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Cardiovascular Risk Evaluation in Patients with Critical Leg Ischemia before Vascular Surgery

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Abstract

Assessment of the role and investigation particularities (comparative and complementary aspects, hierarchies, preferential indication) adapted to the context of a global cardiovascular (CV) evaluation, including clinical elements, non-invasive and invasive imagistic examination in order to estimate the cardiovascular risk (CVR) and to define the revascularization therapeutic strategy in patients with critical leg ischemia (CLI). Complete and accessible evaluation involves accessible means of investigation like clinical exam, electrocardiogram, cardiac biomarkers, arterial, cardiac, and carotid ultrasonography which could be affordable in all cardiovascular departments. Non-invasive stress tests, coronary and arterial cervical angiography imaging leads in selected cases and where is possible to the identification of significant coronary and/or carotid lesions potential responsible for cardiac and cerebrovascular events after vascular surgery. The evaluation algorithm allows better risk stratification of patients with CLI in high and intermediate CVR. The “poly-arterial” status in patients with CLI changes the intervention management with a more intensive pre-operative medical treatment, while the coronary and the carotid arteries revascularization might precedes the peripheral arterial revascularization procedures, in order to reduce the CV risk status.

Keywords: critical leg ischemia (CLI), cardiovascular risk (CVR), poly-arterial (multi-arterial sites lesions), perioperative evaluation, non-invasive stress tests, cardiac biomarkers

1. Introduction

Atherosclerosis (ATS) is a systemic pathological process that affects coronary, cerebral and peripheral arterial circulation. Peripheral arterial disease (PAD) is a distinct athero-thrombotic syndrome marked by stenosis and occlusion of arterial beds [1]. A large proportion of PAD patients are not diagnosed before having a major ischemic cardiovascular (CV) event (MACE), which limits the use of medical therapies with recognized evidence of cardiovascular risk (CVR) reduction [2]. Even if claudication can remain stable over 10 years in 70–80% of patients, the prevalence of myocardial infarction (MI), stroke and CV death is high. PAD patients triple their risk of mortality from any other cause and have a six fold higher risk of death by coronary artery disease (CAD) than those without this ATS lesions. All these problems lead to repeated hospitalizations, low quality of life for patients and increased CV morbidity [3].

2. Predictors of perioperative cardiovascular risk

2.1. The risk of PAD patients in noncardiac vascular surgery

It is estimated that more than 200 million patients suffer a surgery intervention every year worldwide, and the proportion might increase up to 300 million in time. Most of these patients are elderly men, 25% of them having a high or intermediate CVR. The rate of MACE ranges from 11% in patients with one CV risk factor (CVRF) up to 33% in patients with four CVRFs. Perioperative mortality ranges from 0.9% in patients with one CVRF to 11% in patients with four CVRFs. Approximately 60% of patients with PAD have coronary artery disease (CAD), up to 25% of PAD patients have carotid-cerebrovascular atherosclerotic lesions, and the rate of MACE (MI, stroke and CV death) reaches 7% per year. The main causes of mortality in patients with PAD are due to cardiac events, coronary MI (60%) first of all, followed by major or fatal stroke (35%) and only a small proportion (15%) of these patients dies due to complications of critical peripheral arterial ischemia (by gangrene, septicemia and multiorgan failure) [4]. Along with coronary and/or cerebrovascular disease, the type of surgery is an independent predictive risk factor for death of PAD patients with multisite arterial lesions [5, 6]. This is why, patients undergoing vascular surgery have a higher risk of MI (31%), CV death (5%) than general surgery patients (3%) [4, 7, 8]. A good diagnostic and management strategy for PAD patients reduces vital CVR in terms of short outcomes and identifies patients with coronary and/or cervical arterial lesions at risk for long-term CV events. noninvasive tests can provide both diagnostic information (by revealing coronary ischemic heart disease (IHD) or cervical arterial lesions) and CVR prognosis in patients who undergo noncardiac surgery [4, 9, 10].

2.2. Benefits and limits of perioperative risk stratification

Cardiac risk stratification separates patients for vascular surgery into high-risk, intermediate and low-risk categories, adapting the management of perioperative therapy to their needs. Low-risk patients will be further investigated by completing noninvasive and invasive tests, while for high-risk patients, perioperative management primordially changes.

The major objective of CVR stratification is the reduction of perioperative global morbidity and mortality. Clarifying the patient's risk status allows the clinician as well as the surgeon to consent to a better informed patient. From a socio-economic point of view, reducing postoperative complications allowed to reduce perioperative care and treatment costs. The main impediment of perioperative risk stratification procedure is the duration, the cost and the number of investigational tests, which implicitly leads to postponing the intervention moment [4, 7, 8, 10]. And that could be done in elective surgery, but it seems to be quite difficult to be done in emergencies interventions.

2.3. Clinical elements of perioperative cardiovascular risk

2.3.1. Overview

Retrospective clinical studies have shown that a history of coronary artery bypass surgery (CABG), percutaneous transluminal coronary angioplasty intervention (PCI) or coronary angiography without significant lesions indicates a low risk for perioperative cardiac events. The risk is similar to that of patients without clinical signs of significant CAD. The term "protection" given by the presence of a coronary graft cannot be specified. Many studies in large groups of patients have shown the independent predictors of perioperative CVR: the history of MI, angina pectoris (AP), and ischemic ST-T changes on the electrocardiogram (ECG/EKG), as well as the clinical symptoms of congestive heart failure (HF) [9–11].

2.3.2. Several clinical risk assessment scores for postoperative cardiac events

The revised cardiac risk index (RCRI) is used by anesthesiologists and surgeons to assess the perioperative CVR in patients who undergo noncardiac surgery. Parameters included in the evaluation are age over 70 years, estimated risk of surgery, history or presence of IHD (MI or history of AP), congestive heart failure (HF), HT with signs of left ventricular hypertrophy (LVH), presence of Q waves or ischemic ST changes on resting electrocardiogram (ECG) cerebrovascular disease (CVD), the presence of DM (treated with insulin, additional risk) and renal failure (e.g., **Table 1**) [4, 12, 13]. The presence of more than one of these six independent predictors of cardiac complications following surgery is mandatory for further investigation. Patients who do not have active cardiac conditions are stratified into three groups by the RCRI: low (0 risk factor), intermediate (1–2 risk factors) and high (≥ 3 risk factors) [14, 15]. In a meta-analysis of 24 studies that reported the association of the RCRI with MACE or death in the hospital or within 30 days of surgery, the RCRI discriminated moderately well between patients at low versus high risk for cardiac events after mixed noncardiac surgery.

However, its performance was considerably diminished when it was used in patients who underwent vascular surgery and emphasized the necessity of development and validation of a suitable CRI for use in vascular surgery patients [14, 16, 17]. The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database derived from general and other specialty surgery patients have allowed the development of another risk model, in which five risk factors (basically the same from RCRI) were determined to be associated with MI/cardiac arrest following an operation [13]. In the VSG-RCI assessment (published in 2010 by Vascular Study Group of New England (VSGNE), additional

| Clinical risk factors | Clinical elements | Active cardiac condition | Clinical presentation |
|---|--|-----------------------------|---|
| History of ischemic heart disease (IHD) | Previous MI Previous positive result on stress test Use of nitroglycerin Typical angina pectoris ECG Q waves Previous PCI or CABG | Unstable coronary syndromes | Unstable or severe angina (CCS class III–IV) Recent MI (7–30 days) |
| History of compensated previous congestive heart failure (HF) | Previous pulmonary edema Third heart sound Bilateral rales Evidence of heart failure on chest radiograph | De-compensated HF | NYHA functional class IV worsening or new-onset HF |
| History of cerebro-vascular disease (CVD) | Previous TIA disease Previous stroke | Significant arrhythmias | High-grade atrioventricular block Symptomatic ventricular arrhythmias Supraventricular arrhythmias (including atrial fibrillation) with uncontrolled ventricular rate (HR > 100 bpm at rest) Symptomatic bradycardia Newly recognized ventricular tachycardia |
| Diabetes mellitus (DM) | With or without preoperative insulin therapy | Severe valvular disease | Severe aortic stenosis (mean pressure gradient > 40 mm Hg, aortic valve area < 1.0 cm ² or symptomatic) Symptomatic mitral stenosis (progressive dyspnea on exertion, exertional presyncope, or HF) |
| Renal failure | Creatinine level > 2 mg/dL | | |

Adapted from [4, 13]. CCS, Canadian Cardiovascular Society; MI, myocardial infarction; HF, heart failure; NYHA, New York Heart Association; HR, heart rate.

Table 1. Clinical risk factor to predict MACE and active cardiac conditions to be evaluated and to be treated before noncardiac surgery.

risk factors were introduced: CVRF (increasing age, DM insulin-dependent, HT, smoking), clinical features (presence of aortic aneurysm, peripheral arterial ischemic symptoms, CAD, congestive HF, chronic obstructive pulmonary disease, elevated creatinine, abnormal cardiac stress test), previous CV medication administered (β -blockers long-term therapy, antiplatelet, statins) and revascularization interventions (carotid endarterectomy, peripheral arterial bypass, endovascular/surgical interventions for aortic aneurysm). The RCRI predicted risk after carotid endarterectomy reasonably well, but substantially underestimated the other

procedures for low- and higher-risk patients. VSG-CRI risk model predicted more accurately the risk of cardiac complications in vascular surgery patients than the RCRI, which underestimated in-hospital cardiac events in patients undergoing vascular surgery and that new VSGNE index was more accurate than the RCRI in predicting postoperative cardiac event. It should be noted that in this recent study only 45% of patients were evaluated by stress myocardial scintigraphy, the accessibility of the method still being limited [13, 18].

Generally, the type and the conditions of planned surgery cannot be fundamentally changed and can influence the postoperative CVR of patients. Urgent, prolonged (more than 5 h) and long hemodynamic stress (in major vascular interventions, intraabdominal and intrathoracic surgery) increase the risk of perioperative cardiac events. Peripheral vascular procedures present the highest risk (13%); the incidence of postoperative CV events could reach 10–15% [4, 7, 19].

2.4. Noninvasive cardiovascular parameters (biomarkers, coronary artery calcification)

Cardiac biomarkers have been studied for years in prediction of CV long-term outcomes, but less so for preoperative prediction. The most important and evaluated four biomarkers troponinI (TNI), N-terminal brain natriuretic peptide (NT-BNP), cystatin C, and C-reactive protein (CRP) significantly affected the prediction of death from CV causes. The statistical significance increased when the four biomarkers were incorporated into a model with established risk factors [20]. From six risk markers of interest (coronary artery calcium (CAC), carotid intima-media thickness (IMT), ankle-brachial index (ABI), brachial flow-mediated dilation (BFMD), CRP and family history of CAD, at a median follow up of 7.6 years, the CAC (had the highest predictive value), ABI, CRP and family history of CAD were independently associated with incident CAD [21, 22]. The addition of the degree of stenosis measured with computed tomography coronary angiography (CTCA), the presence of significant coronary artery stenosis (>50%) and/or multivessel CAD in completion with the CAC value and the RCRI significantly improved the predictive model for postoperative CV events [23]. Addition of CTCA determines a slight improvement in discrimination for CV death or MI. When added to the RCRI, information from CTCA is five times more likely to overestimate risk in low-risk individuals than to identify a previously misclassified high-risk individual. Thus, current data do not support CTCA as a first-line preoperative screening test for CAD in PAD patients (e.g., **Table 2**) [4, 24].

High CRP levels are positively associated with PAD, independent of smoking, and multiple other cofounders, demonstrating the important role of inflammation in ATS. High levels of inflammatory markers would identify vascular surgery patients at increased risk for adverse events (graft failure, MACE) after lower extremity bypass surgery. Among patients with an elevated CRP (>5 mg/L) before surgery, major postoperative MACE occurred in 60%, compared with a 32% rate in those with a baseline CRP < 5 mg/L (**Table 2**) [25].

High preoperative NT-BNP or CRP are independent predictors of perioperative MACE in noncardiac surgery; the addition of these two markers to the RCRI improves its predictive power for adverse events. There is a statistically significant association between an elevated preoperative NT-BNP level and various CV adverse outcomes within 30 days of surgery (composite of cardiac death, nonfatal MI and atrial fibrillation). NT-BNP concentrations of 99.5 pg./mL predicted cardiac events and 448 pg./mL predicted cardiac death (all-cause

| Biomarker | Indication | Sensitivity | Specificity |
|-----------|---|-------------|-------------|
| NT-BNP | Obtain preoperatively in high surgical risk patients scheduled to undergo non-emergent vascular surgery | 75–88% | 62–100% |
| CRP | | NA | NA |
| TnT | | 97% | 54% |
| CAC | Evidence is currently lacking to recommend preoperative risk stratification with routine measurement | 79% | 61% |

Adapted from [13].

Table 2. Indications and characteristics of various markers in preoperative cardiac risk stratification.

mortality in the short-, intermediate- and long-term postoperative periods). Over the threshold value of 448 pg./mL, NT-BNP had a positive predictive value of 100% and suggested that, if a preoperative NT-BNP level is in this vicinity, then it may be preferable to delay or cancel the procedure. Patients with high preintervention values of both CRP and NT-BNP are 10.6 times more likely to experience MACE than patients with normal CRP and NT-BNP values. Patients with a postoperative BNP ≥ 245 pg./ml or NT-proBNP ≥ 718 pg./ml had a significantly elevated risk for 30-day CV mortality, nonfatal MI, and cardiac failure. In addition, these postoperative elevations are able to predict long-term outcomes (i.e. ≥ 180 days after surgery) (e.g., **Table 2**) [26, 27].

Similar to postoperative troponin (Tn) levels, the current data for postoperative BNP suggest that it is the absolute postoperative threshold, rather than the increase in the BNP between the preoperative and postoperative period, that is associated with postoperative morbidity and mortality. Natriuretic peptides act as a cumulative marker of myocardial damage sustained during the perioperative period, possibly as a result of ischemic injury, volume overload or both. However, it remains unclear what the exact temporal relationship between postoperative BNP and Tn elevations is. In certain circumstances, it is possible that BNP elevation may precede Tn elevation, as may occur during fluid overload. In such cases, BNP elevations may identify patients at risk of subsequently developing myocardial injury and postoperative Tn elevation. Identification of patients at risk may provide a window for therapeutic intervention. It is likely that the more common scenario is postoperative BNP elevation that occurs together with, or shortly after, a postoperative Tn elevation. In these cases, elevated postoperative BNP may reflect the severity of myocardial injury and may prognosticate short- and long-term outcomes (e.g., **Table 2**) [26, 27].

In the perioperative period, it is clear that any Tn elevation is associated with an increased risk of death, even in the absence of a defining features (e.g., ischemic symptoms and ECG changes, evidence of MI on echocardiography) necessary for the diagnosis of MI. Owing to the effects of anesthesia, and widespread use of narcotics, the majority of perioperative ischemic events are clinically silent. In the Perioperative Ischemic Evaluation (POISE) trial, 65% of patients with a perioperative ischemic event did not experience ischemic symptoms [28]. The risk of death at 30 days was 9.7% in patients with a symptomatic MI and 12.5% in patients with an asymptomatic MI. Thus, the universal definition of MI may not be as sensitive in the perioperative period to detect ischemic events that are associated with poor, intermediate and long-term outcomes.

An isolated peak cardiac biomarker elevation (preferably Tn) with or without correlation with ischemia may be the most sensitive tool to detect perioperative ischemic events that are clinically important [29]. A peak postoperative TnT (>0.02 ng/ml) measured within the first 3 days after surgery is the strongest predictor of 30 days mortality and explained 41.8% of the deaths in population [30]. The current data suggest that the absolute postoperative threshold of Tn is a stronger independent predictor of postoperative MI and intermediate-term survival than the increase in the Tn level between the preoperative and postoperative period. Current data therefore suggest that a raised preoperative Tn level may identify patients who are at risk of increased short-term CV morbidity, mortality and long-term mortality (1 year after surgery, but no longer) due to his high sensitivity, but it may be an inappropriate additional test for improving preoperative risk stratification due to its poor specificity (**Table 2**) [26].

Preoperative cardiac biomarkers (especially BNP and Tn) evaluation adds incremental value to the risk stratification (by RCRI) for MACE (i.e. MI, pulmonary edema, CV death) and for in-hospital mortality [26]. While the body of evidence for the use of cardiac biomarkers for risk stratification is not extensive, the utility of assessing certain biomarkers in high-risk vascular surgical patients is suggested. A pharma-economic analysis of routine Tn surveillance in all patients who fulfilled the VISION study, based on a 25% relative risk reduction for vascular mortality and perioperative MI following the introduction of statin and aspirin therapy in high-risk patients who were Tn positive, found routine Tn surveillance to be cost-effective [30, 31].

2.5. Cardiac evaluation

2.5.1. Investigation of inducible myocardial ischemia

An ECG should be obtained in all moderate to high-risk vascular surgery patients and confers well-accepted prognostic information [11]. The two most common forms of stress testing are exercise ECG (not often feasible due to debility of many vascular surgery patients) and exercise or pharmacologic stress testing combined with imaging (e.g. dobutamine/dipyridamole stress echocardiography (DSE) and myocardial perfusion imaging scintigraphy (MPI)). There is an association between a positive test (ST depression) and the likelihood of postoperative cardiac complications [15]. Outpatient ECG monitoring is relatively affordable, but requires manual interpretation from the investigator, being time-consuming. The automatic or manual interpretation of the ischemic score depends on the correctness and the accuracy of the recorded ECG path. At a very variable percentage of patients (12–73%), recording irregularities are an obstacle to correct interpretation [32]. A study involving both noncardiac (general and vascular) surgery patients has not shown benefits in performing this type of ECG screening in preoperative monitoring [33]. Other studies focused only on patient groups in vascular surgery demonstrated both the positive and negative predictive value of the results of ECG monitoring of silent ischemia, but under the significance of the values provided by MPI. However, the combination of the two tests does not increase the predictive value [7, 28]. Ischemia and/or intra- and postintervention endocardial lesions (T-negative or ST-segment elevation) are more predictive for perioperative cardiac events (up to 85% of perioperative MI may also be preceded by episodes of ischemia-lesion on ECG), and the prognostic value increases if the cardiac Tn serum level reaction is associated [7].

2.5.2. Noninvasive clinical imaging tests for cardiac perioperative risk assessment

The American College of Cardiology (ACC) and the American Heart Association (AHA) as well as European Society of Cardiology (ESC) introduced guidelines to detect and manage perioperative cardiac risk and to prevent cardiac complications after vascular surgery [15, 19]. For preoperative noninvasive stress testing (NIST), the guidelines recommended that patients with active cardiac conditions should be evaluated and treated. NIST may be considered for patients with high or intermediate risk, if it will change management.

NIST include left ventricular (LV) function evaluation and inducible myocardial ischemia through ECG holter monitoring, ECG, echocardiography or scintigraphy coupled with exercise trial or pharmacological stress methods (**Table 3**). These noninvasive assessment tests should be able to detect cardiac abnormalities not revealed by clinical scores. The simple observation of some cardiac abnormalities does not necessarily means augmenting perioperative cardiac risk [32, 33].

NIST requires logistical and financial support. The PAD patients have less accessibility to MPI when compared to CAD patients. The interpretation of the investigation results in these studies is quite variable, which decreases the predictive accuracy. The explanations of these variable interpretations could be related to differences between the definition of fixed objectives, the follow-up strategies and the heterogeneity of the evaluated groups. Even though NIST are available and can be performed, they do not provide a “guarantee” for the perioperative period, as long as postoperative events have multifactorial causes that could not be accurately predicted [32, 33].

The perioperative period is characterized by myocardial ischemia due to hypercoagulability, increased consumption and oxygen demand, caused by catecholamine discharges, pain,

| Tests | Prerequisites | Recommended indications |
|---------------------------------|---|--|
| Electrocardiogram (ECG) | None in prior 3 months Perioperative risk death/MI >1% | CAD, PAD, CVD Significant arrhythmia Structural heart disease Document baseline* |
| Echocardiogram | Potential to change management Not for prognosis or as surrogate for exercise capacity | HF with worsening symptoms Dyspnea of unknown origin Clinical suspicion of structural heart disease HF or structural heart disease and no prior test within 1 year [†] |
| Non-invasive stress test (NIST) | Perioperative risk death/MI >1% Elevated risk or known CAD Potential to change management | Unable to perform >4 METs based on subjective assessment or validated tool |

Adapted from [15].*Uncertain utility may be considered. CAD indicates coronary artery disease; CVD, cerebrovascular disease; HF, heart failure; MET, metabolic equivalents; PAD, peripheral arterial disease.

Table 3. Recommendations for preoperative cardiac investigations in vascular surgery.

anemia, anesthetic and surgical stress. Noninvasive clinical screening (via ECG, cardiac, carotid-vertebral and peripheral arterial ultrasound and where possible by NIST) coupled with cardiac Tn serum levels dosing increases the safety of postoperative evolution and improves the prognosis [34, 35].

Although available in many cardiology centers, stress tests could not be performed systematically in all presurgery intervention patients. Due to the pain caused by critical leg ischemia (CLI), 30–70% of PAD patients could not perform the exercise test; they are added to those who could not do it the same because of obesity, degenerative diseases of the hip and knee or postvascular sequelae. In this context, the results of the effort tests were inconclusive in several studies [7, 36]. For these patients, stress tests using pharmacological agents that increase consumption and demand for oxygen represent an alternative for detecting coronary ischemia. These stress tests are dipyridamole-coupled ECG, thallium myocardial scintigraphy and echocardiography coupled with dobutamine or dipyridamole. The presence of “reversible” segmental infiltration defects fixation, or alterations in segmental parietal kinetics has a predictive sensitivity with positive value greater than the presence of “fixed” defects (e.g., **Table 4**) [28].

Stress echocardiography with dobutamine (DSE) (or dipyridamole) has the theoretical advantage for evaluating both segmental ventricular parietal kinetics and altered LVF as determined by inducible myocardial ischemia. Most echocardiography stress studies conducted on vascular surgery patients suggested that DSE had a good negative predictive value, but the positive

| Non-invasive stress tests | Advantages | Disadvantages |
|---|---|---|
| Stress ECG | Most affordable of the common testing modalities Widely available | Unable to use in many vascular surgery patients that suffer from claudication and poor functional capacity, as target heart rates cannot be achieved. No additional information about cardiac function that can be seen with cardiac imaging is provided |
| Stress echocardiography (dobutamine) DSE | If pharmacologic stress testing is necessary, may be preferred in patients with known bronchospastic lung disease or significant carotid stenosis. Preferable choice when any additional information about left ventricular function and/or valvular heart disease is desired. Shorter testing time with results available sooner. No ionizing radiation. | Dobutamine has the ability to induce arrhythmias and increases in blood pressure and/or myocardial contractility; avoid in patients with known arrhythmias and symptomatic or large aortic aneurysms |
| Myocardial perfusion imaging or scintigraphy (MPI with dipyridamole/thallium) | If pharmacologic stress testing is necessary, may be preferred in patients with known arrhythmias and symptomatic or large aortic aneurysms. Preferable for the assessment of myocardial viability in patients with known left ventricular dysfunction, where the extent and severity of inducible ischemia is of importance. | Dipyridamole may induce bronchospasm or decreases in blood pressure; avoid in patients with bronchospastic lung disease or significant carotid stenosis. Longer testing time and delay for results to be available. Ionizing radiation. Failure to detect global ischemia |

Adapted from [13].

Table 4. Comparison of noninvasive stress testing modalities.

predictive value was moderate. This does not increase the discriminatory value of the clinical criteria and does not change the appropriate risk group ranking after the RCRI score. In patients with one or two positive cardiac markers, the negative value of DSE was confirmed by the absence of postoperative cardiac events, while a positive result was followed by an incidence of up to 5% of cardiac events postoperative (MI, sudden death), so preoperative DSE offered no incremental value for determining postoperative adverse cardiac outcomes [7, 28, 37]. The second multicenter Dutch Echocardiographic Cardiac Risk Evaluation study showed no difference between the intermediate risk patients with positive NIST results group and negative results group in cardiac death or MI at 30 days after surgery (1.8 vs. 2.3%) (e.g., **Table 4**) [38].

Myocardial perfusion imaging (MPI) scintigraphy combined with pharmacokinetic stress test and EKG with dipyridamole are most used today in centers that benefit from this availability. Despite the initial expectations of better characterization and stratification of patients, especially from groups initially assessed as having intermediate or low risk for postoperative cardiac events, the results were not what they expected. Stress MPI has a relatively high sensitivity for the prediction of cardiac complications, but the specificity of this method is less satisfactory. Preoperative MPI has a high negative predictive value, but it has not proven to be sufficiently sensitive, and the benefit of MPI was unproven in low-risk patients and probably not cost-effective. There was no association between reversible defects on dipyridamole stress MPI and adverse cardiac events in moderate-risk patients undergoing elective vascular surgery. Based on the scintigraphy results, previously patients in the low-risk group switched to the intermediate risk group, but the rate of postsurgery intervention cardiac events do not change significantly, indicating the limited positive predictive value of these tests and proving no independent prognostic value superior to clinically stratified risk [7, 28]. Information about myocardial perfusion does not accurately predict adverse cardiac outcomes (e.g., as prolonged myocardial ischemia, MI, congestive HF and severe ventricular tachyarrhythmia) following univariate and multivariate analyses. The best correlates of cardiac complications were documented evidence of CAD and age greater than 65 years (e.g., **Table 4**) [12, 24, 39].

Two important questions remain unanswered related to the patient at risk: which stress test is best for which patient and what interventions outside of best medical management are of benefit to reducing perioperative ischemia events. No large head-to-head analyses of DSE versus MPI have been performed, although two well-known meta-analyses have compared the different modalities. DSE showed a positive trend toward better diagnostic performance than the other tests. Relative to MPI, DSE had a similar sensitivity, but significantly greater specificity (70% vs. 49%) (e.g., **Table 3**). Comparison with summary receiver operating characteristic analysis between all modalities revealed a trend toward better performance with DSE, but this was only significant when compared with MPI. DSE has better negative predictive value characteristics than MPI. In addition, a moderate-to-large perfusion defect by either DSE or MPI predicts postoperative MI and death, but DSE is slightly superior to MPI in predicting postoperative cardiac events [24, 39].

A typical pattern has emerged with stress testing for risk stratification prior to surgery; the positive predictive value is usually very low, and the negative predictive value is typically high. Routine preoperative NIST is not necessary in all patients undergoing revascularization for CLI, especially for patients in the low-risk group and for those undergoing endovascular

treatment [40]. Widespread use of NIST in assessing the risk of perioperative CV complications remains controversial due to the low predictive value that affects the accuracy of the information. Therefore, the implications for CV risk stratification remain unclear. Even with the reported subtle differences between MPI and DSE, the fact remains that current guidelines do not distinguish between one or the other NIST for the preoperative workup of surgical patients. In line with current joint guidelines, we would recommend that surgeons take into account the availability and expertise in interpretation of the varying modalities and patients specifics at their respective institutions when deciding which test to obtain (e.g., **Figure 1**) [13]. A reversible defect on NIST is considered a predictor of postoperative MACE, and possible revascularization might be recommended. Some authors have suggested coronary angiography as a routine screening test, due to the significant prevalence of coronary involvement in vascular patients. Because coronary angiography is an invasive method with a risk of up to 0.05%, it was not used in studies as a routine examination in perioperative RCV assessment in noncardiac surgery patients. Last data suggested perioperative MI is quite common in

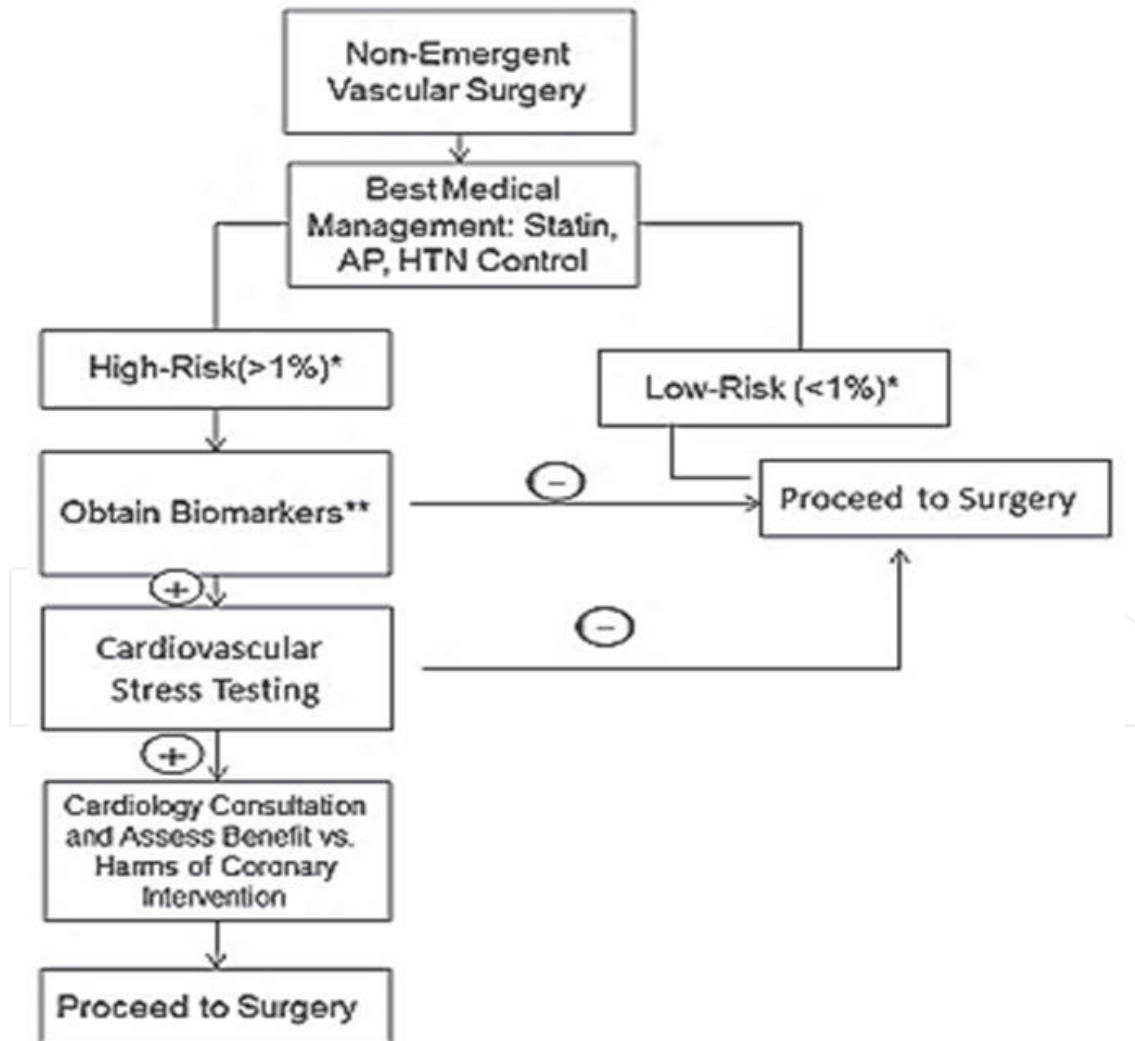


Figure 1. Suggested algorithm for preoperative optimization in vascular surgical patients. AP—Antiplatelet therapy; HTN—Hypertension. Adapted from [13].

nonvascular surgical patients, vascular patients being relatively protected by cardiovascular medication previously administered, and that postoperative events such as anemia play a major role in postoperative MI [41].

2.5.3. Cardiac ultrasound evaluation in perioperative assessment of PAD patients

With cardiac ultrasound (US) (or echocardiography), we can evaluate both the function and the morphology of the heart. The presence of LVH is associated with an increased risk of CV morbidity and all-cause mortality, which emphasizes the importance of diagnosis. The quantitative evaluation of the LV systolic function by LV ejection fraction (LVEF) is a simple and specific predictive index in relation to clinical utility [42]. End-systolic LV volume is an independent predictor of survival in CAD and LVEF has prognostic value for survival in post-MI patients. The presence of diastolic dysfunction represents an early indicator of LV function impairment. Although that high mortality of PAD patients was mainly attributable to coexisting coronary or cervical arteries disease, the prevalence of US abnormalities in patients with peripheral arterial ischemia was not systematically studied. Asymptomatic LV dysfunction is predictive for short- and long-term perioperative CV events in vascular surgery patients; therefore, the echocardiogram should be routinely performed in surgical patients for stratification of CV risk, even in the absence of HF symptoms [43].

The prevalence of CVRF (smoking, DM, dyslipidemia, HT) in PAD patients causes, in addition to peripheral arterial lesions, coronary arteries and myocardial involvement with ischemic, hypertensive and/or diabetic heart disease, aortic and mitral valve calcifications and sometimes myopathic evolution through dilated cardiac disease [44–46]. In PAD patients were found high prevalence of clinically significant cardiac US changes (61.6% vs. 35.3%), especially related to the LV dysfunction and the presence of aortic stenosis (AS) compared to patients without PAD. The presence of PAD is shown to be an independent predictor of LVEF <50%. In PAD patients, MI and HF are the main causes of mortality [47]. PAD patients develop a significantly higher degree of LVH compared with patients with the same means BP but with no PAD. By cardiac US examination, LVH was found in 75% of patients with HT, CAD and PAD and in 46% of patients with HT and CAD but without PAD, respectively. LVH was found in 93% of PAD patients, with ABI <0.6, and 62% of patients with ABI between 0.6 and 0.9 [43, 47–49]. PAD patients with CLI have higher CV morbidity than stable PAD patients. US evaluation is useful in defining the group of patients with low CV risk, in which can be performed with relative safety the revascularization of the limb by interventional/surgery procedures. In the case of the intermediate risk group, additional CV risk assessment tests are required [44–50].

2.6. Perioperative cardiac management strategies

2.6.1. The impact of perioperative risk stratification in the management of PAD patients

Approximately 10% of general surgery patients are included in the high-risk surgical perioperative group after the standard clinical and noninvasive assessment. But for vascular surgery patients, the percentage of high-risk patients may increase by 10–20%. From these, 5–10% may be eligible for myocardial revascularization (PCI or CABG) [7]. In vascular surgery patients in intermediate or low perioperative risk groups, it is advisable to perform NIST. It is possible,

however, that NIST does not provide additional predictive perioperative risk elements. Also, these tests do not provide information about cerebrovascular ischemic risk, derived from cervical arterial lesions, almost equally founded as coronary involvement in vascular surgery patients [7, 29]. Clinical judgment is important in assessing the balance between the relative urgency of identified cardiac and noncardiac surgery problems. A relatively small proportion of surgical patients require urgent preoperative treatment of cardiac conditions: congestive HF, life-threatening arrhythmias or acute coronary syndrome (ACS) (recent MI with significant evidence of ischemic risk or unstable, severe AP). However, there are situations in which the surgical situation with an important vital risk imposes the operative decision, even under an incomplete cardiac evaluation [7, 29].

2.6.2. Impact of coronary revascularization decision on noncardiac surgery patients

Patients in noncardiac surgery are at risk of major perioperative cardiac events (sudden cardiac death, cardiorespiratory arrest, MI). In these patients, the in hospital mortality rate is among 15–25%. Patients who underwent a postsurgery intervention cardiac arrest have a mortality rate in the hospital up to 65% and represent a risk factor for cardiac death within the next 5 years postoperatively. Perioperative MI is an independent risk factor for the risk of CVD and the increase incidence of a new MI over the next 6 months postoperatively [7]. This is why the concern is both for the most discriminatory assessment of noncardiac surgery patients in different risk groups, as well as for finding the best prevention strategies (interventional, medical, etc.) for perioperative CV events. By preoperative coronary angiography, the prevalence of CAD ranged between 50 and 80% and is dependent on the specific distribution of the PAD. It is also clear that periprocedural myocardial ischemia, even non-ST segment MI and Tn leaks, confer a significant 26–55% decreased survival through 5 years, supporting the impetus for careful patient preparation [13].

In retrospective studies, for both vascular and nonvascular surgery patients, the “protective” effects of coronary revascularization in reducing perioperative MACE were controversial [7]. “Prophylactic” preoperative myocardial revascularization of significant lesions could reduce perioperative coronary complications in patients with unstable CAD (ACS) and high CVR. There is a significant difference in mortality among high CVR patients who underwent coronary revascularization prior to noncardiac surgery (0.9%) compared to high CVR patients who did not undergo coronary revascularization procedures (2.4%) [7]. Coronary revascularization performed prior to noncardiac surgery has as a primary objective the reduction of CV mortality in the long-term outcome and as a secondary objective, the reduction of CVR in patients with high coronary risk: unstable refractory AP, left main coronary artery stenosis, coronary multivessel significant lesions, including anterior descendence artery (ADA) and altered LV systolic function. Patients who underwent myocardial revascularization before noncardiac surgery had a lower rate of long-term postoperative cardiac events (up to 5 years after noncardiac surgery). The lowest incidence of CV events in long-term outcome after noncardiac vascular surgery was observed in the group of patients with PCI versus revascularized patients by CABG [50, 51].

The Coronary Artery Revascularization Prophylaxis (CARP) trial showed no difference in the rate of postoperative MI (defined by elevated Tn level) (12 vs. 14%) in 30-day mortality, and MACE and mortality at 2.7 years (22 vs. 23%) in patients scheduled for vascular surgery

with coronary artery revascularization before surgery compared with patients with no revascularization before surgery, but there was a statistically significant survival benefit at 4 years (87% vs. 70%) that persisted up to 8 years. The CARP trial focused on patients who had stable CAD and those without left main coronary disease or significant valvular heart disease. Time to vascular surgery was significantly longer in the revascularization group [52, 53]. Although this evidence is encouraging, caution is warranted. Of note, excellent adherence with cardio-protective drugs was documented. At least one large database review of nonvascular surgical patients concluded opposite findings, suggesting a benefit of revascularization, so the controversy remains open [54].

A prospective study included patients evaluated before vascular surgery by MPI to complete the coronary angiography indication followed by myocardial revascularization by PCI and/or CABG. The results of MPI have increased the rate of coronary revascularization from 4.1% to 14.7%, without significantly improving postoperative MACE (MI, sudden cardiac death in the first 30 days after surgery intervention). However, it should be noted that the patients included in the study had one or two coronary vessels significant lesions with preserved LV systolic function and with optimal medical therapy. Patients with CAD and with severe impairment of LV systolic function, unstable AP and AS were not included. In vascular surgery patients having three coronary vessels significant lesions, there was a slight decrease in the incidence of perioperative cardiac events in myocardial revascularized patients before vascular surgery (43%) versus those treated by standard medical therapy (33%) [7]. Therefore in the coronary revascularization decision made prior to noncardiac surgery, three elements should be considered: the coronary risk of the patient, the risk of bypass surgery and the risk of noncardiac surgery. These results do not suggest that there are benefits in prophylactic coronary revascularization in patients with stable CAD regarding the short-term evolution after vascular surgery intervention [50, 51].

One of the main objectives of preoperative cardiac evaluation should be the identification of patients with high-risk coronary anatomy, amenable to revascularization, by an appropriate and discriminatory noninvasive/invasive cardiac evaluation. Once identified, the next question that needs to be answered is what the best revascularization strategy would be, CABG or PCI? The indication and the accomplishment of PCI before noncardiac vascular surgery are directed toward patients with high coronary risk prior to noncardiac surgery. PCI has the advantage of a low periprocedural risk (0.01%) and avoids the stress of CABG. The disadvantage of the PCI is that some lesions could not be accessed by angioplasty and should be resolved later by CABG [7, 50, 51]. Long-term outcomes appear to be better in patients undergoing CABG when compared to PCI, but incomplete revascularization after PCI, impact of stent-related complications and progressive occlusive CAD should be considered while evaluating the disadvantages of PCI over CABG. The heightened thrombogenic potential of newly implanted stents and prothrombotic state induced by the surgical stress increase the risk of in stent thrombosis. Premature discontinuation of antiplatelet therapy in patients with bare metal stents (BMS) or drug eluting stent (DES) is associated with a high rate of stent thrombosis and perioperative mortality. Elective surgical procedures that carry a potential for increased perioperative bleeding should be postponed until a minimum course of dual antiplatelet therapy (DAPT) has been completed. In patients presenting for emergency

noncardiac surgery after stenting, consideration should be given to the risk of interrupting thienopyridine antiplatelet therapy compared with the risk of bleeding from surgical procedures, to continuation of aspirin in the perioperative period and to restarting thienopyridine as soon as possible [4].

Coronary revascularization is not recommended before surgery for patients with stable CAD in both ACC/AHA and ESC guidelines for the management in patients undergoing noncardiac surgery and it is recommended only in circumstances where it would be indicated even in the nonoperative setting. In general, CABG is recommended for left main disease, triple-vessel disease, complex anatomy or high-risk comorbidities (e.g. diabetes). Given the uncertain benefits of preoperative PCI for improving outcome after noncardiac surgery, current guidelines suggest consideration of PCI only for patients with left main disease whose comorbidities preclude CABG and for patients with unstable CAD (e.g. ST-elevation MI, non-ST-elevation ACS) who are appropriate candidates for emergency or urgent revascularization. If revascularization by PCI is considered, BMS is preferred over DES for vascular surgery patients given the time pressure to proceed with vascular surgery [15, 19].

The additional risk of anesthesia and intervention stress in noncardiac surgery patients who also have simultaneous cardiac problems should be noted. Even under these conditions, the idea of “prophylactic” coronary revascularization, in all cases, could not be accredited to patients who undergo vascular surgery, on the premises that they have multisite arterial lesions and therefore they also have coronary ATS [36]. Probably only prophylactic coronary revascularization of significant lesions in confirmed CAD could prevent perioperative complications in noncardiac surgery patients [8].

In the Reduction of Atherothrombosis for Continued Health (REACH) Registry, more than 50% of PAD patients had a concomitant CAD [2]. This means that modification of ATS risk factors is important in the long term and perioperative CVR is high in the short term [55]. Patients with high CVR should benefit from a sustained medical treatment and control of CVRF, considering the context of a possible myocardial revascularization intervention by PCI or by CABG, as well as the perspective of a future vascular surgery. Patients at risk of having CAD (regardless of the risk group) should be given control of blood pressure, serum cholesterol (via statins), cardiac compensation (angiotensin converting enzyme inhibitors (ACEI), diuretics) and arrhythmia (β -blockers, amiodarone). Numerous scientific studies have demonstrated the beneficial role of β -blockers, antiplatelets, ACEI and statins in reducing perioperative CV mortality in patients undergoing noncardiac vascular surgery. Statins and antiplatelet therapies are also involved in ATS plaque stabilization and improvement of endothelial dysfunction [56–58].

2.7. Cervical arterial ultrasound evaluation in perioperative assessment of PAD patients

With the increase in the use of cardiac and arterial ultrasound (US) in assessing the patient with suspected or known PAD, the diagnostic and prognostic accuracy of these explorations has increased, the sensitivity and specificity of US detection cervical arterial lesions may reach 95%. Noninvasive US methods can also be applied to a wide range of patients including those

at high risk for myocardial stress testing. With respect to CVD, a history should ascertain any previous stroke or transient ischemic attack, as well as detail the associated presentation and deficits. It is important to document the etiology to distinguish ATS carotid stenosis from cardio-embolic disease [44].

Carotid intima media thickness (IMT) measured by US is a noninvasive predictive marker independent of the onset, progression and extension of ATS disease, demonstrated in numerous studies. The increase in carotid IMT is associated with a higher incidence of coronary events and multisite ATS lesions [59]. Increased IMT has common risk factors with the onset and progression of coronary and cerebrovascular ATS lesions (HT, DM, dyslipidemia, smoking) [60, 61]. Furthermore, increased IMT demonstrates good reproducibility for both the progression and regression of ATS disease and has been validated as a vascular marker of ATS evolution in numerous clinical trials. At the same time, invasive studies have shown that treating CVRF for CAD can also significantly reduce progression of IMT [62, 63]. Carotid and femoral IMT thickening are associated with the presence of CVRF; the occurrence of CV events is an indicator of the presence of PAD. It has been shown that these risk factors and CV events are significantly linked to increased carotid and femoral IMT. The treatment of CVRF is associated with a decrease in the progression of IMT thickening, parallel to the reduction of CV events and an improvement in the symptoms associated with PAD. This finding is particularly evident in the context of hypolipemiant therapy. IMT, as an additional predictor of CVR, may influence the decision of therapeutic intervention by medication [59–63].

Significantly elevated IMT values were seen in PAD patients at femoral artery, simultaneous with carotid artery, which allowed the conclusion that the presence of PAD is associated with morphological alterations and dynamic variations of both the femoral and the carotid artery walls. DM patients with PAD had a significantly higher IMT at the carotid bifurcation and at the distal common carotid artery, relative to those without PAD. Thus, carotid IMT may be a marker of ATS with different localizations in patients with type 2 DM and reflects morphological and hemodynamic similarities between arterial beds [64]. Today, IMT is one of the most commonly used parameters of noninvasive assessment of CV-ATS risk. In the initial stages, clinical latency of ATS, the increase of carotid IMT over normal value, often is an indicator of the asymptomatic arterial ATS lesions as well as an accompanied predictor for the increased risk of future CV events in already symptomatic arterial ATS territories [1, 65]. The amount of carotid IMT in PAD patients is correlated with body mass index (BMI), ABI, serum LDL-cholesterol and the number of arterial cervical ATS plaques. These results support the hypothesis that ATS is a systemic, generalized disease, leading to functional and structural changes in each of the segments of the arterial system, as confirmed by many other studies that described the concomitant occurrence of carotid, coronary and peripheral arterial ATS disease. Up to 81% of PAD patients with increased IMT had angiographic coronary artery lesions, while 57% had carotid ATS plaques. Therefore, there is a statistically significant correlation between increased carotid IMT and the severity of CAD and also the presence of carotid ATS plaques and PAD clinically manifested which are positive predictive factors for the presence of CAD [1, 65].

PAD patients had advanced cervical arterial ATS lesions expressed both by a higher IMT and an increased prevalence of ATS plaques. Stenotic and occlusive ATS is a systemic phenomenon commonly coexisting in several arterial territories (coronary, carotid, peripheral

arteries), often symptomatic in one of the arterial areas and asymptomatic in other affected arterial areas [44–46]. There are fewer studies that investigated the lesions in the cervical arterial system in patients with PAD, compared to the large number of studies investigating the coronary-carotid relationship [65]. Noninvasive vascular imaging, especially CV ultrasound, plays a particularly important role in the carotid evaluation system, and in some aspects (the morphological characterization of the ATS lesion and the possibility of analysis in multiple “nonstandardized” incidences) is superior to conventional angiography allowing accurate measurement of the functional diameter and the lumen area of the vessel, precise localization and dimension (thickness/length/extension and volume) of the ATS plaque, the ecostructure and the surface characterization of the ATS plaque and defining the type of vascular remodeling. Thickness, ecogenicity and endoluminal surface of the ATS plaque are the first features related to a possible instability characterized by the US assessment of vascular lesions [67, 68].

There are studies that argue that US technique overestimates the severity of carotid stenosis compared to angiographic assessment, but these results depend on the US way of quantifying stenosis. The two-dimensional US combined with color and pulse doppler modules generally leads to superimposable results with angiographic quantification [68–71]. Carotid angiography is indicated in selected cases and, particularly in cases where US is difficult to perform and poses diagnosis problems, shows particular aspects or atypical pathological pathways. Angiography visualizes intracranial circulation, not quite accessible to extracranial US (even transcranial doppler), which delivers indirect and segmental information related to cerebral circulation, which may present morphological and trajectory abnormalities. Information on the patency of intracranial collateral supply is important in the prognosis of carotid occlusion. Carotid angiography, in this case, helps to diagnose a possible subocclusive carotid stenosis, which would make the patient a candidate for a probably invasive solution [44–46, 66–71].

3. Conclusions

Patients with PAD undergoing elective vascular surgery have a high prevalence of coronary and cerebrovascular ATS with associated comorbidities (DM, renal failure, anemia) and are at an increased risk of perioperative death and MACE (MI or stroke). The management of patients with PAD referred to high-risk vascular surgical procedure for intermittent claudication, CLI or expanding abdominal aortic aneurysm requires risk stratification, optimization of medical therapies and limited use of cardiac imaging prior to surgery. Preventive coronary revascularization in patients with stable CAD, prior to the vascular operation, with the sole intention of mitigating the risk of CV complications in the perioperative period, is not effective and may be associated with significant bleeding and thrombotic risks, in particular, if stents are used. The patient, surgeon and anesthesiologist can be initially informed about the risk of surgery using modern preoperative risk indices (RCRI, NSQIP, VSG-CRI calculator). Modern biomarkers, such as BNP and high-sensitivity Tn assays, are likely to play a more substantial role in preoperative assessment in the future, but for now they are indicated for high-risk patients. A strategy of universal use of cardiac Tn in the perioperative period for active surveillance of myocardial ischemia may be more reasonable and cost-effective than the current standard of care and widespread use of cardiac imaging prior to high-risk

surgery. An elevated cardiac Tn after vascular surgery is recommended and predictive to detect perioperative ischemic events associated with a long-term mortality risk. If the cardiac biomarkers are negative and medical therapy is thought optimized, proceeding with the surgery seems safe. If the cardiac biomarkers are positive, NIST with either DSE or MPI is recommended (particular attention to whether it has potential to change management), taking into account specific patient characteristics that would afford benefit from one modality when compared to another. If the NIST is positive, then a cardiology consultation should be obtained with the appropriate preoperative steps and interventions taken to optimize the patient for their procedure. In general, preoperative coronary revascularization has a limited role, being reserved for the same indications as in routine circumstances. For the most part, chronic CV medications, such as aspirin, ACEI, ARBs and β -blockers, should be continued, but the decision should be individualized to each patient's circumstances. Ideally, thienopyridine antiplatelets therapy should be held before surgery, aside from cases of recent coronary stenting, where expert opinion should be sought. Using clinical risk assessment with biomarkers may decrease further expensive testing and might clarify, optimize risk stratification and indicate whether abnormal cardiac biomarker therapies will change outcomes [71, 72].

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