Effects of platelet glycoprotein IIb/IIIa receptor blockers in non-ST-segment elevation acute coronary syndromes: Benefit and harm in different age subgroups

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Running head: Effects of GP IIb/IIIa blockers by age in NSTE-ACS

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ABSTRACT

Objective*:* To investigate whether beneficial and harmful effects of platelet glycoprotein (GP) IIb/IIIa receptor blockers in non-ST-elevation acute coronary syndromes (NSTE-ACS) depend on age.

Methods: A meta-analysis of 6 trials of GP IIb/IIIa receptor blockers in NSTE-ACS patients (PRISM, PRISM-PLUS, PARAGON-A, PURSUIT, PARAGON-B, GUSTO IV-ACS; n=31,402) was performed. We applied multivariable logistic regression analyses to evaluate the drug effects on death or non-fatal MI at 30 days, and on major bleeding, by age subgroups (<60, 60-69, 70-79, ≥80 years). We quantified the reduction of death or MI as number needed to treat (NNT), and the increase of major bleeding as number needed to harm (NNH).

Results: Subgroups had 11,155 (35%), 9,727 (31%), 8,468 (27%), and 2,049 (7%) patients, respectively. The relative benefit of GP IIb/IIIa receptor blockers did not differ significantly (p=0.5) across age subgroups (odds ratio [95% CI] for death or MI: 0.86 [0.74-0.99], 0.90 [0.80-1.02], 0.97 [0.86-1.10], 0.90 [0.73-1.16]; overall 0.91 [0.86-0.99]). Odds ratios for major bleeding were 1.9 (1.3-2.8), 1.9 (1.4-2.7), 1.6 (1.2-2.1), and 2.5 (1.5-4.1). Overall NNT was 105, and overall NNH was 90. The oldest had larger absolute increases in major bleeding, but also had the largest absolute reductions of death or MI. Patients ≥80 years had half of the NNT and a third of the NNH in comparison with patients <60 years.

Conclusions: In patients with NSTE-ACS, the relative reduction of death or non-fatal MI with GP IIb/IIIa receptor blockers was independent of patient age. Larger absolute outcome reductions were seen in the elderly, but with a higher risk of major bleeding. A close monitoring of these patients is warranted.

Platelet glycoprotein (GP) IIb/IIIa receptor blockers decrease the risk of death or non-fatal myocardial infarction (MI) at 30 days in patients with non-ST elevation acute coronary syndromes (NSTE-ACS) who are not routinely scheduled for early revascularization [1-4]. Age is an important risk factor for these patients, and if the relative benefits of effective interventions are the same across age groups, physicians should treat the elderly even more aggressively than the younger, since the absolute benefit may be larger [5]. However, in clinical practice, the utilization of GP IIb/IIIa receptor blockers is lower among elderly patients [6].

Elderly patients may be undertreated because of several reasons: they were underrepresented or excluded from randomized clinical trials (RCTs), clinicians may believe that benefits in younger may not generalize to the elderly, or they may be worried about harmful effects in elderly patients [5]. Researchers have argued that the benefit of GP IIb/IIIa receptor blockers is greater in younger patients [7], similar in old and younger patients [8], or greater in older patients given their higher baseline risk [5, 9].

Yet, it is difficult to determine how the efficacy of GP IIb/IIIa receptor blockers varies among age subgroups because most trials are not large enough to provide a reliable answer. Individual ACS trials have been inconclusive or even conflicting regarding the presence or absence of relative differences in drug effects across ages [10-15]. Usually, the patient population was only split in two age groups (e.g. <65 years, ≥65 years) [11, 13-15], and different primary endpoints were considered. An evaluation of the drug effects across age groups in a meta-analysis using individual data can better define its relative and absolute efficacies in older vs. younger patients.

One more issue is relevant in the interpretation of the effects of GP IIb/IIIa receptor blockers by age groups. The incorporation of harmful major bleeding rates in the evaluation of effects should be considered to further understand the net drug effectiveness across age strata [5, 9, 16].

We investigated whether the relative effects of GP IIb/IIIa receptor blockers were consistent across age subgroups in non-ST-segment elevation ACS patients. Further, we evaluated whether the absolute benefits and harms differed across age subgroups.

METHODS

Trial selection

A meta-analysis of individual patient data was performed, including trials reported since 1990 with the following characteristics: randomization of patients with NSTE-ACS, comparison of a GP IIb/IIIa receptor blocker with placebo or control therapy, no-recommendation for early (<48h) coronary revascularization during study-drug infusion, and enrolment of at least 1000 patients. Six trials met the inclusion criteria -PRISM, PRISM-PLUS, PARAGON-A, PURSUIT, PARAGON-B, and GUSTO IV-ACS- [10-15] with a total of 31,402 patients. Details of the trial designs are available elsewhere [3].

Patient baseline characteristics

An electronic database consisting of data from individual patients in all eligible trials was available [3]. These data were checked for completeness, for internal consistency of patients' records, and for consistency with the published reports. For this analysis, baseline characteristics regarded as important predictors of the outcome for which information was almost complete (i.e. less than 1% missing) were age, gender, diabetes, smoking, previous myocardial infarction [MI], previous heart failure [HF], previous coronary artery bypass surgery (CABG), previous percutaneous coronary intervention (PCI), and ST-segment depression. Other important predictors had more than 20% of missing data: blood pressure and heart rate were not recorded in the GUSTO IV-ACS trial (n=7800, 25%); and baseline creatine kinase MB (CK-MB) was missing in 7469 patients (24%) across different trials. Blood pressure, heart rate and CK-MB were used in addition to the other predictors in secondary analyses that yielded largely similar results.

Endpoints

For this analysis, the primary efficacy endpoint was defined *a priori* as the composite of death of any cause or non-fatal MI at 30 days. MI was part of the composite outcome of all trials. The MI definitions had subtle differences across trials regarding the CK-MB threshold [3] (Table 1). However, all trials had pre-specified definitions of MI [17, 18]. Secondary endpoints were: death; non-fatal MI; coronary artery bypass graft (CABG); percutaneous coronary intervention (PCI); and CABG or PCI. The primary harm endpoint was major bleeding within 30 days. Individual trial definitions of major bleeding had also at most subtle differences, and trial-specific definitions were retained [3]. We should acknowledge that death or non-fatal MI and major bleeding do not have the same utility, and therefore are not comparable events. A few patients with major bleeding die or have an MI within 30 days, and not all of the remaining patients have long-term negative outcomes. Determining the relative weights of these events is largely subjective. A recent review identified that the weight of a major bleeding related to a drug in the context of an acute coronary syndrome was 0.87, in comparison with the weight of death, which was equal to zero [19].

Table 1: Definitions of primary efficacy and harm endpoints across trials

	PRISM	PRISM-PLUS	PARAGON-A	PURSUIT	PARAGON-B	GUSTO ACS-IV
Primary efficacy end point	Death, MI or refractory ischemia at 48 hours	Death, MI or refractory ischemia at 7 days	Death of MI at 30 days	Death or MI at 30 days	Death, MI or severe, recurrent ischemia at 30 days	Death or MI at 30 days
Required level of CK or CK-MB elevation in MI definition	2xULN	2xULN; in relation to PCI: 3xULN	2xULN	1xULN; in relation to PCI: 3xULN; in relation to CABG: 5xULN	2xULN; in relation to PCI: 3xULN; in relation to CABG: 5xULN	3xULN
Primary harm end point: major bleeding	Intracraneal hemorrhage; bleeding leading to decrease in hemoglobin concentration ≥50 g/L; or cardiac tamponade	Intracraneal hemorrhage; bleeding leading to decrease in hemoglobin concentration ≥40 g/L; bleeding requiring transfusion ≥2 units blood; or bleeding requiring surgery	Intracraneal hemorrhage; bleeding leading to hemodynamic compromise requiring intervention	Intracraneal hemorrhage; bleeding leading to hemodynamic compromise requiring intervention	Intracraneal hemorrhage; bleeding leading to hemodynamic compromise requiring intervention	Intracraneal hemorrhage; bleeding leading to decrease in hemoglobin concentration ≥ 50 g/L

MI: myocardial infarction; CK: creatine kinase; CK-MB: creatine kinase fraction MB; ULN: Upper limit of normal; PCI: Percutaneous coronary intervention; CABG: Coronary-artery bypass graft

Efficacy analysis by age

We divided the patient data into four subgroups according to age: <60, 60-69, 70-79, and ≥80 years old. The decision to group patients in these intervals was made a priori, and was based on decade intervals of common clinical use. The choice of other cut-off points (e.g. quartiles) yielded similar results (not shown). Relative differences between GP IIb/IIIa receptor blockers and placebo/control on the primary endpoint by age subgroups were assessed, within each trial and across all trials. Logistic regression models were used, and odds ratios (OR) and corresponding 95% confidence intervals (95% CI) were calculated. To evaluate GP IIb/IIIa receptor blocker effect modification by age in each individual trial and in all trials, interaction tests were used [20]. These tests also evaluated heterogeneity of effects across trials. The effects of GP IIb/IIIa receptor blockers and the interactions were adjusted for the previously described predictors, for trial, and for potential differences in age-related trends between trials. These effects were combined using random effects calculations [21]. Heterogeneity of interactions across trials was evaluated with the random effects inverse variance model (with trial being the random effect) [22].

Benefit and harm of GP IIb/IIIa receptor blockers by age subgroups

We performed analyses that incorporated the relation among the baseline risk (eBR, proportion of patients in the placebo/control group with the primary efficacy endpoint), the efficacy Odds Ratio (eOR), and the respective number needed to treat [NNT]. The calculation of NNT was done using eBR and eOR, with the formula: [1-eBR(1-eOR)]/ [eBR(1-eBR)(1-eOR)] [22]. The NNT is the number of patients who need to be treated in order to prevent one additional death or non-fatal MI. It is the inverse of the absolute risk reduction (ARR). Further, we looked at the relation among the baseline proportion of the primary harm endpoint in the placebo/control group (hBR), the harm Odds Ratio (hOR), and the respective number needed to harm [NNH]. The NNH was calculated using hBR and hOR, with the formula: [hBR(hOR-1)+1]/[hBR(1-hBR)(hOR-1)] [23]. The NNH is the number of patients who need to be treated in order to cause one major bleeding. It is the inverse of the absolute risk increase (ARI). The NNT and NNH calculations were done overall and by age subgroups.

Role of the funding source

The trials included in this analysis were sponsored by several pharmaceutical companies, which are mentioned in the main trial reports [10-15], and in the acknowledgements. This study was designed, conducted, and interpreted independently of the sponsors. These had the right to review the manuscript, but not censor the findings. No separate industrial grant was obtained for this investigation.

RESULTS

Age subgroups and predictors

Overall, 11,155 (35%) patients were < 60, 9,727 (31%) were 60-69, 8,468 (27%) were 70-79, and 2,049 (7%) were ≥ 80 years-old. Baseline characteristics across age subgroups are shown in Table 2.

Table 2. Patient characteristics by age subgroups.

	<60 years (n=11,155)		60-69 years (n=9,727)		70-79 years (n=8,468)		≥80 years (n=2,049)	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Gender								
Male	8275	74	6274	65	4841	57	997	49
Diabetes								
Yes	1771	16	2360	24	2269	27	461	23
Smoking								
Never	3931	35	3439	36	3269	39	861	42
Former	3144	28	3537	37	3133	37	621	31
Current	4036	36	2709	28	2015	24	552	27
Previous MI								
Yes	3164	28	3445	36	3162	37	877	43
Previous HF								
Yes	578	5	962	10	1191	14	437	21
Previous CABG								
Yes	1088	10	1305	13	1194	14	185	9
Previous PCI								
Yes	1454	13	1251	13	956	11	162	8
ST depression								
Yes	5096	46	5475	57	5441	65	1403	69
Trial								
PRISM	1274	11	1005	10	781	9	172	8
PRISMPLUS	693	6	603	6	495	6	124	6
PARAGON-A	737	7	728	8	631	8	183	9
PURSUIT	4082	37	3553	37	2763	33	550	27
PARAGON-B	1976	18	1513	16	1374	16	362	18
GUSTO IV	2393	21	2325	24	2424	29	658	32

MI denotes myocardial infarction, HF: heart failure, CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention, y: years. Differences among age subgroups were highly significant ($p<0.001$).

Table 3. Treatment effect on various endpoints at 30 days according to age subgroups.

	<60y (n=11,155)			60-69y (n=9,727)			70-79y (n=8,468)			≥80y (n=2,049)		
	Events	%	OR* (95% CI)	Events	%	OR (95% CI)	Events	%	OR (95% CI)	Events	%	OR (95% CI)
Death†												
GP IIb/IIIa	70	1.1	0.86	165	2.9	0.98	281	5.6	0.91	115	9.5	0.90
Placebo/Control	58	1.2	(0.61-1.23)	124	3.0	(0.77-1.24)	215	6.2	(0.75-1.09)	88	10.5	(0.67-1.21)
Nonfatal MI‡												
GP IIb/IIIa	372	5.7	0.83	428	7.6	0.85	437	8.8	1.02	112	9.3	0.91
Placebo/Control	316	6.8	(0.72-0.97)	365	8.8	(0.74-0.99)	299	8.6	(0.87-1.19)	85	10.1	(0.68-1.23)
Death or MI												
GP IIb/IIIa	442	6.8	0.86	593	10.6	0.90	718	14.4	0.97	227	18.8	0.90
Placebo/Control	374	8.0	(0.74-0.99)	489	11.9	(0.80-1.02)	514	14.8	(0.86-1.10)	173	20.5	(0.73-1.16)
CABG												
GP IIb/IIIa	828	12.7	1.00	931	16.6	0.92	860	17.2	0.99	102	8.5	1.07
Placebo/Control	590	12.7	(0.90-1.13)	732	17.7	(0.83-1.03)	603	17.3	(0.88-1.11)	67	8.0	(0.77-1.47)
PCI												
GP IIb/IIIa	1839	28.3	0.92	1369	24.4	1.02	894	17.9	0.89	171	14.2	0.90
Placebo/Control	1404	30.1	(0.84-0.99)	991	24.0	(0.93-1.12)	684	19.7	(0.80-1.00)	131	15.6	(0.70-1.15)
CABG or PCI												
GP IIb/IIIa	2618	40.3	0.93	2264	40.4	0.97	1721	34.5	0.93	268	22.2	0.93
Placebo/Control	1960	42.1	(0.86-1.00)	1699	40.8	(0.89-1.05)	1258	36.2	(0.85-1.02)	197	23.4	(0.76-1.15)
Major bleeding												
GP IIb/IIIa	90	1.5	1.90	118	2.3	1.94	174	3.8	1.58	63	5.7	2.46
Placebo/Control	35	0.8	(1.28-2.81)	46	1.1	(1.38-2.74)	80	2.3	(1.21-2.07)	19	2.3	(1.46-4.14)

* Odds ratio of treatment effect between GP IIb/IIIa and Placebo/Control, GP IIb/IIIa denotes platelet glycoprotein IIb/IIIa receptor blockers; †Death within 30 days; ‡ Non-fatal myocardial infarction in patients who survived at least 30 days. Number of patients per age group: <60 y: GP 6496, Placebo/control 4659; 60-69 y: GP 5602, Placebo/control 4125; 70-79 y: GP 4991, Placebo/control 3477; >80 y: GP: 1207, Placebo/control: 842.

Table 4. Treatment effects on death or MI at 30 days according to age subgroups, by trial and overall.

	PRISM N=3,232	PRISMPLUS N=1,915	PARAGON-A N=2,282	PURSUIT N=10,948	PARAGON-B N=5,225	GUSTO IV-ACS N=7,800	TOTAL* N=31,402
Age <60 years							
OR (95% CI)	1.13 (0.66-1.96)	0.98 (0.54-1.78)	1.65 (0.83-3.30)	0.72 (0.59-0.88)	0.90 (0.64-1.27)	1.01 (0.65-1.55)	0.86 (0.74-0.99)
Age 60-69 years							
OR (95% CI)	0.86 (0.53-1.38)	0.58 (0.35-0.96)	0.87 (0.55-1.39)	0.93 (0.77-1.20)	0.81 (0.59-1.12)	1.19 (0.85-1.67)	0.90 (0.80-1.02)
Age 70-79 years							
OR (95% CI)	0.63 (0.36-1.09)	1.02 (0.61-1.70)	0.83 (0.53-1.31)	0.91 (0.76-1.11)	1.11 (0.82-1.50)	1.15 (0.88-1.50)	0.97 (0.86-1.10)
Age ≥80 years							
OR (95% CI)	0.45 (0.19-1.07)	0.94 (0.39-2.27)	0.82 (0.37-1.81)	1.27 (0.87-1.86)	0.84 (0.48-1.47)	0.80 (0.52-1.22)	0.90 (0.73-1.16)
All subgroups, adjusted for predictors†	0.80 (0.60-1.06)	0.83 (0.62-1.11)	0.95 (0.72-1.25)	0.88 (0.79-0.98)	0.92 (0.78-1.10)	1.07 (0.90-1.27)	0.91 (0.86-0.99)
Age by GP IIb/IIIa Interaction (p)‡	0.01	0.77	0.15	0.03	0.92	0.52	0.15

* Odds ratios of each age subgroup adjusted for trial.
† Predictors included: age, gender, diabetes, smoking, previous MI, previous heart failure, previous CABG, previous PTCA, ST depression.
‡ Odds ratios adjusted for predictors, and age trend. The interactions age by GP IIb/IIIa are significantly different among trials. p: p-value.

The proportion of women and of patients with a history of diabetes, MI or HF, and ST depression increased with age. Further, patients ≥80 years had lower proportions of previous revascularisation procedures than younger patients. The proportion of patients older than 70 years ranged between 30% in the PURSUIT and PRISM trials and 40% in the GUSTO IV-ACS trial.

Endpoints at 30 days by age subgroups

The overall adjusted relative reduction in the odds of death or MI at 30 days was 9% (OR 0.91; 95% CI [0.85-0.99]). There was no difference in the relative benefit of GP IIb/IIIa receptor blockers across age subgroups (p for interaction = 0.5) and this was true also for secondary efficacy endpoints (Table 3). Interestingly, the ratio of non-fatal MI over death decreased with increasing age. The overall adjusted relative increase in the odds of major bleeding was 83% (OR 1.83 [1.5-2.2]). This was especially high for patients ≥80 years (OR 2.5 [1.5-4.1]), but there were no significant differences across ages (p for interaction=0.3) (Table 3).

Benefit of GP IIb/IIIa receptor blockers per trial by age subgroups

With regard to the incidence of death or non-fatal MI, two trials showed significantly different relative effects across age subgroups, but in opposite directions (Table 4). The PRISM trial patients had a clear gradient of GP IIb/IIIa receptor blocker effect across ages: older patients had larger odds reductions than younger ones (p for interaction=0.01). Conversely, younger PURSUIT patients had larger odds reductions than the older ones (p for interaction=0.03). The interactions between GP IIb/IIIa receptor blockers and age subgroup were heterogeneous across trials (p=0.002).

Benefit and harm of GP IIb/IIIa receptor blocker across age subgroups

The absolute risk of death or MI at 30 days correlated with age, varying from 8% in the youngest (<60 years) to 21% in the oldest group (≥80 years). Major bleeding at 30 days also correlated with age, from 0.8% in the youngest to 2.3% in the oldest. For the overall relative reduction in the odds of death or MI of 9%, the NNT was 105. For the overall relative increase in the odds of major bleeding of 83%, the NNH was 90.

The oldest patients had the largest absolute reductions of death or MI, but also had larger absolute increases in major bleeding. Patients younger than 70 years had higher NNTs and NNHs (149 and 163 for those younger than 60 years, and 105 and 110 for those between 60 and 69 years) than those older than 70 years (87 and 55 for those between 70 and 79 years, and 67 and 56 for those older than 80 years). Figure 1 shows the absolute event rate difference between GP IIb/IIIa receptor blocker and placebo/control arms across age subgroups. We noted a rather larger harm in patients ≥70 years and a somewhat variable benefit across all age subgroups.

DISCUSSION

In patients with ACS without ST elevation, the relative reduction in the odds of death or MI at 30 days with GP IIb/IIIa receptor blockers was largely independent of age. The oldest patients had about 3-fold the baseline risk of the youngest ones, not only for death or MI, but also for major bleeding. In the oldest patients, the use of GP IIb/IIIa receptor blockers yielded larger absolute reductions of death/MI, but also larger absolute increases in major bleeding rates in comparison with the youngest patients.

This meta-analysis had more statistical power than individual trials to explore how the GP IIb/IIIa receptor blocker effects vary by age [7-9, 24]. Individual trials did not report these effects in detail across similar age subgroups [10, 11, 13-15], and they analyzed different endpoints. Previous analyses of the age effects in single trials have yielded inconclusive results [25]. Only the PURSUIT and GUSTO IV-ACS reported the same primary endpoint as we used in this paper. Also, these analyses did not adjust for important predictors of the primary endpoint. We found that the PRISM and the PURSUIT trials showed significant differential relative effects of GP IIb/IIIa receptor blockers across ages, but differences were in the opposite direction. We do not fully understand this phenomenon. We speculate that it could be related to the doses used as well as the duration of the study drug infusion. This might have resulted in different levels of platelet inhibition in the PRISM trial (where the dose was later shown to produce suboptimal platelet inhibition in young patients) as compared to the PURSUIT trial (where the dose was not adjusted for older age or modest renal impairment), which might have had different consequences in younger and older patients.

The effects of other antithrombotics have been evaluated in elderly patients with unstable angina or NSTE-ACS [9]. The low molecular weight heparin enoxaparin, compared with unfractionated heparin, appeared to have greater relative and absolute benefit in patients aged 65 years and older, as compared with younger patients. When comparing clopidogrel plus aspirin to aspirin alone, there was a consistent 20% relative reduction in cardiovascular death, myocardial infarction, or stroke in both elderly and younger patients. For GP IIb/IIIa receptor blockers, we found an equivalent relative benefit across age subgroups, which translated into a greater absolute benefit in older in comparison with younger patients.

In order to describe the relative gain in primary efficacy end points by age subgroups, we defined a ratio of reduction of non-fatal MIs to reduction of deaths. For instance, a ratio higher than 1 shows a larger benefit in reduction of non-fatal MIs in comparison to reduction of deaths. Given that the ratio of non-fatal MI to death decreased with increased age, the use of GP IIb/IIIa receptor blockers in the oldest likely aborted more deaths than non-fatal MIs.

Most trials, meta-analyses, and systematic reviews have neglected the contribution of major bleeding rates in the evaluation of the net GP IIb/IIIa receptor blocker effectiveness across age subgroups in NSTE-ACS patients [1-4, 10-15, 26-31]. Elderly patients have higher absolute risks of major bleeding [6, 32]. Therefore, the interpretation of the overall GP IIb/IIIa receptor blocker efficacy needs to incorporate this harm. Although there was a trend for increasing bleeding risk with increasing age, this was nowhere close to being statistically significant, and it should be interpreted cautiously given the small number of patients in the highest age category.

An appropriate dosing of GP IIb/IIIa receptor blockers is a requisite to obtain a higher benefit and a lower harm in elderly NSTE-ACS patients. The CRUSADE registry demonstrated that GP IIb/IIIa receptor blockers were underutilized and mis-dosed in elderly patients, who are at higher risk for adverse cardiac events [33]. An essential factor that increases the risk of major bleeding in elderly patients is low renal function, which is associated with higher serum levels of GP IIb/IIIa receptor blockers. Doses used in early trials were more aggressive than currently recommended doses, which are adjusted for renal dysfunction. Thus, elderly NSTE-ACS patients should receive adequate doses of GP IIb/IIIa receptor blockers to obtain the expected clinical benefit, and these doses should be adjusted for their level of renal function to avoid major bleeding events.

A recent decision analysis evaluated the efficacy of an unspecified potential drug on survival in patients with MI and unstable angina [5], and included serious adverse events (fatal complications) as

an element of the evaluation of benefit-risk balance by age-related baseline risks. The authors used a registry database, and a hard primary endpoint (mortality at 1 year). The estimate of effectiveness was larger than in our randomized data (relative risk reduction 25%, absolute risk reduction 2%), and the registry population was more heterogeneous in risk (baseline risk of 2.3% in the youngest vs.27% in the oldest). They defined a threshold beyond which the treatment benefit would be outclassed by the treatment harm, and found that the fatal complication rate would have to be sevenfold greater in the oldest compared with the youngest age group to outweigh the survival benefits associated with treatment. These results need to be interpreted cautiously given that most major events in these patients do not lead to death. Moreover, retrospective observational data may sometimes inflate estimates of treatment efficacy [34].

Some limitations should be acknowledged. First, even with over 30,000 randomised patients, subtle age interactions could have been missed, especially for rare events such as death. We did not see any age interactions for death based on the available data (not reported) and the clinical significance of subtle interactions is debatable. Second, the total number of patients in the ≥80 age subgroup (n=2049) was small, and less than 25% of each of the other three groups (n>8400). Third, a substantial amount of missing values for a few important predictors (blood pressure, heart rate, CK-MB) limited some possibilities of adjusted analysis. However, the results with imputed data yielded similar conclusions (not shown). Fourth, additional research into the appropriate weighting of events is needed, that can allow a more direct comparison between benefits and harms.

A series of nuances should be considered in interpreting these results. The trials included broad populations of patients with ACS. Through analysis of subgroups, it seems evident that higher risk patients, such as those with positive troponins, diabetes, and perhaps ST segment depression, achieve the greatest benefit. Further, it is likely that patients treated with the aggressive revascularisation strategy achieve more benefit than those treated with the conservative strategy. The trials themselves were heterogeneous, as GUSTO IV-ACS showed no benefit and perhaps a detriment of abciximab, and PURSUIT used a very liberal definition of myocardial infarction that minimized the differences between eptifibatide and placebo. Finally, the category of major bleeding overestimates risk relative to the risk of blood transfusion, which is a more direct measure of risk and occurs less frequently (Mahaffey KW et al., Circulation, in press). The EARLY ACS trial is enrolling patients without age limits, it is testing whether the benefit of antithrombotic drugs is similar between elderly and young patients, and it is also addressing each of the above issues [35]. Allowing for these caveats, our analysis provides estimates for NNTs and NNHs by age subgroups that may be used in clinical decision making for the use of GP IIb/IIIa receptor blockers in NSTE-ACS patients.

In conclusion, the relative risk reduction of death or MI with GP IIb/IIIa receptor blocker is independent of age in patients with non-ST-elevation acute coronary syndromes. Larger absolute reductions of death or MI were observed in the oldest in comparison with the youngest patients, as well as larger absolute increases in major bleeding rates. Attention should be given to optimizing the benefit to elderly patients without increasing bleeding, by ensuring that doses adjusted for renal function are given. Moreover, elderly patients should be monitored more intensively.

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CONFLICT OF INTEREST STATEMENT

D J Moliterno is a consultant for Merck, Centocor, and Eli Lilly, and has received honoraria from the same, as well as from Roche. H White is a consultant for and has received honoraria from Merck. P Théroux was principal investigator and chairman of the Steering Committee for the PRISM-PLUS trial. P W Armstrong has received research grants and honoraria from Eli Lilly and Schering-Plough. R M Califf has worked with Centocor, Lilly, COR, Schering-Plough, and Merck. M L Simoons is a consultant for Merck, Centocor, and Lilly, and has provided paid expert testimony to Schering-Plough.

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FIGURE LEGEND

Figure 1. Absolute event rate differences between treatment arms (GP IIb/IIIa vs. placebo/control) by age subgroups in beneficial (death or myocardial infarction) and harmful (major bleeding) endpoints. GP IIb/IIIa denotes platelet glycoprotein IIb/IIIa receptor blockers.

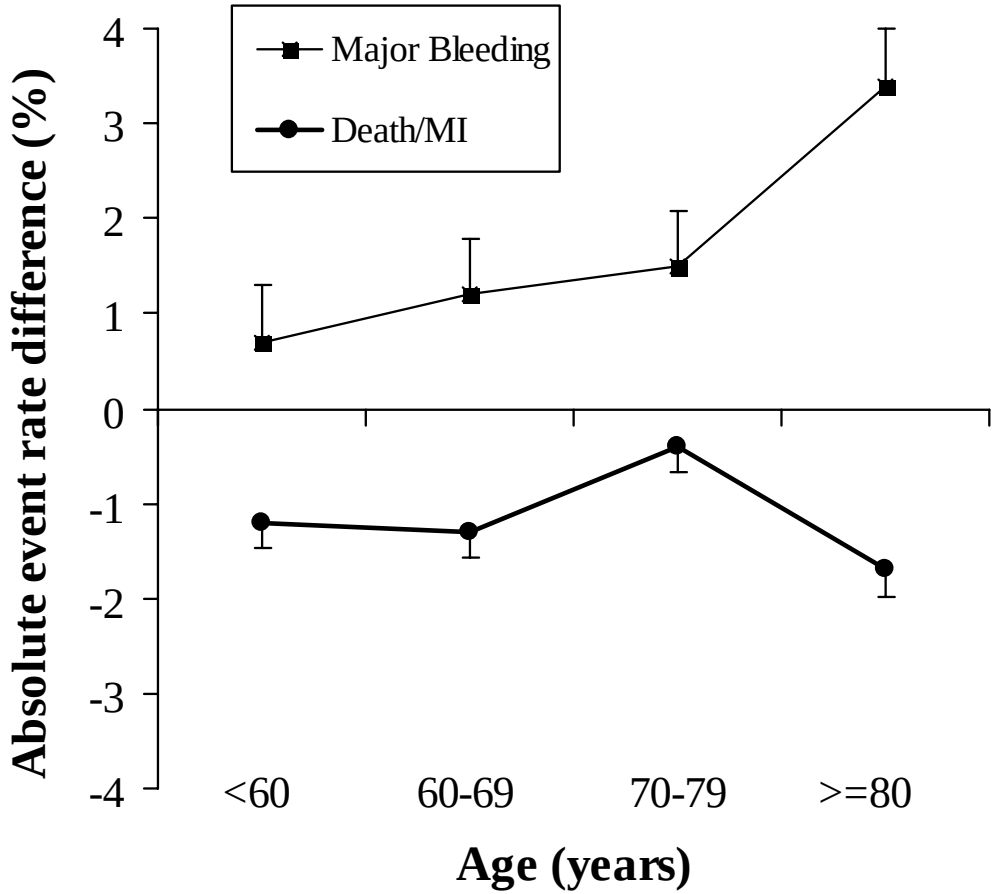

Figure 1