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Systematic Review

Administration of low molecular weight and unfractionated heparin during percutaneous coronary intervention

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ARTICLE INFO

Article history:
Received 1 July 2015
Accepted 11 January 2016
Available online 26 January 2016

Keywords:
Unfractionated heparin
Low molecular weight heparin
Myocardial infarction
Percutaneous coronary intervention
Outcome

ABSTRACT

This systematic review with meta-analysis sought to determine the efficacy and safety of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) on clinical outcomes following percutaneous coronary intervention. Medline, Embase, Elsevier, and web of knowledge as well as Google scholar literature were used for selecting appropriate studies with randomized controlled design. After screening 445 studies, a total of 23 trials (including a total of 43,912 patients) were identified that reported outcomes. Pooled analysis revealed that LMWH compared to UFH could significantly increase thrombolysis in myocardial infarction grade 3 flow ($p < 0.001$), which was associated with similar target vessel revascularization ($p = 0.6$), similar incidence of stroke ($p = 0.7$), and significantly lower incidence of re-myocardial infarction ($p < 0.001$), major bleeding ($p = 0.02$) and mortality ($p < 0.001$). Overall, LMWH was shown to be a useful type of heparin for patients with MI undergoing PCI, due to its higher efficacy and lower rate of complication compared to UFH. It is also associated with increased myocardial perfusion, decreased major hemorrhage, and mortality.

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1. Introduction

Ischemic heart disease is the leading cause of morbidity and mortality worldwide, whereas it is expected to significantly increase the disease burden over the next 10 years.[1] Ischemia-reperfusion injury (IRI) is a well-known phenomenon in thrombolysis, percutaneous coronary intervention, coronary artery bypass grafting, and cardiac transplantation. IRI is clinically manifested as a damage of myocardial cells due to myocardial stunning, microvascular injury, and myocyte necrosis.[2] In patients with ST-segment elevation myocardial infarction (STEMI) or acute coronary syndrome without ST elevation (non-STEMI or unstable angina), early mechanical

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http://dx.doi.org/10.1016/j.ihj.2016.01.014
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or pharmacological reperfusion, anti-thrombotic therapy with aspirin, thienopyridine, glycoprotein IIb/IIIa inhibitors, and unfractionated heparin (UFH) have become the standard of care and have been widely used for decreasing mortality and myocardial infarction (MI).[3,4] However, due to its structural defects, the utilization of UFH has many limitations, such as short half-life, low bioavailability, and non-specific binding to proteins that lead to variability of dose-anticoagulant effects.[5,6] On the other hand, UFH may activate platelets just a few minutes after administration and may lead to thrombocytopenia.[5,6] UFH has unpredictable pharmacokinetics; thus there is a need to monitor activated clotting time for adjusting the dose of UFH.[7–9] Low molecular weight heparin (LMWH) is an alternative anticoagulant characterized by more predictable and stable anti-coagulation without the need for continuous infusion or tight monitoring of activated clotting time.[7–9] Furthermore, it demonstrates less protein binding, less platelet activation and relatively greater inhibition of the coagulation cascade compared to UFH, as it has a ratio of 4.3:1 in its anti-factor Xa to anti-factor IIb activity.[10] Several previous reports indicated that LMWH was shown to be non-inferior to UFH in terms of reducing the risk of morbidity and mortality at 30 days.[11–14] This systematic review with meta-analysis sought to determine the strength of evidence for evaluating the efficacy and safety of UFH and LMWH in patients with MI undergoing PCI.

2. Methods and materials

2.1. Literature search

A comprehensive literature search was conducted in major electronic databases (Medline/Pubmed, Embase, Elsevier, Web of Knowledge and Google Scholar) from their inception through July 20, 2014 to identify randomized controlled trials (RCTs) reporting on the use of UFH vs. LMWH including clinical outcomes in patients with MI undergoing percutaneous coronary intervention. Predefined search terms included: ''unfractionated heparin'', ''UFH'', ''low molecular weight heparin'', ''LMWH'', ''enoxaparin'', and ''myocardial infarction'', ''MI'', ''ST-segment myocardial infarction'', ''STEMI'', ''acute coronary syndrome'', ''non-STEMI'', and ''percutaneous coronary intervention'', ''PCI'', and ''angioplasty''. No language restrictions were applied. All retrieved references of the included RCT 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: thrombolysis in myocardial infarction (TIMI) score, re-MI, stroke, thrombosis, major bleeding, target vessel revascularization (TVR), major adverse cardiovascular events (MACE), and mortality. Abstracts and manuscripts that did not undergo peer-review, duplicate reports and ongoing RCTs were not included.

2.2. Data extraction and outcome measures

Two investigators (S.A.-H.-S. and A.S.) extracted data independently, and discrepancies were resolved via a consensus standardized abstraction check-list used for recording data in each study. Data retrieved from trials included: author's name, country study design, details of therapeutic regimens, clinical scenario, sample size, follow-up duration, mean age and gender, and clinical outcomes of interest. For exploration of heterogeneity among the trials, a subgroup analysis of disparities in the patients' characteristics was performed for[1]: follow-up (≤6 months vs. >6 months),[2] clinical scenario of patients (STEMI vs. ACS and non-STEMI),[3] type of administration (intravenous vs. subcutaneous),[4] and sample size (≤500 vs. >500).

2.3. Definitions of endpoints

TVR was defined as ischemia-driven revascularization of the infarct-related artery with PCI and coronary artery bypass graft. Re-infarction was defined as recurrent symptoms suggestive of ischemia with ST-segment elevation and/or elevation of the levels of cardiac markers. 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; TIMI 3 flow (complete perfusion) is a normal flow, which fills the distal coronary bed completely. Mortality was considered cardiac, unless a non-cardiac cause of death could be established. MACE were defined as composition of death or MI or major cerebrovascular event.

2.4. Statistical analysis, publication bias and quality assessment

Data were analyzed by using STATA version 11.0 utilizing METAN and METABIAS modules. The effect sizes measured were odds ratio (OR) with 95% confidence interval (CI) for categorical variables. OR <1 favored LMWH and OR >1 favored UFH group. RCTs with no events in the two arms were discarded from pooled analysis. Forest plots were created for each outcome. Values of $p < 0.1$ for Q test or $I^2 > 50\%$ indicated significant heterogeneity among studies. Heterogeneity among the trials was accounted for by applying a random effect model when indicated. The presence of publication bias was evaluated using Begg and Egger tests. Quality assessment of RCTs was performed using the Jadad score. The Jadad score assesses 3 items including randomization (0–2 points), blinding of study (0–2 points) and withdrawals and dropouts (0–1 points). Higher scores indicate better reporting (''high'' quality: 5; ''good'' quality: 3–4; ''poor'' quality: 0–2). Results were considered statistically significant at a p-value <0.05.

3. Results

3.1. Literature search strategy and included trials

Our literature search retrieved a total of 445 studies from screened databases of which 295 (66.2%) were excluded after initial review (Fig. 1). Of 150 primary included studies, 127 were excluded after detailed evaluation due to insufficient information on endpoints of interest. Thus, the final analysis included 23 RCTs.

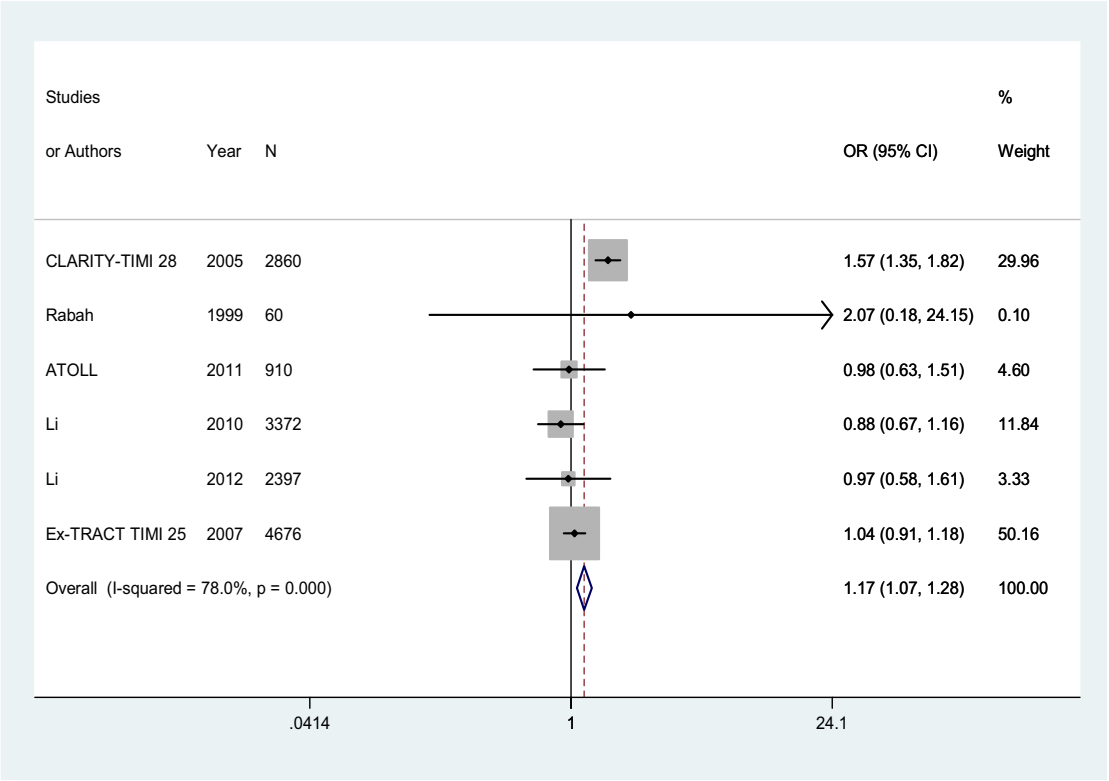

Fig. 1 – Forest plot of odds ratio (OR) for treatment with heparin on incidence of thrombolysis in myocardial infarction score 3 flow.

4. Study characteristics, effect measures and clinical outcomes

4.1. *Thrombolysis in myocardial infarction grade 3 (TIMI-3)*

A total of 14,276 patients were included from 6 RCTs reporting data on TIMI score (Table 1). Patient's populations of the RCTs ranged from 60 to 4676 patients. In this meta-analysis, 6890 patients were allocated to LMWH and 7385 to the UFH group. The overall incidence of TIMI-3 was 60.55% ranging from 9.89% to 97.49% (Table 2). Pooled treatment effect analysis revealed that LMWH compared to UFH therapy significantly increased TIMI-3 flow with an OR of 1.17 (95% CI: 1.074–1.284; $p < 0.001$) using the random effects model (Fig. 1). Significant heterogeneity was observed among the RCTs (chi-squared = 22.72, $I^2 = 78\%$, $p < 0.001$). A subgroup analysis is presented in Table 3. Pooled treatment effect analysis revealed that LMWH compared to UFH therapy significantly increased TIMI-3 flow in patients with STEMI (OR of 1.18; 95% CI: 1.07–1.29; $p = 0.001$) compared to ACS and non-STEMI patients (OR of 0.99; 95% CI: 0.60–1.68; $p = 0.9$), as well as intravenous administration (OR of 1.48; 95% CI: 1.29–1.71; $p = 0.001$) compared to subcutaneous administration (OR of 0.90; 95% CI: 0.70–1.14; $p = 0.3$). Begg and Egger tests showed that there were no potential publication bias among the included RCTs (Begg test, $p = 0.188$; Egger test, $p = 0.188$).

4.2. TVR

A total of 9961 patients were included from 7 RCTs reporting data on the incidence of TVR. Patient's populations of RCTs ranged from 83 to 3528 patients (Table 1). 5335 patients were allocated to LMWH, whereas 4626 to the UFH group. The overall incidence of TVR was 1.29% ranging from 0.38% to 6.02%. TVR occurred in 1.18% in LWMH group and 1.41% in UFH group (Table 2). Pooled analysis revealed that the incidence of TVR was similar between patients receiving LMWH or UFH with an OR of 0.916 (95% CI: 0.641–1.309; $p = 0.6$) using the fixed effects model (Fig. 2). No significant heterogeneity was observed among the RCTs (chi-squared = 7.62, $I^2 = 34.4\%$, $p = 0.17$). Begg and Egger tests showed that there were no potential publication bias among the included RCTs (Begg test, $p = 0.453$; Egger test, $p = 0.453$).

4.3. *Incidence of stroke*

A total of 22,688 cases were included from 8 RCTs reporting data on the incidence of stroke. After removing an RCTs with no events in 2 arms, a total of 22,488 patients were included in the meta-analysis from 7 remaining studies (Table 1). Patient's population of RCTs ranged from 83 to 6299 patients. In this analysis 7909 patients were allocated to LMWH and 14,579 to the UFH group. The overall incidence of stroke was 0.86% ranging from 0.4% to 2.4%. Stroke occurred in 0.82% in LMWH group and 0.88% in UFH group (Table 2). Pooled analysis

Table 1 – Demographic data of included studies.

Follow-up	Study population	Route of administration	Male (%)		Mean age (years)		*n*		Year/country	Author (references)
			UFH	LMWH	UFH	LMWH	UFH	LMWH		
In-hospital	STEMI	N.D.	70.4	66.3	65.7	67.9	5690	609	2008/Germany	Zaymer[15]
In-hospital	ACS	N.D.	62.3	58.2	71.9	72.4	3628	1178	2006/Germany	Zeymer[16]
1 month	ACS	Intravenous	69.3	68	67	67	2364	2323	2006/Germany	SYNERGY Trial[17]
4 years	STEMI	Intravenous	73.3	76.6	61.2	60.5	60	60	2011/China	Li[18]
1 month	STEMI	Intravenous	81.4	80.5	58	58	1431	1429	2005/USA	CLARITY-TIMI 28[19]
1 month	Angina pectoris	Intravenous	73	83	60	61	30	30	1999/USA	Rabah[20]
1 month	Non-STEMI	Intravenous	73.9	75.4	63.5	63.4	1230	2298	2006/France	STEEPLE trial[21]
3 years	STEMI and ACS	N.D.	66.3	69.4	68.9	65.5	922	1932	2012/France	FAST-MI[22]
1 month	STEMI	Intravenous	78	78.4	60	59	460	450	2011/France and Germany	ATOLL trial[23]
1 month	STEMI	Combined	74.1	73.1	63	63	1693	759	2010/USA	FINESSE trial[24]
1 month	Non-STEMI	Intravenous	72	77	64	59	100	100	2005/Canada	ACTION trial[25]
8 months	STEMI	Subcutaneous	75.1	73.2	62.6	62.2	1841	1531	2010/Korea	Li[26]
8 months	Non-STEMI	Subcutaneous	69.4	67.4	63.7	63.7	1219	1178	2012/Korea	Li[27]
1 month	STEMI	Subcutaneous	82.5	82.3	55	56	448	498	2012/Canada	TRANSFER-AMI trial[28]
1.2 years	STEMI	Combined	63.6	66.6	65	58	44	39	2008/USA	Khoobiar[29]
1 month	ACS	Intravenous	63.3	67.6	64.4	61.2	71	68	2006/Korea	Her[30]
1 month	STEMI	Combined	82.7	82.1	57	57	2404	2272	2007/Germany	Ex-TRACT-TIMI trial[31]
In-hospital	STEMI	Intravenous	69.3	74	61	62	49	50	2002/Spain	Galeote[32]
1 month	STEMI and ACS	N.D.	75	77	59	60	624	590	2003/Belgium	ASSENT-3-PCI trial[33]
In-hospital	STEMI and ACS	Intravenous	56.8	54.9	54	54.6	271	222	2009/USA	Diez[34]
1 month	STEMI	Intravenous	81.2	75.7	63.8	61.9	234	346	2010/Australia	Brieger[35]
1 month	STEMI and ACS	Intravenous	75.8	76.7	63.7	63.3	132	129	2003/USA	CRUISE trial[36]
1 month	ACS	Intravenous	N.D.	N.D.	N.D.	N.D.	440	436	2010/Switzerland	Zeus[37]

revealed that the incidence of stroke was similar between LMWH and UFH groups with an OR of 0.941 (95% CI: 0.680–1.302; $p = 0.7$) using the fixed effects model (Fig. 3). No significant heterogeneity was observed among the RCTs (chi-squared = 8.75, $I^2 = 31.4\%$, $p = 0.18$). Begg and Egger tests showed that there were no potential publication bias among the included RCTs (Begg test, $p = 1.000$; Egger test, $p = 1.000$).

4.4. *Re-myocardial infarction*

A total of 40,008 patients were included from 19 RCTs reporting data on the incidence of re-MI (Table 1). After removing a single study with ''zero columns'' in 2 comparative arms, from 39,948 remaining cases, 17,041 patients were allocated to LMWH and 22,907 to UFH group. The overall incidence of re-MI was 4.39% ranging from 0.29% to 12.5%. Re-MI occurred in 3.8% in LMWH group and 4.8% in UFH group (Table 2). Pooled analysis indicated that LMWH compared to UFH significantly decreased the incidence of re-MI with an OR of 0.759 (95% CI: 0.681–0.847; $p < 0.001$) using the random effects model (Fig. 4). Significant heterogeneity was observed among the RCTs (chi-squared = 42.62, $I^2 = 60.1\%$, $p = 0.001$). A subgroup analysis is presented in Table 3. Pooled treatment effect analysis revealed that LMWH compared to UFH therapy significantly decreased incidence of re-MI in patients with STEMI (OR of 0.66; 95% CI: 0.54–0.80; $p = 0.001$) and ACS and non-STEMI (OR of 0.78; 95% CI: 0.68–0.90; $p = 0.001$), whereas intravenous administration (OR of 0.80; 95% CI: 0.71–0.92; $p = 0.001$) was more effective than subcutaneous administration (OR of 0.62; 95% CI: 0.37–1.02; $p = 0.06$). Begg and Egger tests showed that there were no potential publication bias among the included RCTs (Begg test, $p = 0.506$; Egger test, $p = 0.506$).

4.5. *Major bleeding*

A total of 43,912 patients were included from 23 RCTs reporting data on the incidence of major bleeding (Table 1). After removing 2 studies with ''zero columns'' in 2 comparative arms, from remaining 43,573 cases enrolled in the analysis, 18,359 were allocated to LMWH and 25,214 to UFH group. The overall incidence of major bleeding was 2.85% ranging from 0.29% to 8.27%. Major bleeding occurred in 2.12% in LMWH group and 3.37% in UFH group (Table 2). Pooled analysis indicated that LMWH compared to UFH significantly decreased the incidence of major bleeding with an OR of 0.856 (95% CI: 0.751–0.976; $p = 0.02$) using the random effects model (Fig. 5). Significant heterogeneity was observed among the RCTs (chi-squared = 30.51, $I^2 = 34.4\%$, $p = 0.06$). A subgroup analysis is presented in Table 3. Intravenous administration (OR of 0.72; 95% CI: 0.57–0.89; $p = 0.004$) was more efficient than subcutaneous administration (OR of 0.90; 95% CI: 0.54–1.50; $p = 0.6$) for decreasing the incidence of major hemorrhage. Begg and Egger

Table 2 – Clinical outcomes of included studies.

Jadad	MACE		Thrombosis		Mortality		Re-MI		Major bleeding		TVR		TIMI 3 flow		Stroke		Author (references)
	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	
1	842	62	N.D.	N.D.	569	44	302	19	313	40	N.D.	N.D.	N.D.	N.D.	46	9	Zeymer[15]
1	268	46	N.D.	N.D.	123	32	149	14	163	61	N.D.	N.D.	N.D.	N.D.	36	11	Zeymer[16]
4	336	304	N.D.	N.D.	43	39	312	274	38	35	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	SYNERGY Trial[17]
2	4	2	1	1	3	1	3	3	1	0	1	1	N.D.	N.D.	N.D.	N.D.	Li[18]
4	180	109	400	315	68	44	101	54	31	23	N.D.	N.D.	802	952	22	18	CLARITY-TIMI 28[19]
3	N.D.	N.D.	0	0	0	0	0	0	1	1	N.D.	N.D.	28	29	N.D.	N.D.	Rabah[20]
3	70	138	N.D.	N.D.	5	13	65	126	34	28	8	22	N.D.	N.D.	N.D.	N.D.	STEEPLE trial[21]
2	N.D.	N.D.	N.D.	N.D.	85	62	12	37	32	33	N.D.	N.D.	N.D.	N.D.	8	19	FAST-MI[22]
3	155	126	2	4	29	17	20	10	22	20	N.D.	N.D.	46	44	1	3	ATOLL trial[23]
4	135	40	N.D.	N.D.	95	29	N.D.	N.D.	78	21	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	FINESSE trial[24]
2	14	8	N.D.	N.D.	0	0	14	8	0	0	0	0	N.D.	N.D.	0	0	ACTION trial[25]
2	213	149	N.D.	N.D.	116	45	8	2	11	8	26	27	1731	1428	N.D.	N.D.	Li[26]
2	92	89	N.D.	N.D.	16	20	12	3	3	4	25	10	1189	1148	N.D.	N.D.	Li[27]
3	35	36	N.D.	N.D.	11	12	21	22	18	17	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	TRANSFER-AMI trial[28]
2	4	3	0	1	3	1	N.D.	N.D.	2	0	3	2	N.D.	N.D.	2	0	Khoobiar[29]
2	N.D.	N.D.	0	0	0	0	2	1	0	0	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	Her[30]
5	355	261	N.D.	N.D.	71	66	53	53	39	32	N.D.	N.D.	632	615	14	5	Ex-TRACT-TIMI trial[31]
3	7	7	10	12	0	1	3	4	4	1	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	Galeote[32]
2	23	18	N.D.	N.D.	17	15	13	8	16	23	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	ASSENT-3-PCI trial[33]
2	N.D.	N.D.	0	0	0	0	N.D.	N.D.	6	2	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	Diez[34]
2	30	25	N.D.	N.D.	17	11	6	2	21	27	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	Brieger[35]
3	10	11	1	1	0	0	10	11	2	3	1	0	N.D.	N.D.	N.D.	N.D.	CRUISE trial[36]
2	N.D.	N.D.	N.D.	N.D.	0	0	N.D.	N.D.	17	11	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	Zeus[37]

Table 3 – Subgroup analysis for clinical outcomes.

Subgroup	Studies (*n*)	Odd ratio (95% CI)	*p*-Value
S.G.A. for TIMI 3 flow according to OR			
Sample size			
>500	5	1.174 (1.073–1.28)	0.001
≤500	1	2.071 (0.17–24.14)	0.561
Clinical scenario			
STEMI	4	1.181 (1.07–1.29)	0.001
ACS and non-STEMI	2	0.999 (0.60–1.68)	0.997
Type of administration			
Intravenous	3	1.489 (1.29–1.71)	0.001
Subcutaneous	2	0.900 (0.70–1.14)	0.396
Follow-up			
>6	2	0.900 (0.70–1.14)	0.396
≤6	4	1.224 (1.11–1.34)	0.001
S.G.A. for TVR according to OR			
Sample size			
>500	3	0.938 (0.64–1.35)	0.733
≤500	3	0.674 (0.17–2.64)	0.571
Clinical scenario			
STEMI	3	1.193 (0.71–1.98)	0.499
ACS and non-STEMI	2	0.727 (0.43–1.20)	0.218
Type of administration			
Intravenous	3	1.308 (0.62–2.74)	0.477
Subcutaneous	2	0.821 (0.53–1.25)	0.362
Follow-up			
>6	4	0.820 (0.54–1.23)	0.341
≤6	2	1.334 (0.61–2.87)	0.463
S.G.A. for stroke according to OR			
Sample size			
>500	6	0.964 (0.69–1.33)	0.827
≤500	1	0.215 (0.01–4.62)	0.326
Clinical scenario			
STEMI	5	0.898 (0.59–1.36)	0.611
ACS and non-STEMI	1	0.940 (0.47–1.85)	0.859
Type of administration			
Intravenous	2	0.915 (0.50–1.65)	0.770
Subcutaneous	–	–	–
Follow-up			
>6	2	0.971 (0.44–2.10)	0.940
≤6	5	0.935 (0.65–1.33)	0.713
S.G.A. for major bleeding according to OR			
Sample size			
>500	15	0.868 (0.76–0.99)	0.036
≤500	6	0.499 (0.21–1.16)	0.110
Clinical scenario			
STEMI	11	0.860 (0.71–1.03)	0.106
ACS and non-STEMI	6	0.889 (0.71–1.10)	0.284
Type of administration			
Intravenous	11	0.720 (0.57–0.89)	0.004
Subcutaneous	3	0.904 (0.54–1.50)	0.699
Follow-up			
>6	5	0.579 (0.38–0.87)	0.009
≤6	16	0.894 (0.77–1.02)	0.110
S.G.A. for re-myocardial infarction according to OR			
Sample size			
>500	13	0.756 (0.67–0.84)	0.001
≤500	5	0.838 (0.49–1.43)	0.518
Clinical scenario			
STEMI	9	0.665 (0.54–0.80)	0.001
ACS and non-STEMI	6	0.785 (0.68–0.90)	0.001
Type of administration			
Intravenous	10	0.809 (0.71–0.92)	0.001
Subcutaneous	3	0.624 (0.37–1.02)	0.063
Follow-up			
>6	4	0.837 (0.52–1.33)	0.456
≤6	14	0.755 (0.67–0.84)	0.001
S.G.A. for mortality according to OR			
Sample size			
>500	14	0.661 (0.58–0.74)	0.001
≤500	3	0.551 (0.14–2.06)	0.376
Clinical scenario			
STEMI	11	0.659 (0.56–0.76)	0.001
ACS and non-STEMI	4	0.934 (0.72–1.20)	0.600
Type of administration			
Intravenous	7	0.705 (0.55–0.89)	0.004
Subcutaneous	3	0.598 (0.45–0.79)	0.001
Follow-up			
>6	5	0.445 (0.33–0.55)	0.001
≤6	12	0.767 (0.66–0.88)	0.001
S.G.A. for thrombosis according to OR			
Sample size			
>500	2	0.737 (0.62–0.87)	0.001
≤500	4	1.289 (0.56–2.92)	0.544
Clinical scenario			
STEMI	5	0.754 (0.63–0.88)	0.001
ACS and non-STEMI	–	–	–
Type of administration			
Intravenous	5	0.754 (0.63–0.88)	0.001
Subcutaneous	–	–	–
Follow-up			
>6	2	1.778 (0.23–13.58)	0.579
≤6	4	0.750 (0.63–0.88)	0.001
S.G.A. for major adverse cardiovascular events according to OR			
Sample size			
>500	13	0.765 (0.71–0.82)	0.001
≤500	5	0.788 (0.48–1.29)	0.348
Clinical scenario			
STEMI	11	0.714 (0.65–0.78)	0.001
ACS and non-STEMI	5	0.851 (0.75–0.95)	0.007
Type of administration			
Intravenous	9	0.804 (0.72–0.89)	0.001
Subcutaneous	3	0.886 (0.74–1.04)	0.156
Follow-up			
>6	4	0.875 (0.73–1.04)	0.138
≤6	14	0.745 (0.68–0.80)	0.001

tests showed that there were no potential publication bias among the included RCTs (Begg test, $p = 0.235$; Egger test, $p = 0.235$).

4.6. *Incidence of stent thrombosis*

A total 5025 patients were included from 9 RCTs that provided data on thrombosis. Overall incidence of thrombosis was 14.88%; 13.48% in LMWH group and 16.24% in UFH group. In fact, 3 out of 9 comparisons did not present any thrombosis events in 2 comparative arms; therefore, the remaining 6 RCTs (4333 patients) were used to perform the meta-analysis. Pooled analysis indicated that LMWH compared to UFH significantly decreased the incidence of thrombosis with an OR of 0.754 (95% CI: 0.63–0.89; $p = 0.4$) using the fixed effects model. No significant heterogeneity was observed among the RCTs (chi-squared = 7.52, $I^2 = 0.0\%$, $p = 0.6$). Begg and Egger tests

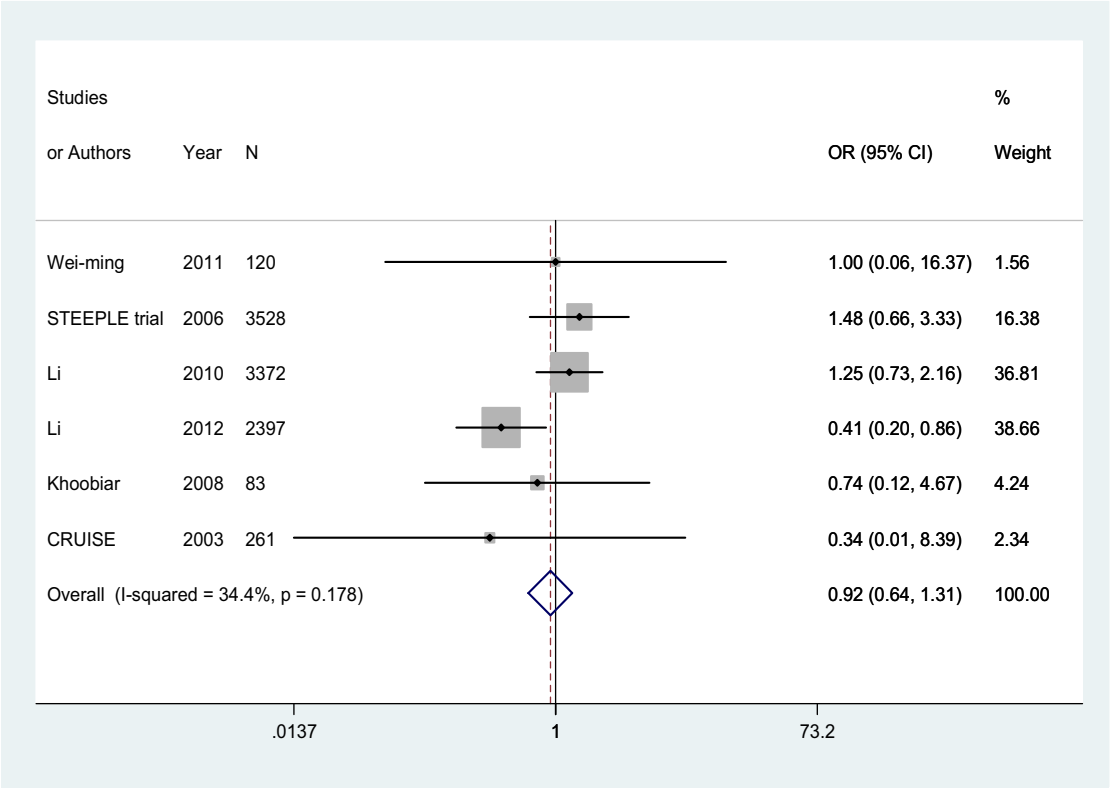

Fig. 2 – Forest plot of odds ratio (OR) for treatment with heparin on incidence of target vessel revascularization.

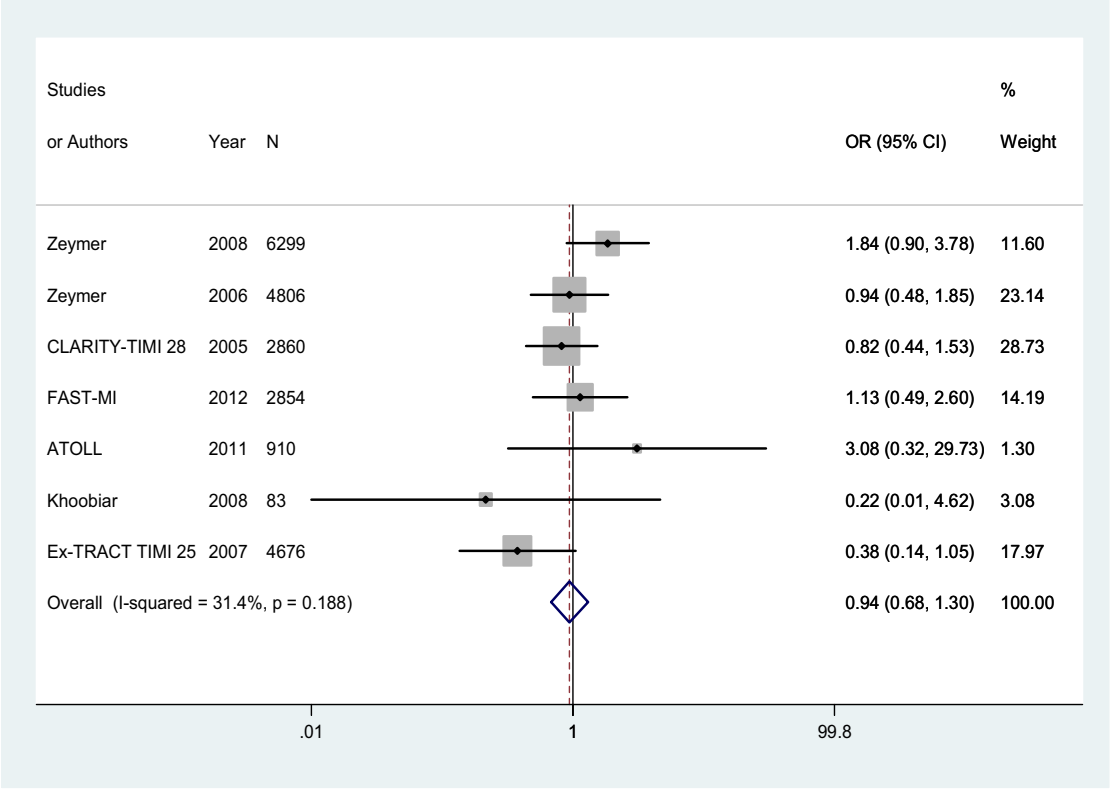

Fig. 3 – Forest plot of odds ratio (OR) for treatment with heparin on incidence of stroke.

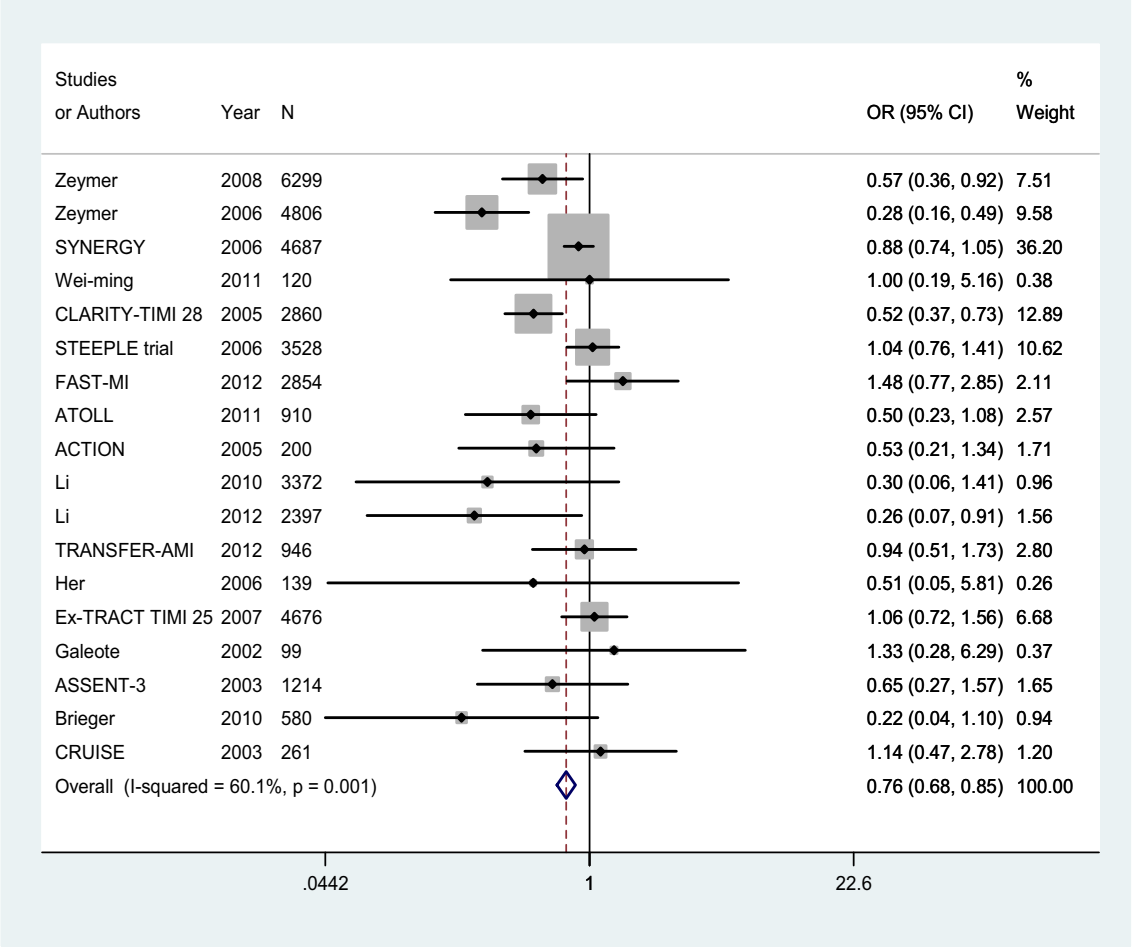

Fig. 4 – Forest plot of odds ratio (OR) for treatment with heparin on incidence of re-myocardial infarction.

showed that there were no potential publication bias among the included RCTs (Begg test, $p = 0.297$; Egger test, $p = 0.297$).

4.7. *MACE*

A total of 39,490 patients were included from 18 RCTs reporting on the incidence of MACE. Overall incidence of MACE was 10.65%; 9.05% in LMWH and 11.7% in UFH group (Table 2). Pooled analysis indicated that UFH compared to LMWH significantly increased the incidence of MACE with an OR of 0.766 (95% CI: 0.71–0.82; $p < 0.001$) using the random effects model. Significant heterogeneity was observed among the RCTs (chi-squared = 29.76, $I^2 = 42.9\%$, $p = 0.02$). A subgroup analysis is presented in Table 3.

4.8. *Mortality*

Twenty-three RCTs (43,912 patients) reported on death. Mortality occurred in 2.43% (452 patients) in LMWH group and 5% (1271 patients) in UFH group. In fact, 6 out of 23 comparisons did not present any postoperative death events in 2 comparative arms; therefore, the remaining 17 RCTs (41,883 cases) were used to perform the meta-analysis. Pooled treatment effect analysis revealed that LMWH significantly decreased mortality with an OR of 0.66 (95% CI: 0.58–0.74; $p < 0.001$) using the random effects model (Fig. 6). Significant heterogeneity was observed among the RCTs (chi-squared = 40.6, $I^2 = 60.6\%$, $p = 0.001$). A subgroup analysis is presented in Table 3. Pooled treatment effect analysis revealed that LMWH compared to UFH therapy significantly decreased mortality in patients with STEMI (OR of 0.65; 95% CI: 0.56–0.76; $p = 0.001$) compared to ACS and non-STEMI (OR of 0.93; 95% CI: 0.72–1.20; $p = 0.6$). Intravenous administration (OR of 0.70; 95% CI: 0.55–0.89; $p = 0.004$) and subcutaneous administration (OR of 0.59; 95% CI: 0.45–0.79; $p = 0.001$) had statistically similar effects in terms of mortality.

5. Discussion

UFH during PCI is a mainstay of thrombotic therapy, whereas it has to be adjusted on the basis of patient's activated clotting time.[4–7] Difficulties in achieving reliable levels of anti-coagulation due to its higher degree of protein binding, inactivation by platelet factor, tendency toward platelet activation and the risk of heparin-induced nephropathy cause limitations of UFH application.[8–10] LMWH represents an alternative anticoagulant that provides more stable and

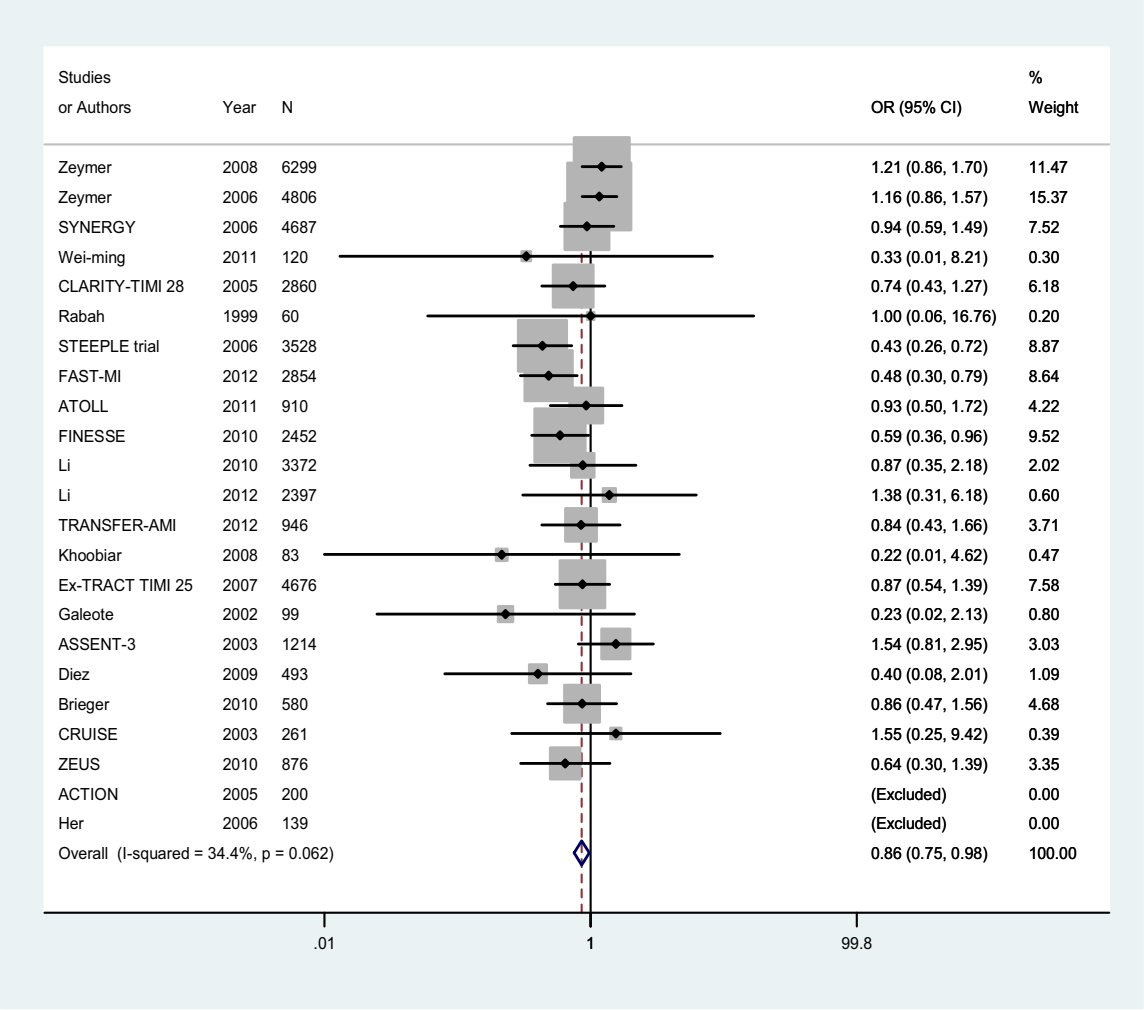

Fig. 5 – Forest plot of odds ratio (OR) for treatment with heparin on incidence of major bleeding.

predictable anticoagulation with no need to continuous infusion and anticoagulant monitoring.[8–10]

It is still unclear as what type of heparin is the most appropriate, safe and efficient anticoagulant for MI patients undergoing PCI. Our findings revealed that using LMWH was associated with significantly better TIMI flow compared to UFH; therefore, administration of LMWH should be preferred in order to achieve complete perfusion. Sabatine et al.[19] also previously suggested that in order to improve TIMI flow and achieve complete perfusion, LMWH should be used, which is consistent with our findings. Our subgroup analysis showed that the incidence of optimal TIMI flow after MI was significantly different between the receivers of LMWH and UFH in terms of the route of administration (either intravenous or subcutaneous) and clinical scenario (either ACS, non-STEMI or STEMI).

TVR was defined as ischemia-driven PCI of target lesions due to re-stenosis or re-occlusion within the stent or in the adjacent 5 mm of the distal or proximal segment. The findings of our study indicated that the incidence of TVR was similar between LMWH and UFH groups; thus both heparin types were associated with comparable TVR. Li et al. claimed that following administration of enoxaparin, the incidence of TVR decreased with a tendency toward reduced re-MI.[26,27] According to our findings enoxaparin also significantly decreased the incidence of re-MI. Previous studies proposed LMWH to be a more potent anticoagulant in terms of decreasing re-MI compared to UFH. Our analysis of a larger body of literature and more subjects confirmed this stronger prophylactic effect of LMWH compared to UFH.

The results of our sensitive analysis showed that in terms of decreasing re-MI LMWH was superior to UFH for both stable and unstable patients especially when administered intravenously. Prophylactic effects against re-MI were shown to be stronger in cases of intravenous compared to subcutaneous administration; therefore, it can be suggested that for patients with a history of MI, intravenous administration of LMWH may be more beneficial than subcutaneous administration or the administration of UFH with the view to avoiding recurrent infarction.

Several studies showed that increased efficiency of LMWH may be accompanied by an increased risk of hemorrhage, especially in high risk patients, such as elderly patients with history of chronic renal impairment. In cases of renal

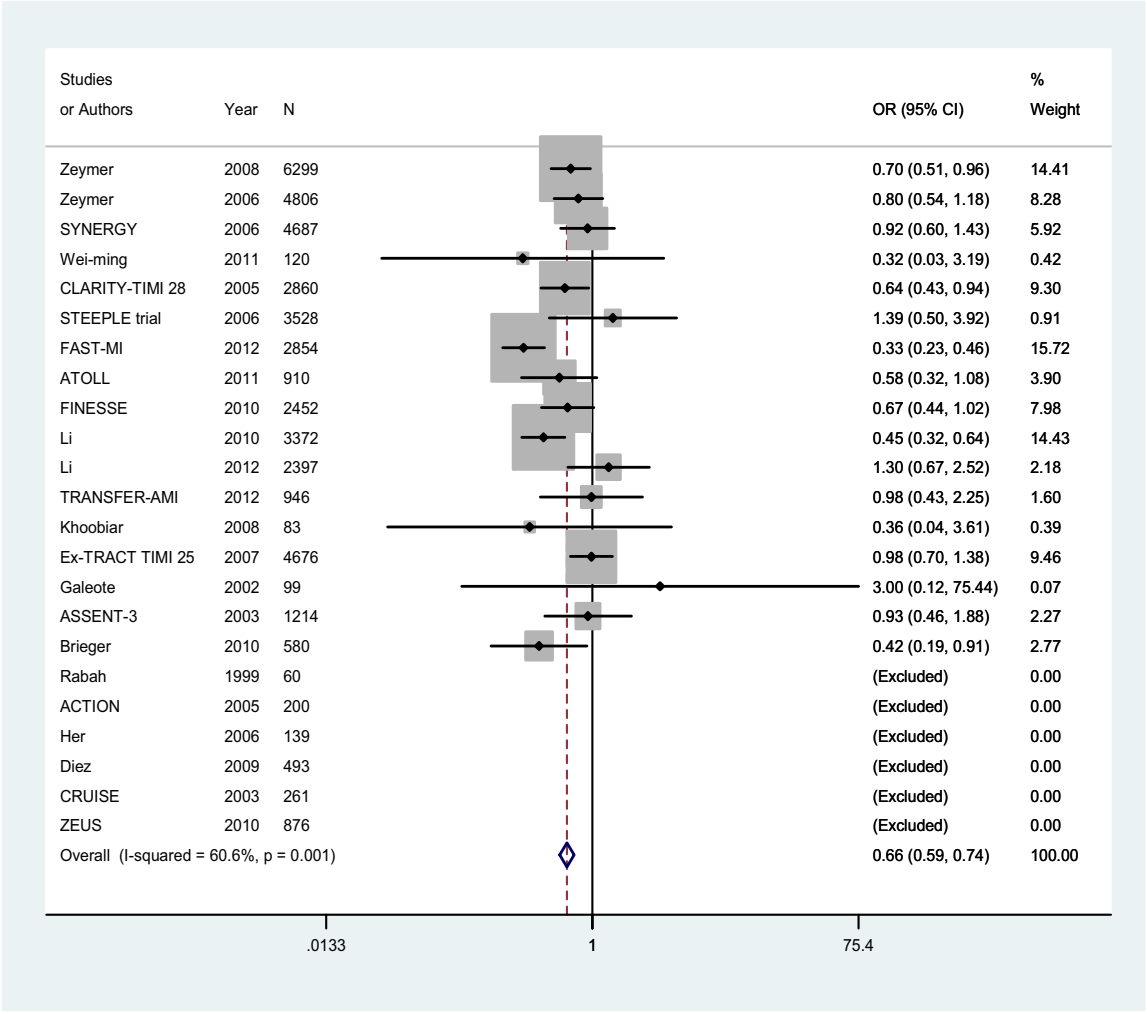

Fig. 6 – Forest plot of odds ratio (OR) for treatment with heparin on incidence of mortality.

impairment there is definite accumulation of LMWH, whereas no antagonist to LMWH is available. This accumulation might subsequently increase the risk of major bleeding episodes. Thus, the dose of LMWH needs to be adjusted in this fragile population.[38–41] Nevertheless, the results of our study showed that the risk of hemorrhage was significantly lower in LMWH receivers compared to UFH, particularly when administered intravenously; it was associated with better therapeutic response as well as less major bleeding. Puymirat et al.[22] also reported that LMWH significantly reduced the risk of major bleeding, and this complication particularly decreased in cases of intravenous injections, which is in agreement with our study. Montalescot et al. stated that subcutaneous administration of enoxaparin was more common in stable and occult coronary syndrome patients; however, intravenous injection could be well adopted to PCI and emergency conditions pharmacologically.[21] In addition, it provided urgent and predictable anticoagulation, which is effective for full 2 h.[23–24] Our findings also revealed that intravenous injection was the most effective route of administration of heparin. This advantage is achieved with a protocol that is simpler than that typically used for UFH: one intravenous bolus without anticoagulation monitoring, the same dose with or without glycoprotein IIb/IIIa inhibitors, and immediate sheath removal after femoral or radial PCI.[42]

Several preoperative risk stratification models such as the additive European System for Cardiac Operative Risk Evaluation (EuroSCORE) and Cardiac Surgery Score (CASUS) are currently in daily use in cardiac surgery.[43,44] These scores are population-based and offer a probability of occurrence in a set of patients with similar characteristics. A prediction of individual outcome especially mortality might be achieved. The present study, analyzing 43,912 patients, claims that administration of LMWH in comparison to UFH, is able to significantly reduce the risk of mortality in patients with MI. Our subgroup analysis demonstrated that administration of LMWH in STEMI patients could considerably reduce mortality, however, that did not have such effect in stable and ACS patients. Also both intravenous administration and subcutaneous administration of LMWH were found to be able to decrease mortality. Silvain et al. reported that LMWH had a remarkable preference to UFH for decreasing the risk of mortality.[45]

Patients may develop in-stent-thrombosis following PCI. This complication is of critical importance due to formation of

blood clot and reduction of blood supply to distal vessels, and a decrease in reperfusion to the myocardium surrounding the site of thrombosis. Our results indicated that patients under LMWH therapy may less frequently develop thrombosis and MACE during PCI compared to UFH.

Finally, we can conclude that the most appropriate type of heparin for patients with MI undergoing PCI seems to be LMWH with higher efficacy and lower incidence of complications compared to UFH. LMWH administration is also more convenient with no need for continuous infusion or tight anticoagulation monitoring. Nevertheless, it is imperative that the outcome after PCI as a procedure in patients receiving either forms of heparin is dependent on many other factors, namely gender, comorbidities, time from onset of symptoms to hospitalization etc.

Conflicts of interest

The authors have none to declare.

Acknowledgments

We would like to thank Dr. Ali Akbar Karimi, and Dr. Ali Mohammad Dehghan for their assistance in writing this manuscript, and Dr. Zahra Ghodratipour, Dr. Zahra Sarrafan, Dr. Arezoo Shahidzadeh, and Dr. Rahimizadeh for their assistance in collecting data and statistical analysis.

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