CHAPTER 228

Renin-Angiotensin System Blockers and Acute Kidney Injury

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Objectives

This chapter will:

1. Describe the role of renin-angiotensin system (RAS) and angiotensin receptor blockers (ARBs) as risk factors of renal impairment in everyday clinical practice.
2. Describe the role of angiotensin-converting enzyme inhibitors (ACEIs) and ARBs in the treatment of acute and chronic kidney dysfunction (CKD).
3. Detail the most important studies describing the risk of acute kidney injury in different subsets of patients receiving ACEIs and ARBs (i.e., patients with heart disease, hypertension, and chronic kidney disease).

The renin-angiotensin system (RAS) is a major factor involved in the progression of renal diseases. Its activation can promote intraglomerular and systemic hypertension and contribute to hemodynamically mediated renal injury. Angiotensin II (Ang II), which is the principal mediator of the system, induces mesangial and tubular cells to proliferate by means of a direct or indirect mechanism and possibly leads to matrix production and tubulointerstitial fibrosis. The RAS also actively participates in the derangement of the heart after ischemic events or since the early stages of heart failure. A reduced capacity to excrete sodium secondary to increased proximal tubular reabsorption and the loss of the renal functional reserve are the two most relevant initial alterations of renal function in which Ang II has been proven to act directly.

Angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin II receptor blockers (ARBs) are considered the gold standard of treatment in patients with chronic kidney disease (CKD), especially if proteinuric. According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines,[1] RAS inhibitors are recommended as first-line treatment in all CKD hypertensive patients with micro- or macroalbuminuria, whether they are diabetic or not.

In addition to CKD, they have extensive treatment indications, from essential hypertension to heart diseases. According to the findings of the Heart Outcomes Prevention Evaluation (HOPE) study, ACEIs can reduce significantly the rates of death, myocardial infarction, and stroke in a broad range of patients at high risk for cardiovascular events in the absence of left ventricular dysfunction or heart failure.

This implies that acute kidney injury (AKI) secondary to RAS use is observed not only in CKD but also in other categories of patients; the coexistence of the primary treatment indication with CKD may amplify the risk of AKI.

In this chapter we critically review the efficacy of RAS blockers given alone or in combination and focus on the risk of AKI after their use.

EFFICACY OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS IN CHRONIC KIDNEY DISEASE

ACEIs and then ARBs had been studied extensively in the 1990s and early 2000s for their antiproteinuric and nephroprotective effects in diabetic and nondiabetic CKD.[2–5] The majority of the patients who were enrolled in the clinical trials were in their adulthood, with a mean age around 50 years old. These findings are then not necessarily applicable to the majority of CKD patients attending nephrology outpatient clinics, who are in general overweight or obese, old, and affected by several comorbidities.

In more advanced CKD, data are less clear. Some years ago, a Chinese trial confirmed the nephroprotective efficacy and relative safety of ACEIs in CKD patients with serum creatinine levels of 3.1 to 5.0 mg/dL.[6] However, the accuracy of the study was questioned by data published in duplicate reporting different sample sizes. Conversely, clinical observations indicate that some patients with advanced CKD may have an improvement in kidney function after RAS blocker withdrawal.[7]

Similar to ACEIs, ARBs reduced the progression of type 2 diabetic nephropathy with overt proteinuria.[8,9] These trial populations were much closer to that observed currently. However, the reduction in the relative risk of reaching the combined primary end point of the doubling of serum creatinine, ESRD, or death was modest (only 16% and 20% in the Irbesartan Diabetic Nephropathy Trial [IDNT][8] and Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan [RENAAL][9] study, respectively).

Although it is acknowledged that RAS blockers are nephroprotective in proteinuric nephropathies, the magnitude of the effect seems less relevant in patients without proteinuria. According to a meta-analysis,[10] the effect of ACEIs disappears in patients with nondiabetic CKD and proteinuria <0.5 g/day. Similarly, treatment with losartan did not significantly reduce the risk of a renal event in type 2 diabetic nephropathy with baseline albuminuria less than 1.5 g/g.[11]

In 2005 a large meta-analysis of RAS inhibitors and renal outcomes raised questions on the renal efficacy of RAS blockade.[12] Even if ACEIs and ARBs were significantly effective, only a small reduction was seen in the risk of end-stage renal disease (ESRD) in favor of either ACEIs or ARBs (relative risk 0.87, CI 0.75–0.99; $p = .04$) compared with other antihypertensive drugs. These results were influenced by the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial,[13] in which there was no evidence for a greater beneficial effect of ACEIs in high-risk hypertensive patients with reduced GFR.

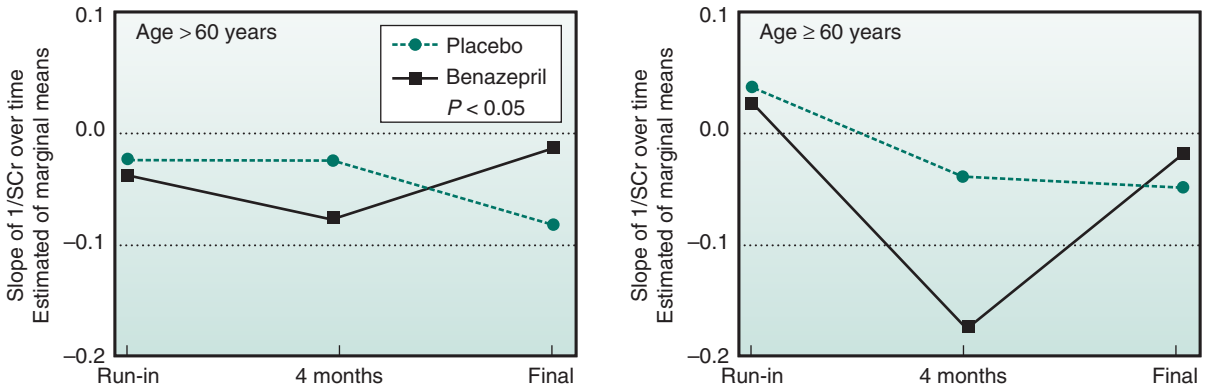

FIGURE 228.1 Trend of the initial decrease in renal function after the start of benazepril therapy according to age in the AIPRI study.[3]

Considering that the progression rate of CKD seems to be very slow in subjects older than 65 years,[14] it is then possible that the follow-up of the majority of randomized trials testing the effect of RAS inhibition may be relatively inadequate to study hypertensive kidney disease at least in Caucasians. Accordingly, a secondary analysis of the ACE Inhibition in Progressive Renal Insufficiency (AIPRI) study[3] showed that at the start of ACEI therapy the short-term worsening of renal function was of higher magnitude in elderly patients compared with younger ones (unpublished data, Fig. 228.1). However, during the long-term follow-up, even the elderly patients treated with ACEIs experienced a trend toward a better GFR compared with those receiving placebo. Moreover, the initial apparent negative effect of benazepril can persist for different periods of time, being longer in the patients with slowly progressive CKD.

Anyway, this relatively scarce benefit is to be balanced with a higher risk of AKI (and hyperkalemia) in this patient population because of the older age, frailty, and high burden of cardiovascular disease. Moreover, it is becoming more often the case that patients with type 2 diabetes develop CKD without overt proteinuria.[15]

TABLE 228.1

Risk Factors for Acute Kidney Injury During Renin-Angiotensin System Blockade

Patient characteristics	Older age
	Male gender
	Chronic kidney disease
	Diabetes
	Renal artery stenosis
	Reduced cardiac ejection fraction
Intercurrent events	Infections
	Hypotension
	Hypovolemia
	Major surgical procedures
Drugs	High number of prescribed drugs
	Diuretics
	Aldosterone receptor antagonists
	Dual RAS blockade
	Nonsteroidal antiinflammatory drugs

RAS, Renin-angiotensin system.

RISK OF ACUTE KIDNEY INJURY WITH RENIN-ANGIOTENSIN SYSTEM BLOCKERS IN EVERYDAY CLINICAL PRACTICE

Renal complications of ACEIs or ARBs are widely recognized. These agents usually cause an initial but reversible worsening of renal function on a hemodynamic basis. However, in some patients the increase in serum creatinine can sustain longer or AKI can develop later during undercurrent events, such as infections or dehydration or surgical procedures.

Several risk factors increase the likelihood of AKI at the start or during RAS blockade (Table 228.1). In particular, the use of diuretics and nonsteroidal antiinflammatory drugs or the presence of a stenosis of the renal artery (often unknown) increase the likelihood of AKI related to RAS blockade use. Excessive doses of RAS blockers, especially at treatment start, may cause AKI resulting from hypotension and renal hypoperfusion.

The risk of AKI secondary to RAS blockade has been studied in several medical conditions. Unfortunately, the definition of AKI varies greatly among studies, preventing an easy comparison of data from different trials and in various clinical settings. This recently has been improving after KDIGO guidelines gave a clear definition of AKI (i.e., an increase in serum creatinine by ≥0.3 mg/dL within 48 hours or an increase in serum creatinine ≥1.5 times from baseline, which have presumably occurred in the prior 7 days).[16] Further complicating matters, patients who normally are seen in everyday clinical practice substantially differ from those enrolled in clinical trials. For instance, in the setting of heart failure or myocardial infarction, most of the large randomized trials aimed at assessing the effect of ACEIs on mortality excluded the very elderly or subjects with renal dysfunction (serum creatinine higher than 2.0 to 2.5 mg/dL). Furthermore, a worsening in renal function during the run-in phases and the suspect of renal artery stenosis were considered as exclusion criteria in many of the studies enrolling patients with chronic nephropathies.

Patients undergoing cardiac surgery are at high risk of AKI; RAS blockers may further increase the risk of AKI by contributing to intraoperative systemic hypotension and enhancing intraglomerular hypotension. However, data in the literature are conflicting. Some authors found an increased AKI risk after RAS blockade[17,18]; others found no effect or reduced risk.[19,20] Treatment indication biases and different comorbidities partially may explain these discrepancies.

The TRIBE-AKI study prospectively observed 1594 subjects undergoing cardiac surgery.[21] According to ACEI/ARB use (none, halted the morning of surgery, or continued), a graded increase of functional AKI was observed (31%, 34%, and 42%, respectively). However, this was not followed necessarily by structural AKI (i.e., the urinary release of markers of kidney injury). A meta-analysis collected data from 23 either retrospective or prospective studies (69,027 patients) examining the effect of preoperative use of RAS blockers in the development of postoperative AKI after cardiovascular surgery.[22] Preoperative RAS-blocker use was associated with increased odds of postoperative AKI (OR, 1.17; 95% CI 1.01–1.36; $p = .04$). However, significant heterogeneity was found across studies, with different definitions of AKI, different durations of follow-up, and inability to exclude outcome reporting bias.

Another possible bias was the long time frame of the selected trials, spanning from the 1950s to recent years. Although this makes the meta-analysis complete, it adds the strong confounding factor of the impressive improvements in the surgical procedures observed over the decades. Moreover, decades ago RAS blockers were not prescribed necessarily as they are now.

Another recent meta-analysis of 24 studies (1 randomized controlled trial and 23 cohort studies; 102,675 patients) assessed the risk of postoperative AKI and preoperative RAS inhibitors use.[23] The majority of the studies were performed again in patients undergoing cardiovascular surgery. The pooled risk ratio (RR) of postoperative AKI in patients receiving RAS inhibitors was higher than in those untreated (1.05, 95% CI 0.92–1.20). When the meta-analysis was limited only to the single RCT and to the cohort studies with propensity score analysis (thus reducing confounding effects), the pooled RR of postoperative AKI was lower in patients receiving preoperative RAS inhibitors than in those not receiving RAS blockade (0.92, 95% CI 0.85–0.99). A subgroup analysis of the patients who had received preoperative RAS inhibitor since more than 2 weeks before surgery showed the strongest association of reduced AKI risk.

In noncardiac surgery, AKI risk is much lower, ranging between 6% and 12% in gastrointestinal surgery and between 23% and 25% in vascular surgery.[24] Also in this setting, results are conflicting. In a mixed Japanese cohort of 2725 subjects, the risk was enhanced by diuretic but not RAS blockade use.[25] Conversely, in patients undergoing major orthopedic surgery, preoperative RAS blockers use was an independent predictor of AKI, with an odds ratio of 1.70 (1.34 to 2.16).[26] In addition to ACEI or ARB use, the other independent predictors of AKI were older age, male sex, diabetes, number of prescribed drugs, lower estimated GFR, and the American Society of Anesthesiologists grade.

A large population-based retrospective study in Ontario, Canada, included cardiac and noncardiac major surgeries but excluded emergency procedures.[27] It showed a 17% lower risk of AKI requiring dialysis in preoperative ACEI/ARB use versus nonuse. The choice of a more severe definition of AKI and the exclusion of patients who were more likely to have hemodynamic instability (i.e., those with emergent conditions) may be a partial explanation of this surprising finding.

During undercurrent illnesses or surgical procedures, patients who already have CKD have a higher risk of AKI when treated with RAS blockers. In the above Canadian study, the inverse association between ACEI/ARB use and AKI requiring dialysis was confirmed in the presence of preoperative CKD.[28] As suggested by the authors, it is possible that CKD patients not receiving preoperative ACEIs/ARBs had more advanced CKD and were not treated with ACEIs/ARBs for this reason.[28]

RISK OF ACUTE KIDNEY INJURY IN CLINICAL TRIALS ENROLLING CHRONIC KIDNEY DISEASE PATIENTS

In the setting of chronic nephropathies, clinical trials report a relatively low incidence of renal impairment secondary to RAS blockade compared with what was observed in everyday clinical practice.

In the 1990s the trials testing ACEIs as nephroprotective agents enrolled mainly middle-aged patients with low cardiovascular risk. In the AIPRI Study,[3] which mainly enrolled patients with nondiabetic nephropathies and creatinine clearance values between 30 and 60 mL/min, 3 out of 300 patients on benazepril (1%) and 6 out of 283 patients on placebo (2.1%) were withdrawn from the trial because of worsening of renal insufficiency. Similarly, a very low incidence of drug-related renal impairment was observed in the Ramipril Efficacy in Nephropathy (REIN) study (0.5% and 1.1% in the ramipril and placebo group, respectively).[4]

Some years later, the Chinese trial mentioned above tested the efficacy and safety of ACEIs in more advanced CKD.[6] All the patients in group 1 (serum creatinine between 1.5 and 3 mg/dL) received benazepril; only 1 (1%) developed AKI. Similarly, only one patient (0.9%) in group 2 (serum creatinine between 3.1 and 5 mg/dL) developed a significant worsening of kidney function after the start of benazepril. The study foresaw a run-in phase in which all the patients were given benazepril for 4 weeks. At this stage, 9 out of 422 patients (2.1%) had an acute increase in serum creatinine of more than 30%.

The Ongoing Telmisartan Alone in Combination with Ramipril Global Endpoint Trial (ONTARGET) compared the effect of ramipril and telmisartan monotherapies or their combination in 25,620 patients with vascular disease or high-risk diabetes.[29] The majority of the patients had substantially normal renal function at baseline and no proteinuria. During the run-in phase, in which all the patients received monotherapy and then dual blockade, only 64 (0.2%) had an elevated creatinine level; after randomization approximately 0.7% of the patients in monotherapy discontinued the study drug because of renal impairment.

Patients with diabetic nephropathy may have a slightly higher incidence of AKI after RAS blockade. In the early 1990s two large trials, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL)[8] and the Irbesartan Diabetic Nephropathy Trial (IDNT),[8] which investigated the effect of ARBs in type 2 diabetes and nephropathy, the majority of the enrolled patients had decreased kidney function at baseline. An increase in serum creatinine leading to study drug discontinuation occurred in 1.5% of the patients receiving losartan in the RENAAL study.[9] As expected, this incidence rate was higher in the highest tertile of serum creatinine at baseline.[30] Conversely, in the IDNT trial only one patient (0.17%) had an early increase in serum creatinine following irbesartan therapy.[8]

Recently, a network meta-analysis of 157 randomized trials (n = 43,256) compared blood pressure–lowering agents in adults with diabetic kidney disease.[31] Despite expectations, RAS blockade did not increase AKI risk significantly compared with other antihypertensive drugs or placebo.

RISK OF ACUTE KIDNEY INJURY IN CLINICAL TRIALS ENROLLING PATIENTS WITH HEART DISEASE

As it is reasonable to expect, data from large trials that assessed the effects of RAS blockers in patients with left-ventricular dysfunction or heart failure indicate a higher incidence of renal failure compared with that observed among patients with chronic nephropathies. In the Assessment of Treatment with Lisinopril and Survival (ATLAS) study, which enrolled patients with an ejection fraction of 30% or less, 68 patients (1.7%) experienced AKI during the run-in phase with lisinopril.[28] After randomization, 112 (7%) and 155 (10%) subjects in the low-dose and in the high-dose lisinopril groups had a worsening in renal function. However, only a minority had to discontinue the trial for this reason. A post-hoc analysis of the Studies of Left Ventricular Dysfunction (SOLVD)[32] showed that the patients assigned to enalapril had a 33% greater likelihood of decreased renal function (defined as an increase in serum creatinine of ≥ 0.5 mg/dL) than controls. Older patients and those receiving diuretics in the enalapril group were more likely to experience an increase in serum creatinine than patients in the placebo group.

Some years ago, an individual-patient meta-analysis from five trials of patients with heart disease reported that renal dysfunction occurred in 281 (5.2%) patients receiving ACEIs.[33]

More recently, Clark et al.[34] performed an ad-hoc meta-analysis addressing the impact of AKI after RAS blockade on long-term outcome in patients with left ventricular systolic dysfunction and heart failure. Data from five major studies (SOLVD, SAVE, RALES, Val-HeFT, and EPHESUS; 20,573 patients) were analyzed. As expected, more subjects developed AKI in the RAS inhibitor than in the placebo group. However, as underlined by the authors, AKI occurred frequently also in the placebo group. This means that patients with heart disease had a high background rate of AKI independent of RAS inhibitor use. The development of AKI shortly after randomization was associated with worsened outcomes compared with no AKI; however, the use of RAS inhibitors was associated with a significant reduction in all-cause mortality also in this setting of patients.

Interestingly, it has been suggested that pre-treatment with beta-blocker may prevent renal impairment in patients with heart failure when treated with ACEIs. Indeed, beta-blockers, which lower plasma renin activity, could decrease dependence on Ang II for maintaining GFR and allow a safer introduction of ACEIs.[35]

RISK OF ACUTE KIDNEY INJURY IN DUAL RENIN-ANGIOTENSIN SYSTEM BLOCKADE

Given that single blockade with ACEIs or ARBs can achieve only partial and not-durable suppression of the RAS system, it had been hypothesized that dual blockage with ACEIs and ARBs would be most beneficial in the management of progressive CKD than either agent alone. Indeed, the combination of these two classes of drugs reduced more proteinuria than one single agent.[36] In addition, in the 2000s dual blockade had gained popularity in patients with heart disease.[37,38] Direct renin inhibitors also have been tested in combination with either ACEIs or ARBs in high-risk patients with diabetes[39] and in patients with heart failure.[40] Despite expectations, dual blockade does not significantly reduce the risk of hard end points and increases the risk of adverse events, such as hyperkalemia and AKI.

Some years ago, the Ongoing Telmisartan Alone in Combination with Ramipril Global Endpoint Trial (ONTARGET) study compared the effect of ramipril and telmisartan monotherapies and their combination on cardiovascular mortality in 25,620 patients with vascular disease or high-risk diabetes.[29] Unexpectedly, the primary renal outcome (dialysis, doubling of serum creatinine, and death) occurred more frequently in patients receiving dual blockade than monotherapies (13.4%, 13.5%, 14.5% for telmisartan, ramipril and dual blockade, respectively).[41] Considering that those receiving the combination therapy had more frequent hypotensive symptoms, excessive hypotension may have caused the acute worsening of renal function. It is also possible that in high-risk patients the presence of unknown stenosis of the renal artery or increased intrarenal vascular resistance may have enhanced the risk of AKI after dual blockade. According to a meta-analysis of more than 60,000 patients with heterogeneous diseases (hypertension, heart failure, high-risk cardiovascular disease, diabetic nephropathy) dual blockade was not associated with any significant benefit for either all-cause mortality or cardiovascular mortality compared with monotherapy (excepting a 18% reduction in the risk of hospitalization for heart failure).[42] However, patients randomized to dual blockade had a 55% increase in the risk of hyperkalemia, a 66% increase in the risk of hypotension, and a 41% increase in the risk of renal failure.

Patients with diabetes are considered at risk of AKI and/or hyperkalemia during dual blockade. In the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) trial, renal impairment and hypotension were reported more commonly in the aliskiren group than in the placebo group; they were the second and third most common adverse events leading to study-drug discontinuation after hyperkalemia. However, renal impairment was also common in the placebo group, with a difference between the two treatment arms only of borderline significance (9.8% and 8.7%, respectively, $p = .07$). The addition of aliskiren to single RAS blockade delayed progression to microalbuminuria and macroalbuminuria and improved regression to microalbuminuria and normoalbuminuria.[43]

More recently, the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D)[44] study tested the safety and efficacy of combination therapy with an ACEI and an ARB as compared with ARB monotherapy in slowing the progression of proteinuric diabetic nephropathy with overt nephropathy. Despite a trend toward a benefit from combination therapy on the secondary renal end point (the first occurrence of a decline in the estimated GFR or ESRD), the study was stopped early because of safety concerns. In particular, the risk of AKI was significantly higher in those receiving dual blockade compared with ACEI alone (12.2 vs. 6.7 events per 100 person-years, respectively; $p < .001$).

In consideration of the small clinical benefits of dual blockade in comparison with a significant risk of adverse events (namely AKI and hyperkalemia), in 2014 the European Medical Agency (EMA) issued an official restriction on the combined use of medicines affecting the RAS. The combination of aliskiren with an ARB or ACEI is now contraindicated strictly in those with kidney impairment or diabetes.

Dual blockade is considered still a possible therapeutic option in patients with nondiabetic CKD and significant proteinuria. However, specialist supervision is needed with close monitoring of kidney function, fluid and salt balance, and blood pressure. A smooth titration of the drugs is warranted to avoid acute hypotension, give time to the kidney to adapt to RAS blockade, and detect early a significant rise in serum creatinine.

Recently, the network meta-analysis by Palmer et al.[31] gave new hope to the use of dual RAS blockade in patients with diabetic nephropathy and CKD with or without albuminuria. Thanks to this statistical methodology, unified hierarchies of evidence for all blood pressure–lowering agents are obtained, overcoming the absence of comparative data in head-to-head trials. ACEI and ARB treatment (alone or in combination) were ranked as the most effective agents for prevention of ESRD; however, only an ARB (alone or combined with an ACEI) was significantly better than placebo. Moreover, dual blockade greatly improved albuminuria. It was estimated that giving 1000 patients the combination of ACEI and ARB for 1 year may prevent 14 patients from developing ESRD and induce regression of albuminuria in 208 subjects. With dual blockade the risk of AKI was only of borderline significance (odds ratio of 2·69, IC 0·98–7·38). A nonuniform definition of AKI across studies may have influenced this finding, because safety end points were defined poorly in clinical trials.[45] In particular, small derangement with kidney function were put together with more serious events, such as acute dialysis (the latter likely much less frequent). Giving 1000 patients the combination of ACEI and ARB for 1 year may cost 55 patients having AKI; however, many of them may have just had physiologic changes in kidney function as a result of hemodynamic changes resulting from treatment.

CONCLUSION

ACEIs and ARBs are effective therapeutic strategies to slow down CKD progression in diabetic and nondiabetic proteinuric nephropathies and improve patient outcome in heart diseases. After the start of therapy with ACEIs or ARBs, an initial small reduction in GFR or a rise in serum creatinine level is a positive prognostic marker of a subsequent reduction in the rate of CKD progression, because of hemodynamic action on glomerular blood flow.[46] However, some patients may develop AKI at treatment start or during chronic treatment in the presence of an undercurrent event. The elderly or high-cardiovascular-risk patients are more likely to be affected by AKI. In this subset of patients, clinical benefits are to be balanced carefully with the risk of adverse events.

Just to add to the complications, it is still unclear which percentage of worsening in renal function is to be considered as the threshold of AKI and thus the indication to stop treatment.

Key Points

1. The RAS is a major factor involved in the progression of renal diseases. Its activation can promote intraglomerular and systemic hypertension and contribute to hemodynamically mediated renal injury.
2. ACEIs and/or ARBs are considered the gold standard of treatment in patients with CKD, especially if proteinuric.
3. Patients undergoing cardiac surgery are at high risk of AKI; RAS blockers may further increase the risk of AKI by contributing to intraoperative systemic hypotension and enhancing intraglomerular hypotension. However, data in the literature are conflicting. A network meta-analysis of 157 randomized trials (n = 43,256) compared blood pressure–lowering agents in adults with diabetic kidney disease showing that RAS blockade did not increase AKI risk significantly compared with other antihypertensive drugs or placebo.
4. Patients with heart disease have a high background rate of AKI independent of RAS inhibitor use. The development of AKI shortly after treatment start may be associated with worsened outcomes compared with no AKI; however, the use of RAS inhibitors was associated with a significant reduction in all-cause mortality also in this setting of patients.
5. In consideration of the small clinical benefits of dual blockade in comparison with a significant risk of adverse events (namely AKI and hyperkalemia), in 2014 the EMA issued an official restriction on the combined use of medicines affecting the RAS.

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