Original Research

Quality of Methodological Reporting of Randomized Clinical Trials of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors

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Abstract

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a new class of medicines approved recently for the treatment of type 2 diabetes. To improve the quality of randomized clinical trial (RCT) reports, the Consolidated Standards of Reporting Trials (CONSORT) statement for methodological features was created. For achieving our objective in this study, we assessed the quality of methodological reporting of RCTs of SGLT2 inhibitors according to the 2010 CONSORT statement. We reviewed and analyzed the methodology of SGLT2 inhibitors RCTs that were approved by the Food & Drug Administration (FDA). Of the 27 trials, participants, eligibility criteria, and additional analyses were reported in 100% of the trials. In addition, trial design, interventions, and statistical methods were reported in 96.3% of the trials. Outcomes were reported in 93.6% of the trials. Settings were reported in 85.2% of the trials. Blinding and sample size were reported in 66.7 and 59.3% of the trials, respectively. Sequence allocation and the type of randomization were reported in 63 and 74.1% of the trials, respectively. Besides those, a few methodological items were inadequate in the trials. Allocation concealment was inadequate in most of the trials. It was reported only in 11.1% of the trials. The majority of RCTs have high percentage adherence for more than half of the methodological items of the 2010 CONSORT statement.

Keywords: CONSORT statement, diabetes mellitus, randomized clinical trials, sodium-glucose cotransporter-2 (SGLT2) inhibitors

Introduction

Randomized clinical trials (RCTs) are the gold standard for evaluating the effectiveness of various types of clinical interventions. However, if they lack methodological rigor, they can yield a biased result. The accurate, complete, and clear methodological information of reporting is essential for the reader in evaluating and judging the validity of clinical trials.[1] Methodological reporting to evaluate the trial design, interventions, blinding, and outcomes of RCTs is important. The poor quality of the methodological feature in RCTs might lead to harmful treatments. The Consolidated Standards of Reporting Trials (CONSORT) statement was developed in 1993 as a standard and updated in 2010. The aim was to reduce the problems arising from the inadequate reporting of RCTs.[2] Diabetes has been increasing in recent years. Globally, according to the World Health Organization,[3] since 1980, the number of adult patients with diabetes has almost quadrupled to 422 million.

Type 2 diabetes made up the great number of people with diabetes around the world, and it is largely the result of obesity and physical inactivity. It was formerly called adult-onset or noninsulin-dependent results due to the relative lack of insulin and insulin resistance.[4] Sodium-glucose cotransporter-2 (SGLT2) inhibitors including canagliflozin, dapagliflozin, and empagliflozin are a new class of medicines approved recently for the treatment of type 2 diabetes.

SGLT2 is found in the proximal tubule in the kidney. It contributes to about 90% of the glucose reabsorption. Once SGLT2 is inhibited, the blood glucose level will come down because of the increase in glucose excretion. These drugs exert their action through improving the sensitivity of insulin and through uptake of the glucose in the muscle cells and also

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Access this article online

Quick Response Code:

Website: www.archivepp.com

DOI: 10.4103/app.app_78_16

How to cite this article: Alfahmi H, Aldawood L, Baz B, Elrggal M, Alsharif HY, Alkahtani SA. Quality of methodological reporting of randomized clinical trials of sodium-glucose cotransporter-2 (sglt2) inhibitors. Arch Pharma Pract 2017;8:78-81.

by enhancing the insulin releasing (phase 1) from beta cells of the pancreas and reduction of gluconeogenesis process. In addition, SGLT2 has an action on the body weight reduction as well as systolic blood pressure reduction.[5]

We believed that evidence-based medicine and RCTs are the cornerstone in clinical research, and the quality of methodological reporting feature is a critical part that may lead to a harmful result; thus, we need to assess the quality of methodological reporting. We used only clinical trials approved by the FDA. Canagliflozin is the first drug approved by the FDA in 2013.

In this study, we aimed to evaluate the methodological reporting of RCTs of SGLT2 that was approved by the FDA according to the 2010 CONSORT statement and providing our recommendations for improving them in the future.

Materials and Methods

Aim

The primary aim was to evaluate the quality of methodological reporting of RCTs of SGLT2 inhibitors.

Data sources

We examined all RCTs included in the FDA label information ofcanagliflozin, dapagliflozin, and empagliflozin from drugs@FDA.

Eligibility criteria

Eligibility criteria for this study are given in Table 1.

Characteristics of the studies

Data were collected based on the general characteristics of studies including number of authors, type and impact factor of journals, year of publication, and interventions (active or placebo).

Data extraction

All RCTs were evaluated according to the 12 items modified from the methods criteria of the 2010 CONSORT statement. These items are important to assess the methodology of RCTs. However, five items (3b, 6b, 7b, 10, and 11b) were not applicable for the evaluation of RCTs in this study.

The three reviewers (H.M., L.M., and B.A.) underwent training in the assessment of RCTs using the 2010 CONSORT statement.

Table 1: Study of eligibility criteria

Inclusion criteria	Exclusion criteria
All phase 3 randomized clinical trials	Non-inferiority trial Trials not published yet Systematic reviews Observational studies

Assessment of reporting quality

For methodological items, each item was assigned as follows: reported, scored as 1; not reported, scored as 2; unclear, scored as 3; and nonapplicable, scored as 4.

Statistical analysis

To assess adherence to the CONSORT checklist items, we calculated the number and proportion of reports describing each of the 12 items. In addition, the percentage of the 12 items was reported in each report. Furthermore, the descriptive analysis was performed. All the analyses were performed using the Statistical Package for the Social Sciences version 18.0 software (SPSS Inc., Chicago, IL, United States).

Results

Study characteristics

A total of 33 articles of RCTs were identified from drugs@FDA [Figure 1]. Of these, six trials did not meet our inclusion criteria. Therefore, it was excluded. Finally, a total 27 articles were included. All these trials were performed at many centers. A total of 5 (18.5%) trials were published in a general journal, while 22 (81.5%) trials were published in a diabetes and endocrinology journal. The placebo was used as comparator in 21 (77.8%) trials, while 3 (11.1%) trials were used as active comparator. Besides those, only 3 (11.1%) trials were used both as placebo and active comparators. A total of 23 (85.2%) trials were published after 2010, while 2 (7.4%) trials were published before 2010. There is a variation between the impact factors of journals, which are summarized in Table 2.

Assessment of methodological items reported

Trial design was reported in 26 (96.3%) out of 27 trials, and it was unclear or not reported in 1 (3.7%) trial. Eligibility criteria were reported adequately in all 27 clinical trials

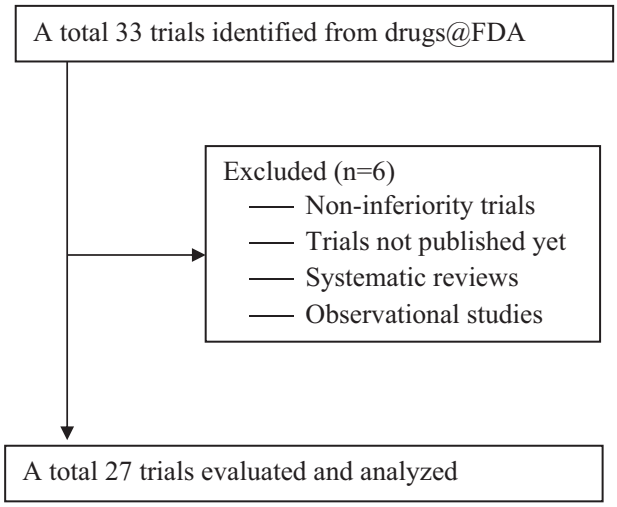

Figure 1: Flow chart for study selection

(100%). Settings were reported in 23 (85.2%) trials, and they were unclear or not reported in 4 (14.8) trials. Interventions were reported in 26 (96.3%) trials, and they were unclear or not reported in one trial. Outcomes of these trials were adequately reported in 25 (92.6%) trials, and they were unclear or not reported in 2 (7.4%) trials. Sample size was reported only in 16 (59.3%) trials, and it was unclear or not reported in 11 (40.7%) trials. Sequence allocation was reported in 17 (63%) trials, and it was unclear or not reported in 10 (37%) trials. The type of randomization was reported in 20 (74.1%) trials, and it was unclear or not reported in 7 (25.9%) trials. Allocation concealment was reported only in 3 (11.1%) trials, and it was unclear or not reported in 24 (88.9%) trials. Double blinding was reported in 18 (66.7%) trials, and it was unclear or not reported in 9 (33.3%) trials. The statistical analysis and additional analysis were reported in 26 (96.3%) trials and 27 (100%), respectively [Table 3].

Table 2: Study characteristics of included articles

Demographics	Number of trials
	n (%)
Number of authors	
<5	2 (7.4%)
5–7	20 (74.1%)
>7	5 (18.5%)
Journals	
General	5 (18.5%)
Diabetes and endocrinology	22 (81.5%)
Interventions	
Placebo controlled	21 (77.8%)
Active controlled	3 (11.1%)
Both	3 (11.1%)
Year of publication	
Published above 2010	23 (85.2%)
Published in 2010	2 (7.4%)
Published below 2010	2 (7.4%)
Impact factor of journals	
Lancet (45.217)	1 (3.7%)
Annals of Internal Medicine (17.810)	1 (3.7%)
Lancet Diabetes & Endocrinology (9.185)	3 (11.1%)
Diabetes Care (8.420)	9 (33.3%)
BMC Medicine (7.360)	1 (3.7%)
Diabetes, Obesity & Metabolism (6.360)	8 (29.6%)
Clinical Endocrinology and Metabolism (6.209)	1 (3.7%)
International Journal of Clinical Practice (2.566)	2 (7.4%)
Journal of Diabetes Investigation (1.825)	1 (3.7%)

Discussion

The methodology of RCTs is a crucial part for quality assessment. However, differences in the methodology of RCTs may lead to biased results. In addition, the interpretation of the results will become difficult. In this study, we assessed the quality of methodological reporting of RCTs of SGLT2 inhibitors. Most of these articles were found in endocrinology diabetes specialty journals, except for 11 of the RCTs.

Our results demonstrate that the majority of RCTs have high percentage adherence for more than half of the methodological items of the 2010 CONSORT statement which indicate that RCTs were conducted for the assessment of efficacy and safety this class have high

Table 3: Methodological quality of randomized clinical trials of sodium-glucose cotransporter-2 (SGLT2) inhibitors

Items checklist			Item percentage of adherence
			n (%)
Trial design	3a	Description of trial design (such as parallel and factorial) including allocation ratio	26 (96.3%)
Participants	4a	Eligibility criteria for participants	27 (100%)
	4b	Settings and locations where the data were collected	23 (85.2%)
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	26 (96.3%)
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	25 (93.6%)
Sample size	7a	How sample size was determined	16 (59.3%)
Randomization			
Sequence generation	8a	Method used to generate the random allocation sequence	17 (63%)
	8b	Type of randomization; details of any restriction (such as blocking and block size)	20 (74.1%)
Allocation concealment analysis	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	3 (11.1%)
Blinding	11a	If performed, who was blinded after assignment to interventions (e.g., participants, care providers, those assessing outcomes) and how	18 (66.7%)
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	26 (96.3%)
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	27 (100%)

quality regarding the methodology. In detail, participants, eligibility criteria, and additional analyses were reported in 100% of the trials. In addition, trial design, interventions, and statistical methods were reported in 96.3% of the trials. Outcomes were reported in 93.6% of the trials. Settings were reported in 85.2% of the trials. Blinding and sample size were reported in 66.7 and 59.3% of the trials, respectively. Sequence allocation and the type of randomization were reported in 63 and 74.1% of the trials, respectively. Besides those, a few methodological items were inadequate in the trials. Allocation concealment was inadequate in most of the trials. It was reported only in 11.1% of the trials. As a result, it should be taken into account by the authors or the editors.

In 2010, a study related to medical disciplines was conducted to evaluate the methodological reporting of RCTs in Respiratory Research. They included 176 articles. From the results of this study, the generation of the allocation sequence was adequate in 93 (53%) of the 176 trials. Furthermore, adequate double blinding was reported in 79 (45%) trials. In addition, eligibility criteria were reported adequately in 176 (100%) trials.[6] These findings were in line with our findings.

In contrast, another study conducted to evaluate the quality of 142 RCT papers published in five Chinese medical journals showed that 26.8% reported random sequence generation, 4.2% reported allocation concealment, 10.6% reported blinding, 0.7% contained flow diagrams, and none of the studies reported sample size determination.[7] Another study was conducted to evaluate and analyze the quality of 305 studies that were retrieved from three major diabetes journals. The generation of the allocation sequence was adequate in 108 (35.4%) of the 305 trials. Allocation concealment was adequate in 87 (28.5%) trials, and blinding was reported adequately in 175 (57.0%) trials including 129 (42.3%) double-blinding trials. In addition, 131 (43.0%) trials reported inadequate blinding, thus indicating that all key methodological items in our study were greater than those reported in other studies.

Limitations

There are a several limitations in this study. First, drugs@FDA was the only database used to examine all RCTs; perhaps, it is possible to miss some relevant studies. Second, we focused on the assessment of the quality of methodological reporting rather than the whole CONSORT 2010 statement which although it gave a clear view of trials robustly, it didn't take into account other important items in the checklist.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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