National Essential Medicine List
Primary Healthcare Medication Review Process
Component: Endocrine medicines

Medication name: Glimepiride

Date of review: October 2013

Indication: Treatment of diabetes mellitus type 2

Executive summary:

Compared with glibenclamide, glimepiride has similar efficacy, is associated with a lower risk of hypoglycaemia, and might be associated with a lower rate of cardiovascular events and mortality.

Introduction and contextualisation:

The current primary and adult hospital level EMLs and STGs for diabetes mellitus type 2 include the sulphonylureas gliclazide and glibenclamide for patients who are not controlled on diet, exercise and metformin. Two external reviewers requested that glimepiride be added. One suggested that it should replace glibenclamide as it is associated with a lower risk of hypoglycaemia and cardiovascular events, and it may be given as a single daily dose which might improve adherence.

This review explores the efficacy and safety (in terms of cardiovascular events and hypoglycaemia) of glimepiride compared to glibenclamide.

Search strategy:

Pubmed search terms:

Randomised controlled trials

(("glimepiride"[Supplementary Concept] OR "glimepiride"[All Fields]) AND ("glyburide"[MeSH Terms] OR "glyburide"[All Fields] OR "glibenclamide"[All Fields])) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomised controlled trial"[All Fields] OR "randomized controlled trial"[All Fields])

Observational studies

("glimepiride"[Supplementary Concept] OR "glimepiride"[All Fields]) AND ("glyburide"[MeSH Terms] OR "glyburide"[All Fields] OR "glibenclamide"[All Fields])

Selection of studies:

Inclusion criteria:

Types of studies: randomised controlled trials (RCTs) or prospective or retrospective observational cohort studies

Participants: patients with diabetes mellitus type 2

Interventions: glimepiride

Control: glibenclamide
Outcomes: Efficacy: glucose concentrations and HbA1c
Safety: risk of hypoglycaemia and cardiovascular effects
Mortality

Results:
Randomised controlled trials

The Pubmed search identified 24 studies. Eight met the inclusion criteria. A further study was identified in the broader (second) search.

Observational studies
The PubMed search identified 255 studies. Twelve met the inclusion criteria.

Evidence synthesis:

Randomised controlled trials
Efficacy and risk of hypoglycaemia

A RCT sponsored by a pharmaceutical company that makes both glimepiride and glibenclamide compared glimepiride plus metformin, with glibenclamide plus metformin in 152 uncontrolled type 2 diabetics.[1] The groups had similar fasting and post-prandial glucose concentrations, and changes from baseline in HbA1c after 12 months' treatment. Adverse events were similar in both groups except for hypoglycaemia, which was more frequent in the glibenclamide group (28.9 versus 17.1%, p=0.047).

A RCT in 172 uncontrolled type 2 diabetics randomised patients to continue their current sulphonylurea (gliclazide or glibenclamide) or to switch to glimepiride.[2] There were no significant changes from baseline in HbA1c after six months' treatment in either group.

A crossover RCT in 29 type 2 diabetic patients compared glimepiride, glibenclamide and placebo over 4 weeks.[3] Mean fasting glucose concentration was lower in glibenclamide than glimepiride (9.5±3.2 versus 10.6±3.4 mmol/L, p=0.003). There was no significant difference in post-prandial glucose concentration.

A RCT sponsored by a pharmaceutical company that made both glimepiride and glibenclamide compared glimepiride with glibenclamide in 1044 type 2 diabetics who were stable on glibenclamide.[4] There was no significant difference in fasting glucose concentration or HbA1c. There were fewer hypoglycaemic episodes in the glimepiride group than the glibenclamide group (105 versus 150).

A RCT sponsored by a pharmaceutical company that made both glimepiride and glibenclamide compared glimepiride with glibenclamide in 577 type 2 diabetics.[5] There was no significant difference in fasting glucose concentration or HbA1c. There were fewer hypoglycaemic episodes in the glimepiride group than the glibenclamide group.

A crossover RCT in sulphonylurea-controlled type 2 diabetics compared glimepiride and glibenclamide over 1 week.[6] There was no significant difference in fasting glucose concentration or insulin secretion.

Vascular effects

A RCT in 40 poorly controlled type 2 diabetics compared glimepiride and glibenclamide over 6 months.[7] There were no significant differences in HbA1c. The mean reduction in arterial stiffness, as measured by the cardio-ankle vascular index, was greater in the glimepiride group (-0.50±0.98 versus -0.04±0.57, p=0.048).

A crossover RCT in 12 type 2 diabetic patients compared glimepiride and glibenclamide over eight weeks.[8] There were no significant differences in HbA1c, blood pressure and forearm vasodilator responses.

A crossover RCT in 20 type 2 diabetic patients compared glimepiride, glibenclamide and diet over eight weeks.[9] There were no significant between group differences in vasodilation after forearm ischaemia, measured by ultrasound.

Observational studies
Mortality
A retrospective cohort study in 17 773 patients in the United States found that glibenclamide, glipizide and chlorpropamide (as well as rosiglitazone, and insulin) were associated with an increased risk of death relative to that expected for patients' demographics and illness severity.[10] Metformin, acarbose, glimepiride, pioglitazone, repaglinide, troglitazone, and dipeptidyl peptidase-4 were not associated with increased mortality.

A retrospective cohort study in 7 320 patients in the United States found no significant difference in mortality between glimepiride plus metformin, glibenclamide plus metformin and glipizide plus metformin.[11]

A retrospective cohort study in 107 806 patients in Denmark found that both glibenclamide and glimepiride monotherapy increased the risk of mortality compared to metformin.[12]

A retrospective cohort study in 3 477 patients with heart failure in Denmark found no difference in mortality between glimepiride, glibenclamide, glipizide, gliclazide or tolbutamide monotherapy.[13]

A retrospective cohort study in 11 141 patients in the United States found no significant difference in mortality between glimepiride, glibenclamide and glipizide monotherapy.[14]

A retrospective cohort study in 9 876 type 2 diabetics who had had a myocardial infarction and who were not treated by percutaneous coronary intervention found that glibenclamide, glimepiride, glipizide and tolbutamide, but not gliclazide, were associated with an increased risk of cardiovascular mortality or non-fatal myocardial infarction compared to metformin. Hazard ratios (95% confidence intervals: 1.31 (1.17 to 1.46); 1.19 (1.06 to 1.32); 1.25 (1.11 to 1.42); 1.18 (1.03 to 1.34); and 1.03 (0.88 to 1.22) respectively.[15]

A prospective cohort study in 1 310 patients in France found that in-hospital mortality after a myocardial infarction was higher in patients on glibenclamide than in those on glimepiride or gliclazide (7.5 versus 2.7%, p=0.019).[16]

A retrospective cohort study in 64 266 patients in the Ukraine found that all-cause mortality was higher in those on glibenclamide than in those glimepiride. However the difference was no longer significant after adjusting for age, sex, diabetes duration, BMI, systolic blood pressure and fasting glucose.[17]

A retrospective cohort study in 2 002 patients in Italy found that glibenclamide plus metformin was associated with an increased risk of mortality compared to other insulin secretagogues plus metformin. Odds ratio (adjusted for age, duration of diabetes, Body Mass Index (BMI), lipid profile, HbA1c, insulin treatment, metformin doses and Charlson co-morbidity score) 2.09 (95% confidence interval 1.07 to 4.11).[18]

Other outcomes
A retrospective cohort study in 1 159 patients in Taiwan found that glimepiride was associated with a lower risk of non-fatal cardiac events (coronary artery disease, peripheral artery disease, stroke, or heart failure) compared to glibenclamide. Hazard ratio 0.31 (95% confidence interval 0.24 to 0.40).[19]

A prospective observational study in 40 type 2 diabetics that compared glimepiride and glibenclamide over 3 years found that glimepiride was better in terms of limiting progression of carotid artery intima media thickness (measured on ultrasound): -0.044±0.171 versus 0.077±0.203 mm, p=0.0474.[20]

A prospective observational study in 45 patients recruited in emergency departments in Germany estimated the incidence of severe hypoglycaemic episodes as 0.86 per 100 person-years for 5.6 per 100 person-years for glimepiride and glibenclamide respectively, based on population numbers and prescribing patterns in the region.[21]

Evidence quality:

This review considers both randomised controlled trials and observational cohort studies. While there are many limitations to the observational studies, they are presented to give an indication of cardiovascular risk and mortality as the RCTs did not have large enough samples or duration of follow up to estimate those outcomes.

Alternative agents:

The EML and STG currently lists gliclazide as an alternative sulphonylurea, especially in the elderly and in those with impaired kidney function.

Summary:

Randomised controlled trials demonstrated that glimepiride and glibenclamide have similar efficacy and vascular effects, but that glimepiride was associated with a lower risk of hypoglycemic events. Most observational cohort studies found similar mortality rates in patients on glibenclamide and glimepiride, but a few found an increased risk of death or cardiovascular events with glibenclamide.

Recommendation:
The Committee recommended an investigation comparing glimepiride *vs.* gliclazide.

References:

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