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Title: Cardiometabolic Risk Factor Control in African American and White Caucasians initiating SGLT-2 Inhibitor: Real-world Study

Running Title: Ethnicity & Cardiometabolic Risk Factor Control with SGLT-2i

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ABSTRACT

Aims: To explore cardiometabolic risk profiles, probability of sustainable control, and the effectiveness of treatment with SGLT-2i in African American (AA) and White Caucasian (WC).

Materials and Methods: Using nationally representative US electronic medical records, 72,690 WC and 10,004 AA adults diagnosed with type 2 diabetes initiating SGLT-2i during 2013-2018, continuing it ≥6 months, and with follow-up ≥12 months, were identified. HbA1c, body weight, SBP, and lipid changes at 6-month and sustainability of control over 18 months post SGLT-2i initiation were explored, separately in those with and without atherosclerotic cardiovascular disease (ASCVD).

Results: WC were older (58 years) with lower mean HbA1c (8.5%), compared to AA (54 years, HbA1c 9.0%). BMI distribution was similar, proportions of uncontrolled SBP /LDL-C /non-HDL-C/ Triglyceride were 24/ 42 /51 /62% in WC and 31/ 51 /49 / 32% in AA.

At 6-month follow-up WC and AA had similar adjusted reduction in HbA1c (1.1%), SBP (8-10 mmHg), LDL-C (10-13 mg/dL) and body weight (1.1-1.4 kg). However, over 18 months follow-up, compared to WC, AA were significantly less likely to achieve a sustainable control in HbA1c (OR: 0.67; 95% CI: 0.63-0.72), body weight (OR: 0.81; 95% CI: 0.72-0.91), SBP (OR: 0.67; 95% CI: 0.61-0.74), LDL-C (OR: 0.77; 95% CI: 0.67-0.89). Triglyceride control was significantly better among AA. AA had significantly higher risk factor burden irrespective of ASCVD status.

Conclusions: While effectiveness of SGLT-2i was similar among AA and WC irrespective of ASCVD status, AA continued to have worse cardiometabolic risk factor burden post SGLT-2i initiation.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality globally, particularly in people with type 2 diabetes [1-3]. In the general US population, studies have reported persistent racial and ethnic differences in cardiovascular morbidity and mortality [4,5], with the higher prevalence of cardiometabolic risk factors reflecting the relatively earlier age of onset of cardiovascular diseases among African Americans (AA) compared to White Caucasians (WC) [6,7]. However, among people with diabetes, there is conflicting evidence about whether AA have an increased risk of cardiovascular disease [8,9]. A recent study by Bancks and colleagues (2019) reported that among people with diabetes, long-term cardiovascular risks were higher among AA compared to WC if non-cardiovascular death is not accounted for as a competing risk, while the risk difference disappears if competing mortality is accounted for [9].

International guidelines suggests proactive management of cardiometabolic risk factors in high-risk people with type 2 diabetes, with early initiation of novel anti-diabetic therapies like GLP-1RA and SGLT-2i, which are considered to be associated with extra-glycaemic benefits [10,11]. Also, the cardio-renal benefits of SGLT-2i are currently being investigated in non-diabetic patients [12,13]. Although clinical trials and observational studies have reported the benefits of treatment with SGLT-2i on cardiometabolic risk factor management in general [14-17], the evidence of the extra-glycaemic benefits of treatment with such therapy among AA with type 2 diabetes is scarce. In fact, most of the randomised clinical trials evaluating the cardiometabolic risk factor control and long-term cardiovascular / mortality risk among type 2

diabetes patients are primarily based on WC patients, with marginal representation of black or AA populations [18]. The meta-analysis of cardiovascular outcome trials evaluating GLP-1RA and SGLT-2i by Hoppe and colleagues (2017, [18]) and Mishriky and colleagues (2019, [19]) reported that less than 5% of the trial populations were AA, and only two of these trials collected race data consistent with FDA guidelines.

Underlying cardiometabolic differences between ethnicities may result in different outcomes of treatment. For example, a comparison of EMPA-REG and CANVAS trials suggests ethnic differences in the cardiovascular outcomes [20,21]. Asian and Caucasians had better cardiovascular benefits than Blacks in the EMPA-REG study, whereas canagliflozin was superior in Blacks and Caucasians as compared to Asian participants [22]. Also, a meta-analysis of 15 RCTs suggested that GLP-1RAs lower HbA1c more in Asian-dominant studies than in non-Asian-dominant studies [23]. International bodies have recommended the use of SGLT-2i in patients with type 2 diabetes and high ASCVD risk [17,23-26]. This necessitates a comprehensive population-level evaluation of cardiometabolic risk factor control in patients receiving SGLT-2i. While RCTs were not powered enough to assess ethnical differences [22], only a few US studies have reported real-world risk factor control with SGLT-2i [27], and separately in a small number of WC and AA patients [28]. We are not aware of any population-level study that holistically evaluated differences in cardiometabolic risk factor control or burden between WC and AA post initiation of SGLT-2i, with comprehensive assessment of patients with and without history of ASCVD.

Using a large representative US electronic medical records (EMR) system, the aims of this retrospective longitudinal cohort study were to examine adults with type 2 diabetes who were initiating a SGLT-2i and to compare WC with AA, in regard to: (1) the cardiometabolic risk factor distribution and therapeutic management; (2) the effect size of treatment with SGLT-2i on HbA1c, SBP, body weight and lipids; and (3) the probability of achieving sustainable control and individual risk factor burden over 18 months of follow-up.

MATERIALS AND METHODS

Data

The Centricity Electronic Medical Records (CEMR) incorporate patient-level data from independent physician practices, academic medical centres, hospitals and large integrated delivery networks in the USA. CEMR partners contribute de-identified patient-level data to enable quality improvement, benchmarking, and population-based medical research. The CEMR database covers over 40,000 health care providers from all USA states, where ~70% are primary care providers. The similarity of the general population characteristics and cardiometabolic risk factors in the CEMR database with those reported in the US national health surveys has been reported by this research group and others [29,30].

The database has been extensively used for academic research [29,31,32]. A robust methodology for extraction and assessment of longitudinal patient-level medication data from the CEMRs has been described by the authors [33]. A detailed account of anti-diabetic drug use in the US population, based on the Centricity EMR, has been also reported by the authors [34]. Longitudinal EMRs were available for more than 46 million individuals from 1995 until September 2018,

with comprehensive patient-level information on demographics, anthropometric measures, disease events, medications, and clinical and laboratory measures.

Study Design and Variables

The study cohort was identified with the following conditions: (1) data available on age and sex, (2) aged 18-80 at the time of type 2 diabetes diagnosis, (3) initiated SGLT-2i (index date, baseline), (4) available follow-up at least 1 year post index, (5) continued SGLT-2i for at least 6 months, and (6) availability of ethnicity identification on WC or AA. The clinically driven machine learning based algorithms to identify patients with type 2 diabetes from EMRs have been described by this research group and others [35,36].

Ethnicity in CEMRs is coded according to the US Census Bureau categorization [37]. HbA1c measures at baseline, 6, 12, 18, and 24 months of follow-up were obtained as the nearest measure within 3 months either side of the time point. Baseline and longitudinal body weight, SBP, and lipids were calculated as the average of available measures within 3 months either side of the time point. With the condition of at least two non-missing follow-up data over 24 months and complete data at baseline, the missing HbA1c and CV risk factor data were imputed using multiple imputation methods adjusting for age, sex and diabetes duration [38]. Percent of non-missing observations for HbA1c /SBP /Weight /Total cholesterol were 60 /94 /95 /49 and 64 /95 /96 /57 prior and post imputation respectively.

A disease was considered as prevalent if its first available diagnostic date was on or prior to the index date. Atherosclerotic cardiovascular disease (ASCVD) was defined by presence of a clinical diagnosis for ischaemic heart disease (myocardial infarction, unstable angina or coronary revascularization, excluding stable angina) or cerebrovascular disease (ischaemic/haemorrhagic stroke, transient ischaemic attack or carotid revascularisation) or peripheral vascular disease. Microvascular disease was defined by a clinical diagnosis of neuropathy, retinopathy, or chronic kidney disease (CKD). CKD definition included diagnostic codes (CKD stages 1-5, end stage renal disease, dialysis, transplant, nephropathy, proteinuria, albuminuria, nephrotic syndrome, and nephritis; excluding non-acute events and pyelonephritis) or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 or urine albumin-creatinine ratio (UACR) > 300 mg/g. Cancer was defined as any malignant neoplasm excludingmalignant neoplasm of skin.

Antihypertensive drugs included all FDA approved diuretics, peripheral vasodilators, beta blockers, calcium channel blockers, and agents acting on renin-angiotensin system. Lipid-lowering drugs included statins, bile acid sequestrants, fibrates, nicotinic acid, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and potent (≥1g) forms of omega-3/fish/krill oil. Antidiabetic drugs (ADDs), other than SGLT-2i, were grouped into 8 groups: metformin, sulfonylurea, thiazolidinedione, DPP-4 inhibitor, GLP-1 receptor agonist (GLP-1RA), alpha glucosidase inhibitor, insulin, and others.

Cardiometabolic Risk Factor Control

For patients with baseline HbA1c 7.5-8.5%, improved control was defined as a reduction of HbA1c below 7.5% at 6-, 12-, or 18-months of follow-up. For those with baseline HbA1c > 8.5% improved control was defined as at least 1% reduction. SBP < 130 / 140 mmHg for those with / without history of ASCVD at baseline was defined as controlled. Similarly, LDL-C < 70/ 100 mg/dL and Non-HDL-C < 100/ 130 mg/dL for those with/ without ASCVD history at baseline were defined as controlled. Triglycerides < 150 mg/dL were defined as controlled. Body weight control was defined in two ways: (1) at least 3kg reduction from baseline body weight, and (2) at least 5% of baseline body weight reduction. Sustainable control for cardiometabolic risk factors was defined as: *control at 6 months AND controlled over 12 OR 18 months of follow-up.*

Statistical Methods

Baseline characteristics were summarised separately for AA and WC as number (%), mean (SD) or median (first quartile, third quartile) as appropriate. Among patients with baseline HbA1c ≥ 7.5% (separately for 7.5-8.5% and >8.5%), the probability (95% CI) of sustainable glycaemic control was estimated using inverse probability weighted Propensity Score approach, adjusting for age, sex, baseline HbA1c, SGLT2-i therapy duration (generalized linear model with probit link function– assuming standard normal distribution), and balancing ethnicity groups by quartiles of time to SGLT-2i initiation from first-line ADD, number of non-insulin ADDs during 18 months of follow-up, use of insulin during 18 months of follow-up, history of microvascular diseases and ASCVD. Odds (95% CI) of sustainable glycaemic control were estimated using logistic regression modelling approach, adjusting and balancing

as described above. Sensitivity analyses were performed among patients who were not exposed to insulin during follow-up and among those who continued SGLT-2i for at least 12 months.

Among patients who were on anti-hypertensive therapy (AHT) at baseline and had uncontrolled baseline SBP (≥ 130 / 140 mmHg for those with / without history of ASCVD), the probability of sustainable control was estimated using inverse probability weighted Propensity Score approach adjusting for age, sex, baseline SBP, SGLT2-i therapy duration (probit model), and balancing ethnicity groups by history of microvascular disease and ASCVD at baseline. Odds (95% CI) of sustainable SBP control were estimated using logistic regression modelling approach adjusting and balancing as above. Sensitivity analyses were performed among those who were uncontrolled and not on AHT during 18 months of follow-up, and among those who were exposed / not exposed to an AHT during follow-up irrespective of baseline control.

Among patients who were on a lipid-lowering therapy (LLT) at baseline and had uncontrolled baseline LDL-C (≥ 70 / 100 mg/dL for those with / without history of ASCVD) / Non-HDL-C (≥ 100 / 130 mg/dL for those with / without history of ASCVD) / Triglycerides (≥ 150 mg/dL), probability of sustainable control was estimated using inverse probability weighted Propensity Score approach adjusting for age, sex, baseline LDL-C / Non-HDL-C / Triglycerides, SGLT2-i therapy duration (probit model), and balancing ethnicity groups by history of microvascular disease and ASCVD at baseline. Odds (95% CI) of sustainable lipid control were estimated using logistic regression modelling approach adjusting and balancing as described above. Sensitivity analyses were performed among those who were uncontrolled

and not on LLT during 18 months of follow-up, and among those who were exposed / not exposed to a LLT during follow-up irrespective of baseline control.

Probability and odds were estimated in the overall study cohort and separately by ASCVD status at baseline for HbA1c, SBP and lipid analyses.

Among those who were exposed to SGLT-2i for at least 12 months, probability (95% CI) of sustainable weight control was calculated by baseline obesity status [Overweight (25-30 kg/m^2), Grade 1 Obesity (30-35 kg/m^2) and Grade 2+ Obesity ($\geq$35 kg/m^2)] using inverse probability weighted Propensity Score approach adjusting for age, sex, baseline weight, SGLT2-i therapy duration (probit model), and balancing ethnicity groups by microvascular disease and ASCVD history. Odds (95% CI) of sustainable weight control were estimated using logistic regression modelling approach adjusting and balancing as described above. Probability and odds were estimated in the overall study cohort and among those who were not exposed to insulin or GLP-1RA during 18 months of follow-up.

RESULTS

Baseline Characteristics

From 3,333,685 patients with type 2 diabetes, 72,690 WC and 10,004 AA patients met inclusion criteria with 2.4 and 2.3 years of median follow-up respectively, and 80% (n=57,896) in WC and 79% (n=7,883) in AA had at least 18 months of follow-up respectively (Supplementary Figure 1, Table 1). WC were older (58 years) and more likely to be male (55%) compared to AA (54 years, 39% male). While the BMI distribution was similar in WC and AA, AA had higher baseline HbA1c (mean: 9.0%; HbA1c > 8.5%: 52%), compared to WC (mean:

8.5%; HbA1c > 8.5%: 41%). HbA1c distribution was similar irrespective of ASCVD status at baseline.

While the proportions with on AHT in AA and WC were 89% and 87% respectively, the proportions with a history of ASCVD and uncontrolled SBP at SGLT-2i initiation was significantly different ($p<0.05$): AA (15 and 31%) compared to WC (21 and 24%). The proportions on LLT at baseline among AA and WC were 72% and 81% respectively, while AA had higher mean LDL-C (100 mg/dL) compared to WC (90 mg/dL). In AA / WC, the proportions with uncontrolled LDL-C and non-HDL-C were 51% / 42% and 49% / 51% respectively. The proportions with CKD among the AA / WC were 25% / 25%, and proportions with microvascular disease were 44% / 43%.

Anti-diabetic and Cardioprotective Therapy Exposure Patterns

A detailed account of exposure to ADDs, AHTs and LLTs prior to SGLT-2i initiation and during follow-up is presented in Table 2. With similar median number of ADDs (median = 3) on or prior to SGLT-2i initiation, 80% were on at least 2 ADDs before initiating SGLT-2i in both ethnic groups. The median (Q1, Q3) months to initiating SGLT-2i from the first known ADD initiation was similar in AA [34 (5, 71) months] and WC [36 (6, 75) months]. The proportions of AA / WC receiving GLP-1RA or insulin prior to SGLT-2i initiations were 23% / 28% and 39% / 37% respectively. The proportions of AA /WC exposed to GLP-1RA for at least 90 days during 18 months of follow-up were 24 /27% ($p=0.09$). Among AA / WC on

insulin at SGLT-2i initiation, 92% / 94% continued insulin over 6 months and 90% / 93% continued it over 12 months of follow-up.

With similar median (Q1, Q3) duration of SGLT-2i therapy in AA [1.7 (1.2, 2.6) years] and WC [1.9 (1.2, 2.8) years], 86% (n=8,642) and 88% (n=64,240), respectively, continued SGLT-2i for at least another 6 months beyond the initial 6 months required by inclusion criteria. In the study cohort 57% / 24% / 19% initiated therapy with canagliflozin / dapagliflozin / empagliflozin respectively. Among AA / WC, 36% / 30% discontinued SGLT-2i during follow-up with a median (Q1, Q3) of 17 (11, 26) months to discontinuation, similar in both ethnic groups. The median number of other than SGLT-2i ADDs with at least 90 days exposure during 18 months post SGLT-2i initiation was 2. Among AA / WC 41% / 39% and 24% / 27% were exposed to insulin and GLP-1RA for at least 90 days during 18 months of follow-up respectively. The proportions of patients receiving AHT and LLT during follow-up among the AA / WC were 90% / 87% and 75% / 83% respectively (Table 2).

Risk Factor Control

HbA1c: Among 3,463/ 18,714 patients with baseline HbA1c >8.5%, the mean baseline HbA1c (95% CI) was 10.5 (10.5, 10.6) / 10.0 (10.0, 10.1) in the AA / WC respectively (Figure 1B), and the mean (95% CI) adjusted reduction in HbA1c at 6 months was similar in both ethnic groups: 1.6 (1.5, 1.6) %. Among 1,782/ 14,474 patients with baseline HbA1c ranging between 7.5 and 8.5%, the mean baseline HbA1c was similar in AA and WC (8.0%) and the mean (95% CI) adjusted reduction in AA / WC was 0.2 (0.1, 0.3)% / 0.4 (0.3, 0.5)%.

Body Weight: Among those with Grade 1 obesity at baseline, the mean (95% CI) baseline body weight was 95 (94, 95) kg / 97 (97, 97) kg among AA / WC, and 22% (95% CI: 21, 24%) / 26% (25, 26%) reduced weight by at least 3 kg at 6 months with a mean (95% CI) weight reduction of 1.1 (1.0, 1.3) kg 1.4 (1.4, 1.5) kg. The proportions of Grade 1 Obese AA /WC who achieved at least 5% body weight reduction were 10 /12% (p=0.07).

Systolic Blood Pressure: Among 2,878 / 15,606 AA / WC who had uncontrolled SBP at baseline and were on AHT, the adjusted mean (95% CI) SBP reduction at 6 months was similar in AA and WC: 8 (8, 9) / 10 (9, 10) mmHg (Figure 1E). For those without history of ASCVD the reductions was 10 (9, 10) / 11 (11, 12) mmHg (Supplementary Figure 2).

Lipid Control: Details on changes in LDL-C, non-HDL-C and triglyceride are presented in Figure 1, Supplementary Table 1, and Supplementary Figure 2. The average change in LDL-C and non-HDL-C at 6 months were similar in the two ethnic groups. Those without a history of ASCVD achieved significantly better lipid control compared to those with ASCVD in both ethnic groups. AA achieved significantly higher median reduction in triglyceride (31 mg/dL) compared to WC (26 mg/dL, Figure 1G, $p<0.05$). The proportion (95% CI) of AA / WC who achieve triglyceride control at 6 months were 27 (25, 29)% / 16 (16, 16)% [$p<0.01$].

Sustainability of Control and Risk Factor Burden

HbA1c: While WC had significantly lower unadjusted HbA1c over 24 months post SGLT-2i compared to AA across baseline HbA1c categories (Figure 1 A and B), both ethnic groups had clinically high HbA1c risk burden post SGLT-2i initiation. Among those with baseline HbA1c

>8.5%, the probability (95% CI) of reducing HbA1c by at least 1% at 6 months and sustaining it over 12 or 18 months was significantly lower for AA [52 (51, 54)%] compared to WC [60 (59, 61)%] (Figure 2, Supplementary Table 1, p<0.01). Among all those with HbA1c ≥ 7.5%, the adjusted probability (95% CI) of achieving control (HbA1c <7.5% or ≥1% reduction for those with baseline HbA1c 7.5-8.4 or ≥8.5%) at 6 months and sustaining it over 12 or 18 months was significantly lower among AA [44 (43, 46)%] compared to WC [52 (52, 53)%] (p<0.01; Supplementary Table 1, Figure 2), and AA were 33% [OR (95% CI): 0.67 (0.63, 0.72)] significantly less likely to achieve a sustainable HbA1c control compared to WC (p<0.01). The probability (95% CI) of achieving sustainable glycaemic control among those who were not exposed to insulin was higher among WC [58 (57, 59)%] compared to AA [49 (47, 51)%].

Body Weight: Among people with grade 1 obesity, the adjusted probability of reducing body weight by at least 3 kg and sustaining it over 12 or 18 months were 18 (16, 19)% and 21 (20, 22)% among AA and WC respectively (Supplementary Table 2). Compared to WC, AA were 19% [OR (95% CI): 0.81 (0.72, 0.91)] less likely to achieve this weight control (p<0.01). Among those without exposure to insulin or GLP-1RA therapy during follow-up, these probability estimates were similar. Among those with Grade 2+ obesity, the WC had 4% higher probability of achieving a sustainable 3 kg weight reduction compared to AA (p<0.001, Supplementary Table 2). The adjusted probability of achieving a sustainable 5% body weight reduction ranged between only 9 and 12% in the cohort of Grade 2+ obese patients.

Blood Pressure: AA had a lower adjusted probability (95% CI) of achieving sustainable SBP control [33 (31, 35)%] compared to WC [43 (42, 44)%; Figure 2; Supplementary Table 1). Similar trends were observed separately in patients with and without history of ASCVD (Supplementary Table 1, Figure 2). Overall, AA were 33% [OR (95% CI): 0.67 (0.61, 0.74)] less likely to achieve a sustainable SBP control.

Irrespective of baseline control, among those who were on AHT during follow-up, AA had consistently higher SBP compared to WC, while among those who were not on AHT during follow-up (13% of the study cohort) AA and WC had similar and well-controlled SBP. Among 100 / 1,010 AA / WC patients who were uncontrolled at baseline and were not exposed to AHT during follow-up, a similar mean (95% CI) of 11 (9, 13) mmHg reduction at 6 months and similar probability (95% CI) of sustainable SBP control for AA [57 (47, 68)%] and WC [58 (55, 61)%] was observed.

Lipids: AA had a lower adjusted probability (95% CI) of achieving sustainable LDL-C control [15 (13, 16)%] compared to WC [20 (19, 20)%]. Irrespective of baseline control, among those who were on LLT during follow-up, AA had consistently higher LDL-C compared to WC, while among those who were not receiving LLT during follow-up (18% of the study cohort) AA had marginally higher LDL-C with a similar probability of sustainable control compared to WC. Among those treated with LLT, both ethnic groups had similar probability (95% CI) of sustainable Non-HDL-C control achievements [18 (16, 20)%; (Supplementary Table 1)].

Triglyceride: AA had consistently better triglyceride control and higher probability (95% CI) of sustainable control [18 (17, 20)%] compared to WC [11 (11, 12)%; (Supplementary Table 1, Figure 2)]. Irrespective of baseline control, those who were on a LLT (82% of cohort), triglycerides were better maintained in AA throughout the follow-up with probability (95% CI) of sustainable triglyceride control of 47 (45, 48)% among AA compared to 38 (38, 38)% among WC [$p<0.01$]. Among 361 / 3,356 AA / WC patients who were uncontrolled at baseline and were not exposed to a LLT, the probability (95% CI) of sustainable triglyceride control was better for AA compared to WC: 19 (15, 23)% vs 13 (12, 14) %.

DISCUSSION

The novelties of this real-world US EMR based pharmaco-epidemiological study include a comprehensive evaluation of the cardiometabolic risk factor control over 18 months post SGLT-2i initiation in more than 82,600 White Caucasians and African Americans. Separate assessment of risk factor control in primary and secondary care populations in conjunction with extensive exploration of exposure to anti-diabetic and cardio-protective therapies ensure robustness in our findings. Given the lack of representation of African Americans in the clinical trials and the paucity of population-level data on the holistic management of cardiometabolic risk factors in patients with type 2 diabetes in different ethnic groups, this study addresses the evidence gap on the possible differences in the effectiveness of novel SGLT-2i on cardiovascular risk factor management by ethnic groups. The effectiveness of SGLT-2i on risk factors was similar for both ethnicities at 6-month of treatment with SGLT-2i, the high risk factor burden continued to remain high in both groups, while the African Americans were

significantly less likely to achieve sustainable risk factor control over 18 month compared to the White Caucasians.

The age and sex distribution, proportion with histories of peripheral vascular disease, micro-vascular diseases, CKD, and the proportions on anti-hypertensive therapies at SGLT-2i initiation in this study are similar to the US Truven MarketScan Data and the overall international population at the time of SGLT-2i initiation reported in the CVD-REAL study [39]. The distributions of HbA1c, BMI and SBP in this study were also similar to those reported in a study based on 1,259 US patients treated with canagliflozin [28].

While the overall adjusted mean reduction in HbA1c at 6 months among those with HbA1c > 7.5% at baseline was similar in both ethnic groups (1.1%), both ethnic groups had a mean HbA1c above 8.0% over the 24 months post SGLT-2i initiation (similar for people with and without ASCVD). However, AA had a significantly higher HbA1c (on average above 8.5%, Figure 1, Supplementary Figure 2) with 33% less likelihood of achieving a sustainable glycaemic control compared to WC. The overall baseline adjusted HbA1c reduction at 6 months (1.1%) is similar to HbA1c control reported in the meta-analysis of 38 clinical trials [40], the recent clinical trial on 150 AA receiving empagliflozin [41], the US EMR based study on 886 WC and 155 AA [28], but lower than the average HbA1c reduction of 2.48% reported in the systematic review reported by Mazidi and colleagues [17]. However, our 6-month analysis is

based on on-therapy patients, not an intention-to-treat analysis, and hence cannot be generalised in a real-world scenario.

In terms of weight change, only a quarter of the obese patients are likely to reduce body weight by at least 3 kg at 6 months and sustain it over 12 or 18 months of follow-up. The observed weight reduction at 6 months among AA is similar to that reported in a recent clinical trial [41], and there is an indication of marginal reduction in body weight over 24 months, although much lower weight reduction compared to that reported in reported in clinical trials [42]. We assessed body weight changes in the overall cohort and in those who were not exposed to insulin or GLP-1RA during the follow-up and observed no change in the estimates. It is possible that in the main cohort, the effects of insulin and GLP-1RA balanced each other out, but a dedicated study would be needed to explore this[43]. While no study to the best of our knowledge evaluated the sustainability of weight reduction in people treated with SGLT-2i under different adiposity levels, our study provides a holistic assessment of weight reduction in people in different BMI categories, with appropriate considerations on exposure to other therapies and confounders.

One of the unique aspects of our study is the comprehensive assessment of blood pressure and lipid control in patients with and without existing ASCVD, while evaluating the control separately in patients with and without exposure to AHTs or LLTs. Among those treated with AHTs and who had high SBP at baseline, the average SBP reduction at 6 months of SGLT-2i therapy initiation was similar in both ethnic groups, but those with ASCVD experienced a 4 mmHg significantly less reduction in SBP compared to those without ASCVD. Among the

relatively small number of patients with high SBP but not treated with any AHT, a clinically significant SBP reduction was also observed. Similar patterns were also observed in LDL-C and non-HDL-C control in primary and secondary care patients. Irrespective of baseline control, AA had consistently higher SBP and LDL-C over 24 months of follow-up compared to WC, while the patients were consistently above clinically acceptable limits of LDL-C in both ethnic groups. Although the AA had only a 18% probability of a sustainable triglyceride control, it was significantly higher than the 11% probability of sustainable control among WC.

The similarity of the general population characteristics and cardiometabolic risk factors in the CEMR database has been shown to be similar to those reported in the US national health surveys by this research group and others [29,30]. While the lack of reliable information on medication adherence is a common problem in all clinical studies, detailed validation studies of US EMRs suggest a high level of agreement between EMR prescription data and the pharmacy claims data, especially in medications for chronic diseases [44]. Other limitations include unavoidable indication bias and residual confounding that remains as a common problem in any EMR based outcome studies, and lack of data on socioeconomic characteristics, diet, physical activity, hypoglycaemic episodes, the nature of insurance, education, income, stress, and other cultural drivers. The weight changes should be interpreted in the light of possible hidden bias due to use of other medications that have weight lowering or increasing properties (certain classes of antipsychotic, epilepsy, or steroid hormone medicines). While 56 / 57% of AA / WC initiated SGLT-2i therapy with canagliflozin, the subclass differences were not explored in this study. Finally, the other pharmacologic effects and potential mechanisms

of treatment of SGLT-2i that benefit cardiovascular and renal health are beyond the scope of this study.

While by design only those who continued the SGLT-2i therapy for at least 6 months were evaluated, raising potential bias in this study, a thorough exploration of those who discontinued the therapy before 6 months reveals similar discontinuation rates and similar baseline characteristics (details in Supplementary Note 1, and the Supplementary Table 3). Although unmeasured confounders including drug dosing and adherence is a common problem in pharmaco-epidemiological studies, use of large nationally representative EMRs appears to be best available resource to explore the risk factor dynamics and therapeutic effectiveness with reasonable robustness. Adjusting and balancing for baseline characteristics and other relevant confounders, we reported probability of sustainable risk factor control using inverse-probability weighted regression modelling approach. Albeit imperfect, this approach has been shown to be more robust compared to the standard propensity-score matching methodology.

In this study we have observed similar reductions in cardio-metabolic risk factors between AA and WC, however AA have significantly lower adjusted probability of achieving a sustainable cardiometabolic risk factor control compared to the WC. Although AA initiated SGLT-2i four years earlier than WC and had lower prevalence of ASCVD, the cardio-metabolic burden was higher in both primary and secondary prevention setups and remained so after 18 months. It should be noted that such difference might be explained by overall metabolic and socio-

economic differences between ethnicities, but also, the role of therapeutic inertia must be recognised here as well.

Conclusions

Although treatment with ADDs, AHTs and LLTs led to a significant improvement in cardiometabolic risk factors within 6 months of SGLT-2i initiation, we have observed significantly high persistent risk factor burden in terms of HbA1c, blood pressure and lipids across ethnicities. This risk factor burden appears to be at higher level among people with established ASCVD, compared to the primary prevention patients. We observed that SGLT-2i is similarly effective in both ethnicities, however AA have significantly lower adjusted probability of achieving a sustainable cardiometabolic risk factor control compared to the WC, leading to significantly higher cardiometabolic risk factor burden in both primary and secondary prevention setup. Overall, AA have worse CV profile before SGLT-2i initiation and remain so after 18 months of treatment.

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SKP and OM conceptualized and designed the study. OM conducted the data extraction. OM and SKP jointly conducted the statistical analyses. The first draft of the manuscript was developed by OM and SKP, while SV and JHS contributed in the interpretation of results and finalisation of the manuscript. SKP and OM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Declaration of interests

SKP has acted as a consultant and/or speaker for Novartis, GI Dynamics, Roche, AstraZeneca, Guangzhou Zhongyi Pharmaceutical and Amylin Pharmaceuticals LLC. He has received grants in support of investigator and investigator initiated clinical studies from Merck, Novo Nordisk, AstraZeneca, Hospira, Amylin Pharmaceuticals, Sanofi-Avensis and Pfizer. OM has no conflict of interest to declare. SV has received honoraria and/or research support from Amgen, AstraZeneca, Boehringer-Ingelheim, Lilly, Janssen, Merck, HLS, Amarin, Sanofi and Novartis. JHS received funding for consultancy and lectures from AstraZeneca, Merck Sharp & Dohme, Mylan, Abbott, Sanofi, Eli Lilly, Boehringer Ingelheim and Mylan.

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Table 1: Baseline characteristics of the study cohort at SGLT-2i initiation.

	statistics	White Caucasian (N= 72,690)	African American (N= 10,004)	Total (N= 82,694)
Prior to SGLT-2i initiation				
ASCVD	N (%)	15,283 (21)	1,452 (15)	16,735 (20)
Heart Failure, Myocardial Infarction or Stroke	N (%)	4,745 (7)	617 (6)	5,362 (6)
Peripheral artery / vascular disease	N (%)	4,211 (6)	506 (5)	4,717 (6)
Microvascular disease	N (%)	31,341 (43)	4,391 (44)	35,732 (43)
Chronic kidney disease	N (%)	18,281 (25)	2,549 (25)	20,830 (25)
Cancer	N (%)	4,242 (6)	535 (5)	4,777 (6)
Antihypertensive therapy	N (%)	63,014 (87)	8,898 (89)	71,912 (87)
Lipid lowering therapy	N (%)	59,214 (81)	7,238 (72)	66,452 (80)
At SGLT-2i initiation				
Male	N (%)	40,210 (55)	3,905 (39)	44,115 (53)
Age, years	Mean (SD)	58 (10)	54 (11)	57 (11)
Age 18-39 years	N (%)	3,646 (5)	888 (9)	4,534 (5)
Age 40-49 years	N (%)	11,641 (16)	2,253 (23)	13,894 (17)
Age 50-59 years	N (%)	24,402 (34)	3,554 (36)	27,956 (34)
Age 60-69 years	N (%)	23,731 (33)	2,642 (26)	26,373 (32)
Age 70+ years	N (%)	9,270 (13)	667 (7)	9,937 (12)
Weight, non-missing	N (%)	69,886 (96)	9,751 (98)	79,637 (96)
Weight, kg	Mean (SD)	104.1 (23.9)	103.4 (24.4)	104.1 (23.9)
BMI, non-missing	N (%)	69,010 (95)	9,616 (96)	78,626 (95)
BMI, kg/m2	Mean (SD)	35.6 (7.4)	36.1 (7.9)	35.7 (7.5)
BMI 25-30 kg/m2	n (% from non-missing)	12,863 (19)	1,797 (19)	14,660 (19)
BMI 30-35 kg/m2	n (% from non-missing)	20,990 (30)	2,774 (29)	23,764 (30)
BMI ≥ 35 kg/m2	n (% from non-missing)	32,605 (47)	4,677 (49)	37,282 (47)
HbA1c, non-missing	N (%)	45,820 (63)	6,747 (67)	52,567 (64)
HbA1c, %	Mean (SD)	8.5 (1.6)	9.0 (2.0)	8.6 (1.7)
HbA1c 7.5-8.5%	n (% from non-missing)	14,474 (31)	1,782 (26)	16,256 (31)
HbA1c > 8.5%	n (% from non-missing)	18,714 (41)	3,463 (52)	22,177 (42)
With ASCVD history				
--- HbA1c, %	Mean (SD)	8.5 (1.6)	8.9 (1.9)	8.5 (1.6)
--- HbA1c 7.5-8.5	n (% from non-missing)	3,066 (34)	283 (30)	3,349 (33)

--- HbA1c >8.5	n (% from non-missing)	3,637 (40)	468 (49)	4,105 (41)
eGFR, non-missing	N (%)	49,635 (68.3)	7,181 (71.8)	56,816 (68.7)
eGFR, mL/min/1.73m2	Mean (SD)	88.9 (24.6)	90.0 (25.6)	89.0 (24.7)
SBP, non-missing	N (%)	69,245 (95)	9,691 (97)	78,936 (96)
SBP, mmHg	Mean (SD)	128.6 (13.6)	131.9 (14.9)	129.0 (13.8)
SBP ≥ 140 mm/Hg	n (% from non-missing)	13,159 (19)	2,613 (27)	15,772 (20)
SBP ≥ 130 mm/Hg	n (% from non-missing)	30,572 (44)	5,080 (52)	35,652 (45)
SBP uncontrolled†	n (% from non-missing)	16,782 (24)	3,008 (31)	19,790 (25)
--- Not on antihypertensive drug during 18M of follow-up	n (% from uncontrolled)	857 (5)	78 (3)	936 (5)
LDL-C, non-missing	N (%)	36,492 (50)	5,075 (51)	41,567 (50)
LDL-C, mg/dL	Mean (SD)	90.2 (35.2)	100.1 (38.6)	91.4 (35.8)
LDL-C ≥ 100 mg/dL	n (% from non-missing)	12,535 (34)	2,349 (46)	14,884 (36)
LDL-C ≥ 70 mg/dL	n (% from non-missing)	25,743 (71)	4,062 (80)	29,805 (72)
LDL-C uncontrolled†	n (% from non-missing)	15,334 (42)	2,611 (51)	17,945 (43)
--- Not on lipid-lowering during 18M of follow-up	n (% from uncontrolled)	1,821 (12)	376 (14)	2,197 (12)
HDL-C, non-missing	N (%)	34,561 (48)	4,977 (50)	39,538 (48)
HDL-C, mg/dL	Mean (SD)	41.8 (11.4)	48.0 (13.5)	42.6 (11.9)
Triglycerides, non-missing	N (%)	44,286 (61)	6,321 (63)	50,607 (61)
Triglycerides, mg/dL	Median (IQR)	174.0 (124.0 254.0)	118.0 (85.0 169.5)	167.0 (117.0 245.0)
Triglycerides ≥ 150 mg/dL	n (% from non-missing)	27,259 (62)	2,049 (32)	29,308 (58)
Non-HDL-C, non-missing	N (%)	39,651 (55)	5,650 (56)	45,301 (55)
Non-HDL-C, mg/dL	Mean (SD)	130.4 (44.7)	129.8 (43.6)	130.3 (44.5)
Non-HDL-C ≥ 130 mg/dL	n (% from non-missing)	17,385 (44)	2,496 (44)	19,881 (44)
Non-HDL-C ≥100 mg/dL	n (% from non-missing)	29,783 (75)	4,237 (75)	34,020 (75)
Non-HDL-C uncontrolled†	n (% from non-missing)	20,064 (51)	2,749 (49)	22,813 (50)
Post SGLT-2i initiation				
Follow-up, years	Median (IQR)	2.4 (1.6, 3.4)	2.3 (1.6, 3.3)	2.4 (1.6, 3.4)
At least 18 months of follow-up	N (%)	57,896 (80)	7,883 (79)	65,779 (80)

At least 12 months SGLT-2i duration	N (%)	64,240 (88)	8,642 (86)	72,882 (88)

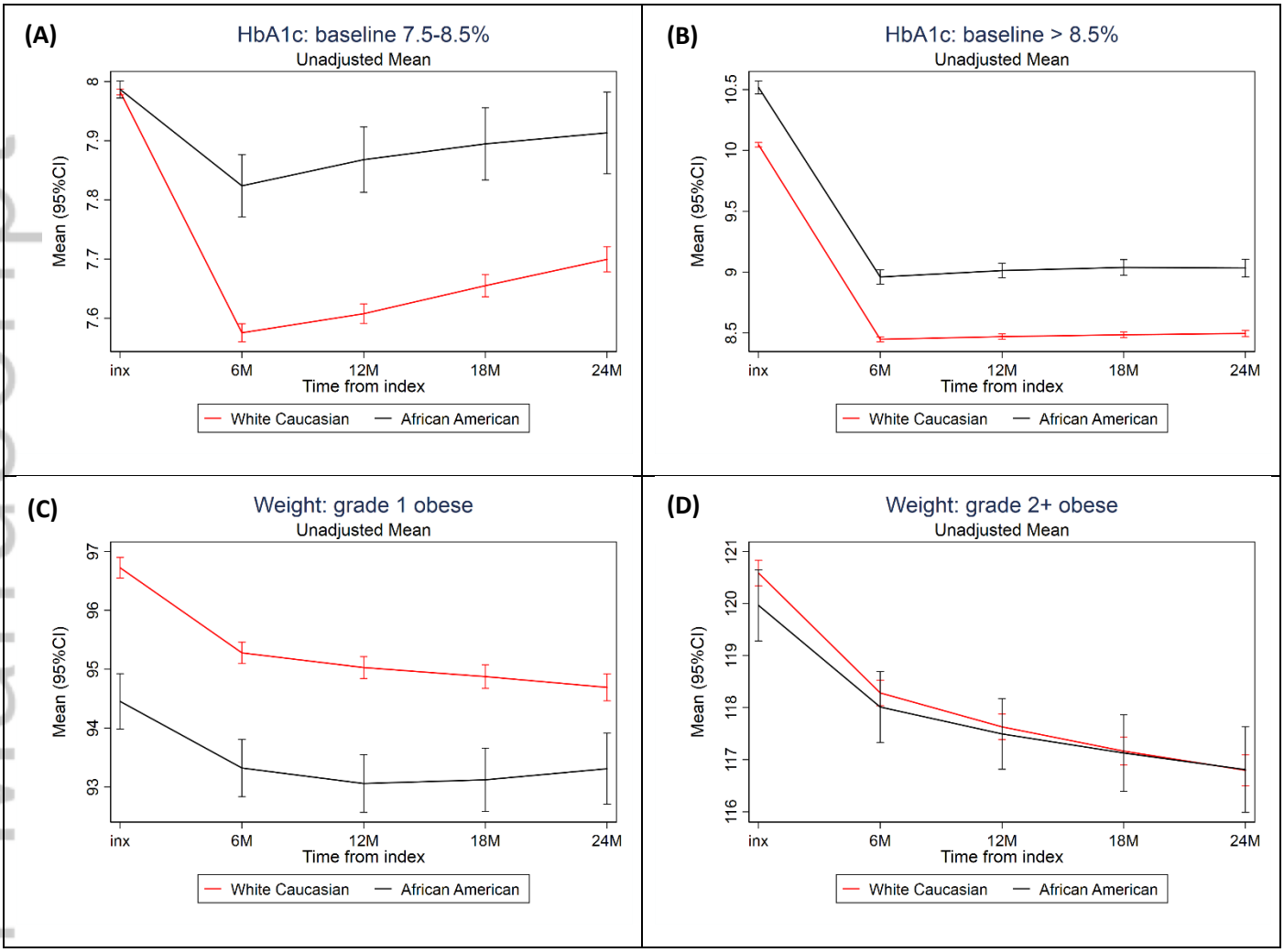
† Among those with / without history of atherosclerotic cardiovascular disease (ASCVD) at the time of SGLT-2i initiation: SBP ≥ 130 / 140 mmHg; LDL-C ≥ 70/ 100 mg/dL; Non-HDL-C ≥ 100/ 130 mg/dL.

Table 2: Drug prescription patterns in the study cohort before SGLT-2i initiation and during 18 months follow-up.

	statistics	White Caucasian (N= 72,690)	African American (N= 10,004)	Total (N= 82,694)
Prior to SGLT-2i initiation				
Number of ADDs prior to SGLT-2i initiation	Median (IQR)	3 (2, 3)	3 (2, 3)	3 (2, 3)
No ADDs prior to SGLT-2i initiation	N (%)	2,332 (3)	339 (3)	2,671 (3)
1 ADD prior to SGLT-2i initiation	N (%)	12,862 (18)	1,710 (17)	14,572 (18)
2 ADDs prior to SGLT-2i initiation	N (%)	20,256 (28)	2,834 (28)	23,090 (28)
3 ADDs prior to SGLT-2i initiation	N (%)	18,400 (25)	2,564 (26)	20,964 (25)
4+ ADDs prior to SGLT-2i initiation	N (%)	18,840 (26)	2,557 (25)	21,397 (26)
Metformin prior to SGLT-2i initiation	N (%)	63,206 (87)	8,576 (86)	71,782 (87)
Sulfonylurea prior to SGLT-2i initiation	N (%)	35,234 (48)	5,016 (50)	40,250 (49)
Thiazolidinedione prior to SGLT-2i initiation	N (%)	14,594 (20)	1,913 (19)	16,507 (20)
DPP-4i prior to SGLT-2i initiation	N (%)	30,361 (42)	4,386 (44)	34,747 (42)
GLP-1RA prior to SGLT-2i initiation	N (%)	20,664 (28)	2,317 (23)	22,981 (28)
Other ADDs prior to SGLT-2i initiation	N (%)	3,011 (4)	357 (4)	3,368 (4)
Insulin prior to SGLT-2i initiation	N (%)	26,667 (37)	3,949 (39)	30,616 (37)
-- continued insulin over 6 months post index	n (%)	25,123 (94)	3,636 (92)	28,759 (94)
-- continued insulin over 12 months post index	n (%)	24,810 (93)	3,568 (90)	28,378 (93)
SGLT-2i				
SGLT-2i duration, years	Mean (SD)	2.1 (1.1)	2.0 (1.1)	2.1 (1.1)
SGLT-2i duration, years	Median (IQR)	1.9 (1.2, 2.8)	1.7 (1.2, 2.6)	1.8 (1.2, 2.8)
Months from first ADD	Mean (SD)	50.5 (60.5)	47.1 (55.0)	50.0 (59.8)
Months from first ADD	Median (IQR)	36.3 (6.3, 74.5)	34.3 (5.4, 71.3)	36.0 (6.2, 74.1)
Initiated SGLT-2i with canagliflozin	N (%)	41,526 (57)	5,558 (56)	47,084 (57)
Initiated SGLT-2i with dapagliflozin	N (%)	16,994 (23)	2,573 (26)	19,567 (24)
Initiated SGLT-2i with empagliflozin	N (%)	14,170 (19)	1,873 (19)	16,043 (19)
Discontinued during follow-up	N (%)	21,771 (30)	3,641 (36)	25,412 (31)
--- months to discontinuation	Mean (SD)	19.7 (11.6)	19.7 (11.3)	19.7 (11.5)
--- months to discontinuation	Median (IQR)	16.4 (10.7, 26.3)	16.7 (11.0, 25.8)	16.5 (10.7, 26.2)
Post SGLT-2i initiation				
Added or switched to any ADD	N (%)	20,520 (28)	2,989 (30)	23,509 (28)

Added any ADD	N (%)	16,148 (22)	2,271 (23)	18,419 (22)
--- month to addition	Median (IQR)	10.5 (4.3, 19.8)	9.9 (3.9, 18.2)	10.4 (4.2, 19.5)
Added insulin	N (%)	4,017 (6)	551 (6)	4,568 (6)
--- month to insulin	Median (IQR)	12.0 (5.2, 22.7)	10.8 (4.1, 19.7)	11.8 (5.0, 22.5)
Added GLP-1RA	N (%)	6,366 (9)	955 (10)	7,321 (9)
--- month to GLP-1RA	Median (IQR)	13.3 (6.3, 24.0)	12.9 (6.3, 23.8)	13.3 (6.3, 24.0)
Exposed for at least 90 days during 18 months post SGLT-2i initiation				
Number of non-insulin ADDs	Median (IQR)	2 (1, 2)	2 (1, 2)	2 (1, 2)
Insulin	N (%)	28,349 (39)	4,076 (41)	32,425 (39)
Antihypertensive therapy	N (%)	63,035 (87)	8,967 (90)	72,002 (87)
Lipid lowering therapy	N (%)	60,301 (83)	7,545 (75)	67,846 (82)

Figure 1: Mean (95% C) or median (95% CI) of the 6-monthly trajectory of risk factors over 24 months of follow-up from SGLT-2i initiation, in African American and White Caucasian



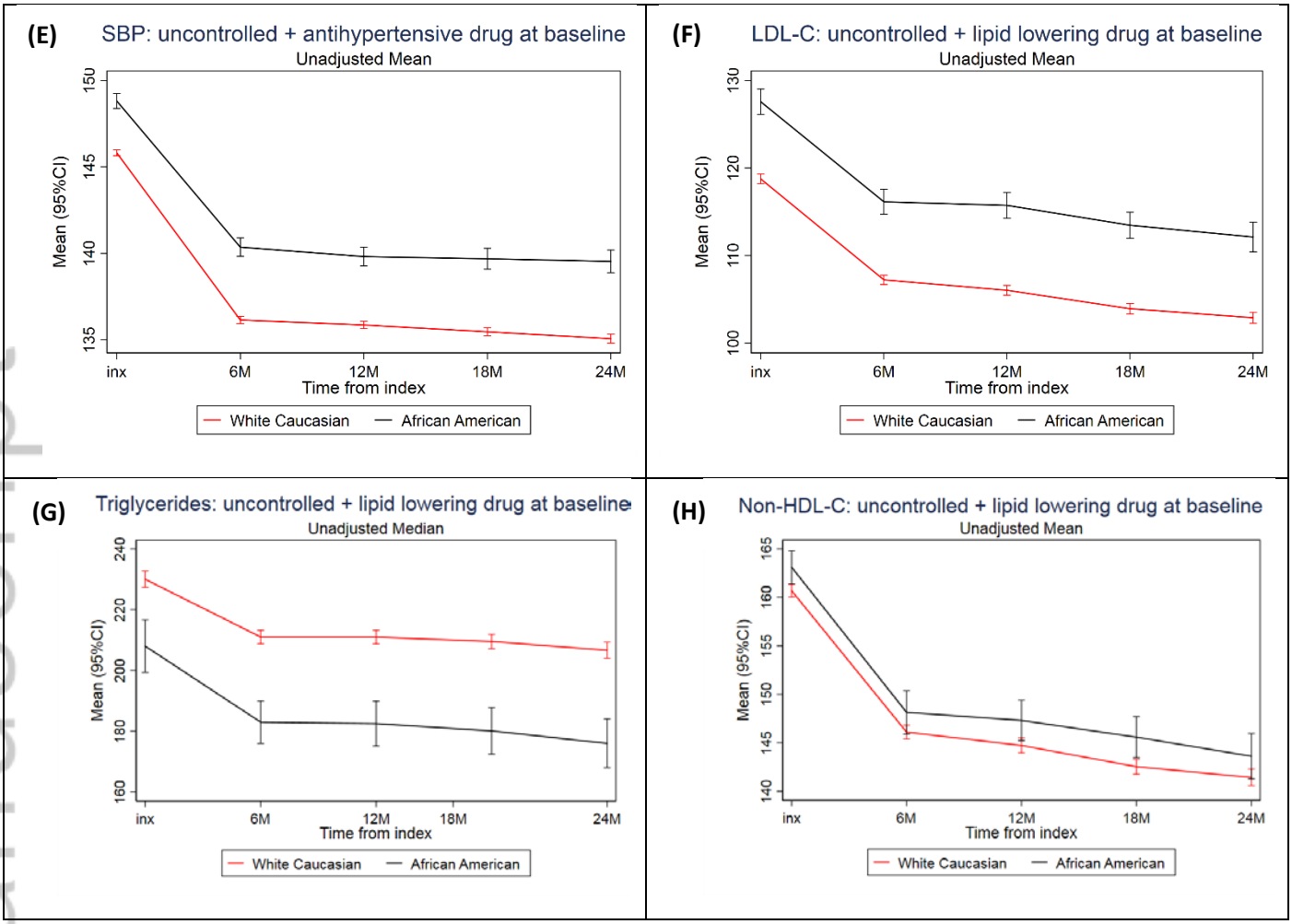


Figure 2: By baseline status of ASCVD, among those with uncontrolled cardiometabolic risks factors at baseline, (A) the probability (95% CI) of achieving control at 6 months and sustaining such control over 12 or 18 months, and (B) the odds of sustainable control in African Americans compared to White Caucasians. For blood pressure and lipid controls, the analyses were conducted among those who were on at least one anti-hypertensive and lipid-lowering therapy at bassline respectively.