Apixaban in atrial fibrillation: Indications of considerable added benefit

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The clot-inhibiting drug apixaban (trade name: Eliquis) has been approved in Germany since November 2012 for the prevention of embolism and stroke in adults with non-valvular atrial fibrillation. In an early benefit assessment pursuant to the "Act on the Reform of the Market for Medicinal Products" (AMNOG), the German Institute for Quality and Efficiency in Health Care (IQWiG) examined the added benefit of apixaban.

IQWiG found an indication of a considerable added benefit of apixaban for each of two patient groups: Patients who can also be treated with a vitamin K antagonist (VKA) have a lower risk of dying, stroke or major bleeding than with warfarin treatment. This only applies to people older than 65 years, however. For younger patients, apixaban does not have an advantage. In patients for whom VKA is not an option, stroke and embolism occur less frequently than with acetylsalicylic acid (ASA).

The G-BA distinguishes between two treatment situations

Atrial fibrillation that is not caused by a leaking heart valve is referred to as "non-valvular atrial fibrillation". Apixaban is an option for patients who also have at least one additional risk factor for stroke, such as hypertension or diabetes mellitus.

The Federal Joint Committee (G-BA) distinguished between two

treatment situations in its specifications for the appropriate comparator therapy: In patients for whom VKAs were an option (VKA population) apixaban was to be compared with a VKA. If VKAs were unsuitable, apixaban was to be compared with ASA.

The G-BA specified warfarin or phenprocoumon as possible VKAs. Doctors in Germany almost exclusively prescribe phenprocoumon, but better data on the benefit of VKA therapy are available for warfarin. In its dossier, the manufacturer therefore compared apixaban with warfarin.

Both approval studies left questions open

Results of one approval study for each of the two patient groups were available. Although both studies were direct comparative randomized controlled trials (RCTs), they left questions unanswered: In the study that directly compared apixaban with warfarin (ARISTOTLE), results largely differed from country to country, and it is unclear whether they adequately represent the effects of apixaban treatment in Germany. In the study that tested apixaban against ASA (AVERROES), it is unclear whether the results can be applied to all patients independent of their individual risk of complications. In both cases, however, there are no fundamental doubts about the advantages of apixaban so that IQWiG derived an indication of an added benefit in each case.

VKA population: added benefit only proven for people aged over 65 years

In comparison with warfarin, the results differed depending on age, i.e. "age" is what is known as an effect modifier. Whereas no added benefit of apixaban could be derived from the study data for people aged under 65 years, this new drug is superior in people aged over 65 years

regarding several outcomes: In the older patients, both death (overall mortality) and stroke were less frequent under apixaban. The difference in strokes was mainly due to haemorrhagic strokes, i.e. strokes caused by bleeding. Regarding bleeding events (major bleeding and clinically relevant non-major bleeding), results were also in favour of apixaban.

Overall, IQWiG rated the extent of added benefit as considerable for people aged over 65 years.

Advantages versus entire ASA population

In patients for whom VKAs were not an option and in whom apixaban was therefore compared with ASA, both stroke and embolism were less frequent in the apixaban group. This was true irrespective of age.

There was also an indication of greater harm in the form of more frequent, mainly non-major bleeding (extent "minor"). But because there also was an advantage in favour of the new drug in the combined outcome of stroke, systemic embolism, and mortality, IQWiG did not consider it appropriate to downgrade the extent of added benefit of apixaban due to the bleeding events. Overall, IQWiG sees a considerable added benefit also in these patients.

First reassessment of a dossier for new therapeutic indication

About a year ago, on 15 March 2012, IQWiG already published a first dossier assessment of apixaban. That assessment however dealt with a different therapeutic indication, namely the "prevention of thrombosis after operations to replace a hip or knee joint". This makes apixaban the first drug to undergo the AMNOG procedure again for an additional therapeutic indication.

G-BA decides on the extent of added benefit

The dossier assessment is part of the overall procedure for early benefit assessments supervised by the G-BA. After publication of the manufacturer's dossier and IQWiG's assessment, the G-BA conducts a commenting procedure, which may provide further information and result in a change to the benefit assessment. The G-BA then decides on the extent of the added benefit, thus completing the early benefit assessment.

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