Causal relationships

Causative factor> **Recipient**	**Ang II**	**AT1r**	**Aldo**	**Pro Re-nin**	**AT 2r**	**Causative factor>** **Recipient**	**S N A**	**NO**	**^ Ins uln**	**Na**	**K**	**Obe-sity**	**O S A**	**Exer cise**
vasoconstriction	+	+				Vasoconstriction	+	--				+ 5		
SNA (10)	+ 5, 10	+ 5, 10				SNA (10)	+		**++ + 5**		--	+5,11	+	
RAAS						RAAS				---	--	+		
Angiotensin II						Angiotensin II				+	--	+ 5		
Aldo release	+	+				Aldo release	+				--9	+ 5,13	+	
Potentiates Ang II by ^ in AT1rs			+			Potentiates Ang II by ^ in AT1rs		--			--			
Renal Na retained	+		+			Renal Na retained	+ 5	--	**++ +5**		-- 12	+13		
	Ang II	**AT1r**	**Aldo**	**Pro Re-nin**	**AT2 r**		**S N A**	**NO**		**Na**	**K**	**Obe-sity**	**O S A**	
Remodel vessels & heart		+			+	Remodel vessels & heart								
Cell growth		+			+	Cell growth		--						
Cardiac fibrosis		+	+	+		Cardiac fibrosis								
Arteriolar hypertrophy		+				Arteriolar Hypertrophy	+							
Vascular stiffness						Vascularstiffness		--						
Cardiac myocyte Hypertrophy		+				Cardiac myocyte Hypertrophy	+							
LVH	+(1)	+				LVH								
CV disease		+				CV disease								
Renal damage		+	+	+		Renal damage				+				
	Ang II	**AT1r**	**Aldo**	**Pro Re-nin**	**AT 2r**		**S N A**	**NO**		**Na**	**K**	**Obe-sity**	**O S A**	
OS (ox stress)	+ (6)	+				O stress					--	+	+	
Inflammation		+			+	Inflammation							+ 3	--(4)
Glucose intolerance		+ 5				Glucose intolerance	+ (5)					+ 5		--
Anti-angiogenesis					+	Anti-angiogenesis								
Cell adhesion Molecules						Cell adhesion Molecules		--						
Endothelin Formation	+					Endothelin Formation		--						
EDHF(2)						EDHF(2)					+			
NO formation	--					NO formation	+			--	+	--		
Endothelial Dysfnctn						Endothelial dysfnctn						+ 5	+	--
MR receptor & ^ENaC			+			MR receptor & ^ENaC								
Platelet aggregat						Platelet aggr'n		--						

(1) independent of BP & amlodipine. (2) endothelial derived hyperpolarizing factor. (3) ^CRP, TNF-a, IL-6.
(4) Exercise increases interleukin 10 (anti-inflammatory) and reduces adipokines (pro-inflammatory and raise BP).
(5) This links HTN to DM. (6) Ang II>>NADPH>>OS>>LDL oxidation & plaque formation. (7) Baro-reflex activation inhibits SNA and increases parasympathetic activity which decrease heart rate, renin release and arterial stiffness, and increase vasodilation and Na excretion. (8) RAAS inhibition promotes endothelial function & decreases OS, PAI1 (anti-coagulant effect) & TGFB. (9) Counterintuitive (10) SNA can be central, peripheral synapses, or in the adrenal medulla (Ang II can cause all three). (11) Obesity increases SNA via OSA!! (12) Hypokalemia causes retention of Na via a) increase in AT1 receptors leading to an in increase in aldosterone, or b) through activating the WNK enzymes. (13) Direct effect postulated.

Section I.
PHYSIOLOGY AND GENETICS OF BP REGULATION
T Giles

Pressure = flow * resistance
CO=stroke volume * HR.
MAP=CO*SVR
MAP=DBP + 1/3 PP

BP response times: SNS: seconds-minutes/ RAAS: minutes-hours/ Kidney: hours-days.
SNA increases with weight, age, BP and SVR

Sympatho-endothelial axis:

Nor epinephrine stimulates B1 and B3 receptors.
B1 stimulation leads to shear stress which increases NOS. B3 recepter stimulation decreases ADMA. ADMA blocks the action of NOS, which converts arginine and O2 to NO+citruline, NO converts guanylate cyclase to an active form, catalyzing GTP to GMP, which leads to relaxation.
ACH and Bradykinin promote EDHF (Endothelial derived hyperpolarizing factor) and PGI2 both of which directly relax smooth muscle. The endothelial function, however, is worsened by Ang II. Also, B1 mediates myocardial growth effects, myocyte damage, apoptosis, and pro-arrhythmia. (i.e., other aspects of B1 stimulation are detrimental.) A1 vasoconstricts.

The renal sympathetics are:
A1 – afferent arteriole constriction & hypertrophy.
B1 – renin release from the JG apparatus >> Ang II formation >> aldosterone release and vasoconstriction).
A1 -- Na-K pump (antagonists: carvedilol, labetolol and doxazosin.)

Aldosterone causes cardiac fibrosis.
Aldosterone is stimulated by K, **ACTH, and NE (via NE effect on renin release and a direct effect on the adrenal medulla)** endothelin and serotonin. Vasodilation by ACH is less in HTN and in those with FH+ of HTN.

Salt sensitivity: Low renin status (elderly, blacks, some diabetics), obesity (normal or hi renin), CKD and NSAID use. BP response is due to increased SVR (counterintuitive).
Obesity

1) **effects the vessel wall causing insulin resistance, OS (oxidative stress), ED (endothelial dysfunction), & VC (vasoconstriction) >> HTN**.
2) **Activates RAAS**
3) F acids in the liver leads to SNA.

Lo renin HTN is more likely to be salt sensitive and responsive to diuretic or CCB and less responsive to non-pharmacologic Rx.

	DBP	SBP
Risk with age	As DBP increases to age 50, Risk increases, then decreases	Increases with age
Hemodynamics	Increased SVR	Increased aortic stiffness
Correlates	Obesity, insulin resistance (CVEs)	CVEs

HTN is defined as the average on 3 visits (at least 2/visit), 2 -4 weeks apart: 140/90+ (per ITC).

EPIDEMIOLOGY OF HTN. M Weber
Each increase in 20/10 of SBP/DBP leads to doubling in CV risk.
HTN prevalence 29% in adults, control: 50%, controlled/treated 70%, Aware 80%, Treated 70%

HTN prevalence 38% in AAs.

Young least aware.
Only 45% of young HTNsvs are treated.
Elderly less well controlled/treated (about60%)
Blacks most aware of HTN
Blacks have poorest control/treated.
Women more likely to be treated.
Prevalence of HTN did not change from 2000 to 2008.
Most uncontrolled HTN is untreated.
Of those treated but uncontrolled:
72% on 1-2 meds ("therapeutic inertia")
28% on 3+ meds ("RH")
For the 72% on 1-2 meds, there is a 2x increased risk of a FRS of 20%+.
Of all treated patients, treatment RH has increased from 16 to 28% from 2005 to 2008. (probably does not exclude poor adherence).
For the 28% with "RH", there is a strong correlation with drs visits, obesity, ckd, FRS of 20%, and AA.
In Framingham, for any given level of SBP, there is an increase in CHD risk with increase in PP.
Most cases of uncontrolled HTN in the US = mild ISH in the elderly.
As SBP increases, the risk from PP increases.
In 1939, authors recognized that >120/80 was a risk factor.

The **TROPHY** trial showed **candesartan reduced incident htn,**

TOHP-II showed that lifestyle change (weight loss & decreased Na consumption) reduced incident HTN by 6-7%.

Elliott: ASH efforts to control BP. ASH htn specialist, taxonomy code, registry initiative (So Carolina)

Section 2.
HORMONAL MECHANISMS. A Gradman:
The 3 determinates of BP are RAAS, Na+volume (i.e., via the kidney), and SNA.
MAP=CO*TPR
AT1Rs link Ang II to
Vasoconstriction, aldosterone release, **NE release (direct effect)**, remodeling of vessels and heart, OS, inflammation, cell growth, cardiac fibrosis, renal damage, CVD, and glucose intolerance.

Ang II has direct effects on NADPH leading to OS which decreases NO; this also leads to oxidation of LDL, which contributes to plaque formation and foam cells.

AT2Rs link Ang II to cell growth, apoptosis, inflammation, remodeling, and anti-angiogenesis

Prorenin is cardiotoxic

Ang II causes LVH, which is not prevented at all by amlodipine (i.e., Ang II effects LVH independently of BP) in animals.
(Conversely, spironolactone blocks cardiotoxicity independent of BP.)

Aldosterone potentiates the effect of Ang II by increasing the number of AT1Rs and by directly potentiating Ang II's effect on BP.

Cardiac fibrosis and renal damage are effected by AT1 receptors, aldosterone, prorenin and Na retention.

Aldosterone directly causes cardiac fibrosis and proteinuria.

Aldosterone antagonists block cardiotoxicity and nephrotoxicity.

Spironolactone prevents myocardial fibrosis independent of BP lowering.

The EPHESUS trial (eplerenone vs placebo) showed reduction in ACM from eplerenone.

Aldosterone (another observation): PA (primary aldosteronism) and RVHTN cause LVH relative to EH.

The PAPY study (primary aldosterone prevalence in Italy) showed increased urinary excretion of albumin in those with IHA and APA (aldosterone producing adenoma).
After treatment with either adrenalectomy or spironolactone, the albuminuria improved in the PA group versus the EH group.
The renal dysfunction, as manifested by albuminuria, is a dynamic reversible rather than structural defect.

Examples of mineralcorticoid HTN: aldosterone: APA, 2ndary aldosteronism, GRA, familial hyperaldosteronism 2, DOC due to CAH, cortisol from Cushings, AME (apparent mineral corticoid excess) & licorice.

Subclinical cushing's syndrome (or non-classical Cushings) occurs in incidental adrenal nodules and BP is improved with surgery. Subclinical Cushings is defined as 2 out of 3 of the following: 1) increase in urinary free cortisol, 2)abnormal 1m Dex suppression test, and 3) low ACTH)

NEURAL MECHANISMS. W Elliott

Ang II increases SNA which effects heart, arterioles, **epi release from the adrenal medulla** and SNA effects of the kidneys.

SNA & kidney:
A1Receptor: Afferent arterioles (constricts) (as with Ang II);
B1Receptor: JG apparatus (renin release) (as with Lo Na);
A1Receptor: Na-K exchange in the CCT (along with aldosterone).

HTN:
Acute effects: increases vasomotor tone, HR, and CO.
Chronic effects: Remodelling of heart and arteries; renin release; renal Na retention.
Rostral Ventrolateral Medulla= prime regulator of SNS, sending excitatory fibers to spinal cord.
Microneurography:
HTN has an increase MSNA (muscle sympathetic neural activity).
Patients with LV diastolic dysfunction with preserved EF have elevated MSNA. (BBs would block this.)

OSA: marked increase in MSNA during apneic episodes via chemoreceptor of carotid body.

Obese patients have higher MSNA in normotensives & in HTNsives.

Patients with hyper-insulinemia have higher SNA which causes HTN (DM-HTN link!!)

Patients on hemodialysis have sympathetic overactivity.

Relative to 3x/ week dialysis, daily dialysis lowers SNA.

ESRD patients with elevated NE have worse survival and more CVEs than those with normal NE. (Could this mean that afferent nerve ablation will improve outcomes independently of BP lowering effect?)

Reflexive (paradoxical) increases in SNA occurs with losartan-HCTZ and with CTDN but not with spironolactone, possibly related to inhibition of aldosterone receptors in the CNS (Menon JCEM 2009;94:1361).

SNA is implicated in EH, obesity related HTN, HTNsive heart disease and CKD.

NE causes vascular remodeling, predicts cardiac events in ESRD and causes cardiac myocyte hypertrophy.

VASCULAR MECHANISMS: T. Giles

The endothelium covers an area of 12 tennis courts.

Normal vessels dilate in response to increases in flow via ACH, NO & EDHF (endothelial derived hyperpolarizing factor).

In those with HTN and a family history of HTN, the response to ACH is impaired.

Reduced flow mediated vasodilation carries a 6 fold increase in risk for HTN (Rossi JACC 2004;44:1636).

NO > guanylate cyclase activation > protein kinase G activation > phosphorylation of myosin light chains >> relaxation.

NO vasodilates but also maintains vascular pliability and natriuresis and inhibits platelet aggregation, smooth muscle proliferation, formation of AT1Rs, cell adhesion molecules, and endothelin formation.

Oxidative stress and ADMA (asymmetric dimethyl arginine) can block NO formation by uncoupling NOS in its enzymatic action, which is to form NO by bringing together arginine and O2.

Arachadonic acid ---(COX)----> PGI2 ---→Vasodilation
This is blocked by NSAIDs. Another cyclo-oxygnase enzyme leads to the formation of vasoconstricting and platelet aggregating TXA2 (thromboxane A2), a vasoconstricting PGH2, and a vasoconstricting Ca++.

Hypokalemia (K depletion) causes a decrease in EDHF, and increase in O2 radicals and an increase in ADMA (both of which block NO formation). **Hypokalemia increases the AT1R population which potentiates Ang II and leading to aldosterone release and Na retention**.

Hypokalemia may also promote Na retention through the LWNK1 activation.

Na enhances angiotensin II activity and decreases NO formation; K does the opposite.

In salt sensitivity, HTN is based on increased PVR, not plasma volume expansion which occurs early and is transient. (Counterintuitive!)

Vitamin D deficiency and PTH may also lead to HTN, particularly in blacks, the obese, the elderly, and those with CKD in whom vitamin D tends to be lower. ½ of the excess HTN in blacks may be due to vitamin D deficiency.

RENAL MECHANISMS. M Weir

The kidneys have one million filtering units.

The glomerulus experiences 50% to 70% of systemic BP and needs to avoid hydraulic injury. CKD is defined as 3 months or more of renal damage.

Microalbuminuria is defined as a spot albumin/creatinine of 30mg/gm +.
There may also be systemic vasculature leaking of albumin into the interstitium.

In chronic HTN, early arteriolar constriction and later vascular smooth muscle hypertrophy reduce renal blood flow and GFR. In chronic HTN, a higher BP is required to maintain pressure-natriuresis.

Na & water depletion increases SNA and RAAS activity, for which RAAS blockers would be more effective. For Na and H2O excess, diuretics and CCBs would be more effective (i.e., Blacks).

Salt sensitivity is defined as a decrease in MABP of 10 mmHg+ after 20 hours of Na deprivation (20 mg furosemide Q 4 hrs x 3 plus a 10 mEq sodium diet) in the setting of Na excess (2L 0.9% NS) (Weinberger Hypertension 2001;37:429.

Salt Sensitivity (about 50% of HTNsvs):
Physiology:

Low renin states (elderly, blacks).

Failure to adequately suppress vasoconstriction leads to an exaggerated BP response to loading of Na and H20.

Populations with salt sensitivity: AAs, elderly, obese (high renin), CKD, DM, NSAID users.

AT1Rs mediate SNA, vasoconstriction, aldosterone release, free radical generation, thirst, ADH release, and hypertrophy of the myocardium and smooth muscle. The thirst and ADH release reflect evolutionary pathways.

SNA and RAAS activation parallel each other and are associated with CKD.

MAP = CO*SVR.

Of course, diuretics are critical in CKD.

DM involves afferent arteriolar disease.

Where the outcome is glomerulosclerosis, for a given SBP level, the ACEI and ARB have lower rates of renal damage than the CCBs.

Glomerulosclerosis is independent of BP change produced by CCBs but is dependent on (or at least correlated with) BP change by an ACEI or an ARB.

Mediators of renal injury include TGF-beta.
A stiff aorta leads to increased PWV, a decreased DBP (hence an increased PP), ISH in the elderly, late systolic augmentation, LVH, and decreased coronary perfusion in diastole.

In the elderly there is an increase in systolic wave reflection and similar central and peripheral BPs, while in the young, there is increased peripheral wave amplification, and a higher peripheral BPs relative to central BPs.

In the CAFÉ substudy of ASCOT, the amlodipine-perindopril arm had lower central aortic BPs than the atenolol-bendroflumethiazide arm despite similar brachial (peripheral) BP. This could explain the fewer CVEs in the amlodipine arm in ASCOT as a whole.

RAAS inhibition confers better endothelial function, less OS, less PAI1 (plasminogen activator inhibitor 1), and less TGF-beta.

CKD is associated with increased SNA.

In CKD, dietary Na should be less than 2.4 gm/day (100 meQ or 6 gm of NaCL).

In CKD, whether DM or non-DM in origin, whether in hypertensives or normotensives, a urinary protein/Creatinine ratio of 200mg/gm+ (abnormal is 150+), should be treated with moderate to high doses of an ACEI or ARB. For 200+mg/gm, begin with diuretic, then ACEI, ARB, BB or CCB.

The BP goal is <130/80. Most will require 2+ medications. Most should be treated with a diuretic (with a loop for GFR < 30) without which BP control is unlikely.

Modify the anti-hypertensive if U Protein/Creatinine is greater than 500 – 1,000 mg/gm. This may lead to much lower BP.

Check BP, GFR and K within 12 weeks of ACEI, ARB, OR diuretic, OR within 4 weeks or sooner for SBP<120 or SBP 140+, GFR< 60, change in GFR > 15%, K > 4.5 or < 4.0.

Section 3.
OFFICE AND OUT OF OFFICE BP. A. Gradman.

	Optimal	Normal	Abnormal
Home	<125/75	<130/80	135/85+
Day	<130/80	<135/85	135/85+
Night	<115/65	<120/70	**125/75+**
24 hr	**<125/75**	**<130/80**	**130/80+**

The above reflects treatment guidelines. WCH has a risk similar to normotensives until 4 to 6 years when it increases to that of hypertensives.
For home BP, take the BP a minimum of 4 days and discard the 1st day.

An algorithm would be: OBP 140/90+ leads to HBP. If Home BP 135/85+, then treat. If < 130/80, do 24 hr ABP. If 24 hr BP <130/80, follow up 1 yr, then Q 2yrs. If latter is 130/80+, Rx. F-U 24 hr ABP Q2 yrs.
Alternatively, a raised clinic BP in the presence of TOD should lead to Rx.
Peak time for CV complications 6AM-12N:Sudden death, Acute MI, angina, ischemia, platelet aggregation.
WCH may have an increased rate of CVA.

CLINICAL EVALUATION AND ASSESSMENT. M Weber

World: In those age 30 or more, Of 16 M deaths, HTN causes 49% (can't be correct??), high cholesterol 27%, and overweight 14%. Ezzati PLOS Med 2005;2(5)E33.

In the U.S. we have 72 million hypertensives (30% of population).

RISK	Millions	%
DM	**20**	**10**
Tobacco	**46**	**21**
Htn	**72**	**29**
Hi chol	**105**	**48**
Overweight	140	66
Inactivity	154	70

% modifiable PAR for 1st MI:

Lipids	50
Smoking	36
Psychosocial	33
Abdominal obesity	20
HTN	**18**
Fruits & veg's	14
Exercise	12
DM	10
Alcohol	7

Heart rate is a strong marker for CV risk in Framingham (2 fold risk for HRof 85+ versus <65).

RR for CV death from proteinuria is 3 fold, and for microalbuminuria is 2 fold.

SBP is the risk factor in the FRS.

The Reynolds score includes:
HgbA1c
CRP
FH of premature MI
Age
Gender
SBP

Total and HDL
Smoking

The following do not have RCTs supporting intervention: Hi salt diet (???), LVH, carotid intimal-media thickness, microalbuminuria, HS-CRP and other inflammatory markers.

HEMODYNAMIC AND TOD. T Giles

DIASTOLIC HTN:
High DBP predicts CVEs in youth, But low DBP independently predicts risk in elderly.
DBP HTN occurs in youth and with abdominal obesity.
DBP HTN of youth has high SNA and RAAS, increased HR and CO, and hi PVR.
NICE says to use BBs in "young" (< age 60) and in high SNA patients.
(This is opposite of the low renin status of the elderly.)

Arteriolar hypertrophy in chronic HTN: arteriosclerosis and nephrosclerosis.
Mechanical factors and Humoral factors (NE, Ang II) cause arteriolar vascular hypertrophy. >> ^ pressure dependency on renal Na and H2O excretion.

SYSTOLIC HTN:

In the young, obese	^DBP, ^HR, **capillary rarefaction**
In the Non-obese with wide PP	Either a Stiff aorta OR a small aorta with NL elasticity
Elderly	Stiff aorta, increased aortic diameter, collagen deposition Increased PP.

Augmentation Index (AI) = (P2-P1)/PP as estimated in the aorta.

P1=the peak cardiac systolic pressure
P2=summation of P1+reflected wave
PP=SBP-DBP.

AI is inversely and strongly related to event free survival.
PWV is strongly and directly related to ACM.
Both of these are strongly related to arterial stiffness.

The central aortic pressures are estimated by radial tonometry using a transfer function.

CLASSIC POSITON: In the elderly, high reflection leads to similar BPs in central and periphery.

GARY MITCHELL STUDY (Hypertension 2004;43:1239): 1) Aortic stiffness measured by Central PWV **(carotid-femoral PWV)** increases dramatically with age. 2) Peripheral stiffness (2^{nd} and 3^{rd} generation branches) measured by **CB-PWV (carotid brachial PWV)** remains flat. 3) **Forward Pressure Wave increases with age**. 4) The AI increases to middle age, then declines in older ages in women; increases with age in men.

In the young, lower reflection leads to higher peripheral SBP compared to central SBP. **With age, Forward Wave pressure increases whereas reflected wave pressure and the AI remain relatively flat. Thus, Forward Wave Pressure rather than wave reflection, are responsible for most of the increase in SBP and PP in the elderly.**

In the young, the peripheral arteries are stiffer than the aorta and there is an increase in stiffness from the aorta to the periphery. With age, the aorta becomes stiffer, whereas the 2^{nd} and 3^{rd} generation muscular arteries have the same stiffness, leading to reversal of the normal central-to-

peripheral arterial stiffness gradient (i.e., central stiffness > peripheral stiffness), a shift of reflecting sites to more distal locations, and a reduction in relative amplitude of the reflected pressure wave.

Increased forward transmission of a larger forward wave may expose the peripheral small arteries and microvessels to damaging levels of pressure pulsatility.

Mathematics of measuring aortic stiffness: PWV=(Eh/r)^0.5, where E=elastic modulus, h=arterial thickness, and r=arterial radius. This explains why the smaller peripheral arteries have higher PWV. Exacerbation of myocardial ischemia is flow-dependent.

Parameter	Young	Old
Aortic stiffness	Baseline	Increased
Forward pressure wave	**Baseline**	**Increased**
Central PWV (Carotid to Femoral)*	Baseline	Increased
PP	**Low**	**Hi**
DBP	**Medium**	**Low (Hence, coronary flow is decreased.)**
ISH	No	Frequent
High amplification of pressure: central to peripheral	Present	Absent
AI: classical presentation	0	Positive
AI: Mitchell	Baseline	In women, AI increases in middle age and declines in old age. In men, AI gradually increases
Reflection: periphery to central	Low	Hi in middle age, Low in old age.
SBP	Peripheral SBP > Central SBP	Peripheral SBP= Central SBP
Susceptibility to peripheral pressure	Baseline	Increased
CAFÉ results	Amlodipine-perindopril (looks Young)	Atenolol-bendrofluthiazide (looks Elderly)
Peripheral PWV (Carotid to brachial)*	Baseline	No change
Stiffness from aorta to periphery	Increasing	No change
Reflected wave amplitude or reflected Pulse wave	Baseline	No change

*PWV is a close correlate of arterial wall stiffness.

In the Mitchell study, there appears to be two distinct patterns: Young: a higher PP in the periphery as compared to central aorta, owing to dissipation of the reflected wave by compliant peripheral vessels. In middle age, the increasing PWV leads to premature return of the reflected pressure wave which leads to a positive AI. However, in elderly patients, the even higher central arterial stiffness actually reduces amplification and reflection and brings AI back down once more.

In HTN, the large arteries undergo fibrosis of the media-adventia causing stiffness. In the peripheral arteries, the pathology is in the intima-media (proliferation of smooth muscle cells) and increased SVR.

Section 4.

HYPERTENSIVE HEART DISEASE T. Giles

LVH criteria: Children: >51 gm/$m^{2.7}$. Men: >131 gm/m^2; women > 100gm/m^2

ECG strain pattern predicts CHF.

LVH doubles the risk for ACM.

***Drug classes can regress LV mass: ARBs 13%, CCBs 11%, ACEIs 10%, Diuretics 8%, BBs 6%.(Meta-analysis by Klingbeil Am J Med 2003;115:41-6).**

LIFE study: Losartan superior to atenolol for CVA but not MI prevention.

(There is a strong correlation of LVH with CVA)

*HTN is the number 1 risk factor for chf.

*In the UKPDS trial, tight (<150/85) vs loose (<180/105) control decreased CVEs by 21 to 56%. The strongest reduction was for chf.

*In HYVET, Indapamide ± perindopril decreased chf by 64%.

*The E:A ratio, EARLY diastolic filling (passive) divided by LATE diastolic filling (atrial kick), ordinarily is >1 (the ventricle relaxes and blood from the atrium is naturally brought into the ventricle more rapidly than during the atrial kick), but is <1 with diastolic dysfunction.

These observational data suggested that BP meds would reduce diastolic CHF (CHF with preserved EF) and reduce CVEs but RCTs failed to support this. (A beautiful theory was slain by an ugly fact!!)

In HFPEF (heart failure with preserved EF), ARBs have not been shown to reduce CVEs.

The I-PRESERVE trial treated patients with NYH 2-4 and EF 45%+ with irbesartan but showed no reduction in CVEs.

In two other trials (CHARM and PEP), RAAS blockers were not shown superior, although the tendency was there.

CAMELOT (IVUS substudy Sipahi JACC 2006;48:833): The observational analysis indicates that a lower SBP (<120/80)is associated with decrease in atheroma volume.

J-Curve pattern: data from INVEST (2006) suggests it reaches a nadir in benefit of DBP of 84, then j's upward (Messerli INVEST Am Ht J 2006;151:1072-9).

However, data from CAMELOT (2006) and Framingham (2005) suggest otherwise.

THE BRAIN AND HYPERTENSION. A. Gradman

1 in 3 North Americans with CVA will become demented.

The PAR of HTN for CVA is 49%.

BBs do not lower CVA risk relative to other drugs.

For CVA,

More effective: Diuretics, ARBS & CCBs.

Less effective: BBs (& ACEIs!!) (Lindholm met-analysis on BBs; PROGRESS trial showed decreased CVEs did not occur until indapamide was added to perindopril.)

Obtain troponins for ischemic CVA.

For Rx of acute CVA:

No TPA, BP goal is <220/120 (the "twenties")

TPA, BP goals is <185/110 and maintain <180/105.

Use labetolol IV, nitropaste or nicardipine IV. If refractory, nitroprusside.

After 24 hours, if stable, restart BP meds:.

Once it is safe to reduce BP:

For DBP, there is no J curve down to 80.

Recurrent CVA: Main guide = PROGRESS trial (perindopril+indapamide vs Placebo): 28% RRR. Perindopril by itself was ineffective! Therefore, PROGRESS would indicate to use both diuretic and ACEI.

Immediately post CVA, the Target BP reduction is 10/5 and eventually 140/90.

Vascular Cognitive Impairment (VCI)

Vascular risk factors for AD: 1) obesity, 2) SBP 140+, 3) cholesterol 251+. Each carries a RR=2. When all 3 are present, the RR=6.

For persons at risk for VCI, treatment of HTN is level IA evidence (!! Unlike the treatment of ^ glucose and ^ lipids which are IIc)

Post CVA BP lowering reduces post CVA dementia: IB.
Primary prevention of dementia: lower BP: IIaB.
For age 80+, this is not well established.

VCI may occur as a result of silent infarcts and "leukoaraiosis" (white matter lesions).
HTN is linked to both dementia and AD.
Lowering BP is recommended to prevent VCI.

HYPERTENSIVE RENAL DISEASE. M. Weir

2 sections: 1) non-DM CKD ± proteinuria; 2) DM CKD.

1) non-DM CKD: MDRD, REIN, REIN-2, and AASK

Bottom line:
>None of the trials examined hard outcomes.
>Lower BP goal may reduce decline in GFR in those with 1+gm proteinuria.
>Proteinuria independently predicts CKD progression.

MDRD: Patients: GFR 13-55. (No insulin-dependent DM).
Target BP <125/75 vs <140/90.; achieved MAP: 93.5 vs 98.5. MAP differs by 5.
In the tighter control (<125/75), the decline in GFR was less, especially for 1+ proteinuria.

REIN2: Patients: GFR=34; BP137/84; no DM. Achieved BP 130/80 vs 134/82. MAP differs by 2. No effect on renal outcomes.

AASK: Patients: hypertensive renal disease (no DM). Urine protein 0.5gm/day. Achieved BP 128/78 vs 141/85 produced no effect on GFR decline.

NB: Hypertension from "In The Clinic" states that BP goal for 1gm+ proteinuria is <125/75 (i.e., lower than for CVD and based on MDRD) and for significant comorbidities (CV dis, DM) <130/80.

2) DM CKD: IDNT & RENAAL

Bottom Line:
RAAS blockade prevents 1) microalbuminuria, 2) progression from micro to macroalbuminuria, 3) progression from macroalbuminuria to renal events or death.
No RCTs examined different goals on renal outcomes.
No RCTs examined targeting lower proteinuria independent of BP.
IDNT: Patients with DM2. Irbesartan vs amlo vs placebo. ARB best at lowering renal endpoints or death. (Correlation of lower BP with better renal outcomes… but didn't adjust for proteinuria.)
RENAAL: Patients with DM2 and advanced renal disease. ARB vs Placebo. RR 28% for ESRD, creatinine doubling, or death. **In RENAAL:**
Change in proteinuria is strongly correlated with renal outcomes after BP adjustment.
Change in BP control was not correlated with renal outcomes after proteinuria adjustment.

Over all trials, RAAS blockade provides a 20% RRR which is more at higher levels of BP (i.e., 140/90+).

3) RAAS blockade is not a substitute for poor BP control. ACCOMPLISH results:
Amlo vs HCTZ reduced progression to CKD and reduced CKD and Death.

INSULIN RESISTANCE, METABOLIC SYNDROME & DIABETES. M. Weber

MS carries 1.8 x risk for CV mortality (NHANES follow up study)/
AASK also showed lower survival in those with metabolic syndrome.
Obesity causes an increase in both SNA and RAAS, both of which lead to HTN.
Increased visceral adiposity >> ^ TNF-a & Leptin > hepatic TGs > peripheral and hepatic insulin resistance.
(Leptin leads to satiety but the obese are resistant to this effect.)
70% of patients with 1st MI have IGT or DM.
Diuretics are most and ARBs are least diabetogenic.
Trandopril-verapamil is better than losartan-HCTZ in preventing new DM (STARLET trial).
Connection between DM & HTN is mediated by hyper-insulinemia causing:

a) cytokines, TNF-a, interleukin &
b) renal pathology (abnormal Na handling and proteinuria)

Both of these cause SNA and thence HTN.
Thus, increased SNA can be caused by Ang II, increased insulin, and obesity.
DM prevalence: 26 M & 8% (versus 72 M & 29% for HTN)
DM incidence: 1.9M/yr
Increased arterial stiffness (from glycation end products & atheromas), hyperinsulinemia (Na retention, SNA activation), and volume expansion are all factors in hypertension in diabetes.
Importance of multiple risk factor intervention in DM: HgbA1c, BP & lipids:
Steno-2 (Gaede NEJM 2008).
In ALLHAT the mean increase in FBS for the CTDN arm was 3 to 4 mg/dL versus the amlodipine and lisinopril arms. (Black. Diab Care 2008;31:353).

Section 5.

RENOVASCULAR HYPERTENSION. A. Gradman

RAS (Renal Artery Stenosis) causes ^ Ang II, which causes 6 things:
Vasoconstriction (via alpha1 receptor)/ Na retention/ aldo release/ ED(endothelin, OS, PGh, remodeling)/ SNA/Myocardial Tox.
The effect of Ang II on SNA is a) via CNS stimulation, b) via adrenal medulla's release of norE and E, c) via facilitation of sympathetic neurotransmission at nerve endings (Reid IA. Endocrinology 1998;126:2749-56).

Goldblatt experiments:
1) Alterations in SNA (e.g., cord transection, adrenalectomy) did not cause long term decrease in BP; 2) Constriction of aorta above kidney caused HTN but below kidney did not.

Renal artery stenosis (RAS) accelerates CHF and CVA and has a 4x increased risk for CAD.
RAS of 75%+ is associated with 25% decrease in survival.

Atherosclerotic-RAS prevalence:

SITUATION	RAS Suspected	Having coronary Angiography	PVD	AAA	ESRD	CHF
Percent prevalence	14	11-18	25	33	41	54

Hemodynamic effects of arterial stenosis: Flow begins to be seriously reduced at 72% stenosis, descending rapidly to 0% at 85%.

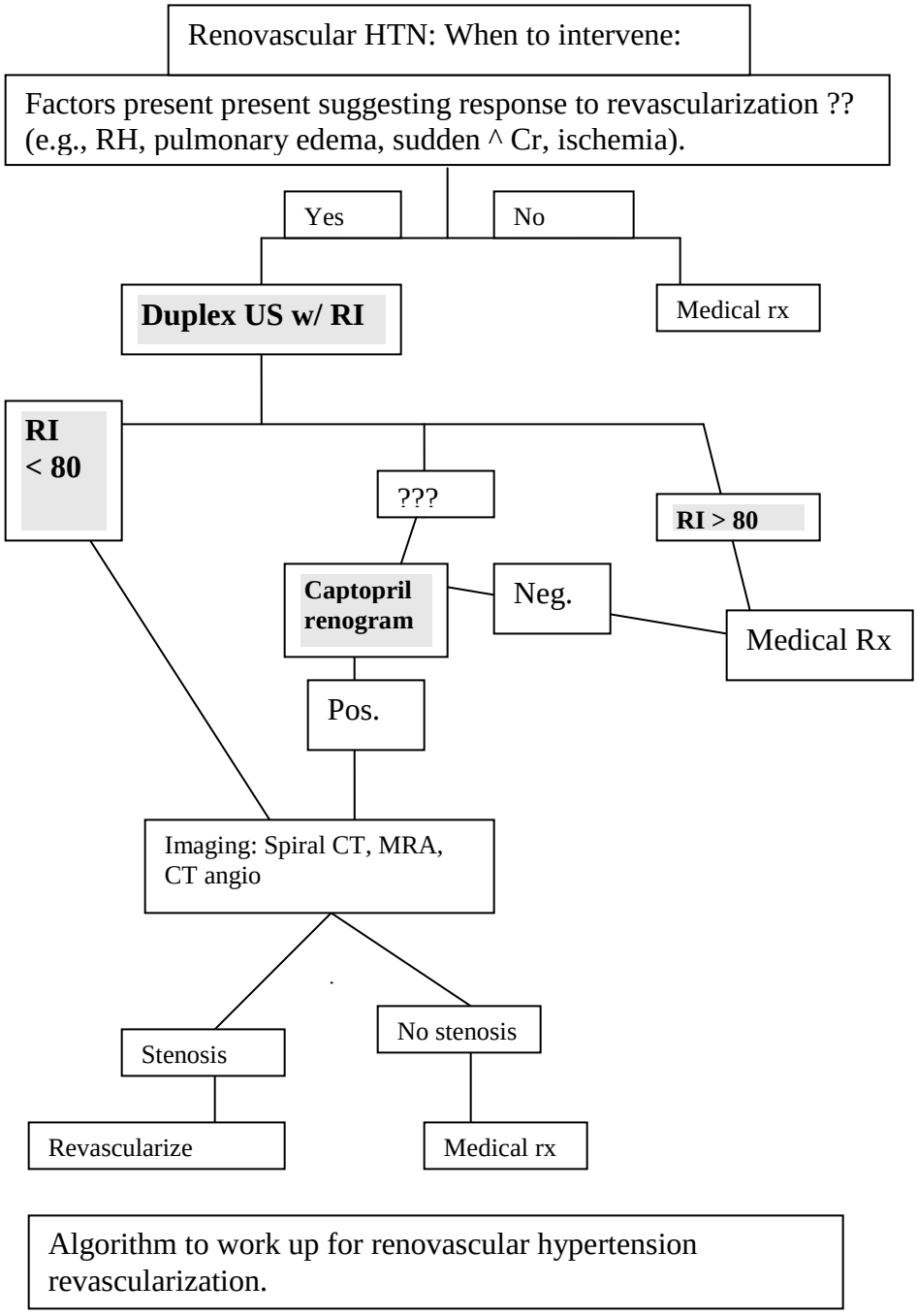
Renin release and Pd/Pa (pressure distal to stenosis /pressure in aorta): At 0.9, renin begins to increase and it peaks at 0.5, after which it falls dramatically. However, even with no flow, renin is still increased. The multiple increase in renin is 3.5, 2.2 and 2 in the stenotic renal vein, the contralateral non-stenotic renal vein, and the aorta, respectively.

FMD(fibromuscular dysplasia)-RAS: Stenting improves or cures HTN in 75%.+
AS-RAS: ASTRAL: Stenting versus medical rx gave no improvement in BP control, GFR decline, or CVEs.

Use ACEI or ARB as part of anti-hypertensive regimen for RAS.
1980s: CCBs and ACEIs; 1990s: ARBs and statins.

Indications for renal vascularization:
RH, recent rise in S-Cr, evidence of reduced diastolic blood flow. Increase in RI (resistive index = (PSV-MDV)/PSV (PSV=peak systolic velocity, MDV=minimum diastolic velocity), loss in GFR during BP rx with an ACE or ARB, flash pulmonary edema.
As stenosis increases, the MDV decreases and the RI increases.

The captopril renogram determines the relative function of each kidney under a challenged test, captopril given 1 hour before imaging which improves GFR in the non-stenotic kidney and worsens GFR in the stenotic



Algorithm to work up for renovascular hypertension revascularization.

kidney.

ALDOSTERONISM. W. Elliott

DDx of Aldosteronism: Primary vs Secondary (hi renin from RAS or Renin tumor)

Primary: APAd, APCa, BAH, GRA, FHA Type II, **OSA**

PA is 1%, 8%, 13% and 20% in thoses with Stage I HTN, Stage II HTN, HTNsve Urgency, and RH respectively.

ARR (aldosterone-renin ratio) interpretation requires a) eukalemia, b) nl sodium diet, c)**cessation of meds other than verapamil, hydalazine, & alpha blockers**, d) mid morning serum sample after 10 minutes of quiet , e) seated.

For the ARR of 30+, the PAC must be in ng/dL (15+ is abnormal) and the RA should be in ng/ml/hr.

The 4 confirmatory tests are:

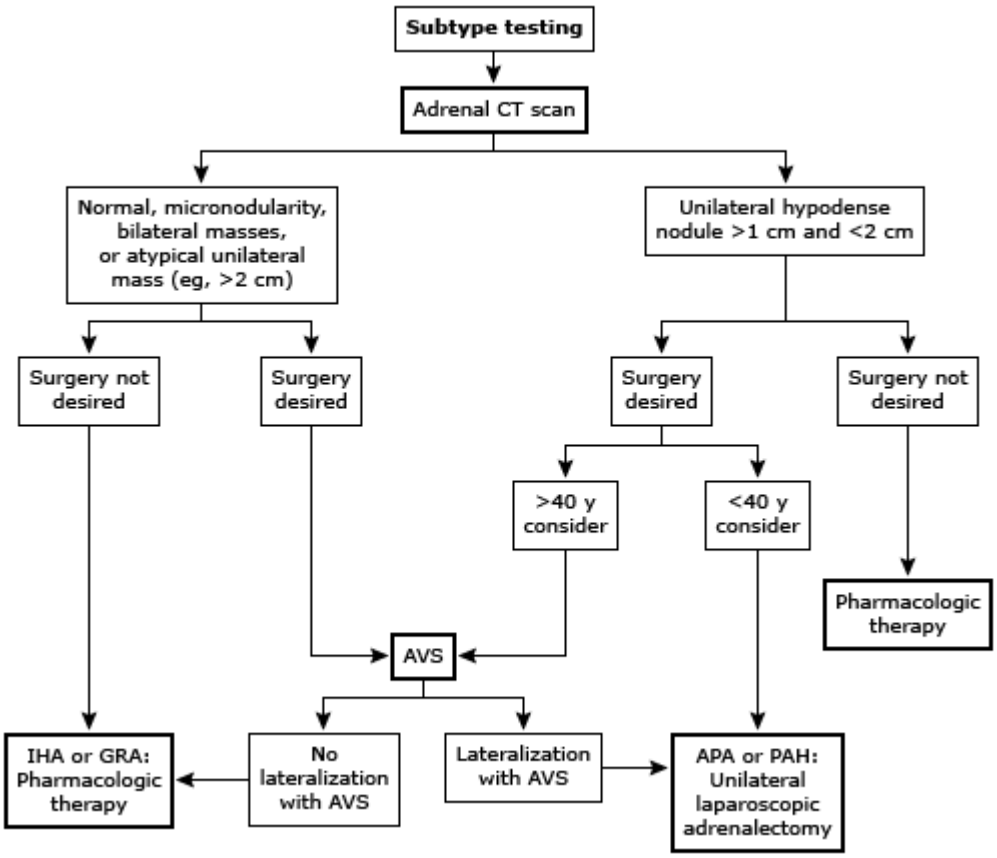
3 day Na loading (6gm NaCl/day) x 3 days and assay 24 hr urine for Na, Cr, & Aldo (confirmed if urinary aldo is 13 mcg/day (reference range 5-20); contraindications: CHF,CKD,uncontrolled BP)

2L NaCL infusion over 4 hrs (8am to noon) and assay plasma aldo post infusion. (confirmed if plasma aldo rises to >10 ng/dL; contraindications as above)

Fludrocortisone suppression: 0.1mg flu q6hr x 4ds. (confirm if plasma aldo >6ng/dLand low PRA and cortisol; may be difficult compliance)

Captopril challenge: 25-50 mg, assay plasma aldo at 0,1 and 2 hrs. Many false negatives.

U.S. Endocrine Society finds these 4 tests similar.



Imaging: Adrenal CT (MRI adds nothing) of chemically documented PA:

*Normal, micronodularity, or bilateral masses: a) if hi probability for APA, do AVS; otherwise begin meds. B) HU < 10 (suggests adenoma), 1cm+ mass and age 40+, do AVS; if age <40, go directly to laparoscopic adrenalectomy.

*APCa is 4cm+, irregular, heterogenous, calcified, enhancing, HU 10+ (suggests CA).

Long term cure of HTN is < 50%. Cure is more likely if there are fewer meds, younger, +FH, +ve BP response to spironolactone, higher pre-op aldosterone/renin activity and urinary aldosterone excretion rate (>13 mcg/day).

Medical Rx: Spironolactone: gynecomastia dose related. 7% to 50% at 50mg to 150 mg.
Eplerenone is more expensive but weaker. Amiloride requires large doses.
Typical reductions in SBP is 7 mmHg versus 19 mmHg for eplerenone and spironolactone respectively.

APA rarely occurs in MEN1 (pituitary, parathyroid hyperplasia, pancreatic tumors)

Licorice inhibits 11betaHSD2 which ordinarily would convert cortisol to cortisone.

PHEOCHROMOCYTOMAS. W. Elliott.
Pheo rule of 10s: 10% extra-adrenal, 10% ca, 10% bilateral, (now 50% familial), 10% recurrent, 10% in children, 10% discovered as incidentaloma.

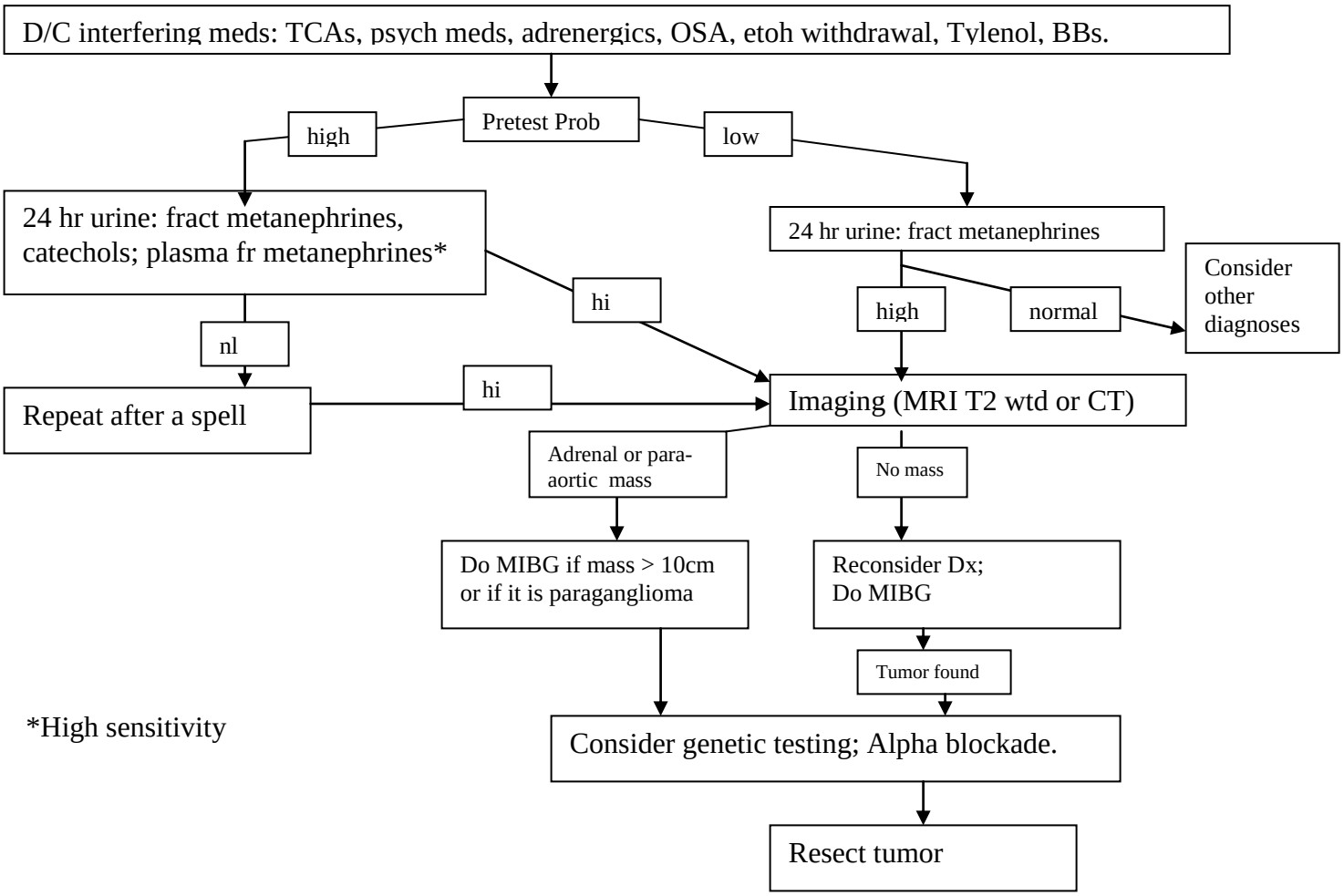
In RH, prevalence may be as high as 14-25%. Also screen pressor response to anesthesia.

Screening: 1) urinary metanephrines & catecholamines. With S & S of 98% and 98%; **2) plasma free metanephrines (special handling) S&S: 99%** & 87%. **Only 77% specificity in those over age 50**. Costs 2x as much as urinary tests. Requires quick refrigeration, centrifugation, separation of plasma, and prompt assay. urinary tests have similar s & s. Plasma free metanephrines are helpful for high probability cases, which would include: High HU, FH of pheo, or presence of an hereditable syndrome.

Interfering meds: tricyclics, L Dopa, adrenergic agonists (amphetamines), OSA, physical stress, antipsychotics, withdrawal from clonidine, ethanol, tylenol, BBs.

(confirmatory tests: clonidine & glucagon suppression tests not done)

Imaging: **MRI is preferred for imaging pheos (unlike imaging for primary aldosteronism). T2 weighted MRI S&S=92&97. MIBG scan is indicated for paraganglioma or metastatic pheo**. S&S 88&84. 98% intra-abdominal, 90% intra-adrenal.
S&S of CT for unilateral adenoma is 78 and 75%.
Imaging algorithm: MRI or CT negative, consider MBIG. If MRI or CT positive and shows >10 cm adrenal mass or a paragangionic location, do MIBG. If MIBG is normal, do genetic testing (i.e., a cancer is excluded, so this makes it more likely to be a genetic syndrome.)



*High sensitivity

Preop: if inpatient, phentolamine. If ambulatory, phenoxybenzamine x 2 weeks. Beta blocker not necessary. **If ca, use metyrosine**. **If BP poorly controlled, CCB.**

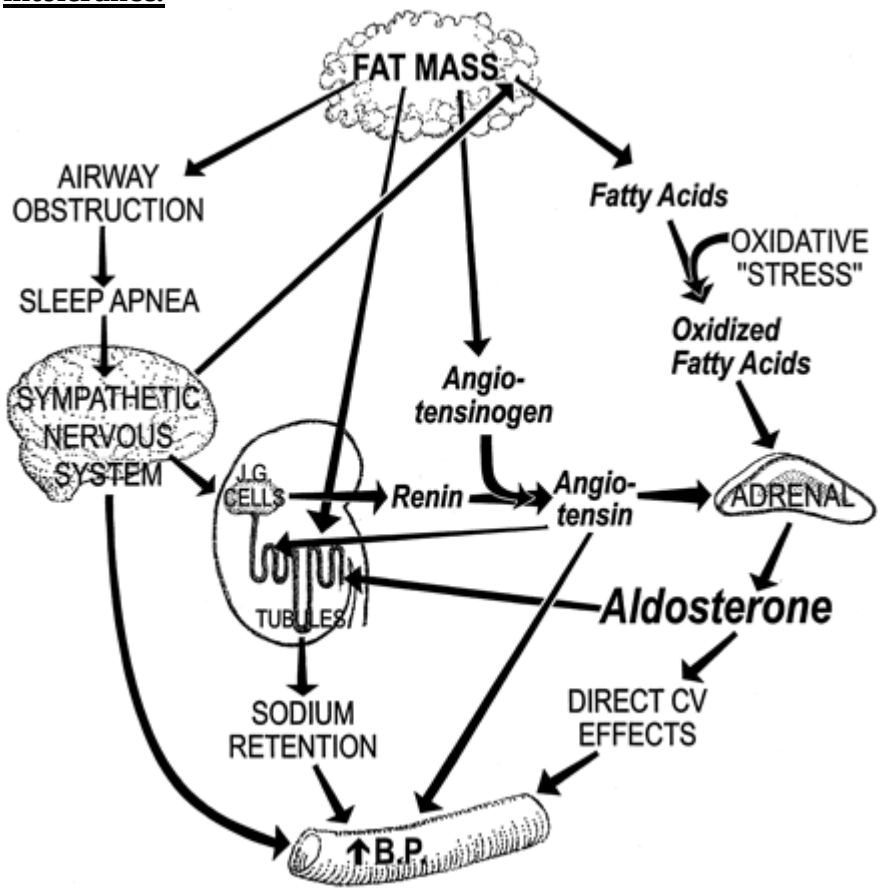
Post Op: 1) screen for genetic diseases. Ca, PTH (MEN II), TSH, AM cortisol, glucose monitoring. If genetic, assess relatives (TSH, cortisol and glucose may be abnormal due to adrenalectomy). 2) repeat chemical test that led to Dx.
For metastatic pheo, use chronic phenoxybenzamine or alpha methyl paratyrosine, obtain MIBG for radiotherapy, and use chemotherapy.

MONOGENIC CAUSES OF HYPERTENSION. T Giles. See tables for pheo & non-pheo.
The inherited tendency to HTN resides primarily in the kidney.

OBSTRUCTIVE SLEEP APNEA. T Giles.
OSA causes SNA, OS, Inflammation (^CRP, TNF-a, IL-6), ED

RH has an estimated prevalence of 10-15% of hypertensives (7 to 10 M in U.S.)
Prevalence of OSA in RH is 83%.
Both PA and Non-PA respond equally to spironolactone.
OSA is the most common cause of RH (64%)
Obesity and OSA both raise aldosterone (Goodfriend Hypertension 2004; 43:518) possibly via SNA.
Aldosterone is correlated with apneic episodes in high aldosterone states but not in normal aldosterone states.
Patients at high risk for OSA were 2x more likely to have primary aldosteronism.
The risk for OSA increases with increasing ARR.

Spironolactone reduces the severity of OSA in RH by 30 – 50%.
All diuretics reduce apneic episodes in HTN.
Na intake is correlated with AHI in CHF.
CPAP decreases MSNA.
In patients with RH and OSA, renal sympathetic denervation lowers BP, AHI, and glucose intolerance.



1. **PATIENT 1: HTN &** Real and theoretical links connecting obesity to hypertension. From left to right, the arrows indicate the effect of excess fat on the upper airway to cause obstructive sleep apnea, with consequent stimulation of sympathetic impulses that cause renin release and vasoconstriction; a poorly understood effect of excess fat on the kidney to cause sodium retention; production of angiotensinogen by adipocytes; and production of nonesterified fatty acids by adipocytes leading to generation of putative adrenal stimuli. Fatty acid release is stimulated by the sympathetic discharge that follows apnea. Aldosterone secretion is postulated to be increased by the activated renin–angiotensin cascade and by oxidized derivatives of fatty acids. Hypertension and vascular pathology is viewed as a result of direct sympathetic stimulation, sodium retention, and the direct and indirect effects of angiotensin and aldosterone, all increased by obesity to levels inappropriately high for a given subject's fluid volume status. (Goodfriend Hypertension 2004; 43:518)

DIABETIC NEPHROPATHY. M. Weber
He went through the DDx of proteinuria without urinary cells.
Foot process disease: lymphoma, leukemia, NSAIDs, ampicillin.
Membranous nephropathy: CA, AI disease

FSGN: heroin, HIV, AA
Membranoproliferative nephropathy: Hep C, other chronic infections, SLE.

In these patients, although lower BP goal (<130/80) is recommended, RCTs are insufficient to support this goal. The following are somewhat supportive:

a) The HOT substudy of diabetics supports DBP $\leq$ 80 vs $\leq$ 90
b) Observational data of multiple trials of a meta-analysis
c) IDNT: The mean achieved SBP strongly correlated to renal endpoints.
d) The UKPDS trial tight BP control reduced CVA, DM endpoints, and microvascular outcomes.

In HOPE, ramipril reduced CVEs in DM with Scr<1.4 and 1.4+ but ramipril was more effective in those with SCr of 1.4+.

RAAS blockade reduces ESRD by 20%.

In DM-2 (IDNT [Irb vs amlo vs plac], RENAAL[Losar vs plac], MicroHope[Ram vs plac]) and in DM1(Lewis 1993), RAAS inhibition reduces ESRD, doubling of Cr & death.
It takes a greater MAP in DM nephropathy versus normals to achieve the same Na excretion.
Proteinuria is a biomarker of therapeutic benefit (RENAAL study).

PATIENT 2: HEART FAILURE. T. Giles

As per the AHA guidelines (2007), the BP target is <130/80 for high CAD risk (10yr FRS 10%+), DM, CKD, CAD equivalent.

The BP target is <120/80 for LV dysfunction.

Rosendorff et al. Circulation 2007; 115:2761-88.

In SOLVD with EF $\leq$ 35%, intervention with enalapril reduced mortality.

In CHARM, in patients with CHF, candesartan reduced CVEs and mortality. There were 3 chf groups: 1) LVEF $\leq$ 40% treated with Arb+ACEI vs ACEI, 2) LVEF $\leq$ intolerant to an ACEI and treated with an ARB, and 3) LVEF >40%. (This last one showed a trend but was not statistically significant.)

Use ACEIs in all patients with decreased LVEF, regardless of symptoms.

In EMPHASIS-HF, for NYHA II, elplerenone reduced ACM & hospitalization.

3 BBs were shown to be most effective in lowering mortality in patients with systolic CHF: Bisoprolol, carvedilol, and metoprolol SR.

In using spironolactone in NY HT 3 & 4,there must be a SCr < 2.5 in men or <2.0 in women and a K of less than 5.

In AAs with NYHT 2-4 on optimal Rx with ACEI, BB and diuretic, use a combo of hydralazine + nitrates (Taylor 2004).

PATIENT 3: DBP has a J curve at 84 mmHg for MI but not for CVA.

Data suggest that the J curve is less pronounced in patients who have undergone revascularization.
Spironolactone may counter the arterial stiffness in ISH.
Eplerenone and nitrates may also be appropriate.
Reducing DBP below 60 to 84 may increase the risk for CAD in some patients.
However, low DBP may simply be a marker of disease risk and not causative.
The impact of lowering BP on dementia is also uncertain (Chobanian NEJM 2007)

No clinical trials have examined the effect of lowering PP.

(Per Messerli JACC 2009;54:1827): RAAS blockers, DHP-CCBs & diuretics all improve arterial compliance and therefore allow greater perfusion in diastole. BBs lower peripheral BP more than central BP (pseudo-antihypertensive effect), with the exception of an a-b blocker such as carvedilol which can be given as XR daily or nebivolol (which causes has a vasodilatory effect via NO and also can be given daily). Decreasing heart rate alone such as with diltiazem and varapamil will improve diastolic perfusion. Short acting CCBs, hydralazine and minoxidil will reduce myocardial perfusion.)

In treating ISH, meds lower SBP more than DBP and diminish PP.

Meds reducing LVH are ARBs 12%, ACEIs 11%, CCBs 9%, diuretics 8%, BBs 6% (counterintuitive).

Drugs that lower HR (BBs, non-DHP-CCBs) allow for more perfusion of the coronaries whereas short acting DHPCCBs and hydralazine may create ischemia.

Patient 4. CHILDREN AND HYPERTENSION. W. Elliott
The BP target is generally <120/80.
Unlike with adults, do not combine meds until the maximum dose is reached.
Use 24 hour monitoring.
In one paper, an elevated LV Mass Index was > 51 gm/m2.7. This girls LV Mass Index was 45, i.e., this is normal (Sorof J et al. Hypertension 2002;39:903.).

Section 6.
LIFESTYLE MODIFICATIONS AND NON-DRUG THERAPY OF HYPERTENSION. S Oparil
Weight loss, exercise, and dietary Na restriction are the most effective BP lowering maneuvers.
Lowering Na may be the easiest to implement.

Reduction in SBP	**1.6**	**1.7**	**3**	**11.3**	**4.5 (MAP)**
Unit of intervention	**1 kg wt loss**	**1 gm K increase**	**1gm Na decrease***	**Exercise**	**d/c NSAID**

Reference for NSAID is from Townsend R. Hypertension Primer, 4th ed, page 481. *1/2 tspn of salt.
Visceral or body fat reduction is more important than weight reduction.
Body fat targets: Men: <16%; Women 22%.

Exercise reduces
***BP before change in weight (mean 11.3/7.5 reduction in meta-analysis).**
***HTN incidence by 18%.**
***adipokines which increase BP and inflammation.**
Exercise improves endothelial function, Coronary blood flow, SVR, insulin resistance, anabolic hormones, and interleukin 10.
Exercise requirement is 6 days/ week of aerobic and resistance training of 20 and 40 minutes, respectively.

DASH diet and low Na diet together lowers SBP by 11 mmHg relative to high sodium normal diet (Sachs nejm 2001; 344:3). The impact of the DASH diet was 2 to 6 mmHg and the impact of sodium ingestion was 3 to 6 mmHg, depending on the intake of Na or DASH, respectively.

Na:
The average is 5 gm/day (range 3 – 20) in the U.S. (about 200 meQ Na/day).
Na 100 meQ/Na 2.4gm ~ 40 meQ Na/gm.
Minimal requirement = 0.5 gm (about 20mEq).

Magnitude of BP reduction is directly proportional to the decrease in Na. (How is this affected by salt sensitive hypertension?)
Low Na has an improved effect with high K, Mg, and Ca.
TOHP I and TOHP II, RCTs, support reduction in CVEs when reducing Na by ~1 gm/day (=40 mEq/day) (1/2 tspn of salt) with RRR 21 – 52.
This is found even in the absence of HTN (all patients in the trial had preHTN DBP). (Cook. TOHP trial. BMJ 2007;334:885)

K:
0.6 gm reduces BP by 1.0/0.5.
The recommended dose is 4.7 gm (120 mEq). For K, there are 25 meQ K/gm K.
This dose was associated with lowering the BP by 8/4 and RRR for CVA and MI of 15% and 11% respectively in epidemiologic studies (observational analysis of TOHP I & II).
Reduction in CVA is BP and Non BP dependent.
The reduction of BP with increasing K is potentiated by low Na, high Mg and Ca, and may be more effective in blacks.
Na & K:
For a 1gm Na increase, ACM increases by 20%
For a 1 gm K increase, ACM decreases by 20% (observational data from NHANES—doubt!!).

In Low renin HTN (which suggests excess Na and volume) and in salt sensitive HTN, it is more important to decrease salt intake.

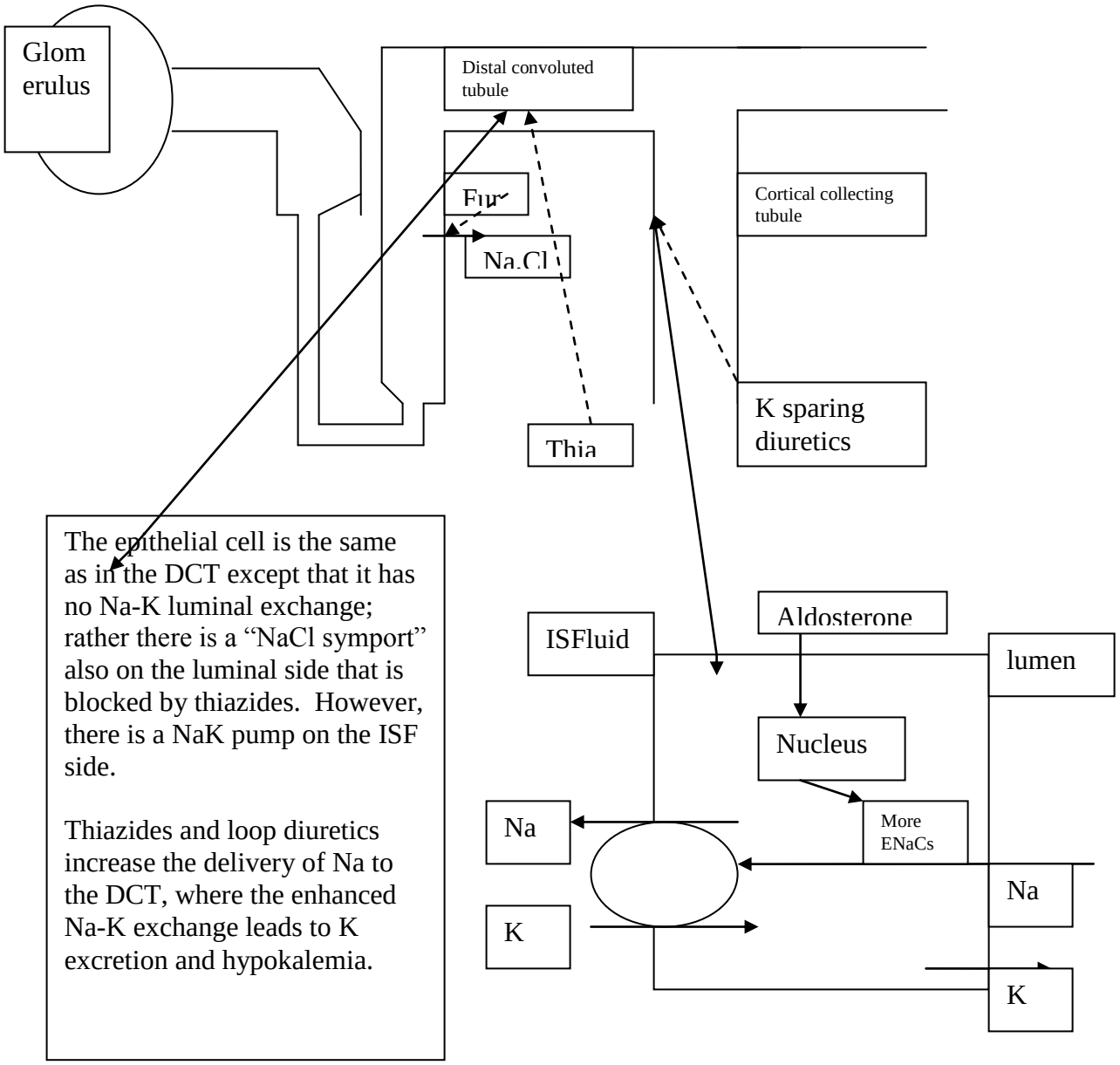
However, in high renin HTN, be cautious about decreasing Na intake.

A J curve may exist for Na but not for K.
Observational data suggest that Na < 3 gm/day (115 mEq) and Na > 7gm/day (270 mEq) increase risk.
A practical recommendation is to decrease Na to 1.5 to 2gm/day and increase K to 5 gm/day (Yang Archives Int Med 2011;171:1183)

Other compounds/nutrients:
Wakame (seaweed in Japan, 3.3 gm/day) also acts as an ACE I and lowers SBP by 14.
Ubiquinone lowers BP by 17/8

Garlic has BP lowering effects but at too high consumptions to be practical.
Natural ACE inhibitors: valyl troysin (sardines)
N3 FAs in high doses may lower BP.
Wakame at dose of 3.3 gm/day decreases SBP by 14.
Vit C not beneficial.
Vitamin D deficiency (<30) is associated with increase prevalence of HTN.
At high doses (5,000 U), BP reduction is 13/7.
Vitamin D decreases renin transcription via thyroid-steroid-retinoid receptor.
B6 reduces BP but only at very high doses, such as 300 mg. RDA =1 – 2 mg.
Cocoa and ubiquinone also may reduce BP.
Monounsaturated fat (olive oil, some nuts) will decrease SBP by 8 at 30-40 gm/day.

CLINICAL PHARMACOLOGY. W. Elliott


Glom
erulus
Distal convoluted
tubule
Fur
Na.Cl
Thia
Cortical collecting
tubule
K sparing
diuretics
The epithelial cell is the same as in the DCT except that it has no Na-K luminal exchange; rather there is a "NaCl symport" also on the luminal side that is blocked by thiazides. However, there is a NaK pump on the ISF side.
Thiazides and loop diuretics increase the delivery of Na to the DCT, where the enhanced Na-K exchange leads to K excretion and hypokalemia.
Aldosterone
ISFluid
lumen
Nucleus
More
ENaCs
Na
K
Na
K

	Contraindications	interactions	The drug potentiates…	The drug is potentiated by or level is raised by	Adverse effects	Lithium Toxicity increased	CYP3A4 metabolism
Thiazides Decrease IV volume.	Sulfa Dig, Li, NSAIDS, decreased intravascular volume.	NSAID v efficacy ^ excretion of asa PTH tests Antagonizes NorE	Muscle relaxants. Dig toxicity due to v K. amphotericin's & prednisone's effect on v K Li Toxicity		V K ED, hyperglycemia, hyperuricemia,	Xx Gastroenteritis; CNS Symptoms.	
Loop D ditto.		Ditto. Except for PTH tests & NorE	Ditto except for muscle relaxants		V K	xx	
K sparing: (3) Block aldosterone effect on kidney or Close Na channels (triamt & amilo)	ACEI, ARB, NSAIDs, **amphotericin B**	Ditto **Drugs metabolized by CYP3A4(1)**	Ditto			xx	Xx (1)
BBs (non selective: B1 & B2 activity) Decrease CO and renin secretion and may stimulate baroreceptor reflex reduce NE release. Membrane stabilizing.	Asthma, copd, pad, Intermittent adherence, SLE, bradycardia, heart block IDDM, PVD, WPW **Interferes with thyroid and glaucoma tests**	NSAIDs v its antihypertensive effect. Although Elliott lists cipro, warfarin, TCAs, & fluconazole, UTD does not find interactions.	**The bradycardia of digoxin** The cardiac effects of CCBs	**Fluoxetine (increases level)**	Sedation, depression, Vivid dreams GI upset vK, agranulocytosis, and Stevens-Johnson syndrome		
BBs selective							
BB a & b (vasodilate and ^ NO production).							
Alpha blockers	Patient at risk for falling. Chf (???)	**Some PDE5 inhibitors**			Dizziness, postural hypotension		
Central acting (only alpha 2 agonists are used) (CAAs)	Intermittent adherence (with clonidine) **AMD: Active liver disease**	**Nsaids and TCAs Antagonize CAAs**.	**Li toxicity**		Dry mouth, lethargy, somnolence, ED, mental slowing, Coomb's + HA	xx	
CCB-DHP Bind to Ca channel and decrease Ca influx into vascular smooth muscle.	**NONE!!**		**Cimetidine cyclosporine**	**Cimetidine Cyclosporine (maybe not amlo)**	Edema, antagonizes oral hypoglycemics, gingival hyperplasia.		
CCB-NonDHP	AV block, SSS, severe LV dysfunction or chf **Acute MI w/ chf.**		**BBs, digkoxin Alcohol, & Arbs, Cimetidine, Carbamazepine, Cyclosporine Cyp3a4(1)**	**Grapefruit juice**	vHR, ht block, constipation(verapamil)		Xx(1)
ACE Is	Pregnancy, ^K, RAS, severe AS, h/o **ACEI associated liver disease**	NSAIDS, K sparers.	**Li (^ risk for Li tox)**		^K, ^Cr	xx	
ARBS(2)	Pregnancy, ^K, RAS	NSAIDs.	**Li (toxicity.)**		^ K (dose dependent), ^ Cr	xx	
Renin inhibitors (Aliskiren)	Pregnancy (1/2 life=1 to 1.5 days)				Minimal, diarrhea		
hydrdalazine	Hi risk in cardiac patient	(3)					

(1) E.g. Azoles, erythromycin, anti-psychotics & diazepines, most chemotherapeutics, cyclosporin, SSRIs & TCAs, CCBs, and statins.

(2) The class of drugs with the fewest dose-related side effects. (Use with ISDN in AAs chf 2-4)

(3) Amiloride & triamterene close Na channels directly and spironolactone acts on the Na-K pump.

LANDMARK CLINICAL TRIALS. A. Gradman. See table.

NICE guidelines place BBs 4th line, except for <age 60, potential child bearers, or evidence of increased SNA. Do not combine BB w/ diuretics.

COMBINATION THERAPY. M. Weber

Inadequate response to monotherapy is often causesd by activation of counter regulatory mechanisms. E.G.: Diuretics >> decrease Na and volume >> Increase Ang II. This is countered by RAAS blockers. Multiple meds are required to achieve BP goals in many clinical trials.

> On average the standard dose reduces BP by only about 20% more than the ½ standard dose. In contrast, symptoms are dramatically increased by more than 4 fold when moving from ½ standard to standard for diuretics, BBs, and CCBs (but not for ACEIs or ARBs). Use of combination therapy at ½ standard dose produced additive effects as compared to ½ standard dose monotherapies.

What are the best combinations?

Additive combinations: there are 7 combos!!:

Diuretic combos: D-BB, D-ACEI, D-ARB, D-CCBs **(i.e., diuretics with all classes)**

CCB combos: CCB-ACEI, CCB-ARB, CCB-BB, CCB-D **(i.e., CCBs with all classes)**

~~ARB-BB, ACEI-BB, ARB-ACEI~~

Preferred combinations (per ASH) I.E., diuretic-CCB combos and BBs are absent!!

Diuretics: D-ACEI, D-ARB OR

CCBs: CCB-ACEI, CCB-ARB

Acceptable combos: All the other combos (including K sparors).

Discontinuation rates range from ARBs having the best and diuretics having the worst.

Documented reductions in CVEs have been shown for diuretics, ACEIs, ARBs, CCBs, and BBs, but not for centrally acting drugs, vasodilators, spironolactone, alpha blockers.

Combination of enalapril and felodipine decreased edema compared to felodipine alone.

In the VALUE study, patients controlled at 6 months compared to those not controlled at 6 months was strongly predictive of CVEs.

Per JNC7, compelling indications:

	Not	D	ACEI	ARB	CCB	BB	Ald Antag
CHF	CCBs	+	+	+		+	+
Post MI	Ds, **CCBs,** AA		+	+		+	
High CAD risk	AAs	+	+	+	+	+	
DM	AAs	+	+	+	+	+	
Post CVA	**CCBs**, BBs, AAs	+	+	+			

JNC7 says to use 2 drugs initially if SBP >20 above goal or DBP > 10 above goal.

Per meta-analysis (Bangalore Am J Med 2007;120:713 and Sanz G. Nat Clin Pract Cardiovasc Med 2008), relative to multiple single pills the fixed-dose combos improved adherence by 24% !!

The STITCH trial (Simplified therapy initially to control HTN) showed that fixed dose combinations of a **diuretic-acei or a diuretic-arb, compared to Canadian guideline** based care, improved BP control at 6 months.

The ACCELERATE trial showed that fixed dose **aliskiren-amlodipine** combination reached BP control faster than **monotherapy with dose doubling**.

In summary: initial combination therapy results in greater BP reduction, higher responder rates and reduced time to reach goal BP.

Section 7. DRUGS FOR COMPELLING INDICATIONS. W. Elliott. See separate tables.

RESISTANT HYPERTENSION. D. Calhoun

Simple definition: Hypertension requiring 4+ drugs (whether or not controlled), one being a diuretic.

In NHANES 2003-2008, the prevalence of RH among all treated hypertensives was 13% and was 9% of all hypertensives.

In Spain, the percent with RH was 15% of hypertensives.
1/3 of RH actually have WCH.

In **ALLHAT, the strongest correlate of poor control was black ethnicity, followed by LVH, CKD, DM, female gender, obesity, and older age.**

Here is the evidence for the role of refractory fluid retention in RH:
1. In RH, the prevalence of PA is 17-22%.
2. In a case-control comparison, RH patients compared to controls (nl BPs or BP controlled on $\leq$ 2 meds) had lower K (3.9 vs 4.3), higher plasma and urinary aldosterone, higher ARRs, lower renins (<1), higher prevalence of hyperaldosteronism, higher ANP and BNP.
3. BNP and ANP correlated with high aldosterone levels.

These findings suggest refractory fluid retention in RH. The mechanisms of this would be hyperaldosteronism, high Na intake, obesity, black ethnicity, CKD.

This is more of a problem in obesity and black ethnicity. (This explains why blacks have an inferior BP response to ACEIs as RAAS is already down regulated.)

The generalized treatment recommendations for RH are to include 1) a diuretic (preferably chlorthalidone), CCB, and ACEI or ARB. 2)spironolactone, eplerenone, amiloride. 3) alpha/beta blocker, 5) an alpha 2 agonist (clonidine or guanfacine), 6) hydralazine or minoxidil.

CTDN is significantly better than HCTZ in reducing 24 hour and night time BP.

In RH, spironolactone lowers SBP by ~25 mmHg in both PA and non-PA patients.
Spironolactone effected PA and non-PA equally.

In another study of RH, the decline in clinic SBP was 14 (de Sousa Hypertension 2010; 55:147-52).

For office SBP, in RH, spironolactone + a RAAS blocker was 2 times more effective than an 2 RAAS blockers (32 vs 13 change respectively).

When using a loop diuretic, hydralazine or minoxidil may be added (minoxidil may cause edema).

The average U.S. diet contains 12 gm of salt per day (200 mEqNa). Reductions of salt intake by one-half (6 gm/day (100 meQ)) lowers SBP by 7 mmHg. For very high salt intake (15 gm/day) versus very low intake (3 gm/day), the change in office BP is 23. The range of NaCl intake in the U.S. is up to 20 gm/day.

Renal nerve ablation has also been used successfully in RH with SBP decrease of 32 at 6 months.

Bedtime dosing of one BP med in RH lowers 24 hr SBP by 6 and nighttime SBP by 15 mmHg.

SUMMARY:
RH is increasing in prevalence.
Aldosterone and high NaCl ingestion contribute to intravascular fluid retention.
RX includes lifestyle change and use of diuretics.

RENAL NERVE ABLATION AND CAROTID BAROSTIMULATION. G. Bakris
SNA stimulates alpha receptors of afferent vessels (vasoconstriction) and ENaC (Na retention) and beta receptors of JG apparatus (renin release).

Renal efferents, but not renal afferents, are likely to regenerate.

SNA causes vasoconstriction in striated muscle, insulin resistance, and Na retention, and also effects the heart causing hypertrophy, arrhythmia, increased O2 consumption, systolic CHF and diastolic CHF.

Renal afferent signals derive from 1) mechanical distortion in the renal pelvis from unilateral obstruction of, say, a stone, and 2) chemical changes (e.g., ionic or osmolar concentration) in the renal interstitium.

In the first full scale RCT (SIMPLICITY 2) in RH, the average SBP decline was 32 (from a baseline of 178).

Baro-reflex activation inhibits SNA and enhances parasympathetic activity, effects which lead to a decreased heart rate, vasodilation, decreased arterial stiffness, increased Na excretion, and decreased renin release.

Baro-stimulation reduces LV mass at 3 and 12 months.

In the Rheos pivotal double blind RCT, the mean decline in SBP was 35 (from 178). Therapeutic efficacy improved over time from 6 to 12 months.
There was sustained and increasing SBP reduction over 4 years, declining by 53 mmHg (!)

A more compact lead has been designed.

Section 8
HYPERTENSIVE CRISES. T. Giles
Emergency: TOD. Immediate reduction in BP required.
The level of TOD determines whether BP should be quickly reduced.
Urgency. No TOD. Manage orally with outpatient f-u.

3 types of Emergency: cerebral, cardiac, and other.
Other may include a pheo, clonidine withdrawal, eclampsia, RPGN.

Emergency:
1) **within 2 hrs, reduce MAP by no more than 25%**
2) **Within 2 – 6 hours, target 160/100**
3) **Avoid excessive falls in BP**.

Hypertensive encephalopathy:

Characterized by cerebral hyperperfusion, loss of blood-brain barrier, vascular necrosis and OS.
Lower MAP to normalized blood flow over 30 to 60 minutes.
In the chronic hypertensive, the goal is to lower MAP to 120 (i.e., 160/100).
Hypertension with intracranial bleed is usually secondary to increased intracranial pressure and irritation of autonomic NS ("Cushing's effect"). It disappears rapidly and has little effect on outcome.
The clues to this are that a CVA will have sudden onset with focal signs, whereas hypertensive encephalopathy will have more gradual onset with n, v, ha, and confusion. Imaging with CT or, preferably MRI, can be done to r/o CVA. Clearly, the CVA should not be treated with aggressive BP lowering.
Pulmonary edema: Use nitroprusside and trimethaphan; avoid hydralazine.
DDx of aortic dissection: MI, PE, rupture of sinus of valsalva, acute abdomen, stroke.
Emergency usually has >220/140; urgency is >180/120 (HA, SOB, epistaxis)
Follow up either the same afternoon to 4 days.
Hypertensive Emergencies (HEs)

Drug	Advantage/ Indication	Disadvantage/ contraindication	AEs
Sodium Nitro-Prusside	Most HEs. Titratable Instantaneous	Light resistant equipment Constant Supervision **May ^ ICP. (however, can use in hypertensive encephalopathy)** **Contraindicated in Eclampsia**	N,V , muscle spasm
NTG	Similar to n-pr Dilates coronaries **Use in coronary ischemia**, LV failure, Post-op.	Careful monitoring Unpredictable Absorption	H,V,**methemo-globinemia**
Fenfoldapam	Most HEs. May not require Intra-arterial monitoring. (1) **Drug of choice in renal insufficiency (renal vasodilation)**	**V K** **Increased intra-ocular pressure, caution with glaucoma** Alpha 1 agonist	**V K,** ^ HR, HA, N, ECG changes, increases Intra-ocular pressure.
Labetolol	Inhibits both A & B receptors. No ^HR Effect persists 24 hrs. Give as boluses or Continuous infusion **Give for aortic dissection(2)**	**Do not use in** **a) heart block OR intrinsic heart disease.** **b) pulmonary edema** **c) sympathetic increase (cocaine, pheo, MAO intoxications, guillain-barre)**	
Nicardipine	Ease of administration Usually effective Reduces both Cerebral and cardiac ischemia.	^ HR ***Caution with coronary insufficiency** ***Do not use nicardipine in heart failure.**	
Phentolamine	Pheos (drug of choice)	^HR Postural hypotension	

(1) This drug, a post synaptic dopamine agonist, causes renal vasodilation, diuresis, and naturesis.
Along with this, you can give a loop diuretic, furosemide 20-40, torsemide 5-10, or ethacrynic acid 25-50.
Do not give sublingual nifedipine. Re-institute meds or if no prior meds:
(2) Give for aortic dissection to heart rate <60 and SBP 100-120 or lower as tolerated.

1) if not volume depleted, give furosemide 20 mg iv over ½ hour OR captopril 6.25 to 12.5 over 15 minutes.

Common mistakes: 1) Did CVA cause HTN or HTN cause the CVA. 2) Excessive duration of iv rx.

Rx for hypertensive urgencies:

Drug	Dose	onset	duration	Comment
Captopril	6.25-12.5	15 min	4-6hrs	
Clonidine	0.2 mg, then 0.1 mg/hr up to 0.8 mg total	0.5 – 2 hrs	6-8hrs	
furosemide	20mg	0.5-1hr	6-8hrs	
Labetolol	100-200mg	0.5-2hrs	8-12hrs	
Nifedipine*	5-10 mg	5-15min	3-5hrs	**Fastest action**

F-U in 1 to 3 days. ***Do not use in chf.**

HYPERTENSION IN CHILDREN: DIAGNOSIS. S Oparil

Three reasons to care:
TOD (particularly LVH, CiMT, & renal damage) occurs frequently in children.
2ndary hypertension is more common in children.
BP in children strongly predicts adult hypertension.
WCH in children may be as high as 35%, suggesting an increased role for 24 hr ABP monitoring.
LVH prevalence is 30% - 40% in those with mild HTN or pre-hypertension.
For 2ndary HTN in children, consider Acute GN, HSP, HUS, hypercalcemia and neuroblastoma.
All children with HTN should have an echo.
LV Mass is related to the following measures in end diastole: interventricular septal thickness, the internal diameter of the left ventricle, and the left ventricular posterior wall thickness.

For LVH a conservative cutpoint is 51 gm/$m^{2.7}$.
If there is LVH, the echo should be repeated periodically.
The prevalence of LVH in hypertensive kids = 30 – 45%.
Carotid intimal medial thickness (cIMT) is strongly related to HTN in children.

HTN and progression of CKD: In children with intensified BP control there was a slower progression to the CKD endpoint (time to decline of GFR by 50%). **The % reaching renal disease in 3 years is about 20% !!**

In the magaement algorithm, **a child with pre-HTN (90-94th p'le) should have BP repeated in 6 months.**
Initiate Rx with a single drug. Increase dose to maximum or if an adverse effect occurs, then add another drug. As with adults, 2+ drugs are usually needed.

BP goals:
Uncomplicated HTN w/o TOD: <95%.
HTN with DM, TOD, or secondary HTN: <90%.
The acceptable drugs are the common adult drugs: diuretics, ACEIs, ARBs, and CCBs (not alpha blockers or cns modifiers).

As in adults, give ACEIs or ARBs in kids with DM or proteinuria.

HYPERTENSION IN CHILDREN: MANAGEMENT G Bakris

Initiate rx with lifestyle only if Stage I HTN and no TOD (UToD).
HTN: percentile 95th+
Pre-HTN: 90-94th
Adolescents with BPs 120/80+ have pre-hypertension.

Prevalence of childhood HTN is 3.2 to 3.5%.

In one High School screening program:
NT: 81%
PreHTN: 16%
Stage I HTN 2.6%
Stage II HTN 0.6%.

For 12 yo, for height in the 50th p'le, systolic BP is

P'le BP	Boys	Girls
50th	105	106
90th	119	120

Levels at which to consult a table:

age	SBP
3	100
6	105
9	110
12	115
15	120

HTN	percentile
Normal	< 90
preHTN	**90-94 OR BP 120/80+ even if <90th percentile**
HTN I	95-98 plus 5 mmHg
HTN II	99+ plus 5 mmHg.

Prior BP and BMI predicted subsequent HTN and pre-HTN. Race did not.

For preHTN, you might check for TOD (???????????????? Not sure of this ??????????) and, if negative, re-check BP again at 6 months.
For Stage I hypertension, recheck BP in 1 – 2 weeks. Same criteria as in adults (3 occasions, with elevation)
For Stage II hypertension, evaluate for TOD and treat.

PreHTN: initiate drug rx only if CKD, DM, CHF, or LVH.

For w/u in children, it is same as in adults (lytes, B, Cr, CBC, u/a) except routinely accomplish the following: FBS, F lipids, **echocardiogram, the renal U/S, and retinal exam.**

Other specific tests:

Loud snoring >>>>>> sleep study

For either:
BP at 99th P'le OR BP at 95th P'le and pre-pubertal:
Do renin, aldosterone, plasma and urine cortisol, plasma and urine catecholamines.
(i.e., check for hyperaldo, cushings & pheo.)
BP at pre-HTN with co-morbidities: Echo and retinal eye exam.
BP at pre-HTN and overweight: F lipids and FBS.

If there is no TOD, do 24 hour monitoring to r/o WCH.

HYPERTENSION IN THE ELDERLY. S Franklin

HTN: usual EH versus Elderly

Essential htn	ISH
160/110	160/80
^ resistance	Arterial stiffening
Small arteries	Large arteries
MAP	Pulse pressure

In ISH of the elderly, at each value of SBP, CV risk increases with decreasing DBP.

Pulse pressure is an indirect but important measure of vascular stiffness. It is associated with:
Cardiac complications: LVH/ Systolic and Diastolic dysfunction & CHF/ A fib
Large artery complications: CVA & MI
Microvascular complications: Renal disease/ White matter lesions/ cognitive decline.

Pulse wave velocity (PWV) and reflection:
In **young compliant arteries, PWV** is low (8 m/sec) and the wave arrives in **late systole**.
In **older stiff arteries, PWV** is high (12 m/sec) and the wave arrives in **early systole** (**hence, ^ PP**).
Consequently, there is decreased coronary perfusion (most coronary perfusion occurs in diastole), increased myocardial demand, and increased ED and atherogenesis.

> **In the Framingham cohort, Higher aortic PWV (carotid femoral PWV) gave a 48% increase in CVEs** whereas peripheral PWV (carotid-radial PWV), augmentation index, central PP and PP amplification bore no detectable risk. (Mitchell 2010)

Central SBP is a marker of cardiac afterload (PVR+stiffness+reflection).
Central DBP is a marker of ventricular-vascular stiffening, LVH and decreased LV relaxation (i.e., "uncoupling disease" of the heart and thoracic aorta).

Increased cardiac afterload presented to the compromised LV leads to diastolic dysfunction and heart failure (grade 2+ ISH).

There is definitely a J curve for DBP associated with ISH, with an inflection point at around DPB = 70.

A lower DBP is related to age, female gender, and Diabetes.

Treating ISH in the elderly is consistently associated with lower CVEs in SHEP, Syst-Eur, and Syst-China.

HYVET, which used indapamide ± perindopril, showed benefits in treating patients 80+.

Practical approach to managing HTN in the elderly:
*Take multiple readings before making a diagnosis
*Start low and go slow.
*Monitor both sitting and standing BP.
*Ask about orthostasis symptoms.
***If there is orthostasis, use the standing BP.**
*Be particularly cautious with the frail.

*for the higher PP, anti-hypertensive treatment causes a greater the fall in SBP for any decrease in DBP and this works to the advantage of decreasing PP.

HYPERTENSION IN BLACKS. G. Bakris

Compared to whites, blacks:

*develop HTN at an earlier age
*have average BPs much higher
*are as aware of their HTN as whites (82% vs 79%)
*are similarly controlled overall (47% and 46%).
*but have higher rates of treatment
*and, among those treated have lower rates of control
*have increased TOD (CKD AND LVH [more than a 10 fold difference]) and higher CHD & CVA
*are much more likely to die of heart disease and stroke and this accounts for the largest discrepancy in life expectancy (a differential of 8 years for males and 5 years for women).

5 life style and non-pharmacologic factors predict most of the non-pharmacologic excess risk: Inactivity, obesity, Na, low K, unhealthy diet(not DASH… low fat, high vegetables, fruits and complex carbohydrates).

IOM recommends 1.5 gm Na diet (63 meQ); JNC7 recommends 2.4 gm Na (100 meQ).

Physician related barriers to HTN control in blacks are a) lower expectations, b) lack of guidelines, c) failure to treat early, aggressively and to target, and d) increased co-morbid conditions making these patients more complex.

In blacks for monotherapy, diuretics (CTDN) and CCBs are the best choice. Thiazides make BBs and RAAS agents more effective.

Compared to whites, blacks have a greater response to diuretics and CCBs but a lesser response to ACEIs and ARBs.

In blacks, the target for primary prevention is 135/85
For secondary prevention, AFRS of 20%+, prediabetes, and diabetes also imply a target of 130/80.

ALLHAT:
Compared to whites, blacks had poorer BP control in each of the 3 arms.

BP control decreased in moving from CTDN to amlodipine to lisinopril.

Comparisons in Relative Risk for CVEs by race and drug comparison.

	Blacks		Whites	
	CTDN/ lisinopril	CTDN/ amlodipine	CTDN/ lisinopril	CTDN/ amlodipine
CHF	<1	<1	<1	<1
CHD	<1	NS	NS	NS
CVA	<1	NS	NS	NS
CVEs	<1	NS	<1	NS

Most of the variation in BP response to ACEIs is within races and not between races.

U.S. guidelines for blacks (Flack 2010):
SBP < 10 above goal, begin monotherapy with a diuretic or CCB.
SBP 15+ above goal, begin with combined therapy CCB+RAAS blocker or a diuretic + RAAS blocker (the latter would be 1st choice for an edematous patient.) They recommend that we use RAAS blockers as 2nd line rather than Diuretic-CCB combo.

2010 Canadian guidelines (for both white and black) (Hackam Can J Card 2010;26:249):
Initiate monotherapy with a thiazide type diuretic.
BB in patients < 60 y.o., and an ACEI in non-blacks, then a long acting CCB or ARB.

For NICE:
Patients < 80 years the target is 140/90; for 80+ the target is 150/90
Begin with an ACEI or an ARB to start, or, if black a CCB. For diuretics, use CTDN or indapamide and not HCTZ.

HYPERTENSION IN PREGNANCY. W. Elliott

There are 4 categories of HTN in pregnancy:

1. Chronic HTN
2. Gestational HTN
3. PE superimposed on chronic HTN
4. PE

Chronic HTN in pregnancy is defined as a BP = 140/90+ before 20 weeks gestation.
Pre-eclampsia or eclampsia (6% prevalence) is defined as a) new-onset proteinuria (300mg+/day) and b) BP 140/90+ after the 20th week. (It's 300mg+/day because it is 10x the criterion for microalbuminuria in women, which is 30 mg/day.)
In chronic HTN, the prevalence of pre-eclampsia increases to 25%.
Gestational HTN is the same as pre-eclampsia but without the proteinuria.

BP is higher in nulliparous compared to parous (at week 0 = 120 vs 115).

Normally, there is systemic vasodilation.
Most patients with stage I or II HTN have "normal" BP in the 1st trimester.
Lack of a BP drop in the 1st trimester also increases risk for pre-eclampsia (which is already 25%).
Many women on 1 – 2 antihypertensives can discontinue them awhile in early pregnancy.
Use Korotkoff phase 5 for diagnosis (disappearance of stound) rather than phase 4 (muffling of sound).

Pre-eclampsia increases the risk for:
*Placental abruption.
*Premature delivery.
*Fetal growth restriction.
*Fetal & neonatal M & M.
Lowering BP decreases the risk of more severe HTN later in pregnancy.
However, there is no proven benefit of tight BP control.
Most would treat women with BP 150/90+.

When to begin Rx is inconsistent among sources:

Source	Jnc7	Kaplan	ASH	UptoDate	NHLBI	ACOG
DBP	105-110	105-110	105	95-99*	100	100

*Or SBP of 150+
Regardless of drug used, bp control does not appear to prevent proteinuria or pre-eclampsia.

All drug classes prevent more severe HTN later in pregnancy.
HTN in pre-eclampsia is primarily due to vasoconstriction.

Normally in pregnancy, all elements of RAAS are increased (renin, Ang II and aldosterone) and yet the response to AT II is blunted, i.e., relatively refractory. Probably progesterone antagonizes the renal effects of aldosterone. However, in pre-eclampsia, the blunted response does not occur and pre-eclamptic women respond as if they were not pregnant, in spite of the fact that Ang II is relatively low. Failure to blunt the response may be due to an increase in AT1 receptors; AT1 receptor antibodies are increased in pre-eclampsia.

In PE:
Endothelium dependent vascular relaxation is impaired.
***SNA is increased due to Ang II activation.**
***OS is increased.**

* Consistent with over production of the 2 antiangiogenic proteins by the placenta, leading to decreases in PIGF and VEGF.
In the last trimester in pre-eclampsia, there is a decline in cardiac output and an increase in SVR.

	PE, no Rx	PE, Rx	Normal
MAP	125*	120*	82
CI	3.3*	4.3	4.2
SVR	3003*	2212	1560
PCWP	7	7	5

*Compared to normal pregnant women, P is less than 0.05.

Augmentation index (a measure of aortic stiffness) is higher in PE compared to normal pregnancy.

	Nullip	Gestational HTN	Pre-eclampsia
AI	6.7	17.7	31.1
PWV m/s	5.1	6.2	7.0

However, increased SVR and increased aortic stiffness still prevail.

Medications in pregnancy (category C unless otherwise specified):

1. AMD (0.5 to 3 gm/day) – **category B**. (drug of choice)
2. **alpha-beta blockers** (fetal growth restriction not a problem): Labetalol 200 – 2400 mg/day. (Some prefer acebutolol.) **Category B**. **Other BBs may cause fetal bradycardia, decreased uteroplacental flow and decreased fetal response to hypoxia and stress, and growth retardation when used in the 1st or 2nd trimester.**
3. Diuretics (thiazides and loop) are safe (**category B)**. However, **avoid diuretics in PE**.
4. Nifedipine (30-120 mg/d) (cat c) are used but have concerns of edema and **inhibition of labor**.
5. Hydralazine (50-300/day) (cat c) is usually **used only with labetalol**. May cause neonatal low platelets.

For urgencies and emergencies: (Note the absence of nitroprusside & NTG.)
***Hydralazine (drug of choice) (5 mg i.v.; repeat 10m q30min to 25mg)**(1)
*Labetolol (20 mg iv then Q 30 min's up to 300 mg(1)
*Nifedipine (possibly block labor)
*Fenoldapam (Category B) (drug of choice in CKD) I.V. 0.1 mcg/kg/min(2)

(1) hydralazine and labetolol are considered equally appropriate as 1st line therapy by UpToDate. Hydralazline has been used longer. Note that hydralazine is 5th line in usual BP treatment in pregnancy.

(2) Fenoldapam is a dopamine agonist.

Other management issues:
*Low threshold for hospitalization.
*Monitor for maternal TOD, fetal well being.

*If no TOD, BP target is 150/95

*Dexamethasone for fetal lung maturation.
*MgSO4 to prevent seizures.

Special concern:
BP 160/105 +
Signs of HELLP (micro-angiopathy).
PRES (Posterior reversible encephalopathy syndrome) (occurs as part of eclampsia with seizures).
The constellation of symptoms include headache, visual disturbances, altered consciousness and seizures. It is thought to be related to a breakdown in the blood-brain barrier.

Prevention of PE:
ASA: small v.
No significant effect with Ca, vit C or E.

PE increases subsequent risk for HTN, CVA, and CVD (RR=3.7, 2.0, 2.2, respectively). Some recommend periodic CV risk screening following PE. (Analogous to gestational diabetes).

ASH statement on HTN in pregnancy (J Clin Hypert 2009;11:214 (Lindheimer, Taler & Cunningham)

Normally, there are marked increases in cardiac output and IV fluid., marked decreases in SVR and creatinine (< 0.9mg/dL !!!), increases in compliance, renal vessel dilation, RAAS, DOC, and progesterone.

For some women, SBP of 120 in mid trimester and 130 in last trimester could represent abnormal elevations.

DBP of 85+ or MAP of 90+ portend increased fetal mortality.

HTN is defined as 140/90+ with 3 readings 5 hours apart.
However, if BP is less than 140/90 but there has been a 30/15 rise, manage this patient as high risk.

The following may be precipitated or unmasked by pregnancy:
*Pheo
*Cushings.
*MR mutation leading to increasing sensitivity (due to progresterone which stimulates the MR).

In pregnancy, primary aldosteronism is more likely to have normal K and minimal BP rise (possibly related to increases in progesterone, which block aldosterone).

PE occurs most often in nulliprous

PE: proteinuria 300 mg/24 hours or a Urine P/C of 0.3 or a U/A of 1+.

In PE, there can be coagulation liver function abnormalities.

Severity is identified by DBP of <100 (mild-moderate) or 100+ as severe.

De novo HTN after mid-gestation in a nulliparous women is sufficient to manage the patient as if she were pre-eclamptic.

Early PE (<34 weeks) has a greater morbidity compared to presentation at 35+ weeks.

Premonitory signs of Eclampsia are HA, visual changes, abdominal pain, constricting sensations in the thorax, apprehension, excitability and hyper-reflexia.

PE leads to HELLP in 5%.

HELLP requires hospitalization and often pregnancy termination.

In women destined to develop PE, the placenta overproduces 2 anti-angiogenic proteins:

1. **Soluble Tms-like tyrosine kinase 1 (sFlt-1)**, a receptor for placental growth factor (PiGF), and for vascular endothelial growth factor (VEGF), leads to **decreases in circulating PiGF (Placental growth factor) and VEGF, changes that lead to endothelial dysfunction.**
2. **Soluble endoglin (sEng)** impairs binding of transforming growth factor 1 to endothelial receptors, which decreases **NO-dependent vasodilaton.**

Glomerular endotheliosis is a factor in increased creatinine.

Shallow and abnormal placentation is a hallmark of PE with failure of normal trophoblastic invasion of the spiral arteries, failing to remodel and dilate.

PE: increased cerebral blood flow; Eclampsia: vessel leak.

PE can have coagulation activation and thrombocytopenia (mild) that are distinct from HELLP.

Hypercoagulability is reflected as reduced antithrobmin II, protein S and C. In HELLP, this is severe.

With Ca supplements, there are small but significant declines in adverse advents including fetal demise.

In PE, deliver the fetus if a) it is near term, b) 1 to 2 days of severe HTN, c) there are premonitory signs of eclampsia (clotting abnormalities, HA, abdominal pain, and increased reflexes), and d) fetal distress.

Chronic HTN: outcomes are worse than in normotensives: placental abruption, Acute renal failure, cardiac problems, CVA, and growth retardation. Extreme obesity is a special risk factor for cardiac problems.

Rx of mild-moderate chronic or gestational HTN does not prevent PE or v adverse outcomes.
NHBPEP and ACOG: withhold antihypertensives unless DBP 100+.

BARRIERS TO OPTIMAL HYPERTENSION CONTROL. S. Oparil

Compared to those whose BP remains high while on treatment, drug-treated hypertensive patients who achieve BP control are less likely to die over a 9.5 year period . Medication adherence at 2 years drops to 66-78% (Flack JM. TOMHS Eur HT J 1995;17(Suppl A):16-20.

Over 18 months, 43% of patients had discontinued their medications. Gregoire J Clin Epi 20002;55:728-35.
16-50% of anti-hypertensives are stopped in the 1st 2 months.

RH prevalence is 25% in patients without DM or CKD or 40% in the latter. (?? Too high)

RH correlates with **high baseline BP, Older age, Obesity, insulin resistance, High salt intake, CKD, DM, LVH, AAs, Females, So East US.**

Medication adherence:
Prevalence 43 – 88%
Using refill data: 52% to 74%.
Within the 1st year of rx, 16%-50% stop their antihypertensive.
In one study, the initial adherence was 81% but dropped to 56% at 1.5 years.

Ephedra or Ma Huang compromise BP control.

COX 2 inhibitors cause RH. Tylenol much better.

To diagnose GRA (glucocorticoid remediable aldosteronism), collect urinary 18-OH cortisol, which should be elevated.

Non-pharmacologic Rx:
Low salt diet (<100 meQ/d); DASH diet (high fiber low fat)
Use CTDN.
Use loop diuretics, particularly if on minoxidil
Na increases risk of CHD and CVA, even in those without high blood pressure.

Origin of salt:
Processed and restaurant foods: 77%
Naturally occurring 12%
While eating 6%
Home cooking 5%.

Meds blocking HTN control: NSAIDs, amphetamines, cocaine, cold pills, OCPs, erythropoietin, licorice, Ma Huang, Ephedra.

Causes of RH:
Common: OSA, hyperaldo, RV HTN, Renal parenchymal disease.
Uncommon: thyroid disease, hyperparathyroidism, pheo, cushings, coarc, IC tumor.

As part of w/u, get Ca & TSH.

Cutting 1 gm of Na/day (40 mEq) will decrease MI or CVA by ¼.

INSTITUTIONAL SYSTEMS FOR EFFICENT BP MANAGEMENT. A. Gradman
Medical home: PMD + team.
Common elements:
*PMD: 1st contact, continuous and comprehensive care.

*Team practice-led by personal doc.
*PMD coordinates care across medical specialties, hospital, home health agencies, and community services.
*IT and analytic tools.
*Expand access to doc: open scheduling, phone, secure e mail.
*Consistency of assignment to doc (bonded)
*3+ visits to assigned PMD at baseline.
*50%+ of primary care visits to assigned PMD

Continuity of PMD is inversely related to hospitalizations and ED visits.

Language concordance increases bonding (72% vs. 42% with language discordance).
Language discordance is associated with missed appointments.

Initial combo therapy in STITCH (D-ACEI or D-ARB versus Canadian guidelines): at 6 months, the BP control was 65% vs 53%

ACEI-HCTZ as initial Rx. If pregnancy potential use CTDN up to 25 or HCTZ up to 50.

COMBO CONTROL RATES: 80% in ACCOMPLISH vs 66% in ALLHAT.

FEVER: Low Dose HCTZ-felodipine vs Low Dose HCTZ. Mean SBP difference was 4; reduced rates of CVA 27%, MI 32%, CHF 30%.

INVEST trial: sustained decreases in office BP control was associated with dramatic reductions in CVEs, particularly in diabetics.

Home BPs are an adjunct. 85% BP control is attainable.

Additional Notes:

Calcineurin inhibitors, tacrolimus and cyclosporine, cause salt-sensitive HTN in transplant patients and hyperkalemia which makes use of ACEIs, ARBs and AAs contraindicated (relative).
Venlafaxine (Effexor) can cause significant HTN when used for depression.

Following CVA or newly diagnosed CAD, treatment of HTN benefits both hypertensive and non-hypertensive patients.

There is no clear evidence on BP goals. The AHA recommends a goal of <130/80 in patients with CAD and <120/80 in patients with CHF.

The presence of copper or silver wiring (no flow in the latter) reflects narrowed arterioles and suggest that the cerebral circulation is compromised and that the MD should go slowly in reducing BP.

RAAS blockade with an ACEI or an ARB causes a marked increase in renin.

Treat acute glomerulonephritis or rapidly progressive GN with salt and water restriction. Treat ischemia induced hypertensive renal disease such as scleroderma, RAAS is activated so rx with ACEI.

RTA type 1 (hypokalemia): amphotericin. RTA type 4: a) no renin & aldosterone: DM, cyclosporine & tacrolimus (these both cause HTN and are treated with diltiazem. HTN is caused by an effect on the NaCl transporter causing Na retention & hyperkalemia), HIV, NSAIDs. No aldosterone: ACEIs, ARBs;

HTN is the most common cause of CVA (hemorrhagic and ischemic) and chf.

In dialysis patients, reasonable goals are pre-dialysis <140/90 and post dialysis <130/80. Finding dry weight BP is key. Restrict Na to 1 gm/day. RAAS blockers, BBs, and CCBs provide similar efficacy. You can give drug QHS. Bilateral nephrectomy can be considered in RH.

For orthostatic hypotension with supine HTN, patient sleeps semisitting. Can give transdermal NTG patch 0.025 to 1mg/hr

STUDY Reference	Population	Intervention 1	Mean Achieved BP	Outcomes RRR%
DOES TREATING HIGH BLOOD PRESSURE REDUCE CVEs AND DEATH?				
VA1 JAMA 1967; 202:1028	**143 men Age 50 DBP 115+**	**HCTZ 50, reserpine, Hydralazine Vs placebo**	HDFP, EWPHE, MRC-1, ANHBP-1, HAPPHY, MAPHY	**CVEs+death 96%**
VA2 JAMA 1970; 213:1143	**DBP 90-114**	**Ditto**		**CVEs+death 63%**
WHAT IS GOAL BP?				
UKPDS BMJ 1998 317:703		**Tight vs not tight**	**144/82 vs 154/87**	**CVA 44% Any DM endpoint 24% Microvasc 36%**
HOT Hansson Lancet 1998;351:1755		**DBP targets: <81 vs <86 vs <91 (used felodipine)**		**All pts: no v in CVEs DM: CVEs: 51%**
AASK JAMA Wright 2002;288:2421	**HTN, renal dis, Gfr45;pr 480/d**	**MAP < 92 vs 102-107**	**128/78 vs 141/85**	**No effect on renal outcomes.**
ACCORD NEJM 2010;362:575	**4,733 DM Age 62**	**120 vs 140**	**119 vs 134**	**CVEs 12% (NS) CVA 41%**
SHOULD WE TREAT SBP IN OLDER PERSONS?				
SHEP JAMA 1991;265:3255	**4,736 men ISH:160+/<90**	**CTDN± atenolol Vs placebo**	**Goal <160 or V by 20 143/68**	**PrimaryO: CVA 36% CHD 27 CHF 54 CVEs 32**
Syst-Eur Staessen Lancet 1997; 350:757	**4,695 BP 160-219/95**	**Active Rx versus Placebo Goal <150 or V by 20. 157/79**	**Decrease bP 10.1/4.5**	**CVEs 31%**
HYVET	**Age 80+, SBP 160-199 BPd <110**	**Perindopril+indapamide Target BP 150/80**	**144/78**	**CVE 30% CVE 34% ACM 21%**
MRC BMJ 1992 304:405	**Elderly**	**HCTZ+amiloride vs Atenolol vs placebo**		HCTZ+amiloride vs either atenolol or placebo ~40%
STOP-1				
TOMHS				
VA monotherapy				
BEST DRUG?: Not BBs. ACEI for renal; hztz-amil; amlo (vs losar); CTDNvs(acei or ccb)allhat				
HCTZ-Amil: MRC BMJ 1992 304:405	**Elderly**	**HCTZ+amiloride vs Atenolol vs Placebo**		HCTZ+Amil vs either atenolol or placebo ~40%
ARB: LIFE DAhlof Lancet 2002;359:995	**HTN & LVH N=9,193**	**Losartan vs Atenolol**	**Atenolol higher by SBP =1.3 mmHg**	**CVEs: 13% CVA: 25% MI: -6% (non-sign)**
CTDN: ALLHAT 2002	**VARIOUS**	**CTDN vs AMLO CTDN vs lisinopril CTDN vs doxazosin**	**CTDN vs AMLO: -1.1 CTDN vs lisin: -2.2 CTDN vs doxazosin -2.4**	**Vs AMLO: v chf Vs lisin: v chf, CVEs, CVA Vs doxaz: ditto**
AMLO:VALUE. Julius Lancet 2004; 353:2022	**N=15,245**	**Amlodipine vs valsartan**	**Valsartan had higher BP than amlo.**	**CVEs: no diff MIs: 16% (2)**
ACEI: AASK(Wright2002)	**Ditto**	**Ramipril vs metoprolol Amlo vs metoprolol**		**22% v in renal outcome for ramipril versus other (2)**
Lancet 2005;366:1545	**Meta-anal**	**Atenolol vs other drugs**		**CVA ^ by 26% with atenolol (1)**
BEST COMBOS? Amlo-Perin(ascot); Amlo-Benaz(accomplish); ACEI=ARB(ontarget)				
ONTARGET Nejm 2008;358:1547	**Hi risk**	**Acei vs arb vs combo**		**2 monotherapies Equally good.**
ASCOT Lancet. 2005 Sep 10-16;366(9489):895-906.	**Hi risk 19,257**	**Amlo+perindopril vs Atenolol+bendroflumethiazide**		**ACM 11% Cva 23% New onset dm 34%**
ACCOMPLISH	**11,506**	**Amlo+benazepril vs HCTZ+benazepril**		**CVEs: 20%**

(1) NICE in the UK place BBs as 4th line Rx. (2). Control at 6 months was strongly predictive of CVEs; i.e., earlier control was better. This is an argument for starting combo.

(2) AASK showed decreased survival in patients with metabolic syndrome.

Trial	population	intervention	Outcome
CHF or LV_Dysfunction: ____">6"=JNC6			
Beta Blockers (particularly, bisoprolol, carvedilol, or metoprolol)__or Hydralazine & ISDN_____			
Meta-analysis. Ann 2001;134:550 >6	**ChF**	**BB, 27 RCTs, 20,313 pts**	**ACM 28%**
A-HEFT nejm 2004;351:2049	**AAs, chf 3-4**	**Hydralazine+ISDN**	**43% for ACM**
LOW EF, All ACEIs: Sympt(consensus, solvd)/ Asympt (solvd rgstry)/_Asympt, P MI(save)			
CONSENSUS-I nejm1987;316:1429 >6	**CHF 4**	**Acei**	**27%**
SOLVD nejm 1991;325:293 >6	**CHF 1-3**	**Acei**	**26%**
SOLVD Rgstry nejm1992;327:685>6	**LVD (1)**	**Acei**	**20%**
SAVE nejm 1992;327:669 >6	**Post mi+lvd(2)**	**Acei**	**22%**
Low EF: ARBS_(VAL-HEFT, charm-alt, charm-added)			
VAL-HEFT nejm 2001;345:1667	**CHF 2-4**	**Arb vs placebo**	**49%**
CHARM-ALTERNATIVE Lancet 2003; 362: 772 & 759	**CHF EF<40%**	**Candesartan vs placebo**	**23%**
Charm-added Lancet2003;362:767	**Nyh2-4,ef<41**	**Candesartan+acei vs acei**	**CVEs 15%**
ELITE II (8)	**CHF 2-4, lo ef**	**ARB vs ACEI**	**No difference(8)**
HF w/ PEF: 1 ACEI (PEP), 3 ARBS (charm, i-preserve, life)			
PEP Eur Ht J 2006;27:2338	**850 HFPEF**	**Perindopril vs placebo**	**PO p=0.06, ^ex cap, v hosp'ns**
CHARM Lancet 2003;362:777	**HFPEF 3,023**	**Candesartan vs placebo**	**Strong trend (3)**
I-PRESERVE nejm2008;359:2456	NYH2-4EF45+	**Irbasartan vs placebo**	**No diff. Weak trend: HR=0.95**
LIFE Lancet. 2002;359:995	**LVH & HTN**	**Losartan vs atenolol**	**CVEs 13%; MI: No difference.**
ALDOSTERONE ANTAGONISTS_for CHF (rales, emphasis) OR LOW EF post MI_(ephesus)			
RALES Pitt nejm 1999;341:709	**Chf 3-4**	**Spironolactone vs placebo**	**30% ACM**
EMPHASIS nejm 2011;364:11	**NYH 2 ef≤35**	**Eplerenone vs placebo**	**34%**
EPHESUS nejm 2003;348:1309	**V EF post MI**	**Eplerenone vs placebo**	**15% ACM (x's cardiac fibrosis)**
POST MI: ANSWER: USE BBs			
Smith JACC 1995; 26:292	**summary**	**Beta blockers**	
POST CVA: Per "PROGRESS", USE indap+perindo			
PROGRESSLancet 2001 358:1033 (4)	**Post cva/tia Htn&nonHtn**	**Perindopril+indapamide**	**CVA/TIA 28%. In htnsvs & non-htnsvs(perind alone no diff)**
HSCSG: Hypertension-Stroke	Cva	Cooperative Study Group,	*JAMA.* 1974;229:409
Post-stroke Antihypertensive	Cva	Treatment Study	(Chinese med;1995)
ELDERLY: hctz-Amil (mrc), Indap (hyvet), ctdn (shep), ccb>acei>diur(syst eur), any drug (STOP2),			
STOP2 Lancet 1999;354:1751	**6614, 180+/105+**	**Old drugs vs New drugs (7)**	**No diff (allhat likeness) (5)**
Shep jama 1991; **265:3255 >6**	Elderly (& ISH)	CTDN+atenolol vs placebo	46-75%
MRC BMJ 1992 >6 304:405 (Like SHEP, this is also for ISH.)	**Elderly (& ISH)**	**HCTZ+amiloride vs Atenolol vs Placebo**	**HCTZ+amiloride vs placebo: CVA: 31% CHD: 44%**
SYST-EUR Lancet 1997; 350: 757 >6	**Elderly (& ISH)**	**Dhp-ccb>>acei>>diuretic vs placebo**	**26%-42%**
HYVET. NEJM 20089;358:1887	**Age 80+; SBP 160+, BPd <110**	**Indapamide+perindopril Target BP 150/80**	**CVE 30% CVE 34% ACM 21%**
HI RISK: Use: Ramipril (hope), amlo+perindo (ascot), acei or arb (ontarget)__			
HOPE nejm 2000; 342:145 (6)	**9,297 cvd, dm 45% w/ htn**	**Ramipril vs placebo**	**22%. RRR in htn and non-htn.**
HOPE Mann Am J Med2001;134:629	**SCr 1.4+ vs <1.4**	**Ramipril vs placebo**	**1) RRR 20% w/ ckd & 21% w/o ckd 2) CKD predicts CV risk.**
ONTARGET Nejm 2008;358:1547	**Cvd,dm25,620 ~50% w/o htn**	**Acei vs arb vs combo**	**2 monotherapies Equally good.**
ASCOT Lancet. 2005;366:895-906.	**HTN+3CVRsk Fctrs n=19,257**	**Amlo+perindopril vs Aten+bendroflumethiazide**	**ACM 11% Cva 23%New onset dm 34%**
DM 2: acei (hope, ukpds), arb(life), ctdn (shep,allhat)			
Shep. Kostis Am J Card 2005;95:29.	DM2	Ctdn	DM&nonDM:22%, DM:31%
Allhat and see Diab Care 2008;31:353	DM2	Ctdn	Similar to non DM (9)
Ukpds	DM2	Captopril vs atenolol	Similar
UKPDS	DM2	144/82 vs 154/85	V macro & micro
MICRO LIFE Lancet 2002;359:1004	**DM2,n=1,195**	**Losartan vs atenolol**	**CVEs 24%**
MICRO HOPE Lancet 2000;355:253	**DM2**	**Ramipril vs placebo**	**CVEs 25%. ACM 24%**

(1) Asymptomatic with EF <41; (2) Asymptomatic with EF <36. (3) Primary outcome: 0.86, p=0.051, v hosp'ns; all CVEs P=0.037. (5) Comparing BBs vs ACEIs vs CCBs gave no difference. (7) Old drugs: atenolol, metoprolol, pindolol, hctz-amiloride. New drugs: enalapril, lisinopril, felodipine, isradipine. (i.e., Old=beta blockers or diuretics; New = ACEIs and CCBs.) (8) ELITE I: Lower ACM on ARB vs ACEI (2ndary endpoint), the primary endpoint gave no difference, & the study was underpowered. Pitt. ELITE-I. Lancet 1997; 249:747. (9) ALLHAT (2002) showed that patients on ctdn had similar RRs in DM and non-DM patients. Black (2008) showed that patients with metabolic syndrome had similar or superior outcomes for patients on ctdn.

"Compelling renal indications"

TRIAL	population	Intervention	Outcome
RENAL OUTCOMES:			
DM-CKD, OUTCOME=GFR, acei (dm1:Lewis), acei (detail), arb (idnt, renaal)			
Lewis nejm 1993;329:1456 >6	**DM 1**	**Captopril vs placebo**	**V doubling of creatinine**
IDNT nejm 2001; 357: 851	**DM-DKD. Proteinuria 0.9mg/d+. SCr up to 3m/dL.**	**Irbesartan vs amlo vs placebo**	Irb (ARB) best for Renal endpoint. v BP <> v renal events (unadjusted for proteinuria)
RENAAL Clin Diabetes 2002; 20: 19	**DM 2 & advanced renal disease. Mean BP 152/82, Urine 1.2 alb/gm Creatinine 1.9 mg/dL**	**Losartan vs placebo**	**28% esrd ** 25% 2x Scr 35% v in proteinuria**
DETAIL nejm 2004; 351:1952	**DM 2 + early nephropathy**	**Arb versus acei**	**Equivalence for change in gfr**
DM-CKD, OUTCOME=proteinuria: acei (microHope), arb (irma, marvel), renin inhib (avoid)			
microHOPE Lancet 2000;355:253	**DM2**	**Ramipril vs placebo**	**Nephropathy 24%**
IRMA-2 nejm 2001; 357:867	**Microalbuminuria**	**Irbesartan vs placebo**	**Overt nephropathy 67% Macroproteinuria: 70%**
MARVAL Vigerti Circulation 2002;106:672	Microalbuminuria	valsartan vs amlo	Normal albuminuria better with valsartan
AVOID nejm 2008; 358:2433	Nephropathy	Aliskiren + losartan vs losartan alone	V urine albumin/creatinine
NON DIABETIC CKD, Outcome=GFR, BP lowering effective if 1 gm proteinuria			
MDRD Sarnak. Ann Int Med 2005;142:342	**GFR13-55, exclude DM w/ insulin**	**125/75 vs 140/90 MAP lower by 5.**	**V GFR loss, especially in 1gm+ proteinuria**
AASK Wright JAMA2002;288:2421	**AAs, HTNsv renal dis Gfr45, Protein 480mg/d**	**Achieved BP 128/78 vs 141/85**	**No effect on renal outcomes**
REIN2(Ruggenenti Lancett 2005;365:939	**nonDMCKD GFR 34 2.9 mg proteinuria. Mean BP 137/84**	**<130/80 vs DBP < 90 MAP lower by 2.**	**No effect on ESRD**
"meta-analysis"	Various	Lowering of BP	V in CKD progression
NON DIABETIC CKD, Outcome=GFR, All ACE's!!, ACEI(rein, aask, aipri, jafar)			
REIN J Am Soc Nephrol. 2001 Dec;12(12):2832-7	**Non-DM nephropathy (proteinuric)**	**Ramipril vs non-acei rx**	**Esrd 33%(1)**
AASK Wright JAMA2002;288:2421	**AAs, HTNsv renal dis Gfr45, Protein 480mg/d**	**Ramipril vs Amlodipine vs Metoprolol (1)(RAM)**	**Ram: 22% for 50%+ decline in GFR, ESRD or death.**
AIPRI J Cardiovasc Pharmacol. 1999;33 Suppl 1:S16-20	**Non DM nephropathy, including proteinuria**	**Benazepril vs other**	**Lower Scr x2 & lower esrd**
Jafar Ann Int Med 2001; 135:73 (meta-analysis)	**Non-DM CKD. No specification as to proteinuria**	**ACE I vs placebo**	**V time to ESRD or Cr x 2**

* Irbesartan: some v in progression of ckd or death. Some on v in BP, unlike RENAAL. Also, HR for CKD decreased with decrease in proteinuria (proteinuria is a biomarker)

** **Lower proteinuria strongly predicted ESRD after adjustment for BP, but BP reduction did not lower ESRD after adjustment for proteinuria.** The entire effect on ESRD was due to reduction in albuminuria.

(1) Benefit was proportional to the baseline rate of albumin excretion.

(2) Renal outcomes were lower for lower proteinuria after adjustment for BP but not lower for BP after adjustment for proteinuria.

OTHER ISSUES

Trial	Population	Intervention	Outcome
NA RESCTRICTION RCT			
TOHP1 & 2 Cook. TOHP trial. BMJ 2007;334:885)	PreHTN	Na v by 1gm/day	21-52%
J CURVE			
INVEST Ann Int Med 006;144:884 JAMA 2003;29:2805	**22 K w/ HTN & CAD**	**Verapamil SR vs atenolol**	**J curve at BPd = 84 CVEs: no difference (1)**
EARLY COMBO THERAPY & BP CONTROL			
STITCH	**Newly diagnosed HTN**	**fixed dose D-ACEI or D-ARB vs Candian guideline-based care**	**Improved control at 6 months.**
ACCELERATE	**ditto**	**Fixed dose aliskaren-amlo Vs monotherapy with doubling**	**Faster BP control**
EARLY COMBO THERAPY & CVEs			
VALUE. Julius Lancet 2004; 353:2022		**Control at 6 months vs not (amlo vs valsartan)**	**V CVEs**
FEVER (Liu J Hyp 2005; 23:2157)	**SBP 140-179**	**HCTZ+felodinpine vs HCTZ (SBP 137 vs 143)**	**V CVEs: 27-30%**
PREVENTS NEW DM			
STARLET		**Trandopril-verapamil vs losartan-hctz**	**Prevents new DM.**
PREVENTS NEW HTN			
TROPHY nejm 2006;354:1685	**PreHTN**	**Candesartan**	**V rate of htn**
SPIRONOLACTONE & BP			
ASCOT Lancet. 2005 366:895-906	**Hi risk**	**Addition of spironolactone vs not**	**V in SBP by 22**
PRIMARY ALDOSTERONISM & RENAL DAMAGE			
PAPY Hypertension 006;48:232	(not an CT)	Prospective study	PA>proteinuria(2)
CENTRAL VERSUS PERIPHERAL PRESSURE			
CAFÉ substudy of ASCOT Circulation 2006;113:1213		amlodipine-perindopril vs atenolol-bendruflumethiazide	Lower central aortic BP Equivalent peripheral BP
REDUCTION IN ATHEROMA VOLUME VIA DECREASE IN BP			
CAMELOT (IVUS substudy Sipahi JACC 2006;48:833)	**130/77, 85% nl dbp<100**	**BP < 120/80**	**Decrease in atheroma volume.**

(1) With sustained **office** BP control there was a dramatic reduction in CVEs.
(2) After rx with either spironolactone or adrenalectomy, the albuminuria is improved.

TRIALS FROM UPTODATE

TRIAL	Population	Intervention1	Outcome 1	Outcome 2	Notes
CAPP 10,985		Captopril Vs BBlckr+ diuretic	CVEs No diff		
INSIGHT >6,000		Nifedipine vs HCTZ-amiloride	CVEs No diff		
NORDIL 11,000		DIURETIC Vs BBlocker	CVEs. No Diff	Diltiazem arm Had v in CVA	
ANBP2 6,083		Enalapril vs HCTZ	CVEs+ACM 0.89		

(1) A lower SBP correlated with a lower atheroma volume. CAMELOT showed no J curve.

Monogenic forms of hypertension, other than pheochromocytoma

Syndrome	Defect	Inheri-ance	Aldo	Age of onset	Rx
LOW RENIN (ALL with Low K except one, where K is hi.)					
Glucocorticoid remedial Aldosteronism (Familial hyperaldo type I).	Chimera: aldosterone synthase gene with 11Bhydroxylase gene. (1)	AD	^	< 20; CVA Dx: **^ urinary 18-HO-cortisol** Or via genetic analysis	Dexa-methasone + Spironolactone, amiloride + thiazide
Familial hyperaldo Type II (may have +FH; MEN I) (2)	**Chromosome 7p22**	AD	^	30+. Occurs in MEN I Looks like BAH. Dx:2 family members	Steroids don't work. Spironolactone works.
Liddle syndrome Nedd4 is a regulatory suppressor that promotes ENaC degradation.	Gain of function ENaC In DCT (chr 16p12).(3)	AD	V	20-29 **^HCO3**	Amiloride or triamterene (**not** spironolactone)
CAH	11 beta hydrox-ylase def >> ^ DOC.(4)	**AR**	V	Boys: early puberty, Girls: virilization vK	Steroids will normalize ACTH.
AME (Apparent mineral Corticoid excess) 11-Beta-hydroxysteroid dehydrogenase deficiency (deficiency = **R**educed <> A**R** inheritance)	11BHSD2 def. can't metabolize cortisol to cortisone (5)	**AR**	V	5-29 **Urinary cortisol/ cortisone very high (nl=0.4)**	Spironolactone. Eplerenone, or amiloride Give K + lo Na diet. If ineffective, Give steroids
Mutation of the mineral corticoid receptor (MCR)	Increased sensitivity to progesterone and cortisone.	AD	V	10-19 **^ w/ pregnancy Due to progesterone**	Delivery. **Spironolactone contraindicated**.
Familial hyperkalemic HTN (pseudohypoaldosteronism Type 2 or Gordon's synd) (chr 17)	WNK kinase mutation ^NaCL Absorption Calcineurin & tacrolimus are involved (6)	AD	V or NL.	10-29. Short, MR, muscle weakness, Lo FNA. ^ Cl acidosis. Salt sensitive **^K**	thiazides Lo salt diet
Renin not helpful.					
Mitochondrial DNA abnl.	TRNA of the IIe codon	Mother	**v K** v Mg ^lipids	Essential HTN	
AD brachydactyly type E	Chr 12p Cause of HTN unkown.	AD	Brachydactyly Short stature. Not salt sensitive		

(1) Usually aldosterone is made in the glomerulosa. The genetic defect is a chimeric gene on chr 8q wherein the 11 B hydroxylase gene is coupled with the aldosterone synthase gene CYP11B2. ACTH activates the 11 B hydroxylase gene and in so doing indirectly activates aldosterone synthase production in the Zona Fasciculata. Normally, 11 oxo cortisol forms cortisol.

(2) Familial hyperaldosteronism type III is characterized by severe, childhood HTN, massive bilateral adrenal glands, unresponsiveness to steroids and spironolactone, and negative genetic studies for types I and II (chr 7p22). (3) A mutation in the ENaC gene prevents binding to Nedd4, a repressor, leading to increase expression of ENaC.

(4) Reduction in cortisol >> ^ ACTH >> increase in steroid production proximal to the blocked step which causes an increase in DOC (deoxycorticosterone) which stimulates the aldosterone receptor. 17 BH deficiency has similar increased production of DOC but causes ambiguous genitalia in boys and delayed puberty in girls.

(5) This leads to excess cortisol which stimulates the MCR. This is the same enzyme that is blocked by glycyrrhetinic acid in licorice or carbenoxolone. The syndrome can also be caused by ACTH secreting small cell lung ca.

(6) The calcineurin inhibitor, tacrolimus, induces salt sensitive HTN by activiating WNK3, WNK4, and SPAK.

Term	Skin/eye CMs	Other CMs.	Genetic Pattern
Primary PHEO	**None**	Usual(1,2)	none
Sturge-Weber	**FACE** Port wine stain Tri-geminal Distribution (St. V's employee)	**CNS PROBLEMS**: MR, Seizures, CVA Leptomeningeal capillary venous malformations (may cause visual problems) **visual defects**.	None
Familial paraganglioma SDHA, -B, - C, -D, -AF2 (succinate dehydrogenase)	(no skin CMs)	Abdominal location is most common. Particularly the organ of Zuckerkendl(3)	AD With 100% penetrance when gene is inherited from father but not the mother ("maternal imprinting")
Tuberous sclerosis TSC gene ("S" then "T")	**FACE** **Facial angiofibromas** **Hypopigmented plaques**. ("adenoma sebaceum") Plaques of forehead & lower trunk **Subungal fibromas.**	**"Tubers" (as in potato):** Multiple benign hamartomas of brain, **eye**, heart, lung, liver, kidney	AD or sporadic
Neurofibromatosis (Von Recklinghausen) NF1 tumor suppressor gene	Facial plaques, Neurofibromas, Hypomelanotic Axillary Freckles **Optic gliomas.**	Short, bony defects, sarcomas, & CML.	AD
Von Hippel-Lindau Dis VHL tumor suppressor Gene	Eyes only: Retinal **Hemangioblastomas** **(Visual defects)**	Cerebellar hemangiomas, Cysts of middle ear, lymphatics & pancreas. Renal cell ca	AD
MENIIa Ret protooncogene		MCT (90%), parathyroid hyperplasia (15%)	AD
MENIIb	Mucosal neuromas (4) Marfanoid	MCT	AD

(1) Precipitants of a crisis are anesthesia, opiates, dopamine agonists, cold meds, contrast, TCAs, cocaine, childbirth.

(2) Horm Metab Res. 2012 Feb 10. Update on the Genetics of Paraganglioma, Pheochromocytoma, and Associated Hereditary Syndromes. Gimenez-Roqueplo AP. **Pheochromocytomas (PCCs) and paragangliomas (PGLs)** are catecholamine-secreting tumors of **neural crest** origin. The proportion of all patients with PCC and/or PGL due to **a genetic disruption in these genes is approximately one half**.

(3) This is a chromaffin body of neural crest origin at the bifurcation of the aorta or at the origin of the inferior mesenteric artery. During gestation it secretes catecholamines in the fetal circulation and regulates BP.

(4) This occurs in 100% of patients; there are sessile, yellow-white nodules on the lips and tongue.

GUIDE LINE SUMMARY 5/12

	Goal	1st line	Combos	Other
JNC7 (2004)	<140/90 DM & CKD: <130/80	Diuretic Dual Rx for >160/100 or with BP>20/10 above target		Compelling indications: CHF all except CCBs P MI all but D, CCB & AA CVA all but BB, CCB,AA DM all but AA Hi CAD risk all but AA
AHA, ASA AmStrokeAss (2011)	No official goal, but if patient has Carotid artery disease, this is CAD equivalent And do <130/80.	Diuretic or diuretic+acei		
AHA (2007) Only CAD risk	CKD or DM or CAD equivalent, Or 10 yr FHR=10%+: <130/80 For LVD <120/80	Any,		
Europe (2007)	<140/90 With CVD, DM, CKD, proteinuria <130/80	Not specified	Several	Don't use BBs+D's in patients with metabolic syndr. Syndrome or DM./ Don't use ACEI or ARB in Bilateral renal artery stenosis. Don't use AA in renal failure.
NICE	<140/90 For age 80+ <150/90	<55: acei or arb Age55+ ccb Any black: ccb Or if chf: D (ctdn or indap, not hctz)	CCB-RAAS blocker If evidence for chf, replace ccb with D. 3 drug Rx: Ccb-raas blocker-D.	No BBs as 1st line Except "younger" people or those with evidence for SNA overactivity.
US-Blacks (2010)	<135/85 With TOD or Pre-clinical CVD: <130/80	Monotherapy D or CCB	CCB+ACEI Or ACEI+D (the latter Preferred for edematous)	Begin Drug at Any value above target Begin 2 drugs At level >15/10 above target
Canada (2010)	<140/90 (all) <130/80 (renal, CKD)	Any (BB in <age 50)	ACEI-CCB	