Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

# Conducting and interpreting results of network meta-analyses in type 2 diabetes mellitus: A review of network meta-analyses that include sodium glucose co-transporter 2 inhibitors

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ARTICLE INFO

*Article history:*
Received 31 July 2018
Received in revised form
4 December 2018
Accepted 4 January 2019
Available online 11 January 2019

*Keywords:*
Network meta-analysis
Sodium glucose co-transporter 2 inhibitor
Systematic review
Type 2 diabetes mellitus

ABSTRACT

*Aims:* Network meta-analyses (NMAs) are valuable ways to generate comparative effectiveness data for therapies available to treat type 2 diabetes mellitus (T2DM). This review assesses NMAs that evaluate sodium glucose co-transporter 2 (SGLT2) inhibitors for treatment of T2DM and discusses potential issues in conducting and interpreting NMAs.

*Methods:* A systematic literature search was conducted on September 13, 2018 using the search terms "network meta-analysis," "SGLT2," variations of these terms, and individual SGLT2 inhibitor names. Extracted data included NMA objectives, methods, target populations, treatments, study endpoints, length of follow-up, and funding. Differences between NMAs were investigated.

*Results:* Thirty-five full-length publications met criteria for inclusion. In most NMAs, the target population was defined by therapeutic regimen (e.g., combination with metformin). Follow-up intervals permitted in NMAs varied considerably (range, 4–208 weeks). Twenty-nine NMAs included dapagliflozin, 28 evaluated canagliflozin, and 27 evaluated empagliflozin. Nine NMAs used frequentist methods; 16 used Bayesian methods. Six NMAs were funded by pharmaceutical manufacturers. Heterogeneity across NMAs was seen in scope, time frame, and other aspects of analytic design.

*Conclusions:* Although this review indicates that methodological guidelines for reporting NMAs were generally followed, it also emphasizes the need for T2DM-specific guidance requiring clear reporting of NMA scope and objectives to aid appropriate interpretation and use of NMA results.



## 1. Introduction

Randomized, controlled trials that include direct comparisons between different treatment modalities are 1 source of evidence for health care decision-making [1]. However, direct comparison between all available treatment options is not feasible when there is a multitude of different approved therapies for a given disease state [2], as is the case for type 2

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https://doi.org/10.1016/j.diabres.2019.01.005
0168-8227/

diabetes mellitus (T2DM). Without comparative effectiveness data between all available therapeutic options, knowledge gaps can restrict health care providers' ability to make evidence-based decisions about treatment [1]. Therefore, indirect methodologic approaches are increasingly being used to evaluate the comparative effectiveness of different treatments [2]. Additionally, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Academy of Managed Care Pharmacy (AMCP), and the National Pharmaceutical Council (NPC) Good Practice Task Force have suggested that indirect comparisons can be valuable as a way to provide more precise estimates of treatment effects even when there is sufficient direct evidence [3].

Network meta-analyses (NMAs) have become a popular way for researchers to perform multiple pairwise treatment comparisons across a range of interventions (e.g., A vs B, A vs C) by utilizing data from direct comparisons (e.g., randomized trials of treatment A vs B) and indirect comparisons (e.g., making inferences about A vs B based on results of direct comparisons of A vs C and B vs C, in which C can be placebo or an active comparator) to generate loops of evidence that preserve randomization and provide overall pooled effects for each treatment [1,4–6].

The ISPOR [1,7] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [8] have published guidances on how to conduct and interpret NMAs to inform health-economic assessments that are recommended in many countries for use in health technology assessments [9]. These guidelines provide checklists and other tools to help researchers improve the standardization and transparency of NMA procedures and data reporting [1,7,8]. These guidelines also define a set of good research practices that should be followed when conducting and reporting NMAs. Specifically, NMAs should follow PICOS (population, intervention, comparators, outcomes, study design) criteria when defining the research question, eligibility criteria, and data sources [8]. Search and reporting strategies should follow relevant PRISMA guidelines for systematic reviews and meta-analyses and should consider iterative search methods to optimize the evidence base for analysis. Descriptions of data extraction methods should include details that allow for assessment of comparability and homogeneity, and statistical methods should include explicit statements of all assumptions and analytic features. Data analysis methods should incorporate strategies, such as meta-regression, that can minimize risks for inconsistency and bias [1,7,8].

To further help decision-makers critically review and interpret data generated by NMAs, a good practice task force with members from ISPOR, the AMCP, and the NPC developed a questionnaire that assesses the relevance of an NMA to the setting of interest (i.e., target patient population and treatments), along with the overall validity of the evidence base, analysis methods, reporting quality, transparency, interpretation of findings, and potential conflicts of interest [3]. These [1,3,7,8] and other NMA user guidelines and tutorials [2,10,11] have emphasized the importance of correctly interpreting the information provided by NMAs within the appropriate context. These guidelines have also increased awareness about the need for appropriate standardized methodology; as a result, the reporting quality of NMAs has improved substantially in recent years, especially with regard to evaluation of underlying assumptions [12]. However, there is often considerable heterogeneity (i.e., variation in treatment effects as a result of differences in factors such as patient population, setting, and bias) [13] between the studies included in NMAs, and many published NMAs still have significant contextual and statistical limitations [12]. A key challenge in conducting an NMA is finding a balance in the size of the evidence network such that it includes a sufficient number of studies to generate precise estimates of treatment effects, while excluding studies that increase heterogeneity, bias, and inconsistency [14]. Formal exploration of ways to reduce heterogeneity and inconsistency has been identified as an important topic for inclusion in future NMA guidelines to further standardize methodology and reporting and to minimize the potential for misinterpretation of results [12,15,16].

The objective of this analysis is to understand how methodological differences among NMAs could have implications for T2DM decision-making by analyzing NMAs in T2DM that have been performed to estimate treatment effects associated with the use of sodium glucose co-transporter 2 (SGLT2) inhibitors.

## 2. Materials and methods

A systematic literature search was conducted on September 13, 2018 to identify NMAs that include assessment of SGLT2 inhibitors for the treatment of T2DM. Searches for full-text publications were conducted without a time restriction using MEDLINE (via PubMed). Conference abstracts were not included. Search terms were (((SGLT2 or sodium glucose cotransporter 2 or sodium glucose cotransporter 2 or canagliflozin or empagliflozin or dapagliflozin or luseogliflozin or tofogliflozin or ipragliflozin or ertugliflozin)) AND (network meta-analysis or NMA or meta-analysis or meta analysis)).

Publications identified in these searches were evaluated for relevance. Data extraction followed the ISPOR-AMCP-NPC Good Practice Task Force questionnaire for determining the relevance and credibility of indirect treatment comparisons and NMAs [3]. Key data extracted from relevant publications included the authors' stated objectives of their analysis; inclusion and exclusion criteria for the clinical studies combined in each NMA; the list of treatments and doses relevant to the comparison; details on how treatments were grouped (e.g., whether SGLT2 inhibitors were analyzed as a class or as separate agents; whether different dose strengths were analyzed together or separately); efficacy and safety endpoints synthesized from the clinical studies; details on the choice of time point; details on the NMA methods, including use of frequentist or Bayesian methods, use of fixed versus random effects, and use of tests to detect heterogeneity and inconsistency; and study funding sources. Based on the data extraction, similarities and differences between the NMAs were summarized; these features were then investigated to determine whether they could explain observed differences in NMA results. The complete summary of data extracted from each article is available in the Supplemental Material.

## 3. Results

In total, 168 articles were identified through the systematic search. Thirty-five articles [17–51], which included 33 articles identified in the systematic search and 2 articles that were not identified in the search but were known to the authors, met eligibility criteria for inclusion in the review (Fig. 1) and are described in detail in Table 1.

The full-text articles were generally of good quality and contained most of the information required by NMA guidelines. Two published articles used the Jadad scale [24,32] and 28 used the Cochrane risk of bias tool [17,18,20,21,25,26,29–31,33–51] to ensure that the evidence base from the included clinical trials met rigorous scientific standards. Additionally, 26 articles included presentation of the data extracted from the clinical trials [17,18,20–22,25,27,29–32,34–44,46,47,50,51], which increases the transparency and reduces the risk of errors.

### 3.1. *Treatment regimens*

Target populations of the 35 identified NMAs are summarized in Table 1. The scope of 23 of the 35 NMAs was defined according to background T2DM therapy (e.g., combination therapy that included an SGLT2 inhibitor) [17,19–22,24–26,28–38,44,45,47,49], with 11 of these also requiring prior treatment failure [19,22,28–30,32–37]. Of note, 1 NMA [27] defined scope solely based on failure of metformin alone or in combination therapy. Among the NMAs included in this analysis, SGLT2 inhibitors were used in monotherapy in 2 NMAs [25,26] and as monotherapy or combination therapy with 1 other antihyperglycemic agent (AHA; metformin and unspecified) in 2 NMAs [38,45]. Nineteen NMAs had requirements for combination therapy with an SGLT2 inhibitor and at least 1 other AHA, with 3 focusing on combination with a sulfonylurea [17,33,35], 7 focusing on combination with metformin [19,22,29,32,34,37,44], and 6 focusing on combinations with 2 other AHAs (i.e., triple therapy; metformin plus another AHA [49], metformin + sulfonylurea [30], metformin + thiazolidinedione [36]; or any 2 other AHAs [21,24,28]). Three NMAs required combination of an SGLT2 inhibitor with insulin [20,31,47]. Eleven NMAs included trials of SGLT2 inhibitors as part of any treatment regimen [18,23,39–43,46,48,50,51].

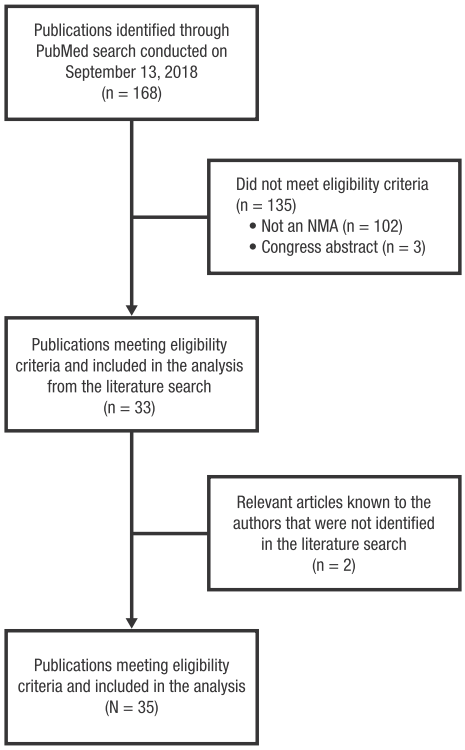


**Fig. 1 – PRISMA flow diagram of literature search results. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NMA, network meta-analysis.**

### 3.2. *Length of follow-up*

The identified NMAs imposed different criteria for the time points at which clinical studies were required to report efficacy and safety results, and the range of permitted time intervals varied considerably (Table 2). Twenty NMAs excluded studies with follow-up duration shorter than 24 weeks, but 15 NMAs permitted inclusion of shorter trials (as low as 4 weeks) and 6 NMAs had no requirement on follow-up duration (Table 1). Only 2 NMAs required the included studies to have comparable lengths of follow-up (24–26 weeks [38] or 46–58 weeks [22]). Twenty NMAs had only a minimum duration requirement [20,21,24–26,28,32,34,35,37,39–43,46–48,50,51].

### 3.3. *Outcomes of interest*

Efficacy, as measured by HbA1c, was included in 22 of the 35 NMAs (Table 1), with all including the efficacy endpoint of absolute change from baseline in HbA1c with an SGLT2 inhibitor relative to the absolute change from baseline observed with another treatment. Seven NMAs additionally included the incremental likelihood of achieving HbA1c < 7% (53 mmol/mol) [20,27,31,32,37,38,47]. Eleven NMAs included the efficacy endpoint of change from baseline in fasting plasma glucose with an SGLT2 inhibitor relative to the change observed with placebo or another AHA [20,27,31,34,35,37,44,45,47–49]. Additionally, 22 NMAs included efficacy results based on body weight outcomes, and 11 provided results on systolic blood pressure outcomes (Table 1). Three NMAs included lipids outcomes [44,48,49], 2 NMAs included diastolic blood pressure [48,49], and 2 NMAs included postprandial glucose [34,37] as an outcome. Two NMAs considered dose changes of concomitant insulin as an efficacy outcome [20,31] and 1 NMA included fasting plasma insulin and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [45].

Thirty-two of the 35 NMAs included safety outcomes, expressed in terms of odds ratios or relative risks of experiencing an event with an SGLT2 inhibitor compared with placebo or another therapy (Table 1). Overall safety and tolerability was reported for any adverse events (AEs) in 3 NMAs [21,44,45], AEs leading to drug withdrawal in 1 NMA [50], and serious AEs in 5 NMAs [21,34,35,45,50]. Specifically, 19 NMAs evaluated risk of hypoglycemic events [19–22,24,28–36,44,47–50], 7 NMAs evaluated urinary tract infections

**Table 1 – Data Extraction Results From Identified NMA Publications.**

| Publication | Date of literature search | Population and setting | Time horizon | Efficacy endpoints | Safety endpoints | SGLT2i included | Statistical model |
|---|---|---|---|---|---|---|---|
| Bain et al. [17] | December 2014 | Efficacy and safety of SU monotherapy or add-on to SU | 14–780 weeks | None | All-cause mortality; CV death; acute MI; stroke | Individual agents NS<br>Analyzed as a class | Bayesian<br>Fixed effects model |
| Balijepalli et al. [18] | November 30, 2016 | Any | Any | None | All-cause mortality, CV death; MACE; HHF; nonfatal MI | EMPA<br>Analyzed individually | Bayesian<br>Fixed effects model |
| Barnett et al. [19] | 2011 to July 2013 | 2nd line<br>DAPA vs other AHAs as add-on to MET | 24 ± 6 weeks or 52 ± 6 weeks | Change from BL in HbA1c, BW, SBP | % of patients with ≥ 1 hypoglycemic event | DAPA 10 mg<br>Analyzed individually | Bayesian<br>Random effects model |
| Cho et al. [20] | December 2016 | 2nd line<br>Efficacy and safety of adjunctive AHAs in patients inadequately controlled on insulin | ≥12 weeks | Change from BL in HbA1c, FPG, BW, insulin dose; % of patients achieving HbA1c < 7% | % of patients with ≥ 1 hypoglycemic event | CANA 100 & 300 mg; DAPA 5 & 10 mg; EMPA 10 & 25 mg; IPRA 50 mg<br>Analyzed by class | NS<br>Random effects model |
| Downes et al. [21] | NS | 3rd line<br>Summarize benefits and harms of triple therapy combinations | ≥24 weeks | Change from BL in HbA1c, BW | % of patients with ≥ 1 hypoglycemic event; SAEs | CANA 100 & 300 mg<br>Analyzed as a class but data were only available for CANA | NS<br>Random effects model |
| Goring et al. [22] | May 2011 & updated in October 2012 | 2nd line<br>DAPA vs other AHAs as add-on to MET | 52 ± 6 weeks | Change from BL in HbA1c, BW, SBP | % of patients with ≥ 1 hypoglycemic event | DAPA 10 mg<br>Analyzed individually | Bayesian<br>Fixed and random effects models applied |
| Kramer et al. [23] | December 1, 2008 to November 24, 2017 | Any combination therapy | Any | None | Incident HF/HHF | CANA; EMPA<br>Analyzed both individually and as a class | Bayesian<br>Random effects model |
| Lee et al. [24] | April 8, 2015 | 3rd line<br>Triple therapy for glycemic control, including effects on weight and hypoglycemia | ≥20 weeks | Change from BL in HbA1c and BW | % of patients with ≥ 1 hypoglycemic event | CANA 100 & 300 mg; DAPA 10 mg; EMPA 25 mg<br>Analyzed as a class | Frequentist<br>Effects model NS |
| Lee et al. [25] | March 2016 | 1st line | ≥24 weeks | None | All-cause mortality; CV mortality; ACS; MI | CANA 100 & 300 mg; DAPA 2.5, 5, & 10 mg; EMPA 10 & 25 mg<br>Analyzed as a class | Bayesian<br>Fixed effects model |
| Li et al. [26] | October 9, 2016 | 1st line<br>SGLT2i vs active comparators (MET, GLIM, SITA, SAXA, & LINA) | ≥24 weeks | None | UTI; genital infection | CANA 100 & 300 mg; DAPA 2.5, 5, & 10 mg; EMPA 25 mg; LUSEO 2.5 mg; IPRA 50 mg<br>Analyzed individually | NS<br>Random effects model |

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**Table 1 – (*continued*)**

| Publication | Date of literature search | Population and setting | Time horizon | Efficacy endpoints | Safety endpoints | SGLT2i included | Statistical model |
|---|---|---|---|---|---|---|---|
| Lorenzi et al. [27] | October 2014 | 2nd line<br>Efficacy of adjunctive AHAs in patients inadequately controlled on MET | Any | Change from BL in HbA1c, FPG, BW; % of patients achieving HbA1c < 7% | None | CANA 100 & 300 mg; DAPA 5 & 10 mg; EMPA 10 & 25 mg<br>Analyzed individually | Bayesian<br>Random effects model |
| Lozano-Ortega et al. [28] | Included studies identified in a 2013 CADTH review and a search in February 2014 | 3rd line<br>Efficacy and safety of SGLT2i with MET + SU relative to other classes of AHAs | ≥4 weeks | Change from BL in HbA1c, BW, SBP | % of patients with ≥ 1 hypoglycemic event | CANA 100 & 300 mg; DAPA 10 mg<br>Analyzed as a class | Bayesian<br>Random effects model |
| Mearns et al. [29] | May 2014 | 2nd line<br>Efficacy and safety of adjunctive AHAs in patients inadequately controlled with MET | 12–52 weeks | Change from BL in HbA1c, BW, SBP | % of patients with ≥ 1 hypoglycemic event; UTI; genital infection | CANA 100 & 300 mg; DAPA 2.5 & 10 mg; EMPA 10 & 25 mg<br>Analyzed individually | NS<br>Random effects model |
| Mearns et al. [30] | May 2014 | 3rd line<br>Efficacy and safety of adjunctive AHAs in patients inadequately controlled with MET + SU | 12–52 weeks | Change from BL in HbA1c, BW, SBP | % of patients with ≥ 1 hypoglycemic event; UTI; genital infection | CANA 100 & 300 mg; DAPA 10 mg; EMPA 10 & 25 mg<br>Analyzed individually | Frequentist<br>Random effects model |
| Min et al. [31] | June 2015 | 2nd line<br>Efficacy and safety of adjunctive AHAs in patients inadequately controlled on insulin | ≥12 weeks | Change from BL in HbA1c, FPG, BW, insulin dose; % of patients achieving HbA1c < 7% | % of patients with ≥ 1 hypoglycemic event | CANA 300 mg; DAPA 10 mg; EMPA 25 mg<br>Analyzed as a class | NS<br>Random effects model |
| Neff et al. [32] | January 1, 1990 to December 16, 2014 | 2nd line<br>Efficacy and safety of adjunctive AHAs in patients inadequately controlled with MET | ≥12 weeks | Change from BL in HbA1c, BW, BMI; % of patients achieving HbA1c < 7% | % of patients with ≥ 1 hypoglycemic event | CANA; DAPA<br>Analyzed as a class | Bayesian<br>Random effects model |
| Orme et al. [33] | March (CENTRAL database) or April (MEDLINE and EMBASE) 2013 | 2nd line<br>Patients inadequately controlled with SU | 24 ± 6 weeks | Change from BL in HbA1c, BW, SBP | % of patients with ≥ 1 hypoglycemic event | DAPA 10 mg<br>Analyzed individually | Bayesian<br>Fixed and random effects models applied |
| Qian et al. [34] | October 2017 | 2nd line<br>Efficacy and safety of adjunctive AHAs in patients inadequately controlled on MET | ≥24 weeks | Change from BL in HbA1c, FPG, BW, 2-h PPG | % of patients with ≥ 1 hypoglycemic event; MACE; all-cause mortality; SAEs; UTI; diarrhea | CANA 100 & 300 mg; DAPA 2.5, 5, & 10 mg; EMPA 10 & 25 mg<br>Analyzed as a class | Frequentist<br>Random effects model |
| Qian et al. [35] | January 1, 1974 to December 28, 2017 | 2nd line<br>Efficacy and safety of adjunctive AHAs in patients inadequately controlled on SU | ≥24 weeks | Change from BL in HbA1c, FPG, BW | % of patients with ≥ 1 hypoglycemic event; SAEs | CANA 100 & 300 mg; DAPA 2.5, 5, & 10 mg<br>Analyzed as a class | Frequentist<br>Random effects model |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Saulsberry et al. [36] | January 8, 2015 | 3rd line<br>Assessment of AHAs used as add-on to MET + TZD | 12–52 weeks | Change from BL in HbA1c, BW, SBP | % of patients with ≥ 1 hypoglycemic event; UTI; genital infection | CANA 100 & 300 mg; EMPA 10 & 25 mg<br>Analyzed individually | Frequentist<br>Random effects model |
| Sharma et al. [37] | August 16, 2017 | 2nd line<br>Efficacy of adjunctive AHAs in patients inadequately controlled on MET | ≥20 weeks | Change from BL in HbA1c, FPG, BW, SBP; % of patients achieving HbA1c < 7% | None | CANA 100 & 300 mg; DAPA 5 & 10 mg; EMPA 25 mg; IPRA 50 mg<br>Analyzed individually | Bayesian<br>Random and fixed effects models |
| Shyangdan et al. [38] | January 2005 to January 2015 | 1st or 2nd line<br>Efficacy of SGLT2i as monotherapy or + MET | ≥24 weeks | % of patients achieving HbA1c < 7%; change from BL to Week 24 in HbA1c, BW, SBP | NS | CANA 100 & 300 mg; DAPA 10 mg; EMPA 10 & 25 mg; LUSEO 2.5 mg; IPRA 50 mg; TOFO 10, 20, & 40 mg<br>Analyzed individually | Bayesian<br>Fixed effects model |
| Tang et al. [39] | January 27, 2016 | Any | ≥24 weeks | None | All-cause mortality, MACE (CV death, nonfatal MI, or nonfatal stroke); HF or HHF; unstable angina or angina requiring hospitalization; AF; TIA | CANA; DAPA; EMPA<br>Analyzed individually | NS<br>Random effects model |
| Tang et al. [40] | January 27, 2016 | Any | ≥24 weeks | None | Fracture | CANA 100 & 300 mg; DAPA 1, 2.5, 5, & 10 mg; EMPA 10 & 25 mg<br>Analyzed individually | NS<br>Random effects model |
| Tang et al. [41] | May 24, 2016 | Any | ≥12 weeks | None | Composite renal events; acute renal impairment/failure | CANA; DAPA; EMPA; LUSEO<br>Analyzed as a class | NS<br>Random effects model |
| Tang et al. [42] | February 15, 2017 | Any | ≥24 weeks | None | Cancer | CANA; DAPA; EMPA; ERTU; IPRA<br>Analyzed individually | NS<br>Random effects model |
| Tang et al. [43] | January 17, 2017 | 1st, 2nd, or 3rd line<br>Comparison of trials of ≥ 1 AHA vs placebo, no treatment, or active comparators (DPP-4i, GLP-1RA, SGLT2i, glinides, AGI, TZD, SU, MET, & insulin) | ≥24 weeks | None | Diabetic retinopathy, including macular edema, vitreous hemorrhage, onset of diabetes-related blindness, and the need for treatment with an intravitreal agent or retinal photocoagulation | CANA; DAPA; EMPA<br>Analyzed as a class | NS<br>Random effects model |
| Wang et al. [44] | March 2017 | 1st and 2nd line<br>Efficacy and safety of adjunctive AHAs in patients inadequately controlled on MET | Any | Change from BL in HbA1c, BW, FPG, total cholesterol, triglycerides | % of patients with > 1 hypoglycemic event; diarrhea; UTI; AEs | DAPA; EMPA<br>Analyzed individually | Bayesian<br>Random effects model |

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**Table 1 – (*continued*)**

| Publication | Date of literature search | Population and setting | Time horizon | Efficacy endpoints | Safety endpoints | SGLT2i included | Statistical model |
|---|---|---|---|---|---|---|---|
| Yang XL et al. [45] | February 2017 | 1st and 2nd line<br>Efficacy and safety of adjunctive AHAs in patients inadequately controlled on MET | Any | Change from BL in HbA1c, FPG, FPI, HOMA-IR | Any AEs; SAEs; diarrhea; nausea; nasopharyngitis | CANA; EMPA<br>Analyzed individually | Bayesian<br>Effects model NS |
| Yang J et al. [46] | April 28, 2016 | Any | ≥12 weeks | None | Fracture | Individual agents NS<br>Analyzed as a class | Frequentist<br>Random effects |
| Yoon et al. [47] | April 2016 | 2nd line<br>Efficacy and safety of adjunctive AHAs in patients inadequately controlled on insulin | ≥12 weeks | Change from BL in HbA1c, FPG, BW, insulin dose; % of patients achieving HbA1c < 7% | % of patients with ≥ 1 hypoglycemic event | CANA 100 & 300 mg; DAPA 5 & 10 mg; EMPA 25 mg; IPRA 50 mg<br>Analyzed by class | Bayesian<br>Random effects model |
| Zaccardi et al. [48] | November 3, 2015 | 1st, 2nd, or 3rd line<br>Licensed doses of CANA, DAPA, and EMPA vs PBO or other AHAs | ≥24 weeks | Change from BL in HbA1c, FPG, BW, SBP, DBP, total cholesterol, HDL-C, LDL-C, triglycerides | Hypoglycemic events; UTI; genital infection; DKA; bone fracture | CANA 100 & 300 mg; DAPA 5 & 10 mg; EMPA 10 & 25 mg<br>Analyzed individually | Frequentist<br>Random effects model |
| Zaccardi et al. [49] | January 2000 to July 2017 | 2nd line<br>Efficacy and safety of adjunctive AHAs in patients inadequately controlled on MET | 24-52 weeks | Change from BL in HbA1c, FPG, BW, SBP, DBP, lipids (total cholesterol, LDL-C, HDL-C, triglycerides) | % of patients with ≥ 1 hypoglycemic event | CANA 300 mg; DAPA 10 mg; EMPA 25 mg<br>Analyzed individually | NS<br>Random effects model |
| Zheng et al. [50] | October 11, 2017 | Any | ≥12 weeks | None | All-cause mortality; CV mortality; HF; all MI; unstable angina; all stroke; hypoglycemia; SAEs; AEs leading to withdrawal | CANA 100 & 300 mg; DAPA 2.5, 5, & 10 mg; EMPA 10 & 25 mg; IPRA 50 & 100 mg; LUSEO 2.5 & 5 mg; ERTU 5 & 10 mg<br>Analyzed as a class | Bayesian<br>Random and fixed effects models |
| Zhuang et al. [51] | January 1, 1980 to June 30, 2016 | Any | ≥24 weeks | None | MACE; all-cause mortality | CANA 100 & 300 mg; DAPA 2.5, 5, & 10 mg; EMPA 10 & 25 mg<br>Analyzed as a class and individually | Frequentist<br>Effects model not specified |

NMA, network meta-analysis; SGLT2i, sodium glucose co-transporter 2 inhibitor; SU, sulfonylurea; CV, cardiovascular; MI, myocardial infarction; NS, not specified; MACE, major adverse cardiovascular event; HHF, hospitalization for heart failure; EMPA, empagliflozin; DAPA, dapagliflozin; AHA, antihyperglycemic agent; MET, metformin; BL, baseline; BW, body weight; SBP, systolic blood pressure; FPG, fasting plasma glucose; CANA, canagliflozin; IPRA, ipragliflozin; AE, adverse event; HF, heart failure; ACS, acute coronary syndrome; GLIM, glimepiride; SITA, sitagliptin; SAXA, saxagliptin; LINA, linagliptin; UTI, urinary tract infection; LUSEO, luseogliflozin; CADTH, Canadian Agency for Drugs and Technologies in Health; BMI, body mass index; CENTRAL, Cochrane Central Register of Controlled Trials; PPG, postprandial glucose; SAE, serious adverse event; TZD, thiazolidinedione; TOFO, tofogliflozin; AF, atrial fibrillation; TIA, transient ischemic attack; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; AGI, alpha-glucosidase inhibitor; FPI, fasting plasma insulin; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; PBO, placebo; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; DKA, diabetic ketoacidosis; ERTU, ertugliflozin.

**Table 2 – Requirements for Reporting Time Points for Identified NMAs.**

| Allowed time point range, weeks | Number of NMAs reporting efficacy only | Number of NMAs reporting safety only | Number of NMAs reporting both |
|---|---|---|---|
| 4+ | – | – | 1 |
| 12+ | – | 3 | 3 |
| 12–26 | – | – | 1 |
| 12–52 | – | – | 3 |
| 18–30 | – | – | 2 |
| 20+ | 1 | – | 1 |
| 24+ | – | 7 | 4 |
| 24–26 | 1 | – | – |
| 24–54 | – | – | 1 |
| 46–58 | – | – | 1 |
| Any | 1 | 3 | 2 |

NMA, network meta-analysis.

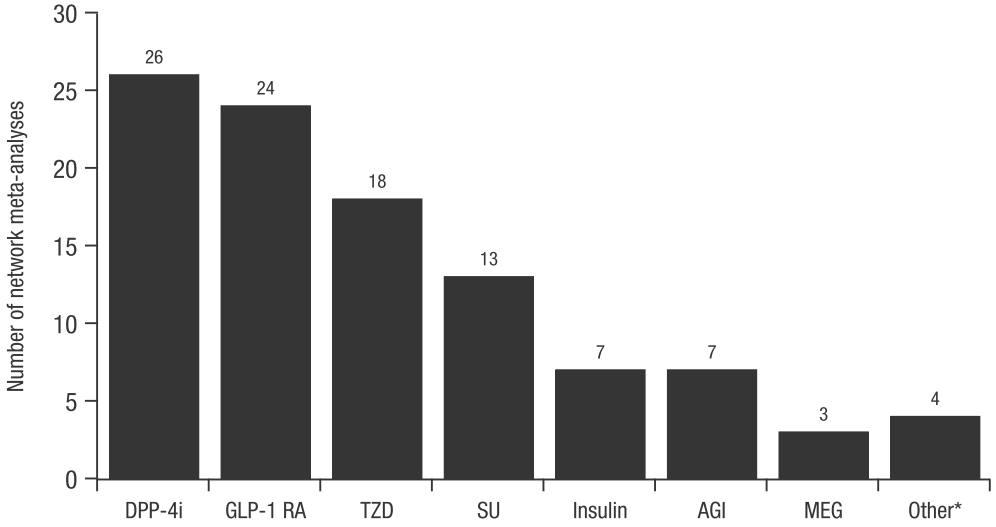


**Fig. 2 – Number of network meta-analyses including drugs from classes other than SGLT2 inhibitors. SGLT2, sodium glucose co-transporter 2; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; TZD, thiazolidinedione; SU, sulfonylurea; AGI, alpha-glucosidase inhibitor; MEG, meglitinide. *Other = bile acid sequestrant (colesevelam).**

[26,29,30,34,36,44,48], and 5 NMAs evaluated genital infections [26,29,30,36,48]. Other safety endpoints investigated in the NMAs were bone fractures [40,46,48], diarrhea [34,44,45], renal safety [41,48], diabetic retinopathy [43], nausea [45], nasopharyngitis [45], and cancer [42]. All-cause mortality was an endpoint in 7 NMAs [17,18,25,34,39,50,51]. Four NMAs reported results for cardiovascular outcomes, including major adverse cardiovascular events (MACE), acute myocardial infarction, stroke or acute coronary syndrome, or cardiovascular mortality [18,34,39,51]; additionally, 4 NMAs reported heart failure or hospitalization for heart failure [18,23,39,50] and 2 NMAs reported other macrovascular outcomes [39,50].

### 3.4. *Treatments included in the NMAs*

As required by the scope of this review, all of the identified NMAs included ≥ 1 SGLT2 inhibitor. The most commonly studied SGLT2 inhibitors were dapagliflozin (included in 29 NMAs) and canagliflozin (included in 28 NMAs), followed by empagliflozin (included in 27 NMAs; Table 1). Additionally, 6 NMAs included ipragliflozin, 4 included luseogliflozin, 2 included ertugliflozin, 1 included tofogliflozin, and 1 did not specify which SGLT2 inhibitors were included. In 19 of the 35 NMAs, each SGLT2 inhibitor was analyzed individually, and in 13 of the NMAs, data from all SGLT2 inhibitors were grouped together and analyzed as a class; 3 NMAs presented results for both individual SGLT2 inhibitors and the class (Table 1). The grouping of SGLT2 inhibitors as a class in 2 NMAs was sometimes motivated by the assumption that efficacy is common to the class, although differences may be more likely in the agents' AE profiles [21,24].

Whether explicitly through their scope or implicitly through the comparators used in the identified relevant studies, all NMAs included AHAs from classes other than SGLT2 inhibitors, most commonly dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists (Fig. 2). AHAs in classes other than SGLT2 inhibitors were generally analyzed together, especially sulfonylureas and

insulins, because titration schedules make it difficult [42,46] to match treatment regimens for different agents. Only 5 NMAs distinguished between different doses of the same agent. While many NMAs required prior therapeutic failure with metformin or considered triple therapeutic regimens that included metformin, metformin was rarely mentioned as a specific comparator.

Due to the scopes of most NMAs, AHA comedications were absent in 2 NMAs or the same across all comparators and thus irrelevant to the analysis (by design in 11 and by chance in 1 of the 35 NMAs). Two NMAs controlled for comedications by requiring that within each study the same comedications apply to all study arms. Sixteen NMAs pooled interventions regardless of comedication [23,24,27,28,31,32,39–42,46–51], and 2 NMAs distinguished between different AHA combinations as distinct comparators [38,45].

### 3.5. *NMA methods*

Sixteen of the 35 NMAs reported using Bayesian NMA methods, and 9 NMAs reported using frequentist methods (Table 1). Ten NMAs did not explicitly state the method that was used. Fixed effects were applied in 4 of the NMAs and random effects were applied in 23 NMAs. In 5 NMAs, both fixed- and random-effects models were applied, including 1 NMA in which the choice of effects was dependent on the endpoint (Table 1). Three NMAs did not specify whether fixed or random effects were used [24,45,51]. Meta-regression was applied and reported in 9 of the 35 NMAs using covariates related to follow-up duration [48]; baseline HbA1c, baseline weight, sex, and baseline disease duration [37]; observed change in HbA1c [43]; and unspecified baseline covariates [20,22,23,31,33,47]. Three NMAs stated that use of meta-regression was considered but not performed or reported [18,26,28].

The $I^2$ statistic was used to assess heterogeneity across the evidence base in 23 of the 35 NMAs [20,23,25,26,29–36,39–48,50]. Three NMAs used Cochran's Q statistic [17,23,36], 2 used inspection of study variance [38,49], and 2 used a chi-squared test [45,47], respectively, to assess heterogeneity.

Thirteen of the 35 NMAs evaluated patient baseline characteristics, treatment and dosing schedules and study designs and found these to be sufficiently similar to one another. Many NMAs pointed out differences between the included studies in terms of patient baseline characteristics (20 NMAs), study designs including duration of follow-up (11 NMAs), and differences in treatment and dosing schedules (9 NMAs). Three NMAs cautioned that their findings might be affected by differences across clinical trials [25,28,49], and only 3 NMAs stated that their findings are likely robust despite some differences across clinical trials [24,38,48]. Twenty-eight of the 35 NMAs carried out formal tests of network inconsistency using the design-by-treatment interaction method [21,24,26,34,35,40–42,48,49,51] or measures of loop inconsistency [18,25–27,29,34,35,37–39,43,45,46,50,51] or stated that inconsistency was not applicable in the case of a star-shaped network [18,23]. Two NMAs found statistical evidence of inconsistency for body weight outcomes [48] and for hypoglycemia [21].

### 3.6. *Study funding*

All 35 NMAs included information about funding. Twenty-seven of the NMAs did not receive funding for their analysis; however, authors disclosed conflicts of interest in 14 of the NMAs. Six of the NMAs acknowledged receiving funding from pharmaceutical manufacturers, 1 received funding from the Australian government, and 1 received no external funding.

## 4. Discussion

This systematic literature review identified 35 NMAs published through September 13, 2018 that were conducted to determine the effects of SGLT2 inhibitors relative to other AHAs for the treatment of T2DM. These NMAs differed markedly in their scope, with 13 NMAs focusing exclusively on safety outcomes and 23 NMAs addressing the use of SGLT2 inhibitors in a range of different treatment settings (e.g., monotherapy or combination therapy with other AHAs), over a broad range of time intervals (ranging from 4 to 208 weeks). Some NMAs evaluated only 1 SGLT2 inhibitor, while other NMAs made comparisons between the different SGLT2 inhibitors or evaluated all SGLT2 inhibitors together as a class. Consistent with the publication of more studies, NMAs with more recent search dates tended to include more clinical trials than NMAs with search dates at earlier time points. Given these substantial differences in scope, target population and treatment setting, and evidence base, results from these different NMAs cannot be expected to match exactly. This observation suggests that heterogeneity may exist even within the relatively narrow topic of SGLT2 inhibitor therapy for the treatment of T2DM and highlights the importance of defining the scope of an NMA according to a relevant patient population. Matching the scope of an NMA to the target population is critical to ensure that results are interpreted correctly by users [1,3,9].

Even when the scope of an NMA consists of a relatively contained question, results can diverge because of differences in methods and assumptions used. In a Warwick Evidence group assessment report produced for the National Institute for Health and Care Excellence (NICE) in the United Kingdom on the use of SGLT2 inhibitors as monotherapy for the treatment of T2DM, 3 separate NMAs were submitted by the manufacturers of canagliflozin, dapagliflozin, and empagliflozin, respectively, and the Warwick Evidence group conducted a fourth NMA [52]. Results of these 4 NMAs (Table 3) indeed illustrate substantive differences. Results from a Bayesian random effects analysis of 23 studies of thiazolidinediones or the DPP-4 inhibitor sitagliptin also illustrate that NMA findings and interpretation of results can vary when combining study populations with different baseline characteristics. For example, adjustments for baseline HbA1c [53], differences in geographical settings or patient ethnicities, as well as choice of time interval for included trials, can affect NMA results [48].

Currently available guidelines for conducting and interpreting NMAs have substantially improved the quality of data published in recent years [12], and these guidelines were generally followed in the NMAs included in this review. Although

**Table 3 – Clinical Effectiveness Estimates of HbA1c From NMAs Conducted by SGLT2 Inhibitor Manufacturers and the Warwick Assessment Group [54].**

| Treatment | Janssen | AstraZeneca | Boehringer Ingelheim* | | Warwick Group |
|---|---|---|---|---|---|
| | Base | Base | 24 week | 52 week | Base |
| SGLT2 inhibitors pooled | | –0.74 | | | |
| Canagliflozin 100 mg | –0.97 | | ■ | | |
| Canagliflozin 300 mg | –1.20 | | ■ | | –1.153 |
| Dapagliflozin 5 mg | | | ■ | | |
| Dapagliflozin 10 mg | –0.64 | | ■ | | –0.704 |
| Empagliflozin 10 mg | –0.73 | | ■ | ■ | |
| Empagliflozin 25 mg | –0.85 | | ■ | ■ | –0.870 |
| DPP-4 inhibitors pooled | | –0.64 | | ■ | |
| Sitagliptin 100 mg | –0.72 | | | ■ | –0.723 |
| Pioglitazone | –0.78 | –0.90 | | ■ | –1.200 |
| Sulfonylurea | –0.59 | –0.95 | | ■ | –1.301 |
| Repaglinide | –1.28 | | | ■ | –1.200† |

NMA, network meta-analysis; SGLT2, sodium glucose co-transporter 2; DPP-4, dipeptidyl peptidase-4.
* Results redacted.
† Assumed as no estimate within NMA.

some forms of heterogeneity can be valuable, findings from this review suggest that the development of T2DM-specific guidance for the interpretation of NMA results would be a useful next step to ensure that health care decision-makers and other consumers of NMAs appropriately use and carefully interpret NMAs based on the study question to inform their decision-making.

## Conflict of interest

M.W. and C.A. are employees of the Swedish Institute for Health Economics, which has provided consulting services for Janssen Global Services, LLC. C.N. is a full-time employee of Janssen Global Services, LLC.

## Author contributions

M.W. and C.A. were involved in the study design and conduct, data extraction, data analysis and interpretation, and manuscript preparation and review. C.N. was involved in the study design and conduct, data analysis and interpretation, and manuscript preparation and review. All authors have approved the final article.

## Acknowledgments

This study was funded by Janssen Global Services, LLC. Medical writing support was provided by Cherie Koch, PhD, of MedErgy, and was funded by Janssen Global Services, LLC.

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