Individual Patient Data Pooled Analysis of Randomized Trials of Bivalirudin Versus Heparin in Acute Myocardial Infarction: Rationale and Methodology

Brief title: Bivalirudin Trials Pooled Database

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ABSTRACT

Background: Individual randomized controlled trials (RCTs) of periprocedural anticoagulation with bivalirudin versus heparin during percutaneous coronary intervention (PCI) have reported conflicting results. Study-level meta-analyses lack granularity to adjust for confounders, explore heterogeneity, or identify subgroups that may particularly benefit or be harmed.

Objectives: To overcome these limitations, we sought to develop an individual patient-data pooled database of RCTs comparing bivalirudin versus heparin.

Methods: We conducted a systematic review to identify RCTs in which ≥1000 patients with acute myocardial infarction (AMI) undergoing PCI were randomized to bivalirudin versus heparin.

Results: From 738 identified studies, 8 RCTs met the pre-specified criteria. The principal investigators of each study agreed to provide patient-level data. The data were pooled and checked for accuracy against trial publications, with discrepancies addressed by consulting with the trialists. Consensus-based definitions were created to resolve differing antithrombotic, procedural, and outcome definitions. The project required 3.5 years to complete, and the final database includes 27,409 patients (13,346 randomized to bivalirudin and 14,063 randomized to heparin).

Conclusions: We have created a large individual-patient database of bivalirudin versus heparin RCTs in patients with AMI undergoing PCI. This endeavor may help identify the optimal periprocedural anticoagulation regimen for patient groups with different relative risks of adverse ischemic versus bleeding events, including those with ST-segment and non–ST-segment elevation MI, radial versus femoral access, use of a prolonged bivalirudin infusion or

glycoprotein inhibitors, and others. Adherence to standardized techniques and rigorous validation processes should increase confidence in the accuracy and robustness of the results.

Keywords: bivalirudin, heparin, pooled analysis, percutaneous coronary intervention, acute myocardial infarction

INTRODUCTION

Optimal periprocedural anticoagulation is fundamental for patients undergoing percutaneous coronary intervention (PCI).[1] Heparin derivatives (predominantly unfractionated heparin) are the dominant agents used for periprocedural anticoagulation and have been successfully used for decades; however, use of heparin is hampered by its indirect mechanism of action (activation of anti-thrombin), unpredictable pharmacodynamics, non-specific protein binding, and paradoxical platelet activation, which can result in either under- or over-anticoagulation with ischemic or hemorrhagic complications or heparin-induced thrombocytopenia.[2]

Bivalirudin, an intravenous direct thrombin inhibitor with intrinsic antiplatelet activity, has been under investigation for use in PCI for the past 2 decades. Initial trials suggested a lower risk of bleeding with bivalirudin-based compared with heparin-based regimens, and some studies even suggested reduced rates of cardiovascular and all-cause mortality.[3,4] These studies led to widespread adoption of bivalirudin, which was—for a while—the most frequently used periprocedural anticoagulant for PCI in the United States[5]; however, an increased rate of acute (<24 hour) stent thrombosis with bivalirudin (likely due to its short-half-life when abruptly discontinued after the procedure)was observed and raised concerns.[3,6,7] Attempts at overcoming this risk with more potent antiplatelet agents offset its bleeding advantage.[8] Some trials have suggested that acute stent thrombosis may be reduced with a prolonged post-PCI bivalirudin infusion, although there is uncertainty as to the optimal infusion dose and duration.[9-11] The differential use of planned or bailout use of glycoprotein IIb/IIIa inhibitors (GPIs) in the randomized arms in many trials has made a comparison between heparin and bivalirudin difficult. In addition, whether these risks and benefits are specific to patients with ST-segment

elevation myocardial infarction (STEMI) versus non-STEMI (NSTEMI), or to those undergoing PCI with radial versus femoral vascular access is unclear.

To explore these issues, several study-level meta-analyses have been performed, reporting variable results.[4,12-14] Such studies, while relatively easy to conduct using widely available statistical software packages, cannot provide in-depth assessment in subgroups, adequately account for heterogeneity of findings across the studies, adjust for confounders, or directly explore time-related effects (Table 1). In contrast, pooling individual patient-level data (IPD) provides the capability for more accurate assessment of the exposure and outcome variables (including multivariable adjustment for confounders), examination of the temporal relationships of therapies, and identification of specific patient subgroups in whom a more favorable risk-benefit profile may be identified.[4,15,16] Such efforts, however, are substantially more complex, time consuming, and resource intensive.

We herein describe the methodology and process of the development of a large pooled database of IPD from RCTs of patients with acute myocardial infarction (AMI) undergoing PCI who were allocated to receive a bivalirudin-based regimen versus a heparin-based regimen.

METHODS

Search strategy. This study was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (PRISMA-IPD) statement[17] and has been registered at the International prospective register of systematic reviews (PROSPERO; https://www.crd.york.ac.uk/prospero/; CRD42019132715). We searched MEDLINE with PubMed interface to identify RCTs that compared the use of bivalirudin-based versus heparin-based regimens in patients with AMI who underwent PCI (broad search query:

("bivalirudin" [Supplementary Concept] OR bivalirudin*[TI] OR hirulog*[TI]) AND (random* OR control* OR trial*)). We also reviewed the existing study-level meta-analyses and reviewed their reference lists to source any additional potential RCTs (date of last search: August 17, 2018).

Study inclusion and exclusion criteria. We assessed the relevance of the studies based on the patients, intervention, control, and outcomes (PICO) principles. To be considered for inclusion, the trials were required to be an RCT of patients with AMI undergoing PCI allocated to bivalirudin-based versus a heparin-based anticoagulant regimen. Prior studies have shown that the accuracy of estimates provided in small randomized trials is uncertain[18] and may have biased estimates of treatment effect. Further, merging numerous small trials at the patient level will create practical challenges for identifying common definitions for the pooled data. We therefore included only RCTs that enrolled at least 1,000 patients with AMI (either NSTEMI or STEMI).

Patient inclusion and exclusion criteria. Among the identified RCTs, we only included patients with AMI meeting at least one of the following criteria: (i) coded by the original trialists as STEMI; (ii) coded by the original trialists as unstable angina or NSTEMI with at least one set of positive pre-procedural cardiac biomarkers in the database; or (iii) coded by the original trialists as NSTEMI along with explicit trial-level protocol processes requiring positive cardiac biomarkers for NSTEMI designation. We excluded patients with stable angina as well as those with biomarker-negative unstable angina (i.e., in the absence of NSTEMI or STEMI).

We included patients randomized to heparin (unfractionated or low molecular weight) with either planned or unplanned (bailout) use of glycoprotein IIb/IIIa inhibitors and patients randomized to bivalirudin with unplanned GPI use. We excluded patients randomized to

bivalirudin plus planned use of GPI since this regimen was never recommended for use in practice nor widely studied. Further, we excluded the patients who did not have a PCI attempt.

Data elements. We collected patient data on demographics, baseline medical history (including diabetes, smoking status, hypertension, dyslipidemia, others), vital signs, laboratory tests (hemoglobin, platelet count, and serum creatinine), procedural information (access site, clinical presentation [NSTEMI, STEMI]), PCI characteristics (including the vessel treated, stent type, and baseline and final Thrombolysis in Myocardial Infarction [TIMI] flow), peri-procedural medications (specifically detailed timing and dosage data for bivalirudin and heparin [pre-, during, and post-PCI]), aspirin, P2Y12 inhibitors, and GPIs), discharge medications, and clinical outcomes (see below). The most essential data elements were pre-specified for inclusion (e.g., clinical presentation, access site, medication regimens, etc.), but all data that were common to the majority of the included studies were collected.

Outcome measures. The main outcome measures are all-cause death, cardiac death, MI, stent thrombosis, ischemia-driven or clinically-driven target-vessel revascularization, stroke, and major adverse cardiovascular and cerebrovascular events (MACCE) events. We defined MACCE as the 30-day composite of all-cause death, MI, stroke, or ischemia/clinically-driven target vessel revascularization.

The definitions of death, cardiac death, MI, stent thrombosis, stroke, and repeat revascularization were sufficiently similar across studies to be pooled. Small differences in the definitions of these endpoints between studies are footnoted. Stent thrombosis was defined according to the Academic Research Consortium (ARC) definite or probable criteria, and further categorized as acute (<24 hours post-PCI), subacute (between day 1 and day 30 post-PCI), and late (after day 30).[19] With respect to bleeding outcomes, no single bleeding classification was

common to all studies. The TIMI and Bleeding Academic Research Consortium (BARC)[20] classifications were most commonly used. Both TIMI major or minor and BARC major bleeding events have been strongly associated with subsequent mortality with similar prognostic correlation,[21] and one or both types were reported in all studies (with TIMI bleeding more commonly available). In the pooled analysis, we therefore *a priori* defined "serious bleeding" as the presence of either TIMI major or minor bleeding (if available), or, alternatively, BARC type 3 or 5 bleeding.

The longest follow-up data available were requested for all outcome measures. Whether outcomes were adjudicated by an independent clinical events committee (CEC) or investigator-reported were noted. CEC-adjudicated data took preference whenever available.

Primary and secondary endpoints. Prior to any analyses the primary efficacy endpoint in the pooled cohort has been pre-specified as the 30-day rate of all-cause mortality, and the primary safety endpoint is the 30-day rate of serious bleeding (as defined above). Secondary endpoints include the rates of cardiac death, MI, stent thrombosis, stroke, repeat revascularization, MACCE, bleeding, thrombocytopenia, and net adverse clinical events (NACE; a composite of MACCE or serious bleeding) at 30 days and 1 year.

Process of data acquisition. The principal investigator of the pooling effort (G.W.S.) contacted the principal investigator of each trial that fulfilled the inclusion/exclusion criteria to solicit their participation. The data received from the studies that met the criteria were stored and validated at the Data Coordinating Center (DCC) of the Cardiovascular Research Foundation (CRF; New York, NY, United States).

Data audit and cleaning. A centralized database was established and validated as follows: Biostatisticians and clinicians from the CRF DCC created table shells based on the case

report forms from each included trial. Raw data from each of the included trials was then transformed into clean patient-level analysis datasets using standardized variable names and data attributes. Tables were then constructed using the actual pooled analysis database. These tables summarizing the individual RCT data were first audited and revised by the DCC for erroneous entries and programming errors. After correction, the tables were delivered to a team of 5 clinician investigators (B.B., S.C., G.M., B.R., G.W.S.), who reviewed the data for clinical meaningfulness, cross-checked the tables with each trial's primary publications, requested additional clinically-relevant data elements from the principal investigator of each trial, and performed additional edit checks. Regular group meetings with participation from the programming and biostatistics team (T.M., A.C., Y.L., Z.Z., M.L., Y.Z.), publications office (D.P.F.), and the clinical investigators (B.B., S.C., G.M., B.R.) under the supervision of G.W.S. took place. Additional contacts were required between the DCC and the principal investigator of each of the included trials numerous times for additional data or for methodological or data clarifications. The above cleaning algorithm was iterated until the raw data included all required elements and the outcomes conformed to the individual primary publications of the included trials. In some cases, small discrepancies were present for explainable reasons (e.g. database updated after the primary report). A publications committee (consisting of the principal investigators from each trial) will consider requests for analyses from outside investigators, which, if approved, will be run at CRF.

Statistical methodology. Continuous variables will be presented as mean and standard deviation (or median with 25th and 75th percentiles) and compared by trial-adjusted analysis of variance (ANOVA) models (or Kruskal-Wallis test for non-normally distributed data). Categorical variables will be reported as percentages and frequencies and compared using a trial-

stratified Cochran-Mantel-Haenszel test. Time-to-event variables will be presented as cumulative event rates estimated by Kaplan-Meier methodology and number of events and compared using a trial-stratified log-rank test.

The primary study objective is to determine the optimal anticoagulant to be used during PCI in patients with AMI. For logistical or study design-related reasons, several of the trials randomized patients in the emergency room, and not all patients were biomarker positive or underwent PCI. However, in the current era, the decision to use heparin vs. bivalirudin for PCI in AMI is usually made in the catheterization laboratory, just before the intervention, and once this decision is made, a PCI attempt always follows. As such, the primary study cohort will be a modified intention-to-treat population consisting of all AMI patients in whom PCI was attempted. AMI patients in whom PCI was not attempted will thus be excluded from the primary analysis. Post-randomization exclusions may introduce differences between groups. To address these issues, we will do the following: (1) The principal analyses will be covariate-adjusted, using a pre-specified set of baseline variables; (2) We will also compare the patients in the main analysis cohort (N=27,407) versus those excluded post-randomization (N=6,510); (3) As a sensitivity analysis, we will report the main analyses in the original ITT populations, recognizing that the inclusion of patients not undergoing PCI will bias the analysis to the null.

Primary analysis will be performed using a Cox regression model (one-stage approach) adjusting for study as a random-effect (frailty term). The frailty term will be assumed to follow a lognormal distribution. Data will be summarized by hazard ratios (HR) with 95% CI. These models have been shown to be robust in cases where the comparison groups are imbalanced between trials.[22] The pre-specified variables for adjustment in the primary analysis include: age, sex, weight, recent smoking, history of diabetes, hypertension, hyperlipidemia, prior myocardial

infarction, radial vs femoral access, presentation with NSTEMI vs STEMI, baseline hemoglobin, baseline calculated creatinine clearance, US vs. EU vs. other enrolling sites, use of pre-randomization heparin, and pre-treatment with no P2Y12 inhibitor vs. clopidogrel vs. prasugrel/ticagrelor, all adjusted by study as a random effect. In addition, multivariable analyses will be performed to adjust for baseline, procedural, and adjunct medication use variables (including adjunct antithrombotic agents, which may have been differentially used across the trial arms across the trials). Further, a study-level meta-analysis (two-stage approach) will be examined using both a Mantel–Haenszel fixed effect model and a DerSimonian and Laird random effect model. Data will be summarized by relative risks (RR) with 95% CI. Heterogeneity between trials will be evaluated with Cochran's Q test and the I2 statistic (with <25%, 25% - 50%, and >50% indicating low, moderate, and high heterogeneity, respectively).

Differences in outcomes across trials and the validity of the Cox proportional hazards model will be tested. Study heterogeneity will be assessed by the Breslow-Day test. The proportionality assumption will be assessed visually with plots of the Schoenfeld residuals versus the log of time for each predictor and formal testing will be performed using the method of Grambsch and Therneau.[23] If the proportional hazards assumption is violated, logistic regression models will be used including trial as a random effect.

Outcomes will also be analyzed across subgroups according to demographic, clinical, and procedural variables that predict high ischemic and bleeding risk. Specifically, the subgroups of greatest interest are: (i) Presentation with STEMI versus NSTEMI); (ii) use of radial versus femoral vascular access; (iii) the use, dose, and duration of a bivalirudin post-PCI infusion; (iv) the planned versus unplanned use of glycoprotein IIb/IIIa inhibitors in heparin-treated patients; (v) the dose and timing of heparin administration; (vi) the adjunctive use of clopidogrel versus

the more potent P2Y12 receptor inhibitors ticagrelor or prasugrel; (vii) use of oral anticoagulants at discharge; (viii) men versus women; (ix) older adults (aged >65 years) versus others, and other demographic, clinical, and procedural variables including but not limited to age, sex, diabetes, anemia, renal function, and stent type (drug-eluting versus bare metal). We will perform multiplicative interaction testing to examine whether treatment-related differences in relative risk exist across the clinical subgroups. A p value of 0.05 will be used for the threshold of significance for these tests.

Sensitivity analysis for missing data will be performed using multiple imputation methods.[24] All statistical tests will be 2-sided, and a p value of <0.05 will be considered statistically significant unless otherwise specified. Finally, in addition to the principal analyses of bivalirudin versus heparin safety and effectiveness, the database may support additional analyses not necessarily related to procedural anticoagulation.

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STUDY SCREENING AND DATABASE CHARACTERISTICS

Study-level screening and inclusion. From 738 identified publications via the PubMed search, 29 were further considered for inclusion (Table 2).[3,6-8,10,25-48] Finally, 8 trials met eligibility criteria for the pooled analysis systematic review (Figure 1).[3,6,7,10,25-28] G.W.S. was the principal investigator of 2 eligible studies that were available for IPD analysis.[3,25] The principal investigators of the other 6 trials[6,7,10,26-28] were contacted for participation. Each investigator

agreed and transferred de-identified IPD to the CRF DCC (Figure 2 and Table 3). The study protocol of each original trial had been approved by appropriate ethics committees at each participating center, and all enrolled patients had provided informed consent.

Patient-level screening and inclusion. The 8 included randomized a total of 38,565 patients. A total of 11,156 patients were excluded from the pooled database, including 4,646 patients who were randomized to bivalirudin plus planned use of glycoprotein inhibitors, 2,471 with biomarker-negative unstable angina, and 4,039 patients who did not undergoing a PCI attempt (Figure 3).

Basic characteristics of the final pooled cohort. The final pooled IPD cohort included 27,409 patients (13,346 randomized to bivalirudin and 14,063 randomized to heparin). The minimum and maximum follow-up duration in the pooled database ranged from 180 to 365 days. Consensus-based definitions for the main outcomes in the pooled database are provided in Table 4. Most of the outcomes among the included trials were adjudicated (Table 5). Table 6 summarizes the Cochrane risk of bias among the included trials.

The project began in December 2015. The validated IPD-pooled database is nearly complete and is expected to be locked in June 2019, after which the analyses will commence.

DISCUSSION

Effective periprocedural anticoagulation for patients undergoing PCI in AMI is required to suppress ischemic complications from the thrombotic coronary syndrome as well as from the interventional procedure itself. An inherent risk of hemorrhagic complications is introduced with use of all such agents. The optimal anticoagulation regimen would most favorably balance these competing risks, a calculus which may depend on individual patient and procedural

characteristics. Despite numerous large-scale RCTs of bivalirudin versus a heparin during PCI in AMI, the optimal anticoagulation regimen remains uncertain, and there is likely no "one size fits all" solution. Specifically, the relative risk: benefit profile of bivalirudin versus heparin may depend on clinical factors such as age, sex, renal function, and the presence of anemia; presentation with NSTEMI versus STEMI, which are characterized by varying patient risk comorbidities and thrombotic potential; procedural factors such as use of femoral or radial access; the dose of heparin used; adjunct medication use such as pre-randomization heparin use, unplanned versus planned GPI, and P2Y12 receptor inhibitor potency; and the use of, dosing, and duration of a bivalirudin post-PCI infusion. Even though numerous study-level systematic reviews and meta-analyses have been published,[4,12,13,49] none has clearly identified subgroups that may particularly benefit from a bivalirudin-based or a heparin-based regimen. Such studies are also unable to account for heterogeneity in endpoint measures, adjust for confounders, or examine the temporal relationships in outcomes. Although an IPD cannot overcome limitations such as treatment differences across trials over time (such as changes in stent technologies or other ancillary therapies), an IPD pooled analysis is the most comprehensive way to explore the comparative effectiveness of these treatment strategies, overcoming many of the limitations inherent in study-level meta-analyses.[50-52] We have therefore endeavored to create a large pooled IPD database of trials of bivalirudin-based versus heparin-based procedural anticoagulation regimens in patients with AMI undergoing PCI.

Recent reviews have emphasized the advantages of IPD pooled analyses compared with standard study-level data meta-analyses.[15] Adherence to PRISMA-IPD standardized techniques for pooling the data,[17] pre-specification of a statistical analysis plan and study registration (PROSPERO), and application of rigorous validation processes should increase confidence in the

accuracy and robustness of the results; however, despite the advantages of IPD pooled analyses, such efforts are inherently more complex, time-consuming and resource intensive. Given the exacting requirements and meticulousness of the processes described herein, the present project took 3.5 years to finalize and validate the database, admittedly much longer than anticipated. Serious challenges were confronted in comprehensive data collection, clarifying data dictionaries and resolving varying study definitions. Some desired data elements were (unfortunately) not collected in all the trials, and some collected data elements had not yet been cleaned, requiring a coordinated effort with each individual trial DCC. Substantial time was also required to reconcile the data provided against that reported in prior publications. Most such discrepancies were minor, but all required investigation and correction or reconciliation. Although a 3.5-year process is not desirable, we believe that a lesser effort would have permitted inconsistencies and errors in the database which would have eroded confidence in the initiative and reduced the precision and accuracy of the results. Our learned experience from the process of pooling these trials may be helpful to other investigators planning large-scale IPD meta-analyses, enhancing the efficiency and validity of such efforts (Figure 4).

In conclusion, this systematic review and IPD pooled meta-analysis will help provide better evidence for the safety and efficacy of bivalirudin-based versus heparin-based procedural anticoagulation in patients with AMI undergoing PCI. It is our hope that these results (expected in late 2019 or early 2020) will impact clinical decision-making, improve patient outcomes, inform societal guidelines, and generate additional hypotheses for subsequent comparative effectiveness research.

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FIGURE LEGENDS

Figure 1. Flow Diagram of Study Selection

Figure 2. Graphical Abstract of the Included Trials

GPI = glycoprotein IIb/IIIa inhibitor.

Figure 3. Flow Diagram of Patient Selection from the Included Studies

NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Figure 4. Process of the Design of the Pooled Analysis Database

AMI = acute myocardial infarction; CRF = Cardiovascular Research Foundation; PI = principal investigator; RCT = randomized controlled trial.

Table 1. Advantages and Limitations of Aggregate Results Meta-analysis and Individual Patient Data Pooled Analysis

	Average-Effect Meta-analysis of RCTs	Individual Patient Data Pooled Analysis of RCTs
Advantages	• Requires less resources • Requires only summary data from each trial • May be done quickly • User-friendly statistical software packages are readily available • Analyses are straight-forward and standardized • All studies meeting the eligibility criteria can be included	• Greater precision in statistical estimates and increased statistical power • Analysis populations can be defined in very specific terms (including specific patient subgroups) • Variable definitions can be standardized across trials • Subgroup analyses and interaction testing can be performed • Multivariable analyses can be performed to adjust for confounders • Permits time-to-event analysis, competing risk analysis, recurrent events analysis and other complex statistical examinations • Consistent with recent policies for clinical trial data sharing
Limitations	• Statistical estimation is crude • Inconsistent variable definitions and heterogeneity across trials cannot be resolved • Subgroup analyses cannot be performed • Temporal relationships in outcomes cannot be assessed • Cannot adjust for measured confounders in individual trials and pooled analysis	• Resource intensive • Requires a team of statisticians and investigators to acquire, compile, and validate the data • Can only include studies from which the principal investigators and sponsors are willing to share the data • Cannot account for unmeasured confounders or resolve all differences between trials

RCT = randomized controlled trial.

Table 2. List of Screened Trials

Study	Included	Year of Publication	Number of Patients	Comment
ACUITY[25]	Yes	2006	13,819	Patients with ACS
MATRIX[10]	Yes	2015	7,213	Patients with ACS
REPLACE 2[33]	No	2003	6,010	Patients undergoing elective or urgent PCI (note: <1000 patients with myocardial infarction)
VALIDATE-SWEDEHEART[28]	Yes	2017	6,006	Patients with STEMI or NSTEMI
ISAR-REACT 3[37]	No	2008	4,570	Patients with stable or unstable angina and negative biomarkers
BAS[29]	No	1995	4,098	Patients with unstable or post-infarction angina (note: only 704 patients had STEMI or NSTEMI)
HORIZONS-AMI[3]	Yes	2008	3,602	Patients with STEMI
EUROMAX[7]	Yes	2013	2,218	Patients with STEMI
BRIGHT[27]	Yes	2015	2,194	Patients with STEMI or NSTEMI
HEAT-PPCI[6]	Yes	2014	1,829	Patients planned for primary PCI
ISAR-REACT 4[26]	Yes	2011	1,721	Patients with NSTEMI
REPLACE 1[34]	No	2004	1,056	Patients undergoing elective or urgent PCI (<1000 with myocardial infarction)
PROTECT-TIMI-30[36]	No	2006	857	Patients with ACS (nearly half with biomarker- negative unstable angina)
ARNO[39]	No	2010	850	Patients with stable or unstable coronary disease undergoing PCI
NAPLES III[47]	No	2015	837	Patients undergoing elective PCI
BRAVE 4[8]	No	2014	548	Patients with STEMI (the trial was stopped prematurely due to slow recruitment)
HERO[30]	No	1997	412	Patients with STEMI
ARMYDA-7-BIVALVE[42]	No	2012	401	Patients undergoing PCI (only 47 having acute myocardial infarction)
TENACITY[41]	No	2011	383	Patients undergoing PCI (the trial was terminated prematurely by the sponsor)
NAPLES[38]	No	2009	335	Patients with diabetes undergoing elective PCI
Kuchulakanti et al.[35]	No	2005	294	Patients with in-stent restenosis
CACHET[31]	No	2002	268	Patients undergoing elective PCI
PROBI-VIRI 2[40]	No	2011	264	Patients undergoing primary PCI
He et al.[48]	No	2016	260	Patients with STEMI (<1000)
Xiang et al.[45]	No	2013	218	Patients undergoing elective PCI
TIMI-8[32]	No	2002	133	Patients with unstable angina or NSTEMI (the trial was terminated prematurely by the sponsor)
Deshpande et al.[43]	No	2012	101	Patients undergoing elective PCI
SWITCH III[44]	No	2013	100	Patients with non-ST-elevation acute coronary syndromes undergoing PCI
Feldman et al.[46]	No	2014	100	Patients undergoing PCI (only 32 with acute myocardial infarction)

ACS = acute coronary syndromes; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Table 3. Basic Characteristics of the Included Studies

Study	Patient Population	Randomized Treatment*	Timing of Randomization	Primary Endpoint	Maximum Follow-up†
ACUITY	Acute coronary syndromes‡	4,603 patients assigned to heparin (unfractionated 60 U/kg bolus [ACT goal of 200-250 sec] or enoxaparin) plus GPI, 4,604 patients assigned to bivalirudin (bolus of 0.1 mg/kg pre-procedurally and infusion of 0.25mg/kg/h pre-procedurally, followed by pre-PCI bolus of 0.5mg/kg and an infusion rate of 1.75 mg/kg/h during PCI) plus GPI, 4612 patients assigned to bivalirudin (bolus of 0.1 mg/kg pre-procedurally and infusion of 0.25mg/kg/h pre-procedurally, followed by pre-PCI bolus of 0.5mg/kg and an infusion rate of 1.75 mg/kg/h during PCI) alone during PCI	Within 72 hours prior to angiography	Ischemic endpoint (composite of death, MI, or unplanned revascularization for ischemia), major bleeding, and net adverse clinical events (composite of ischemia or major bleeding)	365 days
HORIZONS-AMI	STEMI	1,802 patients randomized to unfractionated heparin (60 U/kg bolus, ACT goal of 200-250 sec) plus GPI, 1,800 patients randomized to bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h during PCI) alone	In the emergency room at the PCI hospital	Major bleeding and net adverse clinical events (composite of major bleeding or major adverse cardiovascular events, including death, reinfarction, target-vessel revascularization for ischemia, or stroke)	365 days
ISAR-REACT 4	NSTEMI	861 patients randomized to unfractionated heparin (70 U/kg, no monitoring of ACT) plus GPI, 860 patients randomized to bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h during PCI) alone	After diagnostic catheterization and decision to proceed with PCI	Composite of death, large recurrent myocardial infarction, urgent target-vessel revascularization, or major bleeding within 30 days after randomization	360 days
EUROMAX	STEMI	1,116 patients randomized to unfractionated heparin (100 U/kg bolus), or enoxaparin, with optional GPI (heparin bolus dose was 60 U/kg if GPI given), 1,102 patients randomized to bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h during PCI and 0.25 mg/kg/h [or higher if needed] for at least for 4 hours post-PCI)	In the ambulance or the non-PCI hospital	Composite of death or major bleeding not associated with coronary artery bypass grafting	365 days
BRIGHT	NSTEMI or STEMI	729 patients randomized to unfractionated heparin alone (100 U/kg bolus), 730 patients randomized to unfractionated heparin (60 U/kg bolus) plus GPI, 735 patients randomized to bivalirudin alone (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h during PCI and continued for 30 minutes or up to 4 hours after PCI; after which reduced-dose infusion of 0.2 mg/kg/h was allowed for up to 20 hours)	In the cath lab, prior to angiography	Net adverse clinical events at 30 days, a composite of all-cause death, reinfarction, ischemia-driven target vessel revascularization, stroke, or any BARC bleeding	365 days

HEAT-PPCI	Patients undergoing primary percutaneous intervention (STEMI)	914 patients randomized to unfractionated heparin (bolus of 70 U/kg, aiming for ACT >200 sec), 915 patients randomized to bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h during PCI; re-bolus of 0.3 mg/kg if ACT <225 sec)	In the cath lab, prior to completion of angiography	Composite of all-cause mortality, cerebrovascular accident, reinfarction, or unplanned target lesion revascularization	365 days
MATRIX	Acute coronary syndromes‡	3,603 patients randomized to unfractionated heparin, 3,610 patients randomized to bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h during PCI; bivalirudin-treated patients re-randomized to either post-PCI bivalirudin discontinuation continuation at PCI dose for up to 4 hours or at a reduced dose of 0.25 mg/kg for at least 6 hours)	For patients with STEMI, before angiography, for patients with NSTEMI, after diagnostic catheterization but prior to PCI	Major adverse cardiovascular events by 30 days (a composite of all-cause death, MI, or stroke), and net adverse clinical events (a composite of BARC 3 or BARC 5 bleeding or major adverse cardiovascular events)	365 days
VALIDATE-SWEDEHEART	NSTEMI or STEMI	3,002 patients randomized to unfractionated heparin (total dose of 70-100 U/kg), 3,004 patients randomized to bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h during PCI; post-procedural infusion of bivalirudin was strongly encouraged). Planned GPIs were not allowed.	After angiography but prior to PCI	Composite of death from any cause, MI, or major bleeding at 180 days	180 days

*If there were more randomizations per trial (ie, a factorial design), only the primary randomization related to the bivalirudin-based versus heparin-based regimen is summarized here; †only 2 trials had follow-up for >365 days (ACUITY for up to 395 days, and HORIZONS-AMI for up to 1095 days); we included follow-up of those trials only until 365 days in the pooled database for consistency; ‡in the individual patient-data analysis, only patients with NSTEMI or STEMI meeting the inclusion and exclusion criteria described in the text were included. ACS = acute coronary syndromes; ACT = activated clotting time, BARC = Bleeding Academic Research Consortium; GPI = glycoprotein IIb/IIIa inhibitor; MI = myocardial infarction; NSTE = non–ST-elevation; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Table 4. Outcome Definitions for the Pooled Database

Outcome	Definition
All-cause death	Reported death due to any cause
Cardiac death	Death due to cardiac causes, such as myocardial infarction, heart failure, arrhythmia*; deaths of undetermined cause are also considered cardiac death
Myocardial infarction	According to the trial-specific definitions (most consistent with the Third Universal Definition of MI†)
Stent thrombosis	Definite or probable according to the ARC criteria. Further classified as acute (within the first 24 hours post-PCI), subacute (between day 1 and 30), or late (after day 30)‡.
Revascularization	Ischemia-driven (or clinically-driven) target vessel revascularization§
Stroke	Acute ischemic or hemorrhagic stroke as defined in each trial (not including transient ischemic attack).
Major adverse cardiovascular and cerebrovascular events (MACCE)	A composite of all-cause death, myocardial infarction, stroke, or clinically-driven target vessel revascularization
Serious bleeding	TIMI minor or major bleeding (or if not available, BARC 3 or 5 bleeding)‖
Net adverse clinical events (NACE)	A composite of MACCE or serious bleeding

*VALIDATE-SWEDEHEART did not include cardiac death, but included data related to cardiovascular death. †BRIGHT, EUROMAX, VALIDATE-SWEDEHEART; ‡although ACUITY and HORIZONS-AMI were conducted prior to the development of the ARC consensus document, the definition of stent thrombosis in those trials conforms to the ARC definition. For the stent thrombosis outcome, there was variation between the trials as to whether stent thrombosis related was adjudicated for treated lesions (those stented in the index procedure as well as before or after; available in HORIZONS-AMI, EUROMAX, HEAT-PPCI, and VALIDATE-SWEDEHEART) versus only for lesions stenting during the index procedure (the rest of the trials); §EUROMAX adjudicated all ischemia-driven revascularization but not target vessel versus non-target vessel revascularization separately; ‖HEAT-PPCI and VAILDATE-SWEDEHEART adjudicated bleeding complications using the BARC scale. ARC = Academic Research Consortium; BARC = Bleeding Academic Research Consortium; TIMI = Thrombolysis in Myocardial Infarction.

Table 5. Status of Outcome Adjudication Among the Included Trials

Study	Death	Myocardial Infarction	Stent Thrombosis	Revascularization (Including TLR, TVR, and IDR)	Stroke	Serious Bleeding
ACUITY	Yes	Yes	Yes	Yes (ID-TVR)	No (site-reported)	Yes (TIMI)*
BRIGHT	Yes	Yes	Yes	Yes (ID-TVR)	Yes	Yes (TIMI)
EUROMAX	Yes	Yes	Yes	Yes (IDR)	Yes	Yes (TIMI)*
HEAT-PPCI	Yes	Yes	Yes	Yes (CD-TVR)	Yes	Yes (BARC)
HORIZONS-AMI	Yes	Yes	Yes	Yes (ID-TVR)	Yes	Yes (TIMI)
ISAR-REACT 4	Yes	Yes	Yes	Yes (ID-TVR)	Yes	Yes (TIMI)
MATRIX	Yes	Yes	Yes	Yes (ID-TVR)	Yes	Yes (TIMI)
VALIDATE-SWEDEHEART	Yes	Yes	Yes	No (registry-reported CD-TVR)	Yes	Yes (BARC)

BARC = Bleeding Academic Research Consortium; CD = clinically-driven; ID = ischemia-driven; TVR = target vessel revascularization. *Bleeding events in ACUITY and EUROMAX were adjudicated for 35 days.

Table 6. Risk of Bias Assessment for the Included Trials*

	Random Sequence Generation	Allocation Sequence Concealment	Blinding of Participants	Blinding of Personnel	Blinding Outcome Adjudication	Incomplete Outcome Data	Selective Reporting
ACUITY	+	+	–	–	+	–	–
BRIGHT	+	+	–	–	+	–	–
EUROMAX	+	+	–	–	+	–	–
HEAT-PPCI	+	+	–	–	+	–	–
HORIZONS-AMI	+	+	–	–	+	–	–
ISAR-REACT 4	+	+	+	+	+	–	–
MATRIX	+	+	–	–	+	–	–
VALIDATE-SWEDEHEART	+	+	–	–	+	–	–

Key: + = low risk of bias; – = high risk of bias.

*Unlike most of the existing average effect systematic reviews, the principal investigators of all the included trials were coauthors of the current systematic review and individual patient pooled analysis; therefore, there were no uncertain (yellow) cells in the risk of bias assessment.

Figure 1

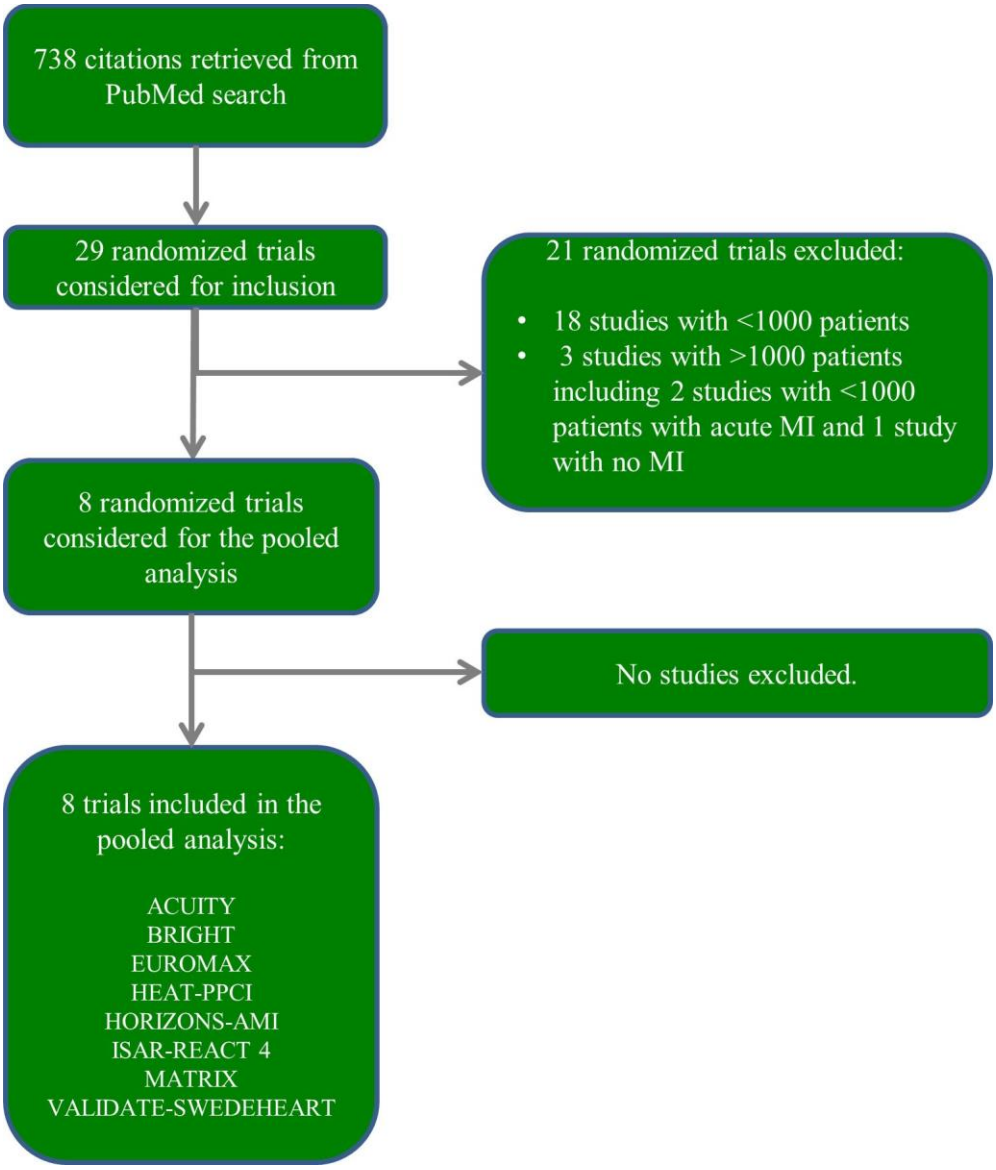

738 citations retrieved from PubMed search
29 randomized trials considered for inclusion
21 randomized trials excluded:
• 18 studies with <1000 patients
• 3 studies with >1000 patients including 2 studies with <1000 patients with acute MI and 1 study with no MI
8 randomized trials considered for the pooled analysis
No studies excluded.
8 trials included in the pooled analysis:
ACUITY
BRIGHT
EUROMAX
HEAT-PPCI
HORIZONS-AMI
ISAR-REACT 4
MATRIX
VALIDATE-SWEDEHEART

Figure 2

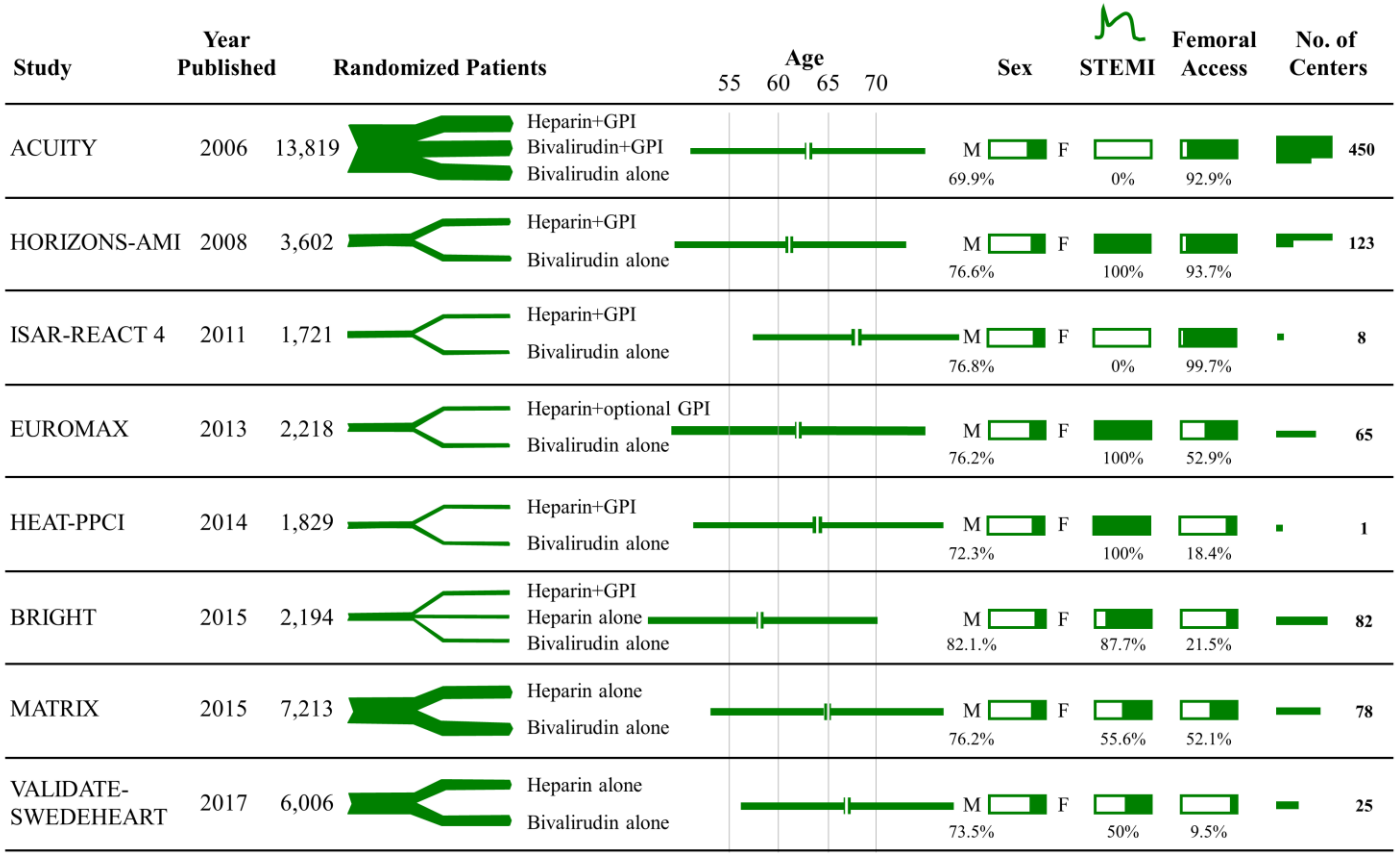

Study
Year Published
Randomized Patients
Age
55 60 65 70
Sex
STEMI
Femoral Access
No. of Centers
ACUITY 2006 13,819
Heparin+GPI
Bivalirudin+GPI
Bivalirudin alone
M F
69.9%
0%
92.9%
450
HORIZONS-AMI 2008 3,602
Heparin+GPI
Bivalirudin alone
M F
76.6%
100%
93.7%
123
ISAR-REACT 4 2011 1,721
Heparin+GPI
Bivalirudin alone
M F
76.8%
0%
99.7%
8
EUROMAX 2013 2,218
Heparin+optional GPI
Bivalirudin alone
M F
76.2%
100%
52.9%
65
HEAT-PPCI 2014 1,829
Heparin+GPI
Bivalirudin alone
M F
72.3%
100%
18.4%
1
BRIGHT 2015 2,194
Heparin+GPI
Heparin alone
Bivalirudin alone
M F
82.1%
87.7%
21.5%
82
MATRIX 2015 7,213
Heparin alone
Bivalirudin alone
M F
76.2%
55.6%
52.1%
78
VALIDATE-SWEDEHEART 2017 6,006
Heparin alone
Bivalirudin alone
M F
73.5%
50%
9.5%
25

Figure 3

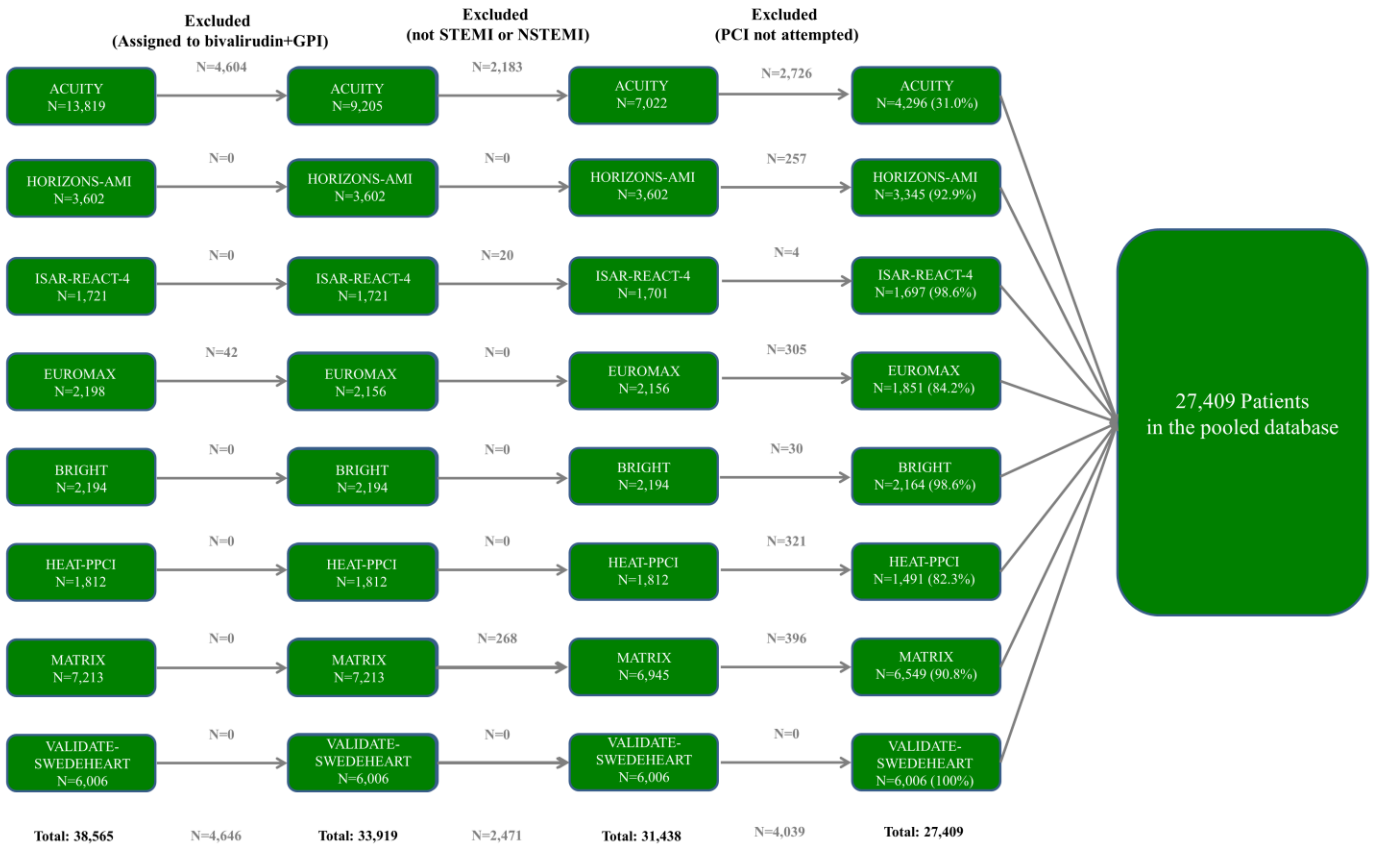
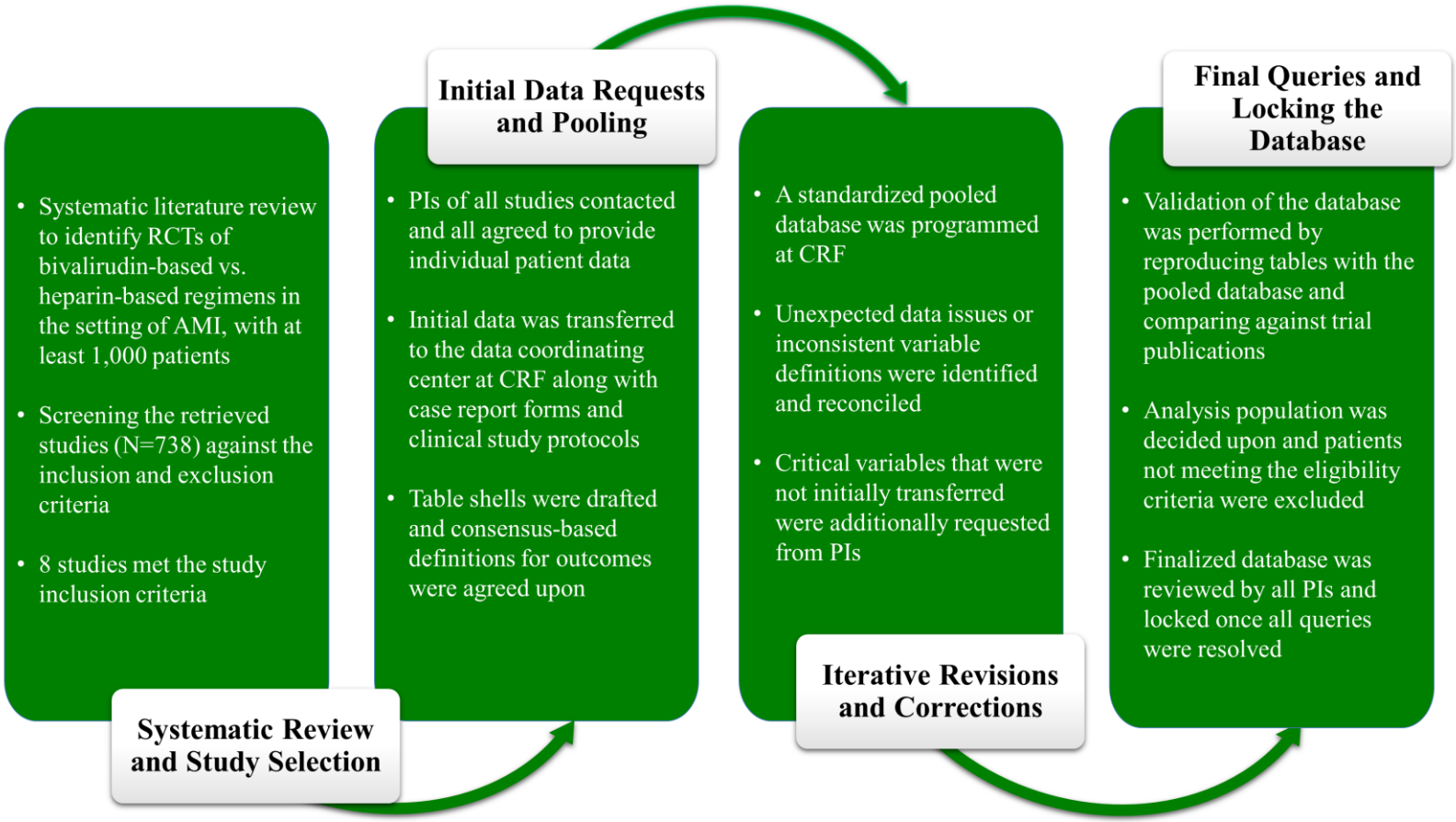

Excluded
(Assigned to bivalirudin+GPI)
Excluded
(not STEMI or NSTEMI)
Excluded
(PCI not attempted)
ACUITY N=13,819
N=4,604
ACUITY N=9,205
N=2,183
ACUITY N=7,022
N=2,726
ACUITY N=4,296 (31.0%)
HORIZONS-AMI N=3,602
N=0
HORIZONS-AMI N=3,602
N=0
HORIZONS-AMI N=3,602
N=257
HORIZONS-AMI N=3,345 (92.9%)
ISAR-REACT-4 N=1,721
N=0
ISAR-REACT-4 N=1,721
N=20
ISAR-REACT-4 N=1,701
N=4
ISAR-REACT-4 N=1,697 (98.6%)
EUROMAX N=2,198
N=42
EUROMAX N=2,156
N=0
EUROMAX N=2,156
N=305
EUROMAX N=1,851 (84.2%)
BRIGHT N=2,194
N=0
BRIGHT N=2,194
N=0
BRIGHT N=2,194
N=30
BRIGHT N=2,164 (98.6%)
HEAT-PPCI N=1,812
N=0
HEAT-PPCI N=1,812
N=0
HEAT-PPCI N=1,812
N=321
HEAT-PPCI N=1,491 (82.3%)
MATRIX N=7,213
N=0
MATRIX N=7,213
N=268
MATRIX N=6,945
N=396
MATRIX N=6,549 (90.8%)
VALIDATE-SWEDEHEART N=6,006
N=0
VALIDATE-SWEDEHEART N=6,006
N=0
VALIDATE-SWEDEHEART N=6,006
N=0
VALIDATE-SWEDEHEART N=6,006 (100%)
Total: 38,565
N=4,646
Total: 33,919
N=2,471
Total: 31,438
N=4,039
Total: 27,409
27,409 Patients
in the pooled database

Figure 4


Systematic Review and Study Selection
• Systematic literature review to identify RCTs of bivalirudin-based vs. heparin-based regimens in the setting of AMI, with at least 1,000 patients
• Screening the retrieved studies (N=738) against the inclusion and exclusion criteria
• 8 studies met the study inclusion criteria
Initial Data Requests and Pooling
• PIs of all studies contacted and all agreed to provide individual patient data
• Initial data was transferred to the data coordinating center at CRF along with case report forms and clinical study protocols
• Table shells were drafted and consensus-based definitions for outcomes were agreed upon
Iterative Revisions and Corrections
• A standardized pooled database was programmed at CRF
• Unexpected data issues or inconsistent variable definitions were identified and reconciled
• Critical variables that were not initially transferred were additionally requested from PIs
Final Queries and Locking the Database
• Validation of the database was performed by reproducing tables with the pooled database and comparing against trial publications
• Analysis population was decided upon and patients not meeting the eligibility criteria were excluded
• Finalized database was reviewed by all PIs and locked once all queries were resolved