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Preoperative Management of Cardiovascular Medications: A Society for Perioperative Assessment and Quality Improvement (SPAQI) Consensus Statement

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Abstract

Cardiovascular conditions such as hypertension, arrhythmias, and heart failure are common in patients undergoing anesthesia for surgical or other procedures. Numerous guidelines from various specialty societies offer variable recommendations for the perioperative management of these medications. The Society for Perioperative Assessment and Quality Improvement identified a need to provide multidisciplinary evidence-based recommendations for preoperative medication management. The society convened a group of 13 members with expertise in perioperative medicine and training in anesthesiology or internal medicine. The aim of this consensus effort is to provide perioperative clinicians with guidance on the management of cardiovascular medications commonly encountered during the preoperative evaluation. We used a modified Delphi process to establish consensus. Twenty-one classes of medications were identified: α-adrenergic receptor antagonists, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, angiotensin receptor–neprilysin inhibitors, β-adrenoceptor blockers, calcium-channel blockers, centrally acting sympatholytic medications, direct-acting vasodilators, loop diuretics, thiazide diuretics, potassium-sparing diuretics, endothelin receptor antagonists, cardiac glycosides, nitrodilators, phosphodiesterase-5 inhibitors, class III antiarrhythmic agents, potassium-channel openers, renin inhibitors, class I antiarrhythmic agents, sodium-channel blockers, and sodium glucose cotransportor-2 inhibitors. We provide recommendations for the management of these medications preoperatively.

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Ischemic heart disease and stroke have remained the top 2 causes of mortality for over a decade, accounting for 27% of deaths worldwide in 2019.[1] Thus, medications prescribed for the management of cardiovascular conditions, such as ischemic heart disease, arrhythmias, hypertension, pulmonary hypertension, and heart failure, are ubiquitous. Moreover, patients presenting for both cardiac and noncardiac operations are frequently taking these medications for the management of their chronic comorbid conditions. Perioperative clinicians must make informed recommendations for the preoperative management of these medications. A blanket statement of holding all antihypertensive medications on the morning of surgery may result in the patient presenting with elevated systemic blood pressure levels on the day of surgery, resulting in a delay or cancellation of the procedure. Conversely, continuation of certain medications such as angiotensin-converting enzyme inhibitors (ACEIs) or

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angiotensin II receptor blockers (ARBs) may precipitate hypotension during surgery.[2]

Preoperative cardiovascular medication management recommendations vary across spectrums of care, individual institutions, and clinical specialties.[3-7] Numerous societies have published recommendations for the perioperative management of cardiovascular medications, often within the context of specific medical conditions or surgical procedures.[8-11] Because there is often a lack of quality evidence to support clinical decision making, there are variable, and sometimes contradictory, recommendations. The perioperative clinician must consult various sources, from expert consensus statements to randomized studies, to make informed recommendations for preoperative medication management. The Society for Perioperative Assessment and Quality Improvement (SPAQI), an interdisciplinary society whose mission is to promote high-value, safe perioperative practices, identified a need to provide multidisciplinary evidence-based consensus recommendations for preoperative medication management.[12] The aim of this consensus effort is to provide perioperative clinicians with guidance on the management of cardiovascular medications commonly encountered during the preoperative evaluation. Physician members were chosen by the SPAQI executive leadership to serve on the consensus committee, and they represent various perioperative clinic practice specialties as well as diverse practice environments, including academic and private practice.

For the purposes of this consensus statement, we did not include anticoagulant, antithrombotic, or antiplatelet agents or medications prescribed for dyslipidemia. We limited our focus to medications used to treat hypertension, arrhythmias, heart failure, and ischemic heart disease. Twenty-one classes of medications were identified on the basis of the mechanisms of action and class.[13]

METHODS

The medications for our consensus statement were chosen by the SPAQI on the basis of a lack of standardized care related to the preoperative management of common cardiovascular medications. Group members were similarly selected for their understanding and expertise on the topic as well as their grasp of evidence-based medicine. A group leader (S.K.S.) was appointed to guide the group through the modified Delphi process and manuscript drafting. The final group consisted of 13 physicians, including the group leader.

A modified Delphi process was used to obtain input from a group of experts in anesthesiology and internal medicine who specialize in perioperative medicine.[14] We used the same methodology as described in previous SPAQI consensus statements[12,15-18] and are explained in detail in Supplemental Appendix (available online at http://www.mayoclinicproceedings.org). An overriding theme during the process was the principle of "first do no harm." In situations in which there was a paucity of evidence or conflicting literature, we recommend that avoidance of harm by holding or continuing a medication should be the guiding philosophy.

RESULTS AND RECOMMENDATIONS

The Table presents the final recommendations of the consensus group after multiple rounds of the Delphi process and several conference calls.[19] For each class of medications, the mechanisms of action and perioperative implications are addressed, followed by our consensus recommendations. As with all clinical situations, we recommend an individualized approach per treating physician and the perioperative team after considering the invasiveness of the planned surgical procedure, the type of anesthesia, the patient's comorbid medical conditions, and institutional protocols.

α-Adrenoceptor Blockers

α-adrenergic receptor antagonists (α-blockers)(α-adrenoceptor blockers) are primarily used for the second-line treatment of hypertension.[4] α-Blockers target the peripheral vasculature and inhibit the uptake of catecholamines in smooth muscle cells, resulting in vasodilation and thereby lowering blood

pressure. These agents are commonly associated with postural hypotension. Thus, patients should be cautioned to maintain their usual hydration status in the immediate preoperative period. α-adrenergic receptor antagonists are indicated for blood pressure control in patients being prepared for the resection of pheochromocytomas who are typically advised to take the medications on the day of surgery.

There are no data on the risks of continuing or discontinuing α-blockers preoperatively, and it is generally accepted that these medications should be continued on the day of surgery. Tamsulosin has a long half-life, and its α_1-adrenoceptor blocking effect is irreversible. There are reports and clinical observations that intraoperative floppy iris syndrome can occur during cataract surgery even after tamsulosin therapy has been terminated years before, which suggests that tamsulosin's detrimental effects on the iris are likely permanent.[20] Because holding α-blockers on the morning of surgery has not been found to decrease the risk of intraoperative floppy iris syndrome, we do not recommend that these agents be held for surgery. However, an accurate medication list is imperative, so surgical modifications can be made by the ophthalmologist.

Consensus recommendation for α-blockers: *Consensus was achieved that* ***α-blockers*** *should be CONTINUED on the morning of surgery.*

Angiotensin-Converting Enzyme Inhibitors and ARBs

Angiotensin-converting enzyme inhibitors prevent the conversion of angiotensin I to angiotensin II (a vasoconstrictor), thereby leading to vasodilation of small arteries and lowering of blood pressure owing to a reduction in peripheral vascular resistance.[21] Angiotensin II receptor blockers prevent the conversion of angiotensin at the level of angiotensin II type 1 subtype receptor and have some clinical advantages over ACEIs.[21] Because bradykinin production is lower in the setting of ARB therapy compared with ACEI, ARBs have a more favorable adverse effect profile in terms of cough and angioedema. Angiotensin-converting enzyme inhibitors and ARBs are predominantly prescribed to treat hypertension and heart failure, prevent diabetic nephropathy progression, and reduce stroke and cardiovascular risk. Many ACEIs and ARBs are commonly incorporated into combination medications, so a careful medication review is needed.[22]

In the past 2 decades, there has been much controversy about the use of ACEIs and ARBs in the perioperative period. Significant and profound intraoperative hypotension during anesthesia has been noted, which is often poorly responsive to fluid resuscitation and conventional vasopressor treatment (eg, phenylephrine). However, studies have reported conflicting data, which led to divergent recommendations.[23-27] Moreover, numerous studies have failed to offer clear guidance.[2,10,28,29] The 2014 American College of Cardiology/American Heart Association (ACC/AHA) perioperative evaluation and management guideline suggests that it is reasonable to continue angiotensin axis blockade (ACEI or ARB) before surgery (class IIa recommendation, level of evidence B).[30] This recommendation was supported by data reporting that intraoperative hypotension associated with the continuation of these agents did not result in a difference in mortality, major adverse cardiac events, stroke, or renal failure.[26,31] Since the 2014 guideline was written, however, in addition to intraoperative hypotension, ACEI or ARB use on the day of surgery has been found to be associated with postoperative acute kidney injury (AKI), major adverse cardiac or cerebrovascular events, and increased hospital length of stay.[9]

In 2017, a large study, later incorporated in a systematic review, again found the correlation between the continuation of ACEI or ARB before surgery and intraoperative hypotension.[2,32] A recent retrospective study by Yoon et al[33] failed to find an increased incidence of hypotension after the induction of general anesthesia in patients taking ARBs. The Canadian Cardiovascular Society

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TABLE. Consensus Recommendations for the Preoperative Management of Cardiac Medications

Medication class	Medications	Continue/hold on the day of surgery	Additional considerations
α-Adrenoceptor blockers (α-blockers)	Doxazosin, phenoxybenzamine, prazosin, and terazosin	Continue	Ensure adequate hydration as postural hypotension may occur with prolonged fasting
Angiotensin-converting enzyme inhibitors	Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, and ramipril	Hold	Consider continuing for low-risk, minimally invasive procedures with minimal sedation or local anesthesia
Angiotensin II receptor blockers	Azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan	Hold	Consider continuing for low-risk, minimally invasive procedures with minimal sedation or local anesthesia
Angiotensin receptor—neprilysin inhibitors	Sacubitril/valsartan	Hold	Consider cardiology input if prescribed for severe heart failure with reduced ejection fraction
β-Adrenoceptor blockers (β-blockers)	Atenolol, bisoprolol, carvedilol, metoprolol, propranolol, and sotalol	Continue	
Calcium-channel blockers	Amlodipine, diltiazem, felodipine, and nifedipine	Continue	
Centrally acting sympatholytic medications	Clonidine, guanabenz, and guanfacine	Continue	
Direct-acting vasodilators	Hydralazine	Continue	
Loop diuretics	Bumetanide, furosemide, and torsemide	Hold	Consider continuing in patients with/at risk of volume overload or those having very low risk surgery (eg, cataract) with minimal sedation or local anesthesia
Thiazide diuretics	Chlortalidone, hydrochlorothiazide, indapamide, and metolazone	Continue	
Potassium-sparing diuretics	Eplerenone, spironolactone, and triamterene	Continue	Assess the fluid status before determination to hold or continue
Endothelin receptor antagonists	Ambrisentan, bosentan, and macitentan	Continue	
Cardiac glycosides	Digoxin	Continue	
Nitrodilators	Isosorbide dinitrate, isosorbide mononitrate, and nitroglycerin	Continue	Delay surgery if recent angina or escalation in nitroglycerin use
Phosphodiesterase-5 inhibitors	Avanafil, sildenafil, tadalafil, and vardenafil	Continue *if* for pulmonary hypertension; hold for 24 h otherwise	
Class III antiarrhythmic agents (potassium-channel blockers)	Amiodarone, dofetilide, dronedarone, and sotalol	Continue	Minimize other medications that prolong the QT interval Carefully monitor electrocardiogram and magnesium and potassium levels Can have a negative inotropic effect that can be worse with the use of halogenated inhalational anesthetic agents
Potassium-channel openers	Minoxidil	Continue	
Renin inhibitors	Aliskiren	Hold	
Class I antiarrhythmic agents (sodium-channel blockers)	Class Ia (disopyramide, procainamide, and quinidine) Class Ib (lidocaine and mexiletine)	Continue	

Continued on next page

TABLE. Continued

Medication class	Medications	Continue/hold on the day of surgery	Additional considerations
	Class Ic (flecainide, propafenone, and tocainide)		
Sodium-channel blocker (late sodium currents)	Ranolazine	Continue	
Sodium glucose cotransporter-2 inhibitors	Dapagliflozin, empagliflozin, canagliflozin, and ertugliflozin	Hold in advance	Discontinue dapagliflozin, empagliflozin, and canagliflozin for 3 days before the procedure Discontinue ertugliflozin for 4 days before the procedure
Minor procedures	For procedures with minimal sedation or with local anesthesia that are low risk, minimally invasive, and without physiologically meaningful hemodynamics changes, we recommend that patients continue all routine cardiovascular medications, including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers		

Mechanisms and pharmacokinetics verified via Micromedex.[15]

perioperative guidelines published in 2017 included an updated review of the literature and provided a strong recommendation to hold ACEIs and ARBs for 24 hours before surgery.[6] Similarly, the Perioperative Quality Initiative, an international multidisciplinary organization, recently provided consensus recommendations for perioperative blood pressure management in elective surgery.[34] This group recommended that, unless clinically contraindicated, ACEIs and ARBs should be held for 24 hours before surgery and with the intention to resume them within 48 hours of surgery, where appropriate.[34]

Currently, the STOP-or-NOT trial, a large multicenter randomized controlled study, is being conducted to provide more clarity.[35] During voting and discussion, ARBs and ACEIs did not generate many differences in opinion. In general, the group supported the principle of "first do no harm," and therefore, most agreed that ACEIs and ARBs should be held on the morning of surgery.

With the recommendation to hold ACEIs and ARBs medications on the day of surgery, the timing and plan for resumption should be addressed. The ACC/AHA perioperative guidelines raise the concern about the nonresumption of ACEIs and ARBs postoperatively, referencing literature suggesting harm when these medications are not reinitiated. This concern was also supported by Mudumbai et al,[36] who reported that 25% of patients did not resume ACEIs within 14 days of surgery. Nonresumption of ACEIs and ARBs was associated with increased 30-day mortality (hazard ratio, 3.44; 95% CI, 3.30 to 3.60; $P<.001$). In addition, Shiffermiller et al[25] reported that although intraoperative hypotension was reduced in those patients who had ACEIs withheld for surgery, the risk of postoperative hypertensive events was elevated.

Consensus recommendation for ACEIs and ARBs: *Consensus was achieved that* ***ACEIs and ARBs*** *generally should be HELD on the morning of surgery.*

Angiotensin Receptor—Neprilysin Inhibitor (Natriuretic Peptides)

Sacubitril (a neprilysin inhibitor) in combination with valsartan (an ARB) is a unique cardiovascular medication called an angiotensin receptor—neprilysin inhibitor (ARNI). This drug combination was developed to block the harmful effects of renin-angiotensin-aldosterone system (RAAS) activation while raising concentrations of potentially beneficial endogenous vasoactive peptides (particularly natriuretic peptides), which are degraded by neprilysin. Blockade of the RAAS by an

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ARNI is a key component in the treatment of patients with heart failure with reduced ejection fraction (HFrEF) with a left ventricular ejection fraction of 40% or less. The major adverse effects of ARNI include hypotension, hyperkalemia, cough, dizziness, and renal failure.[37,38]

No data have been published to date on the perioperative use of sacubitril alone. Therefore, our recommendations for the preoperative management of ARNI are predominantly based on those for ACEIs and ARBs when used for the treatment of patients with heart failure. The 2014 ACC/AHA guidelines consider continuation of ARBs as reasonable. Extrapolating from recommendations for ARBs, if ARNIs are held before surgery, it should be reinitiated as soon as feasible.[30] Similarly, the 2014 European Society of Cardiology/European Society of Anesthesiology guidelines recommend continuation of ARBs, but do not specifically address ARNI, in stable patients with HFrEF.[5] The 2017 Canadian Cardiovascular Society perioperative guidelines did not address ARNI management, although they suggest that ARBs should be held on the morning of surgery.[6]

Discontinuation of ARNI in patients with heart failure remains controversial and is best decided on a case-by-case basis. Consideration should be given to consulting the prescribing physician, as needed.

Consensus recommendation for ARNIs: *Consensus was achieved that* ***ARNIs*** *should be HELD on the morning of surgery.*

β-Adrenoceptor Blockers

β-Adrenoceptor blockers (β-blockers) are commonly used treatments for cardiovascular disease and exert their effects by inhibiting catecholamines from binding to β-receptors. However, they differ in the degree of affinity and selectivity for β_1-receptors (predominantly found in cardiac muscle tissue) and β_2-receptors (in the periphery, with vasodilating effects, and other pharmacologic properties).[21] All β-blockers inhibit cardiac chronotropic and inotropic effects, resulting in decreased oxygen demand. In addition to cardiovascular disease, other Food and Drug Administration—approved indications include treatment of tachycardia, hyperthyroidism, essential tremor, aortic dissection, portal hypertension, glaucoma, and migraine prophylaxis.

β-Blockers are among the most extensively studied class of cardiovascular drugs in the perioperative period. In the past 2 decades, medical practice has evolved from the indiscriminate use of perioperative β-blockers to a more nuanced approach. Several studies have noted that the abrupt discontinuation of β-blockers in the perioperative period increases cardiovascular events and mortality.[11,39] In general, guidelines recommend continuing β-blockers for those patients already taking them and a nuanced approach to initiation in the immediate preoperative period.[6,40,41]

Consensus recommendation for β-blockers: *Consensus was achieved that* ***β-blockers*** *should be CONTINUED on the morning of surgery.*

Calcium-Channel Blockers

Calcium-channel blockers (CCBs) bind to L-type calcium channels present on the sinoatrial and atrioventricular (AV) nodes, cardiac myocytes, and vascular smooth muscles.[13] Calcium-channel blockers are classified into 2 major categories: dihydropyridines and nondihydropyridines.

Patients with atrial fibrillation with rapid ventricular response are sometimes treated with a nondihydropyridine CCB in addition to a β-blocker. This combination depresses cardiac electrical activity and augments the negative inotropic and chronotropic effects of β-blockade alone. Caution should be exercised if both are continued on the morning of surgery.

Continuing CCBs preoperatively appears to be relatively safe. Withdrawal syndrome generally does not occur, although abrupt discontinuation has been reported to cause severe vasospasm in patients having coronary revascularization.[42] Continuing diltiazem may result in stable hemodynamics and lower mortality rates in patients undergoing cardiac surgery.[43,44] A meta-analysis

found that the use of CCBs was associated with reduced ischemia and atrial arrhythmias in patients undergoing noncardiac surgery.[45] Concerns regarding an increased risk of bleeding with CCBs have been raised, but this association has not been confirmed and conflicting data are reported.[46-50]

Consensus recommendation for CCBs: *Consensus was achieved that* ***CCBs*** *should be CONTINUED on the morning of surgery.*

Centrally Acting Sympatholytic Medications

Centrally acting sympatholytic medications reduce sympathetic outflow from the brainstem by acting on α_2-adrenoreceptors.[21] Because of this sympatholytic action, clonidine (the most well-known agent of this class) can cause AV blockade, particularly if given with other sympatholytic medications (eg, dexmedetomidine).

Abrupt discontinuation of centrally acting sympatholytic medications can precipitate tachycardia and rebound hypertension, and interruption is not recommended in the perioperative period. Transdermal clonidine should be continued. However, the absorption of transdermal medications can be variable in the operative setting. Therefore, close monitoring is recommended for patients using a transdermal patch and additional measures to control blood pressure may be required. If oral clonidine is transitioned to the transdermal route perioperatively, therapeutic plasma clonidine concentrations are not achieved for 2 to 3 days after the patch is applied. Oral replacement needs to be overlapped, or other medications may be required. Similarly, plasma concentrations decline slowly after the patch is removed (half-life is ~20 hours), making it difficult to reverse if hypotension or AV block develops.

Consensus recommendation for centrally acting sympatholytic medications: *Consensus was achieved that* ***centrally acting sympatholytic medications*** *should be CONTINUED on the morning of surgery.*

Direct-Acting Vasodilators

Direct-acting vasodilators dilate arterioles, thereby reducing peripheral resistance, with no dilating effect on the venous circulation.[21] This results in a reflex venoconstriction and increased venous return to the heart with reflex positive inotropic and chronotropic effects. Adverse effects include tachycardia and fluid retention (due to vasodilation). Therefore, these agents are often used in combination with a sympathetic inhibitor and a diuretic.

There are no data to guide the management of direct vasodilators perioperatively, and similarly to the other antihypertensive agents, these should be continued preoperatively. Moreover, hydralazine (intravenously) is commonly used in the immediate perioperative period for blood pressure control when bradycardia is a concern.

Consensus recommendation for direct-acting vasodilators: *Consensus was achieved that* ***direct-acting vasodilators*** *should be CONTINUED on the morning of surgery.*

Potassium-Channel Openers

Potassium-channel openers are effective vasodilators. At present, minoxidil is the only approved agent in this class. Minoxidil relaxes smooth muscle cells in small and large arteries, thereby lowering vascular resistance and blood pressure. Minoxidil has been used for the treatment of hypertension, but it is usually a third-line agent in patients with chronic kidney disease.[21]

Consensus recommendation for potassium-channel openers: *Consensus was achieved that* ***potassium-channel openers*** *should be CONTINUED on the morning of surgery.*

Diuretic Medications

Diuretic agents act primarily by impairing sodium reabsorption in the renal tubules. They differ in the specific tubular ion transport system targeted, and the site along the nephron in which they act.[51] The most common diuretics are broadly classified as loop diuretics, thiazide diuretics, and potassium-sparing diuretics.

Loop diuretics block sodium resorption at the loop of Henle, promote sodium diuresis, and decrease extracellular fluid (ECF)

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volume.[21] Hypokalemia is a common adverse effect of loop diuretics.

Thiazide diuretics also increase sodium excretion and diuresis by promoting sodium excretion at the distal convoluted tubule. They are less potent than loop diuretics. Acutely, thiazide diuretics result in increased urine output and a decrease in ECF and plasma volumes. However, within 4 to 6 weeks, plasma and ECF volumes almost fully return to normal, yet blood pressure reduction is maintained.[52] The mechanism by which these drugs chronically lower blood pressure is poorly understood. Possible mechanisms include direct endothelial- or vascular smooth muscle—mediated vasodilation. Thiazide diuretics can also cause hypokalemia.

Potassium-sparing diuretics inhibit sodium resorption in the late distal tubule and collecting duct. Sodium excretion leads to decreased plasma volume and lower blood pressure levels.[21]

Consensus has not been established on the preoperative management of this broad class of agents.[3,53] Physiologic concerns of perioperative continuation of diuretics range from hypovolemia, electrolyte abnormalities (hypokalemia with loop and thiazide diuretics and hyperkalemia with potassium-sparing diuretics), and risk of postoperative AKI.

Preexisting intravascular volume depletion can potentially worsen hypotension from systemic vasodilation with anesthesia. There is concern that patients who continue preoperative loop diuretics may be at risk of volume depletion and subsequent hypotension. However, a double-blinded, randomized, placebo-controlled trial of 193 patients undergoing noncardiac surgery taking chronic furosemide reported that continuation of furosemide on the morning of surgery did not significantly increase (P=0.78) intraoperative hypotension or the risk of developing postoperative cardiovascular events.[54] However, this study lacked adequate power. Of note, these patients were presenting for elective surgery. Thus, these results may not extrapolate to patients who are acutely ill or presenting for urgent or emergency operations.

There is also concern that hypo- or hyperkalemia from chronic diuretic use may increase the risk of perioperative arrhythmias. Holding diuretics on the morning of surgery will not substantially alter chronic electrolyte abnormalities. Hypokalemia has been found to increase the incidence of arrhythmias and the need for cardiopulmonary resuscitation in patients undergoing cardiac surgery.[55] In another observational study, hypokalemia or diuretic therapy did not increase the incidence or severity of ectopy.[56] Severe hyperkalemia can potentiate arrhythmias and can occur in patients taking potassium-sparing diuretics, especially in conjunction with other agents that also increase potassium concentrations, such as ACEI and ARB. Preoperative evaluation of electrolytes in patients taking diuretics should be considered, particularly if the therapy was recently initiated.

Postoperative AKI has been described with continuation of preoperative diuretics. In a large observational cohort study of 3.6 million patients undergoing major surgery, chronic use of ACEIs or diuretics was associated with a slightly higher risk of postoperative AKI.[57] However, it is unclear whether withholding chronic diuretics on the morning of surgery mitigates this risk. A randomized, double-blinded, placebo-controlled trial looking specifically at spironolactone use in patients undergoing cardiac surgery reported that spironolactone was not protective against AKI and there was a trend toward increased risk.[58]

The Perioperative Quality Initiative consensus statement of perioperative blood pressure in elective surgery also recognized the limited evidence to withhold thiazide diuretics and the limited data to suggest that continuation causes harm. The Perioperative Quality Initiative concluded that there is no evidence to hold thiazide diuretics on the morning of surgery.[28] The Perioperative Quality Initiative recommended individualized decisions for loop diuretics owing to the lack of definitive evidence to suggest

that continuing these agents on the morning of surgery is harmful. This group did not address potassium-sparing diuretics in their consensus recommendations.[34]

Our own review of the literature led to a significant discussion on the perioperative use of diuretics. Several video teleconferences and rounds of the Delphi process were devoted to the subject of continuing or holding diuretics on the morning of surgery. Multiple scenarios and medical comorbidities were presented as examples for and against continuing diuretics in the perioperative period. In some cases, the same clinical scenario was used to bolster both views. For example, for an elderly patient undergoing an outpatient procedure, holding the diuretic may lead to hypertension later in the day, whereas continuing the diuretic may result in the patient having a strong urge to urinate during the procedure. Group members commented on the need to assess the fluid status in the preoperative period before making final recommendations. An individualized plan after considering a thorough history and physical examination of the patient and local institutional protocols is recommended.

Consensus recommendations for loop diuretics: *Consensus was achieved that* ***loop diuretics*** *should be HELD on the morning of surgery.*

Consensus recommendations for thiazide and potassium-sparing diuretics: *Consensus was achieved that* ***thiazide and potassium-sparing diuretics*** *should be CONTINUED on the morning of surgery.*

Endothelin Receptor Antagonists

Endothelin receptor antagonists, primarily used in the treatment of pulmonary arterial hypertension (PAH), bind to endothelin receptors and prevent their activation, thereby producing vasodilation.[59,60] High concentrations of endothelin result in vasoconstriction in patients with PAH, which leads to a proliferation of smooth muscle cells and subsequent arterial hypertension.[61] The use of endothelin receptor antagonists in PAH is associated with increased survival.[62-64] Endothelin receptor antagonists are often coadministered with phosphodiesterase-5 (PDE5) inhibitors (sildenafil and tadalafil), requiring extra caution when additional vasodilators (particularly nitrates) are used.

Bosentan is a strong inducer of cytochrome P450 3A4 and may decrease the effectiveness of analgesic agents such as oxycodone and hydrocodone as well as the anticoagulant effect of warfarin.[65] There are few data to inform the perioperative management of these drugs. However, given the increased perioperative morbidity related to PAH and the risk of decompensation, it is generally recommended to continue these agents preoperatively.[66]

Consensus recommendation for endothelin receptor antagonists: *Consensus was achieved that* ***endothelin receptor antagonists*** *should be CONTINUED on the morning of surgery.*

Cardiac Glycosides (Na^+-K^+-ATPase Pump Inhibitors)

Cardiac glycosides are among the oldest medications used to treat cardiovascular diseases. Currently, digoxin is most often used in the treatment of HFrEF and atrial fibrillation with rapid ventricular response with low blood pressure levels.[67] Digoxin has a narrow therapeutic index and a long half-life and is primarily renally excreted. Digoxin toxicity is more prevalent in elderly patients, and the risk of cardiac arrhythmias is increased in patients with hypokalemia, hypomagnesemia, hypercalcemia, and hypoxia. Digoxin also has important drug-drug interactions that increase the risk of digitalis toxicity and complete heart block. Implicated drugs include erythromycin, azithromycin, and clarithromycin, CCBs (verapamil, diltiazem, and nifedipine), β-blockers, thiazide diuretics, metoclopramide, and trimethoprim. It is important to assess renal function and serum electrolytes preoperatively.

Digoxin has a long history of use and is a safe medication when properly dosed. It is generally accepted that digoxin should be continued preoperatively. Moreover, older

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evidence points toward a higher risk of supraventricular arrhythmias or heart failure exacerbation postoperatively if digoxin is discontinued preoperatively.[68]

Consensus recommendation for cardiac glycosides: *Consensus was achieved that* ***cardiac glycosides*** *should be CONTINUED on the morning of surgery.*

Nitrodilators

Nitrodilators mimic the actions of endogenous nitric oxide (NO) by releasing or forming NO within tissues, thereby leading to vasodilation. Their primary mode of action is venous dilation resulting in decreased preload, and they affect afterload to a lesser extent. Nitroglycerin is used in emergencies to lower blood pressure and to relieve angina, whereas longer-acting agents are often used for hypertension and heart failure management.

There are limited studies to support continuing nitrates on the day of surgery. One study reported that continuation of nitrates may be protective. A second study suggested evidence of less ischemia with nitrate use.[69-71] We were unable to identify any studies investigating potential negative consequences of withholding nitrates before noncardiac surgery or large randomized controlled studies informing preoperative nitrodilator management. It seems reasonable to continue this class of medications in patients without significant hypotension given their role in patients with heart disease.

Consensus recommendation for nitrodilators: *Consensus was achieved that* ***nitrodilators*** *should be CONTINUED on the morning of surgery.*

Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 inhibitors are nonadrenergic noncholinergic drugs with inotropic and vasodilatory actions. Their primary effect is to increase the local availability of endogenous NO. These drugs are used to treat PAH (sildenafil and tadalafil), erectile dysfunction, benign prostatic hyperplasia, peripheral arterial disease, and Raynaud phenomenon (off-label use). Phosphodiesterase-5 inhibitors have synergistic effects with many vasodilator drugs and are known to decrease blood pressure levels.[72,73] Anterior ischemic optic neuropathy has been reported with their use.[74,75]

Given the overwhelming benefit of continuing PAH treatment preoperatively, continuation of PDE5 inhibitors in the perioperative period outweighs the risk of hypotension and possible anterior ischemic optic neuropathy. In contrast, when prescribed for erectile dysfunction, it is prudent to discontinue PDE5 inhibitors.[76] Tadalafil has a long half-life, and therefore discontinuation before the day of surgery is necessary to decrease the effects on blood pressure levels.[77]

Consensus recommendation for PDE5 inhibitors: *Consensus was achieved that* ***PDE5 inhibitors*** *should be CONTINUED on the morning of surgery if prescribed for PAH. Consensus was achieved to* HOLD *PDE5 inhibitors used for erectile dysfunction at least 24 hours before surgery.*

Class III Antiarrhythmic Agents (Potassium-Channel Blockers)

Class III antiarrhythmic agents bind to and block potassium channels that are responsible for phase 3 repolarization. This leads to an increase in action potential duration in the effective refractory period and prevents reentry tachycardias.[78] These drugs are indicated for the treatment of atrial fibrillation and flutter (amiodarone, dronaderone, sotalol, ibutilide, and dofetilide) or ventricular tachycardia (sotalol, bretylium, and amiodarone). Ibutilide and bretylium are available only in intravenous formulations to acutely treat arrhythmias. Class III antiarrhythmic agents are both antiarrhythmogenic and proarrhythmogenic because of their potential to increase the corrected QT (QTc) interval and torsades de pointes.[79] This risk is magnified in patients with long QTc syndrome, and the use of other

QTc-prolonging drugs should be avoided. Amiodarone can cause bradycardia and AV block because of its class IV effects. Therefore, it is contraindicated in patients with heart block or sinoatrial node dysfunction. Sotalol shares a β-blocker effect with class II antiarrhythmic agents.

Preoperatively, class III antiarrhythmic agents should be continued, as there is a risk of arrhythmia recurrence when these agents are abruptly discontinued.[5,80-82] Postoperatively, these agents should be reinitiated as soon as feasible.

Consensus recommendation for class III antiarrhythmic agents: *Consensus was achieved that* ***class III antiarrhythmic agents*** *should be CONTINUED on the morning of surgery.*

Renin Inhibitors

Renin inhibitors are 1 of 4 classes of compounds including ACEIs, ARBs, and aldosterone receptor antagonists that affect the RAAS. The antihypertensive effects derive from the inhibition of renin.[13,83] The only renin inhibitor currently available is aliskiren. It is effective alone, but when used with diuretics or ARB, the antihypertensive effects are additive. Renin inhibitors have a low incidence of adverse effects but rarely include angioedema and cough. There is a risk of hyperkalemia when aliskiren is combined with ACEIs, especially in patients with diabetes, and monitoring is warranted. In the presence of volume depletion, aliskiren treatment may adversely affect renal function. Aliskiren is contraindicated during pregnancy.[84]

No guidelines exist for the perioperative management of renin inhibitors. However, prompt resumption of renin inhibitors in the postoperative setting should be carefully considered if volume depletion or intraoperative hypotension is suspected.

Consensus recommendation for renin inhibitors: *Consensus was achieved that* ***renin inhibitors*** *should be HELD on the morning of surgery.*

Class I Antiarrhythmic Agents (Sodium-Channel Blockers)

Sodium-channel blockers reduce the rate and magnitude of depolarization and thus the conduction velocity in the myocardium. This reduction in conduction velocity suppresses tachycardias that are due to abnormal conduction such as reentry arrhythmias.[13,78] Class Ia antiarrhythmic agents (quinidine, disopyramide, and procainamide) prolong the QTc interval, increasing the risk of torsades de pointes. Therefore, the concomitant use of medications that prolong the QTc interval should be used with caution in patients taking class Ia antiarrhythmic agents. As with the other antiarrhythmic agents, there is a paucity of literature regarding perioperative management. Because these agents are commonly used to prevent cardiac arrhythmias, they are usually continued during the perioperative period.

Consensus recommendation for class I antiarrhythmic agents: *Consensus was achieved that* ***class I antiarrhythmic agents*** *should be CONTINUED on the morning of surgery.*

Sodium-Channel Blockers

Ranolazine is approved for the treatment of chronic angina. Its mechanism of action is not well understood but thought to be due to the inhibition of the sodium current in myocytes, thus reducing intracellular calcium overload and diastolic contractile dysfunction.[85] Ranolazine prolongs the QTc interval, and it is recommended that electrocardiography be performed within a few weeks of the initiation of therapy.[85] No data exist as to its perioperative management. As this agent does not affect hemodynamic stability, it was the consensus of the group that it should be continued preoperatively.

Consensus recommendation for sodium-channel blockers: *Consensus was achieved that* ***sodium-channel blockers*** *should be CONTINUED on the morning of surgery.*

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Sodium Glucose Cotransporter-2 Inhibitors

Sodium glucose cotransporter-2 inhibitors are approved for the treatment of HFrEF (class 1A recommendation) in patients with or without diabetes mellitus.[86] They prevent hospitalization for heart failure by several cardiorenal protective mechanisms including increased glucosuria, natriuresis, improved blood pressure control, increased cardiac oxygen delivery, and preventing cardiac remodeling.[87,88] In diabetic patients, adverse effects include euglycemic diabetic ketoacidosis when sodium glucose cotransporter-2 (SGLT2) inhibitors are continued, precipitated by perioperative fasting, dehydration, acute illness, ketogenic low carbohydrate diets, or underlying malignant neoplasm. Although the mechanism is incompletely understood, it is thought to result from an insulinopenic state, increased renal reabsorption of ketones, and ketone body formation.[89,90] Therefore, the Food and Drug Administration recommends discontinuing SGLT2 inhibitors for a 3- to 4-day period, a recommendation supported by the SPAQI's recently published recommendations for patients with diabetes mellitus.[16]

In nondiabetic patients, it is unclear whether there is a risk of euglycemic ketoacidosis if SGLT2 inhibitors are continued perioperatively. Euglycemic ketoacidosis is not described in the pivotal trial on canagliflozin and dapagliflozin for the treatment of heart failure in nondiabetic patients or in a recent meta-analysis.[91] However, a recent case report describes ketoacidosis with hypoglycemia in a nondiabetic patient undergoing a valve replacement who took dapagliflozin on the day of the procedure.[92] Given their recent introduction to the market as well as a lack of long-term safety data, it seems prudent to follow the same recommendations for nondiabetic patients as for diabetic patients.

Consensus recommendation for SGLT2 inhibitors: *Consensus was achieved that* ***SGLT2*** *inhibitors should be HELD IN ADVANCE before surgery. Specifically,* ***discontinue dapagliflozin, empagliflozin, and canagliflozin for 3 days before the procedure,*** *irrespective of a diagnosis of diabetes.* ***Discontinue ertugliflozin for 4 days before the procedure,*** *irrespective of a diagnosis of diabetes.*

DISCUSSION

As previously mentioned, not all clinical scenarios are within the scope of this consensus statement. Our aim was to reach consensus on the perioperative management of the most common cardiovascular medications encountered in the perioperative setting. As always, we recommend an individualized approach per treating physician and the perioperative team after considering the invasiveness of the planned surgical procedure, the anesthesia technique, the patient's comorbid medical conditions, institutional protocols, and future evidence.

Combination Medications and Polypharmacy

Regarding combination antihypertensive agents and other medications, we recommend that the principle of "first do no harm" be followed. If 2 agents are combined in the same medication and consensus states that one can be continued on the morning of surgery but the other should be discontinued, we recommend holding the combination agent. Recent evidence from Takeuchi et al[93] in regard to ARB/CCB combination formulations supports this recommendation. Similarly, if a combination medication contains a component that presents a risk of withdrawal if discontinued abruptly (eg, β-blockers), then it may be reasonable to continue this medication, or at least consider providing a prescription for the β-blocker alone to be taken on the morning of surgery. The perioperative team needs to be made aware through appropriate handoff communications that such patients may be at risk of postoperative hypertension and need to be monitored closely until resumption of their outpatient medication regimen.

Similarly, when patients are taking multiple cardiovascular medications (polypharmacy), the perioperative clinician must decide which medicines to hold and which to continue, given that holding all medications as recommended may lead to an

adverse event (eg, hypertensive urgency) or cancellation. The perioperative clinician may wish to inform the patient to bring their medications to the hospital or ambulatory surgery center so that they may be available to take postoperatively.

Minor Procedures

During the course of the consensus group's deliberations, the subject of minor procedures such as cataract surgery and knee arthroscopy was raised. A blanket recommendation to hold antihypertensive agents such as ACEIs or ARBs may lead to unintended case cancellations because of hypertension on the morning of surgery, which may be avoided by having patients continue their hypertension medications. Hypertension has been cited as a common reason for canceling cataract surgery.[94-96] The consensus group felt that procedures with a low risk of physiologically meaningful fluid shifts should be considered separately from other surgical procedures. As a result, it was decided to add another question to the final Delphi round, in which consensus was achieved.

Consensus for minor procedures, such as cataract surgery: *Consensus was achieved that consideration should be given to continuing all routine cardiovascular medications, including ACEIs and ARBs, on the morning of surgery for procedures under local or minimal sedation techniques that are determined to be low risk, minimally invasive, and without physiologically meaningful hemodynamic changes. Consensus was achieved to consider holding diuretics on the morning of surgery until after the procedure, primarily for patient comfort.*

CONCLUSION

Preoperative management of cardiovascular medications remains highly variable because of geography, specialty, and local practices. The Society for Perioperative Assessment and Quality Improvement sought to obtain consensus on the management of these medications on the basis of the available literature and guidance from a group of perioperative medicine experts. Consensus was achieved on 21 classes of medications after 4 Delphi rounds over 18 months of discussion via e-mail and teleconferences. The Society for Perioperative Assessment and Quality Improvement and the authors are aware that recommendations applied without considering medical issues unique to the patient and planned procedure may lead to unintended consequences. This consensus statement can serve as guidance in most cases, recognizing that individual patient circumstances should always inform medical judgment and compel final care recommendations. During our discussions, the group was guided by the principle of "first do no harm." In many cases, adequately powered and high-quality studies were not available. Although there are ongoing trials for some classes of medications, there is not extensive literature about the management of many of these drugs in the perioperative period. The group relied on mechanisms of action and pharmacokinetic properties to inform their discussions and voting during the Delphi process. Adherence to this consensus statement will not ensure successful treatment in every situation. Furthermore, these recommendations should not be interpreted as setting a standard of care or be deemed inclusive of all proper methods of care, nor exclusive of other methods of care, reasonably directed to obtain the same results. The ultimate judgment regarding the propriety of any specific recommendation must be made by the physicians and the patient considering all the circumstances presented by the individual patient and the known variability and biological behavior of diseases. This consensus statement reflects the best available data at the time the manuscript was prepared. The results of future studies may require revisions to the recommendations.

POTENTIAL COMPETING INTERESTS

Dr Balonov has received payment for expert testimony from Controlled Risk Insurance Company (CRICO)/Risk Management Foundation and served on the Board of Directors of International Society for the Perioperative Care of Patients with Obesity (ISPCOP). Dr

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Merli is a codirector for Mayo Clinic Perioperative Course and a course director for Perioperative Medicine Pre-Course at the American College of Physicians (ACP) National Meeting. Dr Sahai has received royalties or licenses from UpToDate.com and serves on the Governing Board of the Society for Perioperative Assessment and Quality Improvement (SPAQI) (unpaid position). Dr Sweitzer has received royalties from Wolters Kluwer (UpToDate.com and A&A Practice), lecture fees and/or honoraria from several academic centers, and travel expenses to lecture at national meetings and grand rounds. She is President of Society for Ambulatory Anesthesia (SAMBA). She serves on the Board of Directors of SAMBA and SPAQI (both unpaid positions). Dr Urman has received grants or contracts from the National Institutes of Health, Agency for Healthcare Research and Quality, National Science Foundation, AcelRx Pharmaceuticals, and Heron Therapeutics; royalties or licenses from Cambridge University Press, Oxford University Press, Springer, Wolters Kluwer, and Elsevier; consulting fees from Pfizer, Medtronic, Merck, and AcelRx Pharmaceuticals; payment or honoraria from Merck and Medtronic; and payment for expert testimony from Cambridge Medical Experts. He serves on a data safety monitoring board or advisory board of Acacia Pharma and serves on the boards of SPAQI, SAMBA, Enhanced Recovery After Surgery (ERAS USA), American Society of Anesthesiologists (ASA), and Association of Anesthesia Clinical Directors (AACD). The other authors report no competing interests.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ACC/AHA,** American College of Cardiology/American Heart Association; **ACEI,** angiotensin-converting enzyme inhibitor; **AKI,** acute kidney injury; **ARB,** angiotensin II receptor blocker; **ARNI,** angiotensin receptor—neprilysin inhibitor; **AV,** atrioventricular; **CCB,** calcium-channel blocker; **ECF,** extracellular fluid; **HFrEF,** heart failure with reduced ejection fraction; **NO,** nitric oxide; **PAH,** pulmonary arterial hypertension; **PDE5,** phosphodiesterase-5; **QTc,** corrected QT; **RAAS,** renin-angiotensin-aldosterone system; **SGLT2,** sodium glucose cotransporter-2; **SPAQI,** Society for Perioperative Assessment and Quality Improvement

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