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Peripheral Arterial Disease and Outcomes in Patients Undergoing Renal Transplantation

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Research Article

Keywords: renal transplantation, peripheral artery disease, chronic kidney A conservative approach may be adequate in most patients and the decision to intervene should be made individually

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Abstract

Aims: Peripheral artery disease (PAD) is prevalent in renal transplant patients but assessment is seldom considered a routine in pre-transplant workup. We examined the consequences of PAD assessment and evaluated if PAD detection may contribute to identify patients at higher risk of events.

Methods: A retrospective study in 903 renal transplant patients prospectively assessed for PAD by palpation and followed up until death. The endpoint was the composite incidence of death by any cause and/or major cardiovascular events.

Results: The median follow-up was 62 months. PAD occurred in 162/903 patients (18%). The end-point occurred in 71% in patients with PAD and in 57% of those without PAD (log-rank< 0.0001, HR 1.633, 95% CI 1.327-2.010) and was predicted by diabetes (HR 1.782, 95% CI 1.084-2.930) and coronary artery disease (HR 1.799, 95% CI 1.072-3.071). Patients with PAD had more occlusive arterial events (log-rank< 0.0001, HR 1.921, 95% CI 1.320-2.796) independently associated with diabetes and arteriopathy. Occlusive events occurred in only 31 subjects (3.4% of all subjects at risk). Amputation was performed in 18 patients, 2 subjects underwent percutaneous intervention and 11, were managed medically.

Conclusion: PAD is frequent in renal transplant patients, correlates with an increased incidence of major cardiovascular events but the probability of events directly attributed to limb ischemia is modest. PAD must be routinely evaluated because it allows the identification of individuals at higher risk of future cardiovascular events but patients with PAD should not be barred from the wait

list. The decision to intervene in asymptomatic patients should be made individually.

Key words: renal transplantation, peripheral artery disease, chronic kidney A conservative approach may be adequate in most patients and the decision to intervene should be made individually.

Introduction

Peripheral artery disease (PAD) is prevalent in patients with chronic kidney disease (CKD) and is associated with death and major adverse events [1-4]. Given the prevalence and importance of PAD, it should be routinely investigated in patients on renal replacement therapy. Despite this, PAD assessment is seldom considered a routine in pre transplant workup. Consequently, there is relatively little information on the impact of pre-transplant PAD on prognosis of patients undergoing renal transplantation. Moreover, occlusive arterial syndrome is an important cause of death and serious vascular complications, leading to gangrene and amputation. Understandably, physicians may be reluctant to include patients with severe distal vascular disease on the waiting list because of risk of progression after transplantation.

The purpose of this work was to evaluate if PAD detection, using a simple and inexpensive method, may contribute to identify a subgroup of patients at higher risk of ischemic and other significant cardiovascular events or death and should, therefore, be an integral part of pre transplant workup. We also intend to verify if there are grounds for barring patients with PAD from renal transplantation.

Methods

This was a single-center retrospective study in adult patients with CKD undergone renal transplantation prospectively assessed for PAD (the KiHeart cohort). The study was approved by the institutional ethics committee (IRB 3428/10/17) and conducted according to the Declaration of Helsinki. Because this was a retrospective study of a register the institutional ethics committee found that consent to participate in the study was not applicable. This study was

not funded. Patients were being considered to receive a kidney graft at the Renal Transplant Unit, Division of Urology, University of São Paulo Medical School, and they were referred to the Heart Institute (InCor) for cardiovascular assessment before being included on the waiting list. A detailed description of our center's approach to investigating and managing patients with CKD has been reported elsewhere which includes assessment of PAD in all patients [5,6]. Between August 1997 and November 2024, 3213 subjects with CKD stage 5, treated by dialysis, were included in the cohort. Of these, 903 underwent renal transplantation. After the operation patients were followed up prospectively and were evaluated before transplantation, after 6 months, and annually up to the conclusion of the study in November 2024 or death, even if they had returned to dialysis or were retransplanted. Events were verified during clinical visits, by telephone, or by e-mail. Patients were receiving optimal medical treatment for primary or secondary prevention, and risk factor control was vigorously pursued. Medical treatment included statins, antiplatelets, angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers), and beta-blockers. Patients had free access to medication, dialysis, and transplantation. The immunosuppressive treatment was based on calcineurin inhibitors (cyclosporine or tacrolimus), azathioprine or mycophenolate, and prednisone. After 2005, induction therapy with a variety of antibodies became routine. Acute rejections were treated with high doses of prednisolone.

The initial evaluation involved clinical history, physical examination, routine laboratory tests, electrocardiography, and echocardiography. Tobacco use, hypertension, heart failure, dyslipidemia, stroke, and diabetes were defined as previously described [5,6]. Graft failure was defined as return to dialysis or

retransplant. Previous or current cardiovascular disease included myocardial infarction, coronary intervention, stroke, left ventricular dysfunction, and peripheral arterial disease.

Patients were classified into four risk groups according to the modification of the American Society of Transplantation index [7,8] that used age ≥ 50 years, diabetes (Types 1 or 2) and cardiovascular disease to define the risk of future adverse events as follows: low risk—no risk factors, intermediate risk—one factor (age, diabetes or CVD), high risk—two risk factors in any combination and very high risk—all three factors present.

Noninvasive testing for CAD with dipyridamole/adenosine myocardial stress testing by SPECT with Tc-99m Sestamibi was performed in selected cases. Patients with angina, noninvasive testing suggestive of CAD, diabetes, or clinical evidence of cardiovascular disease were eligible for coronary angiography. Significant CAD was defined as luminal stenosis ≥70% in one or more epicardial arteries or a 50% narrowing of a main left coronary artery by visual estimation from two independent experts. The heart team assessed those with significant CAD, and myocardial revascularization procedures following current practice guidelines were indicated.

PAD was defined on clinical grounds as either absence of a pulse in at least one of the main distal arteries of the lower limb (anterior and posterior tibial arteries) or a history of acute vascular syndrome or amputation. PAD was assessed before transplantation through a standardized lower extremity vascular physical examination as recommended for the evaluation of kidney transplant candidates and consistent with contemporary PAD guidelines [9,10]

Aorto-iliac disease was excluded by tomography. Invasive and other noninvasive procedures to assess PAD were not used as a routine. No patient underwent vascular intervention before transplant. Occlusive arterial syndrome was defined as need for amputation or vascular intervention.

Endpoint was the composite incidence of all-cause mortality and/or major cardiovascular events (myocardial infarction, unstable angina, sudden death, stroke, new-onset heart failure, and occlusive arterial syndrome). No patient was lost to follow-up.

Statistical Analysis

Values are expressed as means, standard deviation of the means, and percentages. We used a statistical software package (SPSS Statistics, version 20.0, IBM, Armonk, NY, USA) for data analysis. The differences among the groups were assessed with chi-square test (for categorical data), or the Student t test (for continuous data), when appropriate. To determine independent predictors of PAD and of occlusive arterial syndrome, the univariate binary logistic regression model was performed, using clinical variables associated with outcomes in the univariate model. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards model was used to verify the variables associated with outcomes. $P < 0.05$ was considered significant.

Results

The mean follow-up was 75 ± 63, median 62, and range 0.31-279 months. Table 1 shows the baseline characteristics of the patients according to PAD status. PAD was observed in 162/903 patients (18%). Patients with and without

PAD diverged in many aspects. Patients with PAD were older, more likely to be males and smokers and had been on dialysis for a shorter period of time. A history of diabetes, myocardial infarction and reduced LV ejection fraction and evidence of CAD also predominate in this group. They were less likely to present acute rejection and more often used aspirin after the operation.

Figure 1 compares the combined incidence of death and major adverse events in the 2 groups. The end-point occurred in 71% in patients with PAD and in 57% of those without PAD. The cumulative incidence of events was higher in the PAD group (log-rank< 0.0001). PAD was associated with a HR= 1.633, (95% CI 1.327-2.010).

Figure 2 shows that PAD prevalence increased with severity of clinical presentation, with the majority of patients (91%) having at least 2 major risk factors.

Table 2 depicts the factors associated with PAD on multivariate analysis. Diabetes mellitus (HR 1.782, 95% CI 1.084-2.930) and coronary artery disease as defined by angiography (HR 1.799, 95% CI 1.072-3.071) were the variables independently associated with PAD.

As occlusive arterial syndrome is the major clinical consequence of PAD we assessed the factors associated with that complication. During follow-up 31/903 patients (3.4%) developed an occlusive arterial syndrome: 16 of 162 patients with pre-transplant PAD (9.9%) and 15 of 741 patients without pre-transplant PAD (2.0%), P< 0.0001.

Figure 3 shows the incidence of occlusive arterial events in patients with and without PAD: patients with PAD had significantly more events (log-rank<

188 0.0001). The crude HR associated with occlusive arterial syndrome was 1.921
189 (95% CI 1.320-2.796). Among the 31 patients with an occlusive arterial
190 syndrome, 26 deaths occurred (84%), with 16 (52% of those with occlusive
191 syndrome) directly attributed to a peripheral vascular event. Amputation was
192 performed in 18 patients, 2 underwent percutaneous intervention and, 11 were
193 managed medically.

194 Table 3 compares the prevalence of the most important risk factors between
195 patients who developed and who did not develop an occlusive arterial
196 syndrome. Dialysis duration, diabetes, hypertension, arteriopathy and use of
197 aspirin were associated with the syndrome. Multivariate analysis (Table 4)
198 shows that diabetes (HR 6.446, 95% CI 1.447-28.712) and arteriopathy (HR
199 2.868 95% CI 1.204-6.829) were the sole independent predictors of occlusive
200 arterial syndrome. There was a trend for hypertension and use of aspirin to
201 predict the syndrome that did not achieve statistical significance.

202 **Discussion**

203 In this retrospective investigation with a long follow up in patients undergoing
204 renal transplantation and prospectively evaluated for cardiovascular disease,
205 we observed that PAD was prevalent and strongly associated with adverse
206 events and coronary artery disease, supporting the routine assessment of PAD
207 in patients listed for transplant. Progression of PAD was not a rule and
208 occlusive arterial syndrome occurred in only 3.4%. The data suggest that
209 palpation may be a useful and inexpensive tool to identify individuals at high risk
210 of events. Our data do not support barring patients from transplantation based

211 on the presence of significant PAD because the incidence of complications
212 directly attributed to PAD was low.

213 Our results highlight the recent recommendations of KDIGO that includes the
214 routine evaluation of all renal transplant candidates for presence and severity of
215 peripheral arterial disease based on history and physical examination [10].

216 Here, we used the absence of pulse as the main criterion to define PAD. This
217 method predicted PAD with a specificity of 94% using the Doppler ultrasound as
218 a reference and correlated with the incidence of death and major CV events in
219 patients treated by dialysis from the same cohort [11]. This specificity was
220 comparable with that observed with the most recommended noninvasive
221 method to screen for PAD, the ankle-brachial index, which provides an accurate
222 assessment for the diagnosis of PAD [12]. Using palpation, we identified a
223 subgroup of patients at higher risk of adverse events including occlusive
224 vascular syndrome.

225 PAD prevalence in our patients was 18%, somewhat lower than that reported in
226 other studies but much higher than that observed in patients without CKD. Patel
227 et al [13], using the ankle-brachial index of ≤0.9, found PAD in 46% of
228 transplanted patients. Other reports showed a prevalence varying between 24%
229 and 37% in patients with CKD [12]. In contrary, PAD was reported in only 8% of
230 subjects on the waiting list in a Spanish cohort of 3851 patients [13] and in 17% of
231 patients listed for a kidney transplant in the US Renal Data System [14]. These
232 disparities likely reflect differences in methods and age and in the prevalence of
233 diabetes that are well known risk factors for PAD in the general population.

Unsurprisingly, we detected a close association of PAD with diabetes and other manifestations of atherosclerosis, like CAD, confirming reports by others [13,14]. We found no evidence that sex, dyslipidemia, smoking and hypertension influenced PAD prevalence. Age, an important PAD risk factor in the general population, also showed no correlation, likely due to the relatively young age of our patients, lower than 55 years. PAD had no detrimental effect on graft survival, possibly because we did not include death with functional graft as transplant failure. The close association of PAD with CAD merits a further appraisal. In previous investigation we found that PAD assessed by palpation predicted CAD severity and likelihood of coronary intervention in patients on dialysis [11]. Our present data suggest that in transplanted subjects it may also be a useful and inexpensive tool to identify individuals in need of CAD assessment.

As shown in Figure 1, the HR for death and major adverse events associated with PAD was increased by 60% (HR 1.633, % CI 1.33-2.01). Similarly, 2 studies in a large number of patients undergoing transplant, reported doubled risk of death in those with PAD [13,17] echoing analysis from the US Renal Data System [14]. In our study, this increased incidence of serious events was closely associated with the number of CV risk factors, indicating that PAD is just a particular instance of widespread vasculopathy, prevalent in patients with CKD.

PAD was associated with an increased risk of limb-threatening ischemia suggesting that an aggressive treatment of PAD would be warranted. However we found that only 16/162 (9.9%) patients with PAD developed an occlusive arterial syndrome during a median follow up of 62 months and that the overall incidence of occlusive arterial syndrome was not high (31/903, 3.4%). Other authors also reported a similar incidence of limb ischemia and gangrene, close

to 2% [13]. This indicates that the direct impact of PAD on survival is relatively small and that the risk of progression of PAD after transplantation is not high. Therefore, our data do not support barring patients from transplantation based on the presence of significant PAD.

In renal transplant patients, PAD was useful for identifying subjects at higher risk of CV complications but its direct impact on overall survival was modest. However, when occlusive arterial syndrome does occur, the consequence was important given the mortality rate of over 80%. Interestingly, 15/741 patients without PAD developed acute limb ischemia, indicating that either the palpation method missed the diagnosis or that some patients developed *de novo* PAD. However, the low incidence of occlusive arterial syndrome in our patients without PAD suggests that *de novo* PAD may be a relatively infrequent complication.

Whether to intervene in PAD invasively among asymptomatic kidney transplant candidates is controversial. The American Society of Transplantation recommends endovascular revascularization or surgical intervention for PAD should be reserved for symptomatic patients [7]. Elective aortic bypass surgery in asymptomatic PAD has been associated with high rates of complications and renal transplant patients who underwent revascularization procedures had worse limb salvage rates and higher rates of amputation compared with dialysis patients [18,19]. Therefore, although PAD independently predicts occlusive arterial syndrome, there is no guarantee that intervention will improve prognosis. Our results with a more conservative approach suggest that the decision to intervene should be made individually.

In conclusion, PAD was frequent in patients undergoing renal transplantation. PAD was associated with increased incidence of major CV events, but the probability of events directly attributed to limb ischemia was modest. Patients on the waiting list should be routinely evaluated for PAD to identify those at higher cardiovascular risk, although not necessarily related to limb ischemia. The decision to intervene in asymptomatic patients should be made individually.

Our data indicate that barring patients from transplantation based on the presence of significant PAD is not warranted.

Limitations: this was a retrospective, single-center study and causal relationships cannot be inferred. The palpation method used to diagnosis PAD may have low sensitivity. We did not evaluate functional walking capacity. The method used here to diagnose PAD made impossible to detect non-compressible arteries. Strengths include the large cohort, comprehensive evaluation, and the prolonged follow-up.

Declarations

Abbreviations

CAD: coronary artery disease

CKD: chronic kidney disease

CV: cardiovasular

CVD: cardiovascular disease

HR: hazard ratio

IRB: Institutional Reviewer Board

LV: left ventricle

PAD: Peripheral artery disease

SPECT: single photon emission computed tomography

Ethics approval and consent to participate

The study was approved by the institutional ethics committee, Hospital das Clínicas, Universidade de São Paulo (IRB 3428/10/17) and conducted according to the Declaration of Helsinki. Because this was a retrospective study of a register the institutional ethics committee found that consent to participate in the study was not applicable.

Consent for publication

We agree with the rules for publication established by this journal

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors have no competing interest to declare

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Author´s contributions

JJGL: conceived and wrote the manuscript

LHWG: reviewed the draft

APA: collected data and reviewed the draft

ORJR: reviewed the draft

EDN: reviewed the draft

SATF: collected data and reviewed the draft

LAB: reviewed the draft

Aknowledgements:

Not applicable

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Figure legends

Figure 1. Combined incidence of death and major cardiovascular events in patients with and without PAD.

Figure 2. Prevalence of PAD in accord with the number of cardiovascular risk factors.

Figure 3. Combined incidence of death and major cardiovascular events in patients who developed and did not develop occlusive arterial syndrome.

Table 1. Baseline characteristics of patients (Peripheral artery disease)

Variable	Total	Arteriopathy Yes	Arteriopathy No	P
Number	903	162 (18%)	741 (82%)	
Age, years	51.7 ± 11.1	54.0 ± 9.9	51.3 ± 11.3	0.005
Sex, male	534 (59%)	112 (69%)	422 (57%)	0.005
White race	636 (70%)	121 (75%)	515 (70%)	0.190
Months on dialysis	37 ± 43	28 ± 33	40 ± 45	0.001
Months on the waiting list	31 ± 28	30 ± 25	33 ± 30	0.364
History of				
Dyslipidemia	312 (35%)	58 (36%)	254 (34%)	0.673
Smoking	318 (35%)	77 (47%)	241 (33%)	0.0001
Diabetes	370 (41%)	114 (70%)	256 (35%)	0.0001
Hypertension	676 (75%)	127 (78%)	549 (74%)	0.263
Stroke	69 (8%)	17 (10%)	52 (7%)	0.134
Angina	110 (12%)	22 (14%)	88 (12%)	0.552
Myocardial infarction	85 (9%)	25 (15%)	60 (8%)	0.004
Heart failure	59 (6%)	13 (8%)	46 (6%)	0.630
Pre transplant data				
BMI, Kg/m^2	25.7 ± 4.6	25.9 ± 4.4	25.7 ± 4.7	0.641
Total-cholesterol	169 ± 49	168 ± 48	169 ± 50	0.810
Triglycerides	164 ± 121	160 ± 113	164 ± 123	0.713
Hematocrit	37.5 ± 6.5	37.3 ± 6.0	37.5 ± 6.6	0.799
LV mass index, g/m^2	136 ± 51	129 ± 45	137 ± 52	0.113
LV PWT, mm	11 ± 2.0	11.0 ± 1.6	11.2 ± 2.0	0.586

LV DD, mm	50 ± 7.0	50.1 ± 8.2	50.2 ± 6.7	0.650
LVEF	0.61 ± 0.11	0.59 ± 0.11	0.62 ± 0.11	0.008
Altered myocardial scan	229 (28%)	55 (37%)	174 (26%)	0.007
Coronary artery disease	262 (48%)	92 (65%)	170 (42%)	0.0001
Coronary intervention	50 (17%)	15 (12%)	35 (18%)	0.177
Transplant era				
1998-2013 x 2014-2025	426 (47%)	61 (38%)	361 (49%)	0.007
Post-transplant data				
First transplantation	745 (92%)	146 (95%)	599 (92%)	0.181
Deceased donor	653 (81%)	130 (85%)	525 (80%)	0.171
Delayed graft function	467 (59%)	92 (60%)	375 (59%)	0.693
Acute rejection	154 (20%)	19 (12%)	135 (21%)	0.045
Graft failure	135 (15%)	10 (6%)	125 (17%)	0.571
Post transplant diabetes	83 (9%)	11 (7%)	72 (10%)	0.162
Last creatinine, mg/dL	2.9 ± 2.4	2.6 ± 2.2	2.8 ± 2.4	0.306
Use of statins	627 (78%)	125 (82%)	502 (77%)	0.447
Use of aspirin	532 (66%)	121 (79%)	411 (63%)	0.001

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463 **Table 2.** Factors associated with PAD (multivariate analysis)

Variable	HR	95% CI	P value
Age	0.994	0.970-1.018	0.634
Sex (male)	1.132	0.691-1.852	0.623
Smoking	1.356	0.854-2.153	0.197
Diabetes	1.782	1.084-2.930	0.023
Myocardial infartion	1.291	0.679-2.454	0.436
Months on dialysis	1.003	0.996-1.011	0.399
LV ejection fraction	0.374	0.054-2.585	0.319
Altered SPECT	0.715	0.431-1.186	0.194
Coronary artery disease	1.799	1.072-3.017	0.026
Vintage	1.181	0.724-1.926	0.505
Acute rejection	0.132	0.845-2.341	0.673
Use of aspirin	0.635	0.666-1.949	0.635

Table 3. Baseline characteristics of patients (Occlusive arterial syndrome)

Variable	Total	Occlusive arterial syndrome Yes	Occlusive arterial syndrome No	P
Number	903	31 (3%)	872 (97%)	
Age, years	51.7 ± 11.1	52.2 ± 9.6	51.7 ± 11.2	0.697
Sex, male	535(59%)	23 (74%)	512 (59%)	0.084
White race	637 (70%)	23 (74%)	614 (70%)	0.643
Months on dialysis	37 ± 43	22 ± 18	38 ± 43	0.002
Months on the waiting list	31 ± 28	33 ± 21	32 ± 29	0.097
History of				
Dyslipidemia	312 (35%)	11 (36%)	301 (34%)	0.912
Smoking	319 (35%)	8 (26%)	311 (36%)	0.257
Diabetes	370 (41%)	26 (84%)	344 (39%)	0.0001
Hypertension	678 (75%)	29 (94%)	649 (74%)	0.015
Stroke	70 (8%)	2 (6.5%)	68 (7.8%)	0.783
Angina	110 (12%)	4 (13%)	106 (12%)	0.899
Myocardial infarction	85 (9%)	3 (10%)	82 (9%)	0.959
Arteriopathy	162 (18%)	16 (52%)	146 (17%)	0.0001
Heart failure	59 (6%)	2 (6.5%)	57 (6.5%)	0.982
Pre transplant data				
BMI, Kg/m^2	25.7 ± 4.6	25.5 ± 3.9	25.7 ± 4.7	0.213
Total-cholesterol	169 ± 49	168 ± 56	169 ± 49	0.214
Triglycerides	164 ± 121	180 ± 155	163 ± 120	0.158

Hematocrit	37.5 ± 6.5	38.63 ± 6.0	37.5 ± 6.5	0.926
LV mass index, g/m^2	136 ± 51	127 ± 38	136 ± 51	0.177
LV PWT, mm	11 ± 2.0	11.1 ± 1.3	10.8 ± 2.0	0.138
LV DD, mm	50 ± 7.0	49.2 ± 5.3	50.3 ± 7.1	0.270
LVEF	0.61 ± 0.11	0.60 ± 0.11	0.61 ± 0.11	0.789
Altered myocardial scan	229 (28%)	8 (28%)	221 (27%)	0.933
Coronary artery disease	262 (48%)	15 (60%)	247 (47%)	0.218
Coronary intervention	50 (17%)	2 (13%)	48 (17%)	0.693
Transplant era				
1998-2013 x 2014-2025	428 (47%)	17 (55%)	411 (47%)	0.395
Post-transplant data				
First transplantation	746 (92%)	30 (97%)	716 (92%)	0.334
Deceased donor	656 (81%)	29 (93%)	627 (81%)	0.071
Delayed graft function	467 (59%)	20 (64%)	447 (59%)	0.527
Acute rejection	154 (20%)	3 (10%)	151 (20%)	0.362
Graft failure	147 (16%)	4 (13%)	143 (16%)	0.606
Post transplant diabetes	83 (89%)	2 (100%)	10 (11%)	0.620
Last creatinine, mg/dL	2.9 ± 2.4	2.4 ± 1.9	2.8 ± 2.4	0.399
Use of statins	628 (78%)	27 (87%)	601 (78%)	0.464
Use of aspirin	533 (66%)	28 (90%)	505 (65%)	0.004

476 **Table 4.** Factors associated with Occlusive arterial syndrome (multivariate
477 analysis)

Variable	HR	95% CI	P value
Diabetes	6.446	1.447-28.718	0.015
Months on dialysis	1.001	0.984-1.017	0.936
Hypertension	4.173	0.949-18.360	0.059
Arteriopathy	2.868	1.204-6.829	0.017
Use of aspirin	6.067	0.789-46.623	0.083

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Figure 1.

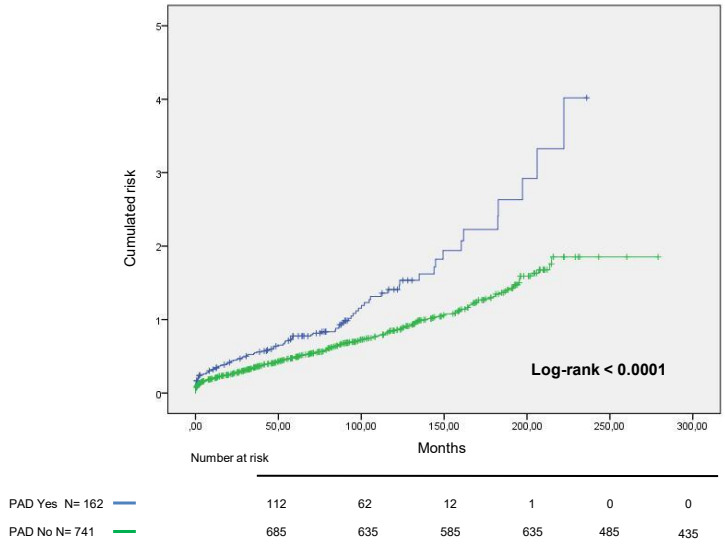
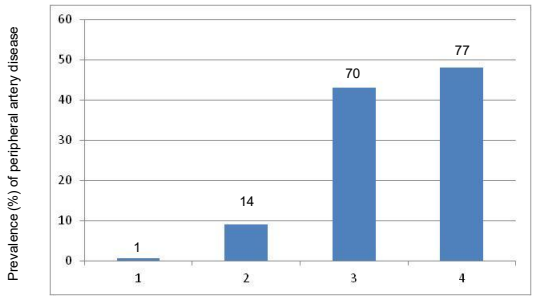

Cumulated risk
0
1
2
3
4
5
Log-rank < 0.0001
,00
50,00
100,00
150,00
200,00
250,00
300,00
Months
Number at risk
PAD Yes N= 162
112
62
12
1
0
0
PAD No N= 741
685
635
585
635
485
435

Figure 2



1- low risk: age< 50 yo, no DM, no CVD

2- moderate risk: one risk facto (any)

3- high risk: 2 risk factors (any combination)

4- very high risk: all 3 risk factors

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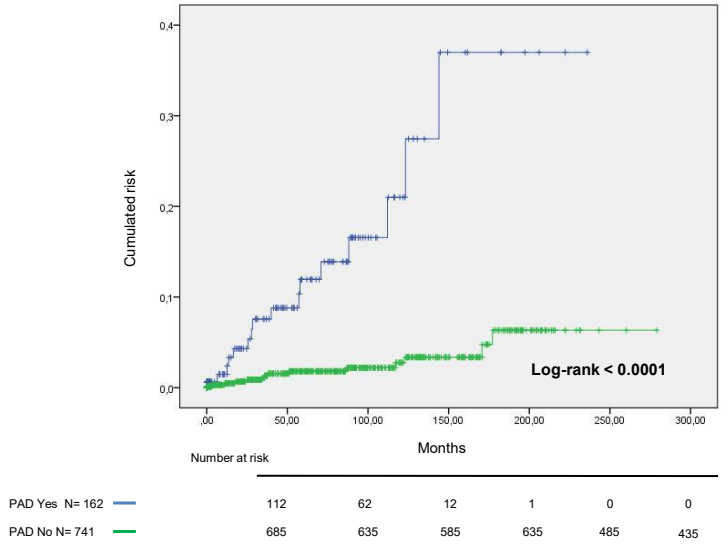
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Figure 3.


Cumulated risk
0,4
0,3
0,2
0,1
0,0
Log-rank < 0.0001
,00
50,00
100,00
150,00
200,00
250,00
300,00
Months
Number at risk
PAD Yes N= 162
112
62
12
1
0
0
PAD No N= 741
685
635
585
635
485
435