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Associations between pre-kidney-transplant risk factors and post-transplant cardiovascular events and death

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Summary

The prevalence of cardiovascular risk factors in renal transplant candidates is high. A better understanding of the relation between these risk factors and cardiovascular morbidity and mortality is mandatory to improve transplantation outcome. In this retrospective cohort study 2187 adult patients who received a first kidney transplant between 1984 and 1997 were included. We analyzed the incidence of post-transplant cardiovascular events and tried to identify independent pretransplant risk factors for post-transplant cardiovascular events and all-cause mortality. The cumulative incidence of post-transplant cardiovascular events was 40%. The incidence was highest in the first 3 months after transplantation. Independent pretransplant risk factors for a post-transplant cardiovascular event were diabetic nephropathy [Hazard ratio (HR) 3.02; 95% CI 2.85–3.98], claudication [HR 2.17 (1.42–3.31)], cardiac event [HR 1.76 (1.32–2.33)], cerebrovascular accident HR 1.53 (1.03–2.28), time-on-dialysis [HR 1.06 (1.02–1.11)], recipient age [HR 1.04 (1.04–1.05)], and body mass index [HR 1.03 (1.00–1.05)]. Diabetic nephropathy and cardiovascular disease were also important predictors for all-cause mortality. Diabetic nephropathy and cardiovascular disease were the most important predictors for cardiovascular events and all-cause mortality after renal transplantation. Early treatment of cardiovascular risk factors and pretransplant cardiovascular evaluation might improve transplantation outcome.

Introduction

Cardiovascular disease is the major cause of death after renal transplantation and the incidence is considerably higher than in the general population [1,2]. The incidence of cardiovascular events and death is highest in the first 3 months after transplantation [2,3]. Several factors seem to play a role in the high incidence of early cardiovascular events in renal transplant recipients. First of all chronic kidney disease is a major risk factor for cardiovascular disease. Patients with a moderate renal insufficiency already have a markedly increased cardiovascular risk [4]. Additionally traditional risk factors are more prevalent in patients with chronic kidney disease [5]. For this reason the prevalence of cardiac disease at the time of transplantation is already high [6].

The high incidence of cardiovascular events late after transplantation also has a multi-factorial origin. Although there is an improved renal function after transplantation, many patients still have a chronic renal insufficiency after transplantation [7]. Besides immunosuppressive medication (e.g. calcineurin inhibitors, corticosteroids) are related to an increased cardiovascular risk [8]. Other non-traditional risk factors such as inflammation and

cytomegalovirus (CMV) infections also have been related to an increased cardiovascular risk [3,8].

Although previous studies have evaluated risk factors for cardiovascular disease and the incidence of cardiovascular events after transplantation, further study on this subject is still necessary [3,9,10]. The first reason is that most previous studies are based on registry (Medicare) data, which probably underestimate the true incidence of cardiovascular events. Besides, these studies have a relative short follow up and are performed in populations that differ in risk and ethnicity from our western European population [3,9,10]. Apart from that, there is still no consensus about which patients should undergo further cardiac evaluation before transplantation and what the consequences of further evaluation are [11].

The aim of our study was to determine the association between pretransplant risk factors and cardiovascular comorbidity and post-transplant cardiovascular events and patient death. Second, we wanted to study the incidence of post-transplant cardiovascular events early and late after renal transplantation. We also tried to find an algorithm that could predict the subset of patients who are at high risk for an early post-transplant cardiovascular event and should undergo extensive cardiac evaluation before renal transplantation. In order to answer these questions, we collected data from all patients transplanted in three transplantation centers in the Netherlands between 1984 and 1997.

Subjects and methods

For this retrospective study, data from patients who received a first renal transplantation in any of the three transplantation centers in the Netherlands were collected. In all three centers, baseline and follow-up data were stored in the Netherlands Organ Transplantation Registration (NOTR). If data were missing, the medical file was called for and extensive research was done to complete the data. All adult patients who received a primary renal transplantation between 1-1-1984 and 31-12-1997 were eligible. Neither the patients who had undergone simultaneous kidney–pancreas transplantations nor those patients who were rejected for pancreas transplantation were included in this study. Before transplantation routine, cardiac examination was performed in all patients (medical history, physical exam, ECG, blood pressure). Additional cardiac examination was done only in patients with diabetic nephropathy, a positive cardiac history or abnormal routine evaluation and comprised a stress echocardiography or a cardiac scintigraphy. In addition, in patients with an abnormal stress test, coronary angiography was performed. Because we were primarily interested in cardiovascular events and mortality, patients with graft loss within 3 months after transplantation were excluded (except when graft loss and patient death occurred on the same day).

The primary endpoints of the study were the occurrence of the first post-transplant cardiovascular event and all-cause mortality. A post-transplant cardiovascular event was defined as a myocardial infarction or revascularization procedure [Percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)], cerebrovascular accident (CVA), or death with a cardiovascular cause after transplantation. An early post-transplant cardiovascular event was defined as the occurrence of an event within 3 months after the transplantation. Patient survival was defined as the time between the date of transplantation and death attributable to any cause. Patient survival was censored at the date of graft failure if the patient was still alive at that time.

To determine independent predictors for a post-transplant cardiovascular event and all-cause mortality the following parameters were collected at baseline: recipient age, recipient gender, type of donor (deceased versus living), date of transplantation, history of a cardiac event [myocardial infarction or revascularization procedure (PCI or CABG)], CVA, claudication, or angina pectoris before transplantation, diabetic nephropathy as primary cause of renal failure (DN), body mass index (BMI), cold ischemia time, dialysis prior to transplantation, and duration of dialysis. Pretransplant systolic and diastolic blood pressure ($n = 1201$), smoking history ($n = 1115$), and the total cholesterol level ($n = 796$) were only collected in one or two centers and were therefore incomplete. To analyze the incidence of post-transplant cardiovascular events we determined the incidence in the first 3 months after transplantation and in each year after transplantation.

Nowadays additional cardiovascular evaluation (dobutamine stress echocardiography or myocardial scintigraphy) is advised for high risk patients (patients over 50 years of age, patients with diabetes mellitus or a cardiovascular history or complaints)[11]. It is generally accepted that additional cardiac evaluation is not necessary in low risk patients. In addition to the overall analysis, we divided our patients into low- and high-risk groups. Patients over 50 years of age, with DN or a cardiovascular history were considered to be at high risk and the other patients were considered low risk. The incidence of cardiovascular events in the low and high-risk group was analyzed. Sensitivity, specificity and the negative and positive predictive value were calculated for this policy. The prevalence of cardiovascular events in our study cohort was used to calculate the predictive values.

Initial immunosuppressive therapy consisted of corticosteroids and a calcineurin inhibitor in all three trans-

plantation centers. From 1990, most patients received azathioprine or mycophenolate mofetil in addition.

Statistical evaluation

In a multivariate Cox proportional hazard model adjusted and unadjusted hazard ratios for a post-transplant cardiovascular event and all-cause mortality were calculated. First, univariate analyses were done to explore the relation between post-transplant cardiovascular events and all-cause mortality and all baseline parameters. In order to investigate which of these parameters were independent predictors for a post-transplant cardiovascular event and all-cause mortality the stepwise selection procedure as suggested by Collet was used [12]. The fit of the models was evaluated by inspection of the Schoenfeld residuals. All baseline parameters were included in the primary analysis, except pretransplant diastolic and systolic blood pressure, total cholesterol, and smoking because these parameters were systematically missing in some centers. However, these variables were included in secondary analyses restricted to the centers they were measured in. In this secondary analysis, we only included the patients in which all four parameters were present.

In an additional analysis, we tried to find a predictive algorithm for the occurrence of a post-transplant cardiovascular event and all-cause mortality within 3 months after the transplantation. For this analysis, occurrences of a post-transplant cardiovascular event and all-cause mortality within 3 months after the transplantation were analyzed using logistic regression. A multivariate analysis was done following the previously mentioned method. On basis of the multivariate logistic regression analysis, a predictive formula was sought. A ROC-curve was used to detect the cut-off point with the optimal sensitivity and specificity and the area under the curve (AUC) to evaluate the overall usefulness of the predictive formula.

A *P*-value of <5% was considered as significant (two-sided). Statistical analyses were carried out with SAS version 9.2 on the AIX 5.2 platform. (SAS Institute Inc. Cary, NC, USA)

Results

Between 1984 and 1997, 2187 patients received a first renal transplant. Seven hundred and five patients received their transplant between 1984 and 1988, 785 between 1989 and 1993, and 697 between 1993 and 1997. At baseline 7% of the patients had a history of a cardiac event, 6.3% of angina pectoris, 2.2% of claudication, and 3.1% of a CVA. Diabetic nephropathy was the primary kidney disease in 6.9% of the patients. The majority of the patients received a kidney from a deceased donor and 92% of the patients were treated with dialysis before the transplantation. All baseline characteristics are given in Table 1. In the latest time period, more patients received a kidney from a living donor and more patients were transplanted pre-emptively. There was no difference in recipient age, DN and cardiovascular morbidity between the three time periods. The median follow-up of the patients was 8 years (interquartile range 4.5–11.4). Mean patient survival after transplantation was 14.8 years (95% CI 14.0–16.1), and mean graft survival was 10.3 years (95% CI 9.7–10.9).

A total of 713 patients (32.6%) experienced a fatal or nonfatal post-transplant cardiovascular event, 115 patients experienced two post-transplant cardiovascular events and 73 patients experienced three or more post-transplant cardiovascular events. The incidence of post-transplant cardiovascular events was highest in the first 3 months after transplantation. Eighty-nine patients (4.1%) experienced a post-transplant cardiovascular event in the first 3 months after transplantation. One-hundred and sixty-seven (7.6%) patients had a post-transplant cardiovascular event in the first year after transplantation. After the first transplant year, the incidence of cardiovascular events declined from 4% in the second year to 3% in the tenth year. The post-transplant cardiovascular event-free survival is given in Fig. 1.

In univariate analyses, a previous cardiac event, angina pectoris, CVA, claudication, DN, duration of dialysis, year of transplantation, BMI, living donor and cold ischemia time were significantly associated with the occurrence of a post-transplant cardiovascular event. In the multivariate Cox regression model DN, claudication, history of a cardiac event, history of a CVA, duration of dialysis, recipient age, and BMI were independent predictors for a post-transplant cardiovascular event. The unadjusted and adjusted hazard ratios and 95% confidence intervals are given in Table 2. The model complied with the propor-

Table 1. Baseline characteristics of all patients.

	All patients (n = 2187)
Recipient age (years)	45.9 ± 13.1
Male (%)	1337 (61.1)
BMI (kg/m^2)	23.5 ± 3.7
Dialysis before transplantation (%)	1990 (92.8)
Time on dialysis (years)	2.3 ± 1.9
History of a cardiac event (%)	151 (7.0)
History of a CVA (%)	68 (3.1)
History of claudication (%)	47 (2.2)
History of angina pectoris (%)	134 (6.3)
Diabetic nephropathy as primary kidney disease (%)	149 (6.9)
Deceased donor (%)	1815 (83.0)
Cold ischemia time (h)	23.8 ± 12.0

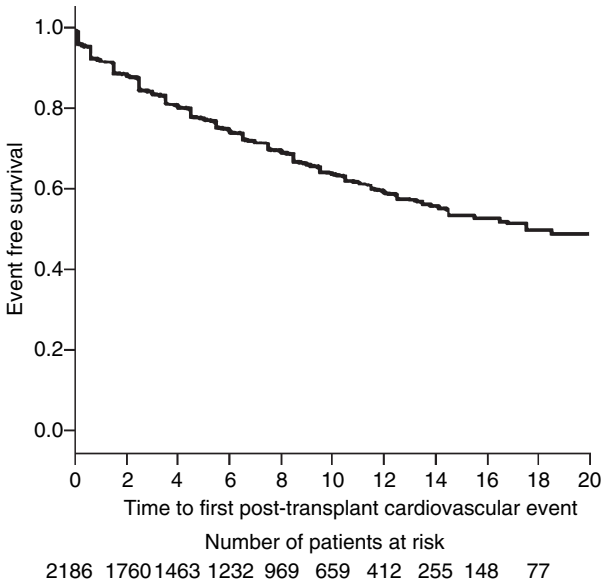

Figure 1 Post-transplant cardiovascular event-free survival.

tional hazard assumption because the correlations between the Schoenfeld residuals and the survival times were less than 0.1 for all predictors. The results of the subgroup analyses restricted to the centers that had recorded blood pressure, cholesterol and smoking data were similar to the results shown in Table 2. None of the additional factors were a significant predictor for a post-transplant cardiovascular event. In the multivariate logistic regression analysis, a previous cardiac event (cardiac event and angina pectoris were combined for this analysis), claudication, DN and recipient age were independent predictors for the occurrence of a post-transplant cardiovascular event within 3 months after transplantation (Table 3). On the basis of the logistic regression analysis, a predictive formula for the risk of occurrence of a post-transplant cardiovascular event within 3 months after transplantation was sought. However, the formula found, did not show an adequate sensitivity and specificity (AUC = 0.72). We also could not find a satisfactory formula for the risk of death early after transplantation (AUC = 0.67).

Table 3. Adjusted HR for predictors of a post-transplant cardiac event within 3 months of transplantation (multivariate logistic regression).

	HR	95% CI	*P*-value
Cardiac event (yes/no)	2.71	1.62–4.54	<0.001
Claudication (yes/no)	2.50	1.02–6.08	<0.05
Diabetic nephropathy as primary kidney disease (yes/no)	2.14	1.10–4.17	<0.05
Recipient age (years)	1.03	1.01–1.05	<0.001

CI, confidence interval; HR, hazard ratio.

One-thousand and sixty-four patients belonged to the predefined low-risk group and 1016 to the high-risk group (age >50 years, diabetes mellitus or a cardiovascular history or complaints). Fourteen patients (1.3%) in the low-risk group and 75 patients (6.8%) in the high-risk group had a post-transplant cardiovascular event within 3 months after the transplantation. Sensitivity and specificity of this algorithm were 84% and 51.2%. The negative predictive value of this policy was 98.7%. The positive predictive value of this policy was 7.3%. At 1 year, 35 patients (3.2%) in the low-risk group and 140 patients (12.8) in the high-risk group had a post-transplant cardiovascular event.

Table 2. Unadjusted and adjusted HR for predictors of a post-transplant cardiovascular event (Cox regression).

		Unadjusted hazard ratio		Adjusted hazard ratio	
	n	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Diabetic nephropathy as primary kidney disease (yes/no)	2173	3.22 (2.86–4.01)	<0.0001	3.02 (2.85–3.98)	<0.0001
Claudication (yes/no)	2154	4.04 (2.86–5.71)	<0.0001	2.17 (1.42–3.31)	<0.001
Cardiac event (yes/no)	2172	2.47 (1.96–3.11)	<0.0001	1.76 (1.32–2.33)	<0.0001
CVA (yes/no)	2175	2.05 (1.46–2.88)	<0.0001	1.53 (1.03–2.28)	<0.05
Time on dialysis (years)	1990	1.07 (1.03–1.10)	<0.001	1.06 (1.02–1.11)	<0.01
Recipient age (years)	2187	1.05 (1.04–1.05)	<0.0001	1.04 (1.04–1.05)	<0.0001
BMI (kg/m^2)	1836	1.05 (1.03–1.08)	<0.0001	1.03 (1.00–1.05)	<0.05
Angina pectoris (yes/no)	2137	1.97 (1.52–2.54)	<0.0001	–	–
Living donor (yes/no)	2164	0.60 (0.48–0.75)	<0.001	–	–
Cold ischemia time <24 h (yes/no)	2184	0.79 (0.68–0.92)	<0.01	–	–
Year of transplantation (years)	2187	0.98 (0.96–1.00)	<0.05	–	–
Recipient gender (male/female)	2187	1.10 (0.95–1.28)	NS	–	–

CI, confidence interval; NS, not significant; HR, hazard ratios; CVA, cerebrovascular accident.

Table 4. Unadjusted and adjusted HR for predictors of all-cause mortality after renal transplantation (Cox regression).

		Unadjusted hazard ratio		Adjusted hazard ratio	
	n	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Diabetic nephropathy (yes/no)	2173	2.49 (1.99–3.12)	<0.0001	2.74 (2.17–3.46)	<0.0001
CVA (yes/no)	2175	2.21 (1.60–3.05)	<0.0001	1.88 (1.36–2.60)	<0.0001
Claudication (yes/no)	2154	2.65 (1.82–3.87)	<0.0001	1.55 (1.05–2.29)	<0.05
Cardiac event (yes/no)	2172	2.46 (1.96–3.08)	<0.0001	1.55 (1.24–1.95)	<0.001
Recipient age (years)	2187	1.07 (1.06–1.08)	<0.0001	1.07 (1.07–1.08)	<0.0001
Year of transplantation (years)	2187	0.98 (0.95–0.99)	<0.01	0.97 (0.95–0.99)	<0.001
Time on dialysis (years)	1990	1.05 (1.02–1.09)	<0.01	–	–
BMI (kg/m^2)	1836	1.045 (1.02–1.07)	<0.001	–	–
Angina pectoris (yes/no)	2137	2.03 (1.59–2.60)	<0.0001	–	–
Living donor (yes/no)	2164	0.54 (0.43–0.68)	<0.0001	–	–
Cold ischemia time <24 h (yes/no)	2184	0.70 (0.60–0.82)	<0.0001	–	–
Recipient gender (male/female)	2187	0.90 (0.78–1.04)	NS	–	–

CI, confidence interval; NS, not significant; HR, hazard ratio; BMI, body mass index; CVA, cerebrovascular accident.

In Table 4 the unadjusted and adjusted hazard ratios for pretransplant risk factors for all-cause mortality are given. Independent pretransplant risk factors for all-cause mortality were DN, history of a cardiovascular event, a CVA, or claudication, recipient age and year of transplantation. Fifty-three percent of the all-cause mortality had a cardiovascular origin. The correlations between the Schoenfeld residuals and the survival times were <0.1 for all predictors apart from age. For the latter variable, the correlation was 0.14. The results of the subgroup analyses restricted to the centers that had blood pressure, cholesterol and smoking data were similar to the results shown in Table 4. Smoking was a significant predictor for all-cause mortality in the univariate and multivariate analyses. In the univariate analysis, the hazard ratio was 1.82 (95% CI 1.28–2.59) and in the multivariate analysis the hazard ratio was 2.34 (95% CI 1.61–3.41).

Discussion

This large retrospective cohort study shows that the incidence of post-transplant cardiovascular events is very high. Ten years after the transplantation, 40% of the patients had experienced at least one post-transplant cardiovascular event. Although our patient cohort had a relatively low cardiovascular risk at baseline compared to other studies, almost half of the patients experienced a post-transplant cardiovascular event within 10 years after transplantation [3,9]. The incidence of cardiovascular events was the highest in the first 3 months after transplantation (4.1%). This is comparable to the results of many other studies [3,9,13]. After the first transplant year, the incidence of post-transplant cardiovascular events slowly declined from 4% in the second year to 3% in tenth year. The decline in the incidence of post-transplant cardiovascular events late after transplantation probably reflects the fact that in patients without cardiovascular risk factors it takes more time before they reach a post-transplant cardiovascular event.

Diabetic nephropathy as primary kidney disease was the strongest predictor for a post-transplant cardiovascular event. Other independent risk factors for a post-transplant cardiovascular event were cardiovascular co-morbidity, time on dialysis, recipient age, and BMI. In the study from Kasiske *et al.* [9] the same independent risk factors, except for BMI, for an acute myocardial infarction after transplantation were found. In contrast to our results Kasiske *et al.* found that patients who were transplanted in the latest part of their study (between 1999 and 2002) had an increased risk for an acute myocardial infarction when compared with patients transplanted between 1995 and 1998. This is probably related to the increase of co-morbidity and age of renal transplant candidates in the last decade [6]. In our patient cohort there was no increase of mean age, DN and cardiovascular disease at baseline between 1984 and 1998. Not surprisingly, year of transplantation was not an independent risk factor for a post-transplant cardiovascular event in our study. In the study from Lentine *et al.* [3] older age, DN and cardiovascular co-morbidity also were the most important predictors for a myocardial infarction after transplantation. In contrast to their study, deceased donor kidney transplantation was not an independent predictive risk factor in our study. This can be explained by the relatively low number of living donor kidney transplantations.

Patients with a previous cardiac event had a more than twofold-increased risk for an early post-transplant cardiovascular event. Increased age, DN and claudication were also independently predictive for an early post-transplant

cardiovascular event. In the study from Humar *et al.* [13] the same risk factors were independently predictive for a peri-operative myocardial infarction. The relevancy of these risk factors was also illustrated by the high incidence of early post-transplant cardiovascular events in the high-risk group. The very low incidence of early post-transplant cardiovascular events in the low risk group confirms the previous findings that extensive cardiac evaluation is unnecessary in low-risk patients [14].

In our study, the risk factors for patient death were almost identical to risk factors for a cardiac event. This is not surprising as more than 50% of the all-cause mortality had a cardiovascular origin. Year of transplantation was an independent risk factor for patient death, with a higher risk for patients transplanted earlier. This might reflect the improvement in the prognosis after a cardiovascular event and the improvement in the treatment of infectious diseases. As we did not collect these data, this remains speculative.

Although our study is limited by its retrospective design, the routine gathering of data and yearly follow up made our database very complete. Data about smoking habits, cholesterol, and blood pressure were not complete because some centers did not routinely collect these data. In the centers that collected these items, data were almost complete. Reporting bias is therefore likely to be minimal. Although inclusion of the missing risk factors could have changed our final results, the subgroup analysis in the centers who reported all parameters does not support this. Another limitation of our study is that all our patients were transplanted before 1998 and that cardiovascular treatment and preoperative evaluation have changed considerably since then. It is not unreasonable to think that standard preoperative treatment with beta-blockers and extensive cardiovascular screening in high-risk patients would have decreased the incidence of early cardiovascular events [15,16]. On the other hand, incidences in more recent analysis are not lower than in our cohort [3,9]. Advantage of our inclusion period is that our study had a very long and complete follow up, which gave us the opportunity to give reliable information about the incidence of cardiovascular events till more than 10 years after transplantation. As far as we know, no study of this size with such a long follow up has been published before. In our study, we focused on pretransplant cardiovascular risk factors and we did not analyze the influence of post-transplant risk factors. It is well known that post-transplant risk factors like renal function and new-onset DM play a role in the occurrence of late cardiovascular events after renal transplantation [7,17]. A last limitation of the study might be the combined endpoint for a post-transplant cardiovascular event. In most recent studies, only cardiac events or myocardial infarction were used as primary endpoint [3,9,18]. Incidences of the events in those studies are not fully comparable to incidences in our study for this reason. On the basis of previous studies, it is expected that the majority of the cardiovascular events in our study had a cardiac origin. Besides, risk factors for stroke are generally the same as for cardiac events [18,19]. This explains the fact that we predominantly found the same independent risk factors in our study compared to other studies [3,9].

In international guidelines cardiovascular evaluation, including nuclear imaging or angiography, has been advised for high risk-patients [11,20]. Unfortunately there is no consensus about which cardiovascular screening test should be done. Sensitivity and specificity of nuclear imaging tests and dobutamine stress echocardiography differ widely between several studies [21]. In the study from De Lima *et al.* [22] angiography had the best sensitivity for the occurrence of cardiac events after transplantation. There is also no evidence that cardiac screening followed by revascularization is beneficial for asymptomatic high-risk renal transplant candidates. Manske *et al.* [23] showed in a small randomized clinical trial that preoperative revascularization in asymptomatic diabetic renal transplant candidates with significant coronary disease was superior to conservative therapy. Limitation of this study is that the conservative therapy was not adequate compared to recent standards. In a recent study from McFalls *et al.* [24] in high risk patients with asymptomatic significant coronary disease, revascularization before a major vascular operation had no benefit compared to conservative therapy. These results show that further prospective research in renal transplant candidates is necessary to elucidate how we can decrease the high incidence of post-transplant cardiovascular events.

The main conclusion of our study is that even in our relatively low risk, western European population the incidence of post-transplant cardiovascular events is high and is responsible for more than 50% of the mortality after transplantation. Traditional risk factors like diabetic nephropathy, older age and previous cardiovascular events are the most important pretransplant predictors for post-transplant cardiovascular events. Unfortunately we could not find a reliable algorithm to predict which patients would experience an early post-transplant cardiovascular event. We propose to do a prospective, randomized-controlled trial in high-risk renal transplant candidates to determine if cardiac screening followed by coronary revascularization is better than medical treatment alone.

Authorship

JA: collection of the data, statistical analysis, writing of the paper. EH: collection of the data and revising of the manu-

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script. JR: collection of the data and revising of the manuscript. WW: collection of the data and revising of the manuscript. JF: collection of the data and revising of the manuscript. AH: collection of the data and revising of the manuscript. GB: statistical analysis.

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