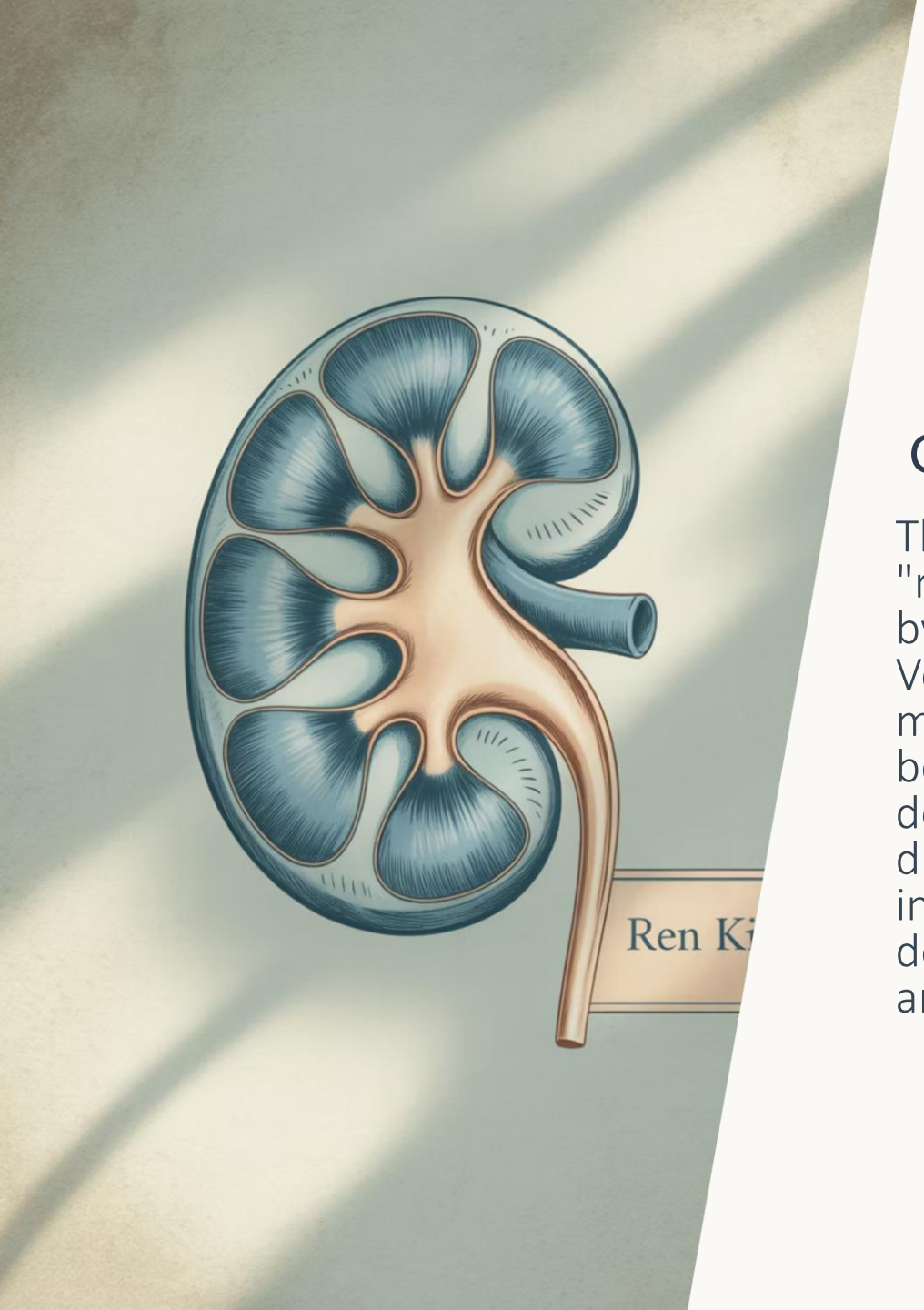
Società Italiana dell'Ipertensione Arteriosa
Lega Italiana contro l'Ipertensione Arteriosa

EVENTO FORMATIVO INTERREGIONALE SIIA
PIEMONTE | LIGURIA | VALLE D'AOSTA
Torino, 29 novembre 2025

Nefronagiosclerosi ed ipertensione nefrovascolare un confine non sempre ben definito

Dott. Maurizio Borzumati
SOC Nefrologia e Dialisi – ASL VCO



Nephroangiosclerosis

German Pioneers

The term "nephrosclerosis" or "renal hardening" was first coined by German physicians Franz Volhard and Theodor Fahr. Their monograph "Bright's Disease" became the nephrology bible for decades, classifying kidney diseases into three groups: inflammatory (nephritis), degenerative (nephrosis), and arteriosclerotic (sclerosis).

Modern Usage

Today, nephrosclerosis, nephroangiosclerosis, and hypertensive renal disease are used interchangeably to describe kidney changes caused by hypertension or ageing. This broad terminology encompasses changes across all kidney compartments, making precise diagnosis challenging.

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Epidemiology

44

Cases per Million

Average annual incidence in Spanish study (1991-2007)

11.6%

Progression Rate

Patients developing end-stage kidney disease

In Spain, hypertension ranks as the second leading cause of chronic kidney disease after diabetes mellitus. However, establishing accurate prevalence and incidence remains challenging due to lack of uniform diagnostic criteria and the overlap with other vascular nephropathies.

The prevalence is likely increasing due to population ageing, rising hypertension rates, and improved cardiovascular disease survival. Yet comprehensive incidence records remain scarce across nephrology departments.

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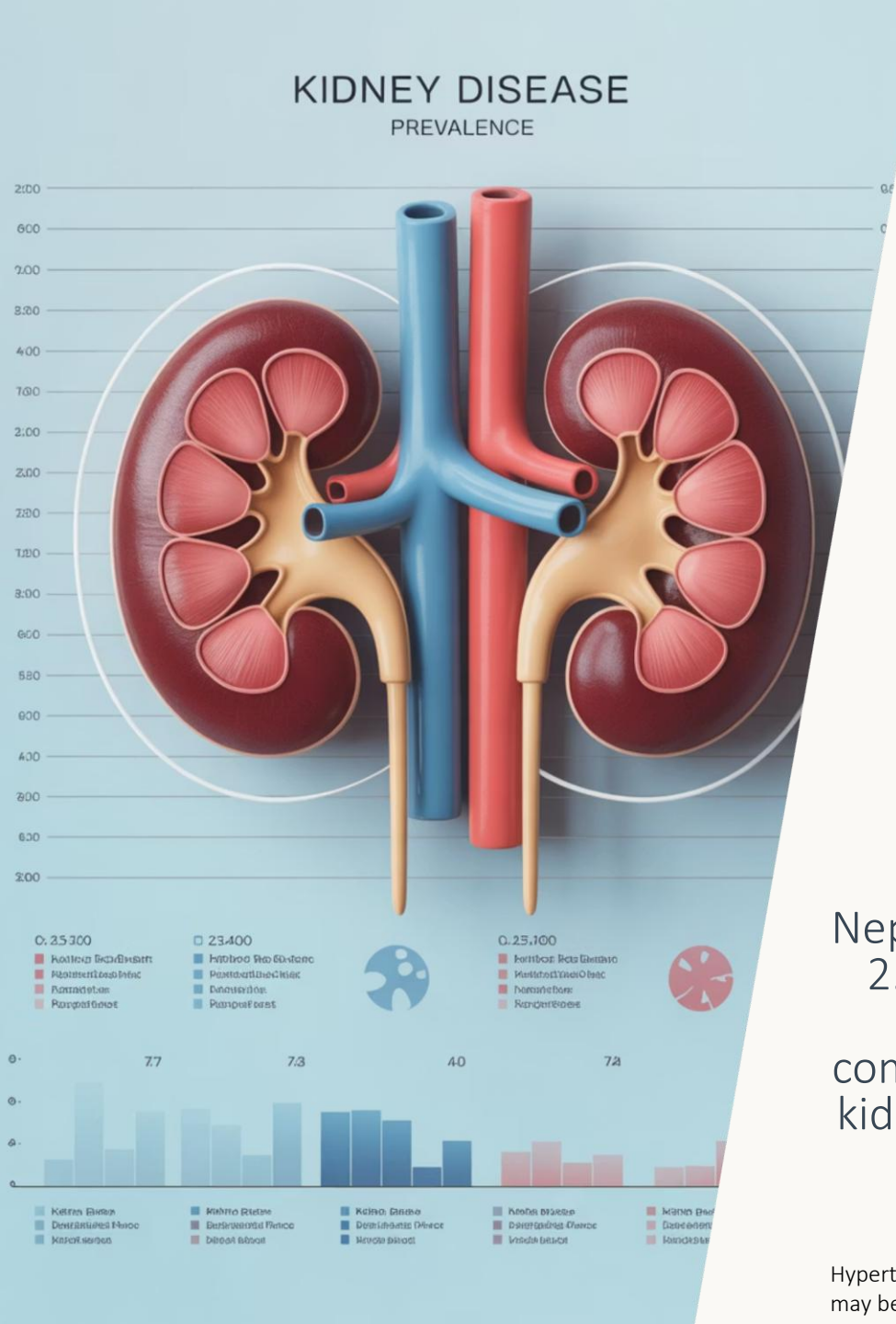


This research analyzed three distinct populations to evaluate and improve diagnostic processes:

- 50,552 adults from the population-based HUNT study
- 7,261 Norwegian CKD patients with kidney biopsies (1988-2012)
- 193 unselected nephrology clinic patients for matching

Prevalence and Population Impact

2.7%

General Population Prevalence

Nephrosclerosis affects 2.7% of the general population, comparable to diabetic kidney disease at 2.0%

6.3%

Other CKD Diagnoses

Additional chronic kidney disease cases not classified as nephrosclerosis or diabetic kidney disease

1.99

Annual eGFR Decline

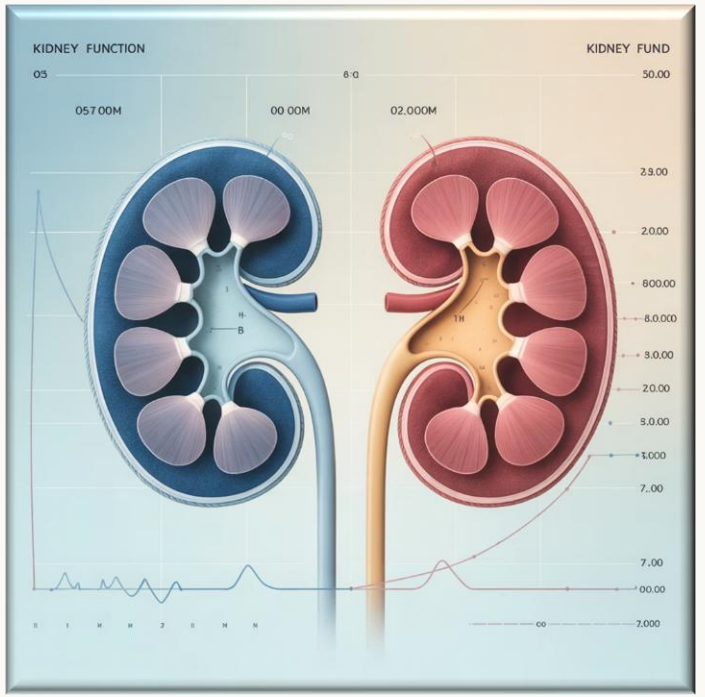
mL/min/1.73m² per year - significantly faster than the 0.71 decline in subjects without CKD

Hypertensive nephrosclerosis: wider kidney biopsy indications may be needed to improve diagnostics

S. I. Hallan et Al - Journal of Internal Medicine, 2021, 289; 69–83

Current Problem

The incidence has increased dramatically over the past 20 years, now constituting 15% of ESKD cases in Europe and 28% in the United States. However, few patients receive biopsy verification, raising questions about diagnostic reliability.



Patient Prognosis: A Serious Condition

Patients with clinically diagnosed hypertensive nephrosclerosis face substantially increased risks for kidney-related outcomes and mortality, challenging the notion that this condition represents merely normal aging.

10-Year Mortality Risk

Half of nephrosclerosis patients died within 10 years, with age-adjusted mortality rate of 30.9% compared to 23.3% in those without CKD

ESKD Risk

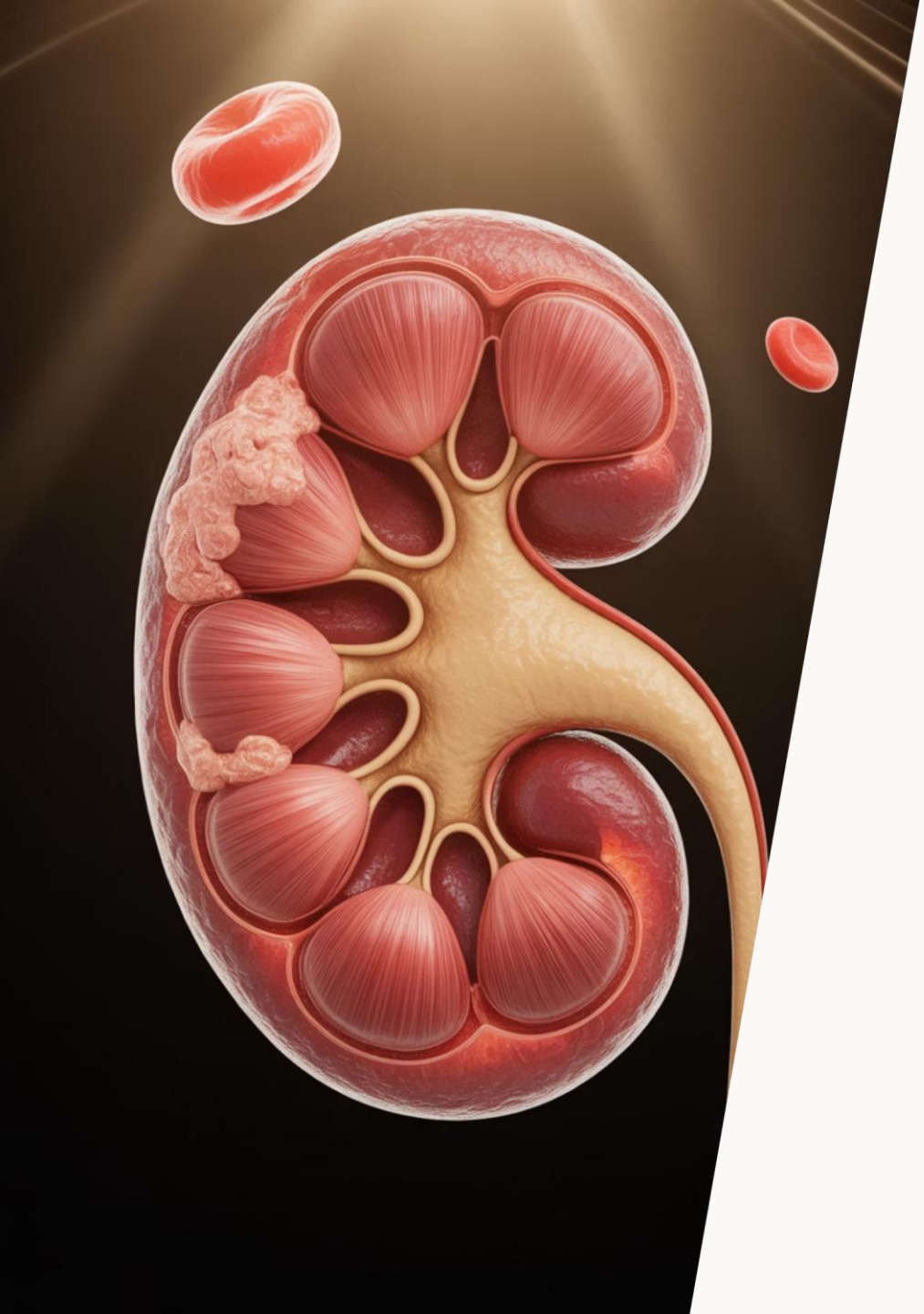
Age-adjusted ESKD risk of 1.3% over 10 years - similar to diabetic kidney disease patients (1.5%) and 26 times higher than those without CKD

Hospital Admissions

CKD-related hospital admissions occurred in 5.7% of nephrosclerosis patients versus 0.5% in those without CKD

The eGFR decline in nephrosclerosis patients was 1.99 mL/min/1.73m² per year, significantly faster than the 0.71 decline in subjects without CKD and comparable to diabetic kidney disease (1.54). Multi-adjusted relative risk for ESKD was similar between nephrosclerosis and diabetic kidney disease, with hazard ratios of 15.4 and 18.8 respectively.

S. I. Hallan et Al - Journal of Internal Medicine, 2021, 289; 69–83



Pathophysiology: The Vascular Cascade

Systemic Hypertension

Uncontrolled blood pressure leads to sustained arteriolar vasoconstriction

Preglomerular Ischaemia

Reduced renal blood flow causes glomerular tuft retraction and decreased filtration

Compensatory Changes

Afferent arteriole vasodilation leads to glomerular hypertrophy and hyperfiltration

Fibrotic Response

Ischaemia triggers angiotensin II, endothelin-1, and TGF-β production, promoting interstitial fibrosis

Clinical Diagnosis: A Process of Exclusion

Typical Patient Profile

Men over 55 years with family history of hypertension, chronic essential hypertension, and mild chronic kidney disease (creatinine 1.3-2 mg/dl) without diabetes mellitus

Laboratory Findings

Negative systematic urine analysis, proteinuria typically <1 g/day, possible hyperuricaemia or dyslipidaemia

Associated Conditions

Peripheral arteriopathy, ischaemic cardiopathy, or cerebrovascular deterioration due to hypertensive damage

The diagnosis remains largely clinical and presumptive, as renal biopsy is reserved for doubtful cases or atypical presentations. This approach creates significant diagnostic uncertainty and potential for misclassification.

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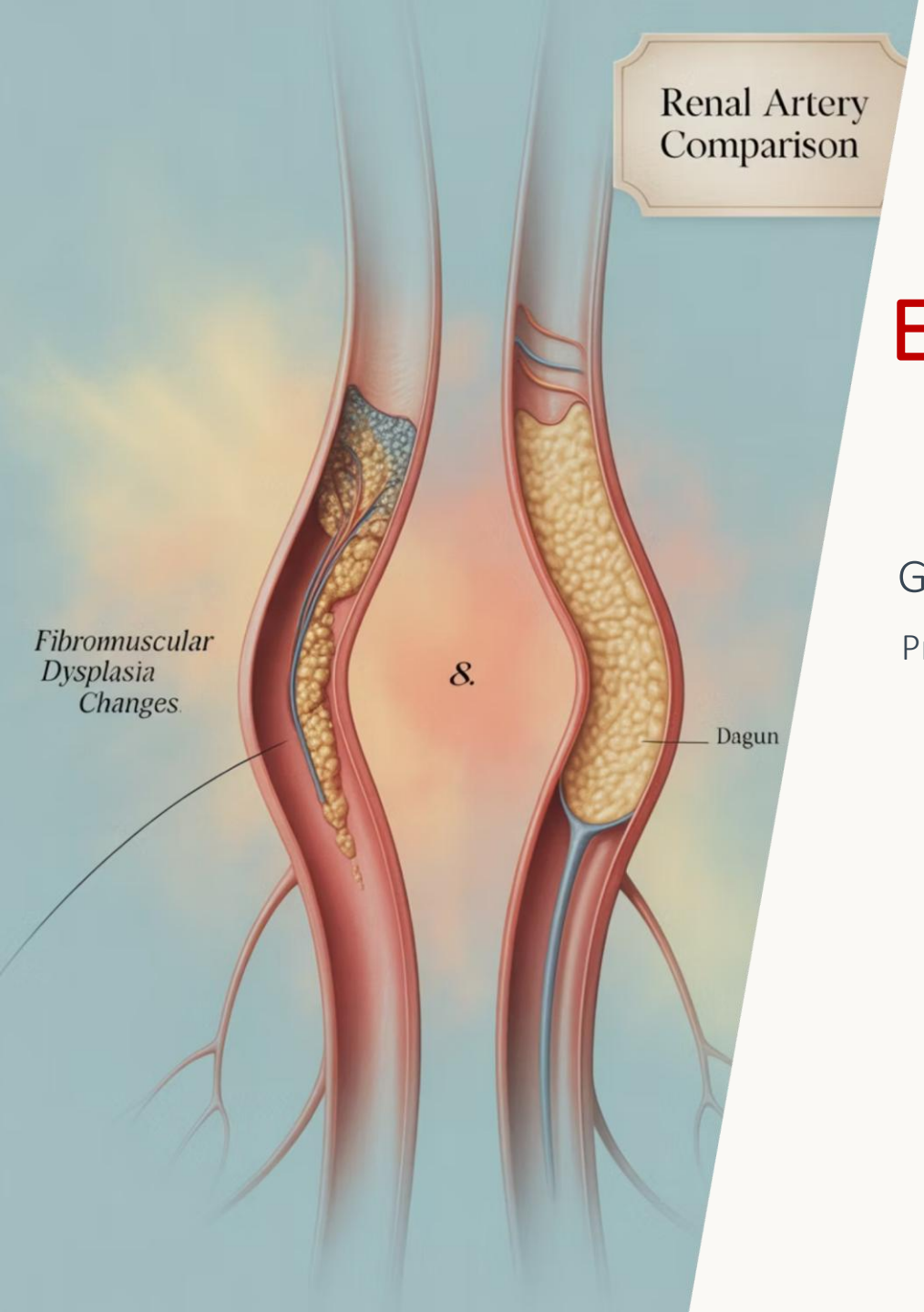


Renovascular disease (RVD) remains a major cause of secondary and treatment-resistant hypertension. Most cases are related to fibromuscular or atherosclerotic lesions, but various other causes can produce the same syndrome.

Epidemiology of Renovascular Disease

1-2%

General Population

Prevalence of RVD in all hypertension cases

6.8%

Elderly Population

Prevalence in patients over 65 years of age

5.8%

Young Adults

Cases of secondary hypertension in young adults

54%

Heart Failure

Patients with heart failure and ejection fraction <50% showing significant prevalence

5-40%

Chronic Kidney Disease

Ranges from 5-22% in middle-aged CKD patients to 40.8% in dialysis patients

Nephrol Dial Transplant , 2023, 38 , 2835–2850

Sandra M. Herrmann and Stephen C. Textor - American Journal of Hypertension 31(2) February 2018

Causes of Renovascular Hypertension

Atherosclerotic Disease

- Renal artery stenosis
- Commonly at vessel origin
- Linked to traditional risk factors

Fibromuscular Disease

- Medial fibroplasia
- Perimedial fibroplasia
- Intimal fibroplasia

Other Causes

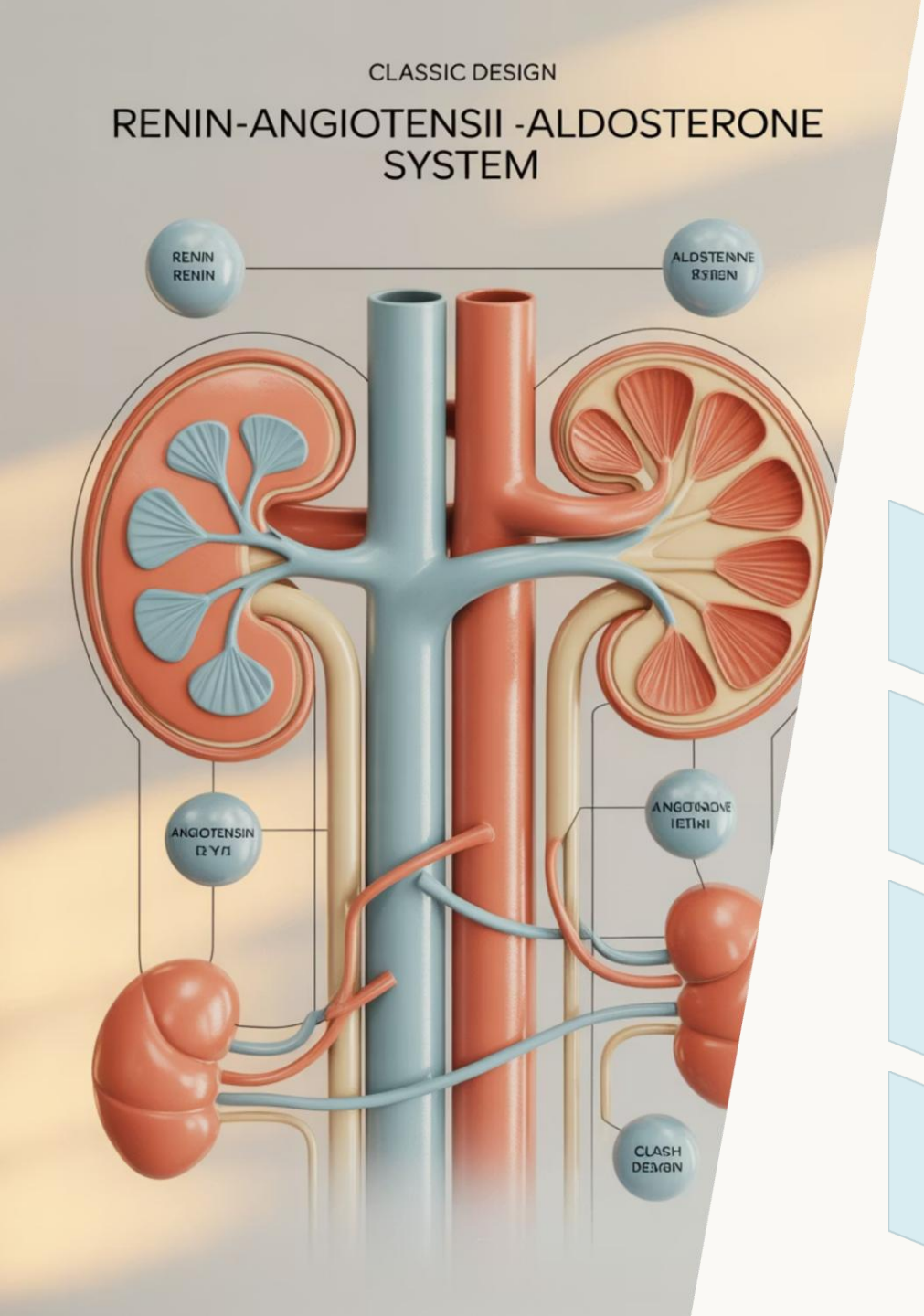
- Arterial dissection
- Renal trauma
- Aortic endograft occlusion

Miscellaneous

- Autoimmune diseases
- Hypercoagulable states
- Malignancy

Atherosclerotic renal artery stenosis (ARAS) and fibromuscular dysplasias (FMD) account for the large majority of cases. Various forms of FMD are non inflammatory, non atherosclerotic arteriopathies most commonly seen in young adults between 15 and 55 years, with clinical manifestations more common in women (nearly 90%).

Sandra M. Herrmann and Stephen C. Textor - American Journal of Hypertension 31(2) February 2018



Pathophysiology of Renovascular Hypertension

Occlusive RVD leading to reduced renal perfusion pressures raises systemic blood pressure, largely attributed to activation of the renin-angiotensin-aldosterone system (RAAS). This activates multiple pressor pathways including peripheral vasoconstriction, sodium retention, vascular remodeling, and inflammation.

Arterial Stenosis >70%

Reduces renal blood flow and causes hypoperfusion of juxtaglomerular apparatus

Renin Release

Stimulates increased production of angiotensin II and aldosterone systemically

Systemic Effects

Increased sympathetic activity, arterial remodeling, inflammation, and sodium retention

End-Organ Damage

Kidney fibrosis, cardiac hypertrophy, diastolic dysfunction, and myocardial fibrosis

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Clinical Presentations

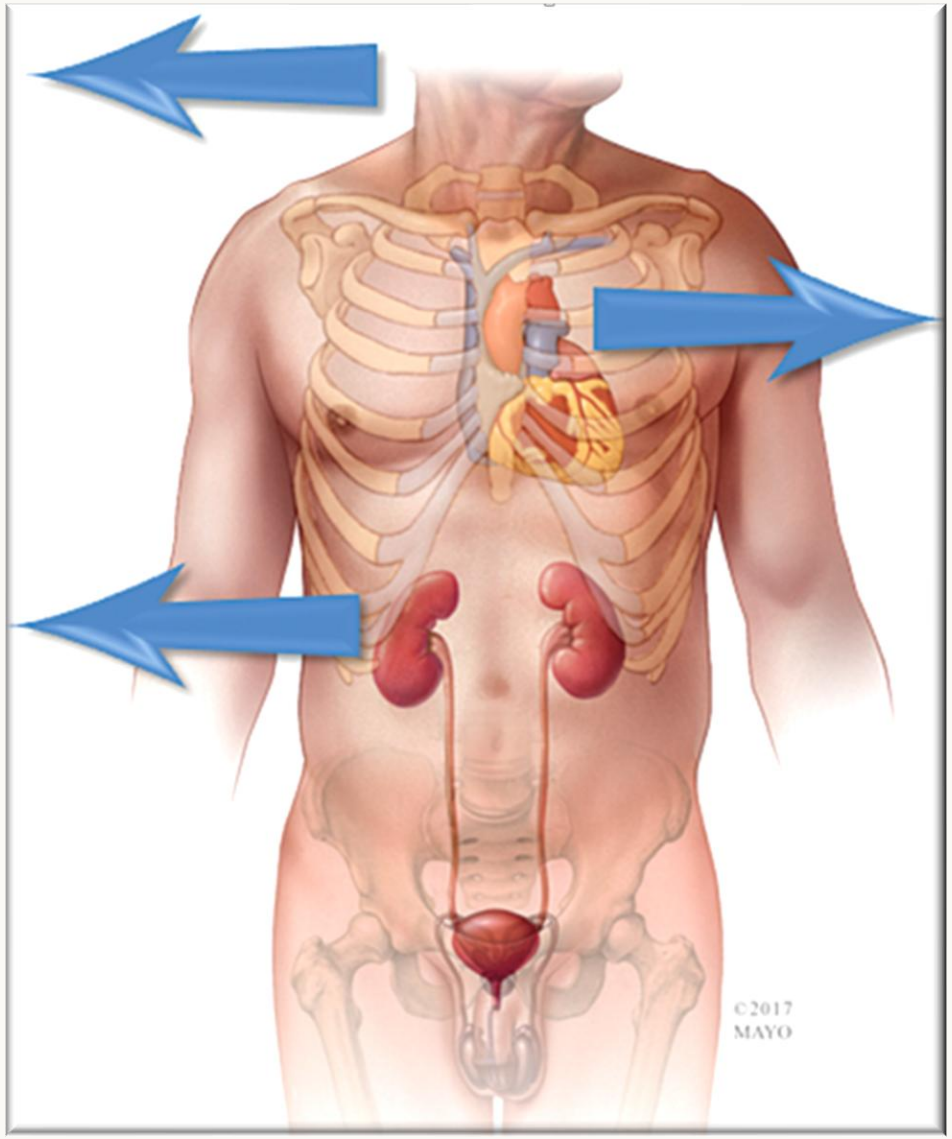
ARVD manifests through diverse clinical presentations, from asymptomatic disease to life-threatening complications requiring immediate intervention.

Hypertension

- Sudden onset or worsening hypertension
- Grade III hypertension with cardiovascular risk factors
- Resistant hypertension despite optimal therapy

Kidney Disease

- Atrophic kidney or size difference >1.5 cm
- Rapid, unexplained kidney function decline
- eGFR decline >30% after starting ACEIs/ARBs



Heart Failure

- Repeated hospitalizations for decompensated heart failure
- Sudden unexplained 'flash' pulmonary edema
- Preserved left ventricular function on echo

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Poor Prognosis Demands Attention

ARVD patients face dramatically higher adverse event rates compared to the general population, making early identification and appropriate management critical.

Cardiovascular Events

- Atherosclerotic heart disease: 303.9 vs 73.5 per 1000 patient-years
- Peripheral artery disease: 258.6 vs 52.2 per 1000 patient-years
- Congestive heart failure: 194.5 vs 56.3 per 1000 patient-years

Mortality & Renal Outcomes

- Death rate: 166.3 vs 63.3 per 1000 patient-years
- Renal replacement therapy: 28.8 vs 1.3 per 1000 patient-years
- CKD patients: 1.5x higher mortality risk
- Dialysis patients: 3.3x higher mortality risk

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Diagnostic Approach

1. **Duplex Ultrasound Screening**
   Most common initial tool. PSV >200 cm/sec has 95% sensitivity and 90% specificity for >50% stenosis

2. **Advanced Imaging**
   CT angiography or MR angiography for detailed visualization. Avoid contrast in severe CKD

3. **Invasive Assessment**
   Digital subtraction angiography remains gold standard. Consider pressure gradients for borderline cases

4. **Functional Evaluation**
   Renal resistive index >0.8 suggests poor response to revascularization

Atherosclerotic renovascular disease: a clinical practice document by the European Renal Best Practice (ERBP) Working Group Hypertension and the Kidney of the European Society of Hypertension (ESH)

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Medical Management Foundation

Comprehensive medical therapy forms the cornerstone of ARVD management, focusing on cardiovascular risk reduction and kidney function preservation.

Antihypertensive Strategy

ACEIs and ARBs are first-line options, supported by observational evidence for mortality reduction. However, initiate with caution and monitor for >30% eGFR decline.

Multiple agents typically needed: dihydropyridine calcium channel blockers, appropriate diuretics, β-blockers, and second-line agents following general guidelines.

Additional Interventions

- Lipid-lowering agents to achieve cholesterol targets
- Low-dose aspirin for cardiovascular protection
- Smoking cessation and lifestyle modifications

Special Considerations:
In bilateral RAS or RAS in solitary kidneys, ACEIs and ARBs should generally be avoided. Evaluate directly for revascularization as these agents may significantly compromise renal function.

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Treatment Philosophy: Medical vs. Interventional

Patient Assessment
Evaluate severity, bilateral involvement, kidney function, and clinical syndrome

Response Evaluation
Monitor blood pressure control and renal function stability

Medical Optimization
ACE/ARB therapy, calcium channel blockers, diuretics, statins

Intervention Decision
Consider revascularization for refractory cases or high-risk syndromes

The overall goal is to reduce morbidity and mortality associated with elevated blood pressure while protecting kidney circulation and function. Many pressor pathways are activated at reductions that are well tolerated by the kidney itself, making medical therapy often effective.

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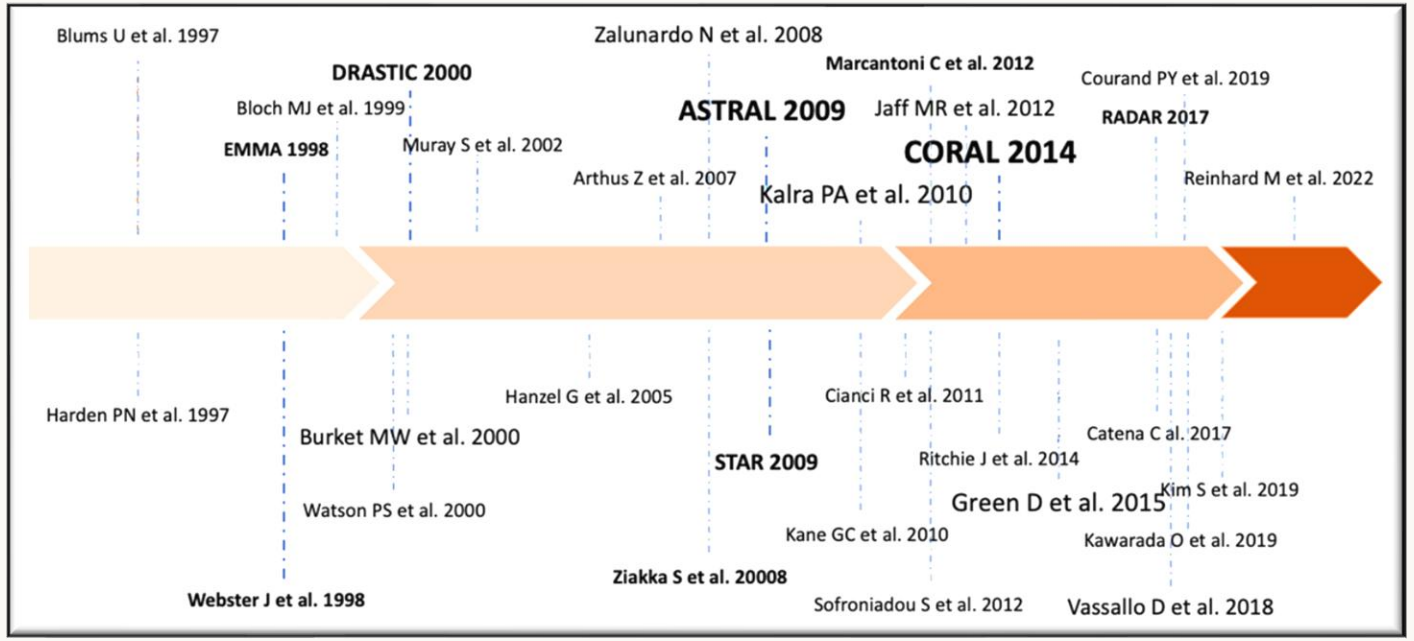
The Rise and Fall of Endovascular Enthusiasm



Pappaccogli et al. - Hypertension. 2023;80:1150–1161

Early Success Era (1990s)

Initial observational studies showed systolic blood pressure reductions up to 25 mmHg and kidney function improvement in 43-69% of patients undergoing percutaneous renal artery angioplasty.

1

First Doubts (2000-2005)

2

DRASTIC, EMMA, and Scottish trials revealed limited blood pressure benefits, with efficacy primarily seen in bilateral disease and medication reduction rather than cure.

Major Disappointments (2005-2010)

3

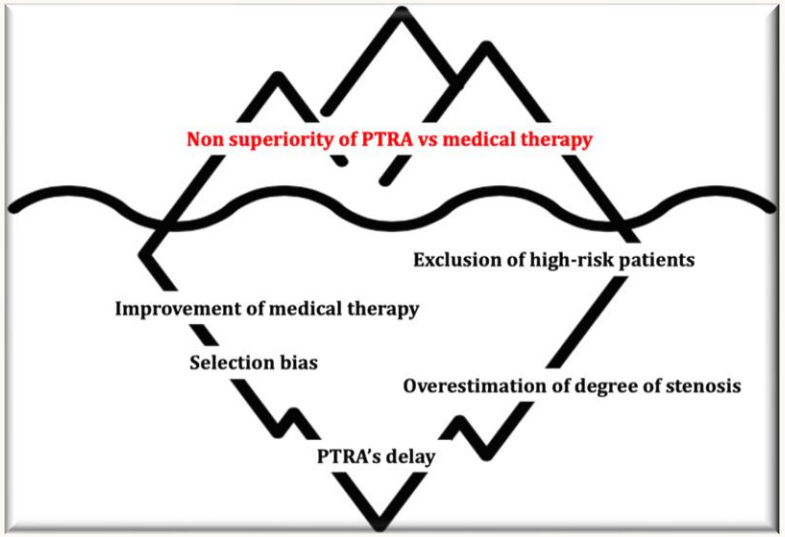
ASTRAL and STAR trials failed to demonstrate renal function benefits, challenging fundamental assumptions about revascularization effectiveness.

Final Verdict (2014)

4

CORAL study's 947 patients showed no cardiovascular or renal event reduction, effectively ending widespread enthusiasm for the procedure.

Diagnostic and Technical Inconsistencies



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Imaging Heterogeneity

Massive variability between studies in diagnostic techniques: duplex ultrasonography, CT angiography, MR angiography, and catheter-based angiography, without universal stenosis severity definitions.

Stenosis Overestimation

CORAL participants had average stenosis of only ~67% despite requiring "severe" stenosis for enrollment. Bax et al. found 18 of 64 intervention patients had <50% stenosis at angiography.

Absence of Functional Assessment

Lack of systematic translesional pressure gradient measurement led to treatment of hemodynamically insignificant lesions, with patients having essential rather than renovascular hypertension.

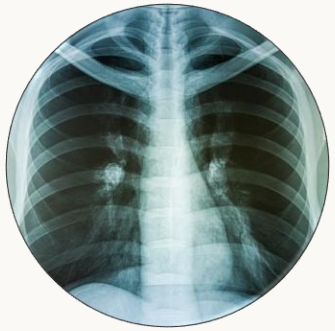
The fundamental problem lies in treating patients with moderate stenosis (50-70%) who may have essential hypertension with collateral circulation preserving renal function, rather than focusing on truly hemodynamically significant lesions causing genuine renovascular hypertension. Modern understanding suggests renal artery stenosis creates a spectrum from pure hemodynamic impairment (reversible) to irreversible parenchymal damage, with intervention timing being crucial.

High-Risk Phenotypes: Who Benefits from Revascularization?

Despite trial limitations, substantial evidence from observational studies, case reports, and single-center cohorts identifies specific patient phenotypes who derive meaningful benefit from endovascular intervention. These represent clinical scenarios where renovascular disease plays a primary pathophysiologic role rather than being a secondary manifestation of systemic atherosclerosis.

Resistant/Malignant Hypertension

Patients with uncontrolled BP despite ≥3 medications including diuretic represent RAAS hyperactivation from severe stenosis. ARVD is an underdiagnosed cause of resistant hypertension, associated with target organ damage and premature cardiovascular events.



Flash Pulmonary Edema

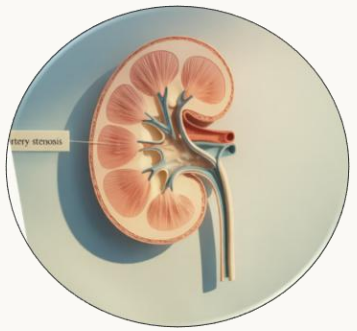
Recurrent acute pulmonary edema reflects RAAS hyperactivation, sodium retention, and cardiac remodeling. Ritchie et al. demonstrated revascularization effectiveness in reducing death risk in 37 patients with flash pulmonary edema and ARVD.

Rapid Renal Decline

Accelerated kidney function deterioration over 6-12 months predicts improved response to intervention. Early revascularization can restore cortical blood flow, reverse tissue hypoxia, and limit progression before irreversible fibrotic changes occur.

RAAS Inhibitor Intolerance

Acute GFR decline with ACE inhibitors/ARBs in bilateral stenosis or solitary kidney indicates hemodynamically significant disease requiring intervention, even with mild-moderate hypertension.



Kidney Transplant Recipients

Transplant RAS occurs in 1-23% of cases. Endovascular treatment is effective with similar long-term graft and patient survival rates.

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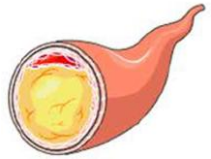
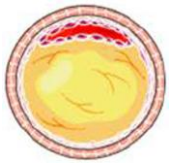
Patient Selection for Revascularization



Criteria for revascularization in ARVD



Strong Indications

- High-grade RAS (>70%) with resistant hypertension
- Acute pulmonary edema or decompensated HF
- Rapid eGFR decline (bilateral or solitary kidney)
- ACEI/ARB intolerance (≥30% eGFR reduction)
- Kidney transplant with RAS

Moderately Strong Indications

- Chronic HF with high-grade RAS
- Asymptomatic bilateral or solitary kidney disease

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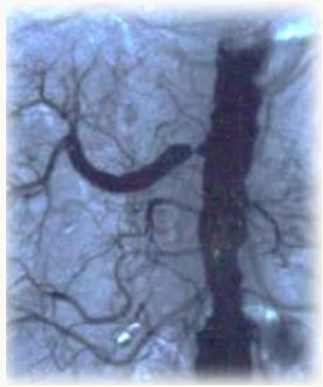
Kidney Viability Assessment

Parameter	Likely Benefit	Unlikely Benefit
RAS degree	>70%	<50%
Kidney length	>8 cm	<7 cm
Resistive index	<0.8	>0.8
Cortical thickness	Distinct cortex	No differentiation



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Post-Procedural Management

1 Immediate Assessment

Evaluate clinical response within first week. Reassess antihypertensive medications, kidney function, and cardiac symptoms.

2 Antithrombotic Therapy

Individualized approach typically involving clopidogrel plus low-dose aspirin for 1-3 months, then single antiplatelet therapy.

3 Restenosis Surveillance

Monitor for unexplained BP increase, kidney function decline, or pulmonary edema. Restenosis rates: 20% at 1 year, 32% at 5 years.

4 Long-term Follow-up

Continue medical therapy optimization and cardiovascular risk factor management along side procedural surveillance.

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Future Directions and Emerging Technologies

Advanced Diagnostics

Blood oxygen-level-dependent MRI (BOLD-MRI) enables functional assessment of renal oxygenation, differentiating salvageable from irreversibly damaged kidneys through the "renal penumbra" concept.

Novel Biomarkers

NGAL and FGF-23 provide early detection of acute kidney injury and functional impairment, potentially guiding intervention timing and predicting response.

Regenerative Therapies

Mesenchymal stem cell infusion and angiogenic growth factors show promise for improving renal perfusion and function beyond mechanical revascularization.

Table 2. Proposal for Improving Diagnosis and Therapeutic Management of ARVD

Current diagnostic tests	Novel diagnostic tests	Novel therapeutic strategies
(1) Wider and earlier screening for ARVD	Functional diagnostic tests (1) BOLD-MRI • Functional and noninvasive technique • Assess kidney's renal oxygenation[94] • Differentiate hypoxic but still functionable and salvable poststenotic kidney from hypoxic and functionally dead and unsalvable poststenotic kidney • Guide patients' eligibility for PTRA • Introduce the concept of renal penumbra[95]	Infusion of (1) Mesenchymal stem cells Improve renal and function perfusion[96,100,101] (2) Angiogenic and growth factors Increase angiogenesis and microvascular density in the poststenotic kidney[102–105]
(2) Wider use of CT- or MR-angiography in patients with: a. Unexplained heart failure b. Kidney function degradation and atherosclerosis c. Atherosclerotic lesions elsewhere		
(3) Wider use of catheter-based angiography as a. Diagnostic tool b. To estimate degree of stenosis, especially in high-risk patients c. To measure translesional pressure gradient	Novel biomarkers (1) NGAL: early biomarker of AKI[99] (2) FGF-23[98]	

AKI indicates acute kidney injury; ARVD, atherosclerotic renal vascular disease; BOLD-MRI, blood oxygen-level-dependent magnetic resonance; CT, computed tomography; FGF-23, fibroblast growth factor 23; MR, magnetic resonance; NGAL, neutrophil gelatinase-associated lipocalin; and PTRA, percutaneous transluminal renal angioplasty.

Pappaccogli et al. - Hypertension. 2023;80:1150–1161

Integrated Management Approach

1 **Initial Assessment**
Examine renal circulation with duplex ultrasound or CT angiography when reduced GFR or high vascular risk present

2 **Medical Optimization**
Progressive antihypertensive therapy including RAAS blockade to achieve goal blood pressures

3 **Monitor Response**
If goal BP achieved and renal function stable, continue medical management with surveillance

4 **Consider Intervention**
For high-risk syndromes with refractory hypertension or progressive dysfunction, proceed with revascularization

More than ever before, clinicians focused on managing complex hypertension will be called upon to balance potential benefits and risks in the management of renovascular hypertension.

CONCLUSION

The therapeutic paradigm must evolve beyond the false dichotomy of revascularization versus medical therapy toward integrated approaches addressing both hemodynamic restoration and parenchymal protection. Future research should establish optimal intervention timing through advanced diagnostics, test combination therapies targeting inflammatory pathways, and validate functional imaging for patient selection. The goal is identifying patients with "renal penumbra"—hypoxic but viable tissue that benefits from revascularization—while avoiding intervention in irreversibly damaged kidneys.

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Based on best available evidence, PTRA should be offered to carefully selected patients with high-risk ARVD phenotypes after thorough evaluation of stenosis severity and kidney viability.

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Lago Maggiore – Verbania Pallanza

Grazie per l'attenzione