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Pharmacological management of South Asians with Type 2 Diabetes: Consensus Recommendations from the South Asian Health Foundation

Running title: Consensus Recommendations from the South Asian Health Foundation on Type 2 Diabetes

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- Compared to White Europeans, South Asians are at a higher risk of developing type 2 diabetes along with cardiovascular, renal and eye complications.
- Cardiovascular outcome trials (CVOTs) for the newer therapies for type 2 diabetes show cardiovascular and renal protection, requiring a shift in management of type 2 diabetes; reflected in the recent European and American management guidelines
- In view of this, there is urgent need for an integrated, evidence-based, cost-effective and individualised approach specific for South Asians.
- This review considers the evidence from these CVOTs and provides best practice recommendations for optimal management of South Asian people with type 2 diabetes

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Abstract: South Asians constitute approximately 1.6 billion people from the Indian subcontinent, comprising Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka; and make up the largest diaspora globally. Compared to the White European population, this group is at a higher risk of developing type 2 diabetes along with cardiovascular, renal and eye complications. Over the recent years, a number of new therapies for type 2 diabetes have become available for which cardiovascular outcome trials (CVOTs) have been published. The recent ADA/EASD consensus guidelines on diabetes, pre-diabetes and cardiovascular diseases' offer a transitional shift in type 2 diabetes management. The new consensus recommendations are based on recent CVOTs, many of whom had representation of South Asian cohorts. In light of this new evidence, there is urgent need for an integrated, evidence-based, cost-effective and individualised approach specific for South Asians. This review takes into consideration the evidence from these CVOTs and provides best practice recommendations for optimal management of South Asian people with type 2 diabetes, alongside the previously published consensus report from South Asian Health Foundation in 2014 [1].

Keywords: Cardiovascular disease; cardiovascular outcome trials; glucagon-like peptide-1 receptor agonists; practice guidelines; South Asians; sodium-glucose transporter 2 inhibitors; type 2 diabetes.

Introduction

Epidemiology of Type 2 Diabetes in the UK South Asian Population – Prevalence rates in the UK

The number of adults with diabetes in the UK has risen from 2.3 million (1980) to 4.7 million (2019), with 1 million people undiagnosed [2]; of which type 2 diabetes contributes to 90.4% (prevalence, 4.5%) [3]. Compared to white Europeans, people of Black and South Asian ethnicity are at a higher risk of developing type 2 diabetes [4]. A cohort study of 1.9 million individuals' extracted data from the CALIBER programme found people with type 2 diabetes were twice as likely to be of either Black or South Asian origin compared to those without diabetes [5]. The UK-based NHS Health Check Programme revealed a higher prevalence of diabetes among South Asian men (9.0% vs. 3.9%; p=0.001), and women (7.4% vs. 3.3%; p=0.001) compared to their white Europeans counterparts [6].

A meta-analysis revealed Bangladeshis to have the highest odds ratio (OR) for type 2 diabetes (6.2; 95% confidence interval [CI], 3.9–9.8), followed by Pakistanis (5.4; 95% CI, 3.2–9.3) and Indians (4.1; 95% CI, 3.0–5.7), compared to white Europeans [7].

Furthermore, Scottish data reported type 2 diabetes to be up to six times more common in South Asians, particularly from the age of 25 years, rather than at 40 years as seen in white Europeans [8]. South Asians were found to be more likely to have undiagnosed diabetes, while among people with diagnosed diabetes, specifically Pakistanis, Indians, and Bangladeshis exhibited poor glycaemic control more often [9].

Risk factors associated with Type 2 diabetes in South Asians

At present, there is insufficient evidence to suggest that there is an increased genetic susceptibility of South Asians to diabetes; with most studies demonstrating that the genetic factors conferring susceptibility to diabetes is not significantly different to other ethnic groups.

Evidence demonstrates greater predisposition of certain ethnic groups towards type 2 diabetes in the presence of identical risk factors. Compared to white European populations, increased levels of pro-inflammatory and pro-thrombotic factors, higher endothelial dysfunction [10], are observed among adult South Asians. Another feature of the South Asian population with type 2 diabetes is the low β-cell pancreatic mass, reducing insulin secretion capacity that could not proportionately compensate

with the severity of insulin resistance.

There have been suggestions regarding the possibility of a South Asian phenotype that predispose this population to the development of insulin resistance, type 2 diabetes and cardiovascular disease (CVD). Fig. 1 depicts various factors that result in an increased risk of diabetes and associated complications in the South Asian population. The disproportionately higher prevalence of type 2 diabetes among South Asians has additionally been linked to a number of lifestyle factors, including increased carbohydrate and fat intake, reduced intake of fruits and vegetables, as well as significantly less physical activity compared to white Europeans.

Data from the ADDITION Leicester Study found that for South Asian men, body mass index (BMI) obesity cut-off points equivalent to 30.0 kg/m^2 in Europeans was 22.6 kg/m^2 (95% CI, 20.7-24.5 kg/m^2); and waist circumference equivalent of 102 cm in white Europeans was 83.8 cm for South Asian men (95% CI, 79.3-88.2 cm) [11]. Similar observations were made in another study comparing associations between anthropometric measurements and cardio-metabolic risk factors in the UK reporting a lower BMI cut-off (22 kg/m^2 vs. 26 kg/m^2) and lower waist circumference cut-off (92 cm vs. 109 cm) for South Asians than white Europeans with dysglycaemia [12].

Diabetes related outcomes in South Asian people

South Asian people with type 2 diabetes have an overall higher risk of developing complications compared to white Europeans, due to genetic predisposition, early onset of diabetes, delayed diagnosis, suboptimal control, and treatment non-compliance.

Macrovascular complications

South Asians were found to have an increased risk of CVD events compared to white Europeans (adjusted OR, 1.4; 95% CI, 0.9-2.2) in the United Kingdom Asian Diabetes Study (UKADS) [13]. Data from Scotland additionally demonstrated that Pakistani ethnicity (Hazard Ratio [HR], 1.45; CI, 1.14-1.85; p=0.002) was an independent risk factor for CVD among those with type 2 diabetes [14].

Studies have reported that South Asians with diabetes have a higher prevalence of coronary artery disease (CAD), with a HR of 1.35 [15]. In a study involving 2,897 people with diabetes from Leicester, UK, shorter life expectancy and higher 30-day mortality after coronary artery bypass

grafting was noted among South Asians (3.8% vs 1.4%, p=0.01) than Caucasians. There was, however, no significant difference in mortality at 5 years (p=0.77) [16]. The West Birmingham Stroke Project studying South Asian people with ischaemic stroke suggested diabetes as an independent predictor of 5-year mortality (OR, 1.65; p=0.039) [17]. The Southall and Brent Revisited (SABRE) study also recorded a higher incidence of stroke in South Asians with type 2 diabetes (HR, 1.97; p=0.038) than Caucasians [18].

However, with the use of culturally appropriate prevention and management strategies over the last two decades, a substantial change in the cardiovascular mortality risk is observed in migrant South Asians; the speculated mechanisms for which are illustrated in Fig. 2.

Microvascular complications

Differences among South Asians and white Europeans have also been observed in relation to microvascular complications. Prevalence rates of diabetic nephropathy have been reported to be higher in South Asians. A recent meta-analysis noted a pooled prevalence ratio of 1.14 (95% CI, 0.99-1.32; p=0.065) for microalbuminuria in South Asians compared to Caucasians, and 1.08 (95% CI, 0.93-1.24; p=0.327) compared to African Caribbeans; in addition to a higher rate of chronic kidney disease (CKD) progression [19].

Initiatives to reduce nephropathy risk in South Asians include earlier diagnosis of diabetes, more aggressive and sustained management of glycaemia, and earlier, more aggressive blood pressure management. Sight-threatening diabetic retinopathy is not only more prevalent in South Asians but also occurs at a younger age compared to white Europeans and is a common cause of visual impairment in the working age group.

Diabetes care research in South Asians

Despite more recent efforts towards inclusion of South Asians with type 2 diabetes in clinical trials, the problem of small cohort sizes and lack of adequate data pertaining to these populations continues to persist. Underrepresentation of South Asians in clinical trials is of particular concern given the high number of people with type 2 diabetes belonging to this ethnic group, which then, hinders prospects for significant sub-group analyses important for ethnic susceptibility and guiding ethnicity specific

guidelines and management.

Barriers to recruitment and retention of participants includes lack of awareness of research, competing priorities, scepticism regarding study purpose and protocols, perceived stigma around research topics, cultural insensitivity, influences pertaining to family, community, and cultural preferences and norms restricting the inclusion of Asian subgroups into trials. As compared to white Europeans or individuals of other ethnicities, significantly higher proportions of South Asians are excluded from participation in research owing to language barriers. [20].

It is essential to train researchers with essential expertise in culturally sensitive techniques to recruit and retain ethnic groups. Various strategies proposed to facilitate South Asian participation in clinical trials are outlined in Fig. 3.

Dietary habits

Given the deep cultural impact of food and the significant social role of diet in sustaining tradition and social relationships, altering diet in the South Asian community is challenging. Moreover, South Asians have an inhibition towards adopting dietary advice by healthcare workers, since they may recommend avoiding certain traditional foods, which is perceived as devaluation of the South Asian diet.

Higher dietary carbohydrates and glycaemic load are associated with an increased risk of type 2 diabetes [21]. Despite few dietary intervention trials among South Asians, results support the improvement of carbohydrate and fat quality in diet plans with an increase in protein intake for enhancing serum insulin, blood glucose, inflammatory markers, hepatic fat and lipids [22].

Exercise and physical activity

Although currently there are no ethnic-specific recommendations for exercise, studies comparing metabolic effects of exercise in South Asian and white European cohorts have shown differences; South Asian adults need to undertake nearly 232 minutes of moderate physical activity per week compared to 150 minutes for white Europeans to gain the same benefits [23].

Low levels of physical activity among South Asians relative to other populations have been reported

in a number of studies. A systematic review of 26 quantitative studies revealed that South Asian women do not engage in the recommended amount of physical activity for health benefits.

Barriers to physical activity in South Asians include carer commitments, lack of time outside long working hours, fear of racial harassment or abuse while exercising, expectations to remain in home, fear for personal safety, lack of same gender venues, concerns over the acceptability of wearing 'western' exercise clothing for women [24]. On a positive note, there is some evidence that attitudes to exercise in South Asians are changing albeit slowly.

Religious rituals, fasting and feasting

For South Asians, religious fasting is an important aspect of life with implications for those with diabetes. Hypoglycaemia, dehydration, postural hypotension, and ketoacidosis [25] are potential risks of fasting undertaken by people with diabetes. For Muslims, the month of Ramadan carries the paradoxical risk of feasting after the end of fast; leading to hyperglycaemia. and weight gain combined with the reduced physical activity during the day [26].

For Muslims with type 2 diabetes, there exists a need to manage their diabetes effectively during Ramadan, as the timing of this period will lead to lengthier fasting periods and more potential health problems over the subsequent decade. Specific structured education programmes focusing on Ramadan could provide clinical benefits and enhanced quality of life for individuals with type 2 diabetes [27].

For Jains with type 2 diabetes, most high-risk fasts may be discouraged in those taking any form of glucose lowering therapy while most low-risk fasts can be practiced with appropriate regime and dose adjustments. Hindu fasts are distinctive owing to the day-long nature compared with the month-long fasts of Ramadan [28]. There is a need for specific dietary advice for the different Hindu festivals involving fasting, feasting or both. Fine-tuning of medications and individualised education are fundamental to avoid hypoglycaemia and ensure safe fasting.

Structured education

The key to better diabetes management is diabetes education. National and international organisations together with the USA National Standards, UK-based National Institute for Health and Care

Excellence (NICE), and International Diabetes Federation International Standards for Diabetes Education endorse diabetes self-management education and ongoing support, in addition to pharmacological therapy, as strategic components of optimal and autonomous self-management care [29].

Diabetes UK advocates all individuals with diabetes to undergo structured education and support to facilitate managing their own diabetes. For type 2 diabetes, the diabetes education programmes currently available include Diabetes Education and Self-Management for On-going and Newly Diagnosed (DESMOND) and X-PERT Diabetes Programme (also developed for the Urdu speaking South Asian community); the former validated in South Asian populations.

The Promotion Of Physical activity through structured Education with differing Levels of ongoing Support for people at high risk of type 2 diabetes (PROPELS) trial suggested that ethnicity may affect the degree to which behavioural and demographic factors act as correlates of sedentary behaviour and physical activity [30]. Efforts to adapt screening and lifestyle interventions to South Asians have hardly triumphed, especially due to low levels of recruitment, retention and follow up. A feasibility study reported community faith centre-based screening and educational intervention to be effective in reducing the risk of type 2 diabetes among South Asians living in the UK [31].

Cost of therapy

Although newer glucose lowering drugs are relatively expensive, these drugs may reduce the overall costs by reduction in hospitalisations due to adverse cardio-renal events and lost Disability-Adjusted Life Years. Recent evaluations based on cardiovascular outcome trials (CVOTs) substantiate the cost-effectiveness of these agents compared to standard therapy in individuals with increased cardiovascular risk.

Risk factor management in South Asian people with Type 2 diabetes

Management of blood glucose

Fundamental objectives of healthcare systems for South Asians should include culturally specific

interventions for earlier diagnosis and timely management with good glycaemic, blood pressure and lipid control along with smoking cessation.

Once diagnosed, a more rapid deterioration in glycaemic control is seen in migrant South Asians with diabetes. This calls for greater efforts to manage hyperglycaemia by encouraging intensive changes in lifestyle and early escalation of oral or injectable therapies to reduce macro- and microvascular risks. There is a potential role of dual therapy at diagnosis in particular groups and frequent healthcare visits to monitor glycated haemoglobin (HbA1c) and disease progression in the early years of diagnosis [32]. Early combination treatment can provide more frequent long-term clinical benefits without tolerability issues compared to standard metformin monotherapy [33].

In people with diabetic nephropathy, with impaired or declining estimated glucose filtration rate (eGFR), several oral glucose-lowering agents are either avoided or need dose adjustments. Such individuals are eventually advised exogenous insulin therapy, which is associated with higher hypoglycaemic episodes (as a result of impaired renal function), exacerbated fluid retention, and weight gain [34]. Preference for therapies with proven efficacy and safety in renal impairment should therefore be considered before progressing to insulin therapy.

Although numerous CVOTs were conducted over the last decade to establish cardiovascular and renal safety of glucose-lowering therapies, the inclusion and participation of people from the South Asian race remains modest in these trials [35]. Evidence from cardiovascular or renal outcome trials for the various glucose-lowering therapies is outlined in Supplementary Material 1. Supplementary Material 2 summarises the dose recommendations for the various glucose-lowering agents.

Lifestyle management

Lifestyle interventions are a cost-effective way to prevent and treat type 2 diabetes and hence advantageous for the South Asian population. A multi-faceted approach including nutritious diet, sufficient physical activity, healthy bodyweight, and preventing use of tobacco products must be promoted for maximum benefit.

Recommended healthy dietary pattern changes for the South Asian communities include increasing consumption of fibre, proteins, pulses and legumes, healthy dairy products, nuts, and reducing

consumption of refined carbohydrates, free sugar to <10% of total energy intake, and high-fat, high-sugar fast foods, beverages and trans fats.

Regardless of a general understanding of the benefits of activity for type 2 diabetes risk reduction, the attitudes of South Asians tend to be laidback, leading to inaction and increasing risk [36]. As a result, greater responsibility for the promotion of physical activity lies in the hands of family physicians, allied health practitioners, and educators in South Asian communities.

The American Heart Association recommendation of moderate intensity aerobic activity for at least 150 minutes to accomplish cardiovascular health benefits may be increased to a minimum of 230 minutes for South Asians due to their elevated cardiovascular and metabolic rate [23]. Culturally appropriate activities for South Asians may include, but are not limited to brisk walking, light jogging, dancing, yoga, and other group activities. Shorter sessions of high-intensity exercise may increase enjoyment and the goal to continue exercising.

Metformin

Metformin is recommended by most diabetes management guidelines as the first-line drug as monotherapy in individuals with newly diagnosed type 2 diabetes and as a combination therapy when glycaemic targets are not met. To improve compliance and facilitate treatment, metformin is frequently administered as a fixed dose combination (FDC) that are available with sulfonylureas, dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium–glucose co-transporter 2 (SGLT2) inhibitors, and pioglitazone.

SGLT2 inhibitors

SGLT2 inhibitors are an attractive option for initial combination therapy with metformin, but certainly should be strongly considered as a second-line agent. Evidence from CVOTs showed a reduction in the risk of a composite outcome of cardiovascular death, myocardial infarction and stroke in people with T2DM and established atherosclerotic CVD (ASCVD) with SGLT2 inhibitor use [37]. The substantial decline in hospitalisation for heart failure shown in the CVOTs suggests that, in the setting of clinical heart failure, treatment with SGLT2 inhibitors might provide substantial benefit and must be specially considered in people with T2DM and ASCVD and/or heart failure. These trials also

suggested a trend towards direct beneficial and consistent effects of SGLT2 inhibitors as a class, in people with type 2 diabetes and CKD. The renoprotective effects of SGLT2 inhibitors' in addition to the induced natriuresis could elucidate the reduction in hospitalisation for heart failure.

Canagliflozin was the first SGLT2 inhibitor approved by the US FDA to reduce the risk of MACE in adults with type 2 diabetes and established CVD, and to reduce the risk of ESRD, doubling of serum creatinine, cardiovascular death, and hospitalisation due to heart failure in adults with type 2 diabetes and diabetic nephropathy with albuminuria [38]. Dapagliflozin is approved to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors. It has also been approved to reduce the risk of cardiovascular death and hospitalisation for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction [39]. Empagliflozin is approved to reduce the risk of cardiovascular death in adults with type 2 diabetes and established CVD [40].

There is a paucity of real-world studies or randomised controlled trials in the migrant South Asian subgroup for this drug class. All such studies have included the Asian population in general, with no clear definition of South Asians. We recommend SGLT2 inhibitors as a preferred class of glucose lowering agents for the South Asian population due to a lower BMI cut-off for obesity, and could be considered appropriate for use during fasting on account of their good hypoglycaemia risk profile; however, volume depletion and therefore dehydration may be a concern. The insulin-independent mechanism of action of SGLT2 inhibitors may be beneficial as South Asians are generally more insulin resistant.

GLP-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists are an important class of drugs with well-established efficacy and safety in people with type 2 diabetes. Selection of a particular GLP-1 receptor agonist by the clinician is based on the differences between these agents in terms of duration of action (short-acting vs long-acting), glycaemic control, weight loss, tolerability profiles and administration routines. Due to their persistent and non-fluctuating concentrations, the long-acting

formulations offer the advantage of providing glycaemic control when needed (fasting and/or postprandial), and have simpler and more convenient administration schedules over the short-acting agents, thereby improving treatment adherence and persistence [41].

The CVOTs of albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, injectable semaglutide and oral semaglutide have demonstrated beneficial or neutral effects on cardiovascular outcomes along with nephroprotective effects in people with type 2 diabetes. The once weekly GLP-1 receptor agonist, albiglutide, was discontinued not due to safety concerns but limited prescribing of the drug and the product is no longer marketed.

A retrospective real-world observational study assessing the effect of sequential addition of liraglutide or dulaglutide in Indian people with type 2 diabetes who had not achieved their glycaemic target (HbA1c, <53 mmol/mol; <7%) on metformin and SGLT2 inhibitors (n=60), reported a meaningful impact of adding a GLP-1 receptor agonist on all metabolic parameters, with additional benefit seen with liraglutide on target HbA1c, weight loss and reduction in systolic blood pressure [42]. Another study evaluating the long-term efficacy of liraglutide in Indian people with type 2 diabetes (n=74) in a real-world setting found a significant and sustained reduction in HbA1c and body weight with liraglutide over a period of one year [43].

Liraglutide has been found to decrease visceral adipose tissue volume, associated with improved glycaemic control in South Asians. There is no need for adjusting dosing regimens for liraglutide based on age, race, ethnicity, and body weight. Its beneficial effects on postprandial lipid profiles with associated reduction in hunger and energy intake have been seen in aiding weight loss [44]. The ongoing MAGNA VICTORIA trial will provide insights on the efficacy of liraglutide in the regression of cardiovascular dysfunction in people with type 2 diabetes of South Asian descent [45].

We recommend GLP-1 receptor agonists as a vital therapeutic option to delay or prevent complications due to the high risk of CVD in South Asians. This class may be preferable for South Asians on account of lower BMI cut-off for obesity, and can be considered appropriate for use during fasting due to their good hypoglycaemia risk profile.

DPP-4 inhibitors

DPP-4 inhibitors appear to be a preferable option in individuals at high risk for hypoglycaemia (i.e. elderly) or in those where a weight-sparing or oral regimen is requisite. This class is increasingly replacing sulfonylureas as insulinotropic agents, but can frequently also be a good therapeutic alternative to other treatment options such as glitazones or glucosidase inhibitors. The CVOTs on alogliptin, linagliptin, saxagliptin, and sitagliptin have demonstrated cardiovascular safety but no beneficial effects in people with type 2 diabetes. Linagliptin may be a good choice as initial therapy in those with CKD or at risk for hypoglycaemia, while other DPP-4 inhibitors might be used in the setting of CKD with appropriate dose adjustment.

In a 24-week, multicentred, Phase III study, to assess the safety and efficacy of linagliptin 5 mg in people with type 2 diabetes, ~50% participants were South Asians. Individuals with mild or moderate renal impairment had similar linagliptin trough concentrations compared to individuals with normal renal function, which supports the concept that there may be no requirement for linagliptin dose adjustment in renally-impaired individuals [46]. A pooled analysis of randomised controlled trials of linagliptin, which including 330 South Asian people with type 2 diabetes, found that it was significantly superior to placebo in reducing mean HbA1c (0.75 ± 0.11 %) and mean fasting plasma glucose (-17.69 mg/dL) [47]. Linagliptin has a protective effect on endothelium and β-cell function [48], which may be relevant to South Asians although there is a lack of evidence in this population.

The role of early dual therapy of vildagliptin plus metformin was studied in the 5-year Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes (VERIFY) trial with 2000 participants (including 18.6% South Asians each in both study arms). Early intervention with a combination therapy of vildagliptin plus metformin provided greater and durable long-term benefits compared with the standard-of-care initial metformin monotherapy for people with newly diagnosed type 2 diabetes. There was also a relative reduction in the risk of treatment failure, which was similarly observed in people of South Asian origin with a HR of 0.45 (95% CI, 0.33-0.62) for time to initial treatment failure [33].

We recommend DPP-4 inhibitors as a preferable class for South Asian people with type 2 diabetes to sulfonylureas due to the lower BMI cut-off for obesity, and their good hypoglycaemia risk profile

during fasting. Linagliptin can be considered in South Asians since there is no dose adjustment needed in people with renal impairment, and is associated with decreased albuminuria and no increased risk of hospitalisation due to heart failure (unlike saxagliptin).

Thiazolidinediones

Pioglitazone has been advocated to be reconsidered in the type 2 diabetes therapeutic armamentarium to address CVD in individuals with insulin resistance, when used in the lower doses of 15 to 30 mg.

Pioglitazone acts by increasing insulin sensitivity; this might be beneficial in South Asians due to increased insulin resistance. Treatments associated with weight gain may not be appropriate in South Asians due to lower BMI cut-off for obesity. Fracture risk may be a concern owing to higher rates of vitamin D deficiency in South Asians.

Sulfonylureas

Sulfonylureas were the first available oral glucose-lowering drugs, and are the most commonly prescribed agents, along with metformin, for the management of type 2 diabetes. Sulfonylureas continue to have a place in the management of type 2 diabetes and should remain an essential component of the armamentarium for its glucose lowering abilities [49]. A comparative CVOT reported a similar incidence of cardiovascular events with sulfonylureas (mostly glimepiride and gliclazide) and pioglitazone as add-on treatments to metformin.

South Asians are at an elevated cardiovascular risk on account of hypoglycaemia compared to White Europeans. As a result, sulfonylureas may not be appropriate, in addition during fasts, due to the risk of hypoglycaemia. Treatments associated with weight gain may not be appropriate in South Asians due to lower BMI cut-off for obesity.

Insulin

Development of long-acting insulin analogues have resulted in improved flexibility of dosing time, simplified insulin dose titration and better glycaemic control in people with type 2 diabetes. Since they provide longer duration of action (~24 h) and reproducible serum concentration relative to Neutral Protamine Hagedorn (NPH) insulin, they mimic the basal slow and steady release of insulin

for narrow glucose level corrections. The long-acting insulins include glargine (U100 and U300), degludec (U100 or U200), and detemir. Insulin glargine has shown a significant incidence of lower nocturnal hypoglycaemia compared with NPH on account of improved time-action profiles. Insulin degludec has an ultra-long duration of action with stable glucose-lowering effect and reduced intra-individual variability.

Findings from a phase 3, multicentre, international, open-label, randomised, treat-to-target trial in patients with type 2 diabetes fasting during Ramadan demonstrated insulin degludec/insulin aspart as a suitable therapeutic agent for patients who need insulin for sustained glucose control before, during and after Ramadan fasting, with a significantly lower risk of hypoglycaemia, compared to biphasic insulin aspart 30 [50]. In Asian adults with type 2 diabetes, the combination was also found to effectively improve long-term glycaemic control, and provide superior reductions in fasting plasma glucose levels with a lower dose, and lesser nocturnal hypoglycaemia [S1].

The concentrated formulations of degludec (U200) and glargine (U300) allow injection of a reduced volume, providing convenience for individuals on higher doses. Though studies showed no reduced risk for CVD for any insulin, the CVOTs for glargine U100 and degludec did not show an increase in the risk for MACE.

Guidelines advocate GLP-1 receptor agonists as initial injectable therapy over basal insulin, based on similar or higher glycaemic efficacy, lower risk of hypoglycaemia, weight reduction, and cardiovascular benefit in people with atherosclerotic CVD (ASCVD). GLP-1 receptor agonists are recommended in most cases, except when HbA1c is >97 mmol/mol (>11%), or there is evidence of catabolism (weight loss, polyuria and polydipsia), or when there is concern of type 1 or pancreatogenic diabetes. [S2].

Due to the cultural aspects of fasting (with the potential increased risk of hypoglycaemic events) as well as the barriers to insulin injection such as frequency of insulin dosing in South Asians, the longer acting basal insulins glargine and degludec are preferable in the South Asian populations compared to NPH insulin.

International Guidelines for South Asians with type 2 diabetes

The recent 2019 ESC EASD guidelines on diabetes, pre-diabetes and cardiovascular diseases offered a paradigm shift in the management of type 2 diabetes. SGLT2 inhibitors and GLP-1 receptor agonists have displaced metformin as first-line glucose lowering therapies in type 2 diabetes drug naïve individuals with ASCVD, or high/very high cardiovascular risk [S3]. This underscores the change in management priorities from a traditional "glucose lowering efficacy" approach to the current emphasis on improving outcomes, and decreasing cardiovascular and renal events.

The South Asian Federation of Endocrine Societies consensus statement advocated customisation of treatment approaches for South Asian people taking into account their body types, dietary patterns and lifestyle; and recommended SGLT2 inhibitors as an initial monotherapy in metformin-intolerant individuals, after appropriate assessment of renal function [S4]. A Pakistani perspective on the use of SGLT2 inhibitors in South Asian population suggested good efficacy and safety of these agents in diabetes management [S5].

The South Asian Task Force highlighted the vital role of GLP-1 receptor agonists in real-world scenario and recommended adding a GLP-1 receptor agonist with demonstrated cardiovascular benefit in the medical regimen of South Asian people with diabetes as it not only confers glycaemic control but also reduce the increased cardiovascular risk [S6].

South Asian Health Foundation's best practice recommendations for selection of glucose-lowering medication in South Asians with Type 2 diabetes: Implications of evidence from CVOTs

Consequent to amalgamation of various higher physical, metabolic, dietary and genetic risk factors, type 2 diabetes often presents almost a decade earlier in South Asians than their Western counterparts. Additionally, disease awareness regarding type 2 diabetes is frequently low among South Asians which leads to a delayed diagnosis and accordingly longer duration of exposure to detrimental diabetic pathophysiologic processes on kidneys and cardiovascular system. South Asians have a comparatively higher HbA1c and glycaemia even at diagnosis, which deteriorates more with disease

progression. Poor compliance and inadequate management of glycaemia and other risk factors further lead to higher cardiovascular morbidity and mortality in South Asians.

The treatment approach of type 2 diabetes in South Asian population thus varies from the western strategy. The 2014 update by South Asian Health Foundation (SAHF) on type 2 diabetes in the UK South Asian population recommended a series of treatment options based on practical considerations while making management choices. On the basis of the new evidence generated in the last five years since that publication, particularly CVOTs, and the worldwide changes in management guidelines, the SAHF provides clear best practice recommendations for appropriate management of type 2 diabetes in South Asian population as outlined in Fig. 4.

Lifestyle management forms the platform over which all the glucose-lowering therapies are placed. A patient-centric individualised approach is advocated with special emphasis on the presence or absence of ASCVD and increased cardiovascular risk (presence of eGFR <60mL/min/1.73m^2, microalbuminuria, younger age, multiple microvascular complications). As the South Asian population with diabetes is frequently younger, have a higher HbA1c at diagnosis with more rapid worsening of glycaemic control and suffer from a rapid deterioration of β-cell function, dual glucose-lowering therapy at diagnosis should be inevitable for optimal benefits.

Therapeutic inertia in type 2 diabetes management, a global phenomenon, with resultant poor glycaemic control also impedes the ultimate aim of achieving better patient outcomes. Delays in treatment intensification occur at all stages of diabetes management from initiation and subsequent stepping-up of oral glucose-lowering therapies after failure of lifestyle management, to escalation to insulin therapy [S7]. Dual initial therapy thus overcomes the barriers of therapeutic inertia achieving two-fold objectives of early glycaemic control and prevention of delays in treatment intensification despite suboptimal control.

Early and aggressive management strategy should be employed in South Asian people with type 2 diabetes, with a clear objective to reduce the risk of microvascular and macrovascular complications. While formulating the current recommendations due emphasis was given to the results of large multicentric CVOTs with various drugs published in the last decade. Dual initial therapy with any of the SGLT2 inhibitors, GLP-1 receptor agonists with or without metformin may significantly improve

cardiovascular, renal and mortality outcomes in this population. Nevertheless, more research is vital to appreciate the extent of beneficial effects of these drugs in the South Asian population.

Overall type 2 diabetes management requires focus on reduction of micro- and macrovascular complications as well as the weight of the individual, and hypoglycaemia risk. The role of treatment compliance should be reinforced and if the HbA1c target is not achieved after three months of treatment, intensification of glucose-lowering regimen is advocated. DPP4 inhibitors, newer sulfonylureas, pioglitazone and basal insulin are the therapeutic options available and the choice of drug should be individualised based on the above-mentioned factors in addition to patient preference and avoidance of side effects. The South Asian Health Foundation's best practice recommendations on therapies for managing hyperglycaemia in type 2 diabetes considering advantages, disadvantages and practical considerations for use in the South Asian population are summarised in Table 1.

Conclusion

Although there is a decrease in diabetes-associated cardiovascular morbidity and mortality in the second-generation migrant South Asian population, the absolute as well as relative risk of diabetes and associated complications in this population still remains high and is a major concern. Consequently, it presents a major challenge for research organisations, non-governmental organisations and policy makers. There is a need to undertake targeted strategies to improve healthcare access and encourage participation of South Asians in clinical trials. The research-based and real-world evidence thus generated will positively guide the various stakeholders in formulating appropriate management programmes. At the level of community-based healthcare professionals, due considerations should be given to cultural practices including differences in physical activity patterns, variations in diet and religious fasting and feasting, while making treatment decisions. The plethora of evidence from CVOTs is encouraging as these novel drugs offer a potential to improving cardiovascular and renal outcomes in this subgroup. A concerted effort by all sections of the healthcare system is required to deliver effective and more tailored individualised care of South Asians with type 2 diabetes in the foreseeable future.

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51.

TABLES

Table 1: Recommendations on therapies for managing hyperglycaemia in South Asians

Medication class	Recommendations	Considerations in South Asian population
Metformin	▪ First line therapy in type 2 diabetes drug naïve persons without ASCVD or high/very high CV risk	▪ Risk of vitamin B12 deficiency may be of concern in vegetarian or vegan South Asians ▪ Modest increase in insulin sensitivity might be beneficial in South Asians due to increased insulin resistance in this population ▪ Extensive experience in South Asian population ▪ Potential ASCVD benefits ▪ Weight neutral
SGLT2 inhibitors	▪ First line therapy in drug naïve people with type 2 diabetes and ASCVD or high/very high CV risk (for drugs with proven CVD benefit) ▪ Canagliflozin is approved by USFDA to reduce the risk of MACE in adults with type 2 diabetes and established CVD, and to reduce the risk of ESRD, doubling of serum creatinine, CV death, and hHF in adults with type 2 diabetes and diabetic nephropathy with albuminuria	▪ Vital therapeutic option to delay or prevent complications due to high risk of CVD among South Asians ▪ Preferable for South Asians owing to lower BMI cutoff for obesity ▪ Appropriate for use during fasting on account of good hypoglycaemia risk profile; however, volume depletion may be a concern ▪ Insulin independent mechanism of action may be beneficial as South Asians are generally more insulin resistant

	▪ Dapagliflozin is approved by USFDA to reduce the risk of hHF in adults with type 2 diabetes and established CVD or multiple CV risk factors ▪ Empagliflozin is approved by USFDA to reduce the risk of CV death in adults with type 2 diabetes and established CVD	
GLP1 receptor agonists	▪ First line injectable therapy in drug naïve people with type 2 diabetes and ASCVD or high/very high CV risk (for drugs with proven CVD benefit) ▪ Dulaglutide is approved by USFDA to reduce the risk of MACE in adults with type 2 diabetes and established CVD or multiple CV risk factors ▪ Liraglutide and injectable semaglutide are approved by USFDA to reduce the risk of MACE in adults with type 2 diabetes and established CVD ▪ Injectable semaglutide is approved by USFDA to reduce the risk of MACE in adults with type 2 diabetes and established CVD	▪ Vital therapeutic option to delay or prevent complications due to high risk of CVD in South Asians ▪ Preferable for South Asians on account of lower BMI cutoff for obesity ▪ Appropriate for use during fasting due to good hypoglycaemia risk profile ▪ Excellent postprandial glycaemic control
DPP-4 inhibitors	▪ Add-on therapy in adults with type 2 diabetes ▪ Saxagliptin is not recommended in individuals at high risk of HF	▪ May be preferable for South Asians due to the lower BMI cutoff for obesity ▪ Good hypoglycaemia risk profile during fasting

	▪ Consider risk benefit ratio in individuals with known risk factors for HF	▪ CV neutral ▪ Weight neutral ▪ Well tolerated
Pioglitazone	▪ Add-on therapy in adults with type 2 diabetes ▪ Not recommended in individuals at high risk of HF	▪ Works by increasing insulin sensitivity; might be beneficial in South Asians owing to increased insulin resistance. ▪ Treatments associated with weight gain may not be appropriate in South Asians due to lower BMI cutoff for obesity ▪ Fracture risk may be a concern owing to higher rates of vitamin D deficiency in South Asians
Sulfonylureas	▪ Add-on therapy in adults with type 2 diabetes ▪ Choose later-generation sulfonylureas with lower risk of hypoglycaemia	▪ South Asians are at elevated CV risk on account of hypoglycaemia compared to White Europeans ▪ May not be appropriate during fasts owing to the risk of hypoglycaemia ▪ Treatments associated with weight gain may not be appropriate in South Asians due to lower BMI cutoff for obesity

Insulins	▪ Basal insulin is the preferred initial formulation ▪ Rapid-acting insulin at mealtime to intensify basal insulin therapy in individuals not meeting glycaemic targets	▪ May not be appropriate during fasts owing to the risk of hypoglycaemia ▪ South Asians are at elevated CV risk on account of hypoglycaemia compared to White Europeans ▪ Doses and timing of administration may need adjustment according to the dietary habits of South Asians ▪ Treatments associated with weight gain may not be appropriate in South Asian people due to lower BMI cutoff for obesity ▪ Stigma surrounding insulin use and reluctance to initiate insulin may be greater in South Asians
Adapted from: Cosentino F, 2019; Das SR, 2018; Davies MJ, 2018. Considerations relevant to South Asian people are based upon the authors' clinical experience.		
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage kidney disease; GI, gastrointestinal; HDL, high-density lipoprotein; HF, heart failure; hHF, hospitalisation for heart failure; MACE, major adverse coronary events; UKPDS, United Kingdom Prospective Diabetes Study; USFDA, United States Food and Drug Administration.		

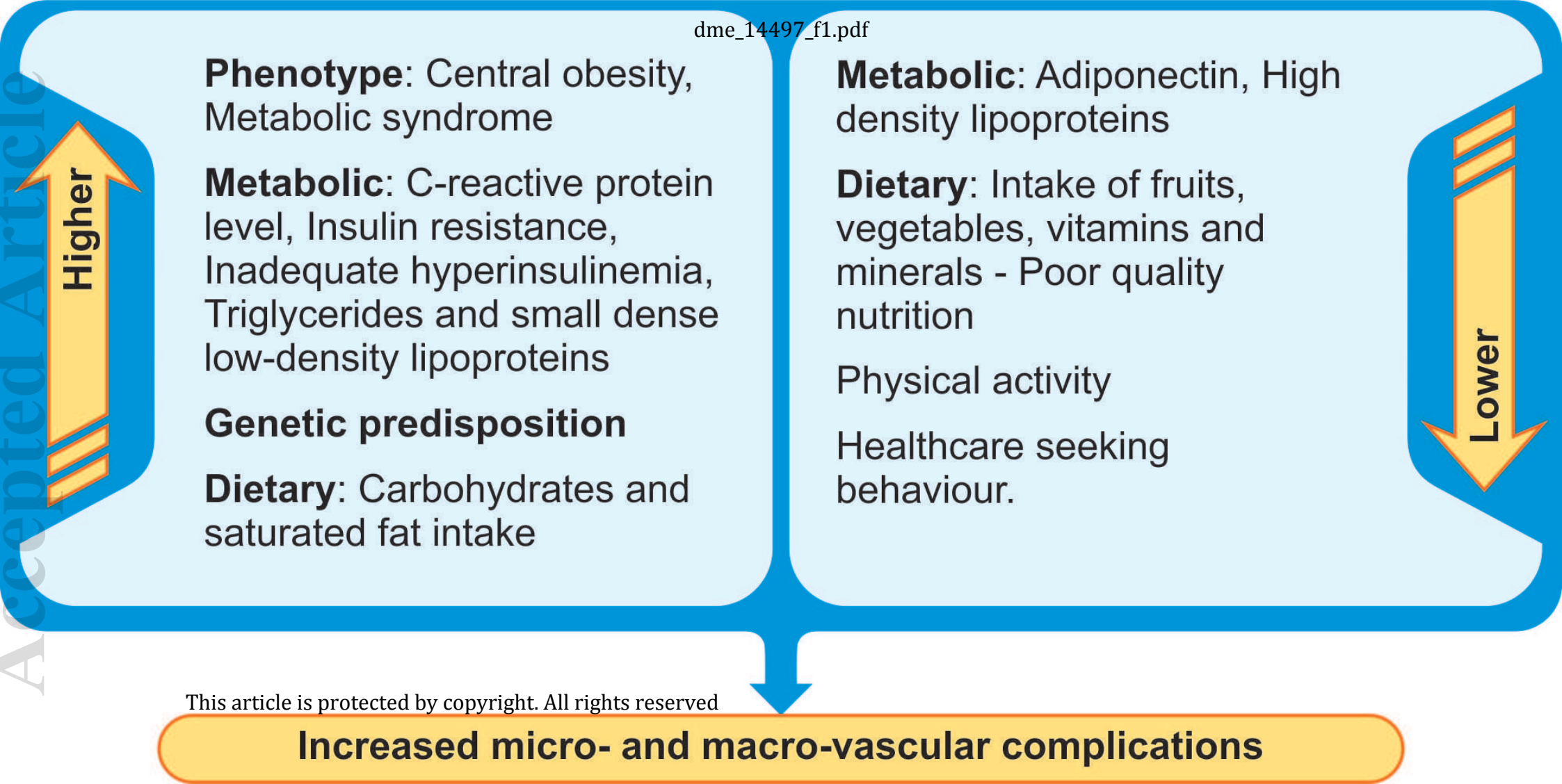
FIGURES LEGENDS

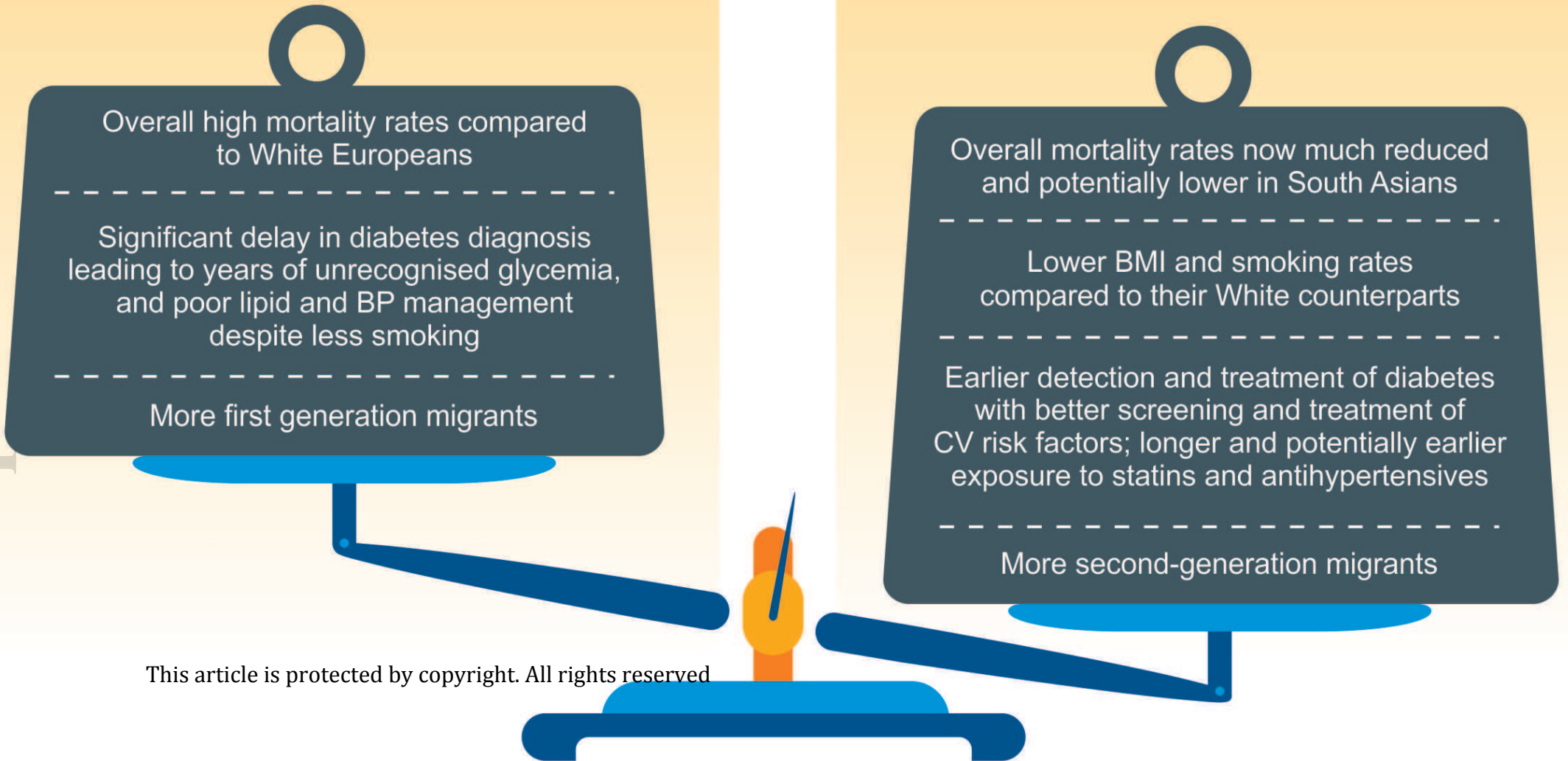
Fig. 1: Amalgamation of various factors leading to increased risk of diabetes and associated complications in the South Asian population

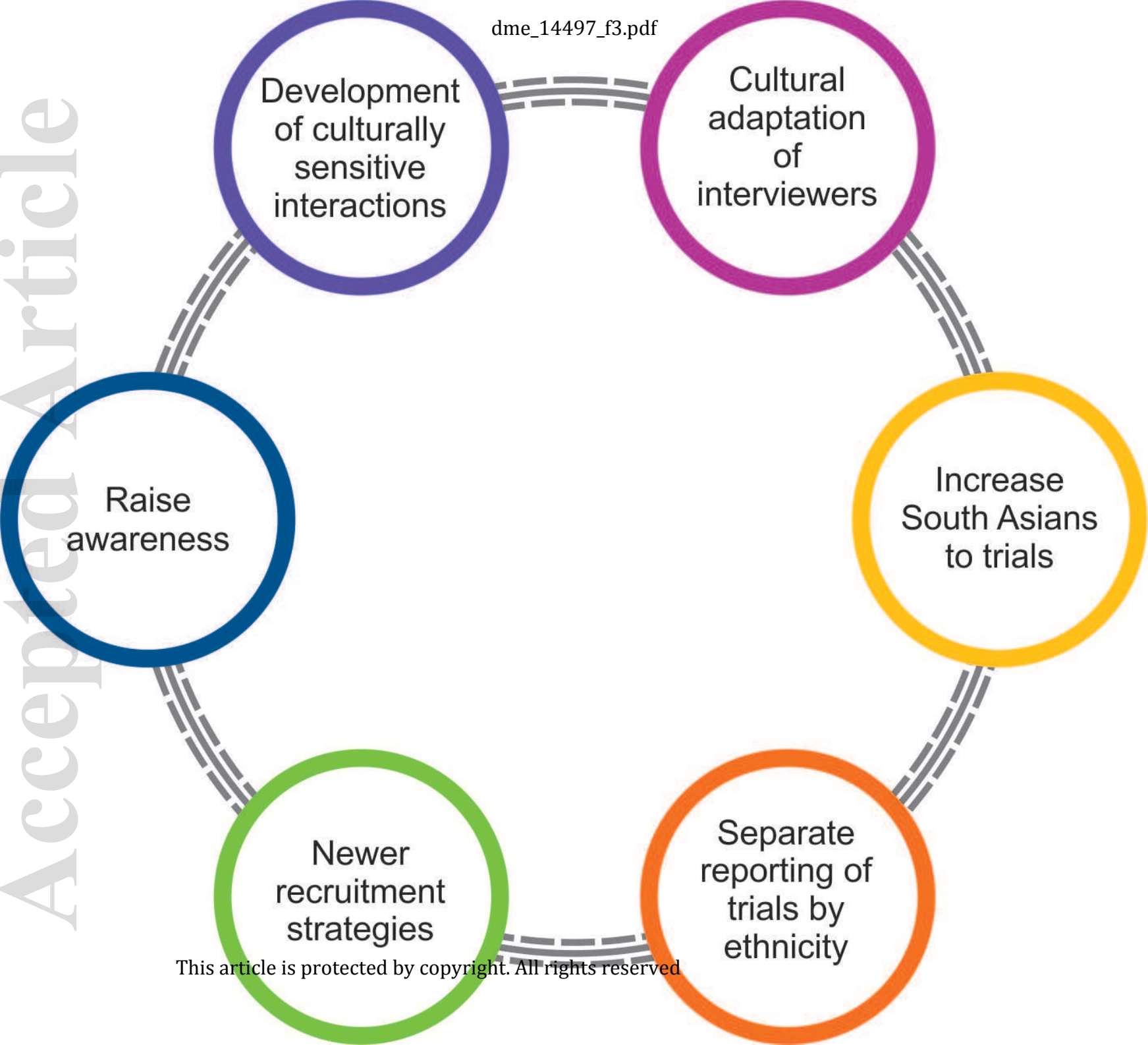
Fig. 2: Speculated mechanisms for changing cardiovascular mortality risks in migrant South Asians with diabetes

Fig. 3: Strategies proposed to facilitate South Asian participation in clinical trials

Fig. 4: The South Asian Health Foundation (SAHF) recommendations for appropriate management of type 2 diabetes in the South Asian population







Therapy	Evidence	Special considerations in South Asian population
Lifestyle management	• High carbohydrate & fat intake, along with decreased physical activity is characteristic of South Asians	• Proven cardiometabolic benefits in this high CV risk population • Fundamental aspect of diabetes management in this group in reducing complications

In patients with ASCVD* or at high risk (HF or eGFR <60 mL/min/1.73 m² or microalbuminuria or multiple microvascular complications or young T2DM)**

Consider dual therapy with any of the following:
Metformin and/or SGLT2i and/or GLP-1 RA (Drugs with proven benefits)

Metformin	• Universally recommended by diabetes treatment guidelines as first line glucose-lowering therapy • Beneficial across wide population subgroups of pre-diabetes, established T2DM and metabolic syndrome • Baseline therapy on which beneficial CV effects of SGLT2i and GLP-1 RA are studied	• Risk of vitamin B12 deficiency may be of concern in vegetarian or vegan South Asians • Modest increase in insulin sensitivity might be beneficial in South Asians due to increased insulin resistance in this population
SGLT2 inhibitors with Proven CVOT ▸ Canagliflozin ▸ Dapagliflozin ▸ Empagliflozin	• Large CV and renal outcome studies demonstrated consistent reduction in MACE and improved renal function parameters ➔ CANVAS: ↓ MACE ➔ CREDENCE: ↓ MACE, renal events (NNT for composite renal outcomes = 28; NNT for 3-P MACE = 40) ➔ DECLARE-TIMI 58: ↓ CV mortality and hHF ➔ DAPA-HF: ↓ hHF (NNT for worsening heart failure or CV mortality = 21) ➔ EMPA-REG: ↓ MACE, all cause mortality (NNT for all-cause mortality = 39)	• South Asian populations are underrepresented and representation varied • Vital therapeutic option to delay or prevent CV/renal complications among South Asians • Appropriate for use during fasting on account of good hypoglycaemia risk profile; however, volume depletion may be a concern • Insulin independent mechanism of action may be beneficial as South Asians are generally more insulin deficient • Expensive
GLP-1 receptor agonists CVOT ▸ Albiglutide ▸ Dulaglutide ▸ Exenatide-extended release ▸ Liraglutide ▸ Lixisenatide ▸ Semaglutide	• First-line injectable therapy • Dulaglutide, liraglutide and semaglutide showed consistent CV events reduction ➔ HARMONY: ↓ MACE ➔ REWIND: ↓ MACE (NNT for 3-P MACE with previous CV event = 18) ➔ EXSCEL, ELIXA: Established CV safety but no benefit ➔ LEADER: ↓ MACE, all-cause mortality (NNT for 3-P MACE = 66; NNT for all-cause mortality = 98) ➔ SUSTAIN-6: ↓ MACE (NNT for 3-P MACE = 45) ➔ PIONEER-6: Established CV safety, ↓all-cause mortality	• South Asian populations are underrepresented and representation varied • Vital therapeutic option to delay or prevent CV/renal complications among South Asians • Preferable for South Asians on account of lower BMI cutoff for obesity • Appropriate for use during fasting due to good hypoglycaemia risk profile • Expensive • Injectables

Further intensifications needed, HbA1c above target at >3 months

In patients without ASCVD or not at high-risk (DPP-4i or Pioglitazone or Sulfonylureas or Basal insulin)

Important considerations: If Hypoglycaemia (DPP-4i, Pioglitazone, SGLT2i), If Obesity (GLP-1 RA, SGLT2i), If Cost (Pioglitazone, Sulfonylureas)

DPP-4 inhibitors CVOT

- Alogliptin
- Linagliptin
- Saxagliptin
- Sitagliptin

- Established CV safety but no benefit
  - EXAMINE
  - CARMELINA
  - SAVOR-TIMI 53
  - TECOS
- Linagliptin: No dose adjustment in patients with renal impairment, no increased risk of hHF, decreased albuminuria
- Increased risk of HF with saxagliptin

- Good hypoglycaemia risk profile during fasting
- Expensive

Pioglitazone

- Some CVD benefit perhaps
  - IRIS
  - PROACTIVE
- Glycaemic durability
- Increased risk of HF

- Works by increasing insulin sensitivity; might be beneficial in South Asians due to increased insulin resistance
- Treatments associated with weight gain may not be appropriate in South Asians due to lower BMI cutoff for obesity
- Fracture risk may be a concern due to higher rates of vitamin D deficiency in South Asians

Sulfonylureas

- Indispensable glucose-lowering therapy due to extensive experience, high efficacy and generic drug availability
- Newer generation sulfonylureas preferred due to lower risk of hypoglycaemia
- CAROLINA did not show increased mortality with Glimepiride compared to Linagliptin
- TOSCA.IT did not show increased mortality with Glimepiride and Gliclazide compared to Pioglitazone

- South Asians are at an elevated CV risk on account of hypoglycaemia compared to White Europeans
- May not be appropriate during fasts due to the risk of hypoglycaemia
- Treatments associated with weight gain may not be appropriate in South Asians due to lower BMI cutoff for obesity

Insulin

- Basal insulin preferred when target HbA1c is not achieved after 2-3 oral glucose-lowering therapies
- Demonstrated CV safety
  - DEVOTE
  - ORIGIN
- Rapid acting insulin at meal time in patients not meeting glycaemic target
- Very high efficacy
- Beta-cell protection

- May not be appropriate during fasts due to the risk of hypoglycaemia
- South Asians are at an elevated CV risk on account of hypoglycaemia compared to White Europeans
- Doses and timing of administration may need adjustment according to the dietary habits of South Asians
- Treatments associated with weight gain may not be appropriate in South Asian people due to lower BMI cutoff for obesity
- Stigma surrounding insulin use and reluctance to initiate insulin may be greater in South Asians

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; CVOT, cardiovascular outcome trial; DPP4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HF, heart failure; hHF, hospitalisation due to heart failure; MACE, major adverse coronary events; NNT, number needed to treat; SGLT2i, sodium glucose co-transporter 2 inhibitor; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; US FDA, United States Food and Drug Administration.

*Including the following scenarios

- New diagnosis of clinical ASCVD in a patient with T2DM on a drug regimen that does not include a GLP-1 RA or SGLT2i
- New diagnosis of T2DM in a patient with clinical ASCVD
- At hospital discharge after admission of an ASCVD- or diabetes-related clinical event

**If HF or CKD predominates in established ASCVD, SGLT2i are preferred (if eGFR is adequate), GLP-1 RA if SGLT2i are not tolerated, contraindicated or eGFR less than adequate.

DPP4i and GLP-1 RA should not be co-administered. GLP-1 RA and SGLT2i are preferred glucose-lowering agents for weight reduction. If cost is a major issue, consider a sulfonylurea and/or thiazolidinedione in addition to metformin.

Drugs to be avoided:

a. In the setting of HF: Thiazolidinediones and Saxagliptin;
b. In the setting of ESRD: Metformin and SGLT2i