The Dark Heart of Type 2 Diabetes Addendum

Baker
HEART & DIABETES INSTITUTE

New evidence to save lives

Recent trials have shown exciting data, indicating that some glucose-lowering drugs protect people with type 2 diabetes from the effects of cardiovascular disease. In particular, the SGLT2 inhibitor empagliflozin lowered the risk of hospitalisation for heart failure by 35%, and reduced CVD and total mortality rates by 38% and 32%, respectively[1]. This translates into a number needed to treat of 39 over three years to prevent one death in this high-risk population. Interestingly, glucose-lowering does not appear to be a major mechanism through which these impressive benefits were achieved. Blood pressure lowering and weight loss likely contributed to the benefits, but the full mechanism is yet to be understood. The EMPA-REG OUTCOME trial, which reported these results, was a large and robust study, conducted in over 7,000 participants at 590 sites in 42 countries[1]. The trial population comprised adults with type 2 diabetes, all of whom had an established history of CVD, with objective evidence of CHD, stroke or peripheral arterial disease.

These findings lead to important questions about the extent to which the use of empagliflozin in Australia could lead to reductions in these important outcomes. The size of the benefit that could be seen depends on the extent to which such drugs are used, and their effectiveness in a non-trial setting.

In order to understand the scope of potential benefit, we have modelled the effects reported in EMPA-REG OUTCOME across the population of people with diabetes in Australia to estimate the impact of the use of empagliflozin on mortality.

Methods

This analysis focused on estimating the total number of deaths that could be saved in a single year if empagliflozin was administered to varying proportions of the estimated national Australian population of people with type 2 diabetes and prior CVD. We focused on total mortality, as this is the most important outcome, and the one for which data sources provide the most reliable estimates.

The source for the national diabetes population was the National Diabetes Services Scheme (NDSS). The NDSS was established in Australia in 1987 to deliver diabetes-related products at subsidised prices and provide information to people with diabetes. Registration of patients is free and is completed by a medical practitioner or credentialed diabetes educator. The NDSS captures 80–90% of all Australians with known diabetes[2]. Diabetes type is assigned by the clinician who completes the registration form. In addition, we reclassified a group of individuals who were initially registered as type 1 to type 2 if they were not taking insulin and had an age of registration >45.

The NDSS was linked to the National Death Index (NDI) using data up to and including 30 June 2016. Linkage was performed by the Australian Institute of Health and Welfare. All-cause mortality rates among those with type 2 diabetes were estimated by Poisson regression using this population. We used the 2015 NDSS population, as this is relatively contemporary, but precedes any significant use of SGLT2 inhibitors.

The NDSS does not include information on the presence of CVD. We therefore used longitudinal data from the national, population-based Australian Diabetes Obesity and Lifestyle Study (AusDiab) to calculate the prevalence of CVD among adults with type 2 diabetes, and the relative risk of death associated with CVD among people with diabetes. We then applied these (in an age-specific manner) to the NDSS population and NDSS total mortality data, using standard methods of apportioning a rate using prevalence and relative risks. This method apportions the all-cause mortality rate for the total NDSS diabetic population into those with prior CVD and those without. The relative risks were then combined with all-cause mortality rates for the year 2015 for the NDSS population, and with age-specific prevalence of prior CVD in diabetes, to calculate the all-cause mortality rate for the population without prior CVD among people with diabetes and the all-cause mortality rate for the population with prior CVD among people with diabetes.

We modelled various different scenarios, all of which were restricted to those with type 2 diabetes and prior CVD. In the primary analysis, we estimated the total number of deaths avoided under the assumption that the effect was to reduce mortality by 30% (i.e. similar to the 32% reported in EMPA-REG OUTCOME[1]), that all people with prior CVD received empagliflozin, and that drug adherence was 75% (i.e. the same as reported in EMPA-REG OUTCOME). In subsequent models, we explored more conservative estimates of the benefits, and reduced the effect of the drug on mortality to reductions of 20% and to 10%, and also varied the uptake of empaglifozin use among the relevant population between 50% and 100%.

Results

There were 963,066 people with type 2 diabetes on the NDSS in 2015, among whom 227,624 were aged 40-79, and were estimated to have prior CVD. Within this group, there were 6,983 deaths in the year 2015. In the primary analysis, we found that the introduction of empagliflozin reduced the number of deaths in a single year by 2,095 (Table 3). As the uptake of empagliflozin fell to 50%, the number of deaths prevented fell to 1,047. If uptake remained at 100%, but the effect on mortality fell to a 10% reduction, the number of deaths prevented became 698. If efficacy and uptake were at their lowest (10% and 50% respectively), 349 deaths were prevented.

Table 3. Number of deaths prevented over 1 year across Australia according to different levels of drug efficacy and uptake.

Uptake (%)	Reduction in mortality (%)		
	10	20	30
100	698	1397	2095
90	628	1257	1885
80	559	1117	1676
70	489	978	1466
60	419	838	1257
50	349	698	1047

Discussion

These findings indicate the likely range of effects of the widespread introduction of empagliflozin on mortality. If the effects of empagliflozin reported in EMPA-REG OUTCOME were reproduced in the general population, and all people with diabetes and prior CVD were prescribed empagliflozin, then over 2,000 deaths would be prevented in a single year. Since the effectiveness of an intervention is often less in a non-trial population than in a trial population, we modelled other more conservative scenarios, but even when both uptake and efficacy were significantly reduced, several hundred deaths were prevented. We could have added a further dimension to account for drug adherence. The trial results were in the setting of a 75% adherence (i.e. 25% discontinued study drug), meaning that the 32% reduction in mortality occurred among a study group in which 25% had discontinued the drug. However, it is likely that adherence outside a trial setting would be somewhat lower than was achieved in EMPA-REG OUTCOME. Adding this extra dimension would have complicated the presentation of findings, but uptake can also be used as a proxy for adherence. Thus, if the effect on mortality is held at 30% and initial uptake were 100% (i.e. all people with type 2 diabetes and prior CVD were prescribed empagliflozin), but 50% discontinued soon after commencement, then the number of deaths prevented would fall from 2,095 to 1,047.

The findings presented take no account of other effects of empagliflozin. They do not include the benefits reported for protection against the serious effects of heart failure, nor on the reduction in the need for kidney dialysis. We also did not include any of the adverse events. Nevertheless, since total mortality is influenced by both the beneficial and harmful effects of an intervention, this measure has significant utility in understanding the net impact of empagliflozin.

This analysis does not examine the costs of empagliflozin. In order to obtain the maximum benefit reported here, over 220,000 people would need to take empagliflozin and over 160,000 people would remain on the drug throughout the 1-year time-period that was considered. However, for many people, empagliflozin would be used instead of another drug in order to achieve adequate glycaemic control. Thus, in considering costs, the difference between drug costs, rather than simply the absolute cost of empagliflozin, needs to be assessed.

In summary, we have shown that, within the Australian population, the introduction of empagliflozin among people with type 2 diabetes and a history of CVD would prevent over 2,000 deaths in one year if uptake is widespread and the effect on mortality is similar to that shown in trials. Even when both efficacy and uptake fall substantially, several hundred deaths could still be avoided.

References:

1. Zinman, B., et al., Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med, 2015. 373(22): p. 2117-28.
2. AIHW, Diabetes Prevalence in Australia. An Assessment of National Data Sources. 2009, AIHW: Canberra.

BAKER HEART AND DIABETES INSTITUTE

Baker Heart and Diabetes Institute is an independent medical research institute with a mission to reduce death and disability from cardiovascular disease, diabetes and related disorders. The Baker Institute is one of the few institutes in the world where the work of world-leading clinicians and researchers spans the spectrum of chronic disease from obesity to type 2 diabetes and cardiovascular disease, and ranges from benchtop to bedside to population. The Institute is acutely aware of the need to meet the significant challenges facing the community as a result of rising rates of diabetes and cardiovascular disease. In particular, the Institute is committed to raising awareness of the important relationship between type 2 diabetes and cardiovascular disease to help improve the quality of life for patients with type 2 diabetes.

Baker
HEART & DIABETES INSTITUTE