diastolic). Self and/or regular BP measurement is useful for the assessment of the treatment effects by the doctor and is valuable for the patients in improving the management of their high BP. However, as many patients (40.6%) do not know their target BP values they cannot accurately report whether it is controlled. Therefore, a major implication of our study is the need for education of patients to their target BP figures so that they can correctly identify whether it is elevated or controlled. Likewise, our findings also suggest the need to improve patient awareness of the cardiovascular risks of hypertension and of the therapeutic indications and usefulness of antihypertensives. It is worth noting that even though these patients have had hypertension for a long period (average number of years in antihypertensive drug treatment was 9.8 ± 7.7 years), their knowledge is inadequate. Recent research points to the need to improve hypertension knowledge and awareness in order to increase medication adherence and BP control.[20, 21] Continuing attention should be given to side effects of antihypertensives, because they are one of the most important causes of nonadherence.[22] Adverse events during antihypertensive treatment are not entirely avoidable because they are partly psychological and are also reported during administration of placebo.[22] However, great effort should be dedicated to limitation of drug-related side effects and preservation of the quality of life either by switching treatment from the responsible drug to another agent or by avoiding unnecessary increases of the dose by using combination therapy.[23] Discussion of patients' side effects and concerns must also be encouraged.

Several features of our study deserve further comment. To our knowledge, this is the first Portuguese study examining barriers to BP control in treated hypertensive outpatients in the Eastern Central Region of Portugal. The study may be relevant to similar Caucasian populations in Portugal and other European countries. Other strengths were the high response rate and the 96.6% completion of questionnaires. The limitations are the size of the study, and the evaluation of BP control based on the measurements performed in one single medical appointment. These BP measurements may or may not be representative of the adequacy of BP control in hypertensive patients. We also were unable to obtain objective measurements of patient compliance (e.g., drug level in biologic fluids, biologic markers, and direct patient observation) or to assess the attitudes of the physicians and nurses toward patients. Behavioral models suggest that the most effective therapy prescribed by the most careful physician will control hypertension only if the patient is motivated to take the medication as directed.[19] Motivation improves when patients have positive experiences with, and trust in, their health care professional team.[19] Moreover, a limited number of covariates were analyzed. Undertreatment and clinical inertia are reported causes of uncontrolled BP[24, 25] that were not evaluated in this cross-sectional study. Further, for some subgroup analyses, there were small cell sizes and the analyses must be considered exploratory in nature.

In conclusion, this study provides a framework for identifying hypertensive patients who are at high risk of poor BP control and since many of the identified factors are modifiable, they signal opportunities to improve BP control in clinical practice. Poor medication adherence and patient unawareness about target BP values, hypertension risks and antihypertensive drug indications, as well as the presence of drug side effects and lack of regular BP monitoring should be considered as possible underlying causes of inadequately controlled BP and must be addressed in any intervention aimed to improve BP control. Strategies to improve medication adherence must be reinforced. Self-monitoring with validated BP devices should be encouraged. Patients with poor knowledge of the goal of their hypertension therapy should be informed about their target BP, to enable them to participate more fully in their own management. To achieve the crucial objective of improving health by controlling high BP, it is important to fully understand the current status of patient knowledge, awareness, and attitudes with respect to hypertension, medication, and lifestyles. It is necessary to understand these patient factors to develop effective strategies and team-based health care professionals' interventions that enroll the patient as a participant in the management of his hypertension.

114

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5.5 Artigo V

"Association of statin therapy with blood pressure control in hypertensive hypercholesterolemic outpatients in clinical practice"

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ABSTRACT

Background: Some clinical evidence revealed that statins, apart from lowering cholesterol levels, also have an antihypertensive effect. Our aim was to evaluate the existence of a possible association of statin therapy with blood pressure (BP) control in clinical practice. **Materials and Methods:** Patients attending a hypertension/dyslipidemia clinic were prospectively evaluated. Those patients with a diagnosis of stage 1 hypertension and hypercholesterolemia who consented to participate were included in the study, either in the statin group (when taking a statin) or in the control group (when not taking a statin). Exclusion criteria included dementia, pregnancy, or breastfeeding, and history or evidence of stage 2 hypertension. Detailed clinical information was prospectively obtained from medical records. A total of 110 hypertensive patients were assigned to the study (82 in the statin group and 28 in the control group). **Results:** Although there were no significant differences ($P > 0.05$) in both groups concerning gender, body mass index, antihypertensive pharmacotherapy, and serum levels of high-density lipoprotein cholesterol and triglycerides, a higher BP control was observed in the statin group ($P = 0.002$). Significantly lower systolic BP (−6.7 mmHg, $P = 0.020$) and diastolic BP (−6.4 mmHg, $P = 0.002$) levels were reported in the statin group. Serum levels of low-density lipoprotein were also significantly lower in the statin group ($P < 0.001$). **Conclusions:** This observational study detected an association of statin therapy with BP control in hypertensive hypercholesterolemic patients in clinical practice. These findings raise the possibility that statin therapy may be useful for BP control in the studied population.

Key words: Antihypertensives, blood pressure, hypercholesterolemia, hypertension, Portugal, statins

INTRODUCTION

Hypertension is a major risk factor in the development of cardiovascular disease, with myocardial infarction and stroke being one of the most important health problems worldwide causing excess morbidity and mortality. The risk of cardiovascular morbidity and mortality is particularly marked when there is insufficient hypertension control and prevention at the community level. Randomized controlled trials (RCTs) have demonstrated that treating high blood pressure (BP) with medication can substantially reduce the risk of stroke by 35–40%, myocardial infarction by 20–25%, and heart failure by more than 50%.[1,2] Hypertension is often associated with other cardiovascular risk factors, including hypercholesterolemia that are present in over 40% of the hypertensive patients.[3] The concomitant presence of both hypertension and hypercholesterolemia in the same patient is associated with a higher rate of cardiovascular events that surpasses the separate contribution of each separate risk factor.[4] The prescription of both antihypertensive and cholesterol-lowering drugs is generally required in these patients.

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Inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (statins) are the most effective and widely used cholesterol-lowering agents in industrialized countries.[5] They significantly reduce the risk of cardiovascular events, particularly in patients showing a combination of high BP and hypercholesterolemia.[6] Although the long-term benefit of statin therapy is largely attributed to their cholesterol-lowering action, additional actions of these drugs, which are independent from 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibition, are thought to be involved in the cardiovascular protection observed shortly after the initiation of treatment.[7] Several RCTs have investigated the antihypertensive effect of statins in patients with hypertension associated with hypercholesterolemia.[8-10] An effect of statins on BP is potentially important and not improbable considering its reported effects on endothelial function, their interaction with the renin–angiotensin system, and their ability to affect large artery compliance.[9,11] However, most significant effects of statins on BP control were reported in controlled clinical trials,[8-10] which involve a highly motivated, closely controlled, and monitored patient population, where any supposed antihypertensive effects of statins would have a greater chance to be detected, when compared to the general population.

The objectives of our study were to prospectively investigate, in the setting of clinical practice, the potential association of self-administered statins with BP control in stage 1 hypertensive outpatients with hypercholesterolemia. We, thus, aimed to evaluate the existence of a possible relationship between statin therapy and BP control and BP levels in hypercholesterolemic hypertensive patients attending a hospital outpatient clinic (ambulatory setting) for routine follow-up.

MATERIALS AND METHODS

Settings

This study was conducted in a secondary care hypertension/dyslipidemia clinic in the university teaching hospital of Cova da Beira Hospital Centre, Covilhã, District of Castelo Branco, located in the Eastern Central Region of Portugal. This outpatient clinic is one of the most important clinics of this region of Portugal in the field of hypertension/dyslipidemia and serves a significant hypertensive population of Covilhã, with a population of 35,000 inhabitants.

Study design

From July 2009 to September 2009, we conducted a cross-sectional study of patients attending the hypertension/dyslipidemia medical clinic. All outpatients attending the medical clinic during that period were asked to give their signed informed consent to be enrolled in the study. The study was approved by the institutional ethics committee for the use of humans in research, and written informed consent was obtained from all participants before their enrollment in the study.

Clinical data for this study, including BP measures, lipid profile, medications prescribed, and medical problems, were prospectively obtained from the Hospital Electronic Medical Records (HEMR) database. The HEMR database of Cova da Beira Hospital Centre comprises detailed patient-level clinical and administrative information of all patients who utilized, at least once, this hospital's services. Available information includes patient demographics, medical problems, various measures of physiological status, and medications prescribed. This database is authorized by the Portugal Department of Health, the government department responsible for public health issues, and patient data confidentiality was ensured. This database was accessed at clinic attendance of patients.

Study population

Eligible participants were all adults (aged ≥18 years) with an established medical diagnosis of stage 1 hypertension (BP measurements, in the clinic, of systolic BP 140–159 mmHg and/or diastolic BP 90–99 mmHg, as defined in current international guidelines[12]) and hypercholesterolemia (fasting total serum cholesterol ≥200 mg/dL). Furthermore, all included patients had been on established antihypertensive treatment for at least 6 months. The recruited hypertensive hypercholesterolemic patients were included either in the statin group (when taking a statin for at least 6 months) or in the control group (when not taking a statin) and BP control and BP levels of both groups were compared. Exclusion criteria included dementia, pregnancy, or breastfeeding, and history or evidence of stage 2 hypertension (BP measurements, in the clinic, of systolic BP ≥ 160 mmHg and/or diastolic BP ≥ 100 mmHg). Hypertensive hypercholesterolemic patients taking a statin for less than 6 months were also excluded.

BP measurements

BP was measured in a seated position after a 5-min rest period, using a mercury sphygmomanometer or automatic device (Omron M4-I), with the mean of two consecutive measurements spaced by 1–2 min. Additional measurements were taken if the first two were quite

120

different. The BP clinic measurement was performed by several nurses blinded to the study.

According to the seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), hypertensive patients without diabetes and chronic kidney disease (CKD) with BP <140/90 mmHg were considered to have their BP controlled.[1] For hypertensive patients with diabetes or CKD, BP control was defined as BP measurements <130/80 mmHg.[1]

Medication adherence assessment

The assessment of medication adherence was determined using a validated five-item compliance scale[13] derived from the four-item scale developed by Morisky *et al.*[14,15] Low medication adherence was defined as answering 'yes' to three or more of five questions.[13] The five-item scale was reported to have predictive validity in that it was able to discriminate levels of hypertension control[14] and to discriminate cases of hypertensive emergency or urgency from hypertensive controls.[16] Cronbach's coefficient alpha,[17] a measure of the internal consistency of the scale, was 0.71 for the five-item scale,[13] better than the 0.61 for the original four-item scale.[14]

Statistical analysis

Demographic variables, clinical data, BP values, and lipid profile of patients included in the study, and also prescribing metrics were examined on a descriptive basis and expressed as the mean ± SD (standard deviation), frequency, and percentages. Student's *t*-test and Mann–Whitney rank-sum test were used to compare continuous variables and χ^2-test and Fisher's exact test were used to test for differences between categorical variables. A logistic regression model was used to adjust the odds ratio (OR) of controlled BP associated with statin therapy for the length of antihypertensive treatment. All statistical analyses were carried out using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA), and a *P*-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

A total of 222 patients attended the medical clinic during

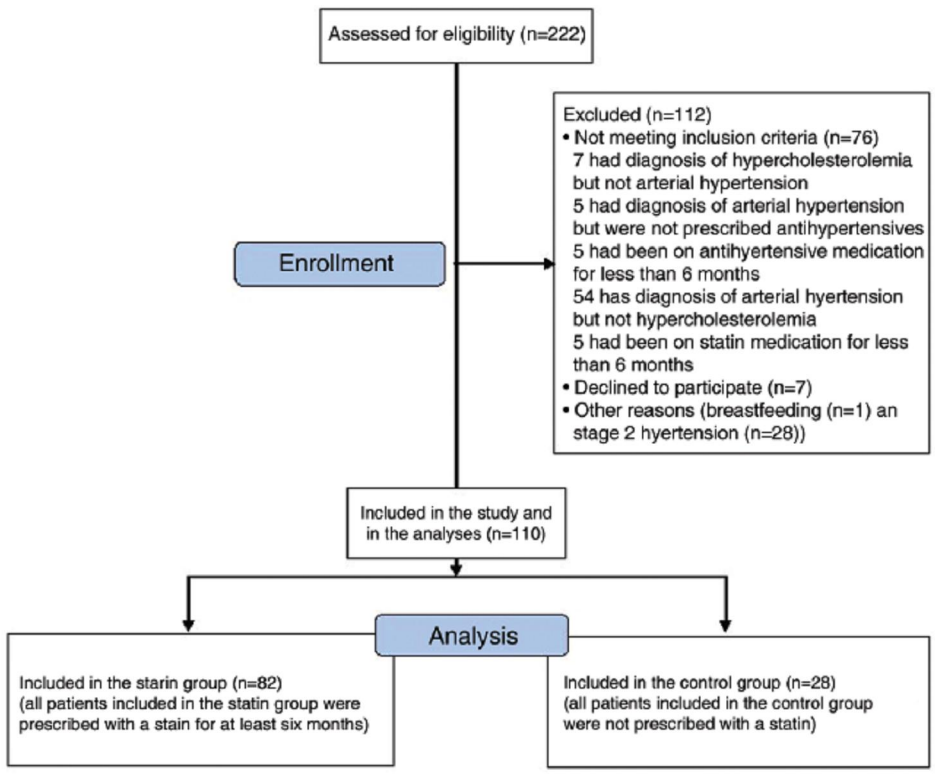

Figure 1: Diagram of patient enrollment

the recruitment period (from July 2009 to September 2009), and all were assessed for eligibility. Of these, 76 were excluded from our study because they did not meet the inclusion criteria, 28 were excluded because of stage 2 hypertension, 1 was excluded because of breastfeeding, and 7 were excluded because they declined to participate (did not sign the informed consent). Of the 110 hypertensive hypercholesterolemic patients meeting the inclusion criteria and consenting to participate, 82 were included in the statin group and 28 were included in the control group [Figure 1].

The overall mean age of the included patients was 59.7 ± 9.5 years, 40.0% being male and 60.0% female. Among these hypertensive hypercholesterolemic patients, 82 (74.5%) were taking a prescribed statin for at least 6 months and were included in the statin group, whereas the remaining 28 (25.5%) were not taking a statin and were included in the control group [Table 1]. In the statin group, patients were receiving both dietary advice and a statin. In the control group, patients were receiving dietary advice alone as a therapeutic measure to control hypercholesterolemia. The use of a statin was considered only when dietary measures alone had proven to be insufficient to control hypercholesterolemia. All statins currently licensed for human use in Portugal were prescribed (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin).

There were no significant differences between patients in the statin group and the control group concerning age (mean 60.2 ± 9.6 years vs. 58.1 ± 9.4 years; $P = 0.306$), gender (39.0% males vs. 42.9%; $P = 0.718$), and body mass index (mean 29.8 ± 4.7 kg/m^2 vs. 29.8 ± 4.6 kg/m^2; $P = 0.963$). Likewise, the proportion of patients with diabetes and/or chronic kidney disease, the number and class of antihypertensive drugs used, and the high-density lipoprotein cholesterol (HDL-C) and triglyceride fasting serum levels did not significantly differ in both groups. Conversely and as expected, fasting total serum cholesterol and low-density lipoprotein cholesterol (LDL-C) levels were significantly lower in the statin group. In addition, the mean duration of antihypertensive drug treatment was significantly higher in the statin group (10.1 vs. 6.9 years, $P = 0.031$), which might represent a possible confounding variable [Table 1].

Blood pressure control according to the JCN 7 guidelines was significantly higher ($P = 0.002$) in the statin group (54.9%) when compared with the control group (21.4%; Table 1). Accordingly, significantly lower systolic BP (−6.7 mmHg, $P = 0.020$) and diastolic BP (−6.4 mmHg, $P = 0.002$) levels were observed in the statin group [Figure 2].

In the light of these results, since the mean duration of

Table 1: Clinical characteristics of the study population

Characteristics	Statin group (n = 82)	Control group (n = 28)	P-value for difference
Mean age (years)	60.2 ± 9.6	58.1 ± 9.4	0.306
Gender (male/female; %)	39.0/61.0	42.9/57.1	0.718
Body mass index (kg/m2)	29.8 ± 4.7	29.8 ± 4.6	0.963
Loop diuretics (%)	15.9	10.7	0.560
Thiazide diuretics (%)	58.5	64.3	0.590
Potassium-sparing diuretics (%)	2.4	3.6	1
Renin inhibitors (%)	1.2	0.0	1
ACE inhibitors (%)	34.1	39.3	0.624
Angiotensin II receptor antagonists (%)	56.1	53.6	0.823
Calcium channel blockers (%)	41.5	25.0	0.120
Beta blockers (%)	45.1	39.3	0.590
Central alpha-2 agonists (%)	7.3	0.0	0.199
Number of antihypertensive drugs per patient	2.6 ± 1.5	2.4 ± 1.1	0.401
Number of years in antihypertensive drug treatment	10.1 ± 7.1	6.9 ± 4.2	0.031*
Total cholesterol (mg/dL)	185.5 ± 39.5	221.3 ± 52.1	<0.001*
LDL cholesterol (mg/dL)	107.1 ± 36.2	140.5 ± 40.9	<0.001*
HDL cholesterol (mg/dL)	50.8 ± 11.7	47.4 ± 8.4	0.169
Triglyceride (mg/dL)	141.9 ± 61.1	172.3 ± 105.0	0.074
Diabetes or chronic kidney disease (%)	22.0	17.9	0.647
BP controlled (JCN 7 guidelines) (%)	54.9	21.4	0.002*
Low, self-reported medication adherence, score ≥ 3 (%)	47.6	57.1	0.380

*Values are mean ± SD unless otherwise stated, *statistically significant difference (P-value < 0.05), ACE, Angiotensin-converting enzyme; BP, Blood pressure; HDL, High-density lipoprotein; LDL, low-density lipoprotein*

122

antihypertensive drug treatment was significantly higher in the statin group, this variable was included into a logistic regression model to adjust the OR of controlled BP associated with statin therapy in hypertensive hypercholesterolemic patients [Table 2].

The crude model presented in Table 2 confirms that statin therapy increases the likelihood of having the BP controlled [OR 4.46; 95% confidence interval (CI) 1.64–12.15]. After adjusting for the length of antihypertensive treatment, the same statistically significant relationship is observed [OR 5.23; 95% CI 1.86–14.67], confirming the hypothesis that statin therapy may be useful for BP control in the studied population.

DISCUSSION

Previous studies found a possible relationship between hyperlipidemia and hypertension that coexist very often in the same patients and exert a cumulative effect on the risk of cardiovascular events.[3,18,19] Several RCTs revealed that statins, beyond their lipid-lowering properties, are also able to significantly reduce systolic and diastolic BP.[8-10,20] However, the capacity of statins to affect systemic BP in clinical practice is still debated and a demonstration of a better BP control, according to JNC 7 guidelines, in self-administered hypertensive, hypercholesterolemic statin outpatients is still lacking. The data recently provided by the Plaque Hypertension Lipid-Lowering Italian Study (PHYLLIS) trial, which enrolled both stage 1 and 2 hypertensive hypercholesterolemic patients (systolic BP 150–210 mmHg and diastolic BP 95–115 mmHg), do not confirm the conclusion of previous studies that statins exert a BP-lowering effect.[21] The results of PHYLLIS revealed that the administration of a statin in hypertensive hypercholesterolemic patients in whom BP is effectively reduced by concomitant antihypertensive treatment does not have an additional BP-lowering effect,[21] which seems to be in line with a few previous studies.[22,23]

In this cross-sectional study, statin therapy was not only associated with an improved lipid profile, through significantly lower fasting total serum cholesterol and LDL-C levels, but also with a higher BP control in stage 1 hypertensive hypercholesterolemic patients from the Eastern Central Region of Portugal. After adjusting for the length of antihypertensive treatment, statin therapy increased 5.23 times the odds of having the BP controlled, this relationship being statistically significant (95% CI 1.86–14.67). The magnitude of systolic and diastolic BP reduction (−6.7 mmHg and −6.4 mmHg, respectively, $P < 0.05$) observed in the statin group when compared to the control group is in agreement with data obtained in some RCTs.[24]

Table 2: Odds ratio of controlled BP associated with statin therapy according to the length of antihypertensive treatment

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
Statin therapy	4.46 (1.64–12.15)†	5.23 (1.86–14.67)†

**Results are adjusted for the length of antihypertensive treatment, †Values are significant at the 0.05 level (two-sided), CI, confidence interval; OR, odds ratio.*

These findings may have some reasonable clinical implications since they help to emphasize the role of statins in the prevention of cardiovascular diseases, particularly in hypertensive hypercholesterolemic patients with stage 1 arterial hypertension. However, adequately powered epidemiological studies need to be considered to test the efficacy and safety of statin therapy in BP control and prevention of cardiovascular events.

Several limitations of this study must be mentioned. First, the sample size power to detect small differences between groups may be questionable. Even though the association observed is statistically significant, the increased precision of confidence intervals is desired. From a methodological point of view, this is a small cross-sectional study and our results must be considered exploratory in nature. Second, the evaluation of BP control is also subject to criticism since it is based on the measurements performed in one single medical appointment. These BP measurements may or may not be representative of the adequacy of BP control in hypertensive patients. Third, we were unable to obtain objective measurements of patient medication compliance

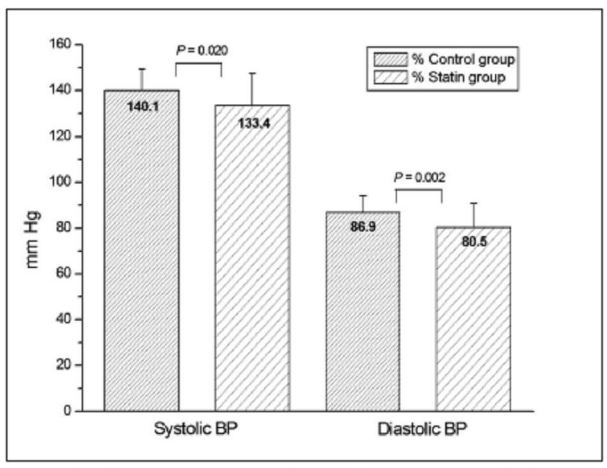

Figure 2: Significant lower systolic blood pressure (–6.7 mmHg, $P = 0.020$) and diastolic blood pressure (–6.4 mmHg, $P = 0.002$) levels were observed in the statin group when compared with the control group. Error bars indicate standard deviation. BP, blood pressure

(e.g., drug level in biologic fluids, biologic markers, direct patient observation) and compare them in both groups. Finally, we did not evaluate whether some combinations of certain statins and antihypertensive drugs might result in a more effective BP control than others, and we did not investigate whether the effect of statins on BP was dose related or not.

In conclusion, our results are aligned with the majority of the medical literature suggesting a statistically significant BP-lowering effect of statins, feasible to be achieved in hypertensive hypercholesterolemic patients in a clinical practice setting. Our findings suggest that, in stage 1 hypertensive patients in whom the prescription of a statin is simultaneously indicated (e.g., because of concomitant hypercholesterolemia), this can improve BP control and reduce, to some extent, the dose and number of antihypertensive drugs required to achieve satisfactory hypertension control. Therefore, our findings might have useful implications for effective and safe prevention of cardiovascular events, particularly in stage 1 hypertensive hypercholesterolemic patients in whom BP is not effectively controlled solely by concomitant antihypertensive treatment. Further studies are needed in this population to clarify the exact magnitude of the effect of statins on BP control, as well as its clinical relevance.

ACKNOWLEDGMENT

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124

Errata do Artigo V

1) Na página 47 do Artigo V (página 122 da tese), na "Table 1", onde se lê:

Characteristics	Statin group (n = 82)	Control group (n = 28)	*P*-value for difference
...	...	...	...
Total cholesterol (mg/dL)	185.5 ± 39.5	221.3 ± 52.1	<0.001
LDL cholesterol (mg/dL)	107.1 ± 36.2	140.5 ± 40.9	<0.001
...	...	...	...
Triglyceride (mg/dL)	141.9 ± 61.1	172.3 ± 105.0	0.074
...	...	...	...

deve ler-se:

Characteristics	Statin group (n = 82)	Control group (n = 28)	*P*-value for difference
...	...	...	...
Total cholesterol (mg/dL), median (IQR)	178.0 (151.5 – 215.0)	208.0 (184.0 – 225.0)	0.002
LDL cholesterol (mg/dL), median (IQR)	103.0 (78.3 – 124.0)	130.0 (113.5 – 158.0)	<0.001
...	...	...	...
Triglyceride (mg/dL), median (IQR)	125.0 (97.0 – 166.8)	150.0 (100.0 – 202.5)	0.317
...	...	...	...

IQR – interquartile range.

5.6 Artigo VI

“Pharmacist intervention program to enhance hypertension control: a randomised controlled trial”

Manuel Morgado, Sandra Rolo, Miguel Castelo-Branco

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128

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RESEARCH ARTICLE

Pharmacist intervention program to enhance hypertension control: a randomised controlled trial

Manuel Morgado · Sandra Rolo · Miguel Castelo-Branco

Received: 17 July 2010 / Accepted: 7 December 2010 / Published online: 13 January 2011

Abstract *Objective* Studies have demonstrated that hypertension remains inadequately managed throughout the world, with lack of adherence to BP-lowering medication being a major factor. The aim of the present study was to evaluate if a pharmaceutical care program could improve antihypertensive medication adherence and blood pressure control. *Setting* This study was conducted in a secondary care hypertension/dyslipidemia outpatient clinic in the university teaching hospital of Cova da Beira Hospital Centre, Covilhã, located in the Eastern Central Region of Portugal. *Method* This report evaluates the pharmacist's interventions during a prospective randomised controlled trial, from July 2009 to June 2010. Patients with diagnosis of essential hypertension attending the clinic for routine follow-up were randomly allocated either to a control group (no pharmaceutical care) or to an intervention group (quarterly follow-up by a hospital pharmacist during a 9-month period). The pharmacist interventions, aimed to increase medication adherence and blood pressure control, involved educational interventions and counselling tips directed to the patient. *Main outcome measure* Systolic blood pressure, diastolic blood pressure and blood pressure control (according to JNC 7 guidelines) assessed at the baseline visit and at the end of pharmaceutical care were the main outcome measures. Blood pressure measurements were performed by blinded nurses. Medication adherence was also evaluated, using a validated questionnaire at baseline and at the end of investigation. *Results* A total of 197 hypertensive patients were randomly assigned to the study (99 in the control group and 98 in the intervention group). Although there were no significant differences ($P > 0.05$) in both groups concerning mean age, gender, body mass index, and antihypertensive pharmacotherapy, blood pressure control was higher in the intervention group ($P = 0.005$) at the end of the study. Significant lower systolic blood pressure (−6.8 mmHg, $P = 0.006$) and diastolic blood pressure (−2.9 mmHg, $P = 0.020$) levels were observed in the intervention group. Medication adherence was also significantly higher in the intervention group at the end of the study (74.5% vs. 57.6%, $P = 0.012$).*Conclusion* Pharmacist intervention can significantly improve medication adherence and blood pressure control in patients treated with antihypertensive agents.

Keywords Blood pressure · Clinical trial · Hospital pharmacist · Hypertension · Medication adherence · Pharmaceutical care · Pharmacist intervention · Portugal

Impact of findings on practice

- Clinical hospital pharmacists can complement physicians in the management of hypertensive patients.
- Pharmacist interventions are effective in improving antihypertensive medication adherence and reducing systolic and diastolic blood pressure.
- Clinical pharmacists can effectively participate in health education and promotion to improve blood pressure control.

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Introduction

Hypertension is a major risk factor in the development of cardiovascular disease and an important public health problem worldwide. It is estimated that over three million Portuguese adults (about 30% of the Portuguese population) suffer from hypertension. In a recently published survey [1] only 11.2% hypertensives had their blood pressure (BP) controlled. This figure is even lower in the Central Region of Portugal, where only 9.7% of the total number of hypertensives have their BP controlled [1]. Although the treatment of hypertension has been shown to prevent cardiovascular disease and to extend and enhance life [2, 3], hypertension remains inadequately managed throughout the world, with lack of adherence to BP-lowering medication being a major factor [4–7]. Hypertensive patients may fail to take their medication because of the symptomless nature of the condition, the long duration of therapy, side effects of medication, complicated drug regimens, lack of understanding about hypertension management and risks, and costs of medication [8, 9]. Antihypertensive medication adherence rates have differed widely depending on the population studied and it is estimated to range between 50 and 70% [6, 10, 11].

The importance of improving adherence to antihypertensive medication has been addressed by "The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high BP" (JNC 7) [2] and emphasis has been put on the role of all health care professionals to improve adherence to treatment [2]. Previous studies have shown that introducing pharmaceutical care to hypertensive patients in community pharmacies improved medication adherence and patient outcomes [12–16]. However, this type of care for hypertensive outpatients in a hospital setting, where collaboration between physician and pharmacist is more feasible, has not previously been undertaken in Portugal and the study presented here is unique in this respect.

Aim of the study

The objectives of the present study were to evaluate the hospital clinic pharmacist's interventions during a prospective randomised controlled clinical trial (RCT), aimed to improve antihypertensive medication adherence and BP control in hypertensive patients in the ambulatory secondary care setting.

Method

This was a RCT, with participants individually randomised to one of two parallel groups (allocation ratio 1:1). Eligible participants were all adults aged 18 or over with an established medical diagnosis of arterial hypertension, whether their BP was controlled or not. According to the JNC 7 guidelines, BP control was defined as BP measurements in the clinic of systolic BP (SBP) <140 mmHg and diastolic BP (DBP) <90 mmHg for patients without diabetes or chronic kidney disease (CKD) and of SBP <130 mmHg and DBP <80 mmHg for patients with diabetes or CKD. Furthermore, all included patients had been on established antihypertensive drug treatment for at least 6 months. Exclusion criteria were dementia, pregnancy and breastfeeding. The study was carried out from July 2009 to June 2010 in a hypertension/dyslipidemia clinic in the university hospital of Cova da Beira Hospital Centre, Covilhã, located in the Eastern Central Region of Portugal. The study was approved by the institutional Ethics Committee for the use of humans in research, and written informed consent was obtained from all participants before their enrollment in the study.

Outpatients attending the medical clinic for routine follow-up were randomly allocated either to a control group [(CG) usual care, where no pharmaceutical care is provided] or to an intervention group [(IG) pharmaceutical care, consisting of quarterly follow-up by a hospital clinical pharmacist during a 9-month period]. Participants were allocated following simple randomisation procedures (equal allocation and without restrictions) using a computer-generated list of random numbers. The allocation sequence was concealed from the clinical pharmacist enrolling and assessing participants in sequentially numbered, opaque, sealed envelopes. The computer generated the allocation sequence and the envelopes were prepared by a researcher with no clinical involvement in the trial. Based on the nature of the intervention, it is not feasible to blind hypertensive patients in pharmaceutical intervention models. Thus, whereas patients, pharmacists and physicians were aware of the patient allocated arm, nurses assessing BP were kept blinded to the allocation.

The pharmaceutical care provided to the IG by a clinical pharmacist consisted in the baseline visit (lasting approximately 30 min) and the follow-up visits (lasting approximately 20 min) conducted with each intervention patient at 3 and 6 months. The clinical pharmacist could also schedule additional optional visits between scheduled visits at his discretion. At each visit, the clinical pharmacist conducted a thorough interview of the patient, identified problems leading to poor BP control, provided patient education (hypertension education, BP self-monitoring recommendation, goal BP to achieve, lifestyle education and counselling, medication education and counselling tips to enhance adherence), and presented recommendations to the physician regarding changes in drug therapy. The recommended lifestyle changes for BP control were in accordance with the JNC 7 guidelines [2]. Patients in the IG were also provided

with written educational material about hypertension and possible complications, as well as healthy lifestyle practices. Furthermore intervention patients were encouraged to bring all empty blisters and boxes of antihypertensive medication to clinic visits for recycling and to verify compliance to therapy. The CG had no clinical pharmacist involvement and control patients received the traditional service provided by the hospital clinic.

The primary outcome measures with respect to pharmaceutical care efficacy were the proportion of patients achieving BP control and reduction in baseline SBP and DBP. The BP clinic measurement was performed by trained nurses blind to the study, according to the published guidelines on proper BP measurement issued by the Portuguese Society of Hipertension [17]. Validated automatic BP measuring devices (Omron M4-I, validated by the British Society of hypertension [18]) and appropriate cuffs were used, the mean of two consecutive measurements being recorded. The secondary outcome measure was antihypertensive medication adherence, which was determined in both arms by a pharmacist using a validated five-item adherence scale [19, 20], derived from the four-item scale developed by Morisky et al. [21, 22]. Low medication adherence was defined as answering yes to 3 or more of 5 questions [23]. Patient knowledge of target BP values and of hypertension risks were also evaluated. Patients were considered knowledgeable of target BP values if they knew both target BP figures (<140/<90 mmHg for hypertensive patients without diabetes and CKD and <130/<80 mmHg for hypertensive patients with diabetes or CKD). They were considered knowledgeable of the negative impacts of hypertension to health if they mentioned at least two potential major negative consequences of uncontrolled hypertension to health. SBP and DBP levels, BP control, medication adherence, patient knowledge of target BP values and of hypertension risks of both groups were assessed and compared at baseline and at the end of a 9-month period. In the final study visit (9-month) the IG did not receive pharmaceutical care and both arms had BP measured by a research nurse, and had medication adherence assessed by a pharmacist. If a subject failed to attend the exit visit despite multiple contact attempts (i.e., drop out), the last available clinic BP was extracted for intention-to-treat (ITT) analysis.

Clinical data for this study, including BP measures, medications prescribed and medical problems were prospectively obtained from the hospital electronic medical records (HEMR) database. The HEMR database is comprised of detailed patient-level clinical and administrative information from all patients that have used the hospital at least once. This database is authorized by the Portuguese government and patient data confidentiality was ensured.

To detect a reduction in SBP of 8–10 mmHg [standard deviation (SD) 16–18 mmHg], which is in agreement with several studies, with a two-sided 5% significance level and a power of 80%, a sample size of 90 patients per group (180 total) was necessary, given an anticipated dropout rate of 10%. To recruit this number of patients a 3-month (July–September 2009) inclusion period was anticipated.

Demographic variables, clinical data, medication adherence and BP values of patients included in the study, as well as prescribing metrics were examined on a descriptive basis and expressed as the mean ± SD, frequency and percentages. Student's test and Mann–Whitney rank sum test were used to compare continuous variables and χ^2 test and Fisher exact probability test were used to test for differences between categorical variables. All statistical analyses were done using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL) and a P-value < 0.05 was considered to indicate statistical significance.

Results

A total of 222 patients attended the medical clinic during the recruitment period (from July 2009 to September 2009) and all were assessed for eligibility. Of these, 17 were excluded from the study because they did not meet the inclusion criteria, 1 was excluded because of breastfeeding and 7 were excluded because they declined to participate. Of the 197 hypertensive patients meeting the inclusion criteria and consenting to participate, 99 were allocated to usual care (CG) and 98 were allocated to pharmaceutical care (IG) (Fig. 1).

The IG and CG were comparable with respect to age, gender, education, marital status, body mass index, smoking status, prevalence of chronic illness, number of antihypertensive drugs per patient, and number of years in antihypertensive treatment (Table 1).

The percentage of patients on angiotensin II receptor antagonists was the only significant difference detected between the two groups at baseline (Table 2).

Baseline SBP and DBP, BP control, stage 1 and stage 2 hypertension and medication adherence did not significantly differ in both groups either (Table 3).

As seen in Fig. 1, a total of 7 subjects (3.6%) withdrew from the study following allocation, 4 (2.0%) from the intervention arm and 3 (1.5%) from the control arm. In the IG, 95 completed the 3-month visit, and 94 completed the 6-month as well as the final study visit. The clinical pharmacist scheduled a mean ± SD of 0.6 ± 0.6 additional visits per patient in the IG, involving a total of 51 patients (7 patients had 2 additional visits).

At the beginning of the study, only 30 of 98 (30.6%) patients in the IG had both SBP and DBP controlled. This was not significantly different from the number in the CG, where 35 of 99 (35.4%) patients had their BP

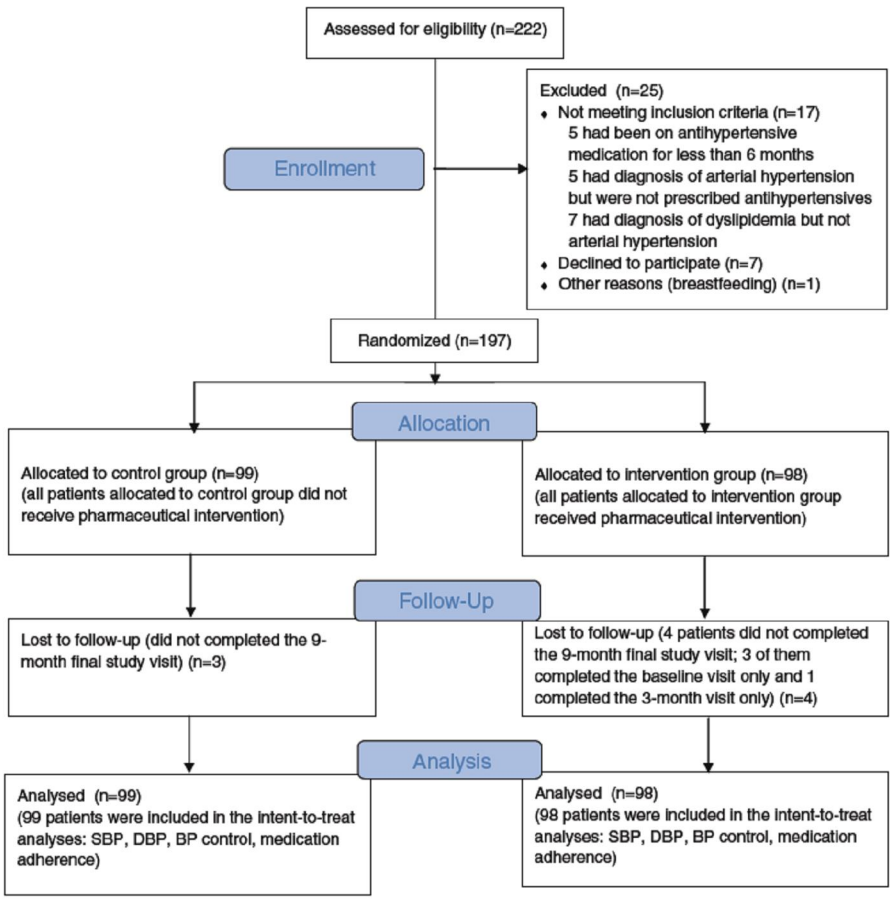

Fig. 1 Flow diagram of patients through the study protocol (according to CONSORT 2010 Statement). *BP* blood pressure, *DBP* diastolic blood pressure, *SBP* systolic blood pressure

controlled ($P = 0.480$). At the end of the study, BP was controlled among significantly more patients in the IG (66.0%) than in the CG (41.7%) ($P = 0.0008$), with an odds ratio of 2.7 (95% CI, 1.5–4.9) (Table 3).

The SBP was reduced by 0.8 mmHg in the CG and 7.6 mmHg in the IG ($P = 0.005$ for between-group SBP comparison). The DBP was reduced by 1.1 mmHg in the CG and 3.0 mmHg in the IG ($P = 0.016$ for between-group DBP comparison) (Table 3).

A sensitivity analysis to determine the robustness of our findings in the presence of informative dropout was performed. The analysis was repeated under the most pessimistic scenario in which all 4 dropouts in the IG had uncontrolled BP and all 3 dropouts in the CG had controlled BP. In this situation, the respective BP control rates would be 63.3 and 43.4% (odds ratio of 2.2; 95% CI 1.3–4.0; $P = 0.005$). Similarly, if we consider the last available clinic BP extracted in all 7 dropouts, SBP was reduced by 0.9 mmHg in the CG and 7.4 mmHg in the IG ($P = 0.006$ for between-group SBP comparison). The DBP was reduced by 1.0 mmHg in the CG and 2.7 mmHg in the IG ($P = 0.020$ for between-group DBP comparison) (Table 3).

The intervention pharmacist made 118 recommendations about antihypertensive therapy, of which 90 (76.3%) were accepted by physicians. These recommendations included maintaining current antihypertensive medication (54.2%), introduction of additional medication (25.4%), dosage increase of existing medication (13.5%), cessation of current medication (5.9%) and dosage decrease of existing medication (0.8%). Despite these recommendations, the mean of overall changes in antihypertensive medication did not differ in IG and CG (0.65 vs. 0.72 changes per subject in the IG and CG, respectively, $P = 0.693$), neither did the number of new antihypertensive medications (0.34 vs. 0.37, $P = 0.768$) or the number of discontinued antihypertensive medications (0.20 vs. 0.19, $P = 0.879$). Likewise, the mean ± SD number of antihypertensive medications was not different between the IG (2.8 ± 1.3 medications) and the CG (2.7 ± 1.4 medications) at the end of the study ($P = 0.682$). Similarly, the antihypertensive medications prescribed did not

Table 1 Patients demographics and clinical characteristics at baseline (n = 197)

Demographic/clinical	Control group (n = 99)	Intervention group (n = 98)	*P* value
Gender, n (%)			0.171
Male	35 (35.4)	44 (44.9)	
Female	64 (64.4)	54 (55.1)	
Age, mean (SD)[a]	60.7 (11.8)	58.3 (11.6)	0.155
Body mass index (kg/m^2), mean (SD)	29.0 (4.7)	29.8 (4.9)	0.261
Married, n (%)	85 (85.9)	75 (76.5)	0.094
Education, n (%)			0.991
Illiterate	5 (5.1)	5 (5.1)	
Elementary schooling	79 (79.8)	77 (78.6)	
High schooling	10 (10.1)	10 (10.2)	
University education	5 (5.1)	6 (6.1)	
Current smoker, n (%)	8 (8.1)	9 (9.2)	0.777
Comorbid conditions, n (%)			
Cerebrovascular disease	15 (15.2)	11 (11.2)	0.417
Chronic kidney disease	6 (6.1)	5 (5.1)	0.764
Diabetes	18 (18.2)	18 (18.4)	1.000
Heart failure	1 (1.0)	0 (0.0)	1.000
Ischemic heart disease	4 (4.0)	1 (1.0)	0.369
Myocardial infarction	2 (2.0)	1 (1.0)	1.000
Left ventricular hypertrophy	2 (2.0)	3 (3.1)	0.683
Dyslipidemia	70 (70.7)	78 (79.6)	0.149
Metabolic syndrome	3 (3.0)	1 (1.0)	0.621
Obesity (body mass index ≥ 30)	43 (43.4)	40 (40.8)	0.708
Advanced age (≥65 years), n (%)	34 (34.3)	30 (30.6)	0.578
None of the above, n (%)	11 (11.1)	8 (8.2)	0.484
Number of antihypertensive drugs per patient, mean (SD)	2.6 (1.4)	2.7 (1.3)	0.437
Number of years in antihypertensive drug treatment, mean (SD)	9.1 (6.6)	8.6 (6.4)	0.572

[a] *SD* standard deviation

significantly differ in both groups at the end of the study (Table 2). Body mass index (BMI) did not significantly differ at the end of the study either (end BMI was 29.9 and 29.3 for IG and CG, respectively, $P = 0.364$) despite the pharmacist's recommendation of lifestyle changes.

Baseline low medication adherence did not significantly differ in both groups (53.1% in the IG and 50.5% in the CG, $P = 0.718$). However, at the end of the study there was a significant difference ($P = 0.0017$) in the percentage of patients with low medication adherence between the IG (22.3%, within group $P < 0.0001$) and the CG (43.8%, within group $P = 0.345$).

Similarly, baseline patient knowledge of target BP values and of the potential complications of high BP to their health did not significantly differ in both groups (Table 3). However, at the end of the study there was a significant difference in the percentage of patients reporting correctly both target BP figures and hypertension risks (Table 3). Both differences remained significant when data were assessed by ITT analysis (Table 3).

Discussion

The pharmacist intervention program developed for this 9-month study resulted in significant reduction of SBP and DBP and in an increase in the proportion of patients with controlled BP according to JNC-7 guidelines. The odds of achieving BP target in the IG were 2.7 times higher than the CG (95% CI, 1.5–4.9; $P < 0.001$). These differences remained significant when data were assessed by ITT analysis. Among hypertensive patients aged 60–69 years, the additional 6.8 mmHg reduction in SBP observed in intervention arm would be expected to yield a 22% reduction in stroke mortality and a 17% reduction in mortality from ischemic heart disease [24]. Thus, inclusion

Table 2 Antihypertensive medication prescribed to hypertensive patients at baseline and at the end of the study

Antihypertensive drug class	Control group (Baseline, n = 99) (End of study, n = 99)[a]	Intervention group (Baseline, n = 98) (End of study, n = 98)[a]	*P* value
Loop diuretics (%)	18.2	11.2	0.168
	18.2	12.2	0.247
Thiazide diuretics (%)	59.6	64.3	0.498
	63.6	67.3	0.584
Potassium-sparing diuretic (%)	6.1	3.1	0.498
	6.1	4.1	0.747
Renin inhibitor (%)	3.0	2.0	1.000
	3.0	4.1	0.721
ACE inhibitors (%)	32.3	33.7	0.841
	32.3	35.7	0.617
Angiotensin II receptor antagonists (%)	47.5	64.3	**0.018**
	52.5	64.3	0.094
Calcium channel blockers (%)	35.4	45.9	0.131
	42.4	44.9	0.729
Beta blockers (%)	47.5	41.8	0.427
	47.5	42.9	0.517
Central alpha-2 agonists (%)	8.1	7.1	0.806
	8.1	6.1	0.590

Bold means that there is a statistically significant difference (*P* value < 0.05)

[a] Includes last medication prescribed before the final study visit (including to dropouts)

of a clinical pharmacist on the hypertension care team represents one possible strategy to address this important public health issue.

Previously reported reduction of SBP and DBP levels in patients receiving pharmaceutical care varied between 6.0 and 31.0 mmHg and 3.0 and 14.2 mmHg, respectively [23, 25, 26]. In the present study, a 7.6/3.0 mmHg reduction was observed in the IG; this may be partly explained by the low mean SBP and DBP level of the study population at baseline (141.8/85.8 mmHg). Indeed, most of those studies only enrolled hypertensive patients with uncontrolled BP, contrary to the current study in which all hypertensive patients taking antihypertensive medications for at least 6 months were included (whether their BP was controlled or not); this approach is closer to the actual context in which the pharmacist could work in our clinic. Nevertheless, the pharmacist intervention was effective in the management of BP and was consistent with the chronic care model in which the hypertension clinic uses team-based care.

The intervention program reported here resulted in significant improvement in antihypertensive medication adherence, which is a likely reason for better BP control in the IG because antihypertensive medications additions did not differ. It must be acknowledged that some studies reported statistically significant improvements in treatment outcomes (SBP, DBP and/or percentage of participants with controlled BP at the end of the study) without significant increases in medication adherence [14, 16, 23, 27–30]. This may be attributed to an intensification of antihypertensive medication and some pharmacist interventions led to a significant improvement in BP control by this mechanism, i.e., overcoming clinical inertia [23, 29, 30]. However, most studies that reported a statistically significant increase in medication adherence also reported a statistically significant improvement in treatment outcomes, which reveals that medication adherence is a key factor (although not the only one) to achieve BP control [12, 13, 15, 31–34]. When baseline medication adherence is high (>75%), pharmacist interventions are not likely to find a statistically significant improvement in this outcome [14, 23, 28, 30]. In the current study, the low baseline medication adherence (<50%) made it feasible for pharmaceutical intervention to have a positive effect in this outcome and hence in treatment outcomes. Increase in medication adherence obtained could be attributed to the hypertension and drug education given to patients. Lack of knowledge about BP targets, hypertension complications and the benefits of antihypertensive medication have been recognized as a barrier to adherence [35–37].

Several limitations of this study must be mentioned. First, although RCTs provide the highest internal validity by controlling confounding bias, their use is limited by contaminating the CG by contact with the intervention program. In the present study, randomisation at the patient level, as opposed to pharmacist or physician, may have resulted in contamination bias. Several patients in the CG asked the pharmacist about their goal BP targets and

Table 3 Clinic BP figures, BP control, antihypertensive medication adherence and knowledge about hypertension (baseline, end of the study and ITT analysis)

Variable	Control group	Intervention group	*P* value
Baseline	(n = 99)	(n = 98)	
Baseline SBP, mean (SD), mmHg	141.9 (16.8)	141.6 (16.3)	0.873
Baseline DBP, mean (SD), mmHg	86.4 (11.7)	85.2 (10.2)	0.438
Baseline BP control, n (%)	35 (35.4)	30 (30.6)	0.480
Baseline stage 1 HT, n (%)	39 (39.4)	43 (43.9)	0.522
Baseline stage 2 HT, n (%)	22 (22.2)	20 (20.4)	0.752
Baseline low medication adherence, n (%)	50 (50.5)	52 (53.1)	0.718
Knowledge of target BP values, n (%)	59 (59.6)	58 (59.2)	1.000
Knowledge of hypertension risks, n (%)	54 (54.5)	54 (55.1)	0.920
End of the study	(n = 96)	(n = 94)	
End SBP, mean (SD), mmHg	141.1 (18.0)	134.0 (16.0)	**0.005**
End DBP, mean (SD), mmHg	85.3 (8.9)	82.2 (8.7)	**0.016**
End BP control, n (%)	40 (41.7)	62 (66.0)	**0.0008**
End low medication adherence, n (%)	42 (43.8)	21 (22.3)	**0.0017**
Knowledge of target BP values, n (%)	61 (63.5)	77 (81.9)	**0.005**
Knowledge of hypertension risks, n (%)	63 (65.6)	79 (84.0)	**0.003**
ITT analysis	(n = 99)	(n = 98)	
ITT SBP (includes last value carried forward), mean (SD), mmHg	141.0 (18.0)	134.2 (16.0)	**0.006**
ITT DBP (includes last value carried forward), mean (SD), mmHg	85.4 (9.1)	82.5 (8.6)	**0.020**
ITT BP control[a], n (%)	43 (43.4)	62 (63.3)	**0.005**
ITT low medication adherence[b], n (%)	42 (42.4)	25 (25.5)	**0.012**
ITT knowledge of target BP values[b], n (%)	64 (64.6)	77 (78.6)	**0.030**
ITT knowledge of hypertension risks[b], n (%)	66 (66.7)	79 (80.6)	**0.026**

Bold means that there is a statistically significant difference (*P* value < 0.05)

[a] Admitting that all patients from control group lost to follow-up had their BP controlled at the end of the 9-month study and that all patients from intervention group lost to follow-up had their BP uncontrolled at the end of the 9-month study

[b] Admitting that all patients from control group lost to follow-up were adherent and knew target BP values and hypertension risks at the end of the 9-month study and that all patients from intervention group lost to follow-up were no adherent and did not known target BP values and hypertension risks at the end of the 9-month study

BP blood pressure, *DBP* diastolic blood pressure, *HT* hypertension, *ITT* intention-to-treat, *SBP* systolic blood pressure, *SD* standard deviation

about the possible serious consequences of high BP at the beginning of the study, and, further, physicians in the study cared for patients in both groups. Although contamination was considered during the study design, researchers recognized that it would conservatively represent bias toward the null hypothesis. Second, the evaluation of BP control was based on the measurements performed in two single clinic appointments (baseline and after a 9-month follow-up period). These BP measurements may or may not be representative of the adequacy of BP control in hypertensive patients, even though they were performed by blinded nurses, which contributes to the validity of observed effects. Third, medication adherence was measured by the research (not blinded) pharmacist, which is potentially biased in situations where the patient does not respond with determination to the questionnaire. Finally, the intervention was short, lasting only 9 months. Future research should be of a longer duration to determine if the effect of pharmacist management of hypertension is sustainable.

Conclusion

Pharmacist intervention can modify factors affecting adherence, improve adherence and reduce BP levels in patients treated with antihypertensive agents. This study suggests that one effective method of improving BP control is for pharmacists to recognize inadequate hypertension knowledge and medication adherence and develop strategies that enlist the patient as a participant in the management of his/her health. Thereby, this report also reinforces the pharmacists' role in improving the health care system, leading to superior hypertensive patient outcomes.

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Conflict of interest None.

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Errata do Artigo VI

1) Na página 136 do Artigo VI (página 133 da tese), na "Table 1", onde se lê:

Demographic/ clinical	Control group (n = 99)	Intervention group (n = 98)	*P* value
...	...	...	...
Body mass index (kg/m^2), mean (SD)	29.0 (85.9)	29.8 (4.9)	0.261
...	...	...	...

deve ler-se:

Demographic/ clinical	Control group (n = 99)	Intervention group (n = 98)	*P* value
...	...	...	...
Body mass index (kg/m^2), median (IQR)	28.9 (25.6 - 31.4)	29.4 (26.9 - 32.0)	0.447
...	...	...	...

IQR - interquartile range.

2) Na página 136 do Artigo VI (página 133 da tese), no texto primeira coluna, linha 4, onde se lê:

$P = 0.364$

deve ler-se:

$P = 0.371$

138

Capítulo 6

Resultados Publicados a Nível Nacional

Para além dos resultados já publicados em revistas com arbitragem e indexadas em bases de dados de referência (Morgado et al. 2010; Morgado et al. 2010; Morgado et al. 2011; Morgado et al. 2011; Morgado et al. 2011; Morgado et al. 2011), o ensaio clínico controlado e aleatorizado produziu outros resultados que foram apresentados num trabalho submetido a um concurso de abrangência nacional no âmbito da Farmácia Hospitalar [Prémio Associação Portuguesa de Farmacêuticos Hospitalares (A.P.F.H.) – IPSEN] (Anexo V).

De acordo com o regulamento do referido concurso [disponível em www.apfh.pt/xfiles/scEditor/File/Regulamento%20Prémio%20APFH-IPSEN%202009-2010.pdf (acedido em 18/12/2010)], atendendo a que o trabalho submetido foi premiado (**1ª Menção Honrosa**) (Anexo V), o mesmo será publicado no Boletim da A.P.F.H. e/ou no sítio oficial da A.P.F.H., na íntegra, ou sob a forma de excertos.

Na secção seguinte será apresentada a totalidade dos resultados obtidos no ensaio clínico controlado e aleatorizado. Embora alguns resultados já tenham sido referidos no último artigo apresentado, optou-se, neste capítulo, pela apresentação da totalidade dos resultados obtidos no ensaio clínico, a fim de tornar mais integrada e clara a exposição dos resultados publicados a nível nacional.

6.1 Resultados obtidos no ensaio clínico controlado e aleatorizado

Dos 197 doentes hipertensos incluídos no estudo (na 1ª fase do projecto), 99 foram alocados para o grupo controlo (sem acompanhamento do farmacêutico hospitalar) e 98 foram alocados para o grupo de intervenção (com acompanhamento do farmacêutico hospitalar). A Figura 10 ilustra o diagrama do fluxo dos doentes através do ensaio clínico.

Os grupos de intervenção e controlo revelaram-se semelhantes no que respeita à idade, género, nível educacional, estado marital, índice de massa corporal, tabagismo, presença de patologias concomitantes, número de medicamentos anti-hipertensores por doente, número de anos a fazer medicação anti-hipertensora, adesão à medicação, conhecimentos na área da HTA, monitorização regular da TA e presença de RAMs (Tabela 15).

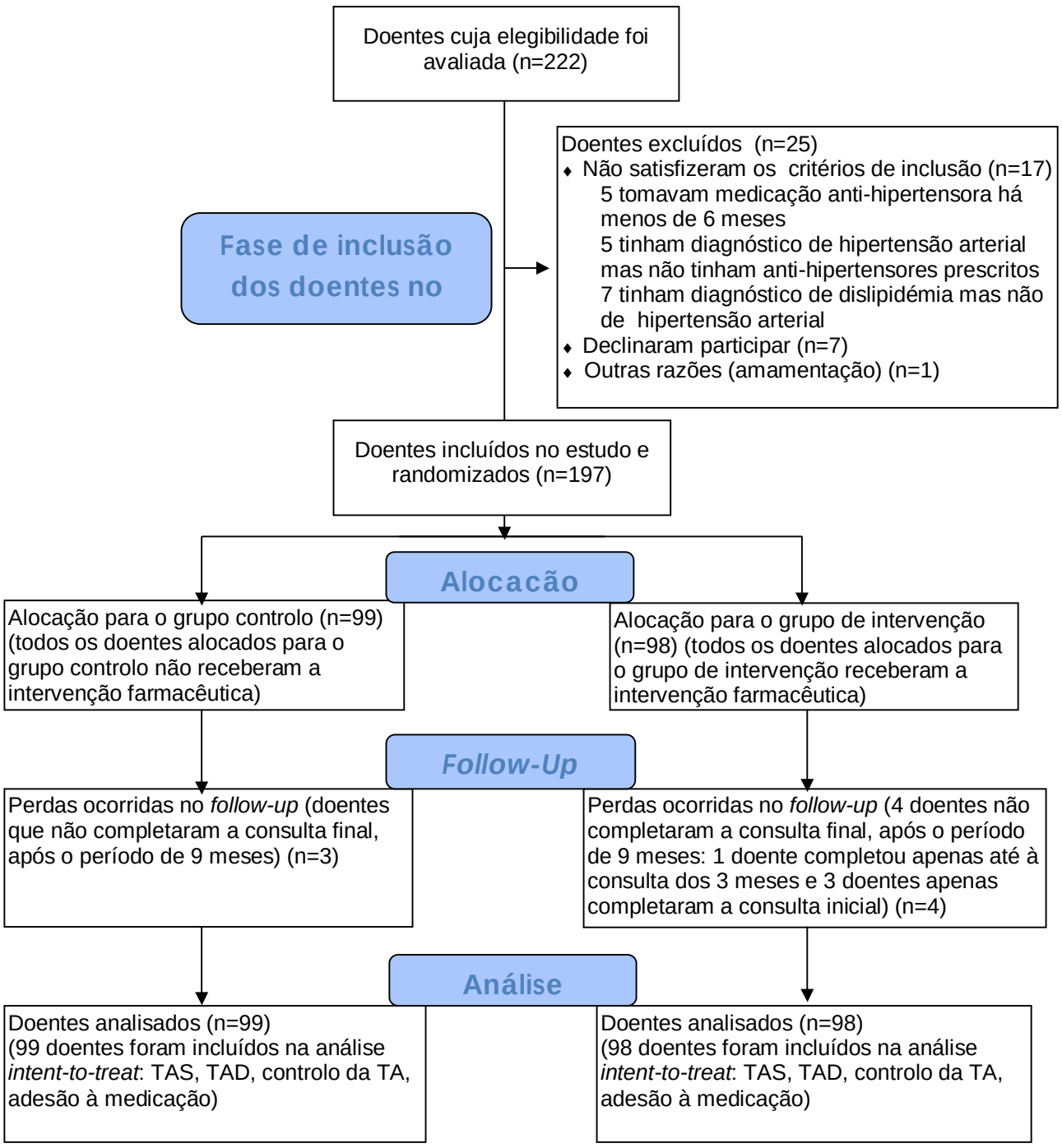

Figura 10 - Diagrama do fluxo dos doentes através do ensaio clínico (em conformidade com o *CONSORT 2010 Statement* (Moher et al.; Schulz et al.)). Abreviaturas: TA – tensão arterial; TAD – tensão arterial diastólica; TAS – tensão arterial sistólica.

Tabela 15 - Características demográficas e clínicas, adesão à terapêutica, conhecimentos acerca da HTA, monitorização da TA e presença de reacções adversas nos grupos controlo e de intervenção no início do estudo.

Parâmetros analisados	Grupo controlo (n=99)	Grupo de intervenção (n=98)	Valor de *P*
Sexo, n (%) Masculino/Feminino	 35 (35,4)/64 (64,4)	 44 (44,9)/54 (55,1)	0,171
Idade, média (DP)	60,7 (11,8)	58,3 (11,6)	0,155
IMC (kg/m^2), mediana (IIQ)	28,9 (25,6 – 31,4)	29,4 (26,9 – 32,0)	0,447
Casado, n (%)	85 (85,9)	75 (76,5)	0,094
Nível educacional, n (%) Analfabeto 1º – 6º ano de escolaridade 7º - 12º ano de escolaridade Educação universitária	 5 (5,1) 68 (68,7) 21 (21,2) 5 (5,1)	 5 (5,1) 66 (67,3) 21 (21,4) 6 (6,1)	0,989
Hábitos tabágicos, n (%)	8 (8,1)	9 (9,2)	0,777
Patologias concomitantes, n (%) Doença cerebrovascular Doença renal crónica Diabetes Insuficiência cardíaca Doença cardíaca isquémica Enfarte do miocárdio Hipertrofia ventricular esquerda Dislipidémia Síndrome metabólica	 15 (15,2) 6 (6,1) 18 (18,2) 1 (1,0) 4 (4,0) 2 (2,0) 2 (2,0) 70 (70,7) 3 (3,0)	 11 (11,2) 5 (5,1) 18 (18,4) 0 (0,0) 1 (1,0) 1 (1,0) 3 (3,1) 78 (79,6) 1 (1,0)	 0,417 0,764 1,000 1,000 0,369 1,000 0,683 0,149 0,621
Obesidade (IMC ≥ 30 kg/m^2), n (%)	43 (43,4)	40 (40,8)	0,708
Idosos (≥65 years), n (%)	34 (34,3)	30 (30,6)	0,578
Nenhuma das condições acima, n (%)	11 (11,1)	8 (8,2)	0,484
Nº de anti-hipertensores por doente, média (DP)	2,6 (1,4)	2,7 (1,3)	0,437
Nº de anos a fazer tratamento com medicação anti-hipertensora, média (DP)	9,1 (6,6)	8,6 (6,4)	0,572
Baixa adesão à medicação, classificação ≥ 3, n (%)	50 (50,5)	52 (53,1)	0,718
Conhecimento dos valores alvo de TA, n (%)	59 (59,6)	58 (59,2)	1,000
Conhecimento dos riscos da HTA, n (%)	54 (54,5)	54 (55,1)	0,920
Conhecimento da indicação dos medicamentos, n (%)	69 (69,7)	70 (71,4)	0,791
Monitorização regular da TA, n (%)	71 (71,7)	68 (69,4)	0,718
Presença de reacções adversas atribuídas à medicação anti-hipertensora, n (%)	24 (24,2)	21 (21,4)	0,639

Abreviaturas: DP – desvio padrão; HTA – hipertensão arterial; IIQ – intervalo interquartil; IMC – índice de massa corporal; n – frequência; TA – tensão arterial.

A percentagem de doentes a fazer antagonistas dos receptores da angiotensina foi a única diferença observada no início do estudo entre os grupos controlo e de intervenção (Tabela 16).

Do mesmo modo, a TAS, a TAD, a percentagem de controlo da TA e a percentagem de doentes com HTA de estádio 1 e HTA de estádio 2 não foi significativamente diferente em ambos os grupos do estudo (Tabela 17).

Como se observa na Figura 10, houve um total de 7 doentes (3,6%) que, após a inclusão num dos grupos, não permaneceu no estudo até ao fim, sendo 4 (2,0%) do grupo de intervenção e 3 (1,5%) do grupo controlo. No grupo de intervenção, 95 doentes completaram a consulta do 3º mês com o farmacêutico e 94 completaram a consulta do 6º mês bem como a avaliação final do 9º mês. O farmacêutico hospitalar fez uma média ± DP de 0,6 ± 0,6 consultas adicionais por doente do grupo de intervenção.

Tabela 16 - Medicação anti-hipertensora prescrita no início e no fim do estudo.

Classe de anti-hipertensor	**Grupo controlo (*Baseline*, n=99) (Final do estudo, n=99)[1]**	**Grupo de intervenção (*Baseline*, n=98) (Final do estudo, n=98)[1]**	**Valor de *P***
Diuréticos da ansa (%)	18,2 18,2	11,2 12,2	0,168 0,247
Diuréticos tiazídicos (%)	59,6 63,6	64,3 67,3	0,498 0,584
Diuréticos poupadores de potássio (%)	6,1 6,1	3,1 4,1	0,498 0,747
Inibidor da renina (%)	3,0 3,0	2,0 4,1	1,000 0,721
Inibidores da enzima de conversão da angiotensina (%)	32,3 32,3	33,7 35,7	0,841 0,617
Antagonistas dos receptores da angiotensina (%)	47,5 52,5	64,3 64,3	**0,018** 0,094
Bloqueadores da entrada do cálcio (%)	35,4 42,4	45,9 44,9	0,131 0,729
Bloqueadores beta (%)	47,5 47,5	41,8 42,9	0,427 0,517
Agonistas alfa 2 centrais (%)	8,1 8,1	7,1 6,1	0,806 0,590

[1]Inclui a última medicação prescrita antes da última visita do estudo (mesmo no caso dos *dropouts*).

Tabela 17 - Valores de TA medidos, controlo da TA e adesão à terapêutica anti-hipertensora (*baseline*, final do estudo e análise *intent-to-treat*).

Variável	Grupo controlo	Grupo de intervenção	Valor de *P*
Baseline	**(n = 99)**	**(n = 98)**	
TAS, média (DP), mm Hg	141,9 (16,8)	141,6 (16,3)	0,873
TAD, média (DP), mm Hg	86,4 (11,7)	85,2 (10,2)	0,438
TA controlada, n (%)	35 (35,4)	30 (30,6)	0,480
HTA Estádio 1, n (%)	39 (39,4)	43 (43,9)	0,522
HTA Estádio 2, n (%)	22 (22,2)	20 (20,4)	0,752
Elevada adesão à medicação, n (%)	49 (49,5)	46 (46,9)	0,718
Final do estudo	**(n = 96)**	**(n = 94)**	
TAS, mean (DP), mm Hg	141,1 (18,0)	134,0 (16,0)	**0,005**
TAD, mean (DP), mm Hg	85,3 (8,9)	82,2 (8,7)	**0,016**
TA controlada, n (%)	40 (41,7)	62 (66,0)	**0,0008**
Elevada adesão à medicação, n (%)	54 (56,3)	73 (77,0)	**0,0017**
Análise *ITT*	**(n = 99)**	**(n = 98)**	
TAS (inclui a última medição efectuada), média (DP), mm Hg	141,0 (18,0)	134,2 (16,0)	**0,006**
TAD (inclui a última medição efectuada), média (DP), mm Hg	85,4 (9,1)	82,5 (8,6)	**0,020**
TA controlada[1], n (%)	43 (43,4)	62 (63,3)	**0,005**
Elevada adesão à medicação[2], n (%)	57 (57,6)	73 (74,5)	**0,012**

[1] Admitindo que, no final do estudo, todos os doentes do grupo controlo perdidos no *follow-up* tinham a sua TA controlada e que todos os doentes do grupo de intervenção perdidos no *follow-up* tinham a sua TA não controlada. A TA foi considerada controlada para valores de < 130/80 mm Hg no caso dos doentes diabéticos ou com doença renal crónica e para valores de < 140/90 mm Hg no caso dos doentes sem qualquer uma destas patologias.

[2] Admitindo que, no final do estudo, todos os doentes do grupo controlo perdidos no *follow-up* eram aderentes à medicação e que todos os doentes do grupo de intervenção perdidos no *follow-up* não eram aderentes à medicação.

Abreviaturas: DP – desvio padrão; HTA – hipertensão arterial; *ITT* – *intent-to-treat*;
n – frequência; TA – tensão arterial; TAD – tensão arterial diastólica; TAS – tensão arterial sistólica.

No início do estudo, apenas 30,6% dos doentes do grupo de intervenção tinham a TAS e a TAD controlada. Este valor não era significativamente diferente (*P* = 0,480) do observado no grupo controlo, onde 35,4% dos doentes tinham a TA controlada. Contudo, no final do estudo, a percentagem de doentes com a TA controlada era significativamente maior (P = 0,0008) no grupo de intervenção (66,0%) do que no grupo controlo (41,7%), sendo o *odds ratio* de 2,7 (IC 95%: 1,5-4,9) (Tabela 17).

Comparando os valores de TA no início e no final do estudo, verifica-se que a TAS foi reduzida de 0,8 mm Hg no grupo controlo e de 7,6 mm Hg no grupo de intervenção (sendo *P* = 0,005, quando se compara a TAS nos dois grupos no final do estudo). Paralelamente, a TAD foi reduzida de 1,1 mm Hg no grupo controlo e de 3,0 mm Hg no grupo de intervenção (sendo *P* = 0,016, quando se compara a TAD nos dois grupos no final do estudo) (Tabela 17). Esta análise

foi também efectuada tendo em conta as perdas ocorridas no *follow-up*, afim de avaliar a robustez daqueles resultados atendendo aos doentes que não acompanharam o estudo até ao fim (análise *intent-to-treat*). A análise dos valores de TA foi, então, repetida tendo em conta o cenário mais pessimista, em que se considerou que, no final do estudo, todos os 4 *dropouts* do grupo de intervenção tinham a TA não controlada e todos os 3 *dropouts* do grupo controlo tinham a TA controlada. Nesta situação, a taxa de controlo da TA foi de 63,3% no grupo de intervenção e de 43,4% no grupo controlo (*odds ratio* de 2,2; IC 95%: 1,3-4,0; *P* = 0,005). Do mesmo modo, se considerarmos o último valor de TA registado nos 7 *dropouts*, a TAS foi reduzida de 0,9 mm Hg no grupo controlo e de 7,4 mm Hg no grupo de intervenção (sendo *P* = 0,006, quando se compara a TAS nos dois grupos no final do estudo). Paralelamente, a TAD foi reduzida de 1,0 mm Hg no grupo controlo e de 2,7 mm Hg no grupo de intervenção (sendo *P* = 0,020, quando se compara a TAD nos dois grupos no final do estudo) (Tabela 17).

Durante o período em que decorreu o estudo, o farmacêutico hospitalar fez um total 118 recomendações envolvendo a terapêutica anti-hipertensora, das quais 90 (76,3%) foram aceites pelos médicos. Estas recomendações incluíram a manutenção da terapêutica anti-hipertensora (25,4%), a introdução de medicação adicional (25,4%), o aumento da dose de medicamentos já prescritos (13,5%), a suspensão de medicação prescrita (5,9%) e a diminuição da dose de medicamentos prescritos (0,8%). Apesar destas recomendações, a média do número total de alterações efectuadas à terapêutica anti-hipertensora por doente não diferiu significativamente em ambos os grupos do estudo (0,65 *vs* 0,72, respectivamente, no grupo de intervenção e no grupo controlo, *P* = 0,693). Do mesmo modo, também não se observaram diferenças estatisticamente significativas no número de novos medicamentos anti-hipertensores adicionados por doente (0,34 *vs* 0,37, respectivamente, no grupo de intervenção e no grupo controlo, *P* = 0,768), no número de medicamentos anti-hipertensores descontinuados por doente (0,20 *vs* 0,19, respectivamente, no grupo de intervenção e no grupo controlo, *P* = 0,879) e no número de alterações da dose de medicamentos por doente (0,10 *vs* 0,15, respectivamente, no grupo de intervenção e no grupo controlo, *P* = 0,321). No final do estudo, o número de medicamentos anti-hipertensores prescritos por doente não diferiu significativamente em ambos os grupos (2,8 ± 1,3 *vs* 2,7 ± 1,4, respectivamente, no grupo de intervenção e no grupo controlo, *P* = 0,682). De igual modo, também não se observaram, no final do estudo, diferenças significativas nas classes de anti-hipertensores prescritas nos dois grupos do estudo (Tabela 16).

Apesar das recomendações do farmacêutico hospitalar no que respeita à adopção de estilos de vida saudáveis, no final do estudo, não se observou uma diferença significativa no índice de massa corporal em ambos os braços do estudo (29,9 *vs* 29,3 kg/m^2, respectivamente, no grupo de intervenção e no grupo controlo, *P* = 0,371).

No que respeita à adesão à terapêutica farmacológica anti-hipertensora, não se observou, no início do estudo, uma diferença significativa em ambos os grupos na percentagem de doentes com elevada adesão à medicação (46,9% *vs* 49,5%, respectivamente, no grupo de intervenção e no grupo controlo, *P* = 0,718). Contudo, no final do estudo, foi observada uma diferença estatisticamente significativa (*P* = 0,0017) em ambos os grupos na percentagem de doentes com elevada adesão à medicação (77,0% no grupo de intervenção e 56,3% no grupo controlo). Em conformidade com estes resultados, observou-se, dentro de cada grupo, do início para o final do estudo, uma diferença significativa na adesão à medicação no grupo de intervenção (*P* < 0,0001) mas não no grupo controlo (*P* = 0,345).

O conhecimento dos valores alvo da TA, dos riscos da HTA não controlada e da indicação dos medicamentos foram parâmetros em que se observou uma melhoria significativa no grupo de intervenção mas não no grupo controlo. Embora, no início do estudo, não existissem diferenças significativas nestes parâmetros nos dois grupos (Tabela 15), no final do estudo, a percentagem de doentes que demonstraram ter conhecimento dos valores alvo da TA, dos riscos da HTA não controlada e da indicação dos medicamentos foi significativamente maior no grupo de intervenção (Tabela 18).

Relativamente à monitorização regular da TA, não se observou, no final do estudo, uma diferença significativa entre os dois grupos do estudo (Tabela 18). Contudo, no que respeita a este parâmetro, foi detectada uma diferença estatisticamente significativa entre o início e o final do estudo no grupo de intervenção (*P* = 0,010), o que não aconteceu no grupo controlo (*P* = 0,390).

O único parâmetro analisado em que não se observou uma diferença significativa, no início e no final do estudo, quer inter- quer intra-grupos, foi a nível das reacções adversas atribuídas à medicação anti-hipertensora (Tabelas 15 e 18).

As diferenças estatisticamente significativas mencionadas para os parâmetros estudados mantiveram a significância estatística quando os dados foram avaliados por análise *intent-to-treat* (Tabela 18).

Tabela 18 - Conhecimentos acerca da HTA, monitorização da TA e presença de reacções adversas nos grupos controlo e de intervenção no final do estudo.

Parâmetros analisados	Grupo controlo	Grupo de intervenção	Valor de *P*
Final do estudo	**n=96**	**n=94**	
Conhecimento dos valores alvo de TA, n (%)	61 (63,5%)	77 (81,9%)	**0,005**
Conhecimento dos riscos da HTA, n (%)	63 (65,6%)	79 (84,0%)	**0,003**
Conhecimento da indicação dos medicamentos, n (%)	69 (71,9%)	83 (88,3%)	**0,005**
Monitorização regular da TA, n (%)	74 (77,1%)	80 (85,1%)	0,158
Presença de reacções adversas atribuídas à medicação anti-hipertensora, n (%)	19 (19,8%)	12 (12,8%)	0,190
Análise *ITT*	**n=99**	**n=98**	
Conhecimento dos valores alvo de TA, n (%)	61 (61,6)	77 (78,6)	**0,009**
Conhecimento dos riscos da HTA, n (%)	66 (66,7)	79 (80,6)	**0,026**
Conhecimento da indicação dos medicamentos, n (%)	71 (71,7)	86 (87,8)	**0,005**
Monitorização regular da TA, n (%)	76 (76,8)	83 (84,7)	0,158
Presença de reacções adversas atribuídas à medicação anti-hipertensora, n (%)	19 (19,2)	12 (12,2)	0,181

Abreviaturas: n – frequência; *ITT* – *intent-to-treat*; HTA – hipertensão arterial; TA – tensão arterial.

Capítulo 7

Discussão

Os resultados obtidos na 1ª fase do estudo (Julho a Setembro de 2009) permitiram caracterizar demográfica e clinicamente os doentes hipertensos atendidos no Centro Hospitalar Cova da Beira, E.P.E., bem como avaliar o seu grau de controlo da TA e de adesão à terapêutica medicamentosa anti-hipertensora (Morgado et al. 2010). Tanto quanto é do nosso conhecimento, não existia, até ao momento, qualquer estudo observacional que tivesse determinado a percentagem de doentes hipertensos, da zona de influência do Centro Hospitalar em causa e tratados com medicação anti-hipertensora, com a TA controlada de acordo com as orientações definidas nacional e internacionalmente (Chobanian et al. 2003; Direcção-Geral da Saúde 2004). Este estudo revelou que 33,0% dos doentes hipertensos, a quem foi prescrita medicação anti-hipertensora, tem a sua TA controlada de acordo com as referidas orientações, sendo a percentagem de controlo da TA significativamente maior nos doentes sem diabetes nem doença renal crónica do que nos doentes com, pelo menos, uma daquelas patologias (39,2% *vs* 11,4%, *P* = 0,009). De acordo com um estudo epidemiológico, transversal, realizado em Portugal, em 2003, a taxa de hipertensos da região Centro, tratados com anti-hipertensores, com valores de TA < 140/90 mm Hg é de apenas 26,1% (De Macedo et al. 2007). Este valor é consideravelmente mais baixo do que o obtido no presente estudo (37,1% doentes com TA < 140/90 mm Hg), o que parece indicar uma maior eficácia no tratamento dos doentes incluídos no estudo actual relativamente aos incluídos no estudo de 2003. É muito provável que a Circular Normativa da Direcção-Geral da Saúde Nº 2/DGCG, de 31/03/2004 ("Diagnóstico, tratamento e controlo da hipertensão arterial") (Portuguese Department of Health 2004. Available at http://www.dgs.pt/. Accessed on 07/15/2010) e as "Normas sobre detecção, avaliação e tratamento da hipertensão arterial da Sociedade Portuguesa de Hipertensão" (Polonia et al. 2006), publicadas em 2006, tenham contribuído para melhorar o tratamento e o controlo da HTA em Portugal. Ambos os documentos apresentam consideráveis e inequívocas semelhanças entre si e com o JNC 7 (Chobanian et al. 2003).

Os resultados do presente trabalho aproximam-se dos obtidos por Ragot et al. num estudo observacional realizado numa população de doentes hipertensos tratados (n = 1015) do Oeste-Central de França (Ragot et al. 2005). Neste estudo cerca de 39% dos doentes tinha valores de TA < 140/90 mm Hg, sendo que apenas 13% (18/134) dos hipertensos diabéticos apresentavam a TA controlada de acordo com as recomendações internacionais (< 130/80 mm Hg). Na realidade, os valores mais baixos de TA recomendados nos diabéticos e nos insuficientes renais (< 130/80 mm Hg) não são atingidos na grande maioria destes doentes (Mancia and Grassi 2002; Mancia et al. 2005; Andros et al. 2006; Mancia et al. 2009). É importante

salientar, contudo, que, actualmente, os valores de TA tradicionalmente mais baixos recomendados nos diabéticos, estão, cada vez mais, a ser postos em causa devido à falta de evidência científica que sustente essa recomendação (Cooper-DeHoff et al.; Cushman et al.; Fagard; Mancia et al. 2009). A Sociedade Europeia de Hipertensão (SEH) na sua reavaliação das *guidelines* europeias para o tratamento da hipertensão recomenda que os doentes diabéticos iniciem o tratamento anti-hipertensor tal como a generalidade dos doentes hipertensos, isto é, quando os valores de TA forem ≥ 140/90 mm Hg (Mancia et al. 2009). De acordo com esta reavaliação, o início do tratamento dos diabéticos quando os valores de TA se situam no intervalo 130 – 139 mm Hg não é actualmente suficientemente sustentado por evidência científica obtida em ensaios clínicos (Mancia et al. 2009). Os mesmos autores reconhecem, contudo, que o tratamento anti-hipertensor, na presença destes valores de TA (130 – 139 mm Hg), possa ser recomendado quando existe microalbuminúria, com base na evidência de um efeito favorável na regressão e progressão deste sinal de lesão de órgão alvo (Mancia et al. 2009).

A análise de regressão logística revelou que as covariáveis com influência significativa no controlo da TA são a adesão à terapêutica anti-hipertensora, o estado marital e a diabetes, de tal forma que a probabilidade de um doente hipertenso, não aderente à medicação, não casado e diabético ter a TA não controlada é de 98,6%. No extremo oposto, a probabilidade de um doente hipertenso, aderente à medicação, casado e não diabético ter a TA não controlada é de apenas 39,3%. Certamente que existirão outras variáveis independentes não estudadas que influenciam significativamente o controlo da TA (p. ex., a medicação anti-hipertensora prescrita, factores genéticos, factores ambientais, etc.). A possível existência de inércia clínica e sub-tratamento deverá também ser investigada nos doentes com diabetes e/ou doença renal crónica, tendo em vista encontrar uma explicação para a percentagem significativamente mais baixa de controlo da TA observada nestes doentes, mesmo quando comparada com os resultados obtidos por outros autores (28% - 37,5%) (Andros et al. 2006; Ong et al. 2007; Jackson et al. 2008). No entanto, é de salientar que o modelo de regressão logística obtido (Equação (1)) apresentou uma sensibilidade, uma especificidade e um poder discriminante [dado pela área sob a curva ROC (*Receiver Operating Characteristic*)] aceitáveis (Morgado et al. 2010).

Das três covariáveis mencionadas, a adesão à medicação é a única variável independente que pode ser favoravelmente influenciada por uma equipa multidisciplinar de saúde, tendo em vista aumentar o controlo da TA. A falta de adesão à terapêutica anti-hipertensora constitui, de facto, um factor de risco, muitas vezes negligenciado, para a existência de TA não controlada em doentes hipertensos tratados, contribuindo, desta forma, para o desenvolvimento dos efeitos cardiovasculares adversos causados pela HTA (Munger et al. 2007). Embora as taxas de adesão à terapêutica anti-hipertensora variem com a população estudada, na grande maioria dos estudos efectuados em doentes hipertensos tratados essas

taxas situam-se, arredondadamente, entre 50% e 70% (Psaty et al. 1995; Caro et al. 1999; Krousel-Wood et al. 2004; Schroeder et al. 2004). Ramalhinho e Cabrita, num estudo que incluiu 95 hipertensos tratados da região suburbana de Lisboa, obtiveram uma taxa de adesão à terapêutica anti-hipertensora, avaliada pelo método da contagem de medicamentos, de 46,3% (Ramalhinho and Cabrita 1998). Neste estudo, foram considerados aderentes os indivíduos que tomaram entre 80% e 120% da medicação prescrita (Ramalhinho and Cabrita 1998). Deste modo, a percentagem de adesão à terapêutica da população hipertensa estudada (48,2%) situa-se dentro do intervalo de adesão descrito na literatura. As *guidelines* do JNC7 salientam claramente a importância das intervenções tendo em vista o aumento da adesão à terapêutica anti-hipertensora, tendo destacado o papel de todos os profissionais de saúde, incluindo os farmacêuticos, no desenvolvimento daquelas intervenções (Chobanian et al. 2003).

A análise de regressão logística revelou, ainda, que o conhecimento dos valores alvo de TA, a presença de reacções adversas atribuídas à medicação anti-hipertensora, a monitorização regular da TA, o conhecimento da indicação dos medicamentos e o conhecimento dos riscos da HTA foram as variáveis independentes estudadas que influenciam significativamente a adesão à terapêutica medicamentosa. Essa influência é de tal forma que a probabilidade de um doente hipertenso que desconhece os valores alvo de TA, as indicações dos medicamentos e os riscos da HTA, que apresenta RAMs e que não mede regularmente a TA de ser não aderente à medicação é de 97,4%. Pelo contrário, a probabilidade de um doente hipertenso que conhece os valores alvo de TA, as indicações dos medicamentos e os riscos da HTA, que não apresenta RAMs e que mede regularmente a TA de ser não aderente à medicação é de apenas 17,6%. Embora, também aqui, pudessem ter sido estudadas outras variáveis independentes com influência na adesão à terapêutica (p. ex., crenças do doente relativamente à eficácia dos medicamentos, confiança na equipa multidisciplinar de saúde, etc.) é de salientar que o modelo de regressão logística obtido (Equação (2)) apresentou uma sensibilidade, uma especificidade e um poder discriminante aceitáveis (Morgado et al. 2010).

A análise de regressão logística não identificou o sexo, a idade e o nível educacional como covariáveis com influência significativa na adesão à terapêutica, encontrando-se estes resultados em alinhamento com os obtidos por Ramalhinho e Cabrita numa população portuguesa (Ramalhinho and Cabrita 1998). Ragot et al. também não identificaram diferenças significativas entre homens e mulheres no que respeita à adesão à medicação; contudo, os doentes que relataram RAMs eram significativamente ($p < 0,001$) menos aderentes à medicação do que os doentes sem RAMs (Ragot et al. 2005). A falta de conhecimento dos valores alvo de TA tem também sido associada a uma menor adesão à terapêutica medicamentosa e a um menor controlo da pressão arterial (Knight et al. 2001).

Embora uma percentagem considerável de doentes (70,6%) meça a TA regularmente, apenas 59,4% (*P* = 0,020) tem um conhecimento correcto dos valores alvo de TAS e de TAD. A medição regular da TA e o seu registo são extremamente importantes para a avaliação, pela equipa multidisciplinar de saúde, do efeito do tratamento anti-hipertensor, sendo também muito importantes para a monitorização, pelo próprio doente, do controlo da HTA. Contudo, uma percentagem considerável de doentes (40,6%) desconhece os valores alvo de TA, pelo que não consegue avaliar eficazmente se a mesma se encontra controlada. Desta forma, uma implicação *major* do presente estudo é a necessidade de educação dos doentes no que respeita aos valores alvo de TA, para que possam avaliar correctamente se a mesma se encontra elevada ou controlada.

Os resultados obtidos sugerem, igualmente, a necessidade de melhorar os conhecimentos dos doentes no que respeita aos riscos cardiovasculares da HTA não controlada e às indicações terapêuticas e potenciais benefícios dos medicamentos anti-hipertensores prescritos. É importante notar que, embora a população em estudo tenha HTA há já vários anos (o valor médio do número de anos a tomar medicação anti-hipertensora foi de 9,8 ± 7,7 anos), o seu conhecimento no que respeita à HTA revelou-se inadequado. Diversos estudos revelaram a necessidade de melhorar os conhecimentos na área da HTA tendo em vista o aumento da adesão à terapêutica e o controlo da TA (Gonzalez-Fernandez et al. 1990; Oliveria et al. 2005).

Deve, igualmente, ser dada atenção às reacções adversas provocadas pelos medicamentos anti-hipertensores, uma vez que constituem uma importante causa de não adesão à terapêutica (Mancia et al. 2007). De referir, contudo, que nem sempre é possível resolver totalmente as RAMs associadas aos anti-hipertensores, uma vez que estas podem ter, em parte, uma componente psicológica, sendo igualmente referidas, nos ensaios clínicos, durante a administração do placebo (Mancia et al. 2007). No entanto, é indiscutível que deve ser desenvolvido um esforço considerável tendo em vista limitar a ocorrência de RAMs e melhorar a qualidade de vida do doente, quer através de uma alteração da medicação prescrita (para eliminar o medicamento responsável pelos efeitos adversos), quer evitando aumentos desnecessários da dose recorrendo à terapêutica combinada (associação de dois ou mais princípios activos) (Gradman et al. 2010). A discussão, entre o doente e os profissionais de saúde, acerca da existência de RAMs deve igualmente ser encorajada.

O estudo observacional transversal realizado no subgrupo de doentes com HTA de estádio 1 e hipercolesterolémia conduziu a resultados que estão em alinhamento com os obtidos noutros estudos (Glorioso et al. 1999; Ferrier et al. 2002; Ikeda et al. 2004), sugerindo um efeito clinicamente significativo das estatinas na diminuição da TA (Morgado et al. 2010). Do ponto de vista metodológico, o estudo transversal realizado envolveu uma amostra de reduzidas dimensões, sobretudo do grupo controlo (n =28), pelo que os seus resultados poderão, apenas,

ser considerados de natureza exploratória. Embora estes resultados necessitem de ser confirmados através de dados prospectivos obtidos em estudos experimentais e observacionais, eles sugerem que em doentes com HTA de estádio 1 nos quais está indicada a prescrição de uma estatina (p. ex., devido á presença concomitante de hipercolesterolémia), esta poderá melhorar o controlo da TA e/ou reduzir a dose e o número de anti-hipertensores necessários para a obtenção de um controlo adequado da HTA.

A revisão sistemática e meta-análise efectuadas inicialmente (Morgado et al. 2011), bem como os resultados obtidos na primeira fase do estudo (Julho a Setembro de 2010) (Morgado et al. 2010) foram determinantes para o planeamento do programa de intervenção farmacêutica implementado, subsequentemente, numa fracção da mesma população hipertensa (grupo de intervenção), durante um período de 9 meses (Morgado et al. 2011). Este programa de intervenção farmacêutica conduziu a uma redução significativa da TAS e da TAD e a um aumento significativo da proporção de doentes com a TA controlada de acordo com as recomendações da DGS (Direcção-Geral da Saúde 2004) e do JNC 7 (Chobanian et al. 2003). A probabilidade de atingir os valores alvo de TA no grupo de intervenção foi 2,7 vezes maior do que no grupo controlo (IC 95%: 1,5-4,9; $P < 0,001$). Estas diferenças permaneceram significativas quando os dados foram submetidos a uma análise *intent-to-treat*. Em doentes hipertensos com idades entre 60-69 anos, a redução adicional de 6,8 mm Hg observada na TAS do grupo de intervenção deverá conduzir a uma redução de 22% na mortalidade por acidente vascular cerebral e de 17% na mortalidade por doença cardíaca isquémica (Lewington et al. 2002). Desta forma, a inclusão do farmacêutico hospitalar na equipa multidisciplinar de saúde, responsável pelo tratamento dos doentes com HTA, constitui uma estratégia vantajosa para combater este importante problema de saúde pública.

O programa de intervenção farmacêutica conduziu a um aumento significativo da adesão à terapêutica anti-hipertensora, o qual foi provavelmente a causa do melhor controlo da TA no grupo de intervenção, uma vez que as alterações à medicação anti-hipertensora não diferiram significativamente em ambos os grupos.

De referir que existem alguns estudos de intervenções farmacêuticas em que se observou uma melhoria significativa nos *outcomes* clínicos (TAS, TAD e/ou percentagem de doentes hipertensos com a TA controlada) sem aumentos significativos na adesão à terapêutica (Mehos et al. 2000; Vivian 2002; Chabot et al. 2003; Zillich et al. 2005; Roumie et al. 2006; Carter et al. 2008; Carter et al. 2009). Estes resultados podem ser atribuídos a uma intensificação da terapêutica anti-hipertensora e, de facto, algumas intervenções farmacêuticas conduziram a um aumento significativo do controlo da TA através deste mecanismo (Vivian 2002; Carter et al. 2008; Carter et al. 2009). Diversos estudos revelaram que, frequentemente, a terapêutica anti-hipertensora não é intensificada mesmo quando a TA não se encontra controlada, um fenómeno descrito na literatura anglo-saxónica como *clinical inertia* (Chobanian et al. 2003;

Milchak et al. 2008; Carter et al. 2009). As percentagens de controlo da TA mais elevadas nos Estados Unidos da América do que em alguns países Europeus tem sido atribuída a uma maior intensificação da terapêutica anti-hipertensora (Wolf-Maier et al. 2004; Ong et al. 2007). Através de uma optimização da terapêutica farmacológica anti-hipertensora (p. ex., aumento das doses dos anti-hipertensores prescritos, substituição de um anti-hipertensor por outro com diferente mecanismo de acção, adição de um diurético tiazídico caso este não faça ainda parte do regime terapêutico, simplificação do regime terapêutico através da utilização de associações de anti-hipertensores na mesma preparação farmacêutica) o farmacêutico pode contribuir para a modificação de regimes farmacoterapêuticos ineficazes e para a selecção de outros com maior probabilidade de sucesso.

No entanto, na grande maioria dos estudos em que se observou um aumento significativo na adesão à terapêutica observou-se, igualmente, uma melhoria significativa nos *outcomes* clínicos, o que revela que a adesão à terapêutica é um factor chave (embora não seja o único) no controlo da TA (Blenkinsopp 2000; Brouker et al. 2000; Sookaneknun et al. 2004; Lee et al. 2006; de Souza et al. 2007; Lai 2007; Aguwa et al. 2008). Quando a adesão à terapêutica no início do estudo (*baseline*) é elevada (> 75%), as intervenções farmacêuticas não conduzem, frequentemente, a uma melhoria significativa deste *outcome* (Chabot et al. 2003; Roumie et al. 2006; Carter et al. 2008; Carter et al. 2009). No nosso estudo, a baixa adesão à terapêutica observada no início (< 50%) tornou possível ao farmacêutico hospitalar melhorar significativamente este *outcome* e, consequentemente, os *outcomes* clínicos.

De acordo com os resultados obtidos na primeira fase do estudo (Equação (2)), o aumento da adesão à terapêutica medicamentosa poderá ser atribuído à melhoria dos conhecimentos dos doentes no que respeita aos valores alvo da TA, aos riscos da HTA não controlada e à indicação dos medicamentos (Tabela 18). De facto, a falta de conhecimento dos valores alvo da TA, das complicações da HTA e dos benefícios da terapêutica anti-hipertensora foram, em diversos estudos, reconhecidos como barreiras à adesão à terapêutica anti-hipertensora (Whelton et al. 2002; Oliveria et al. 2005; Ragot et al. 2005).

Capítulo 8

Limitações do Ensaio Clínico

Embora os ensaios clínicos controlados e aleatorizados possibilitem a mais elevada validade interna através do controlo do viés de confundimento, apresentam como potencial limitação a contaminação do grupo controlo, através do contacto deste com o programa de intervenção. No nosso estudo, a aleatorização ao nível dos doentes, ao invés dos farmacêuticos ou médicos, poderá ter originado viés de contaminação. Alguns doentes do grupo controlo questionaram o farmacêutico hospitalar, no decurso da consulta inicial, acerca dos valores alvo da TA e dos riscos da HTA não controlada e, além disso, os médicos que participaram no estudo estiveram envolvidos no tratamento dos doentes de ambos os grupos. Embora este viés de contaminação tivesse sido considerado aquando do desenho do estudo, tendo em vista a sua minimização, é importante reconhecer que a sua presença favorece a hipótese nula, de acordo com a qual a intervenção do farmacêutico não conduz a uma melhoria significativa dos *outcomes* estudados.

A avaliação do controlo da TA baseou-se na medição da TA efectuada em apenas duas consultas (*baseline* e após um período de *follow-up* de 9 meses). Estas duas determinações da TA podem ou não ser representativas do controlo da TA nos doentes hipertensos em estudo, pese embora o facto de terem sido efectuadas por enfermeiras cegas-para-o-estudo, o que contribui para a validade dos efeitos observados.

A determinação da adesão à terapêutica foi efectuada pelo farmacêutico hospitalar envolvido no projecto de investigação (não cego-para-o-estudo), o que constitui um potencial factor de viés nas situações em que o doente não responde com determinação ao questionário de adesão à terapêutica, aplicado sob a forma de entrevista estruturada. A realização de um questionário sob a forma escrita, em que um impresso contendo as questões seria entregue ao doente para este as responder por escrito, foi um modelo de inquérito inicialmente equacionado. Contudo, a baixa literacia de uma percentagem significativa da população em estudo tornou desaconselhável a utilização deste modelo de inquérito.

A intervenção farmacêutica foi de curta duração (apenas 9 meses). São necessários estudos adicionais, de maior duração, para verificar se os benefícios observados, da intervenção farmacêutica no controlo da TA, são sustentáveis ao longo do tempo.

Não foi possível utilizar métodos objectivos na determinação da adesão à terapêutica (p. ex., determinação dos princípios activos, ou produtos do seu metabolismo, nos fluidos biológicos, utilização de marcadores biológicos, observação directa do doente a tomar os medicamentos)

ou de avaliar as atitudes dos profissionais de saúde em relação aos doentes. Diversos modelos comportamentais sugerem que a terapêutica farmacológica mais eficaz, prescrita pelo médico mais experiente, apenas controlará eficazmente a TA se o doente estiver motivado para tomar a medicação conforme foi prescrita (Chobanian et al. 2003). A motivação melhora quando os doentes têm experiências positivas e confiam na equipa multidisciplinar de saúde envolvida no seu tratamento (Chobanian et al. 2003). A boa empatia dos profissionais de saúde aumenta a confiança, motivação e adesão dos doentes à terapêutica. É possível que a intervenção farmacêutica tenha conduzido a um aumento da adesão à terapêutica através, também, de um aumento desta confiança e motivação dos doentes. São necessários estudos adicionais, no âmbito das ciências sociais, para avaliar o grau de satisfação dos doentes com os diversos profissionais de saúde.

Outra limitação, esta respeitante apenas à primeira fase do estudo, diz respeito ao número limitado de covariáveis analisadas em ambos os modelos de regressão logística desenvolvidos. Por exemplo, o sub-tratamento e a inércia clínica constituem causas reconhecidas de TA não controlada (Milchak et al. 2004; Carter et al. 2009) que não foram avaliadas no primeiro modelo de regressão logística desenvolvido. Outras variáveis independentes que não foram analisadas dizem respeito, por exemplo, às crenças dos doentes relativamente à eficácia dos medicamentos, à confiança na equipa multidisciplinar de saúde e à motivação do doente, induzida por esta equipa de saúde, para a realização do tratamento. Estas, são exemplos de variáveis independentes que não foram analisadas e que poderão influenciar significativamente, quer a adesão à terapêutica, quer o controlo da TA.

Capítulo 9

Conclusões Gerais e Perspectivas para o Futuro

Os resultados deste estudo revelam que uma percentagem significativa de doentes hipertensos a quem foram prescritos medicamentos anti-hipertensores não apresenta a TA controlada, sendo a taxa de adesão a estes medicamentos muito inferior à que seria desejável.

Através da análise de regressão logística foi possível proceder à identificação de diversas covariáveis com influência significativa na adesão à terapêutica anti-hipertensora e no controlo da tensão arterial, algumas das quais passíveis de serem favoravelmente influenciadas por uma equipa multidisciplinar de saúde.

A baixa adesão à terapêutica, o desconhecimento, por parte do doente, dos valores alvo de TA, dos riscos da HTA não controlada e das indicações dos medicamentos, bem como a ocorrência de RAMs e a falta de monitorização regular da TA devem ser estudados como possíveis causas de TA não controlada e devem ser considerados em qualquer intervenção que tenha como objectivo aumentar o controlo da TA.

Desta forma, qualquer intervenção que tenha em vista aumentar o controlo da TA deverá desenvolver estratégias para aumentar a adesão à terapêutica. Deverá encorajar a monitorização regular da TA. Os doentes deverão ser informados acerca dos valores de TA a atingir, de forma a poderem participar mais eficazmente na monitorização da sua TA. Deverão, igualmente, ser informados acerca dos riscos da HTA não controlada e das indicações terapêuticas dos medicamentos. A adopção de estilos de vida saudáveis deve ser incentivada. As RAMs devem ser resolvidas ou minimizadas. Qualquer intervenção desenvolvida por uma equipa multidisciplinar de saúde deverá, desta forma, envolver o doente como um participante activo no tratamento e monitorização da sua HTA.

Encontra-se em desenvolvimento um sistema de telemonitorização da pressão arterial, constituído por um aparelho de medição da TA portátil que comunica sem fios com um telefone informando o médico dos valores do doente e lançando alertas, se necessário. O doente também recebe informação de volta, para saber como está a correr o processo, e o sistema vai recordá-lo na altura em que for necessário fazer novas medições ou tomar medicação. Este sistema, destinado a ser utilizado pelos doentes hipertensos da consulta de hipertensão / dislipidémia do Centro Hospitalar Cova da Beira, E.P.E., permitirá um maior acompanhamento da evolução do tratamento anti-hipertensor, uma maior interacção entre o doente e os profissionais de saúde e contribuirá para aumentar a adesão à terapêutica.

Permitirá, igualmente, uma monitorização regular da TA, permitindo ao profissional de saúde fornecer mais rapidamente uma orientação ao doente caso a HTA não se encontre controlada. Os valores de TA medidos em regime ambulatório contribuirão também para uma avaliação mais eficaz do controlo da TA, permitindo ultrapassar as desvantagens decorrentes da medição realizada em ambiente hospitalar. A TA ambulatória (MAPA ou auto medição da TA no domicílio) é melhor factor preditivo dos eventos cardiovasculares e da mortalidade do que a TA avaliada no consultório, tanto na população em geral como nos grupos de alto risco.

Os resultados obtidos sugerem a possibilidade da prescrição de estatinas poder estar associada a um maior controlo da TA no subgrupo de doentes com HTA de estádio 1 e hipercolesterolémia, sendo, contudo, necessários estudos de maiores dimensões, experimentais e observacionais, que confirmem esta associação. Esta associação, a ser confirmada, poderá ter implicações vantajosas na prevenção eficaz e segura de eventos cardiovasculares no subgrupo de doentes mencionado.

O ensaio clínico realizado demonstrou que a intervenção farmacêutica hospitalar pode modificar os factores que afectam a adesão à terapêutica e aumentá-la significativamente, conduzindo, deste modo, a um aumento do controlo da TA em doentes hipertensos tratados com anti-hipertensores.

Para atingir o objectivo final de melhorar o estado de saúde da população hipertensa, através do controlo da TA, é importante avaliar os conhecimentos e as atitudes dos doentes no que respeita à HTA e aos anti-hipertensores. Este trabalho revela que um método eficaz de melhorar o controlo da TA consiste na detecção de não adesão à terapêutica medicamentosa e no desenvolvimento de estratégias que incluam o doente como participante activo no tratamento e monitorização da sua HTA. O ensaio clínico realizado revela, igualmente, o importante papel do farmacêutico hospitalar na equipa multidisciplinar de saúde, tendo em vista a obtenção de resultados clínicos mais favoráveis para os doentes hipertensos.

Capítulo 10

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Capítulo 11

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11.1 Abstract I

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172

11.1 Abstract I

PC-108 Pilot study of blood pressure control and medication adherence in a hypertensive population

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Background and objective Antihypertensive therapy reduces blood pressure (BP) and cardiovascular morbidity and mortality. However, only 26.1% of treated patients with hypertension in the Central Region of Portugal have BP values of <140/90 mmHg. The objective of this study was to assess BP control according to current guidelines, and patient's medication adherence, and knowledge about hypertension (HT) in a hypertensive population of Eastern Central Region of Portugal.

Design Cross-sectional survey. Patients attending a HT/dyslipidemia medical clinic during July and August 2009 were randomised for participation in a structured interview including lifestyle, adherence to medication, and knowledge about HT and target BP values. Detailed clinical information, including BP measures, medications prescribed and medical problems was obtained from medical records. The study was approved by the institutional Ethics Committee, and written informed consent was obtained from all participants before their enrolment in the study.

Setting HT/dyslipidemia clinic in the University Teaching Hospital of Cova da Beira Hospital Centre, Covilhã, located in the Eastern Central Region of Portugal.

Main outcome measures The primary outcomes are BP control based on evidence-based guidelines [<140/90 mm/Hg for patients without diabetes and chronic kidney disease (CKD) and <130/80 mm/Hg for patients with diabetes and/or CKD] and adherence to prescribed medication.

Results A total of 119 patients attended the medical clinic of whom 76 were asked to complete the structured interview. Of those who completed the interview (100%), two were excluded from our study because they had not arterial HT. Overall, 49.1% (27/55) of patients with a target BP <140/90 mmHg and 31.6% (6/19) of patients with a target BP <130/80 mmHg had their BP controlled ($P = 0.186$). Only two patients had their BP controlled without antihypertensive medication. According to the best practice recommendations, almost all of patients (17/19) with the comorbidity diabetes were treated with an angiotensin converting enzyme inhibitor or angiotensin receptor antagonist. Only 54.2% patients were considered to be adherent to medication. In all, 20.3% patients were aware of their target BP figures (systolic an diastolic), 29.7% indicated only a correct single target BP figure and 50% gave no correct figure. Only 35.1% knew that HT increases the risk of stroke or heart attack.

Conclusions Many hypertensive patients who het antihypertensives prescribed fail to achieve BP control in clinical practice. Behavioural and educational interventions to improve medication adherence and patient knowledge in HT are needed to address inadequate BP control. We will develop and implement such interventions.

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PC-11 Unintended modifications of chronic medication due to admission to an intensive care unit

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Background and objective Admission to an intensive care unit (ICU) may entail an elevated risk of drug discrepancies (DD) due to the focus of care on stabilization of the patient.

The objective of the study was to investigate whether an ICU stay leads to more DD's in particular with respect to chronic medication.

Design Observational, prospective, controlled cohort study. At hospital admission, the medication history was documented by a pharmacist. For drugs administered during hospitalization and prescribed at discharge, physicians' medication records were consulted. For patients transferred from the ICU to another ward, and who were later discharged from the hospital, the medication list and the medication scheme in the discharge letter, respectively, were compared with the pharmacist-acquired medication history with special focus on chronic drugs.

Setting Two adult ICU's (study group) and one cardiologic care unit (control group) of a Belgian university hospital (UZ Brussel).

Main outcome measures The percentage of patients with unintended DD and the incidence as well as the type of DD in chronic medication.

Results The study group consisted of 24 patients and the control group of 12 patients. In the study group 67% of the patients had one or more discrepancies in the medication history vs. 83% in the control group. There was no statistically significant difference in the number of DD between the two groups (Mann–Whitney test; $U = 135.5$; $n1 = 24$; $n2 = 12$; $P = 0.77$; $\alpha = 0.05$). The most common discrepancy was omission of a chronic medication.

At the time of transfer from the ICU to another medical ward, 83% of the patients had one or more DD. The most common discrepancy was again omission of a chronic medication.

At hospital discharge, the percentage of patients with unintended DD was remarkably higher for the study group (81%) than for the control group (55%). There were significantly more DD in the study group than in the control group (Mann–Whitney test; $U = 63.5$; $n1 = 21$; $n2 = 11$; $P = 0.036$; $\alpha = 0.05$). The most common discrepancy was omission of a chronic medication in the discharge letter. The percentage of unintended DD at discharge due to the ICU stay was 36%.

Conclusions The stay in an ICU leads to more unintended DD in chronic medication. Some discrepancies are solved during the further hospitalization, but an important number results in DD at hospital discharge. At transition periods, structural medication reconciliation is necessary to prevent drug discrepancies. The complete and accurate transfer of information between hospital health care providers, patients and health care providers at home is crucial to prevent drug related problems.

Keywords Clinical pharmacy, Drug discrepancies, Intensive care

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PC-12 Medicines reconciliation: developing quality indicators

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Background and objective Evaluating quality of care is essential when redesigning or improving practice. Medicines reconciliation (MR) on hospital admission is now policy in the UK. It is the process of obtaining an up-to-date and accurate medication list and documenting any discrepancies. The overall aim of this work was

174

11.2 Abstract II

were infrequent: dizziness (2.9%) and hypotension (1.9%). Forty-three pts discontinued (12 AEs; 10 pt request; 10 protocol violation; 7 lost to follow-up; 4 other). AML/OM±HCTZ was well tolerated, produced significant SeBP reductions and enabled 61.7% of pts with diabetes and hypertension to reach a SeBP goal of <130/80 mm Hg at Week 18.

SeBP Endpoints at End of Titration Period

	AML 5 mg	AML/OM 5/20 mg	AML/OM 5/40 mg	AML/OM 10/40 mg	AML/OM+HCTZ 10/40+12.5 mg	AML/OM+HCTZ 10/40+25 mg
n	200	188	176	163	144	100
Baseline SeBP mm Hg (±SD)	158.8±12.9/89.0±10.0	158.8±12.9/89.0±10.3	159.2±12.6/89.6±10.1	159.4±12.6/89.5±10.1	159.5±12.8/89.7±10.6	160.3±13.0/89.8±10.7
SeBP Reduction mm Hg (±SEM)[a,b]	10.4±0.9/4.1±0.5	18.0±0.9/8.2±0.6	19.3±1.1/9.2±0.7	22.6±1.0/10.4±0.6	27.6±1.3/14.0±0.7	28.0±1.5/13.7±1.0
Patients achieving SeBP goal[c](%)						
<130/80 mm Hg	5.0	21.0	31.8	42.8	55.2	61.7
<125/75 mm Hg	2.0	10.5	16.9	25.9	39.3	46.3
<120/80 mm Hg	1.0	7.5	13.4	21.4	33.8	40.3

[a]p<0.0001 vs baseline.[b]Last observation carried forward.[c]SeBP goals are cumulative percentages using the number of subjects with valid cuff BP values.

Keywords: Diabetes; Olmesartan medoxomil; Amlodipine; Seated BP goals

PO-234

HIGH DOSE CANDESARTAN CILEXETIL IN COMBINATION WITH HYDROCHLOROTHIAZIDE FOR SECOND STAGE HYPERTENSION: CAESAR (CANDESARTAN EFFECT IN SECOND STAGE ARTERIAL HYPERTENSION) STUDY

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Objective: Angiotensin receptor blockers, such as candesartan cilexetil (candesartan), exert dose-dependent blood pressure lowering effects. In patients with second stage hypertension, we compared the blood pressure lowering effect of candesartan 16 mg/hydrochlorothiazide (HCT)12.5 mg and candesartan 32 mg/HCT 12.5 mg to candesartan 16 and 32 mg monotherapy.

Methods: This 8-week randomized, multicenter, open-labeled study enrolled 253 patients with second stage hypertension. Treatment started with candesartan 16 mg or candesartan 16 mg/HCT 12.5 mg. After 4 weeks, candesartan dose was forced-titrated to 32 mg in both groups.

Results: Baseline sitting systolic/diastolic blood pressures (mean±standard deviation) were 160.7±13.0/104.6±9.5 mm Hg. After 4 weeks, sitting systolic (SBP) and diastolic blood pressures (DBP) were significantly decreased by 28.7±17.5/17.8±10.2 mm Hg with candesartan 16 mg/HCT12.5 mg, which was more effective than candesartan 16 mg monotherapy lowering SBP/DBP by 20.5±14.5/14.0±10.1 mm Hg (p<0.001 for both SiSBP and DBP). And after 8 weeks, forced-titration of candesartan further reduced SBP/DBP by 4.1±12.7/3.8±8.3 mm Hg in candesartan 32 mg/HCT 12.5 mg group and by 4.0±11.6/2.0±8.5 mm Hg in candesartan 32 mg monotherapy group, of which reduction was significant compared with SBP/DBP in 4 weeks in both groups (p<0.001 for both SBP and DBP), but was not different between two groups. After 8 weeks, 68.5% of patients in candesartan/HCT combination group attained goal BP (SBP/DBP <140/90 mm Hg, but <130/80 mm Hg for diabetes mellitus and chronic kidney disease), which was greater than candesartan monotherapy group (52.2%, p=0.014). High dose candesartan was well tolerated both as combination with HCT and as monotherapy. Dizziness was the most common adverse event in both groups (five and two patients, respectively).

Conclusions: High dose candesartan/HCT combination showed excellent blood pressure lowering efficacy, enabling more than two third patients with second stage hypertension attaining target goal, which was more effective than candesartan monotherapy. Even at higher doses, up-titration of candesartan further reduced DBP and SBP without increment in adverse events.

Keywords: Candesartan; Combination; Hypertension

PO-235

PHARMACIST INTERVENTIONS TO ENHANCE PATIENT ADHERENCE TO ANTIHYPERTENSIVE MEDICATION: A SYSTEMATIC REVIEW

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Objective: To systematically review published data on pharmacist interventions targeting antihypertensive medication adherence and reporting blood pressure (BP) outcomes in adults with high BP.

Methods: A search of MEDLINE, The Cochrane Library and ISI Web of Knowledge was performed for records from January 1999 through May 2009, to identify relevant articles of all pharmacist interventions intended to improve adherence to antihypertensive medications. We also hand searched bibliographies in articles on patient adherence to identify relevant articles of pharmacist interventions. Studies were included if they reported an unconfounded pharmacist intervention to improve adherence with antihypertensive drugs, with adherence to medication and BP control as outcomes. Two authors selected studies and extracted the data independently.

Results: We included 15 studies testing 16 different interventions and containing data on 3280 enrolled patients. Studies were too heterogeneous in terms of the interventions and methods used to measure adherence to warrant meta-analysis. Although 87.5% of the interventions tested reported statistically significant improvements in treatment outcomes, only 43.8% of the interventions tested were associated with statistically significant increases in medication adherence, with a relative increase in adherence of 8.0% to 58%, with an average of 26%, from studies reporting positive sensitive outcomes. Almost all the interventions that were effective in increasing adherence to BP-lowering medication were complex, including combinations of simplifying doses regimes, educational strategies directed to the patient, reminders, BP self-monitoring, scheduling more frequent follow-up appointments, and other forms of additional supervision.

176

11.3 Abstract III

Methods: A retrospective study was carried out to evaluate the lipid profiles from individuals registered at the healthy center, State University of Campinas, during 8 years. The studied population was composed of individuals of both sexes and at all ages totalizing 27,543 participants and 228,748 laboratory exams. Normolipidemic and dyslipidemic individuals, classified according to Brazilian guidelines on Dislipidemias, participated in the study. The frequencies of cardiovascular disease were obtained from the Brazilian data base DATASUS. Statistical analyses were carried out using the SAS program and the temporal analysis used the Cosinor method.
Results: In normolipidemic cases (n = 11,892) significant seasonal rhythmicity was observed only in LDL and HDL-cholesterol (respectively $p \leqslant 0.018$ and $p \leqslant 0.031$), with higher values in winter and lower in summer. In the dyslipidemic group (n = 15,651) significant seasonal rhythmicity was observed in Triglycerides ($p \leqslant 0.001$), higher in summer and lower in winter, and in Cholesterol ($p \leqslant 0.021$), LDL-cholesterol ($p \leqslant 0.001$) and HDL-cholesterol ($p \leqslant 0.010$) all higher in winter and lower in summer. Positive cross-correlations were observed between the rhythms of LDL-cholesterol and atherosclerosis in normolipidemic individuals and in dyslipidemia of LDL-cholesterol with atherosclerosis, myocardial infarction and vascular diseases.
Conclusion: Dyslipidemia increased the number and amplitude of lipid biorhythms. The correlation between these rhythms with the ones of prevalence of atherosclerosis manifestations indicates the impact of lipid and lipoprotein seasonality on cardiovascular disease in Brazil.

MS431 THE RELATIONSHIP OF STRESS TO PATHOLOGY, PHYSIOLOGY, ANESTHESIA AND ANALGESIA

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This paper proposes a "Stress Mechanism" that continuously repairs and maintains the vertebrate body. It explains how Stressors induce stress. It consists of the Vascular Endothelium, the Autonomic Nervous System, and the enzymatic interaction of blood-borne Factors VII, VIII, IX and X. The Vascular Endothelium is an autonomic nervous gland, ubiquitous throughout the body, that responds to Stressors, including both stressful forces and stressful stimuli. It controls the enzymatic interaction, and thereby determines the location, magnitude, and speed of production of Thrombin, Soluble Fibrin and Insoluble Fibrin, whose multiple effects explain all Stress Mechanism manifestations. Positive Feedback in the Stress Mechanism produces disease. When Stressors subside, Negative Feedback restores Stress Mechanism activity to a "resting state". Stress Mechanism activity explains Eustress, Distress, Fight-or-Flight, the General Adaptation Syndrome, hemodynamic physiology, Malignancy, Apoptosis, Capillary Hemostasis, Infarction, Anesthesia, Analgesia, Atherosclerosis, Eclampsia, Multi-System Organ Failure (MSOF), Adult Respiratory Distress Syndrome (ARDS), High Altitude Pulmonary Edema (HAPE), Angiodysplasia, Angioneurotic Edema, and the Surgical Stress Syndrome.

MS432 COMPUTER SIMULATION OF PLAQUE FORMATION AND DEVELOPMENT

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Atherosclerosis is a progressive disease characterized by the accumulation of lipids and fibrous elements in the large arteries. Over the past decade, scientists come to appreciate a prominent role for inflammation in atherosclerosis.
In our computer model we firstly assume the passive penetration of LDL in particular areas of the intima. Once in the intima the LDL is immediately oxidized and when the LDLox exceeds a threshold there is recruitment of monocytes which immediately differentiate into macrophages. Monocytes evolve in macrophages which phagocyte LDLox and evolve in (foam cells) by massive ingestion of LDLox.
The steady and pulsatile flow field with plaque formation and development is analysed in simplified 2D and 3D mild stenosis model. The blood flow is simulated by the three-dimensional Navier-Stokes equations, together with the continuity equation. LDL transport in lumen of the vessel is coupled with convective-diffusion equation and inflammatory process was solved with three additional reaction-diffusion partial differential equations. The plaque growing was modeled by Stokes equation.
The computed results show velocity profiles, shear stress distribution and LDL distribution in blood lumen. Computed concentration oxidized LDL, macrophages and cytokines indicate that there is a newly formed matter in the intima, especially in the flow separation region of the coronary artery.
A full three-dimensional model of plaque formation and development, coupled with blood flow and LDL concentration in blood, was created. The plaque location and progression in time for a specific patient shows a clear benefit for future vascular modeling and prediction using computer simulation.

MS433 TOTAL ANTIOXIDANT STATUS IN CORONARY ARTERY DISEASE PATIENTS

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Background and Aims: Coronary artery disease (CAD) and atherosclerosis represent leading cause of death in the world. Reduced antioxidant protection is considered to play an important role in pathogenesis of CAD. We investigated if total antioxidant status (TAS) is reduced in patients with CAD and the possibility of using TAS as a confident diagnostic CAD parameter.
Methods: The study comprehended 96 CAD patients and 31 healthy persons as control group. Using method of coronary angiography CAD diagnosis was set. TAS values were measured with ABTS as chromogen. The diagnostic value of TAS was checked by determining other oxidative injury indicators.
Results: Patients had significantly lower TAS values (0.890 mmol/L ±0.4337) compared to control subjects (1.239 mmol/L ±0.3185). Comparing patients without clinical significant stenosis (lower than 50%) to those with clinical significant stenosis at one, two or three blood vessels, the firt ones had significantly higher TAS concentrations ($p < 0.05$). There is no significant difference between patients with clinical significant stenosis. The positive correlations are noticed between TAS and SOD enzymatic activity ($\rho = 0.236$; $p = 0.027$), while negative ones are obtained with fibrinogen ($\rho = -0.233$; $p = 0.027$), HDL diameter ($\rho = -0.444$; $p = 0.000$) and superoxide anion ($\rho = -0.198$; $p = 0.068$).
Conclusions: Significant correlations with other oxidative stress parameters indicate possibility of using TAS as a diagnostic parameter. Lack of difference in TAS values depending on number of blood vessels with significant stenosis, restricts usage in atherosclerosis progression degree assessment, but suggests need for further research in order to better uderstand the antioxidant protection role in CAD prevention.

MS434 THE VALUE OF D-DIMER IN ACUTE AORTIC DISSECTION: THE EXPERIENCE OF CHINA

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Background: Acute aortic dissection (AAD) is a uncommon lethal medical emergency, with a high mortality. D-dimer is a fibrin fragment and always elevates in AAD patient. However, the diagnostic role of D-dimer for AAD remains uncertain. We evaluated the sensitivity, specificity and likelihood ratios of D-dimer in diagnosing AAD in China.
Methods: In this retrospective single-center study, a total of 343 patients with symptoms onset within 24 hours were enrolled. Of them, 127 were diagnosed with AAD by enhanced computed tomography, and 216 non-AAD controls with other diagnoses, including angina (92), acute myocardial infarction (49), pulmonary embolism (8), and other uncertain diagnoses (67). The plasma D-dimer was detected by stago-evolution (France).
Results: The median D-dimer level was significantly higher in AAD patients (4.0ug/mL) than in non-AAD controls (0.39ug/mL) ($P = 0.000$). The median D-dimer level in AAD patients with false lumen (4.40ug/mL) was markedly higher than in AAD cases without false lumen (1.49ug/mL) ($P = 0.000$). Receiver operating characteristic curves analysis showed that D-dimer was predictive to diagnosis AAD, with a sensitivity of 92.9% and specificity of 70.4%. In cutoff level of 0.5ug/mL, the negative likelihood ratio was 0.10, with positive predictive value of 0.64, negative predictive value of 0.94 and positive likelihood ratio of 3.13.
Conclusion: D-dimer levels is a useful indicator to exclude AAD within 24 hours after symptoms onset.

MS435 EVALUATION OF THE EFFECT OF STATINS ON HYPERTENSION CONTROL IN HYPERTENSIVE HYPERCHOLESTEROLEMIC PATIENTS IN CLINICAL PRACTICE

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Introduction: Some clinical evidence revealed that statins, aside from lowering cholesterol levels, also have an antihypertensive effect.
Objectives: To evaluate the effect of statin therapy on blood pressure (BP) control and levels in hypertensive hypercholesterolemic patients in clinical practice.
Methods: Prospective evaluation of patients attending the hypertension/dyslipidemia medical clinic in the hospital of Cova da Beira Hospital Centre, Covilhã, located in the Central Region of Portugal, from July to November 2009. Hypertensive patients with hypercholesterolemia were randomisedly assigned to the study. Patients were allocated either to the statin group (when taking a statin) or to the control group (when not taking a statin) and BP control and levels of both groups were compared.
Results: A total of 106 hypertensive patients with hypercholesterolemia were randomisedly assigned to the study (78 in the statin group and 28 in the

control group). Although there were no significant differences (P >0.05) in both groups concerning mean age, gender, body mass index, antihypertensive pharmacotherapy and serum levels of high-density lipoprotein cholesterol and triglyceride, BP control was higher in the statin group (P = 0.016). Significant lower systolic BP (−7.9 mmHg, P = 0.031) and diastolic BP (−5.8 mmHg, P = 0.006) levels were observed in the statin group.
Conclusions: These results indicate that statin therapy significantly improves BP control in hypercholesterolemic hypertensive patients in clinical practice, consistent with results obtained in some randomized clinical trials. These findings might have useful implications for the prevention of cardiovascular events in primary care patients.

MS436 SERUM hsCRP CONCENTRATION ⩾2.0 mg/L IS ASSOCIATED WITH CAROTID ATHEROSCLEROSIS, IN WOMEN WITH VARYING DEGREES OF GLUCOSE TOLERANCE

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Background: Rosuvastatin treatment of subjects with high-sensitivity CRP (hsCRP) ⩾2.0 mg/L has been shown to powerfully reduce cardiovascular risk. We hypothesized that hsCRP ⩾2.0 mg/L was associated with increases in carotid intima media thickness (C-IMT), plaque burden and plaque echolucency in the carotid arteries.
Material and Methods: A population sample of 64-year-old women (n = 635) with varying degrees of glucose tolerance underwent risk factor assessment including measurement of hs-CRP and bilateral ultrasound examinations of the carotid arteries for measurement of IMT, plaque number and area, and plaque echogenicity.
Results: Subjects with hsCRP⩾2.0 mg/L had elevated mean and maximum IMT in the carotid bulbs independently of other cardiovascular risk factors compared with those with hsCRP < 2.0 mg/L. There was no difference between the groups in mean plaque area, although the subjects with plaques in the high hsCRP group had larger total plaque area than the subjects with plaque in the low hsCRP group. Plaque echolucency did not differ between the groups.
Conclusion: In this high risk female cohort hsCRP⩾2.0 mg/L was accompanied by elevated IMT in the carotid bulbs independently of other cardiovascular risk factors. Total plaque area was greater among women with plaques in the high vs the low hsCRP subgroup. There was no difference in plaque echolucency between the two groups.

MS437 STRONG UP-REGULATION OF *RUNX2* IN DCC-SUSCEPTIBLE *C3H/HE* MICE AFTER FREEZE–THAW-INJURY

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Introduction: *C3H/He* mice were used as model for Dystrophic Cardiac Calcification (DCC) using freeze-thaw-injury. DCC shares many features with osteogenesis.
Aim: The aim of this study was to analyze the expression-level of transcription-factors involved in osteogenesis and to identify respective target-genes of these for a better understanding of initiation and development of DCC.
Methods: DCC-susceptible *C3H/He* and DCC-resistant *C57BL/6* mice (n = 3) were subjected to freeze-thaw-injury to induce calcification. Early at 24 and 72 hours necrotic and healthy myocardium from each mouse were separated. tRNA and cryo-sections from each tissue were prepared for histological analysis and relative-real-time-PCR using the $\Delta\Delta C_t$-method.
Results: Using Calcein-staining calcification-like deposits appear in resistant and susceptible mice 1 day after injury. Calcification progresses in *C3H/He* but not in *C57BL/6* mice 2 days later. Among the tested transcription-factors a 30.26-fold up-regulation of *Runx2* was detected in calcified tissue of *C3H/He*. Low expression was found for *Sox9, Vdr, Nfkb, Msx1, Smad1*, *Smad2* and *Smad4*, none for *Msx2, Twist1* and *Smad3*. Based on this finding we further tested downstream-genes of *Runx2*: *Vdr, Dmp1, Phex, Osterix, Col1a2, IBSP, MMP2, MMP8, MMP9, MMP13, Bglap II, Opn* and *Akp2*. An up-regulation of *Col1a2* (4.45-fold of induction), of *MMP8* (16.55-fold) and of *MMP13* (15.17-fold) was observed.
Conclusion: Infiltrating cells differentiate into osteoblast-like-cells following injury through high expression of *Runx2*, which activates in turn the MMPs-pathway to cleave collagen (type-I, -II, -III). The MMPs/collagen-interactions and their contribution in repair-processes and tissue-remodelling may explain calcification in myocardium of susceptible mice.

MS438 CORONARY ARTERY ECTASIA: CLINICAL AND ANGIOGRAPHICAL EVALUATION

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Objectives: We investigated the prevalence, risk factors and distribution of coronary artery ectasia (CAE) in patients undergoing coronary angiography for suspected coronary artery disease (CAD).
Design: From 2004 to 2005, 12514 consecutive patients were submitted to coronary angiography. Coronary angiograms were independently reviewed by two operators. Distribution of CAE was made according to the classification of Markis and Ramappa.
Results: CAE was detected in 201 patients (1.6%) and was isolated in 30 patients (14.9%) and associated with aterosclerotic coronary artery disease (ACAD) in 169 patients (84.1%). Among CAE patients, there was a marked male preponderance with 78.6%. Baseline features were similar between isolated CAE and ACAD group.
The RCA was most commonly affected by CAE (45.3%). (Cx and LAD, 39.3%, 31.5% respectively) According to the classification of Markis and Ramappa, the majority of patients had type IV and type 4a ectasia. (77.6%, 57.7%respectively).

Table: Markis and Ramappa classification of CAE patients

Markis Class	Ramappa Class	Number of patients in		Percentage of patients in	
		Markis Class	Ramappa Class	Markis Class	Ramappa Class
Type 1	Type 1a	7	3	3.5	1.5
	1b		3		1.5
	1c		1		0.5
Type 2	Type 2a	24	15	11.9	7.5
	2b		9		4.5
Type 3	Type 3	14	14	7.0	7.0
Type 4	Type 4a	156	116	77.6	57.7
	4b		37		18.4
	4c		3		1.5

MS439 ASSOCIATION OF RS7138803 IN *FAIM2* GENE AND RS7561317 IN *TMEM18* GENE WITH ANTHROPOMETRIC VARIABLES IN A HIGH CARDIOVASCULAR-RISK MEDITERRANEAN POPULATION

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Introduction: Abdominal obesity is associated with higher cardiovascular risk. Several novel obesity genes have emerged from genome-wide association studies (GWAs) as powerful candidates. Moreover, some of these genes have also been linked to the mechanisms regulating food intake. However, the associations are highly dependent of the population characteristics.
Objective: To study the association between some polymorphisms in two relevant novel obesity genes, transmembrane protein 18 (*TMEM18*) and fas apoptotic inhibitor molecule 2 (*FAIM2*) with anthropometric variables and dietary intake in a high-risk Mediterranean population.
Methods: We included 945 subjects with high cardiovascular risk (average age: 67±6 years) participating in the PREDIMED (PREvención con Dieta MEDiterránea) Study, Valencia, Spain. Anthropometric, clinical, biochemical, genetic and life-style data were obtained. We selected the rs7138803 (*FAIM2*) and the rs7561317 as the most relevant for analysis.
Results: Minor allele frequencies (MAF) for the rs7138803 (*FAIM2*) and rs7561317 (*TMEM18*) were A = 0.445 and A = 0.188, respectively. We found a statistically significant association between the rs7561317 in the *TMEM18* gene with waist circumference after multivariate adjustment (AA:99.8±12; AG:103.5±11.2; GG:104.8±12 cm; p = 0.042). Waist circumference and body weight were also higher in AA homozygous subjects for the rs7138803 in *FAIM2*, without reaching the statistical significance (p = 0.255 and p = 0.110 respectively). However, we found that AA subjects had higher energy intake than individuals carrying the G allele (GA+GG) after adjustment for sex and age (AA 2107.5±605.3 *vs* GA+GG 2261.3±660.8 Kcal; p = 0.045).
Conclusion: The rs7561317 in *TMEM18* was associated with waist circumference and the rs7138803 in the *FAIM2* gene with energy intake in this elderly Mediterranean population.

11.4 Abstract IV

Mitochondrial electron transport chain (ETC) and NADPH oxidase have been proposed as possible oxygen sensors underlying hypoxic pulmonary vasoconstriction (HPV), with derived reactive oxygen species (ROS) playing key roles in coupling the sensor(s) to the contractile machinery. However, the true significance of ROS as players in HPV is controversial. We have recently reported that activation of neutral sphingomyelinase (nSMase) and protein kinase C zeta (PKCz) participate in the signaling cascade of HPV (Cogolludo A et al., Cardiovasc Res 2009; 82: 296-302). Herein, we studied the relationship between nSMase and ROS production in rat pulmonary artery (PA). Global tissue ROS production (analyzed by dichlorofluorescein and dihydroethidium fluorescence) was increased by hypoxia in endothelium-denuded distal PA segments. Inhibitors of mitochondrial ETC (rotenone) and NADPH oxidase (apocynin) prevented hypoxia-induced ROS production and vasoconstriction. Further supporting a role for ROS production, hypoxia induced p47phox phosphorylation and its interaction with caveolin-1. Inhibition of nSMase (GW4869), PKCz or mitochondrial ETC (rotenone) prevented p47phox phosphorylation and ROS production. nSMase-derived ceramide (analyzed by immunocytochemistry) was inhibited by rotenone. However, mithocondrial superoxide production (analyzed by MitoSOX Red fluorescence) was decreased by hypoxia in PA segments suggesting a more complex regulation of ROS which may differ among subcellular compartments (Waypa GB et al., Circ Res 2009; Epub.) We propose an integrated signaling pathway for HPV which includes the mitochondrial ETC as the sensor and nSMase-PKCz-NADPH oxidase as a necessary redox amplification pathway required for ROS production and vasoconstriction.

Paper No.: 905
FOCUSED CONFERENCE GROUP: P15 - ENDOTHELIUM IN HEALTH AND DISEASE
ANTIHYPERTENSIVE EFFICACY OF ALISKIREN/ HYDROCHLOROTHIAZIDE COMBINATION: A META-ANALYTICAL APPROACH

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Introduction: Aliskiren/hydrochlorothiazide (A/H) single-pill combinations havebeen approved by the European Medicines Agency on the 16th January 2009 for thetreatment of essential hypertension in adults. The purpose of this study was toassess the antihypertensive efficacy of A/H in hypertensive patients. Methods: Asearch in MEDLINE was performed (January 2000 - November 2009), to identifyrandomised clinical trials (RCTs) using A/H for the treatment of hypertension.Studies were included if they evaluated the antihypertensive efficacy of A/H inpatients with mild or moderate essential hypertension and age ≥ 18 years. Twoauthors selected studies and extracted the data independently. The efficacy oftreatment was calculated using the weighted average reductions of systolic anddiastolic BP for each daily dosage combination. Results: We included 5 RCTstesting several combinations of A/H and containing data on 5448 patients. In allstudies, BP was assessed at inclusion (baseline) and after 8 weeks of therapy.Mean systolic and diastolic BP were 152.5/98.0 mmHg at inclusion and weresignificantly reduced by the several combinations of A/H: -15.8/-10.3 mmHg(150/25 mg); -15.9/-11.8 mmHg (300/12.5 mg); -16.9/-11.6 mmHg (300/25 mg). BPcontrol rates (%) for the above combinations were, respectively: 43.9; 50.1 and51.9. BP reductions and control rates were significantly higher with the A/Hcombinations than with the same dosages of aliskiren or HCTZ monotherapy.Conclusion: A/H provides clinically significant additional BP reductions andimproved BP control rates over aliskiren or HCTZ alone and the single-pillcombination offers the convenience of a single-tablet treatment regimen.

Paper No.: 3336
FOCUSED CONFERENCE GROUP: P05 - TRANSLATIONAL SCIENCE IN THE METABOLIC SYNDROME: BASIC AND CLINICAL PHARMACOLOGY
EFFECT OF KAMPO, CHINESE TRADITIONAL MEDICINE ON CLOCK- AND METABOLISM-RELATED GENE EXPRESSION IN MICE

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Background: circadian clock gene is expressed not only in the suprachiasmatic nucleus, a main oscillator, but brain and peripheral organs. Clock system controls the physiological function through clock gene expression spread over whole body. Recently, it is elucidated that expression of clock gene is controlled by AMPK, Ppar α and Sirt1 suggesting interaction between circadian clock and nutrition metabolism. On the other hand, Kampo drugs, Chinese traditional medicine have been used for disease and for health promoting effect through whole body. Then, we studied whether Kampo may affect clock- and metabolism-related gene, and improve circadian rhythm disorders and obesity. We selected Juzen-taiho-to from 12 Kampo drugs through preliminary screening experiments. Method: mouse body weight changes were examined under ad lib feeding of powdered normal or high-fat diet containing 3% Juzen-taiho-to or 0.3% each Shyoyaku herb which is a component of Juzen-taiho-to. Then mice were sacrificed and gene expression of Per2, PGC-1α, Sirt1 in the liver and visceral fat were measured by RT-PCR. Results and Discussion: Juzen-taiho-to reduced the gene expression of Per2 and increased that of PGC-1αand Sirt1. Moreover, in the experiment of 0.3% each Shyoyaku herb, Touki increased PGC-1, Sirt1 gene expression, and Saiko reduced Per2 gene expression. The present results suggest that Juzen-taiho-to may affect the metabolic syndrome and circadian system disorder through Shoyaku herbal components such as Touki and Saiko.

Paper No.: 1338
FOCUSED CONFERENCE GROUP: P11 - G PROTEIN-COUPLED 7TM RECEPTORS: FROM MOLECULAR TO PHYSIOLOGICAL FUNCTION
NOVEL PATHWAY OF SMOOTH MUSCLE CONTRACTION BY UTP IN RAT AORTIC MYOCYTE

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Introduction: UTP is one of important substances, released from cells surrounding vascular smooth muscle, for regulation of vasoconstriction. It is broadly known that UTP is an agonist selective to P2Y receptors, such as P2Y2, 4and 6 receptors, but not P2X receptors. However, we identified that UTP activated P2X1-like receptors and thus caused vasoconstriction by activation of L-type voltage dependent calcium channel (VDCC). Materials: Male Sprague-Dawleyrats (10-11 weeks old) were used. Tension measurement, patch-clamp method, RT-PCR and Western blot analysis were used for evaluation. Results: UTP(≥10 μM) caused a biphasic, phasic and tonic, contraction. The phasic contraction was almost completely inhibited by removal of extracellular Ca^{2+}, application of nifedipine (10 μM) or TNP-ATP (30 μM), a selective P2Xreceptor antagonist, while the tonic contraction was abolished by thapsigargin(2microM) in a Ca^{2+}-free bath solution. Patch-clamp recording also

180

Capítulo 12

Comunicações Orais

12.1 Comunicação Oral I

Development and assessment of interventions to enhance patient adherence to antihypertensive pharmacological therapy
Morgado M., Verde I., Castelo-Branco M.
Oral Presentation, Nº 30, IV Annual CICS Symposium, Faculdade de Ciências da Saúde, Universidade da Beira Interior, 7th July 2009, Covilhã, Portugal
http://www.fcsaude.ubi.pt/cics/images/stories/pdf/iv_cics_abstract_book.pdf

12.2 Comunicação Oral II

Study of blood pressure control and adherence to antihypertensive medications in a hypertensive population of Central Region of Portugal
Morgado M., Rolo S., Castelo-Branco M.
Oral Presentation, Nº 26, V Annual CICS Symposium, Faculdade de Ciências da Saúde, Universidade da Beira Interior, 6th July 2010, Covilhã, Portugal
http://www.fcsaude.ubi.pt/cics/images/stories/pdf/abstract_book_v_symposium_cics.pdf

182

12.1 Comunicação Oral I

30

DEVELOPMENT AND ASSESSMENT OF INTERVENTIONS TO ENHANCE PATIENT ADHERENCE TO ANTIHYPERTENSIVE PHARMACOLOGICAL THERAPY

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Introduction: Hypertension (HT) is a highly prevalent disease worldwide as well as in Portugal, where, according to estimates, there are about three million adults with high blood pressure. Although the treatment of HT has been shown to prevent cardiovascular disease and to extend and enhance life, HT remains inadequately managed in Portugal, with the Central Region presenting the lowest proportion of treated hypertensives. Low adherence to prescribed antihypertensive (ATH) drugs is a ubiquitous problem and undermines pharmacological therapy benefits. Improving the effectiveness of adherence interventions to these drugs may have a great impact on the health of the hypertensive population. In this study we reviewed the published data about interventions to assist patient's adherence to prescribed ATH drugs, feasible to be applied to the hypertensive outpatients of Centro Hospitalar Cova da Beira.
Methods: A search of Medline and The Cochrane Library databases was performed for records from 2000 to current date to identify relevant articles of randomized controlled trials of interventions intended to improve adherence to self-administered ATH drugs.
Results: Several interventions aimed to improve compliance with ATH treatment and feasible to be applied in our local hospital were identified: informing the patient of the risk of HT and the benefit of effective treatment; providing clear written and oral instructions about treatment; tailoring the treatment regimen to patient's lifestyle and needs; simplifying treatment by reducing, if possible, the number of daily drugs by using controlled release dosage forms; paying great attention to side effects and changing drug doses or types if needed; dialoguing with patient regarding adherence and be informed of existing problems, trying to solve them and including patient in decision making; reminding patients about appointments, monitoring adherence with treatments and appointments, calling patients who have missed appointments for needed follow-up care and reinforcing the importance of high adherence at each visit; encouraging self-monitoring with validated blood pressure devices; scheduling more frequent appointments

184

12.2 Comunicação Oral II

26. STUDY OF BLOOD PRESSURE CONTROL AND ADHERENCE TO ANTIHYPERTENSIVE MEDICATIONS IN A HYPERTENSIVE POPULATION OF CENTRAL REGION OF PORTUGAL

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Introduction: Nonadherence to antihypertensive medications is an important factor to inadequate blood pressure (BP) control in patients with hypertension (HT). Among factors contributing to nonadherence to medication is poor patient knowledge of target BP and the consequences of uncontrolled high BP. The objectives of this study were to evaluate BP control, medication adherence and knowledge in HT in a Portuguese hypertensive population. **Methods:** Cross-sectional survey conducted in a HT / dyslipidemia outpatient clinic in the Cova da Beira Hospital Centre, Covilhã, Portugal. Hypertensive patients attending the clinic from July to September 2009 and taking antihypertensive medications for at least 6 months were asked to participate in a structured interview including adherence to medications and knowledge about HT and target BP values. Detailed clinical information was obtained from medical records. **Results:** A total of 197 patients met the inclusion criteria and completed the structured interview. Of these, 33.0% patients had their BP controlled according to the JNC 7 guidelines. Patients with controlled BP had a significant higher rate of medication adherence than patients with uncontrolled BP (73.8% vs 35.6%, $P < 0.0001$). Likewise, patients with controlled BP were significantly more aware of their target BP figures (75.4% vs 51.5%, $P = 0.001$) and of the potential complications of uncontrolled HT (66.2% vs 49.2%, $P = 0.025$) than those with uncontrolled BP. **Conclusions:** Many hypertensive patients prescribed with antihypertensive therapy fail to achieve BP control in clinical practice. Poor medication adherence and patient knowledge about HT consequences and target BP values should be considered as possible underlying causes of inadequately controlled BP and must be addressed in any intervention aimed to improve BP control.

Keywords: hypertension, blood pressure control, antihypertensives, medication adherence, Portugal

Acknowledgements: We thank the FCT (*Fundação para a Ciência e a Tecnologia*) for supporting the fellowship grant SFRH/BD/36756/2007.

186

Capítulo 13

Comunicação Sob a Forma de Poster

13.1 Comunicação Sob a Forma de Poster I

Métodos para medir a adesão à terapêutica farmacológica anti-hipertensora
Manuel Morgado, Sandra Morgado, Miguel Castelo-Branco
Associação Portuguesa de Farmacêuticos Hospitalares, 3ª Semana APFH - VII Congresso Nacional da Associação Portuguesa de Farmacêuticos Hospitalares, Centro de Congressos do Estoril, 24-27 Novembro de 2010, Estoril, Portugal
http://www.apfh.pt/scid/webApfh/defaultScientificArticleViewOne.asp?realizationId=37&scientificArticleID=189&categoryID=803

188

13.1 **Comunicação Sob a Forma de Poster I**

Resumo nº 7 do Livro de Resumos "3ª Semana APFH – VII Congresso Nacional da APFH"

Métodos para medir a adesão à terapêutica farmacológica anti-hipertensora

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Introdução
Um dos principais obstáculos ao controlo eficaz da hipertensão arterial (HTA) está relacionado com a adesão do doente ao tratamento com fármacos anti-hipertensores. A avaliação da adesão à terapêutica com anti-hipertensores e o conhecimento dos diversos factores que a influenciam são determinantes para o desenvolvimento de estratégias tendo em vista aumentar essa mesma adesão, fundamental para o controlo eficaz da HTA e para a prevenção das complicações cardiovasculares graves que lhe estão associadas.

Objectivos
Efectuar uma revisão da literatura tendo em vista efectuar um levantamento dos métodos de avaliação de adesão ao tratamento com fármacos anti-hipertensores, passíveis de serem utilizados nos doentes da consulta externa de hipertensão / dislipidémia do Centro Hospitalar Cova da Beira, E.P.E. (CHCB).

Métodos
A pesquisa bibliográfica na PubMed intersectando o termos "medication adherence" e "essential hypertension" permitiu a identificação de 21 artigos, publicadas desde 1986, que foram analisados tendo em vista a identificação de métodos de avaliação de adesão ao tratamento com fármacos anti-hipertensores, exequíveis de serem aplicados aos doentes da consulta externa de hipertensão / dislipidémia do CHCB. As referências bibliográficas dos artigos anteriormente obtidos foram também manualmente analisadas tendo em vista a obtenção de artigos adicionais relevantes para a matéria em estudo.

Resultados
Os métodos directos de avaliação da adesão à terapêutica anti-hipertensora incluem: a determinação do princípio activo ou dos seus metabolitos nos fluidos biológicos (p. ex., sangue, urina); utilização de marcadores biológicos (p. ex., brometo de potássio) que podem ser adicionados ao medicamento (p. ex., incorporação nas cápsulas); observação directa da toma do medicamento. Os métodos indirectos incluem: questionário / entrevista estruturada (p. ex., teste de Batalla, teste de Haynes-Sackett, teste de Morisky-Green); contagem dos comprimidos remanescentes; verificação das receitas aviadas nas farmácias comunitárias (possível através da colaboração com o Agrupamento dos Centros de Saúde da Cova da Beira); monitorização electrónica da adesão (p. ex. MEMS® - Medication Event Monitoring Systems); grau de controlo da pressão arterial. Apenas os métodos indirectos de determinação da adesão são exequíveis nos doentes hipertensos em causa.

Conclusões
Existem diversos métodos indirectos de determinação da adesão à terapêutica anti-hipertensora, relativamente económicos e fáceis de implementar, que podem ser utilizados nos doentes em estudo. A utilização simultânea de diversos destes métodos e o cruzamento da informação obtida em cada um deles, poderá auxiliar os profissionais de saúde na identificação dos doentes aderentes e não aderentes, tendo em vista o posterior desenvolvimento de estratégias para aumentar a adesão à terapêutica farmacológica anti-hipertensora.

Anexos

192

Anexo I – Método para medir a adesão à terapêutica anti-hipertensora

Entrevista estruturada utilizando o seguinte questionário de Morisky et al. (Morisky et al. 1983; Morisky et al. 1986) modificado por Shea (Shea et al. 1992; Shea et al. 1992):

1) "Do you ever forget to take your high blood pressure pills?"
2) "Are you ever careless in taking your pills?"
3) "Do you ever miss taking your pills when you are feeling better?"
4) "Do you ever miss taking any of your pills because you are sick?"
5) "Do you ever miss taking your high blood pressure medication for any reason?"

A tradução efectuada, para realizar a entrevista estruturada à população hipertensa em estudo, foi a seguinte:

1) "Alguma vez se esquece de tomar os medicamentos para a hipertensão?"
2) "Toma os medicamentos às horas indicadas?"
3) "Quando se sente bem, deixa de tomar os medicamentos?"
4) "Se alguma vez se sente mal, deixa de tomar os medicamentos?"
5) "Alguma vez deixa de tomar os medicamentos por algum motivo (p. ex., os medicamentos acabam antes de renovar a receita; quando vai de férias ou se ausenta por motivos profissionais não leva os medicamentos; dificuldades económicas para adquirir os medicamentos; demasiado atarefado(a) para cumprir o esquema posológico; ingestão de bebidas alcoólicas; pensa que os medicamentos não são absolutamente necessários para o controlo da tensão arterial; depressão; reacções adversas; experimenta interromper o tratamento para verificar se a tensão arterial se mantém controlada sem a medicação anti-hipertensora; etc.)?"

As respostas no sentido da não adesão à terapêutica medicamentosa são:
1- sim; 2- não; 3- sim; 4- sim; 5- sim.

É atribuído 1 ponto por cada resposta no sentido da não adesão à terapêutica medicamentosa. A adesão à medicação foi classificada em elevada (*score* ≤ 2) ou baixa (*score* ≥ 3); os doentes que obtiveram aquelas classificações foram considerados, respectivamente, aderentes ou não aderentes à medicação.

194

Anexo II – Folheto informativo sobre a hipertensão arterial

HIPERTENSÃO ARTERIAL – INFORMAÇÃO AOS UTENTES

Qual é a importância de medir regularmente a tensão arterial?

A hipertensão arterial é um dos mais importantes factores de risco cardiovasculares. Dentro deste contexto, conhecer os níveis de tensão arterial é crucial para prevenir os eventos cardiovasculares graves como os acidentes vasculares cerebrais e o enfarte do miocárdio.

Medições frequentes da tensão arterial:
• Permitem diagnosticar o mais cedo possível a hipertensão arterial;
• Permitem acompanhar a eficácia da medicação.

A hipertensão, geralmente, não dá sintomas. A única maneira de saber se a sua tensão arterial está elevada é medindo-a regularmente. Medir e registar os valores da tensão arterial são fundamentais para não se esquecer dos valores que tem vindo a apresentar. Sempre que possível deve medir à mesma hora uma vez que a tensão arterial varia durante o dia, sendo mais elevada durante a manhã. No Verão a tensão arterial é habitualmente mais baixa do que no Inverno.

Mostre o registo que tem feito ao profissional de saúde que o acompanha.

Quem deve controlar os valores de tensão arterial?

Todas as pessoas que tomam anti-hipertensores devem medir regularmente a tensão arterial para confirmar se a medicação que o seu médico lhe prescreveu está a resultar. Igualmente todas as pessoas não hipertensas devem medir com alguma periodicidade a tensão arterial pois só assim serão diagnosticados os hipertensos que não sabem que o são.

A hipertensão, na sua fase inicial, é uma doença silenciosa pelo que a medição da tensão arterial e o seu tratamento atempado constituem as melhores armas para prevenir o desenvolvimento de complicações cardiovasculares graves.

Estudos indicam que cerca de 30% da população Portuguesa é hipertensa, ou seja, existem aproximadamente 3 milhões de hipertensos em Portugal. Destes, cerca de metade desconhece que é hipertenso.

Quais os valores de tensão arterial recomendados pela Direcção-Geral da Saúde e pela OMS?

Na população hipertensa em geral, o objectivo será a redução da tensão arterial para **valores inferiores a 140/90 mm Hg**.

Nos doentes hipertensos **diabéticos** ou com **doença renal**, objectivo será a redução da tensão arterial para **valores inferiores a 130/80 mm Hg**.

Quais são as consequências da presença de valores de tensão arterial não-controlados?

O acidente vascular cerebral e o enfarte do miocárdio são as complicações mais comuns de uma hipertensão não controlada, com alguns anos de existência. Para além de danos nos vasos sanguíneos do cérebro e do coração, a tensão arterial elevada pode provocar danos nos vasos sanguíneos dos rins e dos olhos. Pode ser tarde quando surgem as primeiras manifestações da doença, que comprometem a esperança e a qualidade de vida.

Quais os factores que podem elevar a tensão arterial e como controlá-los?

•Consumo excessivo de sal → Reduza o consumo de sal

•Dieta inadequada, com excesso de gorduras saturadas → Consuma uma dieta rica em vegetais e fruta e opte pelo leite magro (e derivados de leite magro), de forma a evitar as gorduras saturadas e o colesterol.
•Excesso de peso e obesidade → Pese-se regularmente e faça uma alimentação saudável
•Sedentarismo → Ande a pé com regularidade
•Tabaco → Apague de vez o cigarro
•Consumo excessivo de álcool → Se beber álcool, faça-o com moderação

No caso de já estar medicado **não pare a medicação por sua iniciativa**. Faça a medicação conforme o seu médico lhe prescreveu.

A medicação para a hipertensão arterial é para toda a vida?

Na maioria dos casos a medicação é para toda a vida. O seu médico dir-lhe-á exactamente durante quanto tempo a deverá tomar. Não interrompa o tratamento por iniciativa própria.

Nalguns doentes em que a tensão arterial se mantém bem controlada durante três anos ou mais, poderá ser possível suspender a medicação, principalmente em doentes que fizeram alterações significativas nos seus hábitos de vida que podem afectar a tensão arterial (p. ex., perda de peso, abandono de hábitos tabágicos e/ou alcoólicos). O seu médico informá-lo-á se não precisar de continuar a tomar anti-hipertensores. Se a medicação for suspensa é necessário medir regularmente a tensão arterial. Nalguns casos, a tensão arterial manter-se-á dentro dos valores normais. Noutros casos, voltará a aumentar. Nestes casos poderá ser necessário retomar a medicação.

Os medicamentos para controlar a tensão arterial têm efeitos secundários?

Todos os medicamentos podem causar efeitos secundários, incluindo os medicamentos anti-hipertensores. No entanto, a maioria das pessoas que tomam anti-hipertensores não apresentam efeitos secundários significativos. Em geral, estes efeitos são de natureza passageira e desaparecem gradualmente com a continuação do tratamento.

Os efeitos secundários que podem surgir dependem do anti-hipertensor prescrito. Os mais frequentemente descritos são: cefaleias, tonturas, vómitos, sensação de mal-estar geral, cansaço, edema, obstipação, rubor facial, tosse, impotência e ataques de gota.

Se surgirem efeitos secundários informe o seu médico, pois este poderá decidir alterar a medicação.

Anexo III – Factores de risco para a doença cardiovascular

Factores de Risco para a Doença Cardiovascular

Gorduras sólidas:

▪ Evite manteiga, margarina, banha, queijos curados e natas;

▪ Evite carnes gordas (vaca e carneiro), produtos de salsicharia e charcutaria (toucinho, bacon, chouriços, enchidos) e miúdos de frango;

▪ Evite a utilização de métodos culinários que utilizem muita gordura ou gorduras sobreaquecidas, nomeadamente refogados, fritos, assados no forno e molhos com muita gordura;

▪ Prefira o azeite cru como gordura para tempero e confecção dos alimentos.

Sal:

▪ Reduza a quantidade de sal utilizado na confecção dos alimentos, substituir por cebola, alho, tomate, pimento, louro, especiarias (colorau, açafrão, noz moscada) e ervas aromáticas (salsa, coentros, hortelã, rosmaninho, poejos, alecrim);

▪ Evitar produtos classicamente salgados (batatas fritas de pacote, conservas, aperitivos, caldos de carne/ galinha);

▪ Evite alimentos pré-preparados e confeccionados pela indústria.

Açúcares:

▪ Diminua a ingestão de açúcar (no chá, no café);

▪ Limite o consumo de produtos açucarados (chocolate, mel, compotas, bolachas, bolos e doces de uma maneira geral);

▪ Evite sumos e refrigerantes.

Anexo III – Factores de risco para a doença cardiovascular (cont.)

Outros:

- Modere ou elimine o consumo de bebidas alcoólicas;
- Evite o consumo de café e chá preto;
- Deixe de fumar, se é fumador! O tabagismo constitui uma importante e evitável causa de morte.

Sedentarismo:

- Mexa-se! A prática regular de actividade física ajuda a reduzir o risco de doença cardiovascular.

Anexo IV – Regras gerais para uma alimentação saudável

Regras Gerais para uma Alimentação Saudável

- Repartir as refeições (6 a 7 refeições): Pequeno-almoço, merenda da manhã, almoço, merenda da tarde, jantar e ceia

- Fazer refeições sempre à mesma hora, de preferência no mesmo local
- Mastigar bem os alimentos

- Comer num ambiente calmo
- Iniciar as refeições de preferência com um prato de sopa de legumes

- Combinar alimentos bem coloridos no prato
- Fazer dos cereais a base da alimentação, pois são fontes de energia e nutrientes essenciais

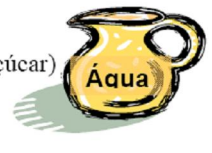
- Evitar as gorduras (gorduras visíveis, fritos, molhos e assados com muita gordura); preferir como gordura de eleição o azeite

- Moderar o consumo excessivo de carne, peixe e ovos

- Moderar o consumo de sal

- Moderar ou eliminar o consumo de bebidas alcoólicas

- Evitar os doces e produtos açucarados. Em situações de festa pode consumir após uma refeição



- Beber abundantemente líquidos ao longo do dia (água e chás de ervas sem açúcar)

200

Anexo V – Prémio A.P.F.H. – IPSEN 2009/2010 - 1ª Menção Honrosa

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2009 /2010

Certifica-se que

Dr. Manuel Augusto Nunes Vicente Passos Morgado

recebeu 1ª Menção Honrosa atribuída pela

IPSEN PORTUGAL

em colaboração com a

ASSOCIAÇÃO PORTUGUESA DE FARMACÊUTICOS HOSPITALARES

a

25 de Novembro de 2010

referente ao trabalho científico apresentado no âmbito da Farmácia Hospitalar, com o título

"Estudo da intervenção do farmacêutico hospitalar na adesão à terapêutica anti-hipertensora e no controlo da pressão arterial. Ensaio clínico controlado e aleatorizado"

Aida Batista
Presidente da A.P.F.H.

António Filipe
Director Geral da Ipsen Portugal