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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Appropriate bolus administration of glycoprotein IIb/IIIa inhibitors for patients with acute coronary syndromes undergoing percutaneous coronary intervention: intracoronary or intravenous? A comprehensive and updated meta-analysis and systematic review

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Abstract

Background and aim: This systematic review with meta-analysis sought to compare the efficacy and safety of intracoronary (IC) vs. intravenous (IV) administration of glycoprotein (GP) IIb/IIIa receptor inhibitors on clinical outcomes following percutaneous coronary intervention in patients with acute coronary syndromes (ST-segment elevation myocardial infarction or non-ST-segment-elevation acute coronary syndrome).

Methods: Medline, Embase, Elsevier, and Sciences online databases as well as Google Scholar literature were used to select appropriate studies with randomised controlled design. The primary end-points were mortality and target vessel revascularisation (TVR), whereas the secondary end points were incidence of thrombolysis in myocardial infarction score 3 flow (TIMI 3 flow means complete perfusion in distal coronary artery bed), re-myocardial infarction (re-MI), major bleeding, stent thrombosis left ventricular ejection fraction (LVEF), and heart failure (HF). The literature search of all major databases retrieved 1006 studies. After screening, a total of 18 trials (5812 patients) were identified with reported outcomes.

Results: Pooled analysis showed IC administration of GP IIb/IIIa receptor inhibitors can significantly increase LVEF (WMD 4.97; 95% CI 3.34–6.60; p = 0.000) and the incidence of TIMI 3 flow (OR of 0.77; 95% CI 0.64–0.92; p = 0.005), and significantly decrease in incidence of HF (OR of 1.927; 95% CI 1.189–3.124; p = 0.008). Incidences of TVR, re-MI, major bleeding, stent thrombosis, and mortality showed no significant differences between the IC and IV groups.

Conclusions: Overall, the most appropriate route of administration of GP IIb/IIIa inhibitors for patients with acute coronary syndromes appeared to be an IC injection that could increase LVEF and TIMI 3 flow and decrease the incidence of HF. Furthermore, the IC administration was not associated with increased adverse event rates when compared to IV injection.

Key words: glycoprotein IIb/IIIa receptor inhibitors, intravenous, intracoronary, acute coronary syndrome, percutaneous coronary intervention

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INTRODUCTION

Ischaemic heart disease is usually caused by thrombotic occlusions of major epicardial coronary arteries in the absence of sufficient collateral blood supply. Early, complete, and sustained reperfusion by prompt recanalisation of infarct related arteries by utilisation of percutaneous coronary intervention (PCI), or alternatively thrombolytic therapy, has been shown to decrease infarct size, preserve ventricular function, improve contractility and reperfusion, and reduce morbidity and mortality [1]. Also, platelets may play an important role in the thrombotic and inflammatory cascades in coronary atherosclerosis [1]. It has been shown that the extent of inhibition of platelet aggregation depends on some factors, such as clinical presentation, antiplatelet agents used, and dose of antiplatelet agents administered [2]. Glycoprotein (GP) IIb/IIIa is an integrin complex on platelets, which represents a receptor for fibrinogen and von-Willebrand factor responsible for platelet activation [2–4]. GP IIb/IIIa inhibitors, such as abciximab, eptifibatide, and tirofiban, are antiplatelet agents, which are often used in combination with angioplasty with or without stent placement in the treatment of patients with unstable angina or myocardial infarction (MI) [2–5]. Administration of GP IIb/IIIa inhibitors may result in high local concentration, which may lead to increased levels of platelet GP IIb/GPIIIa receptor occupancy, destabilisation of platelet aggregates, and promotion of thrombus disaggregation in epicardial arteries and microvasculature [3]. This systematic review with meta-analysis sought to determine the strength of evidence for comparing the efficacy and safety of GP IIb/IIIa inhibitors administrated either as an intracoronary bolus or as an intravenous bolus in patients with acute coronary syndromes (ACS) undergoing PCI.

METHODS

Literature search

A comprehensive literature search was conducted in major electronic databases (Medline/PubMed, Embase, Elsevier, web of knowledge, Sciences online database, and Google Scholar) from their inception until 15th July 2014 to identify randomised controlled trials (RCT) that reported on the comparison of effects of GP IIb/IIIa inhibitors administrated either as an intracoronary (IC) bolus or as an intravenous (IV) bolus on clinical outcomes in patients with ACS undergoing PCI. Predefined search terms were: "glycoprotein IIb/IIIa inhibitors", "abciximab", "eptifibatide", "tirofiban", "GP IIb/IIIa inhibitors", "glycoprotein IIb/IIIa antagonist" and "intracoronary", "intravenous", "bolus", and "myocardial infarction", "MI", "ST-segment myocardial infarction", "STEMI", "non-STEMI", "acute coronary syndrome ", and "percutaneous coronary intervention", "PCI", and "angioplasty". There were no language limitations. All retrieved reference lists of included RCTs were also reviewed to determine additional studies not indexed in common databases. Studies were included into the analysis when they met the following criteria: 1) RCT; 2) reporting at least one of the outcomes of interest, including: left ventricular ejection fraction (LVEF), thrombolysis in myocardial infarction (TIMI) score, re-MI, heart failure (HF), stent thrombosis, bleeding, target vessel revascularisation (TVR), and mortality. In addition, abstracts without peer-review publications of manuscripts, duplicate reports, and ongoing RCTs were not included.

Data extraction and outcome measures

Two investigators (S.A-H-S and A.S) extracted data independently, and discrepancies were resolved via a consensus standardised abstraction checklist used for recording data in each study. Data retrieved from trials included the author's name, country, study design, details of therapeutic regimens, clinical scenario, sample size, follow-up duration, mean age, and gender, and clinical outcomes. For exploration of heterogeneity among trials, a subgroup analysis of disparities in patients' characteristics was performed for (1) average age (> 65 years vs. ≤ 65 years), (2) percentage of males (> 80% vs. ≤ 80%), (3) clinical scenario of patients (ST-elevation MI [STEMI] vs. NSTE-ACS), (4) sample size (≤ 200 vs. > 200), (5) follow-up (≤ 30 days vs. > 30 days), and (6) type of GP IIb/IIIA inhibitors (abciximab vs. small-molecule).

Primary and secondary end-points

The primary end-points were TVR and mortality, whereas the secondary end-points were mean changes of LVEF, incidence of TIMI 3 flow, re-MI, major bleeding, stent thrombosis, and HF.

Definitions of end-points

Target vessel revascularisation was defined as ischaemia-driven revascularisation of the infarct-related artery with PCI and coronary artery bypass graft. Re-MI was defined as recurrent symptoms suggestive of ischaemia with ST-segment elevation and/or elevation of the levels of cardiac markers. LVEF was assessed during hospital stay by echocardiography. TIMI 0 flow (no perfusion) refers to the absence of any antegrade flow beyond the occlusion; TIMI 1 flow (penetration without perfusion) is a faint antegrade flow beyond the occlusion, with incomplete filling of the distal coronary bed; TIMI 2 flow (partial perfusion) is a delayed or sluggish antegrade flow with complete filling of the distal territory; and TIMI 3 flow (complete perfusion) is a normal flow that fills the distal coronary bed completely. Major bleeding was defined as that which occurred during the hospitalisation, using TIMI criteria. Mortality was considered to be cardiac unless a non-cardiac cause of death could be established.

Statistical analysis, publication bias, and quality assessment

All data were analysed by STATA version 11.0 utilising METAN and METABIAS modules. The effect sizes measured were odds ratio (OR) with 95% confidence interval (95% CI) for categorical

variables. For non-categorical data the weighted mean difference (WMD) with 95% CI was used for calculating differences in LVEF between intervention and control groups. OR < 1 favoured intravenous bolus administration and OR > 1 favoured intracoronary bolus administration. RCTs with no events in the two arms were discarded from pooled analysis. Forest plots were created for each outcome. A value of $p < 0.1$ for Q test or $I^2 > 50\%$ indicated significant heterogeneity among studies. Heterogeneity among trials was accounted for by applying a random effect model when indicated. Subgroup analysis was performed to further identify the possible sources of heterogeneity, and a p value of < 0.1 was accepted as significant. Sensitivity analysis was performed to evaluate the robustness of the result with the random-effects method. The presence of publication bias was evaluated using the Begg and Egger tests. Quality assessment of RCTs was performed by using the Jadad score. The Jadad score assesses three items, including randomisation (0–2 points), blinding of study (0–2 points), and withdrawals and dropouts (0–1 points). Higher scores indicated better reporting ("high" quality: 5; "good" quality: 3–4; "poor" quality: 0–2). Results were considered statistically significant at $p < 0.05$.

RESULTS

Literature search strategy and included trials

Literature search retrieved 1006 studies from screened databases, of which 835 (83%) were excluded after initial review. Of 171 primarily included studies, 153 were excluded after detailed evaluation due to insufficient reporting on end-points of interest. The final analysis included 18 RCTs (5812 patients).

Study characteristics, effect measures, and clinical outcomes

Primary end-points

Target vessel revascularisation. A total of 2969 patients were included from 10 RCTs that reported data on the incidence of TVR. The patient population of RCTs ranged from 41 to 1005 patients, with a mean age of 63.07 years, and 72.7% were males (Table 1). From all cases, 1767 cases were allocated to the IV group and 1202 cases to the IC group (Table 1). One in ten comparisons did not present any postoperative death events in two comparative arms; therefore, the remaining nine RCTs (2928 cases) were used to perform the meta-analysis. The overall incidence of TVR was 6.5%, ranging from 0.8% to 24.7%. TVR occurred in 6.69% in the IV group and 6.35% in the IC group (Table 2). Pooled analysis indicated that the incidence of TVR was similar between patients who received IV or IC bolus administration with an OR of 1.14 (95% CI 0.83–1.56; $p = 0.4$) using a fixed model (Fig. 1). No significant heterogeneity was observed among RCTs ($\chi^2 = 8.53$, $I^2 = 6.2\%$, $p = 0.3$).

Mortality. Seventeen RCTs (5763 patients) reported data on death. Mortality occurred in 2.9% (89 cases) in the IV group and 3.4% (91 patients) in the IC group. Three of 17 comparisons did not present any postoperative death events in two comparative arms; thus the remaining 14 RCTs (5632 cases) were used to perform the meta-analysis. Patients had a mean age of 62.3 years, and 75% were males (Table 1). Pooled treatment effect analysis revealed that IV and IC bolus administrations have similar effects on the incidence of mortality with an OR of 1.18 (95% CI 0.87–1.6; $p = 0.2$) using a fixed model (Fig. 2). No heterogeneity was observed among RCTs ($\chi^2 = 9.98$, $I^2 = 0.0\%$, $p = 0.6$).

Secondary end-points

Left ventricular ejection fraction. A total of 400 patients were included from five RCTs that reported data on LVEF. Patient populations of RCTs ranged from 20 to 154 patients, with a mean age of 63.4 years, and 78.1% were males (Table 1). From all patients, 201 cases were allocated to the IV group and 202 cases to the IC group (Table 1). Mean LVEF for all trials was 51.9 ± 8.4 with 50.6 ± 8.1 for IV and 53.3 ± 8.6 for the IC group (Table 2). Pooled analysis with random effect model revealed that IC therapy succeeded in significantly increasing LVEF with a WMD of 4.97 (95% CI 3.34–6.60; $p = 0.000$) (Fig. 3). There was a significant heterogeneity among studies ($\chi^2 = 18.28$, $I^2 = 78.1\%$, $p = 0.00$). Subgroup analysis showed that studies with male percentage ≤ 80%, mean age more than 65 years, small-molecule GP IIb/IIIa inhibitors, and follow-up duration less than six months were the main causes for heterogeneity among trials (Table 3). Sensitivity analysis reported that significant increase of LVEF following IC administration is not dependent on results of most studies (Table 4).

Thrombolysis in myocardial infarction score 3 flow. A total of 3695 patients were included from 13 RCTs that reported data on TIMI-score. Patient populations of RCTs ranged from 40 to 2065 patients, with a mean age of 63.1 years, and 75.7% were males (Table 1). From all cases, 1824 cases were allocated to the IV bolus group and 1871 cases to the IC bolus group (Table 1). The overall incidence of TIMI-3 was 85.5%: 83.1% in the IV group and 87.9% in the IC group (Table 2). Pooled treatment effect analysis revealed that IC, compared to IV bolus administration, could significantly increase TIMI-3 flow with an OR of 0.77 (95% CI 0.64–0.92; $p = 0.005$) using a random model (Fig. 4). Significant heterogeneity was observed among RCTs ($\chi^2 = 19.44$, $I^2 = 38.3\%$, $p = 0.07$). Moreover, subgroup analysis was performed for exploring the cause of heterogeneity, and indicated that the studies with male percentage < 80%, age more than 65 years, sample size less than 200 patients, small molecule GP IIb/IIIa inhibitors, and follow-up duration less than six months was significantly different among treatment groups (Table 3). Begg and Egger tests showed that there was no potential publication bias among RCTs included in the present analysis (Begg test, $p = 0.542$; Egger test, $p = 0.542$). Sensitivity analysis showed that significant increase of TIMI-3 flow following IC administration is not dependent on results of any study (Table 4).

Table 1. Demographic data of included studies

Author	Year/country	Type of GPI	N		Mean age [years]		Male (%)		Drug protocol	Population	Follow-up	Jadad
			IV	IC	IV	IC	IV	IC				
Candemir [4]	2012/Turkey	tirofiban	22	34	70.9	69.4	55	62	High-dose bolus (25 μg/kg), plus maintenance (0.15 μg/kg/min) infusion for 24 h	STEMI	1 month	2
Bertrand [5]	2009/Canada	abciximab	797	208	60	60	79	76	IC and IV bolus 0.25 mg/kg, plus maintenance (0.125 μg/kg/min) infusion for 12 h	NSTE-ACS	12 months	4
Bellandi [6]	2004/Italy	abciximab	23	22	61.4	62.4	78.3	79.3	IC and IV bolus 0.25 mg/kg, plus maintenance (0.125 μg/kg/min) infusion for 12 h	STEMI	1 month	2
Balghith [7]	2014/ /Saudi Arabia	abciximab	248	199	52	55	74	73	IC and IV bolus 0.25 mg/kg, plus maintenance (0.125 μg/kg/min) infusion for 12 h	NSTE-ACS	1 month	2
Wu [8]	2008/China	tirofiban	57	58	74.8	76.4	52.6	56.9	IC and IV bolus 10 μg/kg over 3 min, plus maintenance (0.15 μg/kg/min) infusion for 36 h	NSTE-ACS	1 month	2
Thiele [9]	2012/Germany	abciximab	1033	1032	63	63	75	75	IC and IV bolus 0.25 mg/kg, plus maintenance (0.125 μg/kg/min) infusion for 12 h	STEMI	3 months	4
Wohrle [10]	2003/Germany	abciximab	109	294	60	60	80	79	A 20 mg bolus was given ivor IC, followed by 12 h of IV infusion of 120 mg	STEMI	1 month	4
Thiele [11]	2008/Germany	abciximab	77	77	66	64	77	82	IC and IV bolus 0.25 mg/kg, plus maintenance (0.125 μg/kg/min) infusion for 12 h	STEMI	1 month	3
Secco [12]	2014/Italy	abciximab	42	47	61.8	61.1	78.6	87.2	IC and IV bolus 0.25 mg/kg	STEMI	6 months	2
Dominguez--Rodriguez [13]	2009/Spain	abciximab	25	25	70	66	80	72	IC and IV bolus 0.25 mg/kg, plus maintenance (0.125 μg/kg/min) infusion for 12 h to max. 18 μg/kg/min	STEMI	1 month	3
Namazi [14]	2012/Iran	eptifibatide/ /abciximab	20	20	58.6	53.8	85	90	An IC bolus dose of abciximab (0.25 μg/kg). In the IV, two doses (each 180 μg/kg) of eptifibatide were administrated every 10 min	STEMI	In-hospital	3
Galache Osuna [15]	2006/Spain	abciximab	65	72	59.8	63	77	86	IC and IV bolus 0.25 mg/kg, plus maintenance (0.125 μg/kg/min) infusion for 12 h	NSTE-ACS or SETMI	More than 1 year	3
Kakkar [16]	2004/Louisiana	abciximab	72	101	58.5	55.4	72.2	77.2	IC and IV bolus 0.25 mg/kg, plus maintenance (0.125 μg/kg/min) infusion for 12 h	NSTE-ACS or SETMI	6 months	2
Kirma [17]	2011/Turkey	tirofiban	24	25	56	57	88	92	IC bolus only 25 μg/kg or IV bolus 25 μg/kg plus infusion (18 h at 0.15 μg/kg/min)	STEMI	6 months	4
Iversen [18]	2011/Denmark	abciximab	170	185	62	62	80	82	IC and IV bolus 0.25 mg/kg, plus maintenance (0.125 μg/kg/min) infusion for 12 h	STEMI	1 month	2

→

Table 1. cont. Demographic data of included studies

Author	Year/country	Type of GPI	N		Mean age [years]		Male (%)		Drug protocol	Population	Follow-up	Jadad
			IV	IC	IV	IC	IV	IC				
Gu [19]	2010/ /Netherland	abciximab	263	271	63	63	71	77	IC and IV bolus 0.25 mg/kg	STEMI	1 month	4
Deibele [20]	2009/ /United States	eptifibatide	19	22	58.5	59.9	73.7	63.6	The 180 μg/kg bolus infusion was started at the onset of the bolus at a rate of 2 μg/kg/min (or an infusion of 1 μg/kg/min and continued for 18 h after the initial bolus; the second 180 μg/kg bolus of eptifibatide 10 min after the initial bolus	NSTE-ACS	1 month	3
Yang [21]	2007/China	tirofiban	26	28	59	59	79	79	IC bolus (10 μg/kg) prior to the first balloon inflation or to IV tirofiban bolus at the same dose prior to coronary angiography, followed by a 36-h IV tirofiban (0.15 μg/kg/min) infusion	STEMI	In-hospital	3

GPI — glycoprotein IIb/IIIa inhibitors; NSTE-ACS — non-ST segment elevation-acute coronary syndrome; STEMI — ST segment elevation myocardial infarction; IC — intracoronary; IV — intravenous

Re-myocardial infarction. A total of 5080 cases were included from 13 RCTs that reported data on the incidence of re-MI. After discarding three studies with "zero columns" in two comparative arms, a total of 2642 cases were allocated to the IV group and 2262 cases to the IC group. Patients had a mean age of 63.7 years, and 73.7% were males (Table 1). The overall incidence of re-MI was 2.12% with a range from 0.86% to 7.5%. Re-MI occurred in 2.38% in the IV group and 1.85% in the IC group (Table 2). Pooled analysis reported that IC bolus administration could not decrease the incidence of re-MI when compared to IV application with an OR of 1.259 (95% CI 0.847–1.871; p = 0.2) using a fixed model (Fig. 5). No significant heterogeneity was observed among RCTs (χ^2 = 7.96, I^2 = 0.0%, p = 0.5). Begg and Egger tests showed that there was no potential publication bias among RCTs included (Begg test, p = 0.421; Egger test, p = 0.421).

Major bleeding. A total of 3775 patients were included from 13 RCTs that reported data on the incidence of major bleeding. In fact, two of 13 comparisons did not present any postoperative death events in two comparative arms; therefore, the remaining 11 RCTs (3685 cases) were used to perform the meta-analysis. Patients had a mean age of 63.6 years, and 74.8% were males (Table 1). The overall incidence of major bleeding was 11.72%, accounting for 12.11% in the IV group and 11.34% in the IC group (Table 2). Pooled analysis indicated that the occurrence of major bleeding was statistically similar between patients who received IV or IC bolus administration with an OR of 1.067 (95% CI 0.873–1.305; p = 0.5) using a fixed model (Fig. 6). No significant heterogeneity was observed among RCTs (χ^2 = 8.26, I^2 = 0.0%, p = 0.6). Begg and Egger tests showed that there was no potential publication bias among RCTs included. (Begg test, p = 0.625; Egger test, p = 0.625).

Incidence of stent thrombosis. Four RCTs reported data on stent thrombosis. Overall incidence of thrombosis was 1.77%: 2.26% in the IV group and 1.27% in the IC group (Table 2). Pooled analysis indicated that both routes of bolus administration have similar effects on the incidence of stent thrombosis, with an OR of 1.728 (95% CI 0.703–4.25; p = 0.2) using a fixed model (Fig. 7). No significantly heterogeneity was observed among RCTs (χ^2 = 2.07, I^2 = 0.0%, p = 0.5).

Heart failure. A total of 2334 patients were included from three RCTs that reported data on the incidence of HF. Overall incidence of HF was 3.21%: 4.19% in the IV group and 2.22% in the IC group (Table 2). Pooled analysis indicated that IC, compare to IV bolus administration, can significantly decrease the incidence of HF with an OR of 1.927 (95% CI 1.189–3.124; p = 0.008) using a fixed model (Fig. 8). No significant heterogeneity was observed among RCTs (χ^2 = 0.65, I^2 = 0.0%, p = 0.7). Begg and Egger tests showed that there was no potential publication bias among included RCTs (Begg test, p = 0.602; Egger test, p = 0.602). Sensitivity analysis reported that significant decrease of HF following IC administration is not dependent on results of any study (Table 4).

Table 2. Clinical outcomes of included studies

Author	LVEF		TIMI 3 flow		TVR		Major bleeding		Re-MI		HF		Mortality		Stent thrombosis		MACE	
	IV	IC	IV	IC	IV	IC	IV	IC	IV	IC	IV	IC	IV	IC	IV	IC	IV	IC
Candemir [4]	ND	ND	11	29	2	2	2	2	0	1	ND	ND	1	1	2	0	7	6
Bertrand [5]	ND	ND	ND	ND	51	14	ND	ND	18	7	ND	ND	4	2	ND	ND	69	21
Bellandi [6]	46.3 ± 10.7	53.3 ± 9.5	20	22	ND	ND	ND	ND	ND	ND	ND	ND	1	1	ND	ND	ND	ND
Balghith [7]	ND	ND	ND	ND	16	9	ND	ND	ND	ND	ND	ND	3	2	7	4	ND	ND
Wu [8]	60.7 ± 4.6	67.4±6.2	41	51	1	0	9	7	1	0	6	2	2	1	ND	ND	4	1
Thiele [9]	ND	ND	870	877	ND	ND	129	131	17	17	38	22	34	42	ND	ND	ND	ND
Wohrle [10]	ND	ND	ND	ND	ND	ND	ND	ND	3	1	ND	ND	17	28	ND	ND	22	30
Thiele [11]	46.1 ± 9.7	48 ± 9.5	66	65	2	0	5	4	2	0	5	2	3	2	ND	ND	12	4
Secco [12]	ND	ND	ND	ND	8	14	7	3	2	3	ND	ND	1	2	1	2	12	18
Dominguez--Rodriguez [13]	ND	ND	17	22	ND	ND	3	2	0	0	ND	ND	0	0	ND	ND	ND	ND
Namazi [14]	42 ± 5.9	45.1 ± 9.3	18	19	ND	ND	0	1	0	0	ND	ND	0	0	ND	ND	ND	ND
Galache Osuna [15]	ND	ND	64	72	ND	ND	ND	ND	ND	ND	ND	ND	3	2	ND	ND	4	6
Kakkar [16]	ND	ND	ND	ND	11	20	6	4	8	5	ND	ND	2	1	ND	ND	10	6
Kirma [17]	58 ± 10	53 ± 8.5	23	22	ND	ND	0	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Iversen [18]	ND	ND	124	149	16	7	28	21	8	5	ND	ND	9	2	ND	ND	35	17
Gu [19]	ND	ND	226	241	10	9	27	31	4	3	ND	ND	7	5	3	1	16	15
Deibele [20]	ND	ND	17	21	0	0	0	0	0	0	ND	ND	0	0	ND	ND	2	0
Yang [21]	ND	ND	19	26	ND	ND	3	7	ND	ND	ND	ND	2	0	ND	ND	ND	ND

IC — intracoronary; IV — intravenous; LVEF — left ventricular ejection fraction; TIMI — thrombolysis in myocardial infarction; TVR — target vessel revascularisation; MI — myocardial infarction; HF — heart failure; MACE — major adverse cardiovascular events; ND — no data

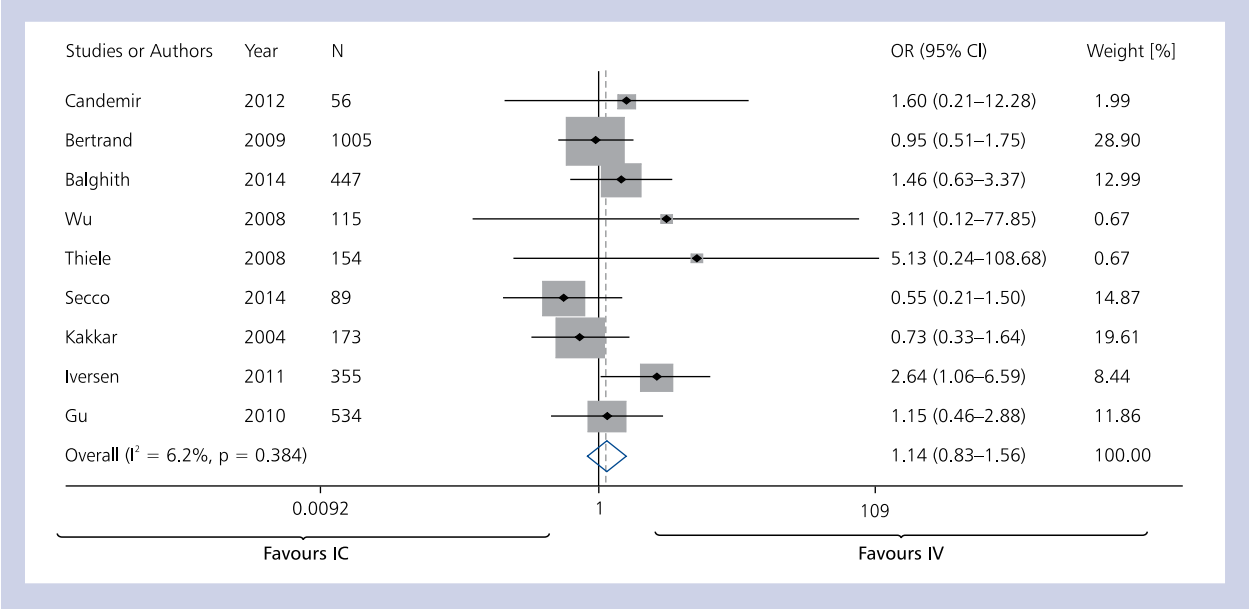

Figure 1. Forest plot of odds ratio (OR) for treatment with glycoprotein IIb/IIIa inhibitors on incidence of target vessel revascularisation; CI — confidence interval; IC — intracoronary; IV — intravenous

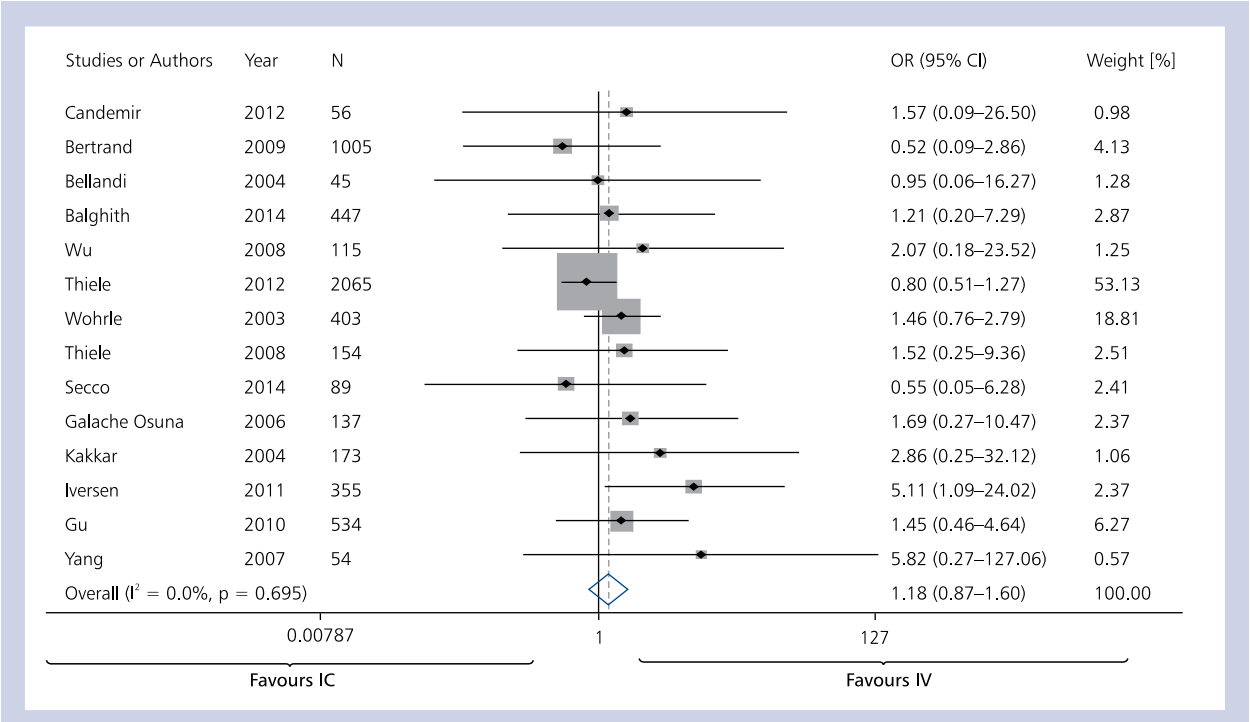

Figure 2. Forest plot of odds ratio (OR) for treatment with glycoprotein IIb/IIIa inhibitors on incidence of mortality; CI — confidence interval; IC — intracoronary; IV — intravenous

DISCUSSION

Ischaemic heart disease is known as the most common cause of morbidity and mortality as well as decrease in quality of life worldwide [22, 23]. Although the formation of atherosclerotic plaques in coronary arteries is a long-term process, genetic and environmental backgrounds, such as hypertension, hyperlipidaemia, and diabetes mellitus, have a strong potential to accelerate that process, resulting in early significant obstructions,

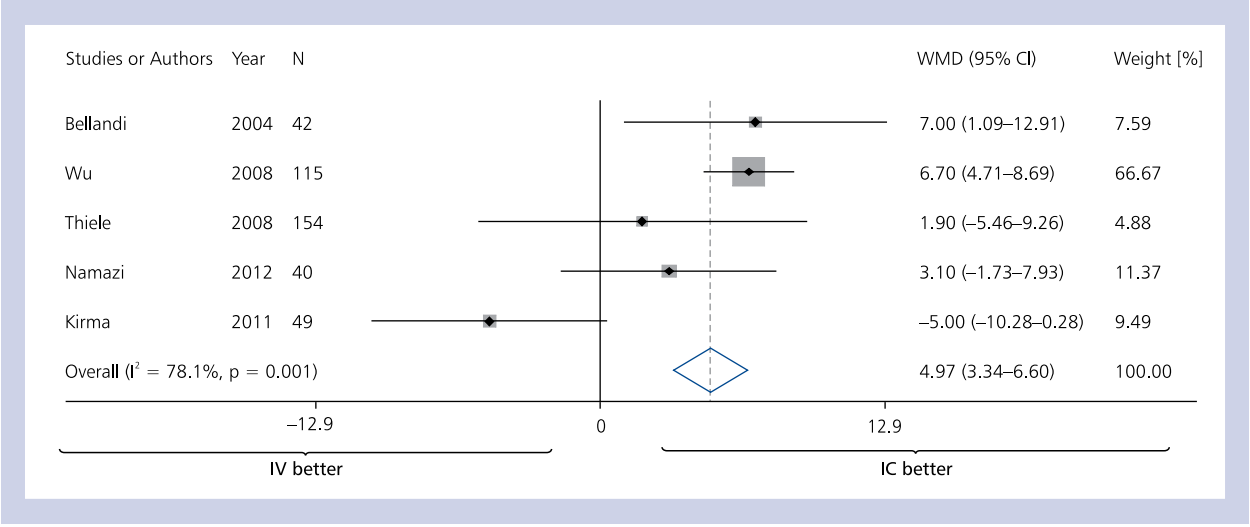

Figure 3. Forest plot of weighted mean differences (WMD) for treatment with glycoprotein IIb/IIIa inhibitors on incidence of left ventricular ejection fraction; CI — confidence interval; IC — intracoronary; IV — intravenous

Table 3. Subgroup analysis for clinical outcomes

Subgroup	Studies (N)	Odds ratio (95% CI)	P
Subgroup analysis for LVEF flow according to SMD			
Age			
> 65	1	1.226 (0.827 to 1.625)	0.000
≤ 65	4	0.160 (–0.155 to 0.476)	0.319
Male (%)			
> 80	2	–0.110 (–0.532 to 0.312)	0.609
≤ 80	4	0.928 (0.622 to 1.323)	0.000
Sample size			
> 200		All studies had sample size ≤ 200	
≤ 200			
Clinical scenario			
NSTE-ACS	1	1.226 (0.827 to 1.625)	0.000
STEMI	4	0.160 (–0.155 to 0.476)	0.320
Follow-up			
> 6 months	1	–0.532 (–1.102 to 0.039)	0.068
≤ 6 months	4	0.826 (0.551 to 1.100)	0.000
Type of GP IIb/IIIA inhibitors			
Abciximab	3	0.465 (0.087 to 0.844)	0.016
Small-molecule	2	0.648 (0.321 to 0.975)	0.000
Subgroup analysis for TIMI 3 flow according to odds ratio			
Age			
> 65	3	0.276 (0.139–0.547)	0.000
≤ 65	10	0.838 (0.694–1.012)	0.066
Male (%)			
> 80	4	0.677 (0.425–1.078)	0.100
≤ 80	9	0.788 (0.648–0.958)	0.017
Sample size			
> 200	3	0.861 (0.706–1.050)	0.138
≤ 200	10	0.444 (0.284–0.696)	0.000
Clinical scenario			
NSTE-ACS	3	0.344 (0.143–0.820)	0.057
STEMI	10	0.801 (0.655–0.963)	0.018
Follow-up			
> 6 months	2	1.185 (0.234–6.000)	0.838
≤ 6 months	11	0.766 (0.638–0.918)	0.004
Type of GP IIb/IIIA inhibitors			
Abciximab	8	0.835 (0.690–1.009)	0.062
Small-molecule	5	0.340 (0.183–0.633)	0.001
Subgroup analysis for TVR according to odds ratio			
Age			
> 65	2	1.981 (0.364–10.78)	0.429
≤ 65	7	1.112 (0.804–1.538)	0.520
Male (%)			
> 80	1	2.642 (1.059–6.590)	0.037
≤ 80	8	0.996 (0.708–1.402)	0.983
Sample size			
> 200	4	1.322 (0.892–1.960)	0.164
≤ 200	5	0.827 (0.473–1.447)	0.507
Clinical scenario			
NSTE-ACS	4	1.008 (0.667–1.525)	0.968
STEMI	5	1.344 (0.819–2.205)	0.242
Follow-up			
> 6 months	3	0.788 (0.512–1.212)	0.278
≤ 6 months	6	1.736 (1.076–2.801)	0.024

→

Table 3. cont. Subgroup analysis for clinical outcomes

Subgroup	Studies (N)	Odds ratio (95% CI)	P
Type of GP IIb/IIIA inhibitors			
Abciximab	7	1.112 (0.804–1.538)	0.520
Small-molecule	2	1.981 (0.364–10.784)	0.429
Subgroup analysis for re-MI according to odds ratio			
Age			
> 65	2	1.262 (0.165–9.639)	0.823
≤ 65	8	1.259 (0.841–1.885)	0.263
Male (%)			
> 80	1	1.778 (0.570–5.544)	0.321
≤ 80	9	1.199 (0.786–1.831)	0.400
Sample size			
> 200	5	1.128 (0.717–1.773)	0.603
≤ 200	5	1.808 (0.796–4.108)	0.157
Clinical scenario			
NSTE-ACS	3	1.169 (0.584–2.343)	0.659
STEMI	7	1.305 (0.807–2.112)	0.278
Follow-up			
> 6 months	3	1.047 (0.540–2.029)	0.892
≤ 6 months	7	1.395 (0.852–2.284)	0.186
Type of GP IIb/IIIA inhibitors			
Abciximab	8	1.259 (0.841–1.885)	0.264
Small-molecule	2	1.262 (0.165–9.639)	0.832
Subgroup analysis for major bleeding according to odds ratio			
Age			
> 65	3	1.442 (0.621–3.352)	0.394
≤ 65	8	1.048 (0.852–1.389)	0.657
Male (%)			
> 80	2	1.442 (0.797–2.608)	0.226
≤ 80	9	1.026 (0.829–1.270)	0.813
Sample size			
> 200	3	1.024 (0.823–1.374)	0.833
≤ 200	8	1.336 (0.802–2.224)	0.265
Clinical scenario			
NSTE-ACS	2	1.654 (0.727–3.762)	0.230
STEMI	9	1.038 (0.843–1.277)	0.727
Follow-up			
> 6 months	2	2.522 (0.967–6.577)	0.058
≤ 6 months	9	1.023 (0.833–1.257)	0.826
Type of GP IIb/IIIA inhibitors			
Abciximab	8	1.076 (0.874–1.325)	0.489
Small-molecule	3	0.952 (0.440–2.060)	0.901
Subgroup analysis for mortality according to odds ratio			
Age			
> 65	2	1.852 (0.296–11.583)	0.510
≤ 65	12	1.162 (0.854–1.582)	0.339
Male (%)			
> 80	2	3.406 (1.082–10.719)	0.036
≤ 80	12	1.067 (0.775–1.468)	0.692
Sample size			
> 200	6	1.107 (0.795–1.539)	0.547
≤ 200	8	1.678 (0.757–3.720)	0.203
Clinical scenario			
NSTE-ACS	5	1.305 (0.542–3.142)	0.553
STEMI	9	1.161 (0.839–1.605)	0.367
Follow-up			
> 6 months	4	1.054 (0.390–2.844)	0.917
≤ 6 months	10	1.191 (0.866–1.639)	0.282
Type of GP IIb/IIIA inhibitors			
Abciximab	11	1.135 (0.831–1.549)	0.426
Small-molecule	3	2.661 (0.575–12.318)	0.211

CI — confidence interval; GP — glycoprotein; SMD — standard mean differences; rest abbreviations as in Table 1 and 2

reduction of blood supply to myocardial tissue, and incidence of MI [22, 23]. Despite several types of pharmacotherapy, such as fibrinolytics and anticoagulants, angioplasty can result in optimal reperfusion. On the other hand, in the presence of simultaneous obstructions in proximal parts of several coronary arteries, or in case of significant stenosis of the left main coronary artery, a coronary artery bypass graft surgery is required [1]. Current guidelines do not recommend routine use of GP IIb/IIIa inhibitors in ACS; however, the IC route may be considered although the IV route should remain the standard of care for administration of GP IIb/IIIa inhibitors [3]. Our findings revealed that GP IIb/IIIa inhibitors injected using the IC route significantly increase the chance of complete perfusion (TIMI 3 flow) compared to IV administration. This can mainly be explained by the high local platelet inhibitor concentration caused by IC injection. Our subgroup analysis also indicated that the IC route had a remarkable preference to the IV route in terms of increasing the incidence of complete perfusion in patients with NSTE-ACS and STEMI, particularly those in older ages. Wu et al. [8] found that IC administration of platelet inhibitors led to a higher rate of complete perfusion; therefore, it might be able to decrease the size of infarcted parts of myocardium. Infarcted myocardium is usually associated with reduced perfusion, decreased ventricular contractility, and subsequently reduced LVEF. Finally, cardiac function can enter a vicious circle with decreasing LVEF, leading to gradually increasing inability of the heart muscle to pump the remaining blood volume, eventually leading to HF. The results of the current study revealed that IC administration of GP IIb/IIIa inhibitors, in comparison with the IV route, could increase LVEF. In addition, the incidence of HF was notably lower in receivers of IC antiplatelets, compared to IV. It can be deduced that IC administration is associated with complete perfusion followed by

Table 4. Sensitivity analysis about role of each study in overall results

Name of removed study	Odds ratio or WMD (analysis except removed study)	P
LVEF (%) according to WMD		
Bellandi	4.80	0.000
Wu	1.50	0.2
Thiele	5.12	0.000
Namazi	5.2	0.000
Kirma	6.01	0.000
TIMI-3 flow according to odds ratio		
Candemir	0.79	0.01
Bellandi	0.77	0.007
Wu	0.79	0.01
Thiele (2012)	0.58	0.000
Thiele (2008)	0.75	0.003
Dominguez-Rodriguez	0.78	0.008
Namazi	0.77	0.005
Galache	0.77	0.005
Kirma	0.76	0.003
Iversen	0.79	0.01
Gu	0.77	0.008
Deibele	0.77	0.005
Yang	0.78	0.009
TVR according to odds ratio		
Candemir	1.12	0.47
Bertrand	1.21	0.30
Balghith	1.08	0.63
Wu	1.12	0.48
Thiele (2008)	1.10	0.53
Secco	1.23	0.22
Kakkar	1.23	0.23
Iversen	0.99	0.98
Gu	1.13	0.47
Major bleeding according to odds ratio		
Candemir	1.01	0.86
Wu	1.01	0.91
Thiele (2012)	1.08	0.62
Thiele (2008)	1.01	0.87
Secco	0.99	0.98
Dominguez-Rodriguez	1.01	0.87
Namazi	1.07	0.49
Kakkar	1.00	0.98
Iversen	0.97	0.79
Gu	1.04	0.69
Yang	1.04	0.70
Re-MI according to odds ratio		
Candemir	1.28	0.22
Bertrand	1.43	0.09
Wu	1.23	0.29
Thiele (2012)	1.41	0.16
Wohrle	1.18	0.42
Thiele (2008)	1.21	0.33
Secco	1.29	0.21
Kakkar	1.15	0.50
Iversen	1.19	0.40
Gu	1.25	0.28
HF according to odds ratio		
Wu	1.82	0.02
Thiele (2012)	2.94	0.07
Thiele (2008)	1.87	0.01
Mortality according to odds ratio		
Candemir	1.17	0.30
Bertrand	1.20	0.23
Bellandi	1.18	0.28
Balghith	1.17	0.30
Wu	1.16	0.32
Thiele (2012)	1.60	0.02
Wohrle	1.11	0.55
Thiele (2008)	1.16	0.32
Secco	1.19	0.25
Galache	1.16	0.33
Kakkar	1.16	0.34
Iversen	1.08	0.63
Gu	1.15	0.35
Yang	1.15	0.36
Stent thrombosis according to odds ratio		
Candemir	1.42	0.47
Balghith	2.14	0.25
Secco	2.11	0.14
Gu	1.52	0.40

WMD — weighted mean differences; rest abbreviations as in Table 2

increased contractility and LVEF, and it may prevent progression from reversible MI to permanent HF. Our subgroup analysis also reported more effective therapeutic response following IC administration of antiplatelets in older ages, but better LVEF was noted in NSTE-ACS and STEMI patients both aged above and below 65 years. According to our findings, the incidence of TVR was similar in both groups. Kubica et al. [24] similarly reported no significant difference in the incidence of TVR between IC and IV GP IIb/IIIa inhibitor receivers. Early recurrent MI or extension of infarction have been clinically recognised for many years as manifested by severe prolonged chest pain

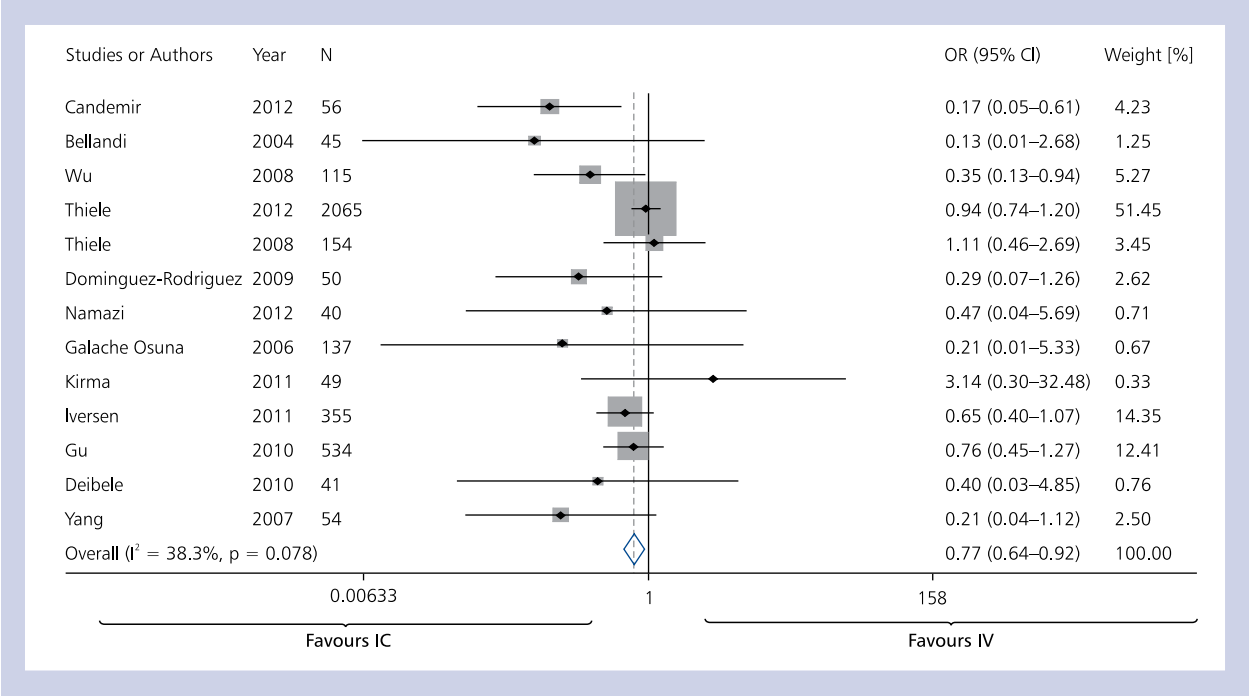

Figure 4. Forest plot of odds ratio (OR) for treatment with glycoprotein IIb/IIIa inhibitors on incidence of thrombolysis in myocardial infarction score 3 flow; CI — confidence interval; IC — intracoronary; IV — intravenous

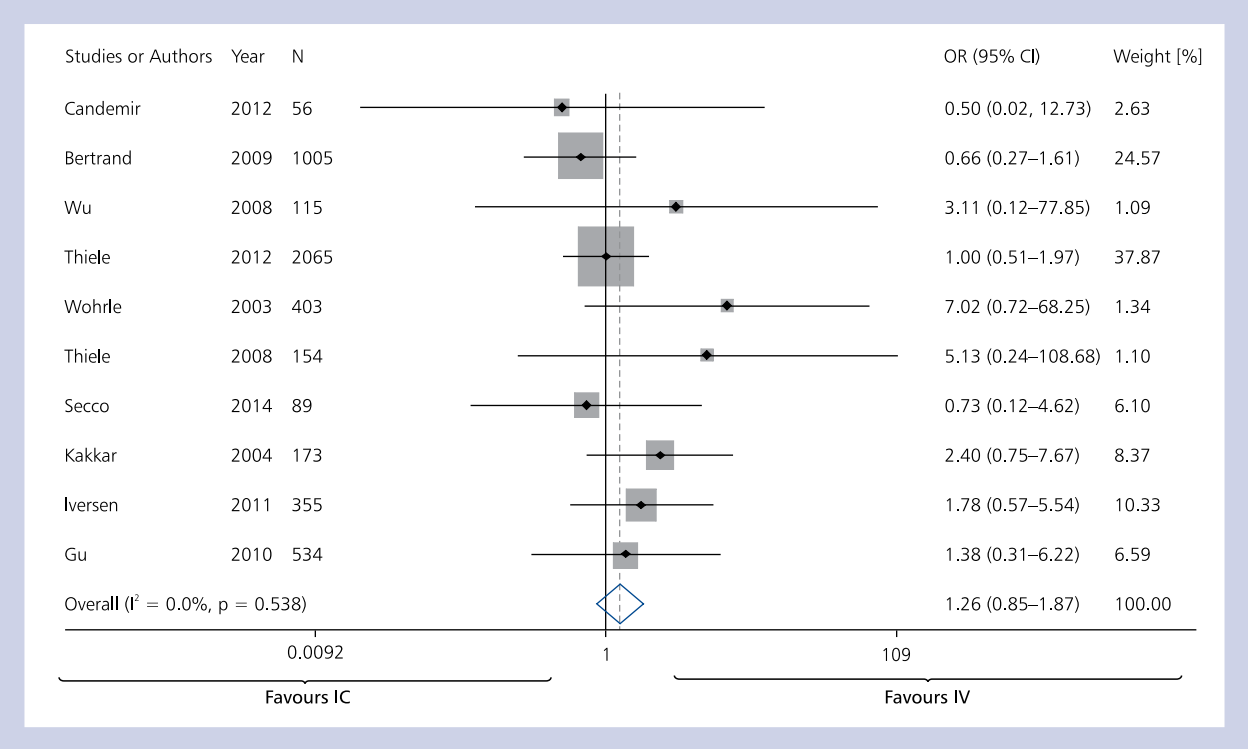

Figure 5. Forest plot of odds ratio (OR) for treatment with glycoprotein IIb/IIIa inhibitors on incidence of re-myocardial infarction; CI — confidence interval; IC — intracoronary; IV — intravenous

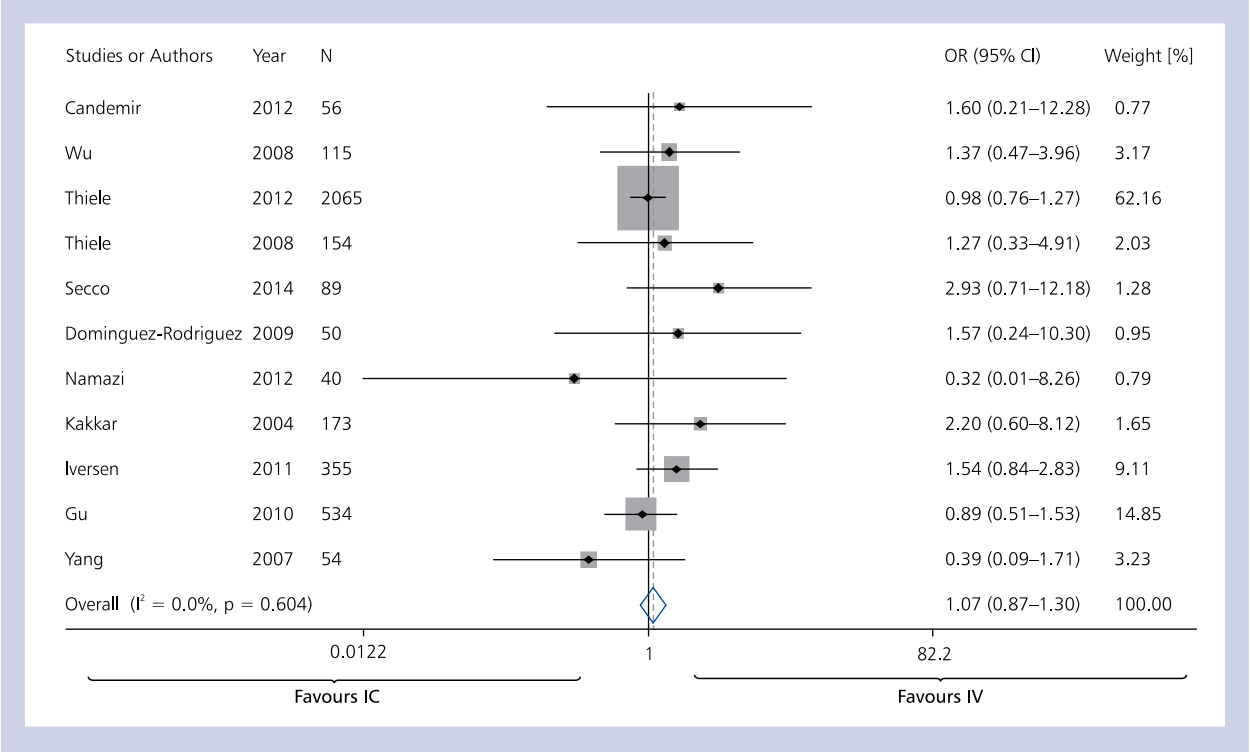

Figure 6. Forest plot of odds ratio (OR) for treatment with glycoprotein IIb/IIIa inhibitors on incidence of major bleeding; CI — confidence interval; IC — intracoronary; IV — intravenous

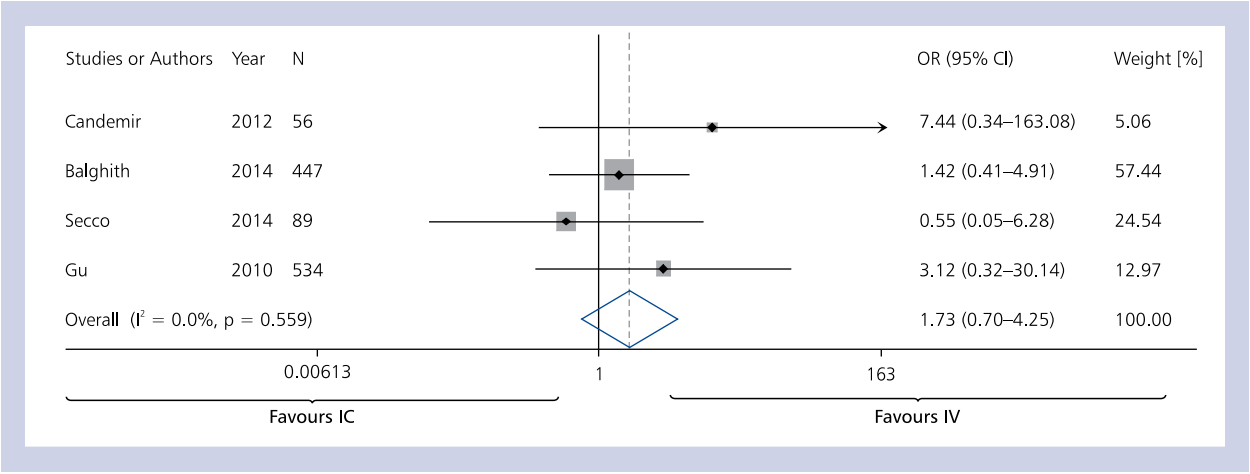

Figure 7. Forest plot of odds ratio (OR) for treatment with glycoprotein IIb/IIIa inhibitors on incidence of stent thrombosis; CI — confidence interval; IC — intracoronary; IV — intravenous

as well as new ST-T wave abnormalities on electrocardiography [25]. Rupture of atherosclerotic plaques leads to the exposure of collagen and vascular media, resulting in platelet and clotting activation and occlusive thrombus formation [25]. Our results demonstrated that IC or IV administration were not significantly different regarding the incidence of re-MI. Regarding the critical role of platelets in blood clotting, GP IIb/IIIa inhibitors, as antiplatelet drugs, inhibit the connection between fibrinogen and von-Willebrand factor to the activated platelets leading to platelet disaggregation. However, administration of antiplatelet drugs may lead to an increased incidence of haemorrhage compared to placebo. The findings of our study found that the incidence of haemorrhage was not different when administering GP IIb/IIIa inhibitors via IC or IV route. Therefore, based on the results of our study we disagree with the theory that the IC route increases the risk of bleeding due

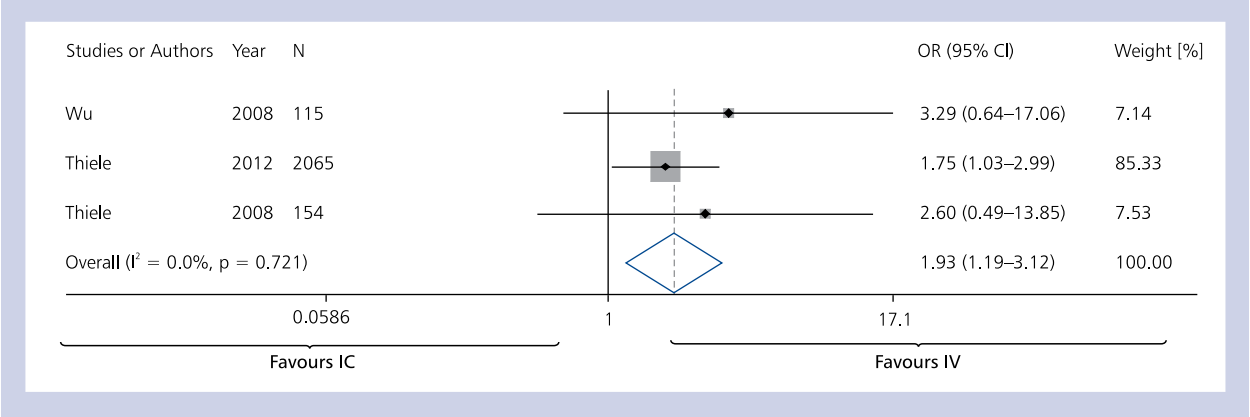

Figure 8. Forest plot of odds ratio (OR) for treatment with glycoprotein IIb/IIIa inhibitors on incidence of heart failure; CI — confidence interval; IC — intracoronary; IV — intravenous

to high local platelet inhibitor concentration. AIDA multicentre trial showed that in patients with STEMI undergoing PCI, IC bolus administration of abciximab did not give any additional benefit compared with standard intravenous bolus administration with respect to the combined primary study end-point death, re-MI, or congestive HF. Since IC abciximab bolus administration was safe and was related to reduced rates of congestive HF [9]. Finally, our study showed that the risk of mortality and incidence of stent thrombosis were not significantly different when administering GP IIb/IIIa inhibitors by either route. However, the primary end-points of this study were not statistically significant; overall, the most appropriate route of administration of GP IIb/IIIa inhibitors appeared to be IC injection, which could increase LVEF and TIMI 3 flow and decrease the incidence of HF.

Limitations of the study

This meta-analysis contains several limitations. First, it was a study-level meta-analysis; second, a comparison of different GP IIb/IIIa inhibitors was performed according to the use of various inhibitors in the RCTs included; third, there was a natural lack of available data on end-points assessed in studies included in the meta-analysis; fourth, several minor deviations definitions of end-points might be present; fifth, there is a lack of data on different GP IIb/IIIa inhibitor concentrations after both IC and IV administrations; and sixth, both STEMI and NSTEMI patients were included in the present analysis in order to increase the number of patients analysed; however, no differentiation or sub-group analysis was performed.

CONCLUSIONS

The most appropriate route of administration of GP IIb/IIIa inhibitors for patients with ACS seems to be IC injection, which can increase LVEF and TIMI 3 flow and decrease HF with comparable adverse event rates as using IV injection.

Conflict of interest: *none declared*

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Odpowiednia droga podania w bolusie inhibitorów glikoproteiny IIb/IIIa u chorych z ostrymi zespołami wieńcowymi poddanych przezskórnej interwencji wieńcowej: dowieńcowo czy dożylnie? Metaanaliza i przegląd systematyczny dostępnych obecnie badań

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Streszczenie

Wstęp i cel: W niniejszym przeglądzie systematycznym z metaanalizą autorzy porównali skuteczność i bezpieczeństwo dowieńcowego i dożylnego stosowania inhibitorów receptora glikoproteinowego (GP) IIb/IIIa, oceniając ich wpływ na efekty terapii po przezskórnej interwencji wieńcowej u chorych z ostrymi zespołami wieńcowymi (zawał serca z uniesieniem odcinka ST lub ostry zespół wieńcowy bez uniesienia odcinka ST).

Metody: Do wyszukania odpowiednich randomizowanych badań z grupą kontrolną wykorzystano internetowe bazy bibliograficzne Medline, Embase, Elsevier i Sciences oraz wyszukiwarkę Google Scholar. Pierwszorzędowymi punktami końcowymi były śmiertelność i rewaskularyzacja naczynia docelowego (TVR), natomiast drugorzędowe punkty końcowe obejmowały częstość trombolizy u osób z zawałem serca, u których przepływ oceniono na 3 w skali TIMI (TIMI 3 oznacza prawidłową perfuzję w dystalnych naczyniach wieńcowych), dorzut zawału serca (re-MI), poważne krwawienie, zakrzepicę w stencie, frakcję wyrzutową lewej komory (LVEF) i niewydolność serca (HF). Po przeszukaniu wszystkich najważniejszych baz literatury medycznej wytypowano 1006 badań. Ostatecznie wybrano 18 badań (5812 chorych), w których były opisane odpowiednie punkty końcowe.

Wyniki: Łączna analiza danych wykazała, że dowieńcowe podawanie inhibitorów receptora GP IIb/IIIa może spowodować istotne zwiększenie LVEF (średnia ważona różnic 4,97; 95% CI 3,34–6,60; p = 0,000) oraz odsetka osób z oceną przepływu TIMI 3 (iloraz szans [OR] 0,77; 95% przedział ufności [CI] 0,64–0,92; p = 0,005) i istotne zmniejszenie zapadalności na HF (OR 1,927; 95% CI 1,189–3,124; p = 0,008). Nie zaobserwowano różnic między grupą otrzymującą lek dowieńcowo a grupą, której podawano lek dożylnie, pod względem liczby przypadków TVR, re-MI, poważnych krwawień, zakrzepicy w stencie i zgonów.

Wnioski: Stwierdzono, że najwłaściwszą drogą podania inhibitorów receptora GP IIb/IIIa u chorych z ostrymi zespołami wieńcowymi jest wstrzyknięcie dowieńcowe, co pozwoliło zwiększyć LVEF i odsetek chorych z przepływem TIMI 3 oraz zmniejszyć zapadalność na HF. Dowieńcowe podanie leków nie wiązało się ze zwiększeniem częstości zdarzeń niepożądanych w porównaniu ze wstrzyknięciem dożylnym.

Słowa kluczowe: inhibitory receptora glikoproteinowego IIb/IIIa, dożylnie, dowieńcowo, ostry zespół wieńcowy, przezskórna interwencja wieńcowa

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