International Journal of Cardiology xxx (2010) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Effectiveness and safety of glycoprotein IIb/IIIa inhibitors in patients with myocardial infarction undergoing primary percutaneous coronary intervention: A meta-analysis of observational studies

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ARTICLE INFO

Article history:
Received 1 January 2010
Received in revised form 13 June 2010
Accepted 8 August 2010
Available online xxxx

Keywords:
Acute coronary syndromes
Angioplasty
Percutaneous coronary intervention
Glycoprotein inhibition

ABSTRACT

Introduction: Meta-analyses of randomized controlled trials (RCT) showed that glycoprotein IIb/IIIa inhibitors (GPI) are associated with reduced adverse events following primary percutaneous coronary revascularization (PCI). However, the external validity of RCTs is generally limited due to their restricted inclusion of patients. The objective of this study is to evaluate the effectiveness and safety of GPI, as adjuvant therapy for primary PCI in real-life patients with myocardial infarction with ST segment elevation (STEMI) from the general population.

Methods: We identified all published peer-reviewed observational studies enrolling STEMI patients who underwent primary PCI. We performed random-effect meta-analyses to determine the association of GPI with major adverse events.

Results: A total of 11 studies, enrolling 12,253 patients, were retained for this meta-analysis. GPI was associated with approximately 53% reduction in short-term mortality (odds ratio (OR): 0.47, 95% confidence intervals (CI): 0.32–0.68). There was a 62% reduction in long-term mortality associated with GPI (OR: 0.38, 95% CI: 0.30–0.50). GPI was associated with a 62% reduction in 30-day re-infarction (OR: 0.38, 95% CI: 0.24–0.60) and 42% reduction in 30-day repeat PCI (OR: 0.58, 95% CI: 0.36–0.94). A non-significant increase in major bleeding with GPI was observed with an OR of 1.55 (95% CI: 0.92–2.62).

Conclusions: GPI is associated with significant reductions in short-term mortality, re-infarction and repeat PCI, long-term mortality and an inconclusive increase in major bleeding. These results provide evidence for the safety and effectiveness of GPI as adjuvant therapy for primary PCI in real-life STEMI patients.

1. Introduction

Meta-analyses of randomized controlled trials (RCT) [1–5] showed reductions in mortality, re-infarction, and target vessel revascularization with glycoprotein IIb/IIIa inhibitors (GPI) for primary percutaneous coronary intervention (PCI) in ST segment elevation myocardial infarction with (STEMI). Therefore, the American Heart Association and the American College of Cardiology have endorsed the use of these medications as adjuvant therapy for primary PCI [6].

However, the external validity of RCTs and meta-analyses of these RCTs is generally limited [7–9]. Findings from RCT may not always be reproducible in real-life context. Well-designed observational studies, and meta-analyses of observational studies, may yield relevant and important results concerning the effectiveness and safety of many medical interventions [10–13]. There is no available systematic review of the safety and effectiveness of GPI in real-life STEMI

Abbreviations: CI, confidence interval; GPI, glycoprotein IIb/IIIa inhibitors; OR, odds ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trials; STEMI, ST segment elevation myocardial infarction.

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doi:10.1016/j.ijcard.2010.08.019

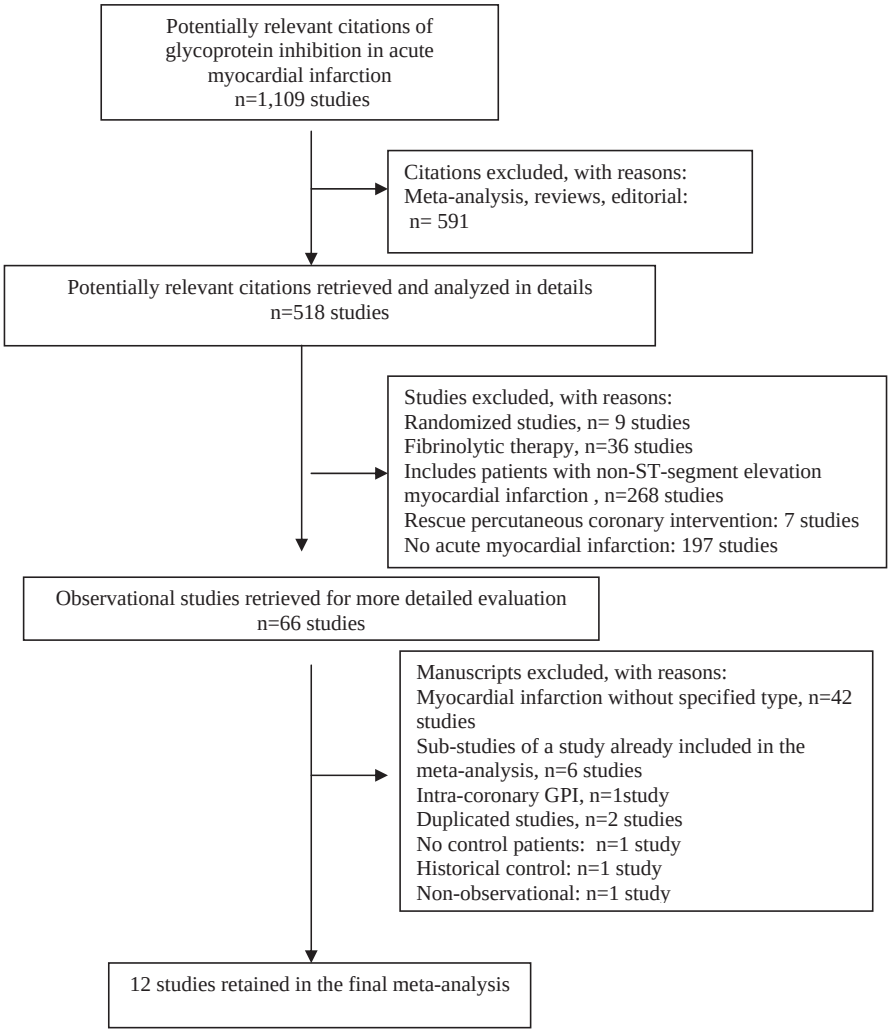

Fig. 1. Quorom flow diagram of study selection.

patients from the general population who may be at higher risk of bleeding than patients enrolled in RCT. Considering the increasing use of primary PCI as the preferred reperfusion strategy [14,15], a systematic review of observational studies is timely and may provide pertinent insights into the effectiveness and safety of GPI for primary PCI for STEMI patients from the general population.

2. Methods

2.1. Literature search

We retrieved all observational studies of GPI for primary PCI in humans from the following databases: BIOSIS, Cinahl, Embase, PubMed, Web of Science, Cochrane Library, health technology assessment agencies and Current Contents (up to 15

Table 1
Baseline clinical characteristics.

First author	No. of GPI	No. of control	Mean age GPI (SD)	Mean age Control (SD)	Female GPI	Female Control	Diabetes GPI	Diabetes Control	Shock GPI	Shock Control	Anterior MI GPI	Anterior MI Control
					%	%	%	%	%	%	%	%
Berger [22]	107	162	60	62	24	30	26	22	15	12	NA	NA
Uyarel [23]	64	51	56 (12)	58 (13)	11	24	13	10	Excluded	Excluded	55	59
Heer [24]	946	1238	63 (NA)	65 (NA)	28	27	23	25	8	4	42	41
Lavi [25]	287	115	57 (12)	60 (13)	16	17	20	20	4	12	72	57
Kalaria [26]	212	45	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Antoniucci [27]	348	213	62 (11)	68 (12)	19	25	14	14	10	11	52	45
Giri [28]	302	348	60 (NA)	62 (NA)	27	33	15	21	16	13	NA	NA
Azar [29]	103	79	60 (13)	61 (11)	30	39	9	24	11	15	37	37
Chan [30]	45	51	65 (NA)	67 (NA)	17	18	18	18	100	100	21	27
Lev [31]	167	49	59 (13)	66 (13)	17	33	19	37	Excluded	Excluded	53	37
Srinivas [32]	5,748	1,573	60 (13)	64 (14)	27	33	19	20	2	2	NA	NA

GPI: glycoprotein IIb/IIIa inhibitor, MI: myocardial infarction.

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Table 2
Methods of administration of glycoprotein IIb/IIIa inhibitors.

First author	Enrollment period	Type of glycoprotein inhibitor	Time of initiation	Duration of infusion
Berger [22]	1998–1999	Abciximab, eptifibatide, tirofiban	NA	NA
Uyarel [23]	2004–2005	Tirofiban	In the PCI laboratory	36 h
Heer [24]	2000–2002	Abciximab	NA	NA
Lavi [25]	1996–2003	Abciximab (30%), eptifibatide (66%), tirofiban (4%)	In the PCI laboratory	14–16 h
Kalaria [26]	1996–1998	NA	NA	NA
Antoniucci [27]	1999–2000	Abciximab	In the PCI laboratory	12 h
Giri [28]	1995–1998	Abciximab	In the PCI laboratory	NA
Azar [29]	1996–1997	Abciximab	NA	12 h
Chan [30]	1993–2000	Abciximab	NA	NA
Lev [31]	2000–2003	Eptifibatide	In the PCI laboratory	18–24 h
Srinivas [32]	2000–2002	Abciximab, eptifibatide, tirofiban	NA	NA

NA: not available, PCI: percutaneous coronary intervention.

September 2009) (no language restriction), using the following keywords: "angioplasty", "acute myocardial infarction", "percutaneous coronary intervention", "reperfusion therapy", "coronary stent", "glycoprotein inhibition" and "glycoprotein inhibitors", "eptifibatide", "abciximab" and "tirofiban". In addition, we hand-searched the references of published articles to ensure identification of all relevant studies and avoid use of duplicate publications.

2.2. Inclusion criteria

We retained only studies that specified the intravenous use of one or more of the following commercially available GPI (abciximab, tirofiban, eptifibatide). The studies had to include a "control" group of patients who did not receive GPI, and reported outcomes for both groups of patients. We excluded studies of patients who received fibrinolytic therapy PCI prior to PCI (rescue or facilitated PCI). Finally, all retained observational studies had to fulfill the quality requirements of a good observational study as suggested by to Concato et al. [10] such as a "time zero" for determination of patient's eligibility, concurrent controls, and clearly defined inclusion criteria.

2.3. Exclusion criteria

We excluded studies with incomplete information on methods of administration of GPI. Studies with intracoronary administration GPI were excluded unless specific outcomes were reported for patients who received peripheral intravenous administration of GPI. We also excluded studies presented or published only as abstracts or conference proceedings, because detailed appraisal of the methodology and detection of potential biases would not be possible.

2.4. Endpoints

All endpoints were analyzed as distinct events rather than as a composite endpoint comprising multiple events. The latter approach can be sub-optimal because of equal contributions to the composite endpoint by endpoints with unequal clinical relevance [16]. Effectiveness endpoints of interest were all-cause mortality, re-infarction and repeat PCI. The safety endpoint of interest was major bleeding which included all hemorrhagic complications, defined by the authors as either severe or life threatening or required transfusion during the index hospitalization. Short-term endpoints included all events up to 30-day after the index STEMI. Long-term endpoints included all events that occurred beyond 6-month after the STEMI. For long-term events, only data on all-cause mortality were available for analysis.

2.5. Study quality

We critically appraised the internal (potential biases) and external validity (generalizability of the results to the real-life context) of all studies retained. We elected not to use scales to evaluate trial quality since this approach can be problematic, with potential inappropriate adjustment of the treatment effects and marked variation in the treatment effects depending on the scale used [17,18]. Our quality evaluation was based on the criteria recommended by the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) Group [19].

The selection, data extraction and quality evaluation of studies were completed independently by two reviewers (RK and TH). Disagreements were resolved by consensus.

2.6. Statistical analysis

We completed separate meta-analysis for each endpoint. Since it was unlikely that the effect of GPI would be similar across studies due to differences in study design and patient characteristics, we did not use a fixed-effect model (where studies were assumed to be similar and that the inter-study variation was due to chance). A random-effects model (DerSimonian and Laird) [20] was selected to take into account the inter-trial variation in treatment effects. In general, the random-effects model provides more conservative estimate of the treatment effect with wider confidence intervals than the fixed-effects models [20,21]. All analyses, funnel plots and forest plots were completed by the Comprehensive Meta-Analysis, version 2.

Table 3
Concomitant therapy.

First author	Aspirin	Heparin	Thienopyridines	Stent % GPI	Stent % Control
Berger [22]	NA	NA	NA	80	80
Uyarel [23]	NA	UFH 5,000 U pre-PCI followed by LMWH 1 mg/kg/day post-PCI	CLOPID 300 mg pre-PCI	100	100
Heer [24]	NA	NA	80% of patients received thienopyridines, method of administration NA	84	78
Lavi [25]	200–350 mg pre-PCI	UFH ,weight adjusted for ACT 250–300 s, discontinued after PCI	Patients with stents: TICLID 250 mg twice daily or CLOPID 75 mg daily for 4 weeks	81	74
Kalaria [26]	NA	NA	NA	NA	NA
Antoniucci [27]	325 mg daily	UFH 12 h for abciximab vs 48 h for control, dose NA	TICLID 250 mg twice daily for 4 weeks	93	84
Giri [28]	NA	UFH 5,000–10,000 U	Patients with stents: TICLID or CLOPID for 21–30 days	66	37
Azar [29]	NA	UFH 5,000 U bolus followed by infusion for ACT >300 s	Patients with stents: TICLID 500 mg load and 250 mg twice daily for 4 weeks	51	43
Chan [30]	NA	NA	NA	27	14
Lev [31]	100–325 mg daily	UFH 70 U/kg bolus followed by infusion for ACT 225–300 s	CLOPID 300 mg loading + 75 mg for 4 weeks	96	98
Srinivas [32]	NA	NA	NA	92	86

U: units, NA: not available, PCI: percutaneous coronary intervention, ACT: activated clotting time, CLOPID: clopidogrel, TICLID: ticlidopine, UFH: unfractionated heparin, LMWH: low molecular weight heparin.

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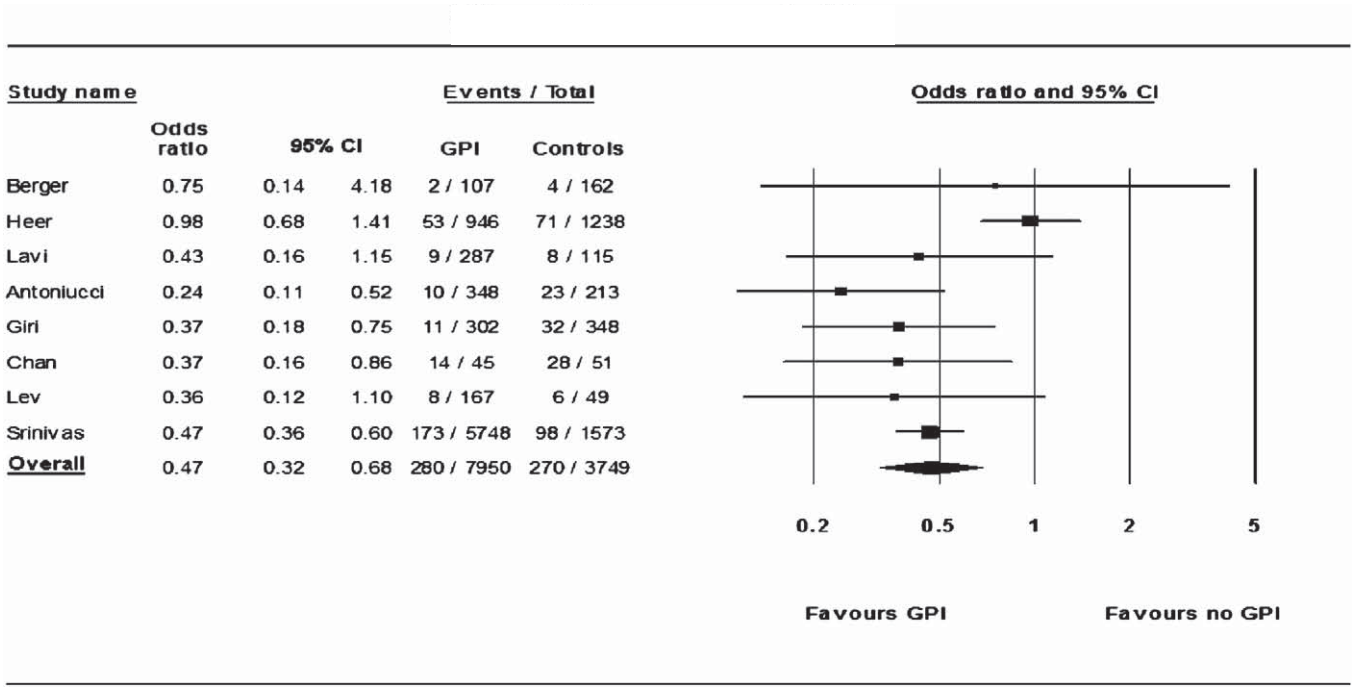

Fig. 2. Short-term mortality.

3. Results

We retained 11 studies [22–32], enrolling a total of 12,253 patients, for the meta-analysis (Fig. 1). We summarized the baseline characteristics of the patients in Table 1. In most studies, there were more males and younger patients in the GPI arm, with abciximab being the most commonly used GPI (Table 1). GPI were most frequently initiated in the PCI laboratory and within 6–24 hours from the onset of STEMI symptoms (Table 2). The majority of patients underwent implantation of an intracoronary stent and concomitant anticoagulation with unfractionated heparin (Table 3). Thienopyridines were prescribed in most patients who received implantation of intracoronary stents.

GPI was associated with approximately 53% reduction in short-term mortality (OR: 0.47, 95% CI: 0.32–0.68) in 8 studies enrolling 11,699 patients (Fig. 2). There was a 62% reduction in long-term mortality associated with GPI (OR: 0.38, 95% CI: 0.30–0.50) in 5 studies that enrolled 2,890 patients (Fig. 3). GPI was associated with a 62% reduction in 30-day re-infarction (OR: 0.38, 95% CI: 0.24–0.60) (Fig. 4) and 42% reduction in 30-day repeat PCI (OR: 0.58, 95% CI: 0.36–0.94) (Fig. 5). A non-significant increase in major bleeding with GPI was observed: 1.55 (0.92–2.62) (Fig. 6).

We reported the associations of exclusive use of abciximab with major adverse cardiac events and major bleedings in Table 4. Abciximab was associated with reductions of 54% in short-term mortality, 30% in re-infarction and 46% in repeat PCI. Finally, the estimate of the treatment effect remained essentially unchanged with imputation of potentially missing studies that might not have shown benefits of GPI in primary PCI.

4. Discussion

Previous meta-analysis of RCTs showed reductions of approximately 30% in short and long-term mortality with abciximab in STEMI patients who underwent primary PCI [3,4]. Abcixmab was associated with relative reductions of 25% to 45% in major cardiac adverse events following primary PCI [1–4]. There is no available meta-analysis of efficacy and safety of eptifibatide and tirofiban for primary PCI.

Despite their generally good internal validity, the external validity of many RCTs of STEMI patients is often limited. Indeed, patients enrolled in RCTs are generally more healthy and younger than real-life

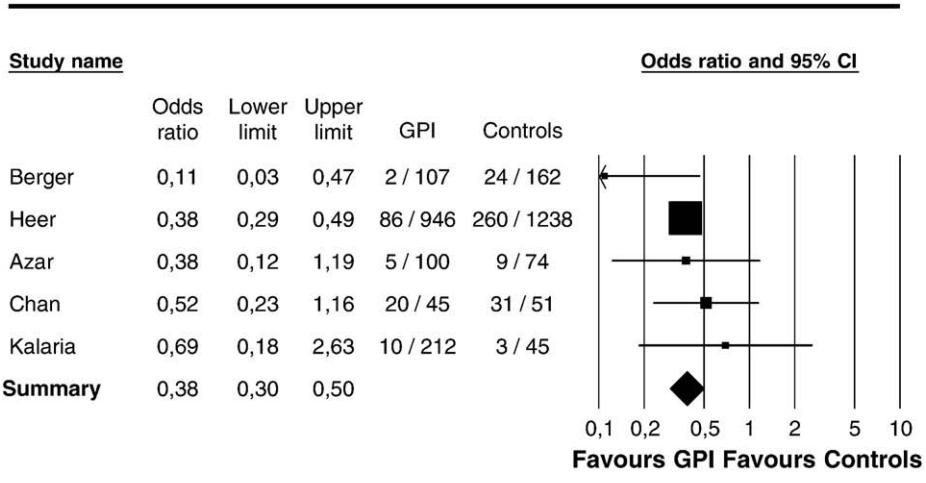

Fig. 3. Long-term mortality.

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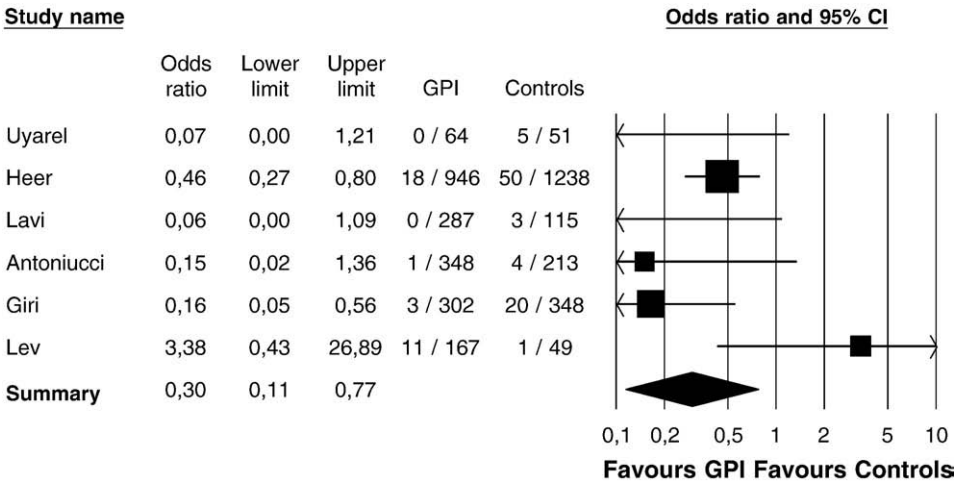

Fig. 4. Short-term re-infarction.

patients [7–9]. Furthermore, administration of GPI in real-life conditions may be sub-optimal than within RCT's context such as delayed initiation, shortened administration or inaccurate dosing. Sub-optimal administration may translate into reduced clinical benefits or increased adverse effects of GPI.

In addition, RCTs generally had limited sample sizes and short duration of follow-up that might be inadequate for detection of infrequent adverse effects or benefits with prolonged latency [12,13]. Patients at increased risk of bleeding such as the elderly, patients with bleeding diatheses or with renal insufficiency were generally excluded or under-represented in RCTs [4,7–9]. Due to all of the above reasons, by inclusion of observational studies with longer follow-up and larger samples sizes, our meta-analysis may provide valuable insights into the effectiveness and safety of GPI for real-life patients within the real-life context.

Recent RCTs [38–40] did not show benefit of GPI in reducing major adverse cardiac outcomes in patients pre-treated with thienopyridines who underwent primary PCI. Seven of the studies included in our meta-analysis mentioned thienopyridines' use in 4,300 patients [23,25–29,31]. Although the authors of two recent studies [24,32] did not report explicitly on the use of thienopyridine, it was highly probable that the patients enrolled in these studies received thienopyridine in view of the recent enrolment periods (2000–2002). Our results suggested potential benefit of GPI in reduction of major adverse events in addition to thienopyridines for primary PCI in "real-life" context.

Long-term data were available from only four RCTs with maximal follow-up only up to 6-month following the index STEMI [33–35,37]. In contrast, four reviewed observational studies had at least 1-year follow-up [22,24,26,30] and 7-month survival data were available in another study [29]. GPI remained consistently associated with reductions in long-term mortality up to 3-year in one study [22]. We observed lower rates of bleeding events with GPI compared to previous meta-analyses of RCTs [1–4]. Judicious physicians' selection of patients at lower-risk of bleeding was the likely explanation for the lack of conclusively increased risk of bleeding with GPI in our study.

The efficacy and safety of GPI in patients with cardiogenic shock are relatively unclear since these patients are generally excluded from most RCTs [4]. There were only four RCTs that enrolled patients in cardiogenic shock [33–36]. There were nine observational studies that enrolled patients in cardiogenic shock [22,24–30,32] with one study that enrolled exclusively patients in cardiogenic shock [30]. The estimates of the treatment effects and risk of major bleeding were similar in these studies, regardless of inclusion or exclusion of patients in cardiogenic shock.

Our sensitivity studies indicated conclusive reductions in short-term mortality, re-infarction and repeat PCI with abciximab as adjunctive therapy for primary PCI. Due to the availability of only a few observational studies that reported exclusive use of eptifibatide and tirofiban [23,26,33], reliable estimate of their treatment effects was not possible. Overall, the results of our meta-analysis indicate conclusive effectiveness of GPI in real-life patients who underwent

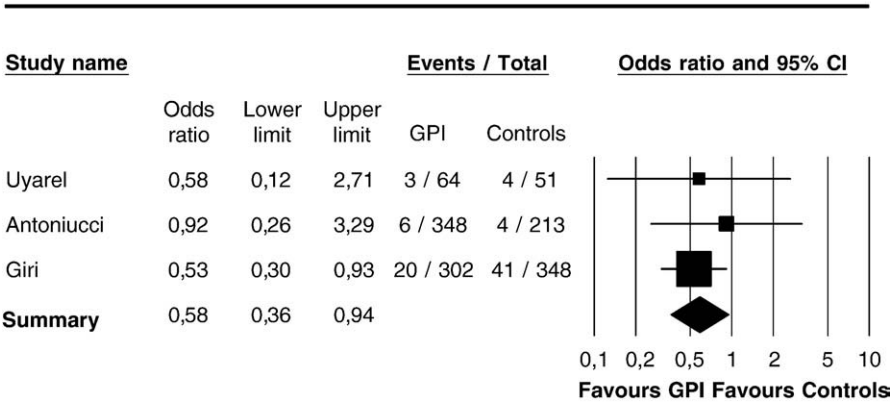

Fig. 5. Short-term repeat percutaneous coronary intervention.

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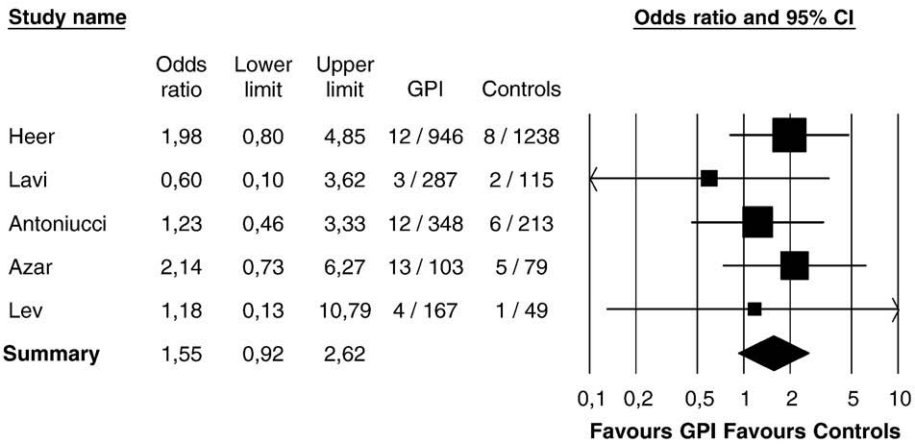

Fig. 6. Major bleeding.

primary PCI within real-life context, despite potentially less ideal conditions and inclusion of sicker patients than those of RCTs.

5. Limitations

Our study has a few potential limitations. First, the more marked relative reductions in major adverse cardiac events (40% to 50%) associated with GPI, observed in our meta-analysis, compared to the relative reductions (30% to 40%) seen in previous meta-analyses of RCTs [1–4] may be explained potentially by selection bias with physicians favouring GPI use in lower-risk patients. Since we did not have access to individual patient data and due to the availability of a limited number of studies, we could not perform meta-regressions to adjust for the differences in baseline characteristics between the patients who received GPI and those who did not receive GPI. Second, unfractionated heparin was used in all of the studies included in this meta-analysis. Therefore, we could not evaluate the safety and efficacy of GPI with low-molecular weight heparin and newer types of anticoagulation such as fondaparinux and bilavirudine. Third, there was heterogeneity in the type of GPI used. However, the recent meta-analysis by Gurm et al. [41] did not show any difference in safety and efficacy between the types of GPI for primary PCI. Fourth, most of the studies included in our meta-analysis were completed before the widespread use of drug eluting stents. Therefore, we could not evaluate the effectiveness of GPI for the different types of stents. Fifth, due to lack of individual patients' data, we could not evaluate the impact of concomitant medications on the safety and effectiveness of GPI. Finally, potential publication bias should be considered. Reports with positive findings were more likely to be reported, published and cited [42]. However, our estimates of the treatment effects were essentially unchanged with imputation of potentially missing observational studies that might not have shown benefits with GPI (Fig. 7).

Table 4
Comparison of abciximab with no glycoprotein inhibition in reduction of major adverse events for primary percutaneous coronary intervention.

Abciximab			
	No. of studies	No. of patients	OR (95% CI)
Short-term mortality [24,26,27,29]	4	3,491	0.45 (0.22–0.92)
Short-term re-infarction [24,27,28]	3	3,395	0.31 (0.14–0.66)
Short-term repeat PCI [27,28]	2	1,211	0.58 (0.35–0. 97)
Major bleeding [24,27,29]	3	2,927	1.73 (0.98–3.05)
Long-term mortality [22,24,25,28,29]	5	2,842	0.60 (0.28–1.26)

PCI: percutaneous coronary intervention, NA: not available.

6. Conclusion

Our meta-analysis shows that GPI is associated with reductions in short-term mortality, re-infarction, repeat PCI and long-term mortality for real-life STEMI patients from the general population who undergo primary PCI. There is no conclusive increased risk of major bleeding with GPI in these patients. Our results confirm the effectiveness and safety of GPI in real-life context, and support the current ACC/AHA recommendation for the use of GPI as adjunctive therapy for primary PCI in patients with STEMI [5].

Acknowledgement

The study was supported by Quebec's Foundation of Research—Axis of Cardiovascular Health, McGill University and McGill Health University Center Research Institute. The authors of this manuscript certified that they have complied with the Principles of Ethical Publishing in the International Journal of Cardiology [43].

Disclosure of conflict of interest: Drs. Dery JP and Huynh T received research grants from Merck, Schering, Elli-Lilly. Dr. Kouz S and Dery JP also received honorarium for speaking engagement and consulting fees from Schering and Merck.

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Please cite this article as: Kouz R, et al, Effectiveness and safety of glycoprotein IIb/IIIa inhibitors in patients with myocardial infarction undergoing primary percutaneou..., Int J Cardiol (2010), doi:10.1016/j.ijcard.2010.08.019