Renovascular Hypertension

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Overview

- Renovascular hypertension (RVHT) reflects the causal relation between anatomically evident arterial occlusive disease and elevated blood pressure.
- The coexistence of renal arterial vascular (ie, renovascular) disease and hypertension roughly defines this type of nonessential hypertension.

Overview

- Current guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) advocate screening for RAS only when a corrective procedure will be considered if renovascular disease is detected

ASRVD

ATHEROSCLEROSIS 75-90%

(more common in OLDER patients)

FMD

FIBROMUSCULAR DYSPLASIA 10-25%

(More Common In Young Patients, Females)

Current Concepts in the Treatment of Renovascular Hypertension

Sandra M. Herrmann[1] and Stephen C. Textor[1]

American Journal of Hypertension 31(2) February 2018

26.03.1401

EPIDEMIOLOGY OF RVD

- Many vascular obstructive lesions can lead to the syndromes of RVH.
- These lesions account for 1% to 2% of all cases of hypertension in the general population and their prevalence may reach up to 6.8% in the population with >65 years of age and 5.8% in cases of secondary hypertension in young adults.
- Atherosclerotic renal artery stenosis (ARAS) and fibromuscular dysplasias (FMD) account for the large majority, but clinicians must be alert to other potential causes

Table 1: Causes of renovascular hypertension

Causes of renovascular hypertension
Atherosclerotic renal artery stenosis
Fibromuscular disease
Medial fibroplasia
Perimedial fibroplasia
Intimal fibroplasia
Medial hyperplasia
Extrinsic fibrous band
Renal trauma
Arterial dissection
Segmental renal infarction
Page kidney (perirenal fibrosis)
Aortic dissection
Arterial embolus
Aortic endograft occluding the renal artery
Miscellaneous:
Hypercoagulable state with renal infarction (e.g., Lupus anticoagulate)
Autoimmune diseases (e.g., Takayasu's arteritis, Polyarteritis nodosa))
Malignancy encircling the renal artery (e.g., Renal cell carcinoma, pheochromocytoma)

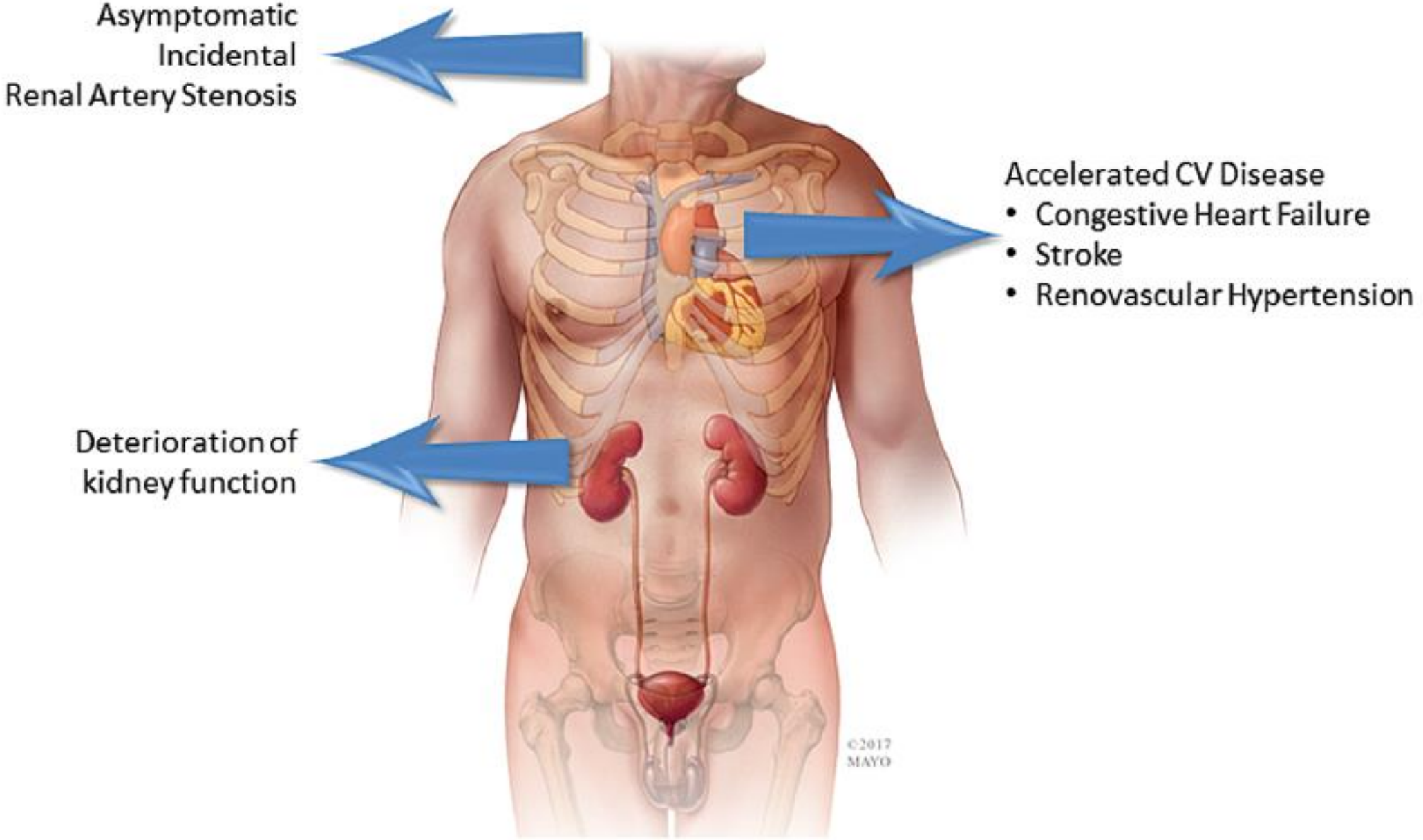

Figure 1. Clinical manifestations of renovascular disease. Abbreviation: CV, cardiovascular disease.

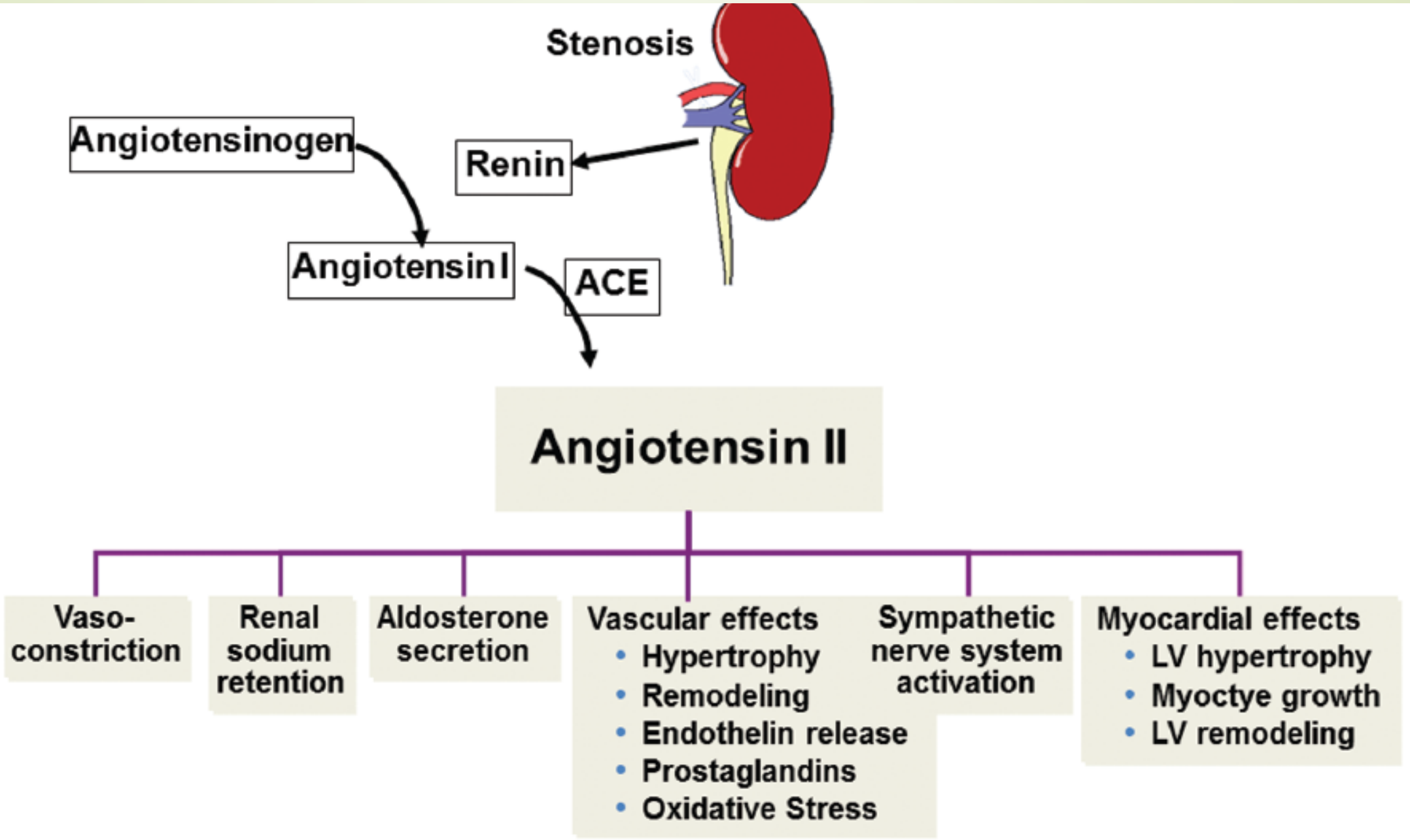

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Figure 2. Pathogenic pathways in renovascular hypertension. Abbreviations: ACE, angiotensin-converting enzyme; LV, left ventricle.

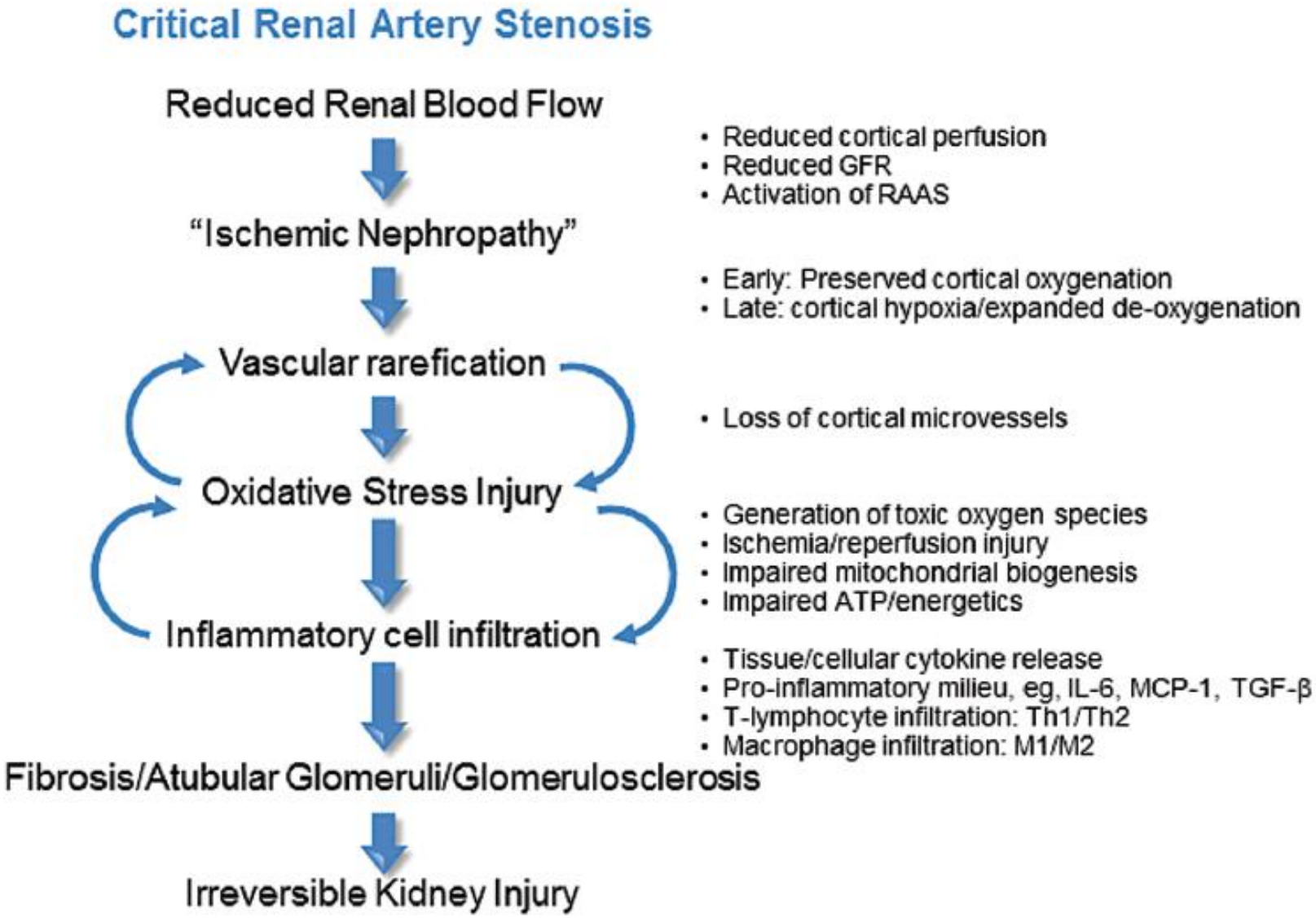

Figure 3. Pathways of kidney injury in atherosclerotic renovascular disease. Abbreviations: GFR, glomerular filtration rate; IL, interleukin; MCP, monocyte chemoattractant protein; RAAS, renin–angiotensin–aldosterone system; TGF, tissue growth factor.

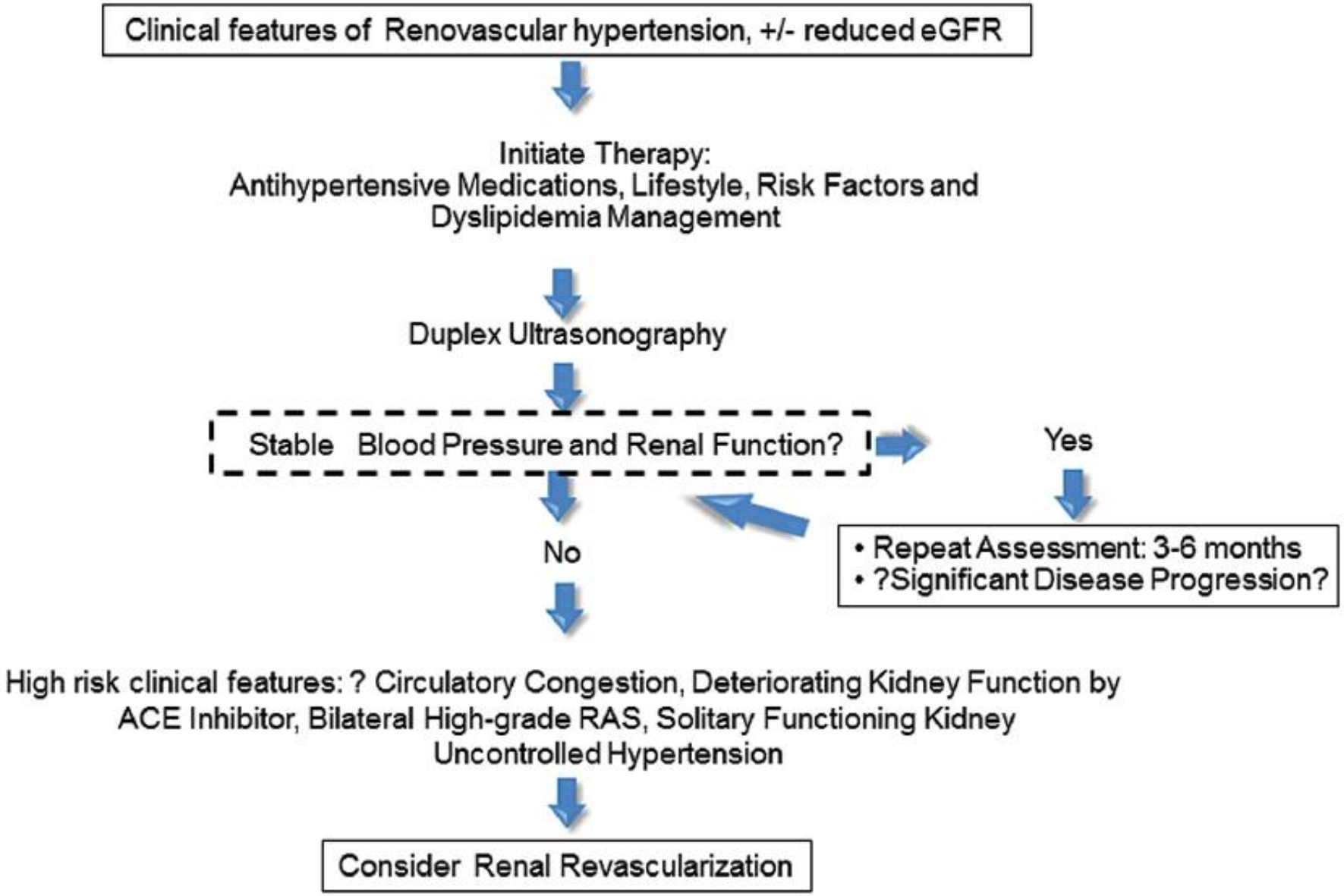

Figure 4. Management of renovascular hypertension and ischemic nephropathy. Abbreviations: ACE, angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate; RAS, renal artery stenosis.

Table 2: Widespread blood pressure variation after PTRAS in randomized and non-randomized studies

Study	Date enrollment	Intervention	*N*	Baseline SBP/DBP [MAP], mean, mm Hg	Blood pressssure ΔSBP/DBP mm Hg	Comments
Ziakka *et al.*,2008[65] (RCT)	NA	PTRAS	36	178/88	Cured: 11% Improved 67%	Mean stenosis 74% ARAS Enrolled 82 patients who had ARAS demonstrated by an angiogram
Scarpioni *et al.*,2005[66] (NITER-RCT)	NA	PTRAS	24	148/79	Cured: 0%	Stenosis ≥70%, renal failure, HTN on ≤5 medications
Bax *et al.*,2009[67] (STAR-RCT)	2000–2005	PTRAS	64	160/83	Δ −9/−6	>50% ostial ARAS with CKD CrCl<80 mL/min per 1.73 m^2 according to the Cockcroft and Gault formula
Wheatley *et al.*,2009[13] (ASTRAL-RCT)	2000–2007	PTRAS	403	149/76	Δ −8/−3	% Stenosis(no data) with substantial ARAS with uncontrolled HTN or unexplained CKD
Marcantoni *et al.*,2012[68] (RASCAD-RCT)	2006–2009	PTRAS	43	133/73	Δ −6/−2	50% and ≤80% ARAS with CKD ≤4 mg/dL and incident HD, but without AMI. ARAS >80% were excluded because at the time the study was design
Cooper *et al.*,2014[45] (CORAL-RCT)	1995–2007	PTRAS	459	150/NA	Δ −17/NA	≥60% ARAS with uncontrolled HTN (SBP≥155 mm Hg while receiving two or more antihypertensive medications) and CKD eGFR<60. However, recruitment and intervention protocols changed over time allowing patients W or WO hypertension
Hanzel *et al.*,2005[69] (NCP)	NA	PTRAS	26	162/82	Δ −15/−8	≥70% ostial ARAS with non−proteinuric CKD scr ≤2.0 mg/dL. Excluded patients with known parenchymal renal disease
Arthurs *et al.*,2007[70] (NCR)	2001–2005	PTRAS	22	162/75	Δ 4/5	≥60% ostial ARAS with >6 mo HTN >140/90 and scr ≥1.5.4/18 in the medical arm had previous angioplasty
Ditchel *et al.*,2010[71] (NCR)	1999–2007	PTRAS	47	145/75	Δ −3/−1	>75% stenosis by MRA or aortic ratio on duplex US >3.5 with CKD (defined as eGFR 15−60 mL/ min/1.73m^{-2})
Kalra *et al.*,2010[54] (NCP)	1995–2007	PTRAS (Germany) PTRAS (UK)	472 89	144/78 157/81	Δ −10/−4 Δ −13/−9	>50% ARAS with a subset with decompensation. UK: after enrolment into the ASTRAL trial. Germany, no ARAS excluded
Kane *et al.*,2010[72] (NCPR)	NA	PTRAS	50	154/NA	Δ −28/NA	70% stenosis and uncontrolled (accelerated or resistant) HTN or CKD 3–5(non-dialysis)
Cianci *et al.*,2011[73] (NCP)	2004–2009	PTRAS	53	160/NA	Δ −5/−2	≥70% stenosis ARAS and without diabetes mellitus
Sofroniadou *et al.*,2012[74] (NCP)	1997–2003	PTRAS	26	177/90	Δ −28/−13	>70% unilateral ARAS and/or FPE, AKI, and refractory HTN:eligible for PTRAS >50% unilateral ARAS w/wo HTN and wo AKI or FPE: medical therapy
Ritchie *et al.*,2014[22] (NCP)	1995–2011	PTRAS PTRAS (RDKF & RHTN) PTRAS (RHTN)	127 11 33	163/83 177/86 175/87	NA Δ−45/−16 Δ−20/−8	>50% unilateral ARAS wo occlusion. Exclusion: unilateral occlusion and insignificant contralateral stenosis
Rocha−Singh, 2011[75]	NA	PTRAS	286	179/83	Δ −25/−6	≥70% de novo or restenotic ARAS with uncontrolled

CLINICAL KIDNEY JOURNAL

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CKJ Review

CKJ REVIEW

Approach to atherosclerotic renovascular disease: 2016

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- Enthusiasm for renal revascularization diminished in the era of statin therapy and renin–angiotensin system (RAS) blockade, which are believed to slow the rate of atherosclerosis progression.

- Major contemporary clinical trials, such as the Cardiovascular Outcomes for Renal Artery Lesions (CORAL) and the Angioplasty and Stenting for Renal Atherosclerotic Lesions (ASTRAL) trials, have failed to show statistically significant benefit of revascularization over optimal medical management in controlling blood pressure (BP) or preserving kidney function.
- These two trials have influenced medical decision making away from vascular intervention.

Current clinical approach

- The current attitudes toward the management and treatment of ARAS have shifted sharply toward optimal medical management.
- This shift was largely driven by the publication of several randomized clinical trials that failed to show superiority of revascularization over optimal medical therapy in terms of BP control, preservation of renal function or major cardiovascular or renal events.

ACCF/AHA Practice Guidelines

Management of Patients With Peripheral Artery Disease (Compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations)

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

(*Circulation*. 2013;127:1425-1443.)

Circulation **is available at http://circ.ahajournals.org**

Clinical Clues to the Diagnosis of Renal Artery Stenosis

- Patients with the onset of hypertension before the age of 30 years. (Level of Evidence: B)
- Patients with the onset of severe hypertension after the age of 55 years. (Level of Evidence: B)
- Accelerated hypertension (sudden and persistent worsening of previously controlled hypertension);

Clinical Clues to the Diagnosis of Renal Artery Stenosis

- Resistant hypertension (defined as the failure to achieve goal blood pressure in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic);

Clinical Clues to the Diagnosis of Renal Artery Stenosis

- Malignant hypertension (hypertension with coexistent evidence of acute end-organ damage, ie, acute renal failure, acutely decompensated congestive heart failure, new visual or neurological disturbance, and/or advanced [grade III to IV] retinopathy). (Level of Evidence: C)

Clinical Clues to the Diagnosis of Renal Artery Stenosis

- New azotemia or worsening renal function after the administration of an ACE inhibitor or an angiotensin receptor blocking agent. (Level of Evidence: B)
- unexplained atrophic kidney or a discrepancy in size between the 2 kidneys of greater than 1.5 cm. (Level of Evidence: B)

Clinical Clues to the Diagnosis of Renal Artery Stenosis

- Patients with sudden, unexplained pulmonary edema (especially in azotemic patients). (Level of Evidence: B)
- Unexplained renal failure, including individuals starting renal replacement therapy (dialysis or renal transplantation). (Level of Evidence: B)

Clinical Clues to the Diagnosis of Renal Artery Stenosis

- The performance of arteriography to identify significant RAS may be reasonable in patients with multivessel coronary artery disease and none of the clinical clues or PAD at the time of arteriography. (Level of Evidence: B)

Clinical Clues to the Diagnosis of Renal Artery Stenosis

- The performance of diagnostic studies to identify clinically significant RAS may be reasonable in patients with unexplained congestive heart failure or refractory angina. (Level of Evidence: C)

Diagnostic Methods

- Duplex ultrasonography is recommended as a screening test to establish the diagnosis of RAS. (Level of Evidence: B)
- CTA (in individuals with normal renal function) is recommended as a screening test to establish the diagnosis of RAS. (Level of Evidence: B)

Diagnostic Methods

- MRA is recommended as a screening test to establish the diagnosis of RAS. (Level of Evidence: B)
- When the clinical index of suspicion is high and the results of noninvasive tests are inconclusive, catheter angiography is recommended as a diagnostic test to establish the diagnosis of RAS. (Level of Evidence: B)

Medical Treatment

- ACE inhibitors are effective medications for treatment of hypertension associated with unilateral RAS. (Level of Evidence: A)
- Angiotensin receptor blockers are effective medications for treatment of hypertension associated with unilateral RAS. (Level of Evidence: B)

Medical Treatment

- Calcium-channel blockers are effective medications for treatment of hypertension associated with unilateral RAS. (Level of Evidence: A)
- Beta blockers are effective medications for treatment of hypertension associated with RAS. (Level of Evidence: A)

Indications for Revascularization

- An asymptomatic bilateral or solitary viable kidney with a hemodynamically significant RAS. (Level of Evidence: C)
- The usefulness of percutaneous revascularization of an asymptomatic unilateral hemodynamically significant RAS in a viable kidney is not well established and is presently clinically unproven. (Level of Evidence: C)

Indications for Revascularization

- Hemodynamically significant RAS and accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with an unexplained unilateral small kidney, and hypertension with intolerance to medication. (Level of Evidence: B)

Indications for Revascularization

- Patients with RAS and progressive chronic kidney disease with bilateral RAS or a RAS to a solitary functioning kidney. (Level of Evidence: B)
- Patients with RAS and chronic renal insufficiency with unilateral RAS.
- Patients with hemodynamically significant RAS and recurrent, unexplained congestive heart failure or sudden, unexplained pulmonary edema. (Level of Evidence: B)

Surgery for RAS

- Patients with fibromuscular dysplastic RAS with clinical indications for interventions (same as for percutaneous transluminal angioplasty), especially those exhibiting complex disease that extends into the segmental arteries and those having macroaneurysms. (Level of Evidence: B)

Surgery for RAS

- Patients with atherosclerotic RAS and clinical indications for intervention, especially those with multiple small renal arteries or early primary branching of the main renal artery. (Level of Evidence: B)
- Patients with atherosclerotic RAS in combination with pararenal aortic reconstructions (in treatment of aortic aneurysms or severe aortoiliac occlusive disease). (Level of Evidence: C)

Current Hypertension Reviews, 2020, *16*, 24-29

REVIEW ARTICLE

BENTHAM SCIENCE

Renovascular Hypertension: Novel Insights

Chrysoula Boutari[1], Eleni Georgianou[1], Alexandros Sachinidis[1], Alexandra Katsimardou[1], Konstantinos Christou[1], Alexia Piperidou[1] and Asterios Karagiannis[1,*]

Medical Therapy

- Management of RVH begins with optimizing medical therapy which includes smoking cessation, administration of statins, glucose control in patients with diabetes and antihypertensive drug treatment.
- ACE inhibitors and ARBs have contributed to the successful control of blood pressure in many patients with RVH.

Medical Therapy

- An observational study with 3,570 patients with the renovascular disease found that the subjects who were receiving angiotensin inhibitors (53%) had a significantly lower risk of the primary outcome (death, myocardial infarction or stroke) (hazard ratio [HR] = 0.70; 95% CI: 0.53-0.90).

Medical Therapy

- The limitation of observational data is selection bias.
- Patients who are able to receive RAAS antagonists have, in general, less severe disease and may have better outcomes anyway.

Medical Therapy

- If the aforementioned approach achieves the intended blood pressure levels with stable renal function, no further action is required.
- If goal blood pressure is not reached, other antihypertensive drugs, such as a thiazide diuretic (chlorthalidone or indapamide), a long-acting calcium channel blocker, a mineralocorticoid receptor antagonist, or a beta blocker, should be added as necessary.

Medical Therapy

- Medical therapy remains the cornerstone of management of ARAS.
- However, the major risk of the available pharmacologic therapy proceeds from the impairment of renal function.
- Important (over 30%) decline in GFR (or an over 0.5 mg/dL rise in serum creatinine) may be a reason to consider renal revascularisation.

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ORIGINAL RESEARCH ARTICLE

WILEY Cardiovascular Therapeutics

Calcium channel blockers are associated with improved survival and lower cardiovascular mortality in patients with renovascular disease

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Summary

Background and objective: Results of interventional trials in renovascular hypertension have been disappointing, and medical therapy is the current recommended gold stand-

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, anonymized data over a 6-year period was analyzed. 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 were 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 were 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: A total of 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) mortality. 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.

Special Report

AJKD

Atherosclerotic Renovascular Disease: A KDIGO (Kidney Disease: Improving Global Outcomes) Controversies Conference

Caitlin W. Hicks, Timothy W.I. Clark, Christopher J. Cooper, Áine M. de Bhailís, Marco De Carlo, Darren Green, Jolanta Małyszko, Marius Miglinas, Stephen C. Textor, Charles A. Herzog, Kirsten L. Johansen, Holger Reinecke, and Philip A. Kalra

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Box 1. KDIGO Consensus on Indications and Nonindications for Renal Artery Revascularization in Atherosclerotic Renovascular Disease

Definite indications

- Acute pulmonary edema or acute decompensations of heart failure and high-grade RAS[96]
- Progressive CKD in high-grade (>75%) RAS (bilateral or solitary kidney)[21]
- AKI due to acute renal artery occlusion or high-grade RAS[83]
- ACEi or ARB intolerance in high-grade RAS
- Kidney transplant with RAS (symptomatic or asymptomatic)[91]

Possible indications

- Chronic heart failure and high-grade RAS[31,73]
- Coexistence of progressive CKD and uncontrolled hypertension[21,84]
- Asymptomatic high-grade RAS (either bilateral or supplying solitary kidney) with viable renal parenchyma (to prevent atrophy)
- New (<3 mo) dialysis patient with nonfunctioning but possibly viable kidney[53-55,83,84]

Nonindications

- Moderate to severe hypertension alone
- Asymptomatic unilateral or bilateral (<75%) RAS[63,70,71]

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; KDIGO, Kidney Disease: Improving Global Outcomes; RAS, renal artery stenosis. Adapted from Johansen et al[1] with permission of the copyright holder; original content ©2021 International Society of Nephrology.

From the Western Vascular Society

Clinical predictors of blood pressure response after renal artery stenting

J. Gregory Modrall, MD,[a,b] Hong Zhu, PhD,[c] *and* Fred A. Weaver, MD,[d] *Dallas, Tex; and Los Angeles, Calif*

Journal of Vascular Surgery
■■■ 2020

CONCLUSIONS

Using prospectively collected data from the CORAL trial, this study independently validated the three clinical markers of BP response to RAS that were previously reported: requirement for four or more antihypertensive medications, preoperative diastolic BP >90 mm Hg, and preoperative clonidine use. Two studies have now confirmed the potential clinical utility of these preoperative variables in predicting BP response to RAS using different data sets and populations of patients.

These clinical markers warrant further study in a prospective trial designed to validate their utility as predictors of BP response after RAS.