

Contemporary Trends and Age-Specific Sex Differences in Management and Outcome for Patients With ST-Segment Elevation Myocardial Infarction

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Background—Age- and sex-specific differences exist in the treatment and outcome of ST-elevation myocardial infarction (STEMI). We sought to describe age- and sex-matched contemporary trends of in-hospital management and outcome of patients with STEMI.

Methods and Results—We analyzed data from 5 Italian nationwide prospective registries, conducted between 2001 and 2014, including consecutive patients with STEMI. All the analyses were age- and sex-matched, considering 4 age classes: <55, 55 to 64, 65 to 74, and ≥ 75 years. A total of 13 235 patients were classified as having STEMI (72.1% men and 27.9% women). A progressive shift from thrombolysis to primary percutaneous coronary intervention occurred over time, with a concomitant increase in overall reperfusion rates (P for trend <0.0001), which was consistent across sex and age classes. The crude rates of in-hospital death were 3.2% in men and 8.4% in women ($P < 0.0001$), with a significant increase over age classes for both sexes and a significant decrease over time for both sexes (all P for trend <0.01). On multivariable analysis, age (odds ratio 1.09, 95% CI 1.07–1.10, $P < 0.0001$) and female sex (odds ratio 1.44, 95% CI 1.07–1.93, $P = 0.009$) were found to be significantly associated with in-hospital mortality after adjustment for other risk factors, but no significant interaction between these 2 variables was observed (P for interaction = 0.61).

Conclusions—Despite a nationwide shift from thrombolytic therapy to primary percutaneous coronary intervention for STEMI affecting both sexes and all ages, women continue to experience higher in-hospital mortality than men, irrespective of age. (*J Am Heart Assoc.* 2016;5:e004202 doi: 10.1161/JAHA.116.004202)

Key Words: percutaneous coronary intervention • registry • sex • ST-segment elevation myocardial infarction

After an acute myocardial infarction, women continue to experience higher mortality than men, despite improvements in reperfusion therapy.^{1,2} This worse outcome is attributed, at least in part, to older age at presentation, though a recent meta-analysis of observational studies has reported that women have a higher risk of in-hospital mortality even after adjustment for baseline differences.³

Over the last 15 years, there has been a progressive improvement in reperfusion therapy for ST-elevation

myocardial infarction (STEMI), with a shift from fibrinolytic therapy to primary percutaneous coronary intervention (pPCI) and an overall increase in reperfusion rates due to the organization of STEMI networks. These improvements in STEMI treatment had the potential to reduce the gap in STEMI outcomes among women, given that in the lytic era they consistently received less treatment and were more exposed to adverse bleeding events following fibrinolysis. On the other hand, use of pPCI virtually eliminates the risk of intracranial

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bleeding and has been shown to be an independent predictor of survival in women.⁴

In the present study, we describe the evolution of reperfusion therapy for STEMI from 2001 to 2014 in Italy, taking into account sex differences in in-hospital treatment and outcome across age groups among patients admitted to cardiac care units (CCUs) with a diagnosis of STEMI and enrolled in nationwide registries.

Methods

Five consecutive prospective registries designed by the Italian Association of Hospital Cardiologists (ANMCO) in patients with acute coronary syndromes (ACS) were conducted in Italy between 2001 and 2014: BLITZ in 2001,⁵ IN-ACS Outcome (Italian Network on Acute Coronary Syndromes Outcome) in 2006–2007,⁶ BLITZ 4 in 2009 and 2010,⁷ MANTRA (Management of patients with ACS in the real world practice in Italy: an outcome research study focused on the use of ANTithrombotic Agents) in 2009–2010,⁸ and EYESHOT (EmploYEd antithrombotic therapies in patients with acute coronary Syndromes HOspitalized in iTalian cardiac care units) in 2013 and 2014.⁹ All surveys were nationwide and included patients with ACS consecutively admitted alive to the participating CCUs during a prespecified period (a few weeks for the BLITZ and EYESHOT registries and 1 year for IN-ACS Outcome and MANTRA) (Table 1). The methods used for each registry have been described previously.^{5–9} Briefly, their primary objectives were to evaluate the clinical characteristics, management, and outcomes of consecutive patients with ACS admitted to Italian CCUs, using a catchment method broad enough to provide data representative of the entire country. Participation in the various registries had been offered to all institutions in BLITZ and EYESHOT, to CCUs able to enroll at least 40 ACS patients over 10 weeks in BLITZ 4, and to a representative sample of CCUs (balanced by

geographical region and hospital complexity) in IN-ACS Outcome and MANTRA. The percentages of Centers with on-site cath-lab are reported in Table 1. Physicians were instructed that participation in the registries should not affect clinical care or management. Informed consent was obtained from all patients who were aware of the nature and aims of the registries. Local Institutional Review Boards were informed of the study according to the Italian rules and approved the protocol.

Data Collection

Data on baseline characteristics, including demographics, risk factors, and medical history, were collected as previously described.^{5–9} Information on the use of cardiac procedures, including coronary angiography, type of revascularization therapy (if any), use of medications during hospitalization and at hospital discharge, and in-hospital major clinical events, were recorded. In the BLITZ 4 registry, door to balloon time was available only for patients presenting to hospitals with on-site pPCI facilities. For the present analysis, only patients with a final diagnosis of STEMI on admission were considered. The definitions of inclusion criteria and outcome events were consistent throughout the surveys. STEMI was defined as ST-segment elevation >1 mm (0.1 mV) in 2 or more contiguous precordial leads or in 2 or more adjacent limb leads, or new or presumed new left bundle branch block associated with symptoms suggestive of ACS. Re-infarction during initial hospitalization was diagnosed in the presence of new ischemic symptoms and a re-elevation of biochemical myocardial necrosis markers with or without concurrent ECG changes. Major bleeding was classified according to the Thrombolysis In Myocardial Infarction (TIMI) criteria.¹⁰ Stroke was identified as an acute neurologic deficit lasting >24 hours and affecting the ability to perform daily activities with or without confirmation by imaging techniques. Cardiogenic shock was defined as systolic blood pressure (BP) of ≤90 mm Hg lasting

Table 1. Characteristics of the 5 Italian Surveys, Incidence of STEMI, and Rate of Women Among STEMI Patients

Study	Enrollment Period	Number of Participating Centers	Percentage of Centers With Cath Lab	No. of Patients Enrolled*	No. (%) of Patients With STEMI	No. (%) of Female Patients With STEMI
BLITZ	October 15–29, 2001	296	45	1959	1374 (70.1)	413 (30.1)
IN-ACS Outcome	December 2, 2005–February 8, 2008	38	47	5894	2281 (38.7)	654 (28.7)
BLITZ-4	September 15–November 30, 2009 and February 15–April 30, 2010	163	83	11 442	5656 (49.4)	1558 (27.6)
MANTRA	April 22, 2009–December 29, 2010	52	65	6394	2858 (44.7)	767 (26.8)
EYESHOT	December 2–22, 2013 and January 27–February 16, 2014	203	67	2585	1066 (41.2)	299 (28.1)

*Excluding 151 patients enrolled in IN-ACS Outcome because they have not been admitted in CCUs and 264 patients from the BLITZ-4 since they underwent a coronary angiography in another hospital. ACS indicates acute coronary syndrome; CCUs, cardiac care units; STEMI, ST-elevation myocardial infarction.

>60 minutes, nonresponsive to fluid challenge or requiring the administration of inotropic drugs in order to obtain a systolic BP of >90 mm Hg, with clinical signs of peripheral hypoperfusion such as sensorial obnubilation, low urine output (<30 mL/h), cold sweat, or cyanosis.¹¹

All data were collected at hospital discharge using a case report form at the participating centers and entered in a centralized database located at the ANMCO Research Center in Florence, Italy. By using a validation plan integrated in the data entry software, data were checked with data queries for missing or contradictory entries and values out of the normal range. The data were also centrally audited at the coordinating center. If the queries were not answered by the investigators, the data were considered as missing.

Statistical Analysis

Categorical variables were reported as numbers and percentages and compared by χ^2 test, whereas continuous variables were reported as means and SDs and compared by *t* test or ANOVA, if normally distributed, or by Mann–Whitney *U*-test and Kruskal–Wallis test, if not. All the analyses were performed considering differences in sex and 4 classes of age: <55, 55 to 64, 65 to 74, and ≥ 75 years.

Temporal trends were tested using the Cochran–Armitage test for binary variables and the Kendall Tau rank correlation coefficient with the Jonckheere–Terpstra test for continuous variables. A multivariable analysis (logistic model) was performed to estimate the risk of in-hospital mortality over time adjusted for study cohort, reperfusion therapy, type of hospital, geographic area, and for risk factors and baseline characteristics significantly associated with in-hospital mortality at a previous univariate analysis. These variables were continuous (age, baseline systolic blood pressure, and heart rate), dichotomous (female sex, smoking, diabetes mellitus, hypertension on treatment, prior angina, prior myocardial infarction, prior heart failure, peripheral artery disease, prior stroke/transient ischemic attack, prior renal dysfunction, Killip class IV at entry, atrial fibrillation, anterior myocardial infarction, hospital with cath-lab) and categorical. In the latter case, dummy variables were introduced to define a reference group: reperfusion therapy (no reperfusion [reference group]; pPCI; lysis), geographic area (north [reference group], center, south), and the study cohort (2001 as reference group). The interaction term between sex and age was also inserted in the model. We also performed the same multivariable analysis for men and women separately. Furthermore, a logistic model on in-hospital mortality was performed with only age, sex, and their interaction term, considering age in the prespecified classes instead of in continuous. Finally, a logistic model on in-hospital mortality was conducted adjusting for sex, study, and their interaction term.

All tests were 2-sided; a $P < 0.05$ was considered statistically significant. All analyses were conducted with SAS system software version 9.2 (SAS Institute Inc, Cary, NC).

Results

Patient Characteristics

Of 28 274 patients with ACS enrolled in the 5 registries, 13 235 (46.8%) were classified as having STEMI (72.1% men and 27.9% women). The overall rates of women with STEMI did not change significantly over time (from 30.1% in 2001 to 28.1% in 2014; P for trend=0.06) (Table 1). The prevalence of women increased significantly with age, being 13.0% in the age class <55 years, 17.5% in the age class 55 to 64 years, 28.0% in the age class 65 to 74 years, and 48.3% in the age class ≥ 75 years (P for trend <0.0001), resulting in a higher mean age of women compared with men (72 ± 13 versus 63 ± 12 years, $P < 0.0001$).

Sex and age differences in clinical characteristics of patients with STEMI enrolled during the study period are listed in Table 2. When compared to men in the majority of corresponding age categories, women were less likely to be active smokers, had more hypertension and lower rates of prior myocardial infarction or revascularization procedures. Killip class IV on admission increased significantly with age in both sexes and was slightly more frequent among women in all age classes, even though a significant difference was observed among patients aged <55 years. The use of antithrombotic therapies during hospital admission was significantly lower with the increase in age classes for both sexes. When compared to men, women aged ≥ 65 years received significantly less unfractionated heparin, glycoprotein IIb/IIIa inhibitors, and dual antiplatelet therapy during hospitalization (Table 2).

Changes in Reperfusion Therapy

As shown in Figure 1, the use of fibrinolytic therapy decreased from 2001 to 2014 in both sexes and at all ages (all P for trend <0.0001), and this trend was mirrored by a dramatic increase in pPCI, also affecting both sexes at all ages (all $P < 0.0001$). The overall rates of no reperfusion therapy decreased significantly (P for trend <0.0001), and the changes were particularly marked among women aged ≥ 75 years (from 64.1% in 2001 to 27.1% in 2014). The no reperfusion rates remained significantly higher in older women until 2010, but tended to disappear in 2014. Among patients receiving pPCI, no significant differences were observed between men and women with regard to door to balloon times (2.2 ± 4.7 versus 1.7 ± 1.6 hours in 2001, 2.2 ± 4.2 versus 2.0 ± 2.4 hours in 2006, 0.8 ± 5.8 versus 0.9 ± 4.3 hours in 2009, 2.7 ± 7.8 versus 2.6 ± 4.8 hours in 2010, and 1.1 ± 4.8 versus 0.9 ± 5.0 hours in 2014). Data on

Table 2. Baseline Characteristics of Patients With STEMI From 2001 to 2014, According to Sex and Age Classes

	<55 Years (Total=2896; Male=2520, Female=376)	55 to 64 Years (Total=3192; Male=2634, Female=558)	65 to 74 Years (Total=3414; Male=2458, Female=956)	≥75 Years (Total=3733; Male=1932, Female=1801)	P for Trend
Age, y (mean±SD)					
Male	48±5	60±3	69±3	81±5	<0.0001
Female	47±6	60±3	70±3*	82±5*	<0.0001
Active smokers					
Male	1751 (69.5)	1414 (53.7)	822 (33.4)	307 (15.9)	<0.0001
Female	229 (60.9)*	249 (44.6)*	222 (23.2)*	126 (7.0)*	<0.0001
Diabetes mellitus					
Male	281 (11.2)	518 (19.7)	572 (23.3)	488 (25.3)	<0.0001
Female	45 (12.0)	120 (21.5)	251 (26.3)	517 (28.7)*	<0.0001
Hypertension					
Male	697 (27.7)	1077 (40.9)	1324 (53.9)	1219 (63.1)	<0.0001
Female	113 (30.1)	300 (53.8)*	623 (65.2)*	1272 (70.6)*	<0.0001
Chronic kidney disease					
Male	36 (1.4)	49 (1.9)	99 (4.0)	245 (12.7)	<0.0001
Female	2 (0.5)	11 (2.0)	36 (3.8)	156 (8.7)*	<0.0001
PAD					
Male	43 (1.7)	124 (4.7)	211 (8.6)	267 (13.8)	<0.0001
Female	13 (3.5)*	20 (3.6)	62 (6.5)*	181 (10.1)*	<0.0001
Previous stroke/TIA					
Male	29 (1.2)	67 (2.5)	105 (4.3)	193 (10.0)	<0.0001
Female	2 (0.5)	20 (3.6)	50 (5.2)	175 (9.7)	<0.0001
History of angina					
Male	150 (6.0)	224 (8.5)	276 (11.2)	246 (12.7)	<0.0001
Female	10 (2.7)*	51 (9.1)	97 (10.2)	181 (10.1)*	0.0003
Previous MI					
Male	180 (7.1)	274 (10.4)	337 (13.7)	338 (17.5)	<0.0001
Female	27 (7.2)	39 (7.0)*	80 (8.4)*	179 (9.9)*	0.01
Previous PCI/CABG					
Male	192 (7.6)	292 (11.1)	323 (13.1)	256 (13.3)	<0.0001
Female	25 (6.7)	26 (4.7)*	77 (8.1)*	116 (6.4)*	0.62
Variables at CCU admission					
Killip IV, n (%)					
Male	28 (1.1)	43 (1.6)	46 (1.9)	80 (4.1)	<0.0001
Female	9 (2.4)*	15 (2.7)	22 (2.3)	81 (4.5)	0.006
SBP, mm Hg (mean±SD)					
Male	133±25	133±27	134±27	133±28	0.44
Female	131±27	133±27	135±27	133±29	0.70
HR, bpm (mean±SD)					
Male	78±17	76±18	76±18	78±20	0.14
Female	79±18	77±18	79±19	81±21	<0.0001

Continued

Table 2. Continued

	<55 Years (Total=2896; Male=2520, Female=376)	55 to 64 Years (Total=3192; Male=2634, Female=558)	65 to 74 Years (Total=3414; Male=2458, Female=956)	≥75 Years (Total=3733; Male=1932, Female=1801)	P for Trend
BMI (mean±SD)					
Male	27.8±4.1	27.4±3.8	26.9±3.5	25.9±3.4	<0.0001
Female	26.3±5.6*	26.9±5.1*	26.7±4.5	25.5±4.6*	<0.0001
LVEF, % (mean±SD)[†]					
Male	51±9	49±9	48±10	45±11	<0.0001
Female	51±9	50±10	48±10	45±11	<0.0001
Atrial fibrillation, n (%)					
Male	38 (1.5)	58 (2.2)	85 (3.5)	191 (9.9)	<0.0001
Female	2 (0.5)	12 (2.2)	36 (3.8)	195 (10.8)	<0.0001
Medications during admission, n (%)					
ASA					
Male	2429 (96.4)	2536 (96.3)	2344 (95.4)	1811 (93.7)	<0.0001
Female	357 (95.0)	537 (96.2)	907 (94.9)	1680 (93.3)	0.02
DAPT					
Male	2179 (86.5)	2250 (85.4)	2051 (83.4)	1528 (79.1)	<0.0001
Female	313 (83.2)	476 (85.3)	754 (78.9)*	1310 (72.7)*	<0.0001
GPI					
Male	1288 (51.1)	1320 (50.1)	1116 (45.4)	680 (35.2)	<0.0001
Female	178 (47.3)	274 (49.1)	385 (40.3)*	564 (31.3)*	<0.0001
UFH					
Male	1912 (75.9)	1996 (75.8)	1835 (74.7)	1299 (67.2)	<0.0001
Female	277 (73.7)	389 (69.7)*	662 (69.3)*	1145 (63.6)*	<0.0001
LMWH					
Male	739 (29.3)	819 (31.1)	775 (31.5)	673 (34.8)	0.0002
Female	122 (32.5)	175 (31.4)	357 (37.3)*	681 (37.8)	0.004

Two-sided *P* values for comparisons across sex for each age category are <0.05. ASA indicates acetylsalicylic acid; BMI, body mass index; CABG, coronary artery bypass graft; CCU, cardiac care unit; DAPT, dual antiplatelet therapy; ECG, electrocardiogram; GPI, glycoprotein IIb/IIIa inhibitors; HR, heart rate; LMWH, low-molecular-weight heparins; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack; UFH, unfractionated heparin.

**P*<0.05 for difference between sexes within same age class.

[†]During hospital stay.

catheterization access site were available only for the BLITZ 4 and EYESHOT study cohorts, where the radial approach was used more frequently in men than in women (31.4% versus 26.4%, *P*=0.002, and 72.7% versus 61.7%, *P*=0.0007, respectively).

In-Hospital Outcomes

As shown in Table 3, crude in-hospital mortality rates increased significantly with age in both sexes, being significantly higher in women at all ages (except in patients <55 years of age, who presented an extremely low in-hospital

fatality rate). The rates of reinfarction increased significantly with age in men, but not in women, whereas the rates of stroke and cardiogenic shock increased significantly with age in both sexes. The rates of TIMI major bleeding were significantly higher in women at all ages compared to men and increased significantly with age in men, but not in women.

Time trends for mortality according to age are shown in Figure 2, with an overall decline in mortality over time affecting both sexes (*P* for trend <0.01) and patients aged ≥75 years (*P* for trend <0.0001). Mortality and reinfarction rates declined significantly over time in both sexes, whereas stroke rates remained fairly stable, being slightly higher

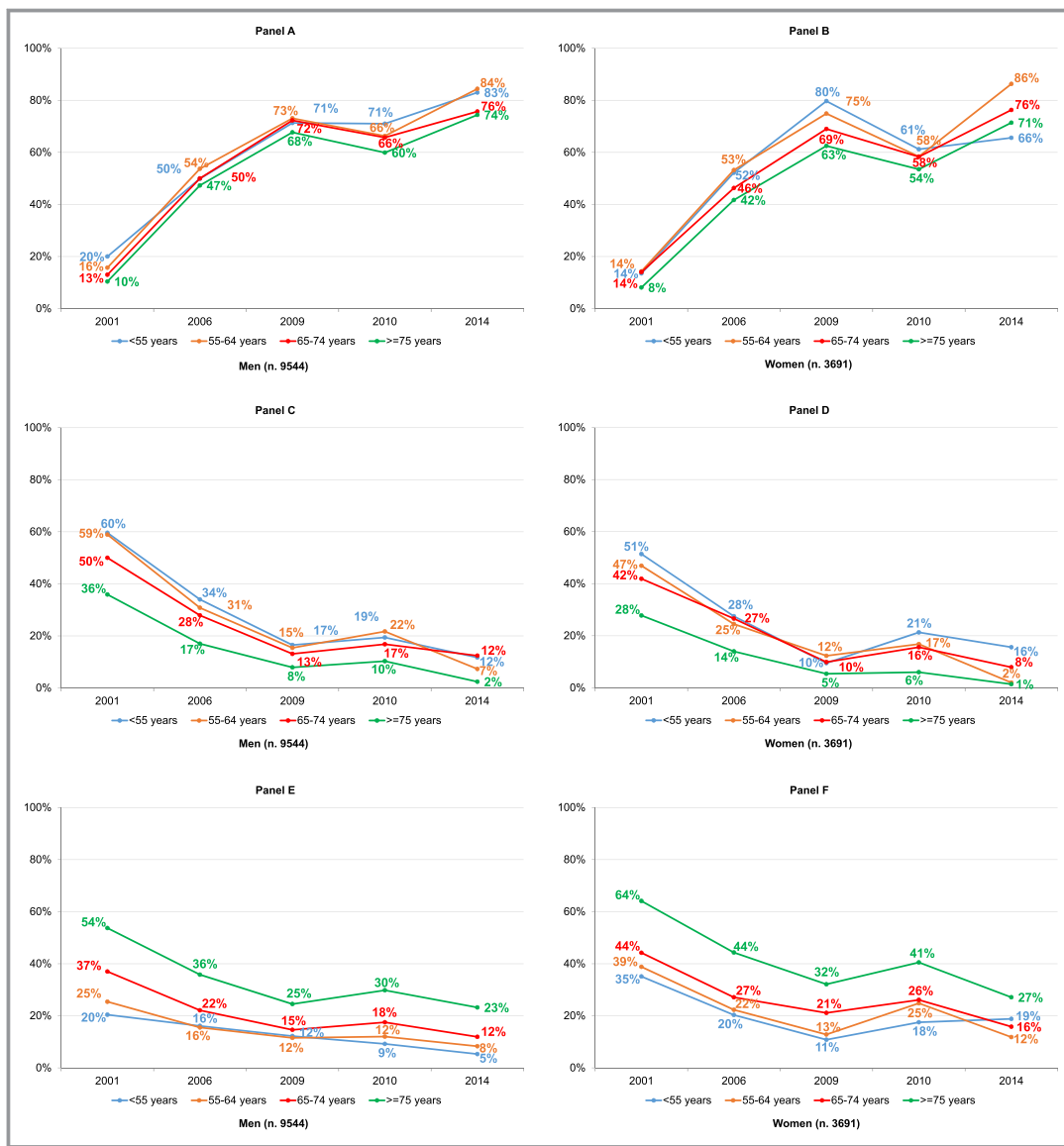


Figure 1. In-hospital rates of primary PCI (A, B), thrombolysis (C, D), and no reperfusion (E, F) over time, among men and women, according to age classes. PCI indicates percutaneous coronary intervention.

among women at all time points (Table 4). Overall cardiogenic shock rates were significantly higher in women (8.6% versus 4.8%, $P < 0.0001$), even though statistically significant only in patients aged 65 to 74 years, and declined significantly over time in women and not in men. Furthermore, cardiogenic shock fatality rates were higher in women at all time points, except for year 2001 (Figure 3), but were statistically significant only in year 2009. Major bleeding rates were significantly higher among women, and there was no significant trend over time in both sexes.

On multivariable analysis, several variables were found to be significantly related to in-hospital mortality (Figure 4), but without a statistically significant interaction between sex and age (P for interaction=0.61). The c-statistic for this

model was 0.881. Many variables remained predictors of mortality even when the model was applied separately to men and women (c-statistic=0.892 and =0.837, respectively) (Figure 5). In a further model adjusted only for sex and age, considering the 4 prespecified age classes, the interaction between sex and age remained not significant (P for interaction=0.21). Comparing women to men, the adjusted odds ratios for in-hospital mortality were 0.74 (95% CI 0.17–3.22) for age <55 years, 2.55 (95% CI 1.43–4.55) for age 55 to 64 years, 1.80 (95% CI 1.22–2.67) for age 65 to 74 years, and 1.48 (95% CI 1.21–1.81) for age ≥ 75 years. Finally, in the model where only sex and year of the study were considered, no significant interaction between these 2 variables was observed (P for

Table 3. In-Hospital Major Clinical Events of STEMI Patients According to Sex and Age Classes

	<55 Years (Total=2896; Male=2520, Female=376)	55 to 64 Years (Total=3192; Male=2634, Female=558)	65 to 74 Years (Total=3414; Male=2458, Female=956)	≥75 Years (Total=3733; Male=1932, Female=1801)	P for Trend
Death					
Male	18 (0.7)	34 (1.3)	64 (2.6)	187 (9.7)	<0.0001
Female	2 (0.5)	18 (3.2)*	44 (4.6)*	246 (13.7)*	<0.0001
Re-MI					
Male	25 (1.0)	40 (1.5)	39 (1.6)	38 (2.0)	0.009
Female	3 (0.8)	7 (1.3)	16 (1.7)	28 (1.6)	0.29
Stroke					
Male	10 (0.4)	12 (0.5)	20 (0.8)	27 (1.4)	<0.0001
Female	2 (0.5)	5 (0.9)	9 (0.9)	29 (1.6)	0.04
Cardiogenic shock[†]					
Male	60 (2.4)	99 (3.8)	103 (4.2)	196 (10.1)	<0.0001
Female	15 (4.0)	25 (4.5)	71 (7.4)*	208 (11.6)	<0.0001
Major bleeding					
Male	9 (0.4)	20 (0.8)	25 (1.0)	35 (1.8)	<0.0001
Female	8 (2.1)*	10 (1.8)*	32 (3.4)*	54 (3.0)*	0.16

Two-sided P values for comparisons across sex are <0.05. Number in parentheses are percentages calculated on males and females within each class of age. MI indicates myocardial infarction; STEMI, ST-elevation myocardial infarction.

*Excluding 151 patients enrolled in IN-ACS Outcome because they have not been admitted in CCUs and 264 patients from the BLITZ-4 since they underwent a coronary angiography in another hospital.

[†]Cardiogenic shock at entry/during hospital stay.

interaction=0.95), suggesting that the risk of death for women was higher than that for men, and this excess risk did not change over the years.

Discussion

The present analysis covers a period of time where reperfusion therapy for STEMI changed dramatically with the nationwide organization of STEMI networks.¹² In the present study, we observed a striking increase in pPCI, a concomitant reduction in fibrinolysis and, more importantly, a significant reduction in the rates of no reperfusion affecting both women and men and all age classes. These positive changes in reperfusion therapy resulted in significantly lower mortality rates for both sexes over time, but the worse outcome of women, as compared to men, remained unchanged among all age classes, except for women aged <55 years. A second point of interest in the present study was the comparison of men and women across age classes to verify whether the unfavorable treatment and mortality gaps reported for women were, at least in part, dependent on women's older age. Our data show that, at least until 2010, the rates of no reperfusion remained significantly higher among women aged ≥75 years compared to men, and this gap disappeared only in 2014. On multivariable analysis, both age and female sex were found to be significantly associated with in-hospital mortality after adjustment for other risk factors, but without any mutual interaction. From the present analysis, 3 causes emerge as possible culprit in persistently higher mortality rates among

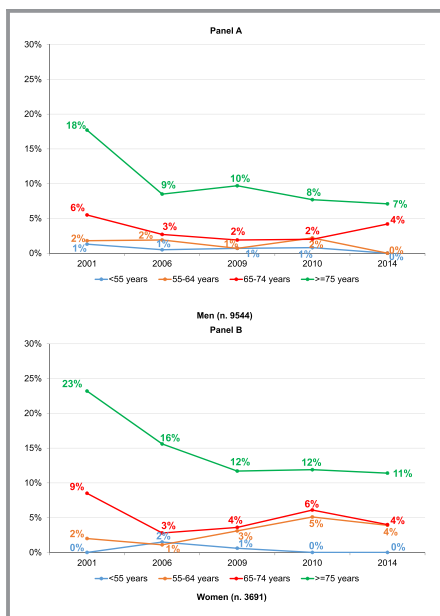


Figure 2. In-hospital mortality rates over time among men (A) and women (B), according to age classes.

Table 4. In-Hospital Major Clinical Events in Men (n=9544) and Women (n=3691) According to Year of the Survey

	2001 (n=1374)	2006 (n=2281)	2008 (n=5656)	2009 (n=2858)	2014 (n=1066)	P for Trend
Death						
Men	5.8	3.1	2.9	2.8	2.6	0.0002
Women	14.0*	8.6*	7.3*	8.1*	7.0*	0.001
Re-MI						
Men	3.1	1.8	1.0	1.7	0.7	0.0002
Women	3.4	0.8	1.3	1.7	0.7	0.07
Stroke						
Men	1.4	0.7	0.6	0.7	0.7	0.12
Women	1.7	1.7*	1.1*	0.9	1.0	0.14
Cardiogenic shock[†]						
Men	6.1	3.9	5.4	3.4	5.5	0.16
Women	12.1*	8.9*	9.1*	6.8*	6.0	0.001
Major bleeding						
Men	1.7	0.7	1.0	0.8	0.8	0.11
Women	4.4*	2.5*	2.4*	3.1*	2.7*	0.42

Two-sided *P* values for comparisons across sex are <0.05. MI indicates myocardial infarction.

*Excluding 151 patients enrolled in IN-ACS Outcome because they have not been admitted in CCUs and 264 patients from the BLITZ-4 since they underwent a coronary angiography in another hospital.

[†]Cardiogenic shock at entry/during hospital stay.

women with STEMI compared to men: (1) significantly less reperfusion therapy; (2) a higher major bleeding rate; and (3) more prevalent and more fatal cardiogenic shock.

Lower reperfusion rates in women, as compared to men, have been reported since the early thrombolytic era,² and this gap continues to persist.^{13–15} In the present analysis, women in any class of age were less likely to receive either pPCI or thrombolysis than men, although the overall rate of reperfusion increased over time. Several reasons can be postulated to explain these findings.² For instance, women with STEMI are more likely to have atypical symptoms possibly leading to

delayed presentation and under-recognition of STEMI at first medical contact, thus precluding early reperfusion strategies.^{2,16–18} Despite an overall increase in emergency coronary angiography, lower reperfusion rates in women can also be explained by a higher frequency of alternative etiologies (eg, spontaneous coronary dissection, coronary vasospasm), and different angiographic findings.¹⁹ Indeed, the OCTAVIA (Optical Coherence Tomography Assessment of Gender Diversity in Primary Angioplasty) study, the first prospective controlled study designed to assess in vivo sex differences in the mechanisms of STEMI, demonstrated that men and women,

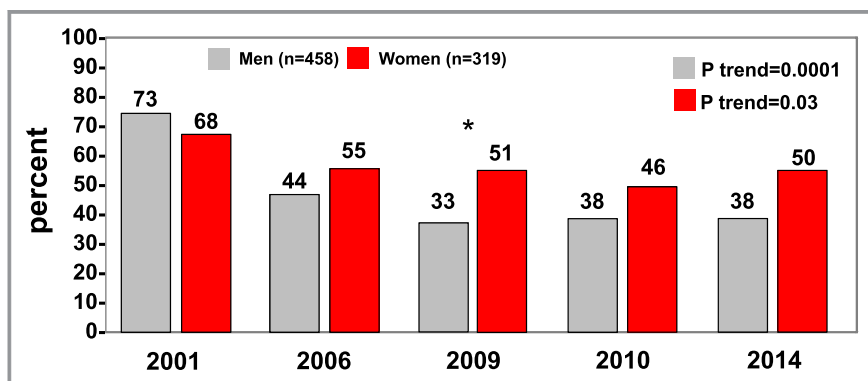


Figure 3. In-hospital mortality rates among men (gray bars) and women (red bars) with cardiogenic shock (at entry/during hospital stay) over the observation time. *Two-sided *P* values for comparisons across sex are <0.05.

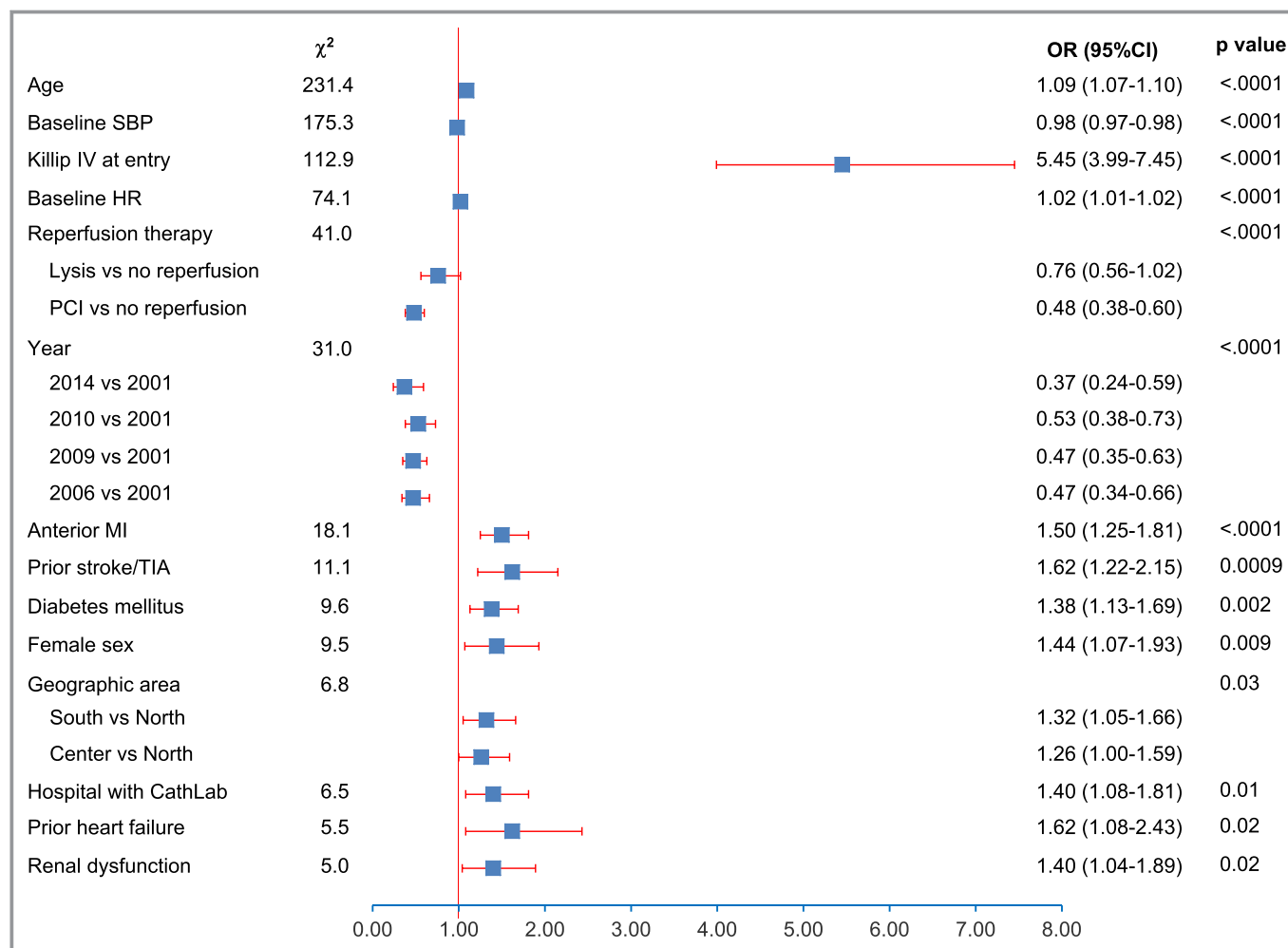


Figure 4. Multivariable logistic regression analysis for in-hospital factors related to mortality over time in the overall population. HR indicates heart rate; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIA, transient ischemic attack.

when matched for age, shared similar prevalence of ruptured and eroded plaques.²⁰ These findings suggest that disparities in environment, behavior, risk factors, and management, rather than different biological mechanisms and response to treatment, might be more relevant in affecting clinical outcome.

We observed higher rates of major bleeding in women than in men, particularly among those aged >55 years, even though no significant trend was observed over age. A higher risk of bleeding in women has been known since the early fibrinolytic era,²¹ when the ISIS-3 collaboration observed a 70% excess in major bleeding among women, as compared to men, after adjustment for age and other risk factors. This increased risk persisted after the reperfusion shift to pPCI²² and is independently associated with a 3-fold increase in mortality.²³ The higher risk of bleeding among women might be partly related to the lack of weight or body mass dose adjustment of most antithrombotic drugs, and also to a

lower use of radial access among women who, compared with men, have smaller radial arteries that may be more prone to spasm, which is a major cause of radial procedure failure.²⁴

The rates of cardiogenic shock due to acute coronary syndromes have decreased in our country during the observation period, as well as overall mortality due to cardiogenic shock.¹¹ Yet, as shown by the present data, case fatality rates have been declining more significantly among men than among women. Women in our study had higher rates of cardiogenic shock as compared to men at any age, both upon admission and during subsequent hospital stay, even though a significant difference was observed among the 65 to 74 years group, and at least part of the excess mortality among women should probably be attributed to a higher incidence of cardiogenic shock. Both female sex and age have been shown to be independent predictors for the occurrence^{20,25} and mortality²⁶ of cardiogenic shock in STEMI, even after the

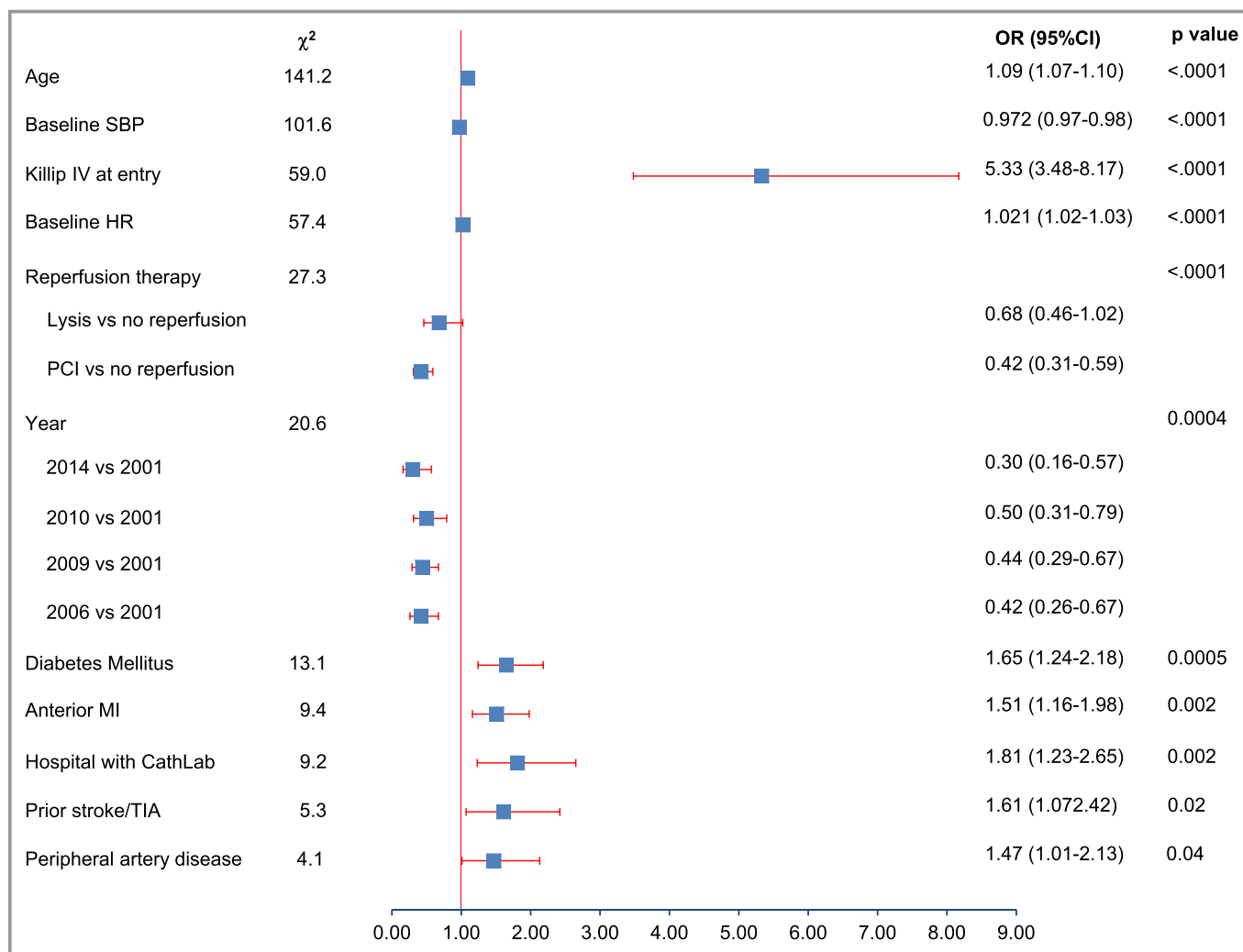


Figure 5. Multivariable logistic regression analysis for in-hospital factors related to mortality over time in men (A) and women (B). HR indicates heart rate; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIA, transient ischemic attack.

widespread use of acute reperfusion therapy. Longer delay to reperfusion among women may be the major reason for both the higher incidence and case fatality of cardiogenic shock.

Focusing future research and quality initiatives on these 3 potential causes of worse outcome in women with STEMI has the potential to reduce the persisting mortality gap for women in STEMI. System efforts to reduce the time from symptom onset to reperfusion are strongly endorsed by practice guidelines,^{27,28} though the effectiveness from public campaigns has not yet been clearly established. According to our data, the implementation of STEMI networks in Italy has improved the rates of reperfusion in both women and men. Among the strategies to reduce bleeding, probably the most effective was the gradual shift from fibrinolysis to pPCI, but also the later shift from the femoral to the radial vascular approach to PCI, which has been shown to improve outcomes

and reduce bleeding particularly among women.²⁹ Finally, according to our data and other all-comers observational studies, mortality in cardiogenic shock complicating acute coronary syndromes remains higher in women than in men. Therefore, further studies are warranted to better define specific treatment strategies in cardiogenic shock.³⁰

Conclusions

Despite a dramatic shift from thrombolysis to pPCI and an overall reduction in no reperfusion therapy over time, affecting both sexes and all age classes, women continue to show a significantly higher adjusted risk of in-hospital mortality, as compared to men. Cardiac societies from both sides of the Atlantic have released specific documents on sex differences in presentation, treatment, and outcomes of

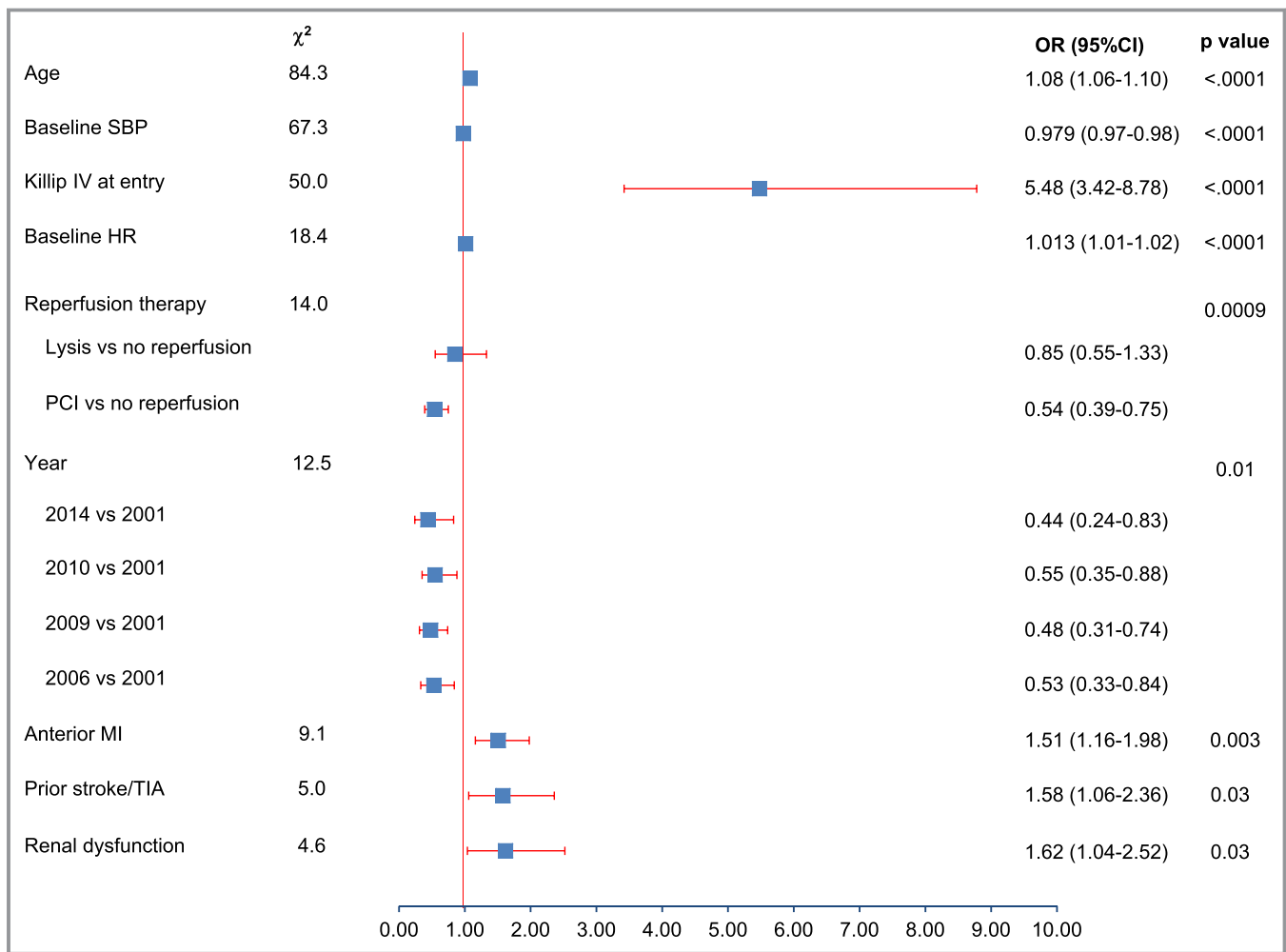


Figure 5. continued.

cardiovascular disease,^{2,31} though prospective studies aimed at investigating the reasons for the persisting worse outcomes of STEMI in women are still lacking.³²

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Disclosures

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References

- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER III, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation*. 2016;133:e38–e360.
- Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE, Wenger NK; American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, and Council on Quality of Care and Outcomes Research. Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation*. 2016;133:916–947.
- Pancholy SB, Shantha GP, Patel T, Cheskin LJ. Sex differences in short term and long-term all-cause mortality among patients with ST-segment elevation myocardial infarction treated by primary percutaneous intervention: a meta-analysis. *JAMA Intern Med*. 2014;174:1822–1830.
- Stone GW, Grines CL, Browne KF, Marco J, Rothbaum D, O’Keefe J, Hartzler GO, Overlie P, Donohue B, Chelliah N. Comparison of in-hospital outcome in men versus women treated by either thrombolytic therapy or primary coronary angioplasty for acute myocardial infarction. *Am J Cardiol*. 1995;75:987–992.
- Di Chiara A, Chiarella F, Savonitto S, Lucci D, Bolognese L, De Servi S, Greco C, Boccanelli A, Zonzin P, Coccolini S, Maggioni AP; BLITZ Investigators. Epidemiology of acute myocardial infarction in the Italian CCU network: the BLITZ study. *Eur Heart J*. 2003;24:1616–1629.
- Rizzello V, Lucci D, Maggioni AP, Giampaoli S, Greco C, Di Pasquale G, Pallotti MG, Mureddu GF, Di Chiara A, Boccanelli A; IN-ACS Outcome Investigators. Clinical epidemiology, management and outcome of acute coronary syndromes in the Italian network on acute coronary syndromes (IN-ACS Outcome study). *Acute Card Care*. 2012;14:71–80.
- Olivari Z, Steffenino G, Savonitto S, Chiarella F, Chinaglia A, Lucci D, Maggioni AP, Pirelli S, Scherillo M, Scorcu G, Tricoci P, Urbinati S. The management of acute myocardial infarction in the cardiological intensive care units in Italy: the ‘BLITZ 4 Qualità’ campaign for performance measurement and quality improvement. *Eur Heart J Acute Cardiovasc Care*. 2012;1:143–152.
- Casella G, Di Pasquale G, Oltrona Visconti L, Pallotti MG, Lucci D, Caldarola P, Scherillo M, Maggioni AP. Management of patients with acute coronary syndromes in real-world practice in Italy: an outcome research study focused on the use of ANTithRombotic Agents: the MANTRA registry. *Eur Heart J Acute Cardiovasc Care*. 2013;2:27–34.
- De Luca L, Leonardi S, Cavallini C, Lucci D, Musumeci G, Caporale R, Abrignani MG, Lupi A, Rakar S, Gulizia MM, Bovenzi FM, De Servi S; EYESHOT Investigators. Contemporary antithrombotic strategies in patients with acute coronary syndromes admitted to cardiac care units in Italy: the EYESHOT study. *Eur Heart J Acute Cardiovasc Care*. 2015;4:441–452.
- Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, Bell WR, Knatterud G, Robertson TL, Terrin ML. Thrombolysis in Myocardial Infarction (TIMI) Trial—phase I: haemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol*. 1988; 11:1–11.
- De Luca L, Olivari Z, Farina A, Gonzini L, Lucci D, Di Chiara A, Casella G, Chiarella F, Boccanelli A, Di Pasquale G, De Servi S, Bovenzi FM, Gulizia MM, Savonitto S. Temporal trends in the epidemiology, management and outcome of patients with cardiogenic shock complicating acute coronary syndromes. *Eur J Heart Fail*. 2015;17:1124–1132.
- Widimsky P, Wijns W, Fajadet J, de Belder M, Knot J, Aaberge L, Andrikopoulos G, Baz JA, Betriu A, Claeys M, Danchin N, Djambazov S, Erne P, Hartikainen J, Huber K, Kala P, Klinecva M, Kristensen SD, Ludman P, Ferre JM, Merkely B, Milicic D, Morais J, Noc M, Opolski G, Ostojic M, Radovanovic D, De Servi S, Stenestrand U, Studencan M, Tubaro M, Vasiljevic Z, Weidinger F, Witkowski A, Zeymer U; European Association for Percutaneous Cardiovascular Interventions. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. *Eur Heart J*. 2010;31:943–957.
- Bangalore S, Fonarow GC, Peterson ED, Hellkamp AS, Hernandez AF, Laskey W, Peacock WF, Cannon CP, Schwamm LH, Bhatt DL; Get with the Guidelines Steering Committee and Investigators. Age and gender differences in quality of care and outcomes for patients with ST-segment elevation myocardial infarction. *Am J Med*. 2012;125:1000–1009.
- Puymirat E, Simon T, Steg PG, Schiele F, Guéret P, Blanchard D, Khalife K, Goldstein P, Cattani S, Vaur L, Cambou JP, Ferrières J, Danchin N; USIK USIC 2000 Investigators; FAST MI Investigators. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. *JAMA*. 2012;308:998–1006.
- Khera S, Kolte D, Gupta T, Subramanian KS, Khanna N, Aronow WS, Ahn C, Timmermans RJ, Cooper HA, Fonarow GC, Frishman WH, Panza JA, Bhatt DL. Temporal trends and sex differences in revascularization and outcomes of ST-segment elevation myocardial infarction in younger adults in the United States. *J Am Coll Cardiol*. 2015;66:1961–1972.
- Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, Kiefe CI, Frederick PD, Sopko G, Zheng ZJ; NRMII Investigators. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA*. 2012;307:813–822.
- Khan NA, Daskalopoulou SS, Karp I, Eisenberg MJ, Pelletier R, Tsadok MA, Dasgupta K, Norris CM, Pilote L; GENESIS PRAXY Team. Sex differences in acute coronary syndrome symptom presentation in young patients. *JAMA Intern Med*. 2013;173:1863–1871.
- Jager B, Farhan S, Rohla M, Christ G, Podczeczek-Schweighofer A, Schreiber W, Laggner AN, Weidinger F, Stefanelli T, Delle-Karth G, Kaff A, Maurer G, Huber K; Vienna STEMI Registry Group. Clinical predictors of patient related delay in the VIENNA ST-elevation myocardial infarction network and impact on long-term mortality. *Eur Heart J Acute Cardiovasc Care*. 2016. doi: 10.1177/2048872616633882. Available at: <http://acc.sagepub.com/content/early/2016/02/17/2048872616633882>. Accessed September 26, 2016.
- De Luca G, Suryapranata H, Dambrink JH, Ottervanger JP, van ’t Hof AW, Zijlstra F, Hoortje JC, Gosselink AT, de Boer MJ. Sex-related differences in outcome after ST-segment elevation myocardial infarction treated by primary angioplasty: data from the Zwolle Myocardial Infarction study. *Am Heart J*. 2004;148:852–856.
- Guagliumi G, Capodanno D, Saia F, Musumeci G, Tarantini G, Garbo R, Tumminello G, Sirbu V, Coccato M, Fineschi M, Trani C, De Benedictis M, Limbruno U, De Luca L, Niccoli G, Bezerra H, Ladich E, Costa M, Biondi Zoccai G, Virmani R; OCTAVIA Trial Investigators. Mechanisms of atherothrombosis and vascular response to primary percutaneous coronary intervention in women versus men with acute myocardial infarction: results of the OCTAVIA study. *JACC Cardiovasc Interv*. 2014;7:958–968.
- Malacrida R, Genoni M, Maggioni AP, Spataro V, Parish S, Palmer A, Collins R, Moccetti T. A comparison of the early outcome of acute myocardial infarction in women and men. The Third International Study of Infarct Survival Collaborative Group. *N Engl J Med*. 1998;338:8–14.
- Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dargas GD, Kirtane AJ, Parise H, Fahy M, Manoukian SV, Feit F, Ohman ME, Witzensbichler B, Guagliumi G, Lansky AJ, Stone GW. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2010;55:2556–2566.
- Kwok CS, Rao SV, Myint PK, Keavney B, Nolan J, Ludman PF, de Belder MA, Loke YK, Mamas MA. Major bleeding after percutaneous coronary intervention and risk of subsequent mortality: a systematic review and meta-analysis. *Open Heart*. 2014;1:e000021.
- Dehghani P, Mohammad A, Bajaj R, Hong T, Suen CM, Sharieff W, Chisholm RJ, Kutryk MJ, Fam NP, Cheema AN. Mechanism and predictors of failed transradial approach for percutaneous coronary interventions. *JACC Cardiovasc Interv*. 2009;2:1057–1064.
- Leor J, Goldbourt U, Reicher-Reiss H, Kaplinsky E, Behar S. Cardiogenic shock complicating acute myocardial infarction in patients without heart failure on admission: incidence, risk factors, and outcome. SPRINT Study Group. *Am J Med*. 1993;94:265–273.
- Klein LW, Shaw RE, Krone RJ, Brindis RG, Anderson HV, Block PC, McKay CR, Hewitt K, Weintraub WS; American College of Cardiology National Cardiovascular Data Registry. Mortality after emergent percutaneous coronary intervention in cardiogenic shock secondary to acute myocardial infarction and usefulness of a mortality prediction model. *Am J Cardiol*. 2005;96:35–41.
- Steg PG, James SK, Atar D, Badano LP, Blömmström-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW,

- Valgimigli M, van 't Hof A, Widimsky P, Zahger D. The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33:2569–2619.
28. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61:e78–e140.
 29. Valgimigli M, Gagnor A, Calabró P, Frigoli E, Leonardi S, Zaro T, Rubartelli P, Briguori C, Andò G, Repetto A, Limbruno U, Cortese B, Sganzerla P, Lupi A, Galli M, Colangelo S, Ierna S, Ausiello A, Presbitero P, Sardella G, Varbella F, Esposito G, Santarelli A, Tresoldi S, Nazzaro M, Zingarelli A, de Cesare N, Rigattieri S, Tosi P, Palmieri C, Brugaletta S, Rao SV, Heg D, Rothenbühler M, Vranckx P, Jüni P; MATRIX Investigators. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomized multicentre trial. *Lancet*. 2015;385:2465–2476.
 30. Thiele H, Desch S, Piek JJ, Stepinska J, Oldroyd K, Serpytis P, Montalescot G, Noc M, Huber K, Fuernau G, de Waha S, Meyer-Saraei R, Schneider S, Windecker S, Savonitto S, Briggs A, Torremante P, Vrints C, Schuler G, Ceglarek U, Thiery J, Zeymer U; CULPRIT-SHOCK Investigators. Multivessel versus culprit lesion only percutaneous revascularization in patients with acute myocardial infarction complicated by cardiogenic shock—design and rationale of CULPRIT-SHOCK trial. *Am Heart J*. 2016;172:160–169.
 31. Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, Franconi F, Gerds E, Foryst-Ludwig A, Maas AH, Kautzky-Willer A, Knappe-Wegner D, Kintscher U, Ladwig KH, Schenck-Gustafsson K, Stangl V; The EUGenMed, Cardiovascular Clinical Study Group. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. *Eur Heart J*. 2016;37:24–34.
 32. Vaccarino V. Ischemic heart disease in women: many questions, few facts. *Circ Cardiovasc Qual Outcomes*. 2010;3:111–115.