UPDATE IN ANTI-HYPERTENSIVE THERAPY

NYACP ANNUAL SCIENTIFIC MEETING

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DISCLOSURES

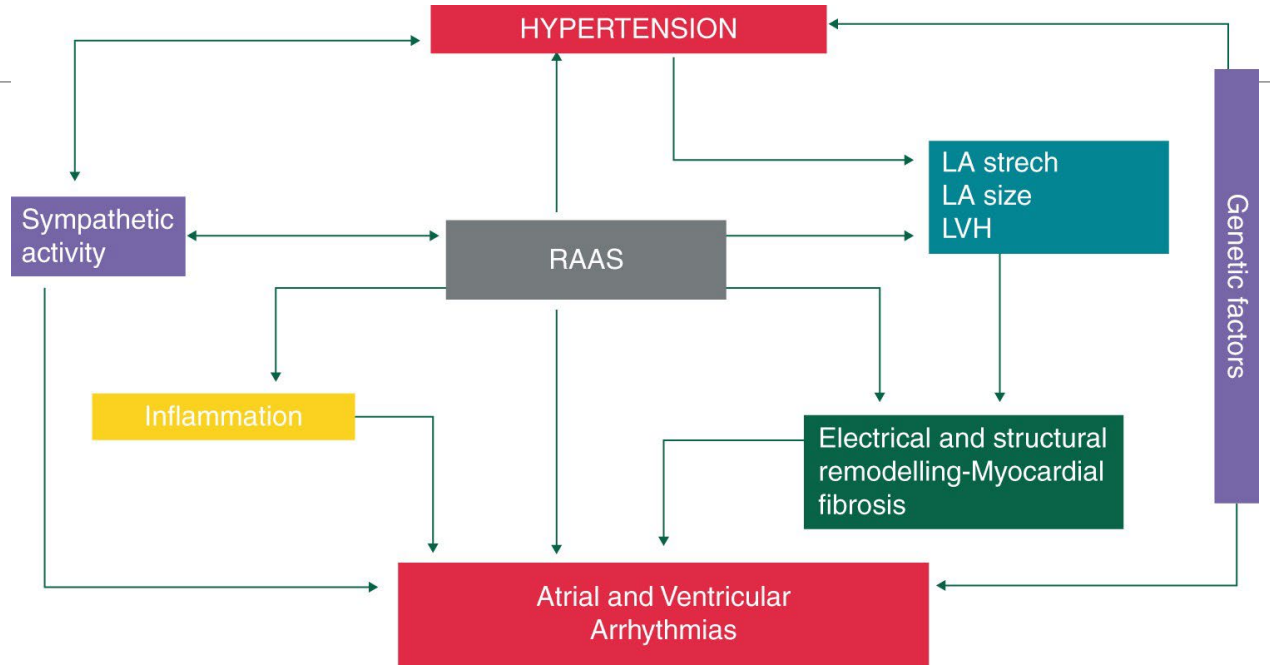
ROCHE – Research

Novo Nordisk – Research

Outset Medical – Research

Eli Lily - Research

Figure 1 Mechanisms of arrhythmias in hypertension. LA, left atrium; LVH, left ventricular hypertrophy; RAAS, ...



Europace, Volume 19, Issue 6, June 2017, Pages 891–911, https://doi.org/10.1093/europace/eux091

HTN - EPIDEMIOLOGY

Approx 35-40% of all adult Americans

Stage 1

Stage 2

Resistant HTN

1.56 Billion adults worldwide

CV Risk

Categories of BP in Adults*

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.
BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure. (ACC/AHA SLIDE)

SPRINT

Multi-center, randomized, controlled

- Nov 2010 – March 2013, 102 sites
- $157 million over 8 years

N = 9361, SBP >/= 130 - 180, age > 50

- CVD, CKD 3, age >/= 75, int-high risk CVD

Target SBP <120 vs <140

- Monthly visits in intensive arm

Primary endpoint: “Composite” CV events

SPRINT CHARACTERISTICS

Baseline: 139.7/78.1

- 90% on anti-htn drug therapy

At 1 yr: SBP 121.4 (intensive) v. 136.2 (standard)

28% w CVD

28% > 75 yrs

36% women

29.9 % black

Intensive control required , on average, addition of one more medication

SPRINT KEY EXCLUSIONS

DM

SBP >180

4+ anti-HTN meds

STANDING SBP <110

STROKE

PCKD

> 1 gm proteinuria

EF <35%

“ADHERENCE FLAGS”

SPRINT FINDINGS

Terminated early - 3.26 years

25% reduction in primary outcome

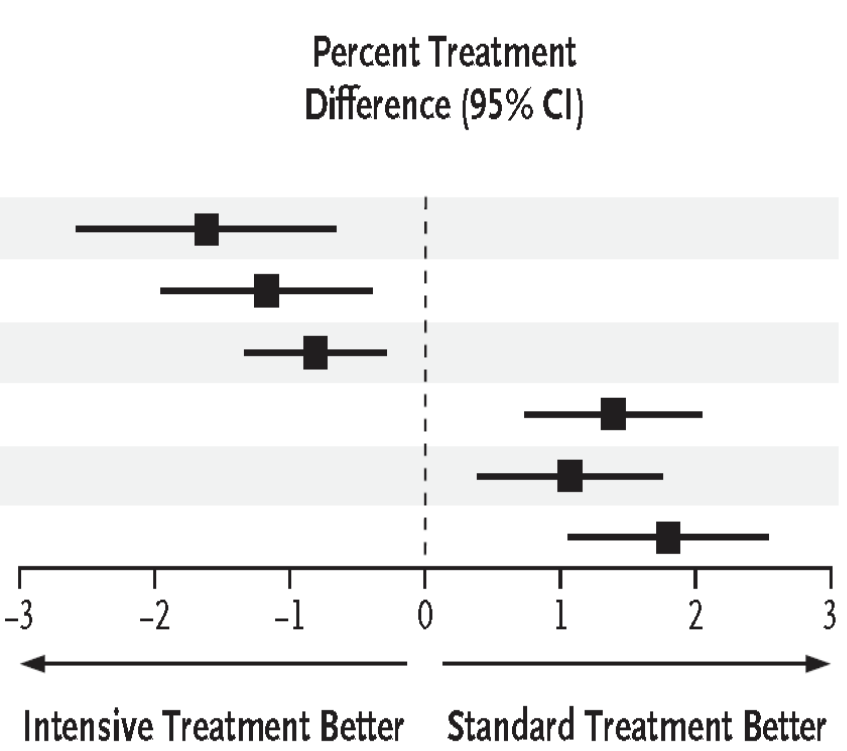
27% reduction in mortality in intensive group

38% reduction in new heart failure

NO difference in MI or Stroke

- Though the trial was not powered to assess individual differences among the primary outcome

Subgroup	Intensive Treatment (N=4678)	Standard Treatment (N=4683)
	no. of events (percent)	
Primary outcome	243 (5.2)	319 (6.8)
Death from any cause	155 (3.3)	210 (4.5)
Heart failure	62 (1.3)	100 (2.1)
Serious hypotensive episode	158 (3.4)	93 (2.0)
Serious syncope episode	163 (3.5)	113 (2.4)
Serious acute renal event	204 (4.4)	120 (2.6)



Pocock NEJM Sept 2016

SPRINT

Targeted high risk CV group

Primary outcome driven almost entirely by reduction in heart failure

NNT = 61

? Similar benefit of intensive reduction in lower risk group

NOT a nephrology focused trial

DID NOT lower event rates for stroke, MI, or ACS

90% patients already on anti-HTN treatment

- What if the CV risk is low and the patient's treatment naïve BP is 138/80 ???

ADVERSE EVENTS

Falls

Electrolyte Abnormalities
- Hyponatremia
- Hypokalemia
- Hyperkalemia

Orthostasis

Acute Kidney Injury

Syncope

ALL HIGHER IN INTENSIVE GROUP

FOR EVERY 100 patients getting to SBP <120, 4 adverse events– hypotension, syncope, and AKI

Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension

Multicenter, Randomized, Controlled Trial in China, 42 centers, Jan – Dec 2017

N = 8511; Mean follow-up time: 3.3 years

Age 60 – 80; mean age 66.2

20% DM; 65% with “high” 10 yr CV Risk

Systolic Targets: 110-130 (intensive) vs 130 – 150 (standard)

Achieved BP (intensive group): 127.5 mm Hg

Achieved BP (standard group): 135.3 mm Hg

Olmesartan (ARB), Amlodipine (CCB), and HCTZ

**Primary CV Composite Outcome: Lower incidence of CV Events with Intensive Control

HYVET (Hypertension in the Very Elderly Trial Beckett et al, NEJM, 2008)

- N = 3845
- SBP >160
- Indapamide +/- Perindopril vs placebo
- Goal: <150/80
- Creatinine > 1.7 excluded
- Achieved SBP: 145
- **Lower rates of all-cause mortality, CV death, stroke, and HF
- 32 % w eGFR < 60 ml/min

ACCORD TRIAL

Randomized, controlled, Type 2 DM

N = 4733, mean age: 62.2

- Oldest patient: 79

Creatinine > 1.5, excluded

SBP <140 v SBP <120

NO difference in CV event rate

LOWER stroke rate

Renal outcomes not specifically addressed

Secondary analysis – NO difference in eGFR

CONCERN for being underpowered

THIAZIDES

Well established therapy for HTN

Short Half Life (2x/day daily dosing): HCTZ

Extended Half Life (1x/daily dosing): Chlorthalidone, Indapamide

Monitor for:

- Hypokalemia
- Hyperuricemia
- Hyperlipidemia
- Hyperglycemia/Insulin Sensitivity

ACEi

Well established therapy for HTN

Sub populations

- Proteinuric CKD
- Systolic HF
- Post-MI
- Scleroderma Renal Crisis

Shorter Half Life (2-3x/day dosing): Captopril, Enalapril, Perindopril

Extended Half Life (1x/daily dosing): Ramipril, Benazepril, Lisinopril

Monitor for:

- Hyperkalemia
- Cough (approx. 20-25%)
- Angioedema

ARB

Well established therapy for HTN

Sub populations

- Proteinuric CKD
- Systolic HF
- Post-MI

Shorter half life: Losartan, Valsartan, Candesartan

Extended half life: Olmesartan, Irbesartan, Telmisartan (** 24 hrs)

Monitor for:

- Hyperkalemia

CALCIUM CHANNEL BLOCKERS

Well established therapy for HTN

Non-dihydropyridines
- Verapamil
- Diltiazem

Dihydropyridines
- Amlodipine
- Nifedpipine

Monitor for:
- Edema
- Reflex tachycardia (Nifedipine)
- Bradycardia (Verapamil, Diltiazem)
- Constipation

BETA-BLOCKERS

Not as well established for HTN relative to other classes

However, well established in setting of CV disease

Nonselective (Beta 1, Beta 2)

- Propanolol

Selective Beta-1

- Atenolol, Metoprolol, Acebutolol, Bisoprolol
- **Nebivolol

Mixed (peripheral alpha-1, beta nonselective)

- Labetalol
- Carvedilol

DIRECT VASODILATORS

Well established therapy for HTN

Plagued by short half

Plagued by side effects

……yet effective potential 5th, 6th, line option

Hydralazine
- Short half life, wide therapeutic index (10 -100 mg, 2-3-4x/day)
- Reflex Tachycardia
- Drug induced ANCA, Drug induced Lupus, Rash

Minoxidil
- Very effective
- Edema
- Pericardial Effusion

CENTRAL ALPHA-2 AGONIST

Well established therapy for HTN

Plagued by side effects, particularly fatigue & bradycardia

Clonidine

- 2-3x/day dosing
- Weekly patch formulation
- “Rebound” relatively quick
- If tapering, replace w “mixed” beta blockers (Labetalol, Carvedilol)

Alpha-Methydopa

PERIPHERAL ALPHA-1 ANTAGONIST

Not first line therapy for HTN

Useful for coexisting conditions

- BPH
- Stone expulsion therapy

Orthostatic Hypotension

Flushing

Tachycardia

ALDOSTERONE BLOCKADE

Spironolactone
- Effective aldosterone blockade
- Gynecomastia
- Hyperkalemia
- Low Cost

Eplerenone
- Effective aldosterone blockade – more specific; also more costly
- Hyperkalemia
- CYP3A4 Subsystem interaction (**Paxlovid)

Finerenone
- Non-steroidal, selective Mineralocorticoid Antagonist
- As opposed to steroidal, non-selective mineralocorticoid antagonist – (Spironolactone & Eplerenone)
- Higher affinity for the mineralocorticoid receptor in cardiac and renal tissue

RESISTANT HYPERTENSION

Definition

- “Uncontrolled” blood pressure despite maximum doses of three antihypertensive medications, at least one of which is a diuretic

Prevalence

- Wide variation in observational studies (5-50%)
- Large clinical trials suggest 20-35%

Prognosis

- Increased CV risk & end organ damage

SECONDARY CAUSES OF HTN

About 10% of all HTN cases have an underlying, potentially treatable etiology

- Renal Artery Stenosis**
- Primary Hyperaldosteronism**
- Obstructive Sleep Apnea**
- Chronic Kidney Disease**
- Pheochromocytoma
- Cushing's Syndrome
- Exogenous prednisone
- Liddle's Syndrome
- Coarctation of the Aorta
- Drug-Induced

ANTI-HTN IN PREGNANCY

Well established safety for specific medications

Labetalol – SAFE

Nifedipine – SAFE

Hydralazine – SAFE

Alpha Methyldopa – SAFE

Thiazide Diuretics (if already established therapy PRIOR to pregnancy)- SAFER

AVOID: **ACE/ARB/Atenolol**

WHAT TO AVOID….

AVOID ACEi & ARBs Combined (negative study)

AVOID Peripheral Alpha-1 blockers as first line

AVOID Combinig Direct Acting Vasodilators

AVOID Combining Multiple Heart Rate Lowering Agents

- Beta-blockers
- Non-dihydropyridine CCBs
- Central Alpha-2 Agonist

Monitor & Even Expect Side Effects

- Potassium flux (either direction)

WHAT TO DO……

ARB (ie Valsartan)

CCB (ie Amlodipine)

Thiazide vs Aldosterone blockade

Nebivolol vs Carvedilol vs Labetalol

Hydralazine vs Minoxidil

Doxazosin

Clonidine

?? ANY Role for SGLT-2i……..(NOT established for HTN, BUT….)

** Consider underlying medical conditions

**Consider secondary causes