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Sex-Stratified Trends in Enrollment, Patient Characteristics, Treatment, and Outcomes Among Non–ST-Segment Elevation Acute Coronary Syndrome Patients: Insights from Clinical Trials Over 17 Years

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Abstract

Background—Adequate representation by sex in trials allows generalizability of results. We examined representation of women in clinical trials during a 17-year period in which inclusion criteria were broadened and federal mandates for representativeness were launched.

Methods and Results—Using mixed models, we studied sex-stratified temporal trends in enrollment, clinical characteristics, treatment, and outcomes among 76,148 non-ST-segment elevation (NSTEMI) acute coronary syndrome (ACS) patients using patient-level data merged from 11 phase III trials conducted from 1994 to 2010. Overall, 33.3% of patients were women, which changed minimally over time. Women were consistently 4–5 years older than men (median age 68 [IQR 61–75] versus 64 [IQR 56–72] years) and more frequently had diabetes, hypertension, and heart failure; men more frequently had prior myocardial infarction and revascularization. GRACE risk scores increased over time for both sexes with the inclusion of older patients with more comorbidities. Use of PCI, in-hospital and discharge angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers, β -blockers, and lipid-lowering drugs also increased among both sexes. Kaplan-Meier estimates of 6-month mortality declined from 7.0% [95% CI 6.5%–7.6%] to 4.5% [95% CI 4.0%–5.0%] among women and 6.3% [95% CI 6.0%–6.7%] to 3.1% [95% CI 2.9%–3.4%] among men during the 17-year period.

Conclusions—The relative proportion of women in NSTEMI ACS trials changed minimally over time. Nevertheless, in parallel with men, use of evidence-based care and outcomes improved significantly over time among women.

Keywords

coronary disease; myocardial infarction; women

Acute coronary syndromes (ACS) are the leading cause of death among women in the United States (US) and worldwide, and each year, more women than men die from cardiovascular disease.¹ With population aging and women's longer life span, women will continue to compose a large proportion of patients with ACS, particularly among patients with non-ST-segment elevation myocardial infarction or unstable angina (NSTEMI ACS).^{1,2} We previously observed that despite trends for enrollment of higher-risk patients into phase III clinical trials of pharmacotherapy for NSTEMI ACS over time, in-hospital and 6-month mortality rates fell concurrently with increases in use of evidence-based pharmacotherapy and invasive treatments.³ Because representativeness of clinical trial populations supports generalizability of safety and efficacy results to the general population of NSTEMI ACS patients, we evaluated trends in representation of women in NSTEMI ACS clinical trials over time.

Although there have been modest successes in increasing the balance of enrollment between women and men in cardiovascular clinical trials, it is less clear that these extend to trials of coronary artery disease secondary prevention and ACS. For example, the proportion of enrollment represented by women in trials of pharmacotherapy and lifestyle interventions for primary and secondary prevention increased from 18% in 1970 to 34% in 2006.⁴ However, in the subset of coronary artery disease (CAD) secondary prevention trials, the proportional enrollment of women in 2008 remained low (25%) relative to their representation in the population of patients with CAD (46%).⁴ Similarly, persistent underrepresentation of women relative to men and the clinical population was noted in federally funded cardiovascular trials,⁵ and in an older series of myocardial infarction (MI) trials.⁶ Data reflecting more contemporary drug registration trials with broader inclusion criteria and fewer age and renal exclusions that might bias against inclusion of women are sparse. Pooling patient-level data from 11 large, multinational, NSTEMI ACS phase III randomized clinical trials (RCTs) of antithrombotic therapy that enrolled 76,148 patients (25,174 women) in a 17-year period from 1994 to 2010 allowed us to examine sex-related temporal trends in enrollment, as well as trends in clinical characteristics, use of evidence-based treatments, and outcomes during a time horizon that saw broadening of inclusion criteria and federal regulations for recruitment and representativeness.^{5,7}

Methods

Study population

We included all phase III clinical trials of antithrombotic therapy in NSTEMI ACS in which the Duke Clinical Research Institute (DCRI) had a coordinating center role (n=8), plus 3 trials conducted elsewhere, for which we had access to patient-level data.^{8–18} A summary of key features of these trials is provided in Table 1.

Study design

Baseline characteristics; in-hospital and discharge pharmacotherapy; coronary angiography and revascularization use; and in-hospital, 30-day, and 6-month outcomes were available on a patient level across 17 years in the combined trial database. To maintain sample size homogeneity for display purposes, time trends were described across 4 pre-specified periods (1994–1997; 1998–2001; 2002–2005; 2006–2010). We did not describe or model trends in the use of glycoprotein IIb/IIIa inhibitors and heparins as these medications were part of the protocol-driven randomized treatment in most of the trials we examined. The Duke University Medical Center Institutional Review Board approved the current study with a waiver of written informed consent and HIPAA authorization.

Endpoints

We studied the following post-randomization outcomes: in-hospital, 30-day, and 6-month mortality; a composite of 30-day death or MI; in-hospital GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) bleeding (mild, moderate, and severe); and transfusion during index hospitalization. Observed 6-month mortality was compared with Global Registry of Acute Coronary Events (GRACE) score predicted mortality, which used variables assessed at initial hospital presentation (age, history of heart failure, history of MI,

presenting heart rate, presenting systolic blood pressure, and ST-segment depression) and during hospitalization (creatinine level, elevation of cardiac enzymes, and no in-hospital percutaneous coronary intervention [PCI]).¹⁹ Analyses and results of observed versus predicted mortality were limited to trials that collected GRACE score variables (Figure 1). We used MI as defined by the adjudication protocol of each trial.

Statistical methods

Categorical variables were summarized using percentages and frequencies, and continuous variables using medians and interquartile ranges (IQRs). To test statistical significance of observed trends over time among women and men, we performed mixed model analyses. Observations with missing data were excluded from our analyses. The models included a temporal variable (actual month since the beginning of 1994) and sex, and the interaction of these. Trial of origin was treated as a random effect in the models to account for differences in patient enrollment. For binary outcomes, we used generalized linear mixed models, and for continuous outcomes, linear mixed models. To compare 6-month mortality, we used survival methods, including Kaplan-Meier estimated rates and a shared frailty model to assess time trends by sex. For 30-day mortality, we assessed homogeneity of trends by sex across trials by fitting additional interactions with trial; the result ($p=0.37$ for homogeneity) supports the merged trial analysis and reporting of aggregate results. Given that women who present with NSTEMI ACS often are older than men and that age is significantly related to mortality, we compared our mixed model analyses for mortality with and without age as a covariate. Statistical significance was set at a p -value <0.05 without adjustments for multiple comparisons. All analyses were performed at the DCRI using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient population

Of 76,148 patients, 46,196 presented with NSTEMI and 28,890 with unstable angina; 33.3% were women ($N=25,174$).

Sex-stratified temporal trends in enrollment

Overall, the relative proportion of women enrolled changed little over time (Table 1). There were no substantial differences in enrollment by sex by region (Supplemental Table 1).

Sex-stratified temporal trends in baseline characteristics

Table 2 displays baseline characteristics stratified by sex for the pre-specified time periods. Over time, there were modest increases in median age. Women were 4–5 years older than men across all time periods. History of diabetes and hypertension increased over time, and women with these preexisting conditions consistently outnumbered men. The same patterns applied for congestive heart failure, although the increase was more moderate. Women had higher median 6-month GRACE risk scores and had GRACE scores ≥ 140 more often than men. Compared with men, women less frequently had prior MI, PCI, and bypass surgery.

Sex-stratified temporal trends in pharmacological and invasive management

During the index hospitalization and at discharge, use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEi/ARBs), thienopyridines, β -blockers, and lipid-lowering drugs significantly increased over time among both women and men (Table 3 and Figures 2 and 3). Use of ACEi/ARBs was lower among women than men during the later time periods, despite starting out higher, and use of lipid-lowering drugs was lower among women than men throughout the entire period of observation (Figures 2 and 3). In-hospital use of aspirin was consistently high among both sexes throughout the entire study period, but aspirin use at discharge was higher from 1994–1997 compared with any subsequent time period for both sexes.

Coronary angiography and PCI increased among both sexes over time (Table 3). Relative to women, significantly more men had coronary angiography and PCI (Figure 4). Use of coronary artery bypass graft surgery (CABG) increased slightly post-2000, but proportions of women and men (40% versus 60%) receiving CABG were consistent throughout the 17-year period (Table 3). In both sexes, median length of stay decreased by approximately 3–4 days from 1994–2001 to 2002–2010.

Temporal trends in clinical outcomes by sex

Over time, observed in-hospital, 30-day, and 6-month mortality decreased significantly among both women and men (Figure 1 and Table 4). Any differences in the magnitude of decline in mortality between women and men were small and not affected by adjusting for age (Supplemental Table 2). Odds ratios for 30-day mortality comparing women with men were not significantly different over time (Supplemental Figure 1).

In a subset of trials in which GRACE risk scores were assessed, women had consistently higher GRACE model-predicted 6-month mortality compared with men; however, declines in observed 6-month mortality rates over time were similar among women and men (Figure 1). Trends for observed 6-month mortality were similar when considering all patients enrolled in trials with available 6-month follow-up information, even if not all variables were available to calculate GRACE-predicted 6-month mortality (Supplemental Figure 2). Substantial differences between GRACE model-predicted 6-month mortality and observed 6-month mortality were evident for both sexes, and while GRACE-predicted 6-month mortality increased over time, observed 6-month mortality fell by approximately half for both sexes (Figure 1).

Bleeding and transfusion rates were higher among women than men across all time periods, although changes in rates over time were similar by sex (Table 4). For both sexes, bleeding and transfusion rates increased from 1994–1997 and 1998–2001, peaked during 2002–2005, then fell to prior levels during 2006–2010. Blood transfusion rates were substantially higher than severe bleeding rates in both sexes, even after excluding CABG-treated patients (Table 4 and Supplemental Table 3).

Discussion

This analysis of 76,148 patients with NSTEMI ACS from 11 multinational, phase III RCTs conducted between 1994 and 2010 revealed no overall change in the proportional enrollment of women relative to men over the 17-year period. Further, the proportion of enrollment represented by women (33%) was well below representation of women in US practice registries, in which women account for approximately 40%–46% of NSTEMI ACS patients.^{2,4,20} During the index hospitalization, use of evidence-based pharmacotherapy and revascularization increased significantly over time among both women and men. Concurrent with increases in evidence-based treatment, observed mortality decreased significantly over time in both groups.

Sex-stratified trends in enrollment and characteristics of NSTEMI ACS trial patients

One might expect that relaxation of age and renal function restrictions to enrollment and selection for patients with diabetes might result in increased proportional representation of women in trials of NSTEMI ACS pharmacotherapy. However, despite these efforts and despite increasing awareness of under-enrollment of women,^{3,5,7} the proportion of women enrolled in the NSTEMI ACS trials in our series was stable at around 33% over the 17-year period. These findings are particularly troubling as they occurred despite the ongoing American Heart Association “Go Red For Women” campaign and the National Institutes of Health Revitalization Act of 1993, which legally required inclusion of women and men in clinical trials to be consistent with the known sex-related prevalence of the disease under investigation.^{4,5,7} The 33% representation of women that we observed was higher than previous assessments among CAD trial populations (25%) and similar to the approximately 30% in other NSTEMI ACS phase III trials contemporary to those we examined but conducted by other centers. However, it is substantially below the 40%–46% representation of women in NSTEMI ACS populations in US registries.^{2,4,20–26}

Overall, between 1965 and 1998, cardiovascular RCTs funded by the National Heart, Lung, and Blood Institute (NHLBI) met the representativeness by sex requirement, but NHLBI-funded phase III and IV RCTs between 1997 and 2006 failed to achieve representativeness according to sex.^{5,7} These observations may reflect that drug intervention trials are more likely to exclude individuals due to concomitant medication use, medical comorbidities, or age (despite apparently more broad inclusion criteria and less restrictive exclusion criteria),^{5,7,21–27} or may reflect unmeasured factors that influence recruitment or participation of women in RCTs. We cannot address these potential factors from our trial series, as parallel registries were not conducted to collect information on individuals screened but ultimately not approached or who did not consent to randomization if eligible.

We speculate there are likely many driving factors for the minimal change in enrollment of women over the 17 years studied. Age, renal function limits, and other comorbidities may select against women even though these have been relaxed somewhat over time.²⁸ Women often present later than men and may fall outside the temporal window for inclusion.²⁸ However, APPRAISE-2,¹⁸ in which patients with NSTEMI ACS within 7 days were eligible, failed to enroll a higher proportion of women than other trials in our series. Likewise, the PROVE IT–TIMI 22 trial only enrolled 22% women, despite having a 10-day window for

inclusion following ACS hospitalization.²⁵ Overcoming this sex-based heterogeneity in trial enrollment is needed to ensure that results of NSTE ACS RCTs are as generalizable as possible.

Sex-stratified trends in care and mortality of NSTE ACS trial patients

In contrast to enrollment trends, there were substantial improvements over time in both evidence-based care and mortality in both sexes. Despite enrollment of patients with increasing numbers of comorbidities and GRACE model-predicted mortality, there were substantial declines in observed mortality rates among both women and men. We hypothesize that this divergence of observed from predicted mortality reflects better care, as use of evidence-based therapies increased concurrently. Although we studied trends in a selected group of RCTs available to us, we saw similar trends in a literature review of similar NSTE ACS phase III RCTs conducted during the same periods but by other centers.^{21–26}

Consistent with US registry trends, we found that women were treated with lipid-lowering drugs and PCI less often than men.^{20,29} Women were also treated less often with ACEi/ARBs during the later time periods, despite having more hypertension, heart failure, and diabetes, for which use of these drugs is highly relevant. Since none of the trials in our merged trial database collected information on relative or absolute contraindications for these treatments or information on patient preferences, rates of use among eligible patients cannot be assessed. As we speculated for differences in enrollment, renal function limits (either age-related or due to diabetes) and other comorbidities may appropriately select more heavily against use of certain treatments in women.²⁸ While some registry-based studies have reported persistent differences in use after accounting for contraindications, others showed narrowing of gaps in rates of treatment among women and men consistent with adequately addressed contraindications to use.^{30–32} Given substantial increases in evidence-based treatment in both sexes and limited gaps in care between women and men, sex-related differences in use in our trial series may reflect appropriate use in the clinical context rather than actual disparities in care. Nevertheless, adequate representation of women in trials may facilitate eliminating remaining barriers to use that could be related to uncertainty about benefits and risks of treatment.

Sex-stratified trends in NSTE ACS bleeding and transfusion outcomes

Relative to men, bleeding and transfusion rates were higher among women in our study. In a secondary analysis from the EARLY ACS trial (included in our pooled dataset), women also had higher bleeding rates than men, but the association between bleeding and mortality was stronger among men than among women.³³ Although female sex is an independent risk factor for bleeding, we found no sex-related differences in bleeding rates over time.

The intense antiplatelet and antithrombotic regimens employed during 2002–2005, in conjunction with a mandate for early invasive care in the SYNERGY and EARLY ACS trials, likely contributed to higher rates of bleeding during this period.^{15,16} Furthermore, the nearly 2-fold higher use of CABG among both women and men may have also played a role in the higher bleeding rates seen during 2002–2005. However, excluding CABG-treated

patients did not fully explain the disproportionate use of transfusions relative to severe bleeding.

Strengths and limitations

No prior study has examined sex-related trends in enrollment, clinical characteristics, care, and outcomes among NSTEMI ACS clinical trial populations this large (>76,000 participants) over such a long period of time (17 years, 1994–2010), during which substantial relaxations in age and other risk factor inclusion/exclusion criteria occurred and federal mandates for increased representativeness of enrollment were enacted.

Although our sample size is large, our analyses are based on a convenience sample of clinical trials. Nevertheless, our observations were comparable to US registries and NSTEMI ACS phase III trials contemporary to those we studied.^{20–26,29} In addition, recent large, multinational, phase III NSTEMI ACS trials had comparable overall findings to the more recently conducted studies in our series, although even fewer women were included.^{34–36}

Trial-to-trial heterogeneity in enrollment criteria, care, and endpoint reporting is inevitable. However, by treating trials as random effects in our mixed model analyses, we adjusted for this heterogeneity to the best of our ability. Increases in some pharmacotherapies (e.g., statins and ACEi/ARBs) reflect their emergence as evidence-based treatments during later time periods. Nevertheless, observed increases likely also reflect improvement in care related to overall process-improvement efforts.

Conclusions

Despite efforts to increase representativeness in clinical trials, women were consistently underrepresented in RCTs of pharmacotherapy for NSTEMI ACS over the last 2 decades. With risk enrichment at inclusion, GRACE model-predicted mortality increased over time. However, concurrent with significant increases in evidence-based pharmacotherapy and invasive treatment, mortality fell by approximately half for both sexes without sex-related differences in bleeding outcomes. Current efforts to representatively enroll women in NSTEMI ACS trials are insufficient. Since safety and efficacy findings may differ according to sex, this disparity could undermine generalizability of clinical trials results to treatment of the overall NSTEMI ACS population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Predicted versus observed 6-month mortality by sex over time.

P-values are from sex and time interaction term with trial as random effect. Insignificant *p*-values indicate that changes in mortality rate over time are similar between women and men. KM=Kaplan-Meier observed rate for patients with calculated GRACE score; Pred=GRACE model-predicted 6-month mortality rate, not available from GUSTO IV-ACS, PRISM, PRISM-PLUS, and APPRAISE-2.

Figure 2.

Sex-stratified trends in discharge use of lipid-lowering drugs.

P-value is from sex and time interaction term with trial as random effect. Significant *p*-value indicates a significant difference in the trends for rates of use between women and men.

Discharge use of lipid-lowering drugs was not available from GUSTO IV-ACS.

Figure 3.

Sex-stratified trends in discharge use of ACE inhibitors/angiotensin II receptor blockers. *P*-value is from sex and time interaction term with trial as random effect. Significant *p*-value indicates a significant difference in the trends for rates of use between women and men. ACE=angiotensin-converting enzyme. Discharge use of ACE inhibitors/angiotensin II receptor blockers was not available from TRACER.

Figure 4. Sex-stratified trends in use of angiography and PCI

a) Trends by sex in catheterization. b) Trends by sex in PCI. P -values are from sex and time interaction term with trial as random effect. Significant p -values indicate a significant change in rates of use between women and men over time. PCI=percutaneous coronary intervention.

Table 1

Summary of clinical trials

Clinical Trials	Enrollment Period	Enrollment Criteria	Treatment Studied	Men	Women	Overall
GUSTO IIb*	1994–1997	Chest discomfort <12 h, ECG changes	Heparin, hirudin	5346 (66.7%)	2665 (33.3%)	8011
PRISM	1994–1997	Chest pain <24 h, ECG changes, CK<2x ULN or CK-MB>ULN	Tirofiban, heparin	2194 (68.0%)	1031 (32.0%)	3225
PRISM-PLUS	1994–1997	Chest pain <12 h, ECG changes, CK>ULN or CK-MB>ULN	Tirofiban, heparin, tirofiban plus heparin	1295 (67.6%)	620 (32.4%)	1915
PARAGON-A	1994–1997	Chest pain <12 h, ECG changes	Low-dose lamifiban with and without heparin, high-dose lamifiban with and without heparin	1499 (65.7%)	783 (34.3%)	2282
PURSUIT	1994–1997	Chest pain <24 h, ECG changes, CK-MB>ULN	Placebo, low-dose eptifibatide, high-dose eptifibatide	7090 (64.8%)	3858 (35.2%)	10948
PARAGON-B	1998–2001	Chest pain <12 h, ECG changes, CK-MB or troponin I or T>ULN	Lamifiban, heparin	3436 (65.8%)	1789 (34.2%)	5225
GUSTO IV-ACS [†]	1998–2001	Chest pain <24 h, ECG changes, troponin I or T>ULN	Heparin, 24 h abciximab, 48 h abciximab	4870 (62.4%)	2930 (37.6%)	7800
SYNERGY [‡]	1998–2001, 2002–2005	Chest pain <24 h, ECG changes, CK-MB or troponin I or T>ULN	Enoxaparin, unfractionated heparin	6598 (66.1%)	3380 (33.9%)	9978
EARLY ACS [‡]	2002–2005, 2006–2010	Chest pain <24 h, ECG changes, CK-MB or troponin I or T>ULN	Early, routine administration of eptifibatide, delayed, provisional administration	6431 (68.4%)	2975 (31.6%)	9406
TRACER [§]	2006–2010	Chest pain <24 h, ECG changes, CK-MB or troponin I or T>ULN	Placebo, voraxapar	9312 (71.9%)	3632 (28.1%)	12944
APPRAISE-2*	2006–2010	Recent ACS (MI, with or without STE or UA within 7 days), symptoms >10 min at rest, ECG changes or elevated biomarkers	Placebo, apixaban	2903 (65.8%)	1511 (34.2%)	4414
				50,974 (66.7%)	25,174 (33.3%)	76,148

*Patients with STE ACS not included.

[†] NSTEMI/UA not undergoing planned early revascularization.[‡] NSTEMI/UA undergoing early invasive management.[§] Patients with transient STE ECG changes (<30 min) enrolled.

ACS=acute coronary syndrome; CK=creatinine kinase; CK-MB=creatinine kinase-MB; ECG=electrocardiogram; MI=myocardial infarction; NSTEMI=non-ST-segment elevation myocardial infarction; UA=unstable angina; STE=ST-segment elevation; UA=unstable angina; ULN=upper limit of normal.

Table 2

Baseline characteristics stratified by sex according to enrollment period

	1994–1997		1998–2001		2002–2005		2006–2010	
	Men	Women	Men	Women	Men	Women	Men	Women
Demographics								
No. of patients	17424	8957	8675	4928	7453	3722	17422	7567
Age, median (IQR)	63 (54–71)	67 (59–74)	64 (54–72)	69 (60–75)	66 (60–74)	70 (63–77)	64 (57–71)	69 (61–76)
<65 yrs	56.1% (17423)	40.5% (8955)	52.4% (8675)	37.2% (4928)	43.6% (7452)	28.7% (3722)	51.8% (17420)	36.3% (7566)
>=65 to 75 yrs	31.0% (17423)	36.9% (8955)	30.6% (8675)	34.4% (4928)	34.8% (7452)	38.1% (3722)	31.4% (17420)	35.6% (7566)
>75 to 80 yrs	8.1% (17423)	12.6% (8955)	10.9% (8675)	16.8% (4928)	12.7% (7452)	17.9% (3722)	10.2% (17420)	14.9% (7566)
>=80 yrs	4.8% (17423)	10.0% (8955)	6.1% (8675)	11.6% (4928)	8.9% (7452)	15.2% (3722)	6.5% (17420)	13.2% (7566)
North America	38.3% (17424)	40.2% (8957)	26.2% (8675)	24.1% (4928)	68.7% (7453)	72.5% (3722)	23.2% (17422)	25.5% (7567)
South America	4.4% (17424)	4.9% (8957)	1.6% (8675)	1.4% (4928)	4.4% (7453)	4.2% (3722)	5.5% (17422)	6.6% (7567)
Europe	50.9% (17424)	48.7% (8957)	67.1% (8675)	69.9% (4928)	21.1% (7453)	18.5% (3722)	58.4% (17422)	57.4% (7567)
Other region *	6.5% (17424)	6.2% (8957)	5.1% (8675)	4.6% (4928)	5.8% (7453)	4.8% (3722)	12.9% (17422)	10.5% (7567)
White race	91.2% (17281)	88.6% (8853)	94.0% (8674)	93.3% (4926)	88.4% (7326)	85.1% (3681)	86.4% (16913)	87.0% (7326)
Past medical history								
Diabetes	18.8% (17424)	25.2% (8957)	19.8% (8675)	26.5% (4928)	28.6% (7453)	32.0% (3722)	32.4% (17422)	37.8% (7567)
Hypertension	47.0% (17424)	62.6% (8957)	48.3% (8675)	65.0% (4928)	65.2% (7453)	75.6% (3722)	69.3% (17422)	80.0% (7567)
Hypercholesterolemia	41.0% (17424)	46.1% (8957)	39.7% (8675)	41.1% (4928)	59.1% (7453)	60.5% (3722)	60.0% (17422)	60.9% (7567)
Chronic renal insufficiency [†]	1.1% (17424)	0.9% (8957)	1.7% (3436) [‡]	1.5% (1789) [‡]	— [‡]	— [‡]	9.3% (12215)	10.8% (5143)
Current smoking	31.5% (17394)	19.6% (8949)	31.3% (8675)	16.1% (4928)	27.8% (7453)	18.7% (3722)	29.1% (17422)	17.7% (7567)
Congestive heart failure	8.4% (17424)	12.2% (8957)	8.0% (8675)	10.9% (4928)	9.2% (7453)	11.5% (3722)	12.9% (17422)	16.0% (7567)
MI	38.2% (17424)	28.8% (8957)	33.7% (8675)	25.1% (4928)	30.9% (7453)	22.2% (3722)	33.8% (17422)	25.6% (7567)
PCI	12.6% (17424)	10.4% (8957)	13.9% (8675)	9.0% (4928)	22.5% (7453)	17.9% (3722)	26.6% (17422)	19.5% (7567)
CABG	14.9% (17424)	8.6% (8957)	13.4% (8675)	7.1% (4928)	18.8% (7453)	12.2% (3722)	13.8% (17422)	8.2% (7567)
PVD	10.0% (17424)	8.6% (8957)	8.9% (3805)	7.2% (1998)	10.4% (7453)	8.9% (3722)	10.4% (17422)	9.1% (7567)
Clinical characteristics								
Number with available data	16489	8458	3689 [‡]	1926 [‡]	7352	3658	17317	7494
BMI, kg/m ² , median (IQR) [‡]	27 (25–29)	27 (24–30)	27 (25–30)	27 (24–31)	28 (25–31)	28 (24–31)	28 (25–31)	28 (24–32)

	1994–1997		1998–2001		2002–2005		2006–2010	
	Men	Women	Men	Women	Men	Women	Men	Women
Number with available data	17419	8955	3758 [‡]	1974 [‡]	7448	3719	17386	7549
SBP, mmHg, median (IQR) [‡]	130 (120–148)	135 (120–150)	140 (122–159)	140 (126–160)	132 (118–150)	134 (120–150)	131 (120–148)	133 (120–150)
Number with available data	17305	8901	3758 [‡]	1971 [‡]	7442	3715	17368	7544
Heart rate, bpm, median (IQR) [‡]	70 (62–80)	74 (65–84)	74 (64–85)	77 (68–89)	71 (62–81)	74 (64–85)	70 (62–80)	73 (64–83)
Killip class >=II [§]	9.7% (13935)	12.4% (7306)	12.9% (3805)	16.3% (1998)	11.7% (7453)	13.4% (3722)	6.5% (14519)	8.6% (6056)
GRACE score, // median (IQR)	101 (82–119)	106 (87–124)	97 (78–118)	105 (85–124)	111 (97–127)	116 (101–132)	103 (89–119)	111 (95–127)
GRACE score // >=140	7.9% (13514)	11.0% (7083)	8.0% (3723)	12.6% (1948)	12.1% (7338)	16.8% (3668)	7.3% (13905)	10.8% (5729)

Data presented as % (N), unless otherwise indicated.

* Primarily Asia and Australia.

[‡] “Chronic renal insufficiency” was not collected in EARLY ACS, GUSTO IV-ACS, and SYNERGY.

[‡] BMI, SBP, and heart rate were not available from GUSTO IV-ACS.

[§] Killip class not collected in GUSTO IV-ACS, PRISM, PRISM-PLUS, and APPRAISE-2.

// GRACE score for 6-month predicted mortality could not be calculated for GUSTO IV-ACS, PRISM, PRISM-PLUS, and APPRAISE-2.

BMI=body mass index; CABG=coronary artery bypass grafting; IQR=interquartile range/first and third quartiles (25%, 75%); MI=myocardial infarction; PCI=percutaneous coronary intervention; PVD=pulmonary vessel disease; SBP=systolic blood pressure.

Concomitant medications and hospital stay by sex according to period of enrollment

	1994–1997		1998–2001		2002–2005		2006–2010	
	Men N=17424	Women N=8957	Men N=8675	Women N=4928	Men N=7453	Women N=3722	Men N=17422	Women N=7567
In-hospital medications								
Aspirin	96.9% (17256)	96.1% (8845)	98.0% (8667)	97.5% (4926)	95.4% (7440)	95.0% (3716)	97.2% (17368)	95.9% (7544)
ACE inhibitors	30.1% (17405)	32.2% (8943)	33.9% (8675)	37.4% (4928)	64.5% (7438)	61.4% (3714)	67.7% (8048)*	65.7% (3901)*
Thienopyridines	13.6% (12071) [‡]	11.6% (6284) [‡]	20.7% (8675)	15.6% (4928)	70.4% (7453)	67.0% (3720)	94.1% (17407)	91.0% (7554)
Beta-blockers	73.7% (17420)	71.7% (8947)	60.3% (8675)	62.0% (4928)	87.2% (7449)	86.1% (3718)	85.4% (17389)	85.5% (7554)
GP IIb/IIIa inhibitors	34.6% (12069) [‡]	34.8% (6287) [‡]	23.0% (8675)	20.7% (4928)	32.4% (7449)	29.8% (3721)	14.3% (17414)	10.3% (7564)
Lipid-lowering drugs	18.2% (17404)	19.3% (8944)	23.7% (3805) [‡]	20.9% (1998) [‡]	75.8% (7453)	72.0% (3722)	91.1% (17420)	86.0% (7566)
Index hospital invasive treatments								
Catheterization	58.8% (17419)	52.4% (8949)	52.8% (8672)	42.1% (4927)	93.3% (7452)	92.0% (3722)	76.6% (17418)	73.1% (7565)
PCI	21.2% (17423)	17.4% (8955)	21.6% (8672)	15.5% (4927)	50.5% (7453)	44.3% (3722)	51.2% (17422)	41.5% (7567)
CABG	13.8% (17414)	9.9% (8953)	11.0% (8672)	6.9% (4928)	20.5% (7448)	13.7% (3721)	10.1% (17418)	6.7% (7565)
Hospital LOS, median (IQR)	9 (6–14)	9 (6–15)	9 (6–13)	10 (7–14)	6 (4–10)	6 (4–9)	6 (4–9)	6 (4–9)
Patients alive at discharge	N=16906	N=8648	N=8430	N=4780	N=7271	N=3623	N=17174	N=7370
Discharge medications[‡]								
Aspirin	71.0% (16731)	70.0% (8532)	99.1% (3691) [‡]	98.2% (1947) [‡]	93.3% (7268)	89.8% (3621)	95.9% (17157)	94.1% (7363)
ACE inhibitors	20.9% (16893)	23.2% (8638)	39.1% (3703) [‡]	40.5% (1950) [‡]	60.8% (7258)	58.1% (3615)	65.0% (7893)*	62.8% (3796)*
Thienopyridines	10.5% (11724) [‡]	8.7% (6081) [‡]	30.6% (3703) [‡]	24.9% (1950) [‡]	63.2% (7266)	56.8% (3622)	78.8% (17129)	73.8% (7347)
Beta-blockers	47.7% (16903)	46.6% (8641)	68.8% (3703) [‡]	65.8% (1950) [‡]	81.8% (7267)	78.4% (3619)	80.1% (17142)	80.0% (7360)
Lipid-lowering drugs	15.5% (16892)	16.4% (8639)	41.0% (3703) [‡]	37.1% (1950) [‡]	78.7% (7271)	74.4% (3623)	88.1% (17172)	83.2% (7369)

Data presented as % (N), unless otherwise indicated.

* Information on ACE inhibitors not available from TRACER.

[‡] Information on thienopyridines and GP IIb/IIIa inhibitors not available from GUSTO IIb.[‡] Information on discharge medications not available from GUSTO IV-ACS.

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ACE=angiotensin-converting enzyme, also including angiotensin II receptor blockers; CABG=coronary artery bypass grafting; GP=glycoprotein; IQR: interquartile range/first and third quartile (25%, 75%); LOS=length of stay; PCI=percutaneous coronary intervention.

Table 4

Clinical outcomes by sex according to time period

	1994–1997		1998–2001		2002–2005		2006–2010	
	Men N=17424	Women N=8957	Men N=8675	Women N=4928	Men N=7453	Women N=3722	Men N=17422	Women N=7567
Mortality								
In-hospital death	3.0% (17423)	3.4% (8956)	2.8% (8675)	3.0% (4928)	2.4% (7450)	2.6% (3720)	1.3% (17395)	2.3% (7542)
30-day death	3.4% (17423)	3.9% (8957)	3.5% (8675)	3.7% (4928)	2.9% (7453)	3.2% (3722)	1.4% (17422)	2.2% (7567)
Kaplan-Meier rates for 6-month death*	927 (6.3%)	537 (7.0%)	204 (5.4%)	108 (5.4%)	402 (5.4%)	209 (5.6%)	525 (3.1%)	325 (4.5%)
Kaplan-Meier rates for 6-month death for patients with GRACE score available ^{†‡}	812 (6.0%)	474 (6.7%)	199 (5.4%)	106 (5.5%)	395 (5.4%)	204 (5.6%)	431 (3.1%)	244 (4.3%)
Patient with follow-up ≥28 days	99.1% (16824)	99.3% (8602)	100.0% (8374)	100.0% (4744)	100.0% (7234)	99.9% (3604)	98.0% (17175)	97.5% (7401)
MI								
30-day MI	9.0% (17423)	9.2% (8956)	7.3% (8675)	6.7% (4928)	13.0% (7453)	10.7% (3722)	5.5% (17422)	5.5% (7567)
Death or MI								
30-day death or MI	11.2% (17422)	11.4% (8956)	9.6% (8675)	9.3% (4928)	14.9% (7453)	12.9% (3722)	6.5% (17422)	7.1% (7567)
MI and death in 30 days	1.3% (17422)	1.7% (8956)	1.1% (8675)	1.1% (4928)	1.0% (7453)	0.9% (3722)	0.4% (17422)	0.6% (7567)
30-day death only	2.2% (17422)	2.2% (8956)	2.3% (8675)	2.6% (4928)	1.9% (7453)	2.2% (3722)	1.1% (17422)	1.6% (7567)
30-day MI only	7.7% (17422)	7.5% (8956)	6.1% (8675)	5.6% (4928)	12.0% (7453)	9.8% (3722)	5.1% (17422)	4.9% (7567)
In-hospital bleeding								
Mild bleeding	20.0% (17413)	23.1% (8953)	20.6% (3805) [§]	26.1% (1998) [§]	29.1% (7434)	30.1% (3702)	12.2% (17280)	14.3% (7471)
Moderate bleeding	7.0% (17413)	10.0% (8954)	14.6% (3805) [§]	14.6% (1998) [§]	11.2% (7434)	14.8% (3702)	2.9% (17280)	4.4% (7471)
Severe bleeding	1.1% (17413)	1.6% (8953)	1.4% (3805) [§]	1.7% (1998) [§]	1.8% (7434)	3.1% (3702)	0.9% (17279)	1.3% (7471)
Transfusion	7.0% (17417)	10.5% (8953)	10.9% (3805) [§]	12.5% (1998) [§]	14.9% (7453)	19.0% (3722)	6.1% (17399)	9.3% (7546)

Data presented as % (N), unless otherwise indicated.

* 6-month mortality is not available from GUSTO IV-ACS and PRISM.

[†] Among patients still alive at 30 days.[‡] GRACE score could not be calculated for GUSTO IV-ACS, PRISM, PRISM-PLUS, and APPRAISE-2.[§] Information on GUSTO bleeding and transfusion not available from GUSTO IV-ACS.

MI=myocardial infarction.

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