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Preventing cardiovascular events with empagliflozin: at what cost?

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The EMPA-REG OUTCOME study,[1] as the first randomised trial to find that a glucose-lowering intervention was associated with reduced cardiovascular events, raises important questions for policy makers. Chief among these is whether the detected effect size produces a cost-effective risk reduction from the studied pharmacological approach. The study has undoubtedly brought good news for the trial sponsors: analysts predict that its findings will propel empagliflozin ahead of other glucose-lowering medications in sales. But will increased empagliflozin use prove affordable for healthcare systems?

In early 2015, the National Institute for Health and Care Excellence (NICE) concluded that empagliflozin was a cost-effective option for patients with type 2 diabetes. The economic model used by NICE simulated diabetes-related long-term complications based on patient characteristics and the drug's impact on HbA1c, systolic blood pressure and body mass index (BMI).[2] Although this model is commonly used by several health technology assessment bodies besides NICE, it has a number of significant limitations.

First, the model assumes that changes in HbA1c, systolic blood pressure, and BMI observed over 26 or 52 weeks continue over the patient's lifetime (the time horizon employed by NICE). However attenuation of effect over time was clearly demonstrated in the 3-year EMPA-REG study.[1]

Second, the model relies on epidemiological rather than interventional studies to predict the long-term effects of glucose lowering, despite the former having been repeatedly shown to overestimate the benefits of glucose lowering. For example, meta-analyses of interventional studies did not detect any benefits of intensive glucose lowering.[3]

Finally, the model compares costs and benefits of empagliflozin when added to metformin to a set of similar (and slightly more expensive) glucose-lowering drug options. Under this scenario, it

is unsurprising that empagliflozin proves cost-effective when compared to its more expensive alternatives. Given the intensive debate about the appropriateness of current HbA1c targets,[3] a more logical analysis (consistent with cost-effectiveness guidelines[4]) would compare adding empagliflozin to metformin versus continuing treatment with metformin alone.

The EMPA-REG OUTCOME study also offers an additional way of estimating the costs and benefits of empagliflozin. Empagliflozin is estimated to reduce the absolute risk of cardiovascular events by 6.5% among a population at very high risk for such events (43.9% over 10 years). In this population the number needed to treat for 10 years to prevent one event would be 16. At an annual cost of £477.30, preventing a cardiovascular event with empagliflozin would cost approximately £73,431 in this high-risk population. If empagliflozin were offered to individuals at substantially lower risk of cardiovascular events (e.g., 10% over 10 years, the NICE threshold for statins), the cost to prevent an event would jump to £322,361.

The recent rise in cardiovascular safety trials like EMPA-REG offers an opportunity to move away from basing economic analyses on epidemiological associations and instead develop more rigorous cost-effectiveness models from trial data. These interventional trials could inform robust cost-effectiveness calculations and compare all relevant glucose-lowering choices which encompass both costs and consequences from the patient's perspective.[5]

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