CADTH

CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Non-Pioglitazone Antihyperglycemic Agents for Secondary Prevention of Stroke in Type II Diabetes or Pre-Diabetes: Clinical Effectiveness and Cost-Effectiveness

Service Line:	Rapid Response Service
Version:	2.0 Corrected Version (see page 7 for Correction Notice)
Publication Date:	July 2020
Report Length:	7 Pages

CADTH

Authors: Shannon Hill, Carolyn Spry

Cite As: *Non-pioglitazone antihyperglycemic agents for secondary prevention of stroke in type II diabetes or pre-diabetes: clinical effectiveness and cost-effectiveness*. Ottawa: CADTH; 2020 July. (CADTH Rapid Response Report: Summary of Abstracts).

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to **requests@cadth.ca**

Research Questions

1. What is the clinical effectiveness of non-pioglitazone antihyperglycemic agents for secondary prevention of stroke in patients with type II diabetes or pre-diabetes?
2. What is the cost-effectiveness of non-pioglitazone antihyperglycemic agents for secondary prevention of stroke in patients with type II diabetes or pre-diabetes?

Key Findings

Four non-randomized studies (all secondary analyses of clinical trial data) were identified regarding the clinical effectiveness of non-pioglitazone antihyperglycemic agents for secondary prevention of stroke in patients with type II diabetes or pre-diabetes. No relevant literature was identified regarding the cost-effectiveness of non-pioglitazone antihyperglycemic agents for secondary prevention of stroke in patients with type II diabetes or pre-diabetes.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were non-pioglitazone antihyperglycemic agents, stroke and type II diabetes. 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 January 1, 2015 and April 28, 2020. Internet links were provided, where available.

Selection Criteria and Summary Methods

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Selection was limited to abstracts that specify inclusion of patients with previous stroke or transient ischemic attack. Full texts of publications were not reviewed. The Overall Summary of Findings was based on information available in abstracts of selected publications.

Table 1: Selection Criteria

Population	Adult patients with type II diabetes or pre-diabetes with previous stroke or transient ischemic attack
Intervention	Monotherapy or combination therapy including metformin, empagliflozin, canagliflozin, dapagliflozin, liraglutide, semaglutide
Comparator	Other antihyperglycemic agents, placebo
Outcomes	Q1: Clinical effectiveness (e.g., stroke, recurrent stroke, transient ischemic attack, safety) Q2: Cost-effectiveness
Study Designs	Health technology assessments, systematic review, randomized controlled trials, non-randomized studies, economic evaluations

Results

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

Four non-randomized studies[1-4] were identified regarding the clinical effectiveness of non-pioglitazone antihyperglycemic agents for secondary prevention of stroke in patients with type II diabetes or pre-diabetes; all four publications presented secondary analyses of clinical trial data. No economic evaluations were identified regarding the cost-effectiveness of non-pioglitazone antihyperglycemic agents for secondary prevention of stroke in patients with type II diabetes or pre-diabetes. In addition, no health technology assessments, systematic reviews, or randomized controlled trials were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Four non-randomized studies providing secondary analyses of clinical trial data[1-4] were identified. The authors of the first non-randomized study[1] evaluated the effectiveness of semaglutide on major adverse cardiovascular events in type II diabetes patients with varying cardiovascular risks, including prior stroke, based on combined data from two randomized controlled trials (one on subcutaneous semaglutide and one on oral semaglutide). The authors found that semaglutide lowered major adverse cardiovascular events versus placebo and concluded that “semaglutide showed consistent effects on [major adverse cardiovascular events] across varying [cardiovascular] risk” groups.[1] The second non-randomized study[2] reported the effects of empagliflozin versus placebo for patients with type II diabetes and prior stroke events. The authors of this study found that empagliflozin showed relative reductions in risk of cardiovascular death, all-cause mortality, major adverse cardiovascular events, and hospitalization for heart failure compared to placebo for patients with and without prior stroke events.[2] The authors of the third non-randomized study[3] reported the effectiveness of canagliflozin on stroke related outcomes in type II diabetes participants with and without a history of stroke or transient ischemic attack. Of a total of 10,142 participants in the original clinical trials, the study authors identified 1958 participants with a history of stroke or transient ischemic attack at baseline. Among 309 participants from both groups with stroke events at follow up, this study found that those who received canagliflozin had a numerically lower incidence rate of stroke events

during follow-up compared to those assigned to placebo, but this difference did not reach statistical significance.[3] The authors concluded there were too few stroke events to conclusively show benefit of canagliflozin.[3] The final non-randomized study[4] evaluated the effectiveness of liraglutide for type II diabetic individuals with and without a history of myocardial infarction and/or stroke. The authors of this study found that liraglutide reduced major adverse cardiovascular events, including non-fatal stroke, in patients with a history of myocardial infarction and/or stroke.[4]

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

No literature identified.

Randomized Controlled Trials

No literature identified.

Non-Randomized Studies

Secondary Analysis of Clinical Trial Data

1. Husain M, Bain SC, Jeppesen OK, et al. Semaglutide (SUSTAIN and PIONEER) reduces cardiovascular events in type 2 diabetes across varying cardiovascular risk. *Diabetes Obes Metab*. 2020 Mar;22(3):442-451. PubMed: PM31903692

2. Fitchett D, Inzucchi SE, Cannon CP, et al. Empagliflozin reduced mortality and hospitalization for heart failure across the spectrum of cardiovascular risk in the EMPA-REG OUTCOME trial. *Circulation*. 2019 Mar 12;139(11):1384-1395. PubMed: PM30586757

3. Zhou Z, Lindley RI, Radholm K, et al. Canagliflozin and stroke in type 2 diabetes mellitus. *Stroke*. 2019 Feb;50(2):396-404. PubMed: PM30591006

4. Verma S, Poulter NR, Bhatt DL, et al. Effects of liraglutide on cardiovascular outcomes in patients with type 2 diabetes mellitus with or without history of myocardial infarction or stroke. *Circulation*. 2018 Dec 18;138(25):2884-2894. PubMed: PM30566004

Economic Evaluations

No literature identified.

Appendix — Further Information

Previous CADTH Reports

5. Nguyen V, Boucher M, Grobelna A. Cardiovascular outcome trials for type 2 diabetes. *CADTH Issues in Emerging Health Technologies; Issue 177*. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/dv/ieht/cardiovascular-outcome-trials-type-2-diabetes. Accessed 2020 May 12.

Randomized Controlled Trial

Alternative Population – Diabetes Not Specified

6. den Hertog HM, Vermeer SE, Zandbergen AA, et al. Safety and feasibiLIty of Metformin in patients with Impaired glucose Tolerance and a recent TIA or minor ischemic stroke (LIMIT) trial - a multicenter, randomized, open-label phase II trial. *Int J Stroke*. 2015 Jan;10(1):105-109. PubMed: PM23489282

7. Osei E, Fonville S, Zandbergen AA, et al. Metformin and sitAgliptin in patients with impAired glucose tolerance and a recent TIA or minor ischemic Stroke (MAAS): study protocol for a randomized controlled trial. *Trials*. 2015 Aug 5;16:332. PubMed: PM26242578

Correction Notice

The original report, published on May 13, 2020, stated: “Two randomized controlled trials and two non-randomized studies were identified regarding the clinical effectiveness of non-pioglitazone antihyperglycemic agents for secondary prevention of stroke in patients with type II diabetes or pre-diabetes.”

However, upon further review, it was determined that all studies should be more appropriately classified as non-randomized studies under the subheading of “secondary analysis of clinical trials data.”

Additionally, a correction was made in the Overall Summary of Findings for the conclusion that was drawn in relation to the non-randomized study by Zhou et al.[3] The summary originally stated: “The study authors identified 1958 participants and found that those who received canagliflozin had a lower incidence of stroke events during follow-up compared to those assigned to placebo.”[1]

A more accurate statement has been made regarding the conclusions about stroke events and characteristics of the included participants that properly reflects the subgroup for which the conclusion was drawn for the non-randomized study by Zhou et al.[3]

Corrections are reflected in the Key Findings, Results, and Overall Summary of Findings.

Finally, further detail about the study design for Husain et al.[1] was added to the Overall Summary of Findings.