Pharmacological Management of Diabetes for Reducing Glucose Levels and Cardiovascular Disease Risk: What Evidence in South Asians?

Short running title: Glucose and outcome Benefits of diabetes drugs in South Asians

Nazim Ghouri[1,2], Hareem Javed[3], Naveed Sattar[1]

[1] Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

[2] Queen Elizabeth University Hospital, Glasgow, UK

[3] NHS Greater Glasgow and Clyde, Glasgow, UK

Corresponding Author

Naveed Sattar

Professor of Metabolic Medicine

Institute of Cardiovascular and Medical Sciences

BHF Glasgow Cardiovascular Research Centre

University of Glasgow

126 University Place

Glasgow

G12 8TA

UK

Tel: +44 (0)141 330 3419

Email: naveed.sattar@glasgow.ac.uk

Abstract

Introduction/Aims

South Asians experience more type 2 diabetes, which is earlier in onset and with more rapid glycaemic deterioration, although average body mass indices are lower than in whites. Cardiovascular outcomes from diabetes drug trials are now reported as standard, with data from newer therapies influencing patient management. However, less is known of the effect of such therapies in South Asians. The aim of this narrative review was to extract, wherever possible, the glucose-lowering efficacy and cardiovascular and renal outcome data for these therapies in South Asians.

Discussion/Conclusions

Despite the higher prevalence and global burden of type 2 diabetes and adverse outcomes in South Asians, they remain underrepresented in global trials. Even when recruited, the current method of classifying ethnicity does not commonly allow South Asian data to be extracted and reported separately from all Asians. Interrogation of available trial data suggests broadly comparable effects on glycaemia and weight in Asians to other ethnicities with use of glucagon-like peptide 1 receptor agonists (GLP-1RA), but a potentially early, albeit marginally, greater glycaemia benefit with Dipeptidyl peptidase-4 inhibitors (DPP4i) which may not be sustained. Furthermore, there appears a potentially greater glycaemia benefit with use of sodium-glucose transport protein 2 inhibitors (SGLT2i) in Asians compared to whites. Whether such findings are true in all Asians subgroups requires further direct study. For cardiovascular outcomes, available data suggest at least comparable and potentially greater outcome benefits in Asians; point estimates were more favourable for Asians in the vast majority of GLP-1RA and SGLT2i outcome trials. It was, however, impossible to determine whether the effects were similar across all Asian subgroups. We conclude that trialists should be encouraged to record ethnicity with better granularity to allow differing ethnic groups data to be better interrogated. In the meantime, doctors should, where possible, confidently follow newer guidelines for the use of newer glucose lowering agents for treating glycaemia and the prevention of cardiovascular and cardiorenal complications in South Asian people with type 2 diabetes.

Keywords

South Asian, type 2 diabetes, CVD, treatment, efficacy, cardiovascular risk, Indian

Background

Diabetes is a well-established causal risk factor for atherosclerotic cardiovascular disease (ASCVD). It shortens life expectancy in high income countries by around 4-6 years on average [1]; such life losses are likely greater in low income countries for multiple reasons [2]. We know from multiple trials in mainly high-income countries that treating glycaemia, cholesterol and blood pressure, as well as helping patients stop smoking, can substantially reduce risk of future complications. The difficulty in some poorer countries is the ready supply of evidence-based medicines to lessen diabetes risks, but efforts are being made to improve such supplies and relevant care processes [3].

The best available evidence suggests modest effects of intensive glucose control *per se* on risks for microvascular outcomes, with potentially even more modest and slower benefits on macrovascular outcomes [4, 5]. There is now also evidence that specific newer diabetes drugs lessen ASCVD risks in groups at elevated risk of with existing ASCVD largely independent of glucose control, leading to a new paradigm in care [6, 7]. Recent guidance from diabetes and cardiology communities has reflected such new findings in relevant algorithms [8, 9]. Whilst such guidance is broadly consistent, some minor but important areas of variance remains and require work to harmonisation. In this article, we review the evidence for the benefits of the more novel diabetes drugs in South Asian populations from a glucose-lowering, as well as ASCVD and cardiorenal outcome perspectives. We show that whilst there is a dearth of sufficiently well-designed trials in this community, indirect evidence suggests cause for optimism that some novel diabetes drugs may offer even greater benefits in South Asians.

T2DM in South Asians – why drug response may be different

The scale and burden of the 'epidemic' of Type 2 Diabetes (T2DM) affecting people in these countries as well their migrants in other, particularly Western countries, is increasing and has not gone unnoticed. It is clear South Asians are more predisposed to type 2 diabetes. Several potential reasons for more diabetes in South Asians have been proposed, including greater insulin resistance, faster loss of beta cell function and altered body compositions with lesser abilities to expand subcutaneous fat depots, and faster accumulation of ectopic stores, and lower lean muscle mass [10, 11]. More recently, in keeping with their greater susceptibility to diabetes, we showed that South Asians are much lighter at diagnosis than whites, with lesser increments in blood pressure or triglycerides compared to their ethnicity matched controls without diabetes [12].

Newer treatments for T2DM and their efficacies

Over the past 10-15 years, three new classes of drugs – dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 receptor analogues (GLP-1 RA) sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged and established themselves as standard second or third-line treatment options in the latest evidence-based international guidance for T2DM management [13]. All three classes of drug share in the favourable feature of being non-weight gaining and not inducing hypoglycaemia [14–18]. Further, these drugs can also be used as first-line treatment options where current 1st line options are not tolerated or contraindicated. DPP-4 inhibitors were the first class of drugs to be marketed and two meta-analyses and systematic reviews for this oral therapy demonstrate their (albeit modest) glucose-lowering efficacy as first-line as well as adjunct therapies [19, 20].

GLP-1 RAs were the next class of drugs to enter the market and generally have strong glucose-lowering efficacy, but with variation within the drug class [15, 21]. Although an injection-based treatment, weekly options such as exenatide, dulaglutide and semaglutide, as well as small needle gauge, make these options more appealing compared to their daily competitors or to insulin [22]. Finally, SGLT2 inhibitors are the most recent of the three classes to market. These oral medications are of high efficacy in lowering glucose in the setting of normal renal function [23–25]. Further, longer-term efficacy is also encouraging for SGLT2 inhibitors both from trial and real-world evidence (RWE) [26–28].

Newer treatments and their glucose-lowering efficacy in South Asians

Whilst global trial data support outcome benefits from GLP-1RA and SGLT2i, and safety for DPP4i, the increased burden of T2DM, and potentially different (or accelerated) pathways to diabetes in south Asians compared to white Europeans means it is important to examine whether diabetes drugs may yield different, either better or lesser, benefits in South Asians compared to other populations. We therefore explored for such evidence in both randomised trials and real word evidence, with the caveat of potential residual confounding in the latter. We first examined glycaemia benefits and then cardiovascular outcome differences for each of the three classes of drugs.

DPP-4 inhibitors and glycaemia changes

DPP-4 inhibitors have an established usage in South Asia, with usage spanning over 10 years [29]. Promising data from the first published study involving subjects from India came from a randomized, double-blind, placebo-controlled, 18-week trial (n = 530). It evaluated efficacy and safety of Sitagliptin amongst Asian population (Korea, China and India), and revealed significant glucose lowering (placebo-subtracted, -1.0%; $P < 0.001$) with Sitagliptin [30]. Although, similar HbA1c reduction was noted in all three subpopulations relative to baseline, Indians and Koreans exhibited better HbA1c lowering (-1.4% each) compared to Chinese (-0.7%), against placebo. However, this apparent difference appears to have been driven by an increase HbA1c in placebo arm in Indians (+0.7%) and Koreans (+0.6%) but HbA1c *decrease* in placebo arm of Chinese (-0.2%) patients. The glucose reduction with DDP4 inhibitors seemed to be broadly similar to European cohorts [19]. Against this, a well analysed recent meta-analysis of glycaemia trials suggested marginally (~0.15%) greater early – within 12 weeks – reduction of HbA1c in trials of DPP4i in Asians compared to whites [31]. However, this glycaemia benefit did not persist to 24 weeks or longer [32]. The authors of the meta-analysis acknowledged the work could not differentiate findings for South Asians compared to those from South East Asia. There was also considerable heterogeneity in the meta-analysed data, suggesting the need for individual participant meta-analyses of trials, or better, for well powered trials of glycaemic agents in South Asians per se.

GLP-1 RAs and glycaemia changes

Data on GLP-1 RAs by ethnicity are more limited. For exenatide, the first GLP-1 RA, a global data analysis included ~25% of subjects resident in India. Results showed better ($p<0.0001$, exenatide bd) or similar (exenatide QW) reductions in HbA1c in Indians compared to whites [33]. However, the Asian group also included East Asians (70% of subjects resident in China, Japan, Korea and Taiwan) and no data were presented on specific ethnicities, nor any adjustments made for ethnicity subgroup. Hence, it is impossible to draw any valid conclusions. Fortunately, the recent meta-analysis by Gan et al [31] also looked at this question and did not find a difference in GLP-1RA-associated glycaemia benefit between whites and Asians. However, once again, the authors were not able to separate data for South Asians versus other groups of Asians so that further specific research is warranted.

SGLT2 inhibitors and glycaemia changes

For SGLT2 inhibitors, whilst detailed analysis exists for East Asian subjects [34], only a paucity of published data includes or makes explicit reference to subjects coming from a South Asian background. Some relevant

patients were included in a systematic review [35] designed to review the clinical effectiveness and cost-effectiveness of dapagliflozin, canagliflozin and empagliflozin in monotherapy versus placebo in people who could not take metformin. Of the seven studies identified, four had subjects from an 'Asian' background, with only one study explicitly making reference to 'Indian subjects [36] and based on geographical data of recruitment, the other studies would suggest that Asians were of an East Asian extraction. There were, however, no Indian-specific data or outcomes adjusted for ethnicity presented from this study.

That noted, the efficacy of canagliflozin 100 mg and 300 mg has been evaluated by racial group using data pooled from four placebo-controlled phase 3 studies and two placebo-controlled sub-studies of a population of patients with inadequately controlled T2DM (N = 4158) [37]. The Sixty-one percent of the 'Asian' racial group were from India. Irrespective of racial group, treatment with canagliflozin 100 mg and 300 mg was associated with greater reductions in HbA1c and body weight (BW) from baseline values compared with placebo. Placebo-subtracted mean changes in HbA1c and bodyweight were generally dose-dependent across all racial groups. Numerically larger reductions in HbA1c were observed with canagliflozin in the Asian and Black/African American groups compared with White. From a baseline HbA1c of 8.1%, a higher proportion of patients treated with canagliflozin 100 mg and 300 mg achieved the HbA1c target of 7.0% in all racial groups versus placebo (Whites: 34.1% and 44.6% vs 17.5% for the two doses relative to placebo, respectively; Black/African Americans: 32.1% and 45.2% vs 19.0%; Asians: 33.5% and 40.3% vs 9.8%; 'Other' racial group: 42.2% and 57.5% vs 20.4%, respectively). These results appear to show canagliflozin lower glycaemia broadly similarly across difference ethnic groups, including Asians, with a hint of potentially greater benefit of SGLT2i's in non-whites.

If we return to the recent meta-analysis by Gan et al [31], here the findings suggest a meaningfully greater reduction in HbA1c with SGLT2i use in Asians versus whites, with a mean difference of around 0.30% in absolute HbA1c levels. This finding occurred despite duration of diabetes being less in Asians, and with lower BMI and similar baseline HbA1c levels. Whilst the overall between-trial heterogeneity was modest, these findings also suggest Asians may have better response to SGLT2is, necessitating formal testing in randomised trials. Of course, once again, whether this greater benefit is similar across all Asians subgroups, including South Asians, is not clear.

Overall, there is now some emerging evidence that SGLT2i therapy may offer better glycaemia benefits in Asians versus whites. If this finding is confirmed subsequent trials, the mechanisms behind this finding merit further study. Finally, to complete the review of glycaemia studies involving SA subjects, it is worth to acknowledge randomised control trials exist in relation the usage of these classes of drugs involving individuals from South Asia the context of fasting during Ramadan [38, 39].

The use of diabetic drugs in lowering cardiovascular risk

As alluded to earlier, T2DM is associated with increased ASCVD burden, and whilst glycaemic control remains integral to the shorter and longer-term management of T2DM, reducing ASCVD risk is of equal importance. Thus, with the emergence of the newer antidiabetic drug classes described above, their efficacy in ASCVD risk reduction across different ethnicities also requires attention.

Initially the U.S. Food and Drug Administration (FDA) issued guidance to the pharmaceutical industry setting out new expectations for the development of antidiabetes drugs for type 2 diabetes, with the intention to focus on CV safety [40, 41], largely in recognition of the excess burden of CVD in T2DM [42]. The FDA was responding to prevailing concerns about the potential for increased CVD risk associated with certain antidiabetes drugs, notably the thiazolidinedione (TZD), rosiglitazone [43, 44]. The guidance — and subsequent similar requirements from the European Medicines Agency [45] — effectively expanded the scope and cost of research necessary to secure approval of new antidiabetes drugs by mandating long-term safety trials.

However, a favourable fallout from these recommendations is the clear evidence of CV safety or indeed benefit from some of these newer drugs. Owing to the size and global/multinational participation in these studies, the opportunity to extract ethnic-specific data an outcome also arises. That noted, FDA guidance presently only requires ethnicity data for Asians to be grouped as one ethnic group, thus combining SAs with East Asians for example. Thus, where available, for DPP-4 inhibitors, GLP-1 RAs and SGLT2 inhibitors, the respective studies with ASCV and cardiorenal outcomes were reviewed, and where available, SA-specific data extracted and commented upon.

DPP-4 inhibitors and cardiovascular outcomes

Trial data on CV outcomes compared to placebo exist for four DPP-4 inhibitors – saxagliptin, sitagliptin, alogliptin [46–48] and linagliptin [49]. None of the three trials lowered CV risk but also none of them increased CV risk overall, although there was a signal of harm for heart failure with saxagliptin which remains unexplained. More recently, one trial using linagliptin have been published, one versus placebo and other against glimepiride [50]. Again, neither trial showed benefit or harm for CV outcomes versus the relevant comparator.

Supplementary data from TECOS study (sitagliptin) included race/ethnicity subgroup analysis [47]. Whist this included a proportion of subjects from India, their data were combined with east Asian subjects. Nonetheless, this subgroup showed no difference in primary outcomes. Further, whilst both linagliptin studies provides supplementary data on Asians, the countries of recruitment were all east Asian. None of the other DPP-4 inhibitors trial data provide primary or supplementary ethnicity. Thus, specific conclusions on the CV benefits or otherwise in SAs cannot be made.

Glucagon-like peptide-1 receptor agonists and cardiovascular and renal outcomes

Six GLP-1 RAs (liraglutide, semaglutide, albiglutide, dulaglutide, lixisenatide and exenatide) with ASCVD outcomes are published to date [6, 51–57], with limited data or textual information presented specifically on SAs. Most studies included data from 'Asian countries or had patients of 'Asian' ethnicity, however as mentioned previously, further subclassification within this geographical location or ethnic group and associated analysis is generally lacking. A summary of these six studies with any SA-specific outcomes or comments are presented in **Table 1**.

Data from the ELIXA, LEADER, SUSTAIN-6, HARMONY OUTCOMES and REWIND trial indicated there was an overall significant improvement in their respective ASCVD outcomes and also had ethnic-specific data [51–55]. EXSCEL and PIONEER-6 trials also indicated risk reduction (albeit statistically nonsignificant) in achieving the primary outcome [56, 57].

Three of the five studies with ethnic-specific data had subjects recruited from India [51, 52, 55]. The ELIXA study showed no heterogeneity in outcomes by ethnic groups [55], but it had limited power to do so (**Table 1**). In LEADER, the intervention yielded a 30% risk reduction (CI -54% to +4%) in the Asian population compared

to placebo [51]. Whilst this result is non-significant, there was no heterogeneity by ethnic group. Notably, 10% of the participants in LEADER were of Asian ethnicity which was the highest proportion found in any trial. SUSTAIN-6 saw a greater risk reduction of 42% with the intervention (CI -75% to +34%) in the Asian subgroup, though again with no formal evidence of heterogeneity by ethnicity.

More recently, the totality of the Asian GLP-1RA CVOT data has been meta-analysed by Singh and Singh [58]. They determined a significant benefit from 3-point MACE in the trials that reported these data with a point estimate of 0.68 and 95% confidence interval between 0.55 to 0.84, with no evidence of heterogeneity. This 32% risk reduction for three-point MACE is impressive and at least as good as, if not better, than the meta-analysis of the full cohorts in each trial, as reported recently by Kristensen et al [6]. That said, it was not clear if three of these CVOTs (EXSCEL, REWIND, HARMONY OUTCOMES) included any South Asians, but HRs in the four other trials were all better in the Asian race than the entire cohort results.

In conclusion, CVOT findings suggesting Asians do just as well at other groups, and potentially better with the use of GLP-1RA's. If amongst these data, the South Asian group also do better, this may be due to their greater propensity towards accelerated atherogenesis (i.e. ASCVD). This suggestion is speculative and requires formal evaluation.

Sodium Glucose co-transporter 2 Inhibitors and CV outcomes

Several trials have investigated the impact of SGLT2 inhibitors on ASCVD and renal outcomes, the vast majority with favourable outcomes, particular on incident renal and heart failure outcomes [7]. More latterly, trials in patients with existing renal disease (CREDENCE and DAPA-CKD [59, 60]) and heart failure (DAPA-HF and Emperor Reduced [61, 62]) have been published. As with the other novel therapy classes, outcome data were not presented separately for the South Asian population. However, all studies include subjects recruited from Asia, including India [24, 63–65], with one from Sri Lanka as well [23]. These outcomes, and more specific SA data (where available) within the trials conducted to date and are summarised in **Table 2**.

Outcome trials in diabetes patients at elevated cardiovascular risk

If we start with Asian specific data in EMPA-REG trial [66], empagliflozin reduced the occurrence of the primary outcome by 32% and CV death by 56%, HR: 0.44 (0.25-0.78) in the Asian subgroup. In all such

analyses, there was no evidence of heterogeneity by ethnicity (**Table 2**). In the CANVAS trial [24], 26.9 per 1000 patient-years in the intervention group vs 31.5 in the placebo group experienced the primary outcome. The result in the Asian cohort [HR: 1.08, 95% CI, (0.72–1.64); P = 0.40] was not as impressive with the main result but there was no formal heterogeneity by ethnicity. With respect to dapagliflozin, the DECLARE trial [64] showed the intervention did not reduce the rate of MACE but did reduce the rate of CV death or hospitalisation from HF. The primary outcome point estimate for Asians with a HR of 0.69 (95% Cl 0.69-1.33), was better than in total population but there was no evidence of heterogeneity by ethnicity. In the VERTIS-CV trial, ertugliflozin did not reduce the primary outcome with a HR of 1.01 (95% Cl 0.87-1.16). The point estimate was lower in the Asian subset with a HR of 0.89, (95% Cl 0.51-1.56), but of course with no evidence of formal interaction [67]. Thus, in three of the four trials in patients with diabetes and elevated cardiovascular risk, the points estimate for the Asian subgroup was lower than for the total cohort.

Renal outcome trials

In CREDENCE [59], the primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. In the Asian subgroup, the HR for benefit was 0.66 (95% Cl, 0.49-1.14), compared to a HR of 0.70 (95% CI, 0.59 to 0.82) for the full cohort, with a P=0.91 for interaction by race. In the DAPA-CKD trial [60], the HR for a similar primary outcome as CREDENCE was 0.61 (0.51 to 0.72), whereas it was 0.66 (0.46 to 0.93) in the Asian subgroup. Thus, for SGLT2i derived renal benefits in patients with CKD, Asians appear to benefit to a near identical degree.

Heart failure trials

In the DAPA-HF study, the primary outcome of heart failure hospitalisation or cardiovascular death occurred less in patients who received dapagliflozin than those receiving placebo and the results did not differ in patients with or without diabetes [61]. DAPA-HF showed a 36% risk reduction (CI 14 to 52%) in achieving the primary outcome within the Asian population compared to a 26% reduction in the white population (although there was no statistical comparison of heterogeneity between ethnic groups for this outcome [61]). In Emperor Reduced trial, which showed a near identical primary outcome benefit of to DAPA-HF, the point estimate was even more notably lower in the South Asian subgroup with a HR of 0.57 (95% Cl 0.41–0.78) [62]. Thus, for SGLT2i derived benefits in patients with pre-existing HF, Asians appear to benefit just as well, if not potentially better, than the total population.

In conclusion, the point estimates for Asians in the SGLT2 outcome trials were lower than in the total population in six of the eight trials (see Table 2). Whilst the Asian subgroups were not specified, the results provide some reassurance for use of these agents in South Asians for benefits in patients with ASCVD or at elevated risk, with existing CKD or HF.

Conclusions

This narrative review examines the efficacy of newer therapies in relation to the management of T2DM and in the prevention of ASCVD and cardiorenal outcomes. Unfortunately, despite the higher prevalence and global burden of T2DM and adverse outcomes in SAs, SAs remain underrepresented in global trials. Even when they are recruited, the current method of classifying ethnicity does now allow South Asian data to be extracted and reported separately. The data that do exist suggest broadly comparable effects on glycaemia and weight in South Asians to other ethnicities with GLP-1RAs but potentially greater benefits with DPP4i (albeit marginal) and perhaps more notably for SGLT2i's. For ASCVD outcomes, the data suggests broadly similar outcome benefits (with point estimates being directionally concordant in most trials) but notably, the point estimates for the Asian subgroup was lower in all GLP-1RA trials reviewed suggesting Asians may gain greater better outcome benefits from such drugs than in whites, but this suggestion needs formal evaluation, and three of the seven GLP-1RA trials did not recruit in South Asian countries. Whilst results for SGLT2i were more mixed, the point estimate for the primary outcome was lower in the Asian group than in the total cohort in six of eight outcome trials reported for this class of drugs, providing strong reassurance that these drugs work to lessen ASCVD, renal progression in those with CKD, and HF outcomes in those with HF, at least as well as in other races. Whilst these results are very reassuring, moving forward, better presentation of data for this ethnic group from global trials is needed, especially given their earlier development of T2DM, propensity to more rapid glycaemic deterioration and subsequent increased burden of adverse outcomes, in particular ASCVD and renal outcomes.

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Table 1 Glucagon-like peptide-1 receptor agonists and South Asian ethnicity specific outcomes.

TRIAL	INTERVENTION	PATIENT GROUP	DURATION (years)	PRIMARY OUTCOME	STUDY OUTCOME	SOUTH ASIAN ETHNICITY-SPECIFIC OUTCOME
ELIXA [55]	Lixistenatide(subcutaneous) 20µg/day	6068 men and woman ≥30 years	2.1	Death from CV causes, non-fatal MI or non-fatal stroke	HR: 1.02, 95% Cl, (0.89-1.17), P=0.78] for superiority.	13.3% of the participants were of Asian ethnicity. This comprised of participants from Australia, China, India, Japan, Korea, Philippines, Taiwan. Asian HR 0.92, 95%CI (0.57-1.48) *
LEADER [51]	Liraglutide(subcutaneous) 0.6mg-1.8mg/day	9340 men and woman ≥50 years	3.5-5	CV death, MI or stroke	HR:0.87, 95 Cl%, (0.78-0.97), P=0.01]	10% of the total patient population were of Asian ethnicity with participants from China, Taiwan, Korea and India. Asian HR:0.70, 95 CI%, (0.46–1.04) P=0.32 for heterogeneity by ethnic subgroups.
SUSTAIN-6 [52]	Semaglutide (subcutaneous) 0.5mg or 1mg/week	3297 men and woman ≥50 years	2	Cardiovascular death, MI or stroke.	HR:0.74, 95%Cl, (0.58-0.95), P=0.02]	8.3% of the total population were of Asian ethnicity including participants from Malaysia, Taiwan, Thailand and India. Asian HR:0.58, 95%CI, (0.25-1.34) for the primary outcome P=0.88 indicated no heterogeneity by ethnic subgroups.
EXSCEL [56]	Exenatide (subcutaneous) 2mg/week	14,000 men and woman	3.2	CV death, MI or stroke	[HR: 0.91, 95%Cl (0.83-1.00), P=0.06)].	9.8% of the population being studied were of Asian ethnicity. Participants were from Australia, China, Hong Kong, Malaysia, Philippines, South Korea, Taiwan and Thailand. Asian HR:0.81, 95%CI (0.57-1.14) P=0.61 indicated no heterogeneity by ethnic subgroups. There were no participants specifically of South-Asian ethnicity.
PIONEER-6 [57]	Semaglutide (oral)14mg/day	3418 men and women ≥50 years	1.3	CV death, MI or stroke	HR:0.79, 95%Cl, (0.57-1.10), P<0.001 for non-inferiority]	19.8% of the total patient demographic were of Asian ethnicity. Participants were from India, Malaysia, Thailand and Taiwan. Asian HR 0.44, 95% Cl (0.20-0.97) P=0.14 for heterogeneity
HARMONY OUTCOMES [53]	Albiglutide(subcutaneous) 30mg or 50mg/week	9463 men and woman ≥ 40 years	1.5	CV death, MI or stroke	[HR: 0.78, 95Cl%, (0.68-0.90), P <0.0001, P=0.0006)]	The Asian subset made up 5% of the total population. Participants were from Hong Kong, Taiwan and South Korea. Asian HR:0.73, 95%CI (0.36-1.48) P=0.065 indicated no heterogeneity by ethnic subgroups.

REWIND [54]	Dulaglutide(subcutaneous) 1.5mg/weekly	9901 men and women ≥50 years	5.4	non-fatal MI, non-fatal stroke, and death from CV causes	HR: 0·88, 95% CI 0·79–0·99; P=0·026)	9.9% of the patient demographic were of Eastern-Asian ethnicity. Asian participants were from Korea and Taiwan. Asian HR:0.54, 95%CI (0.32-0.89) P =0.0080 indicated a significance by the intervention however there were no participants specifically of South Asian ethnicity.

* No Asian data in original paper or supplementary data, HR taken from Singh et.al. *Cardiovascular outcomes with SGLT-2 inhibitors and GLP-1 receptor agonist in Asians with type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials* as author acquired data directly from study team.

MI- myocardial infarction, CV-cardiovascular ELIXA- Evaluation of Lixisenatide in acute coronary syndrome, EXSCEL- Exenatide study of cardiovascular event lowering, LEADER –Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results, MI- myocardial infarction, MACE- major adverse cardiovascular event (cardiovascular death, MI or Stroke), PIONEER 6- Peptide innovation for early diabetes treatment, , REWIND- Dulaglutide and cardiovascular outcomes in type 2 diabetes, UACR-urinary albumin-to-creatinine ratio.

Table 2 SGLT2 inhibitors and South Asian ethnicity-specific outcomes.

TRIAL	INTERVENTION	PATIENT GROUP	DURATION (years)	PRIMARY OUTCOME	STUDY OUTCOME	SOUTH ASIAN/ ASIA RACE SPECIFIC OUTCOME
EMPA-REG [23]	Empagliflozin 10mg and 25mg	7020 men and woman ≥18 years	3.1	Death from CV causes, nonfatal MI/stroke	Primary outcome occurred in 10.5% of the empagliflozin group [HR: 0.86, 95%Cl, (0.74 - 0.99), P=0.04]	21.6% of the population was of Asian ethnicity. This comprised participants from India, Philippines, Sri Lanka, Malaysia, Thailand, Indonesia, Singapore, Japan, Korea, Taiwan and Hong Kong. Asian HR 0.68, 95% Cl, (0.48-0.95), P =0.09 suggesting no heterogeneity by ethnic subgroups.
CANVAS [24]	Canagliflozin 100mg and 300mg	4330 men and women ≥30 years	3.6	Primary outcome - CV death, nonfatal MI and non-fatal stroke	14% reduction in MACE with canagliflozin compared to placebo [HR: 0.86; 95% CI, (0.75–0.97); P < 0.001]	13% of the population was of Asian ethnicity comprising of participants from China, India, South Korea, Malaysia and Taiwan. Asian HR: 1.08, 95% CI, (0.72–1.64) P = 0.40 suggesting no heterogeneity by ethnic subgroups.
DECLARE TIMI 58 [64]	Dapagliflozin 10mg	17,160 men and woman >40years	4.2	CV death, MI or Ischemic stroke	Intervention did not result in a significantly lower rate of the primary outcome [HR 0.93, 95% Cl 0.84 - 1.03); P=0.17]	13.5% of the population was of Asian-Pacific ethnicity comprising of participants from China, Hong Kong, India, Japan, Thailand, Taiwan, South Korea and Vietnam. Asian HR:0.96 (95% Cl 0.69-1.33), P for interaction=0.99 indicated no heterogeneity by ethnic subgroups.
VERTIS-CV [67]	Ertugliflozin 5mg and 15mg	8246 men and women	3.5	CV death, nonfatal MI, nonfatal stroke	MACE occurred in 11.9% in the ertugliflozin group and in 11.9% in the placebo group. [HR 0.97; 95.6% CI (0.85- 1.11); P<0.001 for noninferiority.]	6% of the total population were of Asian ethnicity. It comprised of participants from Hong Kong, Taiwan, and Thailand. Asian HR 0.89, 95% Cl (0.51-1.56)
CREDENCE [65]	Canagliflozin 100mg and 300mg	Men and women ≥30 years	3	eGFR decline, ESKD, renal or CV death	Primary outcome reduced by [0.70 (95% CI, 0.59 to 0.82)]	13% of the total population were of Asian ethnicity. Asian HR:0.66 (95% Cl ,0.46-0.96) P=0.91 indicated no heterogeneity by ethnic subgroups.
DAPA-CKD [60]	Dapagliflozin 10mg	4304 men and women ≥40 years	2.4	eGFR decline, ESKD, renal or CV death	Rate of primary outcome occurred in 9.2% of the dapagliflozin group compared to 14.5% of the	6% of the total population were of Asian ethnicity. It comprised of participants

					placebo group. HR 0.61; 95% CI (0.51-0.72); P<0.001.	from China, India, Japan, Korea and Vietnam. Asian HR 0.66, 95%CI (0.46-0.93)
DAPA-HF[61]	Dapagliflozin 10mg	4744 men and woman ≥18years with class II, III, or IV HF and an ejection fraction of 40% or less plus other criteria	1.5	Hospitalisation for heart failure or CV death	Rate of the primary outcome occurred in 16.3% of the intervention group compared with 21.2% of the placebo group (P<0.001). HR:0.75, 95%CI (0.65-0.85)	24% of the total population was of Asian- pacific origin with participants from China, India, Japan and Taiwan. HR in Asian 0.64 (95% Cl, 0.48-0.86)].
Emperor-Reduced [62]	Empagliflozin 10mg	3730 patients with class II, III, or IV HF and an ejection fraction of 40% or less plus other criteria	16 months	Hospitalisation for heart failure or CV death	0.75; 95% CI, 0.65 to 0.86; P<0.001	HR in Asians 0.57 (95% CI 0.41 - 0.78)

CV-cardiovascular, CANVAS- Canagliflozin cardiovascular assessment study, CREDENCE- Canagliflozin and cardiovascular and renal outcomes in type 2 diabetes mellitus and chronic kidney disease, DAPA-HF- The Dapagliflozin and prevention of adverse outcomes in heart failure trial , DAPA-CKD- Dapagliflozin in patients with chronic kidney disease. DECLARE TIMI 58- Dapagliflozin and cardiovascular outcomes in type 2 diabetes, HF-heart failure, EMPA-REG- Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes, ESKD -end stage kidney disease, MACE-major adverse cardiovascular event. VERTIS- Evaluation of ertugliflozin efficacy and safety cardiovascular outcomes trial.