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Research Article

Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: A systematic review and meta-analysis

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Abstract

Sodium-glucose co-transporter 2 (SGLT2) inhibitors represent a new class of antihyperglycemic agents that block renal sodium and glucose reabsorption and may reduce blood pressure (BP). We assessed the BP lowering ability of these agents using meta-analytic techniques. PubMed, SCOPUS, and Cochrane Central were searched through October 2013. We included fully published randomized controlled trials (RCTs) that evaluated SGLT2 inhibitors in patients with type-2 diabetes mellitus and reported change in systolic and/or diastolic BP. Subgroup analyses were performed for placebo-controlled trials and those with active controls. We also conducted meta-regression to assess for a dose-response effect, and whether baseline BP, changes in body weight, heart rate, and hematocrit were associated with the BP effects. Twenty-seven RCTs (n = 12,960 participants) were included. SGLT2 inhibitors significantly reduced both systolic BP (weighted mean difference, −4.0 mm Hg; 95% confidence interval, −4.4 to −3.5) and diastolic BP (weighted mean difference, −1.6 mm Hg; 95% confidence interval, −1.9 to −1.3) from baseline. Only canagliflozin had a significant dose-response relationship with SBP ($P = .008$). Significant reductions in body weight and hematocrit were seen with the SGLTs. SGLTs had no significant effect on the incidence of orthostatic hypotension ($P > .05$). SGLT2 inhibitors significantly reduce BP in patients with type 2 diabetes. J Am Soc Hypertens 2014;8(4):262–275.

Keywords: SGLT2 inhibitors; blood pressure; diabetes mellitus; meta-analysis.

Introduction

The sodium-glucose transporter 2 (SGLT2) inhibitors are a novel class of oral antihyperglycemic agents that have been developed for the treatment of type 2 diabetes mellitus.[1] Canagliflozin is the first agent in this class approved by the Food and Drug Administration (FDA) in March 2013.[2,3] The SGLT2 transporter is found primarily in the S1 segment of the proximal tubule and accounts for approximately 90% of reabsorbed glucose, with expression limited to within the kidney.[4] SGLT2 couples glucose with the transport of sodium and actively pumps it against a

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Conflict of interest: Dr. Riche serves on the Speaker's Bureau for Janssen, Boehringer Ingelheim, and Merck. Dr. White reports research funding from the National Institutes of Health and is President, American Society of Hypertension, Inc (2012-2014). He receives consulting fees for safety committees for Astra-Zeneca, Forest Research Institute, Roche, Inc, Teva Neurosciences, and Takeda Development Center, North America. No other authors have conflicts of interest germane to this manuscript.Supplemental Material can be found at www.ashjournal.com.

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concentration gradient across the luminal membrane.[5,6] This causes an osmotic diuresis with resultant reductions in plasma volume and blood pressure (BP), which may be associated with symptomatic hypotension and impairments in renal function.[2]

Clinical trials have shown significant reductions from baseline in both systolic and diastolic BP following administration of the SGLT2 inhibitors.[7–10] These effects could have important implications for appropriate patient selection as well as clinical efficacy and safety monitoring. The purpose of this meta-analysis was to more thoroughly characterize the systolic and diastolic BP lowering effects of the SGLT2 inhibitors, evaluate whether these effects have a dose-response relationship, and to evaluate various mechanistic relationships to blood pressure changes.

Methods

The current analysis conforms to standard guidelines and was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[11]

Literature Search

We conducted a systematic literature search using MEDLINE, SCOPUS, and Web of Science through June 25, 2013. The search strategy combined the Medical Subject Headings and keywords canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, remogliflozin, SGLT 2 inhibitors, and sodium-glucose co-transport 2 inhibitors. A manual update of the search was also performed on October 1, 2013 using MEDLINE and an abbreviated strategy. Citations were limited to randomized controlled trials (RCTs) published in English. For the MEDLINE search, the Cochrane Collaboration's Highly Sensitive Search Strategy sensitivity maximizing version for RCTs was utilized.[12] A manual search of references from reports of clinical trials or review articles was performed to identify additional relevant studies.

Study Selection

Two authors (LRS and EMB) reviewed all potentially relevant articles in a parallel manner by using a priori defined criteria. Studies were eligible for inclusion in the systematic review if they were 1) a RCT in humans; 2) evaluated any SGLT2 inhibitor (listed above) compared with either placebo or an active control; and 3) reported data on changes in systolic and/or diastolic BP from baseline in a form suitable for pooling. Only data from fully published manuscripts were considered for inclusion in this analysis.

Data Abstraction and Validity Assessment

For each included study, two authors (LMS and EMB) used a standardized data abstraction tool to independently extract all data, with disagreements resolved by a third investigator (WLB). The following information was sought from each trial: author, year, study design, duration of follow-up, population and setting, sample size, SGLT2 agent evaluated (including dose and frequency), and concomitant therapies. Data on systolic and diastolic BP at baseline, any concomitant antihypertensive medications used, and changes from baseline in BP were collected in addition to frequencies of symptomatic orthostatic hypotension. When available, data from the intention-to-treat analyses were used. Following the Methods Guide for Comparative Effectiveness Reviews, two reviewers assessed the quality of each study by answering ''yes,'' ''no,'' or ''unclear'' to 11 questions regarding similarity of baseline populations, randomization, allocation concealment, blinding of study participants and personnel, outcome adjudication, completeness of follow-up, and conflicts of interest.[13] Studies were given an overall score of good, fair, or poor with disagreements resolved through discussion.

Statistical Analysis

The mean changes from baseline in systolic and diastolic BP were treated as continuous variables, and the weighted mean differences (WMDs) and accompanying 95% confidence intervals (CIs) were pooled using a DerSimonian and Laird random-effects model.[14] We collected and analyzed data for all reported doses of each drug, regardless of its regulatory status. Separate analyses were conducted for placebo-control and active-controlled trials. For each trial, net changes in each of these study parameters were calculated as the difference (SGLT2 − placebo/control) of the changes (baseline − follow-up) in these mean values (also referred to as the change score). Since variances for net changes were not reported directly for all studies, they were calculated from confidence intervals, *P*-values, or individual variances for intervention and placebo/control groups/periods. A pooled variance for net change was calculated for parallel trials in which variance for paired differences were reported separately for each group, using standard methods. A correlation coefficient of 0.5 between initial and final values was assumed.[15] Equal variances during the trial and between intervention and placebo/control groups were also assumed.

Data on the incidence of symptomatic orthostatic hypotension were treated as a dichotomous variable with relative risks (RR) and accompanying 95% CIs pooled using a DerSimonian and Laird random-effects model. The pooled risk difference (RD) was used to calculate the number needed to harm (NNH), and accompanying 95% CI, for symptomatic hypotension.

The likelihood of statistical heterogeneity was assessed using the I-squared statistic (an I-squared >25% is considered representative of important statistical heterogeneity).[16] The presence of publication bias and related biases was