TITLE: Glyburide, Gliclazide or Glimepiride in the Elderly with Type 2 Diabetes: A Review of the Clinical Effectiveness and Safety

DATE: 15 June 2011

CONTEXT AND POLICY ISSUES:

Diabetes mellitus is a chronic disease characterized by the body's inability to produce sufficient insulin and/or properly use insulin. Type 2 diabetes represents 90-95% of the total population living with diabetes in Canada. Type 2 diabetes occurs when the body cannot make enough insulin and/or cannot properly use the insulin it makes. A 2009 estimate reported that 791,816 Canadians age 65 and over had diabetes. Elderly individuals with diabetes are at an increased risk for multiple negative health outcomes including mortality, vascular complications, vascular dementia and Alzheimer's disease.

Sulfonylureas (SUs) are among the oldest class of oral antihyperglycemic agents available for the treatment of type 2 diabetes. They are moderately effective at lowering blood glucose concentrations by 20% and glycated hemoglobin (HbA1c) by 1-2%; their effectiveness is known to decrease over time.

Second generation SUs available in Canada include glyburide (also known as glibenclamide), gliclazide, and glimepiride. The risks related to the use of SUs in the elderly may vary depending on the choice of SU. For example, the risk of any type of hypoglycemia, including severe or fatal hypoglycemia with glyburide increases exponentially for the elderly. The purpose of this review is to examine the comparative clinical effectiveness and safety of glyburide compared to gliclazide, or glimepiride in the elderly (age 65 and over). This is a modified update to the Rapid Response Report entitled, “Glyburide, Gliclazide, or Glimepiride in the Elderly,” published on April 18, 2007.

RESEARCH QUESTIONS:

1. What is the comparative clinical effectiveness of glyburide versus gliclazide or glimepiride in elderly patients with type 2 diabetes?

2. What is the clinical evidence on the patient safety associated with glyburide, gliclazide or glimepiride in elderly patients with type 2 diabetes?
KEY MESSAGE:

There was no evidence identified concerning the clinical effectiveness of glyburide when compared to gliclazide or glimepiride for elderly patients with type 2 diabetes. The evidence available concerning the safety of glyburide, gliclazide or glimepiride is limited and inconclusive. In one study there is some suggestion that glyburide may be associated with a greater risk of all-cause mortality compared to gliclazide.

METHODS:

Literature search strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2011, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between April 19, 2007 and May 16, 2011.

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, and non-randomized studies.

Selection criteria and method

One reviewer (KQ) screened titles and abstracts of the retrieved publications and evaluated the full-text publications for the article selection, according to the selection criteria in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients who are 65 years or older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Glyburide (glibenclamide)</td>
</tr>
<tr>
<td>Comparator</td>
<td>Gliclazide or Glimepiride as a monotherapy or combination therapy</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Clinical Outcomes</td>
</tr>
<tr>
<td></td>
<td>Clinical harms, such as hypoglycemia</td>
</tr>
<tr>
<td>Study designs</td>
<td>Health Technology Assessments (HTAs), Systematic Reviews (SRs), Meta-Analyses (MAs), Randomized Controlled Trials (RCTs), observational studies, and non-randomized studies (only if HTAs, SRs, MAs or RCTs not available)</td>
</tr>
</tbody>
</table>

Exclusion criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications or included in a selected systematic review, or were published prior to April, 2007.
Critical appraisal of individual studies

The quality of the included non-randomized studies was assessed using the SIGN 50 checklist for cohort studies.\(^8\) The quality of these studies will be discussed in the limitations.

**SUMMARY OF EVIDENCE:**

**Quantity of research available**

Two relevant non-randomized studies were identified. No health technology assessments, systematic reviews, or meta-analyses that met the selection criteria were identified in the literature search (see Appendix 1).

Four non-randomized studies not specifically on patients 65 years of age and above but on a broader patient population are included as additional information in Appendix 3. Two guidelines that included information on glyburide, gliclazide and glimepiride in the elderly are included as additional information in Appendix 3.

**Summary of study characteristics**

Greco et al. (2010)\(^9\) conducted a retrospective cohort study with a nested case series (or reports) to examine the incidence and risk factors for developing severe hypoglycemia among patients aged 80 or older with type 2 diabetes admitted to an Italian hospital. Information on numerous risk factors and current treatments for diabetes was collected at the time of admission of the patients 80 years or older with a severe hypoglycemia [number of patients (n) =99].

Monami et al. (2007)\(^10\) conducted a retrospective cohort study with patients who visited a geriatric clinic in Italy to compare all-cause, cardiovascular and non-cardiovascular mortality and cardiac morbidity between patients taking glyburide (n = 378) and gliclazide (n =190) at the time of enrollment. Study characteristics are shown in Appendix 2 (Table 2).

**Summary of critical appraisal**

The quality of evidence identified was generally low. Of the two studies identified one study adjusted for possible confounders in the analysis such as other medications, or comorbidities.\(^10\) In addition, in both studies there was a large discrepancy in terms of the number of patients receiving glyburide compared with gliclazide or glimepiride. Furthermore, little information or in some cases no information was provided on the dose and duration of glyburide, gliclazide, or glimepiride use by patients. In addition, one of the two studies did not include a direct comparison between glyburide and gliclazide or glimepiride.\(^9\)

**Summary of findings**

Greco et al. (2010) conducted a retrospective cohort study with a nested case series (or reports) to determine the incidence and risk factors for developing severe hypoglycemia leading to hospital admission among type 2 diabetic patients age 80 years or older.\(^9\) A total of 591 patients’ age 80 years or older were identified with Type 2 Diabetes. They found that of the patients 80 years of age or older admitted to hospital with Type 2 Diabetes, 99 patients had severe hypoglycemia. Patients with severe hypoglycemia (n=99) were using a variety of oral antidiabetic agents. Patients were taking glyburide monotherapy (n=53) (5-15mg/day), glyburide with metformin (n=22) (1000-2250 mg/day), glyburide with acarbose (unknown dose
regime) (n=1), five patients were taking gliclazide monotherapy (unknown dose regime) and two patients were taking glimepiride monotherapy (unknown dose regime).³

Monami et al. (2007) in a retrospective cohort study⁹ observed that among geriatric patients glyburide was associated with a statistically significantly higher rate of all-cause mortality when compared to gliclazide after adjustment for age, sex, duration of diabetes, HbA1c, insulin and metformin therapy, Body Mass Index (BMI), and Charlson Comorbidity Score (HR= 2.8, 95% CI 1.2 to 6.2). However, glyburide was not associated with a statistically significant increase in cardiovascular mortality or non-cardiovascular mortality after adjusting for the same factors stated above.⁹ Details are provided in Appendix 2 (Table 3).

Limitations

The two non-randomized studies identified were retrospective cohort studies, which relied on medical records or individual recall to ascertain sulfonylurea use. Errors in recall and inaccuracies in medical records of sulfonylurea use could introduce bias. No information was provided on the duration of sulfonylurea use and the basis for medication selection. As a result, the sulfonylurea treatment choice could be subject to prescription bias. Factors related to the disease presentation could have affected prescription choice. A related concern involves the lack of information on the dosage of sulfonylurea. It is possible risk of adverse events in the elderly may be influenced by the dose of sulfonylurea. Nested case series do not consider the frequency of exposure among identified cases and the original cohort or a control group; as a result, they have limited internal and external validity.

An additional concern is the lack comparability of patient groups. In one the studies,¹⁰ patients differed significantly at baseline on possible confounding factors such as HbA1c (%), and duration of diabetes, and cerebrovascular disease between the glyburide and gliclazide groups.¹⁰

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

The lack of good quality evidence concerning glyburide, gliclazide or glimepiride use for the elderly with Type 2 Diabetes makes it difficult to draw conclusions concerning the comparative clinical effectiveness and safety of these SUs. The selected studies did not address the comparative effectiveness of glyburide compared to gliclazide or glimepiride for the elderly with type 2 diabetes

Patient safety concerns were addressed in low quality evidence from retrospective cohort studies. One study suggest patients 80 years of age and above with severe hypoglycemia at time of admission to hospital may more frequently be using glyburide monotherapy or in combination with other oral antidiabetic therapies than gliclazide or glimepiride. However, there are multiple factors that may bias this association including prescription bias, no control for known confounding factors, and the inability to control for unknown confounders. A second study suggested that compared to gliclazide, glyburide is associated with a statistically significant increase in risk of all-cause mortality, however the increase in risk for cardiovascular and non-cardiovascular mortality (excluding patients with malignancies) was not statistically significant. However, it is subject to similar drawbacks as the other included study including prescription bias, and the inability to control for unknown confounders.
Given the drawbacks of the selected studies, definitive conclusions cannot be drawn. The available evidence is inconclusive.

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REFERENCES:


APPENDICES:

APPENDIX 1: Selection of Included Studies

147 citations identified from electronic literature search and screened

127 citations excluded

20 potentially relevant articles retrieved for scrutiny (full text, if available)

20 potentially relevant reports

0 potentially relevant reports retrieved from other sources (grey literature, hand search)

20 potentially relevant reports

18 reports excluded:
- irrelevant population (6)
- irrelevant intervention (1)
- irrelevant comparator (5)
- irrelevant outcomes (5)
- Other (review article) (1)

2 reports included in review
APPENDIX 2: Summary of Study Characteristics

Table 2: Relevant Study Characteristics

<table>
<thead>
<tr>
<th>Name, Year, Country,</th>
<th>Study Type and Design</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greco et al. (2010)</td>
<td>Retrospective Cohort</td>
<td>Patients hospitalized for diabetes age 80 years or older(n= 591)</td>
<td>Glyburide (alone or in combination)</td>
<td>Gliclazide Glimepiride</td>
<td>Therapy at time of admission to study</td>
</tr>
<tr>
<td>Italy</td>
<td>Nested Case Reports</td>
<td>Patients hospitalized for diabetes complications with severe hypoglycemia (n= 99)</td>
<td></td>
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<td></td>
<td>8 year period of admission</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Monami et al. (2007)</td>
<td>Retrospective Cohort Study</td>
<td>Patients who visited a Geriatric Clinic taking glyburide (n= 378) or gliclazide (n = 190)</td>
<td>Glyburide</td>
<td>Gliclazide</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cardiovascular mortality</td>
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<td></td>
<td></td>
<td></td>
<td>non-Cardiovascular mortality</td>
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<td></td>
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<td>Cardiovascular morbidity</td>
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</table>

Table 3 Results, Authors’ Conclusions, and Limitations

<table>
<thead>
<tr>
<th>Name, Year, Country</th>
<th>Results</th>
<th>Authors’ Conclusions</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greco et al. (2010)</td>
<td>53 taking glyburide monotherapy 5-15 mg/ day), 22 glyburide with metformin (1000-2550 mg/day 5 gliclazide monotherapy 2 glimepiride monotherapy</td>
<td>severe hypoglycaemia is a common metabolic condition among elderly patients with type 2 diabetes using long-acting sulfonylurea glyburide should be used with extreme caution for frail elderly people</td>
<td>Prescription bias- possibility that choice of sulfonylurea was based on disease characteristics (e.g. disease severity)</td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td></td>
<td>No information on length of time taking oral antidiabetic drugs</td>
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<td></td>
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<td>Self reported medication use introduces the possibility of recall bias</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Very little data included</td>
</tr>
<tr>
<td>Name, Year, Country</td>
<td>Results</td>
<td>Authors’ Conclusions</td>
<td>Limitations</td>
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</table>
| Monami et al. (2007)** | All-cause mortality HR=2.8* (95%CI 1.2, to 6.2) CV mortality HR= 2.6* (95%CI 0.8, 8.7) Non-CV mortality HR= 2.4* (95% CI 0.8, 7.2)† | Glyburide treatment appears to be associated with higher all-cause mortality when compared to gliclazide | • Prescription bias  
• Differences in baseline characteristics could account for observed differences  
• No information on treatment compliance  
• No explicit operational definition of the elderly (geriatric patients age range not defined) |

* Adjusted for age, sex, duration of diabetes, HbA1c, insulin and metformin therapy, BMI, and Charlson Comorbidity Score  
† Excluded patients with a history of malignancies as well  
BMI= Body Mass Index, CI= Confidence Interval, CV= Cardiovascular, HbA1c=glycated hemoglobin, HR= Hazard Ratio, n= number of patients, NS = not significant
APPENDIX 3: Additional information

Studies Including a Wide Age Range not Specifically the Elderly Population


Patients 15-97 years of age


Patients 38-72 years of age


Patients >18 years of age


Patients 36-75 years of age

Potentially Relevant Guidelines
