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Is there still a role for renal artery stenting in the management of renovascular hypertension – A single-center experience and where do we stand?☆

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ABSTRACT

Background: Renal artery (RA) stenosis has been implicated in the pathophysiological mechanism for resistant hypertension. Despite the increasingly diagnosed frequency of hemodynamically significant lesions, the value of RA revascularization remains controversial. Our group had previously demonstrated significant blood pressure (BP) reduction in a retrospective cohort of appropriately selected patients undergoing RA stenting up to 18-months of follow-up. We herein present long-term clinical outcomes data 5-years post revascularization on 26 subjects who continued follow-up at our institution.
Methods: Retrospective analysis was performed on subjects who underwent RA stenting at our institution for hemodynamically significant (≥70%) RA stenosis and systolic hypertension on ≥3 antihypertensive agents. Clinical outcome data for systolic blood pressure (SBP), diastolic blood pressure (DBP), creatinine level and number of antihypertensive drugs was assessed prior to and then later at 6–12 months and 3–5 years post RA stenting.
Results: Mean age was 69 ± 9 years; 27% (7/26) were male. Median follow-up was 5.1 years. Blood pressure reduction was sustained at long-term follow-up (135/70 ± 18/11 mmHg) compared to initial reduction noted at 6-months (136/69 ± 16/8 mmHg; p ≤0.01 for both) and from baseline (162/80 ± 24/18 mmHg; p ≤0.001 for both). The number of antihypertensive agents also decreased from 4.1 ± 1.0 to 2.7 ± 2.1 (p = 0.002) at 6-months and was sustained at long-term follow-up, 3.4 ± 1.2 (p = 0.03) with no difference in renal function between short- and long-term follow-up compared to baseline.
Conclusions: This study shows sustained benefit of RA stenting in BP reduction in an appropriately selected cohort with significant stenosis ≥70% and uncontrolled hypertension on multiple medications on long-term follow-up.

1. Introduction

Ischemic renal disease from atherosclerotic renal artery stenosis (ARAS) and fibromuscular dysplasia (FMD) have been implicated as the most common etiologies of renovascular hypertension [1, 2]. ARAS accounts for 80–90% cases of renal artery stenosis and is the predominant etiology in patients >50 years of age [3, 4]. Approximately 20% of cases have bilateral disease. ARAS physiologically leads to decreased renal perfusion which causes activation of the renin angiotensin aldosterone system (RAAS) subsequently resulting in sodium and fluid retention and increased systemic blood pressure [1, 5]. In unilateral ARAS, this fluid retention and RAAS activation is compensated by the normally functioning contralateral kidney by the so-called pressure natriuresis [6]. Over time, the pathophysiology transitions to pressor mechanisms independent of angiotensin II, including vasoconstriction owing to oxidative stress, endothelial dysfunction, endothelin release, and sympathetic activation resulting in uncontrolled hypertension [7]. The filtration capacity loss in the ischemic kidney may be due to either hypoperfusion or recurrent micro-embolism resulting in chronic kidney disease (CKD) [8–11]. ARAS is often a manifestation of a systemic atherosclerotic process, as 20% patients with coronary artery disease and 50–60% of patients with peripheral arterial disease can have concomitant ARAS [12–14]. Patients with ARAS have a higher incidence of cardiovascular events and mortality which has been the impetus for the development of various medical and revascularization strategies for the treatment of ARAS [12, 15]. Multiple randomized controlled trials (RCTs) have failed to show any substantial benefit of percutaneous

Abbreviations: ARAS, atherosclerotic renal artery stenosis; DRASTIC, Dutch Renal Artery Stenosis Intervention Cooperative; EMMA, Essai Multicentrique Medicaments vs Angioplastie; FMD, fibromuscular dysplasia; HECULES, Safety and Effectiveness Study of the Herculink Elite Renal Stent to Treat Renal Artery Stenosis; RAAS, renin angiotensin aldosterone system; RAS, renal artery stenting; SNRASCG, Scottish and Newcastle Renal Artery Stenosis Collaborative Group; STAR, Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function.

☆ Conflicts of interest: None

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revascularization in patients with ARAS but have been criticized for design flaws and possible lack of appropriate patient selection [16]. Few non-RCT's have been published in the recent years suggesting a benefit of percutaneous revascularization in selected group of patients with ARAS [17]. Our group has previously published short-term data to suggest significant blood pressure (BP) reduction after renal artery stenting (RAS) in appropriately selected patients with resistant hypertension and severe ARAS [18]. We herein present long-term follow-up data from our single-center cohort evaluating the durability of the RAS and sustained BP reduction along with a brief review of current evidence and guideline recommendations.

2. Methods

We retrospectively collected follow-up data on patients undergoing RAS for uncontrolled renovascular hypertension (≥160/90 mmHg on ≥3 antihypertensive medications) and significant ARAS (angiographically ≥70% unilateral or bilateral stenosis) with kidney size ≥9 cm (when available) at our institution between 2007 and 2015. Patients undergoing renal artery angioplasty alone or RAS for other indications (FMD, flash pulmonary edema, advanced CKD) and inadequate long-term follow-up data were excluded. Data was collected for blood pressure recordings, number of antihypertensive medications and renal function at baseline, 6–12 months post-revascularization and at 3–5 years follow up visits depending on the availability of longest follow-up data. BP recordings for the final 2 outpatient visits were averaged. The angiographic evaluation of renal artery stenosis was performed by the operator, but also reviewed independently by another interventional cardiologist prior to inclusion in the study. The primary endpoint was the change in mean systolic and diastolic blood pressure with secondary endpoints being the change in number of antihypertensive medications, renal function (assessed by serum creatinine levels) and freedom from target vessel revascularization at 6–12 months and 3–5 years follow-up.

2.1. Statistical analysis

Pairwise comparisons were performed using 2-tailed *t*-test to compare baseline measurements with data from 6 to 12 months and 3–5 years follow-up intervals. Significance was determined as a p-value <0.05. Summary statistics are presented as N (%) for categorical variables; continuous variables are presented as mean ± SD. All statistical analyses were performed using IBM SPSS, version 21.0.

3. Results

We identified 26 patients across 7 operators based on our inclusion criteria undergoing RAS for resistant hypertension between 2007 and 2015 who were actively being followed at our institution with at least 3-years of follow-up data. Baseline demographic, clinical data and antihypertensives regimens of our sample are presented in Table 1. Median follow-up duration was 5.1 (IQR, 4.2–6.4) years. Mean age was 69 ± 9 (range 51–87) years. All subjects had uncontrolled hypertension (160/90 mmHg) on at least 3 antihypertensive agents and angiographically significant ARAS. Bilateral ARAS (defined as ≥50% stenosis of the contralateral renal artery) was present in 19% of subjects (n = 5) with 15% (n = 4) of the cohort undergoing RAS for bilateral lesions (≥70% stenosis). There were no major immediate procedural complications. One (1) subject underwent nephrectomy of the ipsilateral side for complicated obstructive uropathy while one (1) subject (with advanced CKD and bilateral renal ARAS at baseline) had progressed to end-stage renal disease at the time of data-collection. Three (3) subjects developed moderate severe in-stent restenosis of the target lesions with two of them requiring repeat interventions; one subject was treated with cutting-balloon angioplasty.

Significant BP reduction was noted at 6–12 months follow-up compared to baseline from 162 ± 25 mmHg to 135 ± 25 mmHg systolic (Δ 27 ± 24 mmHg, p ≤0.001) and from 80 ± 18 mmHg to 69 ± 8 mmHg diastolic (Δ 11 ± 19 mmHg, p = 0.005). These changes were sustained at the long-term follow-up when compared to baseline readings for mean systolic BP of 134 ± 18 mmHg (Δ 28 ± 26 mmHg, p ≤0.001) and mean diastolic BP of 70 ± 11 mmHg (Δ 11 ± 18 mmHg, p = 0.006) (Fig. 1). The number of antihypertensive agents also decreased from 4.1 ± 1.0 to 2.7 ± 2.1 (Δ 1.4 ± 2.0, p = 0.002) at 6-months and sustained at long-term follow-up, 3.4 ± 1.2 (Δ 0.7 ± 1.6, p = 0.03) (Table 2). There was no difference in renal function assessed by serum creatinine values at short-term (Δ0 ± 0.34 mg/dl, p = 0.753) as well as at long-term follow-up (Δ-0.09 ± 0.44 mg/dl, p = 0.342) compared to baseline (Table 2).

Table 1
Baseline demographics, procedural efficacy and clinical outcomes.

Characteristic	(n = 26)
Follow-up duration (years, median [IQR])	5.1 [4.2–6.4]
Age (years, mean ± SD, range)	68.6 ± 8.8 [51–87]
Gender (n, %)	
Male	7 (27%)
Female	19 (73%)
Ethnicity (n, %)	
Caucasian	16 (61%)
African-American	9 (35%)
Other	1 (4%)
Current or former smoking (n, %)	17 (65%)
Hypertension (n, %)	26 (100%)
Diabetes Mellitus (n, %)	10 (38%)
Prior stroke/TIA (n, %)	4 (15%)
Coronary artery disease (n, %)	21 (81%)
Peripheral arterial disease (n, %)	12 (46%)
Congestive heart failure (n, %)	5 (19%)
Chronic kidney disease stage ≥3[a] (n, %)	6 (23%)
Bilateral renal artery stenosis[b] (n, %)	5 (19%)
Bilateral stenting (n, %)	4 (15%)
Major procedural complication (n, %)	0 (0%)
Post-procedure AKI (n, %)	0 (0%)
Ipsilateral nephrectomy at follow-up (n, %)	1 (4%)
Progression to ESRD (n, %)	1 (4%)
Target vessel restenosis (n, %)	3 (11%)
Mortality[c] (n, %)	3 (11%)

Abbreviations: ACEi = angiotensin converting enzyme inhibitor; AKI = acute kidney injury; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor-Neprilysin inhibitors; CD-TVR = clinically-driven target vessel revascularization; ESRD = end-stage renal disease; TIA = transient ischemic attack
[a] Defined as an estimated glomerular filtration rate of <60 ml/min/1.73 m^2 of body-surface area.
[b] Defined as ≥50% stenosis of the contralateral renal artery.
[c] Mortality reported at the time of retrospective data collection.

4. Discussion

Hypertension is one of the most common comorbidities affecting approximately 78 million people in the United States and is a major modifiable risk factor for cardiovascular diseases and stroke [19]. ARAS remains among the most prevalent and important causes of secondary hypertension and renal dysfunction [20]. Furthermore, ARAS has considerable overlap with atherosclerotic disease in other arterial beds and is associated with adverse long-term outcomes [21]. Despite these far-reaching consequences, ARAS remains largely underdiagnosed, and in those with established renovascular hypertension, the management options remain controversial. The advent of new antihypertensive agents, notably RAAS inhibitors, has made achieving goal blood pressures in renovascular hypertension with tolerable inexpensive regimens possible for most patients. Theoretically, RAAS inhibitors can reduce glomerular capillary hydrostatic pressure enough to cause a transient decrease in glomerular filtration rate and raise serum creatinine, meriting caution and close follow-up. However, these drugs have been shown to reduce mortality and morbidity in patients with ARAS in large observational studies [22–24]. Nevertheless, these findings

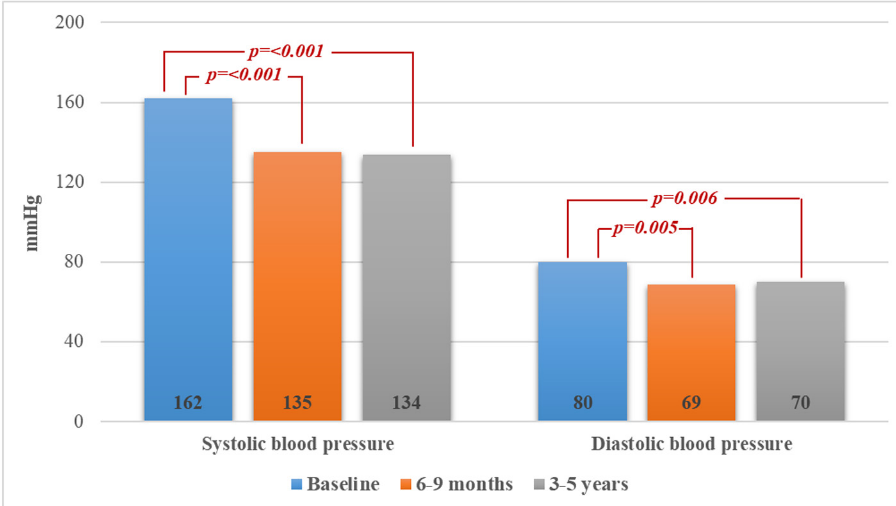

Fig. 1. Change in blood pressure readings at baseline, 6–9 months and 3–5 years follow-up.

could be attributed to a selection bias as patients who cannot tolerate medical therapy tend to have more extensive disease and are more likely to benefit from revascularization.

Restoring blood flow to the stenosed vessel with surgical revascularization in the 1970's and later endovascular angioplasty and stenting in the 1990's was considered largely intuitive for the treatment of resistant renovascular hypertension and ischemic nephropathy for the salvageable kidneys. In a meta-analysis pooling data from the three early RCT's for renal angioplasty including the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC), Essai Multicentrique Medicaments vs Angioplastie (EMMA) and the Scottish and Newcastle Renal Artery Stenosis Collaborative Group (SNRASCG) showed modest transient benefit of angioplasty. Three months follow-up data were used for the DRASTIC trial and 6 months follow-up data for the other two trials [25]. There was a significant decrease in both SBP (7 mmHg; 95% CI −12 to −1 mmHg) and DBP (3 mmHg; 95% CI −6 to −1 mmHg) from baseline in the angioplasty group when compared with medical therapy alone. However, these results should be interpreted with caution as almost 44% of the patients in the DRASTIC trial and 27% in the EMMA trial crossed over to the percutaneous revascularization arm after randomization. In a meta-analysis by Leertouwer et al., comparing succeeding non-randomized studies for RAS with balloon angioplasty, RAS (n = 678) was superior to angioplasty alone (n = 644) with hypertension improvement in 49% of subjects and stabilization of renal function with similar safety profiles [26]. The Safety and Effectiveness Study of the Herculink Elite Renal Stent to Treat Renal Artery Stenosis (HERCULES) trial was a prospective, single-arm trial which evaluated efficacy and safety of RAS in 202 subjects with ARAS and uncontrolled hypertension [17]. At 9 months, the mean SBP significantly decreased (from mean 162 ± 18 mmHg to 145 ± 21 mmHg; p < 0.0001) after stenting with a sustained response in BP at a subsequent 36-month follow-up analysis (146 ± 21 mmHg; p < 0.0001) without change in the number of medications or renal function [27]. Overall procedure-related complication and clinically-driven target vessel revascularization rates were 1.5% and 9.2% respectively.

Table 2
Change in antihypertensive and other guideline-directed medical therapy and renal function at baseline, 6–9 months and 3–5 years follow-up.

Characteristic	Baseline	6–9 months*	3–5 years
Number of antihypertensive medications (mean ± SD, range)	4.1 ± 1.0 [3–7]	2.7 ± 2.1 [0–6]**	3.4 ± 1.2 [1–5]**
Antihypertensive regimen (n, %)			
ACEi/ARB/ARNi	18 (67%)	14 (52%)	15 (56%)
β-blockers	20 (74%)	18 (67%)	20 (74%)
Calcium-channel blockers	20 (74%)	13 (48%)	20 (74%)
Diuretics	19 (70%)	12 (44%)	14 (52%)
Vasodilators	9 (33%)	9 (33%)	13 (48%)
Others	9 (33%)	5 (18%)	2 (7%)
Concomitant guideline-directed medical therapy			
Aspirin/other antiplatelet agent	25 (100%)	21 (100%)	25 (100%)
Statin therapy[a]	25 (96%)	21 (100%)	26 (100%)
Creatinine (mg/dl, mean ± SD)	1.2 ± 0.5	1.2 ± 0.4	1.3 ± 0.5
Chronic kidney disease stage ≥3[b] (n, %)	6 (23%)	6 (28%)	7 (27%)

* 6–9 month data available for 21 subjects.
** p-Value <0.05 compared to baseline values by paired *t*-test.
[a] One subject reported to have statin intolerance and initiated on PCSK-9 inhibitor therapy at follow-up.
[b] Defined as an estimated glomerular filtration rate of <60 ml/min/1.73 m^2 of body-surface area.

Three major randomized studies have evaluated the efficacy of RAS compared to medical therapy but failed to show any clear benefit of RAS. Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function (STAR) trial primarily aimed to assess the efficacy and safety of RAS on the progression of renal impairment in 64 subjects but failed to show any clear benefit, and several complications, including 2 procedure-related deaths [28]. There was no difference in BP between the groups, however, participants were required to have controlled BP, if possible without RAAS antagonists, and subjects with malignant hypertension were excluded. Furthermore, the study was underpowered to provide a definitive estimate of efficacy. Angioplasty and stenting for Renal Atherosclerotic Lesions (ASTRAL) aimed to assess the attenuation of renal function decline while Cardiovascular Outcome for Renal Artery Lesions (CORAL) trial was specifically designed to compare incidence of hard clinical outcomes for subjects with ARAS randomized to medical therapy alone with medical therapy plus renal-artery stenting [29, 30]. Both trials failed to show evidence of clinical benefit from revascularization in patients with ARAS. There was no difference in BP reduction in both arms in ASTRAL (n = 403 each). In the CORAL cohort, the rate of composite end point of death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal insufficiency or the need for renal replacement therapy after a median follow-up period of 43 months was not different between the intervention and medical therapy arms [35.1% vs 35.8%; 95% confidence interval (95% CI) 0.76–1.17; p = 0.58]. There was a consistent modest difference in SBP favoring the RAS group (−2.3 mmHg; 95%CI −4.4 to −0.2; p = 0.03) although the average baseline SBP was lower than in any of the well-controlled nonrandomized trials. However, a post-hoc analysis from the CORAL cohort comparing BP reduction with RAS and medical therapy alone based on stenosis severity, level of systolic blood pressure elevation, or according to the magnitude of the trans-stenotic pressure gradient also failed to show any significant difference in BP reduction with revascularization [31].

These trials were heavily criticized for major section bias and interpretation of the data [16, 32, 33]. A substantial proportion of patients in the renal artery stenting arm of STAR and ASTRAL were excluded from revascularization because of a discrepancy between invasive and non-invasive assessments of the severity of stenosis. Both cohorts in ASTRAL and CORAL had only moderately elevated blood pressure and excluded 'high risk' patients such as those with episodes of flash pulmonary edema or rapidly progressive hypertension and progressive kidney failure. During the course of enrolment, CORAL also modified its inclusion criteria to include subjects with ARAS and chronic kidney disease, defined as an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2 of body-surface area without hypertension. Furthermore, the above mentioned post-hoc analysis by Murphy et al. was underpowered to show differences in the high-risk patients due to parsing the cohort into smaller subgroups [31]. In a systematic review by Raman et al. of published literature between 1993 and 2015 ($n = 2178$ from 57 RCT's and $n = 1828$ from additional nonrandomized controlled studies) regarding the role of renal revascularization compared to medical therapy only for patients with ARAS, the reviewers concluded that most studies were under-powered and had substantial clinical heterogeneity to examine mortality and other major outcomes over the time frames reported [34]. While the pendulum for RAS for resistant renovascular hypertension shifted from vast approbation to being "frowned-upon" in the medical community since the publication of these trials, the current ACC/AHA guidelines on the management of high blood pressure and the SCAI expert consensus statement for appropriate use of RAS maintain a class IIb recommendation for percutaneous RAS for patients with significant ARAS and resistant hypertension or in patients with hypertension and medication intolerance [35, 36]. However, most recently updated ESC/ESVS guidelines do not endorse routine revascularization for ARAS (Class III, level of evidence A) with endovascular therapy reserved for patients with renal artery stenosis secondary to FMD or unexplained recurrent congestive heart failure or sudden pulmonary edema [37].

The findings from our cohort for sustained BP reduction at a median follow-up of 5.1 years are in parallel with other uncontrolled studies and the long-term follow-up data from the HERCULES trial [27]. Similar BP response was noted in a pooled patient-level meta-analysis from the five prospective multicenter Food and Drug Administration-approved investigational device exemption studies of renal artery stent revascularization [38]. In 527 patients with available data, a significant decline in both systolic (164 ± 21 mmHg vs. 146 ± 22 mmHg, $p < 0.0001$) and diastolic (79 ± 13 mmHg vs. 76 ± 12 mmHg, $p < 0.0001$) BP reading at 9-months compared to baseline with a more pronounced effect in subjects with baseline systolic BP reading of >150 mmHg. In our study, patients continued optimized medical therapy without any significant increase in antihypertensive medications at 3–5 years. The immediate post procedure reduction in BP and sustained effects can be physiologically explained by the increased renal flow and reversing the adverse outcome from RAAS activation. The findings of no major procedure related complications or development of acute kidney injury is also not surprising as these were relatively uncommon in the contemporary RCT's with 0.5% procedure-related deaths (none in CORAL) while other adverse events such as pseudo-aneurysm, distal embolization, and acute kidney injury were also infrequent, averaging 3.2% overall [34].

Our study also provides an insight on the long-term patency rates of renal artery stents with hemodynamically significant restenosis noted in only three (3) subjects (11%) in our cohort. RA stents have excellent cumulative patency rates up to 79–85% which could contribute to their sustained long term benefits [39]. One (1) patient underwent nephrectomy and another one (1) progressed to renal replacement therapy with otherwise no significant difference in the serum creatinine levels on long term follow-up in our cohort. These findings of limited renal recovery after revascularization are also consistent with the CORAL cohort where progressive renal failure occurred in 16.8% in the endovascular therapy group compared to 18.9% in the medical therapy group alone ($p = 0.34$) and permanent renal replacement therapy occurred in 3.5% vs. 1.7%, respectively ($p = 0.11$). This could be attributed to the established fibrosis of the renal parenchymal tissue in patients with chronic kidney disease [20]. In addition, atheroembolization is a recognized complication of renal artery stenting which may also add insult to injury. While a dedicated renal embolic protection device is yet to be developed, their use could be vital in attenuation of chronic renal insufficiency in these patients [40, 41].

4.1. Study limitations

This is retrospective single center study and carries inherent limitations. Besides a small sample size, local patient demographics and characteristics could further limit the generalization of these findings. Although adjudicated in our review by a single-reviewer, some procedures were performed based on initial non-invasive screening or "drive-by" non-selective renal angiography during cardiac catheterization for resistant hypertension with subsequent visual estimation of hemodynamic significance without routine assessment of trans-lesion gradients. Visual assessments can routinely over-estimate the lesion severity as was noted in the HERCULES trial where mean operator visual percent stenosis was 81% compared to core laboratory quantitative measurement of 66% [27]. While non-invasive measurement of disease severity and parenchymal involvement like peak systolic velocity and resistive index (RI) may be useful in careful selection of patients [42], utilization of various interventional techniques like intravascular ultrasound (IVUS), measurement of Fractional Flow Reserve (FFR) and translesional gradient in patients with moderate stenosis could further risk stratify patients who will benefit from revascularization approach [43–46]. Finally, variation in medical therapy following the procedures could not be standardized; choice and dose-titration of various antihypertensives was managed by the individual cardiologist.

5. Conclusion

ARAS is the leading cause of secondary hypertension which can lead to progressive renal insufficiency and adverse cardiovascular outcomes. There remains an unmet need for BP optimization in patients who continue to have uncontrolled hypertension despite being on optimal medical regimens including concomitant lipid-lowering therapy, an antiplatelet agent, and lifestyle risk factor modification and could potentially benefit renal revascularization therapies. Furthermore, the majority of the ARAS patients are not candidates for the renal denervation therapies, which also remain under much debate, due to inability to provide catheter/true vessel wall contact deep to plaque [47]. Our single-center long-term experience shows RAS performed by experienced operators in carefully selected 'real life' patients with uncontrolled hypertension can potentially provide long term sustained blood pressure reduction. However, the onus is on the interventional community for development of a large multi-center randomized clinical trial to prove benefit of renal revascularization in these high-risk patients and overcome the short-comings of earlier major clinical trials and using hard endpoints such as cardiovascular morbidity and mortality.

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