Dear Editor,

Anticoagulants-related nephropathy (ARN) came into the public view since the novel oral anticoagulants (NOAC) entered the medical insurance directory. Similarly, warfarin is also known to have adverse renal affects by causing microhemorrhage. However, there is some uncertainty and obstacles in the diagnosis, we are not familiar with ARN. The typical case manifests as unexplained acute kidney injury with diffuse glomerular hemorrhage and often acute tubular necrosis due to renal tubular obstruction by red blood cell casts, accompanied by gross hematuria or not [1,2]. Interstitial nephritis related to NOAC was only reported in sporadic case reports and none was accompanied by ARN. The typical case manifests as unexplained acute kidney injury with diffuse glomerular hemorrhage and often acute tubular necrosis due to renal tubular obstruction by red blood cell casts, accompanied by gross hematuria or not [1,2]. Interstitial nephritis related to NOAC was only reported in sporadic case reports and none was accompanied by ARN [3–7]. Recently we came across a case of biopsy-proven subacute interstitial nephritis accompanied by ARN after oral dabigatran. We would like to present it here for alarm of similar cases. The patient had given the written informed consent to publish her case.

A 62 years old woman with hypertension and paroxysmal atrial fibrillation was admitted because of gross hematuria and elevation of serum creatinine. One month ago, she was prescribed dabigatran (110 mg twice a day) for paroxysmal atrial fibrillation and a high Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack (CHADS2) score of 1, the simplified Canadian Cardiovascular Society Algorithm for patients of non-valvular atrial fibrillation. Gross hematuria occurred a week later with frequent urination at night (4-5 times a night) without pain or urgency when she passed urine. A week ago, her serum creatinine was elevated (215.0 μmol/L) with moderate anemia (hemoglobin 80 g/L). Urinalysis demonstrated massive normal (100%) red blood cells and moderate proteinuria (2426.0 mg/(g.cr))

However, there was no evidence of membranous nephropathy by either electron microscopy or light microscopy. Interesting finding was a lot of intra-tubular protein casts (Figure 2). We further examined the specimens with human hemoglobin antibody staining (Abcam Company Ltd, item number: ab92492) according to instructions of the manual and confirmed the protein in the tubules to be human hemoglobin (Figure 3), which was fit for ARN.

Eleven days after kidney biopsy, prednisone 25 mg/day was prescribed since serum creatinine did not return normal after supportive therapy. Three weeks later, her serum creatinine level reduced to 103 μmol/L with a serum hemoglobin of 109 g/L. Serum creatinine level turned normal at 53 days (89 μmol/L) after steroid and remained normal during the follow-up of more than 1 year with minor proteinuria (0.2–0.3 g/d) and no anemia (hemoglobin 118–120 g/L, Supplementary Table 1). Prednisone dose was gradually reduced and stopped after 3 months under the supervision of physicians. Thereafter, aspirin replaced anticoagulants.

We presented here a case of biopsy-proven subacute interstitial nephritis accompanied by intra-tubular hemoglobin casts, one of the characteristics of ARN, caused probably by dabigatran with a long follow-up of more than a year, which has not been published in literatures. This case manifested with gross hematuria, acute kidney injury, slightly prolonged thrombin time, moderate anemia and a large quantity of intra-tubular hemoglobin casts which presumed to occur around 1 week after dabigatran. Serum creatinine level elevated by
more than 50% with the peak value of 215 μmol/L then it did not continue to elevate after discontinuation of dabigatran. With the subsequent supportive therapy, it decreased to 123 μmol/L then reduced to 89 μmol/L with the help of prednisone (half of the full dose). The patient had no past kidney diseases but kidney biopsy demonstrated focal proliferative glomerulonephritis and minor microscopic hematuria could be traced back to 43 days before admission. In the meanwhile, subacute interstitial nephritis rather than acute tubular necrosis may be one of the causes of acute kidney injury. To our knowledge, ours is the first report of diffuse intertubular hemorrhage confirmed by hemoglobin antibody immunohistochemical staining and the first report of simultaneous interstitial nephritis and some characteristics of ARN probably caused by dabigatran in a senior patient [1,3–7] (Table 1).

The pathophysiological mechanism behind NOAC-induced AIN is not known, which was presumed to be associated with either a type I or type IV [5] or cell-mediated hypersensitivity reaction [6]. Besides, the obstruction of hemoglobin cast, blood loss and metabolites of bleeding may injure the tubular epithelial cells [8]. Even though antibody against PLA2R has high specificity for idiopathic membranous nephropathy, it can occur in other etiologies such as AIN and diabetic nephropathy [9]. Unfortunately, the biopsy specimen was not tested for PLA2R antigens.

Obviously, the protein casts rather than red blood cell casts in this case were remarkable. Even though the hemosiderin could be detected by Prussian blue staining, it may be negative in the acute-phase of hemorrhage when hemoglobin has not degraded, the hemoglobin immunohistochemical staining filled the gap.

Several key points may be derived from this case. At first, when we came across a patient who manifested as hematuria or acute kidney injury with a history of anticoagulants usage, we should think of ARN and pay more attention on history collection. Second, subacute interstitial nephritis may coexist with ARN. Third, hemoglobin immunohistochemical staining may be helpful to make it clear whether the protein casts came from red blood cells. In addition, for those patients who may have decreased kidney function, anticoagulants dose should be reduced to prevent the occurrence of ARN.

Ethical approval
The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.
Table 1. Comparison of literatures of interstitial nephritis as the cause of novel oral anticoagulants related acute kidney injury (AKI).

| Author            | NOAC dose, mg/d | NOAC period, months | Kidney biopsy | AKI pathology | Age, years | Sex | Preliminary CKD | Diabetes mellitus | Other complications | Baseline serum creatinine value, μmol/L | Peak serum creatinine value, μmol/L | Gross hematuria or not | Other bleeding | Proteinuria, g/day | Fever | Rash | Eosinophiluria | Initial pred. dose, mg/day | Period on steroids, months | Scr values after steroids |
|-------------------|-----------------|---------------------|---------------|---------------|-------------|-----|-----------------|-------------------|-------------------|--------------------------------------|--------------------------|-------------------------|-----------------|----------------|----------------|-----------------|----------------|-------------------|-----------------|--------------------------|------------------------|
| Abdulhadi [7]     |                 |                     | Apixaban 0    | AIN           | 76          | F   | 1, CKD 4        | 1                 | Pulmonary hypertension | 5                                     | 6                        | NA                      |                |                 |                 |                 |                 |                   |                 |                           |                        |
| Patel [4]         |                 |                     | Dabigatran 1  | AIN + CIN, nodular DNa + CIN | 59          | M   | 1, CKD 3        | 1                 | Osteomyelitis        | NA                      | 1                        | NA                      |                | NA              | 1.57 g/gcr       | 0               | 0               | 0                 | NA              | 2.73 mg/dL at 1 week |                        |
| DiMaria [6]       |                 |                     | Apixaban 0    | AIN + Mild IgAN | 70          | M   | 0              | 0                 | Hyperlipidemia       | NA                      | 1.3 mg/dL over a 4-month period | About 3.3 mg/dL on the 7th day | 2.73 mg/dL at 1 week |                | NA              | 1.57 g/gcr       | 0               | 0               | 0                 | NA              | 2.73 mg/dL at 1 week |                        |
| Zafar [5]         |                 |                     | Rivaroxaban 0 | AIN           | 76          | M   | 1, CKD 3        | 0                 | Past pulmonary embolism; DVT | NA                      | 1 weeks, then pred. 60 | eGFR 34 ml/(min.1.73 m²) |                |                 |                 |                 |                 |                   |                 |                           |                        |
| Monahan [3]       |                 |                     | Rivaroxaban 1 | AIN           | 82          | M   | 1, CKD 3       | 0                 | Transient epistaxis | 25                      | Less than 90 μmol/L over a period of more than 1-year |                         | 1.3 mg/dL over a 4-month period |                |                 |                 |                 |                 |                   |                 |                           |                        |
| Marcelino [8]     |                 |                     | Rivaroxaban 0 | AIN           | 82          | M   | NA             | 0                 | Dyslipidemia, hyperuricemia | 20                      | 3 weeks                  | eGFR 34 ml/(min.1.73 m²) |                |                 |                 |                 |                 |                   |                 |                           |                        |
| This case         |                 |                     | Dabigatran 1  | AIN, intratubular hemoglobin casts | 62          | F   | 0              | 0                 | None              | 220                     | 3 weeks                  | eGFR 34 ml/(min.1.73 m²) |                |                 |                 |                 |                 |                   |                 |                           |                        |

CKD: chronic kidney disease; DVT: deep vein thrombosis in the right lower extremity; AVB: atrioventricular block; IgAN: IgA nephropathy; NA: not applicable; steroids, Glucosteroids; Pred.: prednisone.

*Diabetic glomerulosclerosis.*
subject has given the written informed consent to publish their case (including publication of images).

Disclosure statement
The authors have no conflicts of interest to declare.

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Supplemental data for this article can be accessed here.

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