Meta-analysis of clinical efficacy and bleeding risk with intravenous glycoprotein IIb/IIIa antagonists for percutaneous coronary intervention

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OBJECTIVE: Percutaneous coronary intervention (PCI) has become the most common mode of coronary revascularization. Inhibition of platelet aggregation via glycoprotein (GP) IIb/IIIa receptor blockade significantly reduces the acute ischemic complications associated with PCI, but the risk of bleeding may also be increased with these agents. The purpose of the present study was to provide an up-to-date meta-analysis on the clinical efficacy and safety of intravenous GP IIb/IIIa antagonists in patients undergoing PCI.

METHODS: A comprehensive search was undertaken to identify all randomized trials of GP IIb/IIIa antagonists versus control in patients intended to undergo PCI. Medline, Embase, Biosis, HealthStar and hand searches were performed. The primary outcome was all-cause mortality. Secondary outcomes included myocardial infarction (MI), repeat revascularization, thrombocytopenia and bleeding. OR and their 95% CI were calculated using the random effects model.

RESULTS: Twenty-one randomized trials were identified, which together included 23,941 patients. The mortality rate at seven days was 0.33% in the GP IIb/IIIa group compared with 0.50% in the control group (OR 0.70, 95% CI 0.29 to 1.68); at 30 days, the mortality rate was 0.83% versus 1.21%, respectively (OR 0.72, 95% CI 0.56 to 0.94); at six months, the mortality rate was 1.92% versus 2.33%, respectively (OR 0.85, 95% CI 0.68 to 1.07); and at one year, the mortality rate was 2.61% versus 3.32%, respectively (OR 0.80, 95% CI 0.64 to 1.00). The number needed to treat at 30 days to save one life was 296. The mortality benefit appeared to dissipate by six months and was of borderline significance at one year. The incidence of MI in the treatment group compared with the control group was reduced at seven days (4.31% versus 6.97%, respectively; OR 0.59, 95% CI 0.46 to 0.75), at 30 days (4.54% versus 6.46% respectively; OR 0.63, 95% CI 0.54 to 0.74) and at six months (5.73% versus 8.29%; OR 0.65, 95% CI 0.55 to 0.77). Repeat revascularization procedures were also significantly lower in the GP IIb/IIIa group compared with the control group at seven days (2.47% versus 4.44%, respectively; OR 0.43, 95% CI 0.29 to 0.84), at 30 days (3.44% versus 5.19%, respectively; OR 0.66, 95% CI 0.56 to 0.77) and at six months (15.21% versus 17.40%, respectively; OR 0.86, 95% CI 0.78 to 0.94). Overall, the composite of death, MI and repeat revascularization was reduced at all time points. An assessment of risk revealed that the incidence of thrombocytopenia (OR 1.41, 95% CI 1.10 to 1.81) and minor bleeding (OR 1.80, 95% CI 1.47 to 2.21), but

not major bleeding (OR 1.29, 95% CI 0.98 to 1.68), was significantly increased in the GP IIb/IIIa group versus the control group.

CONCLUSIONS: Treatment with GP IIb/IIIa inhibitors in the setting of PCI significantly reduces the rates of 30-day mortality, MI and repeat revascularization procedures. These beneficial effects are achieved at an increased risk of thrombocytopenia and minor bleeding, but not major bleeding.

Key Words: *Glycoprotein IIb/IIIa antagonists; Meta-analysis; Percutaneous coronary intervention*

Une méta-analyse de l'efficacité clinique et du risque de saignement des antagonistes de la glycoprotéine IIb/IIIa intraveineux dans le cadre d'interventions coronaires percutanées

OBJECTIF : L'intervention coronaire percutanée (ICP) est devenue le principal mode de revascularisation coronaire. L'inhibition de l'agrégation plaquettaire par le blocage des récepteurs de la glycoprotéine (GP) IIb/IIIa réduit de manière significative les complications ischémiques aiguës associées à l'ICP, mais peut également accroître le risque de saignement. La présente étude visait à fournir une méta-analyse à jour de l'efficacité et de l'innocuité cliniques des antagonistes de la GP IIb/IIIa intraveineux chez les patients subissant une ICP.

MÉTHODOLOGIE : On a entrepris une recherche détaillée pour repérer tous les essais aléatoires des antagonistes de la GP IIb/IIIa par rapport à des sujets témoins chez des patients devant subir une ICP. On a procédé à des recherches manuelles ainsi que dans Medline, Embase, Biosis et HealthStar. La principale issue était la mortalité toutes causes confondues. Les issues secondaires étaient un infarctus du myocarde (IM), une reprise de la revascularisation, une thrombocytopénie et des saignements. On a calculé le RC et l'IC à 95 % au moyen du modèle à effets aléatoires.

RÉSULTATS : On a repéré 21 essais aléatoires qui, ensemble, totalisaient 23 941 patients. Le taux de mortalité était de 0,33 % au sein du groupe de GP IIb/IIIa le septième jour par rapport à 0,50 % au sein du groupe témoin (RC 0,70, 95 % IC 0,29 à 1,68). Le trentième jour, le taux de mortalité atteignait 0,83 % par rapport à 1,21 %, respectivement (RC 0,72, 95 % IC 0,56 à 0,94). Le sixième mois, le taux de mortalité était de 1,92 % par rapport à 2,33 %, respectivement (RC 0,85, 95 % IC 0,68 à 1,07), et à un an, de 2,61 % par rapport à 3,32 %, respectivement (RC 0,80, 95 % IC 0,64 à 1,00). Le nombre nécessaire à traiter pour sauver une vie à 30 jours était de 296. Le bienfait sur la mortalité semblait se dissiper au bout de six mois et avait une signification limite à un an.

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L'incidence d'IM au sein du groupe de traitement par rapport au groupe témoin avait diminué au septième jour (4,31 % par rapport à 6,97 %, respectivement; RC 0,59, 95 % IC 0,46 à 0,75), au trentième jour (4,54 % par rapport à 6,46 %, respectivement; RC 0,63, 95 % IC 0,54 à 0,74) et au sixième mois (5,73 % par rapport à 8,29 %; RC 0,65, 95 % IC 0,55 à 0,77). Les reprises de revascularisation étaient également beaucoup plus rares au sein du groupe de GP IIb/IIIa que du groupe témoin au septième jour (2,47 % par rapport à 4,44 %, respectivement; RC 0,43, 95 % IC 0,29 à 0,84), au trentième jour (3,44 % par rapport à 5,19 %, respectivement; RC 0,66, 95 % IC 0,56 à 0,77) et au sixième mois (15,21 % par rapport à 17,40 %, respectivement; RC 0,86, 95 % IC 0,78 à 0,94). Dans l'ensemble, les éléments composites de décès, d'IM et

de reprise de la revascularisation diminuaient à tous les moments dans le temps. L'évaluation du risque révélait que, contrairement à l'incidence de saignement majeur (RC 1,29, 95 % IC 0,98 à 1,68), l'incidence de thrombocytopénie (RC 1,41, 95 % IC 1,10 à 1,81) et de saignement mineur (RC 1,80, 95 % IC 1,47 à 2,21) augmentait de manière significative au sein du groupe de GP IIb/IIIa par rapport au groupe témoin.

CONCLUSIONS : Le traitement de l'ICP à l'aide d'inhibiteurs de la GP IIb/IIIa réduit le taux de mortalité, d'IM et de reprise de la revascularisation au bout de 30 jours. Ces effets bénéfiques s'accompagnent d'un risque accru de thrombocytopénie et de saignement mineur, mais non de saignement majeur.

Percutaneous coronary intervention (PCI) has become the most common mode of coronary revascularization. Annually, there are over two million procedures performed worldwide (1). Inhibition of platelet aggregation via glycoprotein (GP) IIb/IIIa receptor blockade significantly reduces the acute ischemic complications associated with PCI, but the risk of bleeding may be increased with these agents (2). Currently, there are three available intravenous GP IIb/IIIa antagonists: the monoclonal antibody abciximab and the small molecules eptifibatide and tirofiban. Several randomized trials and earlier meta-analyses (3-39) have examined the efficacy of these GP IIb/IIIa antagonists. Since the completion of these reports, additional trials have been conducted, and although other reports have commented on the effects on mortality and myocardial infarction (MI), little data have been provided on the incidence of repeat revascularization procedures, thrombocytopenia, bleeding complications and survival benefits at very early and later time points.

The purpose of the present study was to provide an up-to-date meta-analysis on the clinical efficacy and safety of intravenous GP IIb/IIIa antagonists. As such, we have included their effects on mortality, MI and the need for repeat revascularization procedures, as well as their impact on thrombocytopenia and major and minor bleeding following PCI.

METHODS

The present meta-analysis was conducted in accordance with the Quality of Reporting of Meta-analysis criteria (40). It included all trials that fulfilled the following criteria: randomized controlled trials of patients undergoing PCI; those that compared treatment arms with and without a GP IIb/IIIa antagonist; and those that reported at least one of death, MI, repeat revascularization or a composite end point (CEP). Two reviewers (CH and JM) independently selected the trials, and disagreements were resolved by discussion. Data were extracted by two reviewers (CH and JM or CH and SB) and verified for accuracy by CH and SB using a structured form. Trial quality was scored using a quality assessment form based on the Jadad scale (41). This scale assesses randomization (zero to two points), double-blinding (zero to two points) and withdrawals or dropouts (zero or one point), with higher values indicating superior quality.

Published literature was obtained by searching multiple databases on the Ovid online system, including Medline, Embase, Biosis Previews, Current Contents and HealthStar. A clinical filter was used to restrict retrieval to relevant studies. A detailed description of the literature search strategy, including key words, is available at <www.ccohta.ca>. There were no date or language restrictions. No foreign language publications were identified by the searches. Regular alerts were set up on the DIALOG system for Medline, Embase and Biosis Previews databases to retrieve newer citations. Selective published bibliographies were hand searched for additional information. In addition, searches were

performed on the CD-ROM version of the Cochrane Library (2001, 2002 and 2003). Updates were performed on PubMed to retrieve pre-Medline and other records. The final date for literature searches was April 2004. Publication bias was explored using the funnel plot for each outcome (42,43).

In most trials, the outcomes investigated included death, MI and revascularization, all of which may have been a component of a CEP. The primary end point of the present study was all-cause mortality at seven days, 30 days, six months and one year. Secondary end points included MI, the need for repeat revascularization and the composites of death, MI and/or revascularization at seven days, 30 days and six months. Safety end points included major bleeding, minor bleeding and thrombocytopenia during the index hospitalization. The definition of MI was as per the study authors' definitions, and was most commonly defined using both electrocardiogram and enzymatic criteria. Repeat revascularization was usually defined as the need for repeat PCI and coronary artery bypass grafting. A major bleeding event was most commonly defined as per the Thrombolysis In Myocardial Infarction (TIMI) criteria (44) or as per the Global Utilization of Streptokinase and tPA for Occluded arteries (GUSTO) trial criteria (45), and included coronary artery bypass grafting-related bleeding. Bleeding was classified as TIMI major if it was associated with a decrease in hemoglobin of 5 g/dL or more or an absolute decrease in hematocrit of 15% or more, or if the bleeding was intracranial. Bleeding was classified as GUSTO severe bleeding if it was intracranial or if hemodynamic compromise resulted. Thrombocytopenia was defined as a patient having a platelet count of less than 100,000/mL.

All comparisons were either between GP IIb/IIIa antagonists (abciximab, eptifibatide or tirofiban) and placebo, or control and no placebo (collectively referred to as 'control'). All eligible randomized trials were included, including those in which the dosage of concomitant therapies, such as heparin, was varied across the different arms. Analyses in the original studies were carried out on an intention-to-treat basis (patients were analyzed according to their allocated treatment).

To compare the outcomes in the different treatment groups, OR with corresponding 95% CI were computed, and forest plots were generated using Stata 7.0 software (StataCorp, USA). If no events were observed in either arm, the trial was omitted from the meta-analysis. A χ^2 test was used to assess effect size variance among trials, and $P < 0.10$ indicated significant heterogeneity across trials. OR and their 95% CI were calculated using the random effects model. Statistical significance was defined as $P < 0.05$ or 95% CI of the OR that did not include unity.

RESULTS

A total of 23,941 patients in 21 randomized controlled trials that compared GP IIb/IIIa inhibitors with controls were included in the analysis. Figure 1 outlines the trial flow. Fifteen trials used

TABLE 1
Patient characteristics according to trial

Trial or authors (reference)	Year published	Jadad score (of 5)	Thienopyridine use	Baseline clinical patient characteristics						
				Mean age (years)	Male sex (%)	DM (%)	HTN (%)	Prior MI (%)	Prior PCI (%)	Prior CABG (%)
Abciximab										
ADMIRAL, n=300 (5)	2001	4	Yes	61	82	18	38	11	14	12
CADILLAC, n=2082 (20)	2002	5	Yes	60	73	17	51	14	11	2
CAPTURE, n=1266 (4)	1997	4	No	61	73	14	42	40	14	3
Chen et al, n=42 (18)	2000	2	No	70	96	36	67	46	12	3
EPIC, n=2099 (14)	1994	4	No	61	72	24	55	57	22	15
EPILOG, n=2792 (10)	1997	4	No	60	72	23	—	21	—	13
EPISTENT, n=1603 (8)	1998	5	Yes	59	75	20	53	51	—	9
ERASER, n=225 (3)	1999	5	Yes	59	79	14	50	—	11	—
Galassi et al, n=106 (16)	1999	1	Yes	62	88	28	34	67	—	—
RAPPORT, n=483 (7)	1998	3	No	61	73	23	48	19	14	—
Simoons et al, n=60 (12)	1994	4	No	61	74	—	—	19	15	4
Tamburino et al, n=107 (21)	2002	2	Yes	62	88	28	34	67	—	—
ISAR-REACT, n=2159 (23)	2004	5	Yes	66	77	21	55	33	—	10
Petronio et al, n=89 (19)	2002	2	Yes	61	65	18	—	10	—	1
ISAR-II, n=401 (6)	2000	3	Yes	61	77	14	63	—	7	4
Eptifibatide										
ESPRIT, n=2064 (13)	2001	5	Yes	62	73	21	59	32	24	10
Harrington et al, n=73 (17)	1995	3	No	60	78	26	71	39	—	31
IMPACT, n=150 (15)	1995	3	No	61	75	20	53	43	40	18
IMPACT-II, n=4010 (11)	1997	5	No	61	75	23	54	41	29	16
Tirofiban										
RESTORE, n=2141 (9)	1997	3	No	59	72	20	55	35	21	7
Juergens et al, n=894 (22)	2002	4	Yes	59	83	15	52	46	—	—

Patient characteristics from each trial include mean age, percentage of men, as well as history of diabetes mellitus (DM), hypertension (HTN), myocardial infarction (MI), percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Also included are the number of patients in each trial, Jadad scores and thienopyridine use. ADMIRAL Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up; CADILLAC Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; CAPTURE c7E3 fab AntiPlatelet Therapy in Unstable REfractory angina; EPIC Evaluation of 7E3 for the Prevention of Ischemic Complications; EPILOG Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade; EPISTENT Evaluation of Platelet IIb/IIIa Inhibitor for STENTing; ERASER Acute Platelet Inhibition With Abciximab Does Not Reduce In-Stent Restenosis; ESPRIT Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy; IMPACT Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis; ISAR-React Intracoronary Stenting and Antithrombotic Regimen – Rapid Early Action for Coronary Treatment; RAPPORT ReoPro in Acute myocardial infarction and Primary PTCA Organization and Randomized Trial; RESTORE Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis

abciximab, four trials used eptifibatide and two trials used tirofiban. Funnel plots showed no evidence of publication bias of any of the clinical outcomes. No clinically important differences in baseline characteristics were apparent between patients randomly assigned to GP IIb/IIIa inhibitors or control. The mean or median age reported in each of the trials ranged from 58 to 63 years; 74% of patients were male, 35% had a history of MI and 21% had diabetes mellitus. Table 1 summarizes the key clinical features of the patients included in the trials. The median Jadad score for the trials was 4.5 points (range two to five points). All studies were double-blinded except for the studies by Galassi et al (16), Petronio et al (19), Tamburino et al (21) and the ISAR-II trial (6). Results did not differ materially when a sensitivity analysis was performed, which excluded the study arms without matched heparin regimens.

Mortality

The overall incidence of death in the GP IIb/IIIa group was 0.33% (eight events in 2436 patients) compared with 0.50% in the control group (12 events in 2419 patients) at seven days (Table 2). There was a 30% reduction in risk of seven-day mortality, which was not statistically significant (OR 0.70, 95% CI 0.29 to 1.68). At 30 days, the overall incidence of death in the GP IIb/IIIa group was 0.83% (114 events in 13,726 patients) compared with 1.21%

Figure 1) Trial selection flow chart. Flow chart indicates the process taken for selecting glycoprotein IIb/IIIa studies used in the present meta-analysis

TABLE 2
Mortality

Time point	Total events/patients (%)		Absolute reduction (%)	OR (95%CI)
	GP IIb/IIIa	Control		
7 days	8/2436 (0.33)	12/2419 (0.50)	0.17	0.70 (0.29–1.68)
30 days	114/13,726 (0.83)	118/9708 (1.21)	0.38	0.72 (0.56–0.94)
6 months	176/9183 (1.92)	157/6712 (2.33)	0.41	0.85 (0.68–1.07)
1 year	186/7139 (2.61)	156/4698 (3.32)	0.71	0.80 (0.64–1.00)

GP Glycoprotein

Figure 2) Mortality at 30 days. Risk ratios and 95% CI are shown for each study and for the combined trials. Heterogeneity $\chi^2=5.81$ (15 degrees of freedom), $P=0.983$. I^2 (variation in OR attributable to heterogeneity) = 0.0%. ADMIRAL Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up; CADILLAC Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; CAPTURE c7E3 fab AntiPlatelet Therapy in Unstable REfractory angina; EPIC Evaluation of 7E3 for the Prevention of Ischemic Complications; EPILOG Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade; EPISTENT Evaluation of Platelet IIb/IIIa Inhibitor for STENTing; ESPRIT Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy; GP Glycoprotein; IMPACT Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis; ISAR-REACT Intracoronary Stenting and Antithrombotic Regimen – Rapid Early Action for Coronary Treatment; RAPPORT ReoPro in Acute myocardial infarction and Primary PTCA Organization and Randomized Trial; RESTORE Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis

in the control group (118 events in 9708 patients). This translates into a statistically significant 28% reduction in the risk of death at 30 days (OR 0.72, 95% CI 0.56 to 0.94), for an absolute risk reduction of 0.38% and a number needed to treat of 296 (Figure 2). At six months, the incidence of death in the GP IIb/IIIa group was 1.92% (176 events in 9183 patients) compared with 2.33% in the control group (157 events in 6712 patients). This difference resulted in a 15% reduction in risk of mortality at six months, which was not statistically significant (OR 0.85, 95% CI 0.68 to 1.07). At one year, there was a trend toward lower mortality in patients treated with GP IIb/IIIa antagonists compared with control (2.61% versus 3.32%, respectively; OR 0.80, 95% CI 0.64 to 1.00). Despite apparent trends in the reduction of mortality, the present analysis revealed that

TABLE 3
Myocardial infarction

Time point	Total events/patients (%)		Absolute reduction (%)	OR (95%CI)
	GP IIb/IIIa	Control		
7 days	114/2644 (4.31)	175/2509 (6.97)	2.66	0.59 (0.46–0.75)
30 days	624/13,748 (4.54)	628/9728 (6.46)	1.92	0.63 (0.54–0.74)
6 months	532/9281 (5.73)	561/6765 (8.29)	2.56	0.65 (0.55–0.77)

GP Glycoprotein

Figure 3) Myocardial infarction at 30 days. Risk ratios and 95% CI are shown for each study and for the combined trials. Heterogeneity $\chi^2=23.03$ (16 degrees of freedom), $P=0.113$. I^2 (variation in OR attributable to heterogeneity) = 30.5%. ADMIRAL Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up; CADILLAC Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; CAPTURE c7E3 fab AntiPlatelet Therapy in Unstable REfractory angina; EPIC Evaluation of 7E3 for the Prevention of Ischemic Complications; EPILOG Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade; EPISTENT Evaluation of Platelet IIb/IIIa Inhibitor for STENTing; ESPRIT Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy; GP Glycoprotein; IMPACT Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis; ISAR-REACT Intracoronary Stenting and Antithrombotic Regimen – Rapid Early Action for Coronary Treatment; RAPPORT ReoPro in Acute myocardial infarction and Primary PTCA Organization and Randomized Trial; RESTORE Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis

GP IIb/IIIa antagonists significantly decreased the incidence of death at 30 days, but not at any other studied time point.

MI

The incidence of MI was significantly reduced with GP IIb/IIIa receptor blockade compared with control at all time points (Table 3). At seven days, the incidence of MI in the GP IIb/IIIa group was 4.31% (114 events in 2644 patients) versus 6.97% in the control group (175 events in 2509 patients), which represented a 41% reduction in risk (OR 0.59, 95% CI 0.46 to 0.75). This beneficial effect was maintained at 30 days, when the incidence of MI in the GP IIb/IIIa group was 4.54% (624 events in 13,748 patients) compared with 6.46% in the control group (628 events in 9728 patients), which represented a relative reduction of 37% (OR 0.63, 95% CI 0.54 to 0.74) (Figure 3). At six months, the overall incidence of MI in the GP IIb/IIIa group was 5.73% (532 events in 9281 patients) compared with 8.29% in the control

TABLE 4
Repeat revascularization

Time point	Total events/patients (%)		Absolute reduction	
	GP IIb/IIIa	Control	(%)	OR (95%CI)
7 days	64/2590 (2.47)	109/2456 (4.44)	1.97	0.43 (0.29–0.84)
30 days	472/13,733 (3.44)	503/9683 (5.19)	1.75	0.66 (0.56–0.77)
6 months	1412/9281 (15.21)	1177/6765 (17.40)	2.19	0.86 (0.78–0.94)

GP Glycoprotein

group (561 events in 6765 patients), representing a 35% RR reduction (OR 0.65, 95% CI 0.55 to 0.77). Results at one year were not analyzed due to insufficient information. Taken together, GP IIb/IIIa antagonists significantly decreased the number of MI by 2.66% at seven days, 1.92% at 30 days and 2.56% at six months.

Repeat revascularization

The need for repeat revascularization was reduced at all time points (Table 4). At seven days, repeat revascularization was required in 64 of 2590 patients (2.47%) in the GP IIb/IIIa group compared with 109 of 2456 patients (4.44%) in the control group. This translated into a significant 51% reduction in the need for repeat revascularization (OR 0.43, 95% CI 0.29 to 0.84). At 30 days, a similar beneficial effect was observed in the GP IIb/IIIa group (472 of 13,733 patients [3.44%]) compared with the control group (503 of 9683 patients [5.19%]). The reduction in risk was 34% (OR 0.66, 95% CI 0.56 to 0.77) (Figure 4). By six months, the need for repeat revascularization remained lower in the GP IIb/IIIa group compared with the control group. There were 1412 of 9281 patients (15.21%) requiring a repeat intervention in the GP IIb/IIIa group compared with 1177 of 6765 patients (17.40%) in the control group, which represented a 14% risk reduction (OR 0.86, 95% CI 0.78 to 0.94). Treatment with GP IIb/IIIa antagonists resulted in an absolute decrease of 1.97%, 1.75% and 2.19% at seven days, 30 days and six months, respectively, for the need for repeat revascularization following PCI.

CEPs

Overall, the composite of death, MI or repeat revascularization was reduced at all time points. At seven days, the risk was reduced by 39% (OR 0.61, 95% CI 0.50 to 0.75); at 30 days, the risk was reduced by 36% (OR 0.64, 95% CI 0.56 to 0.75), and at six months, the risk was reduced by 27% (OR 0.73, 95% CI 0.63 to 0.86). Results at one year were not analyzed due to insufficient information.

Bleeding and thrombocytopenia

Major bleeding events occurred in 533 of 12,598 patients (4.23%) in the GP IIb/IIIa group compared with 249 of 8497 patients (2.93%) in the control group; results were not statistically significant (OR 1.29, 95% CI 0.98 to 1.68) and were associated with significant heterogeneity across the trials (Figure 5). The incidence of minor bleeding was significantly increased in the GP IIb/IIIa group compared with the control group. In the GP IIb/IIIa group, 368 of 6344 patients (5.80%) experienced a minor bleed compared with 157 of 4407 patients (3.56%) in the control group (Figure 6). This translates into a 2.24% absolute increase in minor bleeding events with GP IIb/IIIa antagonists (OR 1.80, 95% CI 1.47 to 2.21). Patients treated with GP IIb/IIIa inhibitors also experienced a greater prevalence of thrombocytopenia. The incidence of thrombocytopenia in the GP IIb/IIIa versus control group was 211 events in 8471 patients (2.49%) compared with 90 events in 5418 patients (1.67%), which represents an

Figure 4) Repeat revascularization procedures at 30 days. Risk ratios and 95% CI are shown for each study and for the combined trials. Heterogeneity $\chi^2=18.60$ (15 degrees of freedom), $P=0.233$. I^2 (variation in OR attributable to heterogeneity) = 19.3%. ADMIRAL Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up; CADILLAC Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; CAPTURE c7E3 fab AntiPlatelet Therapy in Unstable REfractory angina; EPIC Evaluation of 7E3 for the Prevention of Ischemic Complications; EPILOG Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade; EPISTENT Evaluation of Platelet IIb/IIIa Inhibitor for Stenting; ERASER Acute Platelet Inhibition With Abciximab Does Not Reduce In-Stent Restenosis; ESPRIT Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy; EUR CO-OP European Co-operative Study; GP Glycoprotein; IMPACT Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis; ISAR-REACT Intracoronary Stenting and Antithrombotic Regimen – Rapid Early Action for Coronary Treatment; RAPPORT ReoPro in Acute myocardial infarction and Primary PTCA Organization and Randomized Trial; RESTORE Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis

absolute increase of 0.82% (OR 1.41, 95% CI 1.10 to 1.81). Taken together, this indicates that treatment with GP IIb/IIIa antagonists significantly increases the incidence of minor bleeding events and thrombocytopenia, but not major bleeding events, following PCI.

DISCUSSION

Treatment with intravenous GP IIb/IIIa receptor antagonists confers a significant clinical benefit in patients undergoing PCI. With treatment, there is a significant 0.38% absolute reduction in mortality at 30 days. The trend toward benefit appears as early as seven days and is evident at six months and one year, but at these other time intervals, the differences are not statistically significant. The beneficial effects of GP IIb/IIIa antagonists in reducing both MIs and the need for repeat revascularization are observed as early as seven days and persist to 30 days and six months. It is important to note that these observed clinical benefits are achieved with no significant increase in major bleeding, but with a significant increase in the incidence of minor bleeding and thrombocytopenia.

To emphasize the clinical efficacy of GP IIb/IIIa antagonists, it is important to note that at 30 days postprocedure, 296 patients need to have been treated to save one life, 47 patients to prevent one MI and 59 patients to prevent one repeat revascularization procedure. Also, one minor bleed occurs for every 39 patients treated with these medications compared with control patients.

Figure 5 Incidence of major bleeding. Risk ratios and 95% CI are shown for each study and for the combined trials. Heterogeneity $\chi^2=27.95$ (15 degrees of freedom), $P=0.022$. I^2 (variation in OR attributable to heterogeneity) = 46.3%. ADMIRAL Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up; CADILLAC Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; CAPTURE c7E3 fab AntiPlatelet Therapy in Unstable REfractory angina; EPIC Evaluation of 7E3 for the Prevention of Ischemic Complications; EPILOG Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade; EPISTENT Evaluation of Platelet IIb/IIIa Inhibitor for Stenting; ERASER Acute Platelet Inhibition With Abciximab Does Not Reduce In-Stent Restenosis; ESPRIT Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy; EUR CO-OP European Co-operative Study; GP Glycoprotein; IMPACT Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis; RAPPORT ReoPro in Acute myocardial infarction and Primary PTCA Organization and Randomized Trial; RESTORE Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis

Assuming that at least two million PCIs are performed annually worldwide, the routine use of GP IIb/IIIa antagonists would prevent over 6600 deaths, 42,000 MIs and 34,000 repeat revascularization procedures at a cost of 50,000 minor bleeds.

Although previous meta-analyses evaluating the efficacy of GP IIb/IIIa inhibitors have been performed (32,35), not all of these earlier studies have demonstrated a significant reduction in mortality. In those that did, of particular significance is a more recent study by Karvouni et al (33), in which the authors noted a 31% RR reduction in mortality at 30 days (95% CI 0.53 to 0.90) and a 21% reduction in mortality at six months (95% CI 0.64 to 0.97). Kong et al (34) found a 27% reduction in mortality (OR 0.73, 95% CI 0.55 to 0.96) at 30 days and a nonsignificant 16% reduction (OR 0.84, 95% CI 0.69 to 1.03) at six months. Our analysis reported a 30% reduction in mortality at seven days, which was not statistically significant, but by 30 days, the 28% reduction in mortality was statistically significant. At one year, there was a trend toward a beneficial effect on mortality (OR 0.80, 95% CI 0.64 to 1.00). Our meta-analysis, which includes additional contemporary trials, provided data regarding mortality as early as seven days and as late as one year. The effect on mortality at these two time points has not been previously reported.

The present study was unique in demonstrating a GP IIb/IIIa-driven reduction in MI as early as seven days, a benefit that persists to six months. This is consistent with the known pharmacodynamic effects of these agents, whereby potent

Figure 6 Incidence of minor bleeding. Risk ratios and 95% CI are shown for each study and for the combined trials. Heterogeneity $\chi^2=11.04$ (12 degrees of freedom), $P=0.525$. I^2 (variation in OR attributable to heterogeneity) = 0.0%. ADMIRAL Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up; CAPTURE c7E3 fab AntiPlatelet Therapy in Unstable REfractory angina; EPILOG Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade; EPISTENT Evaluation of Platelet IIb/IIIa Inhibitor for Stenting; ESPRIT Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy; GP Glycoprotein; EUR CO-OP European Co-operative Study; IMPACT Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis; RAPPORT ReoPro in Acute myocardial infarction and Primary PTCA Organization and Randomized Trial

GP IIb/IIIa antagonism reduces local platelet deposition at the site of PCI. This results in a reduction in the local platelet-mediated vasoconstriction, distal vessel platelet-thrombin microembolization and abrupt vessel closure, all of which contribute to decreasing MIs in treated patients (2,46).

With decreasing MI rates, GP IIb/IIIa antagonists significantly reduce the need for repeat revascularization procedures. Our meta-analysis was the first to focus on this clinically important end point. At seven days, the need for repeat revascularization was reduced by more than 50%, but there appeared to be some attenuation of benefit, because at six months, there was only a 14% reduction in repeat revascularization procedures. This is likely due to the fact that the GP IIb/IIIa antagonists protect against acute vessel closure, which occurs early after PCI and drives many of the early repeat revascularization procedures. Restenosis, however, is a more chronic process and dominates the repeat revascularization events occurring between 30 days and six months post-PCI. The chronic process of restenosis does not appear to be impacted by this class of drugs, with the exception of abciximab, which may reduce the risk of restenosis in diabetic patients receiving coronary bare metal stents (3,47).

The beneficial effects of intravenous GP IIb/IIIa antagonists may be somewhat offset by their associated increased risk of minor bleeding. More important, however, is that these agents do not have a significant impact on major bleeding. Karvouni et al (33) found that major bleeding was significantly increased, but only in trials in which heparin infusion was continued after the procedure. Most studies have suggested that major bleeding does have a significant impact on long-term outcomes, but that the same is not true of minor bleeding (48,49). The incidence of thrombocytopenia was significantly higher in the GP IIb/IIIa-treated group. Likely, this result was driven by the monoclonal antibody abciximab,

treatment with which is associated with a higher incidence of thrombocytopenia compared with the small molecules, and was used in 15 of the 21 trials included in the present analysis (50).

Limitations

The present meta-analysis was conducted in accordance with the high methodological standards set out by the Quality of Reporting of Meta-analysis recommendations (40). To the authors' knowledge, the meta-analysis represents the most current and comprehensive analysis of available randomized trials of GP IIb/IIIa inhibitors of patients undergoing PCI. Although extensive and comprehensive efforts were used in performing the meta-analysis, it is possible that some studies may have been missed. Because there is a publication bias against negative trials, trials failing to demonstrate benefit may not be present in the medical literature and may therefore not be included in the current meta-analysis, which may result in an overestimation of the benefit of this class of agents. However, we did not detect publication bias in our funnel plots. Given that heterogeneity was not found for most outcomes, further research is not required to confirm the benefit of GP IIb/IIIa antagonists on mortality, MI and revascularization in

patients similar to those treated within the studies included in the present meta-analysis. Nevertheless, changes in the practice of interventional cardiology since the publication of many of these trials may limit the generalizability of the results in this meta-analysis, including the routine use of high-dose loading with clopidogrel, lower doses of heparin and drug-eluting stents.

CONCLUSIONS

The current meta-analysis demonstrates a significant reduction in mortality, MI and repeat revascularization procedures in patients undergoing PCI who are treated with periprocedural intravenous GP IIb/IIIa inhibitors. This beneficial effect is achieved at an increased risk of minor bleeding and thrombocytopenia, but not major bleeding.

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