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Trends in Enrollment, Clinical Characteristics, Treatment, and Outcomes According to Age in Non-ST-Segment Elevation Acute Coronary Syndromes Clinical Trials

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Abstract

Background—Representation by age ensures appropriate translation of clinical trial results to practice, but historically, older patients were underrepresented in clinical trial populations. As the general population has aged, it is unknown whether clinical trial enrollment has changed in parallel.

Methods and Results—We studied time trends in enrollment, clinical characteristics, treatment, and outcomes by age among 76,141 NSTE ACS patients enrolled in 11 phase III clinical trials over 17 years (1994–2010). Overall, 19.7% of patients were ≥75 years; this proportion increased from 16% during 1994–1997 to 21% during 1998–2001 and 23.2% during 2002–2005, but declined to 20.2% in 2006–2010. The number of comorbidities increased with successive time periods irrespective of age. There were substantial increases in use of evidence-based medication in-hospital and at discharge regardless of age. While predicted 6-month mortality increased slightly over time, observed 6-month mortality declined significantly in all age strata (1994–1997 vs. 2006–2010: <65 years: 3.0% vs. 1.9%; 65–74 years: 7.5% vs. 3.4%; 75–79 years: 13.0% vs. 6.5%; 80–84 years: 17.6% vs. 8.2%; and ≥85 years: 24.8% vs. 12.6%).

Conclusions—The distribution of enrollment by age in phase III NSTE ACS trials was unchanged over time. Irrespective of age, post-myocardial infarction mortality decreased significantly over time, concurrent with increased evidence-based care and despite increasing comorbidities.

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Keywords

coronary disease; myocardial infarction

Introduction

In current practice, individuals ≥75 years old account for more than one-third of non-ST-segment elevation acute coronary syndrome (NSTE ACS) episodes and the majority of overall mortality due to NSTE ACS, but represent <10% of NSTE ACS clinical trial populations.[1,2] Substantial differences between trial and community patient characteristics exist and efforts are needed to increase enrollment of older patients in NSTE ACS trials to increase certainty about treatment effects across all age groups.[3]

We previously showed that along with significant increases in discharge evidence-based medications and use of invasive strategies, there was a significant decline in 6-month mortality despite enrollment of increasingly higher-risk patients over time.[4] We explored whether these trends applied to patients of all ages by examining age-related temporal trends in enrollment, clinical characteristics, use of evidence-based hospital and discharge therapies, and clinical outcomes in NSTE ACS clinical trials using the databases of 11 phase III randomized clinical trials that enrolled patients from 1994 to 2010.

Methods

Study population

All phase III clinical trials of antithrombotic therapy in NSTE ACS in which the Duke Clinical Research Institute (DCRI) had a coordinating-center role, plus 3 trials conducted elsewhere, from which we had access to patient-level data, were included (N=11 trials).[5–15] These trials are described in Table 1.

Study design

Baseline characteristics; in-hospital and discharge pharmacotherapy; coronary angiography and revascularization; and in-hospital, 30-day, 6-month, and 1-year outcomes were trended across 17 years and stratified by age. Four prespecified time periods (1994–1997; 1998–2001; 2002–2005; 2006–2010) within 5 age groups (<65 years, 65–74 years, 75–79 years, 80–84 years, and ≥85 years) were designated for display purposes. We excluded glycoprotein IIb/IIIa inhibitors and heparins from our analysis as these medications were part of 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

Study endpoints included in-hospital, 30-day, 6-month, and 1-year mortality; a composite of 30-day death or myocardial infarction (MI); in-hospital GUSTO bleeding (mild, moderate, and severe); and transfusion during index hospitalization. Observed 6-month mortality was

compared with GRACE score-predicted mortality. MI was used as classified by the adjudication protocol of each trial.

Statistical methods

We summarized categorical variables using percentages and frequencies, and continuous variables using medians and first and third quartiles. GRACE risk scores were calculated for 6-month mortality, using previously described methods.[16,17] Complete data for GRACE score determinations were available from GUSTO IIb, PARAGON-A and -B, PURSUIT, SYNERGY, EARLY ACS, and TRACER. Observed versus predicted mortality analyses were limited to these trials.

Regression models assessed trends over time according to age. Actual month since the beginning of 1994 and age as a continuous variable, as well as an age × time interaction term, were included in the models. For short-term (in-hospital and 30-day) binary outcomes (e.g., use of angiography or a medication, and mortality), we used hierarchical logistic regression, and for continuous outcomes (e.g., length of stay and GRACE score) we used linear mixed models. Length of stay was log-transformed for normality. To compare 6-month and 1-year mortality, we use Kaplan-Meier rates and Cox regression with a shared frailty for trial. These models assume and account for clustering of patient outcomes within trials. Statistical significance was set at $P<0.05$ (two-sided) without adjustments for multiple comparisons. Analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient population

Of 76,141 patients, 29,697 (39%) presented with unstable angina and 46,196 (61%) with NSTE MI. Overall, 11.6% of patients were 75–79 years of age, 6.0% 80–84 years, and 2.1% ≥85 years. The distribution of enrollment by age according to time period is shown in Figure 1. Although the changes in distribution of enrollment by age over time were statistically significant in the overall population of >76,000 patients, the changes were qualitatively modest. Enrollment by region by time period is shown in Supplemental Figure 1, and the proportion of US enrollment by age by time is shown in Supplemental Table 1. The higher proportion of North American and US enrollment during the 2002–2005 time period reflects 1) the pattern of early enrollment in EARLY ACS during which US contribution predominated, and 2) enrollment in SYNERGY, in which US enrollment predominated.

Age-stratified temporal trends in baseline characteristics

Age-stratified temporal changes in baseline characteristics are presented in Table 2. Over time, there were clinically modest but statistically significant increases in the number of male ($P<0.0001$) and non-white participants ($P<0.0001$), and a marked increase in patients with diabetes ($P<0.0001$), hypertension ($P<0.0001$), and hypercholesterolemia ($P<0.0001$) in all age groups. In all age strata, the proportion of patients with prior percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) increased over time (both $P<0.0001$).

Age-stratified temporal trends in pharmacological and invasive management

In-hospital use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEi/ARBs), beta-blockers, and lipid-lowering drugs increased in all age strata from 1994–2010 (all P<0.0001; Table 3). Similarly, there were significant increases over time in use of these medications at discharge (all P<0.0001). The trend over time × age interaction terms were statistically significant, indicating that changes in slopes between age groups differed over time, reflecting narrowing treatment gaps between age groups (Figure 2). Within all age groups, in-hospital aspirin use was high throughout the study period, while aspirin use at discharge increased between 1994–1997 and 1998–2001 and then remained high (Table 3, Figure 2).

Coronary angiography and PCI use increased among patients in all age groupings over time (all P<0.0001). Regardless of time period, older patients less often received PCI than younger groups, but these differences narrowed over time (Table 3, Figure 3). Rates of CABG were generally stable over time, and were lowest among the two oldest age groups and highest among patients between 65–74 years. Median length of stay decreased by 3–4 days in all age groupings from 1994–1997 to 2006–2010 (P<0.0001; Table 3).

Temporal trends in clinical outcomes by age

Rates and temporal patterns of observed in-hospital, 30-day, 6-month, and 1-year mortality over the 17-year period are shown in Table 4 and Supplemental Figure 2, respectively, and 30-day death or MI rates are displayed in Supplemental Table 2. Despite slightly increased predicted 6-month mortality within each age stratum over time, observed 6-month mortality fell in all age groups, and the changes in observed mortality rates over time did not vary significantly according to age (P for interaction=0.3345); Tables 2 and 4, Figure 4).

Older groups had higher bleeding and transfusion rates than younger patients, but temporal patterns of GUSTO moderate (P for interaction=0.8860) and severe bleeding (P for interaction=0.4264) were similar by age group (Supplemental Table 3). Rates of blood transfusion were substantially higher than rates of severe bleeding during all time periods regardless of age, even after excluding CABG-treated patients (Supplemental Tables 3 and 4).

Discussion

This analysis of 76,141 patients revealed no overall change in the age distribution of enrollment in randomized clinical trials of NSTE ACS pharmacotherapies over the 17-year period studied, despite inclusion criteria in more recent trials that selected for older patients. Significant increases in use of evidence-based pharmacotherapies in-hospital and at discharge and in use of angiography and PCI and substantial decreases in length of stay occurred regardless of age. Observed mortality declined by approximately half in all age strata despite more comorbidities and a small increase in predicted 6-month mortality.

Age-stratified trends in enrollment and medical care

Despite efforts aimed at increasing enrollment of older patients in randomized clinical trials, particularly in the later trials in our series,[14,15] enrollment by age did not change substantially over time. This may reflect physician bias in enrollment due to concern for bleeding, patient preference, or exclusion criteria related to renal function or other comorbidities that may disproportionately affect the elderly. Because safety and efficacy of pharmacotherapy can differ by patient age, underrepresentation of older patient groups could limit generalizability of clinical trial results to the aging population. To the extent that this creates concern among providers about extrapolating clinical trial results to treatment of older patients, under-treatment may result in both high ischemic risk and potentially high risk of adverse events in this group. To best generalize ACS clinical trials results to actual practice and particularly to ensure that treatment effects are known for the growing older segment of the population, every effort must be made to enroll eligible elderly patients and to avoid restrictive inclusion and exclusion criteria that limit their participation.

Age-stratified trends in treatment, mortality, and ischemic outcomes

Among those enrolled, use of evidence-based pharmacotherapies and angiography increased substantially within all age groupings over time. In general, gaps in care by age were narrowing over time, consistent with observations from registries,[18,19] and mortality declines were more prominent among older groups. Concurrent with increase in use of evidence-based pharmacotherapy and catheterization and shorter lengths of stay, 6-month and 1-year mortality declined significantly, even though GRACE model-predicted mortality increased slightly over time.

Thirty-day death or MI fluctuated across time periods. This may reflect trial-to-trial variation in MI definition or changes in biomarkers used to define MI, but this is less likely given lower death or MI rates in more recent time periods in which troponins were more widely used in endpoint adjudication. The peak in death or MI rates during 2002–2005 may be due to greater use of an invasive strategy, resulting in more procedure-related MI in the trials enrolling during this time period. Because not all trials we examined distinguished between procedure-related and spontaneous MI, we could not directly assess this possibility. However, in previous work we reported a trend for increasing contribution of procedure-related infarction to total MI rates.[4]

Age-stratified trends in NSTE ACS bleeding outcomes

Bleeding and transfusion rates were higher among older age groups, but the temporal patterns of GUSTO moderate and severe bleeding and rates of transfusion were similar by age groupings. Bleeding and transfusion rates were lower in all age groupings and time periods after exclusion of CABG patients, but the disproportionately higher rates of transfusion relative to bleeding persisted in all age groups and point to a need for closer examination of transfusion practices.

Strengths and limitations

Strengths of this study include the large number of included patients, the 17-year time period evaluated, and the quality of information on treatments and outcomes. Despite the large

number of patients, the analyses are based on a convenience sample of clinical trials conducted at the DCRI or by its colleagues, and for which we had access to patient-level data. However, trends over time, including enrollment by age, were comparable to other NSTE ACS trials conducted during the same period.[20–25] Other recent large, multinational, phase III, NSTE ACS trials had comparable findings to the more recent trials in our series, although fewer patients aged ≥75 years were studied.[26–29] Finally, overall rates of treatment and outcomes were comparable to those observed in practice registries.[19,30,31]

We acknowledge trial-to-trial heterogeneity, including in regional distribution of enrollment and endpoint definition (particularly MI) and reporting. We accounted for this by treating the trials as random effects in our mixed model analyses of time trends. Increases in use of some pharmacotherapies (e.g., statins and ACEi/ARBs) reflect their emergence as evidence-based treatments at later time points during our 17-year assessment. However, even for these agents, we observed trends for an increase in use that likely reflect the many efforts to improve use of guidelines-based therapy.

We used the GRACE 6-month mortality model in our predicted versus observed 6-month mortality comparisons. Other models, such as the Thrombolysis In Myocardial Infarction (TIMI) or Predicting Risk of Death in Cardiac Disease Tool (PREDICT) scores, could have been considered and have advantages and disadvantages in both research and clinical practice.[32,33] The discriminative ability of the GRACE model and PREDICT score are superior to the model underpinning the TIMI risk score, likely due to a broader array of laboratory and clinical markers of risk.[16,17,32–35] Conversely, the TIMI score is easily calculated at the bedside, whereas GRACE and PREDICT require programmed algorithms. Adding ejection fraction to PREDICT and TIMI models yielded incremental predictive value from these scores,[32,34,35] but renders them less useful at presentation, although it may be helpful for reassessment in-hospital or at discharge. Because ejection fraction was not available consistently in our dataset, we could not use these modified scores.

Conclusions

Despite efforts aimed at more representative enrollment by age in randomized clinical trials, including elimination of upper age restrictions on enrollment, there was no substantial change in the distribution or enrollment by age in our 17-year series of trials. Use of evidence-based treatments increased in all age strata over the 17-year period, and perhaps due to better treatment, observed mortality fell by approximately half over this time despite slightly increasing predicted 6-month mortality rates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Perspectives

Representation by age is important to support translation of clinical trial results to treatment of older patients in practice, but historically, older patients have been underrepresented in clinical trial populations. Our examination of trends in enrollment of patients with non-ST-segment elevation acute coronary syndrome according to age in 11 phase III trials of antithrombotic therapy during 1994–2010 showed that despite relaxation of age criteria for inclusion in trials during more recent time periods, there were minimal changes in the age distribution of enrolled patients. The proportion of enrolled patients aged ≥75 years remained disproportionate to their representation in clinical practice. However, across all age groups, and despite increasing numbers of comorbidities, in parallel with significant increases in use of evidence-based pharmacotherapies in-hospital and an invasive treatment strategy, mortality fell by approximately half over the 17-year study period. The need to pool trial data to obtain an adequate sample size within the older patient groups to demonstrate these favorable trends highlights potential concerns about extrapolating the results from a single trial to the aging population in clinical practice—such concerns that may lead to underuse of guidelines-recommended care among older, inherently higher-risk patients who may derive greater ischemic benefit but also be at greater risk for adverse effects. To ensure that the clinical trial results that form the basis of evidence-based care adequately reflect the benefits and risks of treatment in the aging population, every effort must be made to ensure enrollment in clinical trials is representative by age.

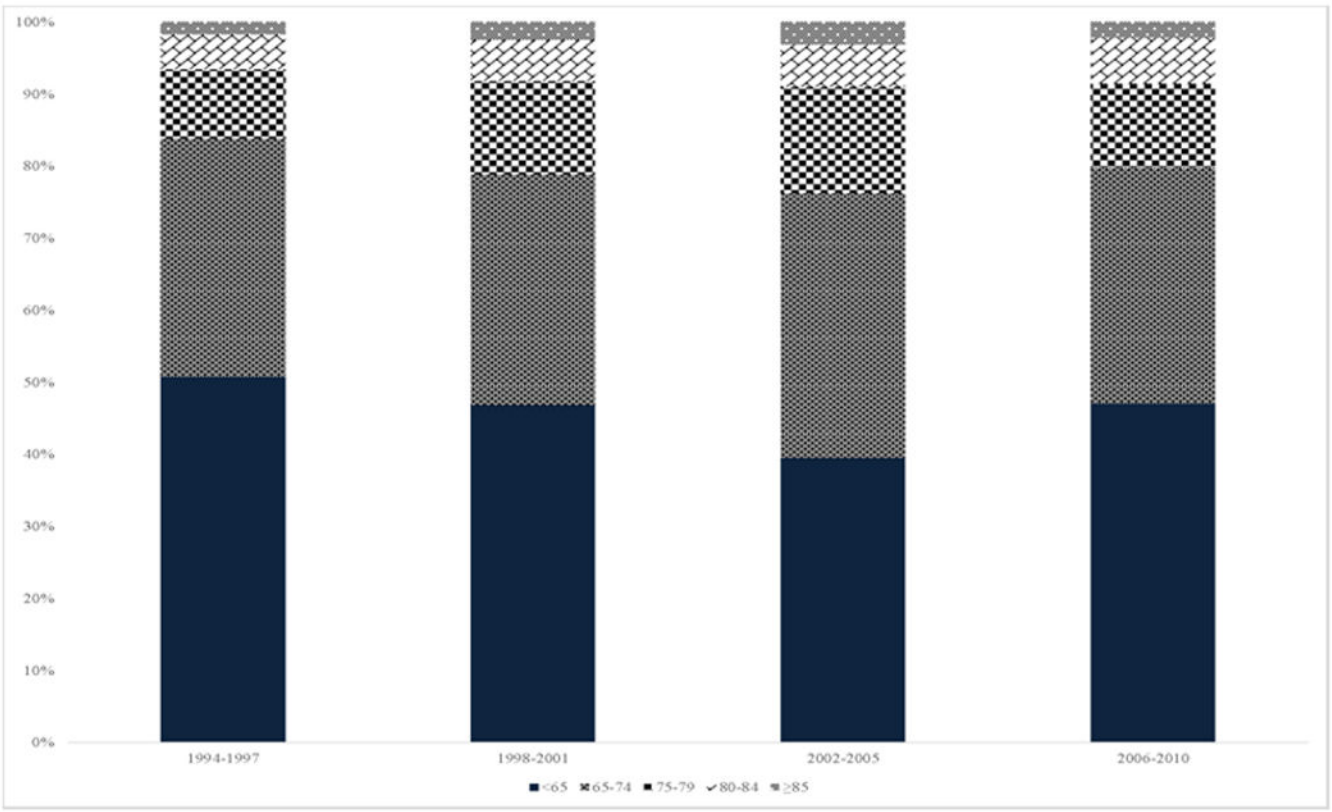

Figure 1. Distribution of enrolled trial participants by age group over time

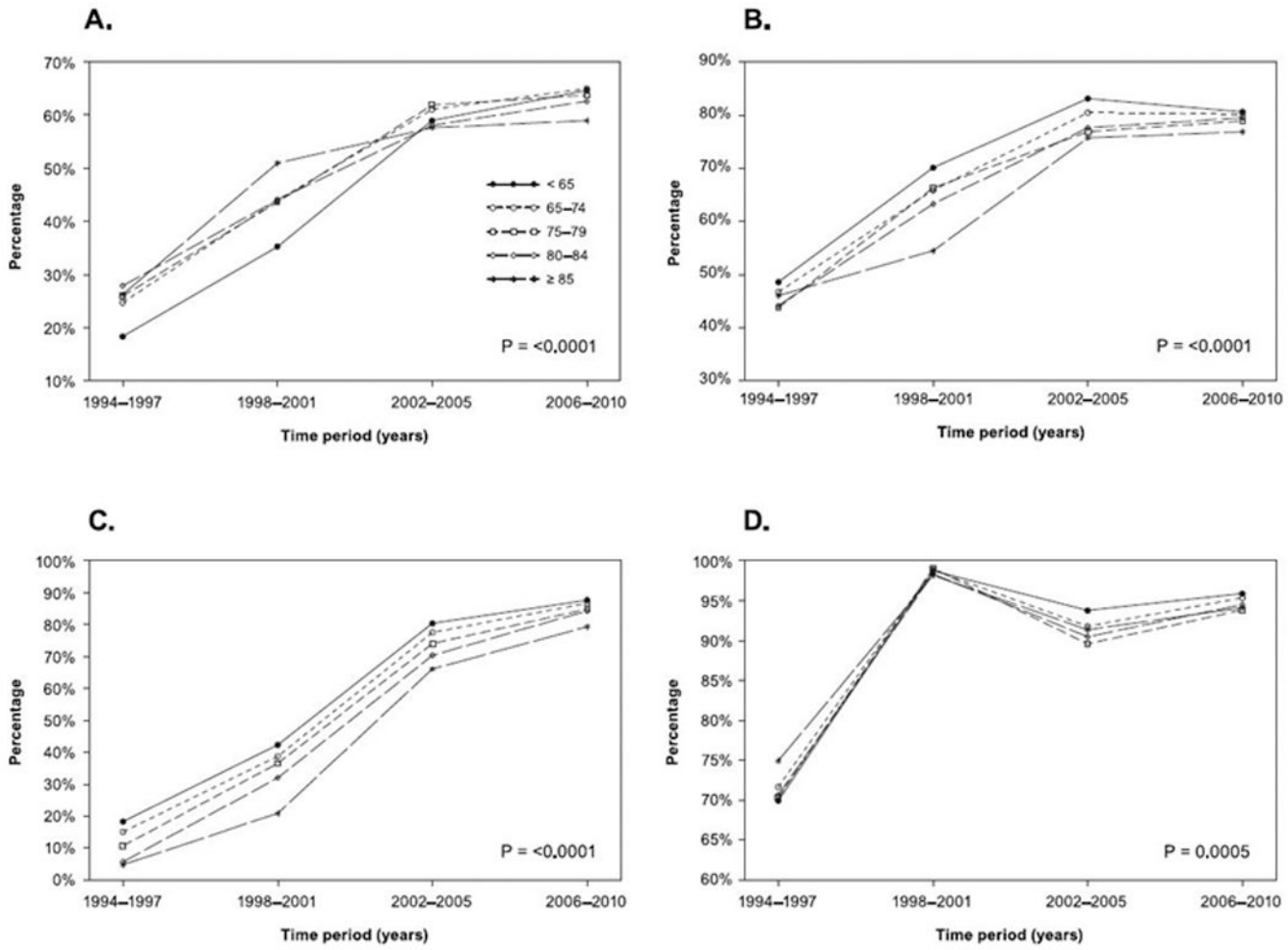

Figure 2.

Selected discharge medication use by age group over time. **A**) Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; **B**) Beta-blocker; **C**) Lipid-lowering drugs; **D**) Aspirin. Age × time interaction P-values are displayed. Significant P-values indicate that changes in use over time differed statistically according to age.

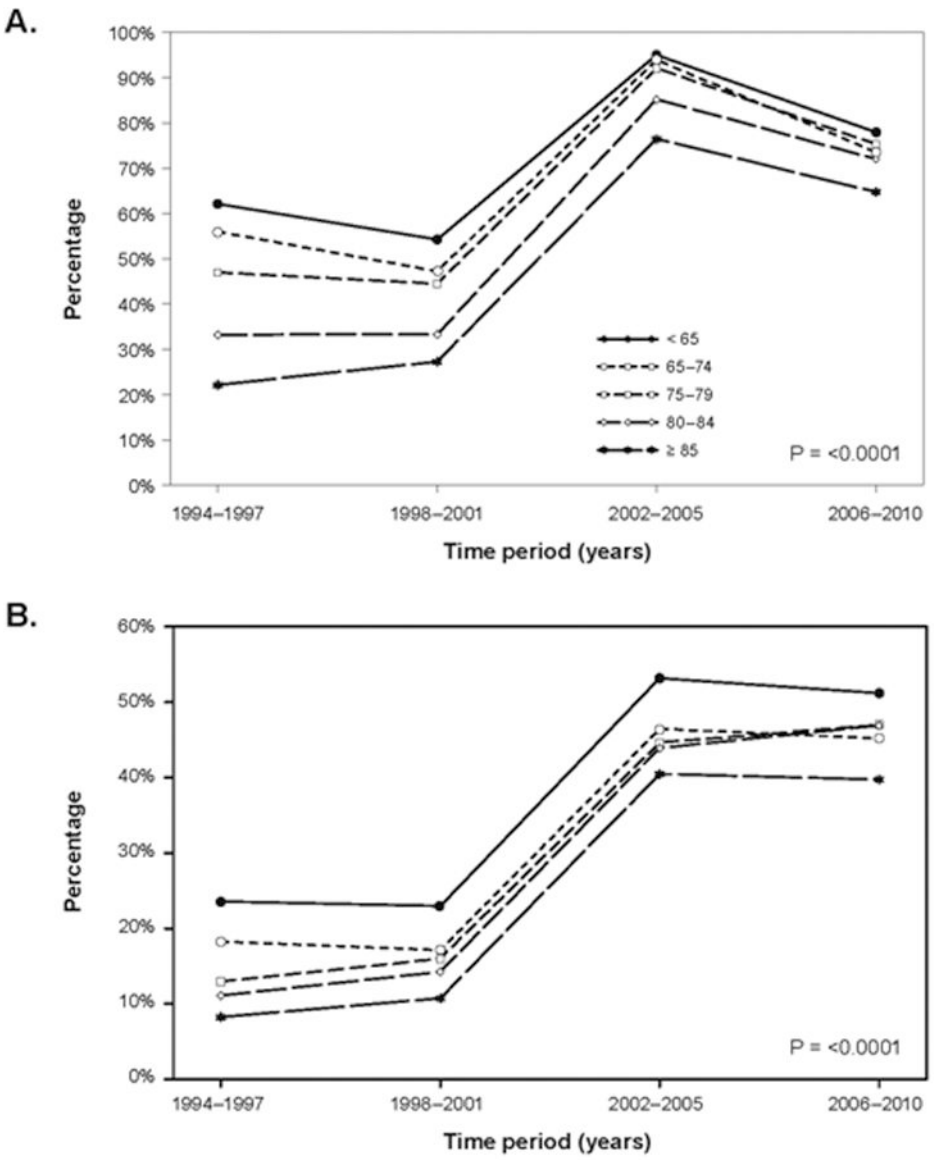

Figure 3.

Use of an invasive strategy by age group over time. **A**) Angiography; **B**) Percutaneous coronary intervention. Age × time interaction P-values are displayed. Significant P-values indicate that changes in use over time differed statistically according to age.

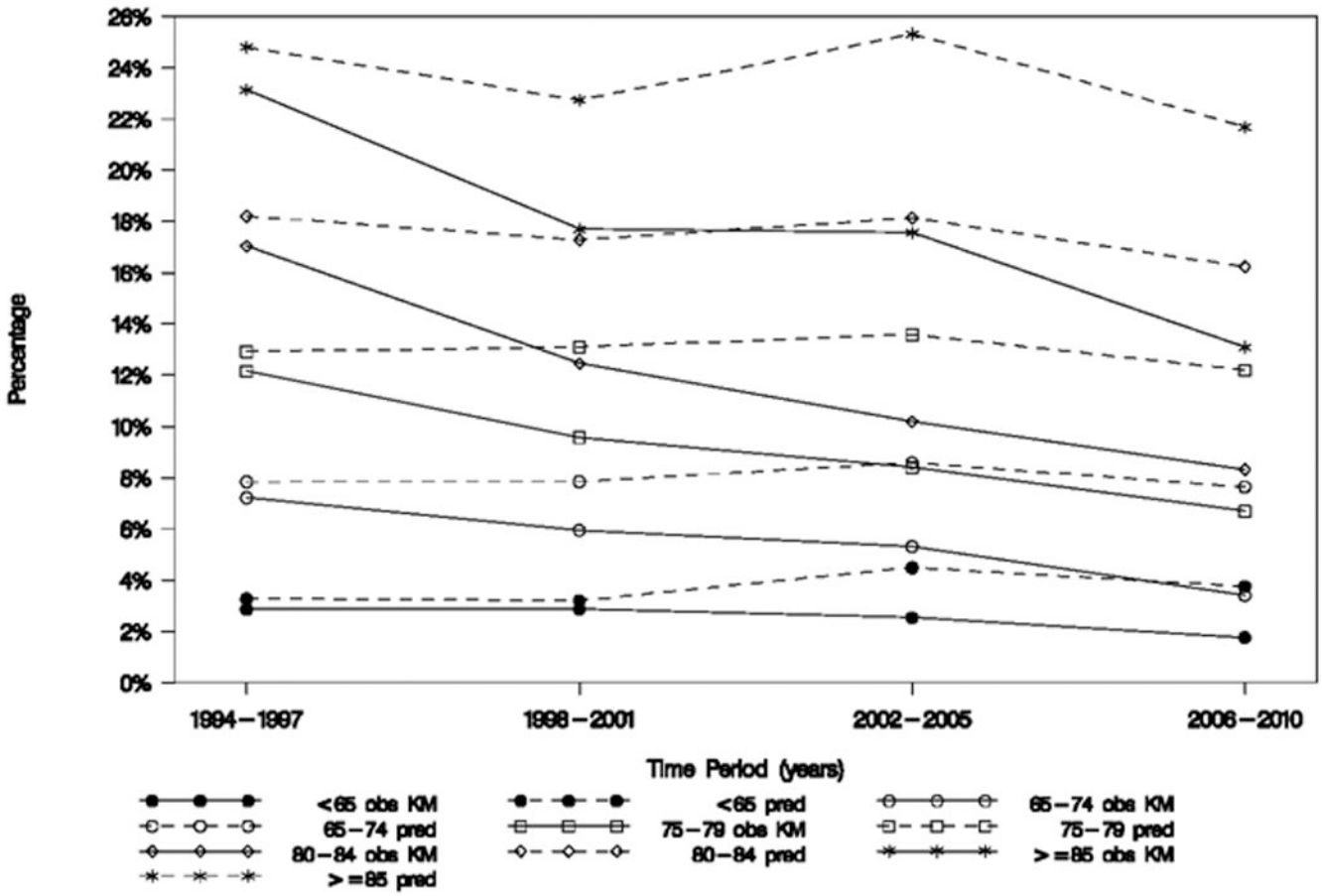

Figure 4.

Predicted versus observed 6-month mortality. The age × time interaction P-value for observed mortality = 0.3345 and is from a model using trials that collected GRACE score data: GUSTO IIb, PARAGON-A and -B, PURSUIT, SYNERGY, EARLY ACS, and TRACER. An insignificant P-value indicates that changes in observed mortality rates over time did not vary significantly according to age. A P-value for GRACE model-predicted mortality was not calculated because age is a variable in the GRACE model.

Table 1

Summary of clinical trials

Clinical Trials	Enrollment period	Enrollment criteria	Treatment studied	<65 years	65–74 years	75–79 years	80–84 years	≥85 years
GUSTO IIb *	1994–1997	Chest discomfort <12 h, ECG changes	Heparin, hirudin	3850 (48.1%)	2598 (32.4%)	868 (10.8%)	504 (6.3%)	191 (2.4%)
PRISM	1994–1997	Chest pain <24 h, ECG changes, CK>2× ULN or CK-MB>ULN	Tirofiban, heparin	1780 (55.2%)	1002 (31.1%)	271 (8.4%)	134 (4.2%)	38 (1.2%)
PRISM-PLUS	1994–1997	Chest pain <12 h, ECG changes, CK>ULN or CK-MB>ULN	Tirofiban, heparin, tirofiban plus heparin	980 (51.2%)	597 (31.2%)	214 (11.2%)	92 (4.8%)	32 (1.7%)
PARAGON-A	1994–1997	Chest pain <12 h, ECG changes	Low-dose lamifiban with and without heparin, high-dose lamifiban with and without heparin	1074 (47.1%)	770 (33.7%)	252 (11.0%)	136 (6.0%)	47 (2.1%)
PURSUIT	1994–1997	Chest pain <24 h, ECG changes, CK-MB>ULN	Placebo, low-dose eptifibatide, high-dose eptifibatide	5717 (52.2%)	3743 (34.2%)	938 (8.6%)	411 (3.8%)	139 (1.3%)
PARAGON-B	1998–2001	Chest pain <12 h, ECG changes, CK-MB or troponin I or T>ULN	Lamifiban, heparin	2709 (51.8%)	1586 (30.4%)	568 (10.9%)	263 (5.0%)	99 (1.9%)
GUSTO IV-ACS †	1998–2001	Chest pain <24 h, ECG changes, troponin I or T>ULN	Heparin, 24-h abciximab, 48-h abciximab	3453 (44.3%)	2577 (33.0%)	1112 (14.3%)	452 (5.8%)	206 (2.6%)
SYNERGY ‡	1998–2001, 2002–2005	Chest pain <24 h, ECG changes, CK-MB or troponin I or T>ULN	Enoxaparin, unfractionated heparin	3836 (38.4%)	3601 (36.1%)	1451 (14.5%)	798 (8.0%)	291 (2.9%)
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	3907 (41.5%)	3119 (33.2%)	1331 (14.2%)	763 (8.1%)	283 (3.0%)
TRACER §	2006–2010	Chest pain <24 h, ECG changes, CK-MB or troponin I or T>ULN	Placebo, voraxapar	6759 (52.2%)	3979 (30.7%)	1329 (10.3%)	685 (5.3%)	192 (1.5%)
APPRAISE-2 *	2006–2010	ACS (MI, with or without STE or UA) within 7 days, symptoms>10 min at rest, ECG changes or elevated biomarkers	Placebo, apixaban	1807 (40.9%)	1675 (37.9%)	500 (11.3%)	308 (7.0%)	124 (2.8%)
				35872 (47.1%)	25247 (33.2%)	8834 (11.6%)	4546 (6.0%)	1642 (2.1%)

ACS: acute coronary syndrome, CK: creatine kinase, ECG: electrocardiogram, MI: myocardial infarction, NSTE: non-ST-segment elevation, UA: unstable angina, ULN: upper limit of normal.

* Patients with STE ACS not included.

† NSTEMI/UA not undergoing planned early revascularization.

‡ NSTEMI, unstable angina undergoing early invasive management.

§ Patients with transient STE ECG changes (<30 min) enrolled.

Table 2
Baseline characteristics stratified by age grouping and time period

	Randomization Year			
	1994–1997	1998–2001	2002–2005	2006–2010
Age <65 years	**(N=13401)**	**(N=6377)**	**(N=4320)**	**(N=11774)**
Demographics				
Age, median (Q1-Q3)	56 (49-60)	55 (50-60)	59 (52-62)	58 (53-61)
Female sex	27.1% (13401) *	28.8% (6377)	24.8% (4320)	23.3% (11774)
White race	87.3% (13236)	91.5% (6376)	83.4% (4226)	84.0% (11378)
Past medical history				
Diabetes	17.8% (13401)	17.9% (6377)	27.0% (4320)	33.1% (11774)
Hypertension	47.8% (13401)	47.4% (6377)	59.7% (4320)	66.4% (11774)
Hypercholesterolemia	46.5% (13401)	43.0% (6377)	59.3% (4320)	60.1% (11774)
Chronic renal insufficiency	0.5% (13401)	0.7% (2709)		5.5% (8566)
Current smoking	40.8% (13381)	41.4% (6377)	42.8% (4320)	39.5% (11774)
Congestive heart failure	6.0% (13401)	5.4% (6377)	6.3% (4320)	11.2% (11774)
MI	32.0% (13401)	25.2% (6377)	23.8% (4320)	32.2% (11774)
PCI	13.0% (13401)	12.5% (6377)	18.5% (4320)	25.0% (11774)
CABG	11.6% (13401)	9.7% (6377)	12.5% (4320)	9.5% (11774)
PVD	6.5% (13401)	4.7% (2924)	6.3% (4320)	9.0% (11774)
Presenting clinical characteristics				
GRACE score risk for 6-month mortality, median (Q1-Q3) †	85 (71-98)	82 (67-95)	96 (87-106)	91 (81-101)
GRACE risk score for 6-month mortality ≥140 †	0.3% (10331)	1.0% (2861)	0.7% (4255)	0.5% (9493)
Age 65–74 years	**(N=8710)**	**(N=4353)**	**(N=4014)**	**(N=8170)**
Demographics				
Age, median (Q1-Q3)	70 (67-72)	70 (67-72)	70 (67-72)	69 (67-72)
Female sex	37.9% (8710)	38.9% (4353)	35.3% (4014)	33.0% (8170)
White race	92.9% (8649)	94.9% (4352)	88.8% (3965)	87.7% (7946)
Past medical history				
Diabetes	24.8% (8710)	26.1% (4353)	32.6% (4014)	35.9% (8170)
Hypertension	56.7% (8710)	59.6% (4353)	72.8% (4014)	75.8% (8170)
Hypercholesterolemia	42.4% (8710)	41.2% (4353)	62.2% (4014)	61.6% (8170)
Chronic renal insufficiency	1.2% (8710)	2.2% (1586)		11.4% (5654)
Current smoking	16.6% (8696)	15.9% (4353)	17.2% (4014)	17.1% (8170)
Congestive heart failure	11.1% (8710)	9.9% (4353)	10.2% (4014)	14.5% (8170)
MI	37.6% (8710)	33.4% (4353)	30.5% (4014)	29.0% (8170)
PCI	11.9% (8710)	12.1% (4353)	22.9% (4014)	24.0% (8170)
CABG	15.2% (8710)	12.5% (4353)	18.7% (4014)	13.6% (8170)
PVD	12.0% (8710)	11.2% (1776)	11.5% (4014)	10.5% (8170)
Presenting clinical characteristics				

	Randomization Year			
	1994–1997	**1998–2001**	**2002–2005**	**2006–2010**
GRACE score risk for 6-month mortality, median (Q1-Q3)[†]	114 (102-124)	111 (99-124)	116 (106-127)	112 (103-123)
GRACE risk score for 6-month mortality ≥140[†]	6.1% (6885)	6.8% (1729)	7.1% (3956)	4.7% (6204)
Age 75–79 years	**(N=2543)**	**(N=1769)**	**(N=1611)**	**(N=2911)**
Demographics				
Age, median (Q1-Q3)	77 (76-78)	77 (76-78)	77 (76-78)	77 (76-78)
Female sex	44.4% (2543)	46.7% (1769)	41.4% (1611)	38.9% (2911)
White race	94.2% (2528)	97.2% (1768)	90.8% (1594)	90.0% (2833)
Past medical history				
Diabetes	25.0% (2543)	27.1% (1769)	32.2% (1611)	34.4% (2911)
Hypertension	57.8% (2543)	64.0% (1769)	76.8% (1611)	81.0% (2911)
Hypercholesterolemia	35.4% (2543)	35.8% (1769)	59.0% (1611)	59.4% (2911)
Chronic renal insufficiency	2.2% (2543)	2.6% (568)		15.2% (1829)
Current smoking	9.0% (2542)	6.8% (1769)	9.6% (1611)	8.5% (2911)
Congestive heart failure	16.0% (2543)	13.8% (1769)	13.2% (1611)	17.2% (2911)
MI	37.4% (2543)	36.2% (1769)	30.4% (1611)	32.9% (2911)
PCI	9.4% (2543)	12.2% (1769)	22.7% (1611)	24.3% (2911)
CABG	13.4% (2543)	13.1% (1769)	20.7% (1611)	15.4% (2911)
PVD	13.5% (2543)	13.7% (657)	12.0% (1611)	11.6% (2911)
Presenting clinical characteristics				
GRACE score risk for 6-month mortality, median (Q1-Q3)[†]	130 (118-141)	125 (115-141)	130 (121-142)	128 (118-138)
GRACE score ≥140[†]	29.0% (1998)	26.4% (640)	30.6% (1584)	21.4% (2313)
Age 80–84 years	**(N=1277)**	**(N=778)**	**(N=888)**	**(N=1603)**
Demographics				
Age, median (Q1-Q3)	82 (81-83)	82 (80-83)	82 (80-83)	82 (81-83)
Female sex	50.0% (1277)	50.6% (778)	45.7% (888)	47.1% (1603)
White race	95.4% (1275)	96.5% (778)	90.6% (883)	91.8% (1566)
Past medical history				
Diabetes	21.5% (1277)	24.8% (778)	28.2% (888)	32.5% (1603)
Hypertension	57.0% (1277)	57.1% (778)	76.4% (888)	82.5% (1603)
Hypercholesterolemia	27.1% (1277)	29.6% (778)	53.3% (888)	58.2% (1603)
Chronic renal insufficiency	3.1% (1277)	4.2% (263)		21.3% (993)
Current smoking	6.3% (1275)	4.8% (778)	6.0% (888)	5.9% (1603)
Congestive heart failure	21.8% (1277)	18.1% (778)	17.5% (888)	19.9% (1603)
MI	41.6% (1277)	42.5% (778)	30.9% (888)	32.8% (1603)
PCI	6.6% (1277)	11.2% (778)	21.8% (888)	23.6% (1603)
CABG	9.0% (1277)	10.7% (778)	18.7% (888)	16.2% (1603)
PVD	14.8% (1277)	12.3% (326)	15.2% (888)	11.2% (1603)
Presenting clinical characteristics				

	Randomization Year			
	1994–1997	**1998–2001**	**2002–2005**	**2006–2010**
GRACE score risk for 6-month mortality, median (Q1-Q3)[†]	141 (130-153)	138 (127-150)	140 (129-151)	137 (128-148)
GRACE score ≥140[†]	52.7% (1017)	44.1% (322)	51.3% (875)	43.4% (1237)
Age ≥85 years	**(N=447)**	**(N=326)**	**(N=341)**	**(N=528)**
Demographics				
Age, median (Q1-Q3)	87 (86-88)	86 (85-88)	87 (86-89)	86 (86-88)
Female sex	57.3% (447)	54.6% (326)	47.2% (341)	45.8% (528)
White race	95.0% (443)	97.2% (326)	92.9% (338)	93.0% (513)
Past medical history				
Diabetes	16.8% (447)	23.6% (326)	23.2% (341)	29.4% (528)
Hypertension	55.0% (447)	60.7% (326)	75.1% (341)	81.3% (528)
Hypercholesterolemia	23.3% (447)	21.8% (326)	49.6% (341)	55.3% (528)
Chronic renal insufficiency	3.8% (447)	5.1% (99)		26.6% (316)
Current smoking	4.9% (446)	2.8% (326)	5.6% (341)	3.2% (528)
Congestive heart failure	21.5% (447)	23.0% (326)	19.1% (341)	24.6% (528)
MI	41.8% (447)	40.8% (326)	34.0% (341)	35.8% (528)
PCI	5.8% (447)	8.0% (326)	18.2% (341)	21.0% (528)
CABG	8.3% (447)	8.3% (326)	19.4% (341)	17.0% (528)
PVD	13.9% (447)	14.2% (120)	13.2% (341)	12.5% (528)
Presenting clinical characteristics				
GRACE score risk for 6-month mortality, median (Q1-Q3)[†]	151 (139-165)	147 (134-159)	151 (141-165)	148 (138-157)
GRACE score ≥140[†]	74.3% (366)	68.9% (119)	77.7% (336)	70.0% (387)

[*] Percentage and denominator for each variable across time is reported.

[†] GRACE score for 6-month death is not available for

GUSTO IV, PRISM, PRISM PLUS and APPRAISE-2. CABG: coronary artery bypass graft, MI: myocardial infarction, PCI: percutaneous coronary intervention, Q1-Q3: first and third quartiles.

Table 3
Concomitant medications and invasive treatment by age group and time period

	Randomization Year			
	1994–1997	**1998–2001**	**2002–2005**	**2006–2010**
Age <65 years	**(N=13401)**	**(N=6377)**	**(N=4320)**	**(N=11774)**
In-hospital medications				
Aspirin	96.7% (13278) *	98.4% (6373)	95.5% (4314)	97.4% (11745)
ACE inhibitors/ARBs	26.6% (13389)	28.6% (6377)	61.2% (4314)	67.1% (4977)
Thienopyridines	14.2% (9546)	21.5% (6377)	71.1% (4319)	94.4% (11763)
Beta-blockers	75.8% (13396)	60.2% (6377)	88.8% (4315)	86.2% (11747)
GP IIb/IIIa inhibitors	35.1% (9545)	24.6% (6377)	32.9% (4318)	15.5% (11772)
Lipid-lowering drugs	21.6% (13387)	24.7% (2924)	76.8% (4320)	91.3% (11774)
Discharge medications				
Patients alive at discharge	13230	6318	4278	11663
Aspirin	69.9% (13104)	98.7% (2882)	93.8% (4274)	95.9% (11658)
ACE inhibitors/ARBs	18.3% (13221)	35.2% (2892)	58.9% (4272)	64.6% (4921)
Thienopyridines	10.9% (9430)	30.8% (2892)	63.6% (4276)	77.7% (11639)
Beta-blockers	48.6% (13225)	70.1% (2892)	83.1% (4273)	80.6% (11636)
Lipid-lowering drugs	18.3% (13219)	42.3% (2892)	80.4% (4278)	87.7% (11663)
Index hospital invasive treatments				
Catheterization	62.2% (13400)	54.3% (6375)	95.0% (4320)	77.9% (11772)
PCI	23.5% (13400)	23.0% (6375)	53.2% (4320)	51.2% (11774)
CABG	11.3% (13396)	8.6% (6375)	18.5% (4317)	8.8% (11772)
Length of stay, median (Q1-Q3)	9 (6-13)	8 (6-12)	5 (4-9)	5 (4-8)
Age 65–74 years	**(N=8710)**	**(N=4353)**	**(N=4014)**	**(N=8170)**
In-hospital medications				
Aspirin	96.5% (8605)	97.6% (4349)	95.4% (4007)	96.3% (8142)
ACE inhibitors/ARBs	34.0% (8695)	39.8% (4353)	64.9% (4003)	67.7% (4164)
Thienopyridines	12.3% (6104)	17.5% (4353)	67.7% (4014)	92.1% (8162)
Beta-blockers	72.0% (8702)	62.3% (4353)	86.1% (4011)	85.0% (8161)
GP IIb/IIIa inhibitors	35.6% (6107)	20.5% (4353)	31.7% (4013)	11.9% (8164)
Lipid-lowering drugs	18.0% (8693)	21.5% (1776)	74.9% (4014)	88.9% (8168)
Discharge medications				
Patients alive at discharge	8382	4208	3917	8031
Aspirin	71.7% (8270)	98.8% (1725)	91.8% (3917)	95.4% (8021)
ACE inhibitors/ARBs	24.7% (8373)	43.9% (1727)	61.0% (3908)	64.9% (4073)
Thienopyridines	9.8% (5876)	26.5% (1727)	58.7% (3916)	76.6% (8007)
Beta-blockers	46.8% (8377)	65.9% (1727)	80.5% (3914)	80.1% (8025)
Lipid-lowering drugs	15.1% (8371)	38.7% (1727)	77.5% (3917)	86.7% (8029)
Index hospital invasive treatments				

	Randomization Year			
	1994–1997	**1998–2001**	**2002–2005**	**2006–2010**
Catheterization	56.0% (8702)	47.3% (4352)	93.9% (4014)	73.6% (8168)
PCI	18.3% (8708)	17.2% (4353)	46.5% (4014)	45.2% (8170)
CABG	15.2% (8705)	11.3% (4353)	19.5% (4013)	10.0% (8168)
Length of stay, median (Q1-Q3)	10 (7-16)	10 (7-15)	6 (4-10)	6 (4-9)
Age 75–79 years	**(N=2543)**	**(N=1769)**	**(N=1611)**	**(N=2911)**
In-hospital medications				
Aspirin	96.9% (2517)	97.2% (1767)	94.6% (1607)	96.2% (2899)
ACE inhibitors/ARBs	36.7% (2537)	43.9% (1769)	65.0% (1607)	67.4% (1565)
Thienopyridines	9.7% (1673)	15.0% (1769)	68.3% (1610)	92.3% (2908)
Beta-blockers	68.6% (2542)	62.7% (1769)	84.7% (1611)	85.0% (2908)
GP IIb/IIIa inhibitors	31.9% (1673)	19.1% (1769)	31.2% (1611)	9.8% (2909)
Lipid-lowering drugs	12.9% (2541)	20.9% (657)	73.4% (1611)	87.6% (2910)
Discharge medications				
Patients alive at discharge	2368	1672	1546	2822
Aspirin	70.3% (2340)	99.0% (621)	89.6% (1546)	93.8% (2817)
ACE inhibitors/ARBS	25.9% (2363)	43.6% (624)	61.8% (1542)	63.7% (1512)
Thienopyridines	6.4% (1554)	26.8% (624)	59.4% (1544)	77.3% (2809)
Beta-blockers	43.8% (2368)	66.3% (624)	76.9% (1546)	78.9% (2820)
Lipid-lowering drugs	10.7% (2367)	36.5% (624)	74.1% (1546)	84.9% (2821)
Index hospital invasive treatments				
Catheterization	47.0% (2539)	44.5% (1768)	92.1% (1611)	75.3% (2910)
PCI	13.0% (2543)	16.0% (1767)	44.6% (1611)	47.0% (2911)
CABG	13.0% (2539)	10.3% (1768)	17.9% (1611)	9.3% (2910)
Length of stay, median (Q1-Q3)	10 (7-16)	10 (7-16)	7 (4-10)	6 (5-10)
Age 80–84 years	**(N=1277)**	**(N=778)**	**(N=888)**	**(N=1603)**
In-hospital medications				
Aspirin	96.6% (1259)	97.2% (778)	94.6% (887)	95.9% (1596)
ACE inhibitors/ARBs	40.2% (1277)	39.3% (778)	64.4% (888)	64.8% (907)
Thienopyridines	9.4% (773)	14.8% (778)	69.3% (888)	91.5% (1599)
Beta-blockers	63.6% (1277)	58.7% (778)	86.0% (888)	83.2% (1598)
GP IIb/IIIa inhibitors	28.2% (772)	21.0% (778)	28.2% (888)	8.6% (1602)
Lipid-lowering drugs	6.8% (1277)	19.3% (326)	68.1% (888)	85.8% (1603)
Discharge medications				
Patients alive at discharge	1174	715	840	1532
Aspirin	70.6% (1155)	98.3% (300)	90.5% (840)	94.5% (1529)
ACE inhibitors/ARBs	27.9% (1174)	44.0% (300)	58.0% (840)	62.5% (867)
Thienopyridines	6.3% (712)	25.0% (300)	62.1% (840)	77.5% (1527)
Beta-blockers	44.2% (1174)	63.3% (300)	77.6% (840)	79.5% (1526)
Lipid-lowering drugs	5.7% (1174)	32.0% (300)	70.4% (840)	84.3% (1532)

	Randomization Year			
	1994–1997	**1998–2001**	**2002–2005**	**2006–2010**
Index hospital invasive treatments				
Catheterization	33.2% (1277)	33.3% (778)	85.2% (888)	72.0% (1602)
PCI	11.1% (1277)	14.3% (778)	43.9% (888)	46.9% (1603)
CABG	7.3% (1277)	7.3% (778)	15.0% (888)	7.3% (1602)
Length of stay, median (Q1-Q3)	10 (7-15)	10 (7-15)	7 (4-11)	7 (5-10)
Age ≥85 years	**(N=447)**	**(N=326)**	**(N=341)**	**(N=528)**
In-hospital medications				
Aspirin	95.4% (439)	96.3% (326)	96.5% (340)	96.0% (527)
ACE inhibitors/ARBS	35.3% (447)	45.1% (326)	65.2% (339)	63.4% (333)
Thienopyridines	6.6% (256)	15.6% (326)	69.5% (341)	89.5% (526)
Beta-blockers	66.0% (447)	53.1% (326)	83.0% (341)	82.7% (526)
GP IIb/IIIa inhibitors	32.0% (256)	16.0% (326)	23.8% (340)	7.2% (528)
Lipid-lowering drugs	5.6% (447)	10.0% (120)	63.3% (341)	82.8% (528)
Discharge medications				
Patients alive at discharge	397	297	313	494
Aspirin	74.9% (391)	98.2% (110)	91.3% (312)	94.1% (493)
ACE inhibitors/ARBs	26.2% (397)	50.9% (110)	57.6% (311)	58.9% (314)
Thienopyridines	5.7% (230)	26.4% (110)	60.9% (312)	78.9% (492)
Beta-blockers	46.1% (397)	54.5% (110)	75.7% (313)	76.9% (493)
Lipid-lowering drugs	4.8% (397)	20.9% (110)	66.1% (313)	79.4% (494)
Index hospital invasive treatments				
Catheterization	22.1% (447)	27.3% (326)	76.5% (340)	64.8% (528)
PCI	8.3% (447)	10.7% (326)	40.5% (341)	39.8% (528)
CABG	4.5% (447)	4.3% (326)	8.5% (340)	2.7% (528)
Length of stay, median (Q1-Q3)	9 (7-15)	10 (7-15)	6 (4-11)	7 (5-10)

*Percentage and denominator for each variable across time is reported. ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; Q1-Q3: first and third quartiles.

Table 4
Clinical outcomes by age according to randomization year

	Randomization Year			
	1994–1997	**1998–2001**	**2002–2005**	**2006–2010**
Age <65 years	**(N=13401)**	**(N=6377)**	**(N=4320)**	**(N=11774)**
Death *				
In-hospital death	1.3% (13401)	0.9% (6377)	0.9% (4318)	0.8% (11758)
30-day death	1.6% (13401)	1.4% (6377)	1.2% (4320)	0.9% (11774)
Kaplan-Meier rates †				
6-month death	331 (3.0%)	82 (2.8%)	108 (2.5%)	212 (1.9%)
6-month death among patients with GRACE score available‡	293 (2.9%)	81 (2.9%)	108 (2.5%)	165 (1.8%)
1-year death	351 (3.8%)	98 (3.6%)	144 (3.4%)	298 (2.7%)
Age 65–74 years	**(N=8710)**	**(N=4353)**	**(N=4014)**	**(N=8170)**
Death *				
In-hospital death	3.8% (8709)	3.3% (4353)	2.4% (4012)	1.5% (8157)
30-day death	4.3% (8710)	3.9% (4353)	2.7% (4014)	1.7% (8170)
Kaplan-Meier rates †				
6-month death	557 (7.5%)	105 (6.0%)	214 (5.3%)	269 (3.4%)
6-month death among patients with GRACE score available‡	495 (7.2%)	102 (5.9%)	210 (5.3%)	208 (3.4%)
1-year death	581 (9.2%)	129 (7.8%)	291 (7.3%)	371 (5.0%)
Age 75–79 years	**(N=2543)**	**(N=1769)**	**(N=1611)**	**(N=2911)**
Death *				
In-hospital death	6.8% (2542)	5.5% (1769)	4.0% (1611)	2.8% (2903)
30-day death	7.7% (2542)	6.3% (1769)	5.0% (1611)	3.2% (2911)
Kaplan-Meier rates †				
6-month death	284 (13.0%)	62 (9.5%)	138 (8.6%)	180 (6.5%)
6-month death among patients with GRACE score available‡	242 (12.2%)	61 (9.6%)	133 (8.4%)	152 (6.7%)
1-year death	278 (14.6%)	72 (11.6%)	180 (11.2%)	231 (8.6%)
Age 80–84 years	**(N=1277)**	**(N=778)**	**(N=888)**	**(N=1603)**
Death *				
In-hospital death	8.1% (1277)	8.1% (778)	5.4% (888)	3.8% (1593)
30-day death	8.9% (1277)	9.5% (778)	6.3% (888)	3.4% (1603)
Kaplan-Meier rates †				
6-month death	194 (17.6%)	42 (12.9%)	91 (10.3%)	125 (8.2%)
6-month death among patients with GRACE score available‡	172 (17.0%)	40 (12.5%)	89 (10.2%)	101 (8.3%)
1-year death	204 (21.1%)	54 (18.2%)	128 (14.5%)	176 (12.1%)

	Randomization Year			
	1994–1997	1998–2001	2002–2005	2006–2010
Age ≥85 years	**(N=447)**	**(N=326)**	**(N=341)**	**(N=528)**
Death *				
In-hospital death	11.2% (447)	8.9% (326)	8.2% (341)	5.5% (523)
30-day death	13.0% (447)	11.7% (326)	11.1% (341)	5.1% (528)
Kaplan-Meier rates †				
6-month death	98 (24.8%)	21 (17.6%)	60 (17.6%)	63 (12.6%)
6-month death among patients with GRACE score available‡	84 (23.1%)	21 (17.7%)	59 (17.6%)	49 (13.1%)
1-year death	94 (26.5%)	29 (26.6%)	83 (24.4%)	88 (18.8%)

*Percentage and denominator for in-hospital and 1-month mortality across time is reported.

†Kaplan-Meier rates are reported for 6-month and 1-year mortality outcomes, as 6-month follow-up is not complete in GUSTO IV and PRISM and 1-year mortality is not complete in GUSTO IV, PRISM, and PRISM PLUS.

‡GRACE score was not available in GUSTO IV, PRISM, PRISM PLUS, and APPRAISE-2.