Direct Oral Anticoagulants[DAOC]

(1) Does the application adequately address the issue of the public health need for the medicine?

- Yes *
- No

Please provide brief details:

There are two applications on DOAC. The first (Karmacharya et al) asked for adding DOAC to the WHO EML for patients with non-valvular atrial fibrillation (NVAF), while the second application (Neumann et al) asked for adding DOAC to the complementary list of the WHO EML for two indications including NVAF and venous thromboembolism. Both applications addressed this global public health important issue very well and included most of available evidence on efficacy, safety, costs, adverse effects. The first is strongly supported by many international agencies.

(2) Have all important studies/evidence of which you are aware been included in the application?

- Yes *
- No

Please provide brief comments on any relevant studies that have not been included:

Both applications covered most of available evidence and did comprehensive review. However, we found two important articles that were not considered among references, probably because of it’s date of publication later than the application submission. They are as below:


(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

- Yes *
- No
(a) Briefly summarise the reported benefits (e.g. clinical versus surrogate) and comment, where possible, on the actual magnitude of benefit associated with use of the medicine:

Both applications addressed efficacy/effectiveness properly according to their main aim which is to add DOAC to the WHO EML.

However, comparing different types of DOACs in terms of efficacy or adverse effects is not among their goals, a subject that has attracted the attention of many scientists in recent years for eg. both dabigatran 110 mg and 150 mg can reduce the risk of ICH compared with rivaroxaban. But prior meta-analysis showed that this difference was significant with the 110 mg dose of dabigatran only [1]. Furthermore, Nielsen et al. showed a lower risk for major bleeding associated with apixaban compared with dabigatran 110 mg [2], and Edoxaban 30 mg was significantly lower in risk of major bleeding compared to apixaban and edoxaban 60 mg[3].

(b) Is there evidence of efficacy in diverse settings and/or populations? Please provide brief details:

Yes there is evidence in both applications. In the first application, authors did a systematic literature review and search, then PICO then synthesized data in Cochrane review manager and summarized the results and assessment quality using GRADE tool. They included studies from many countries in different parts of the world and presented their results accordingly. They referred to different settings like elderly, specific diseases like renal or hepatic failure, blood disorders or bleeding tendency and many others specifically when referring to indications or contraindications.

The 2nd application also addressed diverse setting in terms of DOAC availability, types, marketing, costs/economic evaluation, guidelines etc.

(4) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?
Yes * No □

Please provide brief details:

Yes, both applications addressed safety and side effects properly. The first on AF patients, while the 2d application on both AF and thromboembolic disorders. It seems that DOAC for thromboembolic events has more bleeding risks as shown by studies in the 2d application, and it’s prescribed dose should be more than the dose for AF.

We found differences between DOAC types in terms of side effects (which is beyond the main goal of these applications). For eg:

Among patients treated with standard-dose NOAC for NVAF and warfarin users with similar baseline characteristics, dabigatran, rivaroxaban, and apixaban were associated with more favorable benefit–harm profile than warfarin. Among NOAC users, dabigatran and apixaban were associated with more favorable benefit–harm profile than rivaroxaban[4].
Please comment on the overall benefit to risk ratio of the medicine (e.g., favourable, uncertain etc).

Based on the available evidence in both applications, the efficacy and safety of DOAC in patients with NVAF is favourable to be included in the EML. However, it’s benefit to risk ratio when used in thromboembolic patients is still questionable and uncertain.

**ADDITIONAL CONSIDERATIONS:**

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

|   | Yes | No *
|---|-----|-----

Please provide brief details:

According to the provided evidence, no special requirements or training are needed. The contraindications for each type of DOAC are addressed well in both applications, it doesn’t need specific requirement or training.

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

|   | Yes | No *
|---|-----|-----

Please provide brief details:

All types of DOACs presented in the applications are approved by US/FDA, European Medicines, Australian government, Japanese Pharmaceuticals and Health Canada for NVAF and venous thromboembolism. But none of them exist on international pharmacopoeia.

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

|   | Yes | No *
|---|-----|-----

Please provide brief details:

None of DOACs exists in the current WHO guidelines.

(9) Please comment briefly on issues regarding cost and affordability of this medicine.

The use of DOAC is cost effective compared to VKA. This has been indicated clearly in both applications, furthermore, the cost of DOAC is less than VKA in some settings. However, in countries with no insurance coverage or subsidization, it’s current price might be a barrier, thus not affordable for all patients from different socioeconomic settings.
Any additional comments?

The two applications are well written on DOAC for preventing stroke in patients with NVAF and for venous thromboembolism, both addressed efficacy, safety, side effects, cost effectiveness and economic evaluation as well as regulatory issues. The first application is strongly supported and endorsed by most relevant international agencies.

Please frame the decisions and recommendations that the Expert Committee could make.

I suggest that the Expert Committee approve DOAC to be used for NVAF, but to further discuss its recommendation for venous thromboembolism.

References (if required)