Atrial fibrillation: association between kidney function and major bleeding with warfarin treatment

A Canadian retrospective cohort study in 12,403 people with atrial fibrillation found that the risk of major bleeding with warfarin increases with worsening kidney function, particularly in the first 30 days of treatment. This study supports NICE guidance on atrial fibrillation and chronic kidney disease that the benefits of anticoagulation on the risk of stroke should be considered alongside the risk of bleeding, particularly in people with impaired kidney function.

Overview and current advice

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. If left untreated it is a significant risk factor for stroke and other morbidities, and drug treatments include anticoagulants to reduce the risk of stroke. The NICE guideline on the management of AF recommends that a person’s risk of stroke should be estimated using the CHA²DS²-VASc score. Anticoagulation should be offered to people with AF who have a CHA²DS²-VASc score of 2 or more, taking the person’s bleeding risk into account. The HAS-BLED score is recommended to assess the risk of bleeding. This score takes into consideration several risk factors for bleeding, including abnormal kidney function. However, abnormal kidney function is a dichotomous ‘yes or no’ choice, defined as the presence of chronic dialysis, kidney transplantation or serum creatinine ≥200 micromol/L (in a 70 year old person, that serum creatinine would suggest an estimated glomerular filtration rate [eGFR] of approximately 20–30 ml/min/1.73m² or less). The NICE guideline recommends that anticoagulation should also be considered for men with a CHA²DS²-VASc score of 1 (all women have a CHA²DS²-VASc score of at least 1). Anticoagulation may be with apixaban, dabigatran etexilate, rivaroxaban or a vitamin K antagonist, usually warfarin. The guideline recommends that the options for anticoagulation are discussed with the person and the choice based on their clinical features and preferences. NICE has produced a patient decision aid to facilitate shared decision-making about anticoagulant options.

Chronic kidney disease (CKD) describes abnormal kidney function or structure. It often exists together with other conditions, particularly cardiovascular disease. CKD and AF frequently coexist, and observational studies suggest that AF is 3 times as frequent in people with mild to moderate CKD compared to those without, and that CKD is an independent predictor of stroke. However, impaired kidney function is also associated with a bleeding risk that increases with severity of CKD (see the full NICE guideline on CKD). The NICE guideline on the management of CKD recommends that antiplatelet drugs should be offered to people with CKD for the secondary prevention of cardiovascular disease, but that prescribers should be aware of the increased risk of bleeding. It also recommends that apixaban should be considered in preference to warfarin in people with a confirmed eGFR of 30–
50 ml/min/1.73 m² and non-valvular AF who have 1 or more of the following risk factors: prior stroke or transient ischaemic attack, age 75 years or older, hypertension, diabetes mellitus, or symptomatic heart failure.

The NICE Pathways on atrial fibrillation and chronic kidney disease bring together all related NICE guidance and associated products on these conditions in sets of interactive topic-based diagrams.

New evidence

There are limited data about the bleeding risk associated with warfarin treatment in people with different stages of CKD. To try and add to the evidence base, a Canadian, population-based, retrospective cohort study (Jun M et al. 2015) has determined the rates of major bleeding by level of kidney function in older people with AF who started on warfarin treatment². The study included 12,403 people aged 66 years and older (mean 77 years; 49% women) who started warfarin treatment between 1 May 2003 and 31 March 2010 and had a measure of kidney function at baseline. The index date was defined as the date of the first dispensed warfarin prescription after the participant's 66th birthday, in those with no prescription in the previous year. Kidney function was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation, and participants were categorised based on eGFR: ≥90 (reference group), 60–89, 45–59, 30–44, 15–29 and <15 ml/min/1.73 m². People with end-stage renal disease (those who had received chronic dialysis or renal transplantation at baseline) were excluded.

Over a median follow-up of 2.1 years, 1443 people (11.6%) had a major bleeding episode (defined as first admission to hospital or visit to an emergency department for an intracranial, gastrointestinal or other bleed). Of these bleeding episodes, 58% were gastrointestinal bleeds and 5% were intracranial bleeds. More major bleeding episodes were seen in the first 30 days of warfarin treatment (15.2 per 100 person years) compared with after 30 days (4.2 per 100 person years).

In the analysis, bleeding rates were adjusted for sociodemographic factors, certain comorbidities, previous admission to hospital for a bleeding episode and use of prescription antiplatelet drugs, non-steroidal anti-inflammatory drugs and proton pump inhibitors. During the first 30 days of warfarin treatment, the rates of major bleeding increased with worsening levels of eGFR (p for trend <0.001 for unadjusted and adjusted rates). Adjusted rates of major bleeding in people with eGFR <15 ml/min/1.73 m² were more than 10 times those in people with eGFR >90 ml/min/1.73m² (63.4 per 100 person years, 95% confidence interval [CI] 24.9 to 161.6 compared with 6.1 per 100 person years; 95% CI 1.9 to 19.4; incidence rate ratio 10.33; 95% CI 2.3 to 45.5). For people with eGFR between 15 and 89 ml/min/1.73 m² (see groups above) there were numerical increases in the adjusted rates of major bleeding compared with those with eGFR >90 ml/min/1.73 m², but these were not statistically significant. The authors calculated a number needed to harm of 22 (95% CI 18 to 27) for people with CKD (defined as eGFR <60 ml/min/1.73 m²) compared with people with no CKD (eGFR >60 ml/min/1.73 m²) for a major bleeding episode within the first 30 days of warfarin treatment.

The rates of major bleeding also increased with worsening levels of eGFR in the period after 30 days of warfarin treatment, but to a lesser extent (incident rate ratio 2.22; 95% CI 1.07 to 4.59 for people with eGFR <15 ml/min/1.73 m² compared with eGFR >90 ml/min/1.73 m²).

This study has several limitations inherent in its observational design. It did attempt to adjust for confounding factors but some confounding could remain; in particular, no information was available on non-prescription drug use. Although the cohort was large, the numbers of people in each category of kidney function reduced with increasing severity of impaired kidney function. The group with eGFR 60–89 ml/min/1.73 m² included 6140 people, whereas the reference group (eGFR >90 ml/min/1.73 m²) included only 581 people, and the 15–29 and <15 ml/min/1.73 m² groups included just 586 and 55 people respectively. This could have affected the reliability of the results.
Finally, this study focussed specifically on the safety and not the efficacy of warfarin treatment in people with AF.

**Commentary**

**Commentary provided by the Medicines and Prescribing Centre**

This observational study in people with AF supports the notion that warfarin treatment increases the risk of major bleeding if people have CKD, and suggests that the risk of bleeding increases with worsening eGFR levels, particularly at the start of treatment.

The study looked only at the association between kidney function and major bleeding with warfarin treatment for AF, not treatment with any of the non-vitamin K oral anticoagulants (NOACs). A Medicines Evidence Commentary on the [bleeding risk with apixaban in people with renal impairment: meta-analysis of randomised controlled trials](https://www.medicines.org.uk/evidence/comparison/bleeding-risk-with-apixaban-in-people-with-renal-impairment-meta-analysis-of-randomised-controlled-trials) has recently been published. However, studies included in that meta-analysis excluded people with severe renal impairment (creatinine clearance less than 25 ml/min or 30 ml/min).

The NICE guideline on [chronic kidney disease](https://www.nice.org.uk/guidance/ng192) recommends that apixaban should be considered in preference to warfarin in people with a confirmed eGFR of 30–50 ml/min/1.73 m² and non-valvular AF who have 1 or more of the following risk factors: prior stroke or transient ischaemic attack, age 75 years or older, hypertension, diabetes mellitus, or symptomatic heart failure. This recommendation was based on low and very low quality evidence, primarily from the ARISTOTLE trial in people with AF³. This trial suggested that apixaban was beneficial compared with warfarin for reducing the rate of stroke, death and major bleeding, regardless of kidney function; and people with impaired kidney function seemed to have the greatest reduction in major bleeding with apixaban compared with warfarin (see the full NICE guideline on CKD for details). Apixaban is not recommended for use in people with creatinine clearance <15 ml/min.

Among people with reduced kidney function, particularly in those with much reduced kidney function and during the first 30 days of treatment, Jun et al recommend that the risks of warfarin treatment should be carefully weighed against the potential benefits based on the presence of comorbidities and the assessment of bleeding risk². This is in line with the NICE guideline on the management of AF, which makes a clear recommendation that the options for anticoagulation should be discussed with the person and the choice based on their clinical features and preferences.

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**References**

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