Comparison of Late Cardiac Death and Myocardial Infarction Rates in Women Vs Men With ST-Elevation Myocardial Infarction

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Women and patients with incomplete revascularization (IR) have a worse prognosis after ST elevation myocardial infarction (STEMI). However, the extent to which IR affects outcomes for women with STEMI compared with men is not well characterized. Thus, we examined late outcomes of 589 consecutive STEMI patients who received percutaneous coronary intervention and assessed SYNTAX scores (SS), both at baseline and after all procedures (residual SS). A residual SS >8 defined IR. The primary end point was cardiac death or myocardial infarction (MI), with median follow-up of 3.6 years [interquartile range [IQR] 2.6 to 4.7]. Women (n = 123) had lower baseline SSs 15.0 [IQR 9 to 20], than men (n = 466), 16.0 [IQR 9 to 20; p = 0.02. After all planned procedures, the residual SS was 5.0 [IQR 0 to 9] in women and 5.0 (IQR 1 to 11] in men, p = 0.37. Cardiac death or MI occurred in (97/589) patients (16%), 24% (30/123) in women and 14% (67/466) in men (hazard ratio [HR] 1.75; 95% confidence intervals [CI] 1.14 to 2.69; p = 0.01). In patients with residual SYNTAX score (rSS) >8 cardiac death or MI occurred in 43% (15/35) of women and 23% 36/158 men (HR 2.14; 95% CI 1.17 to 3.91; p = 0.01). In patients with rSS = 0 to 8 cardiac death or MI occurred in 17% (15/88) of women and 10% of men (31/308) (HR 1.68; 95% CI 0.91 to 3.12; p = 0.10; interaction p value 0.58). Multivariate analysis found women were 1.77 times more likely than men to experience cardiac death or MI (95% CI 1.13 to 2.77; p = 0.01). In conclusion, we found despite a lower burden of disease at presentation and no difference in rates of IR between men and women, outcome differences were substantial. Women with rSS >8 were twice as likely as men with the same rSS to experience cardiac death or MI post-STEMI. Differences remained significant postrisk adjustment. **(Am J Cardiol 2020;128:120−126)**

Coronary heart disease is the leading cause of death globally.[1] Lower rates of guideline based medical therapy, and revascularization have been identified as contributors to the poorer late outcomes observed for women with ST elevation myocardial infarction (STEMI).[2] Advanced age and co-morbidities have also been hypothesized to play a role.[3] A disproportionately low number of women have been recruited to clinical trials which limits our ability to address gender-associated outcome differences.[4] Incomplete revascularization (IR) is common[5−7] and is associated with a poorer prognosis in STEMI patients.[5,8−15] A validated method to characterize IR is the residual SYNTAX score (rSS), an rSS >8 defines a high degree of IR .[7,13,14] However rSSs are infrequently reported so the impact of completeness of revascularization is often not assessed. Thus, we sought to determine whether observed gender outcome differences in STEMI were associated with IR.

Methods

Consecutive STEMI patients who underwent percutaneous coronary intervention (PCI) during their initial hospitalization at our PCI center (Liverpool Hospital, Sydney) from December 2010 to April 2014 were included as previously described[13] (Supplementary Figure 1). Patients referred from 3 non-PCI hospitals were also included. STEMI was defined as per the European Society of Cardiology/American College of Cardiology/American Heart Association/World Heart Federation task force.[16] Patients were included if they received primary PCI, rescue PCI, or PCI after successful administration of thrombolytic therapy. High risk subgroups with chronic total occlusion (CTO), >50% left main coronary artery stenosis, and cardiogenic shock were included. Patients were excluded if they had previous or planned coronary artery bypass graft (CABG) surgery due to CABG limiting accurate rSS assessment. Treatment

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decisions were made by the interventional or attending cardiologist including advice regarding angiographic findings and late risk, medical therapies, recommendation of cardiac rehabilitation, and lifestyle modification. Research was performed in accordance with the Declaration of Helsinki and post-PCI follow-up was approved by the Local Health District Human Research Ethics Committee (QA 08/034).

SS was performed by 4 interventional cardiologists trained and calibrated in SS, blinded to the primary end point and not involved in care of the assigned patient. As described in detail previously,[13] training and calibration of SS was completed and included review of online training tools and calibration with core-lab-reported angiograms from the Strategies for Multivessel Revascularization in Patients with Diabetes trial patients from our institution. Each angiogram was reviewed and scored to generate baseline and rSS. Side-by-side paired scoring was used in the first 150 patients to ensure consensus, after which a further 150 patients underwent independent SS from 2 cardiologists with adjudication from a third when consensus of rSS category was not met (n = 13/300; 4%). The remaining patients were scored by one reporting cardiologist. IR with a high burden of residual disease was defined as rSS >8, complete revascularization with a low burden of residual disease was defined as an rSS ≤8, as previously validated.[7,13,14]

Patient supplied information was used to classify gender. All other baseline characteristics were defined as detailed previously.[13] Renal impairment was defined as an eGFR <60 Ml/min/1.73 m^2. Diabetes mellitus was defined using the American Diabetes Association Guidelines.[17] Dyslipidemia was defined as fasting low-density lipoprotein cholesterol of ≥130 mg/dl (≥3.5 mmol/dl), previous dyslipidemia diagnosis or treatment with lipid modifying agents. Selective drug eluting stent (DES) criteria were used before guideline revision regarding DES.[18] Follow-up was performed by contacting cardiologists, general practitioners, patients or next of kin; with review of medical records (including departmental and hospital electronic databases recording vital status), outpatient letters, and laboratory tests.

The primary end point was the composite of cardiac death and myocardial infarction (MI). Cardiac death was defined as death with a demonstrated cardiac cause or sudden unexplained death. When due to co-morbidities the cause of death was uncertain (6 cases) this was adjudicated by the first and last author. In the absence of sudden unexplained death, troponin elevation, electrocardiography or telemetry data, or reported cardiac symptoms close to the time of death these deaths were adjudicated as non-cardiac. MI was defined by ESC/ACCF/AHA/WHF task force guidelines.[16] Type 4a MI was included only where there was also new or recurrent coronary artery occlusion on angiography, new electrocardiographic changes consistent with MI, or new regional wall motion abnormality. Secondary end points included cardiac death, MI, all-cause death, cerebrovascular accident (CVA), unplanned revascularization, congestive cardiac failure (CCF) and major adverse cardiovascular events (MACE), which included all-cause death, MI, unplanned revascularization and stroke. Planned revascularization was defined as nonculprit PCI performed during the index admission or as an outpatient. Outpatient planned revascularization was defined as a documented plan during the index admission to perform staged outpatient coronary revascularization without further clinical evaluation or testing. Stroke and transient ischemic attack were included in the definition of CVA. CCF was defined as signs and symptoms of CCF warranting initiation or up-titration of diuretic medication or hospitalization with new CCF.

Continuous variables were evaluated as mean ± standard deviation for Gaussian variables and median (interquartile range) for non-Gaussian variables and were compared with the one-way analysis of variance test or Kruskal-Wallis test as appropriate. Categorical data were evaluated using the chi-square test or Fisher exact test. For time to event analyses, hazard ratios (HRs) and 95% confidence interval (CI) were estimated using cox regression analyses. Multivariable cox regression was performed considering clinical and angiographic variables of rSS, diabetes, age, gender, periprocedural cardiogenic shock, renal dysfunction, and postprocedure TIMI flow grade; based on previous studies,[2,13,19,20] to identify factors independently associated with end points of cardiac death or MI, cardiac death or MI or CVA, and MACE. Schoenfeld residuals were used to test that global proportional hazard assumptions and covariate specific assumptions were met. Case elimination was used for missing data, a 2-tailed p value <0.05 was considered statistically significant. SPSS Statistics, v21·0 (IBM Corp, Armonk, NY), SAS v 9.4 and STATA v12 (STATA Corporation, TX) were used for analyses.

Results

Of 633 consecutive STEMI presentations, 589 (94%) patients were included, 123 women (21%) and 466 men (79%). Reasons for exclusions were: 17 previous CABG, 11 planned CABG, 7 second STEMI during study, 4 unsuitable images for SS, and 5 refused follow-up. Median follow-up was 3.6 years (IQR 2.9 to 4.7), follow-up duration was ≥1 year in 98% of patients, and ≥2 years in 97%; with no difference in loss to follow-up between women 4 of 123 (3%) and men 13 of 477 (3%) at 2 years (p = 0.76). Women were older than men and had higher rates of diabetes, hypertension, dyslipidemia, and chronic kidney disease (Table 1). Ticagrelor or prasugrel were less frequently prescribed for women, though more women received glycoprotein Iib/IIIa inhibitors.

With respect to angiographic and procedural characteristics, women had lower baseline SS (15.0 [interquartile range; IQR 9 to 20] vs 16.0 [IQR 10 to 22.5], p = 0.02), though there were no differences in disease complexity, such as rates of CTO, calcification, or bifurcations (Supplementary Table 1). There were 1061 nonculprit lesions identified, 953 were not scheduled for planned revascularization, 74% were angiographically assessed as ≥70% stenosed. As peri-infarct physiologic assessment was not well validated at the time of the study[21] only 7 fractional flow Reserves were performed. There were 90 patients with nonculprit proximal left anterior descending artery (LAD) stenosis, of whom 66 had ≥70% stenoses. Nineteen of 66 were

Table 1
Baseline characteristics, angiographic, procedural characteristics, medical therapy, and revascularization status, by gender

	Women (n = 123)		Men (n = 466)		p Value
Variable					
Age (years) median [IQR]	62.7	[52.7-73.2]	58.2	[50.6-65.7]	<0.001
Diabetes mellitus	39	(32%)	88	(19%)	<0.01
Hypertension	84	(68%)	243	(52%)	<0.01
Current Smoker	64	(52%)	252	(54%)	0.67
Dyslipidemia	83	(67%)	253	(54%)	0.01
Family history	28	(23%)	112	(24%)	0.76
Previous MI	9	(7%)	41	(9%)	0.60
Renal impairment (eGFR <60 ml/min/1.73 m^2)	32	(26%)	81	(17%)	0.03
Baseline SYNTAX score median [IQR]	15.0	[9-20]	16.0	[10-22.5]	0.02
Residual SYNTAX score median [IQR]	5.0	[0-9]	5.0	[1-11]	0.37
Residual SYNTAX ≤8	88	(72%)	308	(66%)	0.25
Residual SYTAX >8	35	(29%)	158	(34%)	0.25
Any planned nonculprit PCI*	10	(8%)	63	(14%)	0.11
Primary PCI	96	(78%)	357	(77%)	0.74
Thrombolysis	27	(22%)	109	(23%)	0.74
-Rescue	10	(8%)	45	(10%)	0.61
Femoral Approach	111	(90%)	403	(86%)	0.27
Occluded culprit vessel at PCI	52	(42%)	240	(52%)	0.07
TIMI 3 flow postculprit PCI	117	(95%)	425	(91%)	0.08
Drug eluting stent use	48	(39%)	182	(39%)	0.97
Bare metal stent use	75	(62%)	295	(63%)	0.69
Culprit lesion stent length (mm) median [IQR]	25·1	[22·5-27·6]	25·4	[24·2-26·7]	0.68
Total stent length (mm) median [IQR]	27·2	[24·4-30·0]	29.6	[27·8-31·5]	0.38
Stent diameter (mm) median [IQR]	3.0	[2.5-3.0]	3.0	[2.75-3.5]	0.02
Multivessel disease (≥50% stenosis)	63	(51%)	286	(62%)	0.91
LMCA culprit or nonculprit	0	(0%)	9	(2%)	0.24
Culprit artery Left anterior descending artery	52	(42%)	225	(48%)	0.24
Culprit artery Left Circumflex artery	19	(15%)	59	(13%)	0.42
Culprit artery Right coronary artery	52	(42%)	182	(39%)	0.52
Ejection Fraction ≤35%	15	(12%)	47	(10%)	0.50
Shock	6	(5%)	23	(5%)	0.98
Chronic total occlusion	1	(1%)	14	(3%)	0.09
Medical Therapies					
Antithrombin medications					
Bivalirudin	22	18%	75	16%	0.72
Heparin	102	83%	382	84%	0.72
Glycoprotein IIb/IIIa	72	59%	207	45%	0.01
Antiplatelet medications†					
Aspirin	123	100%	466	100%	NA
Clopidogrel	81	68%	261	56%	0.03
Prasugrel/Ticagrelor	38	31%	202	43%	0.01
Beta-blockers	105	89%	424	92%	0.34
ACE inhibitors/ARB	102	86%	386	84%	0.44
Statins	115	97%	452	98%	0.92

Baseline characteristics, SYNTAX scores, angiographic and procedural characteristics and medications stratified by gender. Dyslipidemia was defined as fasting low-density lipoprotein cholesterol of ≥130 mg/dl (≥3.5 mmol/dl), previous dyslipidemia diagnosis or treatment with lipid modifying agents.

* Planned nonculprit PCI reported as intention to treat.

† As prescribed at hospital discharge. A small proportion of patients received both BMS and DES based on vessel size, therefore the total number of subjects in stent columns is >589. ACE-I Angiotensin converting enzyme inhibitor, ARB = Angiotensin II receptor antagonist, LMCA = left main coronary artery, MI = myocardial infarction, rSS = residual SYNTAX score, SYNTAX = Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery score, TIMI = Thrombolysis in Myocardial infarction. Values are % (n), or median (IQR), for stent lengths mean and 95% CI.

managed with planned (or simultaneous PCI), whereas 47 of 66 were left for further noninvasive or clinical evaluation, or medical management. In women with proximal LAD stenosis ≥70% (n = 17) 4 had planned revascularization (24%), in men with proximal LAD stenosis ≥70% (n = 49) 15 had planned revascularization (31%; p = 0.61).

Overall rates of planned nonculprit PCI were 8% in women vs 14% in men (p = 0.11). After all planned procedures the rSS of women and men were not different (5.0 [IQR 0 to 9] vs 5.0 [IQR 1 to 11], p = 0.37). In patients with an rSS >8, 98% had at least one treatable lesion, and 86% could have achieved an rSS ≤8 without left main or

Table 2
Clinical outcomes by gender

Clinical events at final follow-up (3.6 years)	Women		Men		Hazard ratio (95% CI)	p Value
	n = 123	(%)	n = 466	(%)		
Cardiac death or MI	30	(24%)	67	(14%)	1.75 (1.14-2.69)	~0.01
Cardiac death or MI or CVA	36	(29%)	82	(18%)	1.74 (1.17-2.57)	<0.01
MACE	45	(37%)	132	(28%)	1.33 (0.95-1.87)	0.08
Cardiac death	13	(11%)	20	(4%)	2.50 (1.24-5.03)	0.01
All-cause death	17	(14%)	43	(9%)	1.48 (0.84-2.59)	0.13
Myocardial infarction	24	(20%)	52	(11%)	1.71 (1.06-2.76)	0.01
Cerebrovascular accident	10	(8%)	20	(4%)	0.68 (0.30-1.55)	0.09
Congestive cardiac failure	27	(22%)	43	(9%)	2.42 (1.50-3.92)	<0.001
Unplanned revascularization	22	(18%)	68	(15%)	1.28 (0.79-2.07)	0.37

This table shows both late outcome data by gender. Final follow-up was performed at a median of 3.6 years (IQR 2.9 to 4.7). Hazard ratio expressed as women compared with men. CVA = cerebrovascular accident. MACE = all cause death, MI, unplanned revascularization, and CVA, rSS = residual SYNTAX score.

complex CTO PCI, with no gender differences. Only 6% of patients had a co-morbidity potentially impacting appropriateness of further revascularization, with no gender differences.

The primary end point of cardiac death or MI occurred at 30 days in 9% of women and 4% of men (p = 0.03; Supplementary Table 2), at 1 year in 17% and 9% (p = 0.01), and at final follow-up 24% and 14%, respectively (HR 1.75; 95% CI 1.14 to 2.69; p = 0.01). Secondary outcomes also occurred more frequently in women than men for cardiac death alone, MI, and CCF (Table 2).

Women with rSS >8 had the highest rates of cardiac death and MI (43%) compared to men with rSS >8 (23%), women with rSS ≤8 (17%), and men with rSS ≤8 (10%; log rank p <0.001; Figure 1, Table 3). Kaplan-Meier analysis shows a difference in cardiac death and MI rates between genders in those with rSS >8 (HR 2.14; 95% CI 1.17 to 3.91; p = 0·013), though rSS did not modify the association between gender and outcomes (interaction p value = 0.58). Women compared with men with rSS >8 had poorer outcomes: cardiac death, MI or CVA, MACE, cardiac death alone, and CCF. Differences in gender-associated outcomes were not observed in those with rSS ≤8, except CCF (Table 3).

As bare metal stents (BMS) are now seldom used analysis of patients only treated with DES was also performed. In DES treated patients with rSS ≥8 cardiac death or MI occurred in 46% of women (6/13) and 23% of men (12/53) (p = 0.09), in the full cohort (DES and BMS) rates were 43% and 23% (p = 0.01). In patients with rSS <8, cardiac death or MI occurred in 11% of women (4/35) and 9% of men (11/129) (p = 0.06), in the full cohort (DES and BMS) rates were 17% and 10% (p = 0.10).

Multivariable analyses, after adjusting for age, diabetes, CKD, shock, rSS >8 and postprocedure TIMI flow grade, found being a woman was independently associated with cardiac death or MI HR 1.77 (95% CI 1.13 to 2.77; p = 0.01; Table 4).

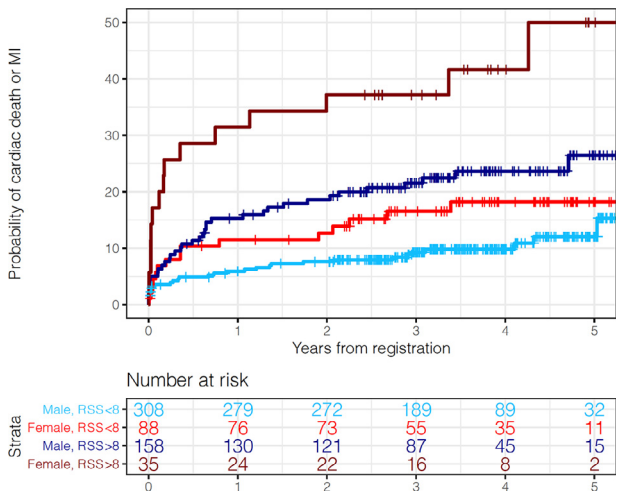

Figure 1. Kaplan-Meier event curve stratified by rSS group and gender for cardiac death or myocardial infarction. Women with IR (rSS >8) had cardiac death and MI rates of 43% (15/35) compared with men with IR with rates of 23% (36/158), women with rSS ≤8 with rates of 17% (15/88), and men with rSS ≤8 with rates of 10% (31/308) (log rank p <0.001). IR = incomplete revascularization rSS >8. rSS = residual SYNTAX score.

Discussion

Our data show worse outcomes for women with STEMI and disproves the hypothesis that differences in outcomes for women with STEMI are due to a higher burden of disease. We found women have a lower burden of disease at presentation, and no gender-associated difference in rSS. We found women with a high level of IR experienced higher rates of cardiac death and MI than men with the same degree of IR.

The difference in outcomes observed between women and men with IR in our study suggests that IR may disproportionately impact outcomes for women. This observation is consistent with trends in subgroup analysis from the [illegible]complete versus lesion only primary PCI trial (CVLPRIT)[9] trial and Preventive Angioplasty in Acute Myocardial Infarction[8] trials but not the Danish Trial in Acute Myocardial Infarction—Primary PCI in Patients With ST-Elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization[10] or the Complete versus Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI (COMPLETE)[12] trials. These trials were

Table 3
Clinical outcomes by gender and incomplete revascularization status

Clinical events at final follow-up (3.6 years)	rSS category	Women		Men		Hazard ratio (95% CI)	p Value	Interaction p value
		n	(%)	n	(%)	Women compared with Men		
Cardiac death or nonfatal MI	rSS <8	15/88	(17%)	31/308	(10%)	1.68 (0.91-3.12)	0.10	0.58
	rSS >8	15/35	(43%)	36/158	(23%)	2.14 (1.17-3.91)	0.01	
Cardiac death or nonfatal MI or CVA	rSS <8	19/88	(22%)	44/308	(14%)	1.51 (0.88-2.60)	0.13	0.24
	rSS >8	17/35	(49%)	38/158	(24%)	2.40 (1.36-4.26)	<0.01	
MACE	rSS <8	24/88	(27%)	64/308	(21%)	1.30 (0.81-2.08)	0.27	0.45
	rSS >8	21/35	(60%)	68/158	(43%)	1.69 (1.04-2.77)	0.04	
Cardiac death	rSS <8	4/88	(5%)	6/308	(2%)	2.28 (0.64-8.09)	0.20	0.66
	rSS>8	9/35	(26%)	14/158	(9%)	3.25 (1.41-7.51)	0.01	
All-cause death	rSS <8	8/88	(9%)	17/308	(6%)	1.52 (0.65-3.52)	0.33	0.81
	rSS >8	9/35	(26%)	26/158	(17%)	1.78 (0.83-3.80)	0.14	
MI	rSS <8	13/88	(15%)	25/308	(8%)	1.80 (0.92-3.53)	0.09	0.76
	rSS>8	11/35	(31%)	27/158	(17%)	2.09 (1.04-4.22)	0.04	
Unplanned revascularization	rSS <8	11/88	(13%)	27/308	(9%)	1.42 (0.71-2.87)	0.33	0.95
	rSS >8	11/35	(31%)	41/158	(26%)	1.48 (0.76-2.88)	0.25	
CCF	rSS <8	16/88	(18%)	21/308	(7%)	2.55 (1.33-4.89)	0.01	0.97
	rSS >8	11/35	(31%)	22/158	(14%)	2.65 (1.28-5.47)	0.01	
CVA	rSS <8	6/88	(7%)	15/308	(5%)	0.30 (0.08-1.09)	0.07	0.03
	rSS >8	4/35	(11%)	5/158	(3%)	2.24 (0.53-9.36)	0.27	

This table shows late outcome data by gender and revascularization status. Final follow-up was performed at a median of 3.6 years (IQR 2.9 to 4.7). CVA = cerebrovascular accident, MACE = all cause death, MI, unplanned revascularization, and CVA, MI = Myocardial infarction, rSS = residual SYNTAX score, CCF congestive cardiac failure.

not powered to demonstrate differences by gender due to low numbers of women,[8–11] or low event rates,[12] as much larger sample sizes are required to demonstrate significant p values for interaction.[22] Reported HRs for women treated with complete revascularization compared with culprit only treatment were between 0.24[8] and 1.05[12] in these trials and for men reported the HRs were between 0.39[8] and 0.67[12].

The CVLPRIT and COMPLETE trials reported more detailed gender data for comparison. We observed rates of cardiac death or MI of 43%, 23%, 17%, and 10% for women with IR, men with IR, women with complete revascularization, and men with complete revascularization, respectively (median follow-up 3.6 years). The CVLPRIT trial reported rates of 27%, 20%, 9%, and 10%, respectively, for their composite primary end point at 1 year. In the COMPLETE trial cardiac death or MI rates were 11%, 10%, 10%, and 7%, respectively, at 3 years. Gender disaggregated rSS data are not available. It is likely, based on event rates, that earlier trials, the CVLPRIT trial and the Preventive Angioplasty in Acute Myocardial Infarction trial, included patients with higher rSS than the COMPLETE trial and may have more closely matched an all-comers cohort, such as ours. In these trials the smallest risk reduction with complete revascularization was seen in the COMPLETE trial. Patients in COMPLETE were noted to be a relatively low risk STEMI cohort, based on event rates and median rSS (7.0 ± 4.7 in the culprit only group). In our study, the rSS for patients with multivessel disease meeting COMPLETE trial inclusion criteria (multivessel disease with ≥70% stenosis) on completion of the index procedure

Table 4
Univariate and multivariable analysis for cardiac death or myocardial infarction

Outcome and variable	Univariate results		Multivariable results	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Renal impairment	3.14 (2.09-4.72)	<0.001	2.62 (1.65-4.17)	<0.001
Cardiogenic Shock	3.05 (1.63-5.71)	<0.001	2.47 (1.29-4.72)	<0.01
Abnormal TIMI flow post-PCI	1.83 (1.00-3.35)	0.05	2.36 (1.27-4.38)	<0.01
Incomplete revascularization	2.47 (1.66-3.68)	<0.001	2.23 (1.46-3.39)	<0.001
Gender (Women)	1.75 (1.14-2.69)	0.011	1.77 (1.13-2.77)	0.01
Diabetes mellitus	1.45 (0.93-2.25)	0.10	1.43 (0.91-2.25)	0.13
Age (in years)	1.02 (1.01-1.04)	<0.01	1.00 (0.98-1.02)	0.84

This table shows univariate and multivariable analysis for cardiac mortality and MI. The univariate hazard ratio for ticagrelor or prasugrel use when compared to clopidogrel was 0.68 (0.44 to 1.07; p = 0.09).This factor was not considered in the prespecified multivariable analysis model. Considered variables included diabetes, renal impairment, incomplete revascularization, periprocedural cardiogenic shock, age in years, TIMI-3 flow post-PCI, as described in methods. Age was considered as continuous variable (All factors included in the model were subsequently found to be significant on univariate analysis with the exception of diabetes, on multivariable analysis renal impairment, cardiogenic shock, TIMI flow, incomplete revascularization and gender were all significant). TIMI = Thrombolysis in myocardial infarction.

was 11(IQR 7 to 17). Our study and other similar studies have shown in STEMI patients with an rSS >8, event rates are ≥threefold higher than those reported in COMPLETE.[13−15,23]

Our study extends the findings of previous studies reporting significant differences in outcomes for women presenting with STEMI.[2,24−26] By including only those who received PCI we have demonstrated that observed outcome differences were not simply attributable to unequal access to primary PCI. By evaluating SS we have also shown that a higher burden of disease at presentation, does not explain our outcomes. We found neither prohibitive complexity of disease nor co-morbidity preventing further invasive treatment explained observed gender outcome differences. Similar outcome differences have been reported from several large studies[2,25,26] reporting death rates post-MI for women 1.19 to 2.17 higher than those for men. In STEMI, IR independently predicts prognosis.[13,14] Among these studies,[2,3,24−28] ours is the only one to include IR in multivariable analysis. We found both gender and IR independently predict prognosis.

Potential pathophysiologic mechanisms can be identified for the higher observed rates of cardiac death or MI among women with rSS >8. Women have smaller coronary vessels than men, their biological response to vascular damage, and inflammatory responses are different and they have more microvascular disease.[29] More data evaluating the impact of these differences are warranted. In the broader STEMI population, it is also imperative to address other factors impacting on outcomes for women, including missed and late diagnoses, and lower rates of culprit PCI provision. Other studies report gender-associated treatment differences for women with STEMI including less culprit revascularization, less guideline-based optimal medical therapy, fewer referrals to cardiac rehabilitation programs,[2,26] and lower rates of representation in clinical trials.[4] Our Kaplan-Meier analyses illustrate the importance of rSS in risk stratification. IR may impact on outcomes for women to a greater degree than it does for men or increase the impact of other differences in treatment. The magnitude of this outcome gap demonstrates an unmet need for strategies to address these differences.

This study adds to previous reports (including ours) regarding the prognostic importance of IR.[5,8−15] Specifically, gender-associated differences in outcomes were evaluated with respect to the completeness of revascularization in patients who underwent PCI for STEMI and found women did not have more complex coronary artery disease at presentation or on completion of all planned procedures. However, substantial gender-associated outcome differences found on univariate analysis persisted on multivariate analysis. The greatest disparity in outcome is apparent amongst those with rSS >8, allowing us to hypothesize that future research targeting this higher risk group may be required to address current gender-based outcome differences. Our study's size may limit power to demonstrate important differences and interaction effects and results should be viewed as hypothesis generating. Physiologic assessment allowing reporting of functional rSS scores, and intraprocedural imaging to evaluate differences in plaque characterization, were also not routinely included. Changes to contemporary STEMI practice over the period required for late follow-up are also noted as limitations, including P2Y12 selection, DES use and increased radial access.

In conclusion, almost half of women with IR experience cardiac death or repeat MI within 4 years of their STEMI. Women with rSS >8 are twice as likely as men with the same rSS to experience cardiac death or MI post-STEMI. This difference in outcome is not simply explained by rates of PCI for STEMI, age, co-morbidity, or acuity of presentation. Despite a lower baseline SS at presentation, outcome differences for women are substantial, particularly for women with rSS >8.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Disclosures

No relevant relationships with industry, other entities, or conflicts of interest exist.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.04.044.

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