



Hypertensive Nephropathy: Nosology, APOL1, and the Autoregulation Paradox

👤 Andrew Bland, MD, FACP, FAAP 📖 UICOMP · UDPA · Butler COM 📅 2026-07-03 ⌚ 18 min read

Learning Objectives

After reviewing this handout, students should be able to:

1. Explain why "hypertensive nephropathy" is both a leading assigned cause of ESRD and a diagnosis of exclusion.
2. Describe how the CMS-2728 attribution inflates the apparent incidence of hypertension-caused kidney failure.
3. Summarize the role of APOL1 in reclassifying kidney disease previously attributed to hypertension.
4. Resolve the autoregulation paradox: how systemic pressure reaches the glomerulus by two distinct routes.
5. Distinguish arteriolar lesions that reverse with blood-pressure control from those that are fixed.
6. Differentiate hyaline from hyperplastic ("onion-skin") arteriolosclerosis and recognize the TMA differential.
7. Apply the mechanism to blood-pressure targets and antihypertensive selection in CKD.

Section 1: What "Hypertensive Nephropathy" Means — and Why It Is Contested

Definition. Hypertensive nephropathy (nephrosclerosis) refers to chronic kidney injury attributed to long-standing high blood pressure. Classically it is diagnosed clinically when a

patient has: long-standing hypertension, reduced GFR, minimal proteinuria, a bland urinary sediment, and **no other identifiable cause** — that is, by *subtraction*.

The core problem is causal circularity. CKD of almost any cause raises blood pressure, so finding hypertension in a patient with a falling GFR tells you very little about which came first. The literature has openly called the term "a term in quest of a disease."

The honest position: some of it is real, much of it is a label of convenience. A genuine entity exists — but any diagnosis defined by what is *missing* will absorb whatever occult disease escapes a non-invasive workup.

Section 2: Epidemiology — The Attribution Problem

Assigned Incidence

In the USRDS registry, hypertension is the **second-most-common assigned primary cause of incident ESRD** (approximately 28–30%), behind diabetes (approximately 45–47%). The attribution comes from the CMS-2728 Medical Evidence form completed at dialysis initiation.

The racial signal is striking: ESRD incidence in Black Americans is roughly **3.8×** that of White Americans, and hypertension is the most commonly assigned cause in Black patients.

The Problem With That Number

The CMS-2728 attribution is a **checkbox, not a diagnosis**. It is filled in by the certifying clinician, typically without a biopsy, and defaults to "hypertension" whenever there is CKD + hypertension + no obvious alternative. This is exactly how a diagnosis of exclusion inflates its own apparent incidence.

Klag's MRFIT cohort (332,544 men, 16-year follow-up) did establish a graded, dose-response relationship between baseline BP and later ESRD — the strongest population-level evidence that BP is doing *something* causal. But population-level risk does not tell you that any one patient's kidney disease was *caused* by their blood pressure.

Clinical takeaway: read the USRDS "hypertension" line as an administrative category. The true incidence of biopsy-provable, genuinely hypertension-caused progressive kidney disease is unknown and certainly lower than the assigned figure.

Section 3: APOL1 and the Reassignment of "Hypertensive" Kidney Disease

This is the discovery that reshaped the field. Two coding variants (G1 and G2) in the **APOL1** gene on chromosome 22 — common on African chromosomes, essentially absent from European ones — protect against African sleeping sickness but substantially raise the risk of kidney disease.

- **Genovese 2010:** APOL1 high-risk variants are strongly associated with FSGS and with *hypertension-attributed* ESKD.
- **Parsa 2013 (AASK):** Among 693 Black participants with CKD "**attributed to hypertension,**" those with the high-risk genotype reached the renal endpoint far more often (58% vs 37%), independent of baseline proteinuria.

In other words, a large share of "hypertensive nephrosclerosis" in Black patients is a genetically driven, FSGS-spectrum disease in which hypertension is the *accompaniment, not the cause*. This is why "APOL1-associated nephropathy" has largely displaced "hypertensive nephrosclerosis" as the operative diagnosis in high-risk-genotype patients.

Practice point: In a Black patient labeled "hypertensive nephrosclerosis" who has FSGS-range proteinuria, unexplained rapid decline, or a family history of kidney disease, APOL1 genotyping or biopsy will frequently reclassify the disease. The label should not end the workup.

Section 4: How Hypertension Injures the Kidney — The Autoregulation Paradox

The paradox: **if the afferent arteriole autoregulates, how does systemic pressure ever reach the glomerulus?** Renal autoregulation holds blood flow and single-nephron GFR roughly constant across a mean arterial pressure of approximately 80–160 mmHg using two *preglomerular* mechanisms:

- **Myogenic response:** the afferent arteriole constricts when wall tension rises. Fast, and the dominant protector against pressure.
- **Tubuloglomerular feedback:** the macula densa senses distal NaCl and adjusts afferent tone via adenosine. Slower fine-tuning.

Because both act upstream of the glomerulus, they attenuate transmission of systemic pressure to the glomerular capillary. In animals with intact autoregulation, even substantial hypertension produces little glomerulosclerosis.

Damage Requires That Protection Fail — by One of Two Routes

The Bidani–Griffin framework resolves the paradox cleanly. Chronic injury requires one of two failure modes:

- **Route A — exceeding the ceiling.** When BP rises above the upper limit of autoregulation, the afferent can no longer hold; pressure breaks through to the glomerulus, producing barotrauma, fibrinoid necrosis, and **malignant nephrosclerosis**. This is threshold-dependent — minimal injury below the critical pressure, severe above it.
- **Route B — impaired autoregulation (the common, chronic route).** In CKD, diabetes, reduced nephron mass, and APOL1 disease, the preglomerular autoregulatory capacity is *itself* impaired. The afferent is relatively vasodilated or unresponsive, so it no longer buffers pressure. Now even *moderate* BP is transmitted to the glomerulus; glomerular hypertension and hyperfiltration follow, and glomerulosclerosis rises roughly **linearly** with BP, at a much lower threshold than in the intact kidney.

The single most important clinical corollary: in patients whose autoregulation is already impaired (established CKD or diabetes), BP must be lowered *into the normotensive range* to protect the glomerulus — there is no preglomerular buffer left to do it.

This is also why **ACE inhibitors and ARBs are renoprotective beyond their systemic BP effect:** they dilate the efferent arteriole, lowering *intraglomerular* pressure specifically. In

the impaired-autoregulation state, glomerular pressure is the true target, and systemic BP is only a proxy for it.

Section 5: Arteriolar Lesions — What Reverses, What Doesn't

A common teaching shortcut — "arteriolar hypertrophy causes the damage and remodels away with BP control" — is only half right. Reversibility tracks the **histology**, not the blood pressure.

STRUCTURAL CHANGE	NATURE	REVERSES WITH BP CONTROL?
Eutrophic / muscular remodeling (same media, smaller lumen)	Adaptive, protective	Yes — substantially, and best with RAAS blockade; <i>not</i> with a beta-blocker at equal BP
Hyaline arteriosclerosis (glassy protein insudation)	Degenerative	No — fixed; causes downstream ischemia and loss of the myogenic reflex
Global glomerulosclerosis / interstitial fibrosis	Scar	No — fixed

Why the muscular thickening is protective: increased preglomerular resistance is exactly what shields the glomerulus by raising the upstream pressure drop. The damage begins when it tips into **hyalinosis**, which is doubly bad — it narrows the lumen (ischemia) *and* converts the vessel into a rigid tube that loses its protective myogenic responsiveness, re-opening Route B.

Human proof of principle: Schiffrin's resistance-artery biopsy studies showed an ACE inhibitor progressively normalized the media-to-lumen ratio of small arteries over 1-2 years, whereas a beta-blocker produced no change despite equal BP reduction — evidence

that adaptive remodeling has an angiotensin-II-driven, pressure-independent component preferentially reversed by RAAS blockade.

Even severe injury can repair: in malignant nephrosclerosis, bringing BP below the critical threshold allows genuine repair of acute microvascular and glomerular injury — the basis for the clinical observation that some patients recover meaningful renal function months after malignant hypertension is controlled.

Section 6: Malignant Nephrosclerosis and Onion-Skinning

Onion-skinning is **hyperplastic arteriolosclerosis**: concentric, laminated layers of proliferating myointimal cells encircling the arteriole, producing severe, often near-obliterative luminal narrowing — the "onion-bulb" appearance. It is the vascular signature of **malignant / accelerated hypertension**, typically accompanied acutely by fibrinoid necrosis of the arteriolar wall and glomerular tuft.

FEATURE	HYALINE ARTERIOLOSCLEROSIS	HYPERPLASTIC ("ONION-SKIN")
Setting	Chronic "benign" HTN, diabetes, aging	Malignant / accelerated HTN
Histology	Homogeneous, glassy, acellular wall thickening (protein insudation)	Concentric cellular myointimal lamination
Companion lesion	Ischemic glomerular obsolescence	Fibrinoid necrosis, thrombosis, glomerular infarct
Tempo	Years	Days to weeks

Critical caveat — the TMA differential. The concentric myointimal lesion is *not specific* to malignant hypertension. It is histologically shared with thrombotic microangiopathies — scleroderma renal crisis, HUS/TTP, antiphospholipid-syndrome nephropathy, radiation nephropathy, and chronic transplant arteriopathy. When onion-skinning is seen,

"malignant hypertension" is a diagnosis of the whole clinical picture (severe BP, fibrinoid

necrosis, retinopathy, LVH) — not of the arteriole in isolation. Work up a TMA when the context does not fit primary hypertension.

Section 7: Clinical Approach and Blood-Pressure Management

- **Target the glomerulus in established CKD/diabetes.** With autoregulation already impaired, lower BP into the normotensive range — every mmHg is transmitted downstream.
 - **Prefer RAAS blockade.** ACEi/ARBs lower intraglomerular pressure specifically and preferentially reverse adaptive vascular remodeling — a benefit beyond the BP number.
 - **Don't anchor on the label.** Significant proteinuria, hematuria, rapid decline, or family history argue against pure hypertensive nephrosclerosis — consider APOL1, biopsy, or a glomerular cause.
 - **Treat malignant hypertension aggressively but with staged reduction.** Injury is threshold-dependent and partly reparable once BP is controlled below the critical level.
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Practice Questions

Question 1: A 54-year-old Black man with long-standing hypertension has an eGFR of 38, urine protein-to-creatinine ratio of 2.4 g/g, and bland sediment. His nephrologist is asked to certify "hypertension" as the cause of CKD. What is the best next step?

- A. Certify hypertensive nephrosclerosis; no further workup needed
- B. Recognize that FSGS-range proteinuria argues against pure nephrosclerosis; consider APOL1 genotyping and/or biopsy
- C. Attribute the proteinuria to hypertension and intensify BP control only
- D. Diagnose diabetic kidney disease empirically

Answer: B — Minimal proteinuria is part of the classic nephrosclerosis picture; 2.4 g/g is not. In a Black patient, APOL1-associated FSGS-spectrum disease is common and frequently reclassifies "hypertension-attributed" CKD. The label should not end the workup.

Specifies "hypertension-attributed" CKD. The label should not end the workup. <https://www.kidney.org>

Question 2: Why must blood pressure be lowered further (into the normotensive range) to protect the kidney in a patient with established CKD than in a patient with normal kidneys?

- A. CKD kidneys have increased renal blood flow that must be reduced
- B. Preglomerular autoregulation is impaired, so systemic pressure is transmitted to the glomerulus even at moderate BP
- C. Antihypertensives are less potent in CKD
- D. CKD raises the upper limit of autoregulation

Answer: B — In CKD the afferent arteriole is relatively vasodilated/unresponsive and no longer buffers pressure (Route B). Glomerulosclerosis then rises roughly linearly with BP, so there is no preglomerular reserve to tolerate higher systemic pressures.

Question 3: A biopsy shows concentric "onion-skin" myointimal proliferation of the interlobular arteries with fibrinoid necrosis. Blood pressure is 210/130 with papilledema. Which statement is most accurate?

- A. Onion-skinning is pathognomonic for malignant hypertension; no other workup is needed
- B. The lesion is shared with thrombotic microangiopathies; malignant hypertension is diagnosed from the whole clinical picture, and a TMA differential is warranted if the context does not fit
- C. This is benign hyaline arteriolosclerosis
- D. Onion-skinning is a fixed lesion that never repairs with BP control

Answer: B — Hyperplastic (onion-skin) arteriolosclerosis is the vascular signature of malignant hypertension, but the same histology appears in scleroderma renal crisis, HUS/TTP, APS nephropathy, and radiation nephropathy. The clinical picture here fits malignant HTN, yet a TMA workup is appropriate when it does not. The vascular lesion can partially repair once BP is controlled below threshold.

Key References

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