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Perioperative management of renin-angiotensin-aldosterone system antagonists

MCQs –

1 Renin-angiotensin-aldosterone system (RAAS) antagonists do not

a. Increase arterial resistance;
b. Decrease venous capacitance;
c. Decrease glomerular filtration pressure;
d. Increase renal excretion of potassium;
e. Decrease natriuresis.

2 In the perioperative period, the RAAS

a. Counteracts activation of the sympathetic nervous system;
b. Stimulates the release of arginine-vasopressin;
c. Potentiates the vasodilatory effect of anaesthetic agents;
d. Promotes myocardial fibrosis and hypertrophy;
e. Decreases venous return to the heart.

3 Chronic treatment with RAAS antagonists has been associated with

a. Refractory hypotension on induction of anaesthesia;
b. Post-operative acute kidney injury;
c. Intra-operative myocardial ischaemia;
d. Increased inflammatory response;
e. Increased risk of red blood cell transfusion.

4 Resuming RAAS antagonists in the post-operative period

a. Increases the risk of hyperkalaemia;
b. Should be delayed for at least 1 week;
c. Decreases the risk of cardiovascular complications;
d. Increases the risk of acute kidney injury;
e. Increases in-hospital length of stay.

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Key points:

- If a patient is maintained on ACEI/ARB treatment before surgery, it is reasonable to withhold it temporarily to prevent hypotension during induction of anaesthesia[1,2]. As most ACEI/ARBs have short half-lives, cessation 24 hours prior to surgery appears the most pragmatic approach. Although a 'withdrawal' state from abrupt cessation of those drugs is theoretically plausible, there is no reliable evidence supporting that.
- In patients on ACEI/ARB treatment for heart failure, it is reasonable to continue it during the perioperative period under close monitoring. If patients are not on those agents pre-operatively, it is recommended to start them after the first post-operative week[2].
- If a patient is on ACEI/ARB treatment pre-operatively, it should be resumed as soon as possible following the surgical procedure [1,2]. Once the patient is haemodynamically stable, the risks associated with post-operative RAAS inhibition are outweighed by the benefits provided that renal function is not compromised.
- If a patient is not on ACEI/ARB therapy, evidence hitherto available does not support starting it pre-operatively (other than possibly in patients undergoing CABG [3]). Further research is warranted to better clarify whether this approach brings any benefit for perioperative or long-term outcomes.

Introduction

The renin-angiotensin-aldosterone system (RAAS) antagonists include ACE inhibitors (ACEIs), angiotensin II receptor subtype 1 blockers (ARBs) and direct renin inhibitors (e.g. aliskiren). Their beneficial cardiovascular and renal effects made them key components in the therapeutic armamentarium of common diseases like hypertension[4], congestive heart failure[5], ischaemic heart disease[6] and diabetic nephropathy[7]. Therefore, most patients presenting for cardiac and non-cardiac surgery are on one or more of those drugs and the alterations they cause in cardiovascular physiology may be problematic in the perioperative setting. The scant literature available on whether they should be stopped or continued in the perioperative period and the lack of guidelines supporting either approach contributes to the wide variation in clinical practice, which is often based on personal experience and local policy. In keeping with this, a survey to 105 cardiac surgeons in the UK

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revealed 63% considered that use of ACEIs causes vasodilatation after CPB, thus increasing the need for fluids, inotropes and vasoconstrictors. However, opinions were divided on whether it was worth stopping ACEIs prior to surgery, with 40% reporting that they used to withhold those drugs preoperatively in elective operations[8]. This practice variation reflects uncertainty regarding the risks and benefits of either approach, which in turn is a consequence of the scant evidence available to support decision making.

Although Wolf and McGoldrick [9]suggested that beta-blockers, calcium channel blockers, amiodarone, and alpha-2 agonists should be continued throughout the perioperative period, whereas ACEIs, ARBs, and diuretics should be discontinued on the morning of surgery and resumed in the immediate postoperative period, controversy is far from being settled.

The purpose of this review is to compare the pros and cons of continuing versus withholding RAAS antagonists in both cardiac and non-cardiac surgery patients in the perioperative period.

Pharmacological considerations and impact in the perioperative period

RAAS antagonists prevent activation of the RAAS and thereby decrease arterial resistance, increase venous capacitance, decrease glomerular filtration pressure, decrease blood pressure, and promote natriuresis. These effects are mediated by the synergistic action of several mechanisms including direct sympathetic blockade, increased bioavailability of vasodilators such as bradykinin, nitric oxide and prostacyclin, inhibition of the direct and indirect vasoconstrictor effects of angiotensin II, and reduced secretion of aldosterone and antidiuretic hormone resulting in a decrease in salt and water reabsorption by the kidney[10].

Physiological activation of the RAAS is crucial to maintain cardiovascular homeostasis, particularly in response to haemodynamic stress or injury. However, overstimulation of this system, for instance in heart failure, can have detrimental consequences like myocardial hypertrophy, fibrosis and inflammation[11]. The RAAS together with sympathetic activation and AVP release is crucial in the perioperative period to maintain venous return and blood pressure and thus counteract the vasodilatory effect of anaesthetic drugs. The vasoconstrictor effect of angiotensin II is twofold: it promotes vasoconstriction directly and it promotes arginine-vasopressin release[12]. Therefore, chronic suppression of the RAAS can have detrimental consequences in the perioperative period by causing “vasoplegia”, that is by blocking the physiological response to increased venous pooling of blood, decreased cardiac output, and arterial hypotension that are caused by anaesthetic agents. Post-induction hypotension can

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affect 10–40% of patients taking ACEI with no cardiac disease and the figures may rise to 75–100% in patients with hypertension [13]. Anaesthesia and surgery disturb the hard-won balance achieved by ACEI/ARB therapy and may uncover the underlying frailty of the patient's haemodynamic system [14,15]. The degree of hypotension reported while on treatment with RAAS antagonists is exacerbated by concomitant use of diuretics [16] and is related to both the duration of discontinuation [17,18], the half-life of the agent [18], and the type of RAAS antagonist (with ARBs appearing to have a more severe effect) [19]. Although stopping those drugs pre-operatively may reduce hypotensive episodes, there is a potential risk that increasing systemic vascular resistance may cause rebound hypertension [18], compromise regional circulation (splanchnic) [12], worsen cardiac failure [20], or cause myocardial infarction [21]. However, those concerns have not been validated in patients with heart failure [20] and hypertension [22].

The multiple pathways influenced directly or indirectly by the RAAS imply that management of intraoperative hypotension associated with RAAS antagonists requires a combination of strategies to increase vascular resistance, venous return and cardiac output. In addition to adequate intravascular volume repletion, AVP and adrenergic agonists (e.g. ephedrine, phenylephrine depending on heart rate [23]) may be useful to compensate for the inhibition of those pathways caused by chronic RAAS blockade [24,25].

On the other hand, recent pharmacogenomics has suggested that individual variations in susceptibility to RAAS antagonists are associated with single nucleotide polymorphisms in genes encoding angiotensinogen and angiotensin II receptor 1 [6,26]. Although genetic variability is still not routinely used to tailor medical therapy, it further compounds the difficulties in managing patients on chronic RAAS antagonists in the perioperative period.

Pre-operative initiation of ACEI therapy

A recent meta-analysis [27] investigated the impact of starting ACEI treatment pre-operatively in patients naïve to RAAS blockade. A total of 7 randomised controlled trials (571 patients) were included from both cardiac and non-cardiac surgery. Overall, this review did not find evidence to support that perioperative ACEI/ARB therapy can prevent mortality, morbidity, and complications (hypotension, perioperative cerebrovascular complications, acute myocardial infarction and cardiac surgery-related renal failure). However, ACEI/ARB seemed to increase cardiac output perioperatively. Due to the low quality, high risk of bias, and lack of power of the included trials, the true

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effect may be substantially different from the observed estimates and hence perioperative (mainly elective cardiac surgery, according to included studies) initiation of ACEIs or ARBs therapy should be individualised.

In contrast with this, there is modest evidence that pre-operative initiation of RAAS inhibitors may be beneficial to patients undergoing cardiac surgery. A small study (14 patients) suggested that IV administration of ACEI for two days prior to CABG improved haemodynamic parameters in patients with heart dysfunction, and sustainably increased renal perfusion up to a week after operation [28]. In keeping with this, another study reported a significant reduction in the incidence of post-operative AKI in patients undergoing cardiac surgery who were started on ACEI pre-operatively [29].

On the other hand, the concerns that RAAS inhibition could increase fibrinolysis and inflammation in patients undergoing cardiac surgery have not been confirmed in a trial that randomised patients to ramipril 5 mg/day, candesartan 16 mg/day, or placebo between one week and 5 days prior to surgery. Although ACEI enhanced intraoperative fibrinolysis, this did not increase the need for RBC transfusion. On the other hand, neither ACEI nor ARB influenced the inflammatory response to cardiopulmonary bypass (CPB) [30].

In conclusion, there is insufficient evidence to recommend routine initiation of ACEI/ARB treatment pre-operatively, although it may be beneficial for certain groups of patients, particularly in those undergoing cardiac surgery.

Stopping versus continuing RAAS antagonists pre-operatively

There have been just 4 prospective, randomized, controlled trials [18,19,21,23] evaluating the effect of pre-operative withdrawal of RAAS antagonists and all showed that it could decrease the associated hypotension. However, none of them was adequately powered or addressed whether it had an impact on postoperative outcomes. One of those trials also demonstrated that withholding ACEI therapy did not increased perioperative hypertension [22].

In addition to those randomised trials, there a many observational studies, some using propensity-score matching, comparing patients who stopped and who continued ACEI/ARB treatment in the perioperative period.

Due to the particular characteristics of the patients and surgical interventions, literature is best analysed considering different populations of patients: cardiac surgery and non-cardiac surgery.

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Cardiac surgery

Most evidence hitherto available comes from observational studies of modest quality and so drawing definite conclusions will not be possible until further data is provided by large randomised clinical trials. Furthermore, those studies often report contradictory findings, which rather than clarify adds to the ongoing controversy on this topic.

In fact, chronic treatment with ACEI/ARB pre-operatively has been associated with increased incidence of post-induction/during CPB hypotension and increased need for vasopressors [31], renal dysfunction and AKI [32-34], AF [32,34,35]. On the contrary, other studies suggested that chronic ACEI/ARB treatment prior to CABG did not influence intraoperative hypotension during CPB [36-38] and clinical outcomes [37,39,40], including in-hospital [41] and long-term mortality [42]. Moreover, ACEI/ARB therapy was associated with a significantly lower incidence of postoperative AKI [43], even in elderly patients [41], and also heparin-induced hypotension in patients undergoing on-pump cardiac surgery [44]. Of note, the risk of hypotension seems to be common to on-pump and off-pump coronary surgery [45] and ARBs in comparison in ACEIs seem to cause more profound hypotension during CPB, perhaps due to blockade of angiotensin II receptors by the former [46].

If observational studies have provided conflicting data, meta-analysis have also failed to demonstrate compelling and consensual findings. A meta-analysis of 5 studies including over 400 patients concluded that administration of ACEI/ARAs in the immediate pre-operative period increased intraoperative hypotension but there was insufficient data to support any other consequences [21]. Furthermore, the association between ACEI treatment and hypotension seemed to be restricted to the intraoperative period [47], and to be directly proportional to the dose of ACEI that the patient was on preoperatively [48]. More recently, a meta-analysis of retrospective studies including almost 70,000 patients demonstrated that preoperative RAAS blockade was associated with increased risk of postoperative AKI and mortality [49] and another meta-analysis including over 30,000 patients found that preoperative ACEI therapy increased the risk of hypotension, myocardial infarction and AKI in patients undergoing on-pump CABG [34]. There was no association with postoperative AF, stroke and early mortality. However, both meta-analyses were based on observational studies of limited quality and thus the possibility of significant biases cannot be underestimated.

To better characterise the nature of the AKI associated with RAS inhibition, a prospective cohort study [50] compared three groups of patients: (1) patients naïve to ACEI/ARB, (2) patients on chronic ACEI/ARB who withheld it on the morning of surgery, and (3) patients on chronic ACEI/ARB who continued it until the operation. Exposure to ACEI/ARB was associated with a graded increased in the incidence of functional (as

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measured by percentage change in serum creatinine) but not structural AKI (as measured by markers of structural kidney damage). This suggests that withholding ACEI/ARB on the day of surgery may reduce the risk of postoperative 'functional' AKI. However, perioperative ACEI/ARB therapy may benefit renal function through enhanced renal cortical perfusion [51], provided that there are no contraindications like concurrent use of nephrotoxic agents and hypotension [52].

Despite considerable evidence suggesting that RAAS blockade prior to surgery is associated with hypotension and increased requirements of vasoactive amines, the benefit of withholding those drugs pre-operatively is uncertain. A small prospective study [19] found that pre-operative omission of ACEI was associated with higher mean arterial pressure and lower utilisation of vasopressors during CPB. On the other hand, those patients required more vasodilators to control hypertension after CPB and in the early postoperative period. The authors did not find any difference in hypotension on induction of anaesthesia or in the use of vasoconstrictors after CPB. In addition, whether continuing (versus stopping) RAAS antagonists pre-operatively influences in-hospital and long-term morbidity and mortality remains controversial. Therefore, evidence hitherto available is insufficient to recommend withholding ACEI/ARB pre-operatively on a routine basis and weighing the pros and cons for each individual patient is paramount. Currently, there is only one registered trial on Clinicaltrials.gov dealing with ACEI/ARB withdrawal in patients undergoing cardiac surgery (nCt02096406).

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Non-cardiac surgery

The scenario in non-cardiac surgery is similar to cardiac surgery, with controversy on the impact of perioperative ACEI/ARB therapy and also lack of high-quality evidence [53], including for spinal anaesthesia [54].

Chronic treatment with ACEI/ARB has been associated with a two-fold higher risk of hypotension after induction of anaesthesia and postoperative AKI [55] in patients undergoing major orthopaedic surgery and a two-fold higher risk of postoperative AKI irrespective of baseline renal function [56] in patients undergoing aortic surgery. Furthermore, a large international prospective study showed that withholding ACEI/ARBs before major non-cardiac surgery was associated with a lower risk of death, stroke, myocardial infarction and intraoperative hypotension [57]. On the contrary, other studies found no association between RAAS antagonists and incidence of post-operative AKI [58], hypotension and cardiovascular complications in patients undergoing non-cardiac surgery [59].

If there is no consensus on the influence of chronic RAAS blockade on perioperative outcomes, whether those agents should be stopped or continued also remains unclear. Comfere et al that retrospectively analysed patients undergoing elective non-cardiac surgery and showed that discontinuation of ACEI/ARB therapy at least 10h before induction of anaesthesia reduced the incidence of post-induction hypotension, although it did not influence vasopressor requirement [17]. On the contrary, da Costa et al did not find any association between ACEI/ARB in the morning of the operation and intraoperative hypotension, thus suggesting that discontinuation of RAAS inhibitors pre-operatively was not justified [60]. On the other hand, discontinuing ACEI/ARB treatment on the day of surgery did not significantly increase the risk of pre- or postoperative hypertension [22] and post-induction hypotension appeared to be more severe in the case of concomitant use of diuretics [55]. Taken together those studies emphasise the importance of assessing patients on an individual basis as the safety of either approach appears identical but depends on the particular circumstances of each patient.

Interestingly, intraoperative hypotension seems to depend on the type of anaesthetic agent, as hypotension was observed after induction with propofol but not etomidate[61]. Therefore, in patients chronically taking ACEIs, low doses of propofol (up to 1.3 mg/kg) are recommended to avoid haemodynamic instability[62]. The underlying mechanism may be related to the additive effect of propofol and ACEI in promoting endothelium-dependent increase the production and release of nitric oxide.

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In addition to the common association with hypotension and renal dysfunction, there have been concerns on whether ACEI treatment could cause upper-airway complications like cough, angioedema, and bronchospasm. However, a propensity-matched retrospective study including almost 80,000 patients found no association between use of ACEIs and intraoperative or postoperative upper-airway complications, vasopressor or fluid requirements and 30-day mortality [63].

To sum up, in patients undergoing non-cardiac surgery, ACEI/ARB therapy might be associated with renal dysfunction and intraoperative hypotension. However, RAAS blockade-related hypotension seemed to be responsive to simple measures and was apparently not associated with adverse outcomes [64]. Evidence on the impact of ACEI/ARBs on cardiac, respiratory or renal complications or mortality is contradictory and flawed with methodological limitations [57,63]. Although some recommend stopping ACEI/ARBs 24h prior to surgery, it seems premature to change clinical practice based on the modest evidence hitherto available [65]. However, there is now equipoise to justify a randomised clinical trial to finally resolve this longstanding controversy.

Resuming RAAS antagonists post-operatively

A prospective study compared patients who underwent coronary artery bypass grafting according to ACEI therapy prior to and following surgery. Withdrawal of ACEI treatment after coronary artery bypass graft surgery was associated with an increase in renal and cardiac adverse events, whilst continuation of ACEI or *de novo* ACEI therapy early after cardiac surgery was associated with improved in-hospital outcomes (significant reduction of cardiovascular events). There was though no difference in in-hospital mortality and cerebrovascular events [66]. In addition, another study showed that failure to resume ACEI treatment in the post-operative period was associated with an increased risk of impaired microcirculation [31].

The randomised controlled trial IMAGINE compared administration of ACEI within 7 days of CABG with placebo in stable patients with normal LVEF. In this group of patients at low risk of cardiovascular events, early initiation of ACEI therapy did not improve clinical outcomes up to 3 years after CABG but it increased the risk of hypotension, particularly in the first 3 postoperative months [67]. In addition, ACEI therapy may be used as a dobutamine substitute as early as the first postoperative day after cardiac surgery without renal consequences in patients with low LVEF [68].

On the other hand, a small trial randomised patients with anaemia to receive either ACEI or placebo at 9 days post-heart surgery in addition to standard treatment, which included iron supplementation. The recovery of haemoglobin and RBC parameters was

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significantly faster in the control arm, thus suggesting that ACEI therapy inhibits erythropoiesis [69]. Although the mechanisms are yet to be understood, this may be important when considering restarting ACEI post-operatively in patients with anaemia.

A small retrospective study analysed the impact of early (within 90 days) reintroduction of ACEI/ARB after renal transplant and concluded that in patients with reasonable allograft function, administration of ACEI/ARB to treat hypertension was well tolerated and did not increase the risk of hyperkalaemia, anaemia, or acute renal dysfunction[70]. In keeping with this, a systematic review suggested that the early (within 12 weeks) initiation of RAAS inhibitors was safe in post-renal transplant patients with functioning grafts and that those drugs could be considered first-line treatment in patients with hypertension and compelling indications (like diabetes or heart failure)[71]. However, data was insufficient to draw conclusions on whether those recommendations could be applied to patients with early graft dysfunction. In this regard, a retrospective study suggested that administration of ACEI/ARB during the immediate post-transplantation period did not impair graft function and it could even shorten the graft recovery in patients with delayed graft function[72].

A large retrospective cohort study, including almost 300,000 patients, investigated whether failure to resume ACEI treatment post-operatively would have an impact on 30-day outcomes. Failure to restart ACEI therapy within 14 days of surgery, which affected 1 in 4 patients, was associated with a three-fold higher 30-day mortality irrespective of the type of surgery [73].

To sum up, evidence suggests that ACEI/ARB therapy should be resumed as soon as safe following cardiac and non-cardiac surgery taking into account concurrent medications, surgical complications and overall cardiovascular risk profile [53,74]. Indeed, failure to restart ACEI/ARB treatment due to concerns over renal function did not seem justified and may have a detrimental impact on postoperative outcomes.

Conclusion

The use of RAAS antagonists (ACEIs/ARBs) has been associated with a variable incidence of hypotension during after induction of anaesthesia; however, these hypotensive episodes have not been conclusively linked to any significant postoperative complications, although recent data suggest an increase in postoperative morbidity and mortality in patients undergoing CABG [75]. Therefore, temporary (on the day of surgery) withdrawal of RAAS antagonists in these patients seems indicated to reduce intraoperative hypotension unless there are contraindications like uncontrolled hypertension or systolic dysfunction. However, further studies are warranted to assess

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whether the organ-protective benefits of RAAS antagonists justify their continuation in the perioperative setting.

Irrespective of the decision to either withhold or continue ACEI/ARB treatment, the anaesthesiologist and the surgeon should be aware and watch for the potential adverse effects of the interactions between anaesthesia and ACEI/ARB therapy in order to be prepared to deal with them. Indeed, the detrimental effect of administering ACEI/ARB immediately before surgery seems to require a combination of common though preventable perioperative physiologic stressors like hypotension, hypovolemia, rapidly changing renal function.

The contradictory evidence available may be at least partially explained by the variable impact of confounding factors related to patient, and anaesthetic and surgical procedures. Confounding factors to ACEI/ARB-induced hypotension are common in patients with cardiovascular comorbidities and include concurrent use of diuretics, negative inotropic agents, the presence of severe hypertension, ventricular dysfunction and volume depletion [13,64]. Even with propensity-score matching there is a risk of residual confounding. In addition, significant associations in observational studies do not prove causality. Until adequately powered randomised controlled trials shed light into this controversial issue, individual patient assessment and joint decision making by the anaesthesiologist and surgeon are crucial to optimise the management of chronic RAAS blockade in the perioperative period.

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