A Strategy to Improve the Cardiovascular Risk Factor Profile in Renal Transplant Patients

Denise Leite e Alexandre Holthausen Campos
Universidade Federal de São Paulo - São Paulo, SP - Brazil

Abstract

Background: Cardiovascular disease represents the leading cause of morbidity, mortality and graft function loss in renal transplant recipients (RTR). Aggressive treatment of risk factors is strongly advocated. However, there is a gap between recommended evidence-based therapy and effective cardiovascular management in that population.

Objective: To establish a cardiovascular risk factor control strategy for RTR.

Methods: The cardiovascular risk of 300 RTR of a renal transplant unit was assessed using the Framingham criteria. Interventions on modifiable risk factors were suggested to attending physicians by letters attached to patients' charts, including lifestyle modifications, blood pressure control and use of antiplatelet and lipid-lowering therapy. Risk factor profiles were re-evaluated after 6 and 12 months.

Results: Most patients were at high cardiovascular risk (58%). After 12 months, the proportion of patients on antiplatelet, antihypertensive and lipid-lowering therapy was significantly increased (29 to 51%, 83 to 92% and 3 to 46%, $p < 0.001$, respectively). Total cholesterol and triglyceride levels decreased (237 to 215 mg/dl, $p = 0.001$ and 244 to 221 mg/dl, $p = 0.03$). Although a non-significant reduction in LDL levels was observed (136 to 116 mg/dl, $p = 0.12$), patients starting statins within the first 6 months of the study presented a significant 25% reduction in LDL (159 to 119 mg/dl, $p < 0.001$). The proportion of patients with complete plasma lipid evaluation was also increased (27% to 49%, $p < 0.001$).

Conclusion: Our results suggest that a simple, inexpensive strategy significantly improves the cardiovascular risk profile of RTR, potentially translating into marked benefits for long-term graft function and life expectancy. (Arq Bras Cardiol. 2010; [online]. ahead print, PP.0-0)

Key words: Risk factors; patients; kidney transplantation; cardiovascular diseases/prevention and control.

Introduction

Renal transplant recipients (RTR) are more prone to cardiovascular disease (CVD) compared with the general population. The incidence of CVD among RTR seems to be three to four-fold higher than that observed in age-matched control populations[1]. In fact, CVD is the leading cause of morbidity and mortality after renal transplantation and, as a consequence of death with functioning graft, represents also the major cause of graft function loss in long-term RTR[1-5]. This high CVD incidence is partially explained by equally high cardiovascular risk factor prevalence and accumulation before and after kidney transplantation. Conventional risk factors, mainly hypertension, diabetes and hyperlipidemia, play a well-recognized proatherogenic role in the development of cardiovascular events after renal transplantation and are strongly associated with the immunosuppressive therapy. In addition, renal dysfunction-related risk factors clearly contribute to the development of CVD in RTR.

To prevent post-transplantation CVD it is necessary to identify and aggressively treat modifiable risk factors. A basic principle of intervention is that the intensity of risk-reduction therapy should be adjusted to the absolute individual risk of each patient[6-7]. Primary and secondary cardiovascular prevention trials in the general population have documented substantial benefits from the administration of statins and antiplatelet drugs. Some evidence has supported the use of those medications in RTR. However, cardiovascular risk management has not been addressed properly in RTR[8-12]. As described for the general population[13], it is very likely that there is a gap between the cardiovascular care recommended in clinical practice guidelines and the effective cardiovascular management for RTR. In this study, we established a relatively simple strategy to optimize cardiovascular risk factor profile evaluation and treatment for RTR followed in a renal transplant unit of São Paulo, Brazil.

Mailing address: Denise Leite •
Alameda dos Nhambiquaras, 596/141 - Moema - 04090-001 - São Paulo, SP - Brazil
E-mail: leitedenise@hotmail.com
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Methods

Sample study

The *Hospital do Rim e Hipertensão*, a partner of the Federal University of *São Paulo*, performs more than five hundred renal transplants per year (656 in 2004[14]). Approximately 80% of the recipients are followed at the outpatient unit indefinitely. In December 2004, almost 3,000 patients were registered for follow-up in that outpatient unit, where sample selection for this study was performed. All patients older than 40 years with stable renal function and that had received a kidney at least 12 months before were identified. Using these criteria, 909 patients were selected and questionnaires, medical records and blood test results were used in each case to evaluate cardiovascular risk factors and calculate the Framingham Heart Study risk score (FRS). HDL was considered to be 50 mg/dl when results were not available. Five hundred, sixty-three patients were excluded due to incomplete information with respect to elements necessary for FRS calculation. During the follow-up, forty-six patients were excluded due to several other causes (Figure 1). The study group consisted of the remaining 300 patients who completed 12 months of follow-up. All patients gave informed consent to participate in this study, which was approved by the local Ethics Committee.

Sample variables

The following variables were collected at the initial evaluation: age, gender, cause of end-stage renal disease (ESRD), time elapsed since transplantation, prior transplantation, and presence of pretransplant diabetes and CVD. CVD was defined as ischemic heart disease (IHD), peripheral vascular disease (PVD) or cerebrovascular disease. IHD included angina pectoris, myocardial infarction, coronary artery revascularization by percutaneous balloon-angioplasty or bypass grafting, or death as a result of IHD (in the follow-up). Deaths were considered attributable to IHD if the autopsy was consistent with the diagnosis or if the events preceding death made IHD the most likely cause. PVD was defined as amputation resulting from vascular insufficiency or history of a limb revascularization procedure (bypass or endarterectomy). Cerebrovascular disease included documented strokes or transient ischemic events.

Variables that could present different values throughout the study were recorded at the initial evaluation and 6 and 12 months thereafter: weight, height, body mass index (BMI; kg/m^2), cigarette smoking status, immunosuppressive agent prescription, serum creatinine, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), blood pressure (mean of the last three measurements) and use of antihypertensive, lipid-lowering and antiplatelet agents. Diabetes and CVD were also reassessed at 6 and 12 months of the study.

Fasting TC and TG concentrations were determined by commercially available standard automated enzymatic assays. HDL was evaluated by dextran sulphate precipitation method and LDL concentrations were calculated using the Friedewald formula. Creatinine clearance (CrCl) was calculated through the Cockroft-Gault formula.

Cardiovascular risk

The FRS was calculated for each subject according to NCEP-ATPIII guidelines[6]. The Framingham Heart Study provides an algorithm to assess the 10-year absolute risk for "hard" coronary events (myocardial infarction and coronary artery disease-related deaths). Risk was then classified as low (0-9%), moderate (10-20%) or high (>20%).

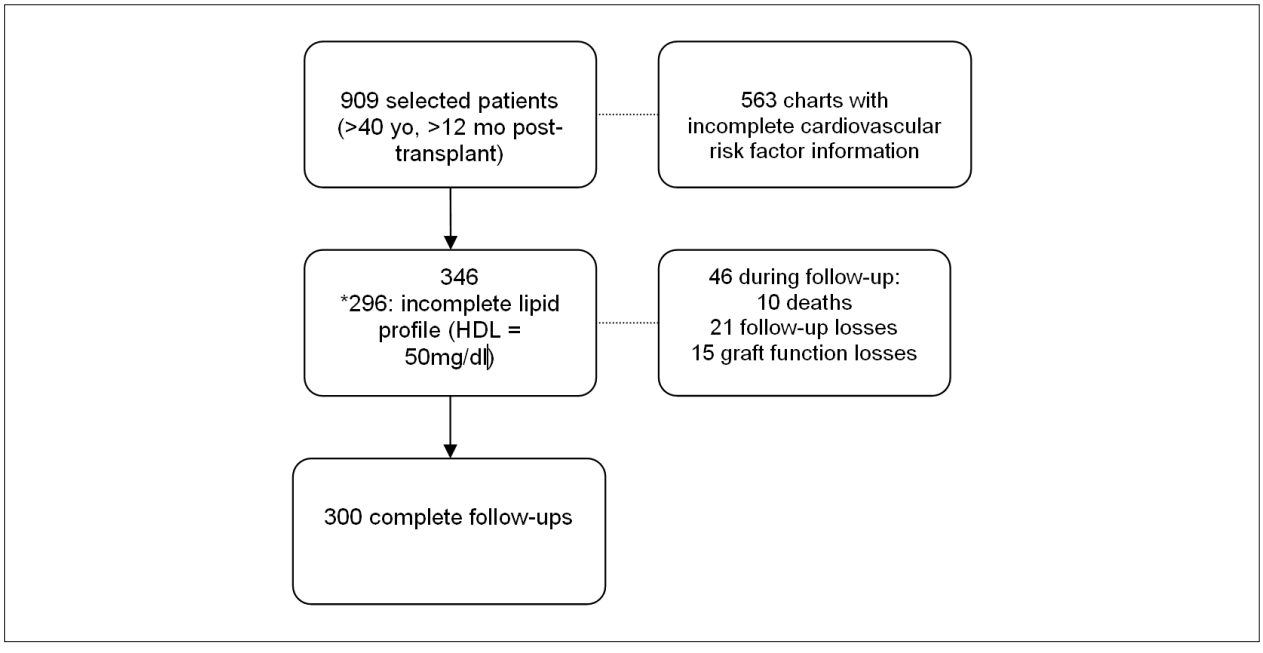

Figure 1 - Eligible and final study sample. Reasons for exclusion before and during follow-up are depicted.

Cardiovascular risk factor control

After cardiovascular risk classification, objective interventions on individual modifiable risk factors, all of them based on clinical practice guidelines, were recommended to attending physicians by means of formal letters attached to each patient's chart. The interventions included, when appropriate: lifestyle modifications (diet and physical activity), aggressive blood pressure control (target < 130 x 80 mmHg), use of antiplatelet (aspirin) and lipid-lowering therapy. In addition, patients who had reported a positive smoking history during evaluation were recommended to seek a specialized program on smoking cessation located in our Institution. Cardiovascular risk factor profiles were then re-evaluated 6 and 12 months after strategy implementation.

Analysis

Values are reported as means and standard deviations (SD), or medians. Analysis of variance for repeated measurements was used for comparisons of numerical data. Non-parametric analysis for ordinal measurements was used for comparisons of categorical data. $P < 0.05$ was considered significant.

Results

Patient characteristics

Three-hundred patients were followed for 12 months. Mean age was 49.9 (6.9) years (median 48), fifty-eight percent were men and only 2% had been submitted to more than one renal transplant. The mean transplantation time was 56.6 months (median 49). The cause of ESRD was undetermined in 40%, hypertension in 24%, chronic glomerulonephritis in 12%, diabetes in 11% and autosomal dominant polycystic kidney disease in 8% of patients. Immunosuppressive treatment at enrollment included, with or without azathioprine or mycophenolate, cyclosporine (CsA, 70%), corticosteroid (28%), CsA plus corticosteroid (66%), or tacrolimus plus corticosteroid (59%). After 12 months there was a slight decrease in the proportion of patients taking CsA (to 66%, $p < 0.001$) and the CsA-corticosteroid association (to 64%, $p = 0.023$). No significant change was seen in the remaining immunosuppressants prescribed.

FRS cardiovascular risk

At the initial evaluation, according to FRS, one hundred and fourteen patients were classified as low, eleven as moderate and 175 as high cardiovascular risk. After the strategy implementation, a gradual and significant decrease in the low-risk group patients was observed - to 101 patients at 6 months and 90 patients at 12 months ($p < 0.001$). Conversely, there was a significant increase in the high-risk patient group - to 187 patients at 6 months and 197 patients at 12 months ($p < 0.001$). There were no differences in the moderate risk group - 12 and 13 patients at 6 and 12 months, respectively ($p = 0.48$, Figure 2).

Diabetes and CVD

Diabetes was present in 126 patients at the initial evaluation. IHD was observed in 51 patients, PVD or cerebrovascular disease in 29, and IHD and PVD or cerebrovascular association was detected in 6 patients. During the 12 months of follow-up there was an increase

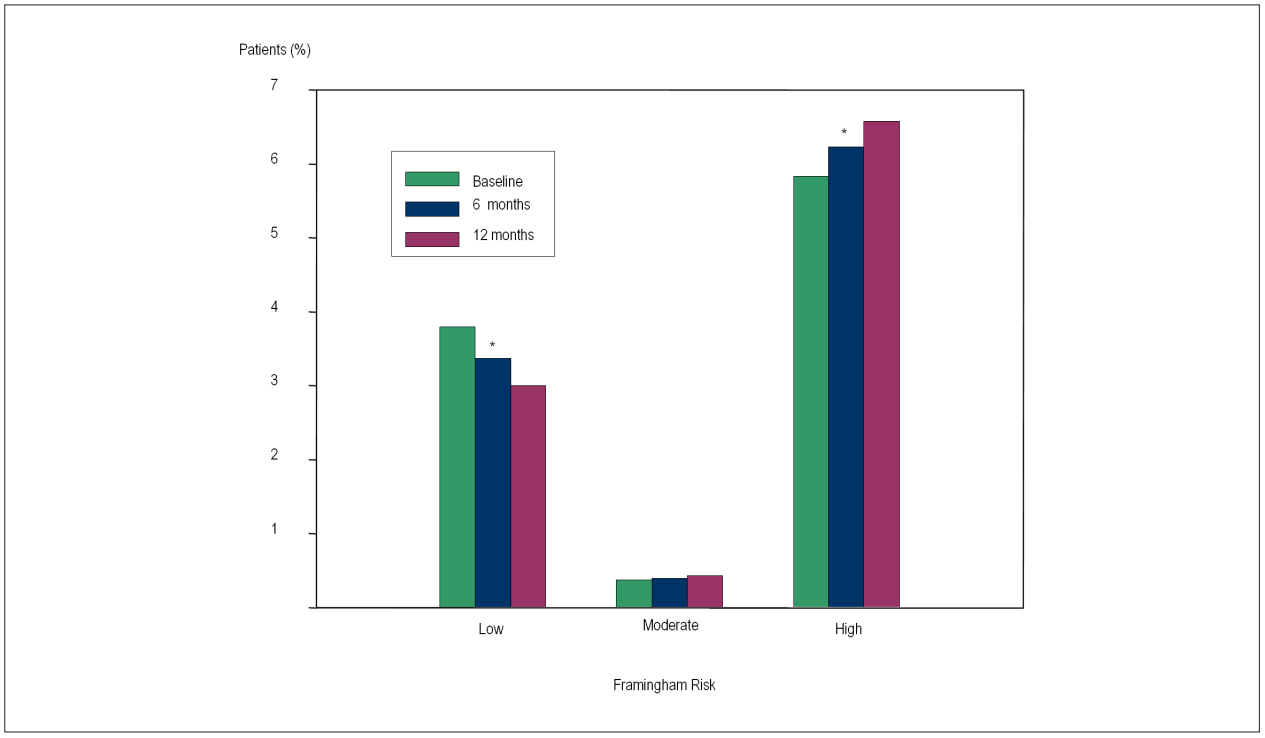

*Figure 2 - Patient relative distribution according to Framingham risk score before and after 6 and 12 months of the strategy implementation (N = 300; * p < 0.001 vs baseline).*

in the prevalence of diabetes and atherosclerotic disease. Diabetes was present in 133 and 145 patients at 6 and 12 months, respectively ($p < 0.001$). IHD was observed in 61 and 69 patients, PVD or cerebrovascular disease was present in 37 and 44 ($p < 0.001$), and IHD and PVD or CVD association was present in 10 and 17 patients in the same period ($p = 0.003$, Figure 3).

Cardiovascular events

Twenty-two cardiovascular events occurred in 19 patients (6%) during the 12 months of follow-up. There were no cardiovascular deaths. Ten patients (3%) presented new coronary artery disease-related events (5 patients had myocardial infarction, three patients had coronary artery revascularization by percutaneous balloon-angioplasty and 2 patients had angina pectoris). Seven patients (2%) had a limb amputation resulting from PVD and 5 patients (1.6%) had confirmed cerebrovascular ischemic events.

Antihypertensive, lipid-lowering and antiplatelet therapy

At the initial evaluation, two-hundred and forty-nine patients were taking antihypertensive drugs, eighty-seven were on antiplatelet therapy and only 10 patients were receiving lipid-lowering drugs. During follow-up, a progressive and significant increase was observed in the number of patients receiving those medications. Antihypertensive drugs were prescribed to 272 patients at 6 months and to 286 at 12 months ($p < 0.001$); antiplatelet therapy (aspirin) to 136 and 154 ($p < 0.001$) and lipid-lowering drugs (statins in all cases) to 110 and 137 patients, respectively ($p < 0.001$, Figure 4).

Renal function, blood pressure, BMI and lipid profile

There were no differences in BMI or CrCl between baseline records and after 6 and 12 months. There was a non-significant reduction in systolic and diastolic blood pressure (SBP and DBP, respectively). At 6 months of follow-up, the strategy implementation resulted in significant decreases in serum TC and TG levels. At 12 months, TC decreased even more and there was no additional significant reduction in TG level. Although only a non-significant reduction in LDL levels was observed after 6 and 12 months, in the subgroup of 128 patients in whom the lipid-lowering therapy was started within the first 6 months of the study, we detected a significant 25% reduction in LDL levels at 12 months (from 159 to 119 mg/dl, $p < 0.001$). A small decrease in HDL levels was observed (58.4 to 54.2 after 6 months and 55.6 mg/dl after 12 months, $p = 0.035$, Table 1).

At the initial analysis, lipid profile evaluation (TC, LDL, HDL or TG) was available in the medical records of 240 (80%) patients. However, dyslipidemia was not properly assessed. Eighty patients had a complete lipid profile, whereas the majority (160 patients) presented only TC and TG in the medical charts. At 6 and 12 months, complete lipid profiles were available for a gradually higher number of patients (138 and 145, respectively, $p < 0.001$, Figure 5).

Smoking status

At study enrollment, 22 (7%) patients were current smokers. Three of them were not directed to the program on smoking cessation as recommended. Of the 19 remaining patients directed to the program, only 1 sought the recommended therapy and successfully quit smoking within 12 months.

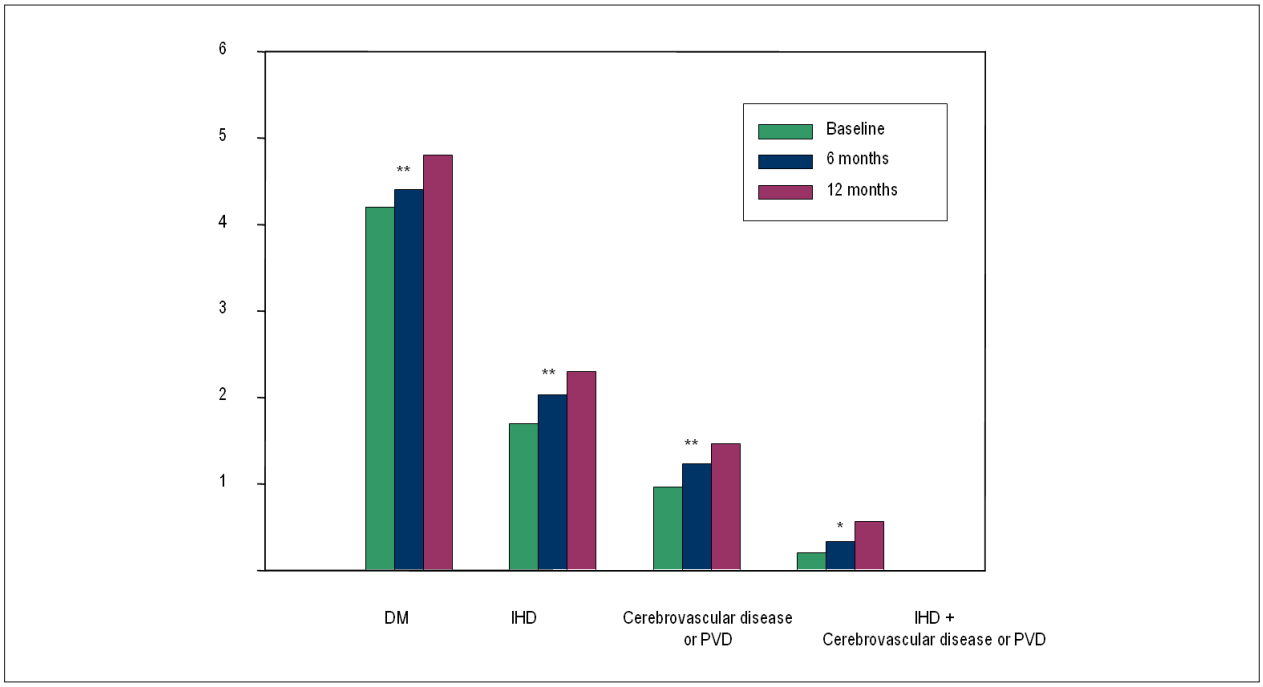

*Figure 3 - Prevalence of diabetes and atherosclerotic disease at baseline, and 6 and 12 months after strategy implementation. (N = 300; *p = 0.003, **p < 0.001 vs baseline). IHD - ischemic heart disease; PVD - peripheral vascular disease; DM - diabetes mellitus.*

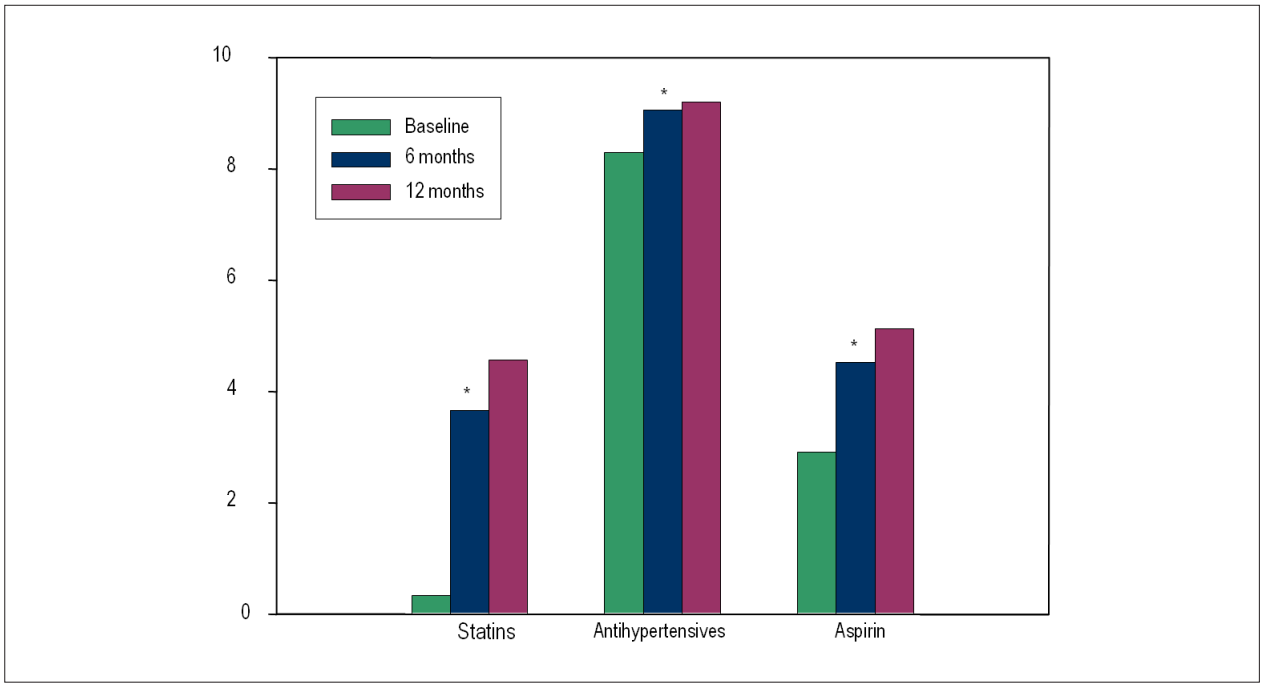

*Figure 4 - Proportion of patients receiving specific cardiovascular medications before, and 6 and 12 months after strategy implementation (N = 300; *p < 0.001 vs baseline).*

Table 1 - Blood pressure, body mass index, renal function and serum lipid levels before and during follow-up

	Basal	6 months	12 months	p
SBP (mmHg)	136 (13.7)	134.2 (14.2)	135.4 (14.6)	0.139
DBP (mmHg)	82.7 (7.7)	81.8 (7.4)	81.6 (7.9)	0.071
BMI (kg/m^2)	26.7 (4.3)	26.8 (4.3)	26.9 (4.5)	0.525
CrCl (ml/min)	60.8 (17.7)	60.5 (18.2)	61.9 (18.9)	0.085
TC (mg/dl)	237.5 (66.8)	222.7 (58.1)	215.1 (55)	0.001
LDL (mg/dl)	136.4 (53.1)	124.7 (41.4)	115.6 (41.7)	0.118
HDL (mg/dl)	58.4 (16.7)	54.2 (15.6)	55.6 (15.7)	0.035
TG (mg/dl)	244.1 (197.3)	218.9 (148.9)	220.8 (232.6)	0.001

SBP - systolic blood pressure; DBP - diastolic blood pressure; BMI - body mass index; CrCl - creatinine clearance; TC - total cholesterol; LDL - low density lipoprotein; HDL - high-density lipoprotein; TG - triglycerides.

Discussion

Despite advances in immunosuppressive therapy and increments in graft survival, RTR have a significantly reduced life expectancy largely due to premature CVD[1-5,15]. Although there is extensive data in the literature concerning the general population, there are no specific guidelines for CVD control in RTR and interventional trials to demonstrate that modifications of traditional risk factors reduce CVD in this population are not available. However, it has been recently demonstrated that patients with renal function impairment should be similarly managed[6]. In addition there is no evidence at all that a patient with renal function impairment should be managed differently from an individual in the general population[6,13]. Due to these facts, the American Heart Association, the American College of Cardiology and the National Kidney Foundation recommend that patients with renal dysfunction be seen as high cardiovascular risk individuals and managed accordingly[2,4,6,7,16-18].

Although widely used, there are some controversies about the relevance of FRS calculation in RTR. Nevertheless, we used the NCEP-ATP III-modified FRS, as it may help to select a high-risk population of RTR[4,19]. We selected patients over the age of 40 years with more than 12 months of renal transplant. Hence, younger patients who were therefore less exposed to cardiovascular risk factors were not included[20]. The minimum time of 12 months since transplantation was adopted as representing enough evaluation and treatment time of cardiovascular risk factors by the attending physician team. We assumed that these patients were on an established, steady situation regarding risk factor control.

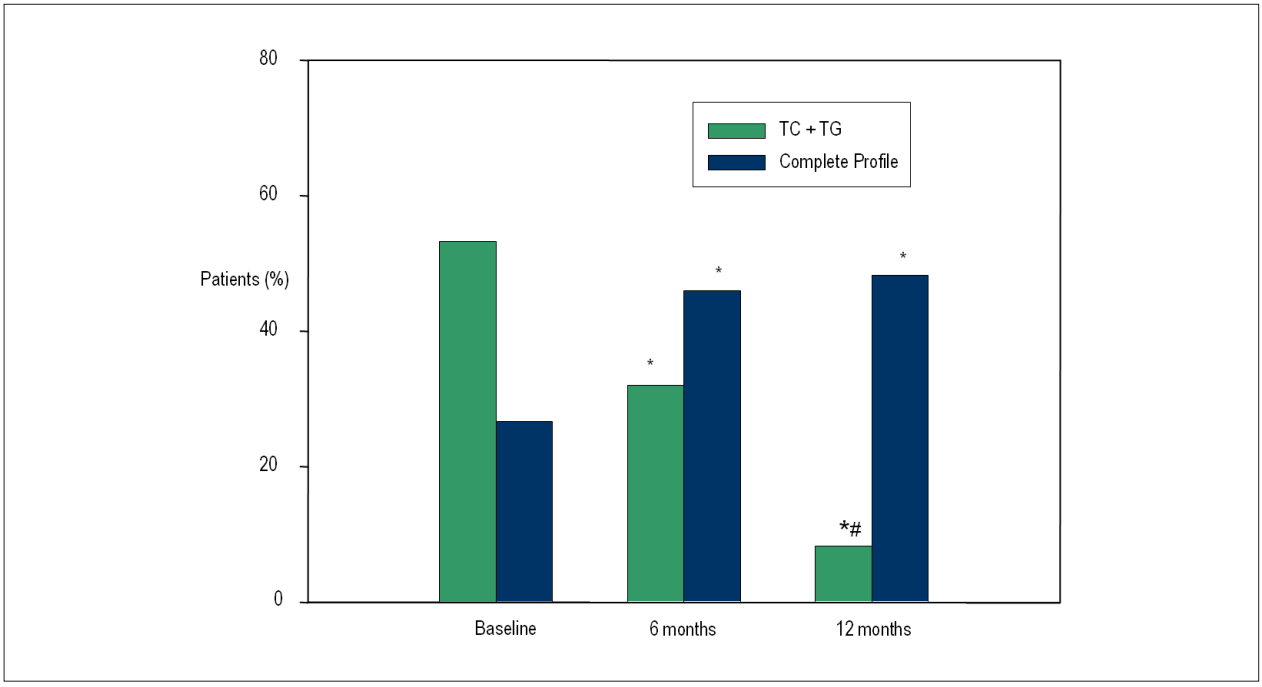

*Figure 5 - Proportion of patients presenting incomplete [total cholesterol (TC) and triglycerides (TG) only] and complete (TC, TG, low- and high-density lipoprotein cholesterol) lipid profile in the medical charts before, and 6 and 12 months after strategy implementation (N = 300; *p < 0.001 vs corresponding baseline, #p < 0.001 vs corresponding 6 months).*

The sample studied presented an extremely unfavorable risk factor profile, even in the presence of satisfactory and stable renal function. Considering the cardiovascular risk profile obtained and the time elapsed since transplantation, the population studied was receiving less than optimal cardiovascular assistance. The majority of patients at the beginning of the study were classified as high-risk group. This is noteworthy, particularly if we consider that the average age of the population was below 50 years. Two factors determined the relatively small proportion of patients included in the moderate risk group (4%). First, the absence of important data in the medical charts, which confirms that, despite the availability and easy access to guidelines and evidence-based medicine information, cardiovascular risk has yet to become a major concern for physicians that treat RTR. Secondly, the high prevalence of diabetes and CVD led to a great proportion of patients automatically classified as high risk.

It is not surprising at all that the proportion of high-risk patients did not improve during follow-up (as a matter of fact it worsened from 58% to 66% in 12 months). The vast majority of high-risk patients were thus classified because they already presented, at some point of their lives, atherosclerotic disease manifestation and/or diabetes. Even with perfect control of blood pressure, cholesterol levels and other risk factors, those patients will continue to be classified as high risk. It should also be mentioned that FRS calculation is not an appropriate tool to detect changes in cardiovascular risk following interventions, but rather an aid to guide decisions regarding the nature and intensity of therapy[6].

The increase in proportion of high-risk patients is also expected: it reflects cardiovascular risk status in previous years and not only in previous months. Worsening in the risk factor profile is strongly associated to renal dysfunction and immunosuppressive therapy[2,5,21-23]. As a significant increase in CVD and diabetes prevalence seen in our study was observed within a short period of time and renal function remained stable throughout the follow-up, the deleterious influence of immunosuppressants was probably the predominant factor. In fact, most patients received corticosteroids (98%) and CsA (70%), drugs clearly linked to the development and aggravation of hypertension, diabetes and unfavorable lipid profile. In addition, we detected a small, but significant reduction in the proportion of patients receiving CsA during the follow-up. This was motivated, in general, by chronic graft rejection, further exposing those patients to non-traditional risk factors.

No specific measure to control risk factors has been demonstrated so far as capable of "erasing" past exposure to risk. In order to detect any improvements in RTR cardiovascular risk control, we evaluated their modifiable risk factor profile during follow-up. Extensive data in the literature indicates that preventive measures, such as the administration of aspirin and lipid-level management, result in long-term benefits in the general population, reducing long-term mortality and morbidity.

Although in the beginning of the study 83% of patients were taking antihypertensive drugs, average SBP and DBP were above recommended levels. After 12 months, we were able to detect a further significant increase in the proportion of patients taking antihypertensive drugs (reaching 92%). However, average SBP and DBP were not reduced as a consequence. This may indicate that increments in blood pressure were blunted by the increase in antihypertensive

prescription. Nevertheless, optimal control was not achieved and increasing doses and/or number of antihypertensive drugs were probably indicated.

Different figures were obtained when analyzing the proportion of patients receiving lipid-lowering drugs in the initial evaluation. Despite the fact that mean total and LDL cholesterol levels were high and the population studied had been followed, on average, for more than 4 years since the renal transplant, only 3% of the patients were on statins at that time. This is a matter of concern, particularly if we consider the data from the ALERT study, which suggest that cardiovascular prevention obtained with statins is more effective when instituted early [within 2 years of transplantation]. After 12 months, the number of patients on lipid-lowering therapy was markedly increased (about 15-fold). Consequently, TC and TG levels were significantly reduced in 12 months. Average LDL levels presented a non-significant decrease and the relatively small proportion of patients with available LDL levels in medical records at the initial evaluation probably contributed to that. However, there was a significant 25% decrease in LDL levels in the subgroup of patients starting statins[6-8] after the implementation of our strategy. The magnitude of the effect of lipid-lowering therapy is comparable to that seen in both general and RTR populations receiving statins. If we extrapolate the long-term follow-up data obtained to the general population, the LDL decrements seen in our study would promote a reduction of approximately 25% in the relative risk for coronary events in 5 years[6]. However, despite these encouraging results and, as previously observed in other RTR studies[8,12], we must emphasize that average LDL levels remained above the recommended levels by the end of the study. The underestimation of the importance of controlling lipid levels can be appreciated if we analyze plasma lipid evaluation. Although 80% of patients were screened for dyslipidemia in some way during the year before the beginning of data collection, only a small proportion of patients presented a complete lipid profile in their charts. Since the complete lipid profile is essential for cardiovascular risk management, we assume that the majority of patients were not properly evaluated and/or treated for dyslipidemia. After 12 months this pattern changed significantly. In spite of a decrease in the total amount of patients being evaluated for dyslipidemia, the proportion of patients with a complete lipid profile was increased from 27% to 48%. This new pattern of evaluation, although sub-optimal, suggested a growing concern of attending physicians towards the analysis of lipid profile and, by extension, of cardiovascular risk.

At the initial evaluation, in spite of the fact that 58% of patients could be classified as high risk, only 29% of the total sample (37% of high-risk patients) was receiving aspirin. These numbers are very unsatisfactory, since primary and secondary prevention of cardiovascular events with antiplatelet therapy is supported by several studies in the general population and clinical guidelines clearly recommend antiplatelet drugs for patients with established atherosclerotic disease and/or diabetes, regardless of their renal function status[24-26]. After 12 months of this study, the proportions of patients receiving aspirin in the whole sample and in the high-risk subgroup almost doubled. Once again, assuming that data from the general population can be applied to RTR, the increment in secondary prevention seen in our study will reduce non-fatal myocardial infarction and cardiac death in 16% and non-fatal ischemic stroke risk in 25% for patients with previous cardiovascular events[26].

In opposition to the significant improvement obtained in matters related to drug prescription and physician compliance (e.g. lipid profile evaluation), our strategy was not effective when changes in lifestyle were analyzed. BMI reduction and tobacco dependence control were poorly achieved. While unaccounted factors, such as prescribed immunosuppressants, may have played a role on BMI stability above recommended levels, it is well known that obesity control in RTR is extremely difficult and more successful when intensified in the immediate post-transplant period[27,28]. There are no interventions on tobacco dependence specifically designed for RTR[29]. In our study, patients were directed to a local program that was not specific for RTR and not linked to the team of attending physicians. Difficulties in implementing lifestyle modifications are a rule in the general population and that is, perhaps, magnified in RTR due to factors that include poorer exercise capacity, prescription of a long list of drugs per patient and the inevitable imposition of a busy schedule. Thus, longer-term, more specific programs, connected to routine medical appointments, might generate more effective results.

All modifications observed occurred in a relatively short period of time after the initiation of our intervention, at relevant magnitudes. Furthermore, the population studied was being followed for an average of 4 years and no abrupt changes related to cardiovascular risk factor control other than our protocol was implemented in the transplant unit. We employed a *quasi*-experimental approach, by which observations were made before and after interventions[30]. That modality was chosen as ethical and logistic issues did not allow us to obtain an adequate control group. As recommendations about proper cardiovascular risk management had to be made to the entire team of attending physicians of the renal transplant unit, it was not feasible to select a group of patients to whom the evidence-based care would not be offered. It has been demonstrated that more pronounced improvements observed after a specific intervention such as the one presented here confirm that changes are attributable to the intervention itself. Concurrent factors are minimized as the impact of these changes increases. An example of pretest/posttest study without controls is the GAP project carried out in Michigan[13]. Acute myocardial infarction quality-of-care measures were assessed among eligible patients at baseline and after the introduction of clinical tools designed to improve them. Significant improvements were detected during hospitalization and at the moment of hospital discharge[13,30]. Thus, although changes detected may be a consequence of chance, it is reasonable to conclude that they were a direct result of our strategy.

It is known that clinical guidelines for cardiovascular management in the general population are not properly applied to all eligible patients[13] and a similar pattern was

verified in our institution concerning RTR. The strategy here described for cardiovascular risk factor identification and control, which is inexpensive and easily implemented, demonstrates that much can still be done for RTR. We believe that results, however, would be potentiated if coordinated actions, involving physicians of different specialties, nurses, nutrition experts, psychologists and social workers, were set in place. Greater, long-lasting benefits, at a relatively low cost, would certainly be granted to RTR, as already demonstrated in the general population[13].

In summary, we established a cost-effective, relatively simple strategy to optimize cardiovascular risk factor profile evaluation and treatment for RTR in a renal transplant unit of São Paulo, Brazil. Considering the impact of comparable approaches in the general population, we anticipate marked benefits for long-term graft function and life expectancy in the specific group of patients studied herein.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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