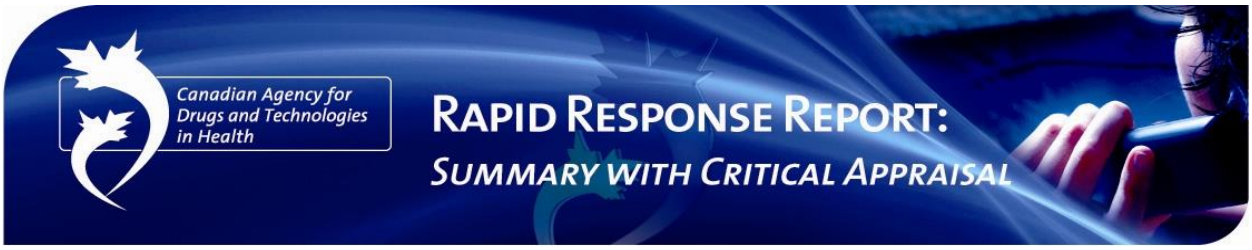

TITLE: Glyburide, Gliclazide or Glimepiride for Elderly Patients with Type 2 Diabetes: A Review of the Clinical Effectiveness and Safety – An Update

DATE: 18 August 2015

CONTEXT AND POLICY ISSUES

Almost two million Canadians (6.5% of the total population) aged 12 and older were reported to have diabetes in 2012, making it the seventh leading cause of death.[1,2] In 2010 the cost of diabetes was estimated at 12 billion in Canada.[2] Type 2 diabetes is the most prevalent form of diabetes comprising approximately 90 to 95% of total cases. It is characterized by persistent hyperglycemia caused by insulin resistance and/or decreased insulin production, which results in micro and macro-vascular complications. It is associated with lifestyle factors (body mass index, physician activity, and tobacco use), genetic factors, ethnicity, socioeconomic status[3] and increasing age,[4-6] and common associated health outcomes include renal failure, ocular morbidities, and risk of amputation due to diabetic ulcers.[7]

Elderly patients with type 2 diabetes exist along a spectrum, which ranges from healthy community dwelling individuals, to frail elderly living in nursing homes and hospitals with significant comorbidities.[5] Physiological changes associated with aging such as reduced hepatic and renal function, comorbidities (e.g., cardiovascular disease, osteoarthritis), and polypharmacy may increase the risk and severity of adverse outcomes associated with the treatment of diabetes, including hypoglycemia, hypotension, other cardiovascular events, and adverse drug interactions.[8] Therapeutic goals for all older persons, particularly frail elderly, may not reflect the same standard as younger patients and more conservative glycated hemoglobin (HbA1c) targets have been proposed for individuals with comorbidities and reduced life expectancy.[5,9]

Sulfonylureas are a class of glucose lowering drugs used to treat type 2 diabetes. These drugs bind to sulfonylurea receptors and stimulate closure of adenosine triphosphate sensitive potassium channels to encourage insulin secretion from pancreatic beta cells.[10,11] Glyburide (also referred to as glibenclamide), gliclazide, and glimepiride are three second-generation sulfonylurea drugs available in Canada. Glyburide has been associated with an increased risk for hypoglycemia and long-term cardiovascular mortality.[12] This may be due to differences in tissue-specific binding of the respective sulfonylureas.[12] A meta-analysis published in 2007

reported an increased risk of hypoglycemia for glyburide compared to other insulin secreting anti-diabetes drugs and alternate sulfonylureas, despite no evidence of improved efficacy.[10] Hypoglycemia can lead to undesirable outcomes including altered mental status, seizures, coma and death.[13-15] It is more strongly associated with the use of long-acting sulfonylureas (e.g., glyburide and glimepiride) than short-acting sulfonylureas (e.g., gliclazide).[5] The American Geriatrics Society's Beers Criteria lists a strong recommendation based on high quality evidence that glyburide be avoided in the elderly due to the potential risks.[16] Based on US market pricing, gliclazide is three times higher in price than glyburide, which may contribute to the persistent use of glyburide.[7]

A previous CADTH review[17] of literature published from 2007 to 2011 reported that there was no evidence regarding the comparative clinical effectiveness of these agents in the elderly, and limited evidence regarding safety, based on the results of two non-randomized studies. One included study reported greater all-cause mortality associated with glyburide use versus gliclazide, and the other reported a numerically higher occurrence of hypoglycemia among patients taking glyburide monotherapy.[17] Thus far, only limited evidence regarding the comparative effects of these drugs in the elderly has been synthesized and recent concerns regarding the cardiovascular effects of these drugs have been noted.[18] Thus, this update will expand on the work of the previous CADTH reports[17,19] to further investigate the comparative clinical efficacy and safety of these medications in older persons.

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 regarding the safety of glyburide, gliclazide or glimepiride in elderly patients with type 2 diabetes?

KEY FINDINGS

Limited evidence from four non-randomized studies suggests an increased risk of progression towards adverse renal endpoints with the use of glimepiride versus gliclazide, as well as conflicting results regarding the risk of progression to cardiovascular endpoints with the use of glyburide versus gliclazide in elderly patients. This indicates a need for further high quality prospective research on this topic. No recent evidence was identified regarding the comparative clinical effectiveness of second-generation sulfonylureas.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, 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 the main focused search to limit retrieval by publication type. The results of a second broader search (with no population age limit) were also included. Methodological filters were applied to the second search to limit retrieval to health technology assessments, systematic reviews, meta-analyses and studies containing safety data. Where possible, retrieval

was limited to the human population. The search was also limited to English language documents published between May 1, 2011 and July 17, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Elderly patients ≥ 60 years of age with type 2 diabetes
Intervention	Q1: Glyburide (as monotherapy or combination therapy with other glucose lowering drugs [e.g., metformin]) Q2: Glyburide, gliclazide, or glimepiride (as monotherapy or combination therapy with other glucose lowering drugs)
Comparator	Q1: Gliclazide or glimepiride (as monotherapy or combination therapy with other glucose lowering drugs) Q2: Alternate sulfonylurea (as monotherapy or combination therapy with other glucose lowering drugs);
Outcomes	Q1: Clinical effectiveness outcomes (i.e., glycated hemoglobin [HbA1c]) Q2: Safety outcomes (e.g., cardiovascular outcomes, hypoglycemia, weight gain, morbidity, mortality)
Study Designs	Health technology assessment reports, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011.

Critical Appraisal of Individual Studies

Non-randomized studies were critically appraised using the Downs and Black checklist.[20] Study quality was assessed in terms of reporting, external validity, internal validity (confounding and bias) and power. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 238 citations were identified in the literature search. Following screening of titles and abstracts, 224 citations were excluded and 14 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these 15 potentially relevant articles, 11 publications were excluded. Of these 11, five publications were excluded because the population did not fit the age restrictions,[21-25] one was excluded due to an inappropriate intervention,[26] four were excluded due to inappropriate comparators,[27-30] and one was excluded due to insufficient review methodology.[7] Four publications met the inclusion criteria and were included in this report.[31-34] The PRISMA flowchart of the study selection is presented in Appendix 1.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Detailed study characteristics are listed in Appendix 2.

Study Design

Four non-randomized studies regarding the safety of glyburide, gliclazide or glimepiride in elderly patients with type 2 diabetes were identified. All included studies utilized administrative health records or hospital databases to collect health information. This included three retrospective cohort studies,[31,32,34] and one nested case control study.[33]

Country of Origin

The included studies were conducted in Canada,[31,33,34] and South Korea.[32] Two of the Canadian studies used Alberta administrative health data,[31,33] and one used data from Ontario.[34]

Patient Population

Patient populations included elderly individuals (aged 60 and over) with diagnosed type 2 diabetes who were treated with the medications of interest.[31-34] Baseline glycated hemoglobin levels were not reported by most studies[31,33,34] with the exception of Lee et al., who reported that over 65% of patients had baseline levels greater than 7%. In some cases other comorbidities were part of the inclusion criteria, including ischemic heart disease,[31] and coronary artery disease.[34]

Interventions and Comparators

Interventions included glyburide, gliclazide, and glimepiride. Comparators could include any alternate sulfonylurea, including those not previously listed, but were primarily limited to the three drugs. One study[31] included an additional comparison to repaglinide.

Outcomes

No efficacy outcomes were assessed by any of the studies. Adverse event outcomes included cardiovascular adverse events and associated hospitalizations and/or death,[31,33,34] and renal endpoints.[32] In addition, secondary outcomes such as pneumonia[33,34] and hemorrhage[34] were recorded.

Summary of Critical Appraisal

A detailed list of critical appraisal points based on the Downs and Black[20] checklist is available in Appendix 3.

Overall, the study information was well reported apart from lacking adverse event profiles. Use of database and administrative health information resulted in good generalizability in most cases, with minor issues related to the reach and size of the databases. Internal validity was limited by the lack of blinding and randomization leading to possible selection and performance bias, as well as the possibility of outcome misclassification bias inherent to database studies. In addition, incomplete consideration of confounders and post-hoc propensity score analysis may have led to under-adjustment of associations. Power was generally poorly reported.

Reporting

A well stated hypothesis or objective was provided for all studies.[31-34] The main outcomes to be assessed were described in the introduction or methods section of the studies.[31-34] The characteristics of patients and interventions, main findings, and confounder distribution were clearly described.[31-34] All studies provided estimates of random variability for the main outcomes listed and probability values and confidence intervals were provided where appropriate.[31-34] Due to the use of administrative health data and healthcare databases there were no apparent losses to follow up, apart from censoring 30 days post index date by one study,[31] and the exclusion of individuals with a dual drug history in another.[32] However, potential unrecorded records or excluded records were not discussed. The main flaw in reporting was the limited adverse event profile. All studies focused primarily on the main outcome and failed to report on common adverse events associated with the use of the interventions such as hypoglycemia, falls, weight gain and gastrointestinal side-effects.[31-34]

External Validity

Based on the use of administrative health data, the participants were representative of the population from which they were drawn. In the case of two studies population health information was used.[31,34] so the generalizability was relatively wide, versus the use of private health plan data[33] and single hospital data from a diabetes care center[32] by the other two studies, which may have excluded some relevant participants. The use of previously collected data precluded any issues regarding differences in willing and unwilling participants. Again, population-based data likely resulted in generalizable facilities, staff and setting of treatment; however, in the case of the diabetes center patients may have had access to more specialized care.[32] The majority of studies were conducted using administrative health records and health databases collected in the Canadian setting,[31,33,34] increasing the generalizability to Canadian clinical practice and populations.

Internal Validity – Bias

None of the studies instituted blinding methods for participants or outcome assessors. Three of the studies adjusted for length of follow-up via the use of survival analysis.[31,32,34] One study failed to adjust for length of follow-up in multivariate models.[33] In general, appropriate statistical tests were used and the main outcome measures were accurate, although there is always the possibility of misclassification of outcomes and reporting bias with the use of database information. It was unclear whether the subgroup and sensitivity analyses were preplanned in three cases,[31-33] and one study did not perform subgroup analysis.[34] Compliance with the study interventions was unclear in all cases; therefore, whether dispensation of medication led to treatment was uncertain.

Internal Validity – Confounding

No randomization of study subjects was completed for any of the studies;[31-34] therefore, only associations between second generation sulfonylurea use and safety outcomes could be explored. Patients in the comparison groups were recruited over the same time period, from the same population pool for all studies. Two studies used propensity scoring to pre-match individuals in the comparison groups,[32,34] while two conducted post-hoc propensity score adjusted analysis.[31,34] In multivariate analysis, all studies considered potential confounders; however, in all cases the included confounders did not necessarily represent all potential confounders.

Power

One study[32] reported a power calculation, but did not discuss whether they enrolled enough subjects to achieve sufficient power to detect the primary outcome. The other studies failed to disclose a power calculation or discuss the power to detect clinically important differences in their main outcomes.

Summary of Findings

Detailed study findings are tabulated in Appendix 4.

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

No relevant evidence was identified regarding the comparative clinical effectiveness of glyburide versus gliclazide or glimepiride in elderly patients with type 2 diabetes; therefore, no summary can be provided.

What is the clinical evidence regarding the safety of glyburide, gliclazide or glimepiride in elderly patients with type 2 diabetes?

Cardiovascular Outcomes

There was disagreement among the three studies[31,33,34] that assessed individual and composite cardiovascular outcomes. One retrospective cohort study[31] reported no difference in the risk of progression to a composite outcome of all-cause mortality, new onset of atrial fibrillation, stroke, heart failure, or myocardial infarction within 30 days of the index date between gliclazide and

glyburide users. As well, each individual outcome analyzed separately showed no difference in the risk of progression between the gliclazide and glyburide groups.[31] One nested case-control study[33] reported increased odds of acute coronary syndrome related hospitalization or death, with a corresponding number needed to harm of 50 for treatment with glyburide versus gliclazide. When the composite outcome was analyzed separately, only hospitalization due to acute coronary syndrome was significantly associated with glyburide use. The other retrospective cohort study[34] observed no difference in the risk of progression towards a composite outcome of death or hospitalization due to acute myocardial infarction or heart failure after index hospitalization between glyburide and gliclazide users. When analyzed separately, risk of progression to individual components of the composite outcome were also similar between groups.[34] There was no data available on the cardiovascular adverse events associated with glimepiride.

Renal Outcomes

One retrospective cohort study concluded that glimepiride was associated with an increased risk of progression to end stage renal disease and a doubling of serum creatinine to at least 132.6 µmol/L in patients aged 62 and older versus gliclazide. No data was available on the renal adverse events associated with glyburide.

Secondary Outcomes

No differences in the odds of pneumonia[33] or risk of progression to pneumonia or hemorrhage[34] were observed between treatment groups for the two studies that assessed tracer outcomes.

Limitations

The use of databases and administrative health data posed several limitations. Firstly, the studies did not report on treatment compliance, which is hard to monitor retrospectively. Dispensation of medication may not perfectly correlate with use and this could increase the risk of exposure misclassification, and thus could result in over-estimation of the risk of medication use. In addition, the two studies that used non-population based databases[32,33] may have restricted analysis to patients who were able to access specialized diabetes care,[32] or those who initiated access to government-sponsored private health coverage.[33] In the latter case, the Alberta government fully subsidizes the coverage that Alberta Blue Cross provides, but some individuals may choose not to enroll.[33] These study populations may represent individuals with greater health seeking behaviors, which could lead to an underestimation of the adverse effects of these medications. The lack of information regarding validation of the various databases that were used suggests the potential for outcome misclassification. For example, if medications were used to ascertain disease state, reason for hospitalization was not correctly coded, or the cause of death was attributed to an acute condition rather than underlying disease then this may have influenced patient classification.

There was general underreporting of adverse events, given the well-known outcomes associated with the use of sulfonylureas. In particular, hypoglycemia, weight gain, falls and other hypoglycemia related sequelae, and gastrointestinal outcomes may have been of interest and may have influenced multivariate analysis.

Some of the studies assessed composite cardiovascular outcomes.[31,33,34] One study[33] reported divergence in the results for the composite outcome and that of the individual outcomes. This

could have resulted for multiple reasons including a lack of power to detect clinically meaningful differences in the individual outcomes (hospitalization and death), or a true lack of risk of progression to death. As such, these results should be interpreted with caution.

One study[34] included patients with a history of the primary outcome in analysis. In this case it was unclear whether treatment exposure occurred prior to the onset of cardiovascular symptoms, which could have resulted in some outcomes being wrongly attributed to exposure.

Lastly, because this review focused on elderly populations, there may be reports on the adverse effects associated with the use of various sulfonylureas in study populations with wider age ranges (e.g., all adults 18 years and older) that were not reviewed. This includes reports on hypoglycemia, mortality, cancer, and weight gain. While the findings of these reports may not be applicable to elderly individuals, and would therefore be considered out of scope, they may be of wider interest and are listed in Appendix 5. The lack of information on these outcomes within this report does not suggest an absence of risk. Rather, there is a lack of evidence available on these outcomes in elderly persons.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Four non-randomized studies were identified regarding the safety of glyburide, gliclazide or glimepiride in elderly patients with type 2 diabetes. Results from one study indicated potential renal risks for elderly patients using glimepiride versus gliclazide,[32] while three studies assessing cardiovascular outcomes were collectively inconclusive with regards to cardiovascular morbidity and mortality associated with glyburide versus gliclazide use.[31,33,34] Two retrospective cohort studies reported no differences between glyburide and gliclazide,[31,34] while one nested case-control study reported a small increased risk of progression towards cardiovascular outcomes with glyburide use, consistent with recent perceived risks associated with the use of this medication.[12,18] No studies compared the efficacy or safety of glimepiride and glyburide.

This report builds on a previous CADTH review conducted in 2011, which concluded, based on the two non-randomized studies identified, that there was a paucity of evidence regarding both the comparative efficacy and safety of glyburide, gliclazide and glimepiride.[17] Further, the available safety data was inconclusive, with a single study reported an increased risk of all-cause mortality for glyburide users relative to gliclazide users. While hypoglycemia was not explored by this review, a non-systematic review article[7] and an earlier systematic review are also available on the topic and provide evidence to suggest that glyburide is associated with an increased risk of severe hypoglycemia[35] compared to other second generation sulfonylureas, especially in the elderly and should not be used in individuals over the age of 60.[7,35] Clinical practice guidelines from the Canadian Diabetes Association state that gliclazide and glimepiride are preferred for the elderly due to a lower frequency of hypoglycemia and cardiovascular events. [36]

Due to the lack of head-to-head data from randomized controlled trials on the various sulfonylureas, network meta-analysis has been conducted to explore indirect comparisons.[23] However, none of these analyses focus on elderly populations. Given that the evidence from well-conducted non-randomized studies is limited and conflicting, indirect comparisons involving data on the elderly or well-designed prospective studies are needed to resolve disagreement. No evidence was identified on the comparative clinical effectiveness of the agents of interest;

however, this topic has been explored in depth by earlier publications that suggest equivalent effectiveness of the various agents.[37]

In conclusion, limited evidence suggests a potential association between both renal and cardiovascular events and the use of certain second-generation sulfonylureas. However; assessed collectively, the evidence is conflicting and inconclusive. The limitations of non-randomized studies and the absence of comprehensive adverse event monitoring should be considered in interpretation of these results.

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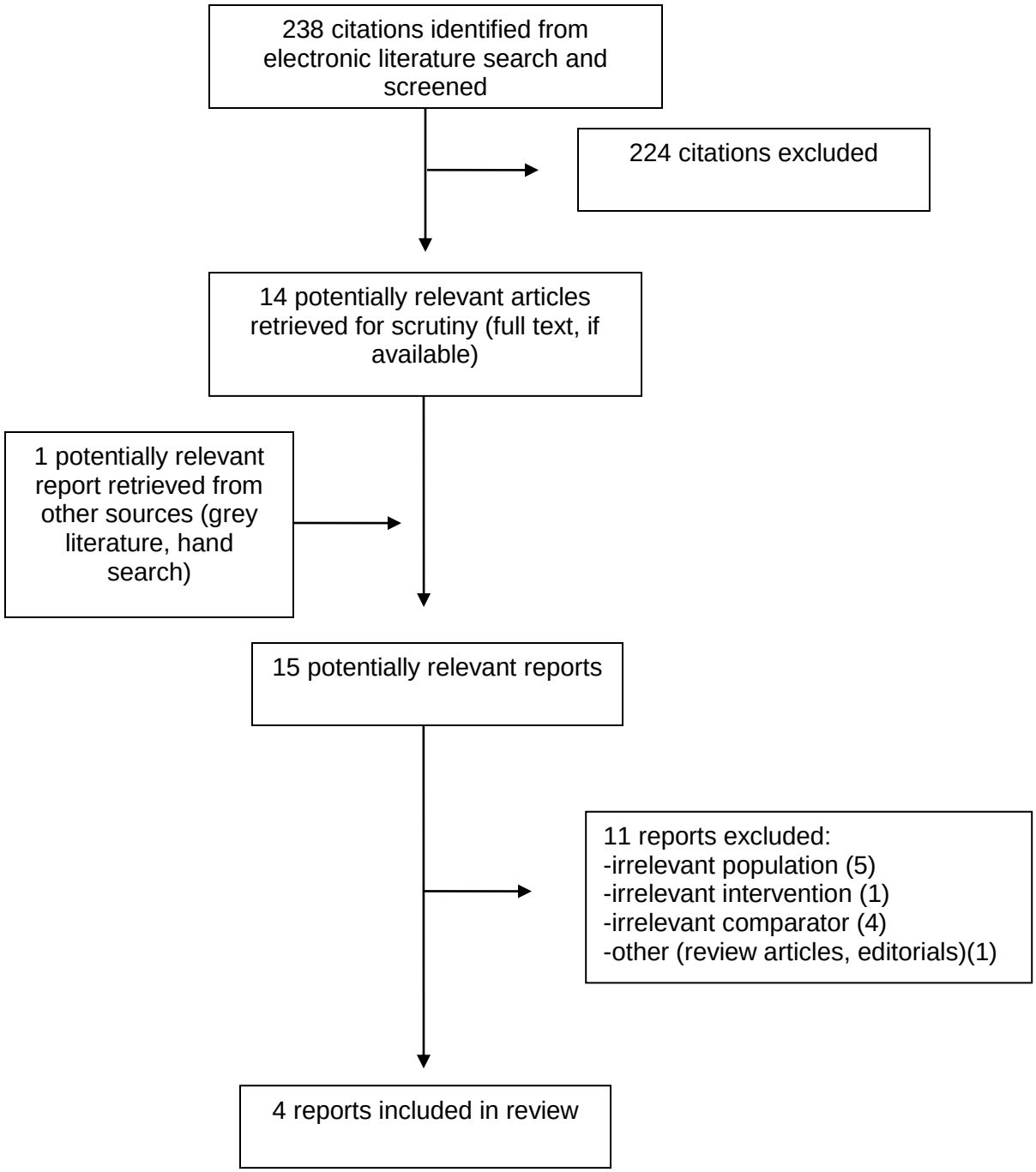
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A2: Characteristics of Included Non-Randomized Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics, Sample Size, Database Source	Intervention	Comparator(s)	Clinical Outcomes	Follow-up Duration
Huang, 2015,[31] Canada	Retrospective cohort study	Patients (≥65 years) with type 2 diabetes and ischemic heart disease (baseline HbA1c not reported) dispensed an oral antidiabetic drug between 1998 and 2010; n = 2254 for gliclazide, n = 3289 for glyburide and n = 740 for repaglinide); Administrative health records from the province of Alberta	Glyburide	Gliclazide; Repaglinide	Composite (all-cause mortality, new onset of atrial fibrillation, stroke, heart failure, or myocardial infarction within 30 days of the index date); Individual components of composite outcome	Follow up restricted to 30 days post ischemic heart disease hospitalization
Lee, 2015,[32] South Korea	Retrospective cohort study	Patients (older than 20 years) with type 2 diabetes (>65% with HbA1c ≥ 7%) who used an oral antidiabetic drug; Subgroup analysis of patients ≥62 years; n = 1427 for glimepiride, n = 1427 for gliclazide; Attended a university-affiliated tertiary-care hospital; patient database accessed for health information	Glimepiride	Gliclazide	End-stage renal disease; Doubling of creatinine	Median follow up = 4.7 years
Abdelmoneim, 2014[33] Canada	Nested case-control study (based on administrative health data)	Patients with type 2 diabetes (≥66 years, baseline HbA1c not reported) who used an oral antidiabetic drug between 1998 and 2010;	Glyburide	Gliclazide	Acute coronary syndrome related hospitalization or death;	Mean follow up (SD) in years: Gliclazide = 5.4(4.1);

Table A2: Characteristics of Included Non-Randomized Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics, Sample Size, Database Source	Intervention	Comparator(s)	Clinical Outcomes	Follow-up Duration
		glyburide (n = 13 884 for glyburide, n = 7441 for gliclazide; Administrative health data of patients with prescription drug coverage from Alberta Blue Cross			Pneumonia	Glyburide = 5.5 (4.0)
Juurlink, 2012[34] Canada	Population-based retrospective cohort study	Patients with type 2 diabetes and active coronary artery disease (≥66 years, baseline HbA1c not reported) dispensed an oral antidiabetic drug between 2007 and 2010; glyburide (n = 1690 for glyburide, n = 984 for gliclazide; Databases included the Ontario Public Drug Program Benefit Program, National Ambulatory Care Reporting System database and Canadian Institute for Health Information Discharge Abstract Database, Ontario Health Insurance Plan Database and Registered Persons Database	Glyburide	Gliclazide	Acute myocardial infarction ; Percutaneous coronary intervention procedure; Secondary: haemorrhage and pneumonia	Median follow up: Glyburide = 318 days; Gliclazide = 220 days

HbA1c = glycated hemoglobin

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Non-Randomized Studies using Downs and Black[20]

Strengths	Limitations
Huang, 2015,[31] Canada	
Reporting • Hypothesis clearly described • Main outcomes described in methods section • Characteristics of patients, and interventions clearly described • Confounder distribution clearly described • Main findings clearly described • Estimates of random variability provided for the main outcomes • Study based on administrative health data; therefore, no loss to follow-up • Probability values and confidence intervals reported for group comparisons and main outcomes *External Validity* • Participants representative of all Alberta residents aged 65 and older with type 2 diabetes and ischemic heart disease dispensed an oral antidiabetic drug between 1998 and 2010 as administrative health data was used • Due to use of administrative health data all eligible subjects were included in analysis; no differences in willing and unwilling participants • Setting and staff involved in treatment representative of Alberta healthcare facilities *Internal Validity - Bias* • Adjustment for length of follow-up using survival analysis • Appropriate statistical tests were used • Main outcome measures were accurate *Internal Validity – Confounding* • Patients in comparison groups recruited from the same population pool over the same time • Multivariable models adjusted for age, sex, index year, type of IHD for index hospitalization, concomitant drug use, comorbidity score, and guideline concordant procedures period • No losses to follow up due to use of administrative health data *Other* • Follow-up and exposure window extended in sensitivity analyses	*Reporting* • Only cardiovascular adverse events were considered *External Validity* • Study subjects limited to Alberta Blue Cross beneficiaries *Internal Validity - Bias* • No blinding of study participants or outcome assessors • Prospective nature of all sub-group analyses unclear • Compliance with intervention unclear • Accuracy of classification methods for main outcomes unclear *Internal Validity – Confounding* • No randomization of study subjects • Several important clinical confounders such as tobacco use and indicators of metabolic syndrome were not available • Post-hoc propensity score adjusted analysis was conducted *Power* • Power to detect clinically important differences unclear *Other* • Follow-up censored if event did not occur within 30 days of index date, the participant moved out of province or the study ended
Lee, 2015,[32] South Korea	
Reporting • Study objective clearly stated • Main outcomes described in methods section • Characteristics of patients and interventions clearly described.	*Reporting* • Only adverse renal outcomes reported *External Validity* • Patients only representative of diabetes patients who attended a diabetes center

Table A3: Strengths and Limitations of Non-Randomized Studies using Downs and Black[20]

Strengths	Limitations
• Confounder distribution clearly described • Main findings clearly described • Estimates of random variability provided for the main outcomes • Database study; therefore, no loss to follow up • Probability values and confidence intervals reported for group comparisons and main outcomes *External Validity* • Due to use of administrative health data all eligible subjects were included in analysis; no differences in willing and unwilling participants *Internal Validity - Bias* • Adjustment for length of follow-up using survival analysis • Appropriate statistical tests were used • Main outcome measures were accurate *Internal Validity – Confounding* • Patients in comparison groups recruited from the same population pool over the same time period • Multivariable models adjusted for age, gender, glycated hemoglobin, total cholesterol, glomerular filtration rate, history of hypertension, duration of medication use, and use of other medications • No losses to follow up due to the use of administrative health data • Propensity scoring used to match participants *Power* • Power calculation carried out for Cox proportional hazards regression	at a hospital in Korea • Patients were treated in a diabetes care center – may not represent all patients treated with sulfonylureas *Internal Validity - Bias* • No blinding of participants or outcome assessors • Prospective nature of all sub-group analyses unclear • Compliance with interventions unclear • Accuracy of classification methods for main outcomes unclear *Internal Validity – Confounding* • No randomization of study subjects *Power* • Power to detect differences in the primary outcome insufficient for subgroup of elderly adults • Stated insufficient power for subgroup analysis
Abdelmoneim, 2014[33] Canada	
Reporting • Objectives and hypotheses clearly stated • Main outcomes described in methods section • Characteristics of patients and interventions clearly described • Confounder distribution clearly described • Main findings clearly described • Estimates of random variability provided for the main outcomes • Administrative health data study; therefore, no loss to follow up • Probability values and confidence intervals reported for group comparisons and main outcomes *External Validity* • Due to the use of administrative health data all eligible subjects were included in analysis; no differences in willing and unwilling participants *Internal Validity - Bias* • Appropriate statistical tests were used • Main outcome measures were accurate *Internal Validity – Confounding*	*Reporting* • Only cardiovascular adverse events and tracer outcomes reported *External Validity* • Use of Alberta Blue Cross data may have excluded individuals who did seek additional healthcare coverage beyond the Alberta Health Care Insurance Plan *Internal Validity - Bias* • No blinding of participants or outcomes assessors • A priori nature of sensitivity analysis unclear • No adjustment for length of follow up conducted in multivariate models • Compliance with interventions unclear • Accuracy of classification methods for main outcomes unclear *Internal Validity – Confounding* • Additional patient characteristics could have been considered in the matching

Table A3: Strengths and Limitations of Non-Randomized Studies using Downs and Black[20]	
Strengths	**Limitations**
• Patients in comparison groups were identified on the basis of occurrence of endpoints and matched based on sex, birth year and cohort entry year • Factors including co-morbidities, past exposure, recent exposure, dispensation for either drug within or more than 120 days of the event date were controlled for in the logistic regression models *Other* • Use of nested case control increased similarities in baseline risk in both cases and controls	of cases and controls • Post-hoc propensity score adjusted analysis was conducted *Power* • Power to detect clinically important differences unclear
Juurlink, 2012[34] Canada	
Reporting • Study objective clearly stated • Main outcomes described in methods section • Characteristics of patients and interventions clearly described • Confounder distribution clearly described • Main findings clearly described • Estimates of random variability provided for the main outcomes • Database study; therefore, no loss to follow up • Probability values and confidence intervals reported for group comparisons and main outcomes *External Validity* • Due to the use of province-wide population data results are representative of all Ontarians that fall under the Ontario Public Drug Program Benefit Program • Due to use of population database all eligible subjects were included in analysis; no differences in willing and unwilling participants *Internal Validity - Bias* • Adjustment for length of follow-up using survival analysis • Appropriate statistical tests were used • Main outcome measures were accurate *Internal Validity – Confounding* • Patients in comparison groups recruited from the same population pool over the same time period *Other* • Propensity matching used to match treatment groups	*Reporting* • Only cardiovascular adverse events and tracer outcomes reported *External Validity* • *Internal Validity - Bias* • No blinding of participants or outcome assessors • No subgroup analysis conducted • Compliance with interventions unclear • Accuracy of classification methods for main outcomes unclear *Internal Validity – Confounding* • No randomization of study subjects • Only factors that were unbalanced after high-dimensional propensity scoring were adjusted for in the Cox proportional hazards regression analyses *Power* • Power to detect clinically important differences unclear *Other* • Patients with a history of the primary outcome were included in analysis – unclear if sulfonylurea exposure preceded onset of cardiovascular outcomes

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A4: Summary of Findings of Included Non-Randomized Studies

Outcome	Intervention	Comparator	Effect estimate	Author's Conclusions
Huang, 2015,[31] Canada				
Composite cardiovascular outcome*	Gliclazide	Glyburide	aHR = 0.91 (95% CI, 0.78 to 1.05)	No difference in the risk of progression to the composite outcome, mortality, new onset atrial fibrillation, new onset stroke, new onset heart failure and new onset myocardial infarction between groups
Mortality	Gliclazide	Glyburide	aHR = 0.84 (95% CI, 0.70 to 1.01)	
New onset atrial fibrillation	Gliclazide	Glyburide	aHR = 0.98 (95% CI, 0.81 to 1.19)	
New onset stroke†	Gliclazide	Glyburide	aHR = 0.92 (95% CI, 0.63 to 1.32)	
New onset heart failure†	Gliclazide	Glyburide	aHR = 0.98 (95% CI, 0.80 to 1.19)	
New onset myocardial infarction†	Gliclazide	Glyburide	aHR = 1.07 (95% CI, 0.79 to 1.44)	
Lee, 2015,[32] South Korea				
Subgroup of patients aged ≥ 62 years				
End-stage renal disease‡	Glimepiride	Gliclazide	HR = 0.35 (95% CI, 0.14 to 0.88)	Despite no differences observed in the overall study population, for patients aged 62 years and older, there was an increased risk of progression to end-stage renal disease as well as doubling of creatinine in the glimepiride group versus the gliclazide group
Doubling of serum creatinine to at least 132.6 µmol/L	Glimepiride	Gliclazide	HR = 0.52 (95% CI, 0.27 to 0.99)	
Abdelmoneim, 2014[33],Canada				
Acute coronary syndrome related hospitalization or death	Glyburide	Gliclazide	aOR = 1.14 (95% CI, 1.06 to 1.23); NNH = 50	• Small but increased odds of acute coronary syndrome related hospitalization or death corresponding to an extra 50 persons needing to be treated with glyburide for one additional patient to suffer from an ACS event • Increased odds of hospitalization or death due to acute coronary syndrome was observed in users of glyburide versus gliclazide • When analyzed separately, glyburide users had an increased odds of acute coronary syndrome related hospitalization but not death
Acute coronary syndrome related hospitalization	Glyburide	Gliclazide	aOR = 1.14 (95% CI, 1.06 to 1.24)	
Acute coronary syndrome related death	Glyburide	Gliclazide	aOR = 1.14 (95% CI, 0.95 to 1.36)	
Pneumonia-related hospitalization or death	Glyburide	Gliclazide	aOR = 1.05 (95% CI, 0.96 to 1.15)	

				• No differences observed in the odds of pneumonia-related hospitalization or death
Juurlink, 2012[34] Canada				
Composite outcome[§]	Glyburide	Gliclazide	aHR = 1.01 (95% CI, 0.86 to 1.18)	Glyburide users had a similar risk of progressing to the composite outcome and individual components comprising the composite outcome as gliclazide users
Myocardial infarction	Glyburide	Gliclazide	aHR = 1.08 (95% CI = 0.85 to 1.38)	
Heart Failure	Glyburide	Gliclazide	aHR = 0.85 (95% CI = 0.65 to 1.13)	
Death	Glyburide	Gliclazide	aHR = 1.04 (95% CI, 0.82 to 1.33)	
Hemorrhage	Glyburide	Gliclazide	aHR = 1.09 (95% CI, 0.76 to 1.57)	
Pneumonia	Glyburide	Gliclazide	aHR = 1.05 (95% CI, 0.79 to 1.39)	

*All-cause mortality or new onset of atrial fibrillation, stroke, heart failure, or myocardial infarction within 30 days following the index date
[†]Excluding patients with a relevant diagnosis within 3 years prior to their index date
[‡]Persistent need for dialysis or kidney transplantation
§ Death or hospitalization for either acute myocardial infarction or heart failure after the index hospitalization
aHR = adjusted hazard ratio; aOR = adjusted odds ratio; NNH = number needed to harm

APPENDIX 5: Additional References not Specific to the Elderly Population

Systematic Review

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Kalra S, Deepak MC, Narang P, Singh V, Uvaraj MG, Agrawal N. Usage pattern, glycemic improvement, hypoglycemia, and body mass index changes with sulfonylureas in real-life clinical practice: results from OBSTACLE Hypoglycemia Study. Diabetes Technol Ther. 2013 Feb;15(2):129-35.

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Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Nutter B, et al. The risk of overall mortality in patients with Type 2 diabetes receiving different combinations of sulfonylureas and metformin: a retrospective analysis. Diabet Med. 2012 Aug;29(8):1029-35.

Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, et al. Increase in overall mortality risk in patients with type 2 diabetes receiving glipizide, glyburide or glimepiride monotherapy versus metformin: a retrospective analysis. Diabetes Obes Metab. 2012 Sep;14(9):803-9.

Schramm TK, Gislason GH, Vaag A, Rasmussen JN, Folke F, Hansen ML, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J. 2011 Aug;32(15):1900-8