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Challenging the use of warfarin in patients on dialysis with atrial fibrillation

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We read with great interest the article from Qamar and Bhatt (Anticoagulation therapy: Balancing the risks of stroke and bleeding in CKD. *Nat. Rev. Nephrol.* **11**, 200–202; 2015)[1] that discussed the observational study by Bonde *et al.* on anticoagulation of patients with atrial fibrillation and chronic kidney disease (CKD) (Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study. *J. Am. Coll. Cardiol.* **64**, 2471–2482; 2014).[2] The original study and the commentary both conclude that anticoagulation with warfarin is safe and reduces the risk of stroke in patients with CKD, and even in dialysis patients. This latter point contrasts with three large registry studies which reported that patients with atrial fibrillation administered warfarin and undergoing haemodialysis have an increased risk of stroke.[3–5] Furthermore, a Canadian study reported that warfarin use is not beneficial in reducing stroke risk but is associated with a higher risk of bleeding in patients with atrial fibrillation and undergoing dialysis.[6]

We therefore question what causes the observed differences between these studies (Table 1)? A central limitation of the study by Bonde *et al.*,[2] and a previous study by the same research group,[7] is that the cohort of patients who were undergoing renal replacement therapy were exposed to different treatment modalities—some were on haemodialysis, some on peritoneal dialysis, and a considerable subgroup had received a kidney transplant. This cohort, therefore, combined patients with varying degrees of CKD and heparin exposure. We previously raised this concern with the prior study—that this mixture of patient situations renders interpretation of the effects of warfarin in patient subgroups difficult.[8]

Uraemia leads to coagulopathy, thrombocytopathy[9] and vitamin K deficiency,[10] and patients undergoing haemodialysis administered warfarin exhibit an increased risk of bleeding, cardiovascular calcifications, and calciphylaxis. In weighing the risks of vitamin K antagonism in patients undergoing dialysis against the poorly documented benefits, we argue against the use of warfarin in patients with atrial fibrillation undergoing haemodialysis.[11]

Table 1 | Administration of warfarin and risk of stroke in patients with atrial fibrillation and CKD

Study	Outcome	HR (95% CI)	Implication
Patients on dialysis			
Chan *et al.*[3]	Stroke and/or death	1.93 (1.29–2.90)	Against warfarin
Wizeman *et al.*[4]	Stroke and/or death (<65 years)	1.29 (0.45–3.68)	No benefit
	Stroke and/or death (65–75 years)	1.35 (0.69–2.63)	No benefit
	Stroke and/or death (>75 years)	2.17 (1.04–4.53)	Against warfarin
Winkelmayer *et al.*[5]	Ischaemic stroke	0.92 (0.61–1.37)	No benefit
	Haemorrhagic stroke	2.38 (1.15–4.96)	Against warfarin
Shah *et al.*[6]	Ischaemic stroke	1.14 (0.78–1.67)	No benefit
Patients undergoing RRT			
Olesen *et al.*[10]	Stroke and/or death	0.44 (0.26–0.74)	Favours warfarin
Bond *et al.*[2]	Death (high risk; CHA_2DS_2-VASc-score* ≥2)	0.85 (0.72–0.99)	Favours warfarin
	Death (low to intermediate risk; CHA_2DS_2-VASc-score 0–1)	1.36 (0.96–1.94)	No benefit

*Note that this score has not been validated in patients with CKD. Abbreviations: CHA_2DS_2-VASc-score, congestive heart failure, hypertension, age >75 years, diabetes mellitus, previous stroke, transient ischaemic attack, or thromboembolism, vascular disease, age 65 to 74 years, sex category; CKD, chronic kidney disease; HR, hazard ratio; RRT, renal replacement therapy.

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Competing interests
The authors declare no competing interests

1. Qamar, A. and Bhatt, D. L. Anticoagulation therapy: Balancing the risks of stroke and bleeding in CKD. *Nat. Rev. Nephrol.* **11**, 200–202 (2015).
2. Bonde, A. N. *et al.* Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study. *J. Am. Coll. Cardiol.* **64**, 2471–2482 (2014).
3. Chan, K. E. *et al.* Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. *J. Am. Soc. Nephrol.* **20**, 2223–2233 (2009).
4. Wizemann, V. *et al.* Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. *Kidney Int.* **77**, 1098–1106 (2010).
5. Winkelmayer, W. C. *et al.* Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. *Clin. J. Am. Soc. Nephrol.* **6**, 2662–2668 (2011).
6. Shah, M. *et al.* Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. *Circulation* **129**, 1196–1203 (2014).
7. Olesen, J. B. *et al.* Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N. Engl. J. Med.* **367**, 625–635 (2012).
8. Schlieper, G., Kruger, T. & Floege, J. Atrial fibrillation and chronic kidney disease. *N. Engl. J. Med.* **367**, 2157–2159 (2012).
9. Schlieper, G. *et al.* The vulnerable patient with chronic kidney disease. *Nephrol. Dial. Transplant*. https://dx.doi.org/10.1093/ndt/gfv041.
10. Schlieper, G. *et al.* Circulating nonphosphorylated carboxylated matrix gla protein predicts survival in ESRD. *J. Am. Soc. Nephrol.* **22**, 387–395 (2011).
11. Kruger, T. *et al.* Sailing between Scylla and Charybdis: oral long-term anticoagulation in dialysis patients. *Nephrol. Dial. Transplant.* **28**, 534–541 (2013).