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Review Article

Evaluation, risk stratification and management of hypertensive patients in the perioperative period

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ABSTRACT

Uncontrolled hypertension represents an important cause for postponing a non-cardiac surgery. Perioperative management of hypertensive patients should focus on cardiovascular risk stratification, evaluation of blood pressure levels and hypertension control, registration of the ongoing antihypertensive regimen and counseling about clinical decisions related to the expected perioperative blood pressure fluctuations. To date, there is a lack of evidence on how hypertensive patients should be perioperatively treated, while an empirical clinical approach is usually pursued in the usual practice. The present review appraises the gaps in the evidence and illustrates the current empirical approach of perioperative management of hypertension in non-cardiac surgery.

1. Introduction

According to the most recent Guidelines published by the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) in 2018, hypertension is defined as the presence of blood pressure levels ≥140/90 mmHg, based on repeated office blood pressure measurements, or out-of-office measurements of ambulatory or home blood pressure, if feasible [1].

Hypertension is closely related to comorbidities, such as ischemic heart disease, heart failure, cerebrovascular disease, and chronic kidney disease; it has just to be emphasized that hypertensive patients develop cardiovascular disease 5 years earlier, compared to normotensive individuals [2]. In fact, almost 7.6 million premature deaths are attributed annually to elevated blood pressure worldwide, with stroke and ischemic heart disease representing the main comorbidities [3]. Target organ damage linked to hypertension, and not high blood pressure levels per se, practically defines the overall perioperative risk, being also associated with increased cardiovascular risk and future adverse events [4]. Consequently, among hypertensive patients undergoing non-cardiac surgery, is expected that baseline cardiovascular risk is higher, and history of clinical cardiovascular disease is more prevalent compared to their normotensive counterparts.

As far as hypertension is concerned, the perioperative period is even more demanding and challenging. Hypertensive patients undergoing non-cardiac surgery are receiving a variety of antihypertensive medications with different blood pressure-lowering intensity and hemodynamic properties, especially in conditions of volume depletion as observed in the usual surgery procedures. Moreover, during preoperative period, pain and stress stimuli represent the clinical phenotype of sympathetic activation accompanied by blood pressure and heart rate changes. Various modalities for the induction and maintenance of anesthesia together with the implementation of intravenous vasoactive drugs or solutions to normalize blood pressure and volume status further contribute to hemodynamic changes during intervention but these changes can be extended in the post-interventional period [5].

Taken together the above, perioperative management of hypertensive patients is rather complicated. This is because the evaluation of cardiovascular risk should take into account not only the medical history but also the eventual sub-clinical hypertension mediated organ damage; the decision about continuation of the underlying antihypertensive treatment should be carefully evaluated; and the hemodynamic effects of different anesthesia procedures, the surgery-

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mediated fluid shift and blood loss, as well as the adjuvant intravenous pharmacological treatment to reverse hemodynamic perturbations can only be hardly predicted during surgery outline especially in hypertension [6].

The aim of the present review is to provide further insights into the management of patients with hypertension in the perioperative setting, based on the most recent available literature.

2. Preoperative assessment and risk stratification

All patients who will undergo surgery should be carefully evaluated by an anesthesiologist and eventually a cardiologist for the assessment of the perioperative overall risk and their general condition, along with the organization of an effective anesthesia plan (14). Initial approach consists of a detailed patient's interview and a meticulous physical examination, including vital signs, along with evaluation of pertinent medical records. Routine and selective preoperative tests should be ordered when indicated, based upon medical history and physical examination [7]. This assessment should, of course, be made on the basis of the surgical risk estimate according to the type of surgery; surgical interventions are divided into low, intermediate and high cardiac risk, according to the 30-day risk of cardiac death and myocardial infarction (< 1%, 1–5% and > 5%, respectively) [8].

Over the past two decades, it has been established that the physical status, as assessed by the criteria of the American Society of Anesthesiologists (ASA), is closely related to the perioperative and postoperative complications and the overall mortality rate [9]. Patient's functional capacity appears to be one of the best prognostic markers of the overall perioperative risk, playing a pivotal role in the preoperative cardiac risk assessment [10]. It is expressed in terms of metabolic equivalents (METs), classified as excellent (> 10 METs), good (7–10 METs), moderate (4–6 METs), poor (< 4 METs), and unknown. According to the most recent guidelines proposed by the American College of Cardiology (ACC)/American Heart Association (AHA) and the European Society of Cardiology (ESC) / European Society of Anaesthesiology (ESA), patients featuring poor functional capacity encounter the greater risk of perioperative cardiac complications and may thus require a more detailed, non-invasive stress testing before proceeding to surgery [11,12]. Functional capacity assessed through the score achieved on the Duke Activity Status Index (DASI) questionnaire arises as a useful measure for the preoperative cardiac risk assessment in patients undergoing a major, non-cardiac surgery, as shown in a recently published prospective cohort study [13].

Several risk-prediction models and indices have been proposed for the preoperative assessment of the patient undergoing non-cardiac surgery; the Revised Cardiac Risk Index [14] and the model developed utilizing the data obtained from the American College of Surgeons' National Surgical Quality Improvement Program (NSQIP) for the prediction of the intraoperative / postoperative myocardial infarction or cardiac arrest (MICA) [15] are the most well-known, while another model, the 9-point S-MPM (Surgical Mortality Probability Model) 30-day mortality risk index, exhibits excellent discriminative value in non-cardiac surgery patients [8] (Table 1). As clearly stated in the 2014 ESC/ESA Guidelines, risk index models “do not dictate management decisions but should be regarded as one piece of the puzzle to be evaluated”. However, it is of utmost importance to carefully evaluate the comorbidities of patients that will undergo non-cardiac surgery, especially those clinical entities not incorporated into the above indices, such as valvular disease, arrhythmias, pulmonary disease, obesity, and obstructive sleep apnea (OSA) syndrome [16–18].

Biomarkers such as B-type natriuretic peptide (BNP) and estimated glomerular filtration rate (eGFR; calculated from serum creatinine) have exhibited a fair predictive value for the incidence of major adverse cardiovascular events (MACEs) in the postoperative period concerning patients undergoing elective, non-cardiac surgery, while C-reactive protein has failed to provide a predictive role [19]. According to the 2014 ESC/ESA Guidelines, assessment of circulating biomarkers is not recommended for routine use but may be considered as an approach in high-risk patients undergoing non-cardiac surgery.

3. Blood pressure and the perioperative period: clinical implications

In a meta-analysis that pooled data from 30 studies on a total of 12,995 patients. Howell et al. demonstrated in 2004 that preoperative hypertension itself increases the odds for cardiovascular complications in the perioperative period by 35% [20]. However, the authors questioned the clinical implications of this statistical analysis, stating that this association reaches statistical, but not clinical significance. Kheterpal et al. also documented in an observational study on 7740 patients undergoing non-cardiac surgery that hypertension represents an independent risk factor for the development of a cardiovascular complication within the first 30 days post-surgery, increasing the corresponding risk by 70% [21].

In a recently published, prospective, observational cohort study, it was confirmed that, among patients undergoing non-cardiac surgery, preoperative hypertension was not associated with intraoperative haemodynamic instability, namely hypotension (mean arterial pressure < 55 mmHg, > 1 min) and tachycardia; however, hypertensive patients required more frequently vasopressor agents and fluid replacement therapy [22]. Despite that fact, during preoperative assessment of the patient, the astute physician should not forget the so called “white-coat effect” and the subsequent risk of intraoperative hypotension due to aggressive therapeutic approach preoperatively.

Some of us have recently published the results of an observational study on patients undergoing orthopedic surgery, showing that there is a significant “white-coat effect” (higher clinic than ambulatory blood pressure values)j over the entire day before surgery as well as just before surgery, the difference between the two sets of values disappearing intraoperatively. It was also noticed that selective treatment discontinuation did not modulate systolic blood pressure trajectories [23]. This “white-coat” effect has been also described, although indirectly, by Schonberger et al., who observed a mean difference in home versus presurgical office systolic/diastolic blood pressure levels equal to −9.2/−1.1 mmHg [24]. The researchers also tested the clinical value of three presurgical blood pressure thresholds (140/90, 150/95, 160/100 mmHg), confirming that elevated presurgical blood pressure values correspond usually to poorly controlled or even undiagnosed hypertension [24].

In the largest available prospective cohort study (data from the UK Clinical Practice Datalink evaluating 251,567 adults who had undergone elective non-cardiac surgery), a dose-dependent association between low blood pressure levels preoperatively and 30-day mortality was demonstrated [25]. Specifically, it was documented that systolic blood pressure levels lower than 119 mmHg increase the odds for postoperative mortality by 2%, while low diastolic blood pressure levels, < 63 mmHg, increase the corresponding odds by 24%. Interestingly, systolic hypertension was not associated with elevated mortality rates; however, diastolic hypertension (> 84 mmHg) increased the odds for death during the first month by 7%. Furthermore, low pulse pressure preoperatively appeared to be a predictor of mortality [25].

Interestingly, in a secondary analysis of the Vascular Events in Non-cardiac Surgery Patients Cohort Evaluation (VISION) international cohort study including 15,057 patients undergoing non-cardiac surgery, Abbott et al. demonstrated that preoperative systolic blood pressure did not have a predictive impact on post-operative myocardial injury, as assessed by serum troponin levels; however, the researchers observed that, independently of systolic blood pressure levels, a pulse pressure > 62 mmHg increases the relative risk of myocardial ischemia up to 25% [26].

The meticulous preoperative assessment of the hypertensive patient and the absolute need for more conservative blood pressure lowering

interventions before surgery are further reinforced by the results of a sub-study of the PeriOperative ISchemic Evaluation 2 (POISE-2) trial in a total of 9765 patients [27].In that study it was demonstrated that, intraoperatively, a 10 min increase in hypotension was associated with an increase in the odds for 30-day myocardial infarction and overall mortality of 8%. Similarly, a 10 min increase of hypotension over the remaining day of surgery was accompanied by a 3% increase in the odds of myocardial infarction or mortality, while considering the first 4 days of hospitalization, the effect of hypotension on the primary outcome, a composite of 30-day mortality and myocardial infarction after randomization, rose up to 183%. [27]. Another analysis of 33,330 non-cardiac surgeries in a total of 27,381 patients showed that intraoperative hypotension even shorter than those defined above increase the odds for myocardial injury in the postoperative period, the 30-day mortality being significantly associated only with intraoperative hypotension lasting at least 20 min [28]. Thus, physicians should be aware of the deleterious effects of hypotension intraoperatively and during the short postoperative period, both preventable and modifiable complications.

The potentially adverse cardiovascular impact of low postoperative blood pressure in patients undergoing non-cardiac surgery has been also confirmed in another prospective cohort study of 2211 patients [29]. Researchers identified a significant association between mean arterial pressure and high-sensitive troponin T (hsTnT) levels in the postoperative period; more specifically, they demonstrated that patients in the lowest mean arterial pressure quartile featured the highest hsTnT levels, establishing the close relationship between postoperative hypotension and myocardial injury [29].

Collectively, based on the above, it seems rationale to conclude that: a) preoperative hypertension and related co-morbidities may increase the risk of perioperative cardiovascular complications; however they do not predict intraoperative haemodynamic instability, unless aggressively treated, achieving systolic/diastolic blood pressure levels lower than 119/63 mmHg, b) low systolic, diastolic, and pulse pressure levels in the preoperative setting serve as predictors of 30-day mortality, c) physicians should not forget the “white-coat effect”, when approaching hypertensive patients in the preoperative setting; however they should thoroughly assess the patient for the identification of other causes (Table 2), d) intraoperative and postoperative hypotension are closely related to myocardial ischemia and overall mortality within the first month post-surgery. However, clinicians should not rely only on day-of-surgery blood pressure measurements but they should use documented blood pressure measurements from the outpatient setting [30]. As clearly stated in the 2018 ESC/ESH Guidelines, home blood pressure monitoring can identify white-coat and masked hypertension, constituting a cheap, easy and widely available method [1]. Twenty four-hour ambulatory blood pressure measurement may be a reasonable solution to this problem, but its role remains to be determined, as far as the management of a patient in the perioperative period is concerned. Unfortunately, no robust evidence currently exists, concerning the optimal blood pressure targets in the perioperative setting. More randomized controlled trials are urgently needed towards this direction (Table 1).

4. Hypertension in the perioperative setting: current recommendations

Despite the fact that hypertension in the perioperative setting is extremely common (with different causes requiring different therapeutic strategies, see Table 2), there is little evidence concerning the optimal blood pressure levels that should be achieved prior to surgery.

According to the Joint Guidelines from the Association of Anaesthetists of Great Britain and Ireland and the British Hypertension Society published in 2016, general practitioners are encouraged to refer hypertensive patients for elective surgery, if systolic/diastolic blood pressure readings are lower than 160/100 mmHg [31]. In patients attending the preoperative clinical evaluation in whom previous blood pressure levels are unknown, elective surgery should proceed, if systolic/diastolic blood pressure are lower than 180/110 mmHg [31].

In their updated Guidelines on hypertension, published in 2017, the ACC and the AHA clearly state that elective major surgery may be deferred if systolic or diastolic blood pressure are higher than 180 or 110 mmHg, respectively (class: IIb, level of evidence: C) [32]. Such patients, along with those experiencing intraoperative hypertension, should be managed with intravenous medications, for the achievement of adequate blood pressure control. Clinicians should always evaluate the patient for the presence of target organ damage.

Regarding the intraoperative management of surgical patients, it seems that an individualized treatment strategy should be followed, especially in high-risk patients, to ameliorate the risk of postoperative organ dysfunction. In the Intraoperative Norepinephrine to Control Arterial Pressure (INPRESS) study, a randomized, parallel-group, controlled clinical trial that enrolled 298 patients (most of whom underwent an abdominal surgery), it was documented that compared to a standard treatment strategy (according to which, patients received intravenous ephedrine, at recommended doses, for every decrease in systolic blood pressure lower than 80 mmHg, or lower than 40% from the patient's reference value, intraoperatively and within the first 4 h after surgery) an individualized treatment strategy that aimed at achieving systolic blood pressure within 10% of the patient's reference value), was superior in terms of preventing the primary composite outcome,i.e. Systemic inflammatory response syndrome and dysfunction of at least 1 among the renal, respiratory, cardiovascular, coagulation, and neurologic systems by day 7 after surgery. [33]. Further, larger randomized controlled trials are required to confirm these observations.

5. The place of antihypertensive drug classes in the perioperative period

5.1. Renin-angiotensin-aldosterone system antagonists

Antagonists of the renin-angiotensin-aldosterone system (RAAS) include angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor subtype 1 blockers (ARBs), direct renin inhibitors, and aldosterone antagonists. They have gained significant ground in the treatment of hypertension and related co-morbidities during the last three decades. However, they have been linked to the development of intraoperative hypotension requiring vasopressor support, questioning their role in the perioperative period of patients undergoing non-cardiac surgery [34].

As far as non-cardiac patients are concerned, Rosenman et al. demonstrated in a meta-analysis that pooled data from 434 patients on chronic ACEI/ARB treatment that immediate preoperative administration of ACEI/ARB is linked to a 51% significant increase in the risk of the development of hypotension requiring vasopressor agents, with no significant effect, however, on the incidence of postoperative myocardial infarction [35]. The authors questioned that the long-term consequences of RAS antagonists mediated intraoperative hypotension, doubting on the continuation or withdrawal of those drug classes preoperatively.

More recently, three large retrospective analyses have provided further insights. Turan et al. analyzed data concerning 9028 ACEI users who underwent non-cardiac surgery and 9028 controls, showing that perioperative use of ACEI (continuation of treatment until the day before surgery) did not have a significant effect on intraoperative hypotension, in-hospital morbidity and mortality and 30-day mortality [36]. Both groups did not differ in terms of vasopressor drug requirements and fluid resuscitation [36], results that are in agreement with those retrieved by another, smaller, observational study conducted by Vijay et al. [37].

Roshanov et al. conducted a subgroup analysis in a sample of

Table 1
Validated risk prediction models in patients undergoing non-cardiac surgery.

Model	Variables	Predictive power
Revised Cardiac Risk Index [16]	1. High-risk type of surgery 2. History of ischemic heart disease 3. History of congestive heart failure 4. History of cerebrovascular disease 5. Diabetes mellitus requiring insulin treatment 6. Preoperative serum creatinine >170 mmol/L	Receiver operating characteristic curve (ROC) analysis: • Entire population: 0.777 ± 0.023 • Validation cohort: 0.806 ± 0.034 • Patients undergoing vascular surgery: 0.774 ± 0.032
NSQIP model [17]	1. Age 2. Functional status 3. Type of surgery 4. ASA status 5. Preoperative serum creatinine >130 mmol/L	C statistic: • Validation cohort: 0.884 • Patients undergoing vascular surgery: 0.746
9-point S-MPM (Surgical Mortality Probability Model) 30-day mortality risk index [10]	1. ASA status 2. Surgery risk class 3. Emergency status	C statistic: • Validation cohort: 0.897

Table 2
Causes of hypertension in the perioperative setting.

Time	Cause
Preoperatively	1. White-coat effect 2. Uncontrolled hypertension 3. Undiagnosed hypertension 4. Pseudohypertension
Intraoperatively	1. Anesthesia induction 2. Insufficient analgesia 3. Extubation 4. Volume overload 5. Pre-existing hypertension 6. Clonidine withdrawal syndrome 7. Major surgery (vascular)
Postoperatively	1. Insufficient analgesia 2. Volume overload 3. Hypoxia / Hypercapnia 4. Hypothermia 5. Urinary retention 6. Stress 7. Clonidine withdrawal syndrome 8. Electrolyte disturbances

patients included in the Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) study. Data included 14,687 patients undergoing non-cardiac surgery, of whom 4802 were taking an ACEI or ARB at baseline [38]. Researchers observed that withholding ACEI/ARB on the day of surgery was associated with an 18% decrease in the risk of the primary composite outcome (30-day all-cause mortality, myocardial injury post-surgery and stroke), the results being consistent, when each outcome was assessed separately [38]. In addition, they demonstrated that withholding ACEI/ARB was associated with a 20% decrease in the risk of intraoperative hypotension which was shown to increase the risk of important postoperative hypotension by 65%, regardless of ACEI/ARB use. ACEI/ARB use was further related to the postoperative incidence of a vascular event, with an increase in the relative risk of 68% [38]. The authors concluded that withholding ACEI/ARB treatment on the day of surgery in patients on chronic treatment should be recommended.

Interestingly, in another retrospective analysis of 30,173 non-cardiac surgical admissions performed by Lee et al., non-resumption of the ARB treatment by the second postoperative day was associated with a significant increase in the 30-day mortality by 47% in the overall cohort, which rose up to 152% for those patients being younger than 60 years old [39]. Similarly, it has been demonstrated in a retrospective study of the Veterans Affairs Healthcare System in a total of 240,978 patients that non-resumption of an ACEI, previously administered, within the first two weeks after surgery increases the risk of 30-day mortality almost by 2.4 times [40]. The most recent meta-analysis of 6022 patients on chronic ACEI/ARB treatment undergoing a major non-cardiac surgery failed to confirm an association between withholding of treatment on the day of surgery and overall mortality or MACEs; however, it documented that withdrawal was associated with a significant decrease by 37% in the odds for intraoperative hypotension [41].

Concerning preoperative discontinuation of ACEIs/ARBs, a former randomized controlled trial on 526 patients assigned either to the continuation or to withdrawal group, confirmed that discontinuation of this drug class was not associated with preoperative and postoperative hypertension, with no deaths or adverse cardiovascular events recorded [42]. Discontinuation of ACEIs/ARBs in the perioperative period in patients undergoing elective, non-cardiac surgery was also not associated with increased odds for postoperative acute kidney injury [43].

A forthcoming randomized controlled trial, namely STOP-or-NOT trial (NCT03374449), is expected to shed light on the place of RAS inhibitors in the perioperative period, assessing major safety and efficacy outcomes [44]. Current knowledge does not provide a definitive answer; original indications for their administration, patient's physical status, type of surgery, blood pressure variability, expected blood loss and haemodynamic instability intraoperatively are factors to be taken into account [45].

5.2. B-blockers

B-blockers constitute the most well studied drug class in the perioperative period. In this setting, beneficial results in overall mortality and cardiovascular morbidity were seen with atenolol in a high-risk population undergoing non-cardiac surgery and assessed in the Multicenter Study of Perioperative Ischemia performed by Mangano et al. [46]. According to a recently published retrospective analysis of data retrieved from the Danish Anesthesia Register and concerning 55,320 patients with uncomplicated hypertension undergoing non-cardiac surgery, perioperative use of b-blockers in a two-drug regimen was associated with a significant increase in the incidence of 30-day MACEs (1.32% vs. 0.84%), all-cause mortality (1.93% vs. 1.32%) and cardiovascular mortality (0.90% vs. 0.45%), compared to patients treated with other antihypertensive drugs, while no significant difference was identified for non-fatal myocardial infarction or non-fatal stroke [47]. Older age, male gender and acute surgery were the major determinants of increased incidence of MACEs in patients administered b-blockers [47].

In the hallmark PeriOperative ISchemic Evaluation (POISE) trial, a randomized controlled trial including 8351 patients with established or at high risk of atherosclerotic disease undergoing non-cardiac surgery, perioperative administration of extended-release metoprolol was associated with a significant decrease in the risk of fatal and non-fatal myocardial infarction of 27% and 30%, respectively; however, use of the drug increased overall mortality by 33% and stroke by almost two

times [48]. Of note, metoprolol increased the risk of clinically significant hypotension by 55% and of bradycardia by 74%, with an increased incidence of death and stroke as well. [48].

According to other more recent meta-analyses, perioperative b-blockade in non-cardiac surgery is associated with a significant increase in overall mortality by 27%, in non-fatal strokes by 73% and in perioperative hypotension by 51%, addressing the need for significant amendment in the current guidelines [49]; these results are also in agreement with a meta-analysis conducted by Bangalore et al., except for the decrease in the odds for myocardial infarction by 35% and for myocardial ischemia by 64% [50].

In the field of randomized controlled trials, the Metoprolol after Vascular Surgery (MaVS) study confirmed that perioperative use of metoprolol in 247 patients undergoing vascular, non-cardiac surgery did not modify the primary efficacy outcome; however, it increased the risk of intraoperative bradycardia and hypotension requiring treatment [51]. In the classic randomized controlled trial conducted by the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography study group, Poldermans et al. demonstrated that perioperative administration of bisoprolol in high risk patients undergoing major vascular surgery resulted in a significant decrease in the incidence of cardiac death and non-fatal myocardial infarction; however, with significant limitations in study design [52]. A recent meta-analysis by Hajibandeh et al. assessing the potential role of b-blockade in the perioperative period in 32,602 patients undergoing vascular or endovascular surgery failed to prove any benefit in the perioperative outcomes, including all-cause and cardiac mortality, cardiovascular morbidity, renal failure, re-hospitalization and re-operation [53].

In non-cardiac surgery, b-blockade correlates with significant increase in all-cause mortality by 25%, in hypotension by 50%, in bradycardia by 123% and in stroke by 59%, which cannot be balanced by the decrease in the risk of myocardial ischemia and supraventricular arrhythmias [54]. The lower risk of myocardial infarction remains of interest and should be evaluated in the light of meticulous stratification of the patient, as high-risk patients may benefit from b-blockade, while low risk patients may not [55].

5.3. Calcium channel blockers

Despite the discrepancy between the results of observational studies concerning the role of calcium channel blockers (CCBs) in the perioperative period [56,57], a meta-analysis of 41 studies, including 3327 patients undergoing CABG or valve surgery, documented that CCBs decreased the occurrence of myocardial infarction by 42% and of ischemic events by 47%, while, non-dihydropyridines were associated with a significant decrease in the odds for supraventricular tachycardia by 38% [58]. No significant correlation between perioperative administration of CCBs and overall mortality, renal function or adverse events was detected [58]. Overall, CABG patients seem to be the population expecting the greatest benefit with CCBs perioperatively.

In a more recent meta-analysis combining data from non-cardiac surgery studies, it was confirmed that CCBs are equally effective and safe, when compared to other antihypertensive drugs, for the management of perioperative hypertension, with no significant differences among the various drug classes [59]. More specifically, it was shown that CCBs induce non-significant decrease in postoperative systolic blood pressure by 7.05 mmHg and in heart rate by 1.05 beats per minute, without increasing the risk of any adverse event or postoperative onset of atrial fibrillation [59]; however, major methodological limitations of this meta-analysis include the use of different CCBs with different route of administration, along with the small overall sample size and the combination of randomized controlled trials and observational studies enrolling patients undergoing non-cardiac surgery.

5.4. Diuretics

No solid evidence exists, concerning the place of diuretics in the perioperative period. Khan et al. demonstrated in their randomized controlled trial of 212 patients who underwent non-cardiac surgery that furosemide administration on the day of surgery was equally safe to placebo, concerning the relative risk of intraoperative hypotension, administration of vasopressor agents and fluid replacement [60]. Interestingly, furosemide compared with placebo did not affect the overall risk of the composite cardiovascular endpoint (i.e. acute coronary syndrome, arrhythmia, stroke or transient ischemic attack, or death), during the postoperative period [60].

5.5. Centrally acting agents

Clonidine, an alpha-2 adrenergic agonist, represents a second-line antihypertensive agent. A published meta-analysis in 2002 by Nishina et al. confirmed that perioperative administration of clonidine decreased the odds for myocardial ischemia by 48% for CABG patients and by 53% for patients undergoing non-cardiac surgery; further analyses indicated a significant superiority of orally administered clonidine versus that given intravenously [61]. No significant effect on incidence of bradycardia or hypotension was identified. A year later, Wijeysundera et al. in their meta-analysis combining data from vascular and non-cardiac surgery studies demonstrated that alpha-2 adrenergic agonists, perioperatively administered, decreased overall mortality by 36% and myocardial ischemia by 24%; however, when the efficacy of clonidine was assessed separately, it was found that it reduced myocardial ischemia by 37%, with no significant impact on the rest cardiovascular outcomes. Further analyses according to type of surgery failed to prove a different association [62].

In 2014, the results of the hallmark Perioperative Ischemic Evaluation 2 (POISE-2) trial were published. In this trial, 10,010 patients undergoing non-cardiac surgery were randomly assigned to receive either clonidine or placebo preoperatively; clonidine did not have a significant effect on the composite outcome of myocardial infarction or death, but it increased the risk of non-fatal cardiac arrest by 2.2 times, mainly due to asystole or pulseless electrical activity [63]. Clonidine was also associated with a significant increase in intraoperative and postoperative hypotension by 32% and bradycardia by 49%, while, hypotension arose as an independent predictor of perioperative myocardial infarction, increasing the corresponding risk by 37% [63].

According to the most recent Cochrane meta-analysis, central alpha-2 adrenergic agonists do not decrease the risk of all-cause mortality, cardiovascular mortality, myocardial infarction and stroke in patients undergoing non-cardiac surgery; in contrast, they increase the risk of bradycardia by 59% and of hypotension by 24% [64]. Overall, this drug class appears to be ineffective in decreasing overall mortality and cardiovascular morbidity and mortality in patients undergoing either non-cardiac surgery.

Regarding the safety and efficacy of moxonidine, a sympatholytic agent acting as alpha-2 imidazoline receptor agonist, in the perioperative period, no evidence practically exists. Only one, small, randomized, controlled trial assessed its efficacy, when administered before surgery and on the following 4 days in 141 patients undergoing major vascular surgery, compared to placebo, failing to provide a protective effect against perioperative myocardial ischemia and overall mortality within the first year [65].

Current recommendations (2014 ACC/AHA and 2014 ESH/ESA Guidelines) for the management of antihypertensive treatment in the perioperative period are presented in Table 3.

6. Conclusion

Clinicians should be aware of the complexity in the approach and management of hypertensive patients during the perioperative period.

Table 3
Recommendations for the management of antihypertensive treatment in the perioperative setting.

Drug class	2014 ACC/AHA Guidelines [13]	2014 ESH/ESA Guidelines [14]
B-blockers	1. Continue in patients in chronic treatment (class: I, level of evidence: B) 2. Guide management after surgery by clinical circumstances (class: IIa, level of evidence: B) 3. It may be reasonable to begin b-blockers in patients with high- or intermediate-risk preoperative tests (class: IIb, level of evidence: C) 4. If Revised Cardiac Risk Index (RCRI) score is ≥3, it may be reasonable to begin b-blocker before surgery (class: IIb, level of evidence: B) 5. Initiating b-blockers in the perioperative period in those patients having a long-term indication but no other RCRI risk factors is of uncertain benefit (class: IIb, level of evidence: B) 6. It may be reasonable to begin a b-blocker long enough in advance to assess safety and tolerability, >1 day before surgery (class: IIb, level of evidence: B) 7. Do not start b-blocker on the day of surgery (class: III, level of evidence: B)	1. Peri-operative continuation of b-blockers is recommended in patients currently receiving this medication (class: I, level of evidence: B) 2. Pre-operative initiation of b-blockers may be considered in patients scheduled for high-risk surgery and who have 2 clinical risk factors or ASA status (class: IIb, level of evidence: B) 3. Pre-operative initiation of b-blockers may be considered in patients who have known ischemic heart disease or myocardial ischemia (class: IIb, level of evidence: B) 4. When oral b-blockade is initiated in patients who undergo non-cardiac surgery, the use of atenolol or bisoprolol as a first choice may be considered (class: IIb, level of evidence: B) 5. Initiation of peri-operative high dose b-blockers without titration is not recommended (class: III, level of evidence: B) 6. Peri-operative initiation of betablockers is not recommended in patients scheduled for low-risk surgery (class: III, level of evidence: B)
RAS inhibitors	1. Continuation of ACEIs or ARBs is reasonable perioperatively (class: IIa, level of evidence: B) 2. If ACEIs or ARBs are withheld before surgery, it is reasonable to restart as soon as possible postoperatively (class: IIa, level of evidence: C)	1. Continuation of ACEIs or ARBs, under close monitoring, should be considered during non-cardiac surgery in stable patients with heart failure and left ventricular systolic dysfunction (class: IIa, level of evidence: C) 2. Initiation of ACEIs or ARBs should be considered at least 1 week before surgery in cardiac-stable patients with heart failure and left ventricular systolic dysfunction (class: IIa, level of evidence: C) 3. Transient discontinuation of ACEIs or ARBs before non-cardiac surgery in hypertensive patients should be considered (class: IIa, level of evidence: C)
Alpha-2 agonists	1. They are not recommended for prevention of cardiac events (class: III, level of evidence: B)	(–)

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A meticulous preoperative assessment, including detailed medical history with emphasis on comorbidities, risk stratification and appropriate amendments in the previous therapeutic regimen, are warranted. Blood pressure thresholds to postpone surgery are higher in the perioperative setting than the thresholds defining hypertension at large, while, an individualized approach is recommended. Intra- and post-operative blood pressure abnormalities are closely linked to short-term morbidity and mortality. Large, prospective, randomized controlled trials are required in order to refine evidence in this field.

Declaration of Competing Interest

None.

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