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CALCIUM CHANNEL BLOCKERS ARE ASSOCIATED WITH IMPROVED SURVIVAL AND LOWER CARDIOVASCULAR MORTALITY IN PATIENTS WITH RENOVASCULAR DISEASE

Short Title: Medical management-Renovascular Disease

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Background and objective

Results of interventional trials in renovascular hypertension have been disappointing and medical therapy is the current recommended gold standard. However, the comparative long-term benefits of different antihypertensive drug classes in atherosclerotic renal artery stenosis are not known. We aim to assess the effect of different antihypertensive drug classes on outcomes in renovascular hypertension

Design, setting, participants, and measurements

Using Tayside Health Informatics Centre database, anonymised data over a 6-year period was analysed. Biochemistry, prescribing data, morbidity, mortality and demographic data were accessed via hospital medical records and electronic data stored in the Tayside Health Informatics Centre Safe Haven. General Registrar's Office data was used to identify patients who died from cardiovascular disease. Independent predictors of survival in each group were analyzed using Kaplan-Meier survival curves and Cox proportional hazard models, adjusted for a range of covariates, using Time-Updated Drug Analysis. Blood pressure data was obtained from primary and secondary care clinic blood pressure records for each patient. Adjustments for mean systolic blood pressure over the follow-up period and baseline blood pressure were made.

Results

579 patients with Atherosclerotic Renal Artery Stenosis were identified. In the unilateral renal artery stenosis cohort, Calcium Channel Blockers but not ACE inhibitors/ARBs, were associated with a significant reduction in all-cause (HR=0.45, CI= 0.31, 0.65; P=<0.0001) and Cardiovascular ((HR= 0.51, CI =0.29-0.90 P=0.019). This was maintained after adjustment for blood pressure. In the bilateral

renal artery stenosis cohort, both classes of drugs reduced all-cause but not cardiovascular mortality. Patients with moderate disease benefitted more than those with mild or severe disease.

Conclusions

Calcium Channel Blockers are associated with significantly increased survival and lower cardiovascular mortality particularly in patients with moderate RAS disease.

Introduction

Atherosclerotic renal artery stenosis (ARAS) accounts for an estimated 90% of renovascular disease[1] and is often complicated by renovascular hypertension, chronic kidney disease (CKD)[2] and increased adverse cardiovascular outcomes. This increased risk of cardiovascular disease and subsequent high cardiovascular mortality has resulted in significant research on how best to approach the management of these patients[3]. Research efforts have largely focused on assessing the efficacy of renal artery revascularisation; however several randomised controlled trials (RCTs) have failed to demonstrate a clear benefit of this intervention over medical therapy[4]. Current guidelines suggest that in view of these trial results, medical management with antihypertensive therapy is the preferred option for patients with renovascular disease. Drugs that interrupt the renin-angiotensin-aldosterone system (RAAS) are regarded as first line therapy in renovascular hypertension[5]. The value of angiotensin converting enzyme inhibitors (ACEi) may extend beyond antihypertensive properties as they protect against angiotensin II (ATII) induced cardiovascular damage, including left ventricular hypertrophy, vascular remodelling and activation of fibrogenic cytokines[6]. However, they reduce blood flow through the stenotic kidney and therefore while blood pressure may fall rapidly, there is often an ensuing deterioration in renal function[7] . Dihydropyridine Calcium channel blockers (CCBs) in clinical use inhibit voltage-gated L-,T- and P-/Q type calcium channels to different degrees of selectivity[8] and have beneficial effects on arterial smooth muscle relaxation without compromising renal function. Furthermore, CCBs have been shown to inhibit adverse vascular

remodelling[9]. However, none of these drug classes have never been specifically trialled in a renovascular hypertension cohort and experimental evidence of their effect on the progression of renal damage has been previously debated[10].

Many patients with renovascular disease have treatment-resistant hypertension and therefore there remain significant challenges in the control of blood pressure, resulting in the use of multiple antihypertensive agents to achieve adequate control[11]. Surprisingly, no RCTs have investigated the comparative efficacy of various antihypertensive drug classes specifically in the management of renovascular hypertension. The aim of this study was to investigate the effect of two commonly used classes of antihypertensive agents, RAAS-blocking agents (ACEi and ARBs) and CCBs on progression of CKD, cardiovascular and all-cause mortality in Unilateral Renal Artery Stenosis (URAS) and Bilateral Renal Artery Stenosis (BRAS).

Methods

Study Population

This was a retrospective population-based cohort study of all hypertensive patients within the population of Tayside, Scotland who underwent a Magnetic Resonance (MR) angiogram or Mercaptoacetyltriglycine(MAG)-3 scan for investigation of renovascular disease (n=579) between Jan 2005 and June 2012. These were contemporaneous investigations of choice for renovascular disease based on local guidelines during the specified time window. Numbers of patients undergoing alternative imaging investigations were too small for inclusion. We excluded patients with no evidence of significant renovascular disease (<50% stenosis), with fibromuscular dysplasia, solitary kidney and those who had already undergone renal transplantation. Further exclusion criteria included ambiguous radiology reports, poor quality images precluding assessment of renal artery stenosis and dual RAAS therapy. These data were linked to biochemistry blood data, prescribing data, co-morbidity information, dates of medical or surgical interventions, demographic data and cause of death (GRO) data provided by Health Informatics Centre (HIC) in Tayside Scotland. The HIC

database contains information on all patients within Tayside who are registered with a General Practitioner (GP). Hospitalisations due to cardiovascular events were captured by linkage to the national hospital admissions Standardised Morbidity Record (SMR-01) data held by the Information Services Division of the National Health Service (NHS) and mortality data was provided by the National Records of Scotland (NRS). The SMR-01 captures all national public sector hospital admissions from 1981 onwards. Cardiovascular disease-related mortality was defined as death with an underlying ischaemic/CHD cause on the death certificate (ICD codes: ICD-9, 410–414; ICD-10 I20–I25) or for cerebrovascular disease including transient cerebral ischaemic attacks and related syndromes (ICD-9 430–43; ICD-10 I60–I69 and G45). These ICD codes were chosen as they are used in the official national statistics for CVD[12]. Definitions of severity of stenosis based on convention used in radiological reports were as follows: mild = <50%, moderate = 50-80% and severe = >80%. ESRD was defined as the first reading of eGFR<15ml/min in during the follow-up period from the date of diagnosis of URAS or BRAS. eGFR was calculated from serum creatinine using the Modified Diet in Renal Disease (MDRD) equation. Longitudinal blood pressure data was obtained using clinic bp data recorded in both primary and secondary care medical records for each patient.

Statistical analysis

The primary outcome was defined as all-cause mortality and all major hospitalised cardiovascular disease (CVD)-related deaths after the date of diagnosis of ARAS. The secondary outcome was defined as time to end-stage renal disease (ESRD). The presence of atherosclerotic renovascular disease was itself an indicator of background vascular disease.

For comparison of the baseline characteristics of the study population we used the chi-square test for categorical variables and t-tests for continuous variables. A value of $P < 0.05$ was considered statistically significant. Time updated cox proportional hazard models (R Software-3.4.1) were used to calculate all-cause mortality and CVD mortality associated with the use of each drug class. In

order to determine the robustness of the findings, we also examined patient survival stratified by severity of RAS, based on the hypothesis that those with severe RAS would have a higher mortality. These time updated Cox proportional hazard models were adjusted for age, sex, stent placement (yes/no), presence of diabetes, use of diuretics, statins, CCB, ACEi/ARB, beta-blockers and severity of RAS at baseline. In order to test the assumption of proportional hazards we generated time-dependent covariates by creating interactions of the predictors and a function of survival time and included these models. ACEi/ARB, CCB and Thiazide Diuretics were modelled as time-dependent variables where the follow-up time was split into intervals of 60 days and drugs use in each of the interval was modelled prospectively. Thus, if in the interval 1 a patient was on ACEi, this patient would have added person years to the ACEi group. If the patient was switched to CCB in the next interval this patient would then add person years to CCB groups. Whereas, if the patient was on both ACEi or ARB and CCB in a particular interval, he would have added person years to both ACEi/ ARB and CCB groups. To check for the effect of blood pressure, the average Mean Arterial Pressure over the duration of follow-up for each subject was calculated.

Results

Baseline characteristics of the study population

Table 1 shows the baseline characteristics of the study population. The study consisted of 394 cases with URAS and 148 cases with BRAS. Those with BRAS were significantly more likely to have stent placement and had significantly higher all-cause and CVD mortality compared to those with URAS (Figure 1). Patients with URAS were also more likely to have a baseline prescription of CCB and ACEi or ARB. There were no differences in statin and aspirin exposure between groups.

Predictors of all cause and CVD related mortality in URAS and BRAS using time updated analysis

In the study population 50.8 %(n=86/169) of patients with BRAS and 36.8% (n=151/410) patients with URAS died during the follow-up period for 3.5 years. We utilised the longitudinal drug prescription data to investigate the effect of ACEi/ARB and CCB on all-cause and CVD related mortality in both URAS and BRAS patients.

Calcium Channel Blockers

In the time–updated analysis (Table 2) CCBs were significantly associated with increased overall survival in URAS (HR=0.45, CI= 0.31, 0.65; P=<0.0001) and BRAS (HR=0.39 CI= 0.22, 0.69; P=0.0013). CCBs also showed a protective effect of CVD related mortality in URAS (HR= 0.51, CI =0.29-0.90 P=0.019) but not for BRAS (HR=0.47, CI= 0.22, 1.02, P=0.056). When the URAS and BRAS cohorts were combined, the results remained consistent. In the combined analysis CCB were significantly associated with lower all cause (HR=0.43 (0.32, 0.59) P<0.0001) and CVD mortality (HR=0.49 (0.31, 0.78) P=0.0022)

ACE inhibitors/ Angiotensin Receptor Blockers

We found that use of ACEi/ARBs was not associated with all-cause mortality reductions in URAS (HR=0.70 (0.48, 1.00) P=0.05) cohort but was associated with reduced all-cause mortality in the BRAS cohort (HR=0.41(0.21, 0.80) P=0.009). However these classes of drugs were not associated with CVD related mortality in both URAS (p=0.80) or BRAS (p=0.20) populations. In the combined analysis, (URAS and BRAS), ACEi/ARBs were associated with lower all-cause (HR=0.60 (0.44, 0.82) P=0.0016) but not CVD mortality (HR=0.73 (0.46,1.16) P=0.19).

Time updated analysis showed that increasing age, lower baseline eGFR, and increasing duration of diabetes were also independent predictors of survival in both URAS and BRAS. Interestingly, statin and aspirin exposure made no statistically significant impact on all-cause or CVD mortality in URAS or BRAS cohorts in our study.

Blood pressure effects

To investigate if the protective effect of CCB on RAS was mediated by a better control of blood pressure we analysed a subset of patients for whom longitudinal blood pressure measurements were available (n=257 for URAS and n=88 for BRAS). After adjustments for mean arterial pressures in this small subset of patients, CCB continued to show a statistically significant reduction in all-cause mortality in URAS population (HR=0.42 CI= 0.23, 0.79; P=0.006) but not in BRAS population. The results were consistent for the ACEi/ARB cohort. This subset analysis also showed that lower MAP, lower baseline eGFR, and increasing duration of diabetes were independent predictors of survival in both URAS and BRAS.

Severity of Stenosis

Finally, we wanted to investigate if the protective effect of CCB varied according to the severity of stenosis and therefore could influence choice of therapy in patients with hypertension and different degrees of RAS. We performed a time –updated analysis, stratified for severity of URAS. These showed that those with moderate stenosis (HR=0.14(0.05,0.39) P=0.0001) were mostly likely to benefit from CCB as compared to those with mild (HR=0.49(0.18,1.29) P=0.15) or severe stenosis ((HR=0.69(0.42,1.13) P=0.14). The effect of ACEi on all-cause mortality in URAS did not vary by the severity of stenosis. Consistent with the findings[13]of the CORAL trial, stent insertion did not improve survival in either URAS or BRAS cohorts (Figure 2a and 2b).

Time to ESRD in URAS and BRAS

In the study population consisting of both URAS and BRAS less than 5% patients developed ESRD. In the URAS and BRAS population combined there was no effect of ACEi/ARBs or CCB on delaying time to end-stage renal disease. As expected, lower baseline eGFR (P<0.0001), higher age of diagnosis of (P=0.02) and the presence of diabetes (P=0.02) was associated with rapid progression to ESRD. In an analysis, stratified by URAS and BRAS subgroups no effect of ACEi/ARBs or CCB was seen.

Discussion

To the best of our knowledge, this is the first cohort head-to-head study comparing effects of two commonly used medical management strategies in hypertension on CVD and overall mortality in patients with URAS and BRAS. Furthermore, we included longitudinal blood pressure control data to examine the blood pressure effect of these drugs. The main finding of our study is that CCBs were associated with a statistically significant overall survival benefit in patients with URAS and BRAS. Treatment with CCBs was also shown to be associated with reduced CVD mortality and the beneficial effects of CCBs on all-cause mortality persisted in the time updated analysis when longitudinal blood pressure was accounted for. This beneficial effect was most pronounced in those with moderate stenosis as compared to mild or severe stenosis suggesting that optimal timing for therapy in ARAS is also an area that requires further research.

Time-updated drug analysis did not show any effect of ACEi/ARBs on CVD mortality in patients with established renovascular disease, either with URAS or BRAS. There was a reduction in all-cause mortality in the BRAS but not URAS cohort on ACEi/ARBs. The all-cause mortality reduction in the combined cohort is likely to be driven by the reductions seen in the BRAS cohort.

There was no effect of the different drug classes on progression of CKD to ESRD in patients with URAS or BRAS. However, numbers of patients who progressed to ESRD were small. The management of ARAS remains controversial. Revascularisation was previously thought to be the mainstay of treatment but over the last few years large randomised controlled trials have favoured aggressive medical therapy. The 2009 Angioplasty and Stent for Renal Artery Lesions (ASTRAL) trial[14] findings were reinforced by the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial in 2014[13]. Justifiably, these trials have shifted the focus of treatment back to medical therapy. Due to the lack of clinical trial evidence in ARAS specific cohorts, the management of hypertension in patients with ARAS has been extrapolated from other populations of patients with hypertension. RAAS blockade is being increasingly used in these patients followed by calcium channel blockers, thiazides and beta blockers. Use of RAAS blockade was, therefore, previously thought to be contraindicated due to concerns about precipitating a decline in renal function. However, there is evidence supporting both its ability to be used in patients with renovascular disease and improved survival[15, 16]. In this present study, we did not find a significant mortality benefit with RAAS blocking agents once patients had already developed URAS or BRAS. However, we did find both overall and CVD survival benefit with CCBs. We are unable to determine with certainty whether the benefits seen with CCBs are due to blood pressure reduction alone but our longitudinal bp data suggest that this is perhaps not the case. There is certainly good experimental evidence to suggest that CCB's positively remodel vasculature in hypertension. Animal studies have suggested that dihydropyridine CCBs attenuate oxidative stress and enhance matrix metalloproteinase expression and activity[9, 17].

Other concerns regarding medical management include potential progression of stenosis and occlusion and damage caused by long-term ischaemia. Studies have shown that progression of URAS to ESRD is rare[18, 19], often because cardiovascular events overtake progression to ESRD. This is in keeping with the findings of this present study. ` Our finding that patients with moderate stenosis benefitted most from CCB treatment would suggest that patients with established disease benefit

less from CCB therapy compared to those with mild RAS and therefore early institution of these drugs for hypertension as per current guidelines may have added benefits.

A strength of our study is that we have examined effects of longitudinal blood pressure and anti-hypertensive treatment according to whether patients have unilateral of bilateral renal artery stenosis. We have also used longitudinal drug prescription data to look at time updated analysis of the effect of treatment rather than examining baseline data alone. Large observational studies, conducted using large health care databases, can be affected by immortal time bias, which can create an impression of remarkable benefit for a drug[20]. However, the modelling of the longitudinal data using a time-updated analysis can control for this bias and helps avoid confounding by indication. In this study we demonstrate the importance of using time-updated analysis as compared to baseline-only analysis. Our baseline analysis showed a protective effect of ACEi/ARBs on survival in RAS, however, this disappeared when we modelled the drug exposure windows using time-updated analysis.

As is common with all observational studies, our study may be subject to selection bias. However, we included all-comers within the stated timeframe. The lack of benefit observed in the BRAS group and CKD progression to ESRD may be due to small sample size and therefore lack of power. Another limitation of our study was that we used office blood pressure rather than the 24-hour Ambulatory blood pressure. However, it would not have been possible to obtain longitudinal bp if restricted to 24-hour ABPM readings alone as ABPMs are not routinely used for follow –up in clinical practice. Another limitation in this study is that we are not able to adjust for longitudinal changes in dose of ACE/ARB and CCB. Whilst we acknowledge the possibility of sub-optimal dosing – which might bias these results, our data reflects real world in clinical practice in which patients with RAS and hypertension are put on the maximum tolerable dose for CCB and ACE/ARB.

The evidence base surrounding the use of anti-hypertensive medication in patients with renovascular disease is lacking and further evidence is required to guide medical management. Our study demonstrates the benefit of treatment of hypertension with CCBs in patients with URAS and BRAS and should provide clinicians with confidence in using this drug in patients with RAS. We would not advocate stopping the prescribing of RAAS blocking agents in patients with URAS or BRAS based on the results of this study alone. Further larger datasets should be analysed to confirm or refute these findings. In conclusion, we have demonstrated an overall and CVD survival benefit of treatment with CCBs in patients in patients with both URAS and BRAS. These results require confirmation in the form of prospective randomized controlled trials. As increasing evidence guides clinicians away from revascularisation, clarification of the optimal anti-hypertensive treatment combination is required in order to guide medical management in this high risk group of patients.

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Table 1: Demographic and clinical characteristics of study population

	URAS(394)	BRAS (148)	P-value
Age at diagnosis (years)	75.3(SD9.1)	76.6(SD8.7)	NS
Sex (Males) n, (%)	205 (52%)	83 (56%)	0.96
Mean Duration of Follow-up (y)	3.5 (SD2.02)	3.3 (SD2.04)	0.8
Stent insertion	22%	42%	<0.0001
% Type II Diabetes	36%	37%	0.9
% Death	36%	50%	<0.0001
% ESRD	14%	11%	0.81
% CVD	40%	50%	0.001
% ACEi or ARBs	9%	6%	0.75
% Thiazide Diuretics	3%	4%	0.80
%CCB	30%	22%	0.01
%Statin	50%	52%	0.90
Mean SBP	145.60 (SD 16.74)	144.13(SD 15.82)	0.46
eGFR	34.2 (SD 11.9)	33.2 (SD 11.5)	0.43

ESRD=End Stage Renal Disease; CVD=Cardiovascular Disease; ACEi= Angiotensin Converting Enzyme inhibitor; ARBs=Angiotensin Receptor Blockers; CCB= Calcium Channel Blocker; eGFR=estimated Glomerular Filtration Rate: Mean BP: Mean blood pressure during the follow-up period

Table 2A: Predictors of survival on URAS and BRAS using time-updated analysis of ACEi/ARBs and CCB

	URAS			BRAS			URAS/BRAS combined		
	HR	95%CI	p	HR	95% CI	p	HR	95% CI	p
Age	1.04	1.01,1.06	0.001	1.04	1.01,1.08	0.02	1.04	1.02,1.06	<0.0001
CCB	0.45	0.31,0.65	<0.0001	0.39	0.22,0.69	0.0013	0.43	0.32,0.59	<0.0001
ACEi/ARBs	0.69	0.48,1.00	0.05	0.41	0.21,0.80	0.0088	0.60	0.44,0.82	0.0016
Baseline eGFR	0.97	0.96,0.98	<0.0001	0.97	0.95,0.99	0.0025	0.97	0.96,0.98	<0.0001
Diabetes	1.06	0.64,1.75	0.82	0.52	0.22,1.20	0.12	0.84	0.55,1.29	0.43
Duration of Diabetes	1.04	1.00,1.07	0.025	1.07	1.025,1.12	0.0025	1.05	1.02,1.07	0.0004

Table 2B: Predictors of survival on URAS and BRAS using time-updated analysis of ACEi/ARBs and CCB, including average Mean Arterial Pressure over follow-up

	URAS			BRAS			URAS/BRAS		
	HR	95%CI	p	HR	95% CI	p	HR	95% CI	p
Age	1.03	0.99,1.07	0.11	1.02	0.95,1.09	0.59	1.03	1,1.07	0.048
CCB	0.42	0.23,0.79	0.0065	0.60	0.25,1.44	0.25	0.46	0.28,0.77	0.0026
ACEi/ARBs	0.64	0.36,1.17	0.15	0.21	0.07,0.67	0.0066	0.49	0.29,0.82	0.0067
Baseline eGFR	0.96	0.94,0.98	<0.0001	0.93	0.88,0.97	0.00069	0.96	0.94,0.97	<0.0001
Diabetes	1.21	0.50,2.93	0.67	0.60	0.17,2.08	0.42	1.03	0.50,2.13	0.93
Duration of Diabetes	1.07	1.02,1.12	0.0089	1.07	1.00,1.14	0.046	1.07	1.03,1.11	0.0012
Avg MAP	0.96	0.93,0.99	0.011	0.96	0.91,1.00	0.074	0.97	0.94,0.99	0.0084

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Figure 1: Mortality in URAS vs BRAS

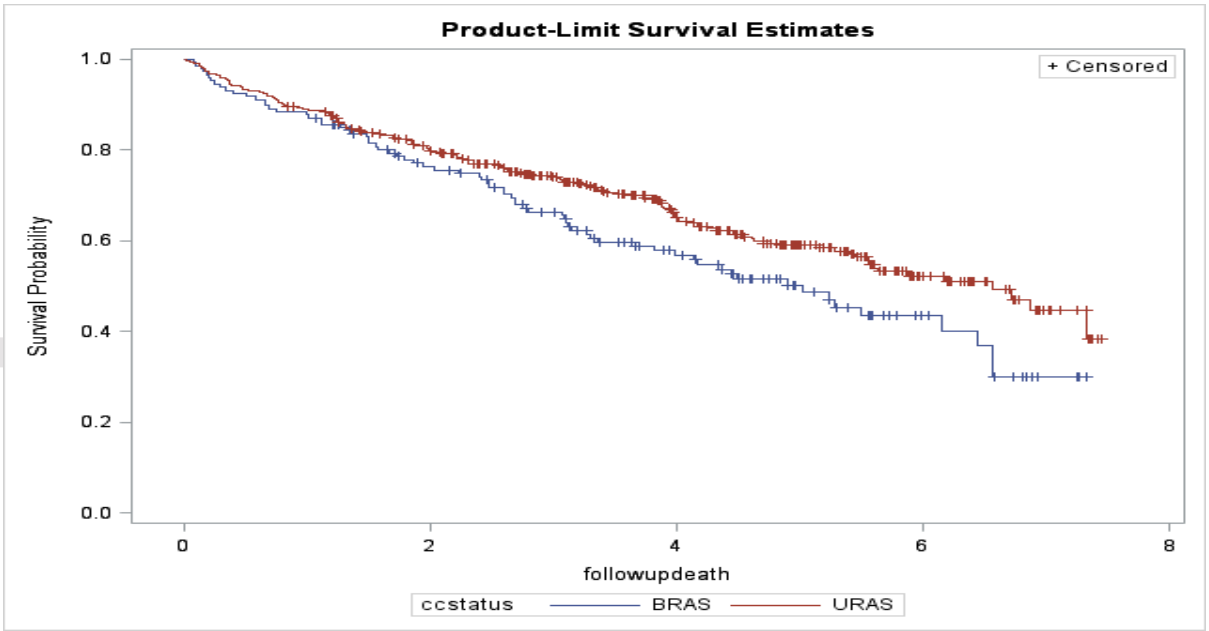

Figure 2a: Effect of Stent on survival on URAS

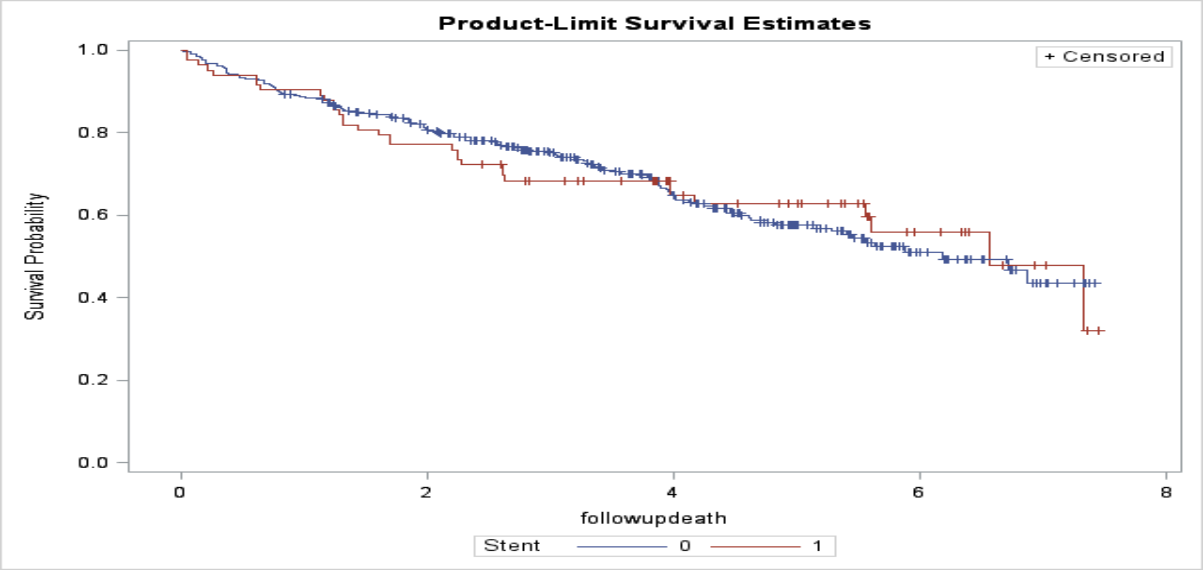

Figure 2b: Effect of Stent on survival on BRAS