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Short- and long-term cause of death in patients undergoing isolated coronary artery bypass grafting: A nationwide cohort study

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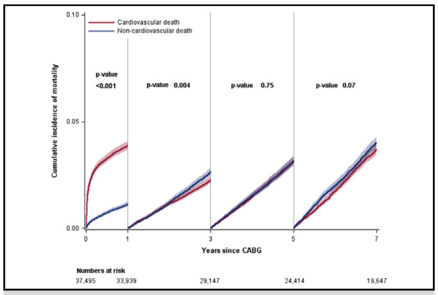
ABSTRACT

Objectives: Knowledge of the association between time and causes of death after coronary artery bypass grafting is sparse. We examined short- and long-term mortality and cause of death in patients undergoing coronary artery bypass grafting.

Methods: With the use of Danish nationwide registries, we identified all patients undergoing isolated coronary artery bypass grafting from 1998 to 2014. Cause of death was classified as cardiovascular or noncardiovascular according to death certificates. Landmark analyses of the cumulative incidences of cardiovascular and noncardiovascular mortality after 1, 3, and 5 years after coronary artery bypass grafting were performed. Multivariable cause-specific Cox regression models were used to evaluate changes over time in the risk of all-cause, cardiovascular, and noncardiovascular mortality after 1 and 7 years after coronary artery bypass grafting, respectively.

Results: Among 37,495 included patients, 12,230 (32.6%) died during a median follow-up of 7.4 years. Causes of death were classified as cardiovascular in 6459 patients (52.8%) and noncardiovascular in 5771 patients (47.2%). Within the first year, the incidence of cardiovascular death was higher compared with noncardiovascular death (3.9% vs 1.1%, $P < .001$). The cumulative incidences of cardiovascular and noncardiovascular were deaths similar in the periods 1 to 3 years (2.3% vs 2.6%, $P = .004$), 3 to 5 years (3.1% vs 3.2%, $P = .75$), and 5 to 7 years postsurgery (3.7% vs 4.0%, $P = .07$). The crude rates and adjusted risks of short- and long-term all-cause and cardiovascular mortality decreased during the study period despite an increase in age and burden of comorbidities.

Conclusions: In patients undergoing coronary artery bypass grafting, cardiovascular causes were responsible for the majority of deaths within the first year. Deaths due to noncardiovascular causes gained importance over time elapsed since coronary artery bypass grafting. (J Thorac Cardiovasc Surg 2018;156:54-60)



Landmark analyses of the cumulative incidences (with confidence intervals) for cardiovascular and noncardiovascular mortality at different time points in patients undergoing CABG.

Central Message

Cardiovascular causes were responsible for the majority of deaths within the first year after CABG. Deaths due to noncardiovascular causes gained importance over time elapsed since CABG.

Perspective

Patients who survived the first year after CABG appeared increasingly likely to die from other causes than cardiovascular, reflecting that the risk of competing diseases increases with age, especially in an aging population. This knowledge will add further to the information provided to the patients at discharge after CABG about long-term prospects and life expectancy.

See Editorial Commentary page 61.

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Over the last 4 decades, revascularization by coronary artery bypass grafting (CABG) has been a well-recognized treatment to relieve symptoms of angina pectoris and to improve survival in patients with coronary artery disease (CAD).[1] Short- and long-term mortality have been

Scanning this QR code will take you to the supplemental figures, tables, and video for this article.

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CAD = coronary artery disease
ICD = International Classification of Diseases
PCI = percutaneous coronary intervention

investigated in patients undergoing CABG[2-15]; however, studies describing the association between time and causes of death after CABG are sparse and limited by a small number of patients or only investigating a subpopulation.[16-21] Evaluating long-term cause of death in patients undergoing CABG is of great importance to enhance current treatment strategies and secondary prevention programs, thereby aiming to reduce mortality in the long-term. From a clinical perspective, knowledge on long-term cause of death will add further to the information provided to the patients at discharge after coronary revascularization about long-term prospects and life expectancy. In patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (PCI), a recent study suggests that cardiovascular death is prevalent in the acute phase, whereas noncardiovascular death gains importance over time.[22] Whether this may be the case in patients undergoing isolated CABG has yet to be determined. To address this gap in knowledge, we conducted a nationwide retrospective cohort study to examine short- and long-term mortality and cause of death in patients undergoing isolated CABG.

MATERIAL AND METHODS

Data Sources

The Danish healthcare system, funded by taxes, provides free and equal access to healthcare for all residents regardless of socioeconomic or insurance status. The assignment of a unique and permanent civil registration number to all residents in Denmark allows accurate linkage of nationwide administrative registries at an individual level. For this study, we used 4 different registries. The Danish National Patient Registry holds information on all hospital admissions since 1977 and all surgical procedures since 1996. Each admission is registered by 1 primary diagnosis and, if appropriate, 1 or more secondary diagnosis according to the International Classification of Diseases (ICD-8 until 1993 and ICD-10 from 1994). All surgical procedures, registered according to the NOMESCO Classification of Surgical Procedures used in Nordic countries, are registered by 1 or more codes depending on the type and scale of the operation.[23] The Danish Registry of Medicinal Product Statistics contains detailed information on all claimed drug prescriptions dispensed from pharmacies in Denmark since 1995. The drugs are classified according to the international Anatomical Therapeutic Chemical system with information on dispensing date, strength, and quantity dispensed.[24] Information on vital status was obtained from the Danish National Population Registry, in which information on all deaths is registered within 2 weeks after their occurrence. Causes of death classified according to the ICD-10 were obtained from the Danish Registry of Causes of Death.[25]

Study Population, Comorbidity, and Concomitant Pharmacotherapy

We identified all patients undergoing first-time cardiac surgery between January 1, 1998, and December 31, 2014. To investigate the association between time and cause of death in patients undergoing first-time isolated CABG, we excluded those who underwent CABG with concomitant valve or other cardiac surgical procedures, were younger than 18 years, and were non-Danish citizens.

Urgency of CABG was classified as elective surgery, urgent surgery (defined as surgery performed during the hospitalization period for acute myocardial infarction), or emergency surgery (defined as surgery within 24 hours after admission for acute myocardial infarction or surgery on the same day as PCI). Patient comorbidity was obtained through the Danish National Patient Registry using hospital discharge diagnoses before admission for CABG (Table E1 shows ICD-8 and ICD-10 codes). Patients with diabetes and hypertension were identified using claimed drug prescriptions as done previously.[26] Concomitant pharmacotherapy was defined through the Danish Registry of Medicinal Product Statistics as a claimed prescription within 180 days before admission for CABG (Table E2 shows Anatomical Therapeutic Chemical codes).

Causes of Death and Outcomes

The Danish Registry of Causes of Death holds information about the date, place, and manner of death (natural, accident, violence, suicide, uncertain), as well as the underlying cause (the disease or condition that started the process that led to death) and, if appropriate, 1 or more contributory causes.[25] On the basis of the underlying cause, we classified causes of death into the following categories: (1) definite cardiovascular; (2) possible cardiovascular; (3) noncardiovascular; and (4) unknown (Table E3 shows ICD-10 codes). On the basis of these categories, we further classified causes of death as cardiovascular or noncardiovascular: The first and second categories were considered a cardiovascular death, and the remaining categories were considered a noncardiovascular death. All-cause mortality, cardiovascular death, and noncardiovascular death were used as end points in separate analyses. Patients were followed from the day of surgery to the occurrence of the event (cardiovascular and noncardiovascular mortality) or the end of the study (December 31, 2014).

Statistical Analyses

Descriptive data were reported as frequencies and percentages or median with 25th and 75th percentiles as appropriate. Baseline characteristics were summarized separately according to 3 time periods in which surgery was performed (ie, 1998-2003, 2004-2009, and 2010-2014), and differences between groups were tested by applying the Cochran–Armitage test for trend for categoric variables and the Kruskal–Wallis test for continuous variables. Cumulative incidence curves were constructed to compare the absolute incidence of cardiovascular and noncardiovascular death while taking into account the competing risk of other causes of death. In addition, landmark analyses of the cumulative incidences of cardiovascular and noncardiovascular mortality were performed and compared using cause-specific hazards by the log-rank test; the first analysis covered the first year after CABG, and additional analyses started at years 1, 3, and 5 and ended 2 years after each time point. The landmarks were selected a priori on the basis of clinically relevant time points. Multivariable cause-specific Cox proportional hazard regression models were used to evaluate changes over time in the risk of all-cause, cardiovascular, and noncardiovascular mortality after 1 and 7 years after CABG, respectively. In addition, factors associated with cardiovascular mortality in the time periods 0 to 1 and 1 to 7 years after CABG were identified using multivariable cause-specific Cox regression models. All models were adjusted for age, gender, urgency of CABG, prior PCI, all comorbidities listed in Table 1, and the time period in which surgery was performed. The proportional hazards assumption was tested and found valid. Clinical relevant interactions including age,

TABLE 1. Baseline characteristics of patients undergoing coronary artery bypass grafting

Characteristics	All patients N = 37,495	Period 1 (1998-2003) N = 16,649	Period 2 (2004-2009) N = 12,213	Period (2010-2014) N = 8633	*P* value
Age, y (median [25th-75th percentile])	66 (59-72)	66 (58-72)	67 (60-73)	68 (61-74)	<.0001
Male, N (%)	30,037 (80.1)	13,150 (79.0)	9860 (80.7)	7027 (81.4)	<.0001
Surgery, N (%)					<.0001
Elective	30,375 (81.0)	14,593 (87.7)	9715 (79.6)	6067 (70.3)	
Urgent	5215 (13.9)	1599 (9.6)	1826 (15.0)	1790 (20.7)	
Emergency	1905 (5.1)	457 (2.7)	672 (5.5)	776 (9.0)	
Prior PCI, N (%)	6462 (17.2)	2080 (12.5)	2404 (19.7)	1978 (22.9)	<.0001
Comorbidities, N (%)					
Myocardial infarction	19,064 (50.8)	8864 (53.2)	6058 (49.6)	4142 (48.0)	<.0001
Heart failure	5398 (14.4)	2225 (13.4)	1846 (15.1)	1327 (15.4)	<.0001
Stroke	2782 (7.4)	1121 (6.7)	936 (7.7)	725 (8.4)	<.0001
Atrial fibrillation	2542 (6.8)	1096 (6.6)	818 (6.7)	628 (7.3)	.05
Hypertension	21,973 (58.6)	9674 (58.1)	7395 (60.6)	4903 (56.8)	.33
Diabetes	6326 (16.9)	2282 (13.7)	2146 (17.6)	1898 (22.0)	<.0001
Peripheral vascular disease	2582 (6.9)	1135 (6.8)	902 (7.4)	546 (6.3)	.34
Malignancy	2947 (7.9)	1067 (6.4)	1015 (8.3)	865 (10.0)	<.0001
Chronic renal failure	676 (1.8)	211 (1.3)	249 (2.0)	216 (2.5)	<.0001
Chronic obstructive pulmonary disease	2234 (6.0)	929 (5.6)	780 (6.4)	525 (6.1)	.04
Liver disease	500 (1.3)	181 (1.1)	183 (1.5)	136 (1.6)	<.0001
Concomitant medical treatment, N (%)					
Statins	23,902 (63.8)	8445 (50.7)	9204 (75.4)	6253 (72.4)	<.0001
Beta-blockers	23,938 (63.8)	11,062 (66.4)	8064 (66.0)	4812 (55.7)	<.0001
Calcium-blockers	13,913 (37.1)	7133 (42.8)	4036 (33.1)	2744 (31.8)	<.0001
Renin-angiotensin-system inhibitors	15,996 (42.7)	5666 (34.0)	5888 (48.2)	4442 (51.5)	<.0001
Thiazide	6179 (16.5)	2628 (15.8)	2253 (18.5)	1298 (15.0)	.87
Loop diuretics	6276 (16.7)	3213 (19.3)	1992 (16.3)	1071 (12.4)	<.0001
Spironolactone	1536 (4.1)	597 (3.6)	577 (4.7)	362 (4.2)	<.0001
Clopidogrel	4444 (11.9)	995 (6.0)	2364 (19.4)	1085 (12.6)	<.0001
Aspirin	25,499 (68.0)	10,833 (65.1)	8829 (72.3)	5837 (67.6)	<.0001
Oral anticoagulants	1464 (3.9)	597 (3.6)	452 (3.7)	415 (4.8)	<.0001

PCI, Percutaneous coronary intervention.

sex, and several comorbidities were tested for and found not significant, unless otherwise stated. There were no missing data for any of the covariates or outcomes. All statistical analyses were performed with SAS statistical software (SAS 9.4, SAS Institute, Inc, Cary, NC).

Sensitivity Analysis

To test the robustness of our findings, we considered deaths due to unknown causes a cardiovascular death.

Ethics

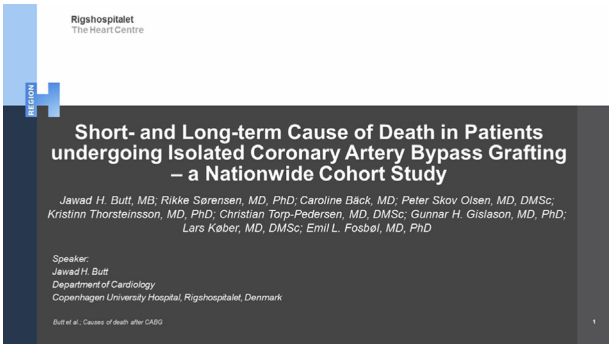
Approval for this study was obtained by the Danish Data Protection Agency (No. 2007-58-0015; internal reference: GEH-2014-014, I-Suite no. 02732), and data were anonymized so that individuals could not be identified. Retrospective registry-based studies do not require ethical approval in Denmark.

RESULTS

A total of 37,495 patients undergoing isolated CABG between January 1, 1998, and December 31, 2014, with no prior cardiac surgery were identified. The median age of the study population was 66 years (25th-75th percentile 59-72 years), and 81% were men. The proportion of patients undergoing emergency and urgent surgery was 5.1% and 13.9%, respectively. Baseline characteristics stratified according to time periods are summarized in Table 1. Patients who underwent CABG between 2010 and 2014 were older, were more often men, were more likely to undergo urgent or emergency surgery, and had generally more comorbidities compared with those who underwent CABG in the period 1998 to 2003.

Cause of Death

A total of 12,230 patients died during a median follow-up of 7.4 years. Cause of death was definite cardiovascular in 5172 patients (42.3%), possible cardiovascular in 1287 patients (10.5%), noncardiovascular in 5320 patients (43.5%), and unknown in 451 patients (3.7%). The most common noncardiovascular causes of death were cancer and infection accounting for 2808 (23.0%) and 544 (4.5%) of the total numbers of deaths, respectively (Video 1).



VIDEO 1. Summary of the main findings. Video available at: http://www.jtcvsonline.org/article/S0022-5223(18)30719-0/fulltext.

Cumulative Incidence of Death

Figure 1 displays the cumulative incidence curves for all-cause, cardiovascular, and noncardiovascular mortality. The cumulative incidences of 30-day, 1-year, and 7-year all-cause mortality were 2.4%, 5.0%, and 21.9%, respectively, and the corresponding cumulative incidences of cardiovascular mortality were 2.1%, 3.9%, and 12.0%, respectively.

Results from the landmark analyses of the cumulative incidences of cardiovascular and noncardiovascular mortality at 1, 3, 5, and 7 years are shown in Central Image/Figure 2. Within the first year after CABG, the incidence of cardiovascular death was higher compared with noncardiovascular death (3.9% vs 1.1%, $P < .001$). However, the landmark analyses showed similar cumulative incidences of cardiovascular and noncardiovascular deaths in the periods 1 to 3 years postsurgery (2.3% vs 2.6%, $P = .004$), 3 to 5 years postsurgery (3.1% vs 3.2%, $P = .75$), and 5 to 7 years postsurgery (3.7% vs 4.0%, $P = .07$).

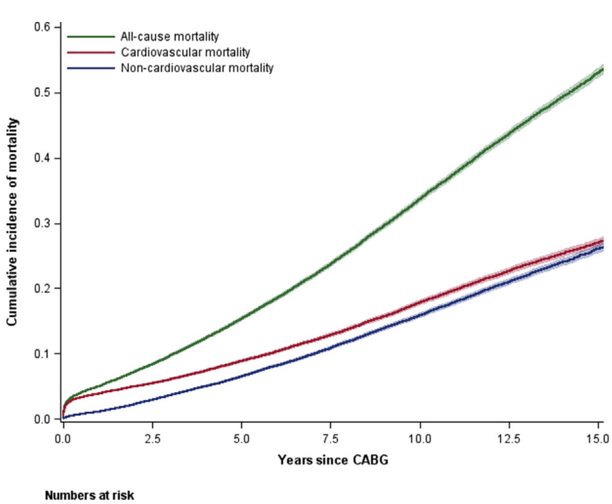


FIGURE 1. Cumulative incidence curves for all-cause mortality, cardiovascular mortality, and noncardiovascular mortality in patients undergoing CABG. *CABG*, Coronary artery bypass grafting.

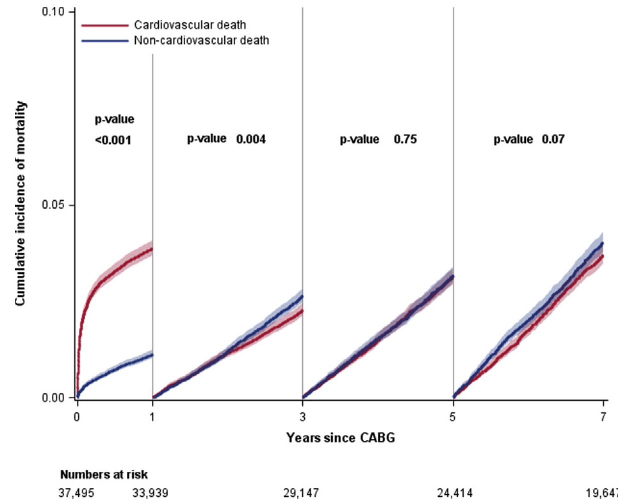


FIGURE 2. Landmark analyses of the cumulative incidences (with confidence intervals) for cardiovascular and noncardiovascular mortality at different time points in patients undergoing CABG. *CABG*, Coronary artery bypass grafting.

Time Trends

The crude rates and adjusted risks of all-cause, cardiovascular, and noncardiovascular mortality according to time of surgery are displayed in Figure 3. The crude rate and adjusted risk of 1-year all-cause and cardiovascular mortality decreased during the study period, whereas the risk of noncardiovascular mortality did not differ significantly. Likewise, a decrease in the crude rates and risks of 7-year all-cause and cardiovascular mortality during the study period were observed.

Concomitant medical treatment 1 year postsurgery stratified according to time of surgery is summarized in Table E4. A higher proportion of patients who underwent CABG between 2010 and 2014 were treated with beta-blockers, statins, aspirin, and renin-angiotensin-system inhibitors compared with those who underwent CABG in the period 1998 to 2003.

Factors Associated With Cardiovascular Mortality

Results from the multivariate Cox proportional hazard analysis for 1-year cardiovascular mortality are presented in Figure E1, *A*. Advanced age, female gender, urgency of surgery, and various comorbidities were associated with short-term cardiovascular mortality.

Factors associated with cardiovascular mortality in the period 1 to 7 years after CABG are displayed in Figure E1, *B*. Advanced age, male gender, and various comorbidities were associated with long-term cardiovascular mortality.

Sensitivity Analysis

To test the robustness of our findings, deaths due to unknown causes were considered cardiovascular.

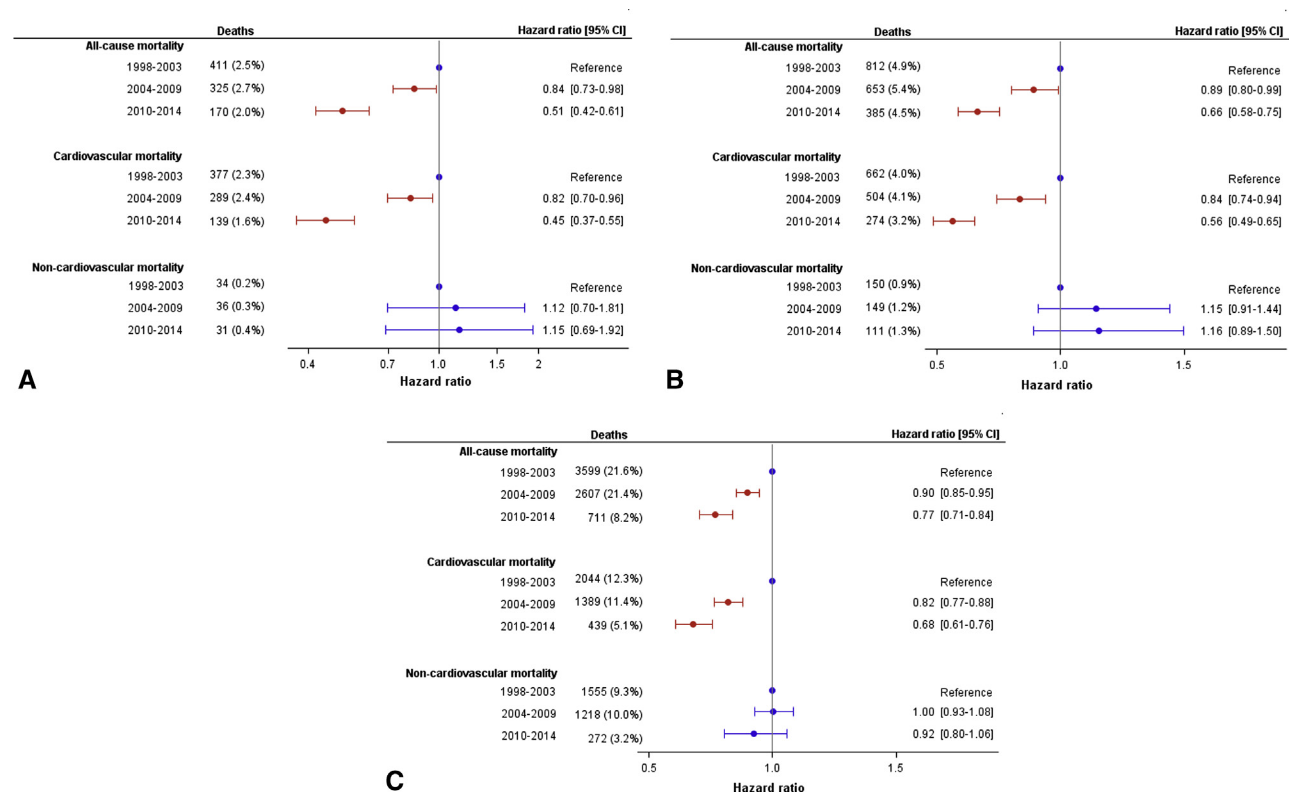


FIGURE 3. Crude rates and adjusted risks of all-cause, cardiovascular, and noncardiovascular mortality according to time of surgery in patients undergoing CABG. A, 30-day mortality. B, 1-year mortality. C, 7-year mortality. *CI*, confidence interval.

This analysis yielded similar results as the main analysis (Figures E2 and E3).

DISCUSSION

In this nationwide cohort study, we examined short- and long-term mortality and cause of death in patients undergoing isolated CABG. Our study yielded the following major findings: First, cardiovascular causes were responsible for the majority of deaths within the first year, whereas deaths attributed to noncardiovascular causes gained importance over time elapsed since CABG. Second, the crude rates and adjusted risks of short- and long-term all-cause and cardiovascular mortality decreased during the study period despite an increase in age and burden of comorbidities.

Previous studies have reported on causes of death after CABG; however, these studies were limited by including a small number of patients, investigating subgroups (eg, patients with heart failure, diabetes, complex CAD), or applying specific inclusion and exclusion criteria, thus not reflecting patients in a real-world setting. To our knowledge, this is the first study to examine short- and long-term causes of death in a large all-comers cohort of patients undergoing CABG on a nationwide scale. In our cohort, 52.5% of all deaths during a median follow-up of 7.4 years were due to a cardiovascular cause. Another observational study found that 58% of all deaths (n = 739) in a cohort of 2000 patients with more than 10 years follow-up were deemed as having a cardiac cause.[16] Data from the 5-year follow-up of the randomized Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial showed that only 49.5% of all deaths in patients treated with CABG were due to a cardiovascular cause. Of note, only patients with complex CAD were enrolled in the SYNTAX trial, and it could be expected that the proportion of cardiovascular deaths was even higher in such a population. However, the low proportion of cardiovascular deaths may partly be explained by the low number of deaths (n = 97) during the follow-up period. In the Surgical Treatment for Ischemic Heart Failure (STICH) trial, 610 patients underwent CABG, and during a median follow-up of 56 months, 218 patients died, in whom 74% the cause was considered cardiovascular.[20] The large proportion of cardiovascular deaths and the high mortality observed in the STICH trial are not surprising because the study population comprised only patients with ischemic cardiomyopathy with reduced ejection fraction.

Knowledge of short- and long-term causes of death is crucial to improve treatment strategies and secondary prevention programs. In a recent study, Pedersen and colleagues[22] examined the association between time and cause of death in patients with ST-segment elevation myocardial infarction undergoing primary PCI. Of note, the authors found the incidence of noncardiac causes of death to be higher than cardiac causes in patients surviving the first month after revascularization.[22] Our findings are in line with these results: We found that cardiovascular deaths were frequent during the first year after CABG, reflecting that the surgical procedure itself is associated with short-term cardiovascular mortality. Patients who survived the first year appeared increasingly likely to die from other causes than cardiovascular. The risk of competing diseases increases with age, especially in an aging population; in line with this, we found that cancer was the most common cause of noncardiovascular death accounting for 23% of all deaths after CABG.

Our study revealed that short- and long-term all-cause and cardiovascular mortality rates decreased during the study period despite an increase in age and burden of comorbidities. Several explanations may contribute to these findings. Marked progress in implementing cardiac rehabilitation programs may play a role in the decrease of cardiovascular mortality. In patients with coronary heart disease, exercise-based cardiac rehabilitation provides important health benefits including reductions in cardiovascular mortality and hospitalization.[27] In Denmark, cardiac rehabilitation is recommended as integrated care with individually planned and coherent rehabilitation across sectors from hospital to municipal; the overall participation rates for patients with coronary heart disease are greater than 70%, although only a part of the patients fulfill a complete comprehensive program.[28] A greater adoption to guideline-directed use of medications postsurgery (ie, beta-blockers, statins, aspirin, and renin-angiotensin-system inhibitors) may also explain the decrease in long-term cardiovascular mortality during the study period. Another possible explanation may be the increased use of arterial grafts. Although the standard method in Denmark is the use of the left internal thoracic artery to the left anterior descending artery and a saphenous vein graft to the remaining vessels, bilateral thoracic artery grafts and radial arteries are being increasingly used. The superior long-term patency of artery grafts compared with vein grafts is now well established, and mounting evidence supports that the superior patency of artery grafts translates into improved clinical outcomes, including death from cardiovascular causes.[29]

Studies examining factors associated with long-term cardiovascular mortality are sparse because focus mainly has been on all-cause mortality.[9,19] We found that advanced age, male gender, cardiovascular comorbidities, chronic renal failure, and chronic obstructive pulmonary disease were associated with cardiovascular mortality in the period 1 to 7 years after CABG. The main causes of chronic renal failure in western societies are diabetes and hypertension, both of which are traditional cardiovascular risk factors, and the main cause of chronic obstructive pulmonary disease is smoking, which is also a cardiovascular risk factor. Therefore, chronic renal failure and chronic obstructive pulmonary disease are surrogate markers for high cardiovascular risk.

Study Strengths and Limitations

The main strength of this study is the completeness of data in a nationwide unselected cohort of 37,495 patients who underwent CABG and were followed for a median 7.4 years in a real-world setting. However, our study has several limitations that need to be acknowledged. The main limitation of this study is inherent to its observational design. Our results are dependent on the classification of causes of death. Determining the exact cause of death is a difficult task and is not always possible. In this study, causes of death were retrieved from the nationwide Danish Registry of Causes of Death. The quality of the data relies mainly on the correctness of the physicians' notification and the coding in the National Board of Health.[25] Likewise, comorbidities were defined using hospital discharge diagnoses that may vary in quality. The possibility of a differential classification bias related to the classification of causes of death (ie, definite and possible cardiovascular deaths were considered cardiovascular, and noncardiovascular deaths and deaths due to unknown causes were considered noncardiovascular) cannot be excluded. However, when deaths due to unknown causes were considered cardiovascular, we found similar results as the main analysis. We were not able to evaluate the impact of cardiac rehabilitation, use of artery grafts, or on- or off-pump surgery on cardiovascular deaths. In addition, we had no information on important clinical parameters such as left ventricular systolic function, coronary lesions, plasma creatinine levels, body mass index, smoking habits, and lipid levels; thus, the effect of unmeasured confounders cannot be excluded. Moreover, the Danish universal health care system and the high life expectancy and socioeconomic status in Denmark may affect the generalizability of our findings. The prevalence of diabetes in our cohort was a little more than 20%, which is less frequent than other similar studies and also may affect the generalizability of our findings. In this study, we applied landmark analyses to estimate the absolute risk of causes of death at different time points. However, landmark analyses may be limited by the arbitrary selection of the landmark times. To minimize the impact of this potential limitation, we selected the landmarks a priori on the basis of clinically relevant time points. In addition, a recognized disadvantage of the landmark analysis approach is the omission of events occurring earlier to the landmark time, that is, entry in the 1- to 7-year period is conditional on surviving to 1 year. However, we did provide data before the landmark time points. Finally, with a large sample size, very small differences between groups may become statistically significant, although not necessarily clinically meaningful (ie, liver disease in this study).

CONCLUSIONS

In patients undergoing first-time isolated CABG, cardiovascular causes were responsible for the majority of deaths within the first year. Deaths due to noncardiovascular causes gained importance over time elapsed since CABG.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: coronary artery bypass grafting, coronary artery disease, epidemiology, mortality

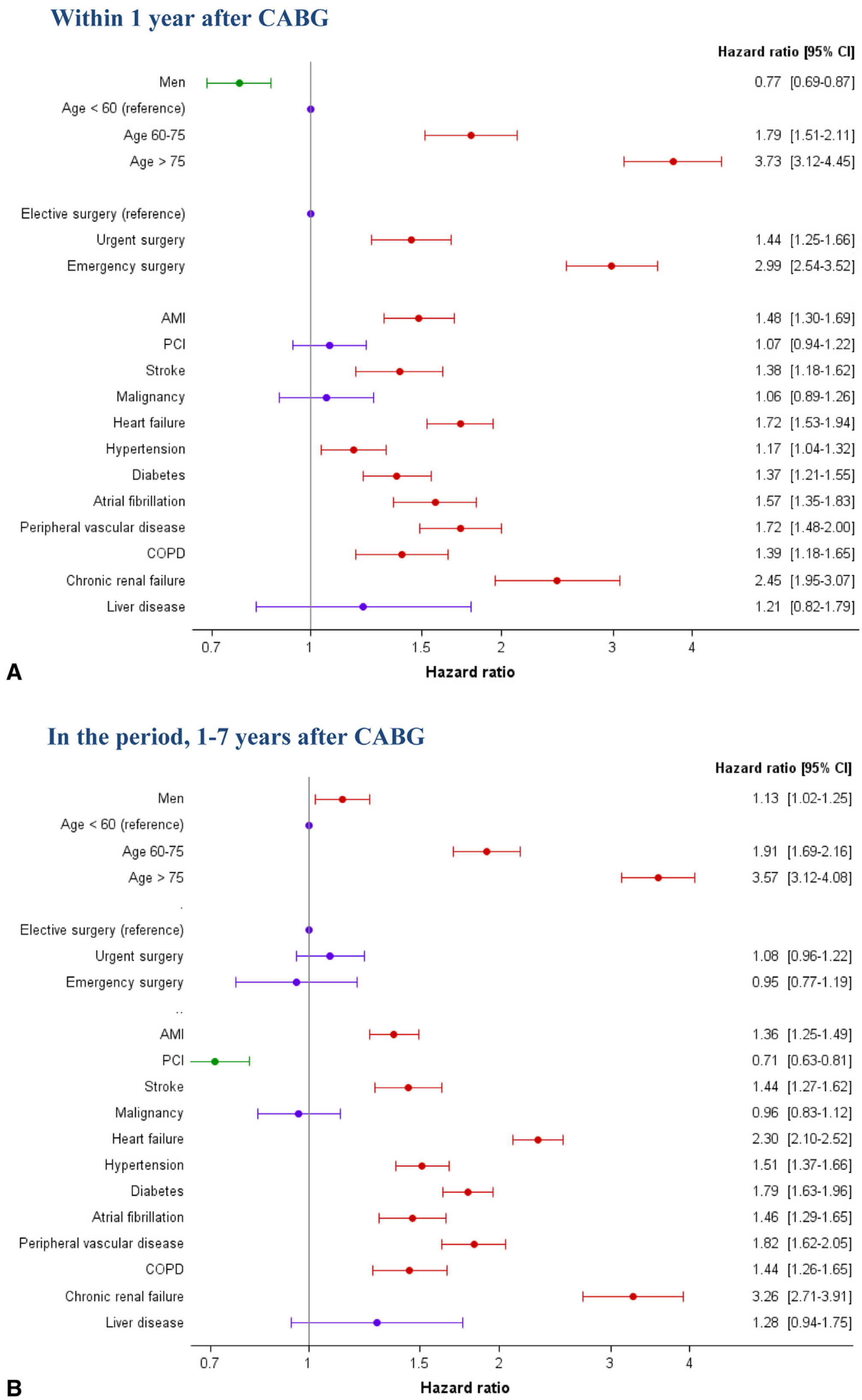

FIGURE E1. Results from the Cox proportional hazard analyses examining factors associated with cardiovascular mortality in patients undergoing CABG. A, Within 1 year after CABG. B, In the period 1 to 7 years after CABG. *CI*, Confidence interval; *AMI*, acute myocardial infarction; *PCI*, percutaneous coronary intervention; *COPD*, chronic obstructive pulmonary disease.

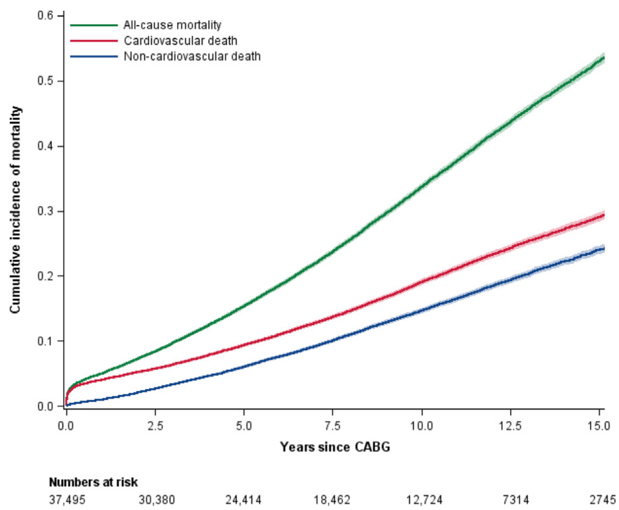

FIGURE E2. Cumulative incidence curves for all-cause mortality, cardiovascular mortality (definite cardiovascular, possible cardiovascular, and unknown), and noncardiovascular mortality in patients undergoing CABG. *CABG*, Coronary artery bypass grafting.

TABLE E1. International Classification of Diseases 8 and 10 codes for comorbidities

Comorbidity	ICD-8 and ICD-10 codes
Acute myocardial infarction	ICD-10: I21, I22 ICD-8: 410
Heart failure	ICD-10: I42, I50, J81, I110, I130, I132 ICD-8: 425, 428, 4270, 4271
Stroke	ICD-10: I60, I61, I63, I64 ICD-8: 430-434, 436
Atrial fibrillation	ICD-10: I48 ICD-8: 4274
Peripheral vascular disease	ICD-10: I70, I74 ICD-8: 443
Malignancy	ICD-10: C00-C97 ICD-8: 140-209
Chronic renal failure	ICD-10: N18, I12, I13, T858, T859, Z992 ICD-8: 585
Chronic obstructive pulmonary disease	ICD-10: J42, J44 ICD-8: 490-492
Liver disease	ICD-10: K70-K77, K704, K766, K711, B150, B160, B190 ICD-8: 571, 572, 456

ICD, International Classification of Diseases.

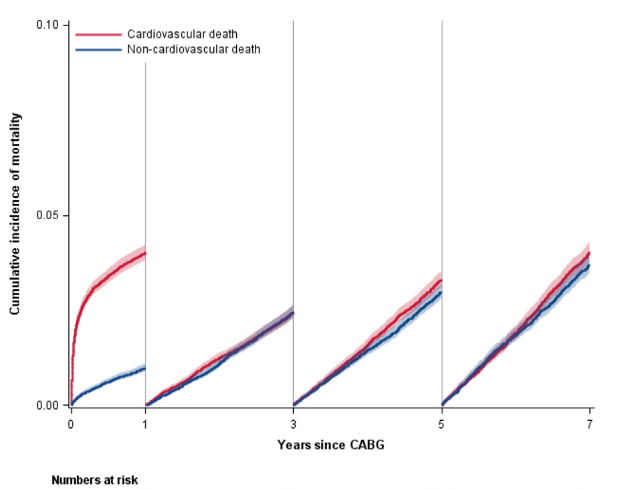

FIGURE E3. Landmark analyses of the cumulative incidences (with confidence intervals) for cardiovascular (definite cardiovascular, possible cardiovascular, and unknown) and noncardiovascular mortality at different time points in patients undergoing CABG. *CABG*, Coronary artery bypass grafting.

TABLE E2. Anatomic Therapeutic Chemical classification codes for pharmacotherapy

Pharmacotherapy	ATC codes
Beta-blockers	C07, C09BX
Calcium channel blockers	C08, C07F, C09BB, C09DB
Renin-angiotensin-system inhibitors	C09
Thiazides	C03A, C07B, C07D, C09XA52, C03EA01
Loop diuretics	C03C, C03EB01, C03EB02
Spironolactone	C03DA01
Statins	C10AA
Anti-diabetics	A10
Acetylsalicylic acid	B01AC06
Clopidogrel	B01AC04
Oral anticoagulants	B01AA, B01AE, B01AF

ATC, Anatomical Therapeutic Chemical.

TABLE E3. International Classification of Diseases 10 codes for causes of death

Cause of death	ICD-10 codes
Definitive cardiovascular	
Acute rheumatic pericarditis	I01.0
Acute rheumatic endocarditis	I01.1
Acute rheumatic myocarditis	I01.2
Rheumatic myocarditis	I09.0
Rheumatic diseases of endocardium, valve unspecified	I09.1
Chronic rheumatic pericarditis	I09.2
Hypertensive heart disease with (congestive) heart failure	I11.0
Hypertensive heart and renal disease with (congestive) heart failure	I13.0
Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	I13.2
Acute myocardial infarction	I21
Subsequent myocardial infarction	I22
Certain current complications following acute myocardial infarction	I23
Other acute ischemic heart diseases	I24
Pulmonary embolism	I26
Acute pericarditis	I30
Other diseases of pericardium	I31
Pericarditis in diseases classified elsewhere	I32
Acute and subacute endocarditis	I33
Endocarditis, valve unspecified	I38
Endocarditis, valve unspecified, in diseases classified elsewhere	I39.8
Acute myocarditis	I40
Myocarditis in diseases classified elsewhere	I41
Cardiomyopathy	I42
Cardiomyopathy in diseases classified elsewhere	I43
Heart failure	I50
Subarachnoid hemorrhage	I60
Intracerebral hemorrhage	I61
Other nontraumatic intracranial hemorrhage	I62
Cerebral infarction	I63
Stroke, not specified as hemorrhage or infarction	I64
Dissection of aorta [any part]	I71.0
Thoracic aortic aneurysm, ruptured	I71.1
Abdominal aortic aneurysm, ruptured	I71.3
Thoracoabdominal aortic aneurysm, ruptured	I71.5
Aortic aneurysm of unspecified site, ruptured	I71.8
Embolism and thrombosis of abdominal aorta	I74.0
Embolism and thrombosis of other and unspecified parts of aorta	I74.1
Possible cardiovascular	
Other I-diagnoses	All I-diagnoses except those mentioned above
Diabetes	E10-E14
Chronic renal failure and diabetes as comorbidity	N18 AND diabetes as comorbidity
Unknown	R95-R99, no information on underlying cause
Noncardiovascular	
Cancer	C00-C97
Infection	A00-B99, J12-J16, J18, J84, J851, J852, J86, N10-N12, N30, N390, G01-G04, G038, G039, K57, R091
Respiratory disease	J00-J99 (except J12-J16, J18, J84, J851, J852, J86)
Renal disease	N00-N99 (except N10-N12, N30)
Other	All ICD-codes not mentioned above

ICD, International Classification of Diseases.

TABLE E4. Concomitant medical treatment 1 y postsurgery in patients undergoing coronary artery bypass grafting according to time of surgery

Concomitant medical treatment, N (%)	All patients N = 33,939	Period 1 (1998-2003) N = 15,837	Period 2 (2004-2009) N = 11,560	Period (2010-2014) N = 6542	*P* value
Statins	27,802 (81.9)	11,238 (71.0)	10,674 (92.3)	5890 (90.0)	<.0001
Beta-blockers	23,322 (68.7)	9516 (60.1)	8861 (76.7)	4945 (75.6)	<.0001
Calcium-blockers	7876 (23.2)	3102 (19.6)	2955 (25.6)	1819 (27.8)	<.0001
Renin-angiotensin-system inhibitors	17,023 (50.2)	6372 (40.2)	6702 (58.0)	3949 (60.4)	<.0001
Thiazide	5161 (15.2)	2395 (15.1)	1955 (16.9)	811 (12.4)	<.0001
Loop diuretics	8534 (25.2)	3928 (24.8)	3057 (26.4)	1549 (23.7)	.50
Spironolactone	2604 (7.7)	1005 (6.4)	985 (8.5)	614 (9.4)	<.0001
Clopidogrel	5163 (15.2)	693 (4.4)	2903 (25.1)	1567 (24.0)	<.0001
Aspirin	27,471 (80.9)	11,756 (74.2)	10,126 (87.6)	5589 (85.4)	<.0001
Oral anticoagulants	2148 (6.3)	772 (4.9)	748 (6.5)	628 (9.6)	<.0001