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Title Sodium-glucose co-transporter 2 (SGLT2) inhibitors versus gliclazide in the treatment of type 2 diabetes mellitus

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Aim

To assess the effectiveness, safety and cost-effectiveness of SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) versus gliclazide in T2DM.

Conclusions and results

Good level of retrievable evidence:

Effectiveness

1) Glycaemic Control (HbA1c reduction)
   Canagliflozin 100mg, dapagliflozin 5mg and 10mg, and empagliflozin 10mg and 25mg were less effective than gliclazide. Only canagliflozin 300mg was found to be as effective as gliclazide.
2) Weight Changes
   SGLT2 inhibitors showed significant reduction in body weight. Gliclazide was associated with weight gain.
3) Blood Pressure Control
   SGLT2 inhibitors had some reduction in systolic blood pressure. There was no retrievable evidence for gliclazide.
4) Cardiovascular Outcome
   SGLT2 inhibitors had moderate benefits on atherosclerotic major adverse cardiovascular events (MACE) and risk of cardiovascular death or hospitalisation for heart failure in patients with established atherosclerotic cardiovascular disease (ASCVD). Patients with multiple risk factors did not benefit from SGLT2 inhibitors in terms of MACE and risk of cardiovascular death or hospitalisation for heart failure. There was limited evidence retrieved for gliclazide.
5) Renal Outcome
   Patients with ASCVD and those with eGFR ≥60ml/min/1.73m^2 would benefit from SGLT2 inhibitors in terms of risk of renal worsening, end-stage kidney disease or renal death. Results were inconclusive for patients with eGFR <60ml/min/1.73m^2. There was no retrievable evidence for gliclazide.

Safety

Gliclazide was associated with significantly higher risk of hypoglycaemia compared with SGLT2 inhibitors. SGLT2 inhibitors were associated with increased risk of genital infections as well as rare occurrences of diabetic ketoacidosis and acute kidney injury. Fournier's gangrene was identified as a safety concern in patients receiving SGLT2 inhibitors. Patients taking canagliflozin had increased risk of bone fractures and were approximately twice as likely to undergo amputation.

Cost /cost-effectiveness

A systematic review and cost-effectiveness modelling showed that all three SGLT2 inhibitors were not cost-effective compared with gliclazide from the perspective of the UK National Health Service and Personal Social Services, using 2014 prices, with costs and benefits discounted at 3.5% per year. However, the cost-effectiveness modelling did not include cost savings from improved cardiovascular and renal outcome of which data were not yet available at the time of assessment.

Recommendations

SGLT2 inhibitors may be used in adults with type 2 diabetes mellitus especially when glycaemic control has not been achieved, cardiovascular disease has been established, or there is compelling need to avoid hypoglycaemia or promote weight loss. There is safety concern for increased risk of amputation and bone fracture with the use of canagliflozin. Hence, continued monitoring of adverse events is advocated for SGLT2 inhibitors.

Methods

Electronic databases were searched via Embase, Ovid MEDLINE® In-process and other Non-indexed citations (1946 to present), EBM Reviews–Cochrane Database of Systematic Reviews (2005 to February 2019), EBM Reviews–Cochrane Central Register of Controlled Trials (January 2019), EBM Reviews–Database of Abstracts of Review of Effects (1st Quarter 2016), EBM Reviews–Health Technology Assessment (4th Quarter 2016), NHS economic evaluation database (1st Quarter 2016) and PubMed. Searches were also run in INAHTA, Horizon Scanning databases, FDA website and general search engine. Additional articles were identified from reviewing the references of retrieved articles. The search was limited to English articles on humans. Last search was run on 29th January 2019. An updated search was conducted between 30th April 2019 and 8th May 2019 based on feedback from one of the external reviewers.

Further research/reviews required

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