Title: Glyburide, Gliclazide or Glimepiride in the Elderly

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Context and policy issues:

Type 2 diabetes is characterized by chronically elevated blood sugar levels and disturbances in carbohydrate, fat and protein metabolism.\(^1\) In 1998, the estimated prevalence of diabetes in Canada for those aged 65 and over was approximately 15.09% or 576,398 people.\(^2\) Older individuals with diabetes have higher rates of premature death, functional disability, and coexisting illnesses such as hypertension, coronary heart disease, and stroke than age-matched individuals without diabetes.\(^3,4\) They are also at increased risk for several common geriatric problems such as depression, cognitive impairment, urinary incontinence, injurious falls, and persistent pain.\(^3,4\) A lower glycosylated hemoglobin (HBA\(_1c\)) indicates better control of blood sugar and is one of the treatment goals for diabetes. Data from uncontrolled studies suggest that improved glycemic control is effective for preventing long-term complications from diabetes in the elderly,\(^5\) although there is no evidence from controlled studies to support this. While there are a number of evidence-base guidelines for diabetes, few guidelines\(^3,4,6\) are specifically targeted toward the control of diabetes and its associated risk factors in elderly people.

Sulfonylureas (SU) are the oldest class of oral hypoglycemic agents available for the treatment of type 2 diabetes.\(^7\) While they are moderately effective at lowering blood glucose concentrations by 20% and HbA\(_1c\) by 1-2%, their effectiveness is known to decrease over time.\(^7\) SU primarily work by stimulating insulin release from pancreatic beta cells, but may also reduce glucose output from the liver and increase insulin sensitivity at peripheral target sites.\(^7-10\) Second generation SU available in Canada include glyburide (also known as glibenclamide), gliclazide, and glimepiride.\(^11\) Second generation SU are favored over the first generation SU, chlorpropamide, due to lower
risk of adverse effects including hypoglycemia. In Canada, the use of second generation SU is increasing among elderly people using oral hypoglycemics to treat type 2 diabetes. In Nova Scotia, the percentage of seniors using glyburide decreased slightly from 68% in 1993 to 59% in 1999, while use of gliclazide increased dramatically from 2% in 1993 to 22% in 1999. In Ontario, SU were the most commonly prescribed oral hypoglycemic drug class in older type 2 diabetics in 2001, with a 25% increase in the number of people using these drugs between 1995 and 2001. These figures are partially explained by the lower cost of SU. The average annual cost to the Ontario Drug Benefit Plan in 2001 for SU was $61.88/person compared with $108.99/person for biguanides, $170.71/person for meglitinides, $169.44/person for alpha-glucosidase inhibitors, $295.16/person for thiazolidinediones, and $373.09/person for insulin.

In the elderly, susceptibility to hypoglycemia is pronounced and often complicated by decreased cognition. Furthermore, diagnosis of hypoglycemia may be hampered by the fact that the classical adrenergic signs of hypoglycemia (palpitation, sweating, tremors) are often absent, and neuroglycopenic symptoms (drowsiness, delirium, and confusion) may be easily misinterpreted as other geriatric syndromes. In addition to cerebral damage, seizures, coma or death in the general population, prolonged hypoglycemia may also provoke a myocardial infarction, atrial fibrillation, or stroke in the elderly. Overall, results from randomized controlled trials in the general adult population indicate similar efficacy in terms of blood glucose control between glyburide, glimepiride, and gliclazide but lower rates of hypoglycemia associated with glimepiride and gliclazide when compared with glyburide. It is important to ascertain whether these findings extend to the elderly population in order to guide treatment in terms of safety and efficacy. This report will provide a review of the evidence evaluating the use of different sulfonylureas in elderly individuals with type 2 diabetes.

**Research questions:**

What is the clinical effectiveness in terms of blood glucose control for glyburide in seniors with Type 2 diabetes? What is the clinical effectiveness of glyburide compared with gliclazide, glimepiride, or other standard treatment in seniors with Type 2 diabetes? What is the cost-effectiveness of glyburide in seniors with Type 2 diabetes? What is the cost effectiveness of glyburide compared to gliclazide or glimepiride in seniors with Type 2 diabetes?

**Methods:**

A limited literature search was conducted on key health technology assessment resources, including PubMed, EMBASE, The Cochrane Library (Issue 1, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI's HTAIS, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2002 and the present, and are limited to English language publications only. Bibliographies of reports were scanned to identify other relevant evidence.
Summary of findings:

The observed differences in hypoglycemic risk among the different SU may be explained by variations in the pharmacological profile for each drug (Table 1). Glyburide and glimepiride are long-acting and the formation of active metabolites increases the risk for prolonged hypoglycemia. Rapid and prolonged hypoglycemia of greater than 12 hours despite glucose injections have been reported with glyburide and glimepiride in elderly patients. This does not appear to be an issue with shorter-acting gliclazide due to metabolism to inactive metabolites. Moreover, a gradual increase in gliclazide plasma concentrations further reduces the risk for hypoglycemia when compared with the sharp increase demonstrated with glimepiride and glyburide. There is evidence that once daily dosing with the long-acting formulation of gliclazide MR significantly improves both compliance and glycemic control when compared with twice daily glyburide.

Table 1: Second Generation Sulfonylureas Available in Canada

<table>
<thead>
<tr>
<th>Drug (Brand Name)*</th>
<th>Dose Range (mg)†</th>
<th>Doses Per Day</th>
<th>Peak Plasma Levels (h)</th>
<th>Duration Of Action (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide (Diabeta®)</td>
<td>1.25-20</td>
<td>1-2</td>
<td>2-4</td>
<td>20-24+</td>
</tr>
<tr>
<td>Gliclazide (Diamicron®)</td>
<td>40-320</td>
<td>1-2</td>
<td>4-6</td>
<td>12-24</td>
</tr>
<tr>
<td>Gliclazide MR (Diamicron MR®)</td>
<td>30-120</td>
<td>1</td>
<td>6-12</td>
<td>~24</td>
</tr>
<tr>
<td>Glimepiride (Amaryl®)</td>
<td>1-8</td>
<td>1</td>
<td>2-3</td>
<td>24+</td>
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</tbody>
</table>

* There are several generic products for each sulfonylurea, except modified-release (MR) gliclazide.
† Starting dose is typically lower with a longer titration period to therapeutic dose for elderly patients.

As the oldest second generation SU with many generic forms, glyburide is the cheapest option, followed by gliclazide, then glimepiride. As there are currently no generic forms available for gliclazide MR, it is currently the most expensive alternative.

No health technology assessments, systematic reviews, meta-analyses, or economic evaluations addressed the use of SU in the elderly population. A few randomized controlled studies of fair methodological quality have been conducted assessing the safety and efficacy of SU in elderly patients. Details of these trials are provided in Table 2.

Tessier et al conducted a small trial (n=22) to compare the effect of glyburide and gliclazide on the frequency of hypoglycemic events and glycemic control in elderly patients. Results revealed that while both were similar for glycemic control after 6 months of treatment, the incidence of hypoglycemic episodes was significantly greater with glyburide when compared with gliclazide. The authors did not comment on the severity of hypoglycemic episodes (i.e. if intravenous administration of glucose was required in any of the cases). Three participants in the glyburide group and one...
participant in the gliclazide group required combination therapy with metformin to achieve adequate glucose control. Only one of the hypoglycemic episodes occurred in a participant who was being treated concurrently with glyburide and metformin; the other episodes occurred in participants receiving glyburide or gliclazide alone. Majority of the hypoglycemic episodes occurred within one month of initiating treatment with either SU (13 of the 17 episodes in the glyburide group and all of the 4 episodes in the gliclazide group).

Schernthaner et al conducted the first large-scale (n=842) head-to-head comparison of two SU designed for once-daily administration (gliclazide MR versus glimepiride). A subgroup analysis of participants over the age of 65 (n=294) revealed that changes in HbA1c from baseline after 27 weeks were significant for each drug but did not differ significantly between the two groups. In agreement with the study by Tessier et al., most hypoglycemic episodes in patients >75 years old, occurred soon after initiating treatment (15 on 30-60 mg gliclazide MR out of 22 episodes, and 48 on glimepiride 1-2 mg out of 56 episodes). However, there was no significant difference in the occurrence of hypoglycemic episodes between the two groups. The sample size for subgroup analysis may not have been large enough to detect a significant difference. It is important to note that when the total study population was analyzed, the difference was significant (p=0.003) with 50% fewer confirmed hypoglycemic episodes reported with gliclazide MR compared with glimepiride. Furthermore, the number of patients experiencing hypoglycemia who were concurrently receiving metformin was also significantly lower in patients receiving gliclazide MR in comparison to glimepiride (p≤0.02). Interestingly, the difference between the two groups was not significant for those concurrently receiving an alpha-glucosidase inhibitor or those receiving either SU alone. Results for entire study population also revealed that even a mild impairment of renal function (creatinine clearance <80 mL/min) significantly increased the incidence of hypoglycemia with glimepiride but not with gliclazide MR (p≤0.02), an important result when considering use in elderly patients with frequently reduced renal function.

Two open-label trials demonstrated significant improvements in glycemic control after 16 weeks with Humalog Mix 75/25 compared with glyburide, and similar rates of hypoglycemia. An open label cross-over trial (n=90) indicated a significant reduction in hypoglycemic episodes when repaglinide was compared with glyburide. There was also a significant improvement in blood glucose control with repaglinide when compared with glyburide after 12 weeks of treatment.
Table 2: Summary of Evidence for Safety and Efficacy of Sulfonylureas in the Elderly

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Results</th>
<th>Conclusions</th>
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<tbody>
<tr>
<td>Tessier et al., 1994</td>
<td>Double-blind, parallel group, RCT</td>
<td>Glyburide 2.5-20 mg daily vs. Gliclazide 40-320 mg daily</td>
<td>HbA1c after 6 months: Glyburide; 7.4±0.2% Gliclazide: 7.9±0.5% (p=NS)</td>
<td>Similar glycemic control between glyburide and gliclazide. Hypoglycemic episodes: Glyburide: 17 (4 patients) Gliclazide: 4 (3 patients) (p&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td>Inclusion age: &gt;65 years old (n=22) 6 months</td>
<td>Both given as monotherapy or in combination w/ metformin 500 mg three times daily</td>
<td></td>
<td>Incidence of hypoglycemic episodes was significantly greater with glyburide, particularly during dose titration.</td>
</tr>
<tr>
<td>Schernthaner et al., 2004</td>
<td>Double-blind, parallel group, RCT</td>
<td>Gliclazide MR 30-120 mg daily vs. Glimepiride 1-6 mg daily</td>
<td>For &gt;65 y subgroup: HbA1c after 27 weeks: Gliclazide MR: 7.2±1.0% Glimepiride: 7.2±1.1% (p=NS)</td>
<td>Gliclazide MR is as effective as glimepiride either as monotherapy or in combination. Fewer hypoglycemic episodes with gliclazide but difference did not reach significance.</td>
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<tr>
<td></td>
<td>Inclusion age: &gt;35 years old (n=842) &gt;65y subgroup: (n=294) 27 weeks</td>
<td>Both given as monotherapy or in combination w/ metformin or α-glucosidase inhibitor (carbbose or miglitol)</td>
<td>Change in HbA1c from baseline after 27 weeks: Gliclazide MR: -1.1±1.2% Glimepiride: -0.9±1.0% (within group: p&lt;0.001)</td>
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<td></td>
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<td></td>
<td>Hypoglycemic episodes: Gliclazide MR: 10 (5 patients) Glimepiride: 17 (14 patients) (p=NS)</td>
<td>No reports of severe hypoglycemia requiring extra treatment occurred.</td>
</tr>
<tr>
<td>Herz et al, 2002</td>
<td>Open-label, parallel group, RCT</td>
<td>Pre-mixed Insulin Pen (Humalog Mix75/25) Twice daily injections (0.3-0.5 units/kg/day) vs. Glyburide 15-20 mg daily</td>
<td>Change in HbA1c from baseline after 16 weeks: Mix75/25: -1.14±0.18% Glyburide: -0.36±0.15% (between group: p=0.001)</td>
<td>Compared with glyburide, Mix 75/25 significantly improved glycemic control in older patients with type 2 diabetes, and could be administered after meals without compromising glycemic control. Rate of hypoglycemia increase from baseline was similar between the two groups.</td>
</tr>
<tr>
<td></td>
<td>Inclusion age: 60-80 years (n=143) 16 weeks</td>
<td></td>
<td>Hypoglycemia rate increase (episodes/patient/30days): Mix 75/25: 0.17±0.02 Glyburide: 0 (p=NS)</td>
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</tbody>
</table>
Various population-based observational studies have provided valuable information regarding the safety of different sulfonylureas in the elderly population. Shorr et al, conducted a four-year retrospective study of 19,932 patients aged 65 years or older with type 2 diabetes. The reported rates of serious hypoglycemia (resulting in hospitalization, emergency room admission or death) were over 2-fold higher in insulin users than in patients using sulfonylureas. In addition, the authors reported that a recent hospitalization was the strongest predictor for the development of hypoglycemia in elderly patients. Other independent risk factors for the development of hypoglycemia were advanced age, black race, and the concomitant use of five or more medications. When the authors compared the incidence of severe hypoglycemia with glyburide, tolbutamide, tolazamide, chlorpropamide, and glipizide, they reported the highest incidence in those patients taking glyburide and lowest incidence among those taking...
The incidence of severe hypoglycemia with chlorpropamide was similar to that with glyburide while shorter-acting drugs such as tolazamide and glipizide were associated with a lower incidence. Holstein et al conducted a prospective observational study to compare the incidence of severe hypoglycemia in elderly patients treated with glyburide or glimepiride by randomly selecting 400 doctors working in acute care hospitals in Germany to fill out a standardized questionnaire. Over the course of 14 months, the number of reported severe hypoglycemic episodes (requiring intravenous glucose) was much higher in those treated with glyburide than in those treated with glimepiride (56 versus 37, respectively; p value not reported). Prolonged hypoglycemia (requiring more than 12 hours of intravenous glucose administration) did not differ significantly between the two groups (8 for glimepiride versus 5 with glyburide; p=0.126). Of the 13 patients with prolonged hypoglycemia, renal impairment was present in 11 and hepatic dysfunction in 1. The authors concluded that the risk for severe hypoglycemia was just as great in elderly patients treated with glimepiride as those treated with glyburide.

During a two-year population survey of type 2 diabetic patients aged 80 years or older, Angilieri et al. reported that out of a total of 1430 medical admissions due to diabetes, 25% were attributable to severe hypoglycemia requiring treatment with intravenous glucose. Majority (68%) of the patients demonstrated prolonged hypoglycemia occurring over a 12-72 hour duration. Among the patients hospitalized for hypoglycemia, more were receiving treatment with SU than insulin (81% versus 19%). Of the SU-related hypoglycemic episodes, 56% occurred in patients receiving glyburide monotherapy (10-15 mg/day), 32% in patients taking glyburide in combination with metformin, 4% in patients receiving combination therapy with acarbose, 4% receiving gliclazide monotherapy, and 4% receiving gliquidone monotherapy. While the patients were found to have an average HbA1c value of 5.1±0.6% (indicating that diabetes was very well controlled), they also had marked co-morbidities (mostly cardiovascular). These results suggest that when considering therapy and treatment goals for diabetes in the elderly, it is important to consider risk for hypoglycemia and co-morbidities.

Additional well-designed trials incorporating an economic component are required to confirm the benefit and cost-effectiveness of gliclazide or glimepiride over glyburide in elderly individuals with type 2 diabetes as well as assess efficacy in comparison to other classes of oral hypoglycemics or insulin.

**Conclusions and implications for decision or policy making:**

In the general adult population, the choice of sulfonylurea is primarily dependent upon cost and availability, as efficacy appears to be similar across the class. However, given the increased risk and sequelae of hypoglycemia in the elderly, choice of drug should be considered carefully. Due to the paucity of high quality evidence for this patient population, the decision is often based on clinical experience. Guidelines developed by the Canadian Diabetes Association recommend gliclazide and glimepiride should be used over glyburide in elderly type 2 diabetics. The European Union Geriatric Society
guidelines recommend that where the risk of hypoglycemia is considered moderate (renal impairment, recent hospital admission) to high (previous history of hypoglycemia, frail patient with multiple co-morbidities, resident of a care home), gliclazide should be considered over glyburide and glimepiride.\textsuperscript{4} When switching between different SU or starting combination therapy with other oral hypoglycemics or insulin, it is important to carefully monitor for signs and symptoms of hypoglycemia.\textsuperscript{38} Therefore, in order to avoid severe hypoglycemia in elderly patients, target glycemic goals should be defined critically with an appreciation for risk factors for hypoglycemia, co-morbidities, quality of life, and life expectancy.

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