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Systematic Review/Meta-analysis

Routine Glycoprotein IIb/IIIa Inhibitor Therapy in ST-Segment Elevation Myocardial Infarction: A Meta-analysis

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ABSTRACT

Background: Guidelines recommend adjunct glycoprotein IIb/IIIa inhibitors (GPIs) only in selected patients with acute ST-segment elevation myocardial infarction (STEMI). This study aimed to evaluate routine GPI use in STEMI treated with primary percutaneous coronary intervention.

Methods: Online databases were searched for randomized controlled trials of routine GPI vs control therapy in STEMI. Data from retrieved studies were abstracted and evaluated in a comprehensive meta-analysis. Twenty-one randomized controlled trials with 8585 patients

RÉSUMÉ

Contexte : Les lignes directrices recommandent le traitement d'appoint par des inhibiteurs des glycoprotéines IIb-IIIa (IGP) uniquement chez certains patients ayant subi un infarctus du myocarde avec élévation du segment ST (STEMI) aigu. Cette étude visait à évaluer l'utilisation systématique des IGP chez les patients ayant subi un STEMI traité par une intervention coronarienne percutanée primaire.

Méthodologie : Une recherche dans les bases de données en ligne a été entreprise pour trouver des études contrôlées à répartition aléatoire ayant comparé l'administration systématique d'IGP à un

Early reperfusion therapy preferably with primary percutaneous coronary intervention (pPCI) has substantially contributed to the improvement of prognosis in acute ST-segment elevation myocardial infarction (STEMI).[1] Adjunct anticoagulants and antiplatelet therapy are routinely used to facilitate dissolution of intracoronary thrombi, reduce microvascular obstruction, and reduce the rate of recurrent ischemic events.[2,3]

Glycoprotein IIb/IIIa inhibitors (GPIs) are potent and rapidly acting intravenous or intracoronary antiplatelet agents and have been an integral part of STEMI management for decades.[4,5] With the advent of the more potent oral P2Y12 receptor inhibitors prasugrel and ticagrelor,[6,7] however, American, Canadian, and European cardiovascular society guidelines have gradually scaled back GPI recommendations from routine therapy[4,5,8] to bail-out-use/selected-patients-only in contemporary iterations,[2,3,9] but the evidence base for these changes remains elusive. Contemporary randomized controlled trials (RCTs) with these agents are lacking, and meta-analyses are largely out-of-date and have focused on a mixture of clinical settings and GPI indications.[10-13]

The conceptual design of this systematic review and meta-analysis thus aimed at evaluating all available RCT evidence on routine GPI therapy in STEMI managed with pPCI, in order to elucidate risk-benefit ratios and improve guidance of intravenous adjunct antiplatelet therapy.

Methods

This work was performed by independent investigators in compliance with accepted standards defined by the Cochrane Collaboration and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for

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were included: 10 trials randomized tirofiban, 9 abciximab, 1 trial eptifibatide, and 1 trial used abciximab+tirofiban; only 1 trial used dual antiplatelet therapy with prasugrel/ticagrelor.

Results: Routine GPI use was associated with a significant reduction in all-cause mortality at 30 days (2.4% [GPI] vs 3.2%; risk ratio [RR], 0.72; *P* = 0.01) and 6 months (3.7% vs 4.8%; RR, 0.76; *P* = 0.02), and a reduction in recurrent myocardial infarction (1.1% vs 2.1%; RR, 0.55; *P* = 0.0006), repeat revascularization (2.5% vs 4.1%; RR, 0.63; *P* = 0.0001), thrombolysis in myocardial infarction flow <3 after percutaneous coronary intervention (5.4% vs 8.2%; RR, 0.61; *P* < 0.0001), and ischemic stroke (RR, 0.42; *P* = 0.04). Major (4.7% vs 3.4%; RR, 1.35; *P* = 0.005) and minor bleedings (7.2% vs 5.1%; RR, 1.39; *P* = 0.006) but not intracranial bleedings (0.1% vs 0%; RR, 2.7; *P* = 0.37) were significantly increased under routine GPI.

Conclusions: Routine GPI administration in STEMI resulted in a reduction in mortality, driven by reductions in recurrent ischemic events—however predominantly in pre-prasugrel/ticagrelor trials. Trials with contemporary STEMI management are needed to confirm these findings.

traitement témoin chez des patients ayant subi un STEMI. Les données tirées des études trouvées ont été résumées et évaluées dans le cadre d'une méta-analyse exhaustive. Vingt-et-une études contrôlées à répartition aléatoire, auxquelles ont participé 8 585 patients, ont été incluses : dix études sur le tirofiban, neuf études sur l'abciximab, une étude sur l'eptifibatide et une autre sur l'association abciximab + tirofiban; une seule étude a utilisé le traitement antiplaquettaire double par l'association prasugrel + ticagrélor.

Résultats : L'utilisation systématique d'IGP a été associée à une réduction significative de la mortalité toutes causes confondues à 30 jours (2,4 % [IGP] vs 3,2 %; rapport des risques [RR] : 0,72; *p* = 0,01) et à 6 mois (3,7 % vs 4,8 %; RR : 0,76; *p* = 0,02), ainsi qu'à une réduction de l'infarctus du myocarde récurrent (1,1 % vs 2,1 %; RR : 0,55; *p* = 0,0006), de la répétition de la revascularisation (2,5 % vs 4,1 %; RR : 0,63; *p* = 0,0001), d'un flux dont le grade TIMI (*Thrombolysis in Myocardial Infarction*) est inférieur à 3 après une intervention coronarienne percutanée (5,4 % vs 8,2 %; RR : 0,61; *p* < 0,0001) et de l'accident vasculaire cérébral (AVC) ischémique (RR : 0,42; *p* = 0,04). Les hémorragies majeures (4,7 % vs 3,4 %; RR : 1,35; *p* = 0,005) et mineures (7,2 % vs 5,1 %; RR : 1,39; *p* = 0,006) ont nettement augmenté avec l'administration systématique d'IGP, mais pas les hémorragies intracrâniennes (0,1 % vs 0 %; RR : 2,7; *p* = 0,37).

Conclusions : L'administration systématique d'un IGP à des patients ayant subi un STEMI s'est traduite par une réduction de la mortalité, principalement attribuable à la diminution du nombre d'événements ischémiques récurrents. Cette réduction a néanmoins été surtout observée dans les études menées avant l'avènement de l'association prasugrel + ticagrélor. Il est nécessaire de mener des études sur les modalités de prise en charge actuelles du STEMI pour confirmer ces résultats.

reporting systematic reviews and meta-analyses in health care interventions.[14,15]

Study design, trial eligibility, and outcome selection

All available prospective RCTs of routine GPI therapy vs control (placebo or no GPI therapy) in unselected patients with STEMI managed with pPCI were eligible for inclusion. Studies had to provide an abstract in English; however, no restrictions on publication date, country, patient characteristics, or reported outcomes were imposed. Observational studies were excluded, as well as trials without pPCI, trials in non-STEMI settings, trials of nonroutine GPI therapy (eg, preselected patients with STEMI or bail-out GPI only), and trials randomizing anticoagulants in addition to GPI (Supplemental Table S1 and Fig. S1).

The primary outcome of interest was all-cause mortality. Efficacy outcomes were recurrent myocardial infarction (MI), repeat revascularization, thrombolysis in myocardial infarction (TIMI) flow grade at the end of pPCI and ischemic stroke; safety outcomes were major and minor bleeding events (defined according to the published report or—where possible—Bleeding Academic Research Consortium [BARC][16]), access site bleeding, transfusions, and hemorrhagic stroke.

Data sources, search strategy, and study identification

Three investigators (G.W., A.K., and Y.L.) performed the systematic review process. Medline, Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, clinicaltrials.gov, and EU Clinical Trials Register were systematically searched up until December 2018 for relevant publications. Search terms included but were not limited to glycoprotein inhibitor IIb/IIIa, GPI, STEMI, acute myocardial infarction, tirofiban, eptifibatide, abciximab, NSTEMI. Clinical trials in humans were used as a filter. Screening was primarily performed at the title and/or abstract level and was continued in full-text reports. Conference proceedings and bibliographic references of identified studies and reviews were additionally checked, and relevant citations were added. Positively evaluated studies were finally selected for inclusion in the meta-analysis. All relevant studies provided a full text in English. All divergences were resolved by consensus.

Data collection and quality assessment

Information on the following was extracted from each included trial into prespecified forms (G.W., A.K., Y.L., and C.P.): trial characteristics (eg, details on trial conduct, publication, intervention, procedures, follow-up, and bias), patient characteristics (eg, age, sex, and comorbidities), and clinical outcomes of interest. The most updated and/or inclusive intention-to-treat data were used, where possible. Cross-checking between investigators ensured internal data validity. Bias assessment was performed by 2 investigators (Y.L. and M.B.) according to the Cochrane collaboration guidelines,[14] who again cross-checked each other for errors. Divergences at any stage of the data collection process were resolved by consensus.

Table 1. Characteristics of included studies

Study	Journal	Multicentre trial (no. of centres)	Enrollment	Year of publication	No. of patients (per group)	Randomization	Oral platelet inhibitors	Anticoagulant	pPCI details	Vascular access	Follow-up duration
Antoniucci et al.[39,40] (ACE)	*Circulation/ JACC*	Yes (n.a.)	2001-2002	2003/2004	200/200	Abciximab 0.25 mg/kg bolus + 0.125 μg/kg/ min for 12 h vs nothing	Aspirin, ticlopidine, clopidogrel	Heparin	BMS	–	30 d, 6 mo, 1 y
Brener et al.[20] (RAPPORT)	*Circulation*	Yes (36)	1995-1997	1998	241/242	Abciximab 0.25 mg/kg bolus + 0.125 μg/kg/ min for 12 h vs placebo	Aspirin, 18% ticlopidine	Heparin	PTCA, 7% BMS	–	30 d, 6 mo
Ernst et al.[21]	*JACC*	No	2002-2003	2004	30/30/29/30	Abciximab 0.25 mg/kg bolus + 0.125 μg/kg/ min for 12 h vs tirofiban 10 μg/kg bolus + 0.15 μg/kg/min for 12 h vs tirofiban 25 μg/kg bolus + 0.15 μg/kg/min for 12 h vs nothing	Aspirin, clopidogrel	Heparin	–	–	In-hospital
Fu et al.[22]	*Chin Med J*	No	2005-2007	2008	72/78	Tirofiban 10 μg/kg bolus + 0.15 μg/kg/min for 24 h vs placebo	Aspirin, clopidogrel	Heparin	–	Radial	6 mo
Han et al.[23] (BRIGHT)	*JAMA*	Yes (82)	2012-2013	2015	629/641	Tirofiban 10 μg/kg bolus + 0.15 μg/kg/min for 18-36 h vs nothing	Aspirin, clopidogrel	Heparin	96% DES	78% radial, 22% femoral	30 d, 1 y
Le May et al.[24] (ASSIST)	*Circ Cardiovasc Int*	Yes (3)	2005-2008	2009	201/199	Eptifibatide 180 μg/kg 2× bolus + 2 μg/kg/min for 18 h vs nothing	Aspirin, clopidogrel	Heparin	76% BMS, 17% DES	87% Femoral	30 d, 6 mo
Liu et al.[25]	*Int J Clin Exp Med*	No	2013-2014	2015	52/53/53	Tirofiban 10 μg/kg bolus IC + 0.15 μg/kg/min for 24 h vs tirofiban 10 μg/kg bolus + 0.075 μg/kg/min for 24 h vs nothing	Aspirin, ticagrelor	Heparin	DES	92% Radial	30 d
Martinez-Rios et al.[26] (SASTRE)	*Am J Cardiol*	Yes (7)	2000-2002	2004	36/36	Tirofiban 0.4 μg/kg/min for 30 min + 0.1 μg/kg/ min for 36 h vs nothing	Aspirin, clopidogrel	Heparin	BMS	–	30 d
Mehilli et al.[27] (BRAVE-3)	*Circulation*	Yes (5)	2003-2008	2009	401/399	Abciximab 0.25 mg/kg bolus + 0.125 μg/kg/ min for 12 h vs placebo	Aspirin, clopidogrel	Heparin	49% BMS, 44% DES	–	30 d
Montalescot et al.[28] (ADMIRAL)	*NEJM*	Yes (26)	1997-1998	2001	149/151	Abciximab 0.25 mg/kg bolus + 0.125 μg/kg/ min for 12 h vs placebo	Aspirin, ticlopidine	Heparin	BMS	–	30 d, 6 mo
Neumann et al.[29]	*Circulation*	No	–	1998	102/98	Abciximab 0.25 mg/kg bolus + 10 μg/min for 12 h vs placebo	Aspirin, ticlopidine	Heparin	BMS	–	30 d
Neumann et al.[30] (ISAR-2)	*JACC*	No	–	2000	201/200	Abciximab 0.25 mg/kg bolus + 10 μg/min for 12 h vs placebo	Aspirin, ticlopidine	Heparin	BMS	–	30 d
Petronio et al.[41]	*Am Heart J*	No	–	2005	30/30	Abciximab 0.25 mg/kg bolus + 0.125 μg/kg/ min for 12 h vs nothing	Aspirin, clopidogrel	Heparin	BMS	90% Radial	30 d, 6 mo
Salarifar et al.[31]	*Iran Red Cres Med J*	No	–	2014	70/43	Tirofiban 25 μg/kg bolus + 0.15 μg/kg/min for 12-18 h vs nothing	Aspirin, clopidogrel	Heparin	51% BMS, 30% DES	–	30 d

Sharma et al.[32]	*Natl J Physiol Pharm*	No	—	2016	51/35	Tirofiban 25 μg/kg bolus + 0.15 μg/kg/min for 24-48 h vs nothing	Aspirin, clopidogrel	Heparin	—	—	30 d
Shen et al.[33]	*Coron Artery Dis*	No	2005-2006	2008	114/58	Tirofiban 10 μg/kg bolus + 0.15 μg/kg/min for 36 h vs nothing	Aspirin, clopidogrel	Heparin	DES	100% femoral	30 d, 6 mo
Steen et al.[34]	*Am Heart J*	No	2000-2002	2005	24/29	Tirofiban 10 μg/kg bolus + 0.15 μg/kg/min for 18 h vs nothing	Aspirin, clopidogrel	Heparin	BMS	—	In-hospital
Tcheng et al.[35,36] (CADILLAC)	*NEJM/ Circulation*	Yes (76)	1997-1999	2002/2003	1052/1030	Abciximab 0.25 mg/kg bolus + 0.125 μg/kg/ min for 12 h vs placebo	Aspirin, ticlopidine	Heparin	42% PTCA, 58% BMS	—	30 d, 1 y
Van't Hof et al.[37,43] (On-TIME 2)	*The Lancet/ JACC*	Yes (24)	2006-2007	2008/2010	491/493	Tirofiban 25 μg/kg bolus + 0.15 μg/kg/min for 18 h vs placebo	Aspirin, clopidogrel	Heparin	24% DES, 78% BMS	—	30 d, 1 y
Wang et al.[38]	*Cell Biochem Biophys*	No	2011-2013	2015	72/47	Tirofiban 10 μg/kg bolus IC + 0.15 μg/kg/min for 48 h vs nothing	Aspirin, clopidogrel	Heparin	DES	—	14 d
Zorman et al.[42]	*Am J Cardiol*	No	1998-2001	2002	112/51	Abciximab 0.25 mg/kg bolus + 0.125 μg/kg/ min for 12 h vs nothing	Aspirin	Heparin	64% BMS	—	In-hospital, 6 mo

ACE, **A**bciximab and **C**arbostent **E**valuation; ADMIRAL, **A**bciximab Before **D**irect angioplasty and Stenting **M**yocardial **I**nfarction **R**egistering **A**cute **L**ong-term Follow-up; ASSIST, A Safety and Efficacy Study of Integrilin-Facilitated Versus Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial; BMS, bare-metal stent; BRAVE-3, **B**avarian **R**eperfusion **A**lternati**v**es **E**valuation-3; BRIGHT, Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial; CADILLAC, **C**ontrolled **A**bciximab and **D**evice **I**nvestigation to **L**ower **L**ate **A**ngioplasty **C**omplications; DES, drug-eluting stent; IC, intracoronary; ISAR-2, **I**ntracoronary **S**tenting and **A**ntithrombotic **R**egimen-2; n.a., nonavailable; On-TIME 2, **On**going **T**irofiban **i**n **M**yocardial Infarction **E**valuation 2; pPCI, primary percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; RAPPORT, **R**eoPro **a**nd **P**rimary **P**TCA **O**rganization and **R**andomized **T**rial.

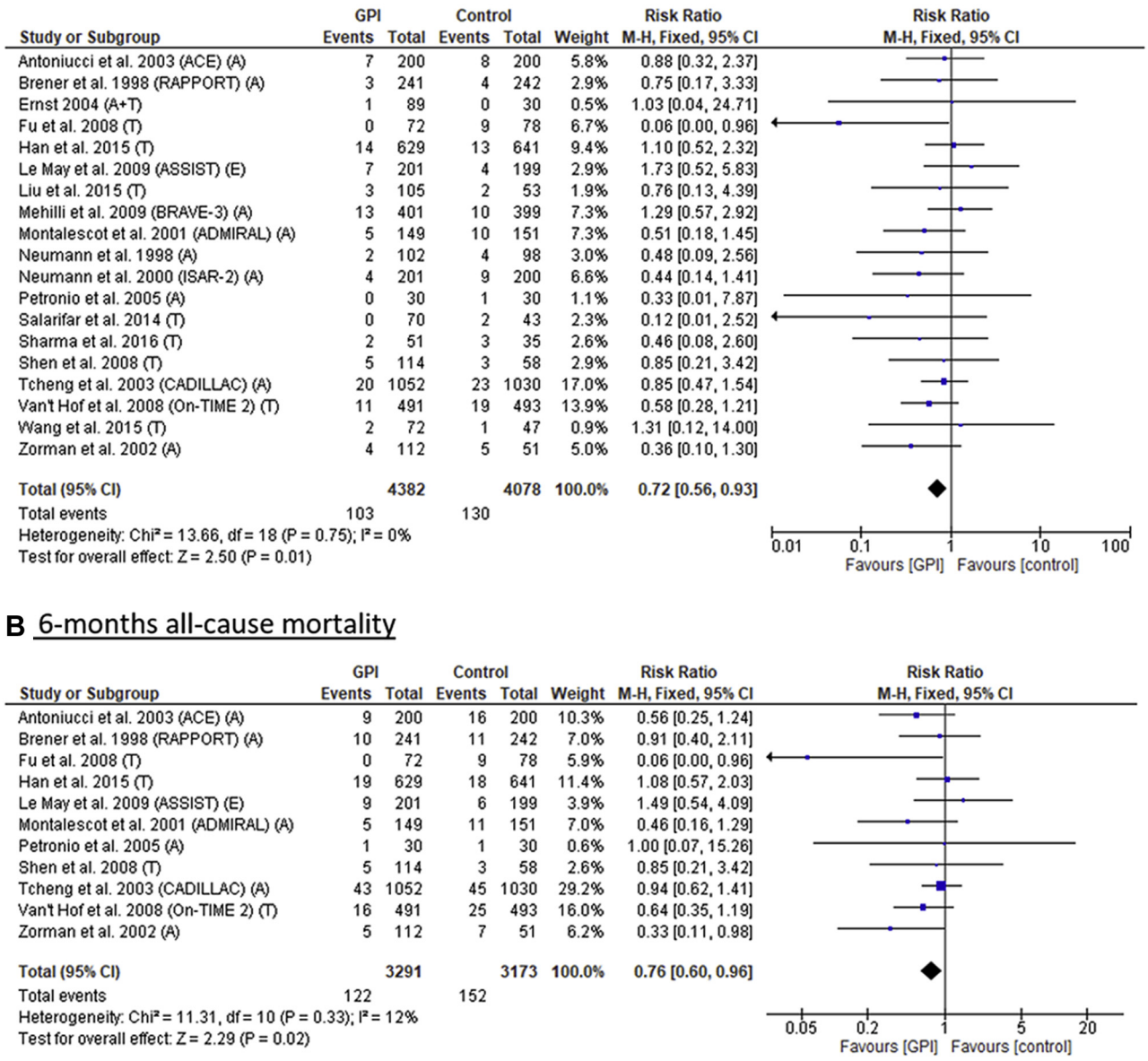


Figure 1. All-cause mortality outcome of routine glycoprotein IIb/IIIa inhibitor (GPI) vs control therapy in ST-segment elevation myocardial infarction: (**A**) all-cause mortality at a median of 30 days; (**B**) all-cause mortality at a median of 6 months. Individual and summary risk ratios with 95% confidence intervals (CIs). M-H, Mantel-Haenszel estimates with a fixed-effects model.

Data synthesis and statistical analysis

Microsoft Excel, SPSS version 23 (SPSS, Chicago, IL), and Review Manager version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) were used for statistical computations.

Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated as individual and summary statistics for effect size. Heterogeneity was assessed by the Cochran Q test,[17] and statistical heterogeneity was summarized by the I^2 statistic.[18] A fixed-effect meta-analysis model was applied for $I^2 <$ 20%; higher statistical heterogeneity prompted the use of the conservative DerSimonian and Laird random-effects model.[19]

Prespecified sensitivity analyses were performed to differentiate the 3 GPI drugs. The statistical level of significance of the Cochran-Mantel-Haenszel statistics estimate for the summary treatment effect was assumed at a 2-tailed P-value of < 0.05.

Results

The systematic literature search, screening, and selection process are described in a PRISMA flow chart (Supplemental Fig. S1): primary searches revealed a total of 2140 sources, which were subsequently condensed to 21 RCTs published between 1998 and 2016 with a total of 8585 patients.[20-42]

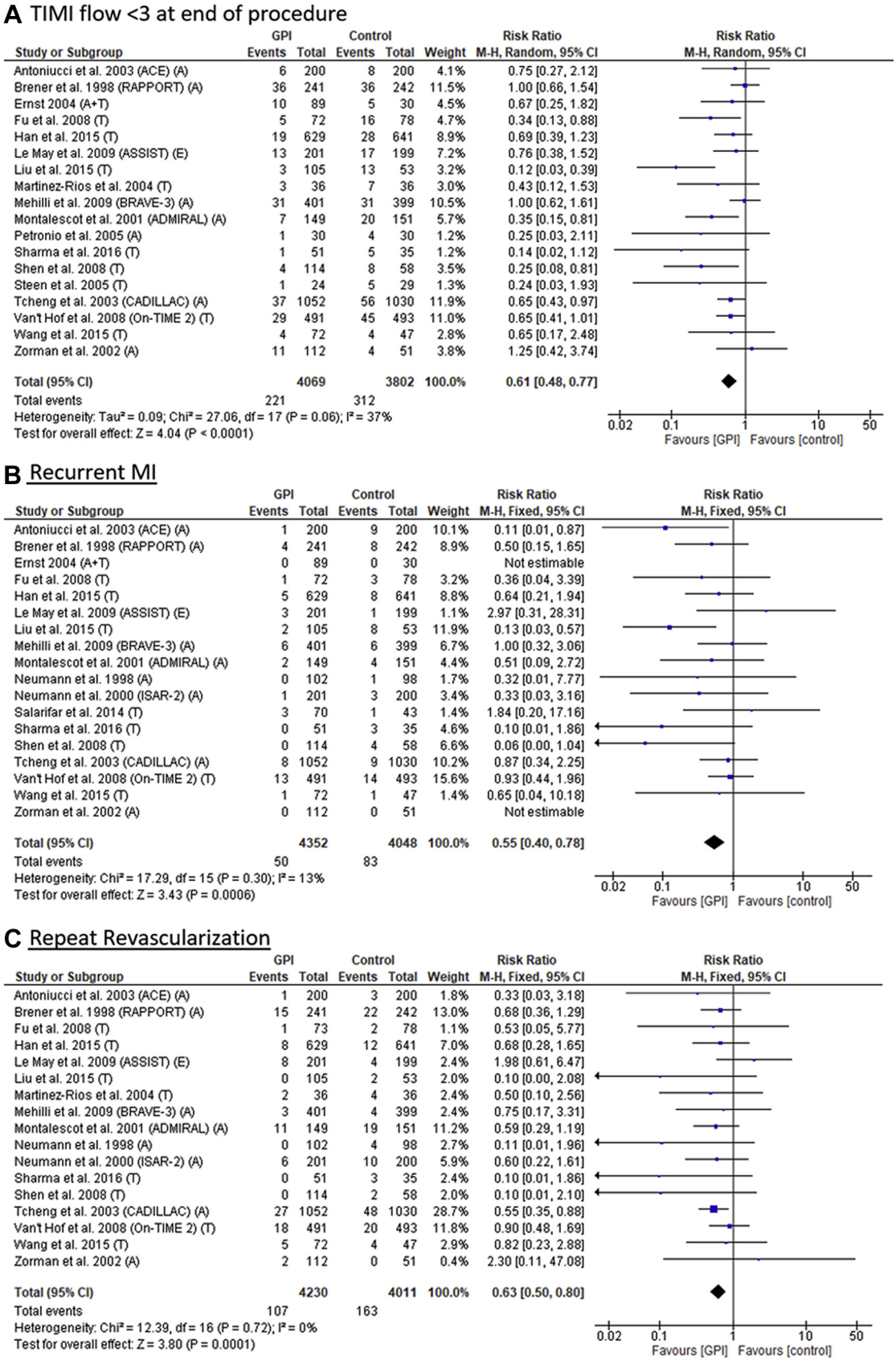


Figure 2. Efficacy outcomes of routine glycoprotein IIb/IIIa inhibitor (GPI) vs control therapy in ST-segment elevation myocardial infarction at a median follow-up of 30 days: (**A**) thrombolysis in myocardial infarction (TIMI) flow < 3 at the end of procedure; (**B**) recurrent myocardial infarction (MI); and (**C**) repeat revascularization. Individual and summary risk ratios with 95% confidence intervals (CIs). M-H, Mantel-Haenszel estimates with a random-effects model used for $I^2 > 20\%$.

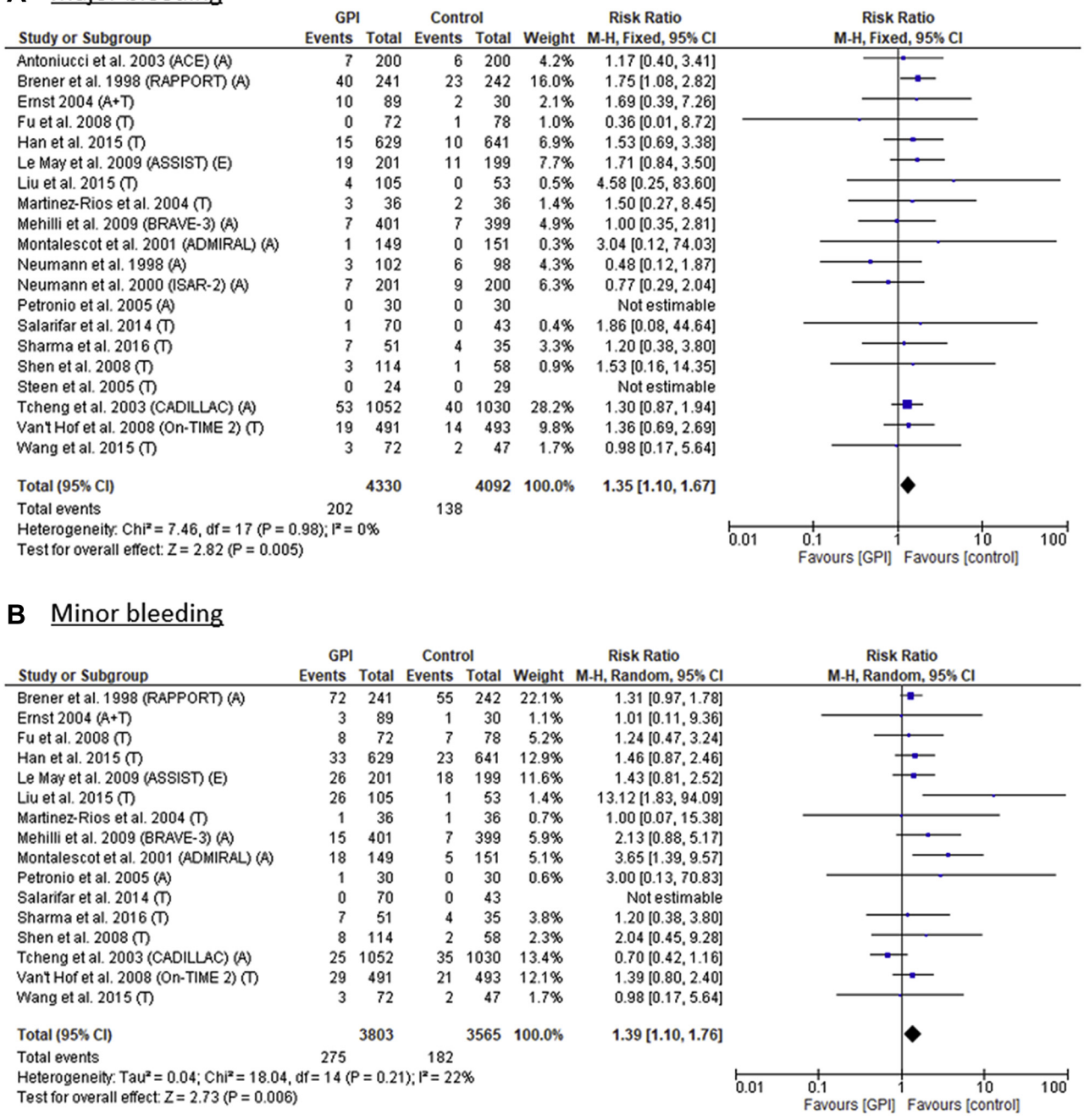
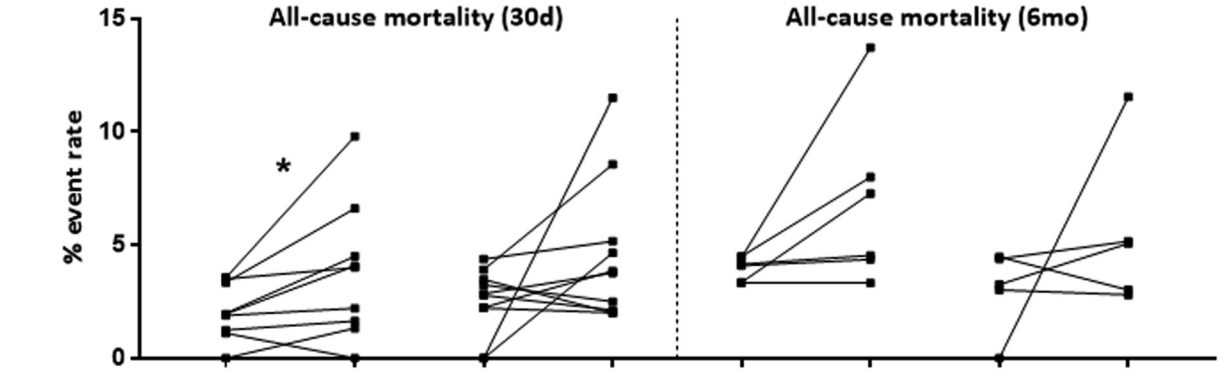


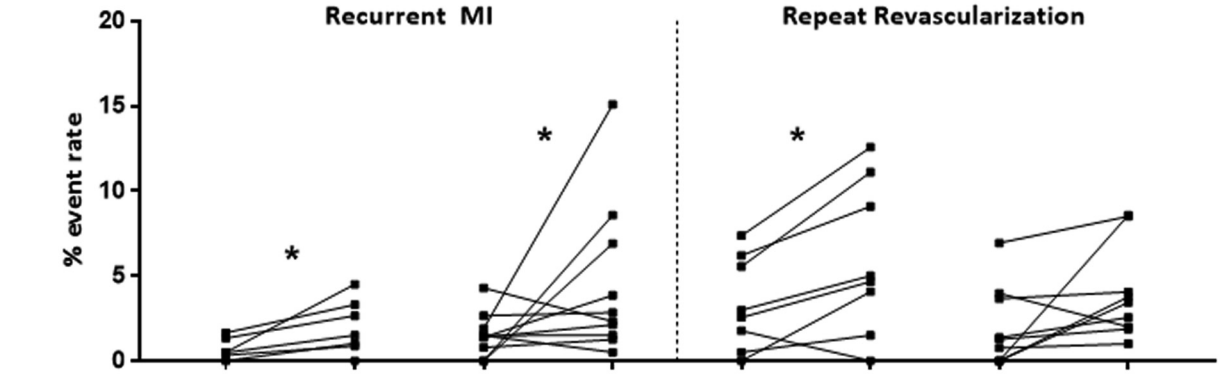
Figure 3. Safety outcomes of routine glycoprotein IIb/IIIa inhibitor (GPI) vs control therapy in ST-segment elevation myocardial infarction at a median follow-up of 30 days: (**A**) major bleeding; (**B**) minor bleeding. Individual and summary risk ratios with 95% confidence intervals (CIs). M-H, Mantel-Haenszel estimates with a random-effects model used for $I^2 > 20\%$.

Excluded studies and reasons for exclusion are listed in Supplemental Table S1.

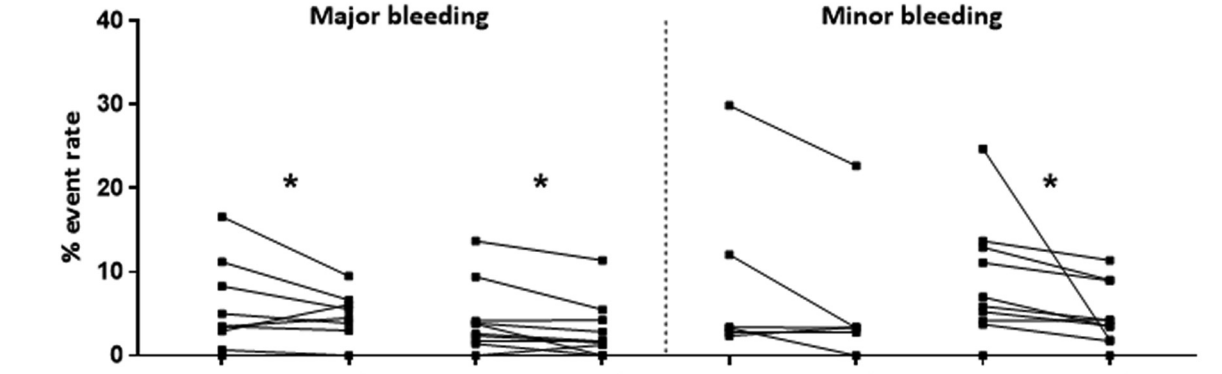
Study characteristics are reported in Table 1. The largest included RCT was **C**ontrolled **A**bciximab and **D**evice **I**nvestigation to **L**ower **L**ate **A**ngioplasty **C**omplications (CADILLAC)[35,36] with 2082 patients and the smallest was by Steen et al.[34] with 53 patients. Eleven trials randomized tirofiban,[21-23,25,26,31-34,37,38,43] 10 trials abciximab,[20,21,27-30,36,39-42] and 1 trial eptifibatide[24] as the investigated GPI to either placebo (8 trials) or standard therapy (13 trials). GPI was initiated as a bolus either upstream to the procedure in 7 trials[22,27,31,33,37,42] or periprocedural for all others; 2 trials administered the intracoronary bolus instead of intravenous.[25,38] The duration of postprocedural GPI infusion varied between 12 and 48 hours. Tirofiban groups of trials randomizing different dosages to control were analysed together.[21,25] Vascular access information was available only in 5 trials.[23-25,33,41] All but one study[22] reported median follow-ups of 30 days; 11 trials provided follow-ups up to 1 year.[20,22-24,28,33,36,37,39-42] Six studies



Group	GPI	Ctrl	GPI	Ctrl	GPI	Ctrl	GPI	Ctrl
Overall mean	2.1%	3.1%	2.6%	3.2%	3.3%	4.2%	4.1%	5.3%
Relative Risk	0.66 (0.46 - 0.96)		0.79 (0.55 - 1.11)		0.75 (0.56 - 1.01)		0.78 (0.54 - 1.12)	
P-value	0.03*		0.17		0.06		0.18	
Time span	**1998 to 2007**		**2008 to 2016**		**1998 to 2007**		**2008 to 2016**	



Group	GPI	Ctrl	GPI	Ctrl	GPI	Ctrl	GPI	Ctrl
Overall mean	0.7%	1.7%	1.5%	2.4%	3.1%	5.5%	2.0%	2.6%
Relative Risk	0.47 (0.26 - 0.85)		0.60 (0.40 - 0.91)		0.57 (0.42 - 0.77)		0.75 (0.51 - 1.10)	
P-value	0.01*		0.02*		0.0003*		0.14	
Time span	**1998 to 2007**		**2008 to 2016**		**1998 to 2007**		**2008 to 2016**	



Group	GPI	Ctrl	GPI	Ctrl	GPI	Ctrl	GPI	Ctrl
Overall mean	5.8%	4.3%	3.5%	2.4%	7.5%	6.4%	7.0%	4.2%
Relative Risk	1.32 (1.01 - 1.72)		1.41 (1.00 - 1.99)		1.29 (0.76 - 2.21)		1.51 (1.16 - 1.97)	
P-value	0.04*		0.05*		0.35		0.0002*	
Time span	**1998 to 2007**		**2008 to 2016**		**1998 to 2007**		**2008 to 2016**	

Figure 4. Summary of glycoprotein IIb/IIIa inhibitor (GPI) effect comparisons stratified by the period of study publication (1998-2007 vs 2008-2016), at a median follow-up of 30 days unless specified otherwise. *Statistical significance. MI, myocardial infarction; RR, relative risk calculated from Mantel-Haenszel estimate and confidence intervals in parentheses.

were partly financed through Eli Lilly (Bad Homburd, Germany), the company producing ReoPro (abciximab). Many of the trials received financial support from the pharmaceutical industry; 3 trials received support from the local government.[19,22,35] Two trials declared no conflicts of interest,[28,29] and there was no financial disclosure provided or it was unclear in 4 of the trials[18,38,31,39] (for details, see Supplemental Table S2).

Patient characteristics are reported in Supplemental Table S3: the majority of patients were male, median age was 60 years, and cardiovascular comorbidities and smoking were frequent. Medical care for STEMI was heterogeneous across studies (Table 1): pPCI techniques in older trials featured balloon dilatation only or bare-metal stents, whereas later trials used drug-eluting stents. P2Y12 inhibitor therapy in addition to aspirin consisted of clopidogrel (14 trials), ticlopidine (5 trials), and ticagrelor (1 trial); 2 trials predominantly used aspirin monotherapy.[20,42] Heparin was used for anticoagulation in all trials, initiated with a bolus of 60 to 100 U/kg and titrated to an activated clotting time of >250 seconds; heparin dosage after pPCI and during GPI infusion was not consistently reported.

The risk of bias of included RCTs is shown in Supplemental Table S4. Bias originated primarily from the lack of blinding of participants or study personnel and unreported methods of randomization and group allocation of patients. Outcome assessors were blinded in 11 of 21 trials, and there was overall little evidence for incomplete outcome data or selective reporting. Funnel plot graphical analysis for the most relevant outcome of 30-day all-cause mortality revealed no evidence for publication bias (Supplemental Fig. S2).

All-cause mortality

Nineteen RCTs including 8460 patients reported 30-day all-cause mortality.[20-25,27-33,35-43] The pooled analysis (Fig. 1A) resulted in a significant reduction in the risk for mortality for routine GPI compared with control (2.4% vs 3.2%; RR, 0.72; 95% CI, 0.56-0.93; $I^2 = 0\%$; $P = 0.01$). Sensitivity analyses for abciximab vs control (10 trials[20,21,27-30,36,39-42]; Supplemental Fig. S3: 2.3% vs 3.0%; RR, 0.74; 95% CI, 0.53-1.04; $I^2 = 0\%$; $P = 0.08$) and tirofiban vs control (9 trials[21-23,25,31-33,37,38,43]; Supplemental Fig. S3B: 2.3% vs 3.5%; RR, 0.64; 95% CI, 0.42-0.96; $I^2 = 0\%$; $P = 0.03$) exhibited similar results.

Mortality after a median follow-up of 6 months was reported in 11 trials,[20,22-24,28,33,35-37,39-43] resulting in a similarly significant reduction in the risk for GPI (3.7% vs 4.8%; RR, 0.76; 95% CI, 0.60-0.96; $I^2 = 12\%$; $P = 0.02$; Fig. 1B).

Efficacy outcomes of TIMI flow, recurrent MI, repeat revascularization, and ischemic stroke

The meta-analysis of 18 RCTs reporting TIMI flow grades at the end of pPCI showed a highly significant reduction in the risk for suboptimal TIMI flow with GPI vs control (5.4% vs 8.2%; RR, 0.61; 95% CI, 0.48-0.78; $P < 0.0001$; Fig. 2A), albeit with considerable statistical heterogeneity (heterogeneity $P = 0.06$; $I^2 = 37\%$) in a random-effects model. There was a modest difference in sensitivity analyses of abciximab (RR, 0.78; $P = 0.09$) and tirofiban (RR, 0.46; $P < 0.0001$; data not shown).

Eighteen RCTs reported recurrent MI events;[20-25,27-33,35-40,42,43] their meta-analysis showed a highly significant reduction in the risk for recurrent MI with routine GPI compared with control (1.1% vs 2.1%; RR, 0.55; 95% CI, 0.40-0.78; $I^2 = 13\%$; $P = 0.0006$; Fig. 2B). Similar results were found for sensitivity analyses in abciximab (RR, 0.55; $P = 0.02$) and tirofiban (RR, 0.46; $P = 0.04$) trials only (data not shown).

Seventeen RCTs reported repeat revascularizations.[20,22-33,35-40,42,43] A highly significant risk reduction was seen in the pooled analysis with GPI vs control therapy (2.5% vs 4.1%; RR, 0.63; 95% CI, 0.5-0.8; $I^2 = 0\%$; $P = 0.0001$; Fig. 2C). Abciximab (RR, 0.58; $P = 0.0004$) and tirofiban alone were equally effective (RR, 0.64; $P = 0.04$; data not shown).

Seven trials reported ischemic stroke events.[23,24,27,30,35-37,40,43] The pooled meta-analyses resulted in a significant reduction in the risk for this rare event under GPI therapy (0.2% vs 0.6%; RR, 0.42; 95% CI, 0.19-0.96; $I^2 = 0\%$; $P = 0.04$; data not shown).

Safety outcomes of bleeding events and intracranial haemorrhage

Bleeding events were reported in all trials.[20-43] The risk of major bleedings was significantly increased under GPI therapy compared with control (Fig. 3A: 4.7% vs 3.4%; RR, 1.35; 95% CI, 1.1-1.67; $I^2 = 0\%$; $P = 0.005$). Similar results, albeit with higher heterogeneity, were observed for minor bleedings (Fig. 3B: 7.2% vs 5.1%; RR, 1.39; 95% CI, 1.10-1.76; $I^2 = 22\%$; random-effects model, $P = 0.006$). Access site bleedings were reported in 6 trials[20,22,24,28,31,41] and were significantly more frequent under GPI (8.5% vs 3.5%; RR, 2.34; 95% CI, 1.51-3.60; $I^2 = 14\%$; $P = 0.0001$; data not shown); the same was true for transfusions (9 trials[20,22,24,27,29,33,35-37,41-43]: 5.1% [GPI] vs 4.0% [control]; RR, 1.3; 95% CI, 1.02-1.66; $I^2 = 0\%$, $P = 0.03$; data not shown).

Intracranial haemorrhage reported in 10 trials[20,21,23,25-27,29,35,36,39-41] was extremely rare: 3 events in total were reported under GPI therapy vs control (0.1% vs 0%; RR, 2.7; 95% CI, 0.3-24.4; $P = 0.37$; data not shown).

Number-needed-to-treat and number-needed-to-harm of GPI therapy

The number-needed-to-treat of GPI therapy to prevent 1 death was 125 during the first 30 days and 91 during the 6-month follow-up. The number-needed-to-harm with major bleeding under GPI therapy was 77 and 1000 for intracranial bleeding.

Impact of study publication period on GPI effects for clinical outcomes

To account for the time span across which studies were included in this analysis (1998-2016), a dichotomous analysis of studies from 1998 to 2007 and from 2008 to 2016 was performed (Fig. 4): GPI reduced 30-day and 6-month all-cause mortality in both older and younger trials (RR, 0.66-0.78; $P = 0.03$-0.18), which was similarly true for recurrent ischemic events (MI and repeat revascularization: RR, 0.47-0.75; $P = 0.01$-0.14). All outcomes showed a slight trend

towards lower GPI efficacy in the younger trial group. Overall, major bleedings became less frequent in the contemporary period; GPI still significantly increased bleeding risk (Fig. 4).

Discussion

The main findings of this meta-analysis of routine GPI use in STEMI were as follows: (1) GPI significantly reduced the risk for mortality compared with control at 30-day and 6-month follow-up; (2) GPI significantly reduced recurrent ischemic events; and (3) GPI significantly increased risk for all bleeding outcomes, except for intracranial haemorrhage.

In high thrombus burden scenarios of STEMI with microvascular obstruction and no-reflow phenomenon, adverse outcomes ensue.[44] Routine thrombus aspiration in this setting has shown limited benefits[45,46] and is not recommended in current guidelines.[2] In this acute setting, oral antiplatelet agents have not yet managed to achieve optimal inhibition related to time, opioid use, and poor gastric absorption in shock. The impressive rapid onset of action of ticagrelor and prasugrel in healthy volunteers[47,48] is not applicable in the acute setting of STEMI, where effective platelet inhibition is achieved not earlier than 2 to 4 hours after oral administration.[49-51] Clopidogrel—still the only option in some subgroup of patients—has considerably slower pharmacokinetics.[52,53] Alternative therapy with intravenous cangrelor[54,55] achieved rapid platelet inhibition leading to a guidelines recommendation for P2Y12-naive patients; nonetheless, high cost hinders large-scale routine application, and it should be considered that the medication was tested mostly on patients receiving clopidogrel. This renders the "old" GPI therapy "new" and interesting again, something that led us to perform this meta-analysis.

Previous meta-analyses studied different routes of administration of GPI or GPI after thrombectomy, but routine GPI therapy in STEMI has not been analysed.[13,56,57] This meta-analysis confirmed GPI efficacy in this setting, finding a robust reduction of recurrent MI, repeat revascularization, and suboptimal TIMI flow after pPCI compared with control. This finding was irrespective of the use of an antibody (abciximab) or small-molecule (tirofiban and eptifibatide) GPI, which is in line with previous analyses.[58] Ischemic strokes were also significantly reduced, reminiscent of the use of GPI in stroke—even though the event rate was low overall.

Compared with oral platelet inhibitors, GPIs have been shown to increase bleeding complications[20,36] leading European guidelines recommending only bail-out use in case of high thrombus burden (class IIa).[2] American guidelines (class IIa/IIb) stress the missing evidence of GPI in combination with modern DAPT,[59] similar to current Canadian guidelines.[9] This meta-analysis made similar observations with an increase in the relative risk of approximately 40% for major and minor bleedings and transfusions in studies predominantly featuring clopidogrel as the second antiplatelet agent in DAPT. Only 1 small trial on GPI therapy as a routine adjunct to modern DAPT with ticagrelor was available.[25]

Overall, this meta-analysis confirms an advantageous bleeding risk vs ischemic benefit balance of routine GPI in patients with STEMI in the pre-prasugrel/ticagrelor era, evident in a significant reduction of approximately 25% in 30-day and 6-month all-cause mortality. Such survival benefit was observed despite low overall mortality in these trials. Results of formal tests of heterogeneity were considered alongside a qualitative assessment of the combinability of studies in this review. Considering heterogeneity present among study designs, protocols, and study size, we analysed the relationship of study size, precision, and treatment effect (see Supplemental Fig. S1), and we accounted for heterogeneity by performing sensitivity analysis and choosing the conservative random-effects method. In addition, no major risk for publication bias or bias within studies could be found. With trials funded from various institutions, the risk of bias was present. Because the impact of trial funding cannot be assessed quantitatively, we included all studies independent of funding. An additional limitation that should be mentioned is the long time span across included studies with evolutions in pPCI techniques and oral antiplatelet therapy. Even with valid results, this meta-analysis cannot overcome the lack of evidence on GPI in combination with modern potent DAPT. This limitation notwithstanding, contemporary access-site management and transradial vascular access[60,61] are bound to reduce bleeding events and increase net GPI benefits. In a contemporary registry of patients with STEMI, we found no differences in bleeding events with or without GPI.[62] That said, we have to consider that GPIs have been shown to be slightly more efficient in older trials (Fig. 4) and might further lose efficacy in ischemic reduction in a setting of modern DAPT and stent technology. Because current evidence is not able to answer these open questions, we think that RCTs of routine GPI in contemporary STEMI management are warranted. Such trials should deliver evidence on clot burden, lesion complexity, and time delay through thrombectomy, while subgroup analyses to identify groups of patients with the largest benefit through such an approach would be of interest, for example, an analysis for patients treated via a transradial vs transfemoral approach. A further consideration would be to test shorter time intervals of GPI infusions, which could further decrease bleeding complications without compromising efficacy. Coadministration of GPIs with cangrelor for the duration of infusion might be another interesting option to increase efficacy while giving an option for fast reversal in case of bleeding.

Conclusions

Routine GPI administration as an adjunct to pPCI in patients with STEMI was found to result in mortality reduction, which was driven by a reduction in recurrent ischemic events. Nevertheless, the majority of trials included were conducted before the era of potent P12Y2 inhibitors. New trials in a contemporary setting of STEMI management are warranted to confirm clinical benefits of routine GPI therapy.

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performed the statistical analysis. A.K., G.W., A.P., C.J., U.Z., and M.K. drafted and revised the manuscript. All authors analysed and interpreted the data and critically revised the manuscript. All authors read and accepted the submitted version of the manuscript.

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Supplementary Material

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