Original Studies

Defining Optimal Activated Clotting Time for Percutaneous Coronary Intervention: A Systematic Review and Bayesian Meta-Regression

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Background: Guidelines recommend routine monitoring of unfractionated heparin (UFH) with activated clotting time (ACT) during percutaneous coronary intervention (PCI). However, the optimal ACT for patients undergoing PCI is unclear. Methods: We sought to determine the association of peak ACT during PCI with 30-day major adverse cardiac events (MACE; all-cause mortality, myocardial infarction, and revascularization) and bleeding events. We searched the Cochrane Central Register of Controlled Trials, EMBASE, and Medline for randomized controlled trials (RCTs) evaluating UFH through May 2015. Only patients randomized to UFH alone or to UFH with a glycoprotein IIb/IIIa inhibitor (GPI) were analyzed using Bayesian meta-regression. Results: Among 13 included RCTs ($n = 17455$), eight ($n = 5521$) included study arms of UFH alone and 12 ($n = 11934$) included arms of UFH with a GPI. Peak ACT ranged from 201 to 460 sec for UFH alone and 248–317 sec for UFH with a GPI. With UFH alone, the probability of MACE was 7.0% (95% credible interval [CrI] 1.5, 31.5) for a peak ACT of 200 sec and 5.8% (95% CrI 2.6, 12.0) for 300 sec. Among UFH with a GPI, the probability of MACE was 2.8% (95% CrI 0.8, 6.8) for a peak ACT of 200 sec and 7.2% (95% CrI 5.4, 9.7) for 300 sec. Conclusion: Among individual RCTs, the probability of MACE and major bleeding events associated with low versus high values of peak ACT is inconsistent. Our meta-regression results are inconclusive, emphasizing the need for RCTs comparing low versus high doses of UFH. © 2016 Wiley Periodicals, Inc.

Key words: activated clotting time; glycoprotein IIb/IIIa inhibitors; meta-regression; percutaneous coronary intervention; systematic review; unfractionated heparin

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INTRODUCTION

The activated clotting time (ACT), which measures the time in seconds needed for blood to clot, is routinely used to monitor the anticoagulant effect of unfractionated heparin (UFH) during percutaneous coronary intervention (PCI) [1]. Patients who receive inadequate anticoagulation may be at risk of acute vessel closure and poor post-PCI thrombolysis in myocardial infarction (TIMI) grade flow [2–4]. In contrast, those who are excessively anticoagulated may be at risk of bleeding complications. The 2013 American College of Cardiology Foundation/American Heart Association guidelines recommend targeting an ACT of 200–250 sec if a glycoprotein IIb/IIIa inhibitor (GPI) is administered and 250–350 sec if no GPI is administered [4]. However, these guidelines are principally based on empirical evidence [5–7] and a few small observational studies [8–10].

Two meta-analyses of randomized controlled trials (RCTs), published early after the advent of coronary stenting, sought to define optimal ACT [11,12]. However, these meta-analyses, limited to low-risk patients and patients undergoing balloon angioplasty, provided opposing results as to whether low or high ACT is optimal. Given the potentially serious complications associated with under- or over-anticoagulation, we conducted a systematic review and Bayesian meta-regression of data from contemporary RCTs to aggregate the evidence on ACT during PCI. The objective of this study was to evaluate the association of ACT values with 30-day major adverse cardiac events (MACE) and bleeding events in order to define the optimal ACT for patients undergoing PCI.

METHODS

Data Sources and Searches

We systematically searched the Cochrane Central Register of Controlled Trials, EMBASE, and Medline databases for articles published from inception through May 2015. We used keywords, Medical Subject Headings terms (for Medline), and Emtree terms (for EMBASE) for heparin ("heparin") and PCI ("percutaneous coronary intervention," "coronary angioplasty," "stent"; a detailed description of our search strategy is found in Appendix A). These search terms were combined with a modified version of the highly specific McMaster RCT hedge for the EMBASE and Medline to restrict results to RCTs [13]. In addition, we hand-searched the bibliographies of previous studies, relevant reviews, and previous meta-analyses to identify additional RCTs not identified in the electronic database search. We conducted our systematic review and meta-regression following a pre-specified protocol and report according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14].

Study Selection

Studies were eligible for inclusion if they randomized patients to UFH with or without a GPI and compared them to any of the following: an alternative dose of UFH, UFH with an alternative GPI, bivalirudin, or low molecular weight heparin. Only patients randomized to UFH or UFH with a GPI were included in our analysis. We restricted our systematic review to RCTs in order to reduce the risk of confounding by indication and selection bias likely to be present in observational studies [15]. Other inclusion criteria were the following: (1) patients aged 18 years and over, (2) patients underwent PCI (i.e., elective, urgent, or primary) in which the majority received at least one coronary stent, (3) patients were administered a $P2Y_{12}$ inhibitor, (4) peak ACT was reported, (5) 30-day outcomes were reported, including all-cause mortality, myocardial infarction (MI), any revascularization, MACE (i.e., composite endpoint of all-cause mortality, MI, and any revascularization), or minor or major bleeding as defined by TIMI bleeding criteria [16], and (6) published in the English or French language. Studies not meeting these criteria were excluded.

Data Extraction

Two reviewers independently extracted data using standardized electronic data extraction forms. Disagreements were resolved by consensus or, when necessary, by a third reviewer. Data were only extracted for patients randomized to UFH or UFH with a GPI. Extracted data included study design, baseline characteristics, procedural characteristics, median and mean peak ACT, and 30-day outcomes. Outcomes were extracted as count data following an intention-to-treat approach. The device used to measure peak ACT (HemoTec or Hemochron) was also extracted. If no GPI is administered, the 2013 American College of Cardiology Foundation/American Heart Association guidelines recommend targeting an ACT of 250–300 sec with the HemoTec device and 300–350 sec with the Hemochron device [4]. However, when a GPI is administered, the recommended ACT is 200–250 sec regardless of the device used.

Quality Assessment

Two reviewers independently evaluated study quality using the Cochrane Collaboration Risk of Bias Tool [17]. We used this tool to assess for the risk of

selection, performance, detection, attrition, and reporting biases, as well as other biases. Each RCT was categorized on the basis of criteria determining the likelihood of potential threats to validity. This tool was used to evaluate the overall quality of RCTs, although data were exclusively extracted for patients randomized to study arms with UFH alone or to UFH with a GPI.

Data Analysis

Differences in study methods, patient characteristics, and intervention characteristics suggested that the true effect from each RCT was likely to vary. First, to account for potential variation caused by GPI administration, we analyzed study arms in which both UFH and a GPI were administered separately from study arms that evaluated UFH alone. Second, we conducted a Bayesian meta-regression model to synthesize our results and account for between-study arm variation in ACT [18]. In this model, the probability of an event was allowed to vary between each study arm. To model the between-study arm variability, the logit of the probability of each outcome variable was assumed to follow a normal distribution. Therefore, the mean of the normal distribution of the logit of probability across study arms represented the average effect in the arms, and the variance represented the variability in the logit of probabilities across arms. Uninformative prior distributions were used throughout. In particular, we used normal (mean 0, standard deviation [SD] 10) prior distributions for means and uniform prior distributions on the range from 0.001 to 4 for SD parameters. Therefore, our estimates of the logit of probability across study arms and their associated 95% credible intervals (CrI) (the Bayesian equivalent of frequentist confidence intervals) were not unduly affected by our choice of prior distribution. In order to change the model from basic meta-analysis to meta-regression, we removed the normal density on the mean parameter of the logit of the probabilities and replaced it with a linear regression component. Hence, the normal densities are given to the intercept and slope of the regression line. Finally, we used the logit of probabilities to calculate the predicted probability of MACE and bleeding events for a peak ACT of 200 and 300 sec. Our Bayesian meta-regression WinBUGS program is found in Appendix B. We used one long chain for our model and assessed convergence by visual inspection of all history plots. All Bayesian analyses were carried out using WinBUGS software (version 1.4.3; MRC Biostatistics Unit, Cambridge, UK). In addition to the Bayesian meta-regression, weighted scatterplots of the risk of adverse events versus ACT were created with the circle for each study proportional to the total size of the population of each included study arm. Scatterplots were created using StataSE (version 13.1; StatCorp, College Station, TX).

RESULTS

Search Results and Study Inclusion

A total of 6468 potentially relevant studies were identified in our initial literature search (Fig. 1). After screening the titles and abstracts, the full-texts of 332 publications were retrieved and assessed for eligibility. Of the retrieved publications, 13 met our inclusion criteria and were included in our systematic review. No additional studies were identified through our handsearch of references from published studies, relevant reviews, or previous meta-analyses.

Study Characteristics

The 13 RCTs ($n = 17455$) included in our systematic review were published between 1998 and 2013 [19–31]. Five RCTs randomized patients to study arms comparing UFH alone to UFH with a GPI [20,23,24,26,29] and four RCTs compared UFH to bivalirudin [25,27,28,31]. One RCT each compared UFH to placebo [19], UFH to low molecular weight heparin [30], UFH with clopidogrel to UFH alone [22], and standard-dose (85 units/kg) to low-dose (50 units/kg) UFH [21]. Among the 13 RCTs in our systematic review, we included eight study arms in which UFH was administered alone ($n = 5521$) and 12 study arms in which UFH was administered with a planned GPI ($n = 11934$). Sample sizes for included study arms ranged from 52 to 3008 patients. According to the Cochrane Risk-of-Bias Tool [17], four RCTs had a high risk of bias due to an absence of blinding of participants, personnel, or outcome assessors (Appendix C) [25,27,28,30].

Baseline Characteristics

The proportion of patients with acute coronary syndrome (ACS; i.e., unstable angina, non-ST-elevation MI, or ST-elevation MI) varied substantially between included RCTs (Table I). Four RCTs were restricted to patients with ACS, while others had proportions of ACS varying from 0 to 75%. Age, which ranged from 57 to 66 years, and the proportion of males, which ranged from 67 to 85%, were also heterogeneous between RCTs. Mean weight was at least 80 kg in seven RCTs and ranged from 69 to 88 kg. Proportions of patients with prior MI and PCI also varied substantially between RCTs.

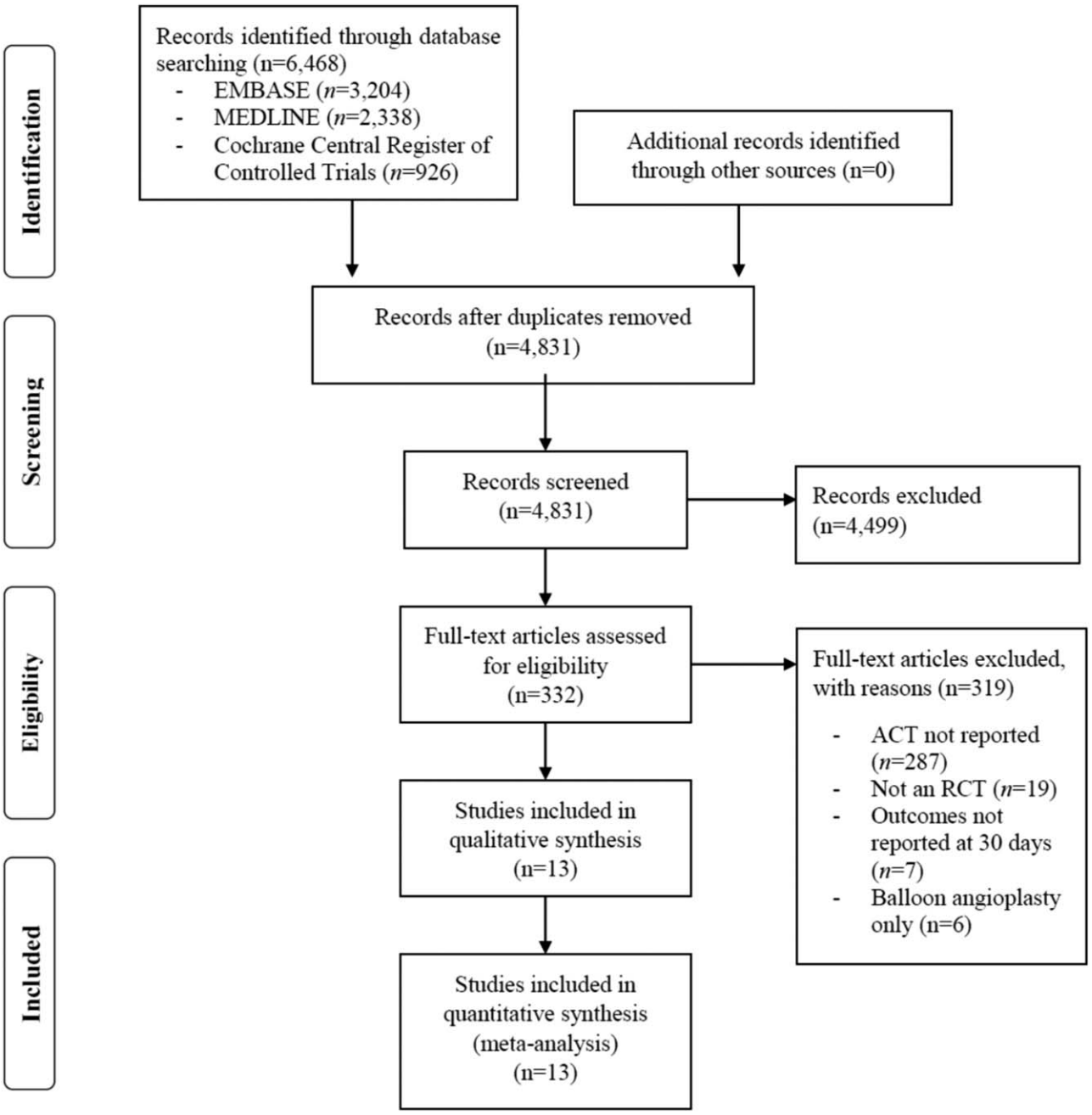

Fig. 1. PRISMA [14] flow diagram of included RCTs. ACT, activated clotting time; RCT, randomized controlled trial.

PCI Characteristics

Among all included RCTs, the vast majority of patients underwent femoral access for PCI (Table II). Among study arms in which UFH was administered without GPI, the minimum ACT targeted by study investigators ranged from 200 to 300 sec. Peak ACT varied considerably, ranging from 201 to 460 sec. Among study arms in which UFH was administered with a GPI, the minimum target ACT was 200, except for the REPLACE-2 Trial (225 sec) [31] and the TARGET trial (250 sec) [29]. There was less variation in peak ACT, which ranged from 248 to 317 sec. Only two RCTs reported the device (HemoTec or Hemochron) used to measure ACT [25,31]. In both of these RCTs, the Hemochron device was used. Also, only the ADMIRAL Trial [31] reported TIMI grade flow 3, which was 11.4% (pre-PCI) and 8.4% (post-PCI) higher in the UFH with abciximab arm versus the UFH alone arm.

TABLE I. Baseline characteristics of included RCTs.

RCT	Study arm	*N*	Peak ACT[a] (sec)	ACS (%)	Age (years)	Males (%)	Weight (kg)	DM (%)	HTN (%)	Current smoker (%)	DLP (%)	Prior MI (%)	Prior PCI (%)	Prior CABG (%)
UFH without GPI														
CIAO 2008 [19]	UFH	350	201[b]	0	63	78	–	35	–	52	57	–	–	–
ESPRIT 2000 [20]	UFH	1024	263	19	62[c]	72	85[c]	21	59	23	59	31	24	10
FUTURA/OASIS-8 2010 [21]	UFH (50 U/kg)	1024	273	100	65	67	76	26	67	–	40	18	16	5
CREDO 2002 [22]	UFH	1053	281[b]	67	62	70	88	28	67	32	74	34	–	–
FUTURA/OASIS-8 2010 [21]	UFH (85 U/kg)	1002	333	100	66	69	77	28	69	–	42	21	18	6
EPISTENT 1998 [23]	UFH	809	346	53	59	75	–	21	55	39	–	39	–	11
ADMIRAL 2001 [24]	UFH	151	346	100	62	78	76	20	41	39	37	7	10	13.3
Xiang 2013 [25]	UFH	108	460[b]	75	59[c]	82	66[c]	–	–	–	–	–	–	–
UFH with GPI														
TEAM 2002 [26]	UFH + tirofiban	56	248[b]	–	–	–	–	–	–	–	–	–	–	–
TEAM 2002 [26]	UFH + eptifibatide	61	256[b]	–	–	–	–	–	–	–	–	–	–	–
TEAM 2002 [26]	UFH + abciximab	63	261[b]	–	–	–	–	–	–	–	–	–	–	–
HORIZONS-AMI 2008 [27]	UFH + abciximab/ eptifibatide	1802	264	100	61[c]	76	80[c]	17	55	45	43	11	11	3
Deshpande 2012 [28]	UFH + tirofiban	52	264[b]	–	57	85	69	42	75	21	6	35	12	2
ESPRIT 2000 (20)	UFH + eptifibatide	1040	273	17	62[c]	73	84[c]	20	59	24	58	32	23	10
TARGET 2001 [29]	UFH + tirofiban	2398	281	–	62	74	86	23	64	65	–	40	29	17
TARGET 2001 [29]	UFH + abciximab	2411	283	–	63	73	86	23	65	64	–	39	30	17
ACTION 2005 [30]	UFH + eptifibatide/ tirofiban	100	307[b]	51	64[c]	72	80[c]	15	56	14	79	42	10	8
EPISTENT 1998 [23]	UFH + abciximab	794	314	52	59	75	–	20	48	37	–	33	–	8
ADMIRAL 2001 [24]	UFH + abciximab	149	316	100	60	85	76	15	34	45	40	14	8	10
REPLACE-2 2003 [31]	UFH + abciximab/ eptifibatide	3008	317	23	63	74	88	26	68	26	–	37	35	19

[a]Median peak ACT measured during PCI. RCTs are in ascending order of peak ACT.
[b]Mean.
[c]Median.
ACS, acute coronary syndrome (consists of ST-elevation MI, non-ST elevation MI, or unstable angina); CABG, coronary artery bypass graft; DLP, dyslipidemia; DM, diabetes mellitus; GPI, glycoprotein IIb/IIIa inhibitor; HTN, hypertension; N, sample size; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; U, units; UFH, unfractionated heparin.

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TABLE II. PCI characteristics of included RCTs.

RCT	Study arm	*N*	Peak ACT[a] (sec)	$P2Y_{12}$ inhibitor (%)	GPI (%)	Minimum target ACT (sec)	Radial access (%)	Stent placed (%)	Pre-TIMI 3 (%)	Post-TIMI 3 (%)
UFH without GPI										
CIAO 2008 [19]	UFH	350	201[b]	100	0	–	0	100	–	–
ESPRIT 2000 [20]	UFH	1024	263	98	0	200	–	97	–	–
FUTURA/OASIS-8 2010 [21]	UFH (50 U/kg)	1024	273	84	26	200	36	94	–	–
CREDO 2002 [22]	UFH	1053	281[b]	100	47	–	–	90	–	–
FUTURA/OASIS-8 2010 [21]	UFH (85 U/kg)	1002	333	86	26	300	37	94	–	–
EPISTENT 1998 [23]	UFH	809	346	100	0	300	0	96	–	–
ADMIRAL 2001 [24]	UFH	151	346	100	0	200	0	100	5.4	86.7
Xiang 2013 [25]	UFH	108	460[b]	100	4	225	27	–	–	–
UFH with GPI										
TEAM 2002 [26]	UFH + tirofiban	56	248[b]	–	100	200	–	91	–	–
TEAM 2002 [26]	UFH + eptifibatide	61	256[b]	–	100	200	–	93	–	–
TEAM 2002 [26]	UFH + abciximab	63	261[b]	–	100	200	–	91	–	–
HORIZONS-AMI 2008 [27]	UFH + abciximab/ eptifibatide	1802	264	100	100	200	–	95	–	–
Deshpande 2012 [28]	UFH + tirofiban	52	264[b]	100	100	200	–	99	–	–
ESPRIT 2000 [20]	UFH + eptifibatide	1040	273	97	100	200	–	95	–	–
TARGET 2001 [29]	UFH + tirofiban	2398	281	–	100	250	–	100	–	–
TARGET 2001 [29]	UFH + abciximab	2411	283	–	100	250	–	100	–	–
ACTION 2005 [30]	UFH + eptifibatide/ tirofiban	100	307[b]	100	100	200	23	94	–	–
EPISTENT 1998 [23]	UFH + abciximab	794	314	100	100	200	0	97	–	–
ADMIRAL 2001 [24]	UFH + abciximab	149	316	100	100	200	0	100	16.8	95.1
REPLACE-2 2003 [31]	UFH + abciximab/ eptifibatide	3008	317	84	97	225	–	86	–	–

[a]Median peak ACT measured during PCI. RCTs are in ascending order of peak ACT.
[b]Mean.
ACT, activated clotting time; GPI, glycoprotein IIb/IIIa inhibitor; N, sample size; RCT, randomized controlled trial; TIMI 3, Thrombolysis in Myocardial Infarction grade flow 3 (i.e., normal coronary blood flow); U, units; UFH, unfractionated heparin.

TABLE III. Thirty-day outcomes of included RCTs.

RCT	Study arm	*N*	Peak ACT[a] (sec)	All-cause mortality (%)	MI (%)	Revascularization[b] (%)	MACE (%)	Minor bleed[c] (%)	Major bleed[c] (%)
UFH without GPI									
CIAO 2008 (19)	UFH	350	201[d]	0.0	3.1	0.6	3.7	1.1	0.0
ESPRIT 2000 (20)	UFH	1024	263	–	–	–	10.4	1.8	0.4
FUTURA/OASIS-8 2010 (21)	UFH (50 U/kg)	1024	273	0.8	3.0	0.9	4.5	0.9	2.1
CREDO 2002 (22)	UFH	1053	281[d]	0.0	4.9	0.9	5.8	3.1	4.7
FUTURA/OASIS-8 2010 (21)	UFH (85 U/kg)	1002	333	0.6	2.5	0.3	2.9	2.1	1.8
EPISTENT 1998 (23)	UFH	809	346	0.6	9.6	2.1	10.8	1.7	2.2
ADMIRAL 2001 (24)	UFH	151	346	6.6	2.6	12.6	20.5	3.3	0.0
Xiang 2013 (25)	UFH	108	460[d]	0.9	1.9	0.0	1.9	6.5	0.0
UFH with GPI									
TEAM 2002 (26)	UFH + tirofiban	56	248[d]	0.0	3.6	1.8	5.4	1.8	0.0
TEAM 2002 (26)	UFH + eptifibatide	61	256[d]	1.6	1.6	0.0	3.3	3.3	1.6
TEAM 2002 (26)	UFH + abciximab	63	261[d]	1.6	1.6	1.6	4.8	1.6	0.0
HORIZONS-AMI 2008 (27)	UFH + abciximab/ eptifibatide	1802	264	3.1	1.8	1.9	4.9	4.6	5.0
Deshpande 2012 (28)	UFH + tirofiban	52	264[d]	0.0	0.0	0.0	0.0	0.0	0.0
ESPRIT 2000 (20)	UFH + eptifibatide	1040	273	–	–	–	6.8	2.8	1.3
TARGET 2001 (29)	UFH + tirofiban	2398	281	0.5	6.9	0.8	7.6	2.8	0.9
TARGET 2001 (29)	UFH + abciximab	2411	283	0.4	5.4	0.7	6.0	4.3	0.7
ACTION 2005 (30)	UFH + eptifibatide/ tirofiban	100	307[d]	0.0	14.0	0.0	14.0	2.0	0.0
EPISTENT 1998 (23)	UFH + abciximab	794	314	0.3	4.5	1.3	5.3	2.9	1.5
ADMIRAL 2001 (24)	UFH + abciximab	149	316	3.3	1.3	7.4	12.1	12.1	0.7
REPLACE-2 2003 (31)	UFH + abciximab/ eptifibatide	3008	317	0.4	6.2	0.5	7.0	3.0	0.9

[a]Median peak ACT measured during PCI. RCTs are in ascending order of peak ACT.
[b]Includes revascularization by repeat percutaneous coronary intervention or by coronary artery bypass graft.
[c]Thrombolysis in myocardial infarction (TIMI) definition of bleed [16].
[d]Mean.
GPI, glycoprotein IIb/IIIa inhibitor; MACE, major adverse cardiac events (consists of all-cause mortality, myocardial infarction, and revascularization); MI, myocardial infarction; N, sample size; RCT, randomized controlled trial; U, units; UFH, unfractionated heparin.

Thirty-Day Outcomes

MACE. Among study arms examining UFH alone, those with a peak ACT less than 300 sec had MACE ranging from 3.7 to 10.4% compared to 1.9–20.5% for those with a peak ACT greater than 300 sec (Table III). The ADMIRAL [31] study arm ($n = 151$), which had a peak ACT of 346 sec, had the highest incidence of MACE (20.5%), largely due to a high incidence of revascularization (12.6%) and all-cause mortality (6.6%). However, the larger FUTURA/OASIS-8 [21] study arm ($n = 1002$), which also had a high peak ACT (333 sec), had a much lower incidence of MACE (2.9%). Overall, there was no major trend to suggest an association of MACE with increasing ACT among study arms (Fig. 2a; scatterplots of the individual components of MACE versus ACT are found in Appendix D). In our Bayesian meta-regression, we found that the probability of MACE was 7.0% (95% CrI 1.5, 31.5) for a peak ACT of 200 sec versus 5.8% (95% CrI 2.6, 12.0) for a peak ACT of 300 sec (Table IV).

Among study arms examining UFH with a GPI, those with a peak ACT less than 300 sec had MACE ranging from 0.0 to 7.6% compared to 5.3 to 14.0% for those with a peak ACT greater than 300 sec (Table III). The ACTION [30] study arm ($n = 100$) and the ADMIRAL [24] study arm ($n = 151$) had the highest incidence of MACE (14.0 and 12.1%, respectively). However, these study arms were small compared to the REPLACE-2 Trial ($n = 3008$) [31] and the EPISTENT Trial ($n = 794$) [23], which had lower incidence of MACE (Fig. 2b). In our Bayesian meta-regression, the probability of MACE was 2.8% (95% CrI 0.8, 6.8) for a peak ACT of 200 sec versus 7.2% (95% CrI 5.4, 9.7) for a peak ACT of 300 sec.

Bleeding events. The incidence of minor bleeds was 6.5% or less for all study arms with the exception of the ADMIRAL [24] study arm, in which patients were randomized to UFH and abciximab (12.1%). The probability of minor bleeds was 0.8% (95% CrI 0.4, 1.6) for a peak ACT of 200 sec versus 1.7% (95% CrI 1.2, 2.4) for a peak ACT of 300 sec.

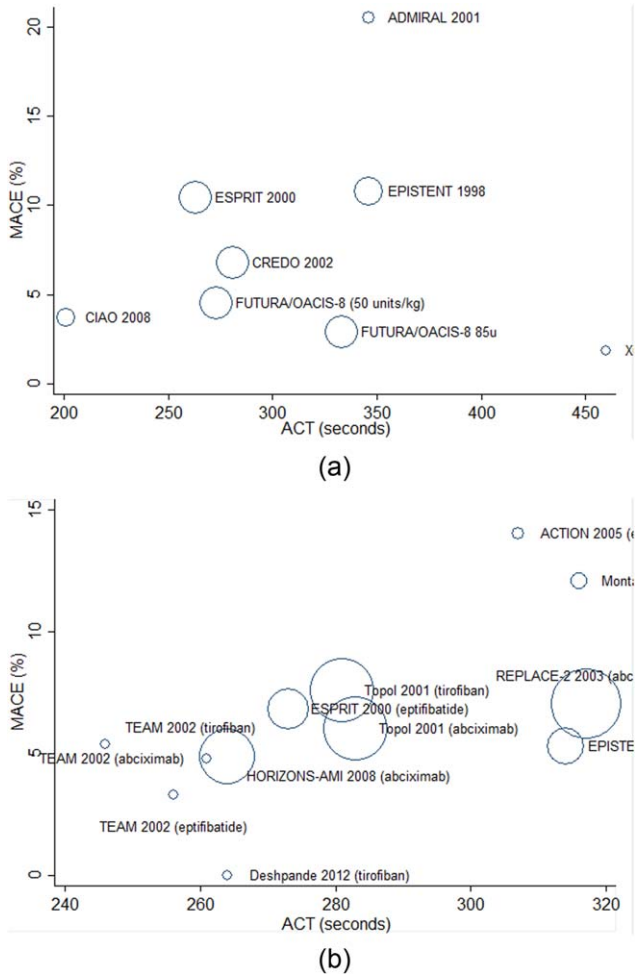

Fig. 2. (a) Proportion of MACE versus ACT at 30 days for individual study arms without GPI. (b) Proportion of MACE versus ACT at 30 days for individual study arms with GPI. ACT, activated clotting time; GPI, glycoprotein IIb/IIIa inhibitors; MACE, major adverse cardiac events (consists of all-cause mortality, myocardial infarction, revascularization). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The incidence of major bleeds was 5.0% or less for all study arms, including those with or without GPI administration (Table III). The two study arms with the highest incidence of major bleeds were HORIZONS-AMI [27] (UFH and GPI; 5.0%) and CREDO [22] (UFH alone; 4.7%). The peak ACTs were 264 and 281 sec for these two study arms, respectively. As with MACE, there was no major trend to suggest an association between major bleeds and ACT (Fig. 3; scatterplots of minor bleeds versus ACT are found in Appendix D). Among patients with UFH alone, the probability of major bleeds was 0.6% (95% CrI 0.0, 28.7) for a peak ACT of 200 sec versus 0.4% (95% CrI 0.0, 2.8) for a peak ACT of 300 sec. Among patients with UFH and a GPI, the probability of major

TABLE IV. Bayesian meta-regression of 30-day outcomes by 100 sec increase of peak ACT[a]

	Without GPI					With GPI				
30-day outcome	Log (odds)[b]	95% CrI[c]	Probability for ACT of 200 sec (%)	95% CrI[c]	Probability for ACT of 300 sec (%)	Log (odds)[b]	95% CrI[c]	Probability for ACT of 200 sec (%)	95% CrI[c]	Probability for ACT of 300 sec (%)
All-cause mortality	1.8	−1.2, 6.6	0.0	0.0, 2.2	0.2	−0.8	0.0, 1.9	−4.1, 2.3	1.4	0.1, 17.7	0.6	0.1, 1.3
MI	0.0	−1.2, 1.1	4.0	1.0, 17.0	3.7	1.3	1.4, 6.7	−1.0, 3.9	1.3	0.1, 8.4	4.4	1.8, 7.4
Revascu-larization	−0.2	−3.1, 2.0	1.5	0.1, 31.6	1.0	0.3	0.1, 5.5	−2.9, 3.8	0.7	0.0, 9.5	0.9	0.2, 2.3
MACE	−0.2	−1.8, 1.0	7.0	1.5, 31.5	5.8	1.0	2.6, 12.0	−0.0, 2.5	2.8	0.8, 6.8	7.2	5.4, 9.7
Minor bleed[d]	0.7	0.1, 1.3	0.8	0.4, 1.6	1.7	0.8	1.2, 2.4	−0.8, 2.8	1.8	0.3, 6.5	3.6	2.2, 5.9
Major bleed[d]	−0.4	−4.4, 2.7	0.6	0.0, 28.7	0.4	−0.8	0.0, 2.8	−3.1, 2.3	1.9	0.1, 13.6	0.9	0.3, 1.8

[a]Peak ACT measured during PCI. Relative risk of 30-day outcome of ACT $\geq$ 300 sec versus ACT $<$ 300 sec.
[b]Log(odds) of 30-day outcome by 100 sec increase of peak ACT.
[c]Bayesian equivalent of standard confidence intervals.
Thrombolysis in myocardial infarction (TIMI) definition of bleed [16].
ACT, activated clotting time; CrI, credible interval; GPI, glycoprotein IIb/IIIa inhibitor; MACE, major adverse cardiac events (consists of all-cause mortality, myocardial infarction, and revascularization); MI, myocardial infarction.

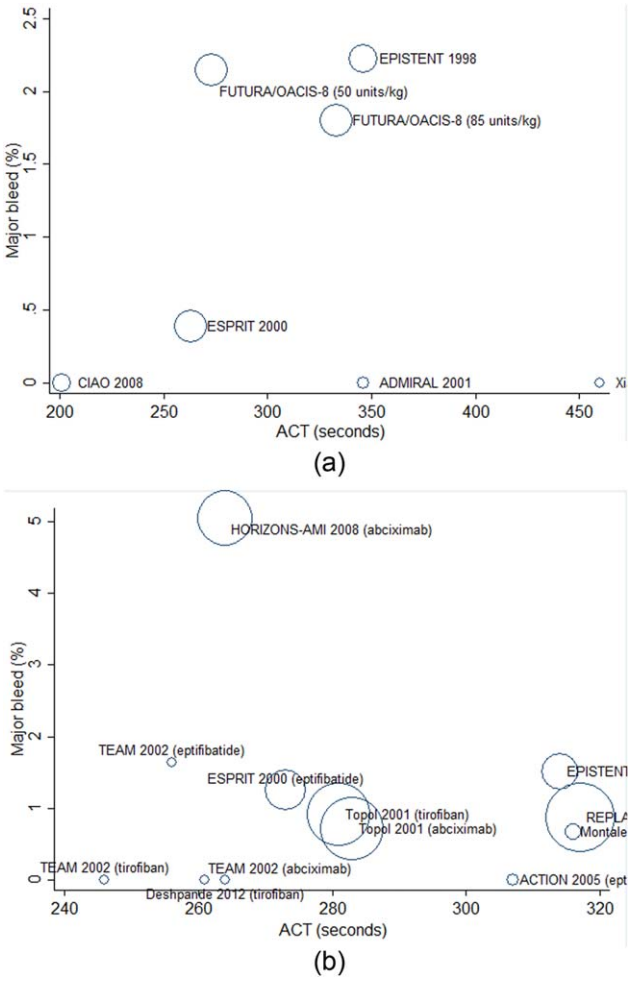

Fig. 3. (a) Proportion of major bleed (thrombolysis in myocardial infarction (TIMI) definition of bleed [16]) versus ACT at 30 days for individual study arms without GPI. (b) Proportion of major bleed (thrombolysis in myocardial infarction (TIMI) definition of bleed [16]) versus ACT at 30 days for individual study arms with GPI. ACT, activated clotting time; GPI, glycoprotein IIb/IIIa inhibitors. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

bleeds was 1.9% (95% CrI 0.1, 13.6) for a peak ACT of 200 sec versus 0.9% (95% CrI 0.3, 1.8) for a peak ACT of 300 sec.

DISCUSSION

Our study was designed to synthesize and evaluate 30-day MACE and bleeding events associated with peak ACTs in patients receiving UFH during PCI. Little data were available to provide direct comparisons of high versus low ACT. Furthermore, among individual RCTs, the probability of MACE and major bleeding events associated with low versus high values of peak ACT was inconsistent. Our Bayesian meta-regression demonstrated that the current literature on ACT and adverse clinical events is inconclusive. The FUTURA/OASIS-8 Trial [21] was the only RCT identified in our literature search to compare low- versus high-dose UFH and to report ACT. This RCT showed a 2.1% increase in MACE in patients with low peak ACT ($\leq$300 sec) versus high peak ACT (>300 sec). However, given the limited and inconclusive data identified in our systematic review and the potentially serious complications that may be associated with UFH, an RCT comparing incremental doses of UFH among patients undergoing PCI is urgently needed. An RCT reporting the associated TIMI grade flow and MACE associated with incremental ACT values may help identify the optimal target ACT.

Evolution of PCI and ACT

The 2013 American College of Cardiology Foundation/American Heart Association guidelines recommend targeting an ACT of 200–250 sec if a GPI is administered [4]. If no GPI is administered, the recommended targets are 250–300 sec (HemoTec device) or 300–350 sec (Hemochron device). However, these reference ranges are largely based on empirical studies examining fibrin deposition within extracorporeal circuits [5–7], as well as small observational PCI studies in the pre-coronary stent era [8–10]. Patients in these early studies predominantly underwent balloon angioplasty alone as opposed to with coronary stenting. Furthermore, fast-acting antiplatelet drugs (i.e., $P2Y_{12}$ inhibitors, GPIs) that are now routinely administered during PCI were not available at the time of those studies. Consequently, patients undergoing PCI in the pre-coronary stent era were at higher risk of thrombotic complications, and consequently, repeat MI, revascularization, stroke, and all-cause mortality [32]. These studies may have favored higher doses of UFH, and thus, higher ACTs than what is currently needed given the relatively elevated risk of thrombotic complications associated with balloon angioplasty and poorer antiplatelets. Conversely, PCI conducted in these previous studies was principally performed via femoral access as opposed to radial access, which is now the preferred method of catheter insertion [33]. PCI via femoral access is associated with a higher risk of groin hematomas, and the use of this approach may therefore have limited the amount of UFH that could be safely administered [34,35]. Furthermore, the utility of ACT measurements with the use of alternative anticoagulants, including direct thrombin inhibitors such as bivalirudin, is unclear. In the context of bivalirudin administration, current practice is to obtain an ACT measurement in order to confirm that the drug was given; however, it is unclear whether or not the ACT correlates to

specific doses of bivalirudin or to MACE in this context [36]. Given the evolution of PCI and the limited and inconclusive data from the coronary stent era for both UFH and alternative anticoagulants, the optimal ACT target remains unclear. There is a need for future RCTs providing head-to-head comparisons of low versus high doses of UFH in order to minimize the incidence of MACE and bleeding events.

Previous Meta-Analyses

Two meta-analyses published in the early 2000s sought to determine the optimal ACT for UFH use during PCI [11,12]. The first, by Chew et al., included six RCTs ($n = 5216$) and divided patients into 25-sec intervals of ACT [11]. This study found a peak ACT of 350–375 sec to be the optimal interval, conferring the lowest risk of MACE at 7 days (6.6%). However, this meta-analysis was primarily limited to patients who did not receive coronary stents or $P2Y_{12}$ platelet inhibitors, and thus, does not reflect current practice. The second meta-analysis, by Brener et al., included four RCTs ($n = 9974$) in a setting where the majority of patients received coronary stenting [12]. In contrast to the previous meta-analysis, this study did not find that MACE varied significantly with increasing ACTs. It found a slight increase in the composite endpoint of major and minor bleeds associated with increasing ACT (i.e., 2.9% for ACT less than 256 sec versus 4.0% for ACT greater than 348 sec). However, this meta-analysis was limited by the fact that only four RCTs were included, the patient population was generally low risk (i.e., majority of included patients did not have ACS), and approximately 20% of patients did not receive a $P2Y_{12}$ inhibitor. Furthermore, results were pooled using a fixed effects model despite substantial between-study heterogeneity.

FUTURA/OASIS-8 Trial

In our systematic review, the FUTURA/OASIS-8 Trial ($n = 2026$), which randomized non-ST-elevation MI patients to low-dose UFH (50 units/kg; median peak ACT 273 sec) or standard-dose UFH (85 units/kg; median peak ACT 333 sec), was the only direct head-to-head comparison identified [21]. MACE at 30 days was higher in the low-dose arm (4.5%) than in the high-dose arm (2.9%) with an adjusted odds ratio 1.6 (95% confidence interval 1.0, 2.5). Furthermore, in a sub-analysis among patients not administered a GPI, MACE was higher in those with an ACT less than 300 sec (4.9%) than in those with an ACT greater than 300 sec (2.8%) (adjusted odds ratio, 1.8; 95% confidence interval 1.1, 3.2) [37]. No difference in MACE was found among patients administered a GPI. In addition, no difference was found in minor or major bleeding events among low versus high ACT. The results of this RCT suggest that non-GPI patients undergoing PCI with a peak ACT less than 300 sec are at higher risk of thrombotic events and may benefit from a higher dose of UFH. A sub-analysis of the STEEPLE Trial, a separate prospective study designed to compare the safety of enoxaparin to UFH in patients undergoing elective PCI, further suggested that patients with a low ACT are at higher risk of thrombotic events [38,39]. The STEEPLE Trial ($n = 3528$) was not included in our Bayesian meta-regression since peak ACT was not reported. However, the STEEPLE Trial authors showed that an increase in MACE was observed when the ACT was <325 sec (odds ratio per 100 sec, 0.7, 95% confidence interval 0.2, 0.8). In contrast, major bleeding increased significantly with an ACT > 325 sec (odds ratio per 100 sec, 1.6, 95% confidence interval 1.1, 2.2). Both the FUTURA/OASIS-8 Trial and the sub-analysis of the STEEPLE Trial challenged the theory that high-dose UFH is no longer needed in the modern era of coronary stenting since low ACT values were associated with a higher MACE [19]. It should be noted, however, that FUTURA/OASIS-8 Trial was underpowered to detect important reductions in bleeding from the use of low-dose UFH, and the sub-analysis from the STEEPLE Trial suggested that a high ACT may significantly increase the risk of bleeding.

Limitations

There are some potential limitations to our study. First, we restricted our systematic review to RCTs only, which reduced the available data for our analysis. Given the lack of studies directly comparing low versus high ACT, we conducted an indirect, observational comparison of study arms in which patients were randomized to receive UFH (with or without a GPI). This type of analysis relies on the similarity assumption; that is, included patients from different study arms are sufficiently similar to be compared [40]. Hence, by restricting to RCTs, we guaranteed a certain degree of similarity between procedural characteristics of different study arms, such as $P2Y_{12}$ inhibitor use and the proportion of coronary stenting. The risk of confounding by indication and selection bias is likely to be lower in RCTs compared to observational studies [15]. Second, despite restricting to RCTs, there were still between-study variations in patient features and procedural characteristics that may potentially confound ACT values. For instance, patients with acute MI may respond differently to UFH compared to patients with stable angina. Also, patients administered different antiplatelet agents may respond differently to UFH. To account for between-trial heterogeneity, we used

Bayesian random-effects models for our meta-regression. Furthermore, we stratified our analysis by GPI use. Third, meta-regression involves certain inherent assumptions. We were limited to data reported in published articles and did not have access to patient-level data. Finally, our systematic review was limited to studies published in the English or French language. However, only 3.7% of studies identified in our literature search were published in another language, and their exclusion is unlikely to substantially affect the conclusions of our systematic review.

CONCLUSION

Our systematic review and Bayesian meta-regression found the overall association between peak ACT and 30-day MACE or bleeding events to be inconclusive. Furthermore, limited data are available to draw direct comparisons of low versus high peak ACT values. The only RCT providing a direct comparison is the FUTURA/OASIS-8 Trial, which suggests that higher peak ACT is associated with lower MACE. However, this finding contradicts common perceptions that coronary stenting and dual antiplatelet therapy have reduced the need for higher ACT. Given these limited and inconclusive data, as well as the potentially serious complications associated with UFH, our study demonstrates the need for more direct comparisons of low versus high UFH dosing.

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APPENDIX A: LITERATURE SEARCH STRATEGY

EMBASE Search (n = 3204)

1. exp heparin/
2. heparin.mp.
3. 1 or 2
4. (((intervent* or stent* or angioplasty* or cath*) and (coronar* or cardiac*)) or pci* or ptca*).mp.
5. exp transluminal coronary angioplasty/
6. exp coronary stent/
7. 4 or 5 or 6
8. 3 and 7
9. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ or (random* or factorial* or crossover* or cross over* or placebo* or (doubl* adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer*).tw.
10. 8 and 9

MEDLINE Search (n = 2338)

1. heparin.mp. or exp heparin/
2. (((intervent* or stent* or angioplasty* or cath*) and (coronar* or cardiac*)) or PCI* or PTCA*).mp. or exp angioplasty,balloon,coronary/ or exp stents/
3. 1 and 2
4. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or randomised.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)
5. 3 and 4

Cochrane Central Register of Controlled Trials (n = 926)

1. heparin.mp. or exp heparin/
2. (((intervent* or stent* or angioplasty* or cath*) and (coronar* or cardiac*)) or PCI* or PTCA*).mp. or exp angioplasty,balloon,coronary/ or exp stents/
3. 1 and 2

APPENDIX B: BAYESIAN META-REGRESSION WINBUGS PROGRAM

i. Below is the Bayesian meta-regression WinBUGS program providing the logit of probability and credible interval of major adverse cardiac events and bleeding events per 100-second increase in activated clotting time.

```
model
{
   for (i in 1:n.studies) {
      cases[i] ~ dbin(p[i],n[i])        #  likelihood function for data for each study
     logit(p[i]) <- z[i]                 #  logit transform
      z[i] ~ dnorm(mu[i],tau)           #  logit of probabilities follow normal distribution
    mu[i] <- alpha + beta*act[i]/100     # meta regression per 100 seconds of activated clotting
                                            time
        }
      alpha ~ dnorm(0, 0.01)   #  prior for intercept
      beta ~ dnorm(0, 0.01)   #  prior for  slope
      sigma ~   dunif(0.001, 4)   # prior distribution for sigma
       tau <-  1/(sigma*sigma)        #  convert standard deviation to precision
        }

# Inits
list(alpha = 0, beta = 0, sigma = 1)

# Data
list(n.studies=x, act =c(x), # number of study arms and their respective values of peak activated
                                clotting time
cases =c(x), n =c(x)) # number of major adverse cardiac events or bleeding events and the total
                            number of patients per study arm
```

ii) Below is the Bayesian meta-regression WinBUGS program providing the predicted probability of major adverse cardiac events and bleeding events for a peak activated clotting time of 200 and 300 seconds.

```
model
{
   for (i in 1:n.studies) {
      cases[i] ~ dbin(p[i],n[i])        #  likelihood function for data for each study
     logit(p[i]) <- z[i]                 #  logit transform
      z[i] ~ dnorm(mu[i],tau)           #  logit of probabilities follow normal distribution
    mu[i] <- alpha + beta*act[i]/100     # meta regression per 100 seconds of activated clotting
                                            time
        }
      alpha ~ dnorm(0, 0.001)   #  prior for intercept
      beta ~ dnorm(0, 0.001)   #  prior for  slope
      sigma ~   dunif(0.001, 4)   # prior distribution for sigma
       tau <-  1/(sigma*sigma)        #  convert standard deviation to precision

# prediction for activated clotting time = 200 seconds
p200 <-exp(alpha + beta*2)/(1+ exp(alpha + beta*2))

# prediction for activated clotting time = 300 seconds
p300 <-exp(alpha + beta*3)/(1+ exp(alpha + beta*3))
        }

# Inits
(alpha = 0, beta = 0, sigma = 1)

# Data
list(n.studies=x, act =c(x), # number of study arms and their respective values of peak activated
                                clotting time
cases =c(x), n =c(x)) # number of major adverse cardiac events or bleeding events and the total
                                number of patients per study arm
```

APPENDIX C: TABLE OF THE ASSESSMENT OF RISK OF BIAS ON THE COCHRANE RISK-OF-BIAS TOOL

TABLE A1. Assessment of risk of bias based on the Cochrane Risk-of-Bias Tool[a]

RCT	Study arm	*N*	Peak ACT[b] (sec)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
UFH without GPI										
CIAO 2008 [19]	UFH	350	201[c]	Unclear	Low	Low	Low	Low	Low	Low
ESPRIT 2000 [20]	UFH	1024	263	Low	Low	Low	Low	Low	Low	Low
FUTURA/OASIS-8 2010 [21]	UFH (50 U/kg)	1024	273	Low	Low	Low	Low	Low	Low	Low
CREDO 2002 [22]	UFH	1053	281[c]	Low	Low	Low	Low	Low	Low	Low
FUTURA/OASIS-8 2010 [21]	UFH (85 U/kg)	1002	333	Low	Low	Low	Low	Low	Low	Low
EPISTENT 1998 [23]	UFH	809	346	Low	Low	Low	Low	Low	Low	Low
ADMIRAL 2001 [24]	UFH	151	346	Unclear	Unclear	Low	Low	Low	Low	Low
Xiang 2013 [25]	UFH	108	460[c]	High	High	High	High	High	Low	Low
UFH with GPI										
TEAM 2002 [26]	UFH + tirofiban	56	248[c]	Unclear	Low	Low	Unclear	Low	Low	Low
TEAM 2002 [26]	UFH + eptifibatide	61	256[c]	Unclear	Low	Low	Unclear	Low	Low	Low
TEAM 2002 [26]	UFH + abciximab	63	261[c]	Unclear	Low	Low	Unclear	Low	Low	Low
HORIZONS-AMI 2008 [27]	UFH + abciximab/ eptifibatide	1802	264	Low	Low	High	Low	Low	Low	Low
Deshpande 2012 [28]	UFH + tirofiban	52	264[c]	Unclear	High	High	High	Low	Low	Low
ESPRIT 2000 [20]	UFH + eptifibatide	1040	273	Low	Low	Low	Low	Low	Low	Low
TARGET 2001 [29]	UFH + tirofiban	2398	281	Low	Low	Low	Low	Low	Low	Low
TARGET 2001 [29]	UFH + abciximab	2411	283	Low	Low	Low	Low	Low	Low	Low
ACTION 2005 [30]	UFH + eptifibatide/ tirofiban	100	307[c]	Unclear	Unclear	High	Low	Low	Low	Low
EPISTENT 1998 [23]	UFH + abciximab	794	314	Low	Low	Low	Low	Low	Low	Low
ADMIRAL 2001 [24]	UFH + abciximab	149	316	Unclear	Unclear	Low	Low	Low	Low	Low
REPLACE-2 2003 [31]	UFH + abciximab/ eptifibatide	3008	317	Low	Low	Low	Low	Low	Low	Low

[a]Assessments presented in terms of risk of bias associated with each item.
[b]Median peak ACT measured during PCI.
[c]Mean.
GPI, glycoprotein IIb/IIIa inhibitor; *N*, sample size; RCT, randomized controlled trial; U, units; UFH, unfractionated heparin.

APPENDIX D: SCATTERPLOTS OF ADVERSE CLINICAL EVENTS AND ACTIVATED CLOTTING TIME (ACT) AT 30 DAYS FOR INDIVIDUAL STUDY ARMS WITHOUT AND WITH GLYCOPROTEIN IIB/IIIA INHIBITORS (GPI)

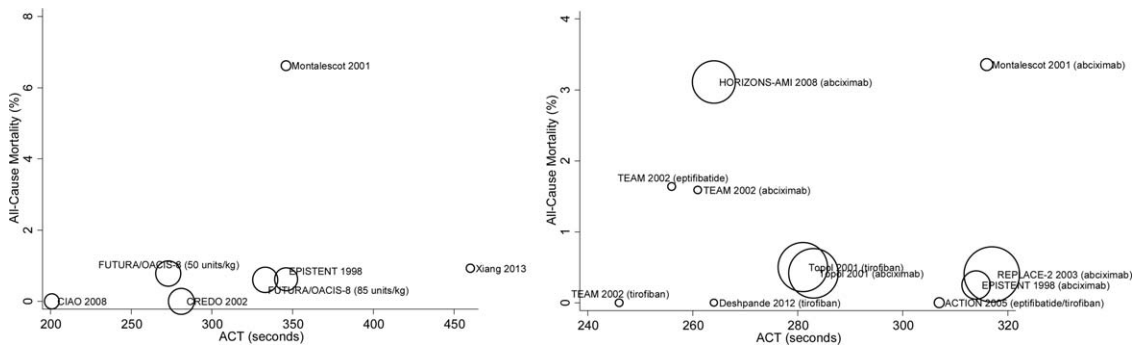

Fig. A1. Proportion of all-cause mortality versus ACT at 30 days for individual study arms without GPI.

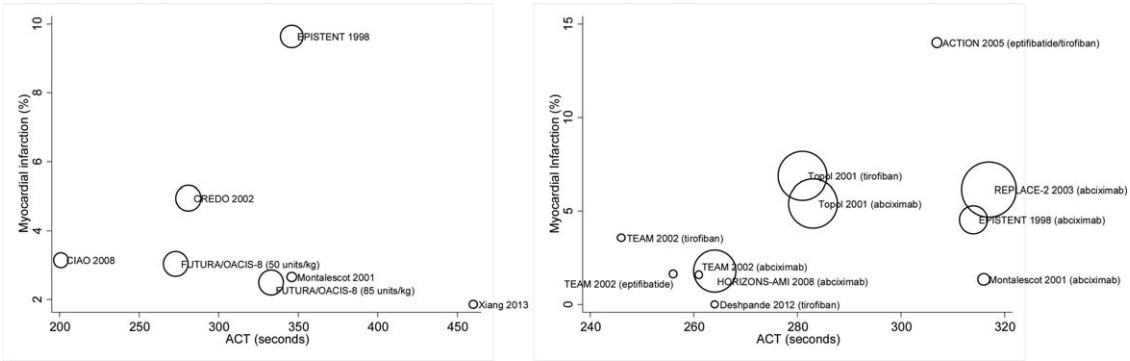

Fig. A2. Proportion of myocardial infarction versus ACT at 30 days for individual study arms without GPI.

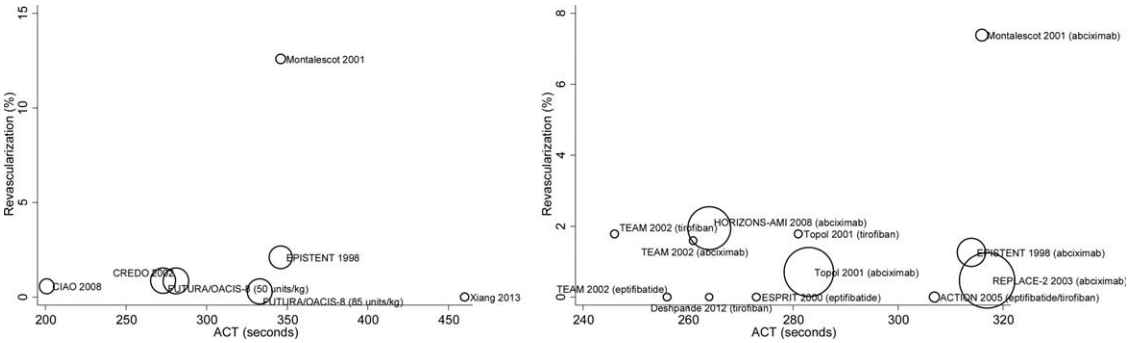

Fig. A3. Proportion of revascularization versus ACT at 30 days for individual study arms without GPI.

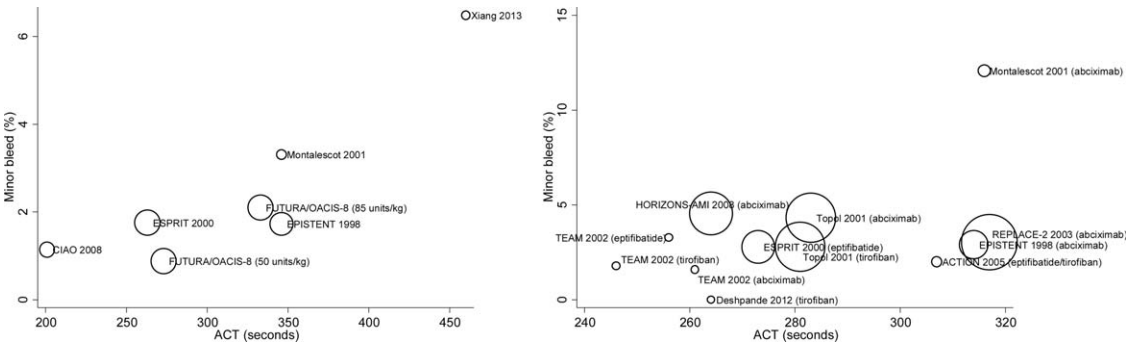

Fig. A4. Proportion of minor bleeding events versus ACT at 30 days for individual study arms without GPI.