Influence of chronic kidney disease on anticoagulation levels and bleeding after primary percutaneous coronary intervention in patients treated with unfractionated heparin

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Abstract Unfractionated heparin (UFH) plasma protein binding and elimination might be impaired in patients with chronic kidney disease (CKD—defined as creatinine clearance <60 ml/min). It is currently unknown at which UFH bolus dose persistent prolongation of activated partial thromboplastin time (aPTT) occurs in ST-segment elevation myocardial infarction (STEMI) patients with CKD. We investigated the effect of different UFH bolus doses on the first aPTT measured within 6 and 12 h after PPCI in 1071 STEMI patients with and without CKD undergoing primary percutaneous coronary intervention (PPCI) between 1-1-2003 and 31-07-2008. In the first 6 h after PPCI, aPTT ratio was 5.1 for patients with CKD versus 3.4 for those without (p < 0.001). The proportion of patients with markedly high aPTTs (aPTT ratio ≥ 4 times control) increased with increasing heparin bolus and beyond 130 IU/kg there was a marked difference between patients with and without CKD (74.1 and 42.3 % respectively, p for interaction = 0.009). By multivariable analysis, CKD was associated with an increased risk of markedly high aPTTs (odds ratio (OR) 2.04; 95 % confidence interval (CI) 1.27–3.27), driven largely by an increased risk of aPTT prolongation in patients treated with UFH boluses ≥ 130 IU/kg (OR 3.69; 95 % CI 1.85–7.36; p for interaction = 0.009). In conclusion, CKD is associated with severe persistent aPTT prolongation in STEMI patients undergoing PPCI, possibly due to impaired plasma protein binding and reduced UFH elimination. A lower heparin bolus dose might result in lower aPTTs and less bleeding complications in patients with CKD undergoing PPCI.

Keywords Unfractionated heparin · Acute myocardial infarction · Chronic kidney disease · Hemorrhage · Percutaneous coronary intervention

Introduction

Chronic kidney disease (CKD) is associated with increased mortality and major bleeding in patients undergoing primary percutaneous coronary intervention (PPCI) for ST-segment elevation myocardial infarction (STEMI) [1, 2]. Therefore, considerable effort has been made to investigate the optimal adjunctive antithrombotic therapy to suppress both bleeding complications as well as recurrent ischemic outcomes in these patients. The European Society of Cardiology (ESC), American Heart Association (AHA) and American College of Cardiology (ACC) currently recommend the use of unfractionated heparin (UFH), enoxaparin or bivalirudin in STEMI patients undergoing PPCI [3, 4]. Of these 3 agents, UFH is currently the most commonly used anticoagulant for this indication [5, 6]. UFH was recently shown to be associated with lower rates of thrombotic events and similar bleeding events as compared to bivalirudin in a large scale all-comer randomized controlled trial reflecting contemporary practice (i.e. bail-out GP IIb/IIIa inhibitor use, radial access PCI and use of novel
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infarction; (2) an aPTT was recorded between arterial sheath insertion and 12 h thereafter and (3) a serum creatinine was recorded pre-procedurally or within 1 h of arterial puncture. We excluded patients who were pre-treated with both UFH and low molecular weight heparin (LMWH).

Measurements and definitions

For each patient we used the first aPTT measured after arterial sheath insertion and categorized these aPTTs in the following time-intervals: from 0 h until 6 h (referred to as: ‘6 h’), from 6 h until 12 h (referred to as: ‘12 h’), and from 0 h until 12 h (referred to as: ‘first 12 h’). All times were expressed relative to the moment of arterial sheath insertion at the start of PPCI. APTT ratios were stratified in the following groups: subtherapeutic (below 1.5 times control), therapeutic: between 1.5 and 2.0 times control; high: between 2.0 and 3.99 times control; and markedly high: ≥4 times control. APTTs are presented in relation to the hospital and reagent specific upper limit of normal. If the electronic laboratory database indicated a value ‘0’ for aPTT, this measurement was treated as not having been performed. In case a patient had no measurements within a given time interval, the value for that time interval was declared missing. The Cockroft Gault formula was used to calculate creatinine clearance [14]. Baseline creatinine clearance was calculated from the serum creatinine measurement that was closest to the moment of arterial sheath insertion. CKD was defined as creatinine clearance <60 ml/min.

Outcome definitions

Primary outcome was aPTT within the first 6 h after PCI. Secondary outcomes included aPTT at different time intervals after PCI (specified above), the in hospital occurrence of Bleeding Academic Research Consortium defined bleeding complications, and the occurrence of major adverse cardiac events (MACE) during the initial hospitalization. MACE was defined as the non-hierarchical composite of cardiac mortality, recurrent MI, stroke or target lesion revascularization (TLR). Recurrent MI and TLR were defined according to the Academic Research Consortium criteria [15]. Stroke was defined as an irreversible neurological deficit, as classified by a neurologist, on the basis of supporting information, including brain images and neurologic evaluation.

Statistical analysis

Normally distributed continuous variables are presented as the median with interquartile range (IQR) and compared with the Mann–Whitney U test. Categorical variables are presented as proportions and compared with the χ² test or Fisher’s exact test.

To investigate the relationship between estimated creatinine clearance and aPTT ratio beyond four times control, we performed 3 sets of logistic regression analyses for each peri-procedural timeframe (6, 12 h, first 12 h): (1) unadjusted; (2) adjusted for age, gender, bodymass, length/size, time to first aPTT measurement and heparin bolus dose, and (3) adjusted for relevant predictors of aPTT ratios beyond four times control. Relevant predictors for aPTT ratios beyond four times control were determined per timeframe, using stepwise backward elimination logistic regression analyses, including the following candidate covariables: gender, body mass, length, heparin bolus dose, time to first aPTT measurement, history of hypertension, diabetes, dyslipidemia, current smoking, stroke or TIA, peripheral artery disease, malignant disease, bleeding, recent surgery, previous MI, family history of CAD, anemia, leucocyte count, thrombocyte count, use of GP IIb/IIIa inhibitor, cardiogenic shock, and use of IABP. A covariate was included in the model if it influenced the model with a p < 0.10 by the likelihood ratio test and was removed if its significance level exceeded p = 0.10. To investigate if there was an interaction between UFH bolus dose and creatinine clearance <60 ml/min/m² we included interaction terms between UFH bolus dose and creatinine clearance. The relationship between creatinine clearance and the in hospital occurrence of BARC type ≥3 bleeding, and MACE was investigated by developing two sets of logistic regression models for each outcome: unadjusted and adjusted for relevant predictors of each outcome. Relevant predictors were determined using stepwise, backward elimination logistic regression analyses including all covariables with a significant unadjusted relationship with each outcome (p < 0.10). As a sensitivity analysis we performed an additional analysis including duration of heparin treatment and vitamin K antagonist treatment in addition to the previously identified predictors of bleeding in the multivariable model for BARC type ≥3 bleeding. All tests were 2-sided and a p value below 0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences software (SPSS version 20.0, Chicago, Illinois).

Results

Between 1-1-2003 and 31-07-2008, a total of 3472 patients with acute myocardial infarction were admitted to our catheterization laboratory with an indication for PPCI. 1928 patients were excluded because these patients did not
| Characteristic                                      | Creatinine clearance (ml/min) | p value |
|----------------------------------------------------|-------------------------------|---------|
|                                                    | <60 (n = 195)                 | ≥60 (n = 876) |
| Male, n/N (%)                                      | 80/195 (41.0)                 | 655/876 (74.8) | <0.001 |
| Age (years), mean (±SD)                            | 76 (±8.6)                     | 59 (± 11.8)    | <0.001 |
| Length (m), median (IQR)                           | 1.67 (1.60–1.75)              | 1.75 (1.70–1.80) | <0.001 |
| Body mass (kg), median (IQR)                       | 70 (62–80)                    | 81 (74–91)     | <0.001 |
| Body mass index, median (IQR)                      | 25.0 (22.6–27.7)              | 26.3 (24.3–29.2) | <0.001 |
| History of n/N (%)                                 |                              |              |
| Diabetes                                           | 35/195 (17.9)                 | 108/876 (12.3) | 0.037 |
| Hypertension                                       | 84/195 (43.1)                 | 304/876 (34.7) | 0.028 |
| Hypercholesterolemia                               | 32/195 (16.4)                 | 206/876 (23.5) | 0.031 |
| Current smoking                                    | 44/195 (22.6)                 | 443/876 (50.6) | <0.001 |
| Previous stroke or TIA                             | 20/195 (10.3)                 | 48/876 (5.5)   | 0.013 |
| Peripheral vascular disease                        | 30/195 (15.4)                 | 39/876 (4.5)   | <0.001 |
| Pre-existent malignant disease                     | 32/195 (16.4)                 | 59/876 (6.7)   | <0.001 |
| Recent surgery (<10 days)                          | 5/195 (2.6)                   | 7/876 (0.8)    | 0.050 |
| Bleeding                                           | 19/195 (9.7)                  | 30/876 (3.4)   | <0.001 |
| Previous MI                                        | 27/195 (13.8)                 | 91/876 (10.4)  | 0.16  |
| Previous PCI                                       | 12/195 (6.2)                  | 69/876 (7.9)   | 0.41  |
| Previous CABG                                      | 2/195 (1.0)                   | 15/876 (1.7)   | 0.75  |
| Family history CAD                                 | 37/195 (19.0)                 | 374/876 (42.7) | <0.001 |
| Laboratory values                                  |                              |              |
| White blood cell count ≥ 11 × 10^9/l, n/N (%)      | 94/191 (49.2)                 | 459/865 (53.1) | 0.34  |
| Anemia, n/N (%)                                    | 73/195 (37.4)                 | 102/875 (11.7) | <0.001 |
| Creatinine clearance, median (IQR)                 | 46.6 (38.7–54.5)              | 99.4 (79.5–122) | <0.001 |
| Thrombocyte count (×10^9/l), n/N (%)                |                              |              |
| <150                                               | 10/193 (5.2)                  | 29/868 (3.3)   |       |
| 150–400                                            | 173/193 (89.6)                | 810/868 (93.3) |       |
| >400                                               | 10/193 (5.2)                  | 29/868 (3.3)   |       |
| Total ischemic time (min),median (IQR)             | 207 (143–297)                 | 182 (130–260)  | 0.005 |
| Cardiogenic shock, n/N (%)                         | 26/193 (13.5)                 | 60/873 (6.9)   | 0.002 |
| IABP, n/N (%)                                       | 40/195 (20.5)                 | 93/874 (10.6)  | <0.001 |
| Loading dose clopidogrel, n/N (%)                   |                              |              |
| 300 mg                                             | 116/194 (59.8)                | 513/865 (59.3) |       |
| 600 mg                                             | 65/194 (33.5)                 | 333/865 (38.5) |       |
| Other                                              | 1/194 (0.5)                   | 6/865 (0.7)    |       |
| Glycoprotein IIb/IIIa inhibitor, n/N (%)            | 23/195 (11.8)                 | 120/876 (13.7) | 0.48  |
| Pre-cathlab heparin bolus (IU/kg), median (IQR)     | 67.6 (55.6–80.6)              | 58.8 (50.0–67.6) | <0.001 |
| Cathlab bolus dose (IU/kg), median (IQR)            | 73.5 (61.7–100)               | 63.3 (54.3–83.3) | <0.001 |
| Total heparin bolus (IU/kg), median (IQR)           | 134 (106–182)                 | 125 (100–149)  | <0.001 |
| Duration of heparin therapy (h), median (IQR)       | 40.5 (21.0–50.0)              | 45.0 (20.5–50.5) | 0.66  |
| Vitamin K antagonist at discharge, n/N (%)          | 22/195 (11.3)                 | 72/876 (8.2)   | 0.17  |
| PCI access site, n/N (%)                            |                              |              |
| Femoral artery                                     | 184/195 (94.4)                | 835/876 (95.3) |       |
| Radial artery                                      | 7/195 (3.6)                   | 34/876 (3.9)   |       |
| Other or combinations                              | 4/195 (2.1)                   | 7/876 (0.8)    |       |
| Infarct related artery, n/N (%)                    |                              |              |
| RCA or LCx                                         | 109/189 (57.7)                | 490/859 (57.0) |       |
| LAD or LM                                          | 80/189 (42.3)                 | 369/859 (43.0) |       |
have an aPTT measured between the start of PCI and 12 h thereafter or because they were not receiving UFH treatment at the time of the aPTT measurement. Of these 1544 patients, baseline creatinine clearance was available in 1332 patients. Of these 1332 patients, we had data on heparin bolus in 1185 patients. 114 patients were excluded from the analysis because they were pretreated with LMWH. Therefore, the study cohort consists of 1071 patients, of whom 195 patients (18.2%) had an estimated creatinine clearance $\leq 60$ ml/min. 16 patients had an estimated creatinine clearance $<30$ ml/min, of whom 2 had end stage renal disease (ESRD (defined as CrCl $<15$ ml/min)). Baseline, procedural, and angiographic characteristics for patients in- and excluded in the analysis are given in supplementary Table 1. Patients included in the analysis were less likely to be male, and less likely to be treated with GP IIb/IIIa inhibitors. They more often presented in cardiogenic shock and were more often treated with intra-aortic balloon pump (IABP). One year mortality was 11.7% in patients included in the analysis, whereas mortality was 10.9% in patients excluded (p = 0.52). The median total UFH bolus was 125 IU/kg (interquartile range (IQR): 100–154), consisting of a median pre-catheterisation laboratory bolus of 60 IU/kg (IQR 50–70) and an additional 66 IU/kg (IQR 56–83) given during the catheterisation procedure. In 87.1% of patients treated with 70–100 IU/kg UFH, the aPTT measured within the first 6 h after PPCI was outside the recommended range (between 1.5 and 2 times control). In as many as 66.3% of patients the aPTT was in excess of the recommended range. In 25.7% of patients, aPTT was markedly prolonged (4 times ULN) after a 70–100 IU/kg UFH bolus dose. Baseline characteristics and treatment strategies by estimated creatinine clearance are presented in Table 1. The aPTT ratio was 3.7 (interquartile range (IQR) 2.1–5.7) in the first 6 h after PPCI, 2.2 (IQR 1.7–4.2) between 6 and 12 h after PPCI and 3.1 (IQR 1.9–5.1) within the first 12 h after PPCI. In the first 6 h after PCI, aPTT ratio was 5.1 for patients with CKD as compared to 3.4 for those without (p < 0.001). In the 6 h timeframe, aPTT measurements were obtained significantly later in patients with CKD (2.4 versus 2.0 h, p = 0.017). There was no statistically significant difference in time to first aPTT measurement in the 12 h time frame.

### Table 1 continued

| Characteristic                        | Creatinine clearance (ml/min) | p value |
|---------------------------------------|-------------------------------|---------|
|                                       | <60 (n = 195)                 | ≥60 (n = 876) |
| Pre-procedural TIMI flow in IRA, n/N (%) |                               |         |
| 0/1                                   | 132/177 (74.6)                | 579/810 (71.5) | 0.41   |
| 2/3                                   | 45/177 (25.4)                 | 231/810 (28.5) |         |
| Post-procedural TIMI flow in IRA, n/N (%) |                               |         |
| 0/1                                   | 15/207 (7.9)                  | 14/840 (1.7) | <0.001 |
| 2/3                                   | 170/207 (91.9)                | 826/840 (98.3) |         |
| Multivessel disease, n/N (%)          | 96/188 (51.1)                 | 273/854 (32.0) | <0.001 |
| Chronic total occlusion, n/N (%)      | 39/188 (20.7)                 | 93/854 (10.9) | <0.001 |

SD standard deviation, IQR interquartile range, TIA transient ischemic attack, MI myocardial infarction, PCI percutaneous coronary intervention, CABG coronary artery bypass grafting, CAD coronary artery disease, IABP intra-aortic balloon pump, RCA right coronary artery, LCx left circumflex artery, LAD left anterior descending artery, LM left main artery, TIMI thrombolysis in myocardial infarction, IRA infarct related artery

a Anemia was defined as baseline hemoglobin less than 13 g/dl for males and less than 12 g/dl for females
b Creatinine clearance was estimated using the Cockcroft Gault equation
c Includes 15 patients who received hemodynamic support with the impella percutaneous left ventricular assist device

**Fig. 1** The first aPTT ratio measurement between sheath insertion and 6 h thereafter according to the administered heparin bolus for patients with and without creatinine clearance <60 ml/min. For each heparin bolus dose, the aPTT ratio was outside the recommended range (between 1.5 and 2 times control). Above 70 IU/kg UFH, aPTT was higher in patients with creatinine clearance <60 ml/min. The difference in aPTT ratio seemed to increase with increasing bolus.
Renal function and anticoagulation with unfractionated heparin

Figure 1 displays the aPTT ratio the first 6 after PPCI for patients with and without CKD according to different categories of UFH bolus. APTT ratios increased with increasing heparin bolus. Above 70 IU/kg, aPTT ratios were higher for patients with CKD and the difference in aPTT ratios between patients with and without CKD seemed to increase with increasing heparin bolus, particularly with heparin boluses in excess of 130 IU/kg. When the currently recommended UFH bolus was used (between 70 and 100 IU/kg), aPTT ratio was significantly higher in patients with CKD. Supplementary Figs. 1 and 2 display aPTT ratios measured between 6 and 12 h after PPCI and the first 12 h after PPCI respectively according to different categories of UFH bolus for patients with and without CKD. Results were similar to aPTT ratios within the first 6 h after PPCI, although the differences between patients with and without CKD were even more prominent. Figure 2a displays the proportion of patients with marked high aPTTs (≥4 times ULN) for patients with and without CKD according to heparin bolus. The proportion of patients with marked high aPTT ratios increased with increasing heparin bolus. For every heparin bolus the proportion of patients with excess anticoagulation was higher in patients with CKD. When the recommended bolus was used, the proportion of patients with excess anticoagulation among those with CKD was as high as 50.0%. Beyond 130 IU/kg the difference between patients with and without CKD who had a markedly high aPTT significantly increased. There was no statistically significant difference in markedly high aPTTs between the patients with CKD treated with ≤70 IU/kg, 70–100 or 100–130 IU/kg UFH bolus dose (p ≥ 0.21). The results were consistent when the relationship between CKD, heparin bolus and aPTT ratio were investigated for the other timeframes (between 6 and 12 h after PPCI and the first 12 h after PPCI; supplementary Figs. 3 and 4 respectively). Figure 2b displays the proportion of patients with subtherapeutic aPTT ratios for patients with and without CKD according to heparin bolus. The proportion of patients with subtherapeutic aPTT ratios decreased as the heparin bolus increased. The proportion of patients with subtherapeutic aPTT ratios tended to be smaller in patients with CKD, as compared to those without CKD. However the differences did not reach statistical significance. Figure 3 shows the distribution of patients with subtherapeutic, therapeutic, high and markedly high aPTT ratios recorded the first 6 h after start of the PPCI for patients with and without CKD according to UFH bolus. Supplementary Figures 5 and 6 show these data for the mean aPTT ratios recorded between 6 and 12 h after PPCI and for the first 12 h after PPCI respectively.

frame and first 12 h timeframe (8.4 and 6.6 h in patients with CKD as compared to 8.3 and 6.5 h in patients without CKD; p = 0.78 and p = 0.25 respectively).
Table 2 provides unadjusted and adjusted odds ratios (ORs) for aPTT beyond 4 times control according to the presence of CKD. CKD was an independent predictor of aPTT beyond four times control. This risk was independent of other components of the Cockcroft-Gault equation of estimated creatinine clearance. The risk of markedly high aPTTs in patients with CKD was mainly driven by the increased risk of markedly high aPTTs when a heparin bolus in excess of 130 IU/kg was administered. To investigate if the increase in proportion of patients with markedly high aPTTs with increasing heparin bolus dose was significantly greater for patients with CKD, as compared to those without, we included an interaction term between heparin bolus and creatinine clearance in the multivariable logistic regression analyses. There was a significant interaction between UFH bolus dose (above or below 130 IU/kg) and CKD, indicating that beyond 130 IU/kg, there was a stronger risk of markedly high aPTTs (measured within the first 6 h and the first 12 h after PPCI) in patients with CKD, as compared to those without.

Supplementary Table 2 provides unadjusted and adjusted ORs for aPTT beyond four times control according to estimated creatinine clearance as a continuous variable. Again, creatinine clearance was an independent predictor of markedly high aPTTs, both between 0 and 6 h after PPCI and 6–12 h after PPCI.

CKD and clinical outcome

Creatinine clearance <60 ml/min was independently associated with in hospital BARC type ≥3 bleeding and MACE (Table 2). Other predictors of in-hospital BARC type ≥3 bleeding and MACE are presented in Tables 2 and 3 of the online appendix. In a sensitivity analysis additionally adjusting for duration of heparin therapy and vitamin K antagonist treatment, CKD remained independently associated with in hospital BARC type ≥3 bleeding.

Discussion

The main findings of this study can be summarized as follows. After repeated UFH boluses a more persistent aPTT prolongation occurs in patients with CKD as compared to those without CKD. After multivariable adjustments, CKD was an independent predictor of aPTT prolongation. Patients with CKD are particularly at high risk of markedly high aPTTs and bleeding when bolus doses in excess of 130 IU/kg are used.

Several mechanisms may be responsible for the persistent aPTT prolongation in patients with CKD. First, the plasma protein binding of UFH might be reduced in patients with renal failure, thus increasing the free concentration in plasma. The strength of a drug’s action is related to the drug’s peak concentration in plasma. The peak concentration of a drug after an initial bolus is dependent on the bolus dose and the volume of distribution, which in turn is strongly dependent on plasma protein binding. Plasma protein bound drugs are largely inactive. Therefore, reduced plasma protein binding may result in more free drug available at the site of action. The binding

![Fig. 3](image-url)
Table 2  Relationship between creatinine clearance <60 ml/min/1.73 m² and aPTT ratio ≥4 times control

| Hours after procedure | Creatinine clearance | Unadjusted | Adjusted<sup>a</sup> | p value for interaction<sup>c</sup> | Adjusted<sup>b</sup> | p value for interaction<sup>c</sup> |
|-----------------------|----------------------|------------|----------------------|-----------------------------------|----------------------|-----------------------------------|
|                       | <60 ml/min % (n/N)   | OR 95% CI  | p value              | OR 95% CI                         | p value              | OR 95% CI                         | p value |
| 6 h<sup>d</sup>        | 65.4 (70/107)        | 2.87  1.73 | <0.001               | 2.21  1.31                        | 0.003               | 2.33  1.43                        | 0.001   |
| <130 IU/kg             | 44.9 (22/49)         | 1.59  0.86 | 0.14                 | 1.28  0.64                        | 0.48                | 0.014               | 1.12  0.56                        | 0.002   |
| ≥ 130 IU/kg            | 82.8 (48/58)         | 4.48  2.15 | <0.001               | 5.07  2.08                        | <0.001              | 6.31  2.69                        | 14.8    |
| 12 h<sup>e</sup>       | 59.1 (52/88)         | 0.14  3.16 | 8.37                 | 1.69  0.92                        | 3.11                | 0.093               | 1.48  0.78                        | 0.23    |
| <130 IU/kg             | 45.7 (16/35)         | 3.69  1.75 | 7.77                 | 1.08  0.43                        | 2.73                | 0.25                | 0.98  0.38                        | 0.48    |
| ≥ 130 IU/kg            | 67.9 (36/53)         | 5.87  3.00 | 11.5                 | 2.68  1.15                        | 6.27                | 0.023               | 2.14  0.87                        | 0.10    |
| First 12 h<sup>f</sup> | 62.6 (122/195)       | 0.4.   2.46 | 4.69                 | 1.98  1.33                        | 2.93                | 0.001               | 1.86  1.25                        | 0.002   |
| <130 IU/kg             | 45.2 (38/84)         | 2.2   1.37 | 3.53                 | 1.19  0.68                        | 2.06                | 0.55                | 1.03  0.58                        | 0.003   |
| ≥ 130 IU/kg            | 75.7 (84/111)        | 4.5   2.78 | 7.28                 | 3.66  2.00                        | 6.70                | <0.001              | 3.62  1.95                        | 6.73    |

APTT activated partial thromboplastin time, CrCl creatinin clearance

<sup>a</sup> Calculated using multivariable logistic regression analyses adjusting for gender, bodymass, length, time to first aPTT measurement and heparin bolus dose

<sup>b</sup> Calculated using multivariable stepwise backward elimination logistic regression analyses including the following candidate covariables: gender, body mass, length, heparin bolus dose, time to first aPTT measurement, history of hypertension, diabetes, dyslipidemia, current smoking, stroke or TIA, peripheral artery disease, malignant disease, bleeding, recent surgery, previous MI, family history of CAD, anemia, leucocyte count, thrombocyte count, use of GP IIb/IIIa inhibitor, cardiogenic shock, and use of IABP

<sup>c</sup> p value for the interaction term between heparin bolus dose (≥130 versus <130 IU/kg) and creatinine clearance (<60 versus ≥ 60 ml/min)

<sup>d</sup> The first APTT determined between arterial sheath insertion and 6 h hereafter

<sup>e</sup> The first APTT determined between 6 and 12 h after arterial sheath insertion

<sup>f</sup> The first APTT determined between arterial sheath insertion and 12 h hereafter
of anion drugs to plasma proteins in patients with renal failure is reduced [16]. Thus, the free fraction of unfractionated heparin, an anion drug, might be enhanced in patients with renal failure, explaining the aPTT prolongation in patients with CKD found in the current study. Second, in low and therapeutic doses, heparin is cleared by the reticuloendothelial system [8]. Renal failure is associated with abnormal function of the reticuloendothelial system and impaired function of macrophages [17–19]. Therefore, we hypothesize that clearance of heparin by the reticuloendothelial system might be reduced in patients with CKD. Third, in high doses UFH is cleared by the kidneys [9, 10]. Therefore, accumulation of heparin and its anticoagulant properties may occur in patients with decreased renal function. Fourth, it is possible that a higher prevalence of other, unmeasured causes of aPTT prolongation may have contributed to aPTT prolongation in patients with CKD, such as vitamin K deficiency [20], coagulation factor deficiencies [21], acquired clotting factor inhibitors [22], disseminated intravascular coagulation [23], and massive blood transfusion leading to a dilutional coagulopathy [24]. These disorders however are extremely rare, therefore it is unlikely that imbalances in the prevalence of these disorders among patients with and without CKD are the causative factors for aPTT prolongation.

Consistent with previous studies, CKD was associated with an increased risk of bleeding after PPCI after adjustment for confounders [1]. Possible explanations for the increased bleeding risk among patients with CKD, include functional abnormalities in platelets, abnormal platelet-vessel wall interaction and adverse effects of anemia [25]. The present analysis suggests an additional, modifiable mechanism. We showed that CKD was associated with high aPTT values, which are known to be associated with an increased risk of severe bleeding [12, 26]. It is possible that this is the result of impaired clearance of UFH secondary to CKD.

### Limitations

Several limitations to the present analysis deserve mentioning. First, in a significant proportion of patients the administered bolus dose heparin exceeded the currently recommended 70-100 IU/kg bolus dose [3, 4]. We used a fixed bolus dose UFH, corresponding to a wide variety of weight-adjusted doses, and this allowed us to investigate the effect of a broad variety of bolus doses on aPTT in patients with and without CKD. Moreover, the evidence in favour of the currently recommended bolus dose is scarce. In fact, in the present analysis, in as little as 16.8% of patients in whom the recommended bolus dose was used the aPTT was in the recommended aPTT range, and in as many as 62% of patients the aPTT was in excess of the recommended range. Second, the ACC/AHA currently recommend using ACT to monitor heparin treatment during PPCI [4]. However, it has been shown that aPTT is more closely related to heparin concentration in blood compared to ACT [27, 28]. Thus, aPTT is the appropriate measure to investigate if accumulation of heparin occurs in STEMI patients with CKD. Finally, as a result of the relatively small number of patients included in the analysis, it is possible that we could not detect significant differences in therapeutic, subtherapeutic high and markedly high aPTT ratios for patient with and without CKD, when different UFH bolus doses below 130 IU/kg were used.

### Table 3

| Outcome                  | Creatinine clearance | No. (%) of patients | Unadjusted | Adjusted |
|--------------------------|----------------------|---------------------|------------|----------|
|                          |                      |                     | OR         | 95% CI   | p value |
|                          |                      |                     |            |          |         |
| In hospital BARC type ≥3 bleeding | <60 (ml/min) | 63/195 (32.3) | 4.33 | 2.98 | 6.29 | <0.001 |
|                          | ≥60 (ml/min) | 87/876 (9.9) | 1 | – | – | – |
| In hospital MACE         | <60 (ml/min) | 51/195 (26.2) | 4.02 | 2.69 | 6.00 | <0.001 |
|                          | ≥60 (ml/min) | 71/876 (8.1) | 1 | – | – | – |

OR odds ratio, CI confidence interval, B ARC bleeding academic research consortium, MACE major adverse cardiac event

a Calculated using logistic regression analysis adjusting for the use of GP IIb/IIIa inhibitor, intra-aortic balloon counterpulsation, gender, body mass index, and multivessel disease (with or without chronic total occlusion). The results of the multivariable model are given in online supplementary Table 3.

b Calculated using logistic regression analysis adjusting for family history of coronary artery disease, GP IIb/IIIa inhibitor, intra-aortic balloon counterpulsation, cardiogenic shock, anemia, platelet count, thrombocyte count, infarct related artery and multivessel disease (with or without chronic total occlusion). The results of the multivariable model are given in online supplementary Table 4.
Conclusion

In STEMI patients with CKD undergoing PPCI, the risk of severe more persistent aPTT prolongation strongly increases with increasing heparin bolus, particularly beyond 130 IU/kg. Therefore, to reduce the risk of bleeding in these vulnerable patients, a UFH bolus dose below 130 IU/kg should be used. Adequately powered randomised controlled trials investigating the optimal UFH bolus dose in STEMI patients undergoing PPCI are needed.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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