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NEPHROLOGY – REVIEW

Anticoagulant-related nephropathy: a case report and review of the literature of an increasingly recognized entity

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Abstract Treatment with oral anticoagulants has been associated with worsening kidney function in patients with chronic kidney disease (CKD) as well as among patients without underlying CKD. Thus, anticoagulant-related nephropathy (ARN) is an increasingly recognized entity nowadays, mainly associated with warfarin anticoagulation. Recent evidence indicates that patients treated with the direct anticoagulants may also be at risk of ARN. However, the true incidence of anticoagulant-related nephropathy is difficult to determine. The typical histological lesion involves renal tubular occlusion by red blood cells (RBCs), tubular red blood cell casts on light microscopy and dysmorphic RBCs in the glomerulus on electron microscopy. In the absence of active glomerulonephritis or other inflammatory changes that could account for glomerular hemorrhage, the above findings confirm the diagnosis. Dabigatran etexilate was the first direct oral anticoagulant approved for stroke prevention in patients with non-valvular atrial fibrillation. In this article, we describe a rare case of dabigatran etexilate-induced nephropathy in a patient with preexisting IgA nephropathy and review the recent literature regarding this increasingly recognized entity.

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Case report

A 78-year-old female patient presented at the emergency room of the University Hospital of Ioannina, Greece, referring nausea, appetite loss and fatigue, with progressive worsening during the last month. Her medical history was significant for chronic atrial fibrillation and arterial hypertension. Her medications included digoxin 0.250 mg od, amlodipine 5 mg od, valsartan 160 mg od, furosemide 20 mg bd, atorvastatin 20 mg od and omeprazole 20 mg od. The patient reported being on anticoagulation with acenocoumarol until a year ago, when she was switched to dabigatran 110 mg twice daily.

The physical examination findings were unremarkable except for irregular heart sounds. Blood pressure was 150/90 mmHg, heart rate 70 beats/min and oxygen saturation on room air 98%. The laboratory tests results revealed severe kidney failure (serum urea and creatinine levels were 237 and 6.8 mg/dl, respectively), anemia (hemoglobin value of 10 g/dl), while serum albumin and potassium levels were 3.8 gr/dl and 5.9 mEq/l, respectively. Coagulation tests results revealed prothrombin time (PT) and activated partial thromboplastin time (aPTT) values of 26 and 150 s, respectively, with an international normalized ratio (INR) 1.9.

The patient reported several episodes of macroscopic hematuria about one month ago, for which she underwent computed tomography (CT) of the abdomen and cystoscopic examination, that did not reveal any abnormal findings. Renal function remained stable the next few weeks after the abdominal CT [serum creatinine was ranged

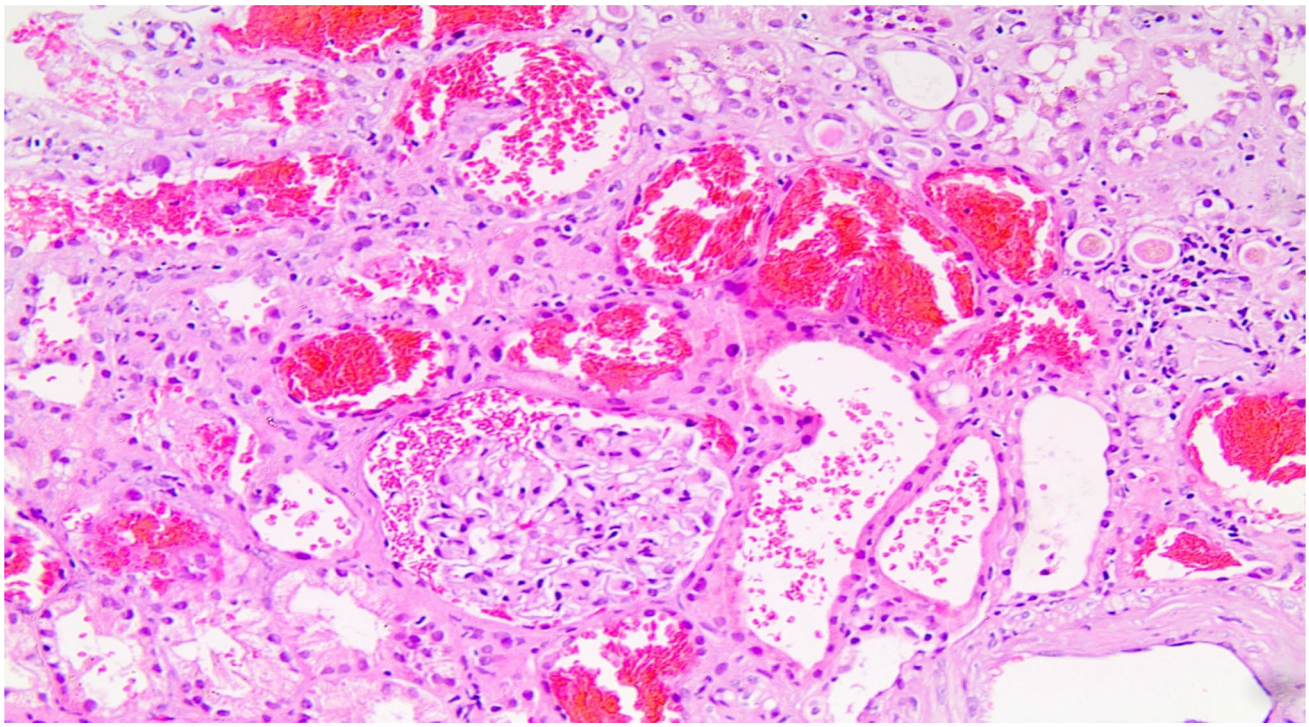

Fig. 1 Occlusion of tubular lumens by red blood cell casts. Red blood cells have entered the Bowman's capsule of a glomerulus (H&E X 200)

from 1.0 to 1.1 mg/dl and estimated glomerular filtration rare (eGFR) was ranged from 48 to 54 ml/min/1.73 m^2 using the CKD-EPI [(Chronic Kidney Disease Epidemiology Collaboration equation)]. On admission, macroscopic hematuria was noticed and a phase contrast microscopic examination of the urinary sediment revealed numerous red blood cells (RBCs) including several dysmorphic erythrocytes, as well as a few white blood cells and granular casts. Urine cytology findings were non-specific. 24-h urinary protein excretion was less than 1(0.6–0.9) g daily. The rest of the laboratory examinations including liver function tests, antinuclear antibodies, pANCA, cANCA and C3, C4 levels were within normal limits. The patient had no clinical or laboratory evidence of an infection related to glomerulonephritis. Thus, severe infections including endocarditis and osteomyelitis were excluded by blood cultures, transesophageal cardiac ultrasound and other appropriate tests. Serum protein electrophoresis, immunofixation and urine immunoelectrophoresis did not reveal any kind of monoclonal gammopathy. The chest X-rays, kidney ultrasound and echocardiographic examination did not reveal any abnormal findings. Dabigatran was discontinued. A kidney biopsy was performed 9 days after the patient's admission, following normalization of the coagulation tests.

In light microscopy, 11 glomeruli were identified; 4 of them were globally sclerosed. Glomeruli showed mild mesangial matrix expansion in association with segmental mild mesangial cell proliferation. Rare foci of segmental endocapillary proliferation were noted. Glomerular capillary walls were of normal thickness. Tubular lumens were occluded by many RBCs. Additionally, acute tubular injury with tubular dilatation and epithelial flattening was observed as well as focally moderate interstitial fibrosis (Fig. 1). In indirect immunofluorescence (in a scale intensity 1–4+), granular deposits for IgA of 3+ were mostly found in the mesangium and rarely along the capillary walls. IgM showed 1+ in a similar pattern of distribution with IgA, whereas IgG was negative. C3 complement component exhibited 3+, while C1q was negative. κ light chain was negative, while λ light chain was evaluated 2+. The final histological diagnosis was IgA nephropathy; score according to Oxford classification, M1E1S0T1. The presence of RBC casts was considered the cause of acute kidney injury (AKI).

The patient was managed conservatively. Urine output was gradually increased. An amount of 1000 ml was noticed the first day of admission which was gradually raised to 2400 ml at the day 3 of hospitalization. She was discharged home after gradual improvement in kidney function, which remained stable at 1-year follow-up (serum creatinine 1.1 mg/dl, eGFR CKD-EPI 48 ml/min/1.73^2).

Glomerular hematuria: not so innocent after all

This case report describes a rare case of ARN of dabigatran etexilate-induced nephropathy in a patient with preexisting IgA nephropathy. There is abundant evidence in the literature linking glomerular hemorrhage and macroscopic hematuria to AKI, sometimes with adverse long-term outcomes [1]. Glomerular hematuria is a common clinical manifestation of glomerular diseases, such as IgA nephropathy and infrequently Alport syndrome or thin basement membrane disease [2–4]. Intratubular obstruction by RBCs or hemoglobin casts was initially considered as the main mediator of tubular injury and AKI. However, experimental evidence has shifted attention toward hemoglobin, heme, iron or other molecules released from RBCs as the main culprits responsible for causing direct tubular toxicity and hematuria-induced renal damage [5, 6]. Hemoglobin released by intratubular degradation of RBCs or directly filtered by the glomerulus is metabolized into the proximal tubules or directly degraded in the tubular lumen, with subsequent release of heme molecules and free iron. Heme redox cycling between ferric and ferryl states induces oxidative damage, generation of radical species and lipid peroxidation [6]. Cell-free hemoglobin may decrease nitric oxide availability, thus inducing intra-renal vasoconstriction and ischemia. Moreover, intratubular cell-free hemoglobin obstructs the renal tubular lumen after precipitating together with Tamm–Horsfall protein. Finally, heme can also indirectly promote chronic renal damage by inducing inflammation and fibrosis via increased renal expression of pro-inflammatory molecules, such as TNF-a and TGF-b [7, 8].

Considering the fact that macroscopic hematuria episodes of glomerular origin are typical of IgA nephropathy, most evidence regarding the development of AKI associated with glomerular hemorrhage and in the absence of associated crescentic glomerulonephritis came from series of patients with IgA nephropathy. Although the real incidence of AKI during episodes of gross hematuria in IgA nephropathy is unknown, early studies have reported that it might be over 35% [1]. The duration of macroscopic hematuria was the most significant predictor of the severity of AKI and residual impairment of renal function [9]. Thus, even though macroscopic hematuria in the setting of IgA nephropathy used to be considered a benign phenomenon in the past, incomplete recovery of renal function has been increasingly observed following AKI associated with macroscopic glomerular hematuria [2, 3].

Anticoagulant-related nephropathy

Likewise, ARN is an entity which has received much attention during the last years as a significant emerging complication of anticoagulation. ARN is associated with chronic kidney dysfunction and increased mortality. It was initially named "warfarin-related nephropathy" as warfarin has been the only available oral anticoagulant until recently; nevertheless, the term currently used is "anticoagulant-related nephropathy", since direct oral anticoagulants have been also associated with episodes of glomerular hematuria and acute kidney injury as well [10, 11]. The true incidence of anticoagulant-related nephropathy is difficult to determine in the absence of biopsy data. Nephrologists are cautious when it comes to perform a kidney biopsy in patients who are under therapeutic anticoagulation, due to the increased risk of hemorrhagic complications from the kidney biopsy site. Additionally patients who receive oral anticoagulants usually have significant comorbidities and AKI might be easily ascribed to other related causes. A high index of suspicion is required in the setting of either macroscopic or microscopic hematuria with dysmorphic red blood cells, red blood cell casts on microscopic urine examination and AKI in patients receiving oral anticoagulants. The characteristic biopsy findings for anticoagulant-related nephropathy include tubular RBC casts on light microscopy and RBCs in the glomerulus on electron microscopy [10]. In the absence of active glomerulonephritis or other inflammatory changes that could account for glomerular hemorrhage, the above findings confirm the diagnosis.

Pathological and clinical implications of anticoagulant-related nephropathy

Glomerular hemorrhage with impairment of renal function as a result of excessive anticoagulation came to notice after reports in the literature published in the early 2000s [4]. A case series of kidney biopsy specimens from 9 patients with warfarin overdose, hematuria and AKI shed more light on anticoagulation-related nephropathy [10]. At presentation with AKI, all patients had a supra-therapeutic level of INR and increased serum creatinine levels. Each biopsy specimen displayed evidence of acute tubular injury and glomerular hemorrhage with RBCs in the Bowman space and abundant occlusive RBC casts in tubules, in the absence of evidence of active inflammatory lesions. It should be noted, however, that all biopsy specimens had additional evidence of chronic kidney injury, manifesting either as mild glomerular immune complex deposits. Focal segmental glomerular sclerosis was noted in 1 patient, and 2 patients had predominantly interstitial findings. Regarding prognosis, there was no improvement in the renal function in 6 out of the 9 patients evaluated [10].

In CKD patients, the risk of hemorrhagic complications due to warfarin is increased more than twofold and patients

with advanced CKD in spite of requiring lower warfarin doses to achieve target INR levels are frequently over-anticoagulated [12]. Treatment with warfarin and supra-therapeutic INR levels has been associated with worsening kidney function in patients with CKD [13]. Brodsky et al. [13] analyzed serum creatinine and INR in 103 patients on warfarin therapy with CKD stages 2–4. They showed that a significant proportion of patients (37%) who experienced at least one episode of INR elevation above 3.0. developed an unexplained increase in serum creatinine coincident with INR elevation. Additionally, the serum creatinine tended to remain elevated in these patients, suggesting that supra-therapeutic anticoagulation is associated with faster progression of CKD.

However, AKI has been reported to occur even among patients without underlying kidney disease in the setting of treatment with oral anticoagulants [14]. A study of 15,258 patients under warfarin therapy showed that of the 4006 patients with an INR level over 3, warfarin-related nephropathy occurred in 20.5% of the entire cohort, 33.0% of the CKD cohort and 16.5% of the no-CKD cohort. Warfarin-related nephropathy was defined by an increase in serum creatinine over 0.3 mg/dl within 1 week after the INR exceeded 3 and with no record of hemorrhage. Risk factors included age, diabetes mellitus, hypertension and cardiovascular disease. Moreover, the 1-year mortality risk was significantly higher among patients with warfarin-related nephropathy compared with those without. These findings were further confirmed by another retrospective large-scale study of 1297 Asian patients who had serum creatinine level measured within 1 week after INR > 3.0 and within 6 months before INR > 3.0. Warfarin-related nephropathy developed in 19.3% of patients having excessive anticoagulation, and it adversely affected renal and patient outcomes [15].

In order to further elucidate the pathogenic mechanisms of anticoagulant-related nephropathy, Brodsky and his associates developed an animal model of AKI based on the 5/6-nephrectomy model. They demonstrated that acute excessive anticoagulation with brodifacoum or "superwarfarin" increased serum creatinine levels in association with hematuria in 5/6-nephrectomized rats but not in controls. Morphologic examination of biopsy specimens of nephrectomized rats showed glomerular hemorrhage, occlusive red blood cell casts and acute tubular injury, as well as an increase in apoptosis of glomerular endothelial cells [16, 17].

Direct oral anticoagulants and the risk of nephropathy

Direct oral anticoagulants or non-vitamin K antagonist oral anticoagulants are oral medications that inhibit a specific enzyme in the coagulation cascade [18]. Available agents include those that directly inhibit thrombin (factor IIa) or factor Xa. Accordingly, dabigatran is the only oral direct thrombin inhibitor available for clinical use [19], whereas rivaroxaban, apixaban and edoxaban are oral direct factor Xa inhibitors [20–22]. They all have a predictable dose–response relationship, which is considered to be associated with an improved safety profile. Due to predictable pharmacokinetics, direct oral anticoagulants may be used without the need for routine monitoring. On the other hand, detecting excessive anticoagulation with the direct oral anticoagulants might be difficult as coagulation parameters are not monitored in routine clinical practice and there are no specific tests available so as to detect excessive anticoagulation with dabigatran. A correlation was observed between dabigatran plasma levels and the degree of anticoagulant effect, as measured by prolongation of activated aPTT, INR, ecarin clotting time (ECT) and thrombin time (TT) [23]. A linear relationship was observed between ECT, INR and TT, whereas a nonlinear increase in aPTT occurred with increasing dabigatran plasma concentrations. Nevertheless, although a linear relationship between dabigatran's plasma concentration and many of these assays exists, they are insensitive within a range of clinically relevant plasma concentrations and are not able to accurately estimate dabigatran's anticoagulant effect [23]. Although TT measures the direct activity of thrombin and might be the most sensitive parameter to the presence of dabigatran's anticoagulant effect, it is not useful for quantitative monitoring of the drug's anticoagulant effect [23]. Moreover, no antidote was available for reversal of dabigatran action. Only recently did the European Medicines Agency (EMA) recommend the approval of idarucizumab, a monoclonal antibody fragment which binds dabigatran with an affinity that is 350 times as high as that observed with thrombin [24]. The Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study was undertaken to examine the efficacy and safety of idarucizumab in dabigatran-treated patients who had serious bleeding or required urgent procedures. Idarucizumab was shown to rapidly and completely reverse the anticoagulant activity of dabigatran in 88–98% of patients [24].

The degree of hemorrhagic complications caused by direct oral anticoagulants as compared to the classic ones has been the subject of extensive investigation. Outcomes of DOAC-associated hemorrhagic complications appear favorable compared with vitamin K antagonists. Thus, a recent meta-analysis that included 13 randomized trials (over 100,000 patients) demonstrated that the case fatality rate for major bleeding was 7.6% in patients taking a DOAC, compared with 11 percent for patients under warfarin treatment [24]. Additionally, the relative risk of fatal bleeding, cardiovascular mortality and all-cause mortality

were also lower in patients receiving the direct oral anticoagulants [25]. The reduced case fatality rate in patients under direct oral anticoagulants who suffer a major bleeding episode should most probably be ascribed to the reduced rate of intracerebral hemorrhage. As all of the direct oral anticoagulants are dependent at least partly on renal clearance, the risk of associated bleeding may be greater in patients with renal failure. Thus, elimination of dabigatran is predominantly via the renal pathway, by glomerular filtration, with negligible contributions from tubular secretion or absorption with ≈80% of the administered dose excreted unchanged in the urine [26]. Nevertheless, the data on course and management of bleeding complications are limited. A prospective observational study of emergency department patients under treatment with dabigatran or warfarin who were admitted with bleeding complications during a 6-month period showed that patients with dabigatran-induced bleeding had a more benign clinical course and shorter hospitalization duration compared with patients with warfarin-induced bleeding [27]. Similarly to previous published works, fewer intracranial hemorrhages were observed in patients receiving dabigatran compared to warfarin. Patients receiving dabigatran were more likely to have gastrointestinal bleeding and less likely to have intracranial bleeding than those receiving warfarin. It should be noted that of patients with dabigatran-induced bleeding, 53% presented with acute kidney injury [27]. Likewise, a large retrospective cohort study which evaluated the risk of bleeding with dabigatran in atrial fibrillation patients compared to warfarin showed that dabigatran was associated with a higher incidence of major bleeding, a higher risk of gastrointestinal bleeding, but a lower risk of intracranial hemorrhage. The risk of major bleeding among dabigatran users was especially high in patients with CKD [28]. On the other hand, another recent population-based case–control study of patients 66 years and older with non-end-stage CKD who received an oral anticoagulant showed that treatment with dabigatran or rivaroxaban was not associated with a statistically significant increased risk of major hemorrhagic events compared with exposure to warfarin [29].

Experimental data regarding dabigatran effects on kidney function in control and 5/6 nephrectomy rats showed that administration of dabigatran resulted in a dose-dependent increase in serum creatinine and hematuria in both control and CKD rats with the effects being amplified in the latter group [11]. Morphological findings in 5/6 nephrectomy rats treated with dabigatran are RBC tubular casts and acute tubular injury, thus being similar to those found previously in animals with warfarin-related nephropathy. An interesting finding is that RBC tubular casts were also found in 1 out of 30 kidneys from control animals treated with dabigatran, suggesting that dabigatran-induced AKI might occur even in the setting of normal kidney function [11]. It should be noted that this finding was not observed in control rats treated with vitamin K antagonists even after fatal excessive anticoagulation [11]. The authors of this study further tried to elucidate the pathogenesis of glomerular injury caused by old and direct oral anticoagulants, considering the fact that the morphological model of glomerular injury caused by both agents is similar. Thus, they proposed that thrombin plays an important role in the glomerular filtration barrier function and its decreased activity owing to anticoagulation results in glomerular filtration barrier abnormalities [11]. Although the anticoagulant mechanism of warfarin and dabigatran is conducted via different pathways, they both ultimately result in diminished thrombin activity. Thrombin participates in the regulation of the endothelial functions, vascular permeability, leukocyte migration and adhesion via protease-activated receptor 1 (PAR-1), which is the thrombin receptor on endothelial cells. Administration of a selective inhibitor of PAR-1 in rat models resulted in increased serum creatinine, hematuria and tubular RBC casts, findings similar to those described in animals with warfarin- or dabigatran-related nephropathy [11, 30, 31].

As far as we know, apart from our case report, there are only three more case reports in the literature describing biopsy-proven, glomerular hemorrhage-induced AKI in patients receiving dabigatran etexilate. In all cases, patients presented with hematuria and had histological evidence of hemorrhage into renal tubules, whereas two of the patients had previously undiagnosed IgA nephropathy, a similar clinical scenario to our case [32–34]. A point of interest, common to all cases of anticoagulant-induced glomerular hemorrhage with AKI, is whether the glomerular hemorrhage is caused by excessive anticoagulation alone or a structurally abnormal glomerular barrier as occurs in IgA nephropathy or thin basement membrane disease is required to be present as well.

Direct oral anticoagulants and CKD

A systematic review and meta-analysis of phase III randomized controlled trials showed that direct oral anticoagulants share a similar risk of renal failure with warfarin [35]. On the other hand, an analysis of the changes in GFR during long-term treatment with warfarin or dabigatran in 16,490 patients with atrial fibrillation enrolled in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial showed that decline in renal function was greater in those taking warfarin compared to dabigatran, and this effect was amplified by diabetes and previous vitamin K antagonist use [36]. Although the GFR declined in all treatment groups after an average of 30 months, the

mean decline in GFR was significantly greater with warfarin compared with dabigatran and patients with poor INR control exhibited a faster decline in GFR [36].

Nevertheless, the mechanism responsible for the chronic exacerbation of the renal function remains unsettled in these large patient groups due to lack of specific information with regard to episodes of macroscopic or microscopic hematuria or kidney biopsy data showing evidence of glomerular hemorrhage. Additionally, there is no consensus definition of AKI within these studies; thus, it remains to be elucidated whether there is an overlap between glomerular hemorrhage-induced AKI and progression of CKD or there is separate mechanism involved in each. Thus, prospective multicenter studies are needed to define the clinical features and prevalence of ARN and define the characteristics of patients at risk, including estimated GFR, proteinuria, quantitative and qualitative evaluation of urinary sediment for RBC and RBC casts, as well as evaluation of different coagulation parameters. It should be kept in mind that the absence of hematuria does not exclude a possible diagnosis of ARN since hematuria might be transient, and as a consequence, it is not detected in all patients at the time of presentation with AKI. Finally, performing a kidney biopsy in the setting of AKI of unknown origin would be possible even in high-risk anticoagulated patients after normalization of the coagulation indices.

Prognosis of anticoagulant-induced nephropathy

Reversal of coagulopathy and general supportive care are the mainstays of treatment of ARN. The most important measure to prevent ARN is proper adjustment of the anticoagulant dose. This is particularly important for patients with CKD, who are more vulnerable to ARN. In most patients with ARN, the serum creatinine stabilizes or improves slightly within the first few weeks after correction of the warfarin coagulopathy. However, some patients may have little or no recovery of kidney function. In the study by Brodsky et al [10] cited above of nine patients with biopsy-proven anticoagulant-related nephropathy, kidney function did not return to baseline or improve in five patients.

Presumptive ARN has been associated with an increase in mortality independent of age, sex, race, hemorrhage, atrial fibrillation, heart failure and diabetes mellitus. In the study of 4006 patients with an elevated INR > 3, patients who developed presumptive ARN had decreased five-year survival compared with those without [14].

Regarding dabigatran, patients with CKD or those who develop AKI are at increased bleeding risk due to drug accumulation, given the significant reduced renal clearance of dabigatran. An increasing number of severe and even fatal bleeding complications due to dabigatran are being reported, and renal replacement therapy has been widely recommended in an effort to improve outcomes in dabigatran-treated patients with uncontrolled bleeding [37].

Conclusions

Considering the increasing utilization of anticoagulation with the direct oral anticoagulants and the adverse renal outcomes associated with ARN, further research is required for the elucidation of the pathogenesis and the identification of the associated risk factors for this entity. However, a careful follow-up of renal function is required in patients on direct oral anticoagulants treatment especially in individuals with underlying CKD. Future reports will hopefully confirm the existence of ARN, with better characterization of its features and predisposing risk factors.

Compliance with ethical standards

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

References

1. Moreno JA, Martin-Cleary C, Gutierrez E et al (2012) AKI associated with macroscopic glomerular hematuria: clinical and pathophysiologic consequences. Clin J Am Soc Nephrol 7:175–184
2. Praga M, Gutierrez-Millet V, Navas JJ et al (1985) Acute worsening of renal function during episodes of macroscopic hematuria in IgA nephropathy. Kidney Int 28:69–74
3. Delclaux C, Jacquot C, Callard P, Kleinknecht D (1993) Acute reversible renal failure with macroscopic haematuria in IgA nephropathy. Nephrol Dial Transpl 8:195–199
4. Abt AB, Carroll LE, Mohler JH (2000) Thin basement membrane disease and acute renal failure secondary to gross hematuria and tubular necrosis. Am J Kidney Dis 35:533–536
5. Martin CC, Moreno JA, Fernandez B et al (2010) Glomerular haematuria, renal interstitial haemorrhage and acute kidney injury. Nephrol Dial Transpl 25:4103–4106
6. Tracz MJ, Alam J, Nath KA (2007) Physiology and pathophysiology of heme: implications for kidney disease. J Am Soc Nephrol 18:414–420
7. Moreno JA, Martin-Cleary C, Gutierrez E et al (2012) Haematuria: the forgotten CKD factor? Nephrol Dial Transplant 27:28–34
8. Gutierrez E, Egido J, Rubio-Navarro A et al (2012) Oxidative stress, macrophage infiltration and CD163 expression are determinants of long-term renal outcome in macrohematuria-induced acute kidney injury of IgA nephropathy. Nephron Clin Pract 121:c42–c53
9. Gutierrez E, Gonzalez E, Hernandez E et al (2007) Factors that determine an incomplete recovery of renal function in macrohematuria-induced acute renal failure of IgA nephropathy. Clin J Am Soc Nephrol 2:51–57
10. Brodsky SV, Satoskar A, Chen J et al (2009) Acute kidney injury during warfarin therapy associated with obstructive

tubular red blood cell casts: a report of 9 cases. Am J Kidney Dis 54:1121–1126
11. Ryan M, Ware K, Qamri Z et al (2014) Warfarin-related nephropathy is the tip of the iceberg: direct thrombin inhibitor dabigatran induces glomerular hemorrhage with acute kidney injury in rats. Nephrol Dial Transpl 29:2228–2234
12. Limdi NA, Beasley TM, Baird MF et al (2009) Kidney function influences warfarin responsiveness and hemorrhagic complications. J Am Soc Nephrol 20:912–921
13. Brodsky SV, Collins M, Park E et al (2010) Warfarin therapy that results in an International Normalization Ratio above the therapeutic range is associated with accelerated progression of chronic kidney disease. Nephron Clin Pract 115:c142–c146
14. Brodsky SV, Nadasdy T, Rovin BH et al (2011) Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. Kidney Int 80:181–189
15. An JN, Ahn SY, Yoon CH et al (2013) The occurrence of warfarin-related nephropathy and effects on renal and patient outcomes in korean patients. PLoS ONE 8:e57661
16. Ware K, Brodsky P, Satoskar AA et al (2011) Warfarin-related nephropathy modeled by nephron reduction and excessive anticoagulation. J Am Soc Nephrol 22:1856–1862
17. Ozcan A, Ware K, Calomeni E et al (2012) 5/6 nephrectomy as a validated rat model mimicking human warfarin-related nephropathy. Am J Nephrol 35:356–364
18. Husted S, de Caterina R, Andreotti F et al (2014) Non-vitamin K antagonist oral anticoagulants (NOACs): no longer new or novel. Thromb Haemost 111:781–782
19. Hauel NH, Nar H, Priepke H, Ries U, Stassen JM, Wienen W (2002) Structure-based design of novel potent nonpeptide thrombin inhibitors. J Med Chem 45:1757–1766
20. Turpie AG, Kreutz R, Llau J, Norrving B, Haas S (2012) Management consensus guidance for the use of rivaroxaban—an oral, direct factor Xa inhibitor. Thromb Haemost 108:876–886
21. Camm AJ, Bounameaux H (2011) Edoxaban: a new oral direct factor xa inhibitor. Drugs 71:1503–1526
22. Wong PC, Crain EJ, Xin B et al (2008) Apixaban, an oral, direct and highly selective factor Xa inhibitor: in vitro, antithrombotic and antihemostatic studies. J Thromb Haemost 6:820–829
23. Dager WE, Gosselin RC, Kitchen S, Dwyre D (2012) Dabigatran effects on the international normalized ratio, activated partial thromboplastin time, thrombin time, and fibrinogen: a multicenter, in vitro study. Ann Pharmacother 46:1627–1636
24. Pollack CV Jr, Reilly PA, Eikelboom J et al (2015) Idarucizumab for dabigatran reversal. N Engl J Med 373:511–520
25. Chai-Adisaksopha C, Hillis C, Isayama T, Lim W, Iorio A, Crowther M (2015) Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials. J Thromb Haemost 13:2012–2020
26. Stangier J, Rathgen K, Stahle H, Mazur D (2010) Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. Clin Pharmacokinet 49:259–268
27. Berger R, Salhanick SD, Chase M, Ganetsky M (2013) Hemorrhagic complications in emergency department patients who are receiving dabigatran compared with warfarin. Ann Emerg Med 61:475–479
28. Hernandez I, Baik SH, Pinera A, Zhang Y (2015) Risk of bleeding with dabigatran in atrial fibrillation. JAMA Intern Med 175:18–24
29. Harel Z, Mamdani M, Juurlink DN et al (2016) Novel oral anticoagulants and the risk of major hemorrhage in elderly patients with chronic kidney disease: a nested case-control study. Can J Cardiol 32:986–1017
30. Carlile-Klusacek M, Rizzo V (2007) Endothelial cytoskeletal reorganization in response to PAR1 stimulation is mediated by membrane rafts but not caveolae. Am J Physiol Heart Circ Physiol 293:H366–H375
31. Rondeau E, Vigneau C, Berrou J (2001) Role of thrombin receptors in the kidney: lessons from PAR1 knock-out mice. Nephrol Dial Transplant 16:1529–1531
32. Moeckel G, Luciano R, Brewster U (2013) Warfarin-related nephropathy in a patient with mild IgA nephropathy on dabigatran and aspirin. Clin Kidney J 0:1–3
33. Kadiyala D, Bum G (2012) Dabigatran induced acute kidney injury The American Society of Nephrology Annual Meeting, San Diego, CA, 1–4 Nov 2012. p. FR-PO1122 [abstract]
34. Shafi ST, Negrete H, Roy P, Julius CJ, Sarac E (2013) A case of dabigatran-associated acute renal failure. WMJ 112:173–175
35. Caldeira D, Goncalves N, Pinto FJ, Costa J, Ferreira JJ (2015) Risk of renal failure with the non-vitamin K antagonist oral anticoagulants: systematic review and meta-analysis. Pharmacoepidemiol Drug Saf 24:757–764
36. Bohm M, Ezekowitz MD, Connolly SJ et al (2015) Changes in renal function in patients with atrial fibrillation: an analysis from the RE-LY Trial. J Am Coll Cardiol 65:2481–2493
37. Knauf F, Chaknos CM, Berns JS, Perazella MA (2013) Dabigatran and kidney disease: a bad combination. Clin J Am Soc Nephrol 8:1591–1597