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Update and review of renal artery stenosis

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Introduction

According to Carey et al., "resistant hypertension (RH) is defined as above-goal elevated blood pressure (BP) in a patient despite the concurrent use of 3 antihypertensive drug classes, commonly including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system (RAAS) (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker), and a diuretic".[1] The causes of RH are: non-adherence with dietary salt restriction, drugs (prescription and non-prescription), obstructive sleep apnea, and secondary hypertension.

Secondary hypertension accounts for about 5–10% of all cases of hypertension, whereas primary or essential hypertension accounts for 90%. In a series of 4494 patients referred to hypertension specialty clinics, 12.7% had secondary causes overall, of which 35% were associated with occlusive renovascular disease.[2]

A more recent series showed that 24% of older subjects (mean age, 71 years) with RH were shown to have significant renal arterial disease, with most cases being caused by atherosclerotic disease.[3] However, the syndrome of renovascular hypertension can also result from other less common obstructive lesions (fibromuscular dysplasias, renal artery dissection or infarction, Takayasu arteritis, radiation fibrosis, and renal artery obstruction from aortic endovascular stent grafts). This paper focuses on renal artery stenosis. Here, we will discuss its epidemiology, clinical presentation, diagnosis and treatment, prognosis as well as future perspectives.

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Epidemiology

Renal artery stenosis is most commonly due to atherosclerotic disease and is generally seen in older patients often with traditional cardiovascular risk factors while the less common cause of FMD is typically seen in younger female individuals.[4] Atherosclerotic RAS was seen in approximately 0.5% of all patients and 5.5% in those with chronic kidney disease in a large Medicare claims data set.[5] As patients with RAS often are asymptomatic or without severe hypertension claims based investigations such as the above may underestimate the true prevalence as cases may go undetected. Illustrative of this, a screening study using duplex ultrasonography in a cohort of patients over the age of 65 found that 6.8% had RAS defined as $a \geq 60\%$ diameter-reducing RAS or occlusion.[6]

In adult patients with renovascular hypertension approximately 10% have FMD.[7] Again, FMD may go clinically unnoticed as shown in a synthesis of four case series of 3181 asymptomatic potential kidney donors were 4.4% were identified by angiography as having FMD.[8] In the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial FMD was an exclusion criteria however 5.8% of patients with images in the trial angiographic core lab had lesions consistent with FMD.[9]

Clinical presentation

The recognition of the clinical features associated with RAS is of crucial importance in the clinical diagnosis of this condition. Renal artery stenosis, a common cause of secondary hypertension, is usually suspected in the patient who initially presents with acute onset of severe hypertension prior to age 30 or after age 55. It is unclear as to why it is not commonly seen in African Americans.[10]

Clinical presentations that should prompt consideration of renal artery stenosis include:

- Onset of acute kidney injury (AKI) with initiation of RAAS inhibitors, i.e., angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB)
- Onset of AKI with aggressive diuresis during treatment of heart failure
- Unexplained CKD in the setting of atherosclerotic cardiovascular disease (ASCVD)
- CKD with asymmetry in kidney size noted on imaging studies
- AKI or CKD with renovascular hypertension
- AKI or CKD with “flash” pulmonary edema
- Unexplained acute elevation in serum creatinine (or decrease in GFR) in a patient with previously stable CKD

The presence of an abdominal bruit (usually epigastric in location), with a systolic and diastolic component, is a noteworthy finding on physical examination. The presence of a diastolic bruit in patients has been correlated with favorable surgical outcomes in patients with fibromuscular dysplasia.[11] It is important to note however, that the absence of a bruit does not necessarily exclude the diagnosis.

Another important finding on physical examination is the presence of high grade (Grade III or IV) hypertensive retinopathy on fundoscopic examination,[12] particularly in those with atherosclerotic renovascular disease.[13] Some patients may exhibit diffuse vasculopathy, that is diffuse atherosclerosis involving other vascular beds, e.g. cerebral, coronary and peripheral. In a way, renovascular hypertension is a retrospective diagnosis, because by definition, the diagnosis of renovascular hypertension can only be made if blood pressure improves after correcting the blockage of the renal artery.

From the laboratory standpoint, renal artery stenosis is associated with hyperreninemic hyperaldosteronism which is characterized by the presence of hypokalemia and metabolic alkalosis. The hyperaldosteronism results in increased urinary sodium retention and increased urinary potassium loss, thereby leading to hypokalemia. Patients with renal artery stenosis may

present with or without kidney dysfunction, e.g., elevated serum creatinine. As noted above, one of notable presentations of a 'hemodynamically significant renal artery disease' that should raise strong suspicion, is that of "onset of AKI with initiation of RAAS inhibitors, i.e., ACE inhibitor or ARB"

Diagnosis

Several societies have released guidelines that provide guidance on the approach to the diagnosis of RAS; the American College of Cardiology (ACC)/American Heart Association (AHA), the European Society of Cardiology (ESC), and the Society for Cardiovascular Angiography and Interventions (SCAI) .[1] The decision to pursue testing for RAS is generally indicated if the clinical presentation suggests secondary hypertension without a clear alternative cause and renal revascularization would be pursued if a significant stenotic lesion was found.

In patients suspected of having RAS, SCAI recommends renal arteriography as the gold standard for making a diagnosis and categorizes stenosis severity as follows:

- Mild: $<$ 50%
- Moderate: 50–70%
- Severe: $>$70%

However there are three non-invasive diagnostic imaging options commonly employed as alternatives; Duplex Doppler ultrasonography, Computed tomographic angiography (CTA), and Magnetic resonance angiography (MRA).

Treatment

The treatment for RAS has been a challenge for clinicians for many decades. It would seem practical that a stenotic lesion in any artery needs to be opened to allow optimal perfusion to its distal organs. We have seen the benefits of angioplasty with stenting in carotid arteries for stroke prevention, coronary arteries for ST segment elevation myocardial infarctions, and superior mesenteric artery for intestinal angina. The data and success for opening and stenting the renal artery has been more controversial in guiding exact treatment therapies.

Prior to 2009, there was a dearth of randomized clinical trials performed in patients with renal artery stenosis. Beginning in that year, the STAR trial was published which included a randomized cohort of patients from the Netherlands and France. One hundred and forty patients with eGFR $<$80 mL/min/1.73 m^2 who had a stable blood pressure $<$140/90 mmHg and ostial RAS of at least 50% were included.[14] These patients were randomized to aggressive medical therapy including anti-hypertensive agents, statins, and aspirin, or to medical therapy plus renal artery stenting. At the conclusion of 24 months, there was no significant difference between the two groups in regards to decline in eGFR, worsening of blood pressure, or cardiovascular events. This study did have a large limitation in that 25% of patients randomized to stenting never actually received a stent. Also concerning, two patients in the stenting group died of complications related to procedure. The STAR trial has been criticized for the small enrollment and exclusion of high-risk patients, as patients with the highest risk may show the most benefit from a revascularization procedure. This critique stems from the knowledge that kidney blood flow perfusion defects and the clinical consequences of RAS do not occur until there is at least 70–80% lumen narrowing.

The year 2009 brought another highly needed clinical trial evaluating stenting therapy. ASTRAL was a larger trial with 806 patients.[15] These patients were eligible for enrollment if they "had substantial anatomic atherosclerotic stenosis in at least one renal artery" and their "doctor was uncertain that the patients would definitely have a worthwhile clinical benefit from revascularization". After a mean of 34 months, there was no significant difference in kidney

outcomes, blood pressure control, or cardiovascular events ($p = 0.06$) between the groups. The study was mired with several limitations that included 40% of enrollees had <70% stenosis and 24% had a normal eGFR. These patients at baseline would be considered low risk for progression and unlikely to show benefit from revascularization. Additionally, only 79% of patients were successfully stented in the revascularization arm. A major criticism of this trial was subjectively allowing physicians to only enroll patients if they felt that revascularization would be beneficial. As a result of the lack of equipoise, there was clear recruitment bias that can be seen with a low rate of randomization in otherwise eligible patients.[16] Both ASTRAL and STAR have been criticized for not including enough high-risk patients to show major clinical and statistical benefit from revascularization.

The RADAR trial was a subsequent study designed to compare medical therapy to stenting in patients with hemodynamically significant RAS.[17,18] The study's main endpoint was change in eGFR over 12 months. Secondary endpoints included clinical events related to cardiac death, stroke, MI, hospitalization or target lesion revascularization, change in average SBP or DBP, or change in left ventricular mass index. Unfortunately, while the design was created to study important outcomes and meaningful inclusion criteria, this trial was terminated early for slow and inadequate enrollment.

The largest trial which currently drives clinical guidelines is the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial published in 2014.[19] This trial was the largest cohort to date with 947 patients who all had SBP >155 mmHg and were on more than two anti-hypertensive medications with an eGFR less than 60 mL/min/1.72 m^2. Patients were excluded from the study if chronic kidney disease was not from ischemic nephropathy, creatinine above 2 mg/dL, or kidney size smaller than 7 cm on imaging. Patients were randomized to medical therapy or stenting with medical therapy and followed for a median of 43 months. Medical therapy included candesartan, with or without thiazide diuretic, and combination of amlodipine-atorvastatin. The primary endpoint was a composite of death from cardiovascular and kidney causes, stroke, MI, hospitalization for congestive heart failure, progressive loss of eGFR, or need for permanent dialysis. The trial was longer and larger than both STAR and ASTRAL and contained a higher risk study population. Despite even more comprehensive clinical criteria to treat those most likely to have some benefit, there was no difference in occurrence of the primary composite endpoint or even any individual endpoints. The only significant finding was lower systolic blood pressure in the stenting arm at the end of the trial (95% CI; $p = 0.03$).

The CORAL trial was limited by difficulty in recruiting adequate patients given the strict inclusion criteria. Despite the careful selection of patients, similar to STAR and ASTRAL, the cohort was not a high-risk group which limited the possibility of showing a significant difference in patients who might benefit from revascularization. The average stenosis in CORAL was verified at only 67%, less than stenosis likely to cause substantial clinical symptoms.[20]

As we examine the three most robust and recent randomized trials, STAR, ASTRAL, and CORAL all of them failed to show a significant benefit from revascularization of a stenotic renal artery. These studies have all been criticized for not including enough high-risk patients. As well, almost all the patients had hypertension and chronic kidney disease, and not a RAS diagnosis alone. These groups would not be expected to show a clinical or measurable benefit from revascularization due to chronic changes. It is not surprising that revascularization of the kidney does not modify pathologic changes in separate distant organs that are already damaged from chronic hypertension, volume overload, or effects of reduced eGFR. Thus it may be difficult for any trial to show a major benefit for revascularization, as stenting treats only one component of a systemic disease.

Several meta-analyses have looked at all the clinical outcomes and trials for RAS and atherosclerotic RAS specifically. Riaz et al. analyzed 7 randomized trials that included 2139 patients and found that stenting was not superior to medical management for any cardiovascular or kidney outcome.[21] Another examination of trials published by Zhu et al. of 1916 patients found that revascularization led to a significant reduction in the number of anti-hypertensive medications, but similar to previous studies there was not an improvement in congestive heart failure or stroke with stenting.[22] Today clinicians remain without randomized evidence to show

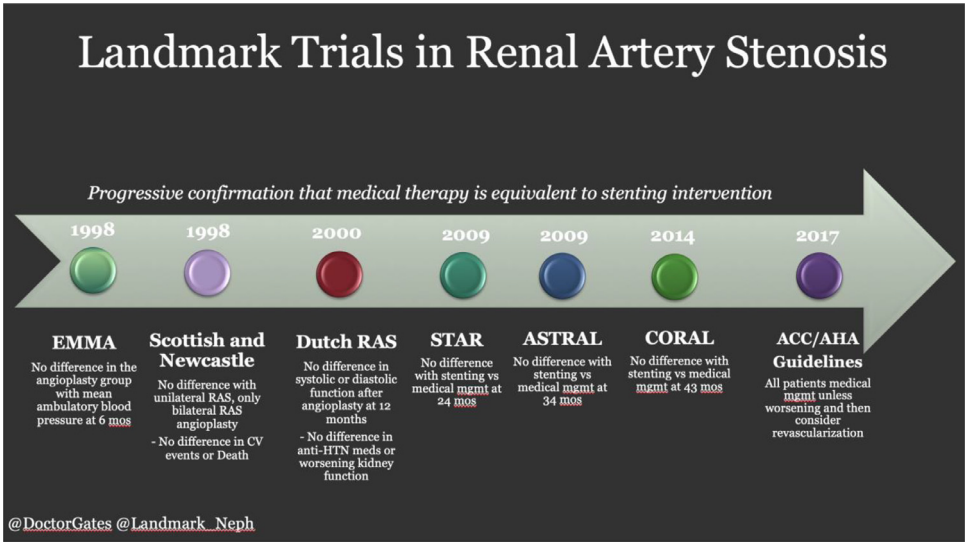

Fig. 1. Landmark trials leading to current guidelines of medical therapy for atherosclerotic renal artery stenosis.

benefit of revascularization in patients with ARAS symptoms and diagnosis. A timeline summary of major trials is included in Fig. 1.

Currently the majority of patients with ARAS can be controlled medically with antihypertensive and cholesterol lower agents. It is not recommended to definitively determine if RAS exists through interventional procedures in most patients. Additionally, routine stenting of cases of RAS does not show meaningful benefit. The most recent 2017 ACC/AHA Hypertension Guidelines have addressed ARAS and treatment guidance.[23] The consensus statement concludes that all patients benefit from aggressive medical therapy citing Level 1A evidence. If patients fail this pathway and continue to have clinical evidence of refractory hypertension, worsening kidney function, or intractable heart failure, revascularization can be considered. The recommendations do not endorse any specific intervention or cite evidence of outcome benefits.

There are many clinicians who remain convinced there must be a benefit to opening the renal artery in some patient subsets. This view is backed both by personal clinical experience and retrospective data. Kalra et al. used the Medicare database between 1992 and 2004 for RAS cases, they found that patients who did not undergo revascularization with a known atherosclerotic renovascular disease had an adjusted mortality hazard ratio between 1.55 and 2.28.[5] In contrast, patients with the same known disease who did undergo revascularization had an adjusted mortality ratio of 0.65 to 0.88. While there may be disease state confounding, lower mortality data with revascularization does exist. Thus, continued exploration is evolving in this treatment space. A recent post-hoc analysis from the CORAL trial showed that patients who underwent stenting and had an albumin/creatinine ratio of less than 22 mg/g showed significantly less cardiovascular disease, progression of CKD, and less death that patients who were randomized to medical therapy alone.[24]

Some subsets of patients have a clear benefit of revascularization. An analysis from a single center showed that patients presenting with flash pulmonary edema or both refractory hypertension and declining eGFR, who underwent revascularization, had a reduced risk of death versus those medically treated alone (HR 0.4 and 0.2).[16] Patients who only had a decline in kidney function or refractory hypertension did not show any benefit. Thus, patients who have an acute change, from a possible new or occlusive renal artery lesion, may have the most promise of showing benefit for improving outcomes. As this was a single center and retrospective cohort, further validation is needed. Renal fraction flow reserve (FFR) has been investigated as a parame-

ter to determine if revascularization provides a benefit. FFR measures the pressure gradient after post-stenotic infusion of an endothelium independent dilating agent, used to achieve maximal blood flow. Unfortunately, several studies have not been able to show benefit FFR measurement as a good predictive technique.[25,26]

Treatment of fibromuscular dysplasia has different recommendations based on its anatomic cause compared with ARAS. Antihypertensive therapy must be addressed first as with all causes of RAS. Unlike ARAS, the majority of patients with focal FMD lesions will have their hypertension cured without need for medication with angioplasty.[27] Focal lesion hypertension occurs at a much younger age than multifocal or ARAS lesions of RAS. One study showed a mean age of FMD focal HTN at age 30 vs multifocal FMD at 49 years.[27] Earlier diagnosis and quick treatment of a focal lesion is associated with the highest changes of intervention cure. If angioplasty is unable to cure hypertension, or multifocal lesions exist, ACEI or ARB are first line recommendation medications.[28] RAASi medications are recommended as the goal is to reduce aldosterone activity from renin stimulation from the FMD stenosis. If the patient does not respond well to a maximally tolerated dose of RAAsi, a calcium channel blocker or thiazide class diuretic should be added to the regimen. As with all forms of RAS, a lab check should occur between 2 and 4 weeks of starting a RAASi to determine hemodynamic eGFR change and to monitor any risk of hyperkalemia.

Currently we do not have any randomized controlled trials comparing revascularization with medical therapy alone in RAS from FMD, unlike the extensive trials mentioned above for ARAS. Current recommendations for revascularization for FMD include patients with recent-onset hypertension, resistant hypertension with a known lesion, patients unable to tolerate medications, and those with bilateral FMD lesions or unilateral lesions in a solitary kidney.[29] Primary goal with revascularization is to prevent atrophy of the kidney from decreased blood flow. Secondary, but equally important for overall health of the patient, minimizing aldosterone stimulation and need for medication control are outcomes that are desired. FMD in non-renal vascular beds is commonly reported such as carotid, coronary, and intracerebral arteries. Patients experiencing conditions such as transient ischemic attack, stroke, claudication, or intestinal ischemia related to FMD should undergo angioplasty similar to renal angioplasty therapeutic goals.[30]

A clinician can choose between open surgery and percutaneous transluminal angioplasty (PTA) when the treatment goal is to open a stenotic lesion. PTA procedures are commonly placed with balloon angioplasty and no stent placement after lesion opening. Currently there are no comparative trials, but patients treated with PTA achieve similar success and has been associated with lower risks of adverse events.[28] If PTA is not technically successful, or if vessel dissection occurs, stent management should be considered. Two indications exist for open surgical correction, they include children with focal FMD and patients with renal artery aneurysms.[28] Once clinical success has been achieved with PTA, restenosis rates range from 12% to 34% over follow-up intervals of six months to two years.[31] Previous reports have cited that it can be difficult to accurately determine if the restenosis is de novo, or if the lesion was incompletely treated, making hard numbers more challenging to cite.

Post PTA success can be determined in several ways. A germaine finding will be drop in blood pressure while the patient is still undergoing the procedure. Physiologic assessments can be determined by pressure gradients before and after angioplasty. Renal artery duplex ultrasound scanning can be used to determine adequacy of lesion relief.[32] Optical coherence tomography (OCT) is occasionally used to evaluate stenosis success as well.[33] Ongoing monitoring is recommended in patients who are treated with medical therapy or PTA procedures. Patients who have serum laboratories and blood pressure measured post procedure, then every six months for two years, and then yearly if stable.[28]

Prognosis

One of the most common effects of RAS is decreased kidney perfusion leading to the activation of the RAAS. This elevation in hormone activation leads to the same long term conse-

quences of other activations of the RAAS, including CKD progression, CV disease, CV mortality, hypertension, and heart failure.[34] Specific to the kidney with RAAS activation, there are known inflammatory and pro-fibrotic cytokines that are activated and lead to glomerular sclerosis, rarefication of the kidney microvascular structures, and interstitial fibrosis with tubular atrophy. Ongoing ischemia of the kidney parenchyma will lead to progressive eGFR loss and contribute to eventual ESKD.[35]

Atherosclerosis is known to occur in multiple vascular beds rather than single locations.[35] It is not surprising that RAS from atherosclerosis is linked to coronary disease and cardiovascular disease. Relief of one stenotic area may not provide much benefit to the already stenotic and narrowed distal vascular beds of other primary organs. This may be best supported by data showing that patients with fibromuscular dysplasia (FMD) show benefit of cardiovascular outcomes after revascularization, while those with ARAS causes do not. Similarly carotid endarterectomy does not improve renal artery blood flow or decrease RAS risk. Single organ system lesion abatement is easier to prove clinical improvement, while systemic disease states like ARAS have less positive data as shown above.

Progression to CKD and eventual ESKD is the greatest risk to patients with a compromised blood flow to the kidney. In patients with incidental RAS, progression may be low risk. A study of 593 patients who underwent angiography for PAD, 397 had renal angiograms performed at the time of study. Of these, 126 had moderate (>50 percent) stenosis of one or more renal arteries. The average eGFR was 58 ml/min per 1.73 m^2at the time of the angiogram. At follow up 10 years later, kidney function remained stable and not a single patient had developed ESKD.[36] This is in contrast to those with worse disease. Another long term study of 51 patients with confirmed bilateral renal artery stenosis (90 percent or greater stenosis in one kidney and 50 percent or worse in contralateral kidney) were monitored for 5 years. The median eGFR declined from 39 to 24 ml/min/1.73 m^2, and 12 percent of patients developed ESKD.[37] These patients did not undergo revascularization and were medically treated alone. While greater stenosis may result in worsening CKD progression, the question of bilateral disease vs unilateral disease was not fully answered.

True RAS is becoming diagnosed less frequently given the current guideline recommendations of limiting intravenous contrast exposure and lacking data showing revascularization provides a major benefit. A clinician cannot diagnose what is not being monitored and measured. Thus, going forward, epidemiology data may be less robust than previous cohorts as the renal artery "drive by" intravenous contrast loads during cardiovascular angiography and dedicated renal angiography becomes less prevalent. Future outcome data may become more limited to those with AKI and acute symptoms warranting aggressive angiography and stenting.

Outcomes of FMD are brighter and more reliable if caught and treated early. Cure rates vary, but hypertension control is achieved in most patients.[38] A previous systematic review of 47 FMD studies of angioplasty reported a mean cure rate of 46 percent.[39] Technical success is reported to be much higher, ranging from 83% to 100% at the time of angioplasty.[40] Thus there is not a perfect correlation with clinical success and procedure success. Single vascular bed lesions have higher cure rates that multiple vascular intrarenal vessels. Additionally, older patients, late intervention cases, and those with multifocal FMD have lower likelihoods of cure potential.[39,41] Renal parenchymal loss is lower in adults compared with children. FMD in children is associated with intimal fibroplasia or perimedial fibroplasia, and thus have higher risks and worse prognosis of progressive chronic kidney disease.[42]

Future

Ongoing investigations continue to determine the best methods to diagnose, risk stratify, and treat patients with RAS. Currently we need better tools to identify who will most likely benefit from revascularization vs medical management therapy. Imaging continues to advance in the field of medicine, including the use of dynamic contrast enhanced MRI and BOLD MRI. Dynamic contrast MRI uses the ability of measuring numerous factors including kidney blood flow, single

Table 1
All ongoing clinical trials involving patients with native and transplant renal artery stenosis. Available on http://www.clinicaltrials.gov.

Treatment	Trial Identification	Enrolled	Outcome
Ciclosporin A	NCT03382301, CicloSAAR	20 with RAS	Kidney perfusion at baseline and 3 months post dilation
Endovascular repair	NCT03530748,	30 with RAS	Syngo Dyna Parenchymal Blood Volume measurement and eGFR at baseline and 3 months
Ultrasound Wave therapy	NCT03914157	30 with ARAS	Change in kidney perfusion, eGFR at 3 months, change in blood oxygen
Endovascular repair	NCT03080519, ETRAS-China	5000 with RAS	Change in blood pressure and eGFR up to 24 months
Aspirin	NCT04260828	368 kidney transplants	RAS result, allograft function, graft loss at 2 years
Paclitaxel-eluting Balloon intervention	NCT04366596	90 with RAS	Blood pressure and artery patency at 9 months
Stem Cells	NCT02266394	42 with RAS	Change in kidney function and biomarkers of injury at 3 months and 2 years
MRI scanning	NCT04423458	110 kidney transplants	Peak systolic velocity, velocity ratio, resistive indices at 12 weeks

kidney GFR and extraction fraction.[43] These factors may be able to be used in future studies as a way to guide outcomes. BOLD-MRI has the ability to reveal areas of kidney ischemia.[44] It has been hypothesized that kidney ischemia as a result of RAS may help risk stratify those who would or would not benefit from a revascularization attempt. Currently there are at least 8 clinical trials ongoing looking at diagnostic tools and therapy options for patients with RAS (Table 1).

In 2021, we continue to rely on the CORAL trial as the gold standard for maximal medical therapy in ARAS as the treatment of choice. Patients with FMD in contrast do show excellent clinical benefits from PTA, despite no randomized trials available for comparison. Those with any known renal artery stenosis must have well controlled blood pressure, guideline driven LDL-C goals with the use of statin medications, healthy diet and exercise lifestyle choices, and maximally tolerated RAASis to prevent CKD and CV progression. Physicians and providers must continually keep a close eye for these patients who may have a benefit from an acute lesion revascularization. As mentioned those with flash pulmonary edema, AKI, and sudden resistant hypertension have all shown some benefits both clinically and in observational studies. Future randomized clinical trials are needed to further stratify these patients and also guide how to predict patients at risk for sudden stenosis.

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