NICE National Institute for Health and Care Excellence

2021 exceptional surveillance of chronic kidney disease (NICE guideline NG203)

Surveillance report

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Surveillance decision

We will update the NICE guideline on chronic kidney disease. The update will focus on the clinical and cost effectiveness of oral antiplatelet therapy in reducing cardiovascular disease (CVD) in people with chronic kidney disease (CKD).

Following this surveillance review we have also replaced the recommendation on oral anticoagulant use with cross-references to the NICE guidelines on atrial fibrillation and venous thromboembolic diseases.

Reason for the exceptional review

The purpose of this exceptional review was to examine any impact on NICE's guideline on CKD based on published evidence for the effectiveness of oral antiplatelet and anticoagulant therapy in reducing CVD in people with CKD.

The original guideline published in 2014 and considered the role of oral antiplatelet and anticoagulant therapy. The guideline recommended offering antiplatelets for the secondary prevention of CVD, and to consider apixaban (a direct-acting oral anticoagulant) in preference to warfarin (a vitamin K antagonist) in people with a confirmed estimated glomerular filtration rate (eGFR) of 30 to 50 ml/min/1.73 m^2 and non-valvular atrial fibrillation who have 1 or more specified risk factors.

The subsequent 2017 surveillance review (see previous surveillance) concluded that although an update of parts of the guideline was needed, there was no new evidence to support an update of the recommendations section on oral antiplatelets and anticoagulants.

During stakeholder consultation on the draft updated guideline, a stakeholder (Daiichi Sankyo UK Ltd, who manufacture pharmaceutical products, including edoxaban and prasugrel) commented on the effectiveness of direct-acting oral anticoagulant (DOAC) therapy in reducing CVD in people with CKD. The stakeholder noted that published evidence, NICE technology appraisals and European guidance support the effectiveness of other DOACs, in particular edoxaban, in reducing CVD in patients with CKD, indicating that the recommendations on oral antiplatelets and anticoagulants may need updating.

Methods

The exceptional surveillance process consisted of:

- Considering the new evidence and information that triggered the exceptional review.
- Considering the evidence used to develop the 2014 version of the NICE guideline and relevant information from a previous surveillance review in 2017.
- Examining related NICE guidance and quality standards.
- A literature search to identify relevant evidence, including any new or updated Cochrane reviews.
- Topic expert input was not sought because the information we obtained was enough to establish whether an update to the guideline was needed.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Evidence considered in this exceptional surveillance review

Information considered when developing the original NICE guideline in 2014

Patients with chronic kidney disease (CKD) have a high risk of cardiovascular disease (CVD) and are more likely to develop atrial fibrillation (AF) than patients without CKD. During development, evidence on the clinical and cost effectiveness of oral antiplatelet and anticoagulant therapy in reducing CVD in people with CKD was examined. Searches found no randomised control trials (RCTs) designed and powered to assess the effectiveness of antiplatelet and anticoagulant drugs specifically in people with CKD, but 12 RCTs had subgroup analyses of people with CKD within larger studies in populations with CVD or hypertension.

Oral antiplatelet agents

Evidence was only available for aspirin, clopidogrel and ticagrelor.

One RCT indicated that, although the bleeding risk with aspirin is increased in people with an eGFR <45 ml/min/1.73 m^2, the increased cardiovascular risk of this group of people meant that the benefits of aspirin, in terms of reduced risk of mortality and cardiovascular events, outweighed the risks. As the data was from a post-hoc subgroup analysis which was not powered to detect changes in the CKD subgroup, a recommendation on using aspirin for primary prevention of CVD was not considered appropriate, so the guideline development group (GDG) decided to make a research recommendation on antiplatelet therapy asking 'for people with CKD at the highest risk of cardiovascular disease, what is the clinical effectiveness of low-dose aspirin compared with placebo for primary prevention of cardiovascular disease?'

Clopidogrel was compared with placebo in 3 studies. All patients in the studies were also taking aspirin. The evidence indicated that there were no benefits from taking clopidogrel and that it may be associated with an increase in harms. However, because people with CKD may be resistant to clopidogrel and the evidence was from a limited number of subgroup analyses not powered to detect differences in this CKD population, the GDG agreed that a recommendation against giving clopidogrel in people with CKD was not appropriate.

One RCT showed some benefit for mortality and cardiovascular events for ticagrelor compared with clopidogrel, however the GDG agreed that this was not sufficient evidence to recommend that people with CKD should be treated with any specific oral antiplatelet over another.

No published economic evaluations focused on a CKD population. The GDG noted that annual cost of aspirin and clopidogrel is small, while the cost of ticagrelor and prasugrel are considerably greater. The GDG judged that although increased bleeding might be greater for CKD patients than for other patients, the benefits of aspirin therapy in terms of reduced cardiovascular events were likely to outweigh the risks and costs.

The GDG agreed that the recommendation on antiplatelets should be to 'offer antiplatelet drugs to people with CKD for the secondary prevention of cardiovascular disease, but be aware of the increased risk of bleeding'.

Oral anticoagulant agents

Evidence was available for warfarin, dabigatran, apixaban and rivaroxaban. Evidence on edoxaban was not searched for as this anticoagulant was not approved in the UK until 2015.

An RCT with a population who had AF or flutter, included a pre-specified subgroup analysis of people with kidney impairment. It found that compared with warfarin, apixaban reduced the rate of stroke, death, and major bleeding regardless of kidney function; and people with impaired kidney function GFR (glomerular filtration rate) between 25 to 50 ml/min/1.73 m^2 seemed to have the greatest reduction in major bleeding with apixaban.

An RCT in people with AF and at least 1 additional risk factor for stroke, with a pre-specified subgroup analysis of people with kidney impairment, found that dabigatran 150 mg twice daily reduced the rate of stroke and systemic embolism compared with warfarin, but there was no consistent benefit at dabigatran 110 mg twice daily. However, at dabigatran 150 mg twice daily, in the group with GFR between 30 to 50 ml/min, warfarin was superior in reducing major bleeding. The GDG therefore agreed that 'as the safety benefits in terms of reduction in major bleeding in the most renal impaired group demonstrated with apixaban were not replicated with dabigatran, that there was not sufficient evidence to recommend that dabigatran should be used in preference to warfarin in this group'.

Two RCTs comparing rivaroxaban with warfarin or placebo reported no difference between the treatments on outcomes.

No relevant published economic evaluations were identified that focused on a CKD population. An original cost-utility analysis was developed to compare anticoagulants for people with CKD and non-valvular AF. There was only clear evidence of survival benefit for apixaban compared with warfarin or aspirin. Apixaban was found to be cost-effective for patients with CKD and non-valvular AF compared with both warfarin and aspirin. For dabigatran 110 mg the cost-utility analysis found that the reduction in stroke/systemic embolism and very small gain in survival was not cost-effective compared with warfarin. For dabigatran 150 mg the very small increase in mortality and the increase in major bleeding meant that there were actually QALYs lost compared with warfarin. The cost-utility analysis was assessed to have direct applicability and only minor limitations.

Based on the evidence, the guideline developers recommended: 'Consider apixaban in preference to warfarin in people with a confirmed eGFR of 30 to 50 ml/min/1.73 m^2 and

non-valvular atrial fibrillation who have 1 or more of the following risk factors:

- prior stroke or transient ischaemic attack
- age 75 years or older
- hypertension
- diabetes mellitus
- symptomatic heart failure.'

Previous surveillance of the NICE guideline in 2017

The guideline underwent a surveillance review in 2017. Four new systematic reviews on oral anticoagulants (Harel et al. 2014; Sardar et al. 2014; Bai et al. 2016; Pathak et al. 2015) and 1 systematic review on aspirin (Major et al. 2016) were identified.

The evidence supported the use of oral anticoagulants, particularly apixaban, in patients with mild renal impairment. For aspirin, the systematic review found no clear benefit of aspirin for the primary prevention of cardiovascular events in CKD, no statistically significant reduction in mortality and a significant increase in major bleeding events. It was concluded that this evidence was unlikely to impact the recommendation on antiplatelet drugs for people with CKD as the recommendation is for the secondary prevention of CVD, not primary prevention, and the increased risk of bleeding is already highlighted.

The surveillance review concluded that an update of the recommendations on oral antiplatelets and anticoagulants was not needed, however other sections of the guideline did need updating.

Other relevant NICE guidance

NICE has published technology appraisal guidance on all 4 DOACs for the prevention of stroke and systemic embolism in people with non-valvular AF, which recommend each of these DOACs as an option for the prevention of stroke and systemic embolism within their licensed indications:

- Apixaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation

- Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation
- Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation
- Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation.

The NICE guideline on atrial fibrillation also has a section with recommendations on stroke prevention, including the use of anticoagulants. It recommends offering 'anticoagulation with a direct-acting oral anticoagulant to people with atrial fibrillation and a CHA_2DS_2-VASc score of 2 or above, taking into account the risk of bleeding. Apixaban, dabigatran, edoxaban and rivaroxaban are all recommended as options, when used in line with the criteria specified in the relevant NICE technology appraisal guidance' and 'If direct-acting oral anticoagulants are contraindicated, not tolerated or not suitable in people with atrial fibrillation, offer a vitamin K antagonist'. It also recommends to 'take into account any contraindications for each drug and follow the guidance in the British National Formulary and the MHRA advice on direct-acting oral anticoagulants, in particular for advice on dosages in people with renal impairment, reversal agents and monitoring'.

In relation to antiplatelets, it recommends 'do not offer aspirin monotherapy solely for stroke prevention to people with atrial fibrillation'. This advice is also reflected in quality statement 2 in NICE's quality standard on atrial fibrillation.

NICE also has a guideline on venous thromboembolic diseases, which includes a section on anticoagulation treatment for deep vein thrombosis (DVT) or pulmonary embolism (PE) with renal impairment or established renal failure, which recommends offering 'people with confirmed proximal DVT or PE and renal impairment (estimated creatinine clearance between 15 ml/min and 50 ml/min) one of:

- apixaban
- rivaroxaban
- LMWH [low molecular weight heparin] for at least 5 days followed by:
  - edoxaban or
  - dabigatran if estimated creatinine clearance is 30 ml/min or above

- LMWH or UFH [unfractionated heparin], given concurrently with a VKA [vitamin K antagonist] for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own.'

It also warns 'note the cautions and requirements for dose adjustment and monitoring in the medicine's SPC [summary of product characteristics], and follow locally agreed protocols or advice from a specialist or multidisciplinary team'.

There is also a section on long-term anticoagulation for secondary prevention, which recommends that 'for people who decline continued anticoagulation treatment, consider aspirin 75 mg or 150 mg daily'. It also says that 'in March 2020, the use of aspirin for secondary prevention of DVT or PE was off label', which remains the case as of June 2021. The guideline also recommends that general health, risk of venous thromboembolism (VTE) recurrence, bleeding risk and treatment preferences are reviewed at least once a year for people taking long-term anticoagulation treatment or aspirin.

New evidence that triggered the exceptional review

The stakeholder referenced the European Heart Rhythm Association 'practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation' (Steffel et al. 2018). This includes guidance on the use of DOACs in patients with CKD. It says that 'Compared with warfarin, all four NOACs [DOACs] showed consistent efficacy and safety in patients with mild to moderate CKD compared with non-CKD patients in the respective subgroup analyses of pivotal NOAC trials'. Details on the recommended dosage of the various DOACs according to renal function are provided, as well as when caution is advised: dabigatran in moderate renal insufficiency; rivaroxaban, edoxaban and apixaban in severe renal insufficiency; and edoxaban in 'supranormal' renal function (creatinine clearance greater than 95 ml/min).

The stakeholder also provided 10 references of published studies. One study (Ando and Capranzano 2017) met the surveillance inclusion criteria. The study was identified as part of the search and selection strategy (see evidence summary).

2021 evidence review

Search and selection strategy

We searched for new evidence related to the review question 'For people with CKD, what is the clinical and cost effectiveness of oral antiplatelet and anticoagulant therapy in reducing cardiovascular disease?'. We re-ran the original search strategy for this review question with the addition of edoxaban as a search term, in order to ensure all relevant oral anticoagulants were retrieved (see section F.3.10 antiplatelet and anticoagulant therapy in appendices A to R from the 2014 full guideline).

We found 444 studies in a search for RCTs and systematic reviews published between 1 September 2016 and 18 March 2021. Inclusion criteria were the same as the criteria used in the original NICE guideline (see appendices A to R, table 13 from the 2014 full guideline), except that edoxaban was also included as an intervention, and 6 months minimum study duration was not required to include a study, as only abstracts were being considered. The main exclusion criteria were that patients on dialysis are excluded, which meant that studies reporting on end-stage CKD or patients with renal failure were also excluded.

We considered 24 studies to be relevant to the review question. As this included 12 systematic reviews which covered the effectiveness of potential oral antiplatelet and anticoagulant therapies, we decided to focus on the findings of systematic review evidence only within this exceptional surveillance review.

Evidence summary

Oral antiplatelet agents

Three systematic reviews examined the effectiveness of oral antiplatelets in people with CKD.

One systematic review (Qu et al. 2020) indicated that aspirin use in CKD patients was associated with no significant preventative effect on cardiovascular events or mortality; and while there was no significant increased risk of major bleeding events, there was a significant increased risk of minor bleeding events and renal events.

For other oral antiplatelets, 1 systematic review (Bonello et al. 2018) reported that in

comparison to clopidogrel, prasugrel and ticagrelor were associated with significantly lower rates of major cardiovascular events, without increased bleeding. A second review (Mavrakanas et al. 2019) found no significant differences in outcomes between CKD patients receiving differing lengths of dual antiplatelet therapy.

Oral anticoagulants

Nine systematic reviews examined the effectiveness and safety of oral anticoagulants (DOACs and warfarin) in people with CKD. As existing NICE guidance covers recommendations on anticoagulant use in patients with renal impairment who have atrial fibrillation or VTE, it was decided that only those assessing the effectiveness and safety of anticoagulants in CKD populations with CVD other than AF or VTE would be considered for an impact on the CKD in adults guideline.

None of the systematic reviews provided evidence on the effectiveness and safety of oral anticoagulants for CKD patients with CVD other than for AF or VTE:

- One Cochrane review (Kimachi et al. 2017) and 4 systematic reviews compared the efficacy and safety of oral anticoagulants in AF patients with CKD (Zou et al. 2017, Ando and Capranzano 2017, Feldberg et al. 2019 and Jin et al. 2020).
- Two systematic reviews included CKD patients with VTE (Alhousani et al. 2021 and Cheung et al. 2020).
- One systematic review included CKD patients with AF and/or VTE (Chen et al. 2021).
- One systematic review included studies on CKD patients with any CVD indication; however 12 of the 15 included studies had CKD patients with AF only, with the remaining 3 studies including CKD populations with AF and additional CVD, 2 of which included patients with VTE (Malhotra et al. 2019).

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

The cumulative evidence from stakeholder feedback, previous surveillance, the current

evidence review and existing NICE guidance indicates that the NICE guideline on CKD should be updated in relation to recommendations on the use of oral antiplatelet and anticoagulant therapy for reducing CVD in people with CKD.

For oral antiplatelet therapy, evidence indicates that aspirin may not have a significant preventative effect on cardiovascular events or mortality in CKD patients, but may be associated with increased risk of bleeding events. While NICE guidance on VTE recommends that aspirin can be considered for the secondary prevention of VTE in people who decline continued anticoagulation treatment, this is off-licence use; and the NICE guidance on atrial fibrillation recommends against aspirin monotherapy solely for stroke prevention in people with AF. Overall, this indicates that the benefits of aspirin therapy on CVD in CKD patients should be further investigated.

While there remains no indication that clopidogrel should be considered for use in patients with CKD for reducing CVD, there is additional evidence that indicates ticagrelor and prasugrel are associated with significantly lower rates of major cardiovascular events, without increased bleeding. No published economic evaluations were identified, so the differences in costs between the oral antiplatelets would need to be considered in an update.

For oral anticoagulant therapy for reducing CVD in people with CKD, newly published evidence was only identified in relation to CKD patients with concomitant AF and/or VTE, which is covered by existing NICE guidance. We therefore removed the recommendation which only recommended apixaban, and added a cross reference to the recommendations for stroke prevention in NICE's guideline on atrial fibrillation, which recommend offering any one of the DOACs to people with AF, in line with the criteria specified in the relevant NICE technology appraisal guidance. We have also added a cross-reference to recommendations on anticoagulation treatment for DVT or PE with renal impairment or established renal failure in NICE's guideline on venous thromboembolic diseases.

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