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Efficacy and Safety of Glycoprotein IIb/IIIa Inhibitors During Elective Coronary Revascularization

A Meta-Analysis of Randomized Trials Performed in the Era of Stents and Thienopyridines

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Objectives The purpose of this study was to investigate the efficacy and safety of glycoprotein IIb/IIIa inhibitors (GPIs) during elective percutaneous coronary intervention (PCI).

Background Studies have documented that GPIs are useful during PCI; however, much of this research was conducted before the routine use of coronary stents and thienopyridines.

Methods We searched the MEDLINE, Cochrane clinical trials, and ClinicalTrials.gov databases from inception for studies that randomly assigned patients undergoing elective PCI to a GPI versus control. Trials were included if stents and thienopyridines were used routinely and clinical outcomes were reported. Outcomes were assessed within 30 days. A DerSimonian-Laird model was used to construct random effects summary risk ratios (RRs) and 95% confidence intervals (CIs).

Results Our search yielded 22 studies with 10,123 patients. The incidence of nonfatal myocardial infarction was 5.1% with GPI versus 8.3% with control (RR: 0.66, 95% CI: 0.55 to 0.79, $p < 0.0001$). Major bleeding was 1.2% versus 0.9% (RR: 1.37, 95% CI: 0.83 to 2.25, $p = 0.22$), minor bleeding was 3.0% versus 1.7% (RR: 1.70, 95% CI: 1.28 to 2.26, $p < 0.0001$), and mortality was 0.3% versus 0.5% (RR: 0.70, 95% CI: 0.36 to 1.33, $p = 0.27$), respectively.

Conclusions In the current era of elective PCI performed with stents and thienopyridines, GPIs provide clinical benefit. These agents reduce nonfatal myocardial infarction without a notable increase in major bleeding; however, they increase the risk of minor bleeding. All-cause mortality is not reduced. (J Am Coll Cardiol 2011;57:1190–9)

Elective percutaneous coronary intervention (PCI) is commonly performed to relieve angina. The risks of PCI include both thrombotic and bleeding events. Antiplatelet agents such as aspirin, thienopyridines, and glycoprotein IIb/IIIa inhibitors (GPIs) are available for use, as are antithrombin agents, which include heparin and bivalirudin. Determining the optimal regimen of adjunctive medications is critical to minimize thrombotic events without increasing major bleeding.

Initial trials demonstrated that GPIs reduce myocardial infarction (MI) and urgent revascularization after angioplasty (1–3). Other advances, such as stents and thienopyridines, also have become available that independently enhance the safety of revascularization (4–9). Some modern trials and systematic reviews, specifically in patients pre-treated with thienopyridines, have failed to demonstrate the benefit of GPIs during elective PCI (10–12). Thus, disagreement still exists about the optimal use of GPIs during elective PCI (13,14). We hypothesized that in elective PCI performed with coronary stents and thienopyridines, GPIs will have minimal benefit and will increase the risk of major bleeding.

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Methods

Selection criteria. We selected studies that randomly assigned patients undergoing elective PCI to a GPI versus control in which the control could be: (1) placebo, or (2) usual care (without a GPI).

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To focus on the current era of PCI, we required that included studies routinely used coronary stents and periprocedural thienopyridines. We excluded trials in which 2 GPIs were compared directly or in which the route of GPI administration was randomized (e.g., intracoronary versus intravenous).

Literature review. A computerized literature search of the MEDLINE database was conducted without language restriction from inception until February 2010 for randomized clinical trials using the medical subject heading terms and keywords listed in Figure 1. To increase sensitivity, we also searched the references of other meta-analyses of GPIs, the Cochrane clinical trials database, and ClinicalTrials.gov.

Outcomes and definitions. The coprimary outcomes of this analysis were nonfatal MI, major bleeding, and all-cause mortality. Additional outcomes included urgent revascularization, stroke, minor bleeding, and thrombocytopenia. Nonfatal MI was defined preferentially as 2 to 3 times the upper limit of the normal range of the locally available creatine kinase-myocardial band assay. If this definition was not available, alternate definitions were included (described in the Results section). Major and minor bleeding were defined preferentially according to the Thrombolysis In Myocardial Infarction (TIMI) criteria (TIMI major bleeding: intracranial hemorrhage or clinically overt bleeding with drop in hemoglobin of >5 g/dl; TIMI minor bleeding: clinically overt bleeding with drop in hemoglobin of 3 to ≤5 g/dl). Similar to nonfatal MI, if a TIMI definition for major bleeding was not available, alternate definitions were included (described in Results). Urgent revascularization was defined as ischemic symptoms that resulted in an urgent need for repeat PCI or coronary artery bypass grafting after the index procedure. Stroke was defined as total stroke (ischemic and nonischemic). Thrombocytopenia was defined as a platelet count after PCI of <100,000/mm^3. All outcomes were tabulated within 30 days, except for all-cause mortality, which also was tabulated at 6 to 12 months.

Data extraction. Outcome data were extracted independently by 2 authors (W.D.B. and K.E.P.), and the information was recorded on a standardized case report form. Data about each trial's baseline characteristics, adjuvant medications, definitions of clinical outcomes, quality components, and duration or completeness of follow-up were extracted. Data were entered into a centralized database by a research assistant, and discrepancies were resolved by consensus of 2 authors (D.E.W. and A.A.B.). Personal communication with study authors was undertaken if additional data or clarification were necessary. Native language-speaking research associates were used when necessary for non-English manuscripts.

Abbreviations and Acronyms

CI = confidence interval
GPI = glycoprotein IIb/IIIa inhibitor
MI = myocardial infarction
PCI = percutaneous coronary intervention
RR = risk ratio
TIMI = Thrombolysis In Myocardial Infarction

Statistical analysis. Random effects summary risk ratios (RRs) were constructed using a DerSimonian-Laird model. Outcomes were assessed by grouping all trials together and by stratifying according to GPI type (abciximab vs. small-molecule GPI). Trial quality was assessed on the adequate description of treatment allocation, blinded outcome assessment, and description of losses to follow-up (15). We assessed for publication bias by Begg and Mazumdar's method (16) and Egger's method (17). Heterogeneity between studies was assessed by calculating a Cochran's Q and an I^2 statistic (18). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for performing a high-quality meta-analysis (19). We conducted sensitivity analyses by restricting our investigation to placebo-controlled trials and by using strict definitions of nonfatal MI and major bleeding.

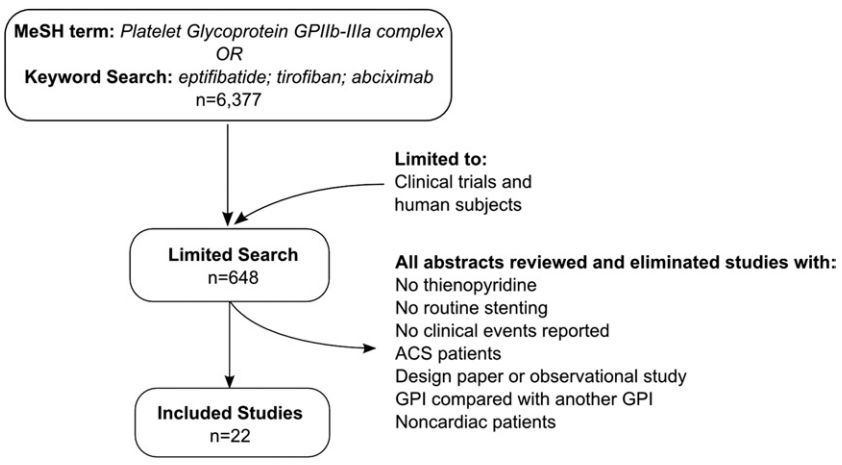

Figure 1 Search Strategy

Flow diagram of the search terms used and the overall search strategy for this analysis.
ACS = acute coronary syndrome; GPI = glycoprotein IIb/IIIa inhibitor; MeSH = medical subject heading.

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Table 1 Patient Characteristics

Study Name/First Author (Ref. #)	Publication Year	n	Age (yrs)	Female (%)	DM (%)	Prior MI (%)	Stented (%)
3T/2R (21)	2009	263*	68/68	26/28	24/28	48/38	92/94
OPTIMIZE-IT (22)	2009	46	66/65	27/29	100/100	17/18	100/100
CLEAR PLATELETS-2 (23)	2009	200	65/64	34/41	34/39	32/26	100/100
De Luca et al. (24)	2008	132	63/63	41/35	100/100	11/14	100/100
Cuisset et al. (25)	2008	149*	66/64	25/23	35/40	NR	100/100
ASIAD (26)	2005	254	62/61	25/28	100/100	40/42	99/100
Prati et al. (27)	2005	140	62/62	17/17	21/11	NR	98/98
Kurowski et al. (28)	2005	50	69/67	16/16	24/16	72/72	100/100
De Luca et al. (29)	2005	122	61/64	30/40	100/100	13/11	100/100
CLEAR PLATELETS (30)	2005	120	61/62	33/47	38/42	27/28	93/93
Claeys et al. (31)	2005	200	69/65†	31/30	17/16	15/23	99/97
ISAR-SWEET (11)	2004	701	68/67	27/24	100/100	35/33	90/90
ISAR-SMART-2 (32)	2004	502	67/66	27/27	26/30	38/36	68/69
Okmen et al. (33)	2004	119	54/58	18/14	8/10	33/26	84/87
DANTE (34)	2004	96	59/61	47/55	100/100	67/33	100/100
ISAR-REACT (10)	2004	2,159	65/66	23/24	21/20	32/33	91/90
Juergens et al. (35)	2002	894	59/59	17/17	17/13	46/46	98/98
Tamburino et al. (36)	2002	107	61/63	13/12	28/27	65/69	100/100
TOPSTAR (37)	2002	96	64/66	26/24	20/26	42/35‡	92/91
ESPRIT (38)	2001	2,064	62/62†	27/28	20/21	32/31	95/97
Galassi et al. (39)	1999	106	61/63	13/12	28/27	65/69	100/100
EPISTENT (40)	1998	1,603	59/59	25/26	20/21	50/55	97/96

All data are formatted as treatment/control and are reported as mean value unless noted otherwise. *Patients were selected for being poor responders to clopidogrel or aspirin. †Median age. ‡Defined as recent MI.

ASIAD = Abciximab in Stenting Inhibits restenosis Among Diabetics; CLEAR PLATELETS = Clopidogrel Loading with Eptifibatide to Arrest the Reactivity of Platelets; DANTE = Diabetes Abciximab SteNT Evaluation; DM = diabetes mellitus; EPISTENT = Evaluation of Platelet IIb/IIIa Inhibitor for Stenting; ESPRIT = Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy; ISAR-REACT = Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment; ISAR-SMART = Intracoronary Stenting or Angioplasty for Restenosis in SMall ARTeries; ISAR-SWEET = Intracoronary Stenting and Antithrombotic Regimen: is abciximab a Superior Way to Eliminate Elevated Thrombotic risk in diabetics; MI = myocardial infarction; NR = not reported; OPTIMIZE-IT = OPtimal TIrofiban bolus to reduce post-PCI Myonecrosis and Improve coronary flow randomized Evalution In diabeTics; TOPSTAR = Troponin in planned PTCA/stent implantation with or without administration of the glycoprotein IIb/IIIa Receptor Antagonist Tirofiban.

Table 2 Primary Study Outcomes and Individual Outcome Definitions

Study Name/First Author (Ref. #)	Primary Study Outcome	Definition of MI (Multiples of ULN)	Definition of Major Bleeding	Definition of Thrombocytopenia
3T/2R (21)	Periprocedural MI	CK-MB >3×	TIMI*	NR†
OPTIMIZE-IT (22)	Periprocedural MI	Troponin I >3×	Major hemorrhage	NR
CLEAR PLATELETS-2 (23)	Platelet reactivity	CK-MB >3×	TIMI	NR
De Luca et al. 2008 (24)	In segment late luminal loss	CK-MB >3×	TIMI	NR
Cuisset et al. (25)	Composite clinical outcomes	Troponin I >1×	TIMI	NR
ASIAD (26)	Angiographic restenosis	CK-MB >3×	TIMI	NR
Prati et al. (27)	Myocardial reperfusion	CK-MB >2×	NR	NR
Kurowski et al. (28)	Periprocedural MI	Troponin I >1×	NR	NR
De Luca et al. 2005 (29)	Target vessel revascularization	NR	NR	NR
CLEAR PLATELETS (30)	Platelet reactivity	CK-MB >3×	NR	NR
Claeys et al. (31)	Periprocedural MI	CK-MB >3×	>3g/dl Hgb drop, ICH, or vascular repair	<100,000/mm^3
ISAR-SWEET (11)	Composite clinical outcomes	CK-MB >3×	TIMI	<20,000/mm^3
ISAR-SMART-2 (32)	Angiographic restenosis	CK-MB >3×	NR	NR
Okmen et al. (33)	Periprocedural MI	CK-MB >2×	NR	NR
DANTE (34)	In-stent percent volume obstruction	CK-MB >3×	NR	NR
ISAR-REACT (10)	Composite clinical outcomes	CK-MB >3×	TIMI	<20,000/mm^3
Juergens et al. (35)	TIMI bleeding	CK-MB >3×	TIMI	NR
Tamburino et al. (36)	Composite clinical outcomes	CK >3×	TIMI	<50,000/mm^3
TOPSTAR (37)	Periprocedural MI	Troponin T >1×	Transfusion	NR†
ESPRIT (38)	Composite clinical outcomes	CK-MB >3×	TIMI	<20,000/mm^3
Galassi et al. (39)	Composite clinical outcomes	CK >3×	TIMI	NR†
EPISTENT (40)	Composite clinical outcomes	CK or CK-MB >3×	TIMI	NR

*TIMI major bleeding is defined as intracranial hemorrhage or clinically overt hemorrhage with drop in hemoglobin of >5 g/dl. †This outcome was reported but not defined.

CK-MB = creatine kinase-myocardial band; Hgb = hemoglobin; ICH = intracranial hemorrhage; TIMI = Thrombolysis In Myocardial Infarction; ULN = upper limit of normal; other abbreviations as in Table 1.

Table 3 Study Medications

Study Name/First Author (Ref. #)	Type of GPI	GPI Bolus (μg/kg)	GPI Infusion (μg/kg/min)	GPI After PCI (h)	GPI in Control Arm (%)	Thienopyridine	Antithrombin Regimen
3T/2R (21)	Tirofiban	25	0.15	14–24	12	300 to 600 mg clopidogrel before	UFH 50-70 U/kg with GPI vs. 100 U/kg with control
OPTIMIZE-IT (22)	Tirofiban	25	0.15	8	NR	300 mg clopidogrel before*	UFH, dose not specified
CLEAR PLATELETS-2 (23)	Eptifibatide	180 × 2	2	18	NR	600 mg clopidogrel before	Bivalirudin 0.75 mg/kg
De Luca et al. 2008 (24)	Abciximab	0.25	0.125	12	0	300 mg clopidogrel before	UFH, ACT >250 s
Cuisset et al. (25)	Abciximab	0.25	0.125	12	3	600 mg clopidogrel before	UFH 50 U/kg with GPI vs. 70 U/kg with control
ASIAD (26)	Abciximab	0.25	0.125	12	0	300 mg clopidogrel before	UFH 50 U/kg with GPI vs. 70 U/kg with control
Prati et al. (27)	Abciximab	0.25	10 μg/min	ND	0	500 mg ticlopidine before	UFH 70 to 100 U/kg
Kurowski et al. (28)	Tirofiban	10	0.15	12–14	NR	300 mg clopidogrel before	UFH 60 U/kg
De Luca et al. 2005 (29)	Abciximab	0.25	0.125	12	0	300 mg clopidogrel after*	UFH, ACT ≥250 s
CLEAR PLATELETS (30)	Eptifibatide	180 × 2	2	18–24	NR	300 to 600 mg clopidogrel after	UFH 60 U/kg
Claeys et al. (31)	Abciximab	0.25	10 μg/min	12	3	450 mg clopidogrel before	UFH, ACT >200 s with GPI vs. >300 with control
ISAR-SWEET (11)	Abciximab	0.25	0.125	12	0	600 mg clopidogrel before	UFH 70 U/kg with GPI vs. 140 U/kg with control
ISAR-SMART-2 (32)	Abciximab	0.25	0.125	12	NR	600 mg clopidogrel before	UFH 70 U/kg with GPI vs. 140 U/kg with control
Okmen et al. (33)	Tirofiban	10	0.15	24	0	500 mg ticlopidine before	UFH 70 U/kg with GPI vs. 10,000 U with control
DANTE (34)	Abciximab	0.25	0.125	12	0	500 mg ticlopidine before	UFH 70 U/kg with GPI vs. 100 U/kg with control
ISAR-REACT (10)	Abciximab	0.25	0.125	12	NR	600 mg clopidogrel before	UFH 70 U/kg with GPI vs. 140 U/kg with control
Juergens et al. (35)	Tirofiban	10	0.1	36	NR	75 mg clopidogrel daily after*	UFH 100 U/kg
Tamburino et al. (36)	Abciximab	0.25	0.125	12	NR	500 mg ticlopidine before	UFH 70 U/kg with GPI vs. 100 U/kg with control
TOPSTAR (37)	Tirofiban	10	0.15	18	NR	375 mg clopidogrel before	UFH 5,000 to 10,000 U, ACT >250 s
ESPRIT (38)	Eptifibatide	180 × 2	2	18–24	4	Loading dose before PCI†	UFH 60 U/kg, ACT 200 to 300 s
Galassi et al. (39)	Abciximab	0.25	0.125	12	2	500 mg ticlopidine before	UFH 70 U/kg with GPI vs. 100 U/kg with control
EPISTENT (40)	Abciximab	0.25	0.125	12	10	500 mg ticlopidine before	UFH 70 U/kg with GPI vs. 100 U/kg with control

In nonplacebo controlled trials, the control arm consisted of all therapies except the study drug. *500 mg ticlopidine could be given in lieu of clopidogrel. †Dose not specified.
ACT = activated clotting time; GPI = glycoprotein IIb/III inhibitor; PCI = percutaneous coronary intervention; UFH = unfractionated heparin; other abbreviations as in Table 1.

Univariate meta-regression analysis was performed in an attempt to explore for any modification of treatment effect according to thienopyridine use after PCI versus before, percentage of diabetics, publication year, and trials that used a higher dose of heparin in the control arm versus a similar dose between treatment arms (20). All statistical tests used 2-tailed p values with significance set at alpha = 0.05 and confidence intervals (CIs) calculated at the 95% level. All analyses were performed using STATA software version 11 (STATA Corporation, College Station, Texas).

Results

Baseline characteristics. Our search identified 22 studies with 10,123 patients (Fig. 1, Table 1) (10,11,21–40). The studies examined a variety of clinical outcomes, including 7 that used a nonclinical primary outcome (Table 2) (23,24,26,27,30,32,34). Details of GPI administration and adjuvant medications are listed in Table 3. Trial dropout rates were low, and slightly more than half of trials were placebo controlled (Table 4). One study was not identified in the MEDLINE search because it was missing the database label *human* and was located through a hand search of references from other meta-analyses (37,41).

Efficacy. Nonfatal MI at 30 days was reported for all but 2 trials (29,32). The incidence of MI was 5.1% with GPI and 8.3% with control (RR: 0.66, 95% CI: 0.55 to 0.79, $p < 0.0001$) (Fig. 2). Low heterogeneity was seen with this analysis ($I^2 = 18.9\%$), and no publication bias was observed (Begg's test: $p = 0.39$, Egger's test: $p = 0.36$). The magnitude of this effect was similar for both abciximab and small-molecule GPIs. The results were unchanged when this analysis was restricted

Table 4 Study Quality

Study Name/First Author (Ref. #)	Generation of Treatment Assignment	Independent Blinded Outcome Assessment	Placebo Controlled	Dropout (%)
3T/2R (21)	Sealed envelope	Yes	Yes	0/0
OPTIMIZE-IT (22)	Computer generated	No*	Yes	8.3/0
CLEAR PLATELETS-2 (23)	Computer generated	Yes	No	NR/NR
De Luca et al. 2008 (24)	Not described	Yes†	Yes	3/3‡
Cuisset et al. (25)	Telephone generated	No	No	0/0
ASIAD (26)	Computer generated	Yes†	Yes	3.1/0
Prati et al. (27)	Not described	No*	No	5.7/0
Kurowski et al. (28)	Not described	No	No	0/0
De Luca et al. 2005 (29)	Not described	Yes†	Yes	0/0
CLEAR PLATELETS (30)	Computer generated	No	No	NR/NR
Claeys et al. (31)	Not described	No	No	0/0
ISAR-SWEET (11)	Sealed envelope	Yes	Yes	3.1/3.7
ISAR-SMART-2 (32)	Computer generated	Yes	Yes	NR/NR
Okmen et al. (33)	Not described	No	No	0/0
DANTE (34)	Sealed envelope	No*	No	0/0
ISAR-REACT (10)	Sealed envelope	Yes	Yes	0/0
Juergens et al. (35)	Not described	Yes	Yes	NR/NR
Tamburino et al. (36)	Sealed envelope	No*	No	0/0
TOPSTAR (37)	Independent study nurse	Yes†	Yes	NR/NR
ESPRIT (38)	Not described	Yes	Yes	0.1/0.1
Galassi et al. (39)	Random number	No*	No	NR/NR
EPISTENT (40)	Telephone generated	Yes	Yes	1/1.2

Data are presented as treatment/control. *Diagnostic studies reviewed in blinded fashion. No mention of blinded clinical outcome assessment. †Double-blind trial; however, no specific mention of independent blinded outcome assessment. ‡Overall percentage of drop-outs over 6 months. Abbreviations as in Table 1.

to placebo-controlled trials (RR: 0.69, 95% CI: 0.55 to 0.86, p = 0.001) and to trials that strictly defined MI based on creatine kinase-myocardial band more than 2 to 3 times the upper limit of normal of the local assay (RR: 0.70, 95% CI: 0.53 to 0.93, p = 0.013). Target vessel revascularization was reported in 10 trials with incidence of 0.8% with GPI versus 1.2% with control (RR: 0.71, 95% CI: 0.46 to 1.10, p = 0.13) (10,11,23,24,26,34,35,38–40).

The logarithm of RR for nonfatal MI plotted against publication year did not reveal any effect modification (p > 0.99) (Fig. 3). Other potential modifiers that were examined by metaregression included: thienopyridine use after versus before PCI (p = 0.99), high percentage of diabetic patients (p = 0.61), and use of a higher dose of heparin in the control arm (p = 0.78).

Safety. Major bleeding was reported in all but 7 trials (27–30,32–34). The incidence of major bleeding was 1.2% with GPI versus 0.9% with control (RR: 1.37, 95% CI: 0.83 to 2.25, p = 0.22) (Fig. 4). Heterogeneity was low (I^2 = 16.2%), and publication bias was not found (Begg's test: p = 0.71, Egger's test: p = 0.91). Results were not different when the analysis was restricted to placebo-controlled trials (RR: 1.17, 95% CI: 0.70 to 1.93, p = 0.55) or to trials that strictly reported TIMI major bleeding (RR: 1.28, 95% CI: 0.71 to 2.32, p = 0.41). Incidence of minor bleeding was 3.0% versus 1.7% with control (RR: 1.70, 95% CI: 1.28 to 2.26, p < 0.0001). Based on 8 trials, the incidence of thrombocytopenia was 0.8% with GPI versus 0.04% with control (RR: 4.77, 95% CI: 1.67 to 13.64, p = 0.004) (10,11,21,31,36–39). The risk of thrombocytopenia significantly increased with abciximab (RR: 6.91, 95% CI: 1.80 to 26.46, p = 0.005), in contrast to small-molecule GPIs (RR: 2.65, 95% CI: 0.49 to 14.34, p = 0.26). Stroke was reported in 5 trials, with an incidence of 0.2% with GPI and of 0.09% with control (RR: 3.01, 95% CI: 0.61 to 14.87, p = 0.18) (30,35,37,38,40).

All-cause mortality. Mortality within 30 days was 0.3% with GPI versus 0.5% with control (RR: 0.70, 95% CI: 0.36 to 1.33, p = 0.27) (Fig. 5). There was no evidence for heterogeneity (I^2 = 0%) or publication bias (Begg's test: p > 0.99, Egger's test: p = 0.91). Data for mortality at 6 to 12 months were available for 8,480 patients with an incidence of 2.9% with GPI versus 3.3% with control (RR: 0.88, 95% CI: 0.66 to 1.18, p = 0.41).

Discussion

Our analysis of 22 studies with 10,123 patients demonstrates that GPIs are beneficial during contemporary PCI. Specifically, the addition of a GPI during stent-based PCI on a background of aspirin and a thienopyridine reduces nonfatal MI without an appreciable increase in major bleeding; however, minor bleeding is increased. All-cause mortality is not reduced. Findings were similar between abciximab and the small-molecule GPIs.

Exploring heterogeneity. There was a small degree of dispersion (heterogeneity) around the nonfatal MI sum-

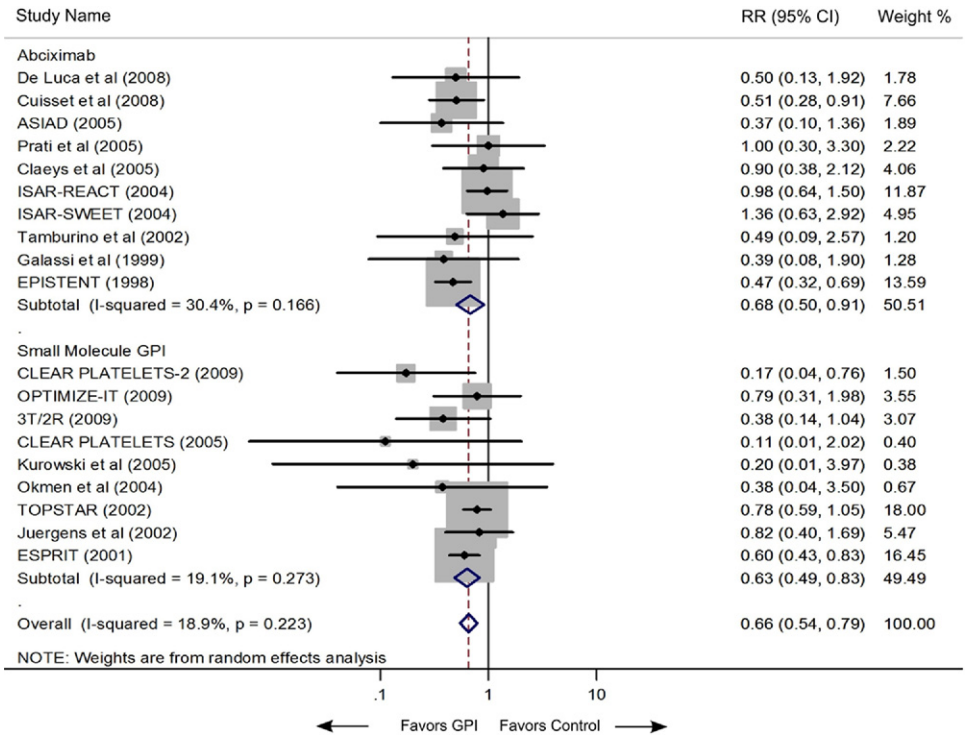

Figure 2 **RRs for Nonfatal Myocardial Infarction**

Trials that did not report nonfatal myocardial infarction were excluded from this analysis. The **size of the data markers** indicates the relative weight of each study. ASIAD = Abciximab in Stenting Inhibits restenosis Among Diabetics; CI = confidence interval; CLEAR PLATELETS = Clopidogrel Loading with Eptifibatide to Arrest the Reactivity of Platelets; EPISTENT = Evaluation of Platelet IIb/IIa Inhibitor for Stenting; ESPRIT = Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy; GPI = glycoprotein IIb/IIIa inhibitor; ISAR-REACT = Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment; ISAR-SWEET = Intracoronary Stenting and Antithrombotic Regimen: is abciximab a Superior Way to Eliminate Elevated Thrombotic risk in diabetics; OPTIMIZE-IT = OPtimal TIrofiban bolus to reduce post-PCI Myonecrosis and Improve coronary flow randomized Evaluation In diabeTics; RR = risk ratio; TOPSTAR = Troponin in planned PTCA/stent implantation with or without administration of the glycoprotein IIb/IIIa Receptor Antagonist Tirofiban.

mary estimate; however, the reduction in nonfatal MI was reduced to a similar magnitude with abciximab and the small-molecule GPIs. This class-effect finding is in contradistinction to the TARGET (Do Tirofiban and ReoPro Give Similar Efficacy Trial), which documented the superiority of abciximab compared with tirofiban (42).

Our selected studies spanned more than a decade, during which time significant refinements in catheters, wires, balloons, and stents took place that have contributed to the current safety of PCI. This was the motivation for performing metaregression as a function of publication year, although the most recent studies seemed to have the same degree of benefit from GPIs as the earlier studies. Additionally, no effect modification was found by examining studies with a large proportion of diabetics or studies that used a relatively high dose of heparin in the control arm (versus similar dose between treatment arms).

Balancing adverse thrombotic and bleeding events. Elevation of postprocedural cardiac enzymes occurred in 8.3% of control patients. The degree of cardiac enzyme elevation has been associated, in a dose-dependent fashion, with an increased risk for long-term mortality (43,44). Our analysis demonstrates that using GPIs

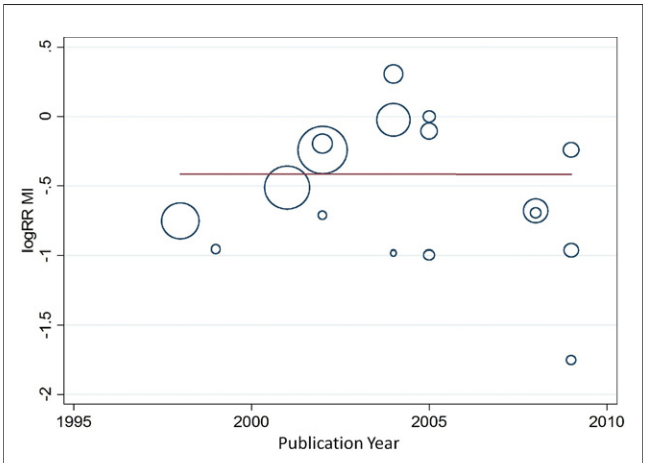

Figure 3 **Metaregression Plot**

Plot of univariate metaregression examining the effect of publication year on the relationship between glycoprotein inhibitors and nonfatal myocardial infarction (MI) ($p > 0.99$). Trials that did not report nonfatal myocardial infarction were excluded. The **area of each circle** is inversely proportional to the variance of the estimate of the log risk ratio. RR = risk ratio.

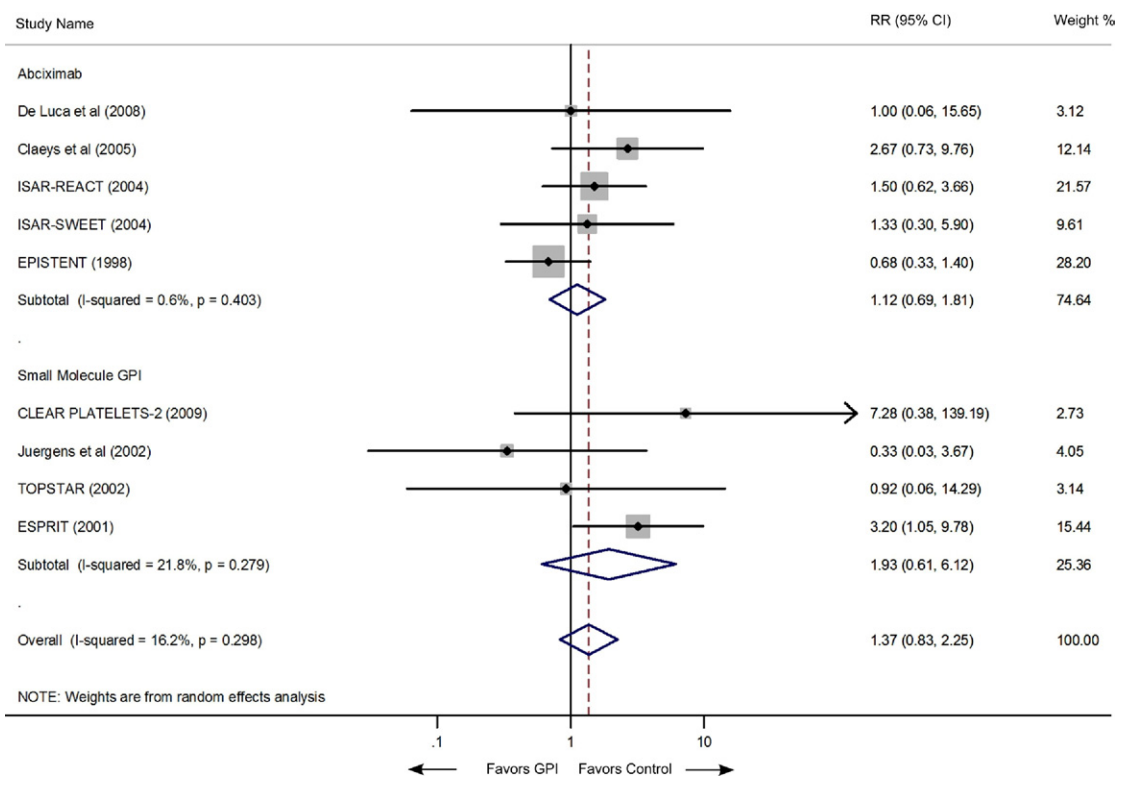

Figure 4 **RRs for Major Bleeding**

Trials that did not report major bleeding were excluded from this analysis. The **size of the data markers** indicates the relative weight of each study. Abbreviations as in Figure 2.

during elective PCI can reduce the risk of postprocedural MI by approximately 30%.

We found that the risk of major bleeding was nonsignificantly increased, although minor bleeding was increased by approximately 70% with GPIs. Major bleeding increases the risk for long-term mortality (45,46); however, even a minor bleed, similar to a small post-procedural MI, can worsen long-term prognosis (45). Although we did not find that GPIs increase major bleeding, their use in acute coronary syndromes may potentiate this hazard (47).We did not expect to find a difference in short-term mortality from GPI use because of the low-risk nature of the studied patients. Had major bleeding occurred more frequently than nonfatal MI, there might have been a signal for increased all-cause mortality.

Clinical use and future directions. Our results are largely applicable to patients pre-treated with thienopyridines, because this group represented approximately 94% of the weight of the nonfatal MI outcome. Despite the benefit of clopidogrel pre-treatment (48,49), some practitioners may choose to give this medication after coronary angiography has been performed in case coronary artery bypass grafting is needed. GPIs may obviate the need for clopidogrel pre-treatment; however, this approach is not supported by our findings and deserves further study.

Current guidelines state that the use of a GPI is recommended as a Class IIa agent (Level of Evidence: B) (13). The European Society of Cardiology guidelines also endorse GPIs as a Class IIa agent (Level of Evidence: C), but only in bailout situations (14). We believe our analysis supports and potentially expands the use of GPIs in appropriate clinical situations.

Further approaches that may be used to enhance the benefit of GPIs while minimizing their risk include the following: intracoronary versus intravenous administration (50), abbreviated infusion (51), and preferential use in patients resistant to thienopyridines (21,25). Lastly, the role of GPIs will need to be reappraised as newer and more potent agents become available (52–54).

Study strengths. We believe our rigorous search strategy has resulted in the most comprehensive review to date of GPI use during elective PCI. We used multiple layers of data verification and sensitivity analyses, which add strength to our meta-analysis. As previously described, this analysis had no publication bias and the level of heterogeneity was low. Also, metaregression was unable to uncover any subtle sources of effect modification.

Study limitations. We were not able to analyze our results by lesion complexity; response to aspirin, clopidogrel, or both; or baseline use of statins, which recently were shown to reduce postprocedural MI (55). Some of the included trials were open label, which might have introduced bias; however, our findings were unchanged after sensitivity analysis with restriction to

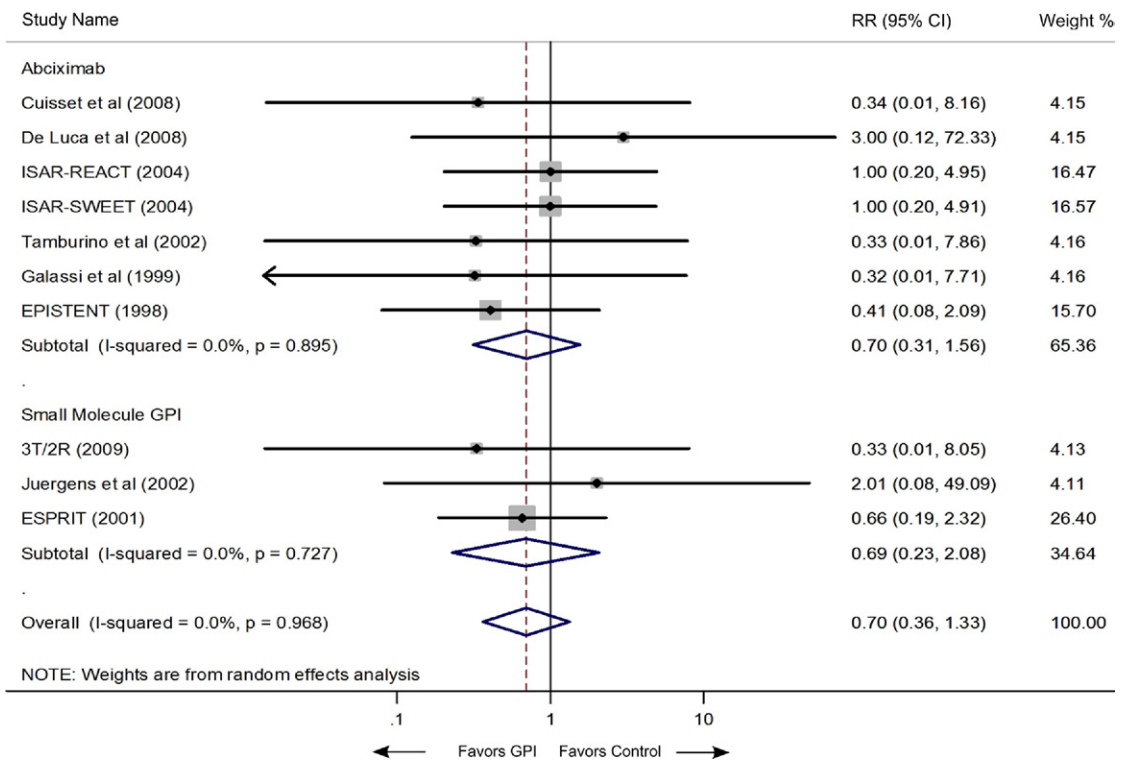

Figure 5 **RRs for Mortality**

Trials that did not report mortality were excluded from this analysis. The **size of the data markers** indicates the relative weight of each study. Abbreviations as in Figure 2.

placebo-controlled trials. These also were the trials that had independent blinded outcome assessment with low participant dropout, thus indicating studies of high quality. We included studies that used ticlopidine; however, because the clinical efficacy of this agent is considered similar to that of clopidogrel, we considered this a reasonable approach (56).

Conclusions

In the current era of elective PCI performed with stents and thienopyridines, GPIs reduce nonfatal MI without a notable increase in major bleeding. However, these agents increase minor bleeding and thrombocytopenia. Overall, the use of GPIs during elective modern PCI seems to be safe and effective.

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Key Words: bleeding ■ glycoprotein IIb/IIIa inhibitors ■ meta-analysis ■ percutaneous coronary intervention ■ post-procedural myocardial infarction.