Sex Differences in 1-Year Rehospitalization for Heart Failure and Myocardial Infarction After Primary Percutaneous Coronary Intervention

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It is unclear whether universal access to primary percutaneous coronary intervention (pPCI) may reduce sex differences in 1-year rehospitalization for heart failure (HF) and myocardial infarction (MI) after ST-elevation myocardial infarction (STEMI). We studied 7,597 consecutive STEMI patients (13.8% women, n = 1,045) who underwent pPCI from January 2007 to December 2013. Cox regression models adjusted for competing risk from death were used to assess sex differences in rehospitalization for HF and MI within 1 year from discharge. Compared with men, women were older (median age 67.6 vs 56.0 years, $p < 0.001$) with higher prevalence of co-morbidities and multivessel disease. Women had longer median door-to-balloon time (76 vs 66 minutes, $p < 0.001$) and were less likely to receive drug-eluting stents (19.5% vs 24.1%, p = 0.001). Of the medications prescribed at discharge, fewer women received aspirin (95.8% vs 97.6%, p = 0.002) and $P2Y_{12}$ antagonists (97.6% vs 98.5%, p = 0.039), but there were no significant sex differences in other discharge medications. After adjusting for differences in baseline characteristics and treatment, sex differences in risk of rehospitalization for HF attenuated (hazard ratio [HR] 1.05, 95% confidence interval [CI] 0.79 to 1.40), but persisted for MI (HR 1.68, 95% CI 1.22 to 2.33), with greater disparity in patients aged ≥60 years (HR 1.83, 95% CI 1.18 to 2.85) than those aged <60 years (HR 1.45, 95% CI 0.84 to 2.50). In conclusion, in a setting of universal access to pPCI, the adjusted risk of 1-year rehospitalization for HF was similar in both sexes, but women had significantly higher adjusted risk of 1-year rehospitalization for MI, especially older women. **(Am J Cardiol 2019;123:1935−1940)**

One in 4 patients with acute myocardial infarction (MI) gets rehospitalized within 12 months of discharge.[1] Women are known to have higher rate of rehospitalization after acute MI than men.[2,3] Sex disparities in post-MI rehospitalization were often attributed by women being less likely to receive primary percutaneous coronary intervention (pPCI).[4] It is unclear if sex differences in outcomes persist in the contemporary era where pPCI is the universal treatment in patients with ST-segment elevation MI (STEMI).

Singapore is a country in South East Asia with a population of 5.5 million and a balanced sex distribution (49% men and 51% women in 2017).[5] The combination of small land mass and available economic resources has enabled Singapore's public healthcare system to provide round-the-clock and universal access to pPCI for all patients with STEMI through its nationwide network of pPCI-capable public hospitals.

We sought to determine whether sex differences in 1-year rehospitalization exist in STEMI patients with pPCI in Singapore. Specifically, we assessed the relation of baseline characteristics and variables related to STEMI care with 2 cardiac-specific causes of rehospitalization: heart failure (HF) and MI. Furthermore, since previous studies have shown that younger women have poorer outcomes after

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MI,[6–8] we sought to ascertain whether sex disparities in rehospitalization for HF and MI differed in young (aged <60 years) and older (aged ≥60 years) patients.

Methods

This is a retrospective study of patients enrolled in the Singapore MI Registry (SMIR). The SMIR is an ongoing population-based registry established in 2007.[9] It captures acute MI treated by the public and private hospitals, as well as out-of-hospital acute MI deaths. More than 95% of acute MI in Singapore are managed at the public hospitals each year. State legislature mandates data collection on acute MI without the need for written informed consent from patients and the quality of acute MI care is closely monitored across all public hospitals by the Ministry of Health. The SMIR identifies MI cases from (1) Hospital Inpatient Discharge Summaries and (2) cardiac biomarker lists from all hospitals, (3) claims data, and (4) Casemix and Subvention data from the Ministry of Health, and (5) death data from the Ministry of Home Affairs, based on International Classification of Diseases (ICD) 9th (Clinical Modification) code of 410 and ICD 10th (Australian Modification) code of I21 and I22. To ensure data accuracy and consistency, yearly internal audit is performed by the Registry to ensure inter-rater reliability of ≥95%. Detailed data collection method has been described in previous publications.[10,11]

The SMIR data was matched with procedural data from the Singapore Cardiac Databank. Further matching was done with claims data from the Ministry of Health to ascertain rehospitalization outcomes.

We included patients who were admitted for STEMI and underwent pPCI from January 2007 to December 2013 in all public hospitals with onsite pPCI capabilities in Singapore. We excluded patients transferred from non-pPCI capable hospitals (n = 417, Supplemental Figure 1).

The 2 primary end points of interest were unplanned fatal and nonfatal rehospitalization for HF and MI within 1 year after discharge for STEMI. The rehospitalization diagnoses were based on claims data submitted to the Ministry of Health by the hospitals. Each patient has a primary diagnosis, which the clinical team deems to be the primary cause of hospitalization, and ≥1 secondary diagnoses, which are deemed to be complications that may have arisen during hospitalization. Rehospitalizations with a primary diagnosis of HF or MI were considered in our study. The full list of primary diagnoses is shown in the Supplemental Materials.

Baseline characteristics and variables related to STEMI care were compared between the sexes using Wilcoxon Rank Sum test for numeric variables and Chi-square test for categorical variables. To account for attrition from mortality and circumvent overestimation of event rate, death was treated as a competing event when examining the relations between sex and time to rehospitalization for HF or MI using cox regression.[12] The cox regression models were built hierarchically, starting with sex only (model 1). Subsequently, other demographic variables (age, ethnicity), past medical history (hypertension, diabetes, hyperlipidemia, cardiovascular disease i.e., MI/ PCI/ coronary artery bypass grafting/stroke/peripheral arterial disease) and presenting features on admission (Killip class, creatinine, number of narrowed coronary arteries, pre-PCI thrombolysis-in-myocardial-infarct [TIMI] flow grade, coronary artery intervened) were added (model 2). Finally, variables related to STEMI care (door-to-balloon time, use of stent, use of thrombectomy, use of intra-aortic balloon pump, procedure success, use of glycoprotein IIB-IIIA inhibitor, aspirin given at discharge, β-blockers given at discharge, lipid lowering drugs given at discharge, renin-angiotensin system inhibitors given at discharge, $P2Y_{12}$ antagonists given at discharge, highest Killip class during hospitalization, lowest left ventricular ejection fraction during hospitalization) were added (model 3). In the independent variables included in the Cox regression models, preprocedure TIMI flow grade had the highest proportion of missing data (10%). Missing data were addressed using multiple imputation with 20 imputed datasets and no auxiliary variable based on the Markov Chain Monte Carlo procedure, which assumes that all variables in the imputation models have a joint multivariate normal distribution.[13,14] Kaplan-Meier survival curves were used to visually assess sex differences in time to rehospitalization for HF and MI. To ascertain whether sex disparities in rehospitalization for HF and MI were equally prevalent in patients aged <60 years and ≥60 years, we tested for interaction between sex and age based on model 3.

This study was conducted according to the Helsinki declaration and the National Healthcare Group Domain Specific Review Board allowed for waiver of patients' consent as the data used were anonymized and analyses were done at a central data repository (National Registry of Diseases Office) with data protection measures in place. All statistical analyses were done using STATA SE (version 13) software. All reported p values were 2-sided and p values <0.05 were considered to be statistically significant.

Results

Between January 2007 and December 2013, there were 7,597 consecutive STEMI patients who underwent pPCI from all public hospitals in Singapore. 1,045 (13.8%) of them were women (Table 1). Compared with men, the median age of women at STEMI onset was a decade older (67.6 vs 56.0 years, $p < 0.001$). Women were less likely to have history of MI (7.8% vs 12.1%, $p < 0.001$), previous PCI (6.7% vs 10.7%, $p < 0.001$) or being current or former smokers (14.0% vs 72.4%; $p < 0.001$), but were more likely to have history of hypertension (69.9% vs 48.6%, $p < 0.001$), diabetes (43.2% vs 24.5%, $p < 0.001$), hyperlipidemia (54.1% vs 42.8%, $p < 0.001$) and stroke (6.7% vs 3.1%, $p < 0.001$). The median creatinine was lower in women (75 vs 92 μmol/L, $p < 0.001$). Women were less likely to have preprocedure complete occlusion of the infarct-related artery (TIMI flow grade 0: 66.8% vs 73.0%, $p < 0.001$), but more likely to have HF on admission (Killip class ≥II: 20.6% vs 14.9%, $p < 0.001$). Although multivessel disease, defined as ≥2 major epicardial arteries with >50% stenosis, was more common in women at the time of emergent coronary angiography (33.4% vs 32.5% with double vessel disease and 32.1% vs 28.9% with triple vessel disease, $p = 0.030$), there was no significant difference in

Table 1
Sex differences in demographics, past medical history and presenting features on admission

Variable	Men (n = 6,552)	Women (n = 1,045)	p
Age (years)	56.0 (49.3−63.2)	67.6 (58.0−76.1)	<0.001
Race			
Chinese	4,052 (61.8%)	662 (63.4%)	0.267
Malay	1,342 (20.5%)	187 (17.9%)	
Indian	1,044 (15.9%)	176 (16.8%)	
Others	114 (1.7%)	20 (1.9%)	
Past medical history			
Hypertension	3,181 (48.6%)	730 (69.9%)	<0.001
Diabetes	1,600 (24.5%)	451 (43.2%)	<0.001
Hyperlipidemia	2,802 (42.8%)	565 (54.1%)	<0.001
Myocardial infarction	794 (12.1%)	81 (7.8%)	<0.001
Percutaneous coronary intervention	701 (10.7%)	70 (6.7%)	<0.001
Coronary artery bypass grafting	71 (1.1%)	12 (1.2%)	0.852
Stroke	97 (3.1%)	33 (6.7%)	<0.001
Peripheral arterial disease	44 (0.7%)	12 (1.2%)	0.094
Current or former smoker	4,700 (72.4%)	143 (14.0%)	<0.001
Killip class on admission			
I	5,575 (85.1%)	830 (79.4%)	<0.001
II	301 (4.6%)	66 (6.3%)	
III	178 (2.7%)	58 (5.6%)	
IV	497 (7.6%)	91 (8.7%)	
Creatinine on admission in μmol/L	92 (80−108)	75 (61−99)	<0.001
Prepercutaneous coronary intervention thrombolysis-in-myocardial-infarct flow grade			
0	4,300 (73.0%)	627 (66.8%)	<0.001
I	376 (6.4%)	87 (9.3%)	
II	574 (9.8%)	99 (10.6%)	
III	639 (10.8%)	125 (13.3%)	
Number of narrowed coronary arteries			
0	14 (0.2%)	0 (0.0%)	0.030
1	2,358 (38.4%)	337 (34.5%)	
2	1,991 (32.5%)	326 (33.4%)	
3	1,771 (28.9%)	314 (32.1%)	
Number of coronary arteries intervened			
Single	6,153 (95.4%)	978 (95.1%)	0.666
Multiple	294 (4.6%)	50 (4.9%)	
Coronary artery intervened			
Left main	118 (1.8%)	21 (2.0%)	0.640
Left anterior descending	3,284 (50.9%)	492 (47.9%)	0.067
Left circumflex	785 (12.2%)	123 (12.0%)	0.847
Right	2,584 (40.1%)	446 (43.4%)	0.045

Values are expressed as n (%) or median (interquartile range).

Table 2
Sex differences in variables related to ST-segment elevation myocardial infarction care

Variable	Men (n = 6,552)	Women (n = 1,045)	p
Door-to-balloon time in minutes	66 (51−87)	76 (60−103)	<0.001
Symptom onset-to-balloon time in minutes	192 (131−312)	233 (165−374)	<0.001
Use of stent	5,928 (92.0%)	912 (88.7%)	<0.001
Use of drug eluting stent	1,549 (24.0%)	200 (19.5%)	0.001
Use of thrombectomy	3,665 (56.9%)	517 (50.3%)	<0.001
Use of intra-aortic balloon pump	217 (3.4%)	61 (5.9%)	<0.001
Procedure success*	6,294 (97.7%)	996 (97.1%)	0.234
Use of glycoprotein IIb−IIIa inhibitor	2,054 (31.9%)	256 (24.9%)	<0.001
Medications given within 24 h from symptom onset			
Aspirin	6,379 (97.4%)	1,006 (96.3%)	0.047
Beta blocker	3,692 (56.4%)	523 (50.1%)	<0.001
$P2Y_{12}$ antagonist	6,499 (99.2%)	1,031 (98.7%)	0.088
Medications given at discharge			
Aspirin	6,074 (97.6%)	881 (95.8%)	0.002
Beta blocker	5,516 (88.6%)	804 (87.4%)	0.286
Lipid lowering drug	6,086 (97.8%)	890 (96.7%)	0.060
Renin-angiotensin system inhibitor	4,801 (77.1%)	695 (75.5%)	0.292
$P2Y_{12}$ antagonist	6,130 (98.5%)	898 (97.6%)	0.039
Killip class during hospitalization			
I	5,872 (89.8%)	883 (84.6%)	<0.001
II	185 (2.8%)	43 (4.1%)	
III	112 (1.7%)	36 (3.5%)	
IV	372 (5.7%)	82 (7.8%)	
Left ventricular systolic dysfunction during hospitalization	3,772 (61.6%)	615 (64.1%)	0.137

Values are expressed as n (%) or median (interquartile range).
* Procedure success is defined as post-percutaneous coronary intervention thrombolysis-in-myocardial-infarct flow grade >II and resolution of ST-segment elevation >50%.

the rate of multivessel PCI performed during hospitalization (4.9% vs 4.6%, p = 0.666).

Women had longer median door-to-balloon (76 vs 66 minutes, p < 0.001) and symptom-to-balloon (233 vs 192 minutes, p < 0.001) time (Table 2). HF during hospitalization was more common in women (Killip class ≥II: 15.4% vs 10.2%, p < 0.001), but not significantly higher for left ventricular systolic dysfunction, defined as left ventricular ejection fraction <50% (64.1% vs 61.6%, p = 0.137). Use of drug-eluting stent (DES, 19.5% vs 24.0%, p = 0.001) and thrombectomy (50.3% vs 56.9%, p < 0.001) were less common in women. Although the prescription rates of aspirin (95.8% vs 97.6%, p = 0.002), $P2Y_{12}$ antagonists (97.6% vs 98.5%, p = 0.039) and glycoprotein IIb-IIIa inhibitors (24.9% vs 31.9%, p < 0.001) were lower in women, there were no significant sex differences in β-blockers, lipid lowering drugs and renin-angiotensin system inhibitors prescription at discharge.

Women had higher unadjusted risk of rehospitalization for both HF (hazard ratio [HR] 1.83, 95% confidence interval [CI] 1.42 to 2.35) and MI (HR 1.78, 95% CI 1.30 to 2.45) (Table 3). After adjusting for baseline characteristics, significant sex difference was no longer observed for HF rehospitalization (HR 1.05, 95% CI 0.79 to 1.40), but persisted for MI rehospitalization (HR 1.68, 95% CI 1.22 to 2.33). Further accounting for variables related to STEMI

Table 3
Risk of rehospitalization for heart failure (HF) and myocardial infarction (MI)

			Women					
			Model 1		Model 2		Model 3	
	Men	Women	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Overall								
Rehospitalized for HF	283 (4.6%)	75 (8.2%)	1.83 (1.42−2.35)	<0.001	1.05 (0.79−1.40)	0.728	1.04 (0.78−1.40)	0.789
Rehospitalized for MI	184 (3.0%)	48 (5.2%)	1.78 (1.30−2.45)	<0.001	1.68 (1.22−2.33)	0.002	1.71 (1.23−2.38)	0.002
Age <60 years								
Rehospitalized for HF	130 (3.2%)	17 (5.8%)	1.89 (1.14-3.13)	0.014	1.37 (0.78−2.38)	0.272	1.27 (0.70−2.29)	0.435
Rehospitalized for MI	124 (3.0%)	14 (4.8%)	1.61 (0.93−2.79)	0.090	1.45 (0.84−2.50)	0.179	1.49 (0.86−2.58)	0.158
Age ≥60 years								
Rehospitalized for HF	153 (7.3%)	58 (9.2%)	1.27 (0.94−1.72)	0.120	1.09 (0.79−1.50)	0.608	1.05 (0.76−1.46)	0.768
Rehospitalized for MI	60 (2.9%)	34 (5.4%)	1.91 (1.26−2.91)	0.002	1.83 (1.18−2.85)	0.007	1.82 (1.16−2.86)	0.009

Men are the reference group for all models.

care yielded similar results (HF rehospitalization: HR 1.04, 95% CI 0.78 to 1.40; MI rehospitalization: HR 1.71, 95% CI 1.23 to 2.38) (Figures 1 and 2).

Stratifying by age, women had significantly higher unadjusted risk of rehospitalization for HF than men in the <60 years age group (HR 1.89, 95% CI 1.14 to 3.13), but not in the ≥60 years age group (p = 0.120) (Table 3). The interaction between sex and age for HF rehospitalization was not statistically significant (p for interaction = 0.671). In contrast, women had significantly higher unadjusted risk of rehospitalization for MI than men in the ≥60 years age group (HR 1.91, 95% CI 1.26 to 2.91), but not in the <60 years age group (p = 0.090) (Table 3). The interaction between sex and age for MI rehospitalization was statistically significant (p for interaction = 0.029). After adjusting for baseline characteristics, the higher risk of rehospitalization for HF in women in the <60 years age group attenuated (p = 0.272) (Supplemental Figure 2). However, the higher risk of rehospitalization for MI among women in the ≥60 years age group persisted after adjusting for baseline characteristics (HR 1.83, 95% CI 1.18 to 2.85), as well as after further accounting for variables related to STEMI care (HR 1.82, 95% CI 1.16 to 2.86) (Supplemental Figure 3).

Discussion

Our study found that in patients with STEMI who underwent pPCI, women were older with higher prevalence of co-morbidities, multivessel disease and heart failure on admission, compared with men. Women had longer ischemic time and were less likely to receive DES, thrombectomy and antiplatelet agents. Women were approximately 1.8 times more likely to be rehospitalized for HF or MI within 1 year from discharge in unadjusted analyses. After adjusting for baseline characteristics, sex differences in risk of rehospitalization for HF attenuated, but persisted in rehospitalization for MI. Further accounting for variables related to STEMI care yielded similar results. The higher risk of rehospitalization for MI in women than men was more pronounced in the ≥60 years age group than in the <60 years age group.

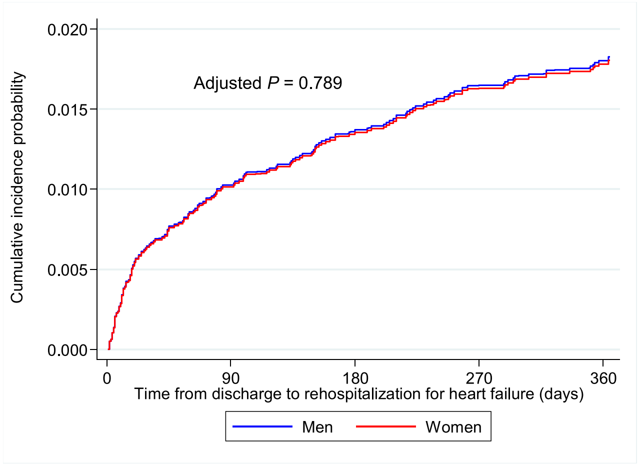

Figure 1. Time to rehospitalization for heart failure.
Event curves show the adjusted rehospitalization events.

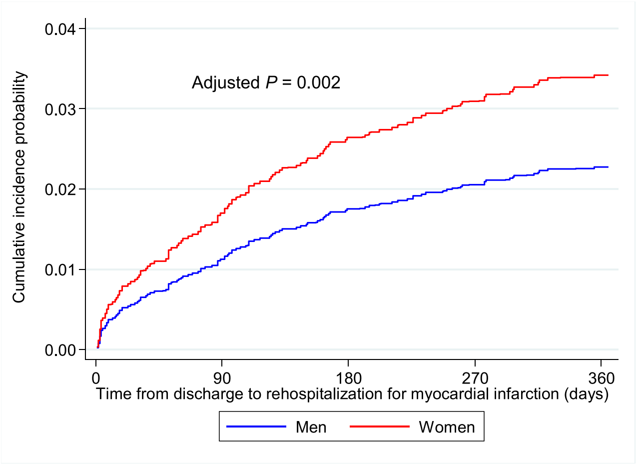

Figure 2. Time to rehospitalization for myocardial infarction.
Event curves show the adjusted rehospitalization events.

HF is a common complication of STEMI.[15] Besides being generally older than men at the onset of STEMI, women also tend to have HF on admission, longer ischemic time and higher burden of hypertension and diabetes—all of which are risk factors that have an established association with HF.[16] The attenuation of statistical significance after accounting for differences in baseline characteristics suggests that the higher risk of rehospitalization for HF in women was largely explained by their higher baseline risk. We further observed high prescription rates of β-blockers and renin-angiotensin system inhibitors at discharge for both sexes. Notably, >75% of women and men received β-blockers and renin-angiotensin system inhibitors at discharge, which was in excess to the prevalence of left ventricular systolic dysfunction in women (64.1%) and men (61.6%). As both β-blockers and renin-angiotensin system inhibitors are known to reduce the risk of adverse ventricular remodeling after a large infarct,[17] it is plausible that the similarly high prescription rates of β-blockers and renin-angiotensin system inhibitors in both sexes may also be responsible in part for the similar adjusted risk of rehospitalization for HF.

In contrast to rehospitalization for HF, the risk of rehospitalization for MI remained higher in women after adjusting for sex differences in baseline characteristics. Despite studies showing that women derive greater benefit from DES than men,[18] there were significantly lower use of DES in women in our study. The lower use of DES in women was limited to patients ≥60 years of age (women 16.9%, men 23.9%, $p < 0.001$). Procedure success was similarly high in both sexes despite higher rate of preprocedure complete occlusion of the infarct-related artery in men. In the same vein, the rate of multivessel PCI was similarly low in both sexes despite multivessel disease being more common in women. However, the interaction between sex and complete revascularization for MI rehospitalization was not statistically significant (p for interaction = 0.441). Unmeasured variables may be postulated to explain the higher risk of rehospitalization for MI in women in our study. Having typically smaller and less compliant conduit arteries, coupled with concomitant risk factors such as diabetes and complex lesions, put women at a higher risk of restenosis.[19,20] Hormonal fluctuation, especially during menopause in women, may lead to macrovascular and microvascular alterations, leaving older women vulnerable to a decreased ability to sustain adequate vascular repair.[21] Smooth muscle cell dysfunction is more commonly seen in women, which may lead to impairment of coronary flow reserve.[22] Spontaneous coronary artery dissection also occurs more frequently in women.[23] Although it is a rare cause of MI, a study by Tweet et al found that revascularization did not protect against recurrent spontaneous coronary artery dissection even in patients presenting with preserved vessel flow.[24] Women are known to have a higher risk of bleeding than men, which could lead to early discontinuation of dual-antiplatelet therapy (DAPT) with a subsequent increased risk of MI.[25] Moreover, women tend to have poorer medical adherence than men.[26,27] Dreyer et al further observed that women had poorer health and psychosocial status after MI and adjusting for health status and psychosocial status attenuated sex differences in post-MI rehospitalization.[2]

As our study covered an unselected STEMI population using national data, which were captured in a standardized manner across all hospitals, it is expected to yield results with high internal validity. Although the long study period of 7 years (2007 to 2013) is a strength, progress in management of STEMI has been rapid and hence there are likely to be time-varying trends that may not be fully accounted in our study. Studies have questioned the accuracy of primary diagnoses coded by hospitals,[28] yet others have shown that major contributory disease conditions can be reliability identified with a positive predictive value >80%.[29] As higher risk of rehospitalization for MI in women persisted after adjusting for all potential confounders available in our study, we can only conclude that these variables are able to partially explain the association between sex and rehospitalization for MI and attribute the unexplained sex disparity to other unmeasured variables, such as duration of DAPT, medication adherence and psychosocial status.

In conclusion, in a setting of universal access to pPCI, sex disparities persist in STEMI treatment and outcomes. Compared with men, women with STEMI are more likely to experience treatment delay, less likely to receive DES and DAPT, and more likely to be rehospitalized for HF and MI. Sex differences in rehospitalization for HF but not MI appear to be largely explained by their differing baseline risk. To better understand how to mitigate the sex disparity in rehospitalization for MI after pPCI, future studies could focus on sex differences in the complexity and severity of coronary artery disease and evaluate their interaction with the impact of intensification of secondary preventive medical therapy and more complete revascularization in women.

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Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.03.021.

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