Mineralcorticoid receptor (MR) antagonists vs. Thiazide Diuretics: Which is the Superior Antihypertensive? →MRAs and New Trials (7 min)

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FINANCIAL DISCLOSURE:
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First line vs. second line: Things to consider

-Efficacy, clinical trial data, mortality-CVD death-stroke-LVH reduction

-**Continuation/Discontinuation rates!**

-Side effects

-ARBs > CCBs check all boxes; ***both thiazide diuretics and MR blockers do not (SE!)***

History of Mineralcorticoid receptor antagonists (MRAs)

1953: Aldosterone as sodium retaining and potassium wasting hormone first discovered

1954: Jerome Conn: suppressed renin, volume expansion, non-suppressible aldosterone; reported the successful removal of an aldosterone overproducing adrenal gland in a patient with HTN and hypokalemia (Conn syndrome)

1960: spironolactone was first marketed as potassium-sparing diuretic but mostly used in patients with hyper-aldosteronism (primary and secondary, e.g., in liver failure)

→Progesterone-like and anti-androgen effects at high doses limited its use

2002: Eplerenone marketed

Jerome W. Conn, MD

University of Michigan
First Division Chief Endocrinology & Metabolism from 1943-1973

Aldosteronism: frequent but under-recognized precursor/cause of HTN

Prevalence in normotensives

- In MESA, normotensive adults with suppressed renin had a 68% greater risk of incident hypertension suggesting that subclinical hyperaldosteronism as risk factor for HTN!
- In another cross-sectional sample of normotensives, 9% had overt hyperaldosteronism (range across studies: 6 to 14%!)

Prevalence in hypertensives

- 2%-19% using elevated ARR followed by confirmatory testing-this likely still underestimates true prevalence.
- When saline suppression testing was used in patients with resistant HTN without ARR prescreening, prevalence was 29%!
- In stage 1 HTN: 16%, in stage 2 HTN 21% in resistant HTN: 24%!

→Yet only 3% of eligible hypertensive patients undergo aldosteronism screening in US!

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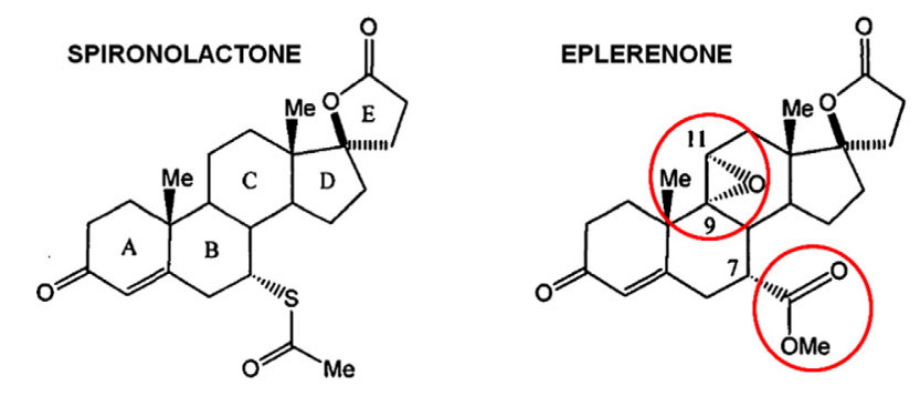
Brown JM et al. Ann Intern Med. 2017;167(9):630-641
Parasiliti-Caprino M et al. J Hypertens. 2020;38(9):1841-1848
Ruhle BC et al. Surgery. 2019;165(1):221-227

MRAs



-longer half-life (12 to 48 hours)
-active metabolites
-more MR receptor affinity and potency
-more hormonal side effects
-increases HbA1c and cortisol levels
-greater incidence of hyper-K+ and AKI

-shorter half-life (3-4 hours)
-no active metabolites
-3% MR receptor affinity but ~60% in-vivo potency of spironolactone
-no (or minimal) hormonal side effects
-no (or minimal) effects on HbA1c

→ ***Requirement of metabolic panel before, after 1 week and 1 month of treatment initiation!***

MR antagonist monotherapy in essential HTN

Spironolactone 25 mg (n=40)

	Baseline	1 months	Treatment difference	p-value
Ambulatory				
SBP	143.55 ± 8.23	137.10 ± 7.57	-4.5	< 0.001
DBP	89.50 ± 4.69	87.15 ± 4.69	-1.3	0.099

Eplerenone (n=1437)

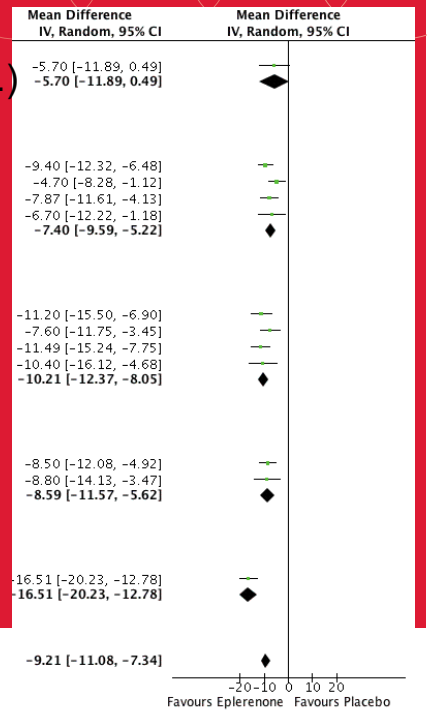
25 mg: -5.7 mmHg (n.s.)

50 mg: -7.4 mmHg

100 mg: -12.4 mmHg

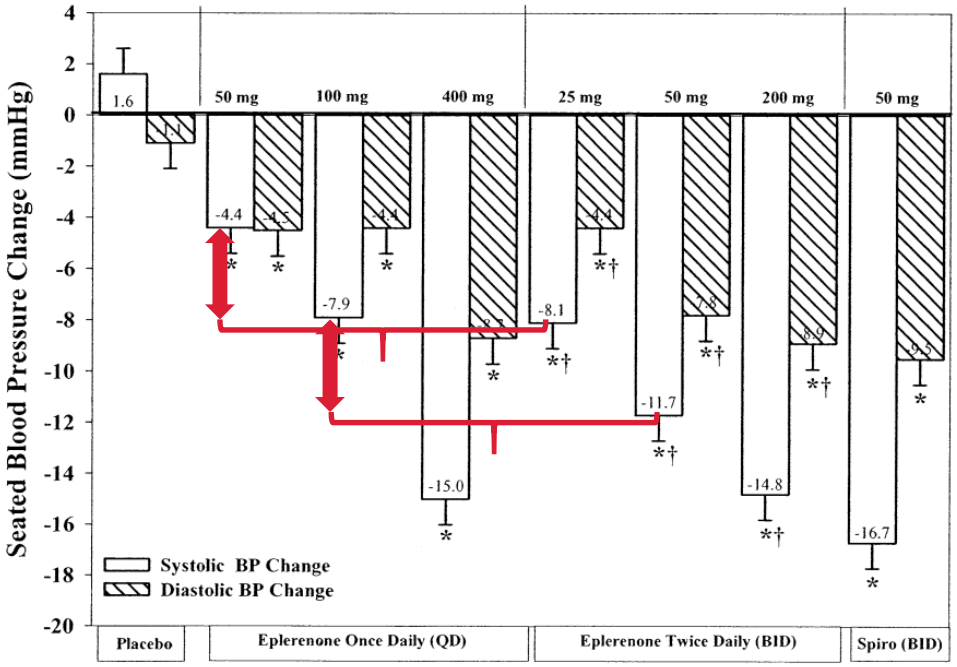
200 mg: -11.6 mmHg

400 mg: -20 mmHg



MR antagonist monotherapy in essential HTN

Eplerenone 50 mg to 400 mg vs. Spironolactone 50 mg



	Placebo	Eplerenone Once Daily 50 mg	Eplerenone Once Daily 100 mg	Eplerenone Once Daily 400 mg	Eplerenone Twice Daily 25 mg	Eplerenone Twice Daily 50 mg	Eplerenone Twice Daily 200 mg	Spironolactone Twice Daily 50 mg
No. of patients	53	54	49	56	55	54	48	48
Discontinued due to AE	(2)	4 (7)	1 (2)	0	1 (2)	1 (2)	1 (2)	2 (4)
Any adverse event	23 (43)	23 (43)	28 (57)	27 (48)	24 (44)	21 (39)	27 (56)	17 (35)
Arthralgia	0	0	0	0	0	1 (2)	3 (6)	0
Dizziness	0	2 (4)	2 (4)	1 (2)	2 (4)	1 (2)	3 (6)	3 (6)
Headache	9 (17)	5 (3)	9 (18)	9 (16)	5 (9)	9 (17)	6 (13)	4 (8)
Leg cramps	0	0	1 (2)	0	0	0	3 (6)	0
Nausea	1 (2)	1 (2)	1 (2)	3 (5)	0	0	2 (4)	0
Respiratory infection	2 (4)	2 (4)	1 (2)	1 (2)	5 (9)	3 (6)	6 (13)	1 (2)
Sinusitus	0	0	4 (8)	0	1 (2)	3 (6)	1 (2)	1 (2)

Weinberger MH et al AJH 2002; 15:709–716

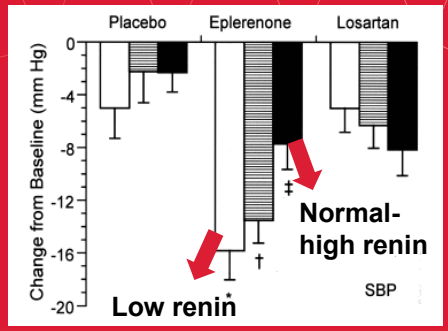
MR antagonist monotherapy in essential HTN

Eplerenone 50 mg vs. Losartan 50 mg

-10.3 vs. -6.9, P<.0001

→ More effective in low-renin patients

→ Equally effective in black vs. white patients



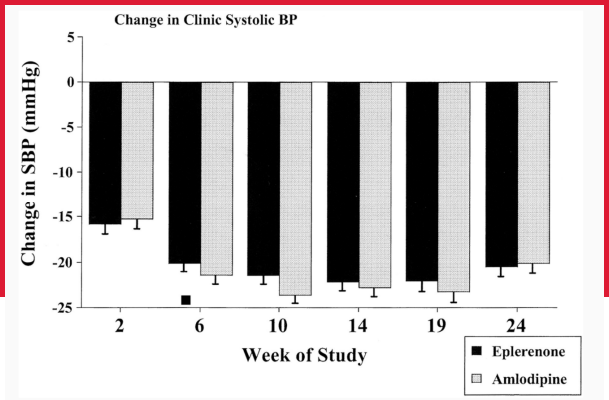
Eplerenone 50 – 200 mg vs. amlodipine 2.5 - 10 mg

-20.5 mm Hg vs. -20.1, p=NS

→ Equally effective

→ Better reduction in urine albumin

→ AEs similar, no gynecomastia reported, potassium elevation was more frequent with eplerenone



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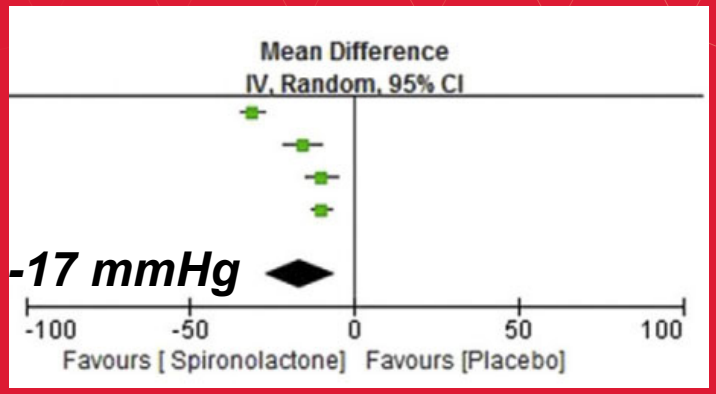
Flack JM et al. J Am Coll Cardiol. 2003 Apr 2;41(7):1148-55

White WB,… Weber MA. Hypertension. 2003 May;41(5):1021-6

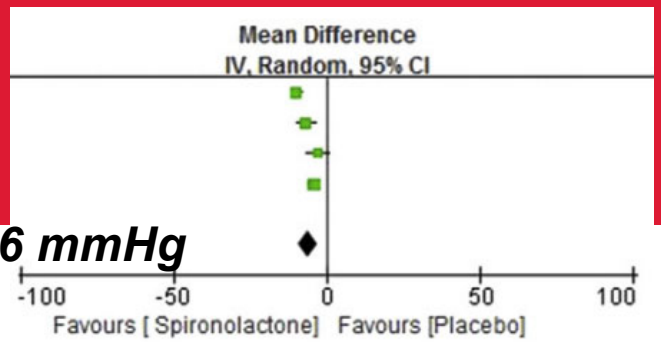
MR antagonist as add-on in resistant HTN

Meta-analysis: 4 trials (n=869)

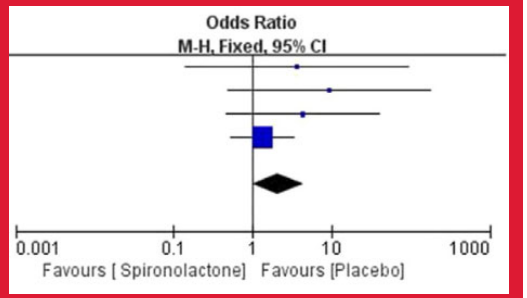
SBP reduction vs. placebo



DBP reduction vs. placebo



But also: 2.1x greater adverse event rate compared to placebo



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Zhao et al. Int J Cardiol. 2017;233:113-117
Colussi et al. Journal of Hypertension 2013, 31:3–15

MR antagonist advantages

-MRAs are equally **reno-protective** and may **reduce proteinuria** as effectively as enalapril both in DM and primary HTN

-MRAs **lowers BP effectively** in resistant HTN and essential HTN irrespective of biochemical evidence for primary hyperaldosteronism, but **specifically in low-renin HTN**

-Have a profound effect on **mortality in HEFrEF** and are possibly useful in HEFpEF

-Eplerenone 50 mg vs HCTZ 12.5 mg **improved coronary endothelial function** (myocardial perfusion reserve: median 1.57 vs. 1.30; P 0.03) with similar effect on BP

Epstein M et al. *Clin J Am Soc Nephrol*. 2006;1:940–951
Nishizuka M et al. *Hypertension*. 2003; 16:925–930
Calhoun DA et al. *J Am Soc Hypertens*. 2008;2:462–468
Butler J et al. *J Cardiac Fail*. 2012;18:265–281
Pfeffer MA et al. 2015 (131);34-42
Joffe et al. J Clin Endocrinol Metab 92: 2552–2558, 2007

Tolerability of MR antagonists

In Heart failure:

	Spironolactone (n = 90)	Eplerenone (n = 90)	p value
Total adverse events	24 (27)	15 (17)	0.102
Gynecomastia in man or breast pain	4 (4)	0 (0)	0.018
Severe hyperkalemia (> 6 mEq/ml)	7 (8)	5 (6)	0.549
Total discontinuation	26 (29)	19 (21)	0.228
Discontinuation because of adverse event	22 (24)	15 (17)	0.135
Hyperkalemia	15 (17)	9 (10)	0.186
Hypotension	0 (0)	2 (2)	0.095
Renal failure	4 (4)	2 (2)	0.402
Gynecomastia in man or breast pain	2 (2)	0 (0)	0.095

Overall (HF, HTN, Liver failure):

Author	Dose of spironolactone (mg/day)	Gynecomastia	Renal failure	Hyperkalemia
Chapman *et al.* (2007) [64]	25–50	6%	–	2%
Tamirisa *et al.* (2004) [91]	12.5–25	–	0.3%	1.6%
Pitt *et al.* (1999) [8]	25–50	10%	0%	2%
Ghose *et al.* (1999) [13]	100–200	54%	–	–
Jeunemaitre *et al.* (1987) [87]	25–400	13%	–	–
Greenblatt and Koch-Weser (1973) [93]	25–400	1.2%	–	8.6%

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Yamamoto et al. Heart Vessels 34, 279–289 (2019)
Flack J et al. *J Am Coll Cardiol*. 2003;41:1148−55

Disadvantages of thiazides

Disadvantages of thiazides

-Non-adherence: 41% to 80% (risk factor for NA: younger age, diuretic use (similar to beta blockers)
OR 1.76 (1.33–2.33)

-Continuation rates:

Alpha blockers worst, CCB and thiazides intermediate, ARBs best

The Silent Epidemic of Thiazide-Induced Hyponatremia

Samuel J. Mann, MD

Hyponatremia occurs in 4 – 30% of patients, elderly being at highest risk

Factors associated with optimal adherence to antihypertensive medications.

	Crude odds ratios	Adjusted odds ratios
First prescription		
ACEIs	1.000	1.000
Alpha blocker	0.338 (0.318, 0.359)*	0.234 (0.215, 0.256)*
Beta blocker	0.375 (0.359, 0.392)*	0.447 (0.420, 0.477)*
CCB	0.404 (0.387, 0.423)*	0.451 (0.423, 0.481)*
Thiazide	0.501 (0.473, 0.531)*	0.431 (0.399, 0.466)*
Combined fixed dose	0.730 (0.404, 1.319)	0.810 (0.266, 2.463)
ARB	0.774 (0.600, 0.997)*	1.322 (0.745, 2.344)
SBP (mm Hg)	1.001 (1.000, 1.002)	0.995 (0.994, 0.996)*
DBP (mm Hg)	1.000 (0.998, 1.002)	

Optimal adherence is defined as Proportion of Days Covered ≥0.80.
* $p<0.05$.

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Gupta et al. Hypertension 2017;69:1113-1120
Wong et al. International Journal of Cardiology 167 (2013) 1438–1442
Mann SJ. J Clin Hypertens 2008;10:(6)

What's new?

Finerenone: nonsteroidal dihydropyridine-based fourth-generation MRA, marketed as same MR-blocking potency of spironolactone but lower incidence of hyper-K+?; studies focused patients with DM +CKD patients: ***FIGARO-DKD***: Reduction in worsening kidney failure (HR 0.82), improvement of albuminuria, reduction in new-onset HF (0.68); Effect on BP modest however (~5 mmHg), more data needed for essential HTN

Esaxerone: Japan, 2.5-5 mg/day, equal BP reduction and side effects as eplerenone in primary HTN

CIN-107: First in-class aldosterone synthase inhibitor (not MR blocker), addresses aldosterone escape (in 40-60% of patient treated with RAAS blockers, correlates with LVH and CKD); lowers aldosterone levels by 75-80%, excellent tolerability in phase ½

→ongoing BRIGHTN randomized trial in resistant HTN and aldosteronism

Filippatos G et al. Circulation. 2021 Nov 13. doi: 10.1161
Ito S. et al. Hypertension. 2020 Jan;75(1):51-58
Bakris GL et al. N Engl J Med. 2020;383(23):2219–29
Cherney DZI, Bakris GL. Kidney Int Suppl 2018;8(1):18-25

The bottom-line

- Neither thiazide diuretics nor MR blockers should be first-line in most patient with primary HTN, evidence for ARBs and CCBs as first-line is compelling
- Think about aldosteronism, low-level conditions are common
- Check renin and aldosterone as one approach to precision medicine BUT…
- *...starting MR antagonist early may be more cost-efficient given low screening and detection rates of aldosteronism in US*
- **Suggestion for add-on decision:**

  →low-normal K+, elderly, low renin: Eplerenone, spironolactone

  →elevated K (low renin): chlorthalidone, indapamide