Journal of Diabetes and Its Complications 33 (2019) 567–571

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Loop diuretic use among patients with heart failure and type 2 diabetes treated with sodium glucose cotransporter-2 inhibitors

Erin R. Weeda [a,*], Christy Cassarly [b,c], Daniel L. Brinton [c], David W. Shirley [a], Kit N. Simpson [c]

[a] Department of Clinical Pharmacy and Outcomes Sciences, College of Pharmacy, Medical University of South Carolina, Charleston, SC 29425, USA
[b] Department of Otolaryngology - Head and Neck Surgery, College of Medicine, Medical University of South Carolina, Charleston, SC 29425, USA
[c] Department of Healthcare Leadership & Management, College of Health Professions, Medical University of South Carolina, Charleston, SC 29425, USA

ARTICLE INFO

Article history:
Received 28 February 2019
Received in revised form 19 April 2019
Accepted 5 May 2019
Available online 10 May 2019

Keywords:
Diabetes mellitus, type 2
Heart failure
Loop diuretic
Canagliflozin
Empagliflozin
Dapagliflozin

ABSTRACT

Aims: To compare loop diuretic use in patients with comorbid heart failure (HF) and type 2 diabetes (T2D) newly initiated on sodium glucose cotransporter-2 inhibitors (SGLT2Is) versus other oral anti-glycemic agents (AGAs).
Methods: This analysis used 2013–2015 MarketScan Medicare Supplemental claims data. HF and T2D patients were identified and SGLT2I users were propensity score matched to other AGA users. The mean daily dose of loop diuretics in furosemide equivalents was ascertained. For those not on baseline loop diuretics, new use was compared between cohorts. For those on baseline loop diuretics, we assessed patterns of use (increased dose, decreased dose, stable dose, no longer using) at 12-months.
Results: A total of 750 SGLT2I users were matched to 750 other AGA users. The distribution of loop diuretic use at mean doses of 0 mg (i.e., no use), ≤20 mg, >20 mg–40 mg, >40 mg–80 mg and >80 mg/day did not differ between cohorts at baseline or 12-months ($p > 0.05$ for both). SGLT2I use was associated with less new loop diuretic use (22.7% [79/348] vs. 34.0% [132/388]; $p = 0.001$). For those on loop diuretics at baseline ($n = 764$), patterns of use at 12-months did not differ between cohorts ($p = 0.14$).
Conclusions: New loop diuretic use was less frequent among SGLT2I users; however, patterns of loop diuretic use did not differ between cohorts in those on loop diuretics at baseline.

1. Introduction

Heart failure (HF) is a common comorbidity among patients with type 2 diabetes (T2D).[1] In randomized controlled trials (RCTs), sodium glucose cotransporter-2 inhibitors (SGLT2Is) reduced the rate of HF hospitalizations by >25% in patients with T2D and high cardiovascular risk.[2–4] These reductions led to ongoing trials assessing SGLT2Is in HF patients with or without diabetes.[5]

Loop diuretics, which are used to treat fluid retention in patients with HF, lead to increases in sodium and water loss in the kidney via inhibition of a sodium-potassium-chloride co-transporter in the ascending limb of the loop of Henle.[6] These diuretics are often titrated to achieve symptom relief but have not demonstrated a consistent mortality benefit in chronic HF patients.[7] SGLT2Is reduce blood glucose by enhancing urinary excretion of glucose in the proximal convoluted tubule and it has been proposed that SGLT2Is may also increase sodium and water loss in the kidney.[8] It is possible that the initiation of SGLT2I therapy results in changes in loop diuretic utilization due to decreases in HF morbidity, increased effectiveness or side effects (e.g., dehydration, hypotension or electrolyte abnormalities) at previously tolerated doses. Therefore, we sought to compare loop diuretic use among patients with comorbid HF and T2D newly initiated on SGLT2Is versus other oral anti-glycemic agents in a real-world setting.

2. Materials and methods

This retrospective study used United States (US) MarketScan Medicare Supplemental claims data from January 2013 to December 2015. Individuals with a medical claim for both HF (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] = 428.X, 398.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93) and T2D (ICD-9-CM = 250.X) were identified. Only those newly initiated on oral anti-glycemic agents (i.e., no claims for the agent in the last 90 days), which included SGLT2Is (i.e., canagliflozin, empagliflozin or dapagliflozin) sulfonylureas, dipeptidyl peptidase-4 inhibitors (DPP-4Is) or thiazolidinediones (TZDs) were included. Although metformin is also a commonly used oral anti-glycemic agent, it was not evaluated as it is often the preferred agent for monotherapy and thus may be used in patients requiring less aggressive treatment in order to achieve glycemic targets when compared to those on the aforementioned agents which are often used for dual therapy.[9] Patients were required

* Corresponding author at: Department of Clinical Pharmacy and Outcomes Sciences, College of Pharmacy, Medical University of South Carolina, 280 Calhoun Street, QE213C MSC140, Charleston, SC 29425, USA.
E-mail address: weeda@musc.edu (E.R. Weeda).

https://doi.org/10.1016/j.jdiacomp.2019.05.001
1056-8727/

to have ≥6-months of continuous insurance coverage prior to and ≥12-months of continuous insurance coverage following the qualifying oral anti-glycemic dispensing (i.e., index) date.

SGLT2I users were 1:1 propensity score matched to those receiving other oral anti-glycemic agents (i.e., sulfonylureas, DPP-4Is or TZDs). Propensity scores were estimated using a logistic regression model that included age, sex, hospitalization in the past 6-months, urban hospital location, hospital region, concomitant HF medications (angiotensin-converting enzyme inhibitors [ACEIs], beta-blockers, angiotensin II receptor blockers [ARBs] and aldosterone antagonists) as well as the presence of myocardial infarction, atrial fibrillation, 31 Elixhauser comorbidities and Charlson Comorbidity Index scores.[10,11] Matching was performed using 6-months of baseline data for each patient and a greedy nearest neighbor algorithm. Balance between cohorts was evaluated by assessing standardized differences for covariates; with differences >0.1 indicating imbalance.

Loop diuretic (i.e., furosemide, bumetanide, torsemide and ethacrynic acid) prescriptions were identified. For each prescription, total milligrams prescribed were calculated by multiplying the quantity by the drug strength. The total milligrams prescribed were then converted to oral (PO) furosemide equivalents by multiplying by a conversion factor (eTable 1).[12–16] The total milligrams of furosemide equivalents for each patient in the 6-months prior and 12-months following the index date was obtained by summing all prescriptions in each period. The mean daily dose in furosemide equivalents for each patient was obtained by dividing the total milligrams of furosemide equivalents prescribed by the sum of the days' supply for all prescriptions in each period. Mean daily doses were classified as 0 mg (i.e., no use) ≤20 mg, >20 mg to 40 mg, >40 mg to 80 mg and >80 mg per day, as furosemide is available in 20 mg, 40 mg and 80 mg strengths in the US.[12] All prescription claims were treated as separate prescriptions; including those with overlapping days' supply, as much of the overlap likely resulted from patients filling prescriptions early and these patients would be expected to finish one prescription before starting the next. Prescriptions that did not allow for an accurate calculation of mean daily dose (i.e., those with a days' supply of 0, a days' supply of 1 but a metric quantity larger than would be expected to be taken in a single day [e.g., 30] and solutions) were excluded.

Baseline characteristics (e.g., age, sex, region, concomitant medications, and comorbidities) are presented as a descriptive analysis. Cohorts were compared with respect to the daily loop diuretic dose category distribution using a Mann-Whitney *U* test. In patients not using loop diuretics prior to the index date, we compared the occurrence of new loop diuretic use (i.e., any use in the 12-months following the index date) between those receiving SGLT2Is versus patients receiving other oral anti-glycemic agents using a chi square test. In patients using loop diuretics in the 6-months prior to the index date, we evaluated patterns of loop diuretic use in the 12-months post-index by comparing the proportion of patients in the following categories between cohorts using a chi square test: increased mean dose, decreased mean dose, stable mean dose and no longer using loop diuretics (i.e., no prescriptions for loop diuretics in the 12-months following the index date). An increase or decrease in mean dose was defined as a change of ≥20 mg, as this is the lowest strength furosemide tablet available in the US.[12] Database management and statistical analysis were performed using SAS statistical software version 9.4 (NC, USA) and SPSSv22 (IBM Corp., Armonk, NY). This study was designated nonhuman research by the university institutional review board.

3. Results

A total of 1500 patients with both HF and T2D newly initiated on either a SGLT2I, sulfonylurea, DPP-4I or TZD were included (750 SGLT2I users matched to 750 patients receiving other oral anti-glycemic agents). The majority of SGLT2I users were on canagliflozin (n = 636; 85%); while patients treated with other oral agents received sulfonylureas (n = 455; 61%), DPP-4Is (n = 243; 32%), TZDs (n = 34; 4.5%) or combinations of these agents (n = 18; 2.4%).

All baseline characteristics demonstrated a standardized difference <10%; suggesting that the cohorts were well-matched. Mean age for all patients was 73.2 years (standard deviation [SD] = 6.4 years) and ~63% of patients were male (Table 1). Approximately 70% of patients were taking an ACEI or ARB; while 71% and 13% of patients were taking beta-blockers and aldosterone antagonists, respectively.

In the 6-months prior to the index date, 764 (50.9%) patients filled a prescription for loop diuretics and the median total days' supply for these patients was 120 days. A total of 904 (60.3%) patients filled a prescription for loop diuretics in the 12-months following the index date (median total days' supply = 270 days). Descriptive data on the number of prescriptions and days' supply for these agents can be found in eTables 2 and 3.

The proportion of patients with no loop diuretic use and the proportion receiving loop diuretic at mean doses of ≤20 mg, >20 mg to 40 mg, >40 mg to 80 mg and >80 mg per day in PO furosemide equivalents is shown in Table 2. There was not a significant difference in the distribution of loop diuretic use between cohorts before or after the index date ($p > 0.05$ for both). In the 12-months following the index date, SGLT2I use was associated with less new loop diuretic use (22.7% versus 34.0%, $p = 0.001$; Table 3). Among those using loop diuretics in the 6-

Table 1
Characteristics of included patients with type 2 diabetes and heart failure.

Characteristic	Total N = 1500 n (%)	SGLT2I N = 750 n (%)	Other anti-glycemic agent N = 750 n (%)	Absolute standardized difference (%)
Age, years (mean ± SD)	73.2 ± 6.4	73.1 ± 6.2	73.3 ± 6.6	3.1
Male	937 (62.5)	467 (62.3)	470 (62.7)	0.8
Region				
Northeast	390 (26.0)	201 (26.8)	189 (25.2)	3.8
Northcentral	439 (29.3)	220 (29.3)	219 (29.2)	0.3
South	533 (35.5)	262 (34.9)	271 (36.1)	2.6
West	134 (8.9)	64 (8.5)	70 (9.3)	2.9
Urban hospital location	1277 (85.1)	630 (84.0)	647 (86.3)	6.1
Previous hospitalization[a]	284 (18.9)	146 (19.5)	138 (18.4)	2.5
Comorbidities				
AF	373 (24.9)	188 (25.1)	185 (24.7)	0.9
Arrhythmias	616 (41.1)	306 (40.8)	310 (41.3)	1.1
COPD	386 (25.7)	194 (25.9)	192 (25.6)	0.6
Depression	99 (6.6)	50 (6.7)	49 (6.5)	0.5
Hypertension (controlled)	156 (10.4)	77 (10.3)	79 (10.5)	0.8
Uncontrolled hypertension	1138 (75.9)	563 (75.1)	575 (76.7)	3.6
Hypothyroidism	251 (16.7)	119 (15.9)	132 (17.6)	5.0
Obesity	250 (16.7)	116 (15.5)	134 (17.9)	7.5
Peripheral vascular disease	245 (16.3)	132 (17.6)	113 (15.1)	6.7
Valvular disease	232 (15.5)	119 (15.9)	113 (15.1)	2.2
Concomitant medications				
Beta blockers	1062 (70.8)	536 (71.5)	526 (70.1)	2.9
ACEI	607 (40.5)	294 (39.2)	313 (41.7)	5.2
ARB	498 (33.2)	254 (33.9)	244 (32.5)	2.9
Aldosterone antagonists	192 (12.8)	98 (13.1)	94 (12.5)	1.6

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; COPD = chronic obstructive pulmonary disease; SD = standard deviation; SGLT2I = sodium glucose cotransporter-2 inhibitors.

[a] Hospitalizations were captured during the 6-months prior to the qualifying oral anti-glycemic dispensing date.

Table 2
Mean daily dose of loop diuretics among patients with type 2 diabetes and heart failure[a].

	SGLT2I N = 750 n (%)	Other anti-glycemic agent N = 750 n (%)	P-value
Six months prior to index date			0.05
None	348 (46.4)	388 (51.7)	
≤20 mg	94 (12.5)	91 (12.1)	
>20–40 mg	169 (22.5)	142 (18.9)	
>40 mg–80 mg	103 (13.7)	94 (12.5)	
>80 mg	36 (4.8)	35 (4.7)	
Twelve months after the index date			0.15
None	313 (41.7)	283 (37.7)	
≤20 mg	94 (12.5)	96 (12.8)	
>20–40 mg	170 (22.7)	191 (25.5)	
>40 mg–80 mg	127 (16.9)	127 (16.9)	
>80 mg	46 (6.1)	53 (7.1)	

mg = milligrams; SGLT2I = sodium glucose cotransporter-2 inhibitors.
[a] Doses are in oral furosemide equivalents. Data are reported as the proportion of patients receiving mean doses in these dosing categories.

months prior to the index date, patterns of use after 12-months did not differ between cohorts (p = 0.14).

4. Discussion

In this retrospective study of US patients with HF and T2D, we compared loop diuretic use among 750 new users of SGLT2Is matched to 750 patients newly prescribed other oral anti-glycemic medications. After 12-months, SGLT2I use was associated with less new loop diuretic use. However, among patients on loop diuretics at baseline, no difference in patterns of loop diuretic use at 12-months was observed between cohorts.

SGLT2I use reduced HF morbidity among patients with T2D at high cardiovascular risk in several large, RCTs.[2–4] Among 7020 patients in the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG) trial, empagliflozin reduced cardiovascular mortality (HR = 0.62; 95%CI = 0.49–0.77) and hospitalizations for HF (HR = 0.65; 95%CI = 0.50–0.85).[2] Similar to what was observed in our current analysis, the proportion of patients newly initiated on loop diuretics was decreased with empagliflozin use (HR = 0.62; 95%CI = 0.53–0.73).[17] In the Canagliflozin Cardiovascular Assessment Study (CANVAS) and Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58) trials, which both included over 10,000 patients with T2D, HF hospitalizations were also decreased with canagliflozin (HR = 0.67; 95%CI = 0.52–0.87) and dapagloflozin (HR = 0.93; 95%CI = 0.61–0.88) but no difference in cardiovascular mortality was observed (p > 0.05 in both trials).[3,4] Among those with HF and using loop diuretics (N = 379) at baseline in the CANVAS trail, the composite endpoint of cardiovascular death and HF hospitalization was reduced with canagliflozin use (HR = 0.54; 95%CI = 0.37–0.78).[18] Based on these reductions in HF morbidity, the 2019 American Diabetes Association [ADA] Standards of Medical Care in Diabetes state that SGLT2Is are a preferred treatment option among patients with atherosclerotic cardiovascular disease with or at high risk of heart failure (Level of evidence = C).[9] It is important to note that our study included data from 2013 to 2015 and all of the aforementioned RCTs were published after November of 2015.[2–4] As this RCT data prompted changes in the ADA guidelines and would be expected to result in expansion of SGLT2I use, it is possible that patients in our study differ from those prescribed SGLT2Is after 2015.[2–4,18]

Table 3
Changes in loop diuretic use in the twelve months following the initiation of oral anti-glycemic medications.

	SGLT2I % (n/N)	Other anti-glycemic agent % (n/N)	P-value
Not on loop diuretics during the six months prior to the index date (N = 736)			
New loop diuretic use	22.7% (79/348)	34.0% (132/388)	0.001
On loop diuretics during the six months prior to the index date (N = 764)			
Increased mean loop diuretic dose	9.5% (38/402)	12.2% (44/362)	0.14
Decreased mean loop diuretic dose	4.0% (16/402)	6.1% (22/362)	
Stable loop diuretic dose	75.6% (304/402)	74.3% (269/362)	
No longer using loop diuretics	10.9% (44/402)	7.5% (27/362)	

SGLT2I = sodium glucose cotransporter-2 inhibitors.

SGLT2Is have also been associated with reduced HF morbidity in studies utilizing real-world data.[19] The Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors (i.e., CVD-REAL) study compared HF hospitalizations and mortality among those on SGLT2Is versus other glucose lowering drugs across 6 countries, including the US.[19] Data from the US were obtained from MarketScan and Medicare claims data; while other data sources in the remaining countries included electronic health records and registries. Among 309,056 included patients, lower rates of HF hospitalization (HR = 0.61; 95%CI = 0.51–0.73) and mortality (HR = 0.49; 0.41–0.57) were observed with SGLT2I use. Our study adds to this real-world evidence because, to our knowledge, it is the first to assess patterns of loop diuretic use among HF patients receiving SGLT2Is.

Although the mechanism behind the reductions in HF morbidity with SGLT2I use is unknown, SGLT2Is have several non-glycemic effects that may benefit patients with HF.[20–22] For instance, SGLT2Is increase beta-hydroxybutyrate; which could improve cardiac metabolism by increasing the use of ketone bodies by the heart leading to more efficient oxygen consumption.[20] SGLT2Is also decrease sodium reabsorption in the proximal tubules of the kidney.[20–22] This would be expected to alter tubuloglomerular feedback and decrease plasma volume without sympathetic nervous system (SNS) activation.[20] Moreover, it is thought that acetazolamide, a carbonic anhydrase inhibitor, improves the efficiency of loop diuretics by decreasing sodium reabsorption in the proximal tubules and it has been suggested that SGLT2Is could also improve loop diuretic efficiency by this mechanism.[20] If loop diuretic efficiency is improved, these medications could provide increased effectiveness at lower diuretic doses or patients could experience dehydration, hypotension or electrolyte abnormalities at previously tolerated doses; leading to changes in dosing patterns.

Patterns of loop diuretic use in patients on these medications at baseline did not differ between SGLT2I users when compared to those on other oral anti-glycemics in our study. One possible explanation for this is clinical inertia, which is defined as failure to act despite identifying problems.[23] Clinical inertia often involves repeated delays in medication changes and is well described among patients with cardiometabolic disease.[23–25] For instance, in an evaluation of outpatient visits among 7253 patients with hypertension, medication regimens were only intensified in 13.1% of visits where uncontrolled blood pressure readings were documented.[25] In our current analysis, it is possible clinicians were hesitant to prescribe loop diuretics at doses that differed from those initially allowing patients to maintain euvolemia; resulting in fewer than expected dosing changes.

While loop diuretics are used to achieve symptom control in chronic HF, they have not demonstrated a consistent mortality benefit.[7] In fact, diuretic use has been associated with increased mortality in several observational studies.[26–28] In a retrospective analysis of Digitalis Investigation Group (DIG) data (n = 7788), being treated with diuretics was associated with a higher rate of all-cause mortality (HR = 1.31; 95% CI = 1.11–1.51) and HF hospitalization (HR = 1.37; 95%CI = 1.13–1.65).[27] However, this observational study was susceptible to biases. For instance, those with more severe HF and thus at a greater risk of

mortality and HF hospitalization may have been more likely to receive diuretics. Nonetheless, diuretics may activate the SNS, which has been associated with HF progression.[29–32] It is unknown if decreased exposure to loop diuretics in SGLT2I users, as observed in our analysis (i.e., less new use of these diuretics) and the aforementioned analysis of EMPA-REG data, is beneficial.[17]

In the Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) registry, 78% of the 5229 patients with HF and diabetes were on ACEI/ARBs versus 70% of patients in our analysis.[33] Similarly, 88% and 71% of patients in the IMPROVE HF registry and our analysis were on beta-blockers, respectively. This somewhat higher proportion of patients receiving these medications in the registry may reflect the inclusion of only patients with HF with reduced ejection fraction (HFrEF); whereas patients with both HFrEF and HF with preserved ejection fraction (HFpEF) are likely represented in our analysis.[7,33] Despite this slightly lower use of standard HF medications in our study, included patients likely had HF. Patients were identified through the use of ICD-9 diagnostic codes, which have shown acceptable accuracy for the identification of HF patients.[34] In a meta-analysis of 11 studies, the pooled specificity for identifying HF based on diagnostic codes was high (96.8%; 95%CI = 96.8%–96.9%); while sensitivity was moderate (75.3%; 95%CI = 74.7%–75.9%).[34] This suggests that most individuals with diagnostic codes for HF truly have HF but some HF patients are not captured with this coding.

This study has several limitations worthy of discussion. First, we could not account for left ventricular ejection fraction or New York Heart Association Functional Classification in our analyses as these variables are not available in MarketScan claims data. However, patients were successfully matched based on the use of several standard HF medications. Similarly, HBA1c and measures of renal function (e.g., creatinine clearance values) are not available in this data set. We also could not evaluate signs of volume overload (e.g., edema) or depletion (e.g., hypotension, dehydration) in these patients. Moreover, we assessed loop diuretic use through prescription claims and were unable to definitively measure whether patients took these medications or capture medications purchased with cash (i.e., those not processed through insurance). Reasons for prescriptions with overlapping days' supply also cannot be determined using administrative data. Prescriptions with overlapping days' supply were treated as separate prescriptions in our analysis as much of the overlap likely resulted from patients filling prescriptions early and these patients would be expected to finish one prescription before starting the next. Patients could have also filled prescriptions at local pharmacy to bridge a period before a mail-order prescription was delivered; which would also likely lead to a patient finishing one prescription before starting the next. Alternatively, patients could have been started on a new dose and received a prescription for a new medication strength or been instructed to take two different strengths of a loop diuretic simultaneously. However, the latter would increase the complexity of patients' medication regimens and is generally avoided. It is also unclear how changes in SGLT2I dose impacted our results. These changes would only impact the SGLT2I group and not those receiving other oral anti-glycemic agents. Moreover, SGLT2I changes would likely be dose increases occurring after the index date and thus after the six month period where baseline data were obtained to match patients.[35–37] Therefore, we did not match on this variable. Lastly, patients receiving other oral anti-glycemic agents could have received TZDs; which are contraindicated in patients with NYHA class III and IV HF.[38,39] Nonetheless, these agents may be used in those without symptomatic HF and < 3% of patients in the study received TZDs.

5. Conclusion

In this analysis of 1500 patients with HF and T2D, less new loop diuretic use was observed with SGLT2Is compared to other oral anti-glycemic agents. However, among patients on loop diuretics at baseline, patterns of use after 12-months did not differ between cohorts. This could reflect a decrease in HF morbidity but not a pronounced increase in loop diuretic efficiency with SGLT2I use. The mechanism behind reductions in HF morbidity with SGLT2I therapy is not well understood.

Acknowledgements

None.

Funding

The project described was supported by the NIH National Center for Advancing Translational Sciences (NCATS) through Grant Number UL1 TR001450. Data analytic support for the study was provided through the CEDAR core funded by the MUSC Office of the Provost and by the South Carolina Clinical and Translational Research (SCTR) Institute, with an academic home at the Medical University of South Carolina, through NIH grant number UL1 RR029882.

Declaration of Competing Interest

The authors report no conflicts of interest.

Appendix A. Supplementary tables

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2019.05.001.

References

1. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 1974;34:29-34.
2. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.
3. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl JMed 2017;377:644-57.
4. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 380 2019:347-57.
5. Boehringer Ingelheim. EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced). Available from: https://www.dovepress.com/author_guidelines.php?content_id=2967
6. Roush GC, Kaur R, Ernst ME. Diuretics: a review and update. J Cardiovasc Pharmacol Ther 2014;19:5-13.
7. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-239.
8. Kimura G. Diuretic action of sodium-glucose cotransporter 2 inhibitors and its importance in the management of heart failure. Circ J 2016;80:2277-81.
9. American Diabetes Association. Summary of revisions: standards of medical care in diabetes – 2019. Diabetes Care 2019;42:S4-6.
10. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130-9.
11. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
12. Lasix [package insert]. *Bridgewater.* NJ: Sanofi-Avantis. 2011.
13. Bumex [package insert]. *Parsippany.* NJ: Validus Pharmaceuticals. 2008.
14. Demadex [package insert]. *Somerset.* NJ: Meda Pharmaceuticals. 2012.
15. Edecrin [package insert]. *Parsippany.* NJ: Edenbridge Pharmaceuticals. 2014.
16. Devore AD, Hasselblad V, Mentz RJ, et al. Loop diuretic dose adjustments after a hospitalization for heart failure: insights from ASCEND-HF. Eur J Heart Fail 2015;17:340-6.
17. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME trial. Eur Heart J 2016;37:1526-34.
18. Rådholm K, Figtree G, Perkovic V, et al. Canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS program (Canagliflozin Cardiovascular Assessment Study). Circulation 2018;138:458-68.
19. Kosiborod M, Cavender MA, Fu AZ, et al. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose Cotransporter-2 inhibitors). Circulation 2017;136:249-59.
20. Martens P, Mathieu C, Verbrugge FH. Promise of SGLT2 inhibitors in heart failure: diabetes and beyond. Curr Treat Options Cardiovasc Med 2017;19:23.
21. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes: cardiovascular and kidney effects, potential mechanisms and clinical applications. Circulation 2016;134:752-72.

22. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZI. Sodium glucose cotransporter-2 inhibition in heart failure: potential mechanisms, clinical applications, and summary of clinical trials. Circulation 2017;136:1643-58.
23. Phillips LS, Branch WT, Cook CB, et al. Clinical inertia. Ann Intern Med 2001;135: 825-34.
24. Basile J, Neutel J. Overcoming clinical inertia to achieve blood pressure goals: the role of fixed-dose combination therapy. Ther Adv Cardiovasc Dis 2010;4:119-27.
25. Okonofua EC, Simpson KN, Jesri A, Rehman SU, Durkalski VL, Egan BM. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. Hypertension 2006;47:345-51.
26. Ahmed A, Husain A, Love TE, et al. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. Eur Heart J 2006;27:1431-9.
27. Felker GM, O'connor CM, Braunwald E. Loop diuretics in acute decompensated heart failure: necessary? Evil? A necessary evil? Circ Heart Fail 2009;2:56-62.
28. Mielniczuk LM, Tsang SW, Desai AS, et al. The association between high-dose diuretics and clinical stability in ambulatory chronic heart failure patients. J Card Fail 2008;14:388-93.
29. Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). Circulation 1990;82:1724-9.
30. Sigurdsson A, Swedberg K. Neurohormonal activation and congestive heart failure: today's experience with ACE inhibitors and rationale for their use. Eur Heart J 1995;16:65-72.
31. Packer M. Beta-blockade in the management of chronic heart failure. Another step in the conceptual evolution of a neurohormonal model of the disease. Eur Heart J 1996;17:21-3.
32. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. Br Heart J 1987;57:17-22.
33. Mccormick N, Lacaille D, Bhole V, Avina-zubieta JA. Validity of heart failure diagnoses in administrative databases: a systematic review and meta-analysis. PLoS ONE 2014;9, e104519.
34. Fonarow GC, Yancy CW, Albert NM, et al. Heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. Circ Heart Fail 2008;1: 98-106.
35. Invokana [Package Insert]. *Titusville*. NJ: Janssen Pharmaceutical Companies. 2013.
36. Farxiga [Package Insert]. *Princeton*. NJ: Bristol-Myers Squibb. 2014.
37. Jardiance [Package Insert]. *Ridgefield*. CT: Boehringer Ingelheim Pharmaceuticals. 2016.
38. Avandia [Package Insert]. *Research Triangle Park*. North Carolina: GlaxoSmithKline. 2019.
39. Actos [Package Insert]. *Deerfield*. IL: Takeda. 2011.