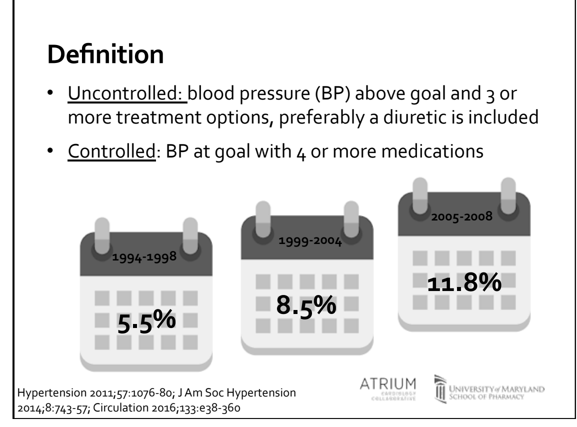
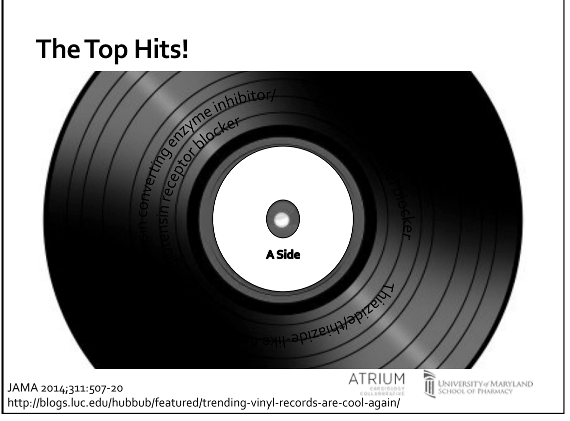




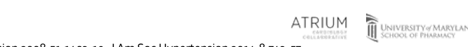
Learning Objective

- Discuss the place in therapy of spironolactone, hydralazine, clonidine and alpha-antagonists in the management of treatment resistant hypertension.
- Given a patient with treatment resistant hypertension, develop a pharmacological treatment regimen.

Before you add another track…

Conduct a Thorough Assessment

- Pseudoresistance
  - Adherence to medications
  - "White coat" phenomena
  - Drug-induced causes
- Obstructive sleep apnea
- Primary aldosteronism
- Renal artery stenosis
- Others: Cushing's syndrome, pheochromocytoma, aortic coarctation



Hypertension 2008;51:1403-19; J Am Soc Hypertension 2014;8:743-57

The Who and The Why

At-Risk Groups

- Increasing age*
- Obesity*
- Left ventricular hypertrophy
- Chronic kidney disease (CKD)
- Diabetes
- African American
- Female

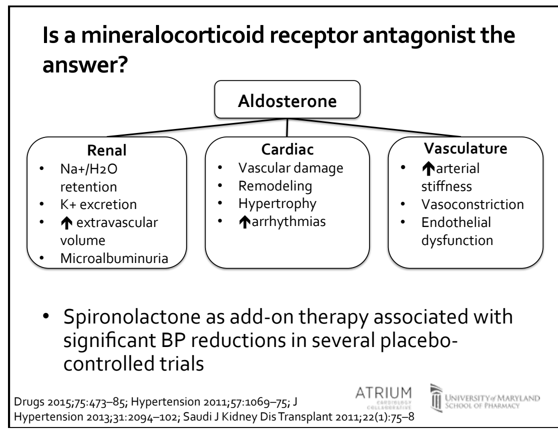
Pathophysiology

- Normal cardiac output with:
  - ↑ systemic vascular resistance
  - ↑ plasma volume
- Degree of plasma aldosterone levels elevation and renin suppression

ATRIUM

Hypertension 2008;51:1403-19; Drugs 2015;75:473–85

Is a mineralocorticoid receptor antagonist the answer?



- Spironolactone as add-on therapy associated with significant BP reductions in several placebo-controlled trials

Drugs 2015;75:473–85; Hypertension 2011;57:1069–75; J Hypertension 2013;31:2094–102; Saudi J Kidney Dis Transplant 2011;22(1):75–8

PATHWAY-2 Trial

- Spironolactone vs. bisoprolol, doxazosin and placebo (n=322)
- 230 received all four treatments; each "cycle" was 12 weeks
- Notable exclusion criteria:
  - Type 1 diabetes
  - estimated Glomerular Filtration Rate (eGFR) < 45 ml/min
  - Recent cardio/cerebrovascular event
  - Active cancer therapy
- Spironolactone associated with improved BP reduction compared to other therapies/placebo

Take home point: spironolactone 25-50 mg/day as 4th agent for BP treatment in general population

Lancet 2015; 386:2059–68

Mineralocorticoid receptor antagonist: safety

- Hyperkalemia risk increased:
  - Diabetes
  - Renal disease
  - Advanced age
  - Concurrent non-steroidal anti-inflammatory agent use
- Start at lower dose when renal disease present
- Use in hemodialysis, Stage 3 or 4 CKD not well established

Monitoring is KEY!!!

Drugs 2015;75:473–85; Am J Nephrol 2009;30:418-24; J Am Coll Cardiol 2013;62:1585-93

What else should we put on the B side?

- Direct renin inhibitor
- Mecamylamine
- Methyldopa
- Loop diuretic
- Minoxidil
- Beta-blocker
- Hydralazine
- Clonidine
- Alpha-antagonist

Second line options?

Aliskerin (Tekturna®)
- Should not be used in patients with diabetes or CKD receiving an angiotensin converting enzyme inhibitor/ angiotensin receptor blocker

Mecamylamine (Vecamyl®)
- Not for use in those with significant atherosclerosis
- Side effects heightened in those with renal disease
- Cumbersome regimen
- Sodium restriction *not* recommended

Methyldopa
- Adverse effect profile
- Typically reserved for use during pregnancy

Tekturna® (aliskerin). Novartis. East Hanover, NJ 2015; Vecamyl® (mecamylamine). Turing Pharmaceuticals. New York, NY 2015; Methyldopa. Mylan Pharmaceuticals. Morgantown, WV 2015.

Second line options?

Loop diuretic
- Maybe necessary in those with advanced renal disease instead of a thiazide
- For volume overload

Minoxidil
- Reflex tachycardia and other adverse effects
- Concomitant diuretic therapy (and often beta-blocker) required

Beta-blocker
- Not as effective, as first line therapy, in reducing BP and clinical outcomes compared to other agents
- For use in those with compelling indications
  - Heart failure
  - Coronary disease
  - Arrhythmias

Am J Kidney Dis. 2004;43(5 Suppl 1):S1-290.Hypertension 2008;51: 1403-19; J Am Coll Cardiol 2015;65:1998-038; JAMA 2003;289:2534-44

Second line options?

Hydralazine
- Thrice daily
- Adverse effect profile

Clonidine
- Side effect profile limits use in the elderly
- Transdermal patch available

Alpha-antagonists
- Male patient with benign prostatic hypertension
- Orthostatic hypotension risk

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J Am Geriatr Soc 2015;63:2227–46; Hypertension 2008;51:1403-19

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Non-Pharmacological Strategies

Renal denervation
- Initial trials encouraging
- SYMPLICITY-HTN-3: large, prospective, randomized, controlled trial did not show benefit
- PRAGUE-15: BP control similar to spironolactone; both in addition to standard medications

Others
- Ultrasonic sound technology
- Carotid baroreflex activation therapy

Hypertension 2012; 60:596-606; J Am Coll Cardiol 2012;59:901-9; N Engl J Med 2014;370:1393-1401; Hypertension 2016;67:397-403; J Am Soc of Hypertension 2014;8:743–757

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- 74 y/o obese woman
- Systolic BP above 160 mmHg x 3 months; HR 60 BPM
- PMH:
  - Diabetes
  - Hypertension
  - Hypothyroidism
- Labs within normal limits; CrCl ~ 65 ml/min
- BP medications:
  - chlorthalidone 25 mg/d
  - lisinopril 40 mg/d
  - felodipine 10 mg/day
- Secondary causes ruled out

Which medication should be added next?

A. clonidine
B. doxazosin
C. hydralazine
D. spironolactone

CrCl = creatinine clearance

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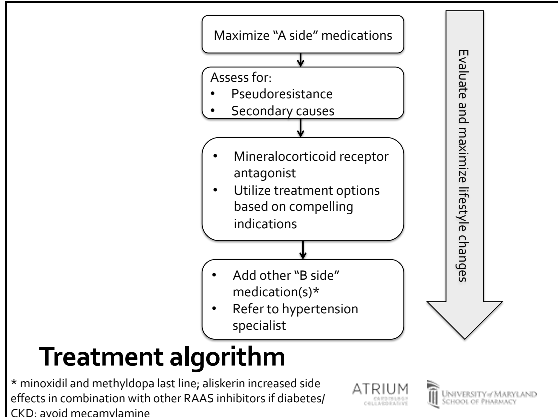

Treatment algorithm

* minoxidil and methyldopa last line; aliskerin increased side effects in combination with other RAAS inhibitors if diabetes/ CKD; avoid mecamylamine

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More tracks on the way…

- Prevalence of Resistant Hypertension with Directed Observed Therapy (DOT)
  - DOT x 1 month followed by 24 hour ambulatory care BP monitoring
  - No adjustments in medication therapy
- Safety and Efficacy Study of LHW090 in Resistant Hypertension Patients
- Resistant Hypertension Optimal Treatment (ReHOT) Study
  - Traditional backbone 3 medication regimen
  - Sprinolactone vs. clonidine x 3 months
- TRIUMPH Study
  - Exercise training, sodium and calorie reduction, and weight management compared to physician advice and standard education

https://clinicaltrials.gov/ct2/show/NCT02513524
https://clinicaltrials.gov/ct2/show/NCT02515331
Clin Cardiol 2014;27:1-6; Am Heart J 2015;170:986-94

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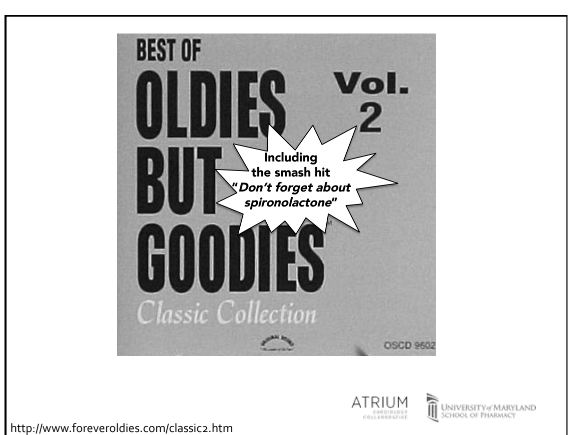
BEST OF
OLDIES
BUT
GOODIES
Vol.
2
Including
the smash hit
"Don't forget about
spironolactone"
Classic Collection
OSCD 9602
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http://www.foreveroldies.com/classic2.htm