Impact of Modifiable Risk Factors on Long-Term Outcomes after Coronary Artery Bypass Surgery

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Abstract

Background Risk factors control and secondary prevention measures are often reported to be suboptimal in patients undergoing coronary artery bypass grafting (CABG) and may lead to worse clinical outcomes. We aimed to examine potentially modifiable risk factors in patients undergoing CABG and investigate their association with long-term coronary events.

Methods Cardiovascular risk factors were recorded preoperatively in the setting of a cardiac catheterization laboratory and were analyzed in relation to long-term coronary events, defined as acute coronary syndrome (ACS) or revascularization after CABG.

Results Study population included 1,125 patients undergoing CABG without previous revascularization. Modifiable risk factors included hypertension (71%), hyperlipidemia (67%), diabetes (42%), obesity (28%), and smoking (21%). Only 8% did not have any of the five risk factors. During the mean follow-up of 93 ± 52 months after CABG, 179 patients (16%) experienced a coronary event. Incidence rates were higher in patients with than without the presence of each of the modifiable risk factors, except obesity. Active smoking (hazard ratio [HR]: 1.51; 95% confidence interval [CI]: (1.07–2.13); $p = 0.020$), presence of diabetes (HR: 1.61; 95% CI: 1.18–2.18; $p = 0.002$), and hyperlipidemia (HR: 2.13; 95% CI: 1.45–3.14; $p < 0.001$) were independent predictors of future coronary events after CABG; they also displayed a progressive stepwise increment in the risk of long-term coronary events when cumulatively present.

Conclusions In patients undergoing CABG, diabetes, hyperlipidemia, and smoking, as documented preoperatively, were potentially modifiable risk factors that were independently and cumulatively associated with long-term risk of ACS or coronary revascularization, highlighting the importance of early identification and risk factors control for improving cardiovascular health after CABG.

Keywords
- coronary artery bypass graft surgery
- acute coronary syndrome
- risk factors
- coronary revascularization
- secondary prevention

Introduction

Advanced coronary artery disease (CAD) is commonly seen in patients undergoing coronary artery bypass grafting (CABG) and is often associated with a significant burden of cardiovascular risk factors.[1] In recent years, an increase in the operative age and the prevalence of comorbidities is noted in patients undergoing cardiac surgery, with a general trend toward the older and sicker patient population.[2] Although considered to be among the highest risk groups of patients

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with CAD, risk factor control and secondary prevention measures in patients undergoing CABG are reported to be significantly suboptimal and may be associated with worse clinical outcomes.[3,4] These may include ischemic coronary events occurring due to the progression of native CAD, graft failure, or attrition, leading to the need for repeat or further coronary revascularization.[5]

Research studies have focused on the investigation of treatment adherence and guideline-based care for patients after CABG.[4,6] However, the differential influence and prognostic impact of preoperative modifiable cardiovascular risk factors on long-term coronary outcomes after CABG are less known. The aim of this study was to evaluate potentially modifiable risk factors in patients undergoing CABG, as recorded preoperatively during cardiac catheterization, and investigate their association with long-term coronary events after CABG.

Patients and Methods

The Cardiac catheterization laboratory database of Carmel Medical Center, Haifa, Israel, was searched retrospectively for consecutive patients who were referred to CABG surgery between the years 2000 and mid-2015 in a single center. Patients with previous coronary revascularizations and patients aged 80 years and older were excluded. The final study population included 1,125 patients who underwent CABG during the study period. Data regarding the presence of modifiable cardiovascular risk factors were prospectively documented in the cardiac catheterization laboratory database. Modifiable risk factors evaluated included hypertension, hyperlipidemia, active smoking, obesity (defined as body mass index [BMI] $\geq 30\ kg/m^2$), and diabetes mellitus. Database information was gathered from patients' electronic files and computerized medical records. Risk factor diagnosis was usually given by primary care physicians according to clinical judgment and customary definitions. In cases of missing data regarding the presence of a specific risk factor, direct questioning of the patient and investigation of laboratory blood tests were performed. Dietary patterns and physical activity were not routinely recorded and therefore were not included in the current analysis. Age, gender, presence of chronic kidney disease, and the occurrence of acute coronary syndrome (ACS) leading to the preoperative cardiac catheterization were also documented. The primary study outcome was coronary events, defined as ACS or the need for coronary revascularization after CABG, during long-term follow-up period ending in June 2018. The study database was approved by the Ethics Committee of Carmel Medical Center, with waiving of the need for individual patient consent.

Data Analysis

Continuous data are presented as means and standard deviation or median with interquartile range, and categorical variables are presented as numbers and percentages. Independent samples *t*-test were used to compare continuous variables, and chi-square test was used to compare categorical variables. Preoperative modifiable cardiovascular risk factors evaluated included hypertension, hyperlipidemia, diabetes mellitus, obesity, and active smoking. The proportion of coronary events (ACS or revascularization during follow-up) and incidence rates per 100 person-years were calculated for each modifiable risk factor. Time-to-event analyses was performed with the use of Kaplan–Meier estimates, presenting coronary events over time in relation to the modifiable risk factors, with comparison performed using the log-rank test.

Univariable- and multivariable-adjusted analyses of the association between the modifiable risk factors and long-term coronary events after CABG were performed using the Cox proportional hazards model, calculating hazard ratios (HRs) and 95% confidence intervals (CI). Age, gender, chronic kidney disease, and the presence of preoperative ACS were additional covariates included in the regression model. The modifiable risk factors that were found to be independently associated with coronary events were additionally investigated for their combined impact on outcome events and calculated according to the cumulative number of risk factors present in each patient.

The results were considered statistically significant when the two-sided *p*-value was <0.05. SPSS statistical software version 20.0 (IBM Corp., Armonk, New York, United States) and MedCalc version 16.8.4 were used to perform all statistical analyses.

Results

Study population included 1,125 consecutive patients less than 80 years of age with no previous coronary revascularization. Mean age was 65 ± 9 years and 79% were males. Preoperative ACS was the clinical presentation in 570 (51%) patients. Potentially modifiable preoperative cardiovascular risk factors included hypertension, evident in 796 patients (71% of the study population), hyperlipidemia (749 patients; 67%), diabetes mellitus (477 patients; 42%), obesity (317 patients; 28%), and active smoking (232 patients; 21%) patients. Only 8.4% of the study population undergoing CABG did not have any of the aforementioned five modifiable risk factors.

Effect of Modifiable Risk Factors on Coronary Events

During a mean follow-up period of 93 ± 52 months (median: 88 months) after CABG, 179 (16%) patients have experienced a coronary event, defined as ACS or the need for coronary revascularization. Coronary event rates and incidence per 100 person-years according to the five modifiable risk factors are presented in ►**Table 1**. Incidence rates of the coronary events were higher in patients with than without the presence of each of the modifiable risk factors, except obesity. This was similarly demonstrated by Kaplan–Meier plots displaying ACS or coronary revascularization rates over time stratified by each of the risk factors (►**Fig. 1a–e**). In a univariate Cox regression analysis, younger operative age, presentation with ACS, chronic kidney disease, diabetes mellitus, hypertension, hyperlipidemia, and smoking were each associated with a significant increase in the HR for coronary event during follow-up (►**Table 2**).

Table 1 Descriptive statistics and crude incidence rate of acute coronary syndromes or revascularization according to preoperative modifiable risk factors

Risk factor		No. of patients (%)	No. of events (%)	Incidence rate per 100 person-years
Hypertension	No	329 (29)	42/329 (12.8)	1.49
	Yes	796 (71)	137/796 (17.2)	2.33
Hyperlipidemia	No	376 (33)	34/376 (9.0)	1.04
	Yes	749 (67)	145/749 (19.4)	2.68
TC / HDL-C ratio	≤5	794 (71)	116/794 (14.6)	1.88
	>5	331 (29)	63/331 (19)	2.49
Active smoking	No	893 (79)	127/893 (14.2)	1.79
	Yes	232 (21)	52/232 (22.4)	3.21
Diabetes mellitus	No	648 (58)	81/648 (12.5)	1.52
	Yes	477 (42)	98/477 (20.5)	2.92
Obesity	No	808 (72)	132/808 (16.3)	2.10
	Yes	317 (28)	47/317 (14.8)	1.96

Abbreviations: HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.
Note: Obesity was defined as body mass index > 30 kg/m^2.

During the 6-month period before CABG, 757 (67%) patients were treated with statins. Preoperative statin treatment was not associated with reduction in long-term coronary events (►**Table 2**). Increased ratio of total cholesterol to high-density lipoprotein cholesterol (>5) was evident in 331 (29%) of the patients and was associated with a higher incidence rate of coronary events but did not reach statistical significance in the regression analysis (►**Tables 1** and **2**).

The statistically significant variables were further examined using a multivariable Cox regression analysis. Younger operative age and chronic kidney disease were independent prognostic predictors. In addition, the modifiable risk factors that were independently associated with the coronary outcome in the multivariable model included active smoking [HR: 1.51; 95% CI: 1.07–2.13; $p = 0.020$), presence of diabetes (HR: 1.61; 95% CI: 1.18–2.18; $p = 0.002$), and hyperlipidemia (HR: 2.13; 95% CI: 1.45–3.14; $p < 0.001$) (►**Table 2**).

Cumulative Effect of Cardiovascular Risk Factors

A cardiovascular risk factor score was calculated between 0 and 3, according to the cumulative number of the independent risk predictors for coronary events (active smoking, diabetes, and hyperlipidemia) present in each patient. One risk factor was evident in 35.5%, two risk factors in 36.5%, and three risk factors in 7%. In 21% of the patients, none of the three independent risk factors were present. Adjusted HRs for long-term coronary events according to the number of preoperative independent risk factors are presented in ►**Fig. 2**. In comparison to those without any of the three risk factors (reference group), a gradual stepwise increase in the risk of long-term coronary events was observed with the increase in the number of cardiovascular risk factors, reaching an adjusted HR of 5.31 (95% CI: 2.74–10.32) for those with all three independent preoperative risk factors (p-value for trend < 0.001). Patients with one or no risk factor (56.5% of study population) had a significantly lower risk of future coronary events compared with those with two to three risk factors (43.5% of study population), with an adjusted HR of 0.435 (95% CI: 0.320–0.591; $p < 0.001$).

Discussion

In patients undergoing CABG, a significant burden of cardiovascular risk factors was observed, and apart from obesity, each of the potentially modifiable risk factors was associated with a higher incidence rate of future coronary events, defined as ACS or the need for coronary revascularization. Hyperlipidemia, diabetes, and active smoking, which were present preoperatively, were independent predictors of long-term coronary events after CABG. Furthermore, they displayed an incremental association with the adverse coronary outcome when cumulatively present.

Cardiovascular risk factors are broadly classified as nonmodifiable, including age, gender, ethnicity, and family history, and as potentially modifiable risk factors, which include smoking, abnormal blood lipids, high blood pressure, obesity, and diabetes mellitus, as well as physical inactivity and unhealthy dietary patterns. These risk factors are often affected by socioeconomic, behavioral, and environmental determinants, along with different life-course influences and genetic factors.[7] The seminal INTERHEART case–control study demonstrated that simple known risk factors, which are potentially modifiable, account for most of the population attributable risk of a first myocardial infarction, consistent across all geographic regions, ethnic groups, and gender.[8] These modifiable risk factors should be targeted by early lifestyle modification and drug-based interventions, at both the individual level and population level. The role of secondary prevention measures and risk-factor control in reducing adverse cardiovascular events and mortality is well established, including after cardiac surgery,[4] as is highlighted by international guidelines for cardiovascular prevention and myocardial revascularization.[9,10] However, studies have shown that there is a wide variation in post-CABG risk factor control and secondary prevention care and that evidence-based discharge therapies are underutilized in patients who undergo CABG.[3,4] Therefore, even though greater use of indicated secondary prevention medications is associated with lower rates of death or myocardial infarction, patients remain at high risk of subsequent major cardiovascular events after CABG.

Although patients undergoing CABG are considered as one of the highest risk groups of patients with CAD, a paucity of real-world data exists regarding the burden of potentially modifiable risk factors at the preoperative phase before undergoing CABG and their association with long-term postoperative coronary outcomes. In this study of patients without previous revascularizations undergoing CABG, hyperlipidemia, diabetes, and active smoking were each independently associated with a higher incidence of coronary outcomes during long-term follow-up. This correlation with increased risk of coronary events was less significant with

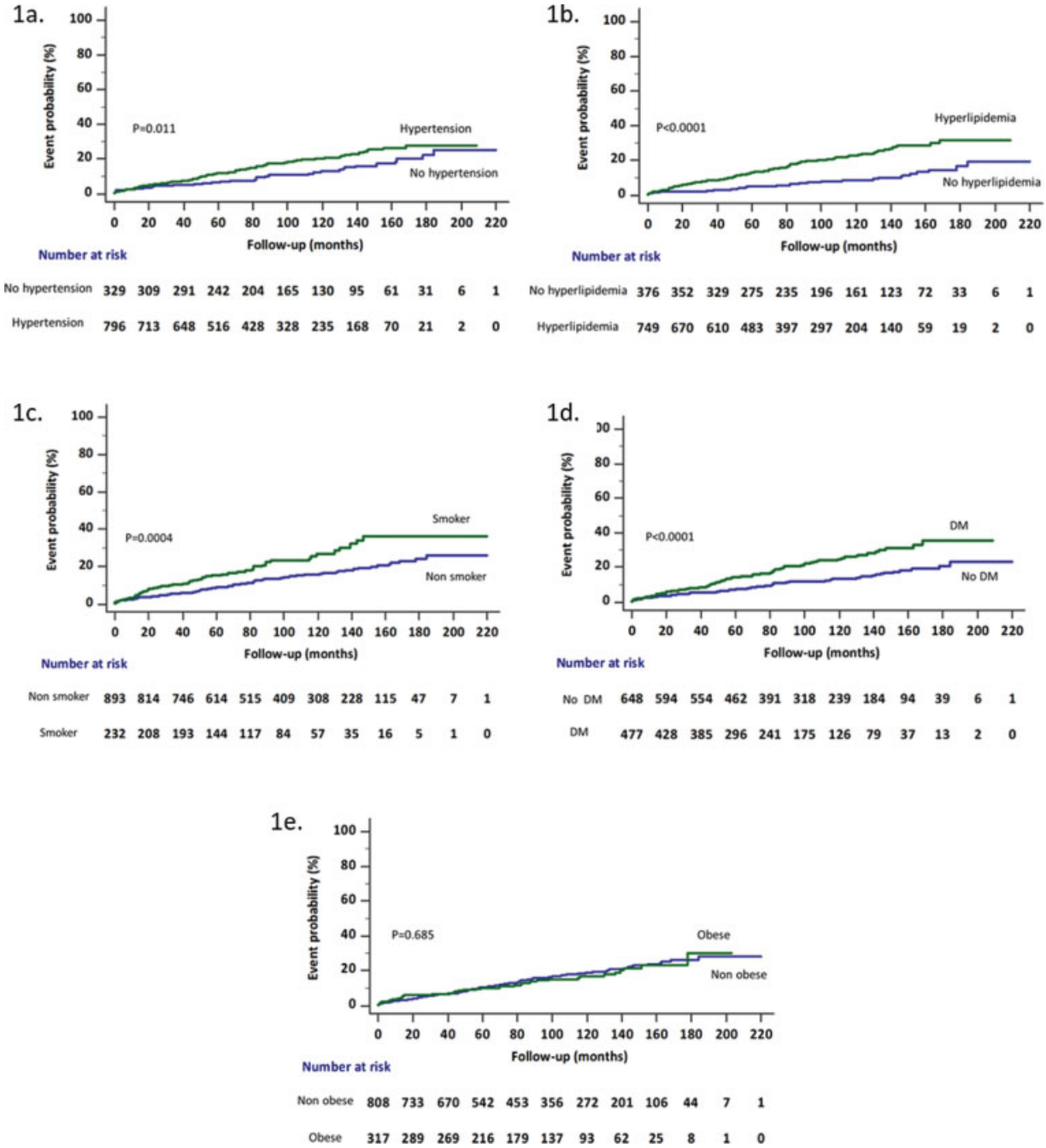

Fig. 1 Kaplan–Meier curves for long-term coronary events stratified by modifiable risk factors. (**a**) Hypertension. (**b**) Hyperlipidemia. (**c**) Active smoking. (**d**) Diabetes. (**e**) Obesity. DM, diabetes mellitus.

hypertension, observed only in univariate analysis, and was not seen with obesity. Obesity may be associated with perioperative complications, such as during anesthesia, and is a risk factor for mediastinitis following CABG. In addition, obesity is considered an established risk factor for the development of cardiovascular disease,[11] and morbid obesity was shown to be associated with increased mortality after CABG.[12] However, others have also suggested that an "obesity paradox" is present in patients undergoing CABG, similarly to various chronic cardiovascular disease states, with unexpectedly lower mortality rates observed in the overweight and mildly obese patients.[13] Our findings demonstrate a lack of association between obesity and adverse events after CABG, though we have investigated an outcome of coronary events, which is different from most of the obesity–CABG studies in which the main outcome analyzed was mortality. In addition, BMI, which is the most common anthropometric parameter used clinically, may not be a reliable method to assess the distribution and degree of adiposity or a good way to correct weight for height, which may limit its prognostic significance.[14]

Hyperlipidemia is a causal factor for the development and progression of atherosclerotic cardiovascular disease.[15] Identifying and targeting plasma lipid abnormalities is one

Table 2 Hazard ratios of variables associated with long-term coronary events after univariate and multivariable Cox regression analyses

Variable	Univariate analysis	Multivariable analysis
Age (at CABG operation)	0.975 (0.959–0.990); $p = 0.001$	0.982 (0.966–0.999); $p = 0.038$
Gender (male)	1.176 (0.799–1.732); $p = 0.412$	–
Chronic kidney disease	2.475 (1.431–4.280); $p = 0.001$	2.086 (1.200–3.628); $p = 0.009$
Preoperative acute coronary syndrome	1.393 (1.036–1.874); $p = 0.028$	–
Active smoker	1.788 (1.293–2.471); $p < 0.001$	1.509 (1.068–2.131); $p = 0.020$
Hypertension	1.561 (1.103–2.208); $p = 0.012$	–
Hyperlipidemia	2.588 (1.778–3.768); $p < 0.001$	2.133 (1.450–3.136); $p < 0.001$
TC/HDL-C ratio (>5 vs. ≤5)	1.322 (0.973–1.797); $p = 0.075$	–
Statin treatment[a]	0.901 (0.662–1.226); $p = 0.507$	–
Diabetes mellitus: Insulin therapy	1.922 (1.430–2.583); $p < 0.001$ 2.472 (1.566–3.902); $p < 0.001$	1.605 (1.183–2.178); $p = 0.002$
Obesity (BMI > 30 kg/m^2)	0.934 (0.669–1.303); $p = 0.686$	–

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.
[a]Patients treated by any type of statin during the period of 6 months before surgery.

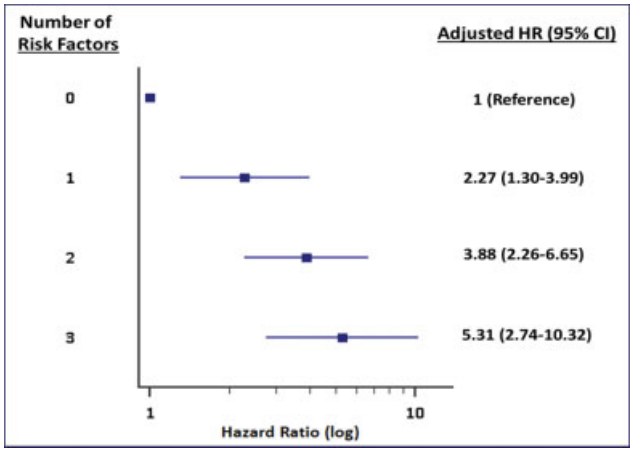

Fig. 2 Adjusted hazard ratios for long-term coronary events according to the number of preoperative cardiovascular risk factors (diabetes mellitus, hyperlipidemia, or active smoking). Adjustment for age, gender, chronic kidney disease, and presence of acute coronary syndrome. CI, confidence interval; HR, hazard ratio.

of the mainstays in cardiovascular prevention and is important for improving long-term outcomes.[9] Significant reduction in the risk of cardiovascular events and mortality was shown in secondary prevention trials, with statins and non-statin therapies.[15,16] After CABG, Statin administration was shown to limit the progression of atherosclerosis in native coronary arteries and saphenous vein grafts and to reduce postoperative cardiac events and mortality.[17] Moreover, initiation of statins preoperatively before CABG has been demonstrated to reduce the risk of short-term mortality, stroke, and atrial fibrillation, and decrease markers of the systemic inflammatory response.[18] In our cohort, diagnosis of hyperlipidemia was highly prevalent in patients undergoing CABG and was the strongest independent variable associated with long-term coronary events. Our findings may be partially explained by the significant underutilization of statin therapy observed in patients after CABG, which may adversely impact patients' outcomes and highlight the importance of early identification and treatment of hyperlipidemia in patients with CAD.

Tobacco use is one of the most important contributing causes of myocardial infarction globally. In a large analysis of 21,534 patients in whom isolated CABG surgery was performed, active smoking preoperatively was noted in 15% of the patients and associated with an increased risk of pulmonary complications and reduced long-term survival after CABG, though smoking status was not associated with early postoperative mortality.[19] This study further demonstrates that preoperative active smoking, which was evident in 21% of the study population, is a long-term independent predictor for coronary events after CABG as well. Smoking cessation after an acute myocardial infarction was shown to be potentially the most effective of all preventive measures,[20] and endeavors to quit smoking should be the primary target for smokers undergoing CABG. Participation in a cardiac rehabilitation program may increase the chances of abstaining from smoking after CABG.[21]

Diabetes mellitus is associated with both microvascular and macrovascular complications, significantly increasing the risk of ischemic heart disease and stroke. As CAD in diabetics is commonly more complex, rapidly progressive, and diffuse, coronary revascularization by CABG is often indicated, as is seen in our patients' cohort of whom 42% were diabetic.[10] Diabetes may lead to unfavorable clinical outcomes and increased risk of postprocedural complications.[22] High rates of repeat revascularizations are observed in diabetics following percutaneous coronary interventions. Even though less pronounced, the risk of late or repeat coronary revascularizations is also seen in diabetics after CABG, especially if insulin treated.[23] As expected, we have found diabetes to be an independent predictor for long-term coronary events after CABG. This highlights the importance

of improving clinical care and cardiometabolic risk factors control in diabetic patients after CABG.

Cardiovascular risk is commonly a result of multiple interacting risk factors. This is the basis for the "total risk approach" to prevention, as reflected by the use of risk estimation calculators.[9] The combined effects of the major cardiovascular risk factors were shown to explain a significant part of coronary heart disease.[7] In the current analysis, hyperlipidemia, diabetes, and active smoking were independent predictors for long-term coronary events after CABG. However, they also displayed a strong combined incremental association with the risk of coronary events. Moreover, those with one or no risk factors had significantly lower risk of coronary events than those with concomitant two to three independent risk factors. These results are in line with the "low-risk concept," which is the cornerstone of population preventive endeavors such as the Ideal Cardiovascular Health Campaign and the American Heart Association's 2020 Strategic Impact Goals, which states that individuals with the lowest number of risk factors experience the lowest rates of cardiovascular disease.[24] A meta-analysis has recently demonstrated a strong inverse, linear, dose–response relationship of seven ideal cardiovascular health metrics with mortality, suggesting that there is life-saving benefit associated with improving cardiovascular health by as little as one health metric.[25] Our findings further extend these results to the CABG population, displaying an incremental association between the presence of major modifiable risk factors and future adverse coronary outcomes.

Several limitations of this study should be noted. The modifiable risk factors investigated were referred to as dichotomous variables (available or absent), and therefore the severity degree of each risk factor was not considered. In addition, no data on medications or compliance to therapy, or information on which of the modifiable risk factors were medically treated, were systematically available. This may have limited the ability to evaluate their predictive value. Moreover, as noted, additional modifiable risk factors such as physical inactivity, sedentary lifestyle, and unhealthy diet were not included in the cardiac catheterization database and therefore were not evaluated. Furthermore, we did not adjust the data to additional known prognostic factors such as the functional class of the patients, the ventricular function, extent of coronary disease, and type of surgical revascularization performed. However, we did take into consideration the presence of chronic kidney disease and recent myocardial infarction. We have also excluded patients with previous revascularizations from our study population to reduce bias regarding the association between modifiable risk factors and coronary outcomes in patients undergoing CABG. Finally, as this is a retrospective analysis of observational data, the association between modifiable risk factors and adverse outcomes do not prove causation.

Conclusions

In patients undergoing CABG, diabetes, hyperlipidemia, and active smoking were independent long-term predictors of ACS or need for future coronary revascularization. Present preoperatively, these cardiovascular risk factors displayed a cumulative adverse prognostic impact, with a stepwise increment in the adjusted risk of coronary events after CABG. These results illustrate the clinical relevance of common modifiable risk factors to the progression of CAD after CABG and highlight that in addition to the surgical approach, lifestyle modification and risk factors control are essential for improving cardiovascular health after CABG and may contribute to a long-lasting postoperative success.

Conflict of Interest
None declared.

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