European Journal of Preventive Cardiology

ESC European Society of Cardiology

Research letter

European Journal of Preventive Cardiology
0(00) 1–3

DOI: 10.1177/2047487319900875
journals.sagepub.com/home/cpr

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Sex differences in optimal medical therapy following myocardial infarction according to left ventricular ejection fraction

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Cardiovascular disease is the number one cause of mortality globally with myocardial infarction (MI) a common form.[1] Prescription of evidence-based optimal medical therapy (OMT) reduces mortality post MI.[2,3] Yet female sex has been associated with lower prescription of OMT.[4,5] Previous studies demonstrating sex-differences in OMT have included a heterogeneous post-MI population, without incorporation of left ventricular ejection fraction (LVEF), a key determinate of appropriate therapy. This study aimed to identify sex differences in discharge OMT following ST-elevation MI (STEMI) and non-STEMI (NSTEMI) treated with percutaneous coronary intervention (PCI), stratified according to impaired or preserved LVEF. Secondary aims including identification of discharge OMT association with mortality.

The Victorian Cardiac Outcomes Registry (VCOR) is a state-wide Australian clinical quality registry that prospectively recruits all patients treated with PCI across 30 Victorian hospitals with 30-day telephone follow-up post discharge. This study included consecutive patients treated with PCI or attempted PCI for a STEMI/NSTEMI from January 2013 to December 2016. The study was approved by the Monash Health Human Research Ethics Committee with an opt-out patient consent. LVEF was collected during the index admission and four weeks post-MI for STEMI patients and within six months of index admission and four weeks post-discharge for NSTEMI patients, as prespecified by VCOR. Patients without LVEF assessment or who died prior to discharge were excluded, while those missing data for individual medications were excluded from the respective group in which the data was missing. The primary endpoint was proportion of patients on OMT at discharge. OMT was defined as medications with level IA evidence and was split according to LVEF.[6] VCOR defined moderate LVEF dysfunction as LVEF ≤ 44, hence we utilised this value to separate impaired and preserved LVEF given it best matched the Australia/New Zealand guidelines.[6] Discharge aspirin, clopidogrel/ticagrelor and moderate-high dose statin fulfilled the requirements for OMT in patients with LVEF $> 44\%$. Addition of an angiotensin-converting enzyme inhibitor or angiotensin receptor inhibitor and beta-blocker met OMT requirements for patients with impaired LVEF $\leq 44\%$. Patients with contraindications could meet criteria for OMT; however, those with a contraindication to statin therapy required an alternative lipid-lowering therapy to be prescribed. Logistic regression was applied to compare associations with sex, with adjustment for confounders (age, inpatient major bleeding, oral anticoagulants, acute renal impairment, cardiogenic shock, previous coronary artery bypass grafting and/or PCI). OMT analysis included outcomes from the time of discharge until 30 days, negating any associated immortal time bias. Analysis of associations with 30-day mortality utilised date of death. Stata version 14 was used for all analysis, with a p-value < 0.05 considered statistically significant.

A total of 14,140 patients underwent PCI for MI with exclusion of 1655 (11.6%) with no LVEF measured and 382 (2.7%) with in-hospital death while 79 (0.6%) patients had one or more discharge medications missing. From the included 12,103 patients, 6291 were

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NSTEMIs (24.4% female) and 5812 were STEMIs (20.5% female). Compared with men, women were older (68.0 ± 12.8 vs. 63.1 ± 12.2, $p < 0.001$; 66.5 ± 13.2 vs. 60.7 ± 12.0, $p < 0.001$), had more diabetes (24.7% vs. 20.7%, $p < 0.001$; 18.9% vs. 14.9%, $p < 0.001$) and previous cerebrovascular events (4.5% vs. 3.3%, $p = 0.03$; 4.4% vs. 2.6%, $p < 0.001$) in NSTEMI and STEMI patients, respectively. Women had lower rates of previous PCI (14.5% vs. 18.4%, $p < 0.001$; 8.2% vs. 10.1%, $p = 0.04$) in NSTEMI and STEMI respectively, compared with men. Overall OMT, including statin therapy, was significantly lower in women than in men, with NSTEMI/STEMI and LVEF > 44% (Table 1). No significant association between OMT and sex was seen in post-MI patients with LVEF $\leq$ 44%.

Total mortality from hospital discharge to 30 days was 0.5% in the NSTEMI cohort (0.4% female vs. 0.5% male, $p = 0.67$) and 0.7% in the STEMI cohort (0.8% female vs. 0.7% male, $p = 0.70$). Discharge OMT was independently associated with lower mortality in STEMI (hazard ratio 0.23, 95% confidence interval (CI) 0.11–0.50, $p < 0.001$) and NSTEMI (hazard ratio 0.41, 95% CI 0.17–0.98, $p = 0.04$) patients. The proportional hazard assumption was met for both NSTEMI and STEMI multivariate analyses.

After adjustment for confounders, women with NSTEMI and STEMI had 34% and 38% lower odds,

Table 1. Discharge Medications for NSTEMI and STEMI patients according to sex.

			Unadjusted			Adjusted[a]		
	Female	Male	OR	95% CI	*p*-value	OR	95% CI	*p*-value
NSTEMI								
n	1535	4756						
Aspirin	1496 (97.5%)	4669 (98.3%)	0.66	0.45–0.97	0.03	0.97	0.62–1.52	0.90
$P2Y_{12}$ inhibitors								
Ticagrelor or thienopyridine	1495 (97.5%)	4681 (98.6%)	0.55	0.37–0.82	0.003	0.57	0.37–0.89	0.01
Ticagrelor	848 (55.3%)	2802 (59.0%)	0.86	0.76–0.96	0.01	0.91	0.79–1.04	0.15
Thienopyridine	650 (42.4%)	1894 (39.9%)	1.11	0.99–1.24	0.09	1.05	0.92–1.19	0.51
Beta blockers	1184 (77.3%)	3703 (78.2%)	0.95	0.82–1.09	0.43	1.01	0.86–1.18	0.95
ACE/ARB	1136 (74.1%)	3593 (75.9%)	0.91	0.80–1.04	0.15	0.97	0.84–1.13	0.73
Statin	1403 (91.8%)	4524 (95.5%)	0.52	0.41–0.65	<0.001	0.58	0.45–0.77	<0.001
Optimal therapy								
LVEF > 44%[b]	1173 (88.7%)	3876 (93.5%)	0.54	0.44–0.67	<0.001	0.66	0.51–0.84	<0.001
LVEF $\leq$ 44%[c]	124 (59.6%)	373 (63.1%)	0.86	0.62–1.19	0.37	0.96	0.66–1.40	0.83
STEMI								
n	1190	4622						
Aspirin	1155 (97.5%)	4527 (98.2%)	0.71	0.47–1.09	0.12	0.91	0.59–1.42	0.69
$P2Y_{12}$ inhibitor								
Ticagrelor or thienopyridine	1154 (97.5%)	4501 (97.6%)	0.93	0.62–1.40	0.73	1.02	0.66–1.57	0.94
Ticagrelor	711 (60.1%)	2939 (63.8%)	0.86	0.75–0.98	0.02	0.92	0.80–1.05	0.22
Thienopyridine	446 (37.7%)	1576 (34.2%)	1.16	1.02–1.33	0.03	1.09	0.95–1.25	0.21
Beta blockers	1004 (85.1%)	4067 (88.4%)	0.75	0.62–0.90	0.002	0.84	0.69–1.02	0.07
ACE/ARB	988 (83.7%)	3959 (86.2%)	0.83	0.69–0.99	0.03	0.90	0.75–1.08	0.27
Statin	1124 (95.2%)	4481 (97.3%)	0.54	0.39–0.74	<0.001	0.58	0.41–0.81	0.001
Optimal therapy								
LVEF > 44%[b]	794 (91.2%)	3170 (95.1%)	0.54	0.41–0.71	<0.001	0.62	0.46–0.84	0.001
LVEF $\leq$ 44%[c]	209 (67.9%)	939 (74.2%)	0.73	0.56–0.96	0.02	0.83	0.62–1.11	0.20

Data presented as *n* (%).

[a]Adjusted for: inpatient major bleeding event, oral anticoagulants, age, new renal impairment, previous coronary artery bypass grafting and/or percutaneous coronary intervention, cardiogenic shock.

[b]Optimal therapy is defined as including (aspirin) AND (P2Y12 inhibitor) AND a (statin) when the ejection fraction is greater than 44%. If there is a contraindication to statin the patient should be on, an alternative lipid lowering therapy to be included.

[c]Optimal medical therapy includes (aspirin) AND (thienopyridine OR ticagrelor) AND (statin) AND (ACE inhibitor OR ARB) AND a beta blocker when the ejection fraction is less than or equal to 44%.

ACE: angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CI: confidence interval; LVEF: left ventricular ejection fraction; NSTEMI: non-ST elevation myocardial infarction; OR: odds ratio; STEMI: ST elevation myocardial infarction.

respectively, of receiving OMT compared with men, with LVEF > 44%. This stark difference in OMT was driven by lower rates of lipid-lowering therapy in women. Women have documented higher medication non-adherence and statin intolerance.[7] We did not preclude these patients from meeting OMT criteria if an alternative lipid-lowering therapy was prescribed. However, women post MI still received significantly less OMT. The current study included only patients treated with PCI for MI. Hence, lower OMT in women cannot be explained by a female-predominance of alternative causes such as MI with non-obstructive coronary arteries. A less comfortable hypothesis is that clinician bias accounts for the lower prescription of OMT in women, due to perceived lower cardiovascular risk.[8]

No significant sex difference was seen in prescription of OMT in patients with impaired LVEF post MI. This may reflect sicker patients being treated more uniformly or may be due to the lower numbers of patients with impaired LVEF, limiting the power to detect a sex difference. However, the proportion of OMT irrespective of sex was significantly lower in the LVEF ≤ 44% group (62.1% vs. 92.4%, $p < 0.001$; 73.0% vs. 94.3%, $p < 0.001$) in NSTEMI and STEMI cohorts respectively, compared with the LVEF > 44% group. This may reflect the difficulty in treating sicker patients due to hypotension or acute kidney injury, but may also demonstrate gaps in secondary prevention measures.

Prescription of OMT was a strong predictor of lower total mortality, independent of confounders. Previous Australian studies have demonstrated that women have 1.7–2-fold the death rate of men post MI.[9,10] The current study did not associate female sex with higher mortality. However, the exclusion of patients who died in-hospital and those without an LVEF measured would likely have accounted for this. Despite this, lower prescription of OMT, driven primarily by lower statin use, may still play a role in the poorer outcomes observed around the world in women versus men post MI.

This large Australian study highlights the independent association of female sex with lower prescription of OMT in post-MI patients with preserved LVEF, but not impaired LVEF. We need to promote guideline-driven medical care if we are to reduce sex inequities in our post-MI patients. This study is limited by its observational nature and the ability to adjust only for measured confounders. Furthermore, medication adherence was not analysed, only discharge OMT prescription.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: SZ has been supported by a fellowship (101993) from the National Heart Foundation of Australia.

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