

Common Cardiac Medications During Surgical Procedures

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INTRODUCTION

Preoperative medical consultation and perioperative management of surgical patients before non-cardiac surgery is one of the most important issues in the clinical practice of the anesthesiology and surgery. The preoperative assessment process is designed to evaluate risk factors related to the perioperative period, including anesthesia, surgery and the recovery period. Preoperative medical status and the intensity and/or invasiveness of surgery are the main factors that determine the risk to the patient for surgery and anesthesia^[1].

Urological conditions are seen more frequently in the elderly. Most of urological problems particularly malignancies are highly age related thus the medical practitioners facing with urological patients will have to encounter the added challenges associated with aging. Older age is characterized by aging of tissues and organs, a greater occurrence of cognitive decline, and functional impairment and an increasing number of additional problems that may affect perioperative mortality and morbidity^[2,3]. The patient population over 65 years has increased rapidly in the recent years and demographic data projects a progressive increase in the future^[4]. Medical specialties enhance with improvements in both science, technology and pharmacology, and social and economic changes. Along with the development of anesthesia and surgical technical methods, many more elderly patients are scheduled for both elective and emergency surgical operations. There is a prediction that the rate of surgical operations for elderly people is four times of the rest of the population^[5].

Cardiac complications occur in 1-5% of patients undergoing non-cardiac surgery, and associated increased mortality makes them the center of interest in preoperative evaluation^[6,7]. There are several significant clinical risk factors listed in The European Society of Cardiology (ESC) guidelines for cardiac risk stratification^[8] (Table 1). Definition and diagnosis of perioperative cardiac risk factors

ABSTRACT

Elderly patient undergoing major urologic surgery can be a complex case and anesthesiologist usually has to pay great attention to the patient due to comorbid medical and/or surgical conditions and related medications. Number of this group of patients who are chronically taking a range of cardiovascular medications increased rapidly in the recent years and demographic data projects a progressive increase in the future. This review article presents the most frequent issues of commonly cardiac medications encountered with this group of patients, and strategies and maneuvers regarding these medications during a perioperative period according to the current literature, which may be a major challenge for the anesthesiologist.

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such as angina pectoris, prior myocardial infarction, and heart failure vary and can be highly subjective. Therefore, to perform essential preoperative examination having objective information about the patient (e.g. functional capacity, results of single photon emission computed tomography (SPECT), echocardiographic LV assessment, and ongoing medical therapies) is an important issue in the daily clinical practice.

Type of surgery is a significant factor in estimating the cardiac risk for non-cardiac surgical procedures when evaluating a particular patient undergoing surgical intervention^[9,10]. Surgical interventions can be divided into different surgical risk groups regarding risk of myocardial infarction (MI) and cardiac death within 30 days after surgery^[6] (Table 2). Although urologic surgery covers a wide variety of surgical interventions (Table 3), most of common urologic surgical interventions do not locate in a high-risk group (Table 1). Hence perioperative consultation in urologic surgery has to focus on both patients' co-morbid conditions and complications^[11].

In urological procedures, to reduce perioperative cardiac morbidity and mortality, various pharmacological agents have been used. These are ranked as beta-blockers, statins, calcium (Ca) channel blockers, alpha 2 adrenoceptor agonists, angiotensin converting enzyme II inhibitors, and angiotensin II receptor blockers.

Table 1 Clinical risk factors used for preoperative cardiac risk stratification.

1. Ischemic heart disease (angina pectoris and/or myocardial infarction)
2. Surgical risk
3. Heart failure
4. Stroke/transient ischemic attack
5. Diabetes mellitus requiring insulin therapy
6. Renal dysfunction/hemodialysis
7. Age

Table 2 Surgical risk estimate (risk of MI and cardiac death within 30 days after surgery) (Modified from Glance *et al.*).

Low-risk (<1%)	Intermediate-risk (1-5%)	High-risk (>5%)
<ul style="list-style-type: none"> • Superficial surgery • Breast • Dental • Endocrine: thyroid • Eye • Reconstructive • Carotid asymptomatic (CEA or CAS) • Gynecology: minor • Orthopedic: minor (meniscectomy) • Urological: minor (transurethral resection of the prostate) 	<ul style="list-style-type: none"> • Intraoperative: splenectomy, hiatal hernia repair, cholecystectomy • Carotid symptomatic (CEA or CAS) • Peripheral arterial angioplasty • Endovascular aneurysm repair • Head and neck surgery • Neurological or orthopedic: major (hip and spine surgery) • Urological or gynecological: major • Renal transplant • Intra-thoracic: non-major 	<ul style="list-style-type: none"> • Aortic and major vascular surgery • Open lower limb revascularization or amputation or thromboembolism • Duodeno-pancreatic surgery • Liver resection, bile duct surgery • Oesophagectomy • Repair of perforated bowel • Adrenal resection • Total cystectomy • Pneumectomy • Pulmonary or liver transplant

Table 3 Type and extent of most common urologic surgery.

Major Surgery	Intermediate Procedure	Minor Surgery
<ul style="list-style-type: none"> • Nephrectomy • Percutaneous nephrolithotripsy • Bladder augmentation • Urinary diversion 	<ul style="list-style-type: none"> • Retropubic prostatectomy • Urinary bladder diverticulectomy • Transurethral resection of prostate • Transurethral resection of bladder tumor 	<ul style="list-style-type: none"> • Internal urethrotomy • Cystoscopy with/without biopsy • Extracorporeal shock-wave lithotripsy

BETA BLOCKERS

Most of the studies of patients undergoing non-cardiac surgery have focused on beta-blockers. Beta-blockers are drugs that bind to beta adrenoceptor and prevent the binding of norepinephrine and epinephrine to these receptors and inhibit sympathetic effects. So, beta-blockers are sympatholytic drugs. There are three types of beta receptors, beta₁ (β₁), beta₂ (β₂) and beta₃ (β₃).

Some beta-blockers partially activate the receptor while preventing norepinephrine from binding to the receptor. These are called partial agonist beta-blockers and their effects on sympathetic activity are referred to as intrinsic sympathomimetic activity (ISA). These partial agonists have special sympathetic activity while preventing regular and enhanced sympathetic activity. Some beta-blockers have membrane stabilizing activity (MSA) similar with sodium-channels blockers that are identified as Class I anti-arrhythmic.

Usually, beta-blockers are categorized in a few different ways (Table 4). Cardioselective beta-blockers affect the heart and blood vessels rather than other parts of the body. There are also ISA (+) beta-blockers that have intrinsic sympathomimetic activity and dual blockers that block alpha-receptors, as well as beta-receptors. Some beta-blockers fall into more than one category. Sotalol is unique among beta-blockers because it also blocks potassium channels in the heart.

Table 4 Beta-blockers in different categories.

Cardioselective beta-blockers	ISA (+) beta-blockers	Alpha and beta-blockers	Others
Acebutolol	Acebutolol	Carvedilol	Levobunolol
Atenolol	Carteolol	Labetolol	Metipranolol
Betaxolol	Penbutolol		Nadolol
Bisoprolol	Pindolol		Propranolol
Esmolol			Timolol
Nebivolol			
Metoprolol			

Beta blockers are used in the treatment of various medical conditions such as cardiac arrhythmias, heart failure, high coronary artery disease risk, diabetes, angina pectoris and myocardial infarction, and hypertension as well as glaucoma, anxiety, hyperactive thyroid gland, and migraine.

Beta-blocker drugs reduce the effects of epinephrine and other stress hormones so they have negative chronotropic and inotropic effect. They may also restrict the activation of inflammatory activity including leukocyte recruitment, metalloproteinase activity, monocyte activation, growth factor release, and inflammatory cytokine responses^[12]. They prevent coronary endothelial damage and inhibit the atheroma formation and plaque rupture. Beta-blockers reduce energy usage of myocardium via decreasing catecholamine release. They prevent lipolysis and reduce the amount of free fatty acids. In this way, myocardium may be protected from ventricular fibrillation and sudden cardiac death. Anti-renin/angiotensin attribution is another mechanism that reduces blood pressure^[13].

Originally there was a compelling and a small number of publications about the usage of beta-blockers in the perioperative period. More recent and extensive studies have been made including different inclusion criteria, doses and types of beta-blockers^[14-20]. Among them, the largest multicenter randomized controlled trial is the Perioperative Ischemic Evaluation (POISE) Study^[14]. This study reported an increase in mortality, disabling strokes, and hypotension

besides significant cardiac protection. According to this study, only indicated patient population to continue perioperative beta-blocker therapy is the patients who are treated chronically with beta-blockers. Bangalore *et al* confirmed cardiac protection and same risks in their meta-analysis in 2008 when beta-blockers launched shortly before surgery^[15]. After POISE study beta-blocker treatment described in two guidelines in 2009; American College of Cardiology/American Heart Association (ACC/AHA^[16]) and ESC endorsed by the European Society of Anesthesiology (ESA). Both of these guidelines recommended continuing long-term beta-blocker therapy with avoiding high-doses. Considering the introduction of beta-blockers in patients with known coronary artery disease, reversible ischemia on stress test, and in those at risk for coronary artery disease undergoing high-risk surgery, especially vascular surgery is also recommended^[16]. ESC guideline suggested different from ACCF/AHA guideline that beta-blockade could be initiated in patients undergoing intermediate-risk surgery^[8]. In both of these guidelines titration of beta-blockade to slow heart rates (ESC 60-70 beats min⁻¹; ACCF/AHA 60-80 beats min⁻¹) with a limit of at least 100 mmHg systolic arterial pressure before administration of the next dose of beta-blocker (ESC), or no hypotension (ACCF/AHA) was recommended. Both advocated starting beta-blockade at least 7 days, preferably 30 days before surgery. Besides these guidelines, there are also some studies that support the continuing of chronic beta-blockade in the perioperative period^[17-20].

Discontinuing antihypertensive therapy before surgery due to interference with hemodynamic adjustments and profound cardiovascular collapse can be seen as an option but more recent studies have shown that this approach is associated with significant increases in perioperative morbidity and mortality^[17-19]. Also, Ellenberger *et al* found that a chronic treatment was superior to the introduction of beta-blockers within the first two days of surgery^[21].

In light of the current literature a reasonable approach to the perioperative beta-blockade may be as follows: (1) Current beta-blockade should be maintained; (2) Initiating beta-blockade should be limited to high-risk patients undergoing high-risk surgery, particularly in those who would be given beta-blockade for co-existing medical reasons such as coronary artery disease, reversible ischemia on stress test; (3) High-dose beta-blockade should be avoided; (4) Titration is recommended but avoidance is also critical; (5) Starting beta-blockade and titrating its effects over at least 7 days is seen reasonable; (6) Because anemia has been shown to markedly increase the risk of cardiac morbidity and mortality in the face of beta-blockade, blood transfusion should be considered for these patients.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers are used to treat various conditions such as hypertension, myocardial ischemia, cardiac arrhythmias, pulmonary hypertension, cerebral vasospasm, and esophageal spasm. They bind to L-type Ca⁺² channels located on the vascular smooth muscle, cardiac myocytes, and sinoatrial and atrioventricular nodes. These channels regulate the influx of the Ca⁺² into the muscle cells and stimulate smooth muscle and cardiac myocyte contraction. The role of L-type Ca⁺² channels in cardiac nodal tissue is important. They prevent Ca⁺² entry into the cell and cause vascular smooth muscle relaxation (vasodilation), decreased myocardial contraction force (negative inotropy), decreased heart rate (negative chronotropy), and decreased conduction velocity especially on the atrioventricular node (negative dromotropy)^[22].

The anti-anginal effects are obtained from their vasodilator and cardiodepressant features. Systemic vasodilation reduces arterial pressure and causes ventricular afterload reduction thereby decreases myocardial oxygen demand. Verapamil and diltiazem, more cardioselective Ca⁺² channel blockers, decrease heart rate and contractility and used as antianginal drugs. Ca⁺² channel blockers also increase oxygen supply to the myocardium by dilating coronary arteries and prevent reverse coronary vasospasm. The antiarrhythmic features of Ca⁺² channel blockers (Class IV antiarrhythmics) related to their ability to reduce the firing rate of aberrant pacemaker pathways. Also, especially at the atrioventricular node, they decrease conduction velocity and prolong repolarization that helps to suppress the formation of supraventricular tachycardia and prevent reentry block mechanisms.

There are three classes of Ca⁺² channel blockers according to their chemical structure and smooth muscle selectivity. Dihydropyridines that include amlodipine, felodipine, isradipine, nifedipine, nimodipine, and nitrendipine are the most smooth muscle selective ones. These drugs primarily reduce systemic vascular resistance and arterial blood pressure because of their high vascular selectivity; consequently they are ranked among antihypertensive drugs. They are less desirable choice for cardiac angina treatment because of their systemic vasodilatation, and pressure-lowering effects can lead to reflex cardiac stimulation. They also activate sympathetic reflexes, and can cause side effects such as flushing, headache, and reflex tachycardia.

Non-dihydropyridines are verapamil (phenylalkylamine class) and diltiazem (benzothiazepine class). Verapamil differs from other Ca⁺² channel blockers with their relative selectivity for the myocardium. This drug has a role in angina and arrhythmia treatment. Verapamil reduces myocardial oxygen demand and prevents coronary vasospasm. Diltiazem is more selective for vascular calcium channels than verapamil. Conversely to dihydropyridines, diltiazem can reduce arterial pressure without generating the same level of reflex cardiac stimulation. Especially, non-dihydropyridines should not be administered with beta-blockers because addition of a Ca⁺² channel blocker augments the effects of beta-blockade^[23].

Calcium channel blockers' documented vasoactive and cardiac effects that include a reduction in systemic vascular resistance, negative inotropic and chronotropic effects can raise questions regarding dangerous additive interactions with potent general anesthetics. According to the evidence from studies, Ca⁺² channel blockers have minimal effect on preventing myocardial infarction and cardiac death when compared with beta-blockers^[24]. However, it appears to be no significant problem about continuing with these medications throughout the perioperative period in the absence of other contributing factors^[25,26]. A combination therapy of beta-blockers and calcium channel blockers for hypertension can induce significantly more episodes of hypotension and bradycardia during the anesthesia induction than in patients treated with only beta-blockers^[27]. However, these episodes are relatively mild and can be easily treated with small bolus doses of vasoactive drugs. Hypertensive patients should continue to take their antihypertensive medication in the perioperative period. However, if hypertension is current diagnosed and/or initiating antihypertensive therapy is crucial to prevent perioperative risk, delaying elective surgery may be inevitable^[28].

Another theoretical concern in patients chronically treated with calcium channel blockers is the potential for heart block. Calcium channel blockers tend to affect sinoatrial and atrioventricular nodes and to prolong atrioventricular conductivity. In a randomized

controlled trial, there was not any difference among all groups in the frequency of first degree heart block and it was concluded that calcium channel blockers could be continue, even concurrently with beta blockers, without any cardiac conduction abnormalities^[29].

It will be better to be aware that calcium channel blockers can potentiate not only the paralysis produced by neuromuscular blocking drugs, but also the theophylline and digoxin effects. The bioavailability of calcium channel blockers was affected by cimetidine and ranitidine in a positive manner while barbiturates reduce their bioavailability. There is also a concern about dangerous interaction between verapamil and dantrolene that is used to treat malignant hyperthermia. Although dantrolene's mechanism of action is not understood precisely, it is thought that reducing calcium release from the sarcoplasmic reticulum and intracellular calcium levels is the main effect. Verapamil can potentiate dantrolene's effects by decreasing calcium influx and produce hyperkalemia and critically serious myocardial depression^[30].

ALPHA-2 ADRENORECEPTOR AGONISTS

Alpha-2 agonists are known as centrally acting vasodilators and alpha-2 receptors in the vasomotor center of the medulla oblongata are the main target in decreasing the production of systemic adrenaline and noradrenaline and enhancing vagal tone^[31,32]. The most widely known of the members of the group are clonidine, α -methyldopa, and dexmedetomidine. Clonidine has a partial agonist effect with an alpha-2 to alpha-1 selectivity of 39:1 and its half-life is approximately 20 hours while Dexmedetomidine is a much shorter-acting intravenous alpha-2 agonist, the distribution half-life of 8 minutes and a terminal half-life of 3.5 hours, with an alpha-2 to alpha-1 selectivity ratio of 1300:1^[33]. Besides its antihypertensive action, clonidine reduces the anesthetic requirement (by $\geq 40\%$) for volatile drugs or opioids and provides central analgesia and anxiolysis. It also has a beneficial anti-shivering effect. Withdrawal of chronic clonidine treatment may result in rebound hypertension thus continuing clonidine treatment is recommended.

Dexmedetomidine exerts its antihypertensive, analgesic and sedative properties by inhibiting the release of endogenous catecholamine at adrenoreceptors located on vascular smooth muscle cells, substantia gelatinosa of the spinal cord, and locus ceruleus of the brain, respectively^[34]. It is typically used for sedation rather than for its antihypertensive effect.

Alpha-2 agonists decrease the adrenergic response to the trauma of surgery^[35] and improve hemodynamic stability in the perioperative period^[36,37]. This effect may also create cardioprotective effect in the perioperative period. A meta-analysis of alpha-2 agonists to prevent perioperative cardiovascular complications found that their usage reduced mortality and myocardial infarction in patients undergoing non-cardiac, vascular surgery^[37]. In the same meta-analysis, it was found that hypotensive response was not significantly occurred in the non-cardiac surgical patients and the side-effect profile of alpha-2 agonists might be preferable to that of beta-blockers. Authors of this review conducted another meta-analysis according to the Cochrane methodology to determine the efficacy and safety of alpha-2 agonists for reducing mortality and cardiac complications among adult patients undergoing surgery. They found that alpha-2 adrenergic agonists were associated with statistically significant reductions in all-cause mortality, cardiac mortality, and myocardial ischemia after surgery and they also concluded that these potential benefits were counterbalanced by a significantly increased risk for perioperative hypotension and bradycardia^[38].

Alpha-2 agonists' significant side effects are sedation, dry mouth and nasal mucosa (due to increased vagal activity), bradycardia, orthostatic hypotension^[39]. Fluid retention and edema is also a problem for especially urological patients with chronic therapy; therefore, concurrent treatment with a diuretic may be necessary. Sudden disconnection of clonidine can lead to rebound hypertension hence maintaining therapy with this drug is recommended. Perioperative discontinuation of chronic medication of this drug class can be dangerous in hypertensive patients due to possible complications such as delirium, rebound hypertension, and myocardial ischemia^[40].

RENIN ANGIOTENSIN ALDOSTERONE SYSTEM ANTAGONISTS

Renin Angiotensin Aldosterone system (RAAS) antagonists include ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and direct renin inhibitors. Many elderly patients scheduled for surgery are already on RAAS antagonist treatment for hypertension^[41], congestive heart failure^[42], coronary artery disease^[43], or diabetic nephropathy^[44,45].

Perioperative continuation of the management of ACEIs or ARBs has traditionally been controversial because of the risk of worsening myocardial conditions. The vasodilatory actions of RAAS antagonists include various mechanisms such as direct sympathetic blockade, increased bioavailability of vasodilators such as bradykinin, nitric oxide and prostacyclins, 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^[46]. The RAAS, together with sympathetic nervous system activation and arginine vasopressin (AVP) release, is one of the major responsible for the maintenance of venous return and systemic blood pressure during periods of acute hemodynamic stress such as the induction of anesthesia. Thus, patients chronically treated with RAAS antagonists are potentially at higher risk of developing clinically significant hypotension after the induction of anesthesia because of the decreased vascular resistance and cardiac filling^[47,48]. Intraoperative hypotension due to RAAS blockade can be treated with replacement of intravascular volume and AVP agonists (terlipressin, vasopressin) and/or adrenergic agonists.

Own genetics is a significant factor that may influence the hemodynamic response to RAAS antagonists in the perioperative period. Variable genetic susceptibility to RAAS antagonists via single-nucleotide polymorphisms in the genes that is functional for RAAS was proved^[49,50]. One of these RAAS polymorphisms is ACE insertion/deletion polymorphism that is associated with resistance to ACE inhibitors and increased adverse cardiovascular and renal effects^[51,52].

Several studies focused on the effect on hemodynamic responses after intubation in patients taking ACEIs before surgery. In a randomized controlled study, effect of sublingual captopril on the pressor response to intubation was studied and the patients in the captopril group developed more hypotension than the patients in the placebo group^[53]. In another randomized controlled study, two groups of patients undergoing non-cardiac surgery chronically treated with ACEIs for hypertension were compared, and rate of post-induction hypotension was significantly higher in patients who were administered ACEIs on the morning of surgery than in patients ACEIs were withdrawn^[54].

ARBs are increasingly being used as alternatives to ACE inhibitors in patients intolerant to the side effects. The difference in hemodynamic response between ACEIs and ARBs was demonstrated in several studies. It is showed in one pre-study report that all patients taking ARBs for hypertension on the morning of surgery experienced hypotension after induction of anesthesia compared with 60% taking beta-blockers or calcium channel blockers up to the same time and 67% of those taking ACE inhibitors up to the night before vascular surgery^[55]. In addition, the degree of hypotension was increased in patients receiving ARBs. In a follow-up study from the same group, patients taking ARBs in the morning of the surgery had longer duration and increased level of hypotension, with an increased demand for vasoconstrictor therapy, than those in whom ARBs were stopped the day before surgery^[56]. The effects of ARBs appear to be more exaggerated in patients receiving diuretic therapy but, as ACE inhibitors, serious adverse outcomes, such as myocardial infarction and renal failure are not seen mostly^[57].

The timing of withdrawing of RAAS antagonists before surgery was investigated in several studies^[56,58,59] and it was found that the administration of ARBs on the morning of surgery was associated with more frequent episodes and longer duration of hypotension than if ARBs was withheld. Moreover, hypotension was more common in patients receiving an ARB/ACEI dose within 10 h of anesthesia induction than 10 h before the induction of anesthesia^[56,58]. It is recommended that patients chronically treated with ACEIs and ARBs should receive the last dose on the day before surgery.

Despite the recommendations regarding withholding the RAAS antagonists on the morning of surgery, some authors suggest the continuation of them in some circumstances. The American College of Physicians supports the continuation of RAAS antagonists with the condition of maintaining normovolemia^[60]. In the presence of congestive heart failure, continuation of ACEIs is recommended as it was found more beneficial than interruption and probable hypotensive episodes due to ACEIs are usually responsive to volume expansion and vasoconstrictors^[43,61].

Preoperative use of RAAS antagonists may induce the development of postoperative renal failure^[62,63]. Also, it is known that combination of ARBs or ACE inhibitors, diuretics and NSAIDs has been responsible in drug-induced renal failure^[64]. In a retrospective cohort study, it is reported that preoperative use of ACEI/ARB was associated with a higher risk for AKI postoperatively^[65].

In line with the current literature, the decision of continuation or discontinuation of RAAS antagonists depends on the factors related to the patient such as cardiovascular status, surgical operation. A consideration after a full discussion with the anesthesiologist and surgeon, along with the maintenance of careful intraoperative hemodynamic monitoring and adequate intravenous volume status before induction of anesthesia will be better. Careful selection of proper anesthetic agents for induction and maintenance that do not disrupt hemodynamic stability (eg. Etomidate) is also necessary to prevent hypotensive response.

STATINS

Statins inhibit the enzyme HMG-CoA reductase in order to reduce low-density lipoprotein (LDL) and triglyceride levels and increase high-density lipoprotein (HDL) effectively. In addition to this, statins, or HMG-CoA reductase inhibitors, have pleiotropic effects by different mechanisms that promote endothelial morphology and function and stabilize coronary plaques^[66,67]. Thus, statins are being evaluated for their potential benefit in the perioperative period for

different mechanisms.

In the literature many studies have focused on non-lipid-lowering or pleiotropic effects of statins^[68-70]. In the West of Scotland Coronary Prevention Study (WOSCOPS) cardiovascular event rates were examined in statin and control groups with the same cholesterol level and it was found that the risk was lower in the statin group^[69]. Statins have vasodilatory, anti-inflammatory, and anti-thrombogenic effects through increased endothelial nitric oxide synthase expression and the reduced expression of cytokines, chemokines, and adhesion molecules^[70]. They also tend to lower C-reactive protein (CRP) levels that have been shown to correlate with cardiovascular disease risk^[71,72]. In healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, it was found that rosuvastatin significantly reduced the incidence of major cardiovascular events such as stroke, myocardial infarction, and death from cardiovascular causes^[73]. Many of these pleiotropic effects of statins occur before a significant reduction in serum cholesterol levels and endothelial function improved within 24 hours of statin initiation^[74,75].

There is strong evidence that statins decrease coronary artery plaque size, reduce the incidence of coronary events, and improve survival and cardiovascular outcomes in patients with coronary heart disease^[76-80]. However, the role of statin use in the perioperative period is less clear and all of the few studies were conducted in patients undergoing vascular surgery. Durazzo *et al* randomized 100 patients undergoing vascular surgery to 20 mg atorvastatin daily or placebo 30 days prior to surgery for a total of 45 days and they found that the incidence of cardiovascular complications was significantly lower in the atorvastatin group than the placebo group^[81]. The evidence for a beneficial effect of statins has also been augmented by a large randomized controlled trial, DECREASE III^[82]. This trial showed that extended-release fluvastatin significantly reduces myocardial ischemia and the combined endpoint of cardiovascular death and MI in high-risk patients undergoing major vascular surgery. In DECREASE IV study the effect of bisoprolol and fluvastatin on 30-day cardiac outcome in intermediate-risk patients after elective non-cardiac surgery was evaluated. But the study was terminated early because of slow patient recruitment, and as a result, it may have lacked statistical power to detect clinically relevant differences with respect to fluvastatin therapy^[83]. These trials conclude that statins may have a greater benefit in patients with more cardiovascular risk factors.

Statins are tolerated well however low frequency of side effects can be seen. The possible side effects associated with statin therapy are gastrointestinal symptoms, headache, rash that are relatively mild and often transient, asymptomatic increases in liver transaminases and myopathy that can range from myalgia to myositis and, most severely, rhabdomyolysis^[84,85]. Kashani *et al* performed a systematic overview of randomized statin trials to quantify the risks of musculoskeletal, renal, and hepatic complications associated with therapy and they concluded that statin therapy is associated with a small excess risk of transaminase elevations, but not of myalgias, creatine kinase elevations, rhabdomyolysis, or withdrawal of therapy compared with placebo^[86]. Patient age, statin dosage and comorbid conditions are the factors that can induce the side effects.

There is evidence that preoperative discontinuing of chronic statin therapy is associated with adverse perioperative outcome. In a retrospective cohort study of vascular surgery patients withholding statin postoperatively for 4 days was an independent predictor of postoperative myonecrosis^[87]. In another retrospective analysis of patients undergoing major vascular surgery, statin discontinuation for

a mean duration of 3 days was associated with an increased risk for postoperative troponin release and a combination of nonfatal MI and cardiovascular death^{88]}.

In a systematic review^[89] non-atheroprotective effects of statins were investigated and consistent benefits of statin use in improving outcomes of ventricular arrhythmias, sudden cardiac death, cardiac transplant rejection, chronic obstructive pulmonary disease, and sepsis were reported. But the authors concluded that for these conditions, the level of evidence was inadequate to recommend statin use. Use of statins also may be the most cost-effective therapy for patients with cardiac disease undergoing non-cardiac surgery^[90]. Discontinued statin therapy before the surgery due to inability to take oral medications should be restarted as soon as possible.

CONCLUSION

Performing an individual risk-benefit analysis is one of the most important parts of preoperative assessment of geriatric urologic patients. There is unequivocal evidence that current beta-blockade should be maintained in the perioperative period and initiating beta-blockade should be limited to high-risk patients undergoing high-risk urological surgery. Starting beta-blockade and titrating its effects over at least seven days is seen reasonable. High-dose beta-blockade can be detrimental, thus should be avoided. Although it appears to be no significant problem about continuing with calcium channel blocker medication along with the perioperative period, it should be better to be aware of possible drug interactions. The use of RAAS antagonists on the day of surgery has been associated with a variable incidence of intraoperative hypotension after induction of anesthesia that can be reduced by stopping these drugs the day before. Although there is growing evidence regarding the preoperative use of these agents with postoperative adverse effects including worsening of renal function, continuation of RAAS antagonists may be considered with a careful intraoperative hemodynamic monitoring and adequate intravenous volume status before induction of anesthesia. There is need for further randomized controlled studies conducted with large samples that focused on perioperative cardiac medications particularly in the geriatric population undergoing non-cardiac surgery.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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