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ORIGINAL ARTICLE

Major adverse cardiac events in vascular surgery patients with peripheral arterial disease

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Summary

Introduction: Major adverse cardiac events (MACE) are the primary cause of morbidity and mortality in patients undergoing vascular surgical procedures. This is why it is essential to understand the relationship between coronary artery disease and peripheral arterial disease. In this paper, we aimed to determine predictors and risk factors related to the occurrence of MACE in patients undergoing vascular surgery for peripheral arterial disease.

Material and Methods: This is a retrospective study of 310 in-hospital patients treated at a high-volume vascular centre. The outcome was classified through the three-point MACE (myocardial infarction, stroke and cardiovascular mortality).

Results: We found that the majority of initial MACE happened in patients with aortobifemoral bypass surgery compared to other types of reconstruction (p=0.009). No significant correlation was established between the procedures performed and the short-term primary outcome. In the initial period, MACE was detected in 14 (5.8%) patients. Among them, six (1.9%) experienced a myocardial infarction (MI), three (1%) had a stroke, and five (1.6%) died within the first 30 days. All deaths were linked to cardiac ischemia, which ultimately culminated in cardiogenic shock and subsequent death. Short term MACE was observed in 2 (0.6%) patients both of whom had an MI.

Conclusion: Major vascular surgery in patients with coronary artery disease is a highly morbid procedure and perioperative MACE places them at a significantly high risk of mortality. Early detection of coronary heart disease and preoperative optimization can play a major role in reducing the risk of MACE.

Keywords: peripheral arterial disease, coronary artery disease, MACE, myocardial infarction, stroke

INTRODUCTION

Atherosclerosis is a progressive and diffuse inflammatory disease characterized by the accumulation of lipids and fibrous elements in the arteries (1). The accumulation of these metabolic products and a subsequent inflammatory response leads to the narrowing of the arterial blood vessels and reduced oxygen supply to the tissues (2). This can lead to different clinical manifestations depending on the involved vascular beds (3–5). Both coronary artery disease (CAD) and peripheral arterial disease (PAD) represent a manifestation of atherosclerosis with coronary complications being the primary cause of postoperative morbidity and mortality in patients undergoing surgical treatment for PAD (6,7). Although it is commonly assumed that patients with severe PAD have concurrent and severe CAD as well, the prevalence of significant CAD in patients with severe PAD varies widely, with figures ranging between 30% and 90% (7).

Every other inhabitant of the Republic of Serbia dies from cardiovascular disease. Compared to 2020, when mortality from heart and blood vessel diseases was 801.6 per 100,000 inhabitants, in 2021 the mortality rate increased to 828.3 per 100,000 inhabitants (8). With an ever-ageing population, we can expect a further increase in morbidity and mortality of cardiovascular diseases in the following decades.

Major adverse cardiac events (MACE) are used as composite outcomes in randomized controlled trials and observational studies (9). According to the United States Food and Drug Administration and European Medicines Agency, the three-point MACE outcome consists of acute myocardial infarction (AMI), stroke, and total cardiovascular mortality (10). Furthermore, four-point MACE and five-point MACE outcomes are used as well, adding hospitalization for unstable angina or revascularization procedures and heart failure (9,11).

It is essential to understand the relationship between CAD and PAD since MACE are the primary cause of morbidity and mortality in patients undergoing vascular surgical procedures(12,13).

In this paper, we aimed to determine predictors and risk factors related to the occurrence of MACE in patients undergoing vascular surgery for PAD.

METHODS

This is a retrospective study of 310 in-hospital patients treated at a high-volume vascular centre from January 2022 to June 2022. We obtained data from available medical records. All patients provided informed consent, and the Ethical Committee of the Institution approved the study. The data included 1) basic demographic data, 2) clinical presentation and course of the disease, 3) preoperative and postoperative therapy, 4) type of vascular procedure, 5) coronary angiography findings, 6) echocardiographic findings, and 7) primary outcome classified through the three-point MACE (AMI, stroke and cardiovascular mortality). The patients were followed up for 6 months. We analyzed the primary outcome at 30 days (initial) and 6 months (short-term) (14,15).

Risk factor-related data included 1) previous myocardial infarction (MI) within the past 5 years, 2) angina pectoris (AP), 3) previous myocardial revascularization procedures (percutaneous coronary intervention – PCI and coronary artery bypass grafting – CABG), 4) hypertension (HT), 5) hyperlipoproteinemia (HLP), 6) diabetes mellitus (DM), 7) chronic obstructive pulmonary disease (COPD), and 8) chronic kidney disease (CKD) and creatinine levels. We used The Vascular Study Group of New England Cardiac Risk Index (VSG-CRI) and the Revised Cardiac Risk Index (RCRI) based on the criteria presented in **Table 1** (16–18).

Table 1. Risk indexes and the scoring system used in the study

RCRI		VSG-CRI	
Factor	**Score**	**Factor**	**Score**
Elevated-risk surgery (intraperitoneal, intrathoracic, suprainguinal, vascular)	1	**Age**	
		≥80	4
		70-79	3
		60-69	2
History of IHD (History of MI, history of positive exercise test, current chest pain considered due to myocardial ischemia, use of nitrate therapy or ECG with pathological Q waves)	1	**History of IHD**	2
History of CHF (Pulmonary oedema, bilateral rales or S3 gallop, paroxysmal nocturnal dyspnoea, CXR showing pulmonary vascular redistribution)	1	**History of CHF**	2
History of cerebrovascular disease (prior TIA or stroke)	1	**COPD**	2
Preoperative treatment with insulin	1	**Insulin dependent diabetes**	1
Preoperative creatinine >176.8 µmol/L	1	**Preoperative creatinine >160 µmol/L**	2
		Smoking	1
		Long term β-blocked	1
		History of CABG and PCI	-1

RCRI: Revised Cardiac Risk Index, VSG-CRI: Vascular Study Group of New England Cardiac Risk Index, IHD: Ischemic Heart Disease, MI: Myocardial infarction, ECG: electrocardiogram, CHF: congestive heart failure, CXR: Chest X-ray, TIA: Transient ischemic attack, COPD: chronic obstructive pulmonary disease, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention.

Statistical analysis

We analyzed data by parametric and nonparametric methods. Normality was tested using Kolmogorov–Smirnov test and Q-Q diagrams. The observed characteristics were expressed as mean values, standard deviation, median, and interquartile range (IQR). We used the Mann–Whitney U test for continuous nonparametric data, whereas Student's t-test was used for continuous parametric data. Categorical data were analyzed using the Chi-square test and Fisher exact test, to determine the statistically significant difference. Significance was set at a 2-sided $p < 0.05$. IBM SPSS Statistics 26 (Armonk, New York, USA) was used for the analysis.

RESULTS

Demographic parameters and risk factors are given in **Table 2**. No significant difference was observed regarding the frequency of risk factors and sex ($p > 0.05$). A significant proportion of patients (>25%) had undergone a prior myocardial revascularization procedure before the admission, and almost 15% had experienced a prior MI. Diabetes mellitus was highly prevalent, affecting >50% of patients, while 58 (32.7%) diabetic patients were insulin

Table 2. Demographic and risk factors

Factor	N (%)
Age (years)	
(median, min-max)	66 (38-86)
BMI (kg/m²)	
(median, min-max)	25.79 (17-42.6)
Male sex	221 (71.3)
Previous MI	45 (14.5)
Angina pectoris	29 (9.4)
CHF	64 (20.7)
Fontain grade	
II	157 (50.6)
III	62 (20)
IV	91 (29.4)
HLP	267 (86.1)
HTA	282 (91)
DM	177 (57.1)
Previous myocardial revascularization	
PCI	43 (13.9)
CABG	36 (11.6)
History of smoking	249 (80.3)
CKD	12 (3.9)
COPD	20 (6.5)
Previous TIA/CVI	30 (9.7)
RCRI	
(median, min-max)	1 (1-5)
VSG-CRI	
(median, min-max)	4 (2-12)

RCRI: Revised Cardiac Risk Index, VSG-CRI: Vascular Study Group of New England Cardiac Risk Index, IHD: Ischemic Heart Disease, MI: Myocardial infarction, ECG: electrocardiogram, CHF: congestive heart failure, CXR: Chest X-ray, TIA: Transient ischemic attack, COPD: chronic obstructive pulmonary disease, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention.

dependent. The majority of patients had complaints on admission that according to Fontaine could be classified as category II (intermittent claudication), rest pain (Fontain III) was reported by 62 (20%) patients, while the presence of wound and tissue loss (Fontain IV) was reported in 91 (29.4%) patients. Significantly more patients with DM had complaints in Fontaine IV category compared to patients who did not suffer from DM ($p = 0.001$).

A significant majority of patients, exceeding 75%, underwent aortobifemoral bypass surgery. Iliacofemoral reconstruction was undertaken in 2.3% of patients, while above-the-knee femoropopliteal (FP) bypass was performed in 9.7%, and below-the-knee FP bypass in 6.5%. We found that the majority of initial MACE happened in patients with aortobifemoral bypass surgery compared to other types of reconstruction ($p = 0.009$). No significant correlation was established between the procedures performed and the short-term primary outcome. However, it was noted that patients who received below-the-knee FP bypass required additional interventions like necrotomy and toe amputation in comparison to patients who underwent other types of reconstructions.

Table 3. Performed open surgical procedures

Surgical procedure	N (%)
Aortobifemoral bypass surgery	234 (75.5)
Iliacofemoral reconstruction	7 (2.3)
Above-the-knee femoropopliteal bypass	30 (9.7)
Below-the-knee femoropopliteal bypass	20 (6.5)
Other	19 (6.1)

In the initial period, MACE was detected in 14 (5.8%) patients. Among them, six (1.9%) experienced a myocardial infarction (MI), three (1%) had a stroke, and five (1.6%) died within the first 30 days. All deaths were linked to cardiac ischemia, which ultimately culminated in cardiogenic shock and subsequent death. Short term MACE was observed in 2 (0.6%) patients both of whom had an MI. Significant risk factors related to initial MACE are given in **Table 4**. No factors were found to significantly contribute to short-term MACE in our cohort.

Table 4. Risk factors for the occurrence of initial major adverse cardiac event

Factor	OR	95% CI	p
Age >65 years	1.075	1.038-1.113	<0.001
Creatinine level	1.005	1.001-1.009	0.015
CKD	4.063	1-976-8.354	<0.001
Dialysis	3.635	1.149-11.504	0.028
Previous myocardial revascularization	2.789	1.2-6.481	0.017
Emergency admission	4.968	2.297-10.748	<0.001

CKD: chronic kidney disease

The median calculated RCRI was 1 and VSG-CRI was 4 for the entire cohort. There was a significantly higher RCRI score in patients who had initial MACE (3 vs. 1; $p < 0.001$). Same was observed for VSG-CRI score (5 vs. 2; $p = 0.011$).

DISCUSSION

A study by Thomas et al. reported MACE in patients undergoing major vascular surgery to be as high as 11% with overall mortality of 6.4% (56.2% mortality in all patients with MACE) (19). However, their cohort consisted of patients with known CAD making this a high-risk group of patients. We already analyzed the prevalence of CAD in vascular surgery patients and the implications of preoperative coronary angiographies and myocardial revascularization and found significant prevalence of CAD in PAD patients (20). Furthermore, Thomas et al. found a significant difference in the occurrence of MACE in patients with prior revascularization compared to nonrevascularized patients (22% vs. 7%). Other studies, however, have found that the presence of a coronary stent (i.e., prior myocardial revascularization) is a predictor of MACE and that these patients should be carefully managed. We obtained similar results in our cohort, where it was shown that prior myocardial revascularization was a significant predictor of an adverse cardiac event. This can be explained by hemodynamic changes during operations on the aorta and large blood vessels. A detailed subcohort analysis is needed to better stratify these patients.

In the study by Smeili et al., the risk of MACE was related to advanced age, obesity, reduced functional lung capacity, renal impairment, aortic surgery, and altered troponin levels. RCRI and VSG-CRI had an area under the curve of 0.635 and 0.639, respectively, for early cardiovascular complications and 0.562 and 0.610 for 30-day death (21). The reported MACE in this study is lower compared to the available data in literature (19). Overall mortality of 1.6% can be considered an excellent result, but a more detailed analysis of subgroups of patients is necessary for a better stratification of risk factors and better management in the perioperative period.

The association of MACE with vascular surgical treatment can be explained in several ways. This may be due to large intra- and extravascular fluid shifts, prolonged duration of aortic cross-clamping during open surgical treatment of aortic disease, large volume loss and insensible fluid losses, as well as the induction of hypothermia (22). This is associated with an enhanced stress response, characterized by elevated levels of circulating cortisol and catecholamines in the perioperative period, promoting a hypercoagulable state and an increased myocardial oxygen demand (23). In addition to the risks inherent in the surgery itself, patients are at high risk of developing MACE due to the underlying medical comorbidities prevalent in this patient population, all of which are associated with atherosclerosis (24).

Limitations

Our study has some limitations. Primarily, due to the intrinsic characteristics of observational studies, the capacity to establish causal relationships remains limited. In addition, the analysis relies exclusively on a group of individuals admitted to hospital, thus mitigating its generalizability to a wider spectrum of PAD patients. Our decision to include consecutive patients was based on their representation in the wider population of vascular patients encountered in our clinical practice.

CONCLUSION

Major vascular surgery in patients with coronary artery disease places them in high-risk group of mortality due to the occurrence of perioperative MACE. Factors such as age > 65 years, elevated creatinine levels, chronic kidney disease and emergency admission played a significant role in the development of perioperative MACE. Early detection of coronary heart disease and preoperative optimization can play a major role in reducing the risk of MACE.

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VELIKI NEŽELJENI KARDIOVASKULARNI DOGAĐAJI KOD VASKULARNIH HIRURŠKIH PACIJENATA SA PERIFERNOM ARTERIJSKOM BOLEŠĆU

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Sažetak

Uvod: Veliki neželjeni srčani događaji (*MACE*) su primarni uzrok morbiditeta i mortaliteta kod pacijenata koji su podvrgnuti vaskularnim hirurškim procedurama. Zbog toga je neophodno razumeti vezu između koronarne bolesti i periferne arterijske bolesti. Cilj ovog rada je utvrđivanje prediktora i faktora rizika koji se odnose na pojavu velikih neželjenih srčanih događaja kod pacijenata koji su podvrgnuti vaskularnoj hirurgiji zbog periferne arterijske bolesti.

Materijal i metode: Ovo je retrospektivna studija na 310 bolničkih pacijenata lečenih u vaskularnom centru velikog obima. Ishod je klasifikovan kroz tri tačke (infarkt miokarda, moždani udar i kardiovaskularni mortalitet).

Rezultati: Otkrili smo da se većina *MACE* desila kod pacijenata sa aortobifemoralnim bajpasom u poređenju sa drugim tipovima rekonstrukcija (p=0,009). Nije ustanovljena značajna korelacija između urađenih zahvata i kratkoročnog primarnog ishoda. U početnom periodu *MACE* je otkriven kod 14 (5,8%) pacijenata. Među njima, šest (1,9%) je doživelo infarkt miokarda (IM), troje (1%) je imalo moždani udar, a pet (1,6%) je umrlo u prvih 30 dana. Svi smrtni slučajevi su bili povezani sa srčanom ishemijom, koja je na kraju kulminirala kardiogenim šokom i kasnijom smrću. Kratkotrajni *MACE* je primećen kod 2 (0,6%) pacijenta od kojih su oba imala IM.

Zaključak: Velika vaskularna hirurgija kod pacijenata sa koronarnom bolešću je visokorizična procedura i perioperativni *MACE* ih stavlja u značajno visok rizik od smrtnosti. Rano otkrivanje koronarne bolesti srca i preoperativna optimizacija mogu igrati glavnu ulogu u smanjenju rizika od *MACE*.