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Real-world opportunity of empagliflozin to improve blood pressure control in African American patients with type 2 diabetes: A National Cardiovascular Data Registry "research-to-practice" project from the diabetes collaborative registry

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Abstract

The 1245.29 trial recently showed that empaglifozin improved both blood pressure and glucose control in African American (AA) patients with type 2 diabetes (T2D) and hypertension. Using the Diabetes Collaborative Registry (DCR), a large-scale US registry of outpatients with diabetes recruited from primary care, cardiology, and endocrinology practices, we sought to understand the potential impact of these observations in routine clinical practice. Among 74,290 AA patients with T2D from 368 US clinics, 60.4% had hypertension, of whom 34.5% had systolic blood pressure ≥140 mm/Hg (20.8% of the total AA T2D population). Only 1.7% of this eligible population had been prescribed an SGLT2 inhibitor. The mean estimated 5-year risk of cardiovascular death was 7.7%, which could be reduced to 6.2% when modelling the antihypertensive effect of empagliflozin across the eligible population (based on an 8-mmHg blood pressure reduction). These findings may represent a potential opportunity for better management of cardiovascular risk factors and improved outcomes in this vulnerable cohort.

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Keywords

hypertension; diabetes; cardiovascular disease

Empagliflozin selectively inhibits the sodium-glucose cotransporter 2 (SGLT2), resulting in glycosuria, natriuresis, and diuresis, along with a number of secondary vascular effects. In addition to reducing blood glucose, SGLT2 inhibitors also reduce blood pressure—an effect that has been consistently observed across studies[1, 2] and appears to be durable.[3] Although SGLT2 inhibitors likely impact cardiovascular risk through a number of mechanisms, the antihypertensive effect of SGLT2 inhibitors could, by itself, contribute to risk reduction. Clinical trials have shown that when systolic blood pressure is elevated, lowering it by ~10 mmHg reduces risk of myocardial infarction by 20–25%, stroke by 35–40%, heart failure by ~50%, and cardiovascular death by 20–25%.[4, 5]

African American (AA) patients with diabetes and hypertension could benefit from SGLT2 inhibitors, as they: 1) tend to have more salt-sensitive hypertension[6] and may be more responsive to the blood pressure effects of SGLT2 inhibitors; 2) have a greater prevalence of blood pressure not meeting therapeutic targets; and 3) have more cardiovascular complications of hypertension,[7] which could translate into greater absolute risk reductions. Unfortunately, AA patients were under-represented in the pivotal SGLT2 inhibitor trials.[2, 3, 8] As such, the 1245.29 trial was conducted in AA patients and found that treatment with empagliflozin for 24 weeks resulted in an 8-mmHg reduction in blood pressure and 0.8% reduction in HbA1c.[9] We used the Diabetes Collaborative Registry (DCR), a large outpatient registry of US patients with diabetes, to understand the generalizability of this trial to routine clinical practice and to estimate the potential reduction in cardiovascular risk in eligible patients.

METHODS

Patient Population.

DCR is a US quality improvement registry designed to describe the outpatient care of diabetes through the spectrum of primary and specialty care.[10] Patient data (including self-reported race) are extracted from electronic health records from 2014–2016 with the most recent visit used. Because registry participation requires no data collection beyond that of the routine clinical care and due to the de-identified nature of the collected information, waiver of written informed consent and authorization for this study was granted by Chesapeake Research Review Incorporated.

1245.29 Trial.

The 1245.29 trial randomized 154 AA patients with diabetes from 92 sites to empagliflozin or placebo for 24 weeks between 2014–2017.[9] Key inclusion criteria included age ≥18 years, self-described AA race, type 2 diabetes (T2D), HbA1c 7–11%, and systolic blood pressure 140–180 mmHg on 1 to 4 antihypertensive medications. For the present study, to mimic the 1245.29 trial eligibility criteria, we defined potentially eligible as age ≥18 years, AA race, T2D, and systolic blood pressure ≥140 mmHg on ≥1 antihypertensive medication.

We did not exclude patients based on HbA1c or for blood pressures that were too high, as these were felt not to be clinically relevant exclusions (as these patients are likely eligible for SGLT2 inhibitors in the real world).

Statistical Analysis.

We estimated the percentage of patients potentially eligible for the 1245.29 trial as the ratio of patients eligible to the total number of AA patients in DCR with T2D and available data elements to determine potential eligibility. We also compared the prevalence of hypertension not at target in AA patients who have T2D with those who are of White or other races. In order to understand possible cardiovascular implications of using empagliflozin in this potentially eligible cohort, we calculated the 5-year risk of cardiovascular mortality using a pooled analysis from 8 clinical trials of antihypertensive treatments, which included the following risk factors: age, sex, smoking, systolic blood pressure, total cholesterol, height, creatinine, history of myocardial infarction, history of stroke, diabetes, and left ventricular hypertrophy.[11] Given the observed average 8-mmHg reduction in systolic blood pressure in 1245.29,[9] we assumed a 20% relative reduction (RRR) in the risk cardiovascular death with empagliflozin—an assumption based on 3 large studies [4, 5, 12]: meta-analysis of 33 trials/107,647 patients: 20% RRR in cardiovascular death with a 9.1 mmHg blood pressure reduction; meta-analysis of 49 trials/73,738 patients with diabetes: 13% RRR in cardiovascular death with treatment of blood pressure 140–150 and 25% RRR with treatment of blood pressure >150; and an analysis (22,071 men from the Physicians' Health Study and 39,876 women from the Women's Health Study): 20% and 25% RRR in cardiovascular death with a 5- and 10-mmHg blood pressure reduction. Although these studies included but did not specifically evaluate treatment effects among AA patients, prior hypertension treatment trials showed no significant difference in cardiovascular risk reduction by race[13]. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina) and IVEWare (Institute for Social Research, University of Michigan).

RESULTS

Analytic Population.

There were 655,552 patients with T2D and documented race from 368 sites in DCR, of whom 600,483 had blood pressure recorded thereby allowing for determination of study eligibility. Among these patients, 74,290 (12.4%) were self-described AA race (507,780 [84.6%] White and 18,413 [3.1%] other race). Of the AA patients with T2D, 44,883 had medically-treated hypertension, of whom 15,475 (34.5%) had systolic blood pressure ≥140 mm/Hg (20.8% of the total AA population with T2D) and were considered potentially eligible for the 1245.29 trial. Within this potentially eligible group, mean systolic blood pressure was 157 ± 15 mmHg (≥160 mmHg in 10.1%), mean diastolic blood pressure was 84 ± 13 mmHg (≥100 mmHg in 2.5%); patients were on an average of 2.1 ± 1.1 antihypertensive medications, and 13.8% were on ≥4 medications. In contrast, among 240,149 White patients with hypertension, 62,120 (25.9%) had systolic blood pressure ≥140 mmHg (12.2% of the total White population with T2D) and 14,400 (6.0%) had systolic blood pressure ≥160 mmHg (Table 1). Similar rates of blood pressure not at target were

observed among the 7541 patients of other race (≥140 mmHg: 26.9% [11.0% of the total other race population with T2D]; ≥160 mmHg: 7.1%).

Mean age of the potentially eligible AA patients was 65.4 ± 12.1 years, 38.8% were men, 15.1% were current smokers, and mean body mass index was 34.6 ± 8.4 kg/m^2(Table 2). Mean HbA1c was 7.5 ± 1.9, 73.0% were on at least 1 glucose-lowering medication, and 26.8% were on insulin. Among patients potentially eligible for an SGLT2 inhibitor based on the 1245.29 Trial, 256 (1.7%) of patients were currently treated with an SGLT2 inhibitor (canagliflozin in 64.2%, dapagliflozin in 19.2%, and empagliflozin in 16.6%).

Cardiovascular Risk Reduction.

Among potentially eligible AA patients, the mean 5-year risk of cardiovascular death was estimated to be 7.7%. If all potentially eligible patients were treated with empagliflozin, this risk may decrease to 6.2% based on the model prediction (assuming a durable 8-mmHg reduction in blood pressure). This would translate to a number needed to treat of 65 AA patients with T2D and hypertension for 5 years to prevent 1 cardiovascular death.

DISCUSSION

In a recent trial of AA patients with T2D and hypertension not at target, empagliflozin effectively reduced both blood pressure and HbA1c. In the present analyses, we examined the potential generalizability of this trial in routine clinical care and its possible impact on patient outcomes. Compared with other races, AA patients had both a higher prevalence of hypertension and poorer blood pressure control; these patients may be candidates for an SGLT2 inhibitor not just from the standpoint of glycaemic control but also blood pressure lowering. Among potentially eligible patients, SGLT2 inhibitors were uncommonly prescribed, indicating a potential opportunity for additional cardiovascular risk reduction.

This study supports prior data showing a high burden of hypertension not at target in AA patients.[6] Although AA patients represent only 12% of patients with T2D in our cohort, they were 19% of patients with hypertension not at target and 23% of patients with systolic blood pressure ≥160 mmHg. The diagnosis of T2D can complicate the treatment of hypertension, as some commonly used medications worsen glycaemic control[14][15]. Furthermore, the number of medications that patients with T2D and hypertension (and their associated comorbidities) are prescribed can make it more difficult to get blood pressure and glucose controlled. In our cohort, 71% of patients were on ≤2 antihypertensives despite an average blood pressure of 158 mmHg. The blood pressure reduction with empagliflozin is similar to that typically achieved with other traditional antihypertensives[16] and therefore could be a metabolically beneficial supplement to AA patients with T2D. It is also important to note that AA patients with T2D have high rates of both obesity and heart failure, and SGLT2 inhibitors result in significant weight reduction (2.2 kg in 24 weeks in 1245.29 trial[9]) and lower risk of heart failure hospitalizations[2, 3], illustrating the potential multi-modal benefits of SGLT2 inhibitors in these patients. We modelled the estimated absolute risk reduction in cardiovascular death if AA patients with hypertension were treated with empagliflozin, but this estimation was based only on its impact on blood pressure, while SGLT2 inhibitors could impact outcomes via multiple mechanisms). While there are clearly

financial limitations to the widespread use of SGLT2 inhibitors, AA patients with T2D may represent an especially vulnerable group of patients who may benefit from their use.

Limitations.

First, we assumed a durable blood pressure effect with empagliflozin, which, if not maintained, would blunt the projected cardiovascular risk reduction. Furthermore, it is unclear whether the modelled reduction in cardiovascular death would be consistent across SGLT2 inhibitors. This is a particularly relevant question given numerically favourable but not statistically significant effect on cardiovascular death observed in the Canagliflozin Cardiovascular Assessment Study.[2] Second, as all included sites in DCR had electronic health records, our cohort had a low proportion of patients at low socioeconomic status. This translated into a lower proportion of AA patients compared with national data.[17] In addition, as DCR is a quality improvement registry, the rate of hypertension not at target is probably higher outside of DCR practices. Taken together, it is likely that an even higher proportion of AA patients with T2D in the general US population would be eligible for empagliflozin than our estimates. Finally, the cardiovascular death risk model available was based purely on blood pressure reduction and was not race-specific, and therefore we may have underestimated the true underlying risk of the analytic cohort (and therefore the potential absolute cardiovascular risk reduction).[7]

Conclusion.

AA patients with T2D have a high prevalence of hypertension that is not at target and may be candidates for empagliflozin (and other SGLT2 inhibitors, if a class effect) for lowering of blood pressure, in addition to glycaemia, which may translate into significant cardiovascular risk reduction. SGLT2 inhibitors are uncommonly used in this population, highlighting a potential opportunity for better management of cardiovascular risk factors and, possibly, improved outcomes in this cohort.

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Table 1.

Patients potentially-eligible for 1245.29

	n=15,475
Age (y)	65.4 ± 12.1
Male sex	38.8%
Body mass index (kg/m^2)	34.6 ± 8.4
HbA1c (%)	7.5 ± 1.9
On glucose-lowering medication	73.0%
On insulin	26.8%
Dyslipidaemia	76.8%
Coronary artery disease	47.1%
Heart failure	31.8%
Peripheral arterial disease	16.2%
Prior stroke	11.8%
Atrial fibrillation/flutter	13.4%
Chronic kidney disease	14.1%
Current smoker	15.1%
Systolic blood pressure (mmHg)	158±15
Diastolic blood pressure (mmHg)	84±13
Mean # of antihypertensive medications	2.1 ± 1.1
1 antihypertensive	34.0%
2 antihypertensives	37.0%
3 antihypertensives	15.2%
4+ antihypertensives	13.8%
Angiotensin converting enzyme-inhibitor	45.5%
Angiotensin II receptor blocker	38.9%
Calcium channel blocker	77.7%
Diuretic	56.4%
Beta blocker	73.5%

Table 2.

Prevalence of hypertension among DCR patients with T2D according to race

	AA Race n=74,290	White Race n=507,780	Other Race n=18,413	p-value
Medically-treated hypertension	44,883 (60.4%)	240,149 (47.3%)	7541 (41.0%)	<0.001
Systolic blood pressure ≥140 mmHg	15,475 (20.8%) (34.5% of patients with hypertension)	62,120 (12.2%) (25.9% of patients with hypertension)	2032 (11.0%) (26.9% of patients with hypertension)	<0.001
Systolic blood pressure ≥160 mmHg	4539 (6.1%) (10.1% of patients with hypertension)	14,400 (2.8%) (6.0% of patients with hypertension)	536 (2.9%) (7.1% of patients with hypertension)	<0.001

T2D, type 2 diabetes mellitus; AA, African American