Managing cardiovascular disease risk in South Asian kidney transplant recipients

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abstract

South Asians (SA) are at higher cardiovascular risk than other ethnic groups, and SA kidney transplant recipients (SA KTR) are no exception. SA KTR experience increased major adverse cardiovascular events both early and late post-transplantation. Cardiovascular risk management should therefore begin well before transplantation. SA candidates may require aggressive screening for pre-transplant cardiovascular disease (CVD) due to their ethnicity and comorbidities. Recording SA ethnicity during the pre-transplant evaluation may enable programs to better assess cardiovascular risk, thus allowing for earlier targeted peri- and post-transplant intervention to improve cardiovascular outcomes. Diabetes remains the most prominent post-transplant cardiovascular risk factor in SA KTR. Diabetes also clusters with other metabolic syndrome components including lower high-density lipoprotein cholesterol, higher triglycerides, hypertension, and central obesity in this population. Dyslipidemia, metabolic syndrome, and obesity are all significant CVD risk factors in SA KTR, and contribute to increased insulin resistance. Novel biomarkers such as adiponectin, apolipoprotein B, and lipoprotein (a) may be especially important to study in SA KTR. Focused interventions to improve health behaviors involving diet and exercise may especially benefit SA KTR. However, there are few interventional clinical trials specific to the SA population, and none are specific to SA KTR. In all cases, understanding the nuances of managing SA KTR as a distinct post-transplant group, while still screening for and managing each CVD risk factor individually in all patients may help improve the long-term success of all kidney transplant programs catering to multi-ethnic populations.

Key Words: Cardiovascular risk; South Asians; Diabetes; Dyslipidemia; Metabolic syndrome; Health behavior; Novel cardiovascular risk factors

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Cardiovascular disease in South Asians

Core Tip: South Asian kidney transplant recipients are at higher risk for cardiovascular disease. Aggressive management should begin before transplantation and continue into the post-transplant phase. Each risk factor should be managed individually to reduce cardiovascular risk and improve post-transplant outcomes.

INTRODUCTION

Kidney transplantation (KT) provides the highest survival benefit for patients once chronic kidney disease (CKD) progresses to end-stage kidney disease (ESKD)[1]. Registry analyses of KT recipient (KTR) outcomes indicate that cardiovascular disease (CVD) substantially contributes to post-transplant mortality[2]. South Asian (SA) KTR in particular are at higher CVD risk than other population groups[3]. Worldwide experience with post-transplant care in patients of SA origin is increasing[3-5] and as access to KT within SA itself also gradually increases[6], further SA KTR experience will accumulate. According to the Transplantation Society website (accessed February 11, 2019), there were almost 7000 KT performed in India alone. Despite the known higher post-transplant CVD risk in SA[3], preventive and management recommendations for SA KTR have not been made even with available SA-specific general population and CKD population information[7,8]. This review summarizes available literature on CVD in the SA population more generally, and integrates this with post-transplant CVD more specifically so that focused recommendations can be considered to both study and guide CVD management in SA KTR.

CARDIOVASCULAR DISEASE INCIDENCE AND MORTALITY IN SOUTH ASIANS

South Asia typically refers to the Indian subcontinent (India, Pakistan, Nepal, Bangladesh, Sri Lanka, Bhutan, and Maldives), and these two geographical terms are often used interchangeably. SA have emigrated to many parts of the world. SA ethnicity is a risk factor for CVD, whether SA live in their country of origin or have emigrated to countries outside SA. Within India, SA’s largest country, about 2.8 million people died from CVD in 2016 alone[9]. CVD leads mortality across both urban and rural areas[10]. With improved longevity, CVD prevalence also increased by 4 to 7-fold between 1970 and 2013[11].

Emigrating Indians facilitate comparisons to other ethnic groups in their new countries. Coronary artery disease (CAD) is more incident and prevalent in SA[12]. A review of 124 articles indicates that SA have twice the CAD prevalence compared to age- and sex-adjusted Caucasians[13]. In Canada, the age-standardized incidence of acute myocardial infarction (MI) in SA men was 4.97/1000 population per year compared to 3.29/1000 population per year in Caucasian men[14]. In the United Kingdom, SA were almost four times as likely to report a history of MI compared to other groups[15]. CVD incidence may even be higher as succeeding generations of SA live outside South Asia[16].

SA experience acute MI about 10 years earlier than the global population[17]. In India, the mean age for CAD documented by angiography is 48 years, with one-third of cases occurring under 45 years[18]. Young Indians typically over-represent CAD outside SA, such as in the Middle East[19]. Mortality from CAD in SA is also higher[20] and occurs earlier[21]. Sex-standardized mortality rates from CAD are about 50% higher in SA compared to Caucasians for both men and women[22]. SA have a greater burden of triple-vessel disease and a greater atheroma score[23]. CAD may thus be more incident, prevalent and severe in SA.

How well do such epidemiological studies apply to SA KTR? Death with graft function (DWGF) is a leading cause of late kidney allograft loss, and CVD is its leading
cause[24]. Unselected KTR have an annual cardiovascular event rate of 3.5%-5%[25]. Major adverse cardiovascular events (MACE), a term encompassing acute coronary syndrome, coronary revascularization, hospitalization for congestive heart failure and cardiac death, contribute significantly to overall post-transplant morbidity and mortality[24]. A current estimate indicates about 8000 KT are performed across over 267 transplant centres in SA patients annually[6]. KT rates will increase further as deceased donor organ procurement and paired donations increase[6]. Many SA already reside in countries such as Canada, the United States, and the United Kingdom, where KT rates are high and comparisons across ethnic groups will become possible. Therefore, studying and comparing cardiovascular risk factors in SA KTR is worthwhile.

Few studies report post-transplant cardiovascular events in SA. A single-centre study from Canada[3] reported a post-transplant MACE rate of 4.4/100 patient years in SA, compared to 1.31 in Caucasians, 1.16 in blacks, and 1.61 in East Asians (P < 0.0001 vs each). SA also experienced a greater incidence of post-transplant MACE in the first three months compared to each of the other groups[3]. The pre-transplant prevalence of CVD was similar across ethnic groups. In a study from India, CAD was diagnosed in 28% post-KT, and was a major cause of DWGF for up to 15 years[26]. An evaluation of elderly South Indian KTR found that CVD was a major contributor to the post-transplant mortality rate of 12% over 4 years[27]. The increased cardiovascular risk in SA KTR is thus consistent with that of the corresponding SA general population. CKD per se confers increased CVD risk[28], but to accommodate KT potential candidates are usually subject to rigorous pre-transplant cardiovascular screening and risk mitigation[29]. Yet focused study of post-transplant CVD risk and mortality in SA KTR is tragically scarce.

In view of the dearth of studies on CVD in SA KTR, it may be helpful to first look at studies relating CKD to CVD more generally. CKD strongly associates with CVD mortality[30]. Low estimates of glomerular filtration rate (eGFR) and albuminuria are multiplicative in populations at risk for CKD, where risk factors include hypertension, diabetes, or CVD, but they are not interactive with respect to all-cause and CVD mortality[31]. In the SA general population the urine albumin-to-creatinine ratio may better estimate CVD risk and mortality[32], although eGFR in SA using existing equations may be inaccurate[33]. Vagueness results in CVD risk estimation when eGFR estimates are inaccurate and the unique post-transplant milieu compounds this vagueness further.

There is a need for awareness that MACE is both more common and more severe in SA KTR, just as during other CKD phases. A pre-transplant history of CVD remains an important risk factor for post-transplant MACE. Well-studied risk factors mirror those of the general population. In a large multi-ethnic sample from Canada that included a substantial number of South Asians, the Framingham Risk Score calculator under-predicted MACE[34]. Few studies examine either traditional or novel cardiovascular risk factors specifically in SA KTR, but managing cardiovascular risk is best targeted to individual risk factors, as with the KTR population as a whole.

**CARDIOVASCULAR DISEASE SCREENING**

Management of cardiovascular risk begins well before transplantation. Recording SA ethnicity during the pre-transplant evaluation process enables programs to assess cardiovascular risk in greater depth and potentially intervene earlier. Regular pre-transplant screening for CVD remains controversial[35]. Findings from clinical trials regarding CVD screening should be cautiously applied to SA KTR due to their differential risk, unless adequate SA representation in such trials can be ensured. Critical ischemic lesions when detected may be more advanced, and if occurring at a younger age should preclude lower age limits for initial pre-transplant screening. Pre-transplant screening for diabetes incidence and control through an oral glucose tolerance test or HbA1c may permit further focus to managing pre- and post-transplant cardiovascular risk[36].

SA transplant candidates with stable CAD are likely to receive aspirin, but may be at risk for suboptimal utilization of beta blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers, and statins[37]. These medications are commonly used for pre-transplant optimization. However, based on non-SA specific data, initiating a beta-blocker just prior to non-cardiac surgery may prevent perioperative non-fatal MI but increase risk for stroke or death[38]. SA representation in similar clinical trials is needed. Besides screening at a
younger age, lower thresholds for blood pressure (BP) treatment may also be required [39]. SA may even be underrepresented in statin trials[40]. In the case of pre-dialysis KT candidates, SA-specific eGFR equations can be explored[41]. Among dialysis modalities, peritoneal dialysis may decrease post-transplant graft dysfunction[42]. In all cases, SA candidates require special attention to pre-transplant cardiovascular risk reduction to optimize post-transplant success.

Despite widely practiced pre-transplant screening, routine screening for post-transplant CVD is rarely practiced by busy transplant programs. Awareness of the increased CVD risk in SA KTR however may allow earlier post-transplant referral to cardiologists and other specialists, and ensure continuity of cardiovascular care from the pre-transplant to the post-transplant phase of CKD. A major role of post-transplant programs is to ensure that CVD risk factors are adequately managed.

**INDIVIDUAL CARDIOVASCULAR RISK FACTORS**

**Diabetes**
Diabetes is the most significant cardiovascular disease risk factor in SA KTR[43]. One estimate indicates 87 million Indians will have diabetes by 2030[44]. The crude prevalence of diabetes in a population-based study of 1.3 million Indian adults, based on fasting or random glucose measurement was 7.5%[45]. In a United States study, diabetes prevalence was 17% in SA compared to 8% in non-Hispanic whites[46]. SA demonstrate a higher degree of insulin resistance[47] and early pancreatic β-cell dysfunction[48]. Diabetes in SA also clusters with other metabolic syndrome components such as lower high-density lipoprotein (HDL) cholesterol, higher total-to-HDL cholesterol (HDL-C) ratio, and hypertension[7]. SA are more centrally obese[49], the phenotype of which includes less subcutaneous adipose tissue compared to Caucasians, combined with more deep cutaneous and visceral fat[7]. A body mass index in SA of over 35 kg/m² associates with increased mortality from CAD[50]. Duration of residence in the United States inversely correlates with being overweight or obese and the likelihood of leading a sedentary lifestyle, while being directly correlative to fruit and vegetable consumption[51].

SA more likely transport an existing diabetes burden to their post-transplant phase. Pre-existing diabetes increases the risk of post-transplant CVD threefold[52]. Significant CAD is detectable by angiography in a third to half of diabetic patients with ESKD[53]. Diabetes in SA is also likely to occur 5-10 years earlier[54], likely increasing post-transplant CVD attributable to diabetes. Post-transplant diabetes mellitus (PTDM) is also increased in SA, with an incidence at median 50 mo higher in SA (35%) compared to Caucasians (10%, \( P < 0.001 \) for difference)[55]. Calcineurin inhibitors (CNI) and steroids blunt insulin secretion and increase insulin resistance and dysfunction[56] in a population already at higher risk in this milieu of immune stress and ischemia-reperfusion injury[55]. Tacrolimus is generally more diabetogenic than cyclosporine. Differing predisposition to PTDM by CNI type may occur in SA based on the human leukocyte antigens profile[57]. However, there are no studies to prospectively modify PTDM risk in SA KTR.

PTDM portends a worse post-transplant prognosis in SA KTR[58]. There is no proven benefit to avoiding tacrolimus or prednisone to prevent or control diabetes in any population, so immunological concerns primarily should motivate choice of immunosuppressive medication. Glucagon-like peptide 1 receptor agonists (GLP-1RA) may similarly affect glycemia and weight in non-KTR SA, while dipeptidyl peptidase-4 inhibitors may provide greater glycemic benefit[59]. Sodium-glucose transport protein 2 inhibitors (SGLT2i) are safe, and may also provide greater benefit in non-KTR SA compared to Caucasians[59,60]. GLP-1RA and SGLT2i outcome trials demonstrated benefit in some subgroups, although granularity of ethnicity data remains a concern. Linagliptin either as monotherapy or combined with metformin or glimepiride may be effective in SA KTR[61].

**Hypertension**
Hypertension is also widely prevalent in the SA general population, with one estimate being 25% when defined as systolic BP (SBP) ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic[45]. Even among the youngest adults (18-25 years of age), the prevalence of hypertension was around 12%[45]. Based on echocardiography the left-ventricular mass index and left-ventricle remodeling index are lower in SA compared to Caucasians[62], despite no significant differences between them in electrocardiographic voltage[63]. By contrast, diabetes may impact left ventricular function...
adversely in SA compared to Caucasians[64].

Similar to diabetes, hypertension is widely prevalent at transplantation, is exacerbated by CNI particularly cyclosporine, and may occur de-novo or worsen as a result of stable or progressive graft dysfunction. A report suggests that each 10 mmHg systolic BP increase relates to an 18% increase in mortality[65]. Although hypertension is widely prevalent among SA, there is little literature to suggest that its risk in SA is increased compared to other ethnic groups, either with or without CKD. Awareness of hypertension is low in India[66], but might be higher in emigrant Indians[67], so one might also expect higher awareness in SA KTR.

There are no BP-lowering trials specific to SA KTR. The AIM-HY-INFORM trial in the United Kingdom plans to recruit one-third SA, using amlodipine, lisinopril, and chlorthalidone in varying combinations[68]. A review of 16 randomized controlled trials with BP outcomes in 1719 SA hypertensive patients showed no significant differences in BP-lowering efficacy among drugs[39]. SA may generally respond to antihypertensive therapy similar to Caucasians[69]. Vitamin D deficiency may also play a role in hypertension[70]. In a sub-analysis of the Anglo-Scandinavian Cardiac Outcomes Trial study, BP response to amiodipine monotherapy, or adding a diuretic to atenolol did not differ significantly by ethnic group. However, adding perindopril to amiodipine resulted in a greater SBP response in SA compared to Caucasians [-6.2 (-10.2 to -2.2) mmHg vs -1.7 (-2.8 to -0.7) mmHg][70]. Adherence to ACE inhibitors may be concerning[71].

**Dyslipidemia**

SA consistently demonstrate higher triglycerides and lower HDL-C levels, in addition to having more pro-inflammatory small-dense HDL-C even if the HDL-C level is normal[72]. SA also have higher small dense-low-density lipoprotein cholesterol (LDL-C)[73] and non-esterified fatty acids[74], indicating a defective insulin response in adipose tissue leading to pancreatic β-cell dysfunction[75]. Apparently normal total cholesterol levels can therefore be quite deceptive to conventional CVD risk assessment in SA KTR.

Dyslipidemia affects almost half of KTR. The association between post-transplant dyslipidemia and CVD may not be as strong as for diabetes and CVD, especially when considering dyslipidemia as a stand-alone risk factor[76]. However, according to one estimate in non-SA populations, a 2 mmol/L increase in LDL-C doubles the risk for MACE[77], while a low level of HDL-C associates with a threefold increase in post-transplant MACE[78]. A composite measure, non-HDL-C may be a powerful predictor of MACE in KTR[79]. Both low HDL-C and hypertriglyceridemia are components of the metabolic syndrome, to which SA are prone[80]. Hypertriglyceridemia is associated with progressive coronary artery calcification[81]. While CVD risk data for metabolic syndrome may be stronger than for dyslipidemia alone and the unique contribution of dyslipidemia in SA KTR is unclear[82], dyslipidemia should not be ignored.

There are no lipid-lowering trials in SA KTR, although statins are effective at lowering both total cholesterol and LDL cholesterol in non-transplant SA populations[82]. There is no difference in lipid-lowering response compared to Caucasians[83]. Statins may also lower BP in KTR population samples with significant SA representation[84]. Statin use in SA KTR requires close monitoring. Rosuvastatin doses should be kept lower in SA due to increased plasma exposure[85].

**Obesity**

SA possess a greater waist-to-hip circumference ratio than native United Kingdom populations[86], and SA possess 6% more body fat for a given waist circumference or body mass index (BMI)[87]. In the United States, migrant Indians have greater total abdominal fat and intra-abdominal adipose tissue[88]. Skinfold thickness is also greater, even in children[89]. Increased hepatic steatosis[90], intra-myocellular triglyceride deposition, and adipocyte size in subcutaneous adipose tissue[88], as well as lower skeletal muscle mass[91] are all seen more in SA compared to Caucasians.

A meta-analysis of 165 studies with 1.5 million participants with any stage of CKD failed to demonstrate an association between obesity and mortality in CKD, but sparse data regarding waist and hip measurements did not allow further analyses[92]. However, the increased MACE risk in KTR is real[3] and SA have numerous increased obesity-related CVD risk factors[86-91]. Overweight in SA doubles the risk for CKD, more than for any other ethnic group[95]. In a European study higher age and female sex were associated with more post-transplant obesity, which in turn was associated with increased PTDM and lower eGFR[94], both of which increase CVD risk. An increased waist-to-hip ratio in KTR samples with large SA representation indicates less
impact compared to other cardiovascular risk factors[43], but monitoring the waist-to-hip ratio may help motivate positive health behavior.

**Metabolic syndrome**

Metabolic syndrome is more prevalent in SA compared to Caucasians[95]. Once the metabolic syndrome develops, SA have a higher blood pressure, serum triglycerides, and fasting insulin levels, along with lower HDL-C levels compared to Caucasians[72]. Insulin resistance, which is the cardinal feature of metabolic syndrome, also occurs at a lower age in SA, occurring often in adolescents[96] and perhaps even at birth[97]. Insulin resistance in turn correlates with adipocyte size[87] and hepatic steatosis[90].

Metabolic syndrome is present in over one-fourth of KTR in India and is associated with female gender and hypertriglyceridemia[98]. Metabolic syndrome increased post-transplant MACE in a population in which SA were over-represented[43]. Metabolic syndrome also increases the risk of graft failure generally, but its contribution to graft loss in SA KTR specifically remains unknown. Nonetheless, metabolic syndrome definitions that contain information on insulin resistance correlate best with post-transplant MACE[43]. Non-diabetic KTR with metabolic syndrome but without diabetes will likely eventually develop diabetes, and metabolic syndrome components can enhance the effect of diabetes on post-transplant MACE. Therefore, it may be helpful to screen for metabolic syndrome components in SA KTR.

**Novel biomarkers**

Only one-third of measured metabolic factors such as insulin resistance, dyslipidemia, and central obesity explain the excess CVD risk that SA face[51]. Novel biomarkers that may correlate with increased CVD include increased serum leptin and C-reactive protein, as well as adiponectin levels that are lower in SA compared to Caucasians despite similar BMI[99]. The correlation between decreased adiponectin and increased insulin resistance is particularly strong for SA[100]. Both total and high molecular weight adiponectin levels are lower in SA KTR[101]. KTR with metabolic syndrome have significantly lower serum adiponectin levels than those without metabolic syndrome. Leptin levels are higher even after adjusting for body fat, suggesting increased adipocyte production[74]. Leptin inversely correlates with adiponectin, increases with decreasing eGFR, and is associated with inflammation[102]. Similar to adiponectin, lectin has not yet been linked to post-transplant MACE.

The association between hs-CRP and mortality in KTR is J-shaped, with both very low and very high levels associated with a two-fold increase risk of post-transplant mortality[103]. Serum homocysteine levels are higher in SA[46]. Although observational studies in CKD suggested homocysteine was associated with increased cardiovascular risk, lowering homocysteine with a multivitamin in the Folic Acid for Vascular Outcome Reduction in Transplantation trial did not improve post-transplant cardiovascular outcomes[104]. Apolipoprotein B (ApoB) predicts new-onset diabetes in KTR samples with a significant proportion of SA[105]. The LDL-C/ApoB ratio and the non-HDL-C/ApoB ratio were both significantly lower in SA than NHANES participants in the United States[106]. Other promising biomarkers in SA include reduced endothelial nitric oxide[107], increased plasminogen-activator inhibitor-1[108], and increased fibrinogen[109], all of which may correlate with insulin resistance.

The greatest attention among novel biomarkers has been given to elevated lipoprotein (a) [Lp(a)] levels[17,72]. Lp(a) levels are largely genetically determined, varying over 1000-fold among individuals and 5-fold across populations. SA have a median Lp(a) concentration of 16 mg/dL compared to 6 mg/dL in Caucasians[99]. Elevated Lp(a) levels associate with vulnerable plaques and culprit lesions in acute coronary syndromes, including premature CAD, correlating with the extent and severity of both acute coronary syndrome, CAD, and coronary artery calcium score[17]. Lp(a) might be the most promising novel biomarker to explain the excess SA CVD risk. Lp(a) levels decrease post-KT[110] despite an increase from cyclosporine[111]. Lp(a) remains a promising biomarker for targeting cardiovascular risk based on data from statin-based lipid-lowering trials[112], but more data in SA KTR are needed.

At the present time there are no interventions confirmed to influence novel biomarkers, which are at best secondary endpoints, but these biomarkers may be useful to monitor post-transplant CVD risk and guide interventions towards more established risk factors. Enriched recruitment of SA in clinical trials that include novel biomarker measurement may ultimately allow their incorporation into post-transplant cardiovascular risk modifying strategies, thereby benefiting all ethnic groups.
| Epidemiology | Clinical features | Laboratory features |
|--------------|------------------|---------------------|
| ↑ Prevalence, ↑ mortality | ↑ Type 2 diabetes | ↑ Serum triglycerides |
| ↓ Age at presentation, ↓ age at mortality | ↓ Hypertension awareness | ↓ Serum HDL cholesterol |
| ↑ Severity by angiography | ↑ Central obesity | ↑ Small-dense HDL cholesterol |
| ↑ Difficult revascularization | ↑ Intra-abdominal adiposity | ↑ Small-dense LDL cholesterol |
| ↑ Carbohydrate intake | ↑ Insulin resistance | ↓ Serum total and high molecular weight adiponectin |
| ↑ Saturated fat intake | ↓ Age at pancreatic β-cell dysfunction | ↑ Serum leptin |
| ↓ Physical activity | ↑ Fatty liver | ↑ Serum homocysteine |
| ↑ Metabolic syndrome | ↓ Vitamin D deficiency | |
| ↓ Left ventricular mass index | ↓ Non-HDL-cholesterol/apolipoprotein B ratio | |
| ↓ Skeletal muscle mass | ↓ Endothelial NO | |
| ↓ Accurate estimate of glomerular filtration rate | ↑ Lipoprotein (a) | |
|                      |                  | ↑ Fibrinogen        |

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; NO: Nitric oxide.

**Health behaviors**

Using a composite score that included non-smoking, moderate alcohol intake, physical activity, and fruits and vegetables consumption, the attributable fraction of lack of adherence to positive health behavior for CAD and CVD overall was 63% and 51% in SA, compared to 43% and 28% in Caucasians[113]. Besides ethnicity itself, diet and lifestyle may be particularly important to cardiovascular risk in low- and middle-income countries[114]. Dietary sodium intake in India approximates 3.7 g/d, very similar to the intake in the United States and United Kingdom[115]. SA diets are higher in carbohydrate, saturated fatty acids, trans-fatty acids, and ω-6 polyunsaturated fatty acids content, while being lower in monounsaturated fatty acids and fiber[116]. Vitamin D deficiency is especially common in SA[117].

Physical activity correlates inversely with established cardiovascular risk factors in KTR[118]. SA KTR in particular may be prone to a sedentary lifestyle before transplantation, potentially leading to increased post-surgical recovery times and associated complications. Decreased muscle strength and fatigue can affect post-transplant quality of life, thus emphasizing the need for graded exercise training[119]. SA are also more likely to report joint pain[120], further challenging participation in physical activity.

Physical activity is generally lower in SA, especially SA women. Although walking does not have a significant benefit on lipids, it may benefit insulin levels[121]. Cardiorespiratory fitness in SA is generally lower[122]. Therefore, SA KTR may benefit from more intense focus regarding education on physical activity, as well as structured exercise programs. Such programs will need to be culturally sensitive, especially in multiethnic regions of the world. Exercise training improves maximal exercise capacity, quadriceps muscle strength, health-related quality of life and diastolic BP[123].

Table 1 summarizes the cardinal features of CVD in SA. Table 2 summarizes some recommendations to manage CVD in SA KTR.

**CONCLUSION**

SA KTR are a group of transplant recipients at higher cardiovascular risk than other KTR groups. This increased risk in SA KTR is consistent with that seen in the corresponding SA general population. SA KTR are at higher risk for MACE both early and late after transplantation. CVD risk management should therefore begin well before transplantation. Recording SA ethnicity during the pre-transplant evaluation process may enable programs to more accurately assess individual cardiovascular risk and allow for earlier intervention to improve both pre-transplant and post-transplant.
Table 2 Possible interventions to manage cardiovascular risk in South Asian kidney transplant recipients

| Pre-transplant | Post-transplant |
|----------------|-----------------|
| No lower age limit for screening | Diabetes | Screen for post-transplant diabetes |
| Consider earlier cardiologist referral | Consider using any oral antihyperglycemic including newer agents |
| Use oral glucose tolerance test/HbA1c | Hypertension | Consider using any antihypertensive agent |
| Maximize cardioprotective medication | Monitoring potential for increased exposure from standard statin doses |
| | | Monitor for adherence |
| | Dyslipidemia | Recognize that lipid profiles do not necessarily reflect increased cardiovascular risk |
| | | Monitor HDL cholesterol and triglycerides |
| | | Recognize potential for increased exposure from standard statin doses |
| | Obesity and metabolic syndrome | Monitor waist-hip ratio |
| | | Target counseling about potential weight gain and abdominal girth increase even if body mass index is normal |
| | | Screen for presence of metabolic syndrome |
| | | Target interventions to individual components of metabolic syndrome |
| | Health behavior | Decrease carbohydrate and saturated fat intake |
| | | Increase monounsaturated fat and fiber intake |
| | | Implement structured, graded exercise programs |

HbA1c: Glycosylated hemoglobin; HDL: High-density lipoprotein.

Cardiovascular outcomes. Diabetes remains the most prominent post-transplant cardiovascular risk factor, and corresponds to insulin resistance and pancreatic β-cell dysfunction. Hypertension is widely prevalent. Dyslipidemia, metabolic syndrome, and obesity are all significant CVD risk factors in SA KTR, and contribute to increased insulin resistance. Novel biomarkers may be especially important to study in SA KTR. Focused interventions to improve health behaviors in SA KTR may be particularly beneficial. However, there are few clinical trials specific to SA, and none are specific to SA KTR. In all cases, understanding the nuances of managing SA KTR while still approaching each CVD risk factor individually will facilitate improvement in the long-term success of all kidney transplant programs catering to multi-ethnic populations.

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