

openheart Culprit vessel: impact on short-term and long-term prognosis in patients with ST-elevation myocardial infarction

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ABSTRACT

Background ST-elevation myocardial infarction (STEMI) occurs as a result of rupture of an atherosclerotic plaque in the coronary arteries. Limited data exist regarding the impact of culprit coronary vessel on hard clinical event rates. This study investigated the impact of culprit vessel on outcomes after primary percutaneous coronary intervention (PCI) of STEMI.

Methods A total of 29 832 previously cardiac healthy patients who underwent primary PCI between 2003 and 2014 were prospectively included from the Swedish Coronary Angiography and Angioplasty Registry and the Registry of Information and Knowledge about Swedish Heart Intensive care Admissions. Patients were stratified into three groups based on culprit vessel (right coronary artery (RCA), left anterior descending artery (LAD) and left circumflex artery (LCx)). The primary outcome was 1-year mortality. The secondary outcomes included 30-day and 5-year mortality, as well as heart failure, stroke, bleeding and myocardial reinfarction at 30 days, 1 year and 5 years. Univariable and multivariable analyses were done using Cox regression models.

Results One-year analyses revealed that LAD infarctions had the highest increased risk of death, heart failure and stroke compared with RCA infarctions, which had the lowest risk. Sensitivity analyses revealed that reduced left ventricular ejection fraction on discharge partially explained this increased relative risk in mortality. Furthermore, landmark analyses revealed that culprit vessel had no significant influence on 1-year mortality if a patient survived 30 days after myocardial infarction. Subgroup analyses revealed female sex and multivessel disease (MVD) as significant high-risk groups with respect to 1-year mortality.

Conclusions LAD and LCx infarctions had a relatively higher adjusted mortality rate compared with RCA infarctions, with LAD infarctions in particular being associated with an increased risk of heart failure, stroke and death. Culprit vessel had limited influence on mortality after 1 month. High-risk patient groups include LAD infarctions in women or with concomitant MVD.

INTRODUCTION

Mortality rates due to acute coronary syndromes (ACS) have decreased substantially over the last 30 years.¹ However, despite numerous medical advances, a substantial degree of patients with ACS experience

Key questions

What is already known about this subject?

- Despite numerous advances in the treatment of acute myocardial infarction, a residual high mortality rate remains.
- Contemporary data on hard clinical outcomes in a modern population treated with primary percutaneous coronary intervention, stratified by infarct vessel, are limited.

What does this study add?

- Patients with left anterior descending artery (LAD) infarctions have a higher rate of mortality.
- However, landmark analyses at 30 days show no difference in long-term mortality between infarct vessels, suggesting that early mortality explains the excess mortality in LAD infarctions.
- LAD infarctions more often lead to depressed ejection fraction (EF), but for a given EF the outcome is similar, regardless of culprit vessel.
- LAD infarction in women and in patients with multivessel disease are especially high-risk groups.

How might this impact on clinical practice?

- Patients with high-risk coronary features like LAD infarction in women or in patients with multivessel disease might warrant more intense monitoring, treatment and follow-up, especially during the first 30 days (online supplementary file 1).

subsequent clinical events, including death. Ischaemic heart disease thus constitutes the global leading cause of death.²

Clinical presentation in ST-elevation myocardial infarction (STEMI) varies depending on the affected coronary artery. Several studies have compared outcome in anterior versus non-anterior infarctions, stratifying patients based on electrocardiography (ECG) patterns, rather than angiographic findings.^{3–5} A comparison of anterior infarctions with inferior, using ECG-based stratification, concluded that anterior infarction resulted in larger infarct size, lower left ventricular ejection fraction (LVEF) on admission, more heart failure, more in-hospital deaths and more cardiac mortality (even



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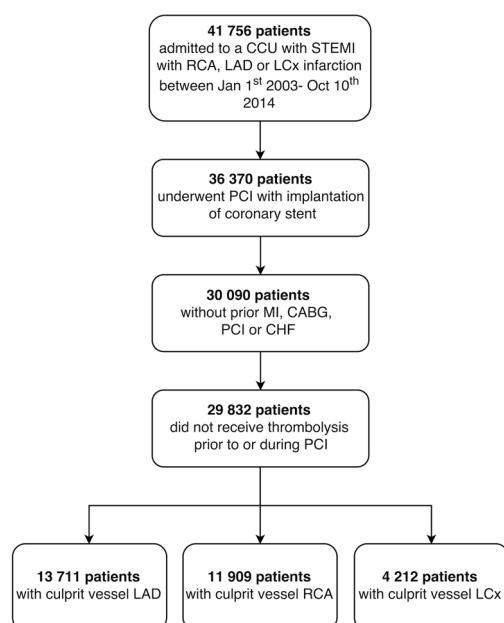


Figure 1 Flow chart of patient exclusion. The initial 53 093 patients were patients who underwent primary PCI with STEMI indication after year 2003. CABG, coronary artery bypass grafting; CHF, congestive heart failure; CCU, coronary care unit; LAD, left anterior descending artery; LCx, left circumflex artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction.

after adjusting for infarct size). Califf and colleagues⁶ have also demonstrated more severe outcomes with more proximal left anterior descending artery occlusion, as well as with multivessel disease (MVD). However, these studies predate the primary percutaneous coronary intervention (PCI) era and therefore may not be applicable in modern clinical practice.^{3,4} Data with angiographic stratification by Brener and colleagues⁷ suggest that proximal left anterior descending artery occlusions are associated with a higher mortality and infarct size. However, this study was limited by a small sample size and did not evaluate other culprit vessels.

Infarction in the left main (LM) artery is less common, but gives significant ischaemia and poor clinical outcome.⁵ Limited published data exist regarding outcomes after myocardial infarction (MI) stratified by infarct vessel (left anterior descending artery (LAD), right coronary artery (RCA) and left circumflex artery (LCx)) rather than ECG patterns in a modern population undergoing primary PCI and receiving modern coronary care.

The purpose of our study was to, in an exploratory analysis, assess short-term (30 days and 1 year) and long-term (5 years) hard clinical endpoints and complications following primary PCI of STEMI, in an otherwise cardiac healthy population, stratified by infarct vessel. We used the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART)

registry. This study is, to our knowledge, the largest study to date investigating this topic.

METHODS

National registries

The SWEDEHEART registry includes all patients with MI and undergoing coronary angiography or PCI, as well as patients undergoing cardiac surgery or percutaneous valve implantations in Sweden. Using each patient's unique personal identification, the registry can be merged with other national registries. The SWEDEHEART subregistries used in this study were the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) and the Swedish Registry of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA). These registries were merged with the national Swedish hospital discharge registry and the national population registry.

Patient screening as well as variables pertaining to catheterisation and PCI were obtained from SCAAR. Variables pertaining to in-hospital events were obtained from RIKS-HIA. Endpoint variables for heart failure, myocardial reinfarction, bleeding and stroke were acquired from the Swedish hospital discharge registry. Death was obtained from the national population registry. All registries above, with the exception of the national population registry, were used for screening of comorbidities and were merged into a single database from which all analyses were performed.

Since all patients were anonymised in the study (with their social security number substituted by a unique SWEDEHEART specific ID number), no informed consent was deemed necessary by the scientific ethics committee.

Study population

The inclusion criteria were as follows:

- ▶ Patients admitted to coronary care unit with STEMI and registered in SCAAR and RIKS-HIA.
- ▶ Patients treated with primary PCI between 1 January 2003 and 14 October 2014.

The exclusion criteria were as follows:

- ▶ Patients with prior MI, heart failure, coronary artery bypass grafting (CABG) or PCI.
- ▶ Patients with PCI to LM or graft vessels.
- ▶ Patients not undergoing coronary stenting.
- ▶ Patients undergoing thrombolytic therapy prior to or during PCI.

Included patients were stratified by culprit vessel. The LM group was excluded since it was too small to render sufficient statistical power, and bypass vessels were deemed too heterogeneous to add value to the study hypothesis. In order to study long-term outcome in an otherwise cardiac healthy population, patients with prior MI, heart failure, CABG and prior PCI were excluded. Patients undergoing thrombolytic therapy prior to or during PCI were excluded since we wanted to study a

Table 1 Baseline demographics

Variable	RCA	LAD	LCx	P values
Age, median (IQR)	66 (58–74)	66 (57–75)	65 (57–73)	<0.001
Sex				<0.001
Male symptom to FMC time	7935 (66.6%)	10 083 (73.5%)	3122 (74.1%)	
Female	3974 (33.4%)	3628 (26.5%)	1090 (25.9%)	
Smoking status				<0.001
Never smoked	3762 (35%)	5523 (45%)	1412 (37.2%)	
Ex-smoker (>1 month)	2924 (27.2%)	3083 (25.1%)	1006 (26.5%)	
Smoker	4076 (37.9%)	3675 (29.9%)	1381 (36.4%)	
BMI, median (IQR)	26.2 (23.9–29)	26.2 (24–28.8)	26.3 (24.2–29)	NS
Clinical presentation				
Heart rate, median (IQR)	70 (58–81)	77 (66–90)	73 (62–86)	<0.001
Systolic BP, median (IQR)	138 (120–158)	140 (120–160)	143 (125–165)	<0.001
Diastolic BP, median (IQR)	80 (70–91)	85 (75–100)	85 (73–99)	<0.001
Cardiogenic shock	346 (3%)	292 (2.2%)	114 (2.8%)	<0.001
Symptom to FMC time	2:30 (1:30–4:30)	2:20 (1:22–4:20)	3:59 (1:30–4:45)	<0.001
FMC to PCI time, median (IQR)	1:08 (0:45–1:43)	1:11 (0:47–1:48)	1:15 (0:50–2:00)	<0.001
FMC to PCI >1 hour	6047 (57.4%)	7283 (60%)	2391 (63.7%)	<0.001
Previous comorbidities				
Diabetes	1910 (16%)	2260 (16.5%)	672 (16%)	NS
Hypertension	4675 (39.3%)	5027 (36.7%)	1627 (38.6%)	<0.001
Stroke	658 (5.5%)	717 (5.2%)	212 (5%)	NS
Kidney failure	114 (1%)	98 (0.7%)	35 (0.8%)	NS
COPD	487 (4.1%)	420 (3.1%)	146 (3.5%)	<0.001
Peripheral artery disease	250 (2.1%)	203 (1.5%)	80 (1.9%)	<0.01
Cancer	250 (2.1%)	203 (1.5%)	80 (1.9%)	<0.05
PCI variables				
Femoral catheterisation	6736 (56.6%)	7622 (55.7%)	2239 (53.3%)	<0.01
DES	3526 (29.6%)	5576 (40.7%)	1473 (35%)	<0.001
MVD	6011 (50.7%)	5051 (37%)	2299 (54.9%)	<0.001
>1 stent	4274 (35.9%)	4080 (29.8%)	1259 (29.9%)	<0.001
Periprocedural medication				
ASA before PCI	9967 (83.8%)	11 281 (82.4%)	3547 (84.3%)	<0.01
Clopidogrel before PCI	6422 (54%)	7268 (53.1%)	2352 (55.9%)	<0.01
Prasugrel before PCI	421 (3.5%)	461 (3.4%)	125 (3%)	NS
Ticagrelor before PCI	1727 (14.5%)	1990 (14.5%)	631 (15%)	NS
Heparin before PCI	3651 (30.7%)	4132 (30.2%)	1278 (30.4%)	NS
Heparin during PCI	7166 (60.2%)	8274 (60.4%)	2516 (59.8%)	NS
Bivalirudin during PCI	4940 (41.5%)	5634 (41.1%)	1775 (42.1%)	NS
GPIIb/IIIa antagonists during PCI	5445 (45.7%)	6126 (44.7%)	1817 (43.2%)	<0.05
LMWH during PCI	1121 (9.4%)	1413 (10.3%)	505 (12%)	<0.001
Discharge medications				
ACEi or ARB	8725 (74.2%)	11 249 (83.3%)	3166 (76.3%)	<0.001
Warfarin or NOAC	337 (2.9%)	827 (6.1%)	128 (3.1%)	<0.001
ASA	11 340 (96.4%)	12 787 (94.6%)	3969 (95.7%)	<0.001
Beta blockers	10 385 (88.3%)	12 544 (92.9%)	3767 (90.9%)	<0.001
Calcium antagonists	899 (7.7%)	761 (5.6%)	308 (7.4%)	<0.001
Diuretics	1542 (13.1%)	2766 (20.5%)	609 (14.7%)	<0.001

Continued

Table 1 Continued

Variable	RCA	LAD	LCx	P values
Statins	11 021 (93.7%)	12 527 (92.7%)	3872 (93.4%)	<0.01
p2y12 inhibitors	11 328 (96.3%)	12 929 (95.7%)	3977 (95.9%)	<0.05
Clopidogrel	8654 (73.6%)	9969 (73.8%)	3011 (72.6%)	
Prasugrel	300 (2.6%)	353 (2.6%)	134 (3.2%)	
Ticagrelor	2351 (20%)	2580 (19.1%)	825 (19.9%)	
Optimal discharge medication	7382 (62.7%)	9875 (73.1%)	2777 (66.9%)	<0.001
Variable	RCA	LAD	LCx	P values
Prehospital CPR	208 (1.8%)	508 (3.8%)	98 (2.4%)	<0.001
Resuscitated cardiac arrest in-hospital	541 (4.6%)	747 (5.5%)	183 (4.3%)	<0.01
New atrial fibrillation in-hospital	534 (4.5%)	655 (4.8%)	199 (4.8%)	<0.001
Bleeding in-hospital	152 (1.3%)	139 (1.0%)	55 (1.3%)	NS
Pacemaker	92 (0.8%)	63 (0.5%)	28 (0.7%)	<0.01
LVEF				<0.001
LVEF ≥50%	6401 (67.4%)	3839 (34.4%)	2051 (60.8%)	
LVEF 40%–49%	2222 (23.4%)	3548 (31.8%)	905 (26.8%)	
LVEF 30%–39%	687 (7.2%)	2868 (25.7%)	328 (9.7%)	
LVEF <30%	181 (1.9%)	911 (8.2%)	90 (2.7%)	

Percentages represent proportions for each culprit group. Percentages presented represent % within each group. Missing percentages represent % of total study population.

ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; DES, drug-eluting stent; FMC, first medical contact; LAD, left anterior descending artery; LCx, left circumflex artery; LMWH, low-molecular weight heparin; LVEF, left ventricular ejection fraction; MVD, multivessel disease; NOAC, novel oral anticoagulants; PCI, percutaneous coronary intervention; RCA, right coronary artery.

pure primary PCI population. A total of 29 832 patients were thus eligible for final analysis (figure 1).

Endpoints

The primary endpoint was 1-year mortality following hospital admission for STEMI. The secondary endpoints were 30-day and 5-year mortality, as well as clinical event rates of myocardial reinfarction, heart failure, bleeding and stroke at above-mentioned time points.

Statistical analyses

Normality for continuous data was tested using skewness and kurtosis tests (within 2 for normality) and visual evaluation of histograms. Baseline characteristics were compared, stratified by infarct vessel, using analysis of variance for continuous parametric data and Pearson's χ^2 test for categorical data. The Kruskal-Wallis test was used for non-parametric continuous data. A two-tailed p value threshold of <0.05 was chosen for significance of all data results. For each variable, percentages of missing data were also calculated.

Kaplan-Meier curves were generated for the crude mortality event rates using the log rank test to identify significant differences between culprit vessel groups. Adjusted HRs were compared between groups using Cox proportional hazards models for multivariable analysis. An adjustment model was created by selecting covariates fulfilling the following three criteria: (1) the variable was deemed clinically relevant as a confounder

without having a role in the chain of events leading to the outcome in question; (2) the variable had a p value <0.1 when comparing culprit groups; and (3) the variable had to fulfil the global proportionality of hazard assumptions for our primary endpoint (1-year mortality) using Schoenfeld residuals. These covariates were added to the multivariable analysis in two blocks to give a better picture of the impact of various variables on HR. The first block (comorbidity adjustment) consisted of age, sex, smoking status, comorbidities (previous hypertension, previous peripheral artery disease, atrial fibrillation) and previous relevant medication (ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs) prior to admission, diuretics prior to admission, statins prior to admission). The second block (expanded adjustment) consisted of both comorbidity adjustment, as well as various angiographic characteristics and administered periprocedural antithrombotic medications (MVD), >1 stent given during the procedure (dichotomised), femoral catheterisation versus non-femoral, drug-eluting stent (DES) versus bare metal stent, acetylsalicylic acid prior to PCI, prasugrel prior to PCI, clopidogrel prior to PCI, GPIIa/IIIb inhibitors during PCI and low-molecular weight heparin (LMWH) during PCI. Variables for previous cancer and chronic obstructive pulmonary disease did not fulfil hazard assumptions for 1-year mortality and were thus excluded from the adjustment model.

Table 2 Unadjusted Kaplan-Meier event rates for each culprit vessel group

Variable	Total	RCA	LAD	LCx	P values
Mortality					
Within 30 days	1072 (3.6%)	325 (2.8%)	610 (4.5%)	137 (3.3%)	<0.001
Within 1 year	1763 (6.0%)	562 (4.8%)	974 (7.2%)	227 (5.5%)	<0.001
Within 5 years	3510 (14.3%)	1262 (13.1%)	1783 (15.5%)	465 (13.5%)	<0.001
Reinfarction					
Within 30 days	2014 (6.8%)	747 (6.3%)	966 (7.0%)	301 (7.1%)	0.03
Within 1 year	2935 (9.8%)	1128 (9.5%)	1370 (10.0%)	437 (10.4%)	NS
Within 5 years	3900 (13.1%)	1557 (13.1%)	1790 (13.1%)	553 (13.1%)	NS
Stroke					
Within 30 days	113 (0.4%)	25 (0.2%)	67 (0.5%)	21 (0.5%)	<0.01
Within 1 year	428 (1.4%)	146 (1.2%)	210 (1.5%)	72 (1.7%)	<0.05
Within 5 years	1054 (3.5%)	380 (3.2%)	518 (3.8%)	156 (3.7%)	<0.05
Bleeding					
Within 30 days	182 (0.6%)	66 (0.6%)	79 (0.6%)	37 (0.9%)	NS
Within 1 year	761 (2.6%)	301 (2.5%)	351 (2.6%)	109 (2.6%)	NS
Within 5 years	1453 (4.9%)	597 (5.0%)	651 (4.8%)	205 (4.9%)	NS
Heart failure					
Within 30 days	808 (2.8%)	158 (1.4%)	560 (4.2%)	90 (2.2%)	<0.001
Within 1 year	2129 (7.1%)	513 (4.3%)	1368 (10%)	248 (5.9%)	<0.001
Within 5 years	3298 (11.1%)	897 (7.5%)	2006 (14.6%)	395 (9.4%)	<0.001

A significant p value indicates any difference between the groups.

LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery.

When not specified, adjusted analyses are always presented after expanded adjustment.

Missing data were imputed using multiple imputation.

Subgroup and sensitivity analyses

Predefined, unadjusted subgroup analyses were done to study specific subgroups: age ≥ 75 versus < 75 years, first medical contact (FMC) to PCI ≥ 1 hour versus < 1 hour, sex, current smokers versus non-smokers, diabetes versus no diabetes, hypertension versus no hypertension, DES versus no DES, MVD versus no MVD, and LVEF $\geq 40\%$ versus $< 40\%$. P values for interaction for subgroup analyses were generated using an interaction test. A p value of interaction < 0.05 was considered significant.

Subgroup analyses were also done for patients who survived admission and received the so-called optimal discharge medication with dual antiplatelet therapy, ACEi or ARBs, statins and beta blockers. This was done separately as the inclusion criteria needed to change to exclude patients who deceased in-hospital in order to avoid an immortal time bias.

Three separate sensitivity analyses were done to explore possible explanatory mechanisms behind differences in HR for mortality between culprit groups. The impact of heart failure was first tested by adding unimputed ventricular function to the Cox regression. Second, the impact of symptom to FMC time and FMC to PCI time was tested by separately adding dichotomised imputed versions of the variables to the Cox regression analyses. Finally,

landmark analyses were done looking at HRs between various vessel groups after a landmark of 30 days. Kaplan-Meier failure estimate curves were generated for landmark analyses. Statistical analyses were performed using STATA V.14.1.

RESULTS

Baseline demographics

A total of 29 832 patients were included, of whom 13 711 (46%) composed the LAD group, 11 909 (40%) the RCA group and 4212 (14%) the LCx group (see [figure 1](#) for inclusion flow chart).

Several differences in baseline characteristics were observed between the RCA, LAD and LCx groups. The LCx group was slightly younger compared with the LAD and RCA groups ([table 1](#)). Men constituted the majority of all culprit groups, but a relatively higher proportion of women were observed in the RCA group. Some differences were also noted in periprocedural medication, the most pronounced being LMWH prior to PCI ([table 1](#)). Symptom to FMC time (patient delay) was highest in the LCx group. Likewise, FMC to PCI time (system delay) was also greatest in the LCx group ([table 1](#)). Prehospital cardiopulmonary resuscitation (CPR) was most common in the LAD group, while clinical presentation with cardiogenic shock at arrival was most common in the RCA group ([table 1](#)). LAD patients were more commonly discharged with ACEi or ARBs as well as diuretics. Patients with

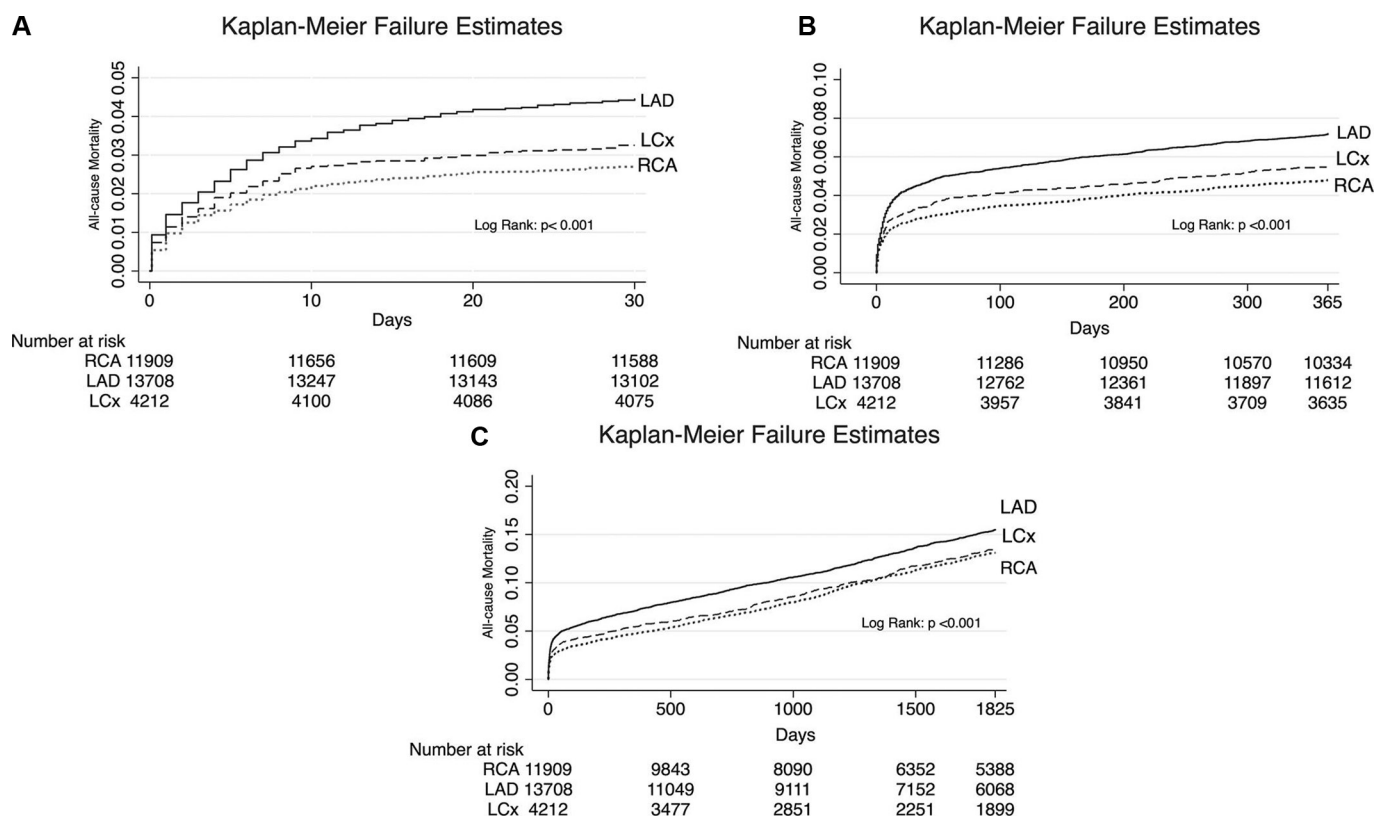


Figure 2 (A) Kaplan-Meier event rate for mortality up to 30 days after admission. (B) Kaplan-Meier event rate for mortality up to 1 year after admission. (C) Kaplan-Meier event rate for mortality up to 5 years after admission. LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery.

optimal discharge medication (dual antiplatelet therapy, ACEi or ARBs, statins and beta blockers) were also most commonly seen in the LAD group (table 2).

Considering procedural variables for PCI, DES deployment was most common in the LAD group, MVD was most common in the LCx group, and the RCA group was most often given multiple stents during primary PCI (table 1).

Differences in clinical presentation

Heart rate at presentation was lowest among RCA patients and highest among LAD patients (table 1). Similarly, the lowest median blood pressures were also found in the RCA group. The LAD group also received prehospital CPR to a significantly larger extent compared with other culprit groups.

Mortality

Because data on death are obtained from the Swedish National Population Registry, follow-up data on our primary outcome were obtained for virtually all patients as in previously published research from the SWEDEHEART registry.^{8–10} Unadjusted mortality was the highest among LAD patients for all time periods, including the primary endpoint of 1-year mortality (4.8%, 7.1%, 5.4% for RCA, LAD and LCx, respectively, $p < 0.001$; figure 2). Unadjusted Cox regression analyses showed that LAD had significantly higher unadjusted risk of death compared with RCA for all time periods (HR 1.64 (95% CI 1.44 to 1.88), 1.52 (95% CI 1.37 to 1.69) and 1.25 (95% CI 1.16 to

1.34) for 30-day, 1-year and 5-year mortality, respectively), while LCx had no significant increase in mortality for any time period compared with RCA (table 3). After comorbidity adjustment, both LAD and LCx showed statistically significantly higher mortality for all time periods compared with RCA. Similar results were obtained after expanded adjustment (table 3).

Secondary endpoints

The unadjusted 5-year incidence of stroke was highest in the LAD group (3.2%, 3.8% and 3.7% for RCA, LAD and LCx, respectively, $p < 0.001$ for comparison of LAD vs RCA). After expanded adjustment, both LAD and LCx showed statistically significantly higher event rates for stroke both short term and long term compared with RCA (table 3).

After expanded adjustment, both LAD and LCx had a higher rate of myocardial reinfarction compared with RCA for all time periods, except for LCx at 5 years (table 3).

No differences in long-term bleeding rates were noted between groups (table 3), both in unadjusted and adjusted models.

Both 30-day and 1-year risk of heart failure were significantly increased within the LAD group compared with both LCx and RCA, as well as between LCx compared with RCA. The HR for heart failure at 1 year was for LAD and LCx compared with RCA 2.74 (95% CI 2.47 to 3.04,

Table 3 Cox regression analysis showing unadjusted and adjusted HRs of clinical endpoints for 30-day, 1-year and 5-year time periods

Clinical event	Time from admission	Infarct vessel*	Unadjusted		Comorbidity adjustment		Expanded adjustment	
			HR (95% CI)	P values	HR (95% CI)	P values	HR (95% CI)	P values
Mortality	30 days	LAD	1.64 (1.44 to 1.88)	<0.001	1.89 (1.64 to 2.17)	<0.001	2.04 (1.78 to 2.35)	<0.001
		LCx	1.19 (0.98 to 1.46)	NS	1.46 (1.20 to 1.79)	<0.001	1.47 (1.20 to 1.80)	<0.001
	1 year	LAD	1.52 (1.37 to 1.69)	<0.001	1.72 (1.54 to 1.91)	<0.001	1.85 (1.66 to 2.06)	<0.001
		LCx	1.15 (0.98 to 1.34)	NS	1.37 (1.18 to 1.61)	<0.001	1.38 (1.18 to 1.61)	<0.001
	5 years	LAD	1.25 (1.16 to 1.34)	<0.001	1.38 (1.28 to 1.48)	<0.001	1.46 (1.35 to 1.57)	<0.001
		LCx	1.05 (0.94 to 1.16)	NS	1.22 (1.10 to 1.36)	<0.001	1.22 (1.10 to 1.36)	<0.001
Reinfarction	30 days	LAD	1.13 (1.03 to 1.24)	<0.05	1.14 (1.04 to 1.26)	<0.01	1.22 (1.10 to 1.34)	<0.001
		LCx	1.14 (1.00 to 1.31)	<0.05	1.16 (1.01 to 1.33)	<0.05	1.16 (1.01 to 1.32)	<0.05
	1 year	LAD	1.06 (0.98 to 1.15)	NS	1.08 (1.00 to 1.17)	NS	1.19 (1.09 to 1.29)	<0.001
		LCx	1.10 (0.99 to 1.23)	NS	1.12 (1.00 to 1.25)	<0.05	1.12 (1.00 to 1.25)	<0.05
	5 years	LAD	1.00 (0.94 to 1.07)	NS	1.02 (0.95 to 1.09)	NS	1.12 (1.04 to 1.20)	<0.01
		LCx	1.01 (0.92 to 1.11)	NS	1.02 (0.93 to 1.13)	NS	1.03 (0.93 to 1.13)	NS
Stroke	30 days	LAD	2.33 (1.47 to 3.69)	<0.001	2.23 (1.40 to 3.54)	<0.01	2.45 (1.53 to 3.91)	<0.001
		LCx	2.38 (1.33 to 4.25)	<0.01	2.39 (1.34 to 4.29)	<0.01	2.46 (1.37 to 4.41)	<0.01
	1 year	LAD	1.25 (1.01 to 1.55)	<0.05	1.26 (1.02 to 1.56)	<0.05	1.38 (1.11 to 1.72)	<0.01
		LCx	1.40 (1.05 to 1.85)	<0.05	1.47 (1.11 to 1.95)	<0.01	1.50 (1.13 to 1.99)	<0.01
	5 years	LAD	1.19 (1.04 to 1.36)	<0.05	1.19 (1.04 to 1.36)	<0.05	1.30 (1.13 to 1.49)	<0.001
		LCx	1.16 (0.97 to 1.40)	NS	1.21 (1.00 to 1.46)	<0.05	1.26 (1.04 to 1.51)	<0.05
Bleeding	30 days	LAD	1.04 (0.75 to 1.44)	NS	1.03 (0.74 to 1.44)	NS	1.03 (0.73 to 1.44)	NS
		LCx	1.59 (1.06 to 2.37)	<0.05	1.63 (1.09 to 2.44)	<0.05	1.66 (1.11 to 2.49)	<0.05
	1 year	LAD	1.01 (0.87 to 1.18)	NS	1.01 (0.87 to 1.18)	NS	1.05 (0.90 to 1.23)	NS
		LCx	1.03 (0.82 to 1.28)	NS	1.05 (0.84 to 1.30)	NS	1.07 (0.86 to 1.33)	NS
	5 years	LAD	0.95 (0.85 to 1.06)	NS	0.95 (0.85 to 1.06)	NS	1.01 (0.90 to 1.13)	NS
		LCx	0.97 (0.83 to 1.14)	NS	0.99 (0.85 to 1.17)	NS	1.02 (0.87 to 1.20)	NS
Heart failure	30 days	LAD	3.12 (2.62 to 3.73)	<0.001	3.20 (2.68 to 3.82)	<0.001	3.42 (2.85 to 4.09)	<0.001
		LCx	1.62 (1.25 to 2.09)	<0.001	1.71 (1.32 to 2.21)	<0.001	1.72 (1.33 to 2.23)	<0.001
	1 year	LAD	2.39 (2.16 to 2.65)	<0.001	2.50 (2.26 to 2.78)	<0.001	2.74 (2.47 to 3.04)	<0.001
		LCx	1.38 (1.19 to 1.61)	<0.001	1.46 (1.26 to 1.70)	<0.001	1.47 (1.27 to 1.72)	<0.001
	5 years	LAD	2.04 (1.88 to 2.20)	<0.001	2.12 (1.96 to 2.29)	<0.001	2.32 (2.14 to 2.52)	<0.001
		LCx	1.26 (1.12 to 1.42)	<0.001	1.34 (1.19 to 1.51)	<0.001	1.36 (1.21 to 1.54)	<0.001

*HRs shown with RCA as the reference vessel (HR 1.00) and all p values are compared with RCA.
LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery.

$p < 0.001$) and 1.47 (95% CI 1.27 to 1.72, $p < 0.001$), respectively (table 3).

Similar results were obtained when looking at 5-year data. Unadjusted incidence of heart failure at 5 years was the highest in the LAD group (14.6%, 9.4% and 7.5% for LAD, LCx and RCA, respectively, $p < 0.001$ for all comparisons vs RCA) (tables 2 and 3). Expanded adjustment showed a continued significant increase in heart failure at 5 years for LAD compared with all groups and for LCx compared with RCA (table 3).

Sensitivity analysis

The impact of heart failure on mortality was tested by sensitivity analysis. Adjusting for LVEF at discharge caused a reduction in HR for LAD mortality (HR for LAD 1-year mortality reduced from 1.85 (95% CI 1.66 to 2.06,

$p < 0.001$) to 1.55 (95% CI 1.35 to 1.76, $p < 0.001$)), while LCx mortality barely was affected.

In addition, as baseline demographics revealed significantly longer patient and doctor delays for LCx compared with other culprit groups, a similar sensitivity analysis was done by separately adding these variables to the adjustment model. There was, however, no substantial impact on HRs when adjusting for either symptom to FMC time or FMC to PCI time.

Landmark analysis

A landmark analysis for patients surviving 30 days was conducted with 1-year mortality from the landmark as endpoint. The excess mortality for LAD and LCx infarctions was attenuated when landmark analysis was performed for all culprit vessel comparisons, and no

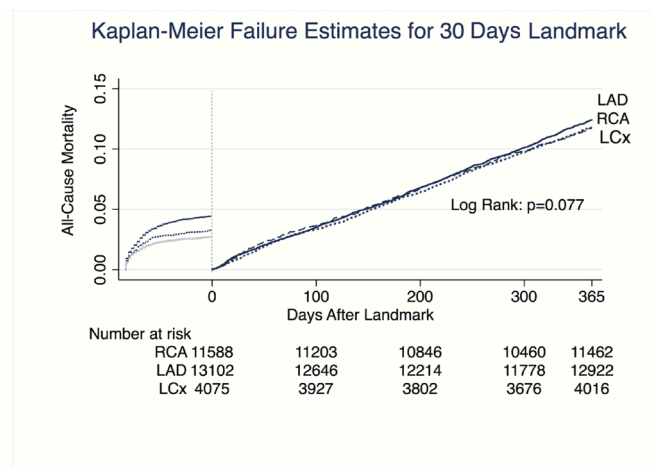


Figure 3 Kaplan-Meier landmark analysis for mortality with cut-off at 30 days. LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery.

statistical significance between culprit groups remained at 1 year (figure 3).

Subgroup analysis

Subgroup analyses were performed in multiple subgroups for 1-year mortality. After considering p value for interaction, only two subgroups showed statistically significant p value for interaction: gender and MVD. For gender, HRs for women in the LAD group were significantly higher compared with men (HR for men in the LAD group: 1.44 (95% CI 1.25 to 1.65) vs women in the LAD group: 1.84 (95% CI 1.57 to 2.16), p value for interaction=0.02) (figure 4).

For MVD, the HR for MVD in the LAD group compared with patients without MVD in the LAD group was 1.85 (95% CI 1.62 to 2.11) vs 1.45 (95% CI 1.23 to 1.71) (p value for interaction=0.025) (figure 3).

Mortality was also stratified according to LVEF at discharge. The increased mortality in the LAD group was attenuated when stratifying data according to LVEF at discharge (forest plot in figure 4), with no statistically different mortality rates for all infarct types within similar ranges of LVEF.

DISCUSSION

The main findings of this large nationwide study indicate that differences in mortality in patients with STEMI undergoing primary PCI between culprit vessels are due to excess mortality the first 30 days. LAD infarctions have the worst prognosis, with heart failure partially explaining this increase in mortality, despite this group being more extensively medically treated at discharge. Furthermore, our data indicate that for a given ejection fraction, the mortality is similar in all three coronary vessels. However, LAD infarctions more often yield depressed LVEF in-hospital than RCA or LCx, as well as more long-term heart failure, which partially could explain the excess mortality. Furthermore, female patients more rarely have LAD

infarctions; however, when they do experience LAD infarctions, they present with worse outcomes. Similarly, patients with LAD infarctions and MVD also constitute a high-risk group.

Endpoints

The LAD group had the highest mortality compared with the remaining culprit groups, a finding consistent with many other studies comparing LAD with non-LAD infarctions.¹¹ There was a significantly higher risk of having an in-hospital LVEF <30% in the LAD group compared with RCA. When adjusting for differences in LVEF at discharge, a significant proportion of the excess HR was reduced in the LAD group, implying that the mortality seen in the LAD group is to some extent driven by reduced LVEF in this patient population. However, patients who died before an ultrasound could be performed were not included in this analyses, and the impact of heart failure on excess LAD mortality is thus probably higher than what we could observe.

An interesting finding is the loss of significance in mortality in patients who survived the first 30 days after admission. Reasons for the higher relative short-term mortality among LAD patients may thus be due to acute and subacute sequelae of their infarction, including heart failure as well as several potentially deadly complications such as mural wall thrombi or mechanical complications (ventricular septum defect, tamponade or papillary muscle rupture).¹²

Furthermore, the attenuation of culprit vessel mortality as well as the total mortality after 30 days is consistent with findings from Pedersen *et al*,¹³ who found that prognosis was excellent after 30 days and that non-cardiac death was the main cause of long-term mortality.

The higher relative risk of stroke in LAD (and LCx) infarction could be explained by the anatomical myocardial supply, since LAD supplies the apex of the heart where apical dyskinesia may lead to increased risk for mural thrombi.¹⁴ The fact that both the absolute and relative risks for bleeding remained non-significant when comparing culprit vessel groups suggests a low level of residual confounding. However, this cannot be ruled out (see the Limitations section).

Clinical presentation

Low blood pressure on clinical presentation is a constituent of cardiogenic shock, likely explaining why the RCA group had slightly higher frequency of cardiogenic shock on clinical presentation. However, it is important to note that the RCA-related cardiogenic shock is generally more benign and responds well to fluid therapy compared with the more dramatic cardiogenic shock seen in LAD infarctions.¹⁵ This finding is not surprising considering the large portion of myocardium supplied by LAD, which is in line with our finding of higher incidence of LVEF <30% after LAD infarction, a finding also consistent with other studies.¹⁶ Clinical delays were more pronounced in

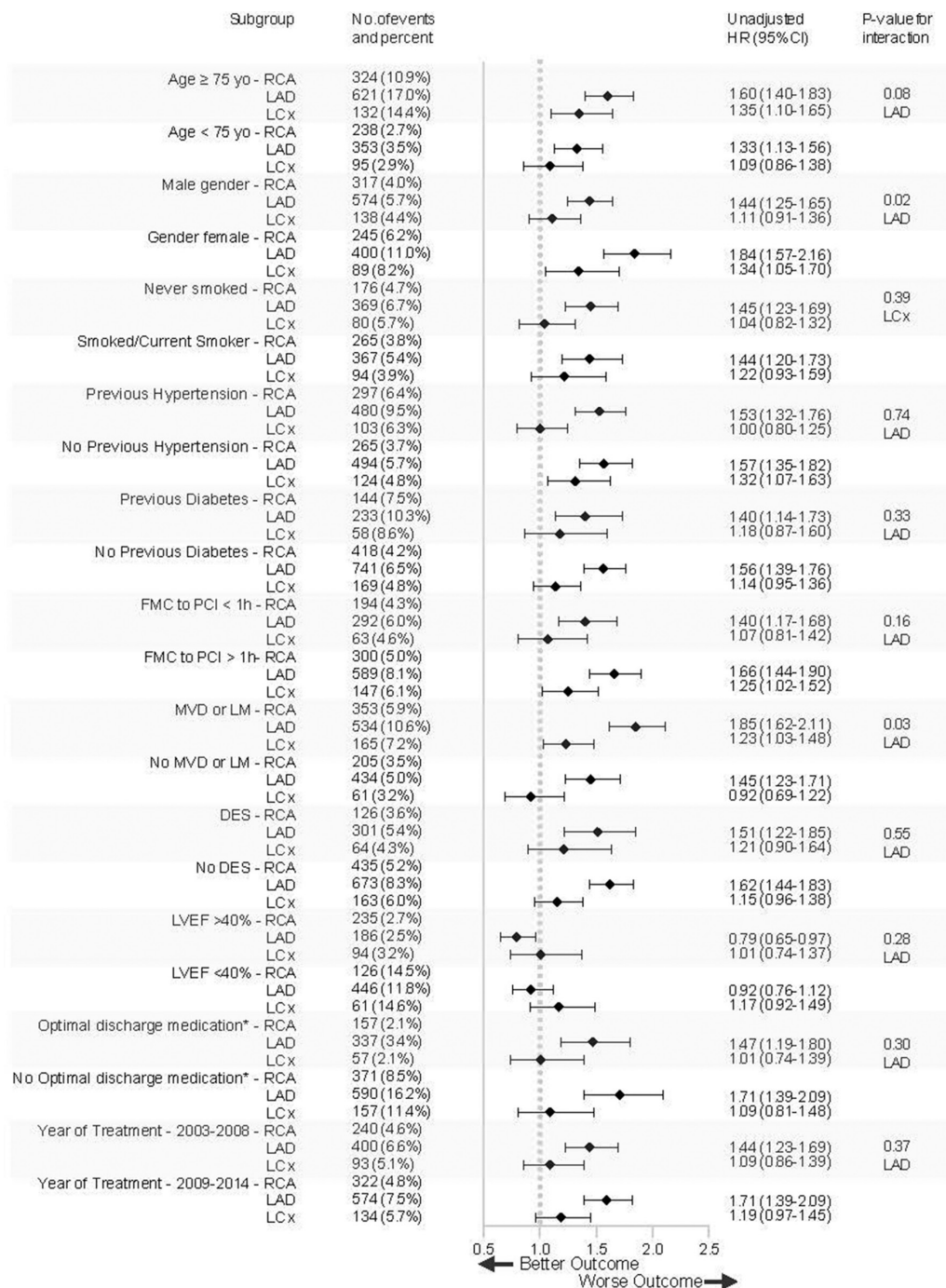


Figure 4 Forest plot of subgroup analyses. *Only patients who survived their admission were included in these subgroup analyses. DES, drug-eluting stent; FMC, first medical contact; LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main; LVEF, left ventricular ejection fraction; MVD, multivessel disease; PCI, percutaneous coronary intervention; RCA, right coronary artery.

the LCx group, probably due to the diffuse symptomatology and difficulty in ECG diagnosis in LCx infarcts.

Subgroup analyses

From an epidemiological point of view, majority of patients with STEMI are men, and male sex increases the risk of cardiovascular disease. However, cardiovascular disease is still one of the leading causes of death in European women under the age of 75.^{17 18} With increasing age, both sexes become exposed to more common risk

factors, and women eventually catch up but with a later presentation as well as more atypical symptoms than men.¹⁹ Although LAD infarctions are less common in women, they seem to have a significantly higher mortality risk when they do occur, compared with men.

In our study, MVD is observed in around 50% of patients. Analyses showed a statistically significantly increased risk for mortality in LAD patients with MVD. It is unclear how many of the patients with MVD underwent culprit-only

PCI or whether all affected vessels were treated in the initial PCI, as new evidence for which option is optimal is emerging.^{20–22}

Infarctions resulting in similar LVEF (>40% or <40%) had similar prognosis no matter which culprit group we looked at. Our results therefore do not support the idea that culprit-specific anatomical structures such as the septum supplied by the LAD have a unique role in mortality. LAD culprits simply more often lead to depressed LVEF compared with the other vessels.²³

Limitations

Because of this study's observational design, residual confounding cannot be ruled out. We tried to limit this by strict inclusion criteria with a study population without prior cardiovascular disease as well as adjustment models which consider a vast array of PCI variables, comorbidities and medications. We believe this is reflected in the lack of significant differences in bleeding rates between culprit groups, indicating a low level of residual confounding, as previously discussed.

The vast majority of patients underwent culprit-only PCI during index procedure and therefore accurate classification of culprit vessel. Misclassification could exist when multivessel PCI was performed since culprit vessel could be difficult to ascertain in those cases. However, these were only a small minority of patients.

CONCLUSIONS

In conclusion, both LAD and LCx infarctions in STEMI undergoing primary PCI had a relatively higher adjusted mortality compared with RCA infarctions, with LAD infarctions in particular being associated with an increased risk of heart failure, stroke and death. There were no relevant differences in risks of bleeding between culprit groups. Landmark analyses performed after 30 days suggested that culprit vessel has limited influence on mortality after 1 month. Global LVEF at discharge is a predictor of death, but for a given LVEF mortality is the same for all culprit groups, with the increased LAD mortality partially being a consequence of a larger proportion of patients having lower LVEF post-MI.

High-risk groups include women with LAD infarctions and patients with LAD infarction and concomitant MVD. Early identification of these patients with more liberal use of haemodynamic monitoring and cardiac support might improve outcomes in these patient groups.

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