Short- and long-term cause of death in patients undergoing isolated coronary artery bypass grafting

A nationwide cohort study

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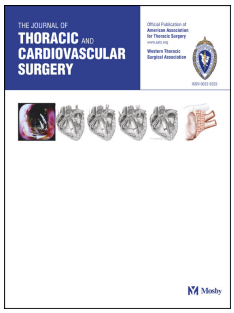

Short- and Long-term Cause of Death in Patients Undergoing Isolated Coronary Artery Bypass Grafting – a Nationwide Cohort Study

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Short- and Long-term Cause of Death in Patients Undergoing Isolated Coronary Artery Bypass Grafting – a Nationwide Cohort Study

Running title: *Butt et al.; Causes of death after CABG*

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Abbreviations

AMI: Acute myocardial infarction

ATC: Anatomical therapeutic chemical

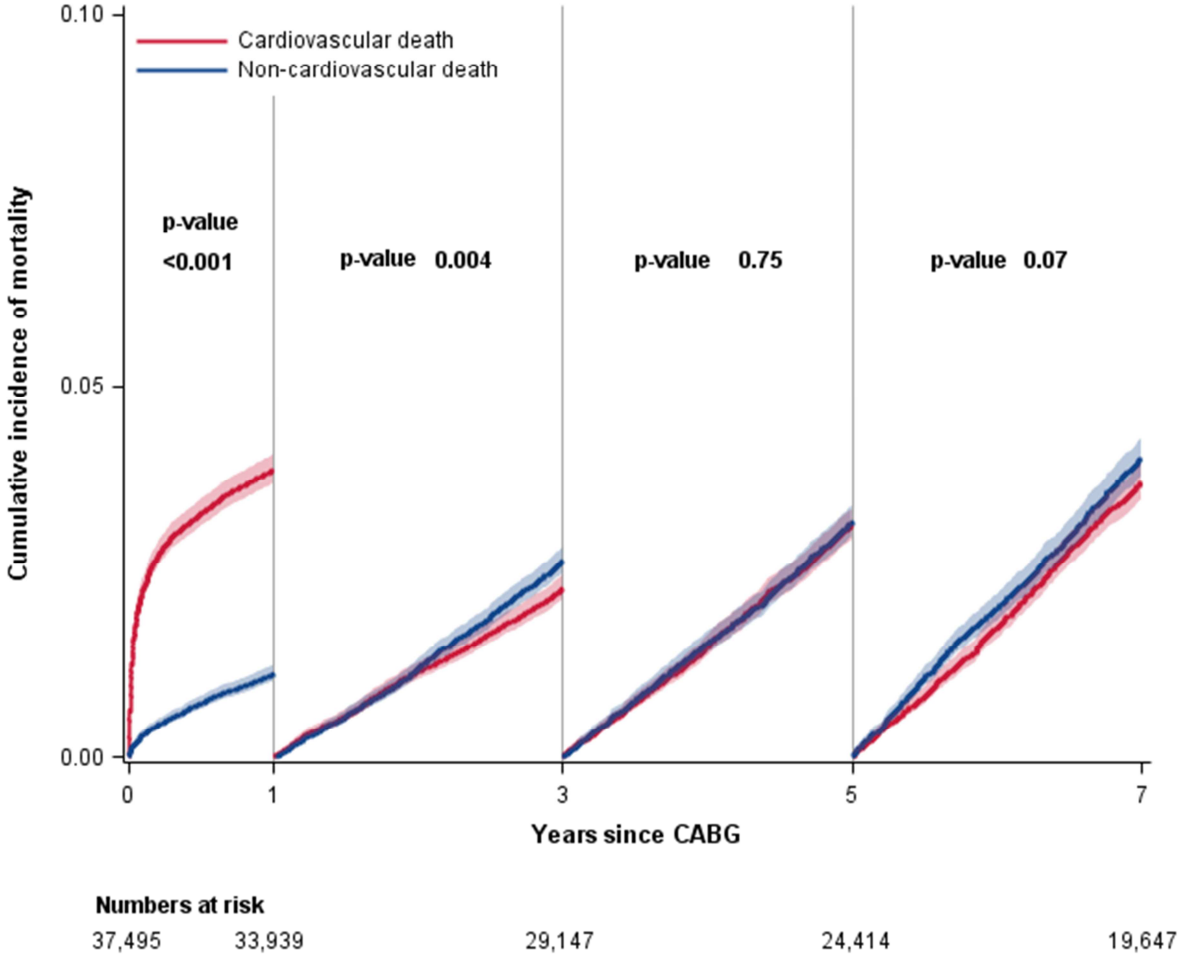
CABG: Coronary artery bypass grafting

CAD: Coronary artery disease

ICD: International classification of diseases

PCI: Percutaneous coronary intervention

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



Central Message

Cardiovascular causes were responsible for the majority of deaths within the first year following CABG. Deaths attributed to non-cardiovascular causes gained importance over time elapsed since CABG.

Perspective Statement

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 ageing population. This knowledge will add further to the information provided to the patients at discharge after CABG about long-term prospects and life expectancy.

Abstract (245 words)

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

Methods: Using Danish nationwide registries, we identified all patients undergoing isolated CABG (1998-2014). Cause of death was classified as cardiovascular or non-cardiovascular according to death certificates. Landmark analyses of the cumulative incidences of cardiovascular and non-cardiovascular mortality after 1, 3, and 5 years after CABG were performed. Multivariable cause-specific Cox regression models were used to evaluate changes over time in the risk of all-cause, cardiovascular, and non-cardiovascular mortality after 1 and 7 years after CABG, 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 (52.8%) and non-cardiovascular in 5771 (47.2%) cases. Within the first year, the incidence of cardiovascular death was higher compared with non-cardiovascular death (3.9% versus 1.1%,p-value <0.001). The cumulative incidences of cardiovascular and non-cardiovascular were deaths similar in the periods 1-3 years (2.3% versus 2.6%,p-value 0.004), 3-5 years (3.1% versus 3.2%,p-value 0.75), and 5-7 years post-surgery (3.7% versus 4.0%,p-value 0.07). 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 CABG, cardiovascular causes were responsible for the majority of deaths within the first year. Deaths attributed to non-cardiovascular causes gained importance over time elapsed since CABG.

Introduction

Over the last four 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 has been investigated in patients undergoing CABG;(2-15) however, studies describing the association between time and causes of death following 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 in order 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 non-cardiovascular 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.

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 four 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 one primary diagnosis and, if appropriate, one 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 (NCSP) used in Nordic countries, are registered by one 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 (ATC) 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 two 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 either elective surgery, urgent surgery (defined as surgery performed during the hospitalization period for acute myocardial infarction (AMI)), or emergency surgery (defined as surgery within 24 h after admission for AMI or surgery on the same day as PCI). Patient comorbidity was obtained through the Danish National Patient Registry using hospital discharge diagnoses prior to admission for CABG (Supplementary Table 1 for 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 prior to admission for CABG (Supplementary Table 2 for ATC 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 which started the process that lead to death) and, if appropriate, one or more contributory causes.(25) Based on the underlying cause, we classified causes of death into the following categories: 1) Definite cardiovascular; 2) possible cardiovascular; 3) non-cardiovascular; and 4) unknown (Supplementary Table 3 for ICD-10 codes). Based on these categories, we further classified causes of death as cardiovascular or non-cardiovascular: The first and second category was considered a cardiovascular death, and the remaining categories were considered a non-cardiovascular death. All-cause mortality, cardiovascular death, and non-cardiovascular death were used as endpoints in separate analyses. Patients were followed from the day of surgery until occurrence of the event (cardiovascular and non-cardiovascular mortality) or the end of the study (December 31, 2014).

Statistical analyses

Descriptive data were reported as frequencies and percentages or median with 25^{th} and 75^{th} percentiles as appropriate. Baseline characteristics were summarized separately according to three time periods in which surgery was performed (i.e. 1998-2003, 2004-2009, and 2010-2014) and differences between groups were tested by applying the Cochran-Armitage test for trend for categorical variables and the Kruskal-Wallis test for continuous variables. Cumulative incidence curves were constructed to compare the absolute incidence of

cardiovascular and non-cardiovascular death while taking into account the competing risk of other causes of death. In addition, landmark analyses of the cumulative incidences of cardiovascular and non-cardiovascular 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 on year 1, 3, and 5 and ended 2 years after each time point. The landmarks were selected a priori based on 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 non-cardiovascular mortality after 1 and 7 years after CABG, respectively. In addition, factors associated with cardiovascular mortality in the time periods, 0-1 and 1-7 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, sex, and several comorbidities were tested for and found not significant, unless otherwise stated. There was no missing data for any of the covariates or outcomes. All statistical analyses were performed with SAS statistical software (SAS 9.4, SAS Institute, Cary, North Carolina, USA). A two-sided p-value <0.05 was considered statistically significant.

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 (25^{th}-75^{th} 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, more often men, more likely to undergo urgent or emergency surgery and had generally more comorbidities compared with those who underwent CABG in the period 1998-2003.

Cause of death

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

Cumulative incidence of death

Figure 1 displays the cumulative incidence curves for all-cause, cardiovascular, and non-cardiovascular 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%.

Results from the landmark analyses of the cumulative incidences of cardiovascular and non-cardiovascular mortality at 1, 3, 5, and 7 years are shown in Central Figure/Figure 2. Within the first year after CABG, the incidence of cardiovascular death was higher compared with non-cardiovascular death (3.9% versus 1.1%, p-value < 0.001). However, the landmark analyses showed similar cumulative incidences of cardiovascular and non-cardiovascular deaths in the periods 1-3 years post-surgery (2.3% versus 2.6%, p-value 0.004), 3-5 years post-surgery (3.1% versus 3.2%, p-value 0.75), and 5-7 years post-surgery (3.7% versus 4.0%, p-value 0.07).

Time trends

The crude rates and adjusted risks of all-cause, cardiovascular, and non-cardiovascular 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, while the risk of non-cardiovascular 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 one year post-surgery stratified according to time of surgery is summarized in Supplementary Table 4. 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 1998-2003.

Factors associated with cardiovascular mortality

Results from the multivariate Cox proportional hazard analysis for 1-year cardiovascular mortality are presented in Supplementary Figure 1a. 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, 1-7 years after CABG are displayed in Supplementary Figure 1b. 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. This analysis yielded similar results as the main analysis (Supplementary Figure 2 and 3).

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, while deaths attributed to non-cardiovascular 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 following CABG; however, these studies were limited by including a small number of patients, investigating subgroups (e.g. patients with heart failure, diabetes, complex CAD etc.), 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 attributed 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 etiology.(16) Data from the 5-

year follow-up of the randomized Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial showed, however, that only 49.5% of all deaths in patients treated with CABG were attributed to a cardiovascular cause. Interestingly, 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 population. However, the low proportion of cardiovascular deaths may partly be explained by the quite 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, of which 74% were considered cardiovascular.(20) The large proportion of cardiovascular deaths and the high mortality observed in the STICH trial is not surprising as the study population comprised only patients with ischemic cardiomyopathy with reduced ejection fraction.

Knowledge of short- and long-term causes of death is crucial in order to improve treatment strategies and secondary prevention programs. In a recent study, Pedersen et al. examined the association between time and cause of death in patients with ST-segment elevation myocardial infarction undergoing primary PCI. Interestingly, the authors found the incidence of non-cardiac 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 ageing population; in line with this, we found that cancer was the most common cause of non-cardiovascular death accounting for 23% of all deaths following CABG.

Our study revealed that 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 CHD, 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 above 70%, though only a part of the patients fulfill a complete comprehensive program.(28) A greater adoption to guideline-directed use of medications post-surgery (i.e. 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 left internal mammary artery to the left anterior descending artery and a saphenous vein graft to the remaining vessels, bilateral mammary 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 support that the superior patency of artery grafts translate into improved clinical outcomes, including death from cardiovascular causes.(29)

Studies examining factors associated with long-term cardiovascular mortality are sparse as focus has mainly 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, 1-7 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.

Strengths and limitations

The main strength of this study is the completeness of data in a nationwide unselected cohort of 37,495 CABG patients 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 upon 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 (i.e. definite and possible cardiovascular deaths were considered cardiovascular, and non-cardiovascular deaths and deaths due to unknown causes were considered non-cardiovascular) 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 as well as the high life expectancy and socioeconomic status in Denmark may affect the generalizability of our findings. The prevalence of diabetes in our cohort was little over 20%, which is less frequent than other similar studies and may also 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 based on 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, i.e. entry in the 1-7 year period is conditional on surviving to one 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 (i.e. liver disease in this study).

Conclusion

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

Acknowledgements

None

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Figure legends

Figure 1. Cumulative incidence curves for all-cause mortality, cardiovascular mortality, and non-cardiovascular mortality in patients undergoing CABG.

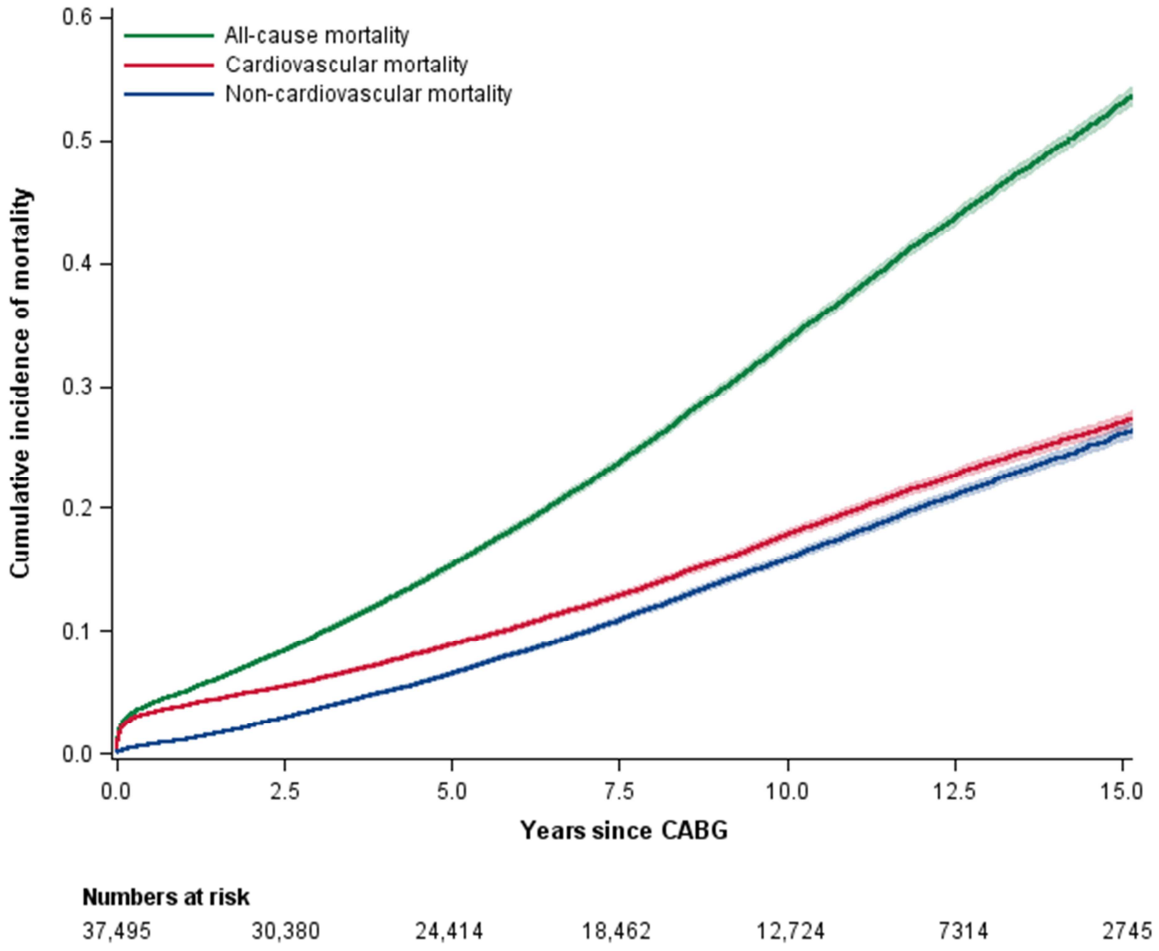
Central Figure/Figure 2. Landmark analyses of the cumulative incidences (with confidence intervals) for cardiovascular and non-cardiovascular mortality at different time points in patients undergoing CABG.

Figure 3. Crude rates and adjusted risks of all-cause, cardiovascular, and non-cardiovascular mortality according to time of surgery in patients undergoing CABG. a) 30-day mortality; b) 1-year mortality; c) 7-year mortality.

Video. Summary of the main findings

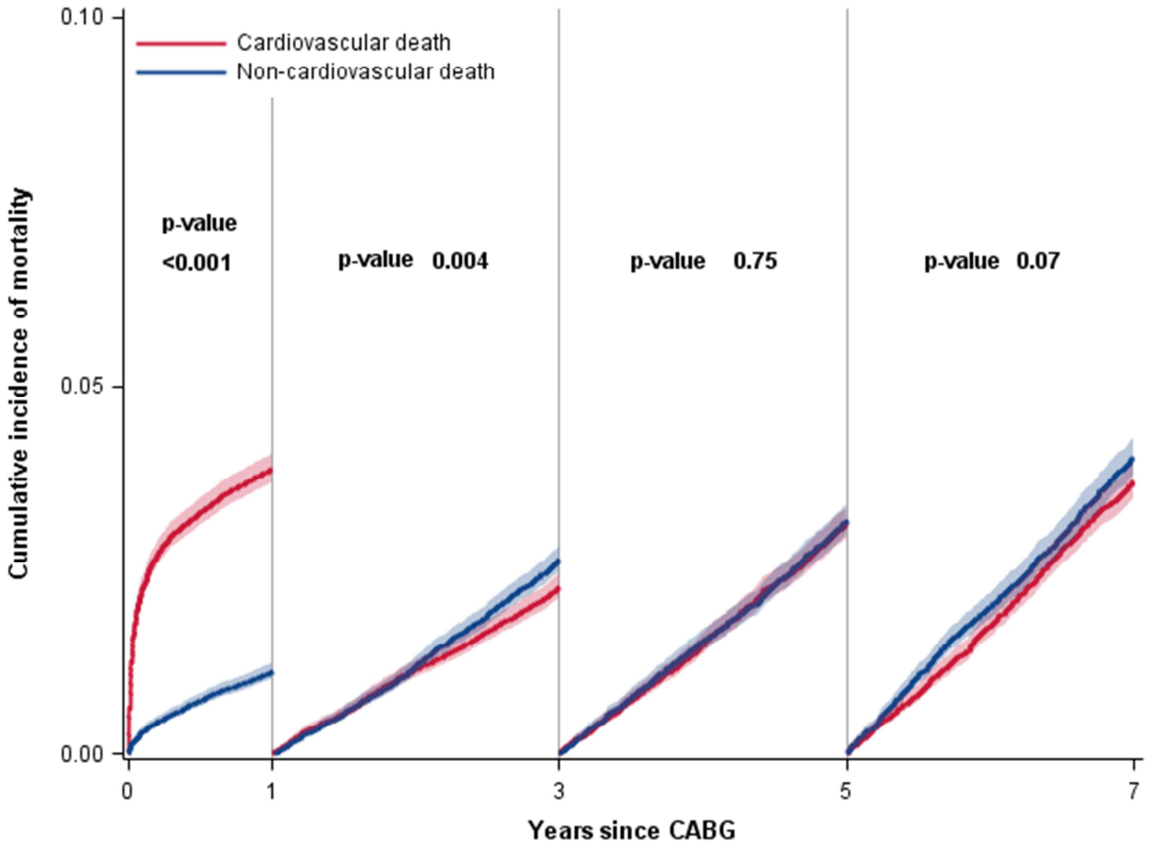
Table 1. Baseline characteristics of patients undergoing coronary artery bypass grafting

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 (median [25th-75th percentile])	**66 (59-72)**	*66 (58-72)*	*67 (60-73)*	*68 (61-74)*	*< 0.0001*
Male, N (%)	**30,037 (80.1)**	*13,150 (79.0)*	*9860 (80.7)*	*7027 (81.4)*	*< 0.0001*
Surgery, N (%)					*< 0.0001*
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)*	*< 0.0001*
Comorbidities, N (%)					
Myocardial infarction	**19,064 (50.8)**	*8864 (53.2)*	*6058 (49.6)*	*4142 (48.0)*	*< 0.0001*
Heart failure	**5398 (14.4)**	*2225 (13.4)*	*1846 (15.1)*	*1327 (15.4)*	*< 0.0001*
Stroke	**2782 (7.4)**	*1121 (6.7)*	*936 (7.7)*	*725 (8.4)*	*< 0.0001*
Atrial fibrillation	**2542 (6.8)**	*1096 (6.6)*	*818 (6.7)*	*628 (7.3)*	*0.05*
Hypertension	**21,973 (58.6)**	*9674 (58.1)*	*7395 (60.6)*	*4903 (56.8)*	*0.33*
Diabetes	**6326 (16.9)**	*2282 (13.7)*	*2146 (17.6)*	*1898 (22.0)*	*< 0.0001*
Peripheral vascular disease	**2582 (6.9)**	*1135 (6.8)*	*902 (7.4)*	*546 (6.3)*	*0.34*
Malignancy	**2947 (7.9)**	*1067 (6.4)*	*1015 (8.3)*	*865 (10.0)*	*< 0.0001*
Chronic renal failure	**676 (1.8)**	*211 (1.3)*	*249 (2.0)*	*216 (2.5)*	*< 0.0001*
Chronic obstructive pulmonary disease	**2234 (6.0)**	*929 (5.6)*	*780 (6.4)*	*525 (6.1)*	*0.04*
Liver disease	**500 (1.3)**	*181 (1.1)*	*183 (1.5)*	*136 (1.6)*	*< 0.0001*
Concomitant medical treatment, N (%)					
Statins	**23,902 (63.8)**	*8445 (50.7)*	*9204 (75.4)*	*6253 (72.4)*	*< 0.0001*
Beta-blockers	**23,938 (63.8)**	*11,062 (66.4)*	*8064 (66.0)*	*4812 (55.7)*	*< 0.0001*
Calcium-blockers	**13,913 (37.1)**	*7133 (42.8)*	*4036 (33.1)*	*2744 (31.8)*	*< 0.0001*
Renin-angiotensin-system inhibitors	**15,996 (42.7)**	*5666 (34.0)*	*5888 (48.2)*	*4442 (51.5)*	*< 0.0001*
Thiazide	**6179 (16.5)**	*2628 (15.8)*	*2253 (18.5)*	*1298 (15.0)*	*0.87*
Loop diuretics	**6276 (16.7)**	*3213 (19.3)*	*1992 (16.3)*	*1071 (12.4)*	*< 0.0001*
Spironolactone	**1536 (4.1)**	*597 (3.6)*	*577 (4.7)*	*362 (4.2)*	*< 0.0001*
Clopidogrel	**4444 (11.9)**	*995 (6.0)*	*2364 (19.4)*	*1085 (12.6)*	*< 0.0001*
Aspirin	**25,499 (68.0)**	*10,833 (65.1)*	*8829 (72.3)*	*5837 (67.6)*	*< 0.0001*
Oral anticoagulants	**1464 (3.9)**	*597 (3.6)*	*452 (3.7)*	*415 (4.8)*	*< 0.0001*



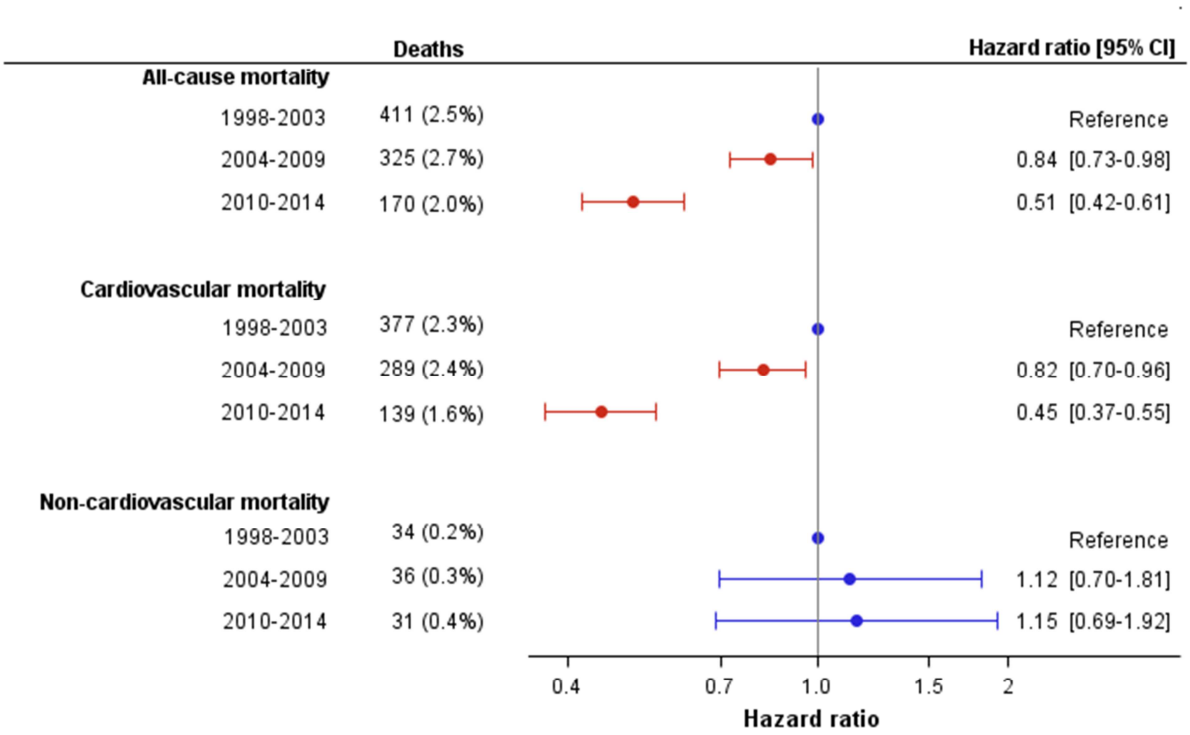
Numbers at risk

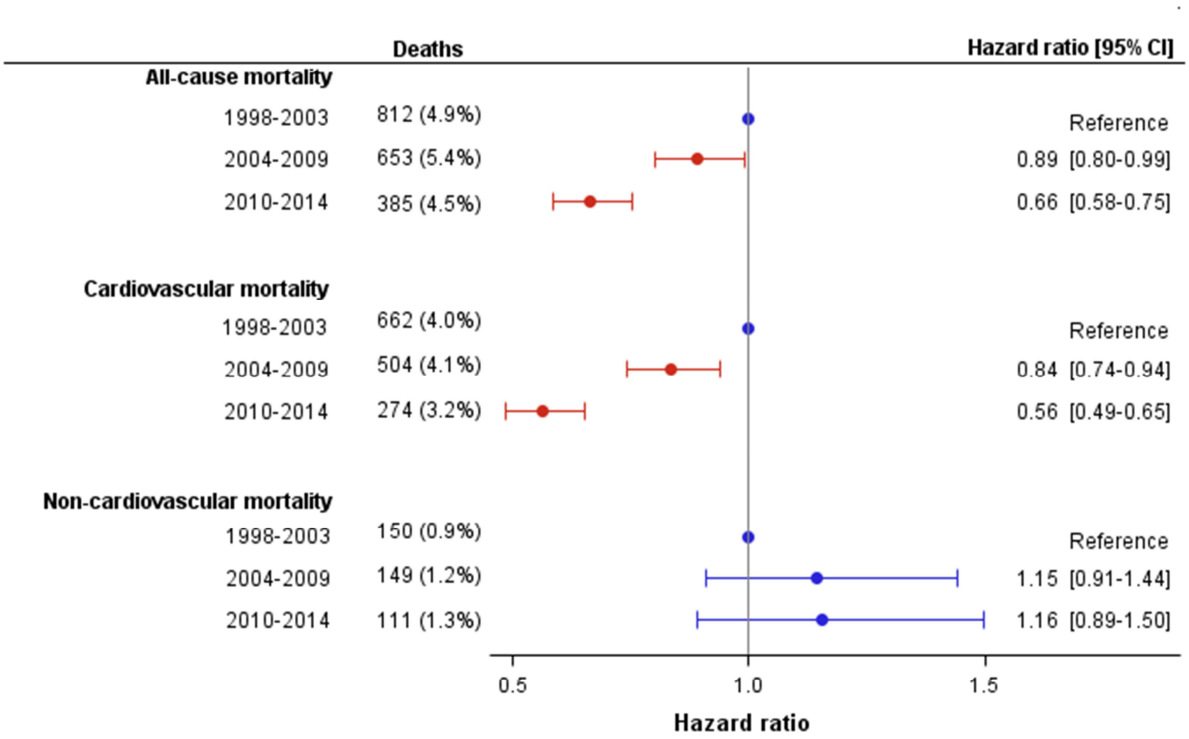
37,495	30,380	24,414	18,462	12,724	7314	2745

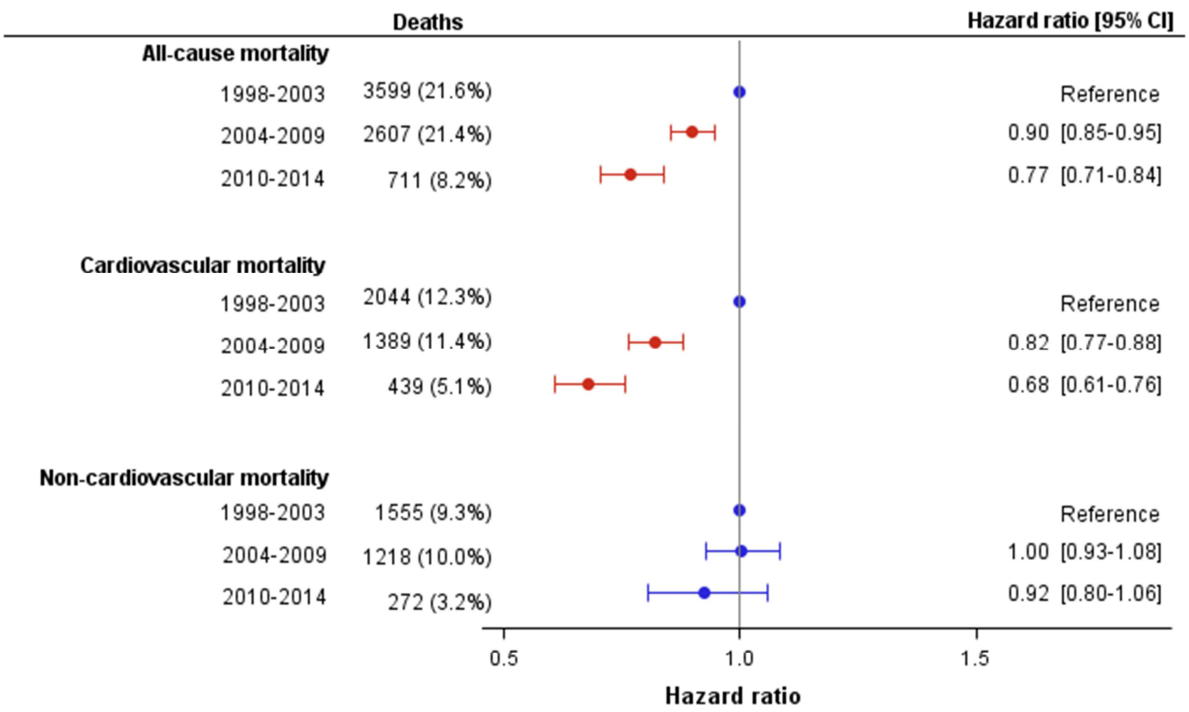


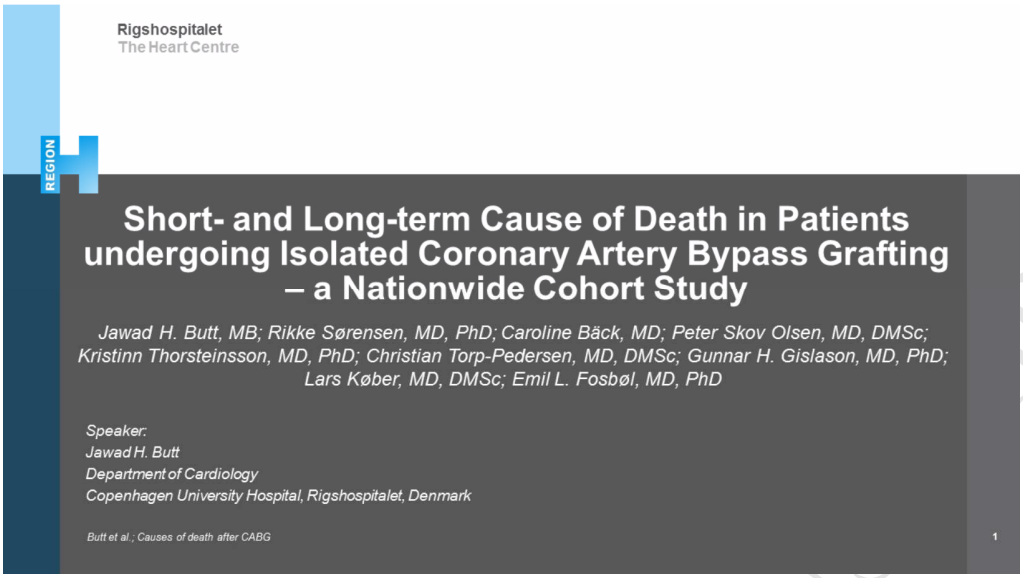
Numbers at risk

37,495	33,939	29,147	24,414	19,647









Supplementary Table 1. International Classification of Diseases (ICD) 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

Supplementary Table 2. Anatomical Therapeutic Chemical (ATC) 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

Supplementary Table 3. International Classification of Diseases (ICD) 10 codes for causes of death

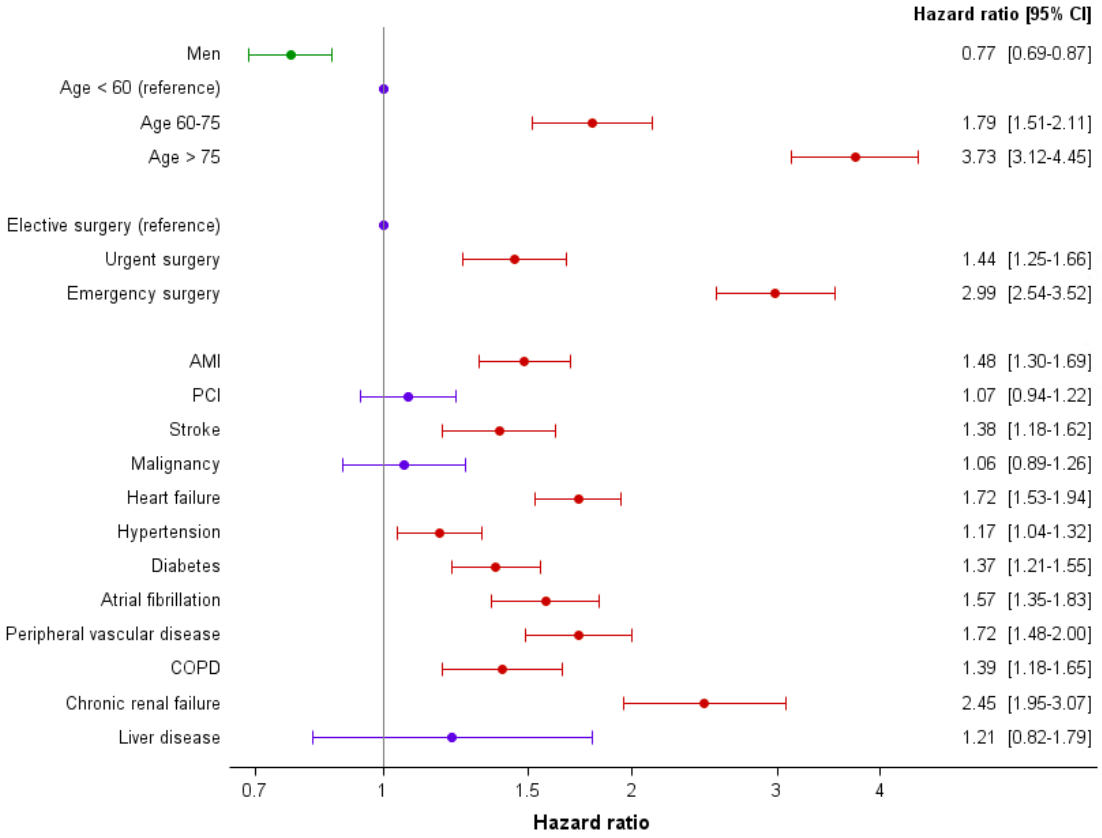
Cause of death	ICD-10 codes
Definitive cardiovascular	
Acute rheumatic pericarditis	I01.0
Acute rheumatic endocarditis	I01.1
Acute rheumatic myocarditis	I01.2
Rheumatic myocarditis	I09.0
Rheumatic diseases of endocardium, valve unspecified	I09.1
Chronic rheumatic pericarditis	I09.2
Hypertensive heart 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 ischaemic 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 haemorrhage	I60
Intracerebral haemorrhage	I61
Other nontraumatic intracranial haemorrhage	I62
Cerebral infarction	I63
Stroke, not specified as haemorrhage 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
Non-cardiovascular	
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

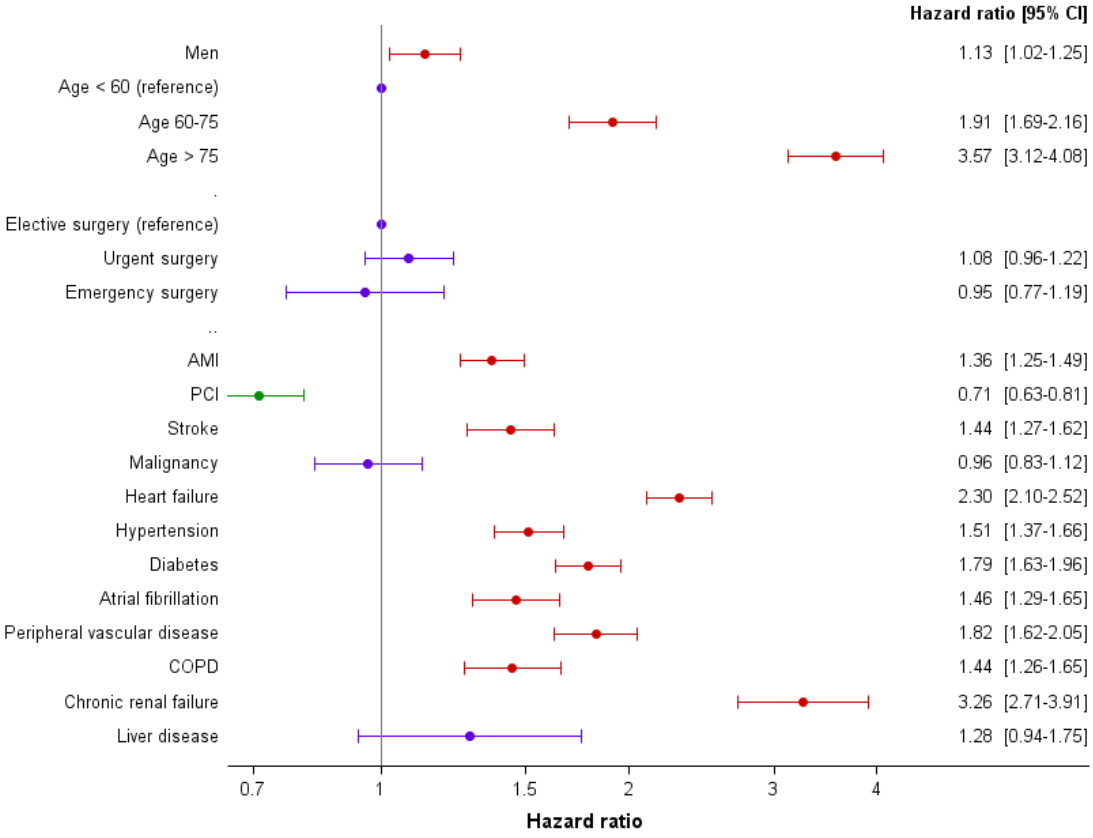
Supplementary Table 4. Concomitant medical treatment one year post-surgery in patients undergoing coronary artery bypass grafting according to time of surgery

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)*	*< 0.0001*
Beta-blockers	**23,322 (68.7)**	*9516 (60.1)*	*8861 (76.7)*	*4945 (75.6)*	*< 0.0001*
Calcium-blockers	**7876 (23.2)**	*3102 (19.6)*	*2955 (25.6)*	*1819 (27.8)*	*< 0.0001*
Renin-angiotensin-system inhibitors	**17,023 (50.2)**	*6372 (40.2)*	*6702 (58.0)*	*3949 (60.4)*	*< 0.0001*
Thiazide	**5161 (15.2)**	*2395 (15.1)*	*1955 (16.9)*	*811 (12.4)*	*< 0.0001*
Loop diuretics	**8534 (25.2)**	*3928 (24.8)*	*3057 (26.4)*	*1549 (23.7)*	*0.50*
Spironolactone	**2604 (7.7)**	*1005 (6.4)*	*985 (8.5)*	*614 (9.4)*	*< 0.0001*
Clopidogrel	**5163 (15.2)**	*693 (4.4)*	*2903 (25.1)*	*1567 (24.0)*	*< 0.0001*
Aspirin	**27,471 (80.9)**	*11,756 (74.2)*	*10,126 (87.6)*	*5589 (85.4)*	*< 0.0001*
Oral anticoagulants	**2148 (6.3)**	*772 (4.9)*	*748 (6.5)*	*628 (9.6)*	*< 0.0001*

Supplementary Figure 1. Results from the Cox Proportional Hazard analyses examining factors associated with cardiovascular mortality in patients undergoing coronary artery bypass grafting. a) Within 1 year after CABG;

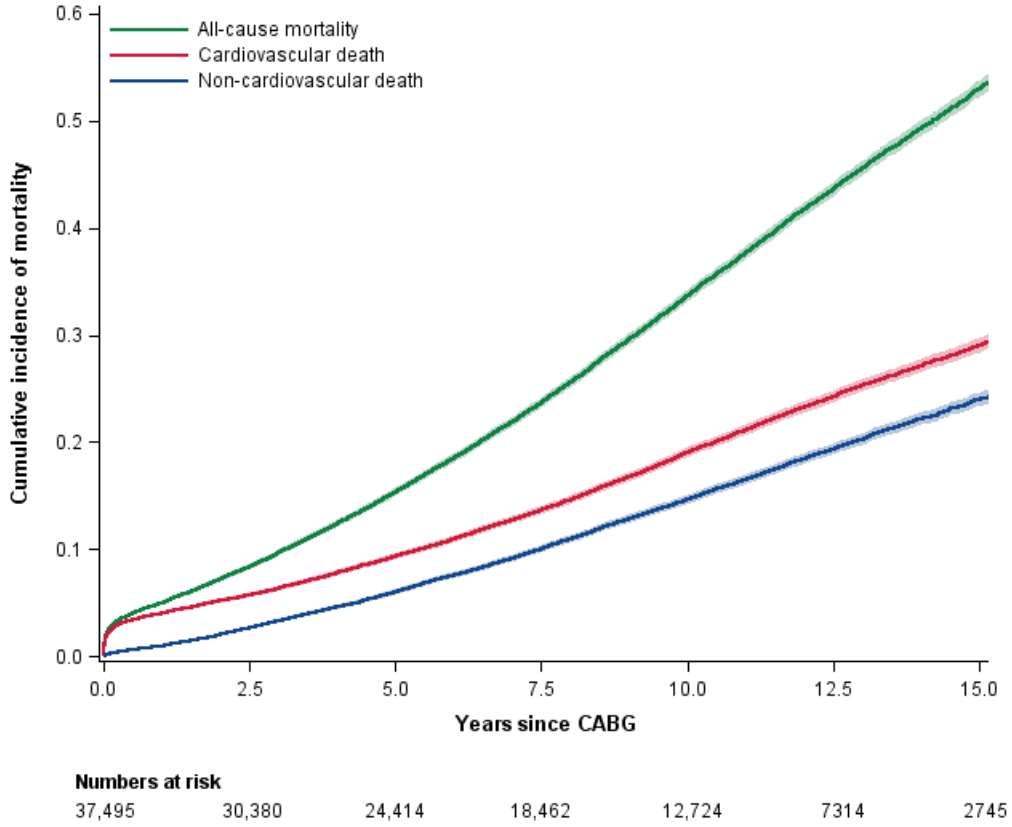


b) In the period, 1-7 years after CABG.



AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; COPD = chronic obstructive pulmonary disease.

Supplementary Figure 2. Cumulative incidence curves for all-cause mortality, cardiovascular mortality (definite cardiovascular, possible cardiovascular, and unknown), and non-cardiovascular mortality in patients undergoing CABG.



Supplementary Figure 3. Landmark analyses of the cumulative incidences (with confidence intervals) for cardiovascular (definite cardiovascular, possible cardiovascular, and unknown) and non-cardiovascular mortality at different time points in patients undergoing CABG.