Arterial Hypertension & Renal disease

Pathophysiology, Clinical management, Therapy prescription and Complications

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Core Curriculum Course Nephrology
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Outline

- Introduction
  → Epidemiology
  → Complications
- Pathophysiology
- Clinical management
- Therapy prescription
- Special populations
Introduction

- Hypertension (HT) is a **major** risk factor for cardiovascular (CV) and renal disease morbidity & mortality.

- Conversely, chronic kidney disease (CKD) is the **most common form of secondary HT** and is an independent risk factor for CV morbidity and mortality.

⇒ Renal disease is a consequence as well as a cause of hypertension
Complications of (untreated) hypertension

Schematic model of the natural history of (untreated) hypertension, showing the progression from prehypertension to hypertension, to target organ damage, to clinical events, and eventually to death.
BP and Stroke-related mortality and Ischemic heart disease-related mortality

Stroke death

IHD death

Meta-analysis of individual data for one million adults in 61 prospective studies.

The probability of a major CV endpoint increased with greater SBP but, at any given value of SBP, this probability increased with lower DBP, suggesting that the wider pulse pressure in the elderly drives the risk of major complications.
Blood Pressure Predicts Risk of Developing End-Stage Renal Disease in Men and Women

Cumulative incidence of ESRD in 46,881 men and 51,878 women*, 20 to 98 years of age, according to the 6 BP categories.

*screened in 1983 in Okinawa, Japan; FU till 2000

Relative risk (95% CI) of development of ESRD for 6 BP categories in men and women.

Relative risks, with optimal BP as the reference category, are adjusted for age and BMI.

Tozawa et al. *Hypertension* 2003;41:1341-1345
Hypertension (HT) is a major risk factor for cardiovascular (CV) and renal disease morbidity & mortality.

Conversely, chronic kidney disease (CKD) is the most common form of secondary HT and is an independent risk factor for CV morbidity and mortality.

⇒ Renal disease is a consequence as well as a cause of hypertension
Population prevalence (%) of CKD stages 1 to 4, by hypertension status, NHANES 1999–2006 (n=17 794).

Crews D et al. Hypertension 2010;55:1102-1109
Prevalence of hypertension in CKD

The prevalence of HT is higher among patients with CKD than in individuals without CKD, progressively increasing with the severity of CKD.

Based on a national survey of a representative sample of non-institutionalized adults in the USA, it is estimated that hypertension occurs in …

The incidence and prevalence of hypertension also vary with the cause (GN and vasculitis > interstitial disease), the type of onset (acute and chronic KD), and the duration of KD;

Hypertension is a frequent finding, particularly in patients with renal artery stenosis (93%), diabetic nephropathy (87%), and polycystic kidney disease (74%)

HR of all-cause and CV mortality according to eGFR/ACR in general population

Lower eGFR and higher albuminuria are associated with mortality and ESRD. A collaborative meta-analysis of KD population cohorts.

**Green**: low risk (if no other markers of KD, no CKD);
**Yellow**: moderately increased risk;
**Orange**: high risk;
**Red**: very high risk

Outline

- Introduction
  - Epidemiology
  - Complications

- Pathophysiology

- Clinical management

- Therapy prescription

- Special populations
Pathophysiology of hypertension

- The genesis of essential hypertension is a complex interplay of various pathophysiologic factors.

- These pathophysiologic factors interact also with genetic (account for 40 – 50% of BP variance), demographic, and environmental influences (account for 10 - 30% of BP variance).

⇒ Explaining the heterogeneity of the hypertensive population.

- Increased vascular stiffness, endothelial dysfunction, inflammation and increased oxidative stress play a role in increasing BP and CV risk.

Pathophysiology of hypertension

- Analysis of BP patterns in families suggest that genetic factors account for 40 – 50% of BP variance. Shared environment accounts for 10 - 30%.

- Single gene mutations play only a minor role, accounting for <1% of cases of hypertension. These genes often lie within pathways managing sodium homeostasis (*Liddle S*: abnormal ENaC; *Gordon S*: overactivity of NCC)

- More recently multiple common genetic variants with modest effects on BP (<1 mm Hg SBP) have been discovered in the population. These variants explain <3% of the BP variance.
Pathophysiologic factors that play a role in the development and maintenance of hypertension
<table>
<thead>
<tr>
<th>Pathophysiologic factor</th>
<th>Increased or decreased activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurohumoral mechanisms</strong></td>
<td></td>
</tr>
<tr>
<td>• SNS activity</td>
<td>↑</td>
</tr>
<tr>
<td>• RAAS activity</td>
<td>↑</td>
</tr>
<tr>
<td>• Production of sodium-retaining hormones</td>
<td>↑</td>
</tr>
<tr>
<td>• Production and expression of vasoconstrictors</td>
<td>↑</td>
</tr>
<tr>
<td>• Production and expression of vasodilators</td>
<td>↓</td>
</tr>
<tr>
<td>• Kallikrein-kinin system activity</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Dietary factors</strong></td>
<td></td>
</tr>
<tr>
<td>• Sodium intake</td>
<td>↑</td>
</tr>
<tr>
<td>• Potassium and calcium intake</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Vascular factors</strong></td>
<td></td>
</tr>
<tr>
<td>• Peripheral resistance</td>
<td>↑</td>
</tr>
<tr>
<td>• Vascular stiffness</td>
<td>↑</td>
</tr>
<tr>
<td>• Endothelial dysfunction</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Cellular mechanisms</strong></td>
<td></td>
</tr>
<tr>
<td>• Cellular ion transport</td>
<td>↑ or ↓</td>
</tr>
<tr>
<td>• Adrenergic receptor activity</td>
<td>↑ or ↓</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
</tr>
<tr>
<td>• Inflammation</td>
<td>↑</td>
</tr>
<tr>
<td>• Oxidative stress</td>
<td>↑</td>
</tr>
<tr>
<td>• Psychosocial stress</td>
<td>↑</td>
</tr>
</tbody>
</table>
Pathophysiology of Hypertension

The Sympathetic Nervous System

- Increased SNS activity is a major determinant of BP elevation.

- The mechanisms of increased SNS activity in hypertension are complex, and they involve alterations in baroreflex and chemoreflex pathways at both peripheral and central levels.
Pathophysiology of Hypertension
Increased sympathetic activity in hypertension

Sympathetic nerve activity in normotensive vs hypertensive persons, showing the resting level of activity of sympathetic postganglionic neurons that innervate muscle resistance arterioles (B). The intensity and frequency of muscle sympathetic nerve activity (MSNA) bursts are higher in hypertensive compared with normotensive persons (B and C). A, The level at which MSNA was measured. (Guyenet PG. The sympathetic control of BP. Nat Rev Neurosci. 2006;7:335-346.)
Increased SNS activity is a major determinant of BP elevation.

The mechanisms of increased SNS activity in hypertension are complex, and they involve alterations in baroreflex and chemoreflex pathways at both peripheral and central levels.
The Sympathetic Nervous System: the afferent signals from peripheral sympathetic and somatic receptors

Rostral ventrolateral nucleus of medulla oblongata

Somatic and sympathetic afferent nerves
Increased SNS activity contributes to both the development and the maintenance of hypertension through stimulation of the heart, peripheral vasculature, and kidneys, causing increased CO, increased vascular resistance and fluid retention.

Chronic sympathetic stimulation induces vascular remodeling and left ventricular hypertrophy by direct and indirect actions of norepinephrine on its own receptors, as well as on release of various trophic factors, including TGF-β, insulin-like growth factor 1, and fibroblast growth factors.
The Sympathetic Nervous System: The sympathetic efferent signals to the periphery

Long-term consequences of increased central sympathetic outflow.
Pathophysiology of Hypertension
The Renin-Angiotensin-Aldosterone System
Pathophysiology of Hypertension
The Renin-Angiotensin-Aldosterone System

Renin-angiotensin-aldosterone system

- Decrease in renal perfusion (juxtaglomerular apparatus)
- **↓** tubular [sodium]
- **↑** SNA

Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.

Legend:
- Blue: Secretion from an organ
- Green: Stimulatory signal
- Red: Inhibitory signal
- Black: Reaction
- Orange: Active transport
- Yellow: Passive transport
Pathophysiology of Hypertension

Dietary factors: Salt sensitivity

- Excess dietary salt produces untoward effects on the CV system and the kidneys

- Salt sensitivity is mediated by activation of central and peripheral SNS

- Excess dietary salt leads to increased BP and TOD via several mechanisms.

- Elderly patients, CKD, DM, African Americans, Low birth weight

High dietary sodium can potentially exert its influence through various mechanisms to cause an increase in BP through alterations in CO and TPR. The change (Δ) in BP varies considerably, even within a given population (as depicted in the distribution). AT1, angiotensin II receptor type 1.
High dietary sodium can cause target organ damage and may have direct effects on the brain, heart, kidneys, and vasculature.

These effects can be independent of changes in BP.
Mechanisms of salt-induced BP elevation and target organ damage. Increased dietary salt activates shear forces and stimulates transforming growth factor-β (TGF-β) and nitric oxide (NO) production. In the setting of increased tonicity and in the presence of aldosterone, NO production is suppressed, leading to unopposed TGF-β activity. Ultimately, these changes result in increased BP and TOD. (*Redrawn from Sanders PW. Vascular consequences of dietary salt intake. Am J Physiol Renal Physiol. 2009;297:F237-243.*)
Pathophysiology of Hypertension
Vascular factors: Arterial Stiffness

Arteriosclerosis results from collagen deposition, SMC hypertrophy, thinning, fragmenting and fracture of elastin fibers in the media.
In addition, endothelial dysfunction contributes functionally to increased arterial rigidity.

Neurohumoral, mechanical, and genetic factors regulate extracellular matrix protein expression and result in increased arterial stiffness, peripheral resistance, and BP. MMPs, matrix metalloproteinases. (Redrawn from Briones AM, Arribas SM, Salaices M. Role of extracellular matrix in vascular remodeling of hypertension. Curr Opin Nephrol Hypertens. 2010;19:187-194.)
Pathophysiology of Hypertension in Kidney Disease

- The kidneys play a vital role in long-term BP regulation[1]
- Virtually all forms of experimental and human HT exhibit impaired sodium excretion by the kidneys at normal BP[2]
- Sodium loading increases BP only when renal sodium excretion is constrained (ablation 2/3 renal mass; administration of angiotensin or aldosterone) \(\Rightarrow\) Initial BP rise is mediated by expansion of extracellular fluid volume and \(\uparrow\) CO (\(\uparrow\)SBP). Over time, ECF volume and CO normalize and high BP results from elevated peripheral resistance (\(\uparrow\)DBP)[1]

Pathophysiology of Hypertension in Kidney Disease (2)

Key components of hypertension in KD include:

- **Inappropriately elevated sympathetic nervous system activity**
  - → efferent arteriolar vasoconstriction ($\alpha$-receptors) → more sodium retention
  - → Stimulate renin release ($\beta$-receptors) ⇒ more AII
    - → efferent arteriolar vc and sodium retention
    - stimulates PTC to recover filtered sodium (Na+/H+ antiporter)
    - stimulates aldosteron production and release ⇒ stimulates distal sodium reabsorption

- **Activation of the RAAS**
  - → Ischemia (particularly in acute vascular disease)
  - → SNS activity
  - → Fall in distal nephron [sodium] is an additional stimulus for renin release

- **Impaired salt and water excretion by the kidneys** → increase in extracellular fluid ⇒ exacerbation of high BP in KD
Pathophysiology of Hypertension in Kidney Disease (3)

- Increased arterial stiffness

Other factors that may explain increased vascular resistance in CKD include:

- ↑production of endothelin and endogenous digitalis-like substance [1,2]
- Reduced generation of vasodilators (NO, Kinins) [3,4]
- Imbalance between VD and VC prostaglandins [5]
- Oxidative stress [6]
- Secondary hyperparathyroidism (↑intracellular calcium ⇒ VC) [7]
- Erythropoietin [8]

Subtle renal defects may underlie the pathogenesis of essential hypertension

- This is supported by
  - Transplant with kidneys from normotensive donors in patients with ESRD due to hypertensive nephrosclerosis results in resolution of their HT[1]
  - NT individuals with family history of HT respond to salt loading with less natriuresis and higher BP than those with no family history [2]
  - HT patients have fewer nephrons than NT counterparts [3,4]

- The exact nature of renal defect(s) for inappropriate sodium excretion remains unclear

Proposed pathogenesis of salt-sensitive hypertension in the setting of subtle renal parenchymal injury.

GFR, glomerular filtration rate.

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Definitions and classification of office blood pressure levels (mmHg)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Normal</td>
<td>120–129</td>
<td>80–84</td>
</tr>
<tr>
<td>High normal</td>
<td>130–139</td>
<td>85–89</td>
</tr>
<tr>
<td>Grade 1 hypertension</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Grade 2 hypertension</td>
<td>160–179</td>
<td>100–109</td>
</tr>
<tr>
<td>Grade 3 hypertension</td>
<td>≥180</td>
<td>≥110</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥140</td>
<td>&lt;90</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The (BP) category is defined by the highest level of BP, whether systolic or diastolic. Isolated systolic HT should be graded 1, 2, or 3 according to systolic BP values in the ranges indicated.

Definitions of hypertension by office and out-of-office blood pressure levels

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office BP</td>
<td>≥140</td>
<td>and/or ≥90</td>
</tr>
<tr>
<td>Ambulatory BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime (or awake)</td>
<td>≥135</td>
<td>and/or ≥85</td>
</tr>
<tr>
<td>Nighttime (or asleep)</td>
<td>≥120</td>
<td>and/or ≥70</td>
</tr>
<tr>
<td>24-h</td>
<td>≥130</td>
<td>and/or ≥80</td>
</tr>
<tr>
<td>Home BP</td>
<td>≥135</td>
<td>and/or ≥85</td>
</tr>
</tbody>
</table>

White coat & Masked hypertension
What do we need to know before treating “high BP”

- True high BP
- Onset (slow vs rapid)
- Has the patient family history of HT
- Does the patient take BP increasing medication
- Is there a secondary cause
- Has the patient risk factors for HT
- Has the patient other CV risk factors
- Is there TOD or symptomatic CV or renal disease
- Has the patient already been taken antihypertensive drugs
What do we need to know before treating “high BP”

- Standardized BP measurement (ev. home and/or 24h ABPM)
- Carefull physical examination
- Blood exam: Hct, sCreatinine, electrolytes, uric acid glucose, lipids
- Urine analysis: microscopic examination, proteinuria
- ECG (echocardiogram)
- Renal US (+ doppler)
- Additional tests, based on history, physical examination, and findings from routine lab tests
Clinical indications for out-of-office BP measurement for diagnostic purposes

<table>
<thead>
<tr>
<th>TRUE HYPERTENSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical indications for HBPM or ABPM</td>
</tr>
<tr>
<td>• Suspicion of white-coat hypertension</td>
</tr>
<tr>
<td>- Grade I hypertension in the office</td>
</tr>
<tr>
<td>- High office BP in individuals without asymptomatic organ damage and at low total CV risk</td>
</tr>
<tr>
<td>• Suspicion of masked hypertension</td>
</tr>
<tr>
<td>- High normal BP in the office</td>
</tr>
<tr>
<td>- Normal office BP in individuals with asymptomatic organ damage or at high total CV risk</td>
</tr>
<tr>
<td>• Identification of white-coat effect in hypertensive patients</td>
</tr>
<tr>
<td>• Considerable variability of office BP over the same or different visits</td>
</tr>
<tr>
<td>• Autonomic, postural, post-prandial, siesta- and drug-induced hypotension</td>
</tr>
<tr>
<td>• Elevated office BP or suspected pre-eclampsia in pregnant women</td>
</tr>
<tr>
<td>• Identification of true and false resistant hypertension</td>
</tr>
</tbody>
</table>

Specific indications for ABPM

| • Marked discordance between office BP and home BP |
| • Assessment of dipping status |
| • Suspicion of nocturnal hypertension or absence of dipping, such as in patients with sleep apnoea, CKD, or diabetes |
| • Assessment of BP variability |

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; HBPM, home blood pressure monitoring.

Clinic and Ambulatory Blood Pressure Recordings and Outcomes in CKD patients

Incidence of (A) ESRD (defined as dialysis therapy initiation) or death, (B) fatal and nonfatal CV event, (C) ESRD, and (D) all-cause mortality in the 4 groups of patients.

Group 1, patients with both clinic and ambulatory BPs **at goal**;
Group 2, patients with **clinic BP not at goal** and ambulatory BP at goal;
Group 3, patients with clinic BP at goal and **ambulatory BP not at goal**;
Group 4, patients with both clinic and ambulatory BPs **not at goal**.

489 hypertensive patients + CKD (stages 1-5)

This long-term study of a prospective cohort of patients with non–dialysis-dependent CKD suggests that having clinic BP not at goal and ambulatory BP at goal is a low-risk condition, whereas having clinic BP at goal and ambulatory BP not at goal is associated with high cardiorenal risk not dissimilar from that observed in patients with both targets not at goal.

These findings support the use of ambulatory BP monitoring in all hypertensive patients with CKD to better stratify their cardiorenal risk and likely to optimize treatment.
Masked hypertension is common in patients with CKD and associated with lower eGFR, proteinuria, and cardiovascular target organ damage.

Masked hypertension is common in patients with CKD and associated with lower eGFR, proteinuria, and cardiovascular target organ damage.

Masked hypertension is associated with cardiovascular target organ damage in patients with CKD.

<table>
<thead>
<tr>
<th>BP Category</th>
<th>Left Ventricular Mass Index (g/m².7)</th>
<th>Pulse Wave Velocity (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted (95% CI)</td>
<td>Adjusted (95% CI)</td>
</tr>
<tr>
<td>Controlled clinic and</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>ambulatory BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White-coat hypertension</td>
<td>4.24 (0.6 to 7.9)</td>
<td>−0.21 (−3.5 to 3.1)</td>
</tr>
<tr>
<td>Masked hypertension</td>
<td>4.34 (2.7 to 6.0)</td>
<td>2.52 (0.9 to 4.1)</td>
</tr>
<tr>
<td>Sustained hypertension</td>
<td>8.37 (6.5 to 10.2)</td>
<td>2.99 (1.1 to 4.9)</td>
</tr>
</tbody>
</table>

95% CI, 95% confidence interval.

Adjusted for age, sex, race, clinical center, tobacco use, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, diuretics, beta blockers, calcium channel blockers, total number of antihypertensives, coronary artery disease, congestive heart failure, diabetes, body mass index, eGFR, urine protein, LDL cholesterol, serum phosphorus, serum calcium, serum uric acid, C-reactive protein, and 24-hour urine sodium.

In patients with CKD, ambulatory BP characterizes the relationship between BP and target organ damage better than BP measured in the clinic alone.
Worse CV outcome in patients with masked HTN

The meta-analysis indicates that the incidence of CV events is not significantly different between WCHT and true normotension, whereas the outcome is worse in patients with masked or sustained HTN.

The size of the squares corresponds to the weight of the study in the meta-analysis. Open and closed squares represent studies that included, resp., 0% and 100% treated hypertensive patients; the half closed squares represent studies with variable numbers of treated patients. The asterisk denotes that the out-of-office BP was obtained by self-measurement at home.
Worse CV outcome in patients with sustained HTN

The size of the squares corresponds to the weight of the study in the meta-analysis. Open and closed squares represent studies that included, resp., 0% and 100% treated hypertensive patients; the half closed squares represent studies with variable numbers of treated patients. The asterisk denotes that the out-of-office BP was obtained by self-measurement at home.
The relationship between BP and CV morbidity and mortality is modified by the concomitance of other CV risk factors.

Metabolic risk factors are more common when BP is high than when it is low\[^{1,2,3}\].

Survival probability for CVD mortality in younger (left) and older (right) men according to the presence of HTN and associated RFs.

Nt = normotensive subjects; Ht 0, HT subjects without RFs; Ht 1-2, HT subjects with 1 or 2 RFs; ... 

The combination of CKD and BP categories on multivariable hazard ratios for CVD (Stroke & MI)

CKD may increase the association of BP and CVD

Kokubo Y et al. Stroke 2009;40:2674-2679
Assessment of total cardiovascular risk

<table>
<thead>
<tr>
<th>Other risk factors, asymptomatic organ damage or disease</th>
<th>Blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High normal SBP 130–139 or DBP 85–89</td>
</tr>
<tr>
<td>No other RF</td>
<td>Low risk</td>
</tr>
<tr>
<td>1–2 RF</td>
<td>Low risk</td>
</tr>
<tr>
<td>≥3 RF</td>
<td>Low to moderate risk</td>
</tr>
<tr>
<td>OD, CKD stage 3 or diabetes</td>
<td>Moderate to high risk</td>
</tr>
<tr>
<td>Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs</td>
<td>Very high risk</td>
</tr>
</tbody>
</table>

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

Stratification of total CV risk in categories of low, moderate, high and very high risk according to SBP and DBP and prevalence of RFs, asymptomatic OD, diabetes, CKD stage or symptomatic CVD. Subjects with a high normal office but a raised out-of-office BP (masked HT) have a CV risk in the HT range. Subjects with a high office BP but normal out-of-office BP (white-coat HT), particularly if there is no diabetes, OD, CVD or CKD, have lower risk than sustained HT for the same office BP.
Primary objective of treating high BP

- To reduce cardiovascular morbidity & mortality

- To retard progression of CKD

- Intermediate endpoints:
  - Controlled BP
  - Less proteinuria
  - Less target organ damage
**BP goals in hypertensive patients**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>A SBP goal &lt; 140 mmHg</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>a) is recommended in patients at low–moderate CV risk;</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>b) is recommended in patients with diabetes;</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>c) should be considered in patients with previous stroke or TIA;</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>d) should be considered in patients with CHD;</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>e) should be considered in patients with diabetic or non-diabetic CKD.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In elderly hypertensives less than 80 years old with SBP ≥ 160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In fit elderly patients less than 80 years old SBP values &lt; 140 mmHg may be considered, whereas in the fragile elderly population SBP goals should be adapted to individual tolerability.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>In individuals older than 80 years and with initial SBP ≥ 160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg provided they are in good physical and mental conditions.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>A DBP target of &lt; 90 mmHg is always recommended, except in patients with diabetes, in whom values &lt; 85 mmHg are recommended. It should nevertheless be considered that DBP values between 90 and 85 mmHg are safe and well tolerated.</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

Proteinuric CKD < 130/< 80 mm Hg (KDIGO 2012)

CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; SBP, systolic blood pressure; TIA, transient ischaemic attack.  
<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.

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In patients with CKD—with or without diabetes—there are two treatment objectives

1. Prevention of CV events (the most frequent complication of CKD) and
2. Prevention or retardation of further renal deterioration or failure.

Unfortunately,

✓ most trials have excluded patients with CKD, and those trials that specifically targeted CKD patients primarily focused on progression of renal disease as the primary clinical endpoint.

✓ evidence concerning the BP target to be achieved in these patients is scanty and confused by the uncertainty about the respective roles of reduction of BP and specific effects of RAS blockers.
Mortality risk is 8x higher than ESRD risk in CKD

In 1996, 27998 patients in a health plan had eGFR < 90 mL/min/1.73 m². FU from index date of 1st GFR < 90 mL/min/1.73 m² until renal replacement therapy, death, disenrollment from the health plan, or June 30, 2001.

<table>
<thead>
<tr>
<th>Table 2. Study End points*</th>
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<tbody>
<tr>
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<tr>
<td>End Points</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>GFR, 60-89; No Proteinuria (n = 14202)</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Disenrolled from plan</td>
</tr>
<tr>
<td>Died (prior to transplant/dialysis)</td>
</tr>
<tr>
<td>Received a transplant</td>
</tr>
<tr>
<td>Initiated dialysis</td>
</tr>
<tr>
<td>None of the above through June 30, 2001</td>
</tr>
</tbody>
</table>

The rate of renal replacement therapy over the 5-y observation period was 1.1%, 1.3%, and 19.9%, resp., for the K/DOQI stages 2, 3, and 4, but the mortality rate was 19.5%, 24.3%, and 45.7%.
Outline

- Introduction
  - Epidemiology
  - Complications
- Pathophysiology
- Clinical management
- Therapy prescription
- Special populations
Initiation of lifestyle changes & antihypertensive drug treatment. Targets of treatment are also indicated. The optimal DBP target in patients with diabetes is between 80 and 85 mmHg. In the high normal BP range, drug treatment should be considered in the presence of a raised out-of-office BP (masked HT). Lack of evidence in favour of drug treatment in young individuals with isolated systolic HT.

### Treatment strategies

**Lifestyle changes**

<table>
<thead>
<tr>
<th>Classes of recommendations</th>
<th>Definition</th>
<th>Suggested wording to use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.</td>
<td>Is recommended/is indicated</td>
</tr>
<tr>
<td>Class II</td>
<td>Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.</td>
<td></td>
</tr>
<tr>
<td>Class IIa</td>
<td><strong>Weight of evidence/opinion is in favour of usefulness/efficacy.</strong></td>
<td>Should be considered</td>
</tr>
<tr>
<td>Class IIb</td>
<td><strong>Usefulness/efficacy is less well established by evidence/opinion.</strong></td>
<td>May be considered</td>
</tr>
<tr>
<td>Class III</td>
<td>Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.</td>
<td>Is not recommended</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level of evidence A</th>
<th>Data derived from multiple randomized clinical trials or meta-analyses.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of evidence B</td>
<td>Data derived from a single randomized clinical trial or large non-randomized studies.</td>
</tr>
<tr>
<td>Level of evidence C</td>
<td>Consensus of opinion of the experts and/or small studies, retrospective studies, registries.</td>
</tr>
</tbody>
</table>

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt restriction to 5-6 g per day is recommended.</td>
<td>I</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Moderation of alcohol consumption to no more than 20-30 g of ethanol per day in men and to no more than 10-20 g of ethanol per day in women is recommended.</td>
<td>I</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Increased consumption of vegetables, fruits, and low-fat dairy products is recommended.</td>
<td>I</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Reduction of weight to BMI of 25 kg/m² and of waist circumference to &lt;102 cm in men and &lt;88 cm in women is recommended, unless contraindicated.</td>
<td>I</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Regular exercise, i.e. at least 30 min of moderate dynamic exercise on 5 to 7 days per week is recommended.</td>
<td>I</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>It is recommended to give all smokers advice to quit smoking and to offer assistance.</td>
<td>I</td>
<td>A</td>
<td>B</td>
</tr>
</tbody>
</table>

A, Based on the effect on BP and/or CV risk profile

B, Based on outcome studies
Weight loss should be considered as an adjunct to medical therapies to prevent or delay progression of CKD in overweight or obese persons with type 2 diabetes.

Cumulative incidence of very-high-risk CKD by treatment group through year 10. Too few observations were available beyond year 10 for reliable estimates.

DSE, Diabetes Support and Education group,
ILI, Intensive Lifestyle Intervention group.

The numbers of persons at risk at the beginning of the even-numbered years since randomization are shown.

The hazard ratio (ILI vs. DSE) is 0.69, 95% CI = 0.55 to 0.87, p=0.002.
Treatment strategies
Pharmacological therapy

- Choice of antihypertensive drugs
  - The main benefits of antihypertensive treatment are due to lowering of BP *per se* and are largely independent of the drugs employed as has been shown by large meta-analysis[^1,^2,^3]^.

  - Diuretics, BB, CCB, ACEI and ARBs are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations[^1].

Relative risk estimates of coronary heart disease (CHD) events and stroke in 46 drug comparison trials comparing each of the five classes of BP lowering drug with any other class of drug (excluding CHD events in trials of β blockers in people with a history of CHD).
Possible combinations of classes of antihypertensive drugs

Green continuous lines: preferred combinations; green dashed line: useful combination (with some limitations); black dashed lines: possible but less well tested combinations; red continuous line: not recommended combination. Although verapamil and diltiazem are sometimes used with a beta-blocker to improve ventricular rate control in permanent atrial fibrillation, only dihydropyridine calcium antagonists should normally be combined with beta-blockers.
### Therapeutic strategies in hypertensive patients with nephropathy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Classa</th>
<th>Levelb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowering SBP to &lt;140 mmHg should be considered.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>When overt proteinuria is present, SBP values &lt;130 mmHg may be considered, provided that changes in eGFR are monitored.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended.</td>
<td>III</td>
<td>A</td>
</tr>
<tr>
<td>Aldosterone antagonists cannot be recommended in CKD, especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalaemia.</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>

### References

- Appel EJ et al. NEJM 2010; 363:918-29
- Parving HH et al. NEJM 2012; 367:2204-13 (ALTITUDE)
- Mann JF et al. NEJM 2008; 358:1547-59
- /-

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# Treatment strategies in patients with diabetes

## References

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ( \geq 160 ) mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ( \geq 140 ) mmHg.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>A SBP goal &lt;140 mmHg is recommended in patients with diabetes.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>The DBP target in patients with diabetes is recommended to be &lt;85 mmHg.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>It is recommended that individual drug choice takes comorbidities into account.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes.</td>
<td>III</td>
<td>B</td>
</tr>
</tbody>
</table>

- **HOPE.** Lancet 2000; 355:253-59
- **ADVANCE.** Lancet 2007; 370:829-40
- **HOT.** Lancet 1998; 351:1755-62
- **SHEP.** JAMA 1996; 276:1886-92
- **SYSTEUR.** NEJM 1999; 340:677-84
- **UKPDS 38.** BMJ 1998; 317:703-13
- **FEVER.** Eur Heart J 2011; 32:1500-08
- **HOPE.** Lancet 2000; 355:253-59
- **ADVANCE.** Lancet 2007; 370:829-40
- **ACCORD.** NEJM 2010; 362:1575-85
- **HOT.** Lancet 1998; 351:1755-62
- **UKPDS 38.** BMJ 1998; 317:703-13
- **BPLTT collaboration.** Arch Intern Med 2005; 165:1410-19
- **Schmieder et al.** Lancet 2007; 369:1208-19

**/-/**

**ALTITUDE.** NEJM 2012; 367:2204-13

---

First-line therapy in CKD: RAAS blockers

- Lewis et al. NEJM 1993
  - Risk reduction, 48%
    - (55% en 17%)

- RENAAL. NEJM 2001
  - Risk reduction, 20%
    - $P=0.01$

- IDNT. NEJM 2001
  - Risk reduction, 23%
    - $P=0.07$
First-line therapy: RAAS blockers

AVOID dual blockade of RAAS

ONTARGET. NEJM 2008

REIN. AJKD 2000 (non-DM np)
**AVOID dual blockade of RAAS**

Table 4. Secondary and Other Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ramipril (N=8576)</th>
<th>Telmisartan (N=8542)</th>
<th>Combination Therapy (N=8502)</th>
<th>Telmisartan vs. Ramipril</th>
<th>Combination Therapy vs. Ramipril</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number (percent)</td>
<td></td>
<td></td>
<td>relative risk (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td>1269 (14.8)</td>
<td>1290 (15.1)</td>
<td>1303 (15.3)</td>
<td>1.03 (0.95–1.11)</td>
<td>1.04 (0.97–1.13)</td>
</tr>
<tr>
<td>Hospitalization for angina</td>
<td>925 (10.8)</td>
<td>954 (11.2)</td>
<td>952 (11.2)</td>
<td>1.04 (0.95–1.14)</td>
<td>1.04 (0.95–1.14)</td>
</tr>
<tr>
<td>Worsening or new angina</td>
<td>567 (6.6)</td>
<td>536 (6.3)</td>
<td>538 (6.3)</td>
<td>0.95 (0.84–1.07)</td>
<td>0.96 (0.85–1.08)</td>
</tr>
<tr>
<td>New diagnosis of diabetes*</td>
<td>366 (6.7)</td>
<td>399 (7.5)</td>
<td>323 (6.1)</td>
<td>1.12 (0.97–1.29)</td>
<td>0.91 (0.78–1.06)</td>
</tr>
<tr>
<td>Any heart failure</td>
<td>514 (6.0)</td>
<td>537 (6.3)</td>
<td>478 (5.6)</td>
<td>1.05 (0.93–1.19)</td>
<td>0.94 (0.83–1.07)</td>
</tr>
<tr>
<td>New atrial fibrillation†</td>
<td>570 (6.9)</td>
<td>550 (6.7)</td>
<td>537 (6.5)</td>
<td>0.97 (0.86–1.09)</td>
<td>0.96 (0.85–1.07)</td>
</tr>
<tr>
<td><strong>Renal impairment‡</strong></td>
<td>871 (10.2)</td>
<td>906 (10.6)</td>
<td>1148 (13.5)</td>
<td>1.04 (0.96–1.14)</td>
<td><strong>1.33 (1.22–1.44)§</strong></td>
</tr>
<tr>
<td>Renal failure requiring dialysis</td>
<td>48 (0.6)</td>
<td>52 (0.6)</td>
<td>65 (0.8)</td>
<td>1.09 (0.74–1.61)</td>
<td>1.37 (0.94–1.98)</td>
</tr>
</tbody>
</table>

* The numbers of patients included in this analysis were 5427 in the ramipril group, 5294 in the telmisartan group, and 5280 in the combination-therapy group.
† This category includes only patients who did not have atrial fibrillation at baseline: 8296 in the ramipril group, 8259 in the telmisartan group, and 8218 in the combination-therapy group.
‡ No specific definitions were used. A determination of renal impairment was based on the clinical investigator’s report of an event that led to the discontinuation of a study drug.
§ P<0.001.

K>5.5 mmol/L: 283 (3.3) - 287 (3.4) - 480 (5.6) p<0.001

Second-line therapy in CKD: CCB or DIUR → third-line

Composite of a CV event and death from CV causes

11,506 HT patients at high risk for CV events (60%DM and 6% CKD)

Figure 2. Kaplan–Meier Curves for Time to First Primary Composite End Point.
There were 552 patients with events (9.6%) in the benazepril–amlodipine group, as compared with 679 patients with events (11.8%) in the benazepril–hydrochlorothiazide group. The relative risk reduction was 20% (hazard ratio, 0.80; 95% CI, 0.72 to 0.90; P<0.001).

Second-line therapy in CKD: CCB or DIUR → third-line

Figure 1. Effects of Treatment on Systolic and Diastolic Blood Pressure over Time.

The mean systolic and diastolic blood pressures after dose adjustment were 131.6/73.3 mm Hg in the benazepril–amlodipine group and 132.5/74.4 mm Hg in the benazepril–hydrochlorothiazide group. The mean difference in blood pressure between the two groups was 0.9 mm Hg systolic and 1.1 mm Hg diastolic (P<0.001 for both comparisons).

Fourth-line therapy – new/alternative therapies

- $\beta B/\alpha B/ CW/Dir VD$
- SGLT-2 inhibitors
  - $\rightarrow$ Glucosuria
  - $\rightarrow$ FPG↓
  - $\rightarrow$ PPG↓
  - $\rightarrow$ Weight↓
  - $\rightarrow$ Urine volume↑
  - $\rightarrow$ BP↓

It remains to be understood if BP reduction and vascular modulation contributed to the benefit observed.

Potential role of sodium glucose cotransporter 2 inhibitors in the treatment of hypertension.

Impact of SGLT2 inhibition on seated BP in T2DM from studies of individual class members. cana, canagliflozin (Invokana®); empa, empagliflozin (Jardiance®); dapa, dapagliflozin; SGLT2, sodium glucose cotransporter 2; T2DM, type 2 diabetes mellitus.

Possible mechanisms involved in the cardiovascular benefits of SGLT2 inhibitors. SGLT2, sodium glucose cotransporter 2.

Blood pressure control

- In the general population, only a minority of patients achieve recommended treatment goals.

- Reports on CKD patients enrolled in prospective observational studies have described rates of awareness and control of HT as similar to current levels in the general population[1,2]. Rates of hypertension control were suboptimal in a cohort of patients with CKD, despite almost universal HT awareness and treatment[1].

HT prevalence, awareness, treatment and control in adults with CKD (CRIC study. AJKD 2010; 55: 441-51)

SBP & DBP distribution among participants in the CRIC study (n=3612).

Overall rates of HT prevalence, awareness, treatment and control among participants of the Chronic Renal Insufficiency Cohort (CRIC) study. HTN Prevalence among all CRIC participants; Aware and Treated are the percent among all participants with HT. HT control rates are calculated for all CRIC participants with HT.
Resistant hypertension

- A patient whose BP is above goal while concurrently taking three appropriately chosen antihypertensive agents at optimally tolerated doses, one of which is a diuretic, should be considered to have resistant hypertension.

- Cave: non-compliance/adherence; secondary hypertension

- High risk for adverse CV events

- Treatment options are catheter-based renal denervation, or implantation of a carotid baroreflex stimulator, which target different aspects of the sympathetic nervous system, creation of a central arteriovenous anastomosis or new drug treatments
Resistant hypertension
Secondary causes

<table>
<thead>
<tr>
<th>Common causes</th>
<th>Uncommon causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSA</td>
<td>Primary hyperparathyroism</td>
</tr>
<tr>
<td>CKD</td>
<td>Cushing’s disease</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Primary aldosteronism</td>
<td>Aortic coarctation</td>
</tr>
</tbody>
</table>

**Interfering drugs/ agents**

- Non-narcotic analgetics (NSAID, ASA, selective COX-2 inh)
- Sympathomimetic drugs/ agents (decongestants, cocaine)
- Stimulants (amphetamines)
- Alcohol, Licorice, herbal compounds (ephedra)
- Cyclosporine, Erythropoietin
Effect of Spironolactone on BP in Resistant Hypertension

\[ \Delta \text{SBP} = 21.9 \\
\text{(95\%CI 20.8, 23.0)} \]

\[ \Delta \text{DBP} = 9.5 \\
\text{(95\%CI 9.0, 10.1)} \]

Mean BP before and during spironolactone treatment.

Effect in 1411 ASCOT participants who received spironolactone for treatment of high BP with available BP measurements before (pre-), and during (post-), spironolactone treatment.
Resistant hypertension
Mineralocorticoid receptor antagonists

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

Home systolic and diastolic BPs comparing spironolactone with each of the other cycles

The top and bottom of each column represents the unadjusted home SBPs and DBPs, resp., averaged across the mid-cycle (low-dose) and end-of-cycle (high-dose) visits (6 weeks and 12 weeks) in which patients received the drug. Error bars represent 95% CI.
Catheter-based RDN Therapy: Ardian and more

- Standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF Generator
  - Automated
  - Low-power
  - Built-in safety algorithms

COV: One Shot  STJ: EnligHTN  RECOR  BSX: Vessix  KONA

and more...

4 ablations simultaneously
### Six-month response of office SBP to renal denervation (RDN) or to follow-up in the control group.

Solid points represent the effect size in individual studies and have a size proportional to the inverse of the variance. The diamond represents the pooled estimate. Horizontal lines and diamonds denote the 95% CIs. For all trials combined, the pooled within group change is given with 95% CI. P-values refer to the significance of the pooled between-group estimate and Cochran’s Q test for heterogeneity.
Meta-analysis of RCTs of renal denervation in treatment-resistant hypertension

Six-month response of 24 h SBP to renal denervation (RDN) or to follow-up in the control group.

Solid points represent the effect size in individual studies and have a size proportional to the inverse of the variance. The diamond represents the pooled estimate. Horizontal lines and diamonds denote the 95% CIs. For all trials combined, the pooled within group change is given with 95% CI. P-values refer to the significance of the pooled between-group estimate and Cochran’s Q test for heterogeneity.
Meta-analysis of RCTs of renal denervation in treatment-resistant hypertension

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>RDN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N*</td>
<td>Δ (SD)</td>
</tr>
<tr>
<td>SYMPLECTY-2</td>
<td>51</td>
<td>+0.9</td>
</tr>
<tr>
<td>SYMPLECTY-3</td>
<td>171</td>
<td>-1.7</td>
</tr>
<tr>
<td>OSLO</td>
<td>10</td>
<td>-4.7</td>
</tr>
<tr>
<td>PRAGUE</td>
<td>54</td>
<td>-3.1</td>
</tr>
<tr>
<td>DENER</td>
<td>53</td>
<td>-5.3</td>
</tr>
<tr>
<td>SYMPLECTY-F</td>
<td>35</td>
<td>-0.01</td>
</tr>
<tr>
<td>SYMPLECTY-J</td>
<td>19</td>
<td>-3.8</td>
</tr>
<tr>
<td>ALL</td>
<td>393</td>
<td>-2.30</td>
</tr>
</tbody>
</table>

Six-month response of the eGFR to renal denervation (RDN) or to follow-up in the control group, respectively.

Solid points represent the effect size in individual studies and have a size proportional to the inverse of the variance. The diamond represents the pooled estimate. Horizontal lines and diamonds denote the 95% CIs. For all trials combined, the pooled within-group change is given with 95% CI. P-values refer to the significance of the pooled between-group estimate and Cochran’s Q test for heterogeneity.
Catheter-based radiofrequency ablation of renal sympathetic nerves

- Due to the lack of benefit in the Symplicity-3 trial, the large international trial (S-HTN-4) was halted prematurely.

- Several studies are ongoing in more “carefully” selected patients:
  - SPYRAL-HTN-ON-MED
  - SPYRAL-HTN-OFF-MED
  - INSPIRED
  - ….
Therapy resistant hypertension: Baroreflex activation therapy via electrical stimulation of carotid baroreceptors.

Baseline: 192/108 mm Hg

Promising Studies are ongoing

Scheffers et al. J Hypertens 2009 and JACC 2010; 56:1254-58
Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial

Self expanding device creating a 4 mm AVF between iliac artery and vein (shunt ≈ 800 mL/min)

Change from baseline in BP at 6 months

Data are mean (SD).
SBP=systolic blood pressure. DBP=diastolic blood pressure. OBP=office blood pressure. ABP=ambulatory blood pressure. AV=arteriovenous.

Venous stenosis (29%), DVT, artery dissection
Outcome? Long-term safety?

Conclusions

- Hypertension is a frequent CVRF
- Hypertension is a cause and a consequence of CKD
- The pathophysiology of hypertension is complex
- Total CV risk should be calculated
- Treatment and BP control can be ameliorated
- BP target < 140/90 mm Hg
- RAASB – CCB – DIUR are the cornerstone of ©®
Renovascular hypertension
Ischemic Nephropathy

Atherosclerotic RVD

Fibromuscular dysplasia
Renovascular hypertension
Ischemic Nephropathy

- Atherosclerotic renal artery stenosis can cause
  → Hypertension
  → CKD

- Since most lesions are asymptomatic,
  → The true prevalence is not known (1 – 45%)
  → The natural history of the disease is controversial

- When to look for atherosclerotic RAS
  → Recurrent pulmonary edema with normal cardiac function
  → Worsening kidney function with RAAS blokkade or with BP lowering
  → Resistant or severe (malignant) hypertension
Diagnostic algorithm for renovascular hypertension

Suspicion of RVH/ RAS

- Screening test
  - Doppler US
  - CTA or MRA

High

Intermediate

Low

PSV<180 cm/s: no RAS

Suggestive of RAS

Not suggestive of RAS

Angiogram

RAS present

Consider revascularization if*

RAS absent

Treat HT and other CVRF

*Recurrent “flash” pulmonary edema
- Refractory hypertension despite appropriate triple drug therapy
- Progressive unexplained decline in renal function
- Acute but reversible kidney injury after RAAS blockade or BP lowering
- Renal resistive index < 80 mmHg on Doppler US
Renal artery revascularization vs medical therapy CV outcomes

Atherosclerotic RAS

Renal artery revascularization: updated meta-analysis with the CORAL trial summary estimates of CV outcomes for revascularization vs medical therapy.

RR (95% CI)

Included trials: STAR; ASTRAL; SNARSCG; NITER; CORAL; RASCAD; DRASTIC; EMMA

Renal artery FMD
Screening for renal artery FMD

In a patient with HTN, screening for FMD-related RAS is recommended in any of the following cases:

1. Age <30 years, especially in women
2. Grade 3 (180/110 mmHg), accelerated or malignant HTN
3. True Resistant HTN (BP target not achieved despite triple therapy at optimal doses including a diuretic)
4. Small kidney without history of uropathy
5. Abdominal bruit without apparent atherosclerosis
6. FMD in at least another vascular territory

In individuals aged less than 50 years, screening for FMD may also be considered in milder HTN cases.

Renovascular hypertension
Ischemic Nephropathy

- FMD: angioplasty without stenting

- Atherosclerotic RVD: no consensus
  - medical therapy remains the cornerstone of treatment and cardiovascular risk factors should be aggressively targeted.

  - revascularization with balloon angioplasty and stent placement should be considered for selected patients with atherosclerotic renal artery stenosis and poorly controlled hypertension and/or rapidly declining kidney function and/or flash pulmonary edema.
Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States.

- HTN is common and inadequately treated/controlled in chronic HD patients

- 2535 clinically stable, adult HDs patients; HTN was defined as an average predialysis SBP > 150 mm Hg or DBP > 85 mm Hg, or the use of antihypertensive medications.
  - The prevalence of HTN (86%), in contrast to that observed in the general population, did not increase linearly with age and was not affected by sex or ethnicity
  - HTN was controlled adequately in only 30%
  - HTN was untreated in 12%
  - HTN was treated inadequately in 58%

BP goal in hemodialysis patients with HTN

- It is reasonable to aim for a predialysis BP ≤ 140/90 mm Hg or a home BP ≤ 135/85 mm Hg.

- Although the recent KDIGO BP guidelines did not recommend BP goals in dialysis patients due to lack of evidence to support any guidelines in dialysis patients, the general strategies to “Individualize BP targets and agents according to age, co-existent cardiovascular disease and other co-morbidities … and tolerance of treatment” and “Inquire about postural dizziness and check for postural hypotension” are relevant to the management of hypertension in dialysis patients.

Levin et al. KI. 2010;77(4):273–284 and 2012 S2
Chronic kidney disease stage 5D: Hypertension is a ubiquitous finding in HD patients and has major implications for survival.

1. **Accurate measurement** of BP is essential for the management of HD patients. However, a pre-HD BP may not reflect the average BP experienced by the patient. Thus, the question of how and where the measurements should be made is of particular importance, with clear evidence for the superiority of self-measured BP at home over pre-HD BP values.

2. The BP to be pursued by treatment in patients on HD has not been clearly established in this context. A distinct difficulty is that large alterations in sodium and water balance make BP particularly variable and that the extent of BP reductions may depend on the presence of complications such as cardiomyopathy rather than drug-induced BP control.
3. All antihypertensive drugs except diuretics can be used in the hemodialysis patients, with doses determined by the hemodynamic instability and the ability of the drug to be dialyzed. Drugs interfering with homeostatic adjustments to volume depletion (already severely impaired in renal insufficiency) should be avoided to minimize hypotension during the fast and intensive reduction of blood volume associated with the dialytic manoeuvres.

RCTs are rare in hemodialysis and should be encouraged. Longer or more frequent dialysis may solve the hemodynamic problems associated with salt restriction and short dialysis time[1]

[1] Levin NW et al. KI 2010; 77:273-84 (KDIGO)
Factors Contributing to Uncontrolled Hypertension in Hemodialysis

- Sodium and volume excess
- Non adherence with prescribed medications (high pill burden; rebound HT; fear for cramps or hypotension)
- Sleep apnea
- Secondary causes
- Erythropoetin treatment (VC)
Average office BP was 170.8±16.9/89.2±12.1 mm Hg despite the use of 3.8±1.4 antihypertensive drugs. All 5 patients in whom muscle sympathetic nerve activity and noradrenaline spillover was assessed at baseline displayed substantially elevated levels. Three out of 12 patients could not undergo RDN due to atrophic renal arteries.

Compared to baseline, **office systolic BP was significantly reduced** at 3, 6, and 12 months after RDN (from 166±16.0 to 148±11, 150±14, and 138±17 mm Hg, resp.), whereas no change was evident in the 3 non-treated patients. Sympathetic nerve activity was substantially reduced in 2 patients who underwent repeat assessment.
Causes of Posttransplant Hypertension Within the first 3 months

- Pretransplant hypertension
- African American race/ethnicity
- Renal allograft dysfunction
- Renal outflow obstruction
- Hypervolemic
- High-dose calcineurin inhibitors
- High-dose corticosteroids
- Postoperative pain
- Discontinuation of pretransplant antihypertensive medications
Causes of Posttransplant Hypertension During long-term care

**Donor variables**
- Increased donor age
- African American donor
- Hypertensive donor

**Recipient variables**
- Older age
- African American race/ethnicity
- Male gender
- Obesity
- Diabetes mellitus
- Pretransplant hypertension
- Native kidney disease

- Renal allograft dysfunction
- Recurrent primary renal disease
- Immunosuppressive medications
  - Calcineurin inhibitors
  - Corticosteroids
- Transplant renal artery stenosis