Accepted Manuscript

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PII: S0049-3848(18)30553-X
DOI: doi:10.1016/j.thromres.2018.09.062
Reference: TR 7157

To appear in: *Thrombosis Research*

Received date: 26 February 2018
Revised date: 16 August 2018
Accepted date: 27 September 2018

Please cite this article as: Vikram Khanna, Adeel Shahzad, Kala Thayalasamy, Ian Kemp, Christine Mars, Rob Cooper, Claire Roome, Keith Wilson, Scott Harris, Rod Stables, Nick Curzen , Comparison of the antiplatelet and antithrombotic effects of bivalirudin versus unfractionated heparin: A platelet substudy of the HEAT PPCI trial. Tr (2018), doi:10.1016/j.thromres.2018.09.062

Comparison of the antiplatelet and antithrombotic effects of bivalirudin versus unfractionated heparin: a platelet substudy of the HEAT PPCI trial

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Word count - 4311

Abstract

In randomised trials, bivalirudin has been associated with higher rates of acute stent thrombosis (AST) compared to unfractionated heparin (UFH), without mechanistic explanation. Furthermore, data are discrepant regards the antiplatelet effects of bivalirudin. This prespecified study, part of a larger HEAT-PPCI Platelet Substudy, aimed to compare the antiplatelet and antithrombotic effects of bivalirudin and UFH using short thrombelastography (s-TEG), an *ex vivo* whole blood platelet function assay. In HEAT-PPCI, patients were randomised to receive UFH or bivalirudin before angiography. Assay with s-TEG was performed in 184 patients (10.2%) at end of procedure (EOP) and repeated at 24 hours. In addition to adenosine diphosphate- (ADP) and arachidonic acid- (AA) mediated platelet aggregation, thrombin-mediated clotting (TMC) was assessed using kaolin with and without heparinase. There were no significant differences between UFH and bivalirudin in ADP- and AA-mediated platelet aggregation at EOP or 24 hours. Whilst UFH obliterated TMC at EOP, bivalirudin prolonged R time (19.7 min [15.9 – 25.4] vs. 8.4 min [7.5 - 10]; $P < 0.0001$), K time (2.4 min [1.9 - 3.4] vs. 2.2 min [1.8 - 2.7]; $P = 0.007$) and significantly increased maximum clot strength (MA 62.7 mm [58.7 - 67.4] vs. 58.6 [55 - 63]; $P = 0.0005$), compared to control. In conclusion, there were no significant differences in the antiplatelet effects of UFH and bivalirudin. However, whilst UFH obliterated TMC, bivalirudin prolonged clot initiation but potentiated maximum clot strength. As AST is likely multifactorial in aetiology, in patients treated with bivalirudin, increased clot strength may contribute to this hazard in some individuals and this observation warrants further investigation.

Keywords: *bivalirudin; heparin; platelet function; thrombelastography; stent thrombosis; thrombin*

Introduction

In patients undergoing primary percutaneous coronary intervention (PPCI) for ST elevation myocardial infarction (STEMI), the risk of recurrent ischaemic events is important. Despite pharmacological inhibition of periprocedural platelet function with conventional dual antiplatelet therapy (DAPT), platelets remain reactive to a multitude of other mediators, most notably thrombin, a potent platelet agonist and the final effector of the coagulation cascade. Furthermore, recently concerns have been raised in STEMI patients with respect to the delayed onset of action of new oral $P2Y_{12}$ inhibitors [1, 2] previously reported to have a more reliable and superior antiplatelet effect compared to clopidogrel [3, 4]. Consequently, adjunctive antithrombotic therapy remains an important component of treatment in patients undergoing PPCI.

The optimal adjunctive antithrombotic regimen in PPCI remains contentious. Historically, unfractionated heparin (UFH) has been the default anticoagulant administered during PCI. Unlike heparin, bivalirudin has the theoretical advantage that it does not bind plasma proteins, is not neutralised by platelet factor 4, exerts its effector activity on thrombin directly without the need for co-factors and can bind thrombin in the fluid phase as well as circulating clot-bound thrombin [5]. However, despite its favourable profile, the net outcome benefits demonstrated in randomised controlled trials have been largely driven by reductions in bleeding complications rather than incremental benefits in reducing ischaemic events [6-10], and this has generally been when comparing it to a combination of heparin plus a glycoprotein IIb/IIIa inhibitor (GPI).

Evolving trends in PPCI, including the use of potent $P2Y_{12}$ inhibitors, transradial access and selective 'bailout' use of GPI means that these trials no longer closely reflect contemporary practice. The HEAT-PPCI trial was a randomised comparison of UFH and bivalirudin (with selective 'bailout' use of GPI in both arms) in patients undergoing PPCI and demonstrated a significant reduction in major adverse cardiovascular events in favour of UFH without excessive bleeding complications [11]. This benefit was largely driven by a

higher incidence of acute stent thrombosis (AST) in the bivalirudin arm, an observation consistent with previous trials [8, 10]. However, the mechanism of AST in bivalirudin-treated patients remains poorly understood. Furthermore, data on the antiplatelet effects of bivalirudin are discrepant [12-15].

The primary objective of this prespecified HEAT-PPCI platelet substudy was to compare the antiplatelet and antithrombotic effects of bivalirudin and UFH in patients undergoing PPCI for STEMI using Short Thrombelastography (s-TEG), a whole blood platelet function assay, extensively validated in PCI populations [16-20].

Methods

Study Population and Design

All patients in this platelet substudy were part of the HEAT-PPCI (How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention Study) trial [11], a single centre, open label, randomised study comparing bivalirudin to UFH in a PPCI population. The selection inclusion and exclusion criteria were as previously described in the HEAT-PPCI trial [11]. Specifically, we enrolled adults (≥18 years age) presenting with STEMI activating the PPCI pathway, unless they had known intolerance, hypersensitivity, or contraindication to any trial drug; active bleeding at presentation; artificial ventilation, reduced conscious level or other factors precluding the administration of oral antiplatelet therapy; their physician refused to administer antiplatelet loading (uncertain diagnosis or risk of bleeding); or if they had previously been enrolled in the HEAT-PPCI trial.

Patients who received a GPI were additionally excluded from the present platelet substudy. Due to logistic considerations patients were enrolled to this substudy only during the core operational hours of the research laboratory at Liverpool Heart and Chest Hospital.

Platelet function testing with Multiple electrode aggregometry (MEA) at the end of the index procedure (EOP) was planned from inception of the trial to compare the differential effects of $P2Y_{12}$ inhibitors on platelet reactivity and clinical events[21].

In this paper, we present results from a 'second phase' of the platelet substudy designed specifically to compare the antiplatelet and antithrombotic effects of bivalirudin and heparin. We elected to perform this comparison using s-TEG, a well-validated and versatile platelet function assay, given its unique ability to individually assess a variety of different agonist-specific pathways of clotting including adenosine diphosphate (ADP), arachidonic acid (AA) and thrombin-mediated clotting (TMC). In this phase of the platelet substudy, all participants had blood samples taken at EOP, but also repeated at 24 hours. However, recruitment to this phase of the platelet substudy had to be deferred until a substantial amendment to the HEAT-PPCI study protocol relating to obtaining a second blood sample at 24 hours was approved by the Liverpool East, North West Research Ethics Committee.

All patients received DAPT before PPCI as per routine practice at the host institution and its referring emergency departments. Patients received the assigned study drug after entry to the catheter laboratory but before the angiographic findings were known. UFH was given as a bolus dose of 70 U/kg bodyweight before the procedure. Additional doses were administered if activated clotting time (ACT) values 5–15 min after the bolus dose or at EOP were less than 200s. Bivalirudin was given as a bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/hr for the duration of the procedure. A rebolus of 0.3 mg/kg was administered if activated clotting time (ACT) values 5–15 min after the bolus dose or at the EOP were less than 225 s. ACT was monitored with Actalyke XL MAX-ACT system (Helena Laboratories, Beaumont, TX, USA).

Blood Sampling and Sample Analysis

Blood sampling

Whole blood for platelet function testing was obtained via arterial sheath in the cardiac catheterisation lab at the EOP. In patients assigned to receive bivalirudin, the infusion was still running at the time of sampling. Blood sampling at the 24-hour time point was performed via venepuncture from the antecubital fossa. The first 10ml (2 ml during venesection) were discarded and then blood was drawn into one 6 ml lithium heparin Vacutainer®, and one 2 ml Vacutainer® of 3.2% sodium citrate for TEG platelet mapping. The tubes were filled to capacity and inverted gently a few times to ensure proper mixing with the anticoagulant *in situ*. According to manufacturer's instructions, blood samples were incubated at room temperature for at least 15 min for TEG platelet mapping.

TEG Platelet Mapping

Briefly, the TEG® technology is based on a stationary pin on a torsion wire being suspended into an oscillating cup containing a small volume of whole blood at 37°C. As clotting is stimulated with agonists, changes in its viscoelasticity are transmitted to the pin and the resulting torque generates an electrical signal producing a characteristic TEG® trace (Figure 1) [16].

Samples were analysed using the modified TEG® platelet mapping system (Haemonetics Corp, MA, USA) as previously reported [16, 17]. Platelet agonists employed in the standard channels include: (i) **Citrated blood activated by Kaolin (CK)**: kaolin stimulates clotting via the intrinsic coagulation pathway leading to thrombin generation and maximal platelet activation as thrombin is a potent platelet agonist, (ii) **Activator F™ (Act F)**: a mixture of reptilase and factor XIIIa, which generates fibrin clot without causing platelet

activation (iii) **ADP**: a combination of Activator F™ and ADP (2µM), (iv) **AA**: a combination of Activator F™ and AA (1mM). In this platelet substudy we used an additional fifth channel **(CKH)** in which citrated whole blood was stimulated by kaolin in a cup coated with heparinase to neutralise the effects of heparin. This channel provides a pure assessment of thrombin-mediated clotting (TMC) by eliminating the activity of any heparin that is present in the sample (endogenous or administered), thus providing an internal control for TMC in patients who had received heparin. It therefore served as a control channel for comparison of the antithrombotic effects of bivalirudin and UFH. Whole blood (340 µl of citrated blood for CK and CKH channel; 360 µl of heparinised blood for Act F, AA and ADP channels) was manually pipetted into the respective channels. In blood preserved with the calcium chelating agent, citrate (i.e. CK and CKH channel), clotting was initiated by recalcification using 0.2M calcium chloride.

The TEG® 5000 haemostasis analyser (Haemonetics Corp., Massachusetts, USA) and automated analytical software were used to measure the physical properties of clot formation to produce a characteristic TEG trace. Observations were continued for at least 60 minutes. Individual TEG traces were used to derive parameters relating to clot dynamics including R time, K time, α-angle, maximum amplitude (MA) and the Short Thrombelastography (s-TEG) parameter Area under the curve at 15 minutes (AUC15), as illustrated in Figure 1.

Short Thrombelastography

s-TEG is a novel modification of the TEG® platelet mapping assay, as previously described and validated [16, 17], which is based upon the concept of "Area under the curve at 15 minutes" (AUC15). This incorporates both strength and speed of clot formation. AUC15 is calculated using bespoke software (Areafinder 2:1) developed using National Instrument Labview 7.0. AUC15 has been shown to correlate well with the conventional TEG® parameter maximum amplitude (MA) in assessment of responses to APT and is easily reproducible [17].

Statistical analysis

Continuous variables are presented as mean ± 95% confidence interval (CI) of the mean for normally distributed data or median with interquartile range (IQR) if not. Normality of data was tested using the Shapiro-Wilk test. Non-normally distributed continuous data were compared using the Mann-Whitney U test. Categorical variables are presented as frequencies (%). A P value <0.05 was considered to represent statistical significance. Statistical analyses were performed using SPSS version 21 (IBM Corp., Armonk, NY, USA).

Results

This TEG substudy includes 184 patients. As outlined in the substudy flow chart (Figure 2), of the 1,812 patients randomised in the HEAT-PPCI trial, 1,229 (67.8%) presented outside the core operating times of the research laboratory. Four patients were deemed too unwell for blood sampling at EOP as the clinical team were occupied with patient resuscitation. Specifically, 2 patients had multiple VF arrests requiring intubation and ventilation, one had left main stem dissection requiring emergency surgery and one patient had coronary perforation requiring emergency surgery. Furthermore, 86 patients who received GPI were not included. Finally, data from 15 bivalirudin-treated patients were excluded from this analysis as they exhibited a pattern of TMC consistent with heparin contamination. Specifically, TMC was obliterated in the CK channel, consistent with the effects of heparin, but restored in the presence of heparinase (CKH channel), which neutralises heparin activity (as described above). On careful review of source data there was definite evidence of only one patient having received fondaparinux and one patient receiving UFH prior to randomisation. Platelet function data at the 24-hour time point for 21 patients (14 in the UFH arm

and 7 in the bivalirudin arm) bearing this characteristic pattern were also excluded from the analysis.

Baseline characteristics in the substudy population (Table 1) were well matched between patients treated with bivalirudin (n = 92) and UFH (n = 92).

Antiplatelet effects of heparin versus bivalirudin

There were no significant differences in ADP- or AA-mediated platelet aggregation between the two groups at EOP or the 24-hour time point (Table 2).

Antithrombotic effects of heparin versus bivalirudin

End of procedure

In the control channel (i.e. CKH channel in patients treated with UFH where TMC was evaluated in the presence of heparinase), the median and IQR for R time was 8.4 min [7.5 - 10], K time was 2.2 min [1.8 - 2.7], α-angle was 59.8° [54.5 - 65.4], MA was 58.6 [55 - 63], and $AUC15_{CKH}$ was 965.7 [859.8 - 1090.4]. By contrast, in patients treated with UFH in the absence of heparinase (i.e. CK only), clotting in response to kaolin (i.e. TMC) at EOP was obliterated, at least for the duration of the observation period. Consequently, no further TEG parameters relating to time to clot initiation (R time), maximum clot strength (i.e. MA), K-time, α- angle or AUC15 (i.e. s-TEG) could be derived at this time point.

Compared to control (i.e. CKH channel in patients treated with UFH) (n=90), bivalirudin (n = 91) significantly prolonged R time (19.7 min [15.9 – 25.4] vs. 8.4 min [7.5 - 10]; $P < 0.0001$), prolonged K-time (2.4 min [1.9 - 3.4] vs. 2.2 min [1.8 - 2.7]; $P = 0.007$) and increased MA (62.7 [58.6 - 67.4] vs. 58.6 [55 - 63]; $P = 0.0005$). There were no significant differences in the α-angle (58.6° [47.3 - 64.1] vs. 59.8° [54.5 - 65.4]; $P = 0.06$) and $AUC15_{CKH}$ at EOP (1011.2 [808.6 - 1161] vs. 965.7 [859.8 - 1090.4], $P = 0.72$) between patients

treated with bivalirudin compared to control (Figure 3).

24 hour time point

At 24 hours, there were no significant differences in any TEG parameter (R time, K time, α angle, MA or AUC15) between patients treated with UFH and bivalirudin, regardless of whether heparinase was present (i.e. CKH) or not (i.e. CK only) (Figure 4).

Discussion

Two principal findings are reported in this study. Firstly, s-TEG detected no significant differences in ADP- or AA-mediated platelet aggregation between UFH and bivalirudin at either time point (i.e. EOP or 24 hours). Secondly, UFH obliterated TMC, but, whilst bivalirudin prolonged time to clot initiation (R time) and propagation (K time), but was also associated with significantly greater maximum clot strength (i.e. MA) compared to control.

Using flow cytometry, previous studies have compared the effects of bivalirudin and UFH on agonist-mediated platelet activation, both *ex vivo* [13, 22] and *in vitro* [14, 23, 24]. Bivalirudin has been shown to have modest inhibitory effects on platelet activation although some authors have reported that it potentiates P-selectin surface expression [15]. By contrast, UFH has mostly been shown to potentiate platelet activation by initiating outside-in signalling via direct binding to $\alpha_{IIb}\beta_3$ integrin [25], though again there are discrepant data reported [26]. However, the overall significance of differential surface expression of platelet activation markers with these anticoagulant agents on agonist-mediated clotting and clinical outcome measures remains poorly understood.

A study in cardiac surgical patients demonstrated that both bivalirudin and UFH significantly attenuated ADP-mediated platelet aggregation, although the effects of bivalirudin were more pronounced [27]. By contrast, using MEA and light transmittance aggregometry (LTA), Sibbing *et al* demonstrated that in PCI patients preloaded with clopidogrel, whilst UFH had no significant effects, bivalirudin resulted in significant incremental inhibition of ADP-mediated aggregation [12]. Such antiaggregatory effects, albeit modest in magnitude, are significant and therefore, at least in theory, might be expected to mitigate the early hazard of periprocedural ischaemic events including AST. However, despite this theoretical advantage, there are no consistent data from randomised trials supporting superiority of bivalirudin over UFH with respect to ischaemic end points. On the contrary, bivalirudin has been consistently associated with an elevated risk of AST [8, 11, 28], at least in the absence of a prolonged post-PCI infusion [29], a finding which has led to downgrading of recommendations for bivalirudin to class IIa in the recent European guidelines [30].

In the present platelet substudy there were no significant differences in ADP- and AA-mediated platelet aggregation between UFH and bivalirudin at either time point (i.e. EOP or 24 hours). Our findings are consistent with the DEACON study which also found no significant differences between UFH and bivalirudin in ADP-induced aggregation with LTA in patients undergoing PCI, regardless of whether they had been treated with GPI [31]. However, it is noteworthy that we found a trend towards significance in AA-mediated aggregation between UFH and bivalirudin at 24 hours ($p = 0.06$). Whilst it is conceivable that a larger sample size could potentially yield a statistically significant result, it is difficult to speculate a plausible mechanistic explanation for such a finding given that, with their short half lives, neither drug would be expected to have detectable activity at this time point. Further studies adequately powered are required to confirm these findings.

Whilst conventional assays for monitoring heparin-related blood clotting (e.g. ACT and activated partial thromboplastin time) terminate early after fibrin gel formation occurs in response to trace amounts of thrombin (< 5%), TEG continues profiling several aspects of clot dynamics on a temporal basis beyond the

initiation phase (i.e. clot propagation) which is typically characterised by a burst of thrombin generation (> 95%). TEG is therefore ideally suited for comprehensive characterisation of the effects of thrombin inhibitors on the viscoelastic properties of clot formation. Indeed, several studies have already systematically evaluated a range of thrombin inhibitors with TEG, based on *in vitro* testing in healthy volunteers [32-36]. In accordance with our findings, these studies have shown that all thrombin inhibitors, including UFH and bivalirudin, prolong time to clot initiation (i.e. R time) and clot propagation (i.e. K time and α-angle) in a dose-dependent manner. However, the effects of direct thrombin inhibitors (DTIs) in prolonging clot initiation and propagation are modest in comparison to those of UFH, which has the steepest concentration-response curve, again consistent with our findings. In our study, UFH obliterated TMC at EOP, at least for the duration of the observation period. These findings are also consistent with previous reports demonstrating that UFH not only inhibits clot initiation and propagation, but also significantly attenuates clot strength and rigidity in a concentration-dependent manner [32, 35, 36].

To our knowledge, this study is the first to demonstrate that bivalirudin augments maximum clot strength. By contrast, the existing evidence is discrepant with respect to the reported effects of bivalirudin on the maximum tensile strength of a clot (i.e. MA). Specifically, Young *et al* showed that clot rigidity and elasticity were relatively preserved even at high doses of bivalirudin, once kaolin-activated clotting finally commenced following a prolonged lag period [32]. By contrast, Taketomi *et al* showed that at therapeutic concentrations (similar to those employed in PCI) bivalirudin resulted in modest increases in MA in response to direct stimulation with thrombin, when compared to control, though this was not statistically significant in their study [34]. It is noteworthy that we evaluated the pharmacodynamic effects of these anticoagulants *ex vivo* in a real-world population of STEMI patients undergoing PPCI, which likely represents a more prothrombotic state than that prevalent in blood from healthy volunteers tested *in vitro*.

The differences between UFH and bivalirudin reported in this study are consistent with their known pharmacological properties. Specifically, heparin-mediated binding of antithrombin leads to the formation of a ternary complex and irreversible conformational changes to the active site of thrombin. By contrast, bivalirudin comprises a peptide directed against the thrombin active site linked via a tetraglycine spacer to a synthetic dodecapeptide analogue of the C-terminus of hirudin [37] that binds to exosite 1 on thrombin (i.e. the binding site for fibrinogen and thrombomodulin). Once bound in a bivalent fashion (i.e. to the active site and exosite 1), thrombin is rendered inactive only transiently. Circulating proteases including thrombin itself cleave bivalirudin close to the N-terminus liberating the amino-terminal moiety from the active site, thereby allowing resumption of thrombin's catalytic activities [38]. Its relatively short plasma half life (~ 25 minutes) has therefore been cited as a plausible explanation for the higher incidence of AST associated with bivalirudin. Undoubtedly, this mechanistic explanation has greater biological relevance given that there is now also convincing evidence for a delayed onset of action of $P2Y_{12}$ inhibitors in STEMI [1, 39]. Consequently, this has prompted analyses of prolonged post-PCI infusions of bivalirudin as a strategy to mitigate the higher incidence of AST, which has shown encouraging results [29, 40].

Nevertheless, numerous studies have also reported that at low concentrations, bivalirudin [35, 36, 41] and other DTIs [42, 43], produce a paradoxical increase in tissue factor (TF)-triggered thrombin generation (TG) *in vitro*. This exaggerated TG at low concentrations of DTIs has been attributed to the suppression of the thrombin-thrombomodulin (TM)-induced negative-feedback inhibition of thrombin via protein C [42, 43], which when activated naturally exerts a potent anticoagulant effect via proteolysis of factor (F) Va and FVIIIa. Following proteolytic cleavage, the carboxyl-terminal remnant of bivalirudin transforms into a competitive inhibitor of exosite 1 substrates including fibrinogen and TM [38], thus potentially exerting an ongoing inhibitory effect on thrombin-TM mediated activation of protein C.

A mechanism of rebound clotting activation could potentially explain the increase in clot strength noted at EOP in this study. Nevertheless, the increase in clot strength, whilst statically significant is modest and

based on existing evidence is unlikely to independently account for the higher incidence of AST observed in patients treated with bivalirudin. However, the pathophysiology of stent thrombosis, which remains poorly understood, is multifactorial and a variety of factors including patient comorbidities, stent design, lesion morphology, high platelet reactivity and procedural factors including stent underexpansion and malaposition have been implicated in its aetiology. It is therefore conceivable that increased maximum clot strength reported here in bivalirudin-treated patients could contribute to triggering AST in some individuals. Further studies to elucidate the precise mechanism and clinical significance of this observed increase in clot strength in patients treated with bivalirudin are warranted.

This substudy has several limitations. Firstly, we have assumed that baseline platelet reactivity prior to drug administration was similar in both treatment groups, though this was not formally confirmed. Secondly, we were unable to compare the effects of these antithrombotic regimens at therapeutic doses on TG as this was neither measured directly nor assayed via surrogate markers. Finally, we have not examined the validity of using the CKH channel in patients treated with UFH as a control group for comparison against patients treated with bivalirudin, although our previous clinical data strongly supports this assumption.

In conclusion, whilst there were no significant differences between UFH and bivalirudin with respect to their effects on platelet aggregation in response to ADP or AA, we did observe important differences in the viscoelastic properties of clot formation in response to thrombin stimulation. Specifically, whilst heparin obliterated TMC, bivalirudin prolonged clot initiation and propagation, but was also associated with a significant increase in maximum clot strength. This effect could be one factor that contributes to AST in susceptible individuals and warrants further investigation.

Sources of funding

Liverpool Heart and Chest Hospital, UK National Institute of Health Research, The Medicines Company, AstraZeneca, The Bentley Drivers Club (UK), Haemonetics Corporation.

Declaration of Interests

NC received unrestricted research grants from Boston Scientific, Haemonetics, HeartFlow, St. Jude Medical, and Medtronic; speaker/consultancy fees from Haemonetics, St. Jude Medical, Abbott Vascular, and HeartFlow; and travel sponsorship from Biosensors, Abbott, and Lilly/D-S. In particular, this study was supported by an unrestricted research grant from Haemonetics Corporation. RHS reports grants from The Medicines Company and grants and personal fees from AstraZeneca during the conduct of the study.

Legends

Figure 1. Typical TEG trace illustrating the parameters: (i) R time - latent period from start of sample analysis to clot initiation); (ii) K time - time taken to attain a fixed viscoelasticity (i.e. amplitude of 20 mm) which is a measure of clot kinetics; (iii) α-angle - gradient formed by angle of initial trace which represents the rapidity of fibrin build-up and cross-linking in the forming clot; (iv) maximum clot strength (MA) – is the final strength of the clot; (v) AUC15 – is the Area under the curve at 15 minutes (AUC15) which reports on both the speed of clot formation as well as clot strength (shaded area).

Figure 2. Study flow chart.

Figure 3. Comparison of Thrombelastography-derived indices between patients treated with unfractionated heparin and bivalirudin at end of procedure when citrated whole blood was stimulated with kaolin (thrombin-mediated clotting) in the presence (CKH channel) and absence of heparinase (CK channel): (A) R time; (B) K time; (C) α-angle; (D); maximum amplitude (MA) and (E) area under the curve at 15 minutes (AUC15).

Figure 4. Comparison of Thrombelastography-derived indices between patients treated with unfractionated heparin and bivalirudin at 24 hours when citrated whole blood was stimulated with kaolin (thrombin-mediated clotting) in the presence (CKH channel) and absence of heparinase (CK channel): (A) R time; (B) K time; (C) α-angle; (D); maximum amplitude (MA) and (E) area under the curve at 15 minutes (AUC15).

Table 1. Summary of baseline characteristics, laboratory investigations and drug use.

Table 2. Comparison of ADP and AA-mediated platelet aggregation in patients treated with unfractionated heparin to those treated with bivalirudin at the end of the PCI procedure and 24-hour time point.

Figures

Figure 1.

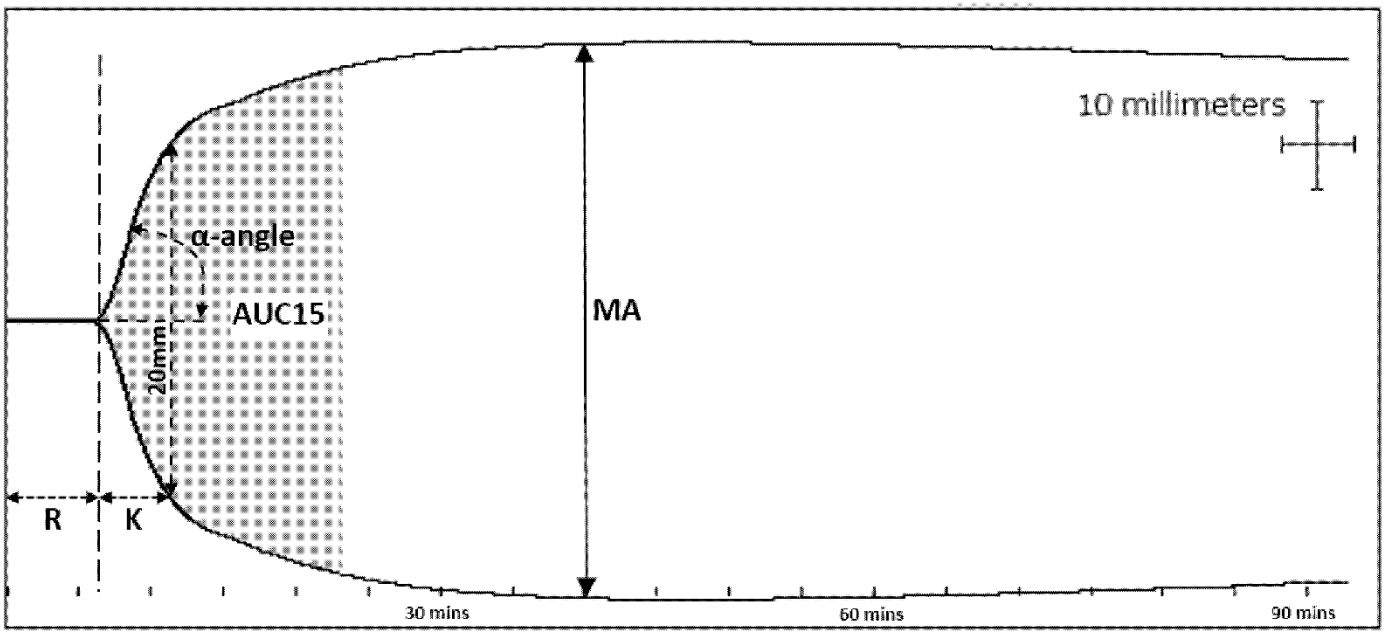


Figure 2.

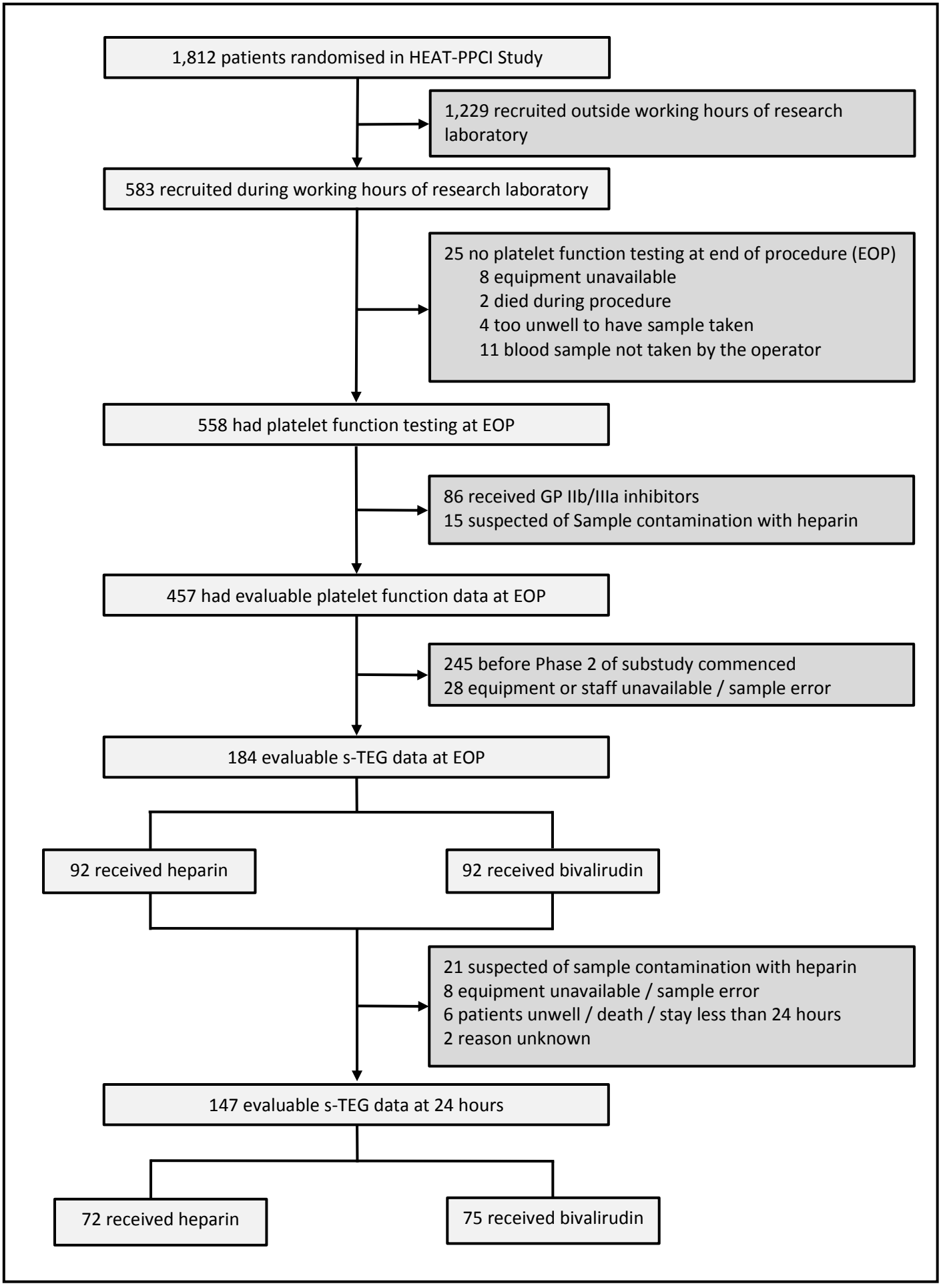
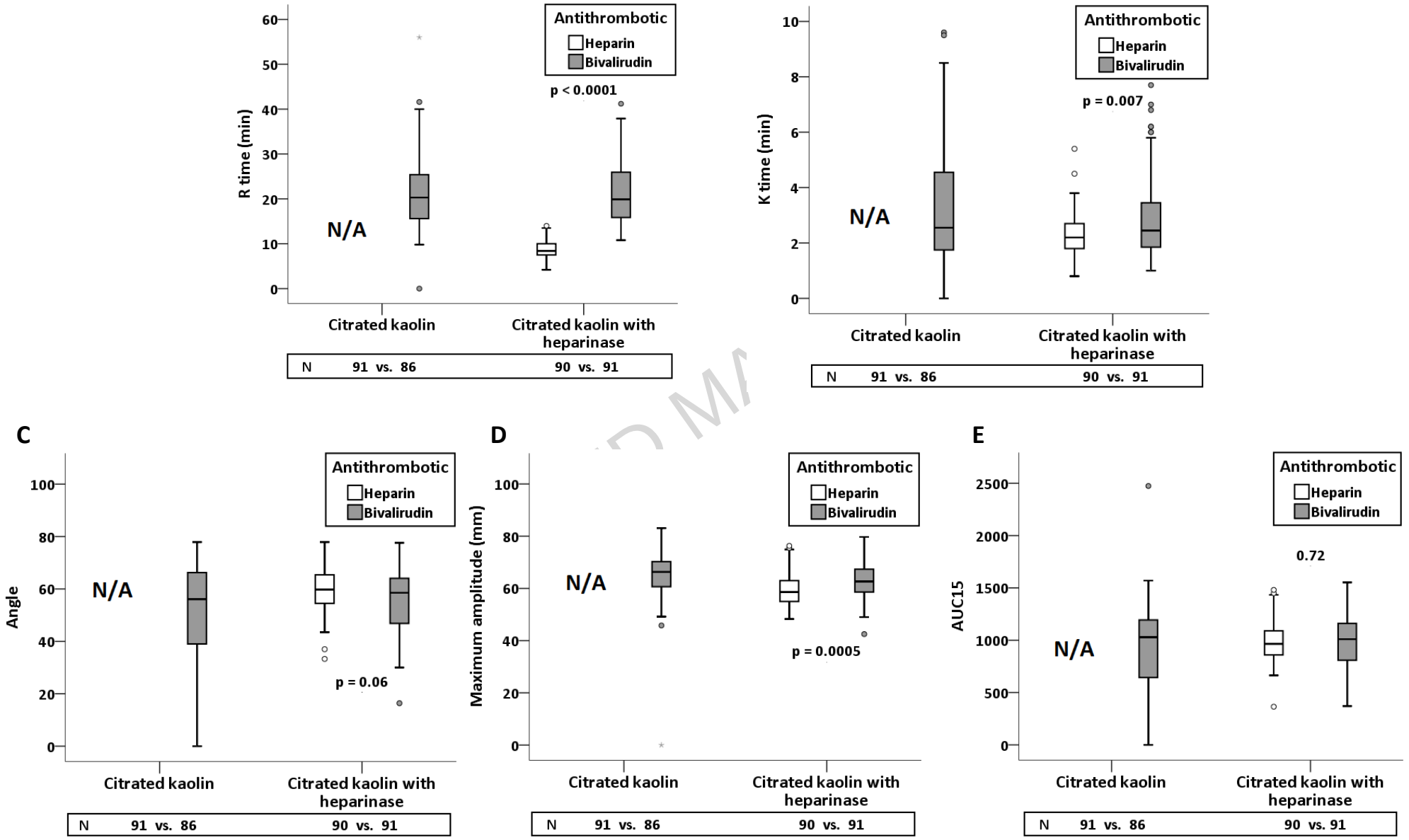


Figure 3.



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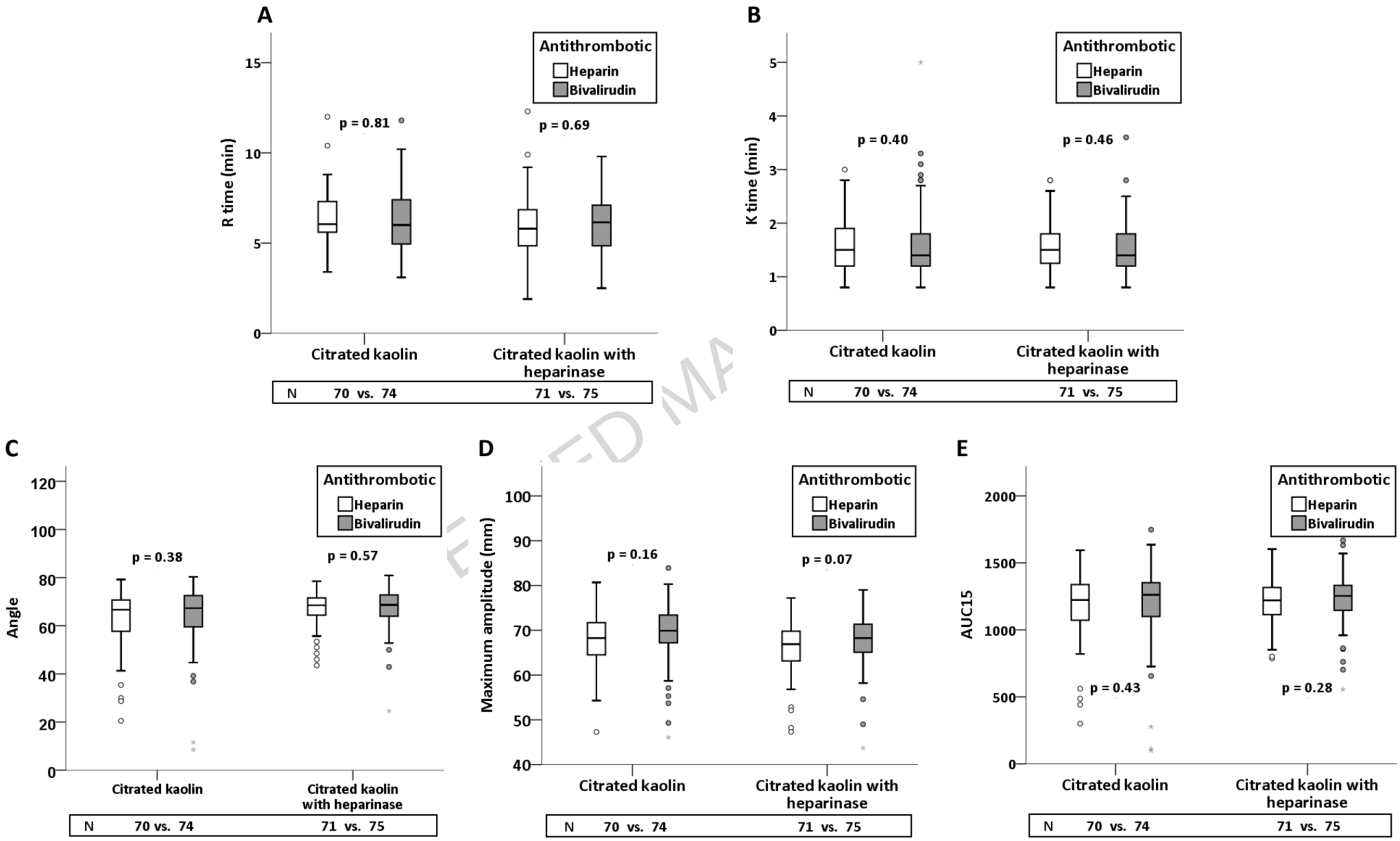

Tables

Table 1.

	Bivalirudin (n = 92)	Heparin (n = 92)
Age, years	65.7 ± 2.6	63 ± 2.7
Sex, female	32/92 (34.8%)	26/92 (28.3%)
Bodyweight, kg		
Data available	74 (80.4%)	82 (89.1%)
Mean ± 95% CI of mean	78.9 ± 3.8	79.1 ± 3.0
Ethnicity, White	85/88 (96.6%)	84/89 (94.4%)
Comorbidities		
Hypertension	36/92 (38.5%)	37/91 (40.7%)
Hyperlipidaemia	29/89 (32.6%)	35/92 (38.0%)
Diabetes Mellitus	12/92 (13.0%)	12/91 (13.2%)
Family history of CVD	40/90 (44.4%)	42/89 (47.2%)
Current Smoker	34/91 (37.4%)	37/89 (41.6%)
Previous myocardial infarction	10/92 (10.9%)	10/92 (10.9%)
Previous PCI	5/92 (5.4%)	6/91 (6.6%)
Previous CABG	3/92 (3.3%)	3/92 (3.3%)
Platelet count		
Data available	89 (96.7%)	91 (98.9%)
Median [IQR]	233 [190 – 282]	222 [186.5 - 263]
Estimated GFR		
Data available	90 (97.8%)	92 (100%)
Median [IQR]	75.5 [60 - 90]	77 [62.5 - 90]
Haemoglobin		
Data available	91 (98.9%)	92 (100%)
Median [IQR]	13.5 [12.1 - 14.6]	13.7 [12.6 -14.8]
$P2Y_{12}$ inhibitor		
Clopidogrel	6/92 (6.5%)	5/92 (5.4%)
Prasugrel	1/92 (1.1%)	1/92 (1.1%)
Ticagrelor	85/92 (92.4%)	84/92 (91.3%)
None	0/92	2/92 (2.2%)
Other anticoagulation		
Warfarin	5/92 (5.4%)	4/92 (4.3%)
Fondaparinux	2/92 (2.2%)	6/92 (6.5%)
Low-molecular weight heparin	1/92	0
Other	1/92	0
Time between LD and EOP sampling (minutes)		
Aspirin		
Data available	91 (98.9%)	85 (92.4%)
Median [IQR]	95 [79 – 117.5]	94 [75 - 110]
$P2Y_{12}$ inhibitor		
Data available	90 (97.8%)	85 (92.4%)
Median [IQR]	67 [44 – 102]	55 [40 - 85]

Table 2.

		End of Procedure				P value	24 hours				P value
		UFH		Bivalirudin			UFH		Bivalirudin		
		N	Median [IQR]	N	Median [IQR]		N	Median [IQR]	N	Median [IQR]	
s-TEG	$AUC15_{AA}$	91	457.3 [225.9 - 648.5]	92	379.4 [251.6 – 573.3]	0.60	68	150.1 [104.7 - 318.7]	73	227.6 [142.7 – 298.8]	0.06
	$AUC15_{ADP}$	91	460.8 [195.2 - 732.9]	92	537.4 [303.1 – 890.2]	0.08	70	140 [77.1 - 309.9]	74	186.5 [119.2 – 301.5]	0.09

s-TEG, Short Thrombelastography; IQR, Interquartile range; UFH, unfractionated heparin

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Highlights

- Comparing the antiplatelet and antithrombotic effects of bivalirudin and heparin
- No significant differences in the antiplatelet effects of bivalirudin and heparin
- Heparin totally obliterated thrombin-mediated clotting
- Bivalirudin prolonged clot initiation/propagation and increased clot strength
- Increased clot strength with bivalirudin may contribute to acute stent thrombosis