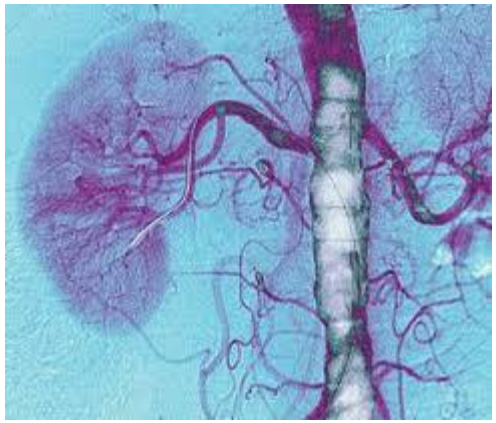
# Νεφραγγειακή υπέρταση – Ισχαιμική νόσος των νεφρών ως εκδήλωση της γενικευμένης αρτηριοσκλήρωσης



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Για τη σημερινή ομιλία δεν έχω να αναφέρω
κάποια σύγκρουση συμφερόντων

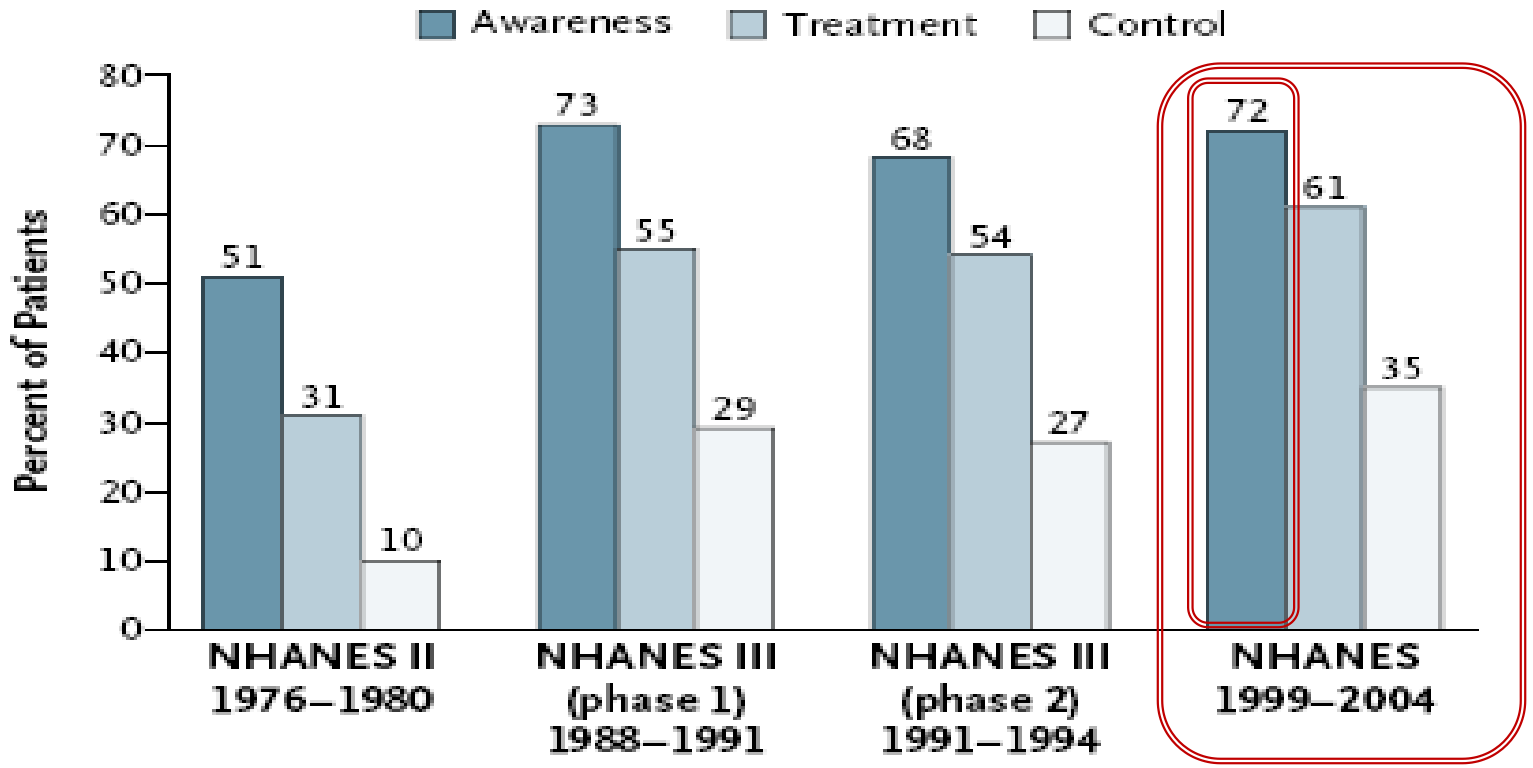



**Figure 2. Rates of Awareness, Treatment, and Control of High Blood Pressure in the United States (1976–2004).**

High blood pressure is defined as a reading of 140/90 mm Hg or more for persons between the ages of 18 and 74 years. Despite major improvements in blood-pressure therapies in recent years, some 28% of Americans with hypertension do not know they have the condition, 39% are receiving no therapy, and 65% have insufficient blood-pressure control. Data are from Chobanian et al.[12] and Cutler et al.[41] NHANES denotes National Health and Nutrition Examination Survey.

# Ten Commandments of the 2018 ESC/ESH HTN Guidelines on Hypertension in Adults

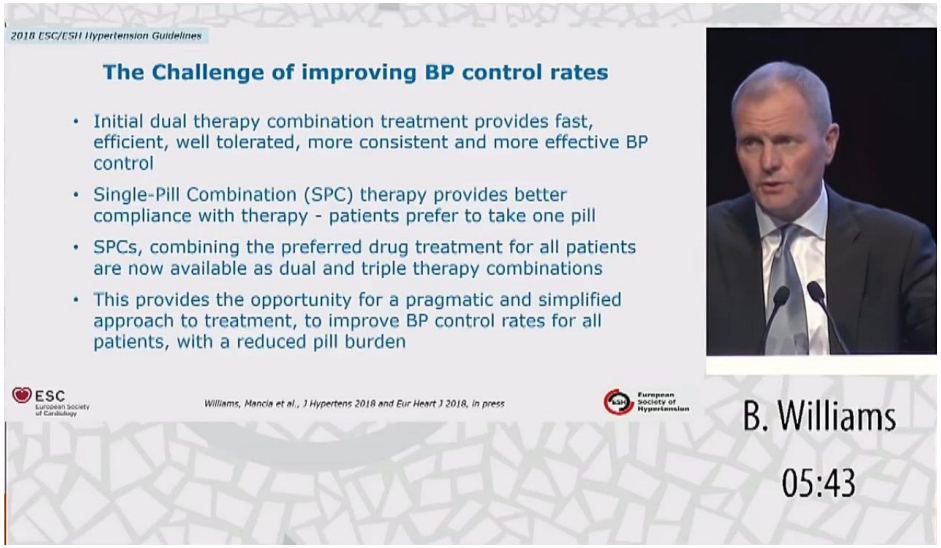
European Heart Journal (2018) **39**, 3007–3019
doi:10.1093/eurheartj/ehy439

**(7) Start treatment in most patients with two drugs, not one**: Monotherapy is usually inadequate therapy for most people with hypertension, especially now that the BP treatment targets for many patients, are lower than in previous guidelines. **Initial therapy with a combination of two drugs** should now be considered usual care for hypertension. The **only exception would** be in a limited number of patients with a lower baseline BP close to their recommended target, who might achieve that target with a single drug, or in some frailer old or very old patients, in whom more gentle reduction of BP may be desirable.

# Ten Commandments of the 2018 ESC/ESH HTN Guidelines on Hypertension in Adults

European Heart Journal (2018) **39**, 3007–3019
doi:10.1093/eurheartj/ehy439

**(8) A single pill strategy to treat hypertension**: **Poor adherence to BP-lowering medication is directly related to the number of pills and is a major factor contributing to poor BP control rates**. Single pill combination therapy is now the preferred strategy for initial two-drug combination treatment of hypertension and for three drug combination therapy when required. This will control the BP in most patients with a single pill and **should improve BP control rates**.



2018 ESC/ESH Hypertension Guidelines

## SBP targets in some hypertensive subgroups

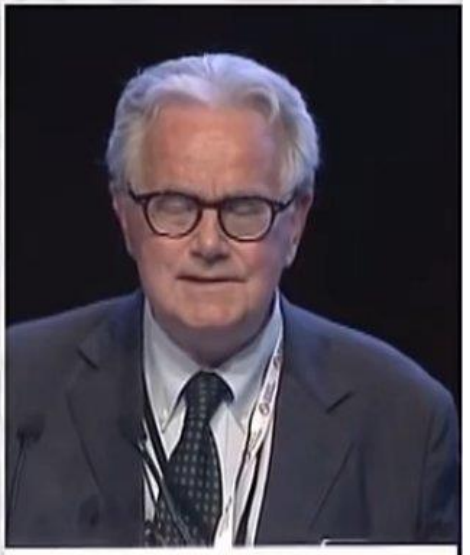
| | | | Class/level |
|---|---|---|---|
| Age < 65 years | 120 to <130 mmHg | (recommended) | IA |
| Age ≥ 65 years | 130 to <140 mmHg | (recommended) | IA* |
| Diabetes | 130 mmHg or lower** | (recommended) | IA |
| CAD | 130 mmHg or lower | (recommended) | IA |
| CKD | 130 to <140 mmHg | (recommended) | IA |
| Post-stroke/TIA | 120 to <130 mmHg | (to be considered) | IIaB |

* Close monitoring of adverse events / ** if tolerated

ESC European Society of Cardiology

Williams, Mancia et al., J Hypertens 2018 and Eur Heart J 2018, in press

European Society of Hypertension

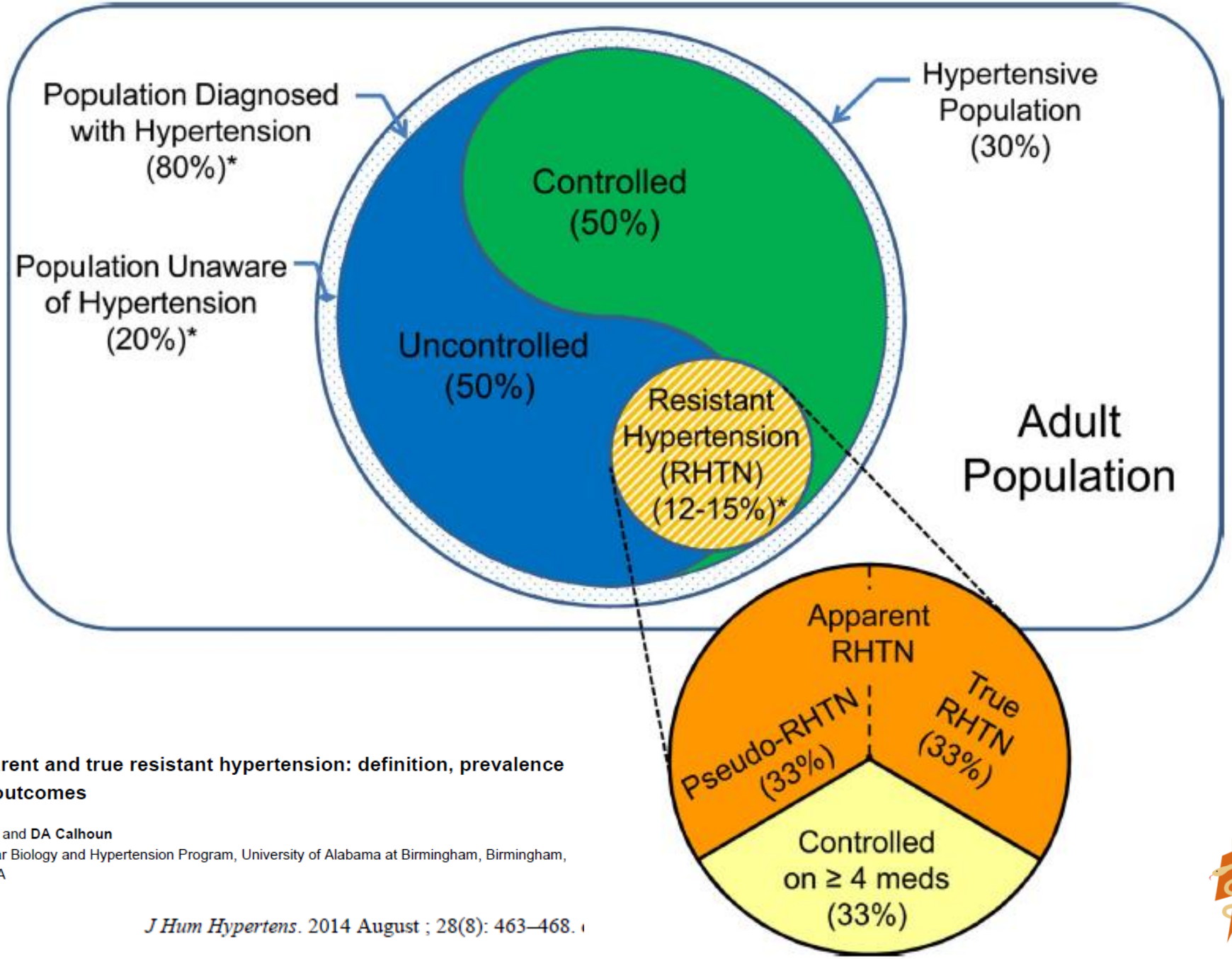


G. Mancia

01:40

**1st group 120-130 mmHg: age<65, post stroke, DM, CAD**

**2ndgroup 130-140 mmHg: age>65, CKD**




**Apparent and true resistant hypertension: definition, prevalence and outcomes**

**E Judd** and **DA Calhoun**
Vascular Biology and Hypertension Program, University of Alabama at Birmingham, Birmingham, AL, USA

*J Hum Hypertens*. 2014 August ; 28(8): 463–468.

# 2018 ESC/ESH Guidelines for the management of arterial hypertension

| Causes of secondary resistant hypertension |
|---|
| **More common causes** |
| • Primary hyperaldosteronism |
| • Atherosclerotic renovascular disease |
| • Sleep apnoea |
| • CKD |

| Secondary hypertension |
|---|
| Skin inspection: cafe-au-lait patches of neurofibromatosis (phaeochromocytoma) |
| Kidney palpation for signs of renal enlargement in polycystic kidney disease |
| Auscultation of heart and renal arteries for murmurs or bruits indicative of aortic coarctation, or renovascular hypertension |
| Comparison of radial with femoral pulse: to detect radio-femoral delay in aortic coarctation |
| Signs of Cushing's disease or acromegaly |
| Signs of thyroid disease |

**Table 27** Incidence and typical causes of secondary hypertension according to age

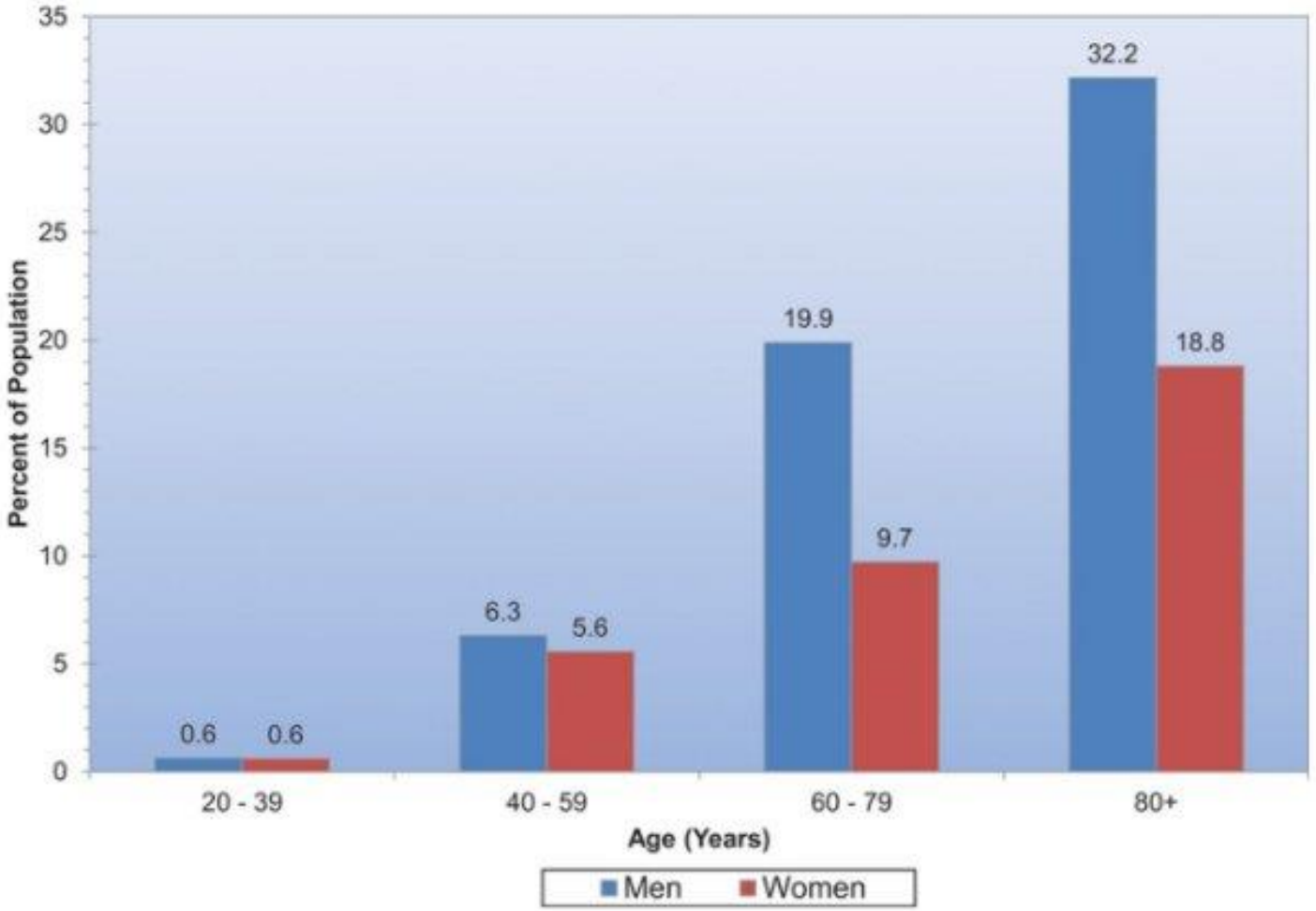
| Age group | Per cent with underlying cause | Typical causes |
|---|---|---|
| Middle-aged adults (41–65 years) | 5–15 | • Primary aldosteronism<br>• Obstructive sleep apnoea<br>• Cushing's syndrome<br>• Phaeochromocytoma<br>• Renal parenchymal disease<br>• Atherosclerotic renovascular disease |
| Older adults (>65 years) | 5–10 | • Atherosclerotic renovascular disease<br>• Renal parenchymal disease<br>• Thyroid disease |

**Table 26** Common causes of secondary hypertension

| Cause | Prevalence in hypertensive patients | Suggestive symptoms and signs | Screening Investigations |
|---|---|---|---|
| **Renovascular disease** | | | |
| Atherosclerotic renovascular disease | 1–10% | Older; widespread atherosclerosis (especially PAD); diabetes; smoking; recurrent flash pulmonary oedema; abdominal bruit | Duplex renal artery Doppler or CT angiography or MR angiography |
| Fibromuscular dysplasia | | Younger; more common in women; abdominal bruit | |


• For the development of clinical atherosclerotic disease, nothing is more dangerous than living a long life!!!.
• The longer you survive other threats, the more likely you are to suffer the consequences of a life's exposure to atherosclerosis risk factors.
• The upsurge in lifespan during the last century, achieved by improvements in socio-economic conditions and health care, has been the central cause of the rise in cardiovascular disease across the world.
EuroIntervention
Official Journal of EuroPCR and the European Association of Percutaneous Cardiovascular Interventions (EAPCI)
Natural history of atherosclerosis: the first shall be the worst
Published on 8 April 2016

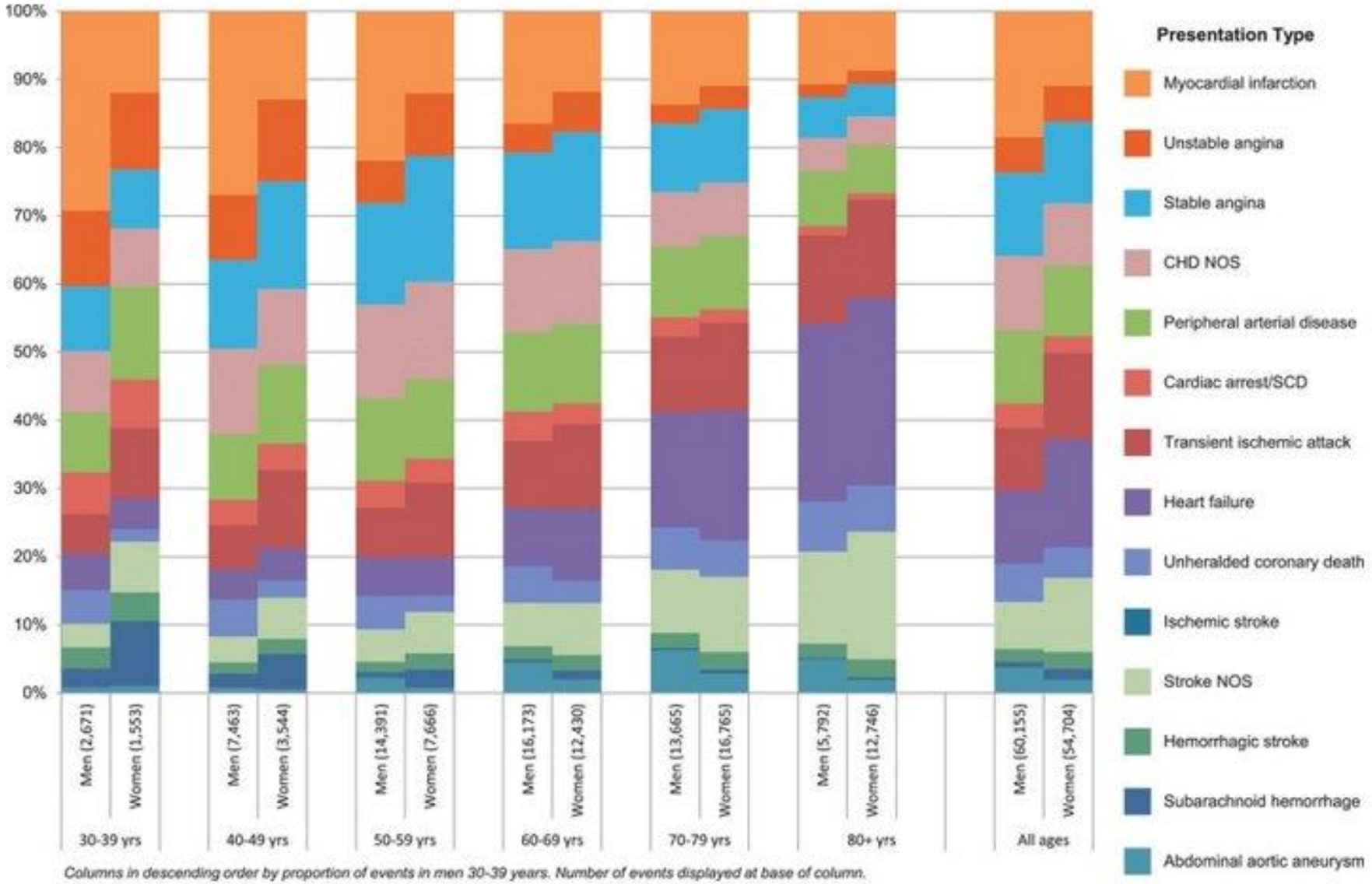
## Prevalence of coronary heart disease by age and sex




National Health and Nutrition Examination Survey: 2009–2012.

American Heart Association.

Mozaffarian D et al. Circulation. 2015;131:e29-e322




*Columns in descending order by proportion of events in men 30-39 years. Number of events displayed at base of column.*

# Σύντομο Ατομικό Ιστορικό (1)

- Άνδρας, 72 ετών, πρώην καπνιστής (διακοπή προ 10 ετών)
- Πολυαγγειακός ασθενής: Χειρουργηθείσα ΣΝ (2008), ΧΝΑ, Αρτηριακή Υπέρταση, Δυσλιπιδαιμία και ΔΕ Νεφρεκτομή λόγω μη κακοήθους μορφώματος (2009).
- ΟΠΟ: Νοσοκομείο Άγιος Ανδρέας (01/15) Cr=1,6mg/dl, EPI= 42 ml/min/1.73
- Ωνάσειο Καρδιοχειρουργικό Κέντρο (03/15), στεφανιογραφικός έλεγχος, ο οποίος ανέδειξε το ενδεχόμενο επαναγγείωσης της δεξιάς στεφανιαίας αρτηρίας. Cr=3.6mg/dl, eGFR EPI =16 ml/min/1.73m2
- Προσφάτου ενάρξεως διαταραχή στη ρύθμιση της αρτηριακής πίεσης
- ΟΠΟ σε έδαφος υπερτασικής αιχμής (200/100 mmHg): Αττικό Νοσοκομείο (4/15) Cr=8.3mg/dl, eGFR EPI= 6 ml/min/1.73

- Ο ασθενής υποβλήθηκε σε συνεδρίες αιμοκάθαρσης με αποτέλεσμα τη βελτίωση της κλινικής του εικόνας και της νεφρικής του λειτουργίας.
- Δυσκολία στη ρύθμιση της αρτηριακής πίεσης παρά την επίταση της αντιυπερτασικής του αγωγής και τη χορήγηση > τριών αντιυπερτασικών στις μέγιστες δόσεις εκ των οποίων το ένα διουρητικό.
- Συνεστήθη κατόπιν καρδιολογικής εκτίμησης να διενεργηθεί Triplex της μονήρους νεφρικής αρτηρίας.

# Σύντομο Ατομικό Ιστορικό (2)- Φαρμακευτική αγωγή

1. Tb Salospir 100 mg 1x1
2. Tb Plavix 75 mg 1x1
3. Tb Ranexa 375 mg 1x2
4. Tb Lipitor 40 mg 1x1
5. Tb Lopresor 100 mg 1/2x2
6. Tb Adalat CR 30 mg 1x2
7. Tb Lasix 500 mg 1/2 -1/4
8. TTS Nitrong 10 mg 1x1
9. Tb Catapresan 0,150 mg 2x2

# Ηχωκαρδιογραφική μελέτη

- Ao root = 3,7 cm
- LA = 55 mm
- **IVSd = 13 mm**
- **PWd = 13 mm**
- LVEDd = 48 mm
- LVEDs = 33 mm

- E bas = 110 cm/sec
- A bas = 76 cm/sec
- **EF = 55%**

- **E/E΄= >15**

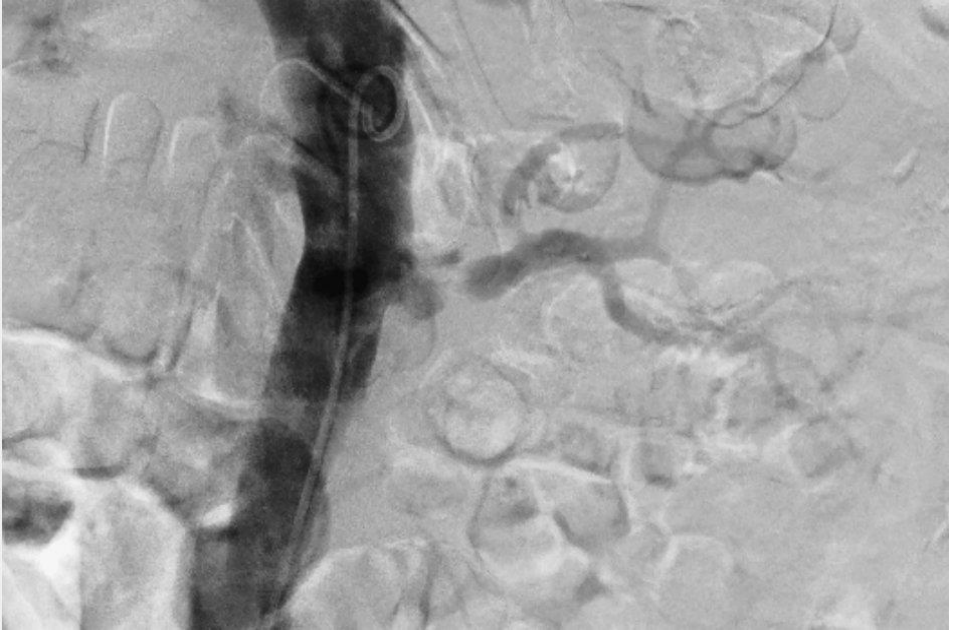
**<u>ΣΥΜΠΕΡΑΣΜΑ</u>** Υπερτροφική αριστερή κοιλία με φυσιολογικές διαστάσεις και καλή συστολική απόδοση.

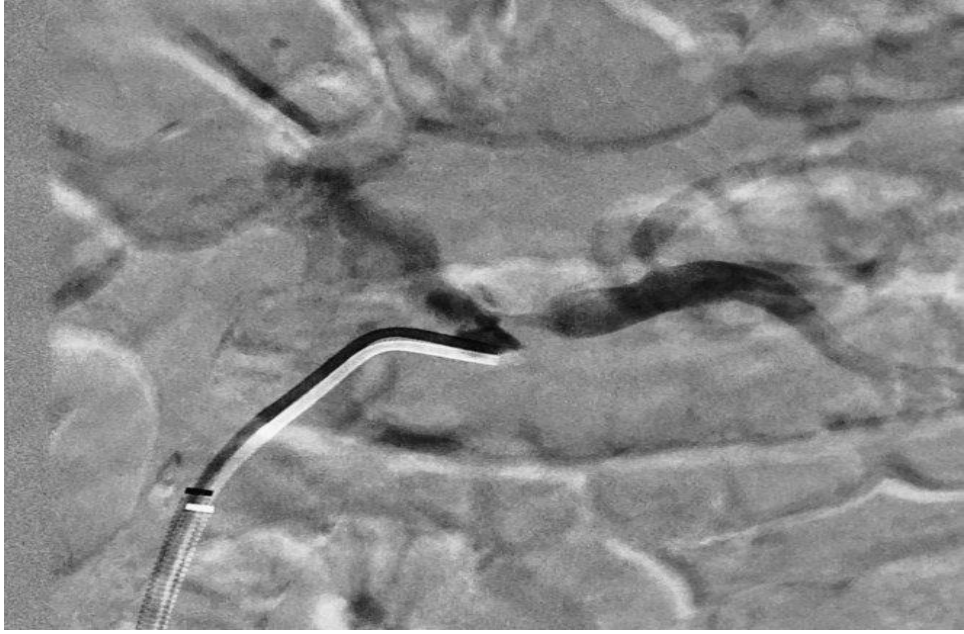
# Απεικόνιση νεφρού και σύστοιχης νεφρικής αρτηρίας

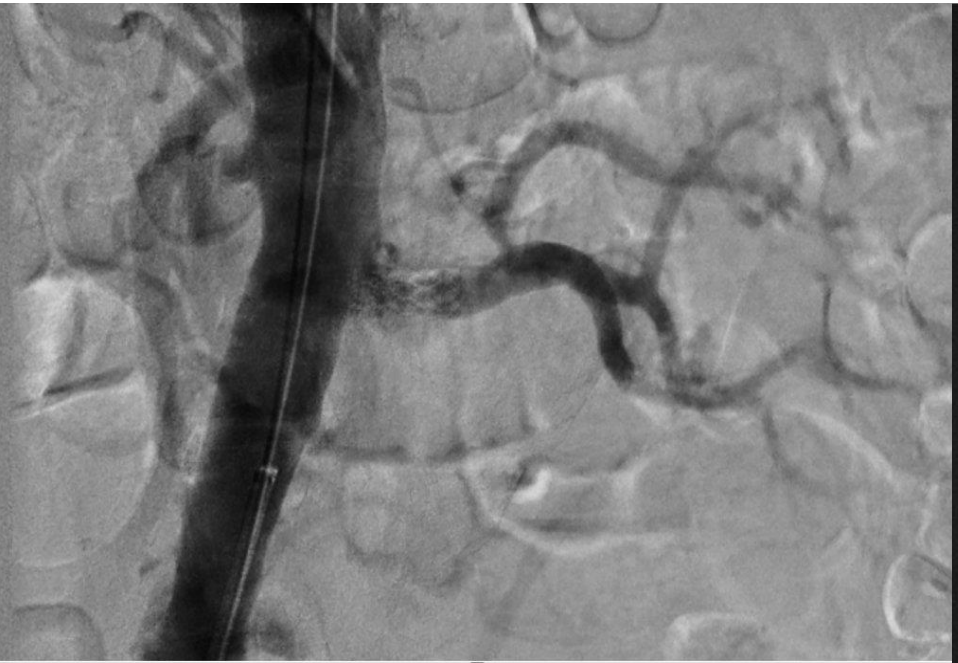
- Αριστερός νεφρός αυξημένου μεγέθους και ηχογένειας, με φυσιολογικό πάχος φλοιού ενώ δεν ελέγχεται ασαφοποίηση της φλοιομυελώδους διαφοράς.

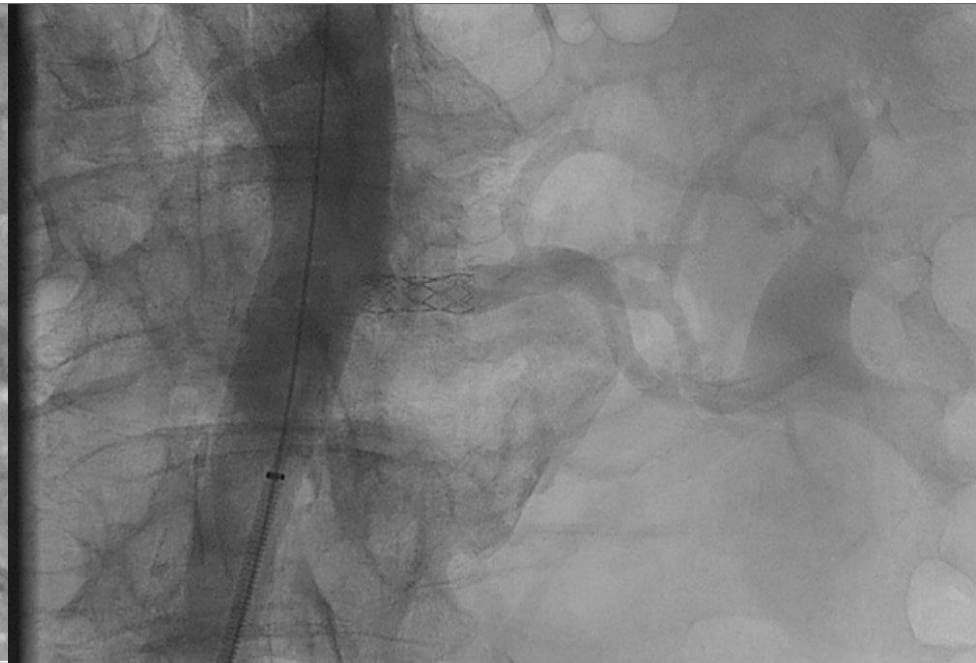
- Από τη φασματική ανάλυση Doppler ελέγχονται σημεία αιμοδυναμικά σημαντικής στένωσης **>95%** στην έκφυση **της αριστερής νεφρικής αρτηρίας** (αυξημένες ταχύτητες ροής **Vmax ≈ 600cm/sec**). Δίδεται δε η εντύπωση ότι αυτή είναι λεπτοφυής και με ελίκωση.

- Δεν κατέστη δυνατή η ανάδειξη και ο έλεγχος των ενδονεφρικών κλάδων λόγω αγγειακής ερήμωσης.









# Επανεκτίμηση ασθενούς μετά τη νοσηλεία του

- Ο ασθενής αναφέρει ικανοποιητική ρύθμιση της αρτηριακής του πίεσης σε επίπεδα ΑΠ=120-130/80mmHg
- Λαμβάνει:

| | |
|---|---|
| Tb Olartan plus 20/12,5 mg | S: 1x1 (08.00) |
| Tb Lopresor 100 mg | S: 1/2x2 (08.00-20.00) |
| Tb Lasix 40 mg | S: 1x2 (08.00-20.00) |

Λοιπή αγωγή ως ελάμβανε.

- Cr=**3mg/dl,** eGFR-EPI= 20 ml/min

CKJ REVIEW

# Approach to atherosclerotic renovascular disease: 2016

Reem Daloul and Aubrey R. Morrison

Renal Division, Department of Internal Medicine, Washington University School of Medicine, 660 South Euclid, Box 8126, St Louis, MO 63110, USA

*Clinical Kidney Journal*, 2016, vol. 9, no. 5, 713–721

- Atherosclerotic renal artery stenosis accounts for >90% of cases of RAS.

- Most commonly seen in older patients (>65 years) and is usually associated with atheromatous disease in other vascular beds.
- The incidence and prevalence are hard to estimate given the asymptomatic nature of the majority of cases.
- **A prevalence of 6.8% in elderly patients**.

- RAS is **progressive** and can **lead to resistant hypertension** and **gradual loss of functional renal mass** resulting in chronic kidney disease.
- It has been **linked to increased rates of cardiovascular events** and **mortality** in patients with atherosclerotic cardiovascular disease.
- This triggered an increasing interest in the treatment of ARAS by surgical or intravascular intervention.

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# Pathophysiology (1)

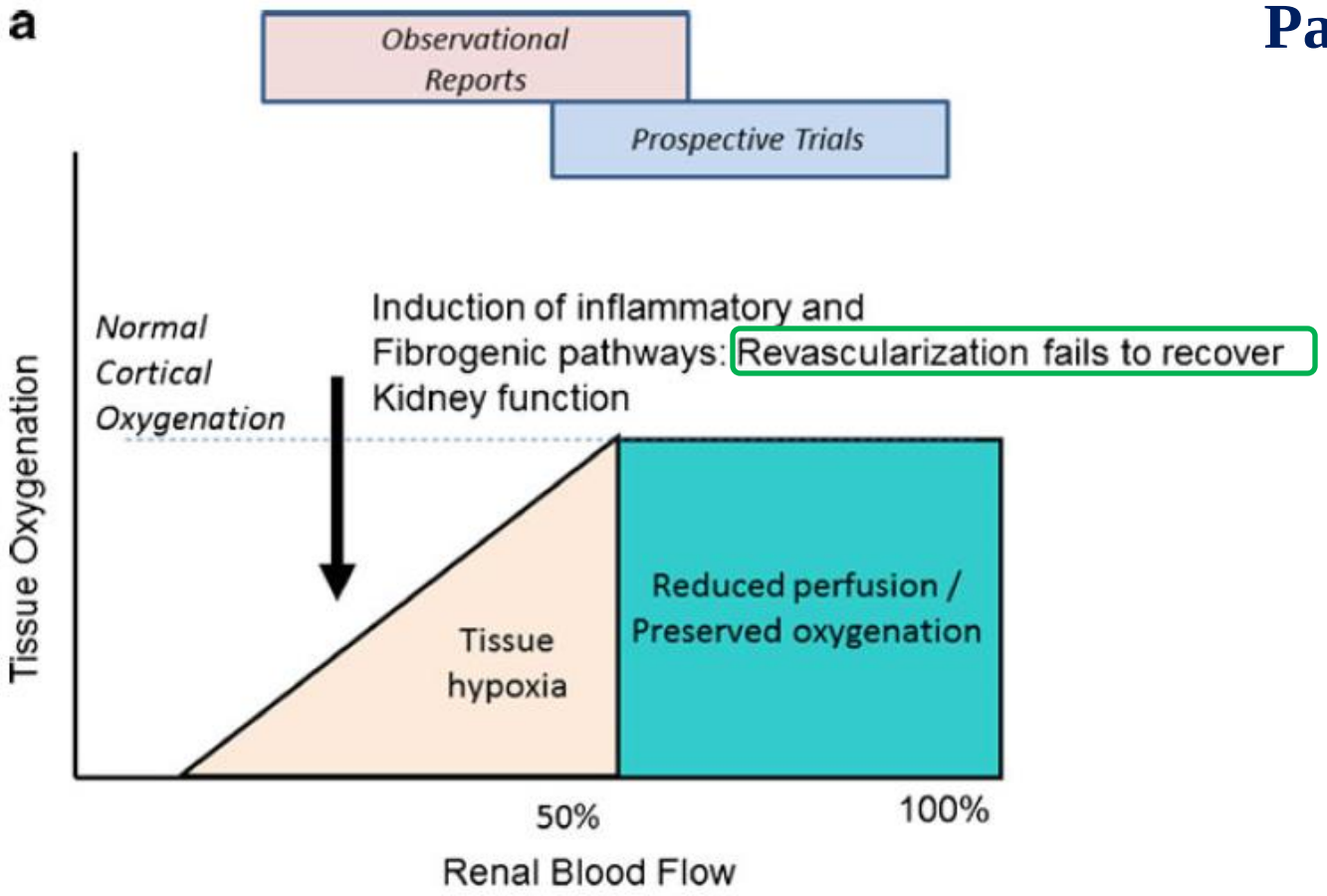
- Renal blood flow largely exceeds tissue metabolic needs. The kidneys receive ~20% of the cardiac output but utilize <10% of the renal perfusion for tissue metabolism.

- A 30–40% reduction in single kidney perfusion in the context of moderate ARAS is associated with preservation of: 1. tissue oxygenation and 2. cortex to deep medulla oxygen gradient due to the high renal perfusion relative to tissue needs.

- More severe stenosis (>70%) did overwhelm the kidneys' adaptive capacity and resulted in overt cortical hypoxia and inflammation.

Renal tissue injury distal to the atherosclerotic renovascular lesion is likely a multifactorial process that includes activation of multiple injurious pathways by the atherosclerotic environment.

# Pathophysiology (2)




Clinical Kidney Journal, 2016, vol. 9, no. 5, 713–721

Textor et al. Curr Cardiol Rep (2013) 15:409

An inflammatory state in the post-stenotic kidney results in parenchymal tissue damage by means of: endothelial injury, increased generation of reactive oxygen species and oxidative stress. Markers of such an inflammatory state can be detected **early** in the course of ARAS before any hemodynamic compromise takes place.

# Εργαστηριακός και Απεικονιστικός έλεγχος

| | |
|---|---|
| Εκτίμηση άξονα RAAS | •PRA+Αλδοστερόνη<br>•Δοκιμασία Καπτοπρίλης<br>•Μέτρηση δραστικότητας ρενίνης νεφρικών φλεβών |
| Λειτουργικές δοκιμασίες νεφρικής λειτουργίας | •Κρεατινίνη ορού<br>•Γενική ούρων<br>•Υπολογισμός CrCl και GFR |
| Εκτίμηση αιμάτωσης νεφρών | •Ραδιενεργό νεφρόγραμμα 99m Tc MAG3 πριν και μετά τη χορήγηση καπτοπρίλης |
| Απεικόνιση νεφρικών αρτηριών | •Dupplex Υπερηχογράφημα<br>•MRA<br>•CTA<br>•Κλασσική Αγγειογραφία νεφρικών αρτηριών |

**Lao D, Mayo Clin Proc. 2011**

# Clinical significance of ARAS (1)

- The **significance of ARAS** has traditionally been **based on estimation of anatomical stenosis.**

- While a luminal cross section reduction of **50–60% has been considered significant in clinical trials,** at least **70–80% is necessary to induce a reduction in blood flow and renal perfusion**.

- **However, it is important to recognize** that the mere presence of an anatomical lesion does not necessarily translate into hemodynamic significance, nor does a certain degree of stenosis exert the same effect on different patients.

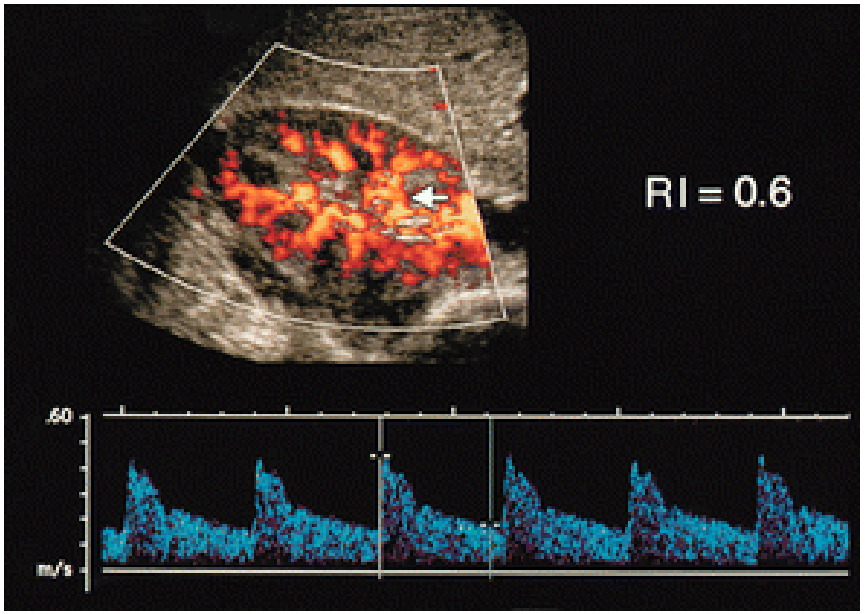
# Clinical significance of ARAS (2)

- Imaging methods likely overestimate the actual severity of luminal stenosis. CT/MRA used by most clinical trials to accurately evaluate the hemodynamic significance of a renal artery stenotic lesion, does not provide any insight **regarding renal flow, translesional pressure gradient or tissue oxygenation.**

- Activation of the RAS and Renin release are believed to be **markers of hemodynamic significance** in renovascular hypertension. Renin release results when the pressure distal to the stenosis dropped by ~10%, correlating with a distal/aortic pressure ratio <0.9 and a luminal occlusion of 70–80%.

- Parameters obtained noninvasively by Doppler ultrasonography have been proposed to better predict the hemodynamic effect of a lesion**. Peak systolic velocity (PSV)** has been reported to have the highest sensitivity (85%) and specificity (92%) among other parameters in evaluating renal artery stenosis.

# Renal artery Doppler




- **RI** =(peak systolic velocity - end diastolic velocity )/ peak systolic velocity
  Normal values ≈ **0.60-0.70**.

- **PSV> 180-200 cm/sec** indicates severe stenosis.

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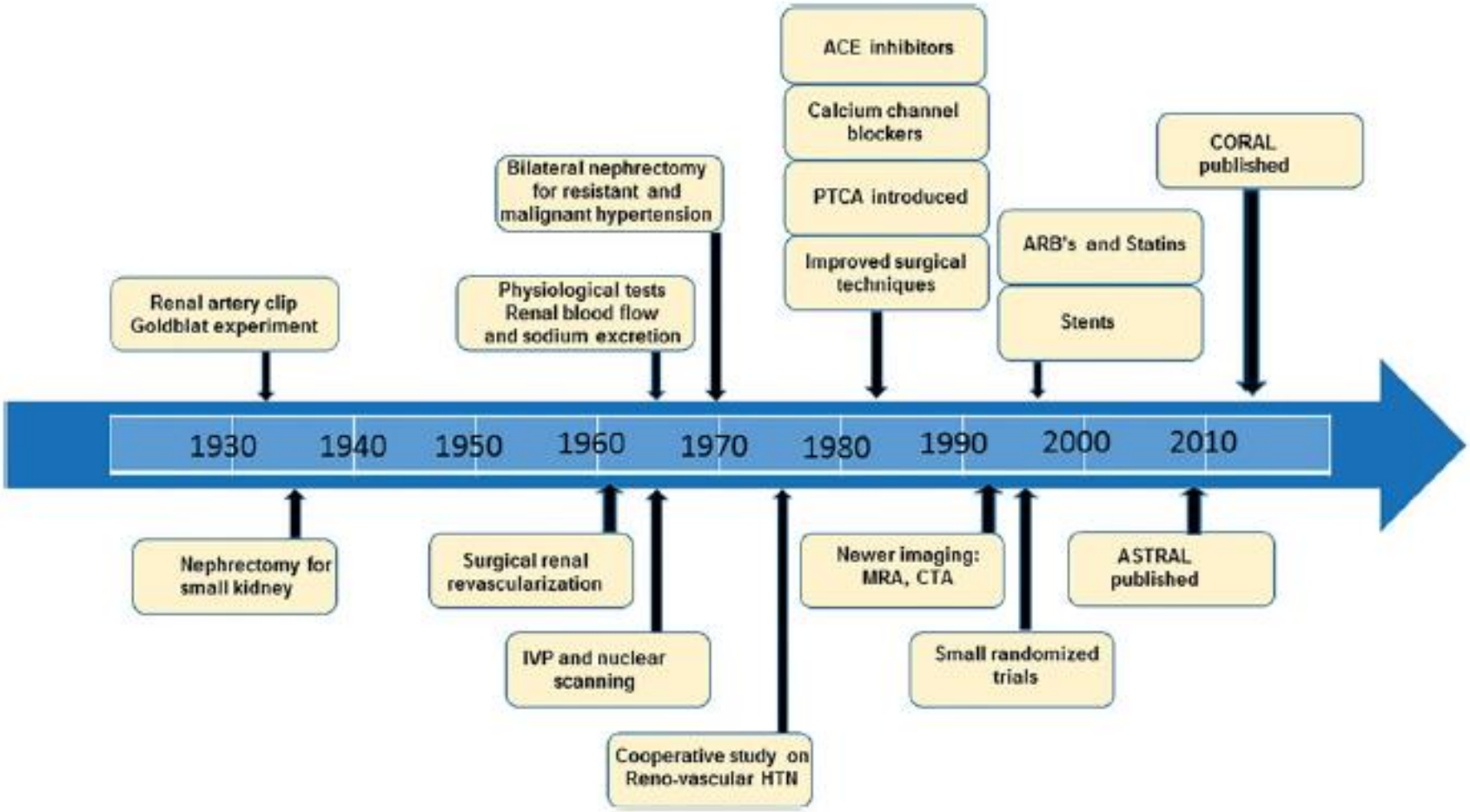


**Fig. 1.** Timeline of the clinical approaches to atherosclerotic renovascular disease.

**Table 1.** Summary of major clinical randomized trials

| Study, number of patients | Inclusion criteria | Exclusion criteria | Baseline renal function, angioplasty versus control | Method of ARAS diagnosis | HTN requirement | Primary outcome |
|---|---|---|---|---|---|---|
| EMMA [30], 49 | – DBP >95 mmHg on three occasions and/or on antihypertensive medications<br>– Renal artery stenosis ≥75% without thrombosis or ≥60% with thrombosis<br>– Stenosis affecting the main renal artery that had not been previously dilated<br>– Functional contralateral kidney without stenosis | – >75 years old<br>– CrCl <50 mL/min<br>– Malignant HTN<br>– Hx of stroke, pulmonary edema or MI within 6 months | CrCl: 73 versus 73 mL/min | – Angiography, no hemodynamic studies | – DBP ≥95 mmHg on at least three occasions and/or receiving antihypertensive medications. | – Ambulatory BP at termination of the study |
| DRASTIC [31], 106 | – DBP ≥95 mmHg on three occasions despite being on two antihypertensive medications<br>– Rise in sCr of ≥0.2 mg/dL with ACEI therapy<br>– Unilateral or bilateral ARAS ≥50% | – Age <18 or >75 years<br>– HTN caused by other condition<br>– Single functioning kidney<br>– sCr >1.7 mg/dL<br>– Affected kidney <8 cm<br>– Total renal artery occlusion<br>– AAA requiring surgery<br>– Unstable CAD or HF<br>– Cancer<br>– Pregnancy | CrCl: 67 ± 23 versus 60 ± 24 mL/min | – Angioplasty, no hemodynamics studies | DBP ≥95 mmHg on three occasions despite being on two antihypertensive medications | SBP and DBP at 3 and 12 months after randomization |
| STAR [33], 140 | CrCl <1.33 mL/s on two measurements 1 month apart<br>Unilateral or bilateral stenosis ≥50%<br>Controlled BP <140/90 mmHg for 1 month prior to randomization | Renal size <8 cm<br>Renal artery diameter <4 mm<br>CrCl <0.25 mL/s<br>Diabetes mellitus with proteinuria >3 g/day<br>Malignant HTN | CrCl: 45 versus 46 mL/min | CTA, MRA, angiography; no hemodynamic testing | Stable BP control with BP <140/90 mmHg for 1 month prior to randomization | Worsening renal function defined as ≥20% decrease in CrCl compared to baseline |
| ASTRAL [14], 806 | Substantial anatomical atherosclerotic stenosis in at least one renal artery<br>Patients' doctor is uncertain that patient would definitely benefit from revascularization. | Requirement of surgical revascularization<br>Have high likelihood of requiring revascularization within 6 months<br>Nonatheromatous cardiovascular disease<br>Previous revascularization of RAS | eGFR: 40.3 versus 39.8 mL/min/1.73m$^2$ | CTA, MRA, angiography, renal US; no hemodynamic studies reported | No clear definition of uncontrolled or refractory HTN | Change in renal function measured by the mean slope of the reciprocal of the sCr level over time |
| CORAL [13], 947 | Severe stenosis defined as<br>– >80% stenosis or 60–80% with peak systolic gradient of ≥20 mmHg by angiography<br>– Systolic velocity >300 cm/s by duplex sonography<br>– MRA, CTASBP ≥155 mmHg on two or more antihypertensive medications or CKD with eGFR <60 mL/min/1.73 m$^2$ | Fibromuscular dysplasia<br>CKD from to other causes<br>sCr >354 μmol/L<br>Kidney length <7 cm<br>Lesion not treatable with a single stent<br>Hospitalization for HF in the last month | eGFR: 58 ± 23.4 versus 57.4 ± 21.7 mL/min/1.73m$^2$ | CTA, MRA, angiography, renal US; duplex study not done in all patients | SBP ≥155 mmHg on two or more antihypertension medications | Major cardiovascular or renal events |

# Treating ARAS by clinical studies

- The resulting study cohorts consisted predominantly of **patients with normal to moderate renal dysfunction and hypertension that is best described as not optimally controlled.**

- Clinical trials **failed to show superiority of revascularization over optimal medical therapy** in terms of: 1. BP control, 2. renal function preservation, 3. major cardiovascular/renal events.

- **Patients** who were considered to be '**high risk**' but who exhibited the clinical features traditionally believed to be associated with renovascular disease (**advanced kidney disease, malignant or accelerated HTN, history of unstable heart failure or recent acute coronary syndrome**) have been **excluded**.

- Subsequently, **management and treatment of ARAS have shifted sharply toward optimal medical management.**

# Conclusions (1)

➢Both ASTRAL and CORAL trials **have answered part of the question of when to intervene in the case of ARAS**. They have shown that in patients with stable kidney function and adequate BP control, the mere presence of renal artery stenosis does not require intervention. Clinical evidence for the benefit or lack of benefit in patients with the high-risk clinical presentations is lacking. A large, well-designed, randomized clinical trial targeted towards a such population is still needed.

Table 2.

| Pretest probability | Clinical characteristics | Recommended approach | Recommended imaging |
|---|---|---|---|
| Low risk | Stable renal function and good control of BP | Conservative management | No screening |
| Moderate risk | (a) Hard to control BP<br>(b) Acute or subacute worsening in renal function | (a) Assess medication and diet compliance. Confirm poor control of hypertension (24-h ambulatory BP measurement)<br>(b) Evaluate for other possible etiologies for renal dysfunction including glomerulopathy, nephrotoxins and others | Renal duplex ultrasonography |
| High risk | (a) Resistant, accelerated or malignant hypertension<br>(b) Unexplained acute or subacute deterioration of renal function<br>(c) Recurrent flash pulmonary edema in the context of patient compliance | (a) Obtain imaging studies<br>(b) Weight benefits versus risks of interventions<br>(c) Consider intervention in patient with both clinical symptoms and imaging findings suggestive of significant lesion | Renal duplex ultrasonography<br>(a) If negative and strong clinical suspicion, get CTA or MRA<br>(b) If positive, proceed to angiography and stenting if significant lesion presents |

# Conclusions (2)
# Clinical scenarios to raise suspicion of significant ARAS and lead to intervention

The **benefit** of invasive intervention should be **weighed against the risks** in **each patient individually**. Patients that will probably have benefit from intervention are those with:

- **Malignant** hypertension on the background of previously well controlled BP.
- Recent increase in antihypertensive requirement in patients with previously stable BP control (**accelerated** hypertension).
- Rapid **deterioration of renal function** (>30% reduction in eGFR over ≤3 months) in patients with previously stable or slowly progressive renal disease.
- **Recurrent flash pulmonary edema** (Pickering syndrome) in the setting of bilateral ARAS