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Sex-Related Differences in Thrombus Burden in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention

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ABSTRACT

BACKGROUND Women have a worse prognosis after ST-segment elevation myocardial infarction (STEMI) than men. The prognostic role of thrombus burden (TB) in influencing the sex-related differences in clinical outcomes after STEMI has not been clearly investigated.

OBJECTIVES The aim of this study was to assess the sex-related differences in TB and its clinical implications in patients with STEMI.

METHODS Individual patient data from the 3 major randomized clinical trials of manual thrombus aspiration were analyzed, encompassing a total of 19,047 patients with STEMI, of whom 13,885 (76.1%) were men and 4,371 (23.9%) were women. The primary outcome of interest was 1-year cardiovascular (CV) death. The secondary outcomes of interest were recurrent myocardial infarction, heart failure, all-cause mortality, stroke, stent thrombosis (ST), and target vessel revascularization at 1 year.

RESULTS Patients with high TB (HTB) had worse 1-year outcomes compared with those presenting with low TB (adjusted HR for CV death: 1.52; 95% CI: 1.10-2.12; $P = 0.01$). In unadjusted analyses, female sex was associated with an increased risk for 1-year CV death regardless of TB. After adjustment, the risk for 1-year CV death was higher only in women with HTB (HR: 1.23; 95% CI: 1.18-1.28; $P < 0.001$), who also had an increased risk for all-cause death and ST than men.

CONCLUSIONS In patients with STEMI, angiographic evidence of HTB negatively affected prognosis. Among patients with HTB, women had an excess risk for ST, CV, and all-cause mortality than men. Further investigations are warranted to better understand the pathophysiological mechanisms leading to excess mortality in women with STEMI and HTB. (J Am Coll Cardiol Intv 2022;15:2066–2076) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Several studies have documented the existence of sex-related differences in early- and long-term prognosis after myocardial infarction (MI).[1,2] In particular, female sex has been associated with higher mortality and complication rates compared with male sex, especially during the first 30 days after MI.[2] Although the underlying mechanisms of excess mortality in female patients remain unclear, recent studies have demonstrated sex-specific differences in thrombus formation and stabilization, with enhanced platelet activation in women compared with men.[3,4] Such differences may adversely modulate the thrombotic milieu in female patients with acute coronary syndrome and, potentially, lead to enhanced thrombogenicity in the acute phases of ST-segment elevation myocardial infarction (STEMI).

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It has been previously shown that in patients with STEMI, a higher burden of intracoronary thrombus predicts periprocedural complications and in-hospital adverse events after primary percutaneous coronary intervention (PCI).[5,6] Building on this concept, randomized clinical trials have investigated the potential benefits of routinely removing thrombus by manual thrombus aspiration. However, these trials failed to demonstrate any prognostic benefit of routine thrombus aspiration.[7]

To date, it remains unknown whether differences in thrombus burden (TB) may help explain, at least in part, the sex-related differences in prognosis seen after MI. Using data on TB and clinical outcomes collected in 3 large trials of manual thrombus aspiration, we sought to assess sex-related differences in TB and their clinical implications in a large cohort of patients with STEMI undergoing primary PCI.

METHODS

PATIENT POPULATION. The study population included 19,047 subjects who underwent primary PCI for STEMI and were enrolled in 1 of 3 randomized clinical trials: TAPAS (Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study), TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia), and TOTAL (Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI Undergoing Primary PCI).[8-13] These studies were selected because they met the following criteria: 1) randomized clinical trial; 2) including patients with STEMI within 24 hours of symptom onset; 3) with available data on clinical outcomes and TIMI (Thrombolysis In Myocardial Infarction) thrombus grade; 4) performing follow-up of at least 12 months; and 5) a large study cohort (n = ≥1,000). We excluded trials that did not meet these criteria.[14]

After obtaining agreement from the steering committee of each trial and ethical approval, the individual patient-level data from these studies were merged into a unique database.[7] The design and primary results of the 3 trials included in this analysis have been previously described in detail,[8-13] and a brief description of each study is reported in the Supplemental Appendix.

The merged study population was dichotomized according to sex and burden of thrombosis. Consistent with previous studies, we divided the study population into 2 groups according to TIMI thrombus grade: low TB (LTB), including patients with TIMI thrombus grades <3, and high TB (HTB), encompassing patients with TIMI thrombus grades ≥3.[15,16]

DEFINITIONS AND OUTCOMES OF INTEREST. Detailed definitions of STEMI, TB, recurrent MI, heart failure, stroke, transient ischemic attack, stent thrombosis, and target vessel revascularization are reported in the Supplemental Appendix.

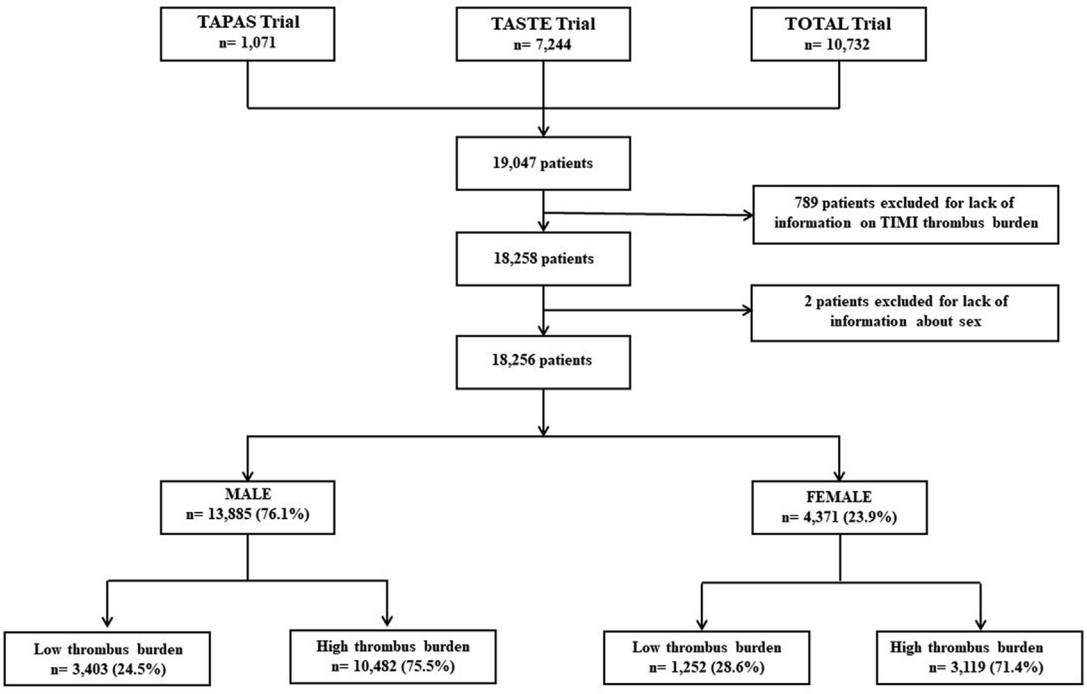
The primary outcome of interest of this analysis was cardiovascular death up to 1 year. The secondary outcomes of interest included recurrent MI, heart failure, all-cause mortality, stroke or transient ischemic attack, stent thrombosis, and target vessel revascularization up to 1 year. All clinical outcomes were assessed at 30, 180, and 365 days after the index procedure.

STATISTICAL ANALYSIS. The study population was dichotomized according to sex and TB. Categorical variables are expressed as number (percentage) and continuous variables as mean ± SD. Differences in baseline characteristics were investigated using the standardized mean difference, and values >0.2 were considered to indicate a clinically relevant imbalance between groups. The cumulative incidence of events during follow-up was calculated according to the Kaplan-Meier method. Across the different TB strata, the HR for each outcome of interest was calculated using Cox proportional hazards regression models. The Cox models were adjusted for age, diabetes, hypertension, prior MI, prior PCI, smoking status, time from symptom onset to PCI start, use of glycoprotein IIb/IIIa inhibitors during PCI, proximal lesion location, and culprit lesion in the left anterior descending coronary artery. All multivariable Cox regression models also accounted for clustering of patients

ABBREVIATIONS AND ACRONYMS

HTB = high thrombus burden
LTB = low thrombus burden
MI = myocardial infarction
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TB = thrombus burden

FIGURE 1 Flowchart of the Study Population



TAPAS = Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study; TASTE = Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia; TIMI = Thrombolysis In Myocardial Infarction; TOTAL = Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI Undergoing Primary PCI.

across the 3 randomized trials. Finally, we assessed the interaction between sex and randomized treatment arm with respect to clinical outcomes. In all analyses, $P < 0.05$ was used as the threshold of statistical significance. All statistical analyses were performed using SPSS Statistics version 26 (IBM) and R statistical software (R Foundation for Statistical Computing).

RESULTS

STUDY POPULATION AND BASELINE CHARACTERISTICS. The flowchart of the study population is presented in Figure 1. From the initial merged study cohort of 19,047 patients, we excluded 791 patients (4.2%) because of missing information on sex or TIMI thrombus grade. The final study population comprised 18,256 patients, of whom 13,885 were men (76.1%) and 4,371 were women (23.9%). Follow-up at 1 year was complete in the study, and the median follow-up duration was 365 days. The baseline clinical characteristics of male and female patients across the TB strata are presented in Table 1. The majority of subjects (n = 13,601 [74.5%]) had HTB at the time of PCI, and the prevalence of HTB was lower in female patients compared with men (n = 3,119 [71.4%] vs n = 10,482 [75.5%]; $P < 0.0001$). A detailed overview of TB prevalence in male and female patients is shown in Figure 2. Overall, patients with HTB had worse 1-year outcomes compared with those presenting with LTB (adjusted HR for cardiovascular death: 1.52; 95% CI: 1.10-2.12; $P = 0.01$).

The clinical characteristics of male and female patients and of patients presenting with HTB and LTB are presented in Supplemental Tables S1 and S2. In both groups, women were older than men and presented more often with a history of arterial hypertension. Women had longer median ischemic times compared with men (on average, excess median ischemic time of about 20 minutes). Female patients were less likely to have had a previous MI and previous PCI compared with men (standardized mean difference ranking from 0.1 to 0.2). No relevant differences were observed in medical therapy before and during PCI between groups, except for a numerically more frequent use of glycoprotein IIb/IIIa inhibitors during PCI in male patients.

TABLE 1 Baseline Clinical Characteristics and Medications According to Sex and Thrombus Burden

	Low Thrombus Burden				High Thrombus Burden			
	Male (n = 3,403)	Female (n = 1,252)	SMD	*P* Value	Male (n = 10,482)	Female (n = 3,119)	SMD	*P* Value
Age, y	63.4 ± 11.4	68.9 ± 12.0	0.471	<0.001	61.2 ± 11.7	67.4 ± 12.3	0.518	<0.001
Clinical history								
Current smoking	1,213 (37.4)	444 (37.6)	0.004	0.925	4,437 (43.4)	1,162 (38.6)	0.098	<0.001
Hypertension	1,435 (42.5)	617 (50.2)	0.156	<0.001	4,623 (44.3)	1,772 (57.1)	0.258	<0.001
Diabetes	467 (13.8)	202 (16.2)	0.068	0.042	1,606 (15.4)	587 (18.9)	0.093	<0.001
Previous MI	394 (11.7)	101 (8.2)	0.118	0.001	1,117 (10.7)	229 (7.4)	0.116	<0.001
Previous PCI	339 (10.0)	70 (5.6)	0.164	<0.001	1,007 (9.6)	187 (6.0)	0.135	<0.001
Killip class 4	23 (0.7)	6 (0.5)	0.026	0.595	81 (0.8)	32 (1.0)	0.027	0.209
Killip class ≥2[a]	129 (4.1)	49 (4.4)	0.014	0.760	452 (4.5)	180 (6.1)	0.071	0.001
Time from symptom onset to PCI start, min	180 (125-290)	195 (135-328)	0.118	<0.001	183 (123-295)	210 (139-334)	0.130	<0.001
Medication before PCI								
Clopidogrel/ticlopidine[a]	1,865 (58.8)	652 (57.3)	0.029	0.420	6,276 (62.9)	1,869 (63.7)	0.017	0.445
Ticagrelor[a]	585 (18.4)	199 (17.5)	0.024	0.510	1,716 (17.2)	521 (17.8)	0.015	0.501
Prasugrel[a]	281 (8.9)	91 (8.0)	0.030	0.417	1,043 (10.5)	223 (7.6)	0.100	<0.001
Medication during PCI								
Unfractionated heparin	2,908 (85.8)	1,074 (86.1)	0.090	0.818	8,751 (83.6)	2,646 (85.1)	0.043	0.042
Low-molecular weight heparin	178 (5.2)	52 (4.2)	0.051	0.157	719 (6.9)	193 (6.2)	0.027	0.212
Bivalirudin	2,015 (59.5)	727 (58.3)	0.023	0.517	3,635 (34.7)	1,136 (36.6)	0.038	0.064
GP IIb/IIIa inhibitors	816 (24.1)	291 (23.4)	0.017	0.647	4,042 (38.6)	994 (32.0)	0.139	<0.001
Medication at hospital discharge								
Clopidogrel[a]	1,776 (56.8)	710 (62.5)	0.116	0.001	5,869 (60)	1,811 (62.7)	0.056	0.008
Prasugrel[a]	320 (10.2)	78 (6.9)	0.121	0.001	1,290 (13.2)	237 (8.2)	0.161	<0.001
Ticagrelor[a]	896 (28.7)	305 (26.8)	0.041	0.258	2,221 (22.7)	650 (22.5)	0.004	0.854
Beta-blocker[a]	2,811 (89.9)	1,024 (90.1)	0.007	0.880	8,129 (83.1)	2,350 (81.4)	0.044	0.039
ACE inhibitor[a]	2,404 (77.0)	814 (71.7)	0.120	0.001	7,196 (73.5)	1,984 (68.7)	0.107	<0.001
Aspirin[a]	3,026 (97.6)	1,073 (95.8)	0.102	0.003	9,564 (97.9)	2,747 (95.6)	0.132	<0.001
Statin[a]	3,024 (96.7)	1,075 (94.7)	0.100	0.003	9,365 (95.7)	2,673 (92.6)	0.134	<0.001

Values are mean ± SD, n (%), or median (IQR) unless otherwise indicated. [a]Data were available only in the TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) and TOTAL (Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI Undergoing Primary PCI) trials.

ACE = angiotensin-converting enzyme; GP = glycoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention; SMD = standardized mean difference.

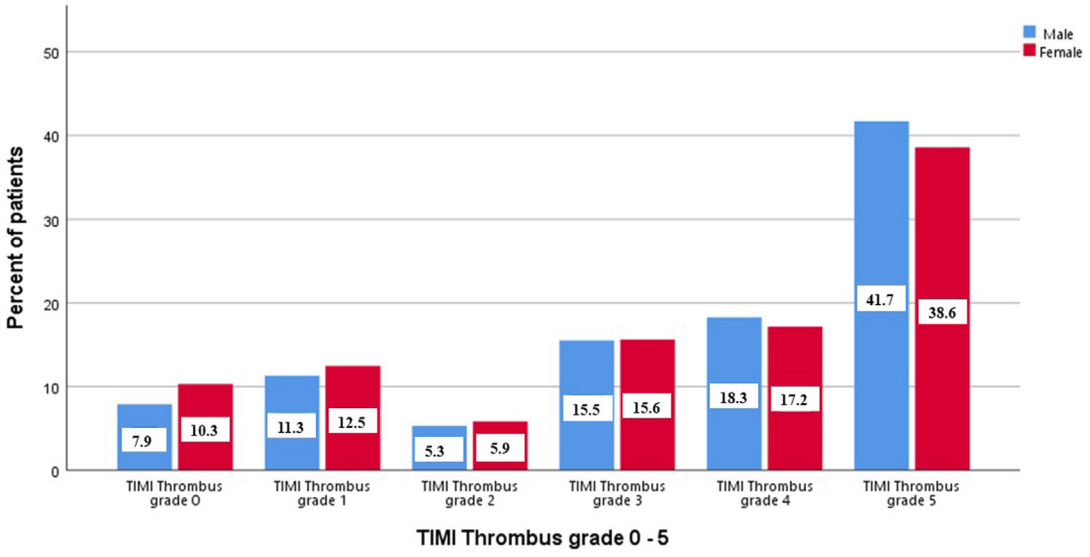
Procedural characteristics and angiographic results of the index primary PCI are presented in **Table 2**. Women in both groups (HTB and LTB) were treated with stents of a smaller mean diameter compared with men. Additionally, radial access was used less often in women than in men.

CLINICAL OUTCOMES. Clinical outcomes according to sex are presented in **Table 3**. In unadjusted analysis, women had a significantly higher risk for cardiovascular and all-cause mortality, stroke or transient ischemic attack, and heart failure than men, in both the short and long terms after index PCI. After adjustment for confounders, female sex remained associated with an increased risk for cardiovascular and all-cause mortality compared with male sex. Moreover, the risk for stent thrombosis and MI at 1 year was higher in women, as well as the risk for heart failure through 30 and 180 days.

The incidence of cardiovascular death in patients categorized by sex and TB is shown in **Figure 3**. Irrespective of TB, women had higher mortality rates than men, with divergence in survival curves primarily occurring early after the index PCI. A landmark analysis for cardiovascular death (landmark point at 30 days) is shown in Supplemental Figure 1.

Adjusted clinical outcomes across both sex and TB strata are shown in **Table 4**. No differences in the risk for cardiovascular death were found among female and male patients in the LTB group. In patients with HTB, women had higher risk for cardiovascular death compared with men. This difference was more pronounced during the first 30 days after the index PCI (adjusted HR for 0-30 days: 1.36; 95% CI: 1.26-1.48; $P < 0.001$) and decreased after the first month and up to 1 year (adjusted HR for 31-365 days: 0.99; 95% CI: 0.83-1.17; $P = 0.863$). Women with HTB had a significantly higher risk for all-cause death and stent thrombosis compared with men. In addition, women with HTB had a higher risk for heart failure through 30 and 180 days, but not at 1 year. The risk for stroke or transient ischemic attack was higher in women with LTB at 30 days. No data were available on the ischemic or hemorrhagic etiology of the events. Similarly, female sex was associated with an

FIGURE 2 TIMI Thrombus Grade by Sex



Prevalence of TIMI (Thrombolysis In Myocardial Infarction) thrombus grades in study population by sex.

increased risk for recurrent MI at 1 year in the LTB group. There was no significant difference in target vessel revascularization between groups in either of the TB strata.

The unadjusted Cox regression analysis is shown in Supplemental Table S3. The outcomes of interest across the TB strata (not stratified for sex) are reported in Supplemental Table S4.

No interaction terms between the randomized treatment arm and sex with respect to clinical outcomes were significant (Table 4). Similarly, no significant interaction terms among sex and use of

TABLE 2 Procedural Characteristics According to Sex and Thrombus Burden

	Low Thrombus Burden				High Thrombus Burden			
	Male (n = 3,403)	Female (n = 1,252)	SMD	*P* Value	Male (n = 10,482)	Female (n = 3,119)	SMD	*P* Value
Treated vessel								
Left main coronary artery	28 (0.8)	15 (1.2)	0.038	0.309	98 (0.9)	24 (0.8)	0.018	0.458
Left anterior descending coronary artery	1,657 (48.8)	554 (44.4)	0.088	0.008	4,508 (43.1)	1,224 (39.4)	0.075	<0.001
Left circumflex coronary artery	670 (19.7)	178 (14.3)	0.146	<0.001	1,545 (14.8)	406 (13.1)	0.049	0.020
Right coronary artery	1,247 (36.8)	548 (43.9)	0.147	<0.001	4,781 (45.7)	1,577 (50.7)	0.120	<0.001
Graft/bypass	20 (0.6)	4 (0.3)	0.040	0.368	45 (0.4)	5 (0.2)	0.050	0.045
Lesion location proximal vessel	2,288 (67.4)	900 (72.2)	0.103	0.002	6,004 (57.3)	1,809 (58.2)	0.017	0.406
Radial access[a]	2,333 (73.4)	749 (65.8)	0.165	<0.001	6,743 (67.6)	1,781 (60.7)	0.144	<0.001
Direct stenting	1,001 (29.7)	378 (30.6)	0.020	0.567	3,202 (30.8)	912 (29.6)	0.025	0.232
Drug-eluting stent	1,441 (42.5)	507 (40.7)	0.037	0.282	4,767 (45.5)	1,339 (43.1)	0.049	0.017
Bare-metal stent	1,871 (55.1)	680 (54.5)	0.012	0.735	5,422 (51.8)	1,583 (50.9)	0.017	0.415
TIMI flow grade 0 or 1 before PCI	1,897 (56.3)	660 (53.1)	0.065	0.055	8,563 (82.3)	2,486 (80.5)	0.046	0.025
Number of stents (per patient)	1.35 ± 0.75	1.33 ± 0.76	0.022	0.507	1.37 ± 0.72	1.36 ± 0.69	0.021	0.313
Stent length, mm	27.14 ± 15.58	26.64 ± 15.33	0.032	0.350	28.50 ± 15.67	27.95 ± 14.37	0.037	0.091
Stent diameter, mm	3.10 ± 0.48	2.96 ± 0.45	0.293	<0.001	3.21 ± 0.49	3.04 ± 0.45	0.365	<0.001
Fluoroscopy time, min	12.33 ± 24.47	11.92 ± 18.34	0.019	0.586	12.88 ± 20.73	13.09 ± 27.44	0.008	0.658
Contrast volume, mL[a]	155.60 ± 80.33	145.56 ± 87.22	0.120	<0.001	177.87 ± 110.21	164.61 ± 75.97	0.140	<0.001

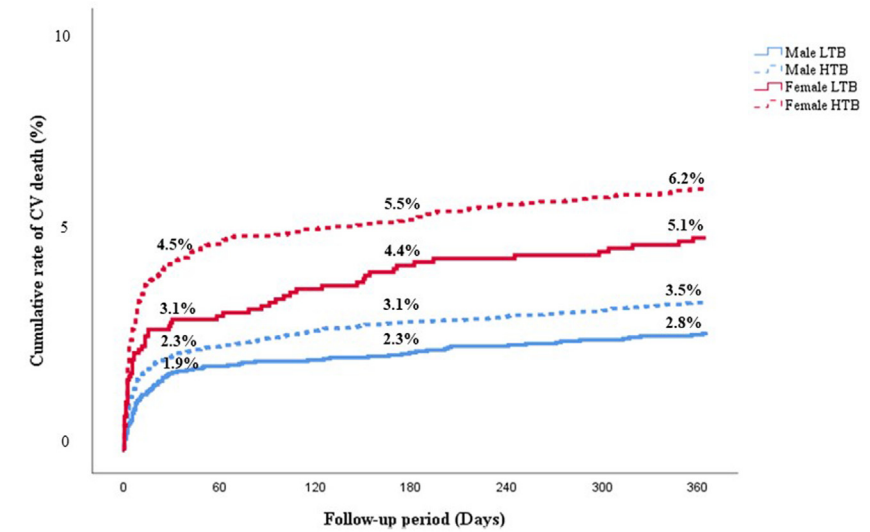
Values are n (%) or mean ± SD unless otherwise indicated. [a]Data were available only in the TASTE and TOTAL trials.
TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

TABLE 3 Clinical Outcomes According to Sex in the Overall Cohort

	Male (n = 13,885)	Female (n = 4,371)	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Outcomes at 30 d						
CV death	299 (2.2)	180 (4.1)	1.93 (1.61-2.33)	<0.0001	1.28 (1.12-1.46)	<0.001
MI	150 (1.1)	51 (1.2)	1.09 (0.80-1.50)	0.577	1.14 (0.90-1.43)	0.280
HF	172 (1.3)	96 (2.3)	1.82 (1.42-2.34)	<0.0001	1.38 (1.30-1.47)	<0.001
All-cause mortality	312 (2.2)	188 (4.3)	1.94 (1.62-2.32)	<0.0001	1.30 (1.17-1.44)	<0.001
Stroke/TIA	69 (0.5)	44 (1.0)	2.04 (1.40-2.98)	<0.0001	1.55 (0.87-2.75)	0.137
Stent thrombosis	101 (0.7)	43 (1.0)	1.37 (0.96-1.96)	0.085	1.49 (1.17-1.89)	0.001
TVR	345 (2.5)	106 (2.4)	0.99 (0.79-1.23)	0.904	0.96 (0.73-1.25)	0.739
Outcomes at 180 d						
CV death	399 (2.9)	226 (5.2)	1.83 (1.55-2.15)	<0.0001	1.17 (1.07-1.27)	<0.001
MI	262 (1.9)	99 (2.3)	1.22 (0.97-1.54)	0.088	1.12 (0.96-1.31)	0.160
HF	285 (2.2)	152 (3.7)	1.75 (1.44-2.13)	<0.0001	1.25 (1.18-1.33)	<0.001
All-cause mortality	449 (3.2)	254 (5.8)	1.83 (1.56-2.13)	<0.0001	1.14 (1.03-1.26)	0.009
Stroke/TIA	122 (0.9)	61 (1.4)	1.61 (1.18-2.19)	0.002	1.13 (0.54-2.38)	0.744
Stent thrombosis	138 (1)	51 (1.2)	1.19 (0.86-1.64)	0.284	1.30 (1.04-1.62)	0.019
TVR	639 (4.6)	176 (4)	0.89 (0.75-1.05)	0.163	0.90 (0.76-1.06)	0.197
Outcomes at 365 d						
CV death	462 (3.3)	257 (5.9)	1.79 (1.54-2.09)	<0.0001	1.19 (1.11-1.26)	<0.001
MI	328 (2.4)	143 (3.3)	1.42 (1.16- .72)	0.001	1.32 (1.08-1.62)	0.007
HF	350 (2.7)	171 (4.2)	1.61 (1.34-1.93)	<0.0001	1.18 (0.96-1.44)	0.117
All-cause mortality	576 (4.1)	309 (7.1)	1.74 (1.51-1.99)	<0.0001	1.11 (1.03-1.19)	0.005
Stroke/TIA	153 (1.1)	80 (1.8)	1.68 (1.29-2.21)	<0.0001	1.21 (0.48-3.01)	0.688
Stent thrombosis	156 (1.1)	57 (1.3)	1.18 (0.87-1.60)	0.284	1.27 (1.06-1.52)	0.010
TVR	777 (5.6)	215 (4.9)	0.89 (0.77-1.04)	0.143	0.92 (0.84-1.01)	0.068

Values are n (%) unless otherwise indicated.
CV = cardiovascular; HF = heart failure; MI = myocardial infarction; TIA = transient ischemic attack; TVR = target vessel revascularization.

FIGURE 3 Kaplan-Meier Curves Showing CV Death Up to 1 Year



No. risk

Male LTB	3.403	3.316	3.309	3.298	3.190	3.178	3.163
Male HTB	10.482	10.153	10.100	10.066	9.790	9.760	9.713
Female LTB	1.252	1.203	1.191	1.183	1.165	1.161	1.154
Female HTB	3.119	2.940	2.921	2.912	2.832	2.821	2.806

Unadjusted rate of cardiovascular (CV) death in patients with ST-segment elevation myocardial infarction (STEMI) categorized by sex and thrombus burden. HTB = high thrombus burden; LTB = low thrombus burden.

TABLE 4 Clinical and Procedural Outcomes According to Sex and Thrombus Burden

	Low Thrombus Burden						High Thrombus Burden					
	Male (n = 3,403)	Female (n = 1,252)	Adjusted HR (95% CI)	*P* Value	*P* Value for Interaction[a]	*P* Value for Interaction[b]	Male (n = 10,482)	Female (n = 3,119)	Adjusted HR (95% CI)	*P* Value	*P* Value for Interaction[a]	*P* Value for Interaction[b]
Outcomes at 30 d												
CV death	63 (1.9)	39 (3.1)	1.01 (0.88-1.17)	0.88	0.764	0.756	236 (2.3)	141 (4.5)	1.37 (1.22-1.54)	<0.001	0.187	0.697
MI	29 (0.9)	8 (0.6)	0.95 (0.47-1.94)	0.89	0.191	0.837	121 (1.2)	43 (1.4)	1.20 (0.90-1.59)	0.22	0.828	0.789
HF[c]	36 (1.1)	20 (1.7)	1.28 (0.78-2.10)	0.33	0.882	0.153	136 (1.4)	76 (2.6)	1.42 (1.37-1.48)	<0.001	0.510	0.828
All-cause mortality	69 (2.0)	43 (3.4)	1.03 (0.84-1.25)	0.78	0.775	0.620	243 (2.3)	145 (4.6)	1.39 (1.24-1.55)	<0.001	0.176	0.691
Stroke/TIA[c]	14 (0.4)	10 (0.8)	2.01 (1.48-2.74)	<0.001	0.052	0.747	55 (0.5)	34 (1.1)	1.45 (0.68-3.11)	0.33	0.857	0.412
Stent thrombosis	16 (0.5)	4 (0.3)	0.66 (0.20-2.19)	0.50	0.380	0.324	85 (0.8)	39 (1.3)	1.68 (1.38-2.06)	<0.001	0.828	0.456
TVR	81 (2.4)	23 (1.8)	0.72 (0.48-1.09)	0.12	0.439	0.681	264 (2.5)	83 (2.7)	1.04 (0.79-1.36)	0.80	0.497	0.985
Outcomes at 180 d												
CV death	79 (2.3)	55 (4.4)	1.13 (0.82-1.56)	0.47	0.922	0.496	320 (3.1)	171 (5.5)	1.19 (1.06-1.35)	0.005	0.122	0.666
MI	63 (1.9)	29 (2.3)	1.25 (0.94-1.66)	0.13	0.391	0.367	199 (1.9)	70 (2.2)	1.08 (0.82-1.43)	0.57	0.621	0.514
HF[c]	67 (2.1)	43 (3.8)	1.22 (0.80-1.86)	0.37	0.830	0.294	218 (2.2)	109 (3.7)	1.27 (1.03-1.57)	0.02	0.747	0.721
All-cause mortality	96 (2.8)	66 (5.3)	1.05 (0.77-1.44)	0.75	0.702	0.322	353 (3.4)	188 (6.0)	1.17 (1.02-1.35)	0.02	0.119	0.559
Stroke/TIA[c]	28 (0.8)	16 (1.3)	1.07 (0.88-1.32)	0.50	0.422	0.368	94 (0.9)	45 (1.4)	1.14 (0.47-2.74)	0.77	0.674	0.116
Stent thrombosis	26 (0.8)	8 (0.6)	0.85 (0.31-2.28)	0.74	0.294	0.852	112 (1.1)	43 (1.4)	1.43 (1.23-1.65)	<0.001	0.486	0.699
TVR	158 (4.6)	47 (3.8)	0.81 (0.61-1.09)	0.16	0.887	0.759	481 (4.6)	129 (4.1)	0.93 (0.79-1.08)	0.34	0.549	0.478
Outcomes at 365 d												
CV death	95 (2.8)	63 (5.0)	1.07 (0.78-1.46)	0.67	0.344	0.906	367 (3.5)	194 (6.2)	1.23 (1.18-1.28)	<0.001	0.122	0.877
MI	81 (2.4)	43 (3.4)	1.39 (1.05-1.84)	0.02	0.478	0.162	247 (2.4)	100 (3.2)	1.29 (0.98-1.71)	0.08	0.159	0.917
HF[c]	91 (2.9)	46 (4.0)	0.95 (0.70-1.29)	0.74	0.931	0.298	259 (2.6)	125 (4.2)	1.26 (0.96-1.67)	0.10	0.943	0.527
All-cause mortality	133 (3.9)	79 (6.3)	0.89 (0.61-1.30)	0.56	0.474	0.324	443 (4.2)	230 (7.4)	1.18 (1.12-1.25)	<0.001	0.081	0.869
Stroke/TIA[c]	40 (1.2)	19 (1.5)	0.90 (0.56-1.47)	0.68	0.261	0.178	113 (1.1)	61 (2.0)	1.30 (0.53-3.22)	0.57	0.712	0.385
Stent thrombosis	30 (0.9)	10 (0.8)	0.91 (0.57-1.44)	0.68	0.197	0.729	126 (1.2)	47 (1.5)	1.38 (1.21-1.57)	<0.001	0.428	0.895
TVR	186 (5.5)	56 (4.5)	0.83 (0.64-1.08)	0.16	0.805	0.467	591 (5.6)	159 (5.1)	0.95 (0.88-1.03)	0.19	0.660	0.484

Values are n (%) unless otherwise indicated. [a]Interaction *P* value (univariate) by sex and thrombus aspiration with respect to individual clinical outcomes. [b]Interaction *P* value (univariate) by sex and glycoprotein IIb/IIIa inhibitors during percutaneous coronary intervention with respect to individual clinical outcomes. [c]Data were available only in the TASTE and TOTAL trials.

Abbreviations as in Tables 1 and 3.

glycoprotein IIb/IIIa inhibitors were found in patients with LTB and HTB.

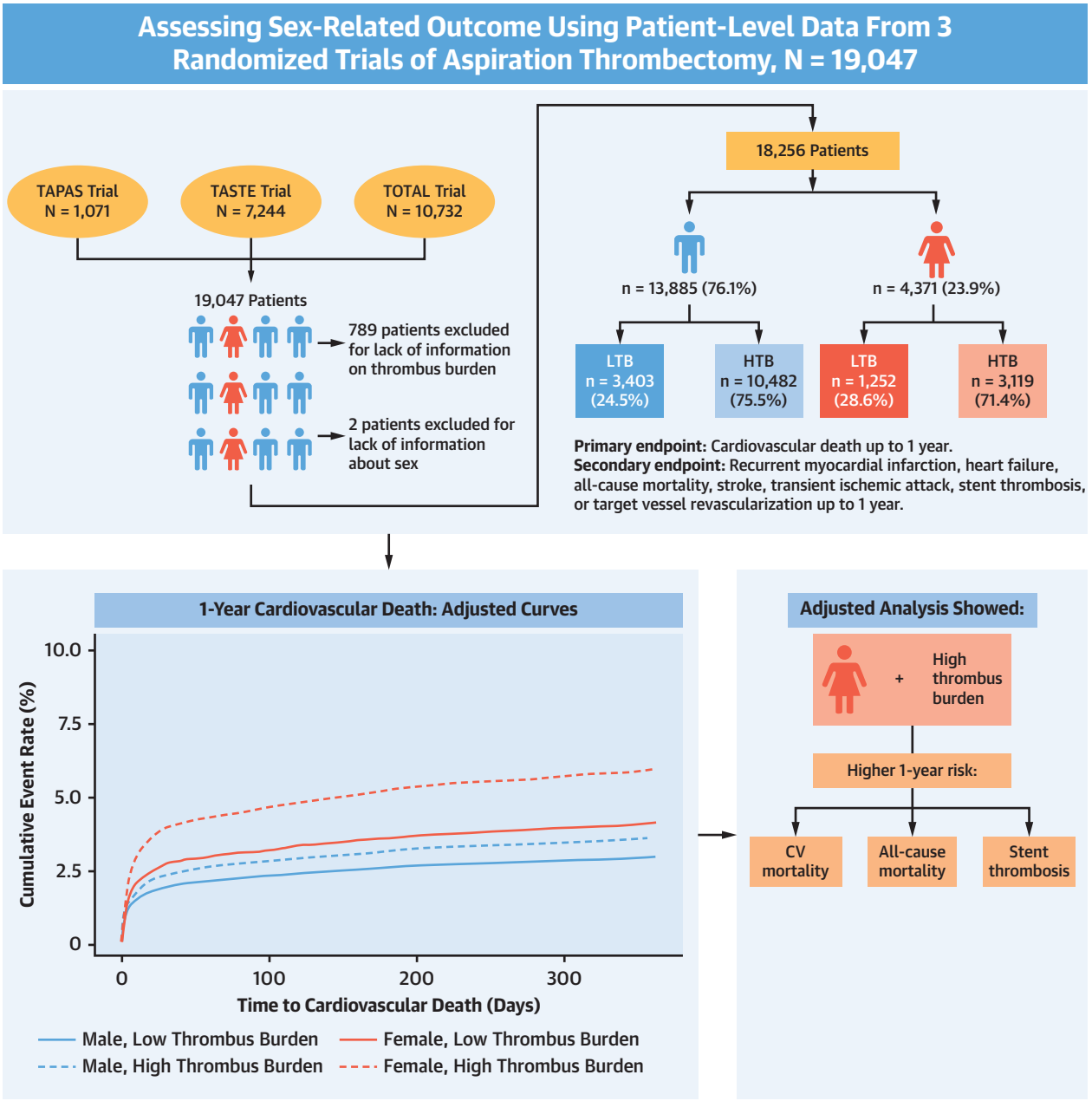
DISCUSSION

The principal findings of this study may be summarized as follows: 1) in the overall study cohort, angiographic evidence of HTB was associated with increased risk for cardiovascular events in both sexes; and 2) women presented less often with HTB at the time of primary PCI, but among patients with HTB, female sex was associated with an excess risk for cardiovascular and all-cause mortality, as well as an increased risk for stent thrombosis compared with male sex (**Central Illustration**).

The overall negative prognostic impact of HTB, as identified in our study, is consistent with previous reports. In a retrospective analysis of 812 patients with STEMI undergoing PCI, HTB was found to be an independent predictor of short- and long-term mortality and major adverse cardiac events, including MI, stent thrombosis, and infarct-related artery revascularization, in patients with STEMI.[5,6] Several studies have also shown that the presence of HTB is associated with a higher rate of distal embolization and no-reflow phenomenon, which is a known predictor of heart failure and mortality.[17,18] In a prospective study of 327 patients with STEMI treated with primary PCI, HTB predicted transmural necrosis and was associated with a larger infarct size and greater myocardial damage, as assessed by contrast-enhanced cardiac magnetic resonance imaging.[18]

Several studies have shown that women with coronary artery disease have worse early and long-term prognosis compared with men.[19-22] In particular, in an international observational cohort study of 458,261 patients undergoing PCI for stable angina pectoris, non-STEMI, unstable angina pectoris, or STEMI, it was found that female sex was associated with a higher risk for procedure-related complications and was an independent predictor of mortality at 30 days and 1 year after PCI.[1] More recently, a retrospectively analyses of 62,048 patients with STEMI from the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to

CENTRAL ILLUSTRATION **Sex-Related Differences in Thrombus Burden in Patients With ST-Segment Elevation Myocardial Infarction: Summary of Study Design and Results**



Manzi MV, et al. J Am Coll Cardiol Intv. 2022;15(20):2066–2076.

CV = cardiovascular; HTB = high thrombus burden; LTB = low thrombus burden; TAPAS = Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study; TASTE = Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia; TOTAL = Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI Undergoing Primary PCI.

Recommended Therapies) registry confirmed that women had an excess risk for all-cause mortality at 30 days and also showed that this difference was particularly evident in women without standard modifiable cardiovascular risk factors.[20] A study from the coronary angiography and PCI registry of the German Society of Cardiology, encompassing data from 185,312 PCIs, demonstrated that the risk for in-

hospital mortality in women with STEMI was 20% higher than that in men.[2] However, it remains unclear whether the association between sex and clinical outcomes is truly dependent on different pathophysiological and biological mechanisms or is instead confounded by differences in clinical characteristics and prevalence of cardiovascular risk factors.

To our knowledge, our study is the largest to examine sex-related differences in the prevalence and prognostic implications of TB in patients with STEMI undergoing primary PCI. Interestingly, although our unadjusted data showed a significantly higher risk for cardiovascular mortality in women irrespective of TB, after adjustment for clinical and procedural confounders, the excess risk for cardiovascular mortality was limited to female patients in the HTB stratum. In aggregate, these findings hint at the prognostic relevance of HTB in women and support the hypothesis of a more aggressive thrombotic process in women that may eventually result in differences in prognosis after acute MI.

Several factors may contribute to explain the excess risk for ischemic events and mortality encountered in women with HTB STEMI. One plausible explanation is the existence of sex-related differences in thrombogenicity. Indeed, sex-related differences in platelet activation and function have been reported.[4] Recently, a study of 134 patients with angina and angiographic evidence of nonobstructive coronary artery disease showed that women had higher platelet fibrin clot strength than men as assessed by thromboelastography.[3] These results support the hypothesis that women may have a more enhanced prothrombotic milieu than men, which may be related primarily to the effect of sex hormones.[4] In contrast, in a multicenter, prospective study of 100 patients with STEMI, no sex-dependent differences in thrombus composition were found, with the only exception being women younger than 55 years, who had reduced levels of thrombogenic substrate (fibrin, p-selectin, and von Willebrand factor) despite having worse prognosis.[23] In addition, potential differences in the response to antiplatelet therapy have been reported.[24] In particular, in a cohort of 1,282 healthy patients treated with low-dose aspirin as primary prevention for cardiovascular disease, women had higher levels of reactive platelets compared with men before and after aspirin treatment.[25] A prospective analysis of 533 stented patients showed that women had a greater risk for hyporesponsiveness to clopidogrel than men.[26] This latter aspect is relevant in our analysis, as more than one-half of the patients in our study were treated with clopidogrel as part of dual-antiplatelet therapy.[27]

Of interest, in patients with HTB, the pattern of risk evolution after the index event was not constant during follow-up, and differences in cardiovascular mortality among male and female patients were observed primarily during the first 30 days after the index event. These data corroborate the concept of the time-varying nature of ischemic risk evolution in STEMI, especially in patients presenting with HTB. In this group of patients, the early phase after STEMI is an important time window for implementing more potent antithrombotic strategies. Given the attenuation of ischemic risk following the early phases after the index event, de-escalation of antithrombotic strategies may be particularly attractive in women who are known to be more prone to bleeding.[28]

Thrombus aspiration was thought to be a promising technique to limit the negative consequences of acute thrombosis in STEMI. An individual patient-level meta-analysis of the TAPAS, TASTE, and TOTAL trials, investigating routine thrombus aspiration use in patients with STEMI, yielded neutral results with respect to efficacy and raised concerns for safety because of an increased risk for stroke.[7] In our analysis, we have demonstrated that the efficacy and safety of thrombus aspiration were similar in male and female patients in both LTB and HTB strata (all P values for the interaction between randomized thrombus aspiration treatment and sex with respect to clinical outcomes were >0.05). The higher risk for adverse events seen in patients with HTB, particularly in women, raises important issues regarding the optimal management of this high-risk patient group. Although thrombus aspiration may be considered in selected patients with HTB during PCI, further research investigating more effective pharmacologic and interventional strategies, especially in this group of patients, is warranted.

It is important to underline that the proportion of women included in our study, on the basis of pooled data from the 3 major trials of thrombus aspiration, was less than one-fourth of the entire study cohort. Regrettably, the issue of underrepresentation of women in trials of cardiovascular diseases is not novel. Indeed, several studies have shown that the percentage of women enrolled in ischemic heart disease trials ranged from 24% to 28%.[29] The fact that women with HTB had an excess risk for adverse events in our study poses important implications for the design of future studies in the field. Indeed, it would be advisable that future trials of cardiovascular therapy in STEMI target the current unmet needs in the management of patients with STEMI with HTB while also enrolling a larger proportion of female patients (ie, stratified randomization and powered subgroup

analyses by sex) in order to narrow the existing gaps in early and long-term prognosis related to sex.

STUDY LIMITATIONS. First, this was a retrospective analysis based on data from 3 randomized trials, and therefore, our study population may not be representative of a real-world population. Second, data on radial access, heart failure, stroke or transient ischemic attack, and medication use before PCI and at hospital discharge were unavailable in the TAPAS trial.[8]

Third, more than one-half of the patients in our study were treated with clopidogrel or ticlopidine as part of dual antiplatelet therapy. It is known that clopidogrel is less effective in reducing the risk for coronary thrombotic events in patients with acute coronary syndrome than new potent $P2Y_{12}$ inhibitors (ticagrelor and prasugrel).[30,31]

Fourth, no information about bleeding events was available for analysis. Although it is well known that women have a higher rate of bleeding compared with men and that bleeding is an independent predictor of mortality in MI, the EARLY ACS (Early vs Delayed Provisional Eptifibatide in Acute Coronary Syndromes) trial showed that the association between bleeding and 30-day mortality was stronger in men than in women.[19,32]

Fifth, no data were available about the etiology of stroke (ischemic or hemorrhagic) or on the incidence of atrial arrhythmias during the index hospitalization (ie, atrial fibrillation) that may increase the risk for cerebrovascular events.[33] Sixth, no information about adherence to treatment and other secondary preventive measures was collected.

Finally, in TAPAS and TOTAL, TIMI thrombus grade was evaluated before wire crossing, whereas in TASTE it was evaluated after wire crossing.[7] However, it has been shown that wire crossing has a minimal impact on the quantification of TB.[6]

CONCLUSIONS

In patients with STEMI, the presence of HTB confers a detrimental impact on prognosis. In patients with STEMI and HTB, women had an excess risk for cardiovascular mortality at 1 year over men. TB stratification should be taken into account in therapeutic decision making to identify patients with STEMI who may benefit from more aggressive treatments. Further investigations are warranted to better understand the pathophysiological mechanisms leading to the excess mortality in women with STEMI and HTB.

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PERSPECTIVES

WHAT IS KNOWN? Several studies have reported on the association between female sex and worse prognosis after STEMI. It has also been demonstrated that a high burden of intracoronary thrombus is an independent predictor of mortality and periprocedural complications after PCI in patients with STEMI. The prognostic role of TB in influencing the sex-related differences in clinical outcomes after STEMI has not been investigated.

WHAT IS NEW? Consistent with previous research, the presence of HTB was found to negatively affect prognosis in patients with STEMI. For the first time, we have shown that HTB confers an excess risk for cardiovascular mortality and other adverse ischemic events in women vs men. This study therefore highlights the risk-amplifying effects of female sex and HTB in patients with STEMI.

WHAT IS NEXT? Further investigations are warranted to better understand the pathophysiological mechanisms leading to the excess mortality in women with STEMI and HTB.

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KEY WORDS ST-segment elevation myocardial infarction, TAPAS, TASTE, TIMI thrombus burden, TOTAL, women

APPENDIX For supplemental methods, tables, and a figure, please see the online version of this paper.