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Original Article

# Effects of Bivalirudin and Unfractionated Heparin on Liver and Renal Function in Chinese Patients with Coronary Artery Disease Undergoing Coronary Angiography with/without Percutaneous Coronary Intervention

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## Abstract

***Background and Aims:*** Unfractionated heparin (UFH) and bivalirudin are widely used as anticoagulants in cardiovascular medicine, including for thrombosis prevention during coronary angiography (CAG) and percutaneous coronary intervention (PCI). Little is known of the effects of UFH and bivalirudin on liver and kidney function in patients subjected to these procedures. This study compared the effects of bivalirudin and UFH on liver/renal function in patients with coronary artery disease who underwent CAG, with or without PCI. ***Methods:*** The study comprised 134 consecutive patients (40–89 years-old), who underwent CAG (or CAG and PCI); among them, 66 and 68 patients were subject to, respectively, bivalirudin or UFH. The following indicators of liver/renal function were measured before and after the procedures: plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, estimated glomerular filtration rate (eGFR), creatinine clearance, and serum creatinine. Patients were further stratified by severity of chronic kidney disease (CKD), based on original eGFR. ***Results:*** Relative to baseline, in the bivalirudin group, ALT and AST were higher after CAG ($p$=0.005, 0.025), while blood urea nitrogen and serum creatinine were lower ($p$=0.049, <0.001). In the UFH group, ALT, AST, eGFR, and creatinine clearance were lower after CAG ($p$≤0.001, all). Patients given bivalirudin with moderate or severe CKD, but not those with mild CKD, gained significant improvement in kidney function. ***Conclusions:*** Relative to UFH, bivalirudin may better safeguard the renal function of patients with coronary artery disease who undergo CAG, especially patients with moderate-to-severe renal insufficiency. UFH may cause less liver damage than bivalirudin.

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## Introduction

Coronary angiography (CAG) and percutaneous coronary intervention (PCI) are recommended for patients with a high risk of acute coronary syndrome. These procedures require adjunctive antithrombotic therapy with anticoagulants and antiplatelet agents.[1] However, there is no gold standard antithrombotic agent, with both optimal clinical benefits and acceptable risk of complications.

Unfractionated heparin (UFH) is one of the oldest agents applied for prevention and treatment of arterial and venous thromboembolism, and is used widely as an anticoagulant during CAG and PCI for its convenience, safety, and low cost. In addition, many new anticoagulation agents have appeared in clinical practice in recent decades. Bivalirudin is a direct thrombin inhibitor, extracted from the derivative hirudin fragment, which is widely used in patients undergoing PCI. Compared with UFH or glycoprotein IIb/IIIa inhibitors, the clearance of bivalirudin is less dependent on renal function,[2] and bivalirudin is characterized by rapid onset and fewer complications, with a short half-life of 25 minutes under normal renal function.[3]

Bivalirudin is currently considered an alternative for patients with progressed and advanced chronic kidney disease (CKD).[4] CKD is prevalent among patients with coronary artery disease (CAD) and has been associated with shorter survival, bleeding, and thrombosis as a complication of PCI.[5–7] This may be due to the multiple hemostatic perturbations in patients with CKD.[8–9]

Hemostasis is largely modulated by protein synthesis

**Keywords:** Bivalirudin; Unfractionated heparin; Coronary artery disease; Coronary angiography; Percutaneous coronary intervention; Liver function.

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CAD, coronary artery disease; CAG, coronary angiography; CCr, creatinine clearance; CKD, chronic kidney disease; CK-MB, myoglobin isoenzyme of creatine phosphokinase; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LMWH, low-molecular-weight heparin; MHB, myohemoglobin; PCI, percutaneous coronary intervention; SCr, serum creatinine; TC, total cholesterol; TG, triglyceride; UA, uric acid; UFH, unfractionated heparin.

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and degradation in the liver. In patients with severe liver disease, the hemostatic system is always dysfunctional because of hepatic protein synthesis disorders.[10] Yet, studies concerning the effects of anticoagulants on liver function are limited.

To aid clinicians' selection of anticoagulant, the present study evaluated the relative effects of bivalirudin and UFH on the liver and kidney functions of patients with CAD who underwent CAG, with or without PCI.

## Methods

### *Participants*

Participants were recruited from consecutive patients who underwent CAG with or without PCI at the First Affiliated Hospital of Nanjing Medical University from 8 July 2017 to 30 June 2020. Patients with any of the following were excluded: massive hemorrhage within 1 month; severe thrombocytopenia (blood platelet count $<20\times10^9$/L); dialysis-dependent end-stage renal failure; or allergy to bivalirudin or hirudin. Massive hemorrhage sufficient for exclusion was defined as clinically overt bleeding, accompanied by a decrease in hemoglobin ≥2 g/dL, requiring a transfusion of ≥2 U of packed red blood cells, and occurring at a site of concern (intracranial, intraocular, intraspinal, intra-articular, intramuscular with compartment syndrome, pericardial, or retroperitoneal), or resulting in death.[11]

Finally, the study population consisted of 134 patients, aged 40 to 89 years. Among them, 66 and 68 were administered, respectively, bivalirudin and UFH as antithrombotic therapy during CAG.

### *Application of bivalirudin and UFH during CAG*

Bivalirudin was given intravenously at a loading dose of 0.75 mg/kg before CAG, and then at 1.75 mg/kg/h as intravenous drip until the end of the surgery, with an additional 4 h intravenous drip for those who underwent PCI. During CAG, patients with creatinine clearance (CCr <30 mL/m and not on dialysis were given bivalirudin at a rate of 1.0 mg/kg/h. UFH was given intravenously at a dose of 2,000 U before angiography, with an additional 0-14,000 U of UFH during the operation on an as-needed basis for those undergoing PCI. Iodixanol injection was used as contrast agent for CAG and PCI.[12]

### *Clinical design*

Demographic data, medical history, and the results of laboratory measurements of the patients, including alanine aminotransferase (ALT, in U/L), aspartate aminotransferase (AST, in U/L), blood urea nitrogen (BUN, in mmol/L), serum creatinine (SCr, in μmol/L), total cholesterol (TC, in mmol/L), triglyceride (TG, in mmol/L), fasting high-density lipoprotein (HDL) cholesterol (in mmol/L), fasting low-density lipoprotein (LDL) cholesterol (in mmol/L), fasting blood glucose (FBG, in mmol/L), uric acid (UA, in μmol/L), myoglobin isoenzyme of creatine phosphokinase (CK-MB, in ng/mL), myohemoglobin (MHB, ng/mL), red blood cell count ($\times10^{12}$/L), white blood cell count ($\times10^9$/L), platelet count ($\times10^9$/L), hemoglobin (in g/L), and the Gensini score, were collected and sorted in a dedicated database. The differences in the following laboratory parameters before (baseline) and after CAG were compared between the bivalirudin and UFH groups: ALT, AST, creatinine clearance (CCr), and estimated glomerular filtration rate (eGFR). The results of CAG were reported by at least two experienced cardiologists immediately at the end of the procedure. The Gensini score was used to evaluate the severity of CAD,[13] after all procedures and other data collection.

The CCr was estimated using the Cockcroft-Gault equation, as follows: CCr in mL/m=(140-age, y)×(weight in kg)×(0.85, if female)/(72×SCr in mg/dL).[14] The eGFR in this Chinese population was calculated using the "CKD-EPI" equation as follows, with the GFR expressed as mL/m/1.73 $m^2$, SCr as mg/dL. and age in years. For females with SCr ≤(>)0.7, then $eGFR=(144)\times(SCr/0.7)^a\times(0.993)^{age}$, where a=−0.329 (−1.209). For males with SCr ≤(>)0.9, then $eGFR=(141)\times(SCr/0.9)^a\times(0.993)^{age}$, where a=−0.411 (−1.209).[15]

Patients were stratified according to eGFR as having mild (≥60 mL/m), moderate (30–69 mL/m), or severe (<30 mL/m) CKD.[16]

### *Ethical approval and consent to participate*

All patients provided written informed consent. The ethics committee of Nanjing Medical University approved all the experimental protocols.

### *Data analysis*

The data analysis was performed using the Statistical Package for Social Sciences software (ver. 16.0; SPSS, Chicago, IL, USA). Skewed data are presented as median (interquartile range), normal data as mean±standard deviation, and categorical data as absolute values. Data analyses utilized chi-squared tests to determine differences in sex, smoking status, drinking status, and medical history. Independent samples *t*-tests, one-way analysis of variance, and paired samples *t*-tests were applied to normal data, as appropriate. Other baseline characteristics (non-normal data) were examined by Mann-Whitney and Wilcoxon rank tests. Multi-factor logistic regression analysis was applied to identify the risk factors to liver function and kidney function. A *p*-value of <0.05 was considered significant in the 2-tailed tests.

## Results

### *Baseline characteristics of the subjects*

Compared with the patients given UFH in this study, the patients in the bivalirudin group were significantly older ($p<0.001$), and with higher levels of ALT, SCr, BUN ($p<0.001$, each), and AST ($p=0.002$). In addition, patients in the bivalirudin group had significantly higher rates of hypertension, cerebral infarction ($p=0.002$, both) and CAD ($p=0.011$). The HDL cholesterol ($p=0.280$), LDL cholesterol ($p=0.274$), and FBG ($p=0.836$) (Table 1).

### *Baseline characteristics of the bivalirudin group stratified by CKD severity*

Renal function was judged prior to CAG as mild, moderate, or severe based on eGFR, according to the international standard (Table 2).[16] Among all the baseline characteristics considered, levels of only the following increased significantly with classification of severity: SCr, BUN, UA, and MHB ($p<0.001$, all). Only FBG decreased with severity of CKD ($p=0.032$).

**Table 1. Baseline characteristics of the subjects by the anticoagulants used in CAG and PCI**

| | Bivalirudin | UFH | *p* |
|---|---|---|---|
| Subjects, *n* | 66 | 68 | — |
| Age, years | 71.09±11.53 | 62.68±9.18 | <0.001 |
| Sex, M/F | 51/15 | 50/18 | 0.615 |
| Weight, kg | 69.39±11.05 | 66.72±7.82 | 0.109 |
| Hypertension, Y/N | 55/11 | 40/28 | 0.002 |
| Diabetes mellitus, Y/N | 26/40 | 19/49 | 0.160 |
| Cerebral infarction, Y/N | 23/43 | 8/60 | 0.002 |
| Smoke, Y/N | 25/41 | 31/37 | 0.327 |
| Drink, Y/N | 15/51 | 11/57 | 0.338 |
| ALT, U/L | 22.65 (14.28–34.23) | 35.00 (27.93–44.00) | <0.001 |
| AST, U/L | 22.65 (17.95–31.10) | 27.85 (20.93–40.78) | 0.002 |
| SCr, μmol/L | 117.00 (80.85–186.95) | 61.20 (51.83–73.13) | <0.001 |
| BUN, mmol/L | 8.36 (6.10–13.95) | 5.69 (4.75–6.81) | <0.001 |
| TC, mmol/L | 4.04±1.23 | 3.95±1.05 | 0.664 |
| TG, mmol/L | 1.20 (0.93–1.62) | 1.39 (0.94–2.04) | 0.177 |
| HDL, mmol/L | 0.98±0.29 | 1.02±0.23 | 0.280 |
| LDL, mmol/L | 2.48±0.90 | 2.32±0.78 | 0.274 |
| FBG, mmol/L | 5.03 (4.34–6.13) | 4.99 (4.48–6.26) | 0.836 |
| UA, μmol/L | 427.29±134.88 | 318.81±99.09 | <0.001 |
| CK-MB, ng/mL | 3.79 (2.39–12.18) | 2.05 (1.66–3.62) | <0.001 |
| MHB, ng/mL | 24.00 (11.30–43.64) | 13.18 (10.36–19.95) | 0.003 |
| Gensini score | 86.00 (37.75–126.00) | 48.00 (12.88–93.00) | 0.011 |

Skewed data are presented as median (interquartile range), normal data as mean±standard deviation, and categorical data as absolute values. N, no; Y, yes.

### *Liver and renal function tests before and after CAG*

To evaluate the potential benefits of bivalirudin for patients with CKD, the differences in ALT, AST, BUN, and SCr from baseline after CAG were examined (Table 3). For patients given bivalirudin, the serum levels of ALT and AST were significantly higher after CAG ($p$=0.005, 0.025, respectively), which indicated possible liver injury, while BUN and SCr were lower ($p$=0.049, <0.001), suggesting a renoprotective effect. Significant increases in the calculated CCr ($p$=0.001) and eGFR ($p$=0.022) also indicated improvement in renal function.

In the UFH group, the serum levels of ALT and AST significantly declined after CAG compared with the baseline ($p$<0.001, =0.001); while BUN ($p$=0.009), SCr ($p$<0.001), CCr ($p$<0.001) and eGFR ($p$<0.001) decreased. Thus, UFH may exert some positive effects on the liver but not on the kidney.

### *Differences in eGFR after CAG according to eGFR and Gensini score*

To explore the renal benefits of bivalirudin among patients with different original renal functions, patients were apportioned to three groups according to eGFR; as mild, moderate or severe CKD (Table 4). Patients with moderate or severe CKD gained significant renal benefits ($p$=0.018, 0.039), while patients with mild CKD failed to show obvious improvements in kidney function ($p$=0.890). This suggested that bivalirudin may be more likely to exert renoprotective effects in patients with moderate-to-severe renal insufficiency.

Gensini scoring is widely used for determining the severity of CAD (Table 4). To investigate further the renal benefits of bivalirudin in patients with different severities of CAD, patients were apportioned to three groups according to the range interquartile of Gensini score. The eGFR data after CAG in patients with different severities of CAD showed no significant difference, suggesting that the renal benefits of bivalirudin may be not related to the severity of CAD.

### *Risk factors of liver and renal effects based on multi-factor logistic regression analysis*

To identify risk factors of liver and renal effects among the overall population, a multi-factor logistic regression analysis was conducted (with the forward selection-conditional method; Table 5). The following were determined to affect renal function independently: the anticoagulant used in PCI ($p$<0.001); weight ($p$=0.001); and, Gensini score ($p$=0.030). Bivalirudin increased the probability of improvement in renal function by 82.7% compared with UFH.

Similarly, UFH exerted a hepatoprotective effect that was independent of other potentially confounding factors. In the UFH group, the plasma levels of ALT and AST were, respectively, 82.2% and 65.8% in the bivalirudin group.

## Discussion

In this study, we compared the effects of bivalirudin and UFH on liver and renal function in patients with CAD who

**Table 2. Baseline characteristics of patients' prior bivalirudin by CKD severity**

| | Mild | Moderate | Severe | *p* |
|---|---|---|---|---|
| Subjects, *n* | 26 | 25 | 15 | — |
| Age, years | 67.92±11.92 | 72.84±12.21 | 73.67±8.76 | 0.195 |
| Sex, M/F | 19/7 | 19/6 | 13/2 | 0.595 |
| Weight, kg | 71.87±11.41 | 68.00±10.58 | 67.43±11.11 | 0.343 |
| HTN, Y/N | 19/7 | 22/3 | 14/1 | 0.179 |
| Diabetes mellitus, Y/N | 8/18 | 9/16 | 9/6 | 0.165 |
| CI, Y/N | 11/15 | 9/16 | 3/12 | 0.348 |
| Smoke, Y/N | 10/16 | 9/16 | 6/9 | 0.966 |
| Drink, Y/N | 5/21 | 7/18 | 3/12 | 0.726 |
| ALT, U/L | 26.75 (15.18–39.45) | 19.60 (13.95–31.25) | 24.00 (12.50–31.60) | 0.216 |
| AST, U/L | 25.35 (18.35–35.23) | 23.50 (18.80–29.25) | 18.20 (14.00–21.90) | 0.091 |
| SCr, μmol/L | 74.07±19.33 | 139.50±30.40 | 286.75±93.49 | <0.001 |
| BUN, mmol/L | 6.32±2.83 | 10.26±4.07 | 16.76±4.48 | <0.001 |
| TC, mmol/L | 3.92±1.24 | 4.10±1.24 | 4.15±1.25 | 0.818 |
| TG, mmol/L | 1.55±0.78 | 1.26±0.43 | 1.18±0.52 | 0.112 |
| HDL, mmol/L | 0.89±0.28 | 1.08±0.28 | 0.95±0.27 | 0.068 |
| LDL, mmol/L | 2.36±0.83 | 2.48±1.00 | 2.70±0.89 | 0.517 |
| FBG, mmol/L | 5.46 (4.84–6.69) | 4.91 (4.37–5.96) | 4.47 (4.04–5.35) | 0.032 |
| UA, μmol/L | 346.01±103.48 | 468.71±118.81 | 499.13±142.44 | <0.001 |
| CK-MB, ng/mL | 3.75 (2.39–11.35) | 3.15 (2.06–7.70) | 6.07 (2.52–14.99) | 0.426 |
| MHB, ng/mL | 14.50 (8.54–22.28) | 25.00 (12.26–39.44) | 78.88 (34.78–116.36) | <0.001 |
| Gensini score | 101.13±85.63 | 91.26±60.57 | 81.90±80.82 | 0.730 |

Data points are as reflected by eGFR. Skewed data are presented as median (interquartile range), normal data as mean±standard deviation, and categorical data as absolute values. CI, cerebral infraction; HTN, hypertension; N, no; Y, yes.

underwent CAG, with or without PCI. For data analysis, the subjects were apportioned to either the bivalirudin or UFH group, as appropriate. After rigorous laboratory measurements, data collection, and statistical comparisons, we made some surprising and interesting discoveries.

In the group given UFH, the ALT and AST levels after CAG

**Table 3. Laboratory parameters reflecting liver and renal functions before and after CAG in the bivalirudin and UFH groups**

| | Before PCI | After PCI | *p* |
|---|---|---|---|
| Bivalirudin | | | |
| ALT, U/L | 22.65 (14.28–34.23) | 27.00 (21.55–36.00) | 0.005 |
| AST, U/L | 22.65 (17.95–31.10) | 25.50 (19.20–32.95) | 0.025 |
| BUN, mmol/L | 10.18±5.43 | 9.53±5.10 | 0.049 |
| SCr, μmol/L | 147.19±94.99 | 136.68±84.91 | <0.001 |
| CCr, mL/m | 53.54±33.61 | 58.02±38.56 | 0.001 |
| eGFR, mL/m | 55.21±31.49 | 57.79±32.19 | 0.022 |
| UFH | | | |
| ALT, U/L | 35.00 (27.93–44.00) | 28.70 (19.43–40.58) | <0.001 |
| AST, U/L | 27.85 (20.93–40.78) | 27.00 (19.48–38.48) | 0.001 |
| BUN, mmol/L | 5.81±1.52 | 5.37±1.62 | 0.009 |
| SCr, μmol/L | 64.43±17.20 | 68.83±17.44 | <0.001 |
| CCr, mL/m | 99.37±26.69 | 92.07±21.93 | <0.001 |
| eGFR, mL/m | 100.53±15.41 | 96.80±15.53 | <0.001 |

**Table 4. Baseline and postoperative[a] eGFR values according to severity of CKD and Gensini score in the bivalirudin group**

| | Subjects, *n* | Baseline | Postoperative | *p* |
|---|---|---|---|---|
| CKD[b] | | | | |
| Mild | 26 | 88.73±19.43 | 90.82±22.32 | 0.406 |
| Moderate | 25 | 41.89±7.80 | 45.03±9.73 | 0.018 |
| Severe | 15 | 19.33±6.57 | 21.80±7.31 | 0.039 |
| Gensini score | | | | |
| <37.5 | 16 | 55.31±37.62 | 56.50±36.01 | 0.542 |
| 37.5–126 | 35 | 52.33±28.23 | 55.35±30.47 | 0.099 |
| ≥126.5 | 15 | 61.86±32.91 | 64.84±33.13 | 0.064 |

Data are presented as mL/m. [a]Before and after CAG; [b]eGFR ranges for mild, moderate, and severe CKD were ≥60, 30–60, and <30 mL/m, respectively.

were significantly lower compared with the baseline levels. This appears to conflict with previous studies. According to the National Library of Medicine's LiverTox database, hepatotoxicity is the most frequently reported adverse event associated with heparins,[17–24] and 8% of the events were due to UFH.[18] The association between UFH and elevations in serum AST was first reported in 1975.[19] However, although AST levels were higher after heparin administration, such elevations were asymptomatic and did not lead to severe liver injury. Conjectured mechanisms included non-hepatic sources for the enzymes,[25] induction of these enzymes in hepatocytes,[26] reduction in the clearance of these enzymes from circulation, and hepatocellular membrane modification.[27,28] In a recent randomized study, circulating mir-122 was selected as a biomarker to identify liver cell necrosis. The researchers opined that heparins, including UFH, may cause a transient, low-level death of hepatocytes, and the subsequent activation of innate immune response may promote the injury.[29]

For clarification, we explored the data further. Among the 68 patients in the UFH group, 8 had higher pre-CAG ALT levels than normal and the remaining 60 had normal pre-CAG ALT levels. While among the eight patients who had higher pre-CAG ALT levels, 4 showed ALT descent to a normal level after CAG. Besides, 14 patients had higher pre-CAG AST levels among the 68 subjects, and only 3 patients' AST level descended to a normal level after CAG. After taking an intersection, we found that only two patients with both higher pre-CAG ALT and AST levels among the 68 subjects achieved improved ALT and AST levels, which descended to normal (where elevation of ALT and AST was defined as >69 and >45 U/L).

On the other hand, among the 66 patients given bivalirudin, 64 had normal pre-CAG ALT levels and only 2 had higher pre-CAG ALT levels than normal. While among the 64 patients who had normal pre-CAG ALT levels, 4 patients' ALT rose to an abnormal level after CAG. Besides, 62 patients had normal pre-CAG AST levels among the 66 subjects, and 7 patients' AST level rose to an abnormal extent after CAG. After taking an intersection, two patients with both normal pre-CAG ALT and AST levels in the bivalirudin group showed worse ALT and AST levels, which became abnormal (where normal ALT and AST was considered 13–69 U/L and ≤45 U/L).

It was reported that cardiac hepatopathy, which is used to describe any liver damage caused by cardiac disorders in the absence of other possible causes of liver damage, can be examined as congestive hepatopathy and acute cardiogenic liver injury. Furthermore, acute cardiogenic liver injury is

**Table 5. Multi-factor logistic regression analysis of associations between anticoagulant (bivalirudin or UFH) and basic characteristics of patients and renoprotective effects[a], ΔALT[b], and ΔAST[c]**

| | OR (95% CI) | *p* |
|---|---|---|
| Renoprotective effects[a] | | |
| Anticoagulant | 0.173 (0.073–0.409) | <0.001 |
| Weight | 0.922 (0.878–0.968) | 0.001 |
| Gensini score | 1.007 (1.001–1.013) | 0.030 |
| ΔALT[b] | | |
| Anticoagulant | 0.178 (0.078–0.404) | <0.001 |
| TG | 0.478 (0.244–0.936) | 0.031 |
| ΔAST[c] | | |
| Anticoagulant | 0.342 (0.155–0.755) | 0.008 |
| Sex | 0.395 (0.159–0.980) | 0.045 |
| Gensini score | 1.011 (1.005–1.018) | 0.001 |

[a]The renoprotective effect was calculated as $\Delta eGFR=eGFR_2-eGFR_1$; where $eGFR_1$ and $eGFR_2$ are the eGFR values before and after CAG, respectively. ΔeGFR >0 (<0) indicates positive (negative) renoprotective effects. The covariates were age, sex, weight, medical history, smoking and drinking status, plasma levels of ALT, AST, BUN, TC, TG, HDL, LDL, FBG, UA, CK-MB and MHB, and Gensini score. [b]$\Delta ALT=ALT_2-ALT_1$; where $ALT_1$ and $ALT_2$ are the ALT values before and after CAG, respectively. The covariates were age, sex, weight, medical history, smoking and drinking status, plasma level of AST, SCr, BUN, TC, TG, HDL, LDL, FBG, UA, CK-MB and MHB, and Gensini score. [c]$\Delta AST=AST_2-AST_1$; where $AST_1$ and $AST_2$ are the AST values before and after CAG, respectively. The covariates were age, sex, weight, medical history, smoking and drinking status, plasma level of ALT, SCr, BUN, TC, TG, HDL, LDL, FBG, UA, CK-MB and MHB, and Gensini score.

most commonly associated with acute cardiocirculatory failure caused by acute myocardial infarction, acute decompensated hepatic failure, or myocarditis.[30] In acute cardiogenic liver injury patients, the laboratory measurements showed elevation in transaminase and lactate dehydrogenase levels.[30–32] Thus, we hypothesize that the decline in transaminase in the UFH group was mainly due to the improvement in coronary circulation and myocardial oxygen delivery after the CAG; the liver benefited as well, and the mild liver injury from the UFH was more than compensated for.

Thus, regarding liver function, patients undergoing CAG and PCI may benefit more from UFH, relative to bivalirudin. Notably, heparins were shown to alleviate liver injury in several animal studies.[33,34]

In addition, significant renal improvement was observed in the bivalirudin group compared with the UFH (Supplementary Fig. 1 and 2). This was especially true for patients suffering from moderate or severe CKD; patients with eGFR ≥60 mL/m showed no significant renal benefits from bivalirudin. The paired-samples tests suggested that the renoprotective effects of bivalirudin may not be associated with the severity of CAD. In other words, the renal benefits of bivalirudin may be enjoyed by patients with either mild or severe CAD.

This study has several limitations. First, the sample size is small, which may lead to inaccuracy of the results and conclusions. Further studies with large samples are warranted. Second, the results would be more convincing if patients with similar renal function were matched with the bivalirudin group as a control group. The mechanisms of the effects on liver and kidney of bivalirudin and UFH have not been clarified, and we intend further explorations of these questions in the future.

Despite its limitations, this study is the first to discuss the renal benefits of bivalirudin, and to suggest a possible liver benefit associated with UFH, in patients undergoing CAG and PCI. This report may help physicians choose anticoagulants for patients with abnormal liver and kidney function. We have planned a future multicenter, large-sample, and multi-ethnic study to verify these conclusions and explore the mechanisms.

## Conclusions

As anticoagulants used for CAG and PCI procedures, bivalirudin may provide better benefit to renal function compared with UFH, especially in patients with moderate-to-severe renal insufficiency. On the other hand, UFH is less likely to cause liver injury than bivalirudin.

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## Conflict of interest

The authors have no conflict of interests related to this publication.

## Author contributions

Guarantor (EJ), conception of the study (EJ), initial drafting of the paper (QJ), enrollment of participants and collection of data (JH), supervision of the enrollment of patients and collection of data (EJ), and data analysis and review of the manuscript for important intellectual content (EJ, QJ, JH).

## Data sharing statement

All data are available upon request.

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