UNIVERSIDADE DA BEIRA INTERIOR
Ciências da Saúde

Drug-induced prerenal acute kidney injury: a review of the literature

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Dissertação para obtenção do Grau de Mestre em

Medicina

(ciclo de estudos integrado)

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Covilhã, maio de 2019

Acknowledgements

A realização desta tese de Mestrado em Medicina contou, direta e indiretamente, com importantes apoios e incentivos sem os quais não seria possível cumprir os meus objetivos e concretizar esta etapa da minha formação académica. Este espaço é dedicado aos que deram o seu contributo para que esta dissertação fosse uma realidade. A todos eles deixo aqui o meu agradecimento sincero.

Quero agradecer em primeiro lugar à minha orientadora, Dra. Catarina Santos, pela sua orientação, apoio, rigor e total disponibilidade.

Um agradecimento muito especial aos meus pais, pela forma como me incutiram valores e capacidades que me permitiram ultrapassar todos os obstáculos ao longo deste percurso, pelo incentivo, força, inspiração e amor. Espero que esta etapa, que agora termino, possa de alguma forma retribuir e compensar todo o carinho, apoio e dedicação que constantemente me oferecem.

Aos meus avós por estarem sempre ao meu lado e por torcerem sempre por mim, nos bons e maus momentos.

Um especial obrigado à Ivanna por acreditar em mim e nas minhas capacidades, por todo o carinho e amor diário, dedicação e confiança, pelo apoio incondicional em todos os momentos, pela inspiração e companhia, pela generosidade e por tudo o que representa para mim.

Aos meus amigos e colegas, por todos os momentos de diversão, apoio, entreajuda, confiança, incentivo, companheirismo e, principalmente pela amizade! Uma palavra especial de obrigado para o Trio Sombrio, por toda a compreensão e paciência, pelo apoio e parvoíce, por tudo.

Abstract

Acute kidney injury is a heterogeneous disorder that is common in hospitalized patients and associated with short- and long-term morbidity and mortality, as well high healthcare costs. It is defined as a rapid decrease in the glomerular filtration rate, occurring over a period of hours to days and by the inability of the kidney to regulate fluid and electrolyte homeostasis appropriately.

Approximately 70% of community-acquired cases of acute kidney injury are attributed to prerenal causes, which include severe hypotension, sepsis, dehydration, heart failure, liver failure, narrowing of renal arteries and exposure to a large number of drugs. Prerenal acute kidney injury results from glomerular hemodynamic alterations leading to reduced glomerular filtration rate with no parenchymal compromise. Autoregulatory mechanisms can partially compensate renal perfusion reduction in order to maintain glomerular filtration rate.

Non-steroidal anti-inflammatory drugs, renin-angiotensin system inhibitors and diuretics - a combination also known as “triple whammy” - can reduce the glomerular filtration rate and lead to prerenal acute kidney injury. A number of different mechanisms are involved, including inhibition of both prostaglandin-mediated control of glomerular afferent arteriolar tone and angiotensin control of efferent arteriolar tone, as well as volume depletion, all contributing to reduced renal plasma flow.

This literature review intends to systematize the different pathophysiological mechanisms by which the different drugs promote prerenal acute kidney injury and, on the other hand, to compare the different groups of drugs in relation to their potential to induce prerenal acute kidney injury.

Keywords

Acute kidney injury; diuretics; nephrotoxicity; non-steroidal anti-inflammatory drugs; renin-angiotensin system inhibitors

Resumo

A lesão renal aguda é um distúrbio heterogéneo, comum em pacientes hospitalizados, associado a elevada morbilidade e mortalidade a curto e longo prazo, assim como a elevados custos em saúde. É definida por uma diminuição rápida na taxa de filtração glomerular, durante um período de horas a dias, e pela incapacidade do rim para regular adequadamente a homeostase dos fluídos e eletrólitos, resultando na retenção de produtos azotados. Essa acumulação é acompanhada por distúrbios metabólicos, como acidose metabólica e hipercalemia, alterações no equilíbrio de fluídos corporais e efeitos em muitos outros sistemas orgânicos, dependendo da gravidade e da duração da disfunção renal. A gravidade da lesão varia de leve a grave e requer, em alguns casos, terapia de substituição da função renal.

Ao longo dos anos, a ausência de consenso em relação aos critérios para a definição e classificação da lesão renal aguda fez emergir a necessidade de padronizar conceitos. Com o progresso do conhecimento médico diversos critérios foram propostos sendo que os mais recentes preconizam que a lesão renal aguda deve ser diagnosticada quando ocorre um aumento da creatinina sérica de pelo menos 0,3 mg/dL (num período de 48 horas) ou quando ocorre um aumento da creatinina sérica em 1,5 vezes em relação ao seu valor basal (documentada ou presumida a sua ocorrência nos 7 dias anteriores) ou ainda, quando for quantificado um volume de urina inferior a 0,5 ml/kg/h em 6 horas.

Clinicamente, a lesão renal aguda pode ser dividida em três categorias principais: pré-renal, renal (ou intrínseca) e pós-renal. A forma pré-renal resulta de alterações hemodinâmicas glomerulares que conduzem à diminuição da perfusão renal, porém sem causar danos estruturais ao parênquima renal. A forma pós-renal é despoletada pela obstrução do fluxo urinário por massas intrínsecas ou extrínsecas, como cálculos ureterais ou tumores ginecológicos ou urológicos. Os restantes casos enquadram-se na forma renal, na qual várias estruturas do nefrónio são afetadas, incluindo glomérulos, túbulos, vasos ou interstício.

Aproximadamente 70% dos casos de lesão renal aguda adquiridos na comunidade são atribuídos a causas pré-renais, as quais incluem hipotensão grave, sépsis, desidratação, insuficiência cardíaca, insuficiência hepática, estenose das artérias renais e exposição a um variado número de fármacos. Mecanismos autorregulatórios podem compensar parcialmente a redução da perfusão renal com o objetivo de manter uma taxa de filtração glomerular apropriada e de evitar o desenvolvimento de lesão renal aguda.

Anti-inflamatórios não esteróides, inibidores do sistema renina-angiotensina e diuréticos - uma combinação conhecida como "*triple whammy*" - podem reduzir a taxa de filtração glomerular e conduzir a lesão renal aguda pré-renal. Vários mecanismos diferentes estão envolvidos, incluindo a inibição do controle mediado pelas prostaglandinas do tónus glomerular arteriolar aferente, a inibição do controle mediado pela angiotensina do tónus glomerular arteriolar eferente, bem como a depleção de volume, todos contribuindo para a redução do fluxo plasmático renal.

Esta revisão da literatura pretende sistematizar os diferentes mecanismos fisiopatológicos pelos quais os diferentes fármacos promovem a lesão renal aguda pré-renal e, por outro lado, comparar os diferentes grupos de fármacos em relação ao seu potencial para induzir lesão renal aguda pré-renal.

Palavras-Chave

Lesão renal aguda; diuréticos; nefrotoxicidade; anti-inflamatórios não esteróides; inibidores do sistema renina-angiotensina

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Abbreviations

ACE – angiotensin-converting enzyme

ACEI - angiotensin-converting enzyme inhibitor

ADH – antidiuretic hormone

AKI – acute kidney injury

AKIN – Acute Kidney Injury Network

ALI – acute lung injury

ARA – angiotensin receptor antagonist

BP - blood pressure

CKD – chronic kidney disease

COX – cyclooxygenase

DMT2 - Diabetes *Mellitus* Type 2

eGFR – estimated glomerular filtration rate

GFR - glomerular filtration rate

GHP – glomerular hydrostatic pressure

h – hours

KDIGO – Kidney Disease: Improving Global Outcomes

MF - metformin

NaCl – sodium chloride

NSAID - non-steroidal anti-inflammatory drug

PG - prostaglandin

RAS – Renin-Angiotensin System

RAAS - Renin-Angiotensin-Aldosterone System

RIFLE - Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease

RRT – renal replacement therapy

SCr - serum creatinine

TXA_2 - thromboxane A_2

UOP – urine output

1. Introduction

Acute kidney injury (AKI, previously termed acute renal failure), a leading cause of nephrology consultation, is a heterogeneous disorder that is common in hospitalized patients and associated with short- and long-term morbidity and mortality, as well high healthcare costs (1,2). Its incidence around the world is not well known and fluctuates according to the differences in parameters used for the classification criteria and different patient populations. However, in a systematic review, Susantitaphong *et al*. verified that 1 in 5 adults (21.6%) and 1 in 3 children (33.7%) experienced AKI worldwide, during a hospital episode of care. They also showed that the pooled mortality rates were 23.9% in adults and 13.8% in children (3).

AKI is currently defined as a rapid decrease in the glomerular filtration rate (GFR), occurring over a period of hours (h) to days and by the inability of the kidney to regulate fluid and electrolyte homeostasis appropriately, resulting in retention of nitrogenous wastes, primarily creatinine and blood urea nitrogen (BUN) (2,4). This accumulation is accompanied by metabolic disturbances, such as metabolic acidosis and hyperkalemia, changes in body fluid balance, and effects on many other organ systems, depending on the severity and duration of the renal dysfunction (5). The magnitude of injury ranges from mild to severe and, in some cases, eventually requiring renal replacement therapy (RRT) (6).

This syndrome has several causes, however, it is more often related to the prerenal disorders which included severe hypotension, sepsis, dehydration, heart failure, liver failure, narrowing of renal arteries and exposure to a large number of drugs (7).

Angiotensin receptor antagonists (ARA's), angiotensin-converting enzyme inhibitors (ACEI's), non-steroidal anti-inflammatory drugs (NSAID's) and diuretics, frequently used in multidrug therapies, represent nephrotoxic or potentially nephrotoxic drugs and have been associated with nephrotoxicity upon chronic exposure and AKI. In this context, the "double whammies" or "triple whammy" therapies are referred as the AKI resulting from combined therapy with NSAID's, ARA's/ACEI's and diuretics (8).

This work therefore has as main objective to make a bibliographical review of the existing literature, explaining and systematizing, the different pathophysiological mechanisms by which the different drugs mentioned (NSAID's, ARA's/ACEI's and diuretics) promote prerenal AKI and compare the different groups of drugs in relation to their potential in mono-, double- or triple therapy to induce prerenal AKI. For this, in a first phase it tries to clarify which classification is more current and accepted for AKI. Afterwards, it intends to explore the different clinical forms of AKI, evidencing prerenal AKI and characterizing its etiology and pathophysiology. Lastly, it is intended to describe the types of drugs that have the capacity to develop AKI and the associated risk factors to finally specify the real potential of the different groups of drugs alone or in combination therapies to induce prerenal AKI.

2. Methods

A bibliographic search was performed in the *PubMed*, *MEDLINE Complete*, *ResearchGate* and *Google Scholar* databases between September 2018 and February 2019, using the terms “prerenal”, “acute kidney injury”, “nephrotoxicity”, “diuretics”, “non-steroidal anti-inflammatory drugs”, “angiotensin receptor antagonists”, and “angiotensin-converting enzyme inhibitors”. Articles in English, Spanish and Portuguese were included, with no temporal limitation.

In the first phase, articles were excluded based on the reading of the title. Then, they were excluded based on the abstract’s analysis. Finally, the articles used in this review were selected based on their reading and analysis.

In addition, reference manuals and reports have been consulted.

After a careful analysis of the relevant material, an evidence-based and in-depth review of the literature was performed.

3. Acute Kidney Injury

3.1. Classification of Acute Kidney Injury

3.1.1. RIFLE Criteria

For years the lack of consensus regarding the criteria for the definition and classification of AKI raised the need to standardize concepts. Therefore, the Acute Dialysis Quality Initiative (ADQI) group proposed the first uniform definition that was the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria for AKI, in 2004. There are based on the definition of three stages of AKI (Risk, Injury and Failure), taking into account changes in serum creatinine (SCr) values along with urinary output to determine the stage of renal dysfunction (9). In this classification of AKI the deterioration of renal function should be both abrupt (within 1-7 days) and sustained (more than 24 h) (10). Additionally, if urine output (UOP) and SCr concentration do not correspond to the same stage, it has been recommended that the highest stage should be considered (11). These criteria are also based on two other stages, defined as clinical outcomes, that correspond to more severe disease and a worse prognosis (Loss and End-stage kidney disease) (**Table 1**) (9). These outcomes were eliminated from the subsequent definitions of AKI however all definitions use common UOP criteria.

Table 1 – RIFLE criteria for AKI staging. Adapted from (9,12,13).

Stage	SCr	UOP
Risk	1.5-1.9 times baseline **or** eGFR decrease >25%	<0,5 mL/Kg/h for 6-12 h
Injury	2.0-2.9 times baseline **or** eGFR decrease >50%	<0,5 mL/Kg/h for ≥12 h
Failure	≥3.0 times baseline **or** eGFR decrease >75% **or** ≥4.0 mg/dL (with acute increase of >0.5 mg/dL)	<0,3 mL/Kg/h for ≥24 h **or** anuria for ≥12 h
Loss	Persistent acute renal failure with complete loss of function >4 weeks	
End-stage renal disease	Complete loss of renal function for >3 months	

eGFR - estimated glomerular filtration rate; h – hours; SCr – serum creatinine; UOP – urine output.

3.1.2. AKIN Criteria

In March of 2007, the Acute Kidney Injury Network (AKIN) workgroup released a modified version of the RIFLE criteria (14). The AKIN classification introduced modifications such as: only after achieving an adequate status of hydration and excluding urinary obstruction,

the diagnosis of AKI can be considered; these criteria not relies on GFR changes, only on SCr; baseline SCr is not necessary, and it requires, within a period of 48 h, at least two values of SCr obtained. The need for these modifications were based on the fact that even small increases in SCr, in a variety of settings, are associated with adverse outcomes and increased mortality (15).

Thus, AKI can be defined by the sudden decrease (in 48 h) of renal function, defined by an increase in absolute SCr of at least 0.3 mg/dL or by an increase in SCr to 1.5 times baseline, or yet by a decrease in the UOP (documented oliguria <0.5 mL/kg/h for more than 6 h) (**Table 2**) (16). Independently of the stage they are at the time of RRT, individuals who receive that treatment are considered to have met the criteria of Stage 3 (15).

Table 2 - AKIN criteria for AKI staging. Adapted from (12,16).

Stage	**SCr**	**UOP**
Stage 1	1.5-1.9 times baseline **or** increase ≥0.3 mg/dL within 48h	<0,5 mL/Kg/h for 6-12 h
Stage 2	2.0-3.0 times baseline	<0,5 mL/Kg/h for ≥12 h
Stage 3	>3.0 times baseline **or** ≥4.0 mg/dL (with acute increase of >0.5 mg/dL) **or** initiation of RRT	<0,3 mL/Kg/h for ≥24 h **or** anuria for ≥12 h

h – hours; RRT - renal replacement therapy; SCr – serum creatinine; UOP – urine output.

3.1.3. KDIGO Criteria

Proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) AKI Work Group, the latest classification (the KDIGO criteria) were merged with RIFLE and AKIN criteria and had the aim of earlier diagnosis of AKI (9,14). According to this definition, AKI was diagnosed as an increase in SCr by at least 0.3 mg/dL within 48 h or an increase in SCr to 1.5 times baseline, which is known or presumed to have occurred within 7 days before, or urine volume of less than 0.5 mL/kg/h for 6 h (**Table 3**). Furthermore, it is important to note that should be added to KDIGO stage 3 patients under 18 years with a eGFR <35mL/min per 1.73 m^2 (13).

These 3 scores (RIFLE, AKIN and KDIGO) were presented as good tools for predicting mortality in critically ill patients, with no significant difference between them in terms of predicting death (9,14).

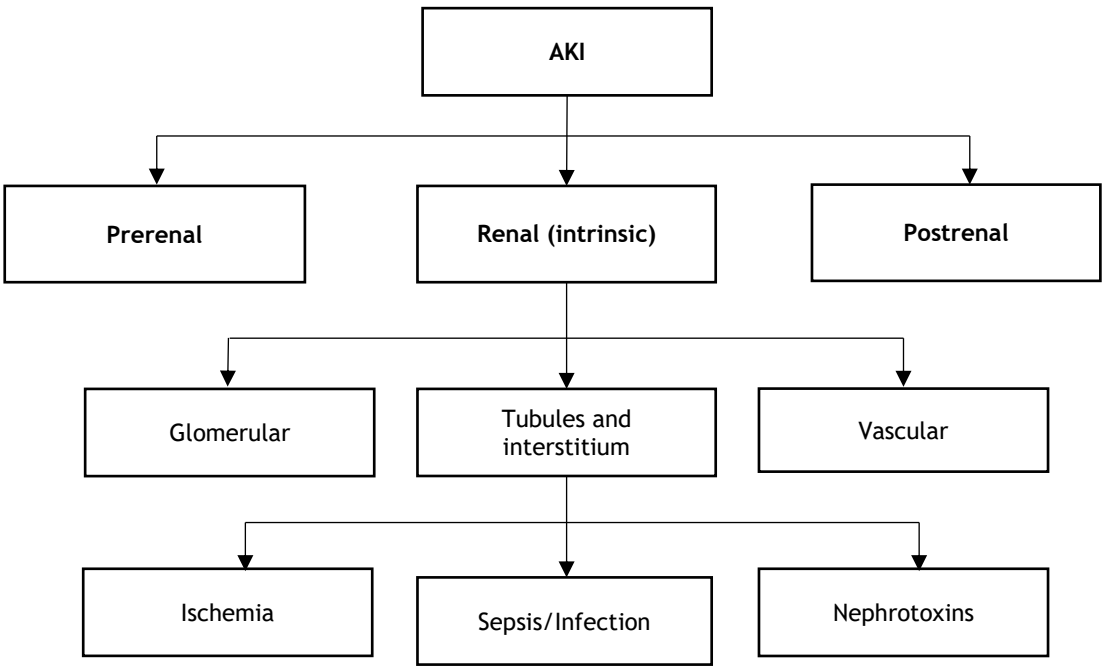
Table 3 – KDIGO criteria for AKI staging. Adapted from (13).

Stage	SCr	UOP
Stage 1	1.5-1.9 times baseline within the prior 7 days **or** ≥0.3 mg/dL increase within 48h	<0,5 mL/Kg/h for 6-12 h
Stage 2	2.0-2.9 times baseline	<0,5 mL/Kg/h for ≥12 h
Stage 3	≥3.0 times baseline **or** increase to ≥4.0 mg/dL **or** initiation of RRT **or** in patients <18 years, decrease in eGFR to <35 ml/min *per* 1.73 m^2	<0,3 mL/Kg/h for ≥24 h **or** anuria for ≥12 h

eGFR - estimated glomerular filtration rate; h – hours; RRT - renal replacement therapy; SCr – serum creatinine; UOP – urine output.

3.2. Types of Acute Kidney Injury

Clinically, AKI can be broadly divided into three primary categories: prerenal, renal (or intrinsic), and postrenal (**Scheme 1**) (2).



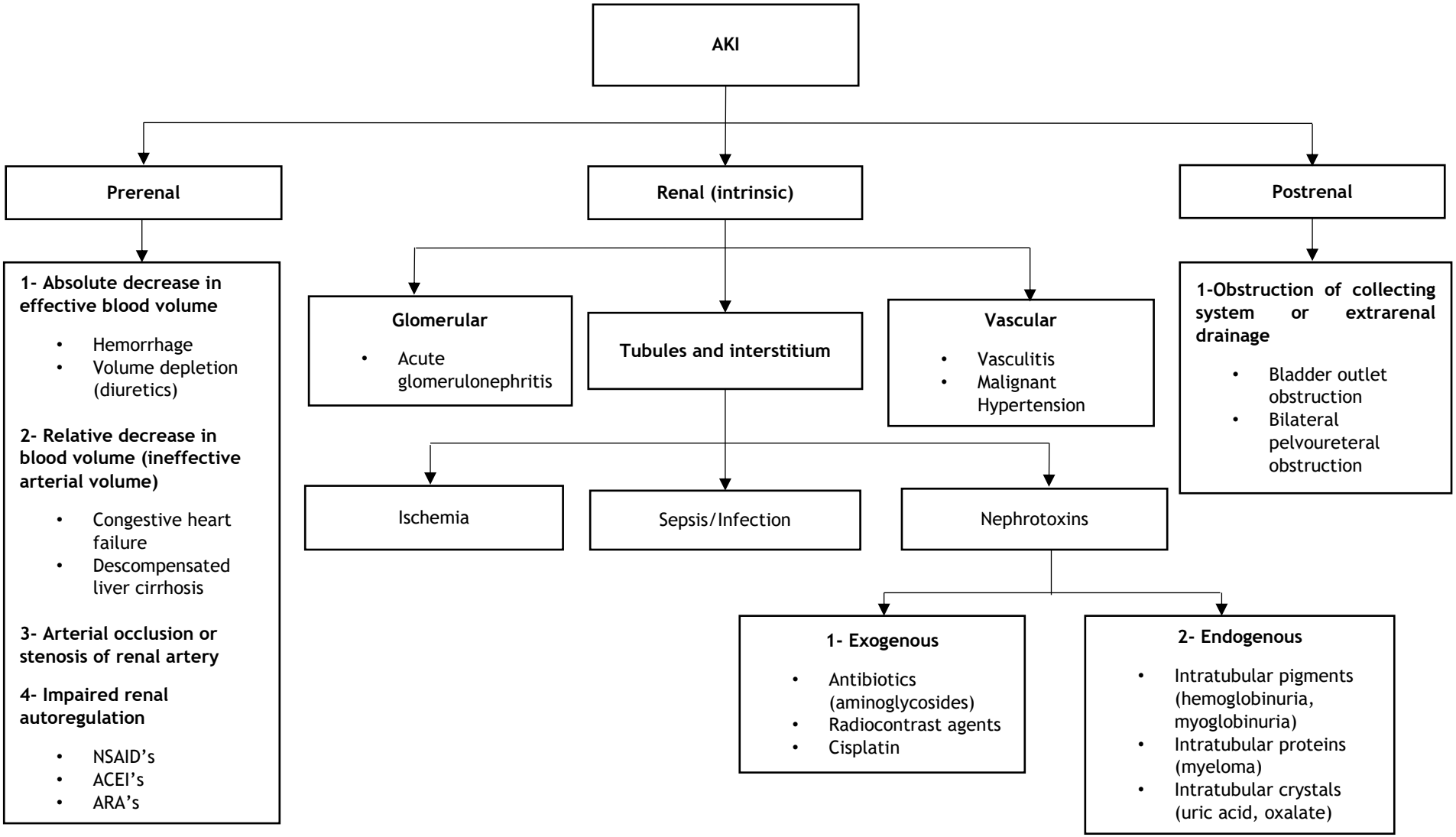
Scheme 1 – Flowchart of AKI categories. Adapted from (17). AKI – acute kidney injury.

The prerenal form of AKI results from decreased renal perfusion, which leads to a reduction in GFR without damage to the renal parenchyma. It is characterized by a reversible increase in SCr and blood urea concentrations. The postrenal form is due to obstruction of the urinary flow by either intrinsic or extrinsic masses, like ureteral stones or gynecological or

urological cancers. The remaining cases have the renal form, in which several structures of the nephron are affected, such as the glomeruli, tubules, vessels, or interstitium (**Schemes 1 and 2**) (2,5).

Actually, only renal AKI represents true kidney disease, while prerenal and postrenal AKI are the consequence of extra-renal diseases leading to the decreased GFR and they will eventually evolve to renal cellular damage and hence intrinsic renal disease, if these prerenal and/or postrenal conditions persist (18).

This review will focus on the prerenal causes of AKI.



Scheme 2 – Etiology of prerenal, renal and postrenal AKI. Adapted from (5,7). ACEI – angiotensin-converting enzyme inhibitor; AKI – acute kidney injury; ARA – angiotensin receptor antagonist; NSAID – non-steroidal anti-inflammatory drug.

3.2.1. Etiology of Prerenal Acute Kidney Injury

Community-acquired cases of AKI are attributed to prerenal causes in approximately 70% of cases (19). In these cases, underlying kidney function may be normal, but decreased renal perfusion associated with intravascular volume depletion or decreased arterial pressure results in a reduced GFR. In an attempt to maintain the GFR, autoregulatory mechanisms often can compensate for some degree of reduced renal perfusion. In patients with preexisting chronic kidney disease (CKD) these mechanisms are impaired and that increases the susceptibility for the development of acute-on-chronic renal failure (6).

Severe hypotension (e.g., from surgical or traumatic blood loss, burns and mild sepsis), dehydration (e.g., from vomiting, diarrhea, bleeding or hypovolemia), heart failure, liver failure, narrowing of renal arteries, and exposure to vasoactive drugs and toxins are commonly causes of prerenal AKI (**Scheme 2**) (2,7,8).

Among the medications that can cause prerenal AKI, namely drugs who interfere with the autoregulation of renal blood flow and GFR, the most commonly involved are ARA's, ACEI's, NSAID's, and diuretics (20).

Kidney function typically returns to baseline after adequate volume status is established, the underlying cause is treated, or the offending drug is discontinued. In contrast, when not corrected, persistent renal hypoperfusion will ultimately lead to ischemic acute tubular necrosis (ATN) (6).

3.2.2. Pathophysiology of Prerenal Acute Kidney Injury

At present the majority of what we understand about prerenal AKI pathophysiology was obtained from research done on animal models (21). The many pathways that are probably implicated and the mechanisms of organ injury were demonstrated in studies of models of acute ischemia induced by acute occlusion of the renal artery (5,21). Generally speaking, the endothelium is injured, coagulation system is locally activated, leucocytes infiltrate the kidney, and adhesion molecules are expressed, toll-like receptors are induced, cytokines are released, intrarenal vasoconstrictor pathways are activated, and apoptosis is induced (22–25). Additionally, changes also occur in the tubular cells with loss of adhesion to the basement membrane and loss or inversion of polarity (5,26).

Unfortunately, more relevant models are needed, because this ischemic model has little clinical relevance to illnesses/states such as sepsis, major surgery (especially open heart surgery), and acute decompensated heart failure, situations where the renal artery is not occluded (27).

Considering that the kidneys receive up to 25% of the cardiac output, any alteration of the systemic circulating blood volume or isolated failure of the intra-renal circulation can have a profound impact on renal perfusion (28).

The kidney responds to changes in renal perfusion pressure by autoregulating renal blood flow and GFR within fairly narrow limits. Under physiological conditions, when the blood

pressure (BP) falls, gradual dilation of the afferent arteriole is mediated by the generation within the kidney of vasodilating products of arachidonic acid (prostanoids) and nitric oxide. Additionally, concomitant vasoconstriction of the efferent arteriole, mainly under the influence of angiotensin II, maintains a constant glomerular hydrostatic pressure (GHP) (**Figure 1**) (29,30).

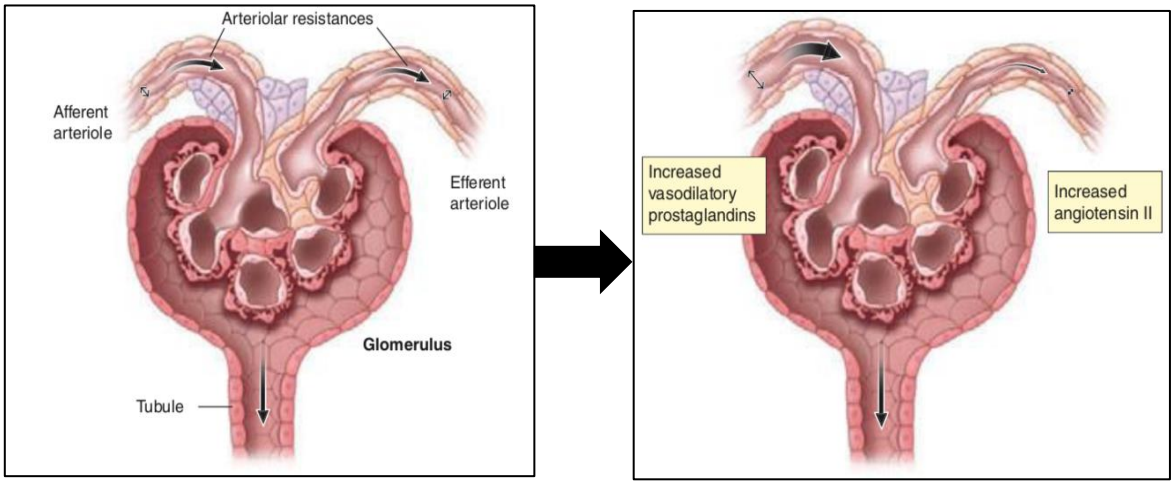
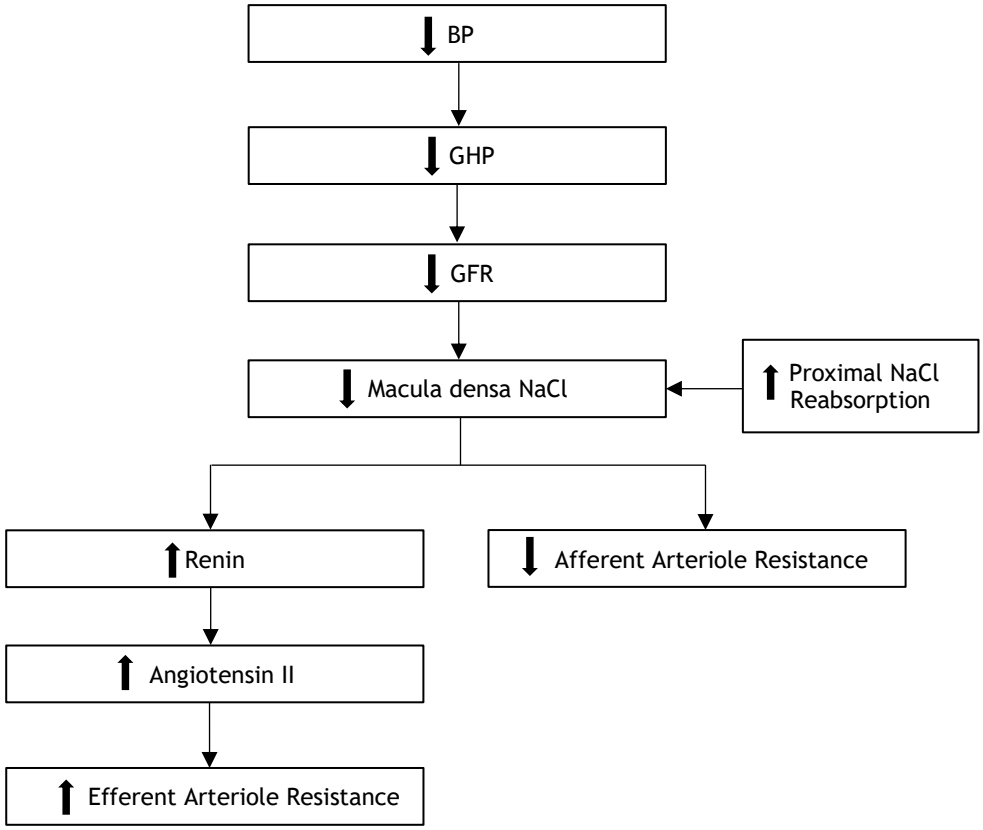


Figure 1 - Kidney autoregulatory mechanisms in response to changes in renal perfusion to maintain the GFR. Adapted from (31).

This process is described as a *tubuloglomerular feedback* mechanism and depends on the special anatomical arrangement of the juxtaglomerular complex, consisting of macula densa cells in the initial portion of the distal tubule and juxtaglomerular cells on the walls of afferent and efferent arterioles. When BP falls, specialized macula densa cells detect the decrease in sodium chloride (NaCl) concentration and initiate a signal that has a double effect: 1) - reduce resistance to blood flow in the afferent arterioles, which elevates the GHP, helping the return of GFR to normal and; 2) - increase the release of renin by the juxtaglomerular cells of the afferent and efferent arterioles, which in turn promotes the formation of angiotensin II that contracts the efferent arterioles, increases the GHP and equally helps the return of GFR to normal (**Scheme 3**) (32).



Scheme 3 – Feedback mechanism of macula densa during BP fall. Adapted from (32). BP – blood pressure; GFR – glomerular filtration rate; GHP – glomerular hydrostatic pressure; NaCl – sodium chloride.

When this autoregulatory function is impaired (e.g., through drug-mediated inhibition or CKD), it might enhance the effect of slight reductions in BP on GFR, leading to AKI. Under these conditions autoregulatory mechanisms attempt to maintain the GFR, although these mechanisms become progressively less effective (as BP and GFR gradually declines) making AKI almost inevitable (8).

4. Drug-induced Acute Kidney Injury

Drugs remain a relatively common cause of acute and chronic kidney injury because patients are exposed to numerous prescribed and over-the-counter medications (33). They seem to contribute to AKI in approximately 15 to 25% of patients, especially in critically ill patients (34).

A combination of factors are involved in the complex process of nephrotoxicity of drugs, such as the inherent nephrotoxic potential of the drug, underlying patient characteristics that enhance their risk for kidney injury, and the metabolism and excretion of the potential offending agent by the kidney (33). Thus, the drug-induced AKI risk factors can be divided into: kidney-specific factors, patient-specific factors and drug-specific factors (**Table 4**) (35).

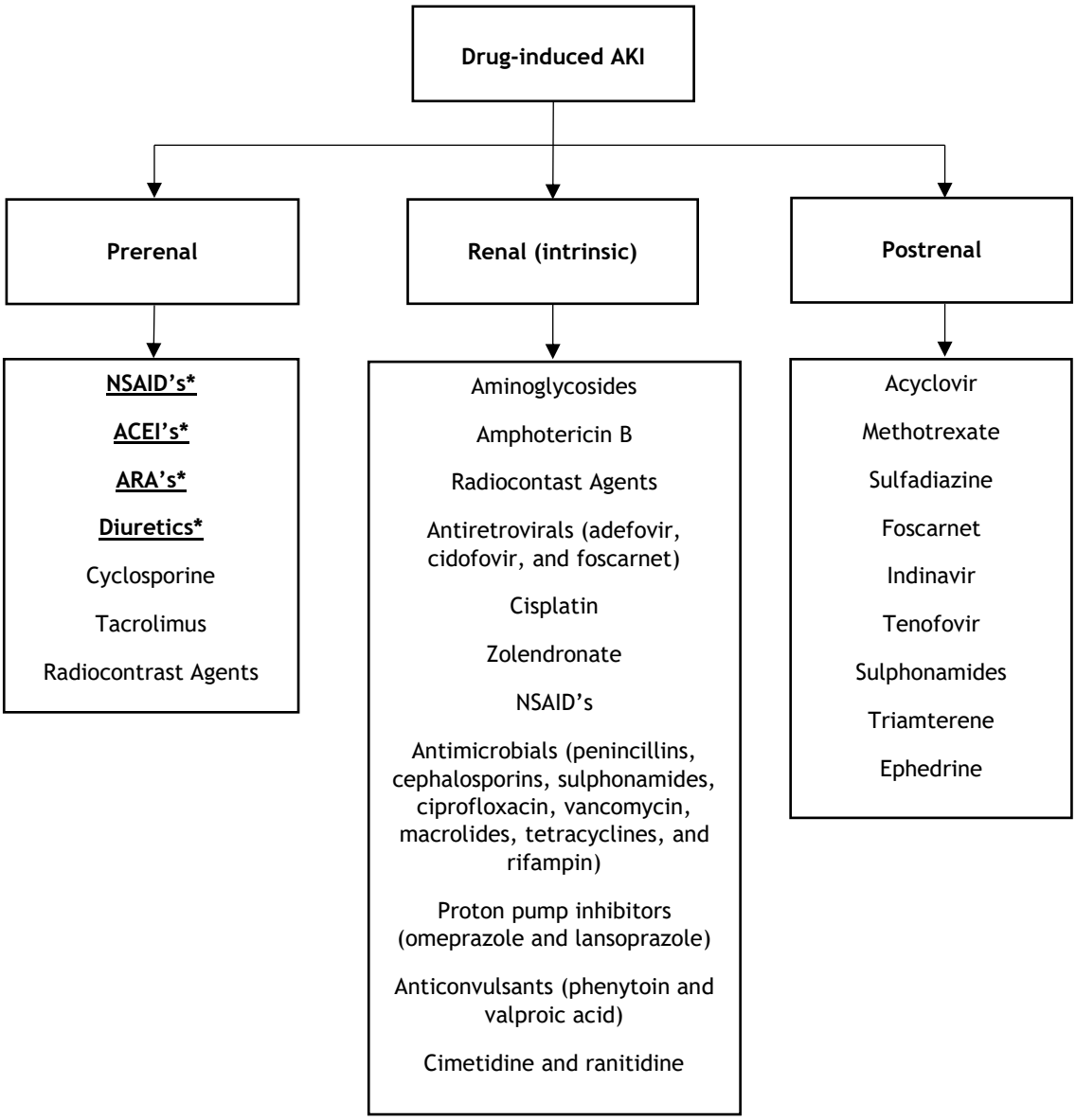
Table 4 – Drug-induced AKI risk factors. Adapted from (35).

Kidney-specific factors	Patient-specific factors	Drug-specific factors
• High blood flow rate (up to 25% of cardiac output) • Differential sensitivity based on metabolic activity with kidney (cells in loop of Henle are most sensitive) • Increased accumulation and concentration of drugs or metabolites • Transport properties of renal tubular epithelial cells • Enzymes specific for biotransformation that can lead to generation of reactive oxygen species	• Older age (>65 years) • Female gender • AKI • CKD • Nephrotic syndrome • Acute and chronic heart failure • Cirrhosis • True or effective volume depletion • Metabolic derangements • Hypercalcemia, hypokalemia, hypomagnesemia • Alkaline or acidic urine pH • Host genetic factors • Gene mutations in hepatic or renal CYP450 enzymes • Gene mutations in renal transport channels	• Prolonged exposure • Direct nephrotoxic effects of a compound • Combinations of medications leading to or enhancing nephrotoxicity • Insolubility leading to crystal precipitation

AKI - acute kidney injury; CKD - chronic kidney disease; CYP450 – cytochrome P450.

Many mechanisms or processes potentially leading to renal injury have been associated with drug nephrotoxicity: acute tubular cell injury, changes in renal hemodynamics, intratubular obstruction, acute interstitial nephritis, hypersensitivity vasculitis, thrombotic microangiopathy, osmotic nephrosis, and rhabdomyolysis. It is important to recognize that the same drug may cause nephrotoxicity by more than one mechanism (36).

Considering the mechanism of renal injury, the medications involved in drug-induced AKI can equally be classified in three groups: prerenal, renal (intrinsic), and postrenal (**Scheme 4**) (34).



Scheme 4 – Classification of drug-induced AKI. (20,34,37). ACEI – angiotensin-converting enzyme inhibitor; AKI – acute kidney injury; ARA – angiotensin receptor antagonist; NSAID – non-steroidal anti-inflammatory drug.

It is pertinent to mention the special status of metformin (MF), a drug widely used in recent years as a first-line therapy in Diabetes *Mellitus* Type 2 (DMT2) (38), often in association with other drugs with proven nephrotoxic potential, especially in the elderly. MF has several

renoprotective effects on various types of renal diseases and does not appear to be directly related to the development of AKI (39). This statement has been supported by Bell *et al.,* in a large observational cohort study of over 25,000 patients with DMT2, who showed no evidence that MF increases incidence of AKI and was associated with higher 28-day survival following incident AKI (the survival rates were higher in patients with AKI previously treated with MF compared to patients with AKI not previously on MF) (40).

In the setting of individuals with normal kidney function, MF is filtered in the glomerulus and secreted from the proximal tubule in a nonmetabolized and nonprotein bound form, but its clearance decreases by 75% when eGFR falls to 30–59ml/min/1.73m^2 (41). Thereby, international guidelines and expert opinion recommend that the drug dose should be reduced according to the eGFR value of individual patients (42).

Although MF does not have the primary potential to develop prerenal AKI, in patients treated with MF, when presenting CKD, AKI and/or volume depletion (for example due to dehydration, vomiting, diarrhea or exposure to nephrotoxic drugs) the accumulation of MF may aggravate kidney function (43,44). In these situations, the associated tubular toxicity impairs mitochondrial function and oxygen consumption, which in turn decreases gluconeogenesis and glycogenolysis, leading to the generation of lactate and the occurrence of lactic acidosis, a syndrome known as metformin-associated lactic acidosis (MALA). Although it is rare, MALA represents a dangerous metabolic adverse effect related to MF therapy, especially when diagnosis and/or treatment are missed or delayed (44–46).

Summarizing, the DMT2 epidemic continues and MF is a central therapeutic agent in its treatment and when used appropriately does not cause nephrotoxicity, however, in the presence of clinical conditions that aggravate the basal renal function (as diarrhea or vomiting) or in the context of its coadministration with potential nephrotoxic drugs (like ARA's, ACEI's, NSAID's or diuretics) may condition the onset or aggravation of AKI and other related complications. Therefore, understanding the indirect mechanisms by which MF result in nephrotoxicity is important and is potentially clinically relevant to guide dose adjustments in the setting of renal impairment and CKD.

In the next subchapters of this review will be studied the individual and combined potential of the drugs highlighted in Scheme 4 (NSAID's, ACEI's/ARA's and diuretics) to induce prerenal AKI.

4.1. Non-steroidal anti-inflammatory drugs

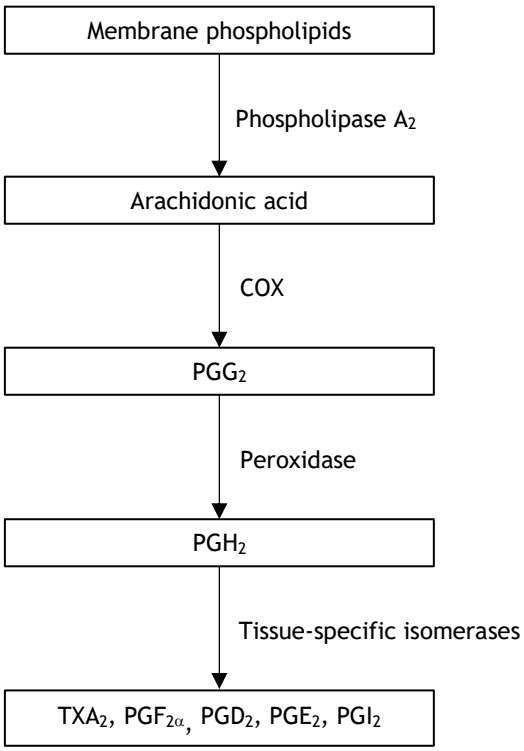
NSAID's, a diverse group of compounds that possess analgesic, antipyretic and anti-inflammatory effects, are one of the most commonly used groups of drugs, despite their several notorious adverse effects, particularly gastrointestinal (GI) bleeding and cardiovascular or renal dysfunction (47,48). The risk of adverse events associated with NSAID's are both duration and dose-dependent (49).

NSAID's are acidic compounds with a relatively high bioavailability and highly bound to plasma proteins. Their metabolization occur mainly by the liver but glucuronidation by the kidney enzyme is also reported for some NSAID's (e.g., naproxen and ibuprofen) (47,50).

The mechanism of action of NSAID's occur by the inhibition of the cyclooxygenase (COX) enzyme, involved in prostanoid synthesis, which has two isoforms (COX-1 and COX-2) and, based on their extent of selectivity for COX inhibition, they can be classified as non-selective (traditional) or COX-2 selective inhibitors. As they are more selective, it was expected that COX-2 inhibitors theoretically reduced the adverse effects related to inhibition of the COX-1 isoform while preserving the anti-inflammatory properties related to COX-2 inhibition, nevertheless they appear to have similar adverse renal event profiles as nonselective NSAID's (51,52).

The two COX isoforms have been described in the kidneys: COX-1 is expressed as a constitutive renal enzyme in the collecting ducts, glomerular mesangial cells and renal vasculature, and is responsible for the control of GFR and renal hemodynamics. In contrast, COX-2 is mainly an inducible enzyme expressed in response to injury or inflammation but it also exists as a constitutive enzyme in the macula densa, cortical thick ascending limb of Henle, medullary interstitial cells, podocytes, arteriolar smooth muscle cells, medullary vasa recta and collecting ducts. This enzyme is also engaged in the control of renal hemodynamics, sodium, water and potassium homeostasis and renin release (53,54).

The synthesis of prostanoids is achieved in four main steps: at first, arachidonic acid is released from membrane phospholipids through phospholipase A_2; after, the arachidonic acid is transformed into the intermediate endoperoxide prostaglandin (PG) G_2 (through COX action) and consequently to PGH_2; at last, PGH_2 is further converted by tissue-specific isomerases to five major prostanoids (PGD_2, PGE_2, PGI_2 or prostacyclin, $PGF_{2\alpha}$, and thromboxane A_2 (TXA_2)) (**Scheme 5**) (55).



Scheme 5 – Biosynthesis of prostanoids. Adapted from (55). COX – cyclooxygenase; PG - prostaglandin; TXA_2 -thromboxane A_2.

The two major prostanoids synthesized in the kidney are PGE_2 and PGI_2. Depending on the receptor stimulated and the renal distribution of the receptors, the biological effects of prostanoids varies (51).

Thus, by inhibiting its synthesis, NSAID's may compromise the vasodilatory effect of PG's under the renal afferent arterioles, which can progress to hemodynamically-mediated AKI (**Figure 2**). Although by other mechanisms, they can also be related with nephrotic syndrome, acute and chronic interstitial nephritis, renal papillary necrosis, and electrolyte and fluid abnormalities (hyperkalemia and sodium and fluid retention) (34).

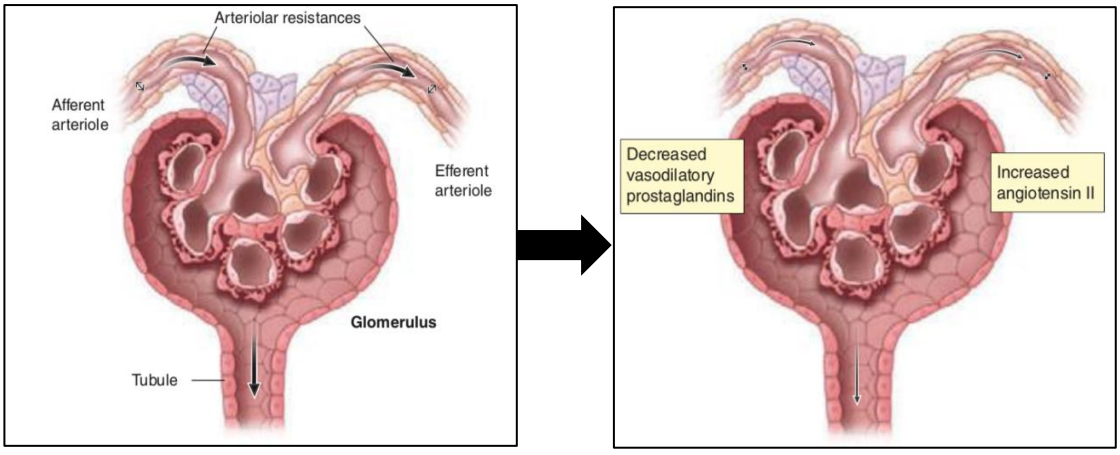


Figure 2 – Effect of NSAID's on the afferent arteriole resistance (trough the inhibition of vasodilatory PG's synthesis). Adapted from (31).

In patients with normal renal function and preserved renal hemodynamics, GFR and renal blood flow are minimally controlled through PG's. However, under hypovolemic circumstances, the maintenance of renal function is dependent on prostanoids, which counteract the numerous vasoconstrictors released to maintain BP. On these cases, the administration of NSAID's might cause severe adverse renal effects like sodium retention and edema (due to inhibition of PGE_2), potassium retention and hyperkalemia (result from the inhibition of PGI_2-derived renin release and aldosterone production) and AKI (in situations in which renal autoregulation is impaired and GFR has been previously altered as severe cardiac/hepatic disease, CKD, volume depletion or elderly) (56).

In a nested case-control study, in 2005, Huerta *et al.* described that, in general population, the current NSAID's use was associated with a 3 times greater risk for AKI compared with non-NSAID's use and that this risk was slightly increased with long-term therapy and high dose of NSAID's (57).

In a systematic review and meta-analysis of cohort studies, in 2015, Ungprasert *et al.* demonstrate a statistically significant elevated AKI risk among most of the included traditional NSAID's (indomethacin, piroxicam, ibuprofen, naproxen, sulindac, diclofenac, and meloxicam). They verified that the highest risk ratio was observed among indomethacin users while the lowest risk was found in sulindac users. By contrast, they conclude that the pooled risk ratios of the two specific COX-2 inhibitors included in the study (rofecoxib and celecoxib), were lower than traditional NSAID's, although the risk differences did not reach a statistical significance. Additionally, they verified that the pooled risk ratios of the two traditional NSAID's with the most COX-2 selectivity (diclofenac and meloxicam), did not achieve a statistical significance as well (**Figure 3**) (58).

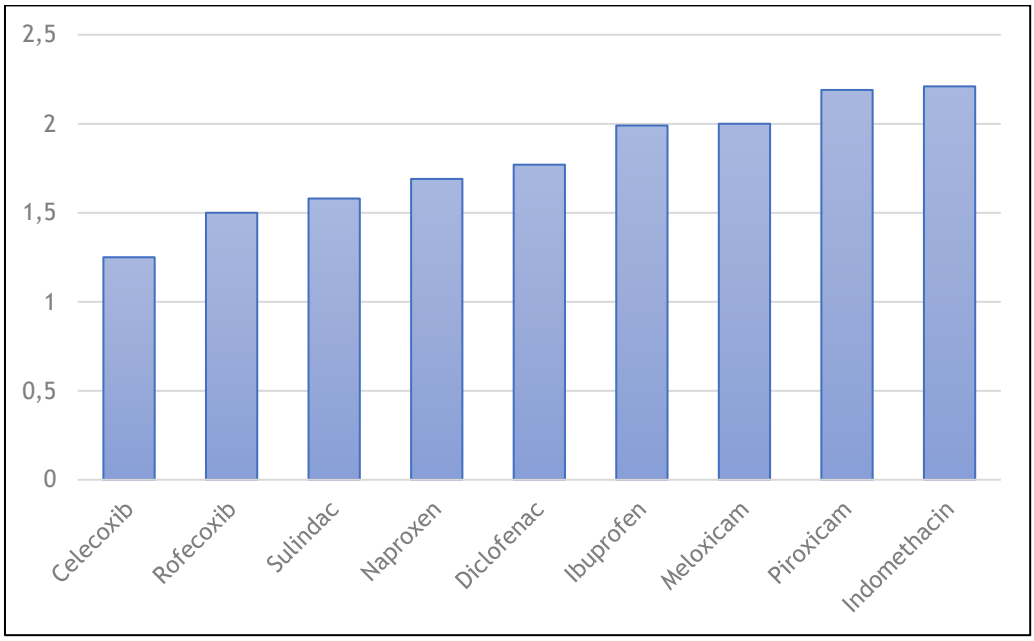


Figure 3 – Risk ratios of AKI for all NSAID's. Adapted from (58).

In another nested-control cohort study, in 2016, *Chou et al.* conclude that the current use of nonselective NSAID's was associated with increased risk of hospitalization for AKI within 1 month after the prescription (in comparison with COX-2-selective NSAID's), however the risk was not increased in past users neither in unexposed controls. They also shown that, except for rofecoxib, the association of COX-2 selective NSAID's subtypes with AKI was consistently insignificant for current use of celecoxib and etoricoxib (59).

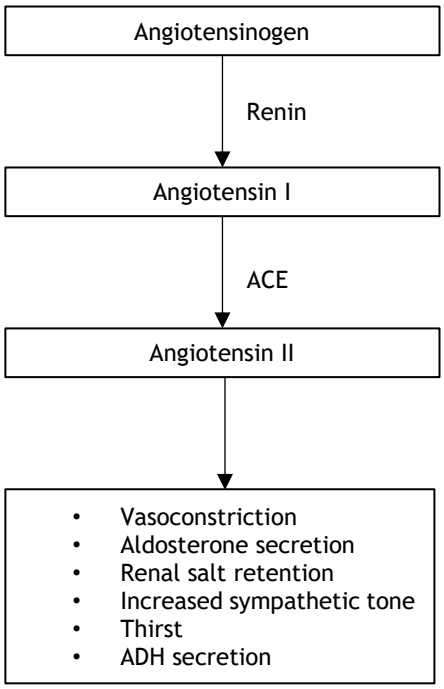
In a systematic review and meta-analysis, in 2017, Zhang *et al.* demonstrated that current exposure to NSAID's, in the general population and in people with CKD, was associated with an approximately 1.5-fold increase in the odds of developing AKI. Additionally, similarly to other studies, there was a non-statistically significant trend that the higher the COX-2 selectivity NSAID's was, the lower the increased odds of AKI (60).

It is widely accepted that traditional NSAID's have significant renal adverse effects (including AKI), however, and although recent studies indicate that selective COX-2 inhibitors also have nephrotoxic potential, further investigation is needed to better characterize the effects of selective COX-2 inhibitors under the renal function and its ability to induce AKI.

4.2. Renin-angiotensin system inhibitors

The utilization of Renin-Angiotensin System (RAS) inhibitors is an effective approach for the management of patients with essential hypertension or a high cardiovascular risk as well for congestive heart failure, diabetes nephropathy, or CKD, since they have been shown to either reduce mortality or to retard disease progression (61). Between them, ACEI's and ARA's are the most commonly used (they have similar ability to lower BP and equivalent antiproteinuric effect) (62). Although their additional antiproteinuric action, the combination of two classes of RAS inhibitors (dual RAS blockade) was associated with a higher incidence of hyperkalemia and AKI and is now formally contraindicated by regulatory agencies such as the European Medicines Agency (EMA) (62).

The Renin-Angiotensin-Aldosterone System (RAAS), a key regulator of BP and blood volume, is activated when juxtaglomerular cells in the kidneys are stimulated to secrete renin into circulation. Plasma renin catalyzes the conversion of angiotensinogen released from the liver into angiotensin I, which is subsequently converted to angiotensin II by the angiotensin-converting enzyme (ACE) mainly detected in the lung endothelium. Angiotensin II is a potent vasoconstrictor and anti-natriuretic peptide that increases BP. It also stimulates the secretion of the hormone aldosterone from the adrenal cortex, with powerful anti-natriuretic and volume expansion properties (**Scheme 6**) (63).



Scheme 6 – The RAAS. Adapted from (64). ACE – angiotensin-converting enzyme; ADH - antidiuretic hormone.

Relatively to their mechanism of action, the mentioned RAS inhibitors act by two different mechanisms: the ACEI's (captopril, ramipril, lisinopril, trandolapril, fosinopril, perindopril, and enalapril) inhibit the synthesis of angiotensin II and the degradation of bradykinin through ACE inhibition and ARA's (losartan, candesartan, valsartan, eprosartan, ibersartan, olmesartan, and telmisartan) prevent the binding of angiotensin II to angiotensin II type I (AT1) receptor, which is implicated in vasoconstriction, aldosterone release, salt and water retention, vascular remodelling and oxidative stress (65). Therefore, they cause preferential vasodilation of the kidney efferent arterioles (by nullifying the vasoconstriction effects of angiotensin II) thereby leading to reduced kidney filtration pressure and consequentially reduced GFR (**Figure 4**), which increases the likelihood of AKI (66).

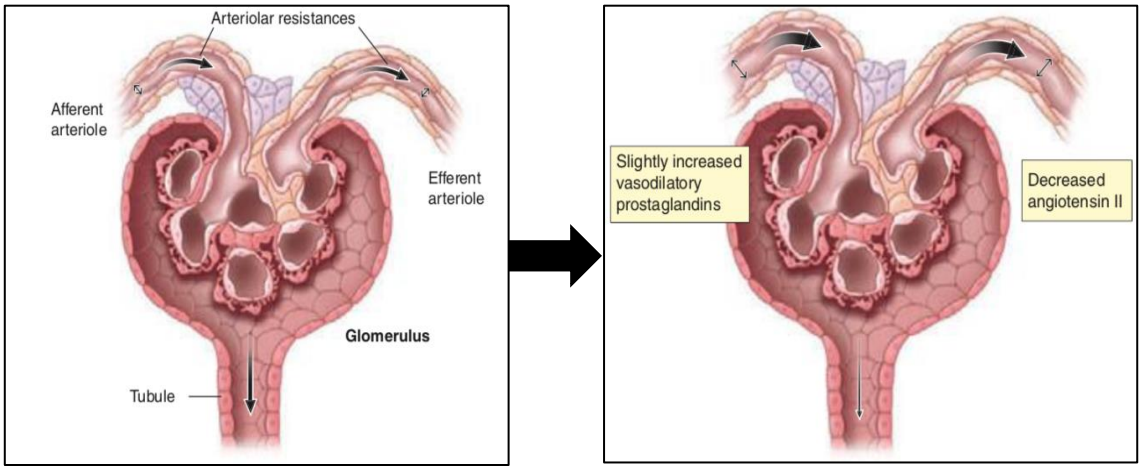


Figure 4 – Effect of ACEI's/ARA's on the efferent arteriole resistance (impaired angiotensin II vasoconstriction). Adapted from (31).

With regard to their route of excretion, the ACEI's dosage must be adapted to account for renal clearance in patients with CKD to avoid AKI, because they are almost exclusively cleared by the kidney but in contrast the ARA's, mainly excreted by the liver, do not need this adjustment (67). Accordingly, in part because of their hepatic clearance, ARA's seem to be less harmful in moderate to severe CKD, which reduces the risk of accumulation in patients with acute-on-chronic renal failure (68).

However, ACEI's and ARA's isolated do not alter GFR but these drugs abolish the RAAS as a response mechanism. The detrimental effect of these drugs on the GFR is observed when the kidney function was challenged by additional circumstances, and the RAAS is necessary to make appropriate compensations. Thus, when GFR is compromised (for example in situations of volume depletion, congestive heart failure, CKD, renal artery stenosis, or the use of vasoconstrictor drugs) ACEI's and ARA's might induce prerenal AKI (69).

In a population-based cohort study, Mansfield *et al*. demonstrates that the treatment with an ACEI or an ARA appear to be associated with only a small increase in AKI risk while patient characteristics (such as age, use of loop diuretics, and comorbidities like diabetes, heart failure or CKD) are much more strongly associated with the rate of AKI (70).

In 2008, the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) study, a large randomized controlled trial in patients at high risk for vascular events, compared telmisartan, ramipril, and the combination thereof. In this study the primary outcome (a composite of cardiovascular death, myocardial infarction, stroke, and admission to hospital for heart failure) was similar in all three groups, but combined treatment with an ARA and an ACEI produced more symptoms attributable to hypotension and worsened the decline in renal function and need for dialysis compared with monotherapy (worst secondary renal outcomes). Additionally, during follow-up, the eGFR values decreased more with telmisartan and with combination therapy than with ramipril alone (71).

In the VA NEPHRON-D study, in 2013, ARA monotherapy (losartan) was compared with the combination of an ACEI and an ARA (losartan plus lisinopril) in adults with proteinuria and diabetes, but this study was finished early because of a high prevalence of AKI and hyperkalemia in patients receiving dual RAS blockade, exacerbating concerns about combined treatment (72).

In a nested case-control study within a cohort of RAS-inhibiting drug users, in 2018, Dörks *et al*. showed an increased risk of AKI in patients with diabetes and/or CKD, however AKI was not significantly associated with dual RAS blockade compared to being treated with one RAS-inhibiting drug class only (73).

Despite the potential benefits of dual treatment with an ACEI and an ARA (in diabetic kidney disease progression, for example), concerns about widespread adoption of this strategy are justified, because information and research on the balance between potential benefits and safety are doubtful and controversial (74).

Although the risk of AKI associated with the administration of ACEI's and ARA's is well characterized and recognized, further studies are needed to study the individual potential of

each RAS inhibitor drug to promote prerenal AKI in order to stratify the risk associated with each drug.

4.3. Diuretics

Diuretics, a chemically heterogeneous class of drugs, are used for the treatment of several cardiovascular and renal diseases associated with edema and hypertension (75). They are also used to prevent and manage diverse forms of AKI, however, themselves might produce or aggravate AKI as a side effect (76), particularly in combination with NSAID's and ACEI's/ARA's (77). A multi-center prospective study in Shanghai showed that, ranked only after antibiotics, diuretics accounted for 22.2% of all cases of drug-induced AKI (78).

Diuretics are grouped into different categories: carbonic anhydrase inhibitors (acetazolamide), loop diuretics (furosemide and torsemide), thiazides (chlorthalidone, chlorothiazide, and hydrochlorothiazide), potassium-sparing (amiloride and triamterene), potassium-sparing and aldosterone antagonists (spironolactone and eplerenone), and osmotic (mannitol) (79). For being the most potent, loop diuretics remain the most commonly used agents in the management of patients with AKI (75).

The majority of diuretics act by reducing renal tubular NaCl reabsorption at different sites in the nephron, thereby increasing urinary sodium which limits water reabsorption and results in diuresis (79). By reducing the extracellular volume, they also reduce blood volume, the main chronic determinant of BP and when this extracellular volume depletion is detected, different regulatory mechanisms are rapidly activated to maintain BP and prevent the development of AKI (80).

These regulatory mechanisms converge to produce systemic vasoconstriction and increase water and electrolyte reabsorption to maintain BP and renal perfusion pressure. In the presence of diuretic drugs, natriuretic/diuretic balance and BP control are realized at the expense of a net reduction in blood volume, an increased sympathetic activity, RAAS and antidiuretic hormone (ADH) tones, and decreased atrial natriuretic peptide (ANP) tone (81). Thus, by reducing the circulating volume excessively and adding a prerenal insult, the use of diuretics can lead to hypovolemia and precipitate or aggravate an AKI, especially when used in elderly or dehydrated subjects (13). In addition to AKI, thiazide and loop diuretics may cause interstitial nephritis (82).

The most common pathological lesion of diuretics associated AKI may be vacuolar degeneration of tubular epithelial cells (77).

Grams *et al.*, in a randomized controlled trial evaluating a conservative *versus* liberal fluid-management strategy in 1000 patients with acute lung injury (ALI), in 2011, evaluated the association of post-renal injury fluid balance and diuretic use with 60-day mortality in patients who developed AKI. They demonstrated that a positive fluid balance after in-hospital AKI carried a strong and consistent association with mortality in patients with ALI, independent of liberal or conservative fluid management and that a higher diuretic dose after AKI onset had a

protective effect on survival (due in part to the reduction of positive fluid balance), with no observed threshold dose above which mortality increased. Thus, considering that these data were obtained in a randomized clinical trial of patients with ALI, clinicians may be reassured that diuretics may not be contraindicated, in selected patients (83).

In a meta-analysis of randomized trials, in 2018, Bove *et al*. showed that, although it may reduce mortality and RRT utilization when used as a preventive measure, intermittent furosemide administration is not associated with an overall improvement in survival or other major outcomes in patients with or at risk for AKI (84).

In accordance with the studies such as those mentioned above, the KDIGO Clinical Practice Guidelines for AKI have recommended against the use of loop diuretics for the prevention and/or treatment of AKI, however, they suggest that diuretics have an adjuvant role to manage fluid overload (13).

In 2012, in a study using rats, Sánchez-Pozos *et al*. demonstrated that spironolactone is able to treat kidney ischemia/reperfusion injury efficiently when administered immediately or up to 3 h after reperfusion. The benefit of spironolactone at 6 h after reperfusion was partial and was lost when administered after longer periods of time. Thus, this study indicates that spironolactone is a promising agent for preventing AKI once an ischemic insult has occurred (85).

Based on the fact that mannitol could cause nephrotoxicity or AKI in a proportion of patients, Shi *et al.*, in a laboratory study, in 2018, examine the cytotoxicity of mannitol on renal tubular epithelial cells *in vitro*, and investigate its potential lesion mechanism. They demonstrated that mannitol could induce renal tubular epithelial cells injury (vacuolization) by increase in oxidative stress, inducing cell apoptosis and cytoskeleton destruction (86).

Despite the ambiguity related to the beneficial therapeutic profile of diuretics in situations of AKI with fluid overload and to the potential for the development or aggravation of AKI associated with its administration, an additional consideration of its risks and benefits is necessary considering the individual characteristics of each patient. In addition, more concrete research is needed on the ability of each specific group of diuretics to cause prerenal AKI, so that in situations where the benefits outweigh the risks, be possible their administration with the best therapeutic profile.

4.4. The “double whammies” and “triple whammy” therapies

Either in dual or triple combination, nephrotoxicity is proposed to occur through the cumulative pharmacodynamic effect of each drug. NSAID’s decrease PG’s synthesis, creating afferent arteriolar vasoconstriction, the RAS inhibitors provoke efferent arteriolar vasodilatation by neutralizing the effects of angiotensin II and, additionally, diuretics decrease renal blood flow through the reduction of plasma volume, which leads to decreased renal perfusion pressure. The interaction between these mechanisms play a pivotal role on the potential of the “double whammies” and “triple whammy” drugs to develop prerenal AKI (87).

As the AKI represents a consequence of multiple combinations of risk factors, such as diverse diseases, drugs, transient situations or functional and structural changes due to advanced age, doctors must adapt the prescription in an individualized way in each patient in order to reduce the likelihood of that pathology (8).

In 2013, in a retrospective cohort study using nested case-control analysis, Lapi *et al*. reported that a triple therapy combination consisting of diuretics with ACEI's or ARA's and NSAID's was associated with an increased risk of AKI (31% higher risk of AKI) in users of antihypertensive drugs in the community, being the risk greatest at the start of treatment. Also, they showed that the current use of a double therapy combination of a diuretic or an ACEI/ARA with NSAID's was not associated with an increased rate of AKI. Thus, they conclude that although antihypertensive drugs have cardiovascular benefits, vigilance may be warranted when they are used concurrently with NSAID's (88). Subsequently, Fournier *et al*. analyzed a French Pharmacovigilance database and found that the AKI caused by the interaction between NSAID's and ACEI's/ ARA's or diuretics was the most frequently reported adverse effect (89).

Similarly, in 2015, in another nested case-control study, Dreischulte *et al*. showed that in NSAID's users the combined use of an inhibitor of the RAS and a diuretic was associated with a significant increase in the risk of AKI in the community. Nevertheless, they found that the risk is also higher in the dual combination with RAS inhibitors or diuretics alone. However, the AKI risk was much higher for NSAID use in triple than in dual combination with RAS inhibitors and/or diuretics (90).

Camin *et al*., in a 15-month retrospective observational study, also showed that the "triple whammy" therapy is associated with a high incidence of hospital admission for AKI. In monotherapy, a relevant incidence appeared for the diuretic group, and it was higher when these were combined in dual therapy with ACEI's/ARA's or NSAID's (being highest for the combination of diuretics plus NSAID's). In contrast, the incidence of AKI associated with ACEI's/ARA's and NSAID's, alone or in combination, was lower. In the users of the "triple whammy", the incidence of associated AKI was similar to that of the users of dual therapies that included diuretics. They also related that in 67% of the cases there was a trigger of AKI, such as fever, vomiting or diarrhea in the previous days (probably an intercurrent disease that causes volume depletion or, simply, an increase in basal metabolism in a patient with decreased intraglomerular pressure). This seems to indicate that it was not the treatment with these drugs, but the appearance of an intercurrent disease that precipitated the AKI (91).

In 2014, on two case reports, Onuibgo and Agbasi described the "quadruple whammy" has a syndrome of accelerated post-operative AKI in CKD patients concurrently on "triple whammy" medications. This state is preventable if "triple whammy" combinations are pre-emptively discontinued four to seven days prior to elective surgical procedures, and if peri-operative hypotension is aggressively prevented or rapidly corrected if and when it develops (92).

In Spain, in an uncontrolled before-after intervention study, Arrufat-Goterris *et al*. conducted a double intervention consisting in an educational part (informative session about

the iatrogenic risk associated with the drugs prescribed), and an individualized part (in which recommendations to general practitioner were assessed after reviewing medical records), in order to reduce the iatrogenic risk associated with the "triple whammy" therapy. The suggested recommendations were: monitoring renal function, suspend NSAID's and/or diuretics, replacing the NSAID with an alternative treatment or associations of the various recommendations referred. At the end, the intervention improved the prescription and reduced the number of patients on the "triple whammy" combination and, therefore, the risk of AKI associated with the concomitant use of these three groups of drugs (93). In conclusion this study reveals that monitoring of patients under "triple whammy" therapy is insufficiently performed and needs to be reinforced through specific interventions and that active and effective interventions can actually reduce the risk of iatrogenic side effects.

Currently, clinicians are faced with difficult decisions regarding which complex medication regimens increase the risk of AKI. Enhanced monitoring and management of patients receiving multiple nephrotoxic drugs can reduce AKI severity (87). Doctors all over the world must be aware of the potential for several agents to induce kidney damage, shall make every effort to limit the use of that drugs to reduce harm to patients, and be ready to discontinue drugs when unexplained AKI is diagnosed (92). This peremptorily highlight the need for higher-quality research in this area to better understand which combinations lead to the greatest risk of AKI (87).

5. Conclusion

Medications are widely prescribed and ingested by patients and remain a relatively common cause of prerenal AKI (33). Risk factors for AKI include age, comorbid conditions (like CKD or heart failure), sepsis, and severity of illness. However, one of the most significant modifiable risk factor for AKI is exposure to nephrotoxic medications and so further understanding of the risk factors for AKI may offer an opportunity to prevent or minimize AKI and the associated consequences (87).

Although drug related AKI is commonly associated with the use of individual classes of drugs, little is still known about the effects of drug-drug interactions on this outcome, despite recent investigations in this area. This aspect is particularly relevant among users of antihypertensive drugs, who often need more than one drug for adequate BP control. For example, in patients with heart failure and hypertension, the concurrent use of ACEI's or ARA's along with diuretics is common. However, many of these patients also have chronic inflammatory diseases or chronic pain, so the add-on use of NSAID's may be indicated (88). This pharmacological cocktail known as "triple whammy" presents an undoubted potential for developing prerenal AKI (8).

It is important to remember not to withhold a class of drugs simply because the patient has some form of renal insufficiency, since there are many instances when the benefits of the drug outweigh the risks of nephrotoxicity. To prevent kidney injury, a correct assessment of kidney function before the medication be administered is of the utmost importance, and this knowledge gives the practitioner the opportunity to adjust dosages and take preventive measures (like hydration and therapeutic drug level monitoring) (94).

Thus, both at the level of primary health care and at the hospital level, effective and individualized follow-up of patients who are under nephrotoxic therapy and who present preponderant risk factors for AKI will reduce the incidence of this pathology, with the respective gains in terms of mortality, morbidity, quality of life and health costs.

However, although it is increasingly attempted to characterize prerenal AKI induced by drugs, it is necessary to continue research in this area to educate health professionals and the general public itself so that in a joint effort it is possible to develop strategies and protocols to minimize the associated socioeconomic impact.

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