Outcomes After ST-Segment Versus Non-ST-Segment Elevation Myocardial Infarction Revascularized by Coronary Artery Bypass Grafting

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The objectives of this study were to investigate the outcome differences between ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) patients treated with coronary artery bypass grafting surgery (CABG). We conducted a multicenter, retrospective cohort follow-up study of consecutive patients with STEMI (surgery ≤48 hours of admission; n = 348) or NSTEMI (n = 1,160) revascularized with first-time isolated CABG in Finland using nationwide registries (median age 68 years, 24% women). The short- and long-term (10-year) outcomes were studied with inverse propensity probability weight adjustment for baseline features. The median follow-up was 5.2 years. In-hospital mortality (11.4% vs 5.3%; adj. odds ratio [OR] 2.27; confidence interval [CI] 1.41 to 3.66; p = 0.001) and re-sternotomy rates (6.9% vs 3.5%; adj. OR 2.07; CI 1.22 to 3.51; p = 0.007) were higher in STEMI patients. Long-term all-cause mortality did not differ between STEMI and NSTEMI patients among all operated patients (30.2% vs 28.3%; adj. HR 1.30; CI 0.97 to 1.75; p = 0.080) or hospital survivors (21.6 vs 24.3%; HR 0.93; CI 0.64 to 1.36; p = 0.713). Occurrence of major adverse cardiovascular event in hospital survivors within 10 years was 34.7% in STEMI versus 29.6% in NSTEMI (adj. HR 1.24; CI 0.88 to 1.76; p = 0.220). Occurrences of cardiovascular death (14.6% vs 14.4%; p = 0.773), myocardial infarction (MI; 15.2% vs 10.3%; p = 0.203), and stroke (10.8% vs 14.8%; p = 0.242) were also comparable. In conclusion, patients with STEMI have poorer short-term outcome compared to NSTEMI patients after revascularization by CABG, but the long-term outcomes are comparable regardless of MI type. Thus, both short- and long-term risks should be considered when evaluating patients for CABG eligibility by MI type. **(Am J Cardiol 2020;135:17−23)**

Myocardial infarction (MI) is a major cause of morbidity and mortality world-wide.[1] In ST-segment elevation myocardial infarction (STEMI), acute total coronary occlusion is regularly present, requiring immediate revascularization.[2] In non-ST-segment myocardial infarction (NSTEMI), the coronary perfusion is impaired, but commonly not totally occluded requiring nonemergent early revascularization.[3] In NSTEMI patients, choice of revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting surgery (CABG) is based on clinical presentation, patient characteristics, and differences in coronary lesions.[3−5] Primary PCI is the first-line treatment in STEMI, but CABG is the treatment of choice in PCI failure, presence of special features (e.g., double antithrombotic treatment cannot be used), or as means to complete revascularization in left-main or multivessel coronary artery disease after culprit-only PCI.[2,4,5] In US 5% to 10% of STEMI and c.a. 10% of NSTEMI patients are treated with CABG with significant interhospital variability.[6,7] Reported early mortality of MI patients treated with CABG varies from 3% to 22%.[7−9] Of MI patients in general, those with STEMI have poorer short-term outcome than NSTEMI patients.[10] Little is however known whether outcomes of CABG-treated STEMI and NSTEMI differ in short-, and especially, on the long term. Thus, we investigated the outcome differences of STEMI and NSTEMI patients treated with CABG in a baseline adjusted real-world population-based cohort.

Methods

Short- and long-term outcomes between STEMI and NSTEMI patients treated with isolated CABG were studied. In-hospital outcomes were all-cause mortality, re-sternotomy, and duration of admission (of hospital survivors). Long-term outcomes were all-cause mortality, combined

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major adverse cardiovascular event (MACE; defined as cardiovascular mortality, MI, or stroke), and individual components of MACE studied for 10-year occurrence of hospital survivors after CABG. Study design and outcomes are described in more detail in the Supplement. The Care Register for Healthcare in Finland was used to identify all patients aged ≥18 who underwent CABG as primary operation for STEMI or NSTEMI between January 1, 2004 and December 31, 2014 in Finland. This obligatory-by-law, nationwide registry includes data on all hospital admissions in Finland.[11] Of STEMI patients, only those with CABG ≤48 hours from beginning of the MI admission were included. Patients with prior CABG or other cardiac surgery, concomitant other cardiac surgery, or CABG using free arterial or gastroepiploic arterial grafts were excluded. Co-morbidities were recognized from the Care Register for Healthcare in Finland and the Nationwide database of permissions for drug reimbursements in Finland using previously described ICD coding[12] and drug purchase reimbursement codes (https://www.kela.fi/web/en/medicine-expenses). Survival data of patients were obtained from nationwide, cause of death registry held by Statistics Finland. Follow-up for mortality ended 10 years after index operation or on December 31, 2016 which ever came first. The National Institute for Health and Welfare of Finland (permissions no: THL/143/5.05.00/2015 and THL/1569/5.05.00/2016), Social Insurance Institution of Finland (91/522/2015), and the Statistics Finland (TK53-1410-15) approved the study. Informed consent was not required due to the retrospective nature of the study.

Baseline differences between study groups were balanced with inverse probability weighting for propensity score (IPW).[13] Propensity score including all baseline features listed in Table 1 was created with logistic regression. IPWs were calculated based on propensity score. To improve balancing patients with nonoverlapping propensity scores were excluded from weighting (1 STEMI and 7 NSTEMI patients). Inverse weighting resulted in balanced study groups (Supplement, Table 1). In order to maintain balance, hospital surviving patients were re-weighted. Effect sizes between study groups were evaluated with standardized difference scores. Differences between groups were studied by two-way Wilcoxon rank-sum test after evaluation of normality assumption with Kolmogorov-Smirnov test and Chi-Square test. In-hospital mortality and re-sternotomy were studied using logistic regression. Long-term outcomes were studied using the Kaplan-Meier method and Cox regression. Proportional hazard assumptions were confirmed by examination of Schoenfeld residuals. Competing risk due to death was accounted for by

Table 1
Features of ST-elevation (STEMI) and non-ST-elevation (NSTEMI) myocardial infarction patient revascularized with coronary artery bypass grafting

	Original cohort					Weighted cohorts	
Variable	All patients (n=1508)	STEMI (n=348)	NSTEMI (n=1160)	P-value	|SMD|	All (n=1500) |SMD|	Hospital survivors (n=1396) |SMD|
Age, years (Median, IQR)	69 (61-77)	67 (60-74)	69 (62-76)	0.0001	0.23	0.06	0.08
Women	361 (23.9%)	77 (22.1%)	284 (24.5%)	0.366	0.06	0.02	0.003
Atrial fibrillation	121 (8.0%)	18 (5.2%)	103 (8.9%)	0.026	0.15	0.07	0.05
Cerebrovascular disease	104 (6.9%)	22 (6.3%)	82 (7.1%)	0.630	0.03	0.02	0.01
Chronic pulmonary disease	123 (8.2%)	24 (6.9%)	99 (8.5%)	0.328	0.06	0.01	0.02
Diabetes mellitus	415 (27.5%)	63 (18.1%)	352 (30.3%)	<0.0001	0.29	0.002	0.03
Heart Failure	196 (13.0%)	35 (10.1%)	161 (13.9%)	0.063	0.12	0.07	0.08
Hypertension	759 (50.3%)	135 (38.8%)	624 (53.8%)	<0.0001	0.30	0.01	0.02
Liver disease	5 (0.3%)	2 (0.6%)	3 (0.3%)	0.368	0.05	0.02	0.02
Malignancy	104 (6.9%)	17 (4.9%)	87 (7.5%)	0.091	0.11	0.04	0.04
Peripheral vascular disease	82 (5.4%)	11 (3.2%)	71 (6.1%)	0.033	0.14	0.04	0.03
Prior myocardial infarcion	466 (30.9%)	96 (27.6%)	370 (31.9%)	0.127	0.09	0.01	0.02
Rheumatic disease	53 (3.5%)	8 (2.3%)	45 (3.9%)	0.160	0.09	0.002	0.004
Renal disease	30 (2.0%)	5 (1.4%)	25 (2.2%)	0.400	0.05	0.004	0.03
Type of bypass graft				<0.0001			
Only IMA	295 (19.9%)	74 (21.3%)	221 (19.1%)		0.06	0.02	0.04
Only venous	187 (11.7%)	71 (20.4%)	116 (10.0%)		0.29	0.002	0.001
IMA and venous	1026 (68.4%)	203 (58.3%)	823 (71.0%)		0.27	0.02	0.03
Number of coronary anastomoses				0.205			
1	299 (19.8%)	79 (22.7%)	220 (19.8%)		0.09	0.02	0.02
2	216 (14.3%)	58 (16.7%)	158 (13.6%)		0.08	0.03	0.03
3	439 (29.1%)	86 (24.7%)	353 (30.4%)		0.13	0.02	0.05
4	336 (22.3%)	74 (21.3%)	262 (22.6%)		0.03	0.02	0.02
5	164 (10.9%)	40 (11.5%)	124 (10.7%)		0.03	0.03	0.04
≥6	54 (3.6%)	11 (3.2%)	43 (3.7%)		0.03	0.001	0.01
Operation year				<0.0001	0.45	0.09	0.09
Surgical center (n = 6)				0.713	0.01	0.04	0.03

Differences between groups for original study cohort and for inverse probability weighted cohorts. SMD = Standardized mean difference, IMA = Internal mammary artery.

application of cause-specific hazard models in outcome analysis. Admission duration from CABG to discharge (beginning days) of hospital survivors was studied using negative binomial regression. ST-elevation MI was used as the reference in regression modelling. Adjustment for baseline covariates was performed by weighting with stabilized IPWs. Results of unadjusted analyses are presented in Supplement Table 1. Robust sandwich type estimates were obtained for regression analyses.[14] Median follow-up for mortality was evaluated by reverse Kaplan-Meier method including all patients. Results are given as the mean, median, percentage, hazard ratio (HR), relative risk (RR), or odds ratio (OR) with 95% confidence interval (CI) or interquartile range (IQR). A P value <0.05 was considered

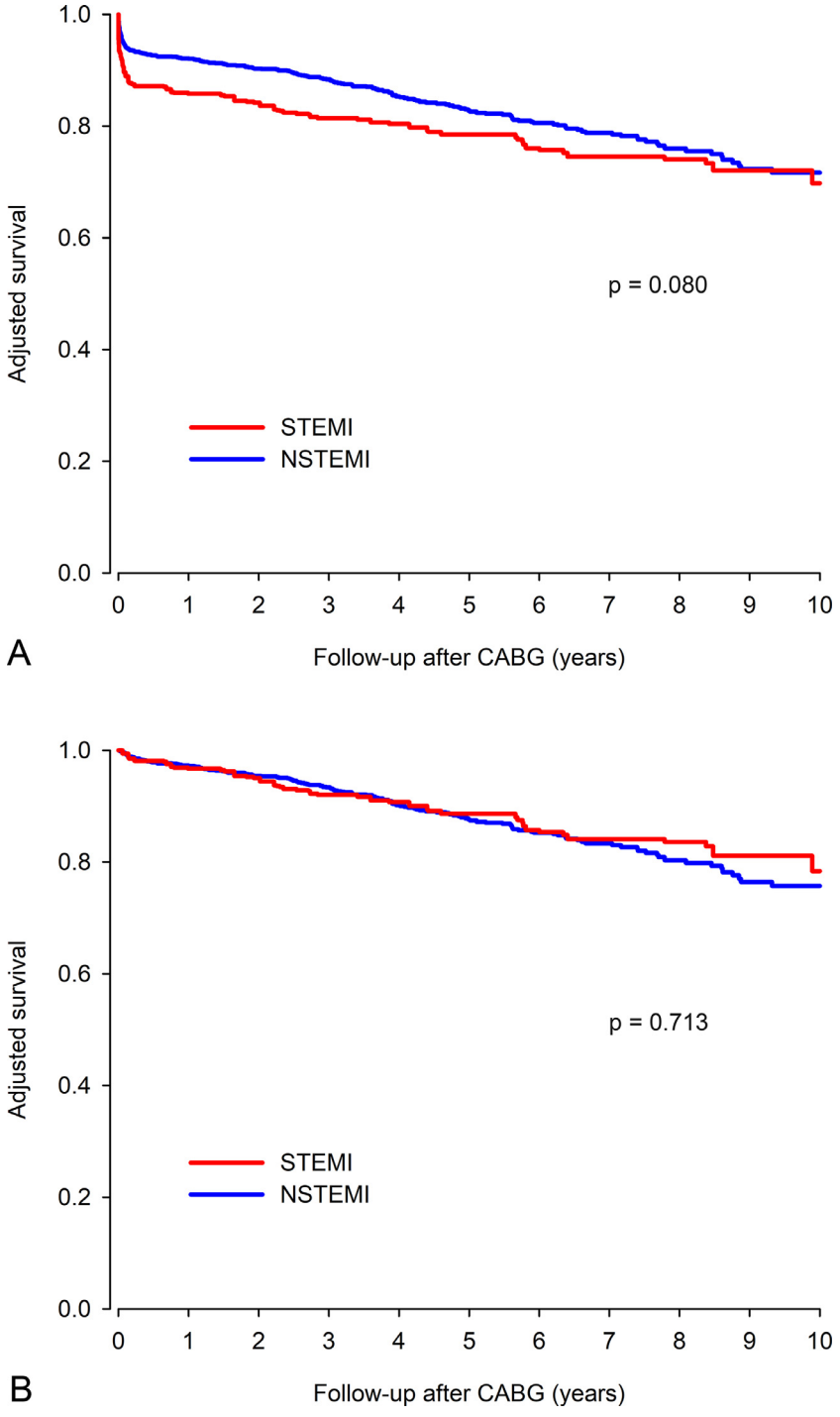

Figure 1. Cumulative adjusted survival in ST-elevation (STEMI) and non-ST-elevation (NSTEMI) patients revascularized with coronary artery by-pass grafting surgery (CABG). Results of all operated patients *(A)* and hospital survivors *(B)*.

statistically significant. Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Baseline features of all operated patients are presented in Table 1. Of all patients treated with CABG, 23% (n = 348) had STEMI and 67% NSTEMI (n = 1,160). Number of CABG operations for these patients increased significantly during study period (Supplement Figure 1). Of STEMI patients 52% had anterior, 30% inferior, and 18% lateral or unspecified location infarction. Differences in baseline features were balanced with IPW (Table 1). The median follow-up was 5.2 years.

Adjusted in-hospital mortality rate was 11% in STEMI and 5% in NSTEMI groups (OR 2.27; CI 1.41 to 3.66; p = 0.001). Re-sternotomy during MI admission was performed to 7% of STEMI and 4% of NSTEMI patients (OR 2.07; CI 1.22 to 3.51; p = 0.007). The median duration of hospital stay after CABG was 13 (IQR 9 to 17) days in STEMI and 12 (IQR 9 to 16) days in NSTEMI patients (p = 0.025).

Long-term mortality was not significantly different between weighted STEMI and NSTEMI patients (Figure 1). Higher in-hospital mortality of STEMI persisted in all revascularized patients at 1-year (14% vs 8%; HR 1.88; CI 1.27 to 2.80; p = 0.002). However, at 10-year follow-up of all operated patients, there was no significant difference in cumulative all-cause mortality (30% in STEMI vs 28% in NSTEMI; HR 1.30; CI 0.97 to 1.75; p = 0.080). Among hospital-survivors, the cumulative all-cause mortality was 21% in STEMI and 24% in NSTEMI patients (HR 0.93; CI 0.64 to 1.36; p = 0.713).

Occurrence of MACE in long-term follow-up after CABG did not differ significantly between the study groups (Figure 2). Ten-year cumulative occurrence of MACE in hospital survivors was 34% in STEMI patients compared to 30% in NSTEMI patients (HR 1.24; CI 0.88 to 1.76; p = 0.220). Occurrence of MACE sub-components was also similar in STEMI and NSTEMI patients within 10-year follow-up after CABG (Figure 3). Cardiovascular mortality rate was 15% in STEMI versus 14% in NSTEMI (HR 1.07; CI 0.67 to 1.72; p = 0.773) patients. New myocardial infarction occurred to 15% of STEMI versus 10% of NSTEMI patients (HR 1.41; CI 0.83 to 2.38; p = 0.203) and stroke to 11% versus 15% of patients (HR 1.18; CI 0.66 to 2.10; p = 0.308).

Discussion

This nationwide multicenter study investigated outcome differences of baseline adjusted STEMI and NSTEMI patients revascularized with CABG. Patients with STEMI had significantly poorer short-term outcome. At long-term, however, outcomes of STEMI and NSTEMI patients were comparable.

The number of MI patients treated with CABG increased significantly in Finland from 2004 to 2014. Number of STEMI patients remained quite stable whereas CABG as the revascularization in patients NSTEMI increased substantially. Similar trends for STEMI/NSTEMI distribution are present in the United States[7] and are likely due to increasing activity of invasive treatment in older and sicker patients, and developments in PCI techniques.

Unadjusted in-hospital mortality rate of CABG treated STEMI was 11% in the current study. Short-term mortality of CABG treated STEMI patients is found to range from

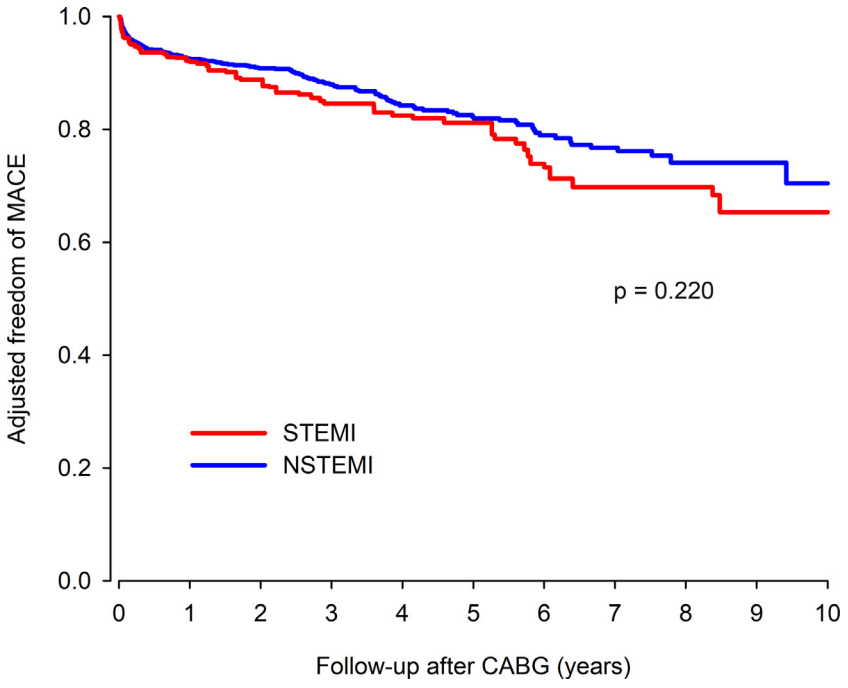

Figure 2. Cumulative adjusted freedom of major adverse cardiovascular event (MACE) after coronary artery by-pass grafting surgery (CABG) in ST-elevation (STEMI) and non-ST-elevation (NSTEMI) myocardial infarction patients (hospital survivors).

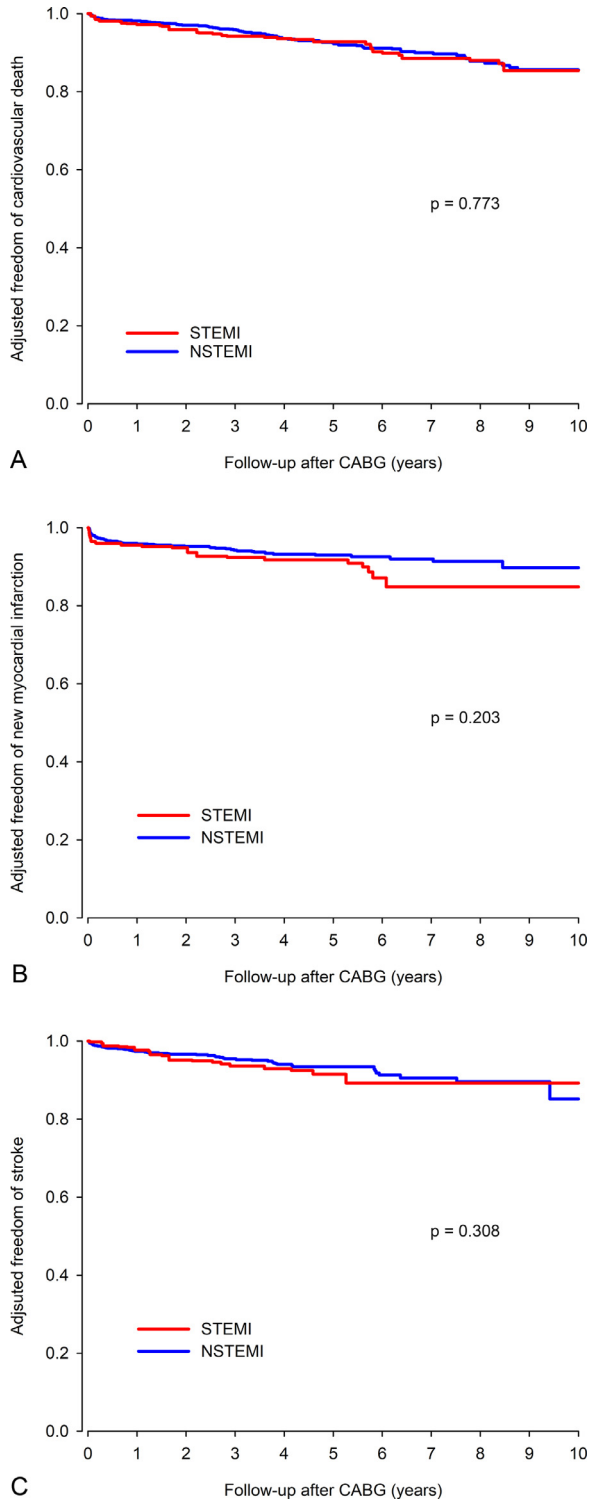

Figure 3. Cumulative adjusted freedom of cardiovascular death *(A)*, new myocardial infarction *(B)*, and stroke *(C)* in ST-elevation (STEMI) and non-ST-elevation (NSTEMI) myocardial infarction patients (hospital survivors) after coronary artery bypass grafting (CABG).

5% to 14% in previous studies.[6,7,15,16] Mortality rates between studies are however not directly comparable due to possible differences in study settings and patient selection. Timing of CABG is associated with mortality in STEMI[8] more than in NSTEMI.[17] The necessity for earlier CABG in STEMI results to poorer outcome.[16,18] In this study, we included STEMI patients requiring early CABG (within 48 hours of admission[19]), although we did not have information regarding symptom onset.

Of all MI patients, those with STEMI are found to be at higher short-term mortality risk compared with NSTEMI patients with approximately 1% absolute difference in mortality in large registry study from UK and Sweden.[10] Comparative data of outcomes in STEMI versus NSTEMI patients treated with CABG is however scarce. Previous US study by Lee et al found identical in-hospital mortality of 3% in analysis of transmural and non-transmural MI in CABG patients when including all operated patients, but STEMI patients operated within 7 days after MI had poorer in-hospital outcome compared to NSTEMI.[20] We found baseline adjusted in-hospital mortality of STEMI patients with early operation to be more than double (11% vs 5%) compared with NSTEMI patients. Yet the mortality of STEMI patients treated with CABG does not dramatically differ from mortality rate of all STEMI patients in Finland (11%), as previously reported.[21] Taken together, these results support the notion that timely CAGB can be safely performed to both STEMI and NSTEMI patients when clinically justified.[6]

Re-sternotomy rate reflecting major uncontrolled bleeding was also increased in STEMI patient (7% vs 4% in NSTEMI). This can be explained by more aggressive antithrombotic and anti-coagulant therapy in STEMI[22] and usage of thrombolysis during the study period.

Importantly, we however found no difference in the long-term outcomes of STEMI and NSTEMI patients. Long-term hazard of both mortality and cardiovascular end-points were comparable between MI types. Of all MI patients, those with STEMI are found to have lower long-term risk of death compared to patients with NSTEMI.[23] The current study is however, at least to our knowledge, the first direct comparison for long-term outcomes of STEMI and NSTEMI patients treated with CABG. Comparable long-term risk in STEMI and NSTEMI patients has important clinical implications. Primarily, early surgery for STEMI should not be denied on basis of poorer projected long-term outcome. Furthermore, follow-up of MI patients treated with CABG may not need to be specially tailored by the MI type in general. Efficient secondary prevention and adequate follow-up is however of pivotal importance in all MI patients with approximately one third of hospital survivors facing cardiovascular death, MI, or stroke during 10 years after CABG.

We acknowledge that the current study has some limitation. The major limitation is the retrospective design. Previously validated nationwide, mandatory by law registries were used,[24] but inherent limitations and sources of bias in registry data are nevertheless possible. Clinicians were responsible for diagnoses in the registries and coding errors are possible. We did not have access to more detailed operative or clinical information, or to usage of pharmacotherapies. Moreover, the information of medication used during hospital admissions was not obtain from these registries. It is however unlikely that these limitations would have significantly different impact on study groups in the current

study setting. Weighting for baseline propensity score was used to balance differences between study groups, but it is possible that additional non-recognizable co-founders may impact the results. Due to these limitations and the fact that we did not study post-CABG confounders (such as pharmacotherapy or extent of myocardial damage in MI) our study is unable to discover detailed mechanisms of outcomes. Follow-up for mortality was complete, but although admission registries used are mandatory and have excellent coverage, it is possible that some non-fatal outcomes may be underestimated.

In conclusion, this nationwide, multicenter propensity adjusted study found that patients with STEMI have poorer short-term outcome than patients with NSTEMI after revascularization by CABG. Long-term outcomes of STEMI and NSTEMI patients after CABG were however comparable. These results indicate that both short- and long-term risks should be considered when evaluating patients for eligibility to CABG by MI type.

Author Contributions Statement

Conceptualization, V.K., M.M and J.G.; methodology, V.K., J.G.; software, V.K.; validation, V.K., J.G., J.S.; formal analysis, V.K.; investigation, M.M, V.K.; resources, V. K., P.R.; data curation, V.K., J.S., P.R.; writing—original draft preparation, M.M., V.K.; writing—review and editing, J.G., P.R., J.S., V.K.; visualization, V.K.; supervision, V.K.; project administration, V.K.; funding acquisition, V.K. All authors have read and agreed to the published version of the manuscript.

Disclosures

Markus Malmberg has received travel grants and congress sponsorship (Abbott, Boston Lifesciences, Medtronic). Jussi Sipilä has received honoraria (Merck, Pfizer, Sanofi), has received a consultancy fee (Rinnekoti Foundation), has received travel grants and congress sponsorship (Abbvie, Orion Pharma, Merck Serono, Sanquin, Lundbeck, Novartis) and holds shares (Orion Corporation). Päivi Rautava has received speaker fee and travel grant (Roche Oy). Jarmo Gunn has received an unrestricted research grant form Vifor Pharma. Ville Kytö has received a scientific consultancy fee (AstraZeneca), speaker fee (Bayer, AstraZeneca, Roche), and travel grants and congress sponsorship (AstraZeneca, Boehringer Ingelheim, Bayer, Pfizer).

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Supplementary materials

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