European Heart Journal (2010) **31**, 35–49
doi:10.1093/eurheartj/ehp376

Tirofiban as adjunctive therapy for acute coronary syndromes and percutaneous coronary intervention: a meta-analysis of randomized trials

Marco Valgimigli[1]*, Giuseppe Biondi-Zoccai[2], Matteo Tebaldi[1], Arnoud W.J. van 't Hof[3], Gianluca Campo[1], Christian Hamm[4], Jurriën ten Berg[5], Leonardo Bolognese[6], Francesco Saia[7], Gian Battista Danzi[8], Carlo Briguori[9], Ertan Okmen[10], Spencer B. King[11], David J. Moliterno[12], and Eric J. Topol[13]

[1]Cardiovascular Institute, Azienda Opedaliera Universitaria di Ferrara, Corso Giovecca 203, Ferrara 44100, Italy; [2]Division of Cardiology, University of Turin, S. Giovanni Battista Hospital, Turin, Italy; [3]Department of Cardiology, Isala Klinieken, Zwolle, The Netherlands; [4]Kerckhoff -Klinik GmbH, Bad Nauheim, Germany; [5]St Antonius Ziekenhuis, Nieuwegein, The Netherlands; [6]Cardiovascular Departments of San Donato Hospital, Arezzo, Italy; [7]Istituto di Cardiologia, Università di Bologna, Policlinico S. Orsola-Malpighi, Bologna, Italy; [8]Division of Cardiology, IRCCS, Fondazione Ospedale Maggiore Policlinico Mangiagalli e Regina Elena, Milan, Italy; [9]Laboratory of Interventional Cardiology and Department of Cardiology, Clinica Mediterranea, Naples, Italy; [10]Department of Cardiology, Siyami Ersek Cardiovascular and Thoracic Surgery Center, Istanbul, Turkey; [11]Saint Joseph's Heart and Vascular Institute, Atlanta, GA, USA; [12]Gill Heart Institute, University of Kentucky, Lexington, KY, USA; and [13]Scripps Translational Science Institute, Scripps Genomic Medicine, La Jolla, CA, USA

Received 12 February 2009; revised 26 August 2009; accepted 20 August 2009; online publish-ahead-of-print 14 September 2009

Aims To perform a thorough and updated systematic review of randomized clinical trials comparing tirofiban vs. placebo or vs. abciximab.

Methods and results We searched for randomized trials comparing tirofiban vs. placebo or any active control. Odds ratios (OR) were computed from individual studies and pooled with random-effect methods. Thirty-one studies were identified involving 20 006 patients (12 874 comparing tirofiban vs. heparin plus placebo or bivalirudin alone, and 7132 vs. abciximab). When compared with placebo, tirofiban was associated at 30 days with a significant reduction in mortality [OR = 0.68 (0.54–0.86); $P = 0.001$] and death or myocardial infarction (MI) [OR = 0.69 (0.58–0.81); $P < 0.001$]. The treatment benefit persisted at follow-up but came at an increased risk of minor bleedings [OR = 1.42 (1.13, 1.79), $P = 0.002$] or thrombocytopenia. When compared with abciximab, mortality at 30 days did not differ [OR = 0.90 (0.53, 1.54); $P = 0.70$], but in the overall group tirofiban trended to increase the composite of death or MI [OR = 1.18 (0.96, 1.45); $P = 0.11$]. No such trend persisted at medium-term follow-up or when appraising studies testing tirofiban at 25 μg/kg bolus regimen.

Conclusion Tirofiban administration reduces mortality, the composite of death or MI and increases minor bleedings when compared with placebo. An early ischaemic hazard disfavouring tirofiban was noted when compared with abciximab in studies based on 10 but not 25 μg/kg tirofiban bolus regimen.

Keywords Tirofiban • Abciximab • Glycoprotein IIb/IIIa inhibitors • Systematic review • Percutaneous coronary intervention

Introduction

Tirofiban is a small molecule, non-peptide tyrosine derivative which belongs to the class of glycoprotein (GP) IIb/IIIa inhibitors (GPI).[1,2] By preventing the binding of fibrinogen and von Willebrand factor to the GP IIb/IIIa receptor on the surface of the platelet, GPIs are currently regarded as the most potent inhibitors of platelet aggregation.[1,2]

Though similar to abciximab in that it has a high affinity for the GP IIb/IIIa receptor, tirofiban dissociates from the GP IIb/IIIa

* Corresponding author. Tel: +39 0532 202143, Fax: +39 0532 241885, Email: vlgmrc@unife.it

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2009. For permissions please email: journals.permissions@oxfordjournals.org.

Downloaded from https://academic.oup.com/eurheartj/article/31/1/35/563591 by guest on 21 August 2022

receptor more rapidly than abciximab.[1,2] Its anti-aggregatory effects reverse within hours after the completion of the infusion, whereas abciximab binds near irreversibly to the receptor resulting in a considerably longer effect.[1,3] Additionally, tirofiban does not inhibit other β3 integrins, such as the vitronectin receptor, at the surface of vascular cells or the activated MAC-1 receptor on leucocytes,[4] which have been traditionally regarded as crucial targets to explain abciximab effects on microcirculation.[5]

Even more importantly, different dosing regimens of tirofiban have been developed over time based on the clinical setting and the timing of percutaneous coronary intervention (PCI) which has resulted in mixed results in clinical trials when compared with either placebo or abciximab.[3,6–10] Thus, uncertainty on the role of tirofiban still largely persists in current clinical practice.

Systematic reviews employing meta-analytic techniques provide quantitative and objective means to pool and assess available clinical evidence, emphasizing internal validity and homogeneity, while affording increased statistical power for hypothesis testing. The aim of this study was thus to perform a thorough and updated systematic review of randomized clinical trials comparing tirofiban vs. placebo or vs. abciximab in patients undergoing treatment for various coronary artery disease (CAD) conditions, with specific emphasis on the role of front-loaded tirofiban regimen and timing of intervention.

Methods

Search strategy

Two expert cardiologists (M.V., M.T.) independently and systematically searched BioMedCentral, CENTRAL, Clinicaltrials.gov, EMBASE, and PubMed for randomized trials comparing tirofiban vs. placebo or any active control in patients with acute coronary syndromes and/or undergoing PCI (updated October 2008), with divergences resolved after consensus.[11] EMBASE and PubMed were searched with explode features according to the following strategy: '(abciximab[all] OR tirofiban[all] OR (glycoprotein[all] AND (iib/iiia OR iibiiia) AND inhibitor*[all])) AND coronary AND (clinical trial*[all] OR random*[all])'.[12]

Articles published in languages other than English or Italian (the native languages of the authors) were systematically searched in multiple online databases, international conference proceedings, references (backward snowballing) or cross-quotations (forward snowballing) from included studies and pertinent available quantitative reviews, and queries to international experts. References were systematically scanned to retrieve additional studies. No language restriction was enforced.

Selection criteria

Shortlisted studies were retrieved as full articles and appraised by three unblinded reviewers independently (M.V., G.B.Z., M.T.), with divergences resolved after consensus, according to the following inclusion criteria: (i) randomized treatment allocation and (ii) comparison of tirofiban vs. placebo or active. Exclusion criteria were: (i) duplicate reports failing to report additional or extended clinical outcomes, (ii) lack of outcome data beyond hospitalization, and (iii) equivocal (i.e. no clear information on modalities for allocating patients to tirofiban vs. placebo or active treatment) or non-random treatment allocation.

Data abstraction and validity assessment

Three reviewers independently abstracted data, with divergences resolved after consensus. In case of incomplete or unclear data, authors were contacted where possible. The co-primary endpoints of the analysis were the 30 days and long-term mortality rates. The incidence of major adverse cardiovascular events (MACE), including the composite of death, myocardial infarction (MI), or urgent revascularization, death or MI, as well as major and minor bleeding [according to the Thrombolysis In Myocardial Infarction (TIMI) criteria][13] and thrombocytopenia were also appraised. We *pre hoc* stratified studies according to the type of control, dosage/timing of tirofiban administration, and type of concomitant oral anti-platelet therapy. Thus, studies where more than one dosage or timing of intervention were tested vs. placebo or active control have been split up into the most suitable pre-specified study categories. Additional pertinent data for baseline and procedural characteristics were abstracted, including type of PCI. Study validity and risk of bias were appraised according to The Cochrane Collaboration methods, i.e. separately appraising means for generating the randomization sequence, allocation concealment, blinding, concurrent treatment, data completion, definitions, outcome reporting, other potential source of bias, and overall risk of bias.[11]

Data analysis and synthesis

Odds ratios (OR) were computed from individual studies and pooled according to DerSimonian-Laird random-effect methods (with 95% confidence intervals) using RevMan 4.2 (The Cochrane Collaboration, Købehavn, Denmark). Inconsistency was appraised by means of I^2. Specifically, $I^2 < 25\%$ suggests mild, statistical inconsistency, whereas I^2 values in the 25–50% range and in the 75–100% represent, respectively, moderate and extensive inconsistency. Statistical heterogeneity was appraised with χ^2 tests, with *P*-values less than 0.10 suggesting underlying heterogeneity. Small study bias and/or publication bias (i.e. the likelihood of small yet nominally significant studies being selectively published in the literature) were appraised by means of visual inspection of funnel plots and Peters test.[14] Random-effect meta-regression was also performed to explore moderators and/or predictors of changes in log-transformed OR, by means of a weighted-least-square inverse-variance weighted method with SPSS 11.0 (SPSS, Chicago, IL, USA). Unadjusted *P*-values are reported throughout, with hypothesis testing set at the two-tailed 0.05 level.

According to absolute risk reduction or increment obtained with random-effect risk differences computed at 30-day follow-up, we calculated the number needed to treat (NNT) to prevent one event, whereas for the safety endpoints, we calculated the number needed to harm (NNH) to determine one adverse event.

Results

Search results and study selection

Database searches retrieved 1952 citations (*Figure 1*). Shortlisted citations were retrieved and checked at the title/abstract level excluding 1894 papers. Complete articles for the remaining 58 studies were checked for compliance to inclusion/exclusion criteria. Reasons for further exclusion included non-experimental design, use of historical controls, duplicate reporting, unconventional study drug regimen, early vs. late study drug administration design, or failure to report/provide upon request clinical data. We finally identified 31 eligible trials of which 22 were controlled

Downloaded from https://academic.oup.com/eurheartj/article/31/1/35/563591 by guest on 21 August 2022

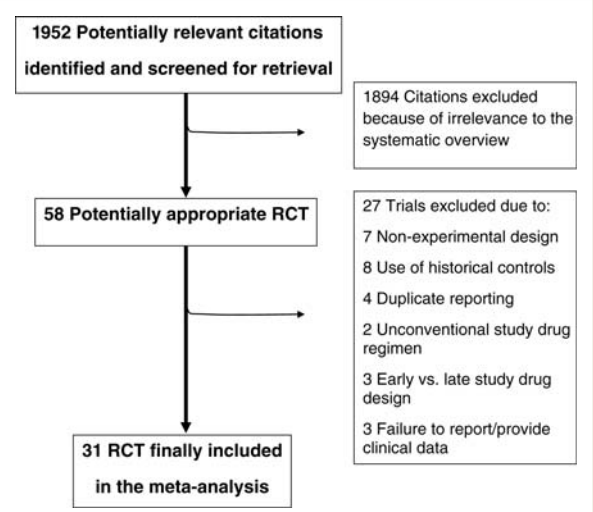

Figure 1 Flow diagram of the systematic literature search indicating the inclusion and exclusion process of studies.

with placebo[6–8,15–35] (*Table 1*), eight with abciximab,[9,10,36–41] and one with both agents[42] (*Table 2*).

Study and patient characteristics

The 31 studies included in the final analysis 20 006 randomized patients (average follow-up 5 months), 12 874 vs. placebo and 7132 vs. abciximab. In seven placebo-controlled trials,[7,8,21–23,26,28] mainly recruiting patients with confirmed or suspected non-ST-segment elevation acute coronary syndrome (NSTEACS) or ST-elevation myocardial infarction (STEMI), tirofiban was co-administered together with unfractioned heparin (UFH) upon presentation (upstream) as a 0.4 μg/kg 30 min bolus regimen followed by 0.1 μg/kg/min infusion apart from PRISM study,[8] where tirofiban was given without UFH at a 0.6 μg/kg 30 min bolus regimen followed by 0.15 μg/kg/min infusion.

In five placebo-controlled studies,[19,20,27,29,31,32] tirofiban was administered upstream in NSTEACS, STEMI, or stable CAD patients at 10 μg/kg 3 min bolus regimen and 0.15 μg/kg/min infusion, whereas in 12 studies, eight placebo-controlled,[6,15,17,18,24,30,32,34] two abciximab-controlled,[9,39,40] one controlled with both agents,[42] and one with bivalirudin,[34] tirofiban was given at 10 μg/kg 3 min bolus regimen and 0.15 μg/kg/min infusion prior PCI (downstream) in patients with stable or unstable CAD. Finally, in 4076 patients tirofiban was administered downstream at high bolus dose (25 μg/kg 3 min bolus regimen and 0.15 μg/kg/min infusion) and controlled with placebo ($n = 1863$)[25,33,35,42] or abciximab ($n = 2213$).[10,36–38,41–43] Study quality and risk of bias were variable, reflecting heterogeneity in setting, sample size, and study design (phase III vs. IV) and is detailed in *Table 3*.

Quantitative synthesis

Tirofiban vs. placebo or bivalirudin

Overall pooled effect estimate analysis showed a significant reduction in short-term (30 days) mortality [OR = 0.68 (0.54–0.86), $P = 0.001$, P for heterogeneity = 0.95, $I^2 = 0\%$] (*Figure 2*), mortality or MI [OR = 0.69 (0.58–0.81), $P < 0.001$, P for heterogeneity=0.33, $I^2 = 10\%$] (*Figure 3*), MI alone [OR = 0.71 (0.56–0.90), $P = 0.004$, P for heterogeneity=0.16, $I^2 = 24\%$], and the composite of death, MI, or target vessel revascularization [OR = 0.73 (0.60–0.89), $P = 0.002$, P for heterogeneity = 0.06, $I^2 = 37\%$] in patients randomly allocated to receive tirofiban at the different bolus and infusion regimens. According to an absolute risk reduction of 2.5%, the NNT is 40 to prevent one death or MI at 30 days, with an NNT of 100 to prevent one death. Comprehensive heterogeneity and inconsistency analyses showed that included trials led to apparently statistically heterogeneous results in terms of MACE rates (P for heterogeneity = 0.06, $I^2 = 37\%$), which is paralleled by the disparities in clinical setting, tirofiban bolus and infusion regimens, interventions, duration of treatment, and outcomes. However, there was no signal of heterogeneity across trials for the composite of death or MI, mortality, or MI alone.

To assess the effect of tirofiban when added to P2Y12 receptor blockers (i.e. ticlopidine or clopidogrel), studies where patients were adequately pretreated with clopidogrel ($n = 13$) or ticlopidine ($n = 1$) were selected, comprising 3424 patients.[17,22,24,25,27–35,42] Consistent to previous analysis, tirofiban was associated with a significant decrease in mortality [OR = 0.56 (0.34, 0.93), $P = 0.02$, P for heterogeneity = 0.93, $I^2 = 0\%$] and the composite of death or MI [OR = 0.61 (0.48, 0.79), $P < 0.001$, P for heterogeneity = 0.62, $I^2 = 0\%$] at 30 days.

The use of tirofiban tended to increase the rate of major bleeding [1.5 vs. 1.8%; OR = 1.21 (0.88, 1.67), $P = 0.24$, P for heterogeneity = 0.97, $I^2 = 0\%$] with an estimated NNH of 286 for one major haemorrhagic event. Minor bleedings [OR = 1.42 (1.13, 1.79), $P = 0.002$, P for heterogeneity = 0.97, $I^2 = 0\%$, 3.8 vs. 2.7%; NNH: 91] and the incidence of any thrombocytopenia [OR = 1.51 (1.06, 2.16); $P = 0.02$, P for heterogeneity = 0.96, $I^2 = 0\%$] were both significantly increased by the use of tirofiban.

After an average of 5-month follow-up, tirofiban remained associated with a significant reduction in mortality [OR = 0.81 (0.66, 0.99), $P = 0.04$, $P = 0.70$ for heterogeneity, $I^2 = 0\%$] and death or MI [OR = 0.73 (0.62, 0.85), $P < 0.001$, $P = 0.24$ for heterogeneity, $I^2 = 16\%$].

Tirofiban vs. abciximab

The overall pooled effect estimate analysis showed that tirofiban at 30 days led to similar mortality rate [OR = 0.90 (0.53, 1.54), $P = 0.70$, P for heterogeneity = 0.62, $I^2 = 0\%$] (*Figure 4*) but tended to increase the composite of death or MI [6.0 vs. 5.1%; OR = 1.18 (0.96, 1.45), $P = 0.11$, P for heterogeneity = 0.58, $I^2 = 0\%$] (*Figure 5*) and MACE rate [6.3 vs. 5.5%; OR = 1.18 (0.97, 1.44), $P = 0.10$, P for heterogeneity = 0.43, $I^2 = 0\%$] when compared with abciximab. Although there was no formal signal of heterogeneity across included studies, likely due to limited statistical power, these results mainly mirrored the findings of the TARGET study (study weight 78.4%) which tested tirofiban at 10 μg/kg 3 min bolus regimen and 0.15 μg/kg/min infusion. Indeed, mortality [OR = 0.73 (0.36, 1.47), $P = 0.38$, P for heterogeneity = 0.61, $I^2 = 0\%$], the composite of death or MI [OR = 0.87 (0.56, 1.35), $P = 0.54$, P for heterogeneity = 0.58, $I^2 = 0\%$] or MACE rate [OR = 0.87 (0.57, 1.32), $P = 0.51$, P for heterogeneity = 0.63,

Downloaded from https://academic.oup.com/eurheartj/article/31/1/35/563591 by guest on 21 August 2022

Table 1 Main characteristics of the placebo-controlled trials

Study	Trial period	No. randomized	Patient population	Tirofiban dose	Setting	Concomitant anti-thrombotics	1° Endpoint	Follow-up
3T/2R[35]	2006–2008	263	ASA and/or clopidogrel poor responders	Bolus: 25 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH or bivalirudin, and clopidogrel	Periprocedural MI defined as troponin >3× ULN within 48 h	30 Days
ADVANCE[25]	2002–2003	202	High-risk PCI	Bolus: 25 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH, ticlopidine or clopidogrel	Death, MI, TVR, or bailout tirofiban	6 Months
ELISA 2[29]	2002–2005	328	NSTEACS	Bolus: 10 μg/kg; infusion: 0.15 μg/kg/min	Upstream	ASA, LWMH, clopdidogrel	Enzymatic infarct size (LDHQ 48)	30 Days
Ercan *et al.*[22]	Not reported	57	NSTEMI	Bolus: 0.4 μg/kg/min × 30 min; infusion: 0.1 μg/kg/min	Upstream	ASA, UFH, clopidogrel	Levels of C-reactive protein at 48 h	30 Days
Ernst *et al.*[42]	2002–2003	60	STEMI	Bolus: 10 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH, clopidogrel	Platelet aggregation inhibition	Hospital stay
Fu *et al.*[30]	2005–2007	150	STEMI	Bolus: 10 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH, clopidogrel	Not reported	30 Days
Ivandic *et al.*[31]	2004–2006	100	NSTEMI	Bolus: 10 μg/kg; infusion: 0.15 μg/kg/min	Upstream	ASA, UFH, clopidogrel	Infarct size based on troponin T elevation	6 Months
Juergens *et al.*[18]	Not reported	894	Elective PCI	Bolus: 10 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH	TIMI bleedings	30 Days
Kereiakes *et al.*[15]	Not reported	44	Elective PCI	Bolus: 10 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH	Platelet aggregation inhibition	Hospital stay
Kim *et al.*[26]	2001–2002	160	NSTEACS	Bolus: 0.4 μg/kg/min × 30 min; infusion: 0.1 μg/kg/min	Upstream	ASA, UFH or dalteparin,	Not reported	6 Months
Kurowski *et al.*[27]	2000–2003	50	Stable or marker-negative unstable angina undergoing SVG stenting	Bolus: 10 μg/kg; infusion: 0.15 μg/kg/min	Upstream	ASA, UFH, clopidogrel	Myocardial necrosis as evidenced by an increase in the cTnT above the ULN within 72 h	21 Months
NAPLES[34]	2005–2008	335	Elective PCI in diabetics	Bolus: 10 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH, clopidogrel	NACE	30 Days
Okmen *et al.*[21]	Not reported	83	NSTEMI	Bolus: 0.4 μg/kg/min × 30 min; infusion: 0.1 μg/kg/min	Upstream	ASA, UFH	Infarct size based on CK-MB >2× ULN	10 Months
Okmen *et al.*[24]	Not reported	119	Stable or unstable angina undergoing PCI	Bolus: 10 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, ticlopidine, UFH	Infarct size based on CK-MB >2× ULN	21 Months
On-TIME 2 open-label study[33]	2004–2006	414	STEMI	Bolus: 25 μg/kg; infusion: 0.15 μg/kg/min	Upstream	ASA, UFH, clopidogrel	None	30 Days
On-TIME 2[33]	2006–2007	984	STEMI	Bolus: 25 μg/kg; infusion: 0.15 μg/kg/min	Upstream	ASA, UFH, clopidogrel	Residual ST-segment deviation at ECG	30 Days
Ozkan *et al.*[28]	1999–2004	47	Stable or marker-negative unstable angina undergoing SVG stenting	Bolus: 0.4 μg/kg/min × 30 min; infusion: 0.1 μg/kg/min	Upstream	ASA, enoxaparin, and clopidogrel	Not reported	30 Days
PRISM[8]	1994–1996	3232	NSTEACS	Bolus: 0.6 μg/kg/min × 30 min; infusion: 0.15 μg/kg/min	Upstream	ASA, UFH in placebo group only	Death, MI, refractory ischemia at 48 h	30 Days

Downloaded from https://academic.oup.com/eurheartj/article/31/1/35/563591 by guest on 21 August 2022

PRISM-PLUS[7]	1994–1996	1570	NSTEACS	Bolus: 0.4 μg/kg/min × 30 min; infusion: 0.1 μg/kg/min	Upstream	ASA, UFH	Death, MI, refractory ischemia at 7 days	6 Months
RESTORE[6]	1995	2212	NSTEACS or STEMI undergoing POBA or DCA	Bolus: 10 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH	Death, MI, TVR, or bailout stenting	6 Months
SASTRE[23]	2000–2002	144	STEMI	Bolus: 0.4 μg/kg/min × 30 min; infusion: 0.1 μg/kg/min	Upstream	ASA, UFH, alteplase	TIMI flow grade 3 in the IRA at 90′	30 Days
Shen *et al.*[32]	2005–2006	115	STEMI	Bolus: 10 μg/kg; infusion: 0.15 μg/kg/min	Upstream	ASA, UFH, clopidogrel	MACE at 30 days	6 Months
TETAMI[19,20]	1999–2002	1224	STEMI ineligible to lysis	Bolus: 10 μg/kg; infusion: 0.15 μg/kg/min	Upstream	ASA, enoxaparin or UFH	Death, MI, recurrent angina	30 Days
TOPSTAR[17]	Not reported	96	Stable angina	Bolus: 10 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH, clopidogrel	Troponin elevation within 48 h	9 Months

ASA, aspirin; LWMH, low-weight molecular heparin; LDH, lactate dehydrogenase; NSTEACS, non-ST-segment elevation acute coronary syndromes; NSTEMI, non-ST-segment elevation myocardial infarction; MI, myocardial infarction; LDHQ48, area under the lactate dehydrogenase release over 48 h curve; POBA, balloon angioplasty; DCA, directional coronary atherectomy; STEMI, ST-segment elevation myocardial infarction; ULN, upper limit of normal; PCI, percutaneous coronary intervention; SVG, saphenous vein graft; IRA, infarct-related artery; MACE, major adverse cardiovascular events; NACE, net adverse cardiovascular events; UFH, unfractionated heparin; TVR, target vessel revascularization.

$I^2 = 0\%$] were similar when tirofiban at high-dose bolus was compared with abciximab.

The rate of major bleedings did not differ in tirofiban- vs. abciximab-treated patients [OR = 1.24 (0.78, 1.98), $P = 0.35$, P for heterogeneity = 0.76, $I^2 = 0\%$], whereas minor bleedings [3.1 vs. 4.8%; OR = 0.64 (0.50, 0.82), $P < 0.001$, P for heterogeneity = 0.95, $I^2 = 0\%$] and any thrombocytopenia [0.3 vs. 2.4%; OR = 0.28 (0.08, 0.94), $P = 0.04$, P for heterogeneity=0.71, $I^2 = 0\%$] were both markedly reduced in the tirofiban group.

At the longest available follow-up, death or MI [OR = 1.09 (0.91, 1.31), $P = 0.34$, P for heterogeneity = 0.87, $I^2 = 0\%$], mortality [OR = 1.03 (0.75, 1.42), $P = 0.86$, P for heterogeneity = 0.71, $I^2 = 0\%$], and MACE [OR = 1.00 (0.87, 1.16), $P = 0.95$, P for heterogeneity = 0.68, $I^2 = 0\%$] rates also did not differ between groups (*Figure 6*).

Additional analyses

Meta-regression was performed to explore moderators of effect estimates for tirofiban vs. abciximab analysis, focusing on the 30 days rate of death or MI, and on the long-term rate of MACE, and appraising type of control, type of administration, concomitant medical treatment, adequate randomization method, adequate concealment of allocation, and adequate patient blinding (*Table 4*). The only potentially relevant finding beyond type of control treatment (i.e. placebo or anticoagulant vs. abciximab) was a trend for interaction between 30 days death or MI rates and the comparison between tirofiban and abciximab when focusing on the bolus regimen of tirofiban [$\beta = -0.646$ (-1.244, 0.103), $P = 0.083$], suggestive of more efficacy for the latter when employed at a high (25 μg/kg) dose.

Inspection of funnel plots for either tirofiban vs. control and tirofiban vs. abciximab and the 30 days rate of death or MI (*Figures 7* and *8*) did not disclose evidence of small study bias, which was also confirmed by analytical testing with Peters test ($P = 0.365$ and $P = 0.921$, respectively).

Discussion

The main finding of this meta-analysis is that adjunctive tirofiban therapy, compared with placebo, is associated with a >30% reduction in all considered ischaemic endpoints including overall mortality, mortality or MI, and MACE rates within 30 days after treatment. In absolute terms, tirofiban administration in 40 patients would prevent one death or MI, whereas 100 treated patients would lead to one fatal event prevention. Importantly, the benefit observed soon after intervention persisted at longest available follow-up. Interestingly, the magnitude of benefit for mortality observed in our analysis for tirofiban was quite similar to the treatment benefit shown by abciximab in a recent meta-analysis.[44]

As expected, the advantage in terms of ischaemic endpoints was counterbalanced by a significant increase in minor, but not major, bleeding and thrombocytopenia. Assuming that the observed insignificant 25% relative increase in major bleeding in the tirofiban group is real, we estimated a NNH of 286, 91, and 227 to lead to one major bleed, one minor haemorrhagic event, and one episode of thrombocytopenia, respectively. Thus, altogether the use of tirofiban at different tested regimens was associated with

Downloaded from https://academic.oup.com/eurheartj/article/31/1/35/563591 by guest on 21 August 2022

Downloaded from https://academic.oup.com/eurheartj/article/31/1/35/563591 by guest on 21 August 2022

Table 2 Main characteristics of the abciximab-controlled trials

Study	Trial period	No. randomized	Patient population	Tirofiban dose	Setting	Concomitant anti-thrombotics	1° Endpoint	Follow-up
Danzi *et al.*[37]	2002	100	STEMI	Bolus: 25 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH	Infarct-zone wall motion score index at 30 days	30 Days
Ernst *et al.*[42]	2002–2003	60	STEMI	Bolus: 10 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH, Clopidogrel	Platelet aggregation inhibition	Hospital stay
EVEREST[36]	2003–2004	61	NSTEMI	Bolus: 25 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH, clopidogrel	TIMI myocardial perfusion rate	30 Days
FATA[38]	2004–2007	692	STEMI	Bolus: 25 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH	≥70% STR at 90′	30 Days
MULTISTRATEGY[10]	2004–2007	744	STEMI	Bolus: 25 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH, clopidogrel	≥50% STR at 90′	8 Months
Neumann *et al.*[40]	Not reported	40	Stable or unstable angina	Bolus: 10 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH, ticlopidine	Inhibition of platelet aggregation after 2 h of infusion	30 Days
STRATEGY[41]	2003–2004	175	STEMI	Bolus: 25 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH, clopidogrel	Death, MI, stroke, binary restenosis	36 Months
TARGET[9]	1999–2000	5308	Urgent and elective PCI	Bolus: 10 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH, clopidogrel	Death, MI, urgent TVR at 30 days	12 Months
TENACITY[43]	2004–2005	383	Medium to high-risk PCI	Bolus: 25 μg/kg; infusion: 0.15 μg/kg/min	Downstream	ASA, UFH, clopidogrel	Death, MI, urgent TVR	30 Days

ASA, aspirin; UFH, unfractionated heparin; NSTEMI, non-ST-segment elevation myocardial infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; MI, myocardial infarction; TVR, target vessel revascularization; STR, ST-segment resolution.

Downloaded from https://academic.oup.com/eurheartj/article/31/1/35/563591 by guest on 21 August 2022

Table 3 Risk of bias assessment

Study	Adequate sequence generation	Allocation concealment used	Blinding	Concurrent therapies similar	Incomplete outcome data addressed	Uniform and explicit outcome definitions	Free of selective outcome reporting	Free of other bias	Overall risk of bias
3T/2R[35]	Yes (computer generated)	Yes (sealed envelopes)	Yes (patients, caring physicians, and outcome assessors)	Yes	Yes	Yes	Yes	Yes	Low
ADVANCE[25]	Yes (computer generated)	Yes (external personnel)	Yes (patients, caring physicians, and outcome assessors)	Yes	No	Yes	Yes	Yes	Low
Danzi *et al.*[37]	Unclear	Unclear	No	Yes	Yes	No	No	Yes	Moderate
ELISA 2[29]	Unclear	Unclear	Yes (outcome assessors)	No	Yes	Yes	Yes	Yes	Moderate
Ercan *et al.*[22]	Unclear	Unclear	No	No	Yes	Yes	Yes	Yes	Moderate
Ernst *et al.*[42]	Yes (computer generated)	Unclear	No	Yes	No	Yes	Yes	Yes	Moderate
EVEREST[36]	Unclear	Unclear	No	Yes	Yes	No	No	Yes	Moderate
FATA[38]	Unclear	Yes (sealed envelopes)	Yes (patients, caring physicians, and outcome assessors)	Yes	Yes	Yes	Yes	Yes	Low
Fu *et al.*[30]	Unclear	Unclear	No	Yes	No	No	Yes	Yes	Moderate
Ivandic *et al.*[31]	Unclear	Unclear	No	Yes	No	No	No	Yes	Moderate
Juergens *et al.*[18]	Unclear	Unclear	Yes (patients and caring physicians)	No	Yes	Yes	Yes	Yes	Moderate
Kereiakes *et al.*[15]	Unclear	Unclear	Yes (patients and caring physicians)	Yes	No	No	No	Yes	Moderate
Kim *et al.*[26]	Unclear	Unclear	No	Yes	No	No	Yes	Yes	Moderate
Kurowski *et al.*[27]	Unclear	Unclear	No	Yes	No	No	No	Yes	Moderate
MULTISTRATEGY[10]	Yes (computer generated)	Yes (sealed envelopes)	Yes (outcome assessors)	Yes	Yes	Yes	Yes	Yes	Low
NAPLES[34]	Unclear	Unclear	No	Yes	No	No	No	Yes	Moderate
Neumann *et al.*[40]	Unclear	Unclear	No	Yes	No	No	No	Yes	Moderate
Okmen *et al.*[21]	Unclear	Unclear	No	Unclear	No	No	Yes	Yes	Moderate
Okmen *et al.*[24]	Unclear	Unclear	No	Yes	No	No	No	Yes	Moderate
On-TIME 2 open-label study[33]	Yes (computer generated)	Yes (centralized system)	Yes (outcome assessors)	Yes	Yes	Yes	Yes	Yes	Low
On-TIME 2[33]	Yes (computer generated)	Yes (centralized system)	Yes (outcome assessors)	Yes	Yes	Yes	Yes	Yes	Low
Ozkan *et al.*[28]	Unclear	Unclear	No	Yes	No	No	No	Yes	Moderate

Continued

Downloaded from https://academic.oup.com/eurheartj/article/31/1/35/563591 by guest on 21 August 2022

Table 3 *Continued*

Study	Adequate sequence generation	Allocation concealment used	Blinding	Concurrent therapies similar	Incomplete outcome data addressed	Uniform and explicit outcome definitions	Free of selective outcome reporting	Free of other bias	Overall risk of bias
PRISM[8]	Unclear	Yes (centralized system)	Yes (patients, caring physicians, and outcome assessors)	Yes	Yes	Yes	Yes	Yes	Low
PRISM-PLUS[7]	Unclear	Yes (sealed envelopes)	Yes (patients, caring physicians, and outcome assessors)	Yes	Yes	Yes	Yes	Yes	Low
RESTORE[6]	Unclear	Yes (centralized system)	Yes (patients, caring physicians, and outcome assessors)	Yes	Yes	Yes	Yes	Yes	Low
SASTRE[23]	Unclear	Yes	No	Yes	Yes	Yes	Yes	Yes	Moderate
Shen *et al.*[32]	Unclear	Yes	No	Yes	Yes	Yes	Yes	Yes	Moderate
STRATEGY[41]	Yes (computer generated)	Yes (sealed envelopes)	Yes (outcome assessors)	Yes	Yes	Yes	Yes	Yes	Moderate
TARGET[9]	Unclear	Yes (centralized system)	Yes (patients, caring physicians, and outcome assessors)	Yes	Yes	Yes	Yes	Yes	Low
TENACITY[43]	Unclear	Yes (centralized system)	Yes (patients, caring physicians, and outcome assessors)	Yes	Yes	Yes	Yes	Yes	Low
TETAMI[19,20]	Unclear	Unclear	Yes (patients, caring physicians, and outcome assessors)	Yes	Yes	Yes	Yes	Yes	Low
TOPSTAR[17]	Unclear	Yes (external personnel)	Yes (patients and caring physicians)	Yes	Yes	No	No	Yes	Moderate

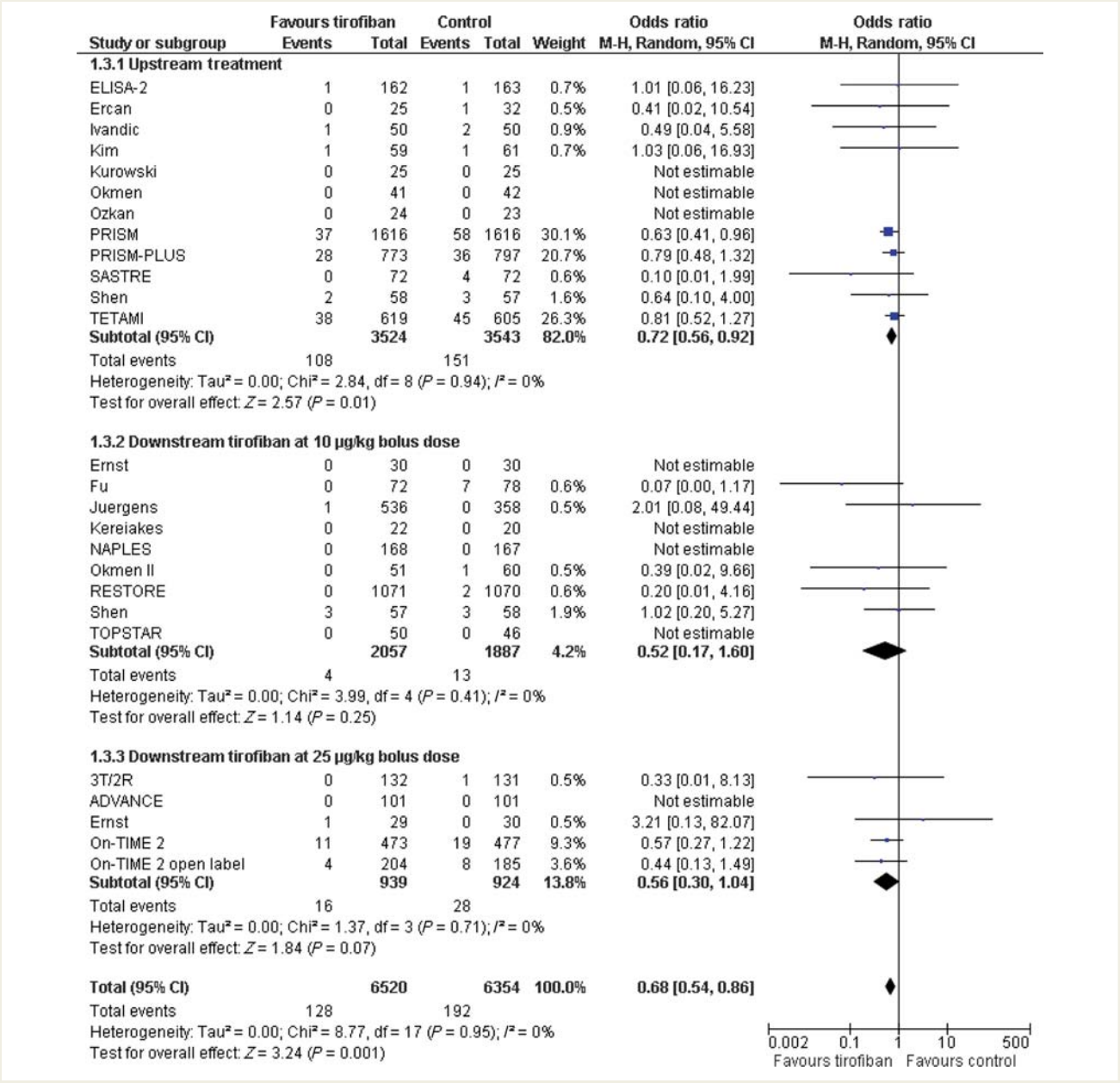

Figure 2 Forest plot of comparison: tirofiban vs. placebo or standard therapy, outcome: 30-day mortality rate. CI, confidence interval; Weight, statistical weight (an indirect estimate of study precision and impact on overall pooled estimates of the single study result).

a favourable efficacy/safety profile in a broad patient population presenting with acute coronary syndromes and/or undergoing PCI.

While several included studies antedated the advent of clopidogrel pre-treatment strategy in patients undergoing PCI, our sensitivity analysis, which focused on patients receiving tirofiban on top of pretreatment with clopidogrel or ticlopidine,[17,22,24,25,27–35,42] suggested the benefit of tirofiban to be additive to first or second generation P2Y12 receptor inhibitors. These findings are in keeping with previous evidence[45,46] and reinforce the importance of the degree and consistency of platelet inhibition to prevent ischaemic complications in patients with acute coronary syndromes undergoing PCI.

Our analysis failed to show heterogeneity of results across the different tested regimens of tirofiban for mortality or the composite of death or MI. However, for both MI rate alone and the composite of MACE rate, some degree of inconsistency was noted throughout. This might be due to various MI definitions, multiple clinical settings and/or different tirofiban tested regimens throughout studies. Interestingly, trials testing tirofiban downstream at high bolus dose, which results in a prompt and significantly greater inhibition of platelet activity compared with both standard 10 µg/kg 3 min and 0.4 µg/kg 30 min bolus regimens,[3,47,48] resulted in overall numerically higher relative and absolute reduction of death or MI, MI alone, and MACE rates within the first 30 days.

Downloaded from https://academic.oup.com/eurheartj/article/31/1/35/563591 by guest on 21 August 2022

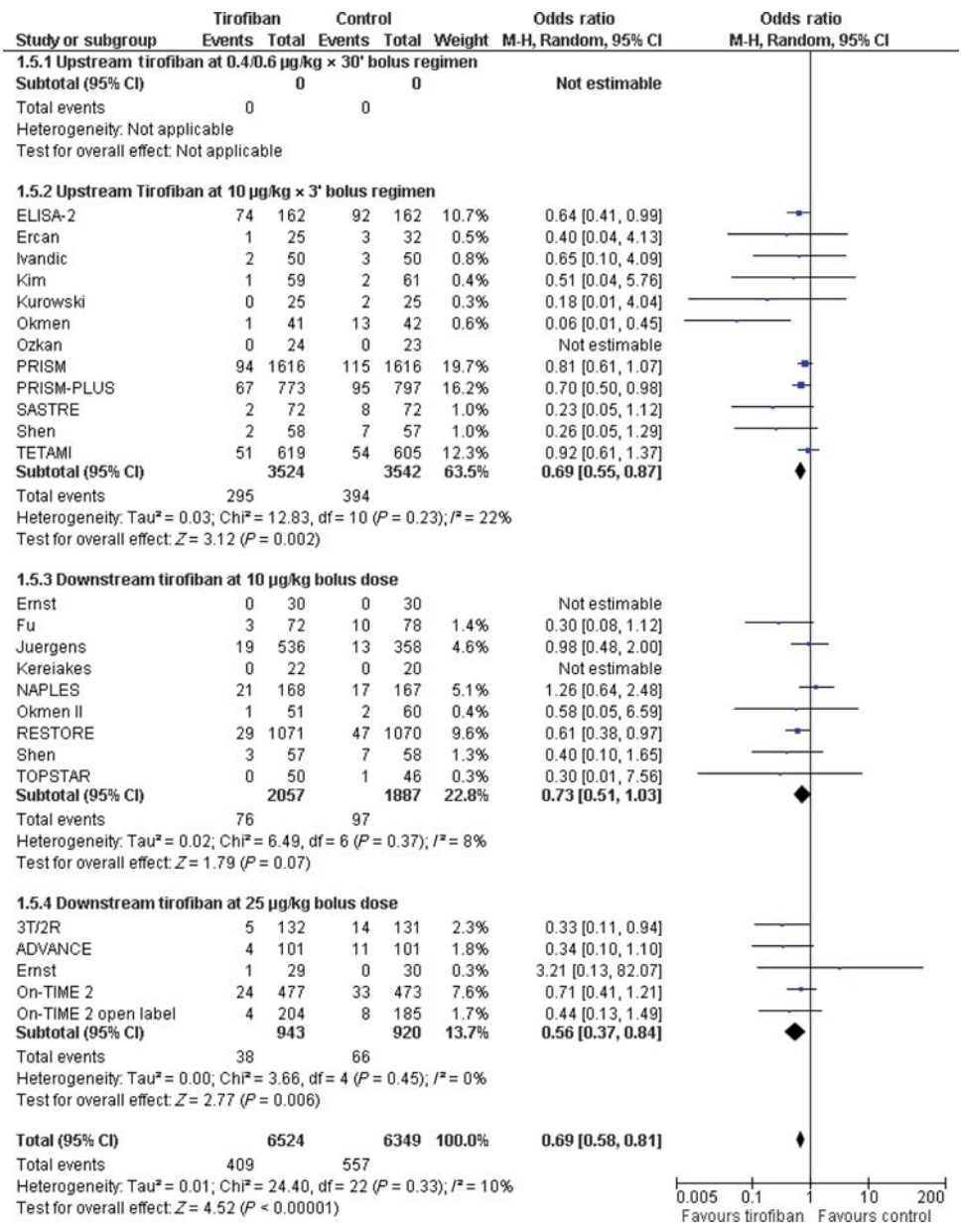

Figure 3 Forest plot of comparison: tirofiban vs. placebo or standard therapy, outcome: 30-day death or myocardial infarction. CI, confidence interval; Weight, statistical weight (an indirect estimate of study precision and impact on overall pooled estimates of the single study result).

In aggregate, ischaemic complications did not significantly differ in tirofiban vs. abciximab-treated patients at short- or medium-term follow-up. However, tirofiban tested at 10 µg/kg bolus regimen, which results in suboptimal platelet inhibition soon after administration,[3,47] increased peri-procedural ischaemic events mainly in terms of MI, compared with abciximab. This was largely driven by the results of the TARGET study, which remains by far the biggest comparison between the two drugs.[9] In contrast, the 25 µg/kg tirofiban bolus regimen which has been developed to more closely mimic abciximab-driven platelet inhibition soon after treatment administration,[48] was not associated with an increase of early ischaemic hazard when contrasted to the latter. Indeed, a trend was noted suggesting an interaction between 30-day death or MI rates and the comparison between tirofiban and abciximab when focusing on dosage of tirofiban administration. While abciximab treatment effect vs. placebo was previously shown to be directly proportional to risk status of treated patients,[49] no such pattern was observed when abciximab was compared with tirofiban at metaregression analysis, suggesting that tirofiban may effectively replace abciximab across the whole spectrum of patients with CAD, particularly with a high-dose bolus regimen.

Downloaded from https://academic.oup.com/eurheartj/article/31/1/35/563591 by guest on 21 August 2022

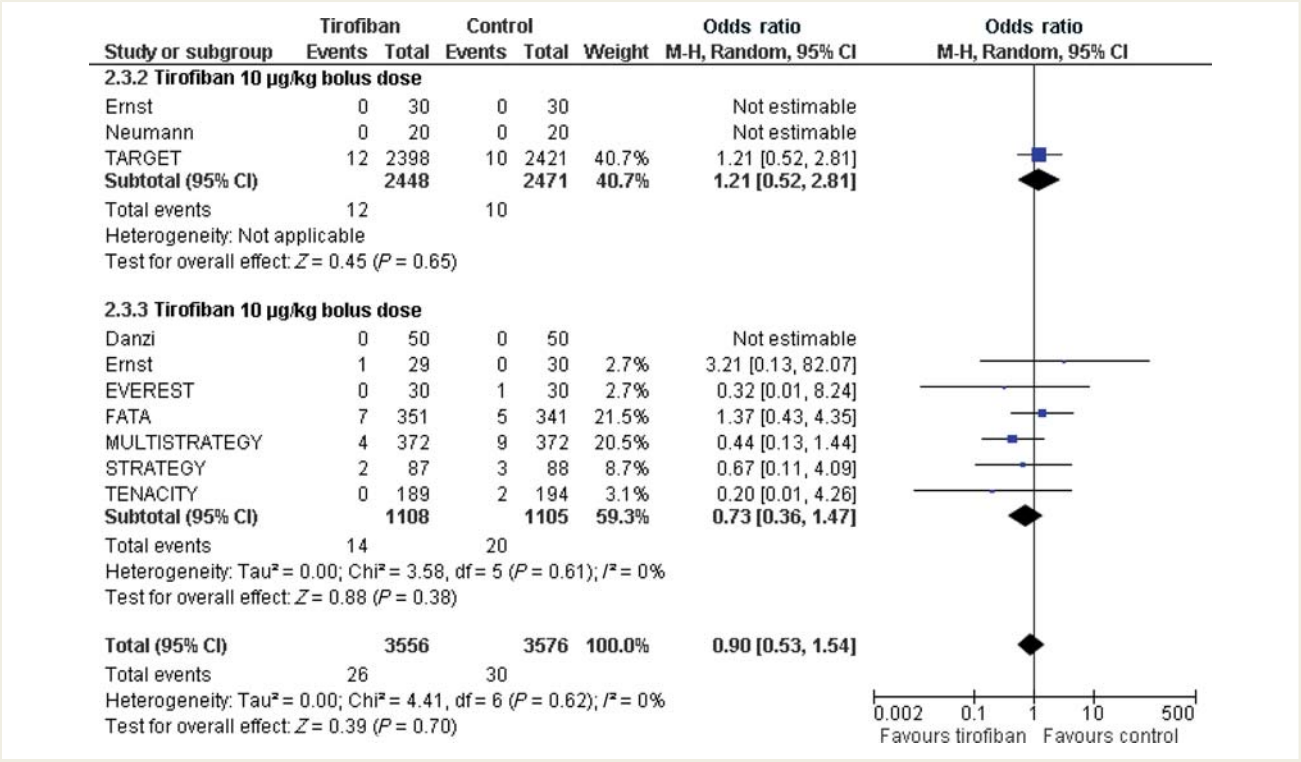

Figure 4 Forest plot of comparison: tirofiban vs. abciximab, outcome: 30-day death. CI, confidence interval; Weight, statistical weight (an indirect estimate of study precision and impact on overall pooled estimates of the single study result).

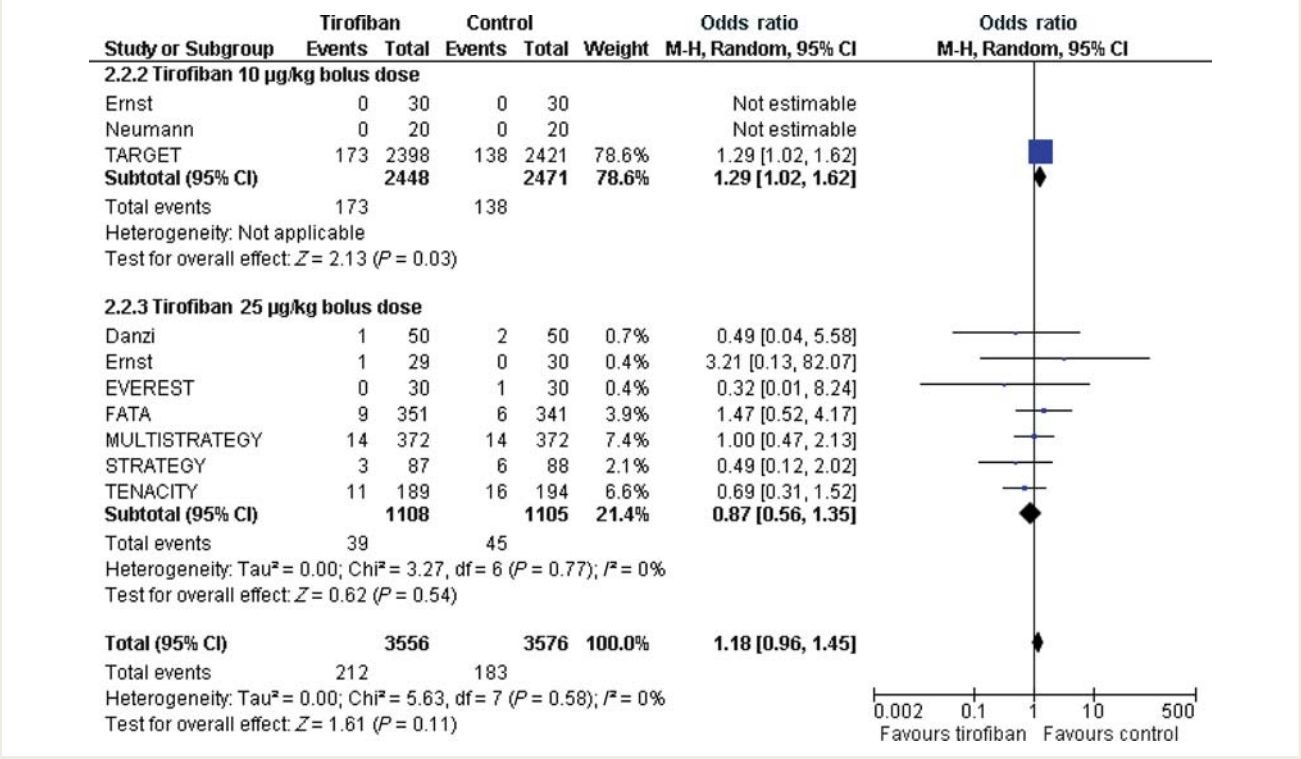

Figure 5 Forest plot of comparison: tirofiban vs. abciximab, outcome: 30-day death or myocardial infarction. CI, confidence interval; Weight, statistical weight (an indirect estimate of study precision and impact on overall pooled estimates of the single study result).

Downloaded from https://academic.oup.com/eurheartj/article/31/1/35/563591 by guest on 21 August 2022

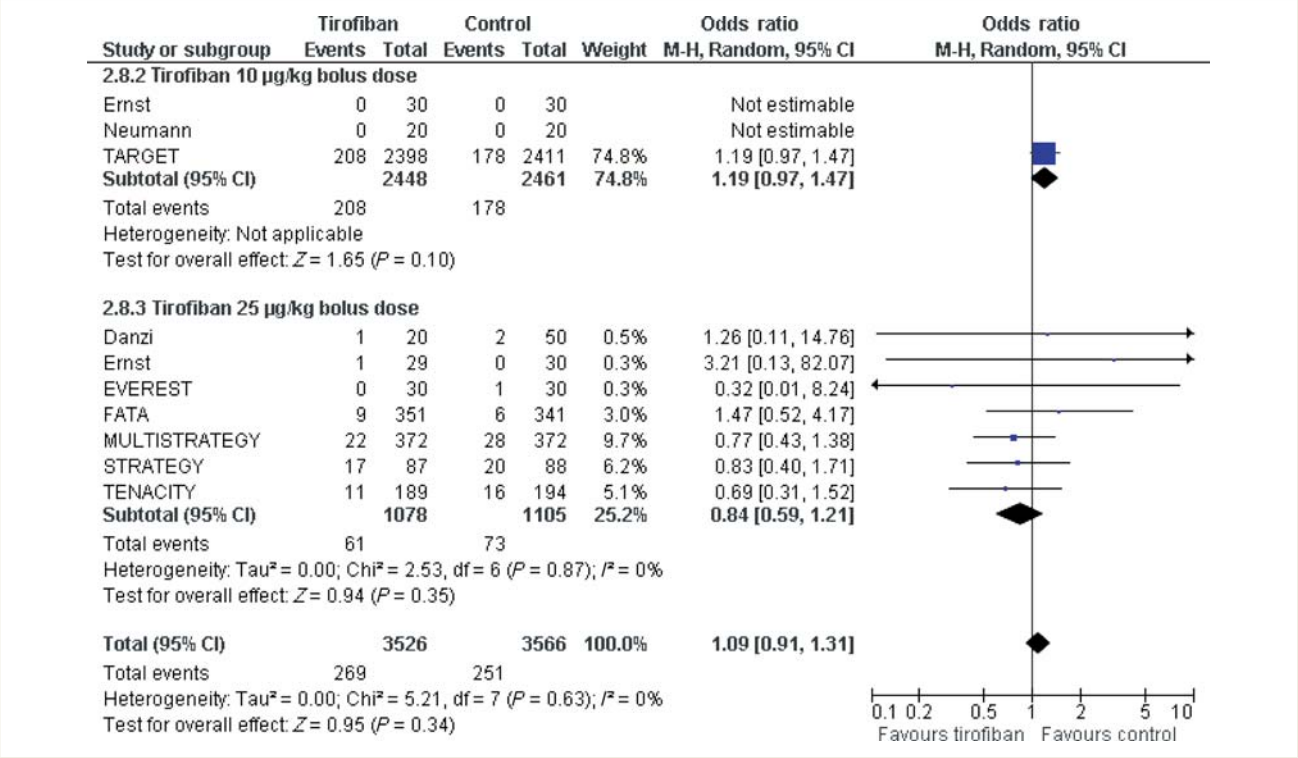

Figure 6 Forest plot of comparison: tirofiban vs. abciximab, outcome: long-term death or myocardial infarction. CI, confidence interval. Weight, statistical weight (an indirect estimate of study precision and impact on overall pooled estimates of the single study result).

Table 4 Results of meta-regression analysis

Variable	30 Days death or myocardial infarction		Long-term major adverse cardiac events	
	Beta (95% confidence interval)	*P*-value	Beta (95% confidence interval)	*P*-value
Type of control	0.469 (0.127; 0.767)	0.008	0.350 (−0.005; 0.574)	0.054
Type of administration	0.056 (−0.136; 0.183)	0.765	0.035 (−0.123; 0.149)	0.850
Concomitant medical treatment	0.166 (−0.190; 0.494)	0.371	−0.052 (−0.336; 0.255)	0.782
Adequate randomization method	−0.220 (−0.887; 0.226)	0.234	−0.203 (−0.639; 0.187)	0.273
Adequate concealment of allocation	0.261 (−0.099; 0.587)	0.157	0.035 (−0.280; 0.337)	0.850
Adequate patient blinding	0.362 (0.007; 0.654)	0.046	0.197 (−0.156; 0.507)	0.289

Based on a univariate fixed-effect model with least-squares weights for sample size to explore moderators and/or predictors of changes in log-transformed odds ratios.

Altogether, the pooled findings from both placebo and abciximab controlled studies suggest that the bolus regimen, especially for patients undergoing PCI and receiving treatment immediately before is of utmost importance to optimize outcomes. Tirofiban, given at a high-dose bolus, by providing a greater and more consistent level of platelet inhibition may be a preferable option than previously developed standard regimens which lead to desirable anti-platelet activity only with some delay after drug administration.[47]

Importantly, confidence intervals around point of estimate for ischaemic events remains wide for the comparison between tirofiban and abciximab and entail the possibility that even at high bolus regimen, the former may lead to a relatively small yet distinct increase in adverse events after PCI. This uncertainty largely reflects the still limited number of patients who have been re-evaluated in head-to-head studies with tirofiban given at high bolus dose. Unfortunately, the planned large ($n = 8800$ patients) TENACITY study which aimed to definitively ascertain whether at proper dosing tirofiban would be non-inferior to abciximab was prematurely stopped for financial reasons after 383 patients were enrolled.[43] All subsequent investigator-driven head-to-head comparisons between these two agents were based on surrogate endpoints such as ST-segment elevation resolution,[10,38,41] myocardial blush,[36] left ventricular ejection fraction,[37] or platelet inhibition[42] which explains the relatively small study populations.

Downloaded from https://academic.oup.com/eurheartj/article/31/1/35/563591 by guest on 21 August 2022

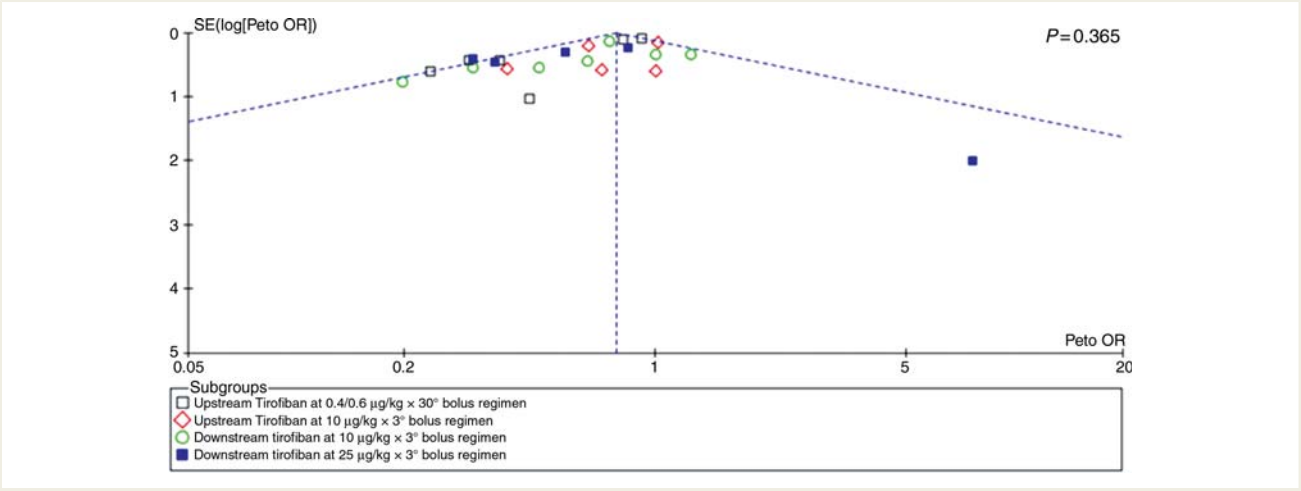

Figure 7 Funnel plot for the long-term risk of major adverse cardiac events (MACE) comparing tirofiban vs. control. This plot shows the association (or lack of) between study effect (*x*-axis) and study size/precision (*y*-axis), and can thus provide a graphical appraisal of the risk of small study bias in the overall systematic review. Specifically, small study bias, also known as publication bias, is due to the selective reporting and publication of small but significant studies and the selective under-reporting and lack of publication of small non-significant studies. If present, small study bias may unduly impact on pooled effect estimates and bias the overall results toward rejecting a null hypothesis which is actually valid. The vertical dashed line represents the summary pooled effect estimate, the oblique dashed lines represent the corresponding 95% confidence intervals, and the *P*-value provided by analytical testing with Peters test. OR, odds ratio; SE, standard error.

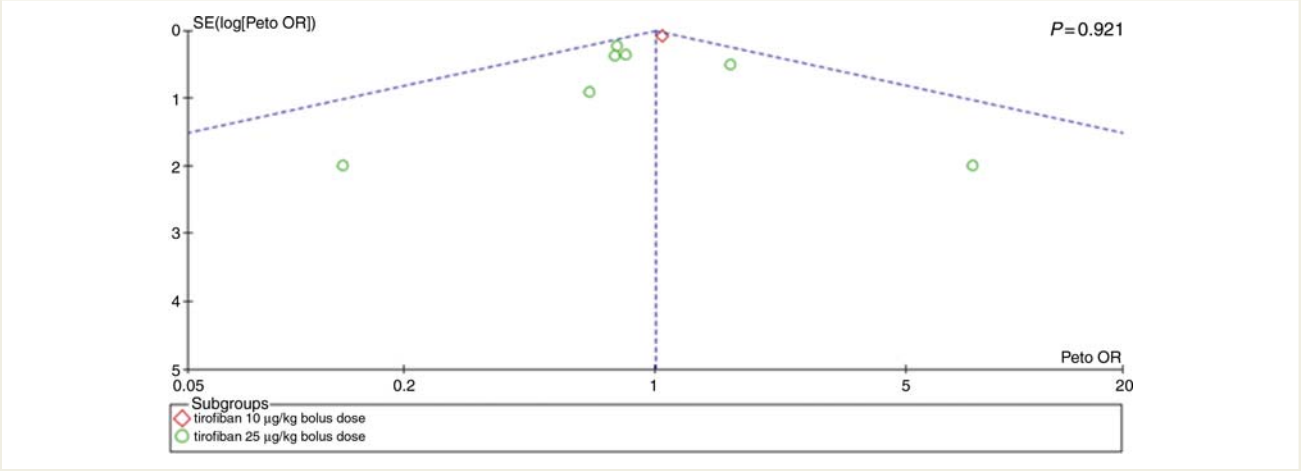

Figure 8 Funnel plot for the long-term risk of major adverse cardiac events (MACE) comparing tirofiban vs. abciximab. This plot shows the association (or lack of) between study effect (*x*-axis) and study size/precision (*y*-axis), and can thus provide a graphical appraisal of the risk of small study bias in the overall systematic review. Specifically, small study bias, also known as publication bias, is due to the selective reporting and publication of small but significant studies and the selective under-reporting and lack of publication of small non-significant studies. If present, small study bias may unduly impact on pooled effect estimates and bias the overall results toward rejecting a null hypothesis which is actually valid. The vertical dashed line represents the summary pooled effect estimate, the oblique dashed lines represent the corresponding 95% confidence intervals, and the *P*-value provided by analytical testing with Peters test. OR, odds ratio; SE, standard error.

An additional finding of potential clinical relevance was that the rate of minor, but not major, bleeding was significantly reduced by the use of tirofiban compared with abciximab. This was consistently noted in studies testing either 10 or 25 µg/kg tirofiban bolus regimens. Since the degree of platelet inhibition provided by a high-dose tirofiban bolus is not inferior to that of abciximab, and indeed many previous studies have shown that tirofiban at this revised bolus regimen might be associated with greater and more consistent antiplatelet activity than abciximab,[41,42,50] this observation of lower minor bleeding rate in tirofiban-treated patients is intriguing and deserves further investigation. Similarly, the rate of thrombocytopenia, which like bleeding complications has been shown to independently predict worse outcomes,[51,52] was reduced by almost 80% by the use of tirofiban. This likely reflects the lower propensity of

Downloaded from https://academic.oup.com/eurheartj/article/31/1/35/563591 by guest on 21 August 2022

tirofiban to elicit an antibody response. Thrombocytopenia has been shown to be associated with bleeding complications,[51,52] and it is tempting to speculate that the lower propensity of tirofiban to trigger an immune response might at least partially explain the improved safety profile in terms of minor bleedings observed in the tirofiban group. Finally, we cannot rule out the possibility that the difference in minor bleedings noted between tirofiban and abciximab is a spurious finding or simply related to the shorter duration of anti-aggregatory effect.

Study limitations

Our results suffer from those limitations which are inherent to all meta-analytic techniques including particularly heterogeneity in patient populations, different study drug regimens, and variable endpoint definitions across studies. This mainly applies to the different criteria employed throughout trials for classifying bleeding and peri-procedural ischaemic endpoints. Importantly, however, a clear reduction of overall mortality in the tirofiban arm has been noted vs. placebo but not vs. abciximab studies which is in keeping with the differences observed between study groups for MI alone or the composite of death or MI.

Conclusions

In our pooled analysis based on over 20 000 patients, tirofiban administration was shown to significantly reduce mortality, the composite of death or MI along with MACE rate when compared with placebo. This benefit in ischaemic endpoints reduction remained significant and of consistent magnitude in studies where tirofiban was tested in addition to thienopyridines but came at an increase risk for minor bleeding and thrombocytopenia. An early ischaemic hazard disfavouring tirofiban was noted when compared with abciximab in studies based on 10 μg/kg bolus regimen but not in those testing the 25 μg/kg bolus regimen. Overall, the safety profile seems to favour the use of tirofiban over abciximab for lower incidence of minor bleeding and thrombocytopenia, likely reflecting different chemical structures more than a difference in anti-platelet potency between these two drugs.

Our findings suggest that the use of tirofiban is an efficacious treatment option to reduce ischaemic events in patients with acute coronary syndromes and/or those undergoing PCI. When employed at high-dose bolus just prior to PCI, tirofiban may provide similar efficacy yet an improved safety profile when compared with abciximab. This hypothesis would require prospective assessment in order to be validated.

Funding

This work was supported by the University of Ferrara, Italy.

Conflicts of interest: M.V. has consulted for Iroko, Eli Lilly and the Medicines Company, has lectured for Iroko, Glaxo SmithKline and received grant support from Iroko and Eli Lilly. G.B.-Z. has consulted for Cordis and The Medicines Company, has lectured for Bristol-Myers Squibb and sanofi-aventis, and has received grant support from Glaxo SmithKline.

References

1. Scarborough RM, Kleiman NS, Phillips DR. Platelet glycoprotein IIb/IIIa antagonists. What are the relevant issues concerning their pharmacology and clinical use? *Circulation* 1999;**100**:437–444.
2. Topol EJ, Byzova TV, Plow EF. Platelet GPIIb-IIIa blockers. *Lancet* 1999;**353**:227–231.
3. Batchelor WB, Tolleson TR, Huang Y, Larsen RL, Mantell RM, Dillard P, Davidian M, Zhang D, Cantor WJ, Sketch MH Jr, Ohman EM, Zidar JP, Gretler D, DiBattiste PM, Tcheng JE, Califf RM, Harrington RA. Randomized COMparison of platelet inhibition with abciximab, tiRofiban and eptifibatide during percutaneous coronary intervention in acute coronary syndromes: the COMPARE trial. Comparison of Measurements of Platelet aggregation with Aggrastat, Reopro, and Eptifibatide. *Circulation* 2002;**106**:1470–1476.
4. Lele M, Sajid M, Wajih N, Stouffer GA. Eptifibatide and 7E3, but not tirofiban, inhibit alpha(v)beta(3) integrin-mediated binding of smooth muscle cells to thrombospondin and prothrombin. *Circulation* 2001;**104**:582–587.
5. Reininger AJ, Agneskirchner J, Bode PA, Spannagl M, Wurzinger LJ. c7E3 Fab inhibits low shear flow modulated platelet adhesion to endothelium and surface-absorbed fibrinogen by blocking platelet GP IIb/IIIa as well as endothelial vitronectin receptor—results from patients with acute myocardial infarction and healthy controls. *Thromb Haemost* 2000;**83**:217–223.
6. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation* 1997;**96**:1445–1453.
7. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998;**338**:1488–1497.
8. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998;**338**:1498–1505.
9. Topol EJ, Moliterno DJ, Herrmann HC, Powers ER, Grines CL, Cohen DJ, Cohen EA, Bertrand M, Neumann FJ, Stone GW, DiBattiste PM, Demopoulos L. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001;**344**:1888–1894.
10. Valgimigli M, Campo G, Percoco G, Bolognese L, Vassanelli C, Colangelo S, de Cesare N, Rodriguez AE, Ferrario M, Moreno R, Piva T, Sheiban I, Pasquetto G, Prati F, Nazzaro MS, Parrinello G, Ferrari R. Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTI-STRATEGY randomized trial. *J Am Med Assoc* 2008;**299**:1788–1799.
11. Higgins JPT, Green SG (eds). In: *Cochrane Handbook for Systematic Reviews of Interventions*. 2008. Version 501. Available from http://www.cochrane-handbookorg (last accessed on 18 May 2009).
12. Wong SS, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. *J Med Libr Assoc* 2006;**94**:451–455.
13. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. *N Engl J Med* 1985;**312**:932–936.
14. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. *J Am Med Assoc* 2006;**295**:676–680.
15. Kereiakes DJ, Kleiman NS, Ambrose J, Cohen M, Rodriguez S, Palabrica T, Herrmann HC, Sutton JM, Weaver WD, McKee DB, Fitzpatrick V, Sax FL. Randomized, double-blind, placebo-controlled dose-ranging study of tirofiban (MK-383) platelet IIb/IIIa blockade in high risk patients undergoing coronary angioplasty. *J Am Coll Cardiol* 1996;**27**:536–542.
16. Gibson CM, Goel M, Cohen DJ, Piana RN, Deckelbaum LI, Harris KE, King SB III. Six-month angiographic and clinical follow-up of patients prospectively randomized to receive either tirofiban or placebo during angioplasty in the RESTORE trial. Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis. *J Am Coll Cardiol* 1998;**32**:28–34.
17. Bonz AW, Lengenfelder B, Strotmann J, Held S, Turschner O, Harre K, Wacker C, Waller C, Kochsiek N, Meesmann M, Neyses L, Schanzenbacher P, Ertl G, Voelker W. Effect of additional temporary glycoprotein IIb/IIIa receptor inhibition on troponin release in elective percutaneous coronary interventions after pretreatment with aspirin and clopidogrel (TOPSTAR trial). *J Am Coll Cardiol* 2002;**40**:662–668.
18. Juergens CP, White HD, Belardi JA, Macaya C, Soler-Soler J, Meyer BJ, Levy RD, Bunt T, Menten J, Herrmann HC, Adgey AA, Tarnesby G. A multicenter study of the tolerability of tirofiban versus placebo in patients undergoing planned intracoronary stent placement. *Clin Ther* 2002;**24**:1332–1344.

Downloaded from https://academic.oup.com/eurheartj/article/31/1/35/563591 by guest on 21 August 2022

19. Cohen M, Gensini GF, Maritz F, Gurfinkel EP, Huber K, Timerman A, Krzeminska-Pakula M, Danchin N, White HD, Santopinto J, Bigonzi F, Hecquet C, Vittori L. The safety and efficacy of subcutaneous enoxaparin versus intravenous unfractionated heparin and tirofiban versus placebo in the treatment of acute ST-segment elevation myocardial infarction patients ineligible for reperfusion (TETAMI): a randomized trial. *J Am Coll Cardiol* 2003;**42**: 1348–1356.
20. Cohen M, Gensini GF, Maritz F, Gurfinkel EP, Huber K, Timerman A, Krzeminska-Pakula M, Santopinto J, Hecquet C, Vittori L. Prospective evaluation of clinical outcomes after acute ST-elevation myocardial infarction in patients who are ineligible for reperfusion therapy: preliminary results from the TETAMI registry and randomized trial. *Circulation* 2003;**108**:III14–III21.
21. Okmen E, Cakmak M, Tartan Z, Cam N. Effects of glycoprotein IIb/IIIa inhibition on clinical stabilization parameters in patients with unstable angina and non-Q-wave myocardial infarction. *Heart Vessels* 2003;**18**:117–122.
22. Ercan E, Tengiz I, Duman C, Onbasili OA, Baris N. Effect of tirofiban on C-reactive protein in non-ST-elevation myocardial infarction. *Am Heart J* 2004; **147**:E1.
23. Martinez-Rios MA, Rosas M, Gonzalez H, Pena-Duque MA, Martinez-Sanchez C, Gaspar J, Garcia H, Gaxiola E, Delgado L, Carrillo J, Leyva JL, Lupi E. Comparison of reperfusion regimens with or without tirofiban in ST-elevation acute myocardial infarction. *Am J Cardiol* 2004;**93**:280–287.
24. Okmen E, Sanli A, Uyarel H, Dayi S, Tartan Z, Cam N. Effects of glycoprotein IIb/IIIa receptor inhibition with tirofiban on minor myocardial damage in angiographically successful percutaneous coronary angioplasty. *Cardiology* 2004;**102**:18–23.
25. Valgimigli M, Percoco G, Barbieri D, Ferrari F, Guardigli G, Parrinello G, Soukhomovskaia O, Ferrari R. The additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high-risk coronary angioplasty: the ADVANCE Trial. *J Am Coll Cardiol* 2004;**44**:14–19.
26. Kim JH, Jeong MH, Rhew JY, Lim JH, Yun KH, Kim KH, Kang DK, Hong SN, Lim SY, Lee SH, Lee YS, Hong YJ, Park HW, Kim W, Ahn YK, Moon Y, Cho JG, Park JC, Kang JC. Long-term clinical outcomes of platelet glycoprotein IIb/IIIa inhibitor combined with low molecular weight heparin in patients with acute coronary syndrome. *Circ J* 2005;**69**:159–164.
27. Kurowski V, Toelg R, Jain D, Richter C, Wiegand UK, Richardt G, Khattab AA. Effect of adjunctive treatment with tirofiban on troponin T elevation during stenting of critically stenosed aortocoronary saphenous vein grafts. *Am J Cardiol* 2005; **96**:681–684.
28. Ozkan M, Sag C, Yokusoglu M, Uzun M, Baysan O, Erinc K, Isik E. The effect of tirofiban and clopidogrel pretreatment on outcome of old saphenous vein graft stenting in patients with acute coronary syndromes. *Tohoku J Exp Med* 2005; **206**:7–13.
29. Rasoul S, Ottervanger JP, de Boer MJ, Miedema K, Hoorntje JC, Gosselink M, Zijlstra F, Suryapranata H, Dambrink JH, van 't Hof AW. A comparison of dual vs. triple antiplatelet therapy in patients with non-ST-segment elevation acute coronary syndrome: results of the ELISA-2 trial. *Eur Heart J* 2006;**27**:1401–1407.
30. Fu XH, Hao QQ, Jia XW, Fan WZ, Gu XS, Wu WL, Hao GZ, Li SQ, Jiang YF, Geng W. Effect of tirofiban plus clopidogrel and aspirin on primary percutaneous coronary intervention via transradial approach in patients with acute myocardial infarction. *Chin Med J* 2008;**121**:522–527.
31. Ivandic BT, Kurz K, Keck F, Staritz P, Lehrke S, Katus HA, Giannitsis E. Tirofiban optimizes platelet inhibition for immediate percutaneous coronary intervention in high-risk acute coronary syndromes. *Thromb Haemost* 2008;**100**:648–654.
32. Shen J, Zhang Q, Zhang RY, Zhang JS, Hu J, Yang ZK, Zheng AF, Zhang X, Shen WF. Clinical benefits of adjunctive tirofiban therapy in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Coron Artery Dis* 2008;**19**:271–277.
33. Van 't Hof AW, ten Berg J, Heestermans T, Dill T, Funck RC, van Werkum W, Dambrink JH, Suryapranata H, van Houwelingen G, Ottervanger JP, Stella P, Giannitsis E, Hamm C. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. *Lancet* 2008;**372**: 537–546.
34. Briguori C. NAPLES: a prospective, randomized trial comparison of bivalirudin and unfractionated heparin plus tirofiban in patients with diabetes mellitus undergoing elective percutaneous coronary intervention. 2008; Presented at TCT; Available at http://www.tctmd.com/txshow.aspx?tid=2434&id=70954&trid=2380.
35. Valgimigli M. Main results of the tailoring treatment with tirofiban in patients showing resistance to aspirin or resistance to clopidogrel study (3T/2R). 2008; Presented at ESC; Available at http://resources.escardio.org/Webcast/ESC%2D2008/3210/.
36. Bolognese L, Falsini G, Liistro F, Angioli P, Ducci K, Taddei T, Tarducci R, Cosmi F, Baldassarre S, Burali A. Randomized comparison of upstream tirofiban versus downstream high bolus dose tirofiban or abciximab on tissue-level perfusion and troponin release in high-risk acute coronary syndromes treated with percutaneous coronary interventions: the EVEREST trial. *J Am Coll Cardiol* 2006;**47**: 522–528.
37. Danzi GB, Sesana M, Capuano C, Mauri L, Berra Centurini P, Baglini R. Comparison in patients having primary coronary angioplasty of abciximab versus tirofiban on recovery of left ventricular function. *Am J Cardiol* 2004;**94**:35–39.
38. Marzocchi A, Manari A, Piovaccari G, Marrozzini C, Marra S, Magnavacchi P, Sangiorgio P, Marinucci L, Taglieri N, Gordini G, Binetti N, Guiducci V, Franco N, Reggiani ML, Saia F. Randomized comparison between tirofiban and abciximab to promote complete ST-resolution in primary angioplasty: results of the facilitated angioplasty with tirofiban or abciximab (FATA) in ST-elevation myocardial infarction trial. *Eur Heart J* 2008;**29**:2972–2980.
39. Mukherjee D, Topol EJ, Bertrand ME, Kristensen SD, Herrmann HC, Neumann FJ, Yakubov SJ, Bassand JP, McClure RR, Stone GW, Ardissino D, Moliterno DJ. Mortality at 1 year for the direct comparison of tirofiban and abciximab during percutaneous coronary revascularization: do tirofiban and ReoPro give similar efficacy outcomes at trial 1-year follow-up. *Eur Heart J* 2005;**26**:2524–2528.
40. Neumann FJ, Hochholzer W, Pogatsa-Murray G, Schomig A, Gawaz M. Antiplatelet effects of abciximab, tirofiban and eptifibatide in patients undergoing coronary stenting. *J Am Coll Cardiol* 2001;**37**:1323–1328.
41. Valgimigli M, Percoco G, Malagutti P, Campo G, Ferrari F, Barbieri D, Cicchitelli G, McFadden EP, Merlini F, Ansani L, Guardigli G, Bettini A, Parrinello G, Boersma E, Ferrari R. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. *J Am Med Assoc* 2005;**293**: 2109–2117.
42. Ernst NM, Suryapranata H, Miedema K, Slingerland RJ, Ottervanger JP, Hoorntje JC, Gosselink AT, Dambrink JH, de Boer MJ, Zijlstra F, van 't Hof AW. Achieved platelet aggregation inhibition after different antiplatelet regimens during percutaneous coronary intervention for ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2004;**44**:1187–1193.
43. Moliterno DJ. Tirofiban Evaluation of Novel Dosing vs. Abciximab with Clopidogrel and Inhibition of Thrombin Study. The TENACITY. 2005; Presented at TCT.
44. De Luca G, Suryapranata H, Stone GW, Antoniucci D, Tcheng JE, Neumann FJ, Van de Werf F, Antman EM, Topol EJ. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *J Am Med Assoc* 2005;**293**:1759–1765.
45. Kastrati A, Mehilli J, Neumann FJ, Dotzer F, ten Berg J, Bollwein H, Graf I, Ibrahim M, Pache J, Seyfarth M, Schuhlen H, Dirschinger J, Berger PB, Schomig A. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *J Am Med Assoc* 2006;**295**:1531–1538.
46. Gurbel PA, Bliden KP, Zaman KA, Yoho JA, Hayes KM, Tantry US. Clopidogrel loading with eptifibatide to arrest the reactivity of platelets: results of the Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) study. *Circulation* 2005;**111**:1153–1159.
47. Kabbani SS, Aggarwal A, Terrien EF, DiBattiste PM, Sobel BE, Schneider DJ. Suboptimal early inhibition of platelets by treatment with tirofiban and implications for coronary interventions. *Am J Cardiol* 2002;**89**:647–650.
48. Schneider DJ, Herrmann HC, Lakkis N, Aguirre F, Lo MW, Yin KC, Aggarwal A, Kabbani SS, DiBattiste PM. Increased concentrations of tirofiban in blood and their correlation with inhibition of platelet aggregation after greater bolus doses of tirofiban. *Am J Cardiol* 2003;**91**:334–336.
49. De Luca G, Suryapranata H, Stone GW, Antoniucci D, Tcheng JE, Neumann FJ, Bonizzoni E, Topol EJ, Chiariello M. Relationship between patient's risk profile and benefits in mortality from adjunctive abciximab to mechanical revascularization for ST-segment elevation myocardial infarction: a meta-regression analysis of randomized trials. *J Am Coll Cardiol* 2006;**47**:685–686.
50. Danzi GB, Capuano C, Sesana M, Mauri L, Sozzi FB. Variability in extent of platelet function inhibition after administration of optimal dose of glycoprotein IIb/IIIa receptor blockers in patients undergoing a high-risk percutaneous coronary intervention. *Am J Cardiol* 2006;**97**:489–493.
51. Merlini PA, Rossi M, Menozzi A, Buratti S, Brennan DM, Moliterno DJ, Topol EJ, Ardissino D. Thrombocytopenia caused by abciximab or tirofiban and its association with clinical outcome in patients undergoing coronary stenting. *Circulation* 2004;**109**:2203–2206.
52. McClure MW, Berkowitz SD, Sparapani R, Tuttle R, Kleiman NS, Berdan LG, Lincoff AM, Deckers J, Diaz R, Karsch KR, Gretler D, Kitt M, Simoons M, Topol EJ, Califf RM, Harrington RA. Clinical significance of thrombocytopenia during a non-ST-elevation acute coronary syndrome. The platelet glycoprotein IIb/IIIa in unstable angina: receptor suppression using integrilin therapy (PURSUIT) trial experience. *Circulation* 1999;**99**:2892–2900.

Downloaded from https://academic.oup.com/eurheartj/article/31/1/35/563591 by guest on 21 August 2022