University
Of Dundee

Update from Recent Trials

Professor Tom MacDonald
Ninewells Hospital and Medical School
University of Dundee
Dundee, Scotland, United Kingdom

Competing Interests Statement

I have lots of competing interests

BMJ

RESEARCH

Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP)

Nancy R Cook, associate professor,[1] Jeffrey A Cutler, former senior scientific adviser,[2] Eva Obarzanek, research nutritionist,[2] Julie E Buring, professor,[1] Kathryn M Rexrode, assistant professor of medicine,[1] Shiriki K Kumanyika, professor of epidemiology,[3] Lawrence J Appel, professor of medicine,[4] Paul K Whelton, president and chief executive officer,[5] for the Trials of Hypertension Prevention Collaborative Research Group

Long-term sodium reduction may also reduce long term risk of CV events.

BMJ 2007;334:885-892

BMJ

BMJ 2013;347:f6954 doi: 10.1136/bmj.f6954 (Published 26 November 2013)

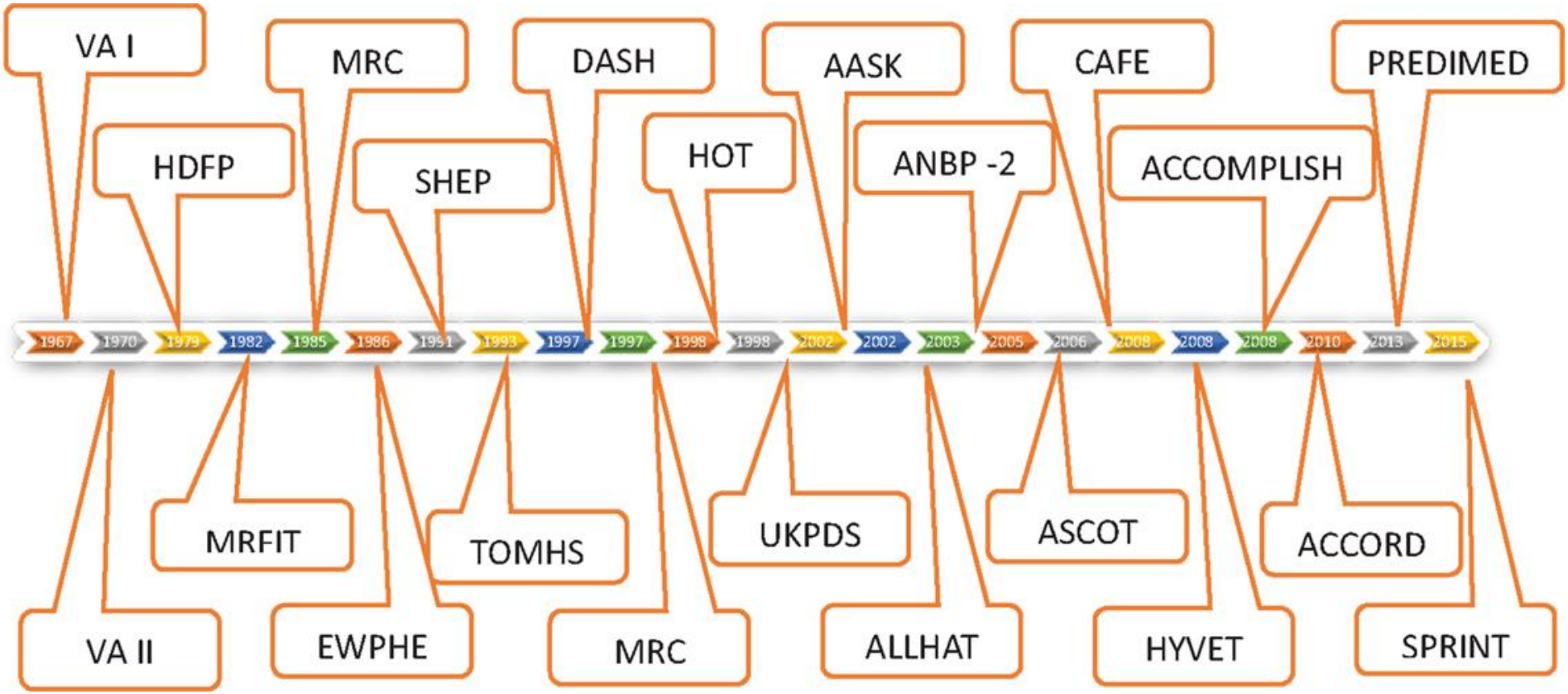
RESEARCH

Association between cardiovascular events and sodium-containing effervescent, dispersible, and soluble drugs: nested case-control study

Jacob George *senior lecturer/honorary consultant in clinical pharmacology*[1], Waseem Majeed *core medical trainee in medicine*[2], Isla S Mackenzie *senior lecturer/honorary consultant in clinical pharmacology*[3], Thomas M MacDonald *professor of clinical pharmacology*[3], Li Wei *senior lecturer in medical statistics*[3 4]

Salty tablets increase hypertension seven-fold

Timeline of BP Treatment Studies

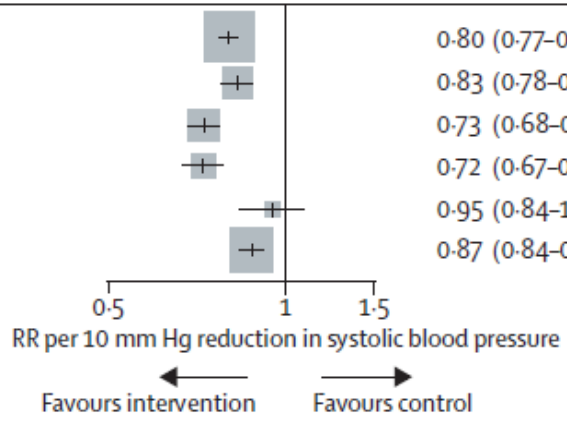


Front. Cardiovasc. Med. 2016;3:3.

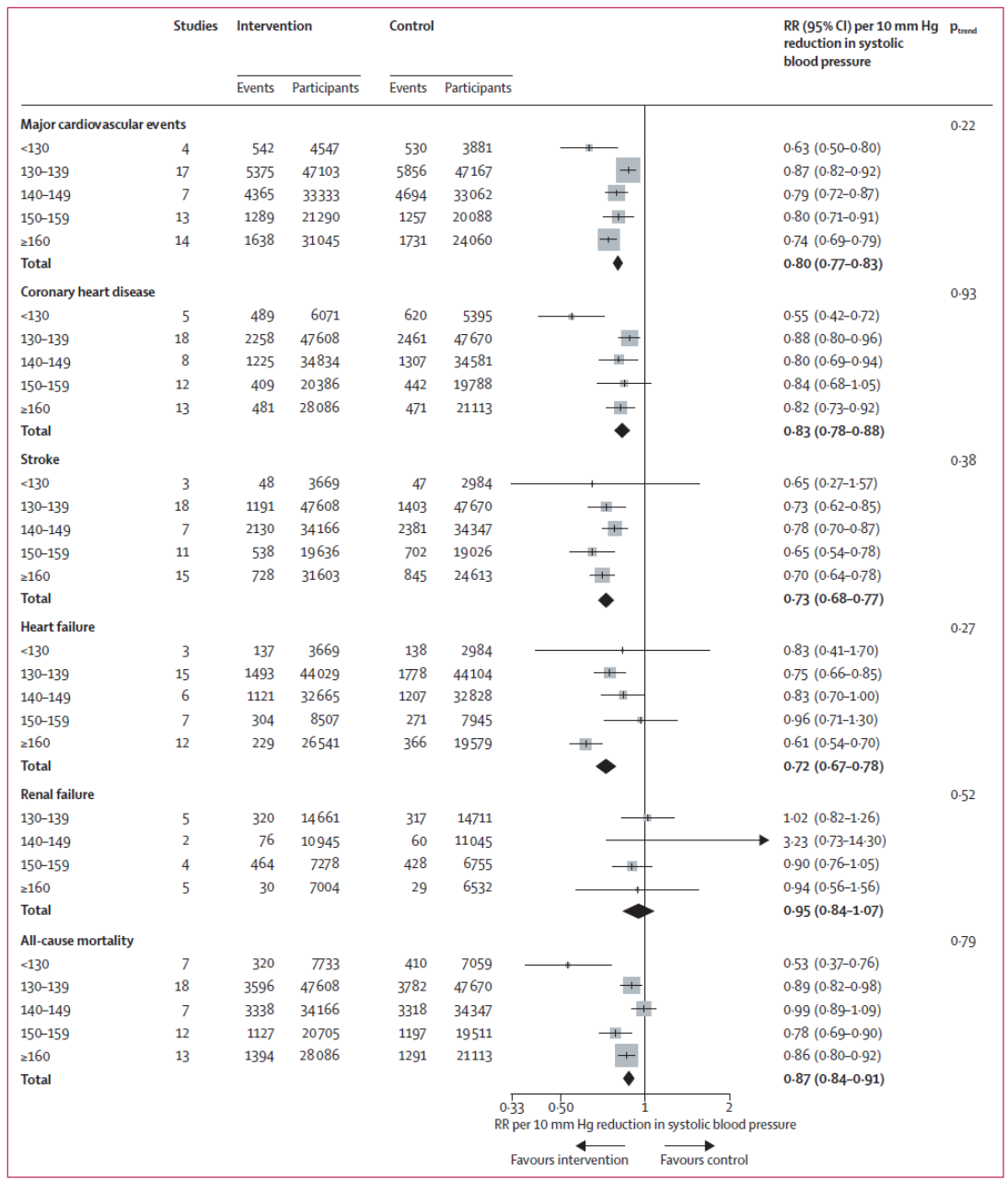
Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis

Dena Ettehad, Connor A Emdin, Amit Kiran, Simon G Anderson, Thomas Callender, Jonathan Emberson, John Chalmers, Anthony Rodgers, Kazem Rahimi

	Studies	Intervention		Control		RR (95% CI) per 10 mm Hg reduction in systolic blood pressure
		Events	Participants	Events	Participants	
Major cardiovascular events	55	13209	137319	14068	128259	0·80 (0·77–0·83)
Coronary heart disease	56	4862	136986	5301	128548	0·83 (0·78–0·88)
Stroke	54	4635	136682	5378	128641	0·73 (0·68–0·77)
Heart failure	43	3284	115411	3760	107440	0·72 (0·67–0·78)
Renal failure	16	890	39888	834	39043	0·95 (0·84–1·07)
All-cause mortality	57	9775	138298	9998	129700	0·87 (0·84–0·91)



Lancet 2016;387:957–67



Lancet 2016;387:957–67

BHS Statement

BRITISH HYPERTENSION SOCIETY ENDORSES THE USE OF SINGLE PILL COMBINATION TREATMENTS IN HYPERTENSION

"In view of the apparent benefits of fixed dose combinations over free-drug combinations, the BHS believes that if there are no significant cost disadvantages "fixed-drug" or single-pill combinations of drugs should be used preferentially for the routine management of hypertension when ≥ 2 drugs are required"[1].

http://www.bhsoc.org/resources/bhs-statements/

Add or Titrate?

Adding a drug
5 x more effective
than titrating

Am J Med 2009;122:290-300

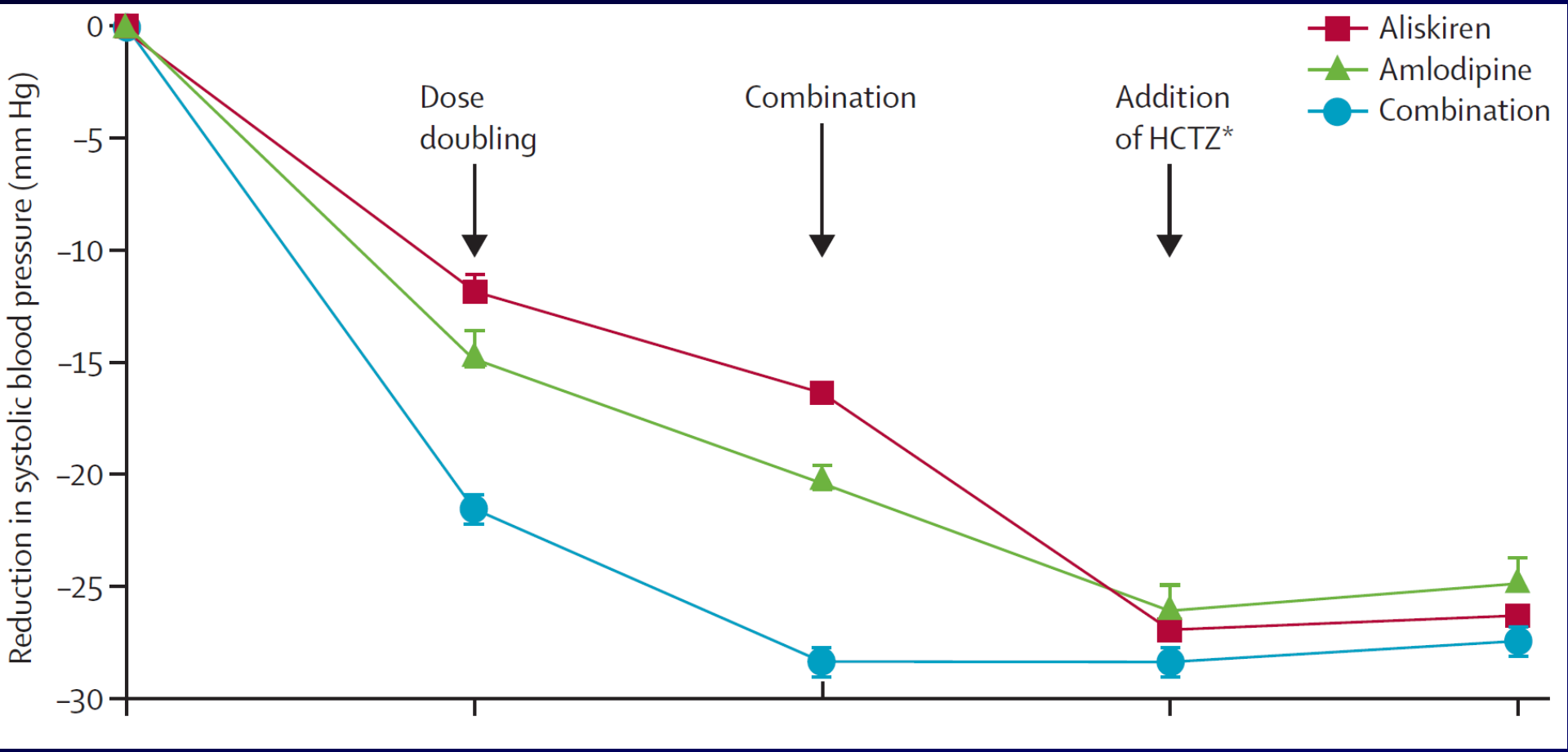
Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial

Morris J Brown, Gordon T McInnes, Cheraz Cherif Papst, Jack Zhang, Thomas M MacDonald

Starting with two drugs always better than starting with one

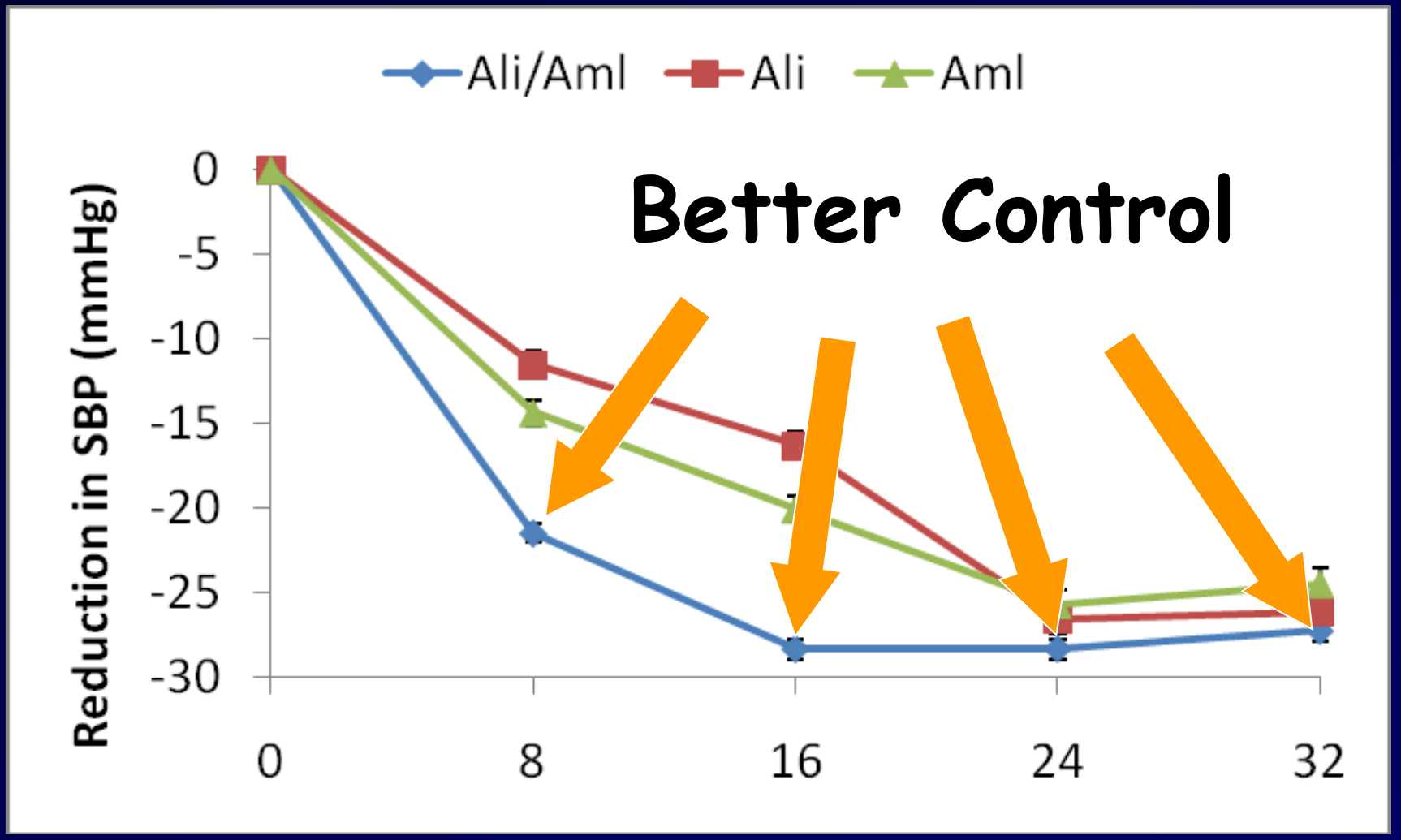
Lancet 2011;377:312-20

Combination v Mono-therapy



Lancet 2011;377:312-20

Start with Combination Rx?



Combination therapy:

Fewer side effects than mono-therapy

Lancet 2011;377:312-20

PATHWAY

Clinical Trials in Hypertension

SCOT

BHF Research Programme

Pathway 1

Combination v Monotherapy for Initial Treatment of Hypertension

Pathway 2

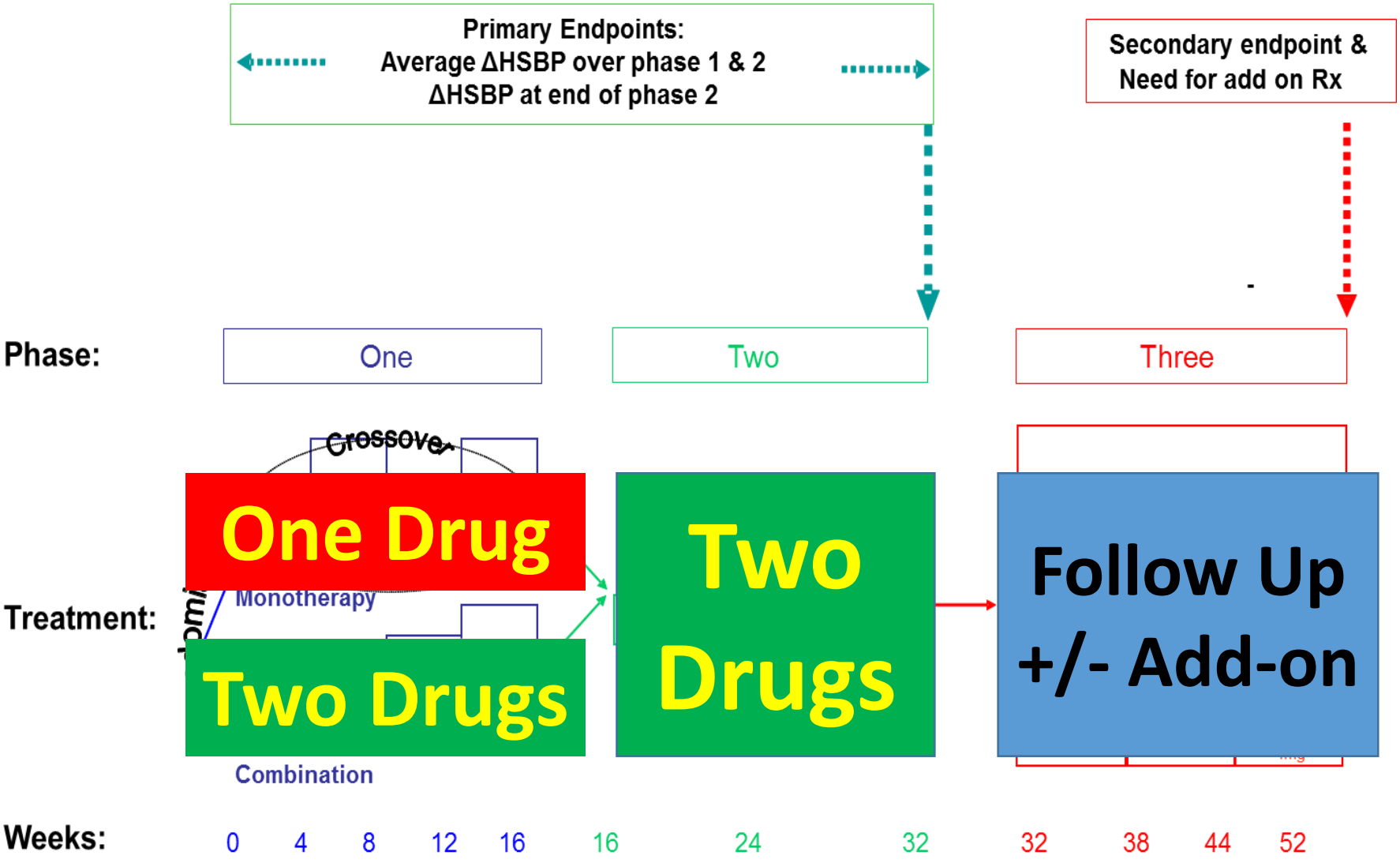
Resistant Hypertension: placebo-controlled crossover

Pathway 3

Thiazide vs K^+-sparing diuretic v Combo

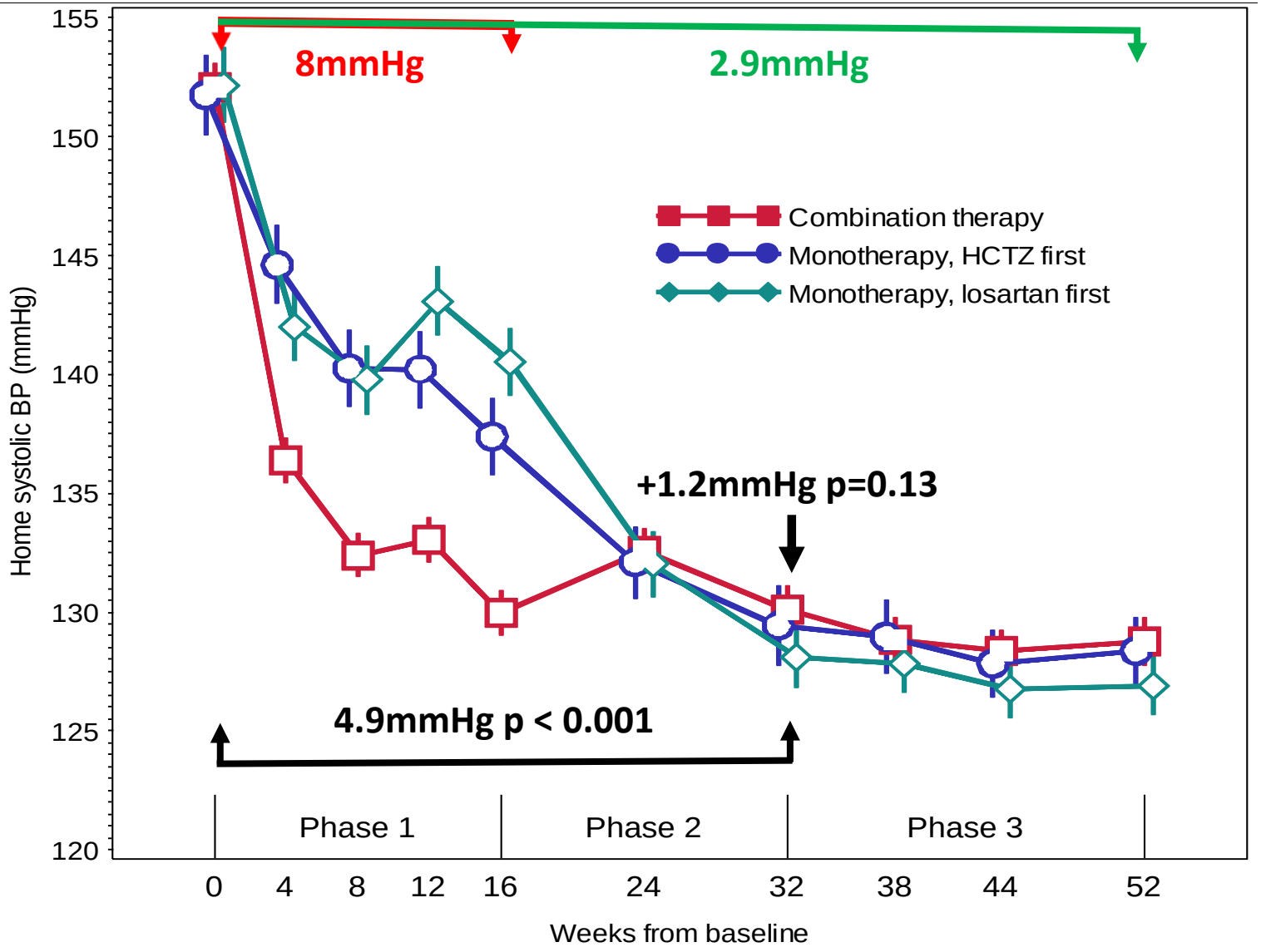
Methods

PATHWAY
Clinical Trials in Hypertension



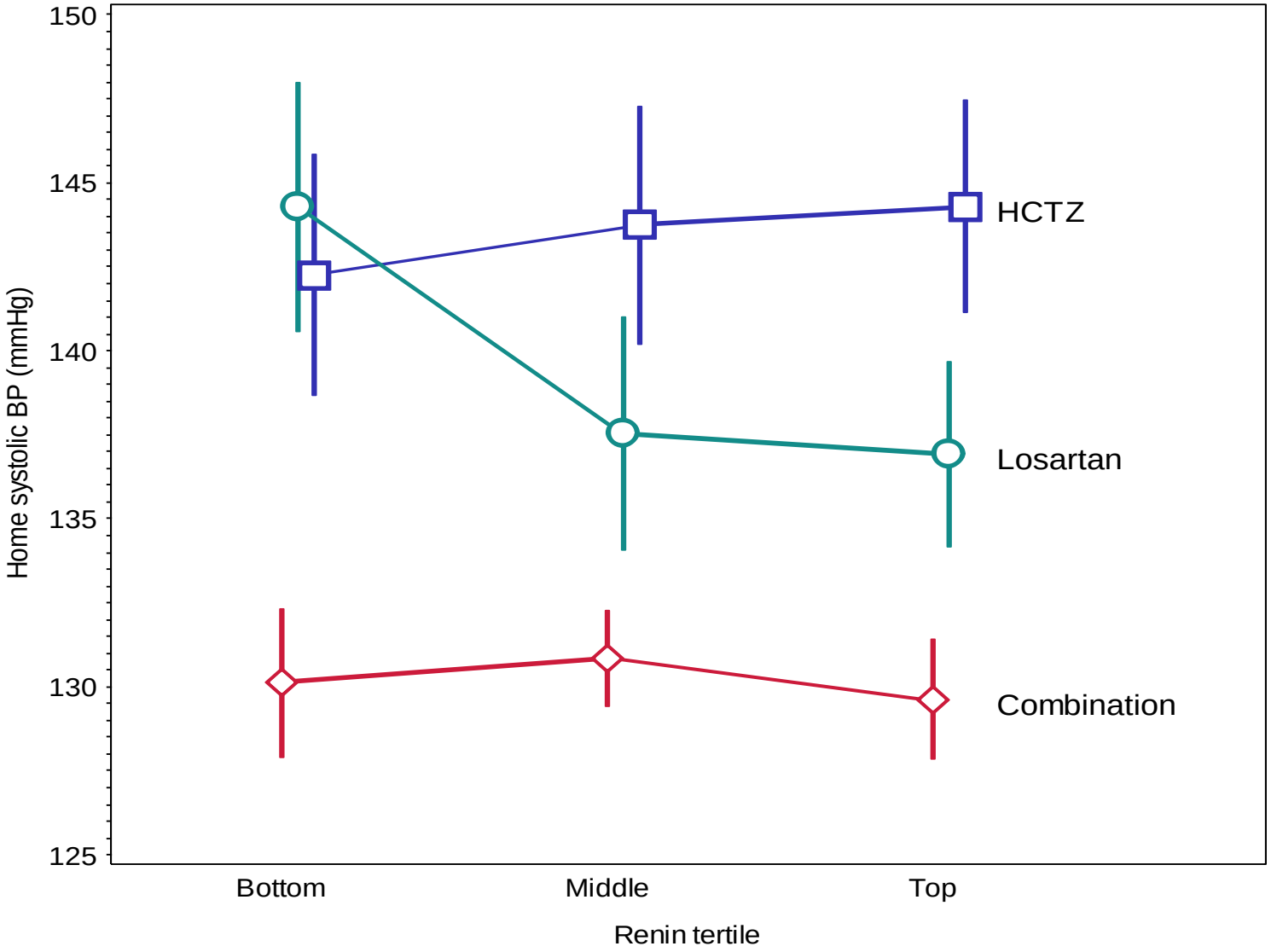
Results: Home SBP

PATHWAY
Clinical Trials in Hypertension



Results: Baseline Renin

PATHWAY
Clinical Trials in Hypertension



PATHWAY
Clinical Trials in Hypertension

Predictors of HSBP Response

	Randomised initial treatment					
	Combination		HCTZ		Losartan	
	Difference (95% CI)	p-value	Difference (95% CI)	p-value	Difference (95% CI)	p-value
Top vs Bottom renin tertile[1]	-1·41 (-3·52,0·71)	0·193	4·31 (-2·26,6·35)	<·001	-3·71 (-5·70,-1·71)	<·001
Aged over 55 vs 55 and under[1]	1·45 (-0·29, 3·19)	0·103	-2·94 (-4·73,-1·15)	0·001	-1·89 (-3·62,-0·16)	0·032
Renin (per 10 fold increase)	-1·80 (-4·75,1·16)	0·235	4·96 (2·12,7·80)	<·001	-3·70 (-6·43,-0·97)	0·008
Age (per 10 years)	0·13 (-0·85,1·12)	0·787	-0·97 (-1·98,0·04)	0·062	-0·20 (-1·18,0·77)	0·682
Baseline HSBP	0·29 (0·22,0·36)	<·001	0·48 (0·42,0·54)	<·001	0·55 (0·48,0·61)	<·001
Never vs previously treated	1·83 (-0·41,4·08)	0·111	-3·01 (-5·26,-0·77)	0·009	-2·85 (-4·96,-0·73)	0·009

Everything Predictive

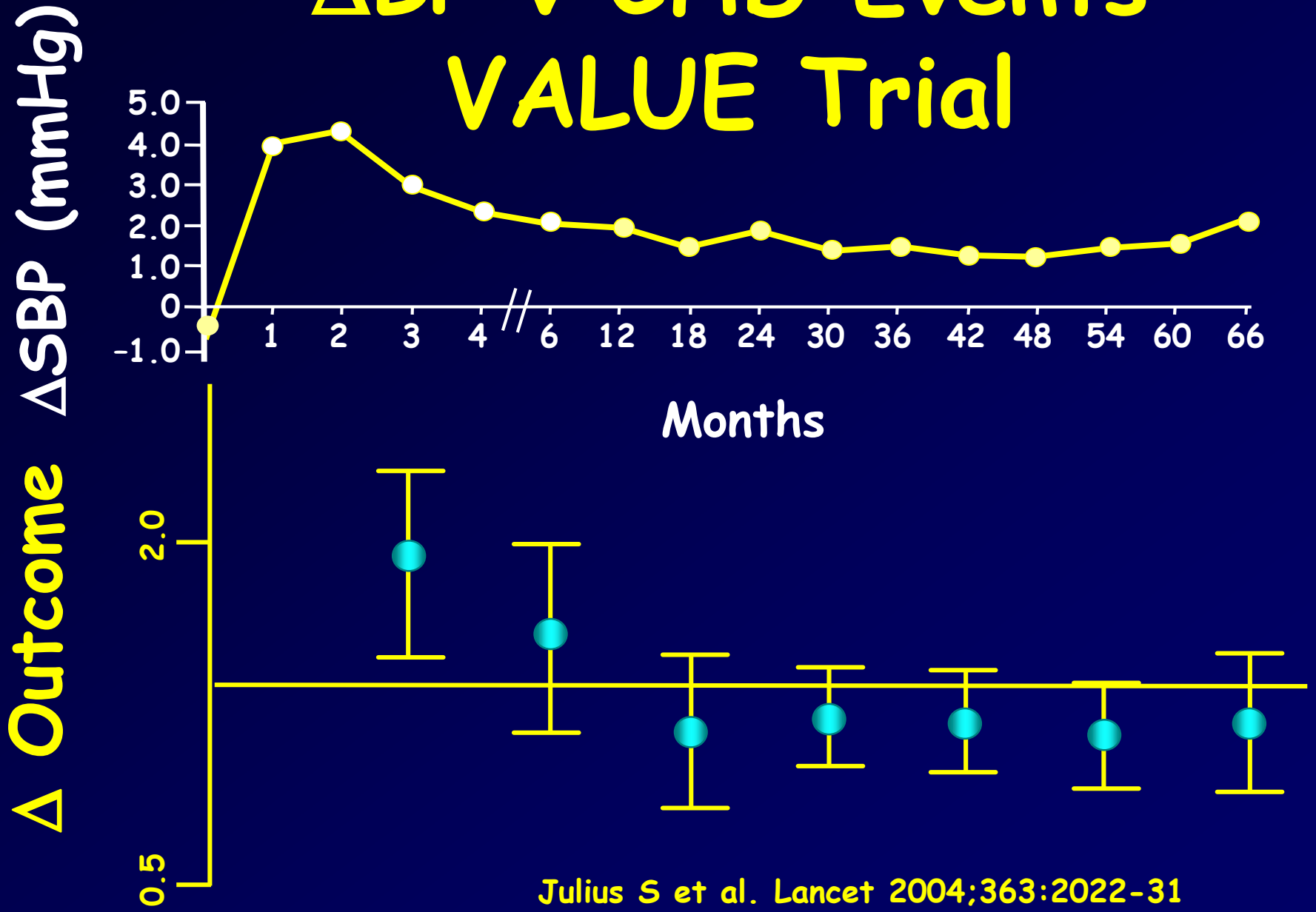
Optimal systolic blood pressure target, time to intensification, and time to follow-up in treatment of hypertension: population based retrospective cohort study

Wenxin Xu,[1] Saveli I Goldberg,[2] Maria Shubina,[3] Alexander Turchin[3]

Delays of > 2.7 months before BP intensification associated with increased risk of a acute cardiovascular event or death

BMJ 2015;350:h158

ΔBP v CHD Events VALUE Trial



Julius S et al. Lancet 2004;363:2022-31

Context

PATHWAY
Clinical Trials in Hypertension

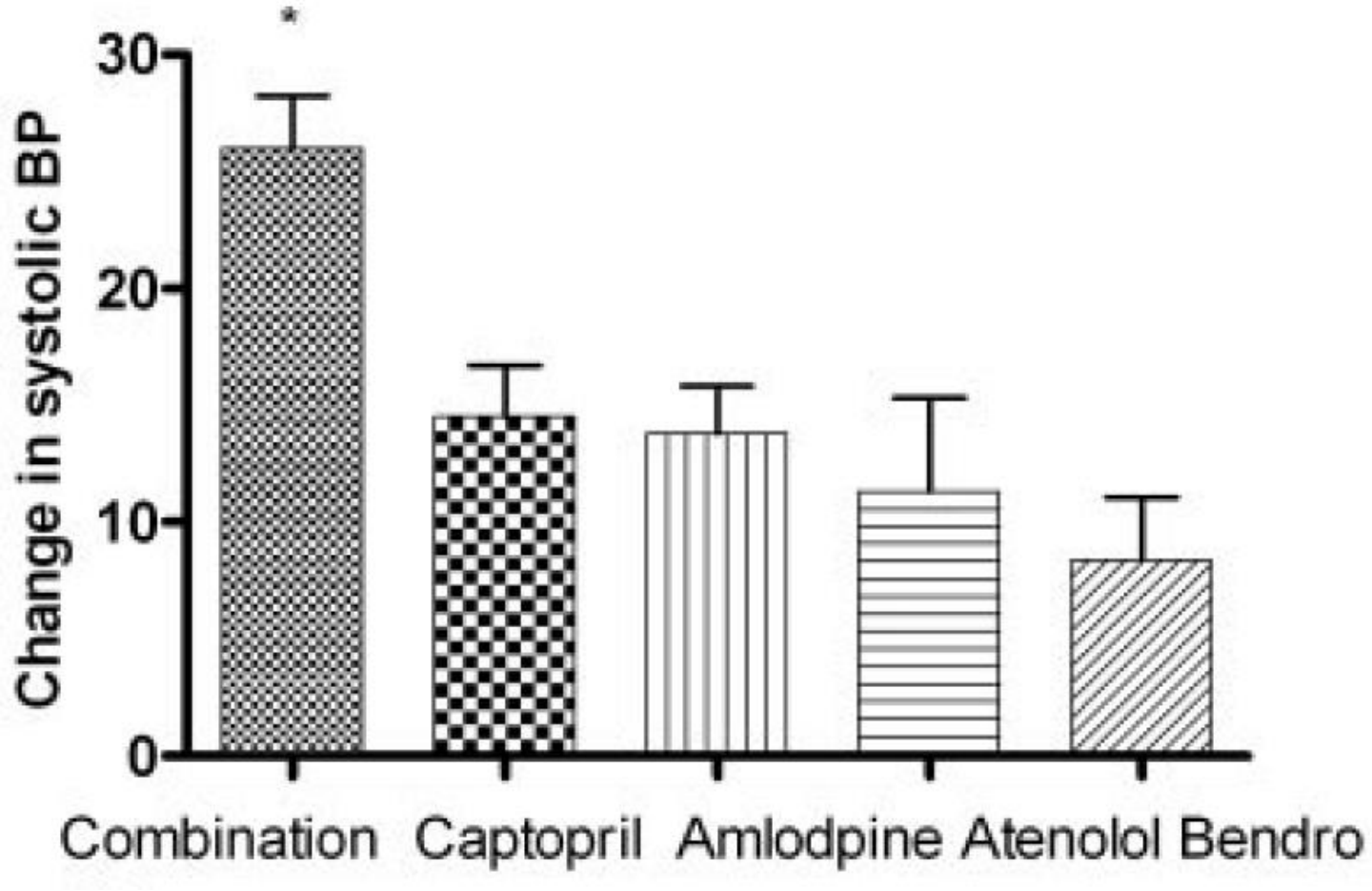
- In VALUE a between treatment difference in clinic SBP of -3.8mmHg over 3 months resulted in increased stroke and mortality.
- In PATHWAY, combination versus sequential monotherapy clinic SBP was;
  - -10.1mmHg over first 4 months
  - -6.8mmHg over first 8 months

PATHWAY
Clinical Trials in Hypertension

Summary

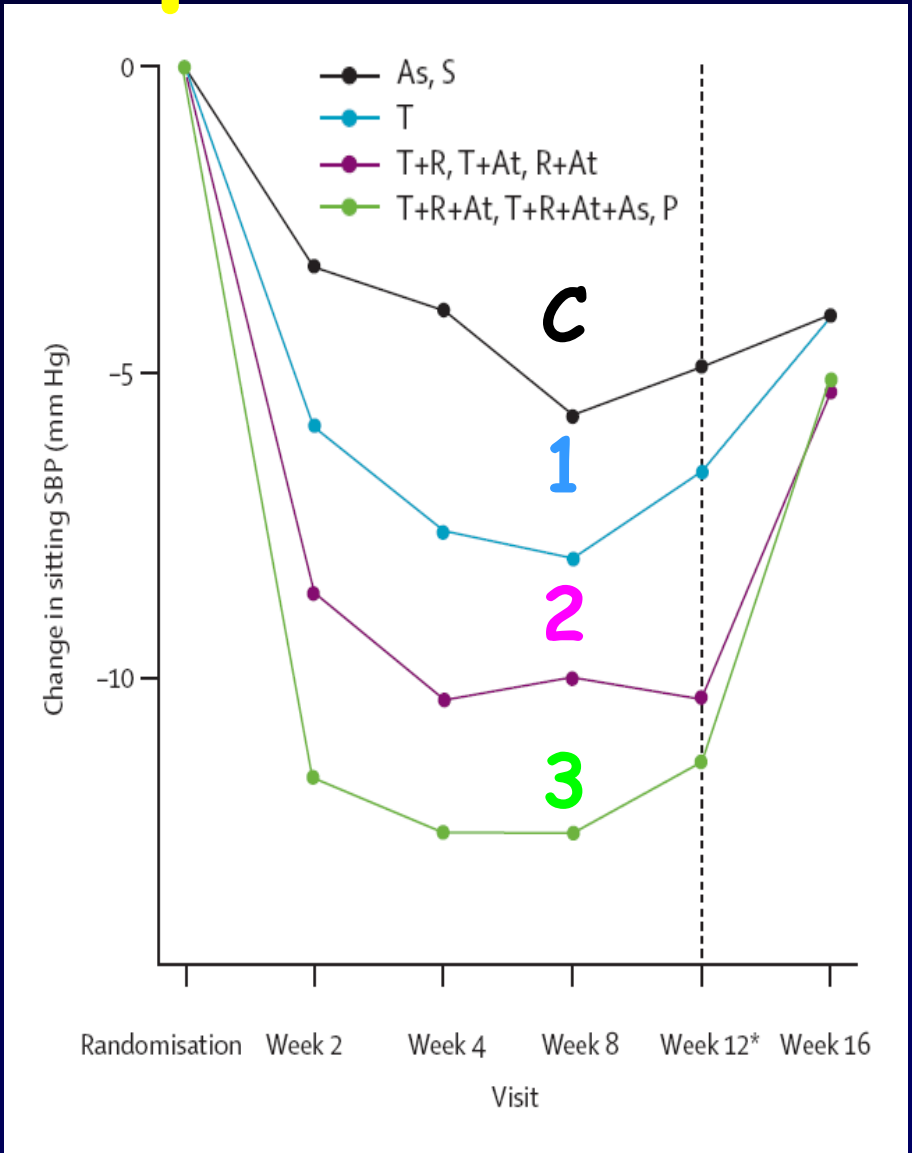
- Initial combination much more effective than optimized initial monotherapy
- No downside in adverse events
- 'Never-Catch-Up' not supported
- Need to change practice & guidelines to start with combination if SBP≥150mmHg

Four ¼ dose v standard dose



Hypertension 2007;49:272-275

PolyCap half-dose Rx



Lancet 2009; 373: 1341-51

Quarter-dose quadruple combination therapy for initial treatment of hypertension: placebo-controlled, crossover, randomised trial and systematic review

Clara K Chow, Jay Thakkar, Alex Bennett, Graham Hillis, Michael Burke, Tim Usherwood, Kha Vo, Kris Rogers, Emily Atkins, Ruth Webster, Michael Chou, Hakim-Moulay Dehbi, Abdul Salam, Anushka Patel, Bruce Neal, David Peiris, Henry Krum, John Chalmers, Mark Nelson, Christopher M Reid, Mark Woodward, Sarah Hilmer, Simon Thom, Anthony Rodgers*

Placebo corrected 24h mean ABPM BP reduction

18.7/14.2 mmHg

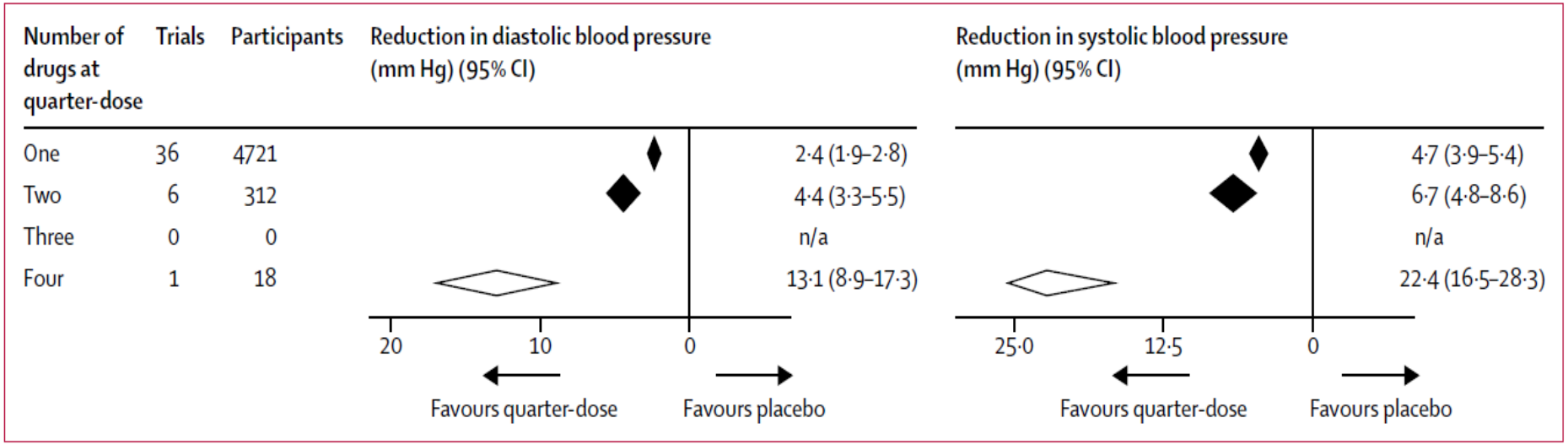
Placebo corrected Daytime mean ABPM BP reduction

22.3/15.3 mmHg

Lancet 2017;389:1035–42

Quarter Dose Studies

meta analysis-placebo controlled studies



Lancet 2017;389:1035–42

Recipe for 80+

Multiple Low-Dose Rx

Resistant Hypertension

Resistant Hypertension

- Non-concordance
- 'White Coat' Effect
- Pseudo-Hypertension
- Lifestyle Factors
- Drug Interactions
- Secondary Hypertension
- True Resistance

"Drugs don't work in patients who do not take them"

C. Everett Koop, M.D.

University Hospitals of Leicester NHS Trust

Pathology Directorate
Enquiries: pathology@uhl-tr.nhs.uk

NHS

[redacted]

Clinical Details

Assay ..

URINE DRUG SCREEN BY LC-MS/MS AND GC-MS:
[Patient on lisinopril, doxasizin, amlodipine, bendrofluazide, moxonidine and aliskiren]
NO DRUGS DETECTED BY ANY OF THESE SCREENING TECHNIQUES.
(Please note that moxonidine and aliskiren are not normally detected by the above screening techniques).

letter to GP to Hepworth dictated 28-9-11

FILE
SHOW WITH NOTES

2/11/11

11:30 15/09/2011

Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

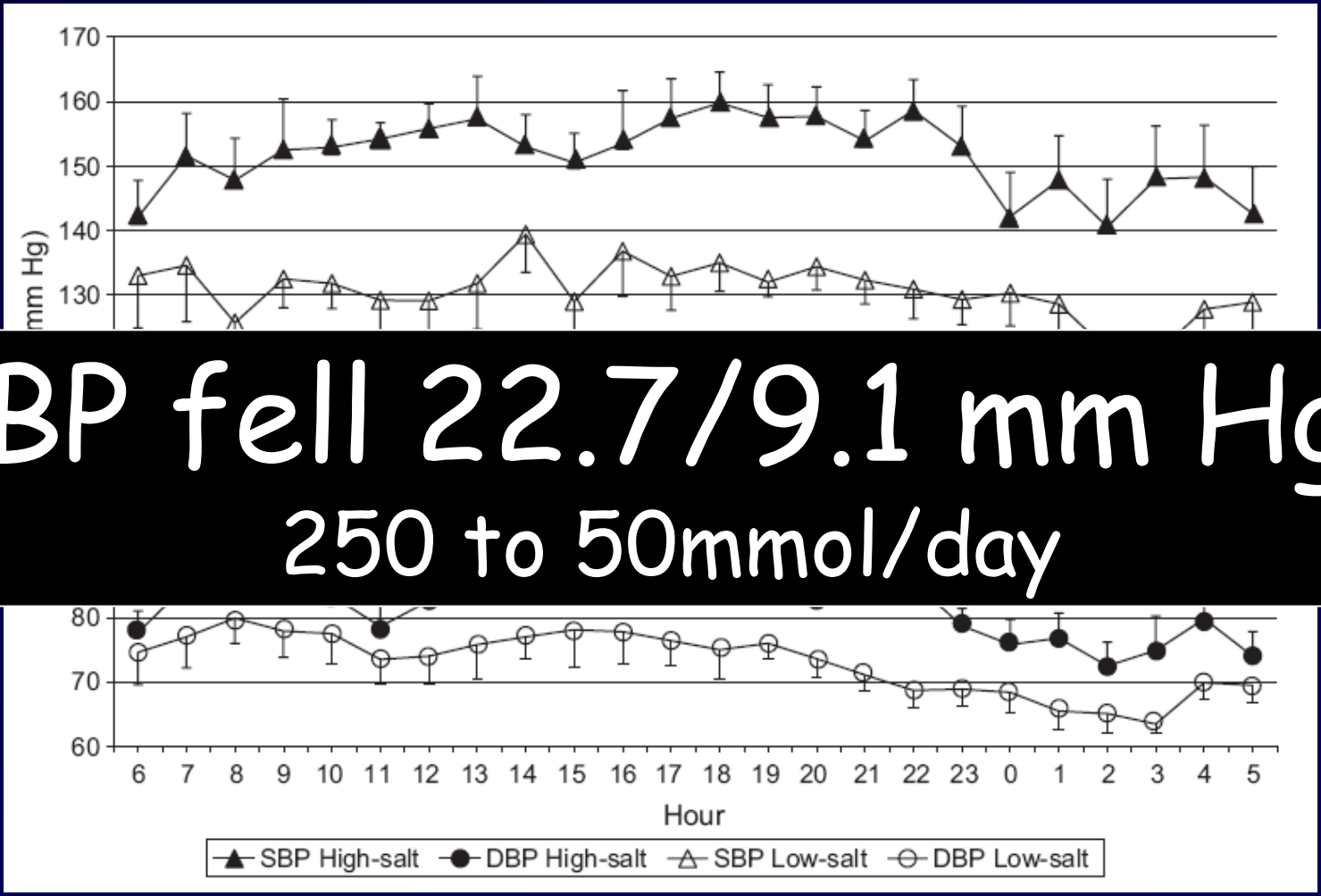
Vitamin D Therapy to Reduce Blood Pressure and Left Ventricular Hypertrophy in Resistant Hypertension: Randomized, Controlled Trial

Miles D. Witham, Sheila Ireland, J. Graeme Houston, Stephen J. Gandy, Shelley Waugh, Thomas M. MacDonald, Isla S. Mackenzie and Allan D. Struthers

Hypertension. published online January 13, 2014;

Vitamin D did not reduce ambulatory blood pressure in resistant hypertension

RCT High v Low Salt Resistant hypertension



BP fell 22.7/9.1 mm Hg

250 to 50mmol/day

Hypertension 2009;54:475-481

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

*Bryan Williams, Thomas M MacDonald, Steve Morant, David J Webb, Peter Sever, Gordon McInnes, Ian Ford, J Kennedy Cruickshank, Mark J Caulfield, Jackie Salsbury, Isla Mackenzie, Sandosh Padmanabhan, Morris J Brown, for The British Hypertension Society's PATHWAY Studies Group**

Lancet 2015

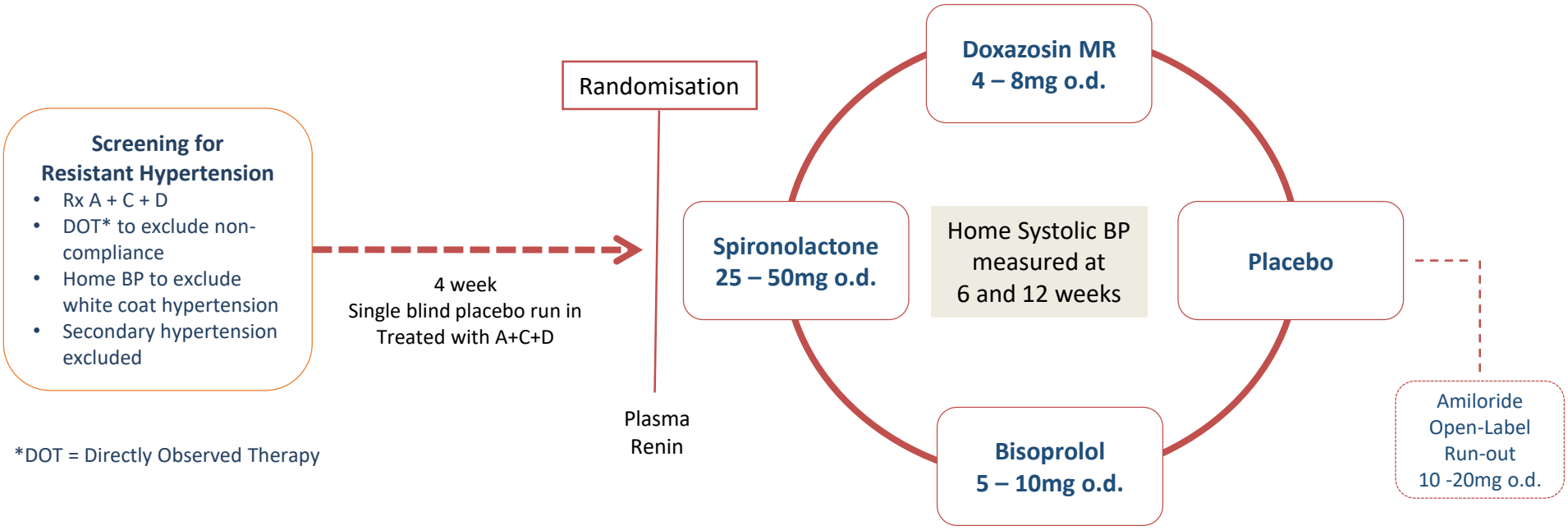
Spironolactone for resistant hypertension—hard to resist?

Lancet Editorial 2015

PATHWAY-2
Clinical Trials in Hypertension

PATHWAY-2 Study Design

Double blind, Randomised, Placebo-Controlled, Cross-over Study



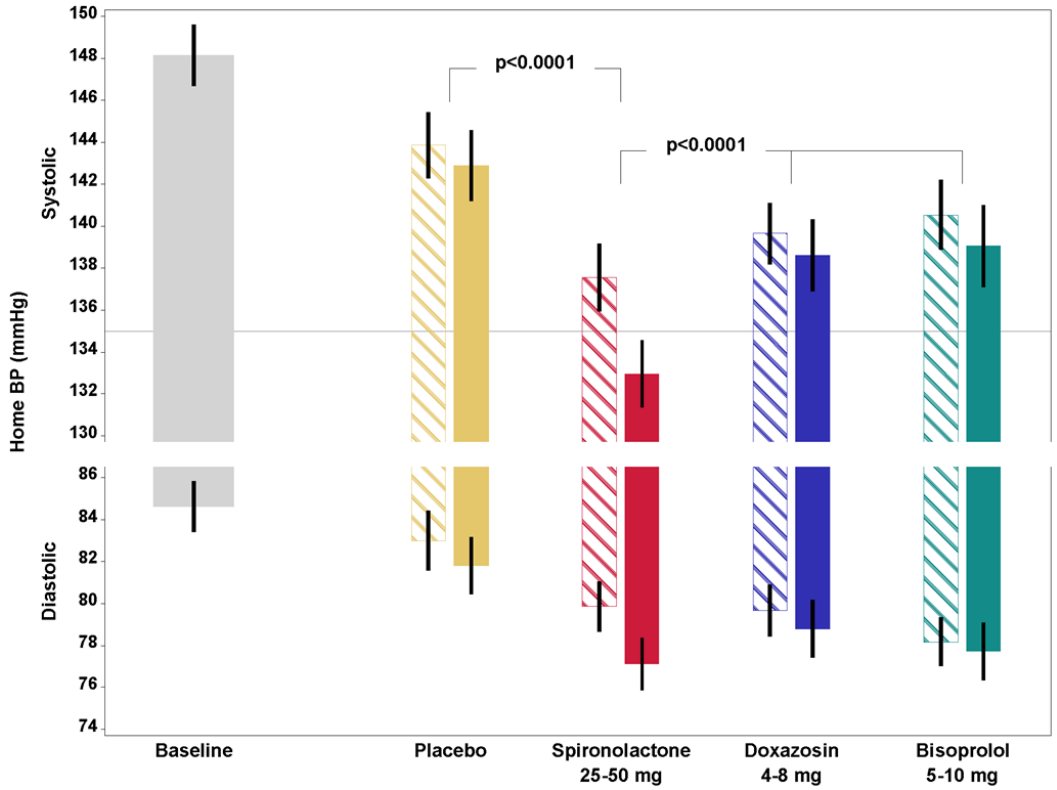
*DOT = Directly Observed Therapy

- 12 weeks per treatment cycle
- Forced titration; lower to higher dose at 6 weeks
- No washout period between cycles

Williams B, et al. BMJ Open, 2015

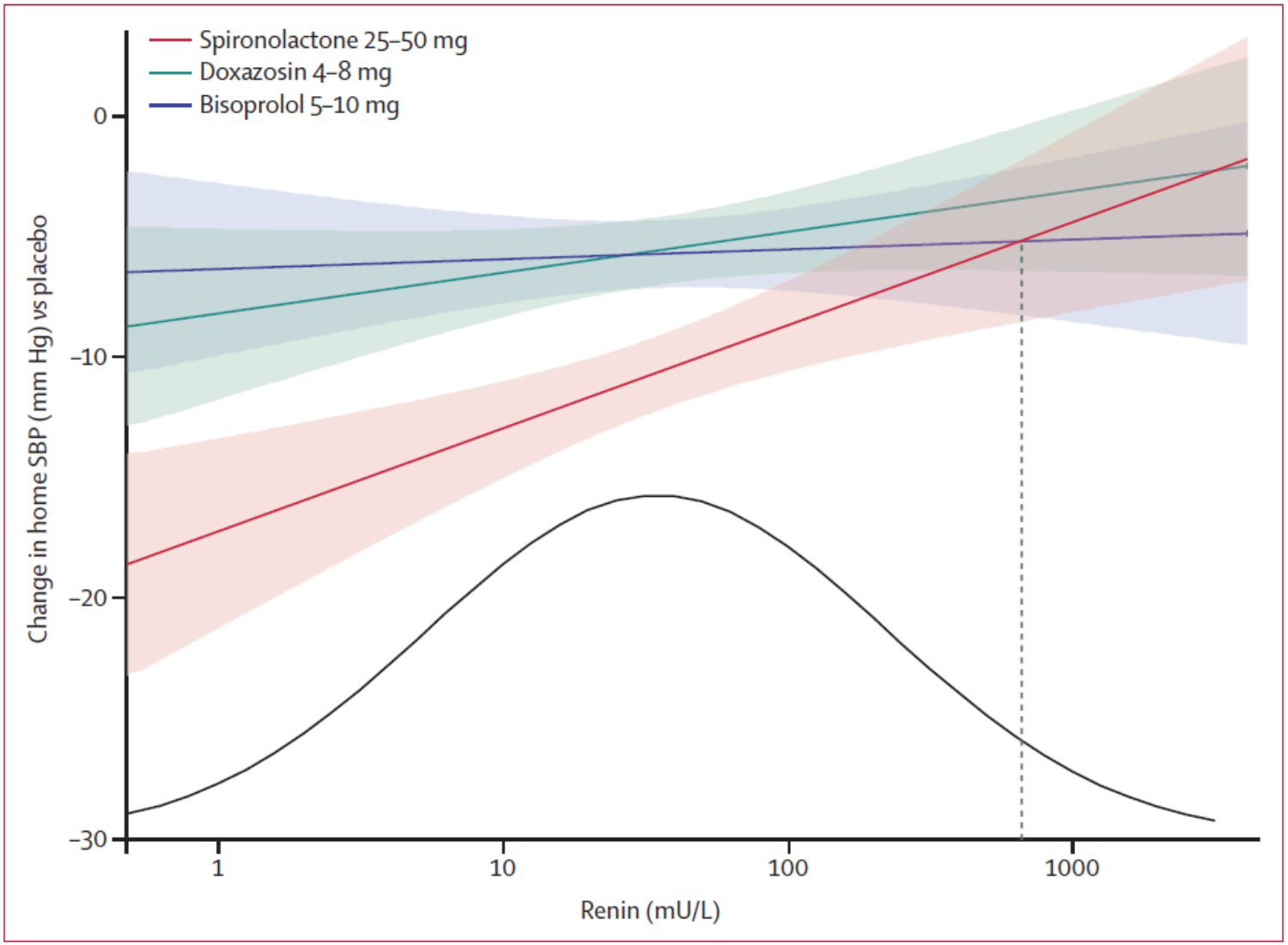
Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

*Bryan Williams, Thomas M MacDonald, Steve Morant, David J Webb, Peter Sever, Gordon McInnes, Ian Ford, J Kennedy Cruickshank, Mark J Caulfield, Jackie Salsbury, Isla Mackenzie, Sandosh Padmanabhan, Morris J Brown, for The British Hypertension Society's PATHWAY Studies Group**



Lancet 2015;386:2059–68

Δhome SBP by Renin Mass

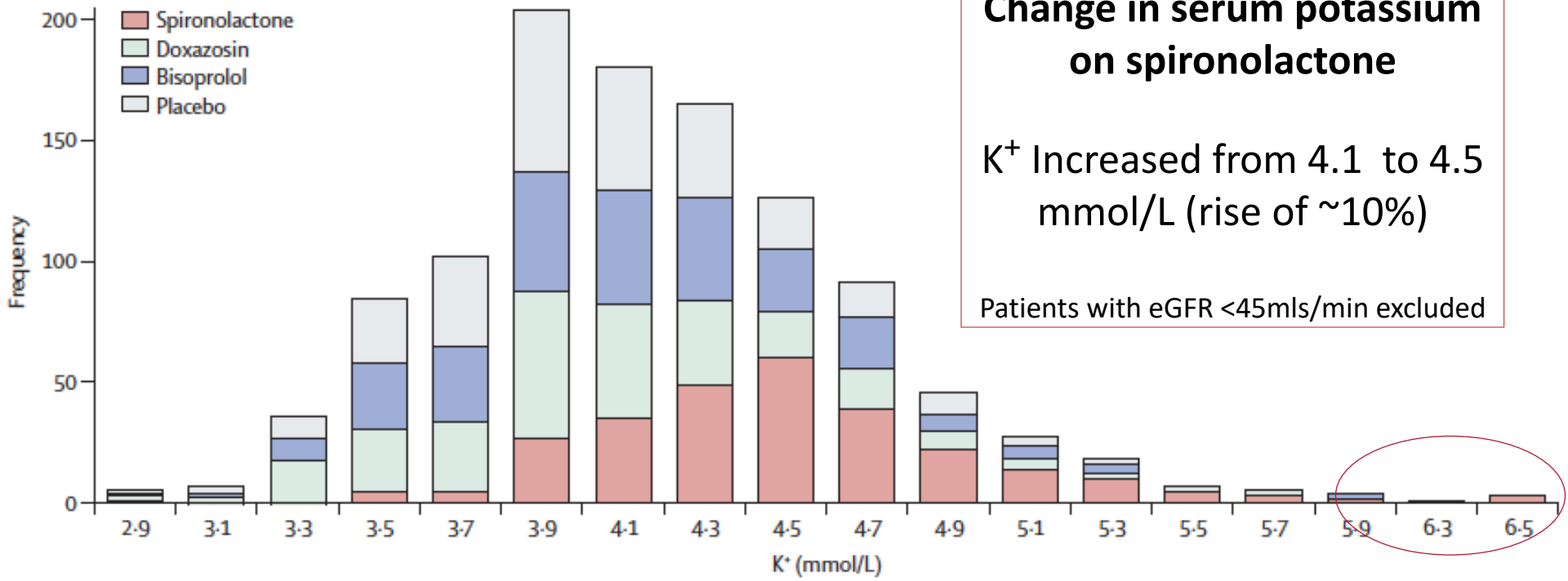


Lancet 2015;386:2059-68

60% of hypertensive patients have inappropriate secretion of aldosterone

J Clin Endocrinol Metab 2015, 100:2853–2855

Distribution of Serum Potassium at End of each Treatment Cycle



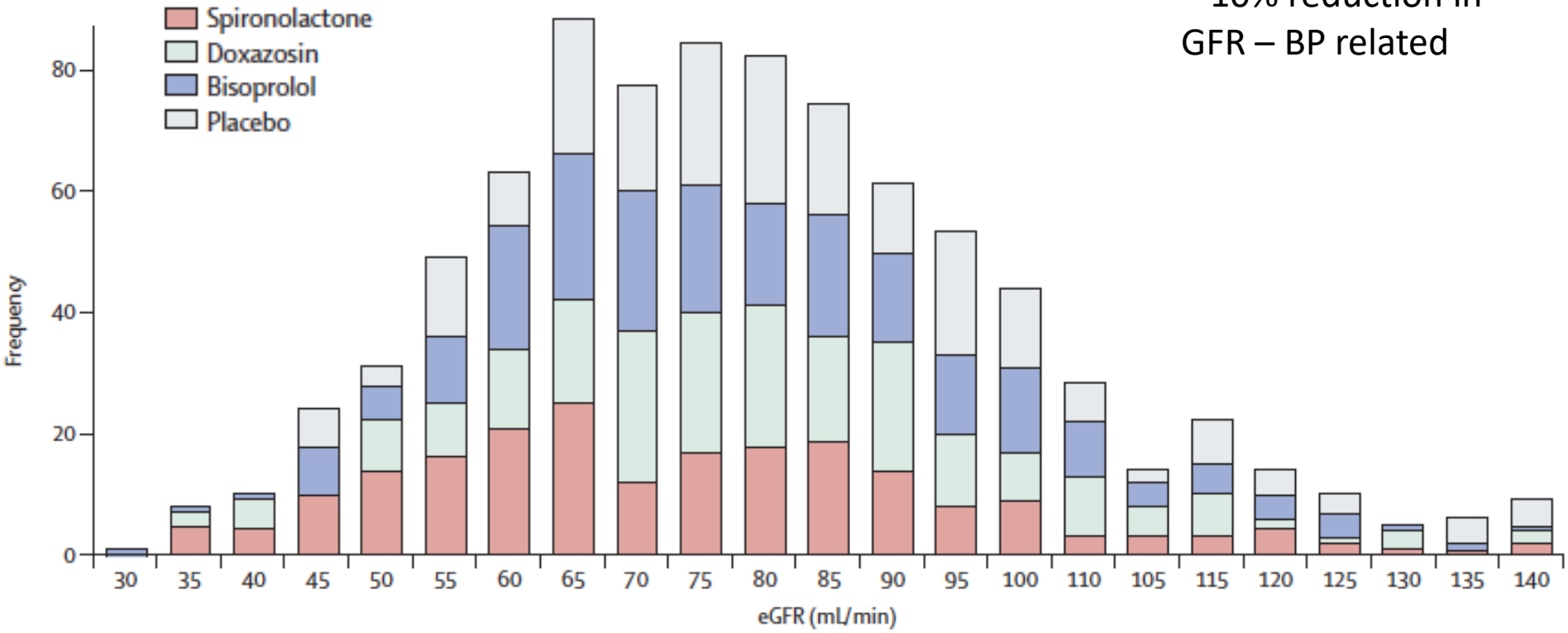
Change in serum potassium on spironolactone

K^+ Increased from 4.1 to 4.5 mmol/L (rise of ~10%)

Patients with eGFR <45mls/min excluded

Distribution of eGFR at end of each treatment Cycle

- Patients with eGFR <45mls/min excluded
- ~10% reduction in GFR – BP related



eGFR Changes with treatment

	Baseline	Follow up	Change	p value	Adjusted change*	p value
eGFR (mls/min)						
Spironolactone	93·20	83·18	-10·02	0·004	-9·68	<0·001
Doxazosin	92·70	85·38	-7·32	0·023	-7·31	0·011
Bisoprolol	92·40	86·35	-6·05	0·006	-6·05	0·031
Placebo	92·52	92·67	0·15	0·923	-0·86	0·773

* Adjusted for change in Mean arterial blood pressure

Reduction of cardiovascular risk in chronic kidney disease by mineralocorticoid receptor antagonism

Murray Epstein

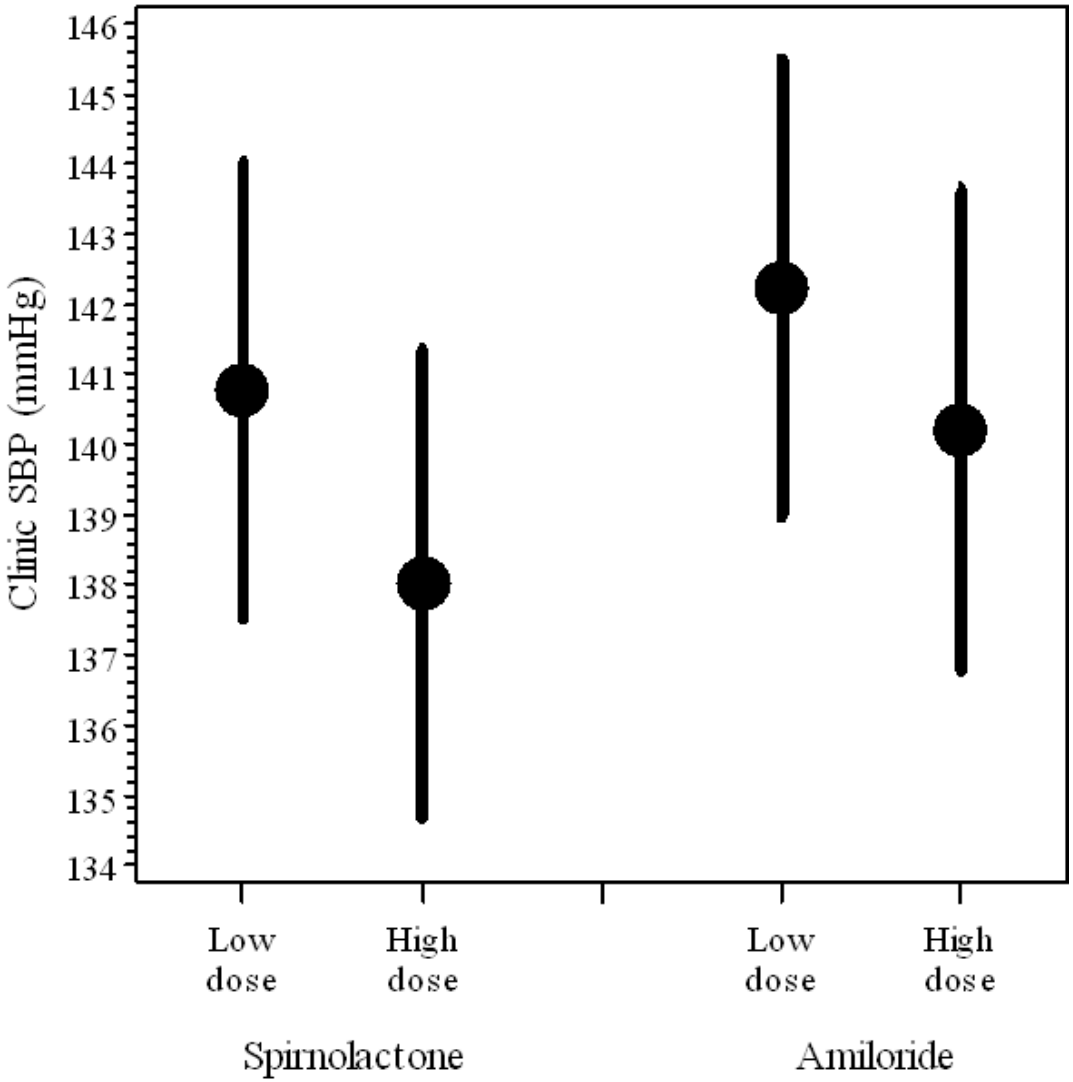
Cardiovascular disease is the leading cause of death and morbidity in people with chronic kidney disease, but there are few evidence-based treatments for reducing cardiovascular events in these patients. The failure of novel drug candidates to delay progression to end-stage renal disease and limit or abrogate cardiovascular morbidity and mortality has led to increased interest in a mineralocorticoid receptor (MR) antagonist-based treatment model to reduce cardiovascular risk in patients with chronic kidney disease and end-stage renal disease. Aldosterone concentrations and MR signalling

Lancet Diabetes Endocrinol 2015
Published Online
September 29, 2015
http://dx.doi.org/10.1016/
S2213-8587(15)00289-2

MR antagonists could provide cardiovascular benefit in patients with chronic kidney disease

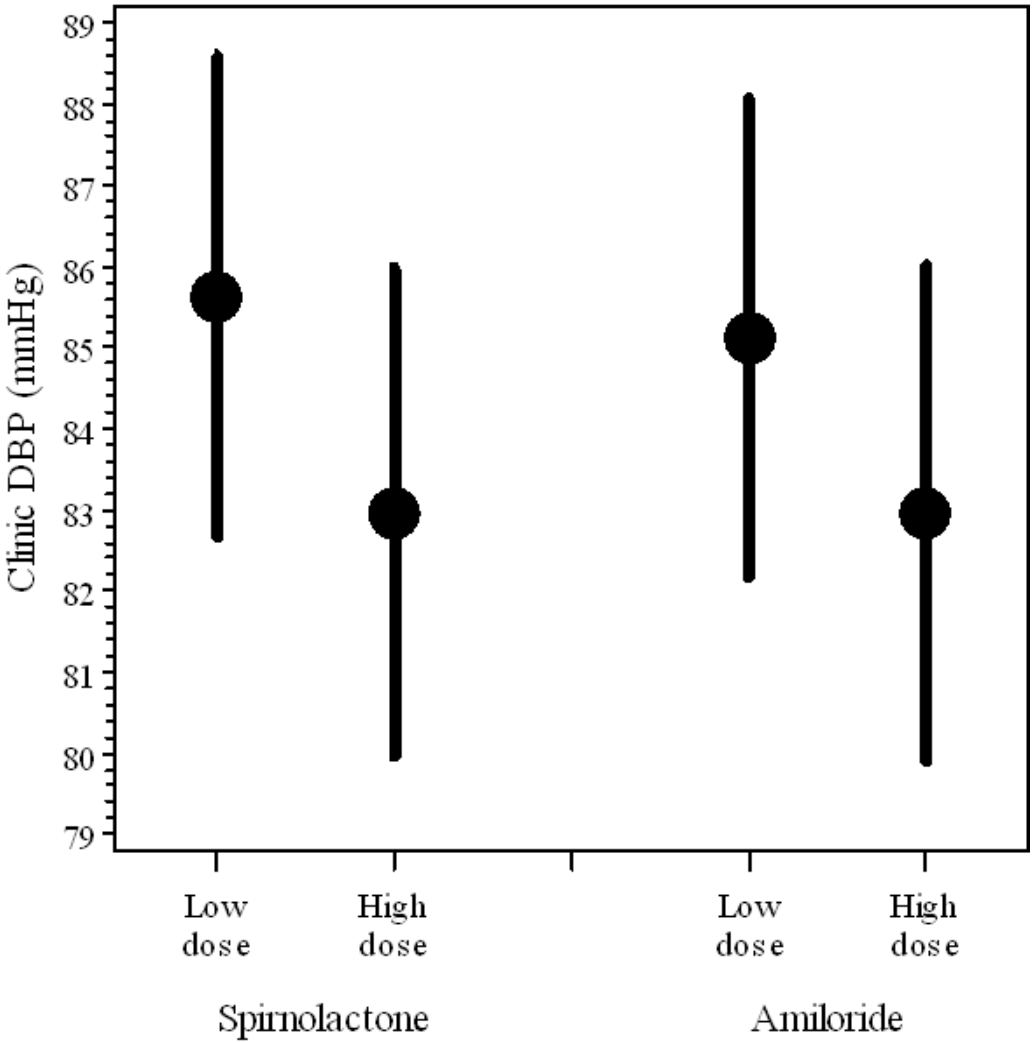
Lancet Diabetes Endocrinol
Published Online September 29, 2015

Run-out: PATHWAY 2



PATHWAY
Clinical Trials in Hypertension

Run-out: PATHWAY 2



Implications of Findings

- **Spironolactone is the most effective treatment for resistant hypertension**
- **These results should influence treatment guidelines globally**
- **Patients should not be defined as resistant hypertension unless their BP remains uncontrolled on spironolactone**

Cameo of the spironolactone responder

Obese resistant hypertensive taking ACEI/ARB/Renin inhibitor/beta blocker, who has a high salt intake, has diabetes and takes a diuretic but despite this has a low renin


Spironolactone
Tablets, USP
25 mg
SANDOZ

Spironolactone

- Complex metabolism – active metabolites
  - Canrenone
  - 7-alpha-thiomethylspirolactone
  - 6-beta-hydroxy-7-alpha-thiomethylspirolactone
- Licence for hypertension withdrawn in UK in 1988 after concerns of malignancy in animal models
  - Myelomonoblastic leukaemia (with potassium canrenoate)
- Licensed in many European countries

Spironolactone safety in practice

- **Interactions?**

BMJ

BMJ 2011;343:d5656 doi: 10.1136/bmj.d5656

EDITORIALS

Co-prescription of co-trimoxazole and spironolactone in elderly patients

The combination should be used with caution because of the risk of hyperkalaemia

Li Wei *lecturer*, Thomas M MacDonald *professor* , Isla S Mackenzie *clinical senior lecturer*

- **Hyperkalaemia / renal toxicity?**

PATHWAY 2
Clinical Trials in Hypertension

ADRs in PATHWAY 2

	Spironolactone	Doxazosin	Bisoprolol	Placebo	p value*
Serious adverse events	7 (2%)	5 (2%)	8 (3%)	5 (2%)	0·82
Any adverse event	58 (19%)	67 (23%)	68 (23%)	42 (15%)	0·036
Withdrawals for adverse events	4 (1%)	9 (3%)	4 (1%)	3 (1%)	0·28

Lancet 2015;386:2059–68

BMJ

RESEARCH

Spironolactone use and renal toxicity: population based longitudinal analysis

Li Wei, lecturer,[1] Allan D Struthers, professor,[2] Tom Fahey, professor,[3] Alexander D Watson, general practitioner,[4] Thomas M MacDonald, professor[1]

Safe with adequate monitoring

BMJ 2010;340:c1768

Spironolactone

- Consider switch to loop diuretic (or add a loop)
- Start low (or v low)
- 6.25mg /day (12.5mg every second day)
- 5mg/5ml Liquid available
- Tolerate 25% rise in K+ & Creat
  - Improves with time

Spironolactone & cancer

- Breast cancer – case reports
- Pharyngeal cancer – small numbers
- Thyroid follicular adenomas
- Leydig cell testicular tumours in rats at high doses

BMJ

BMJ 2012;345:e4447 doi: 10.1136/bmj.e4447 (Published 13 July 2012)

RESEARCH

Spironolactone and risk of incident breast cancer in women older than 55 years: retrospective, matched cohort study

Isla S Mackenzie *clinical senior lecturer in clinical pharmacology*[1], Thomas M MacDonald *professor of clinical pharmacology and pharmacoepidemiology*[1], Alastair Thompson *professor of surgical oncology*[2], Steve Morant *honorary research fellow*[1], Li Wei *lecturer in medical statistics*[1]

[1]Medicines Monitoring Unit (MEMO), University of Dundee, Dundee DD1 9SY, UK; [2]Dundee Cancer Centre, Dundee

British Journal of Clinical Pharmacology

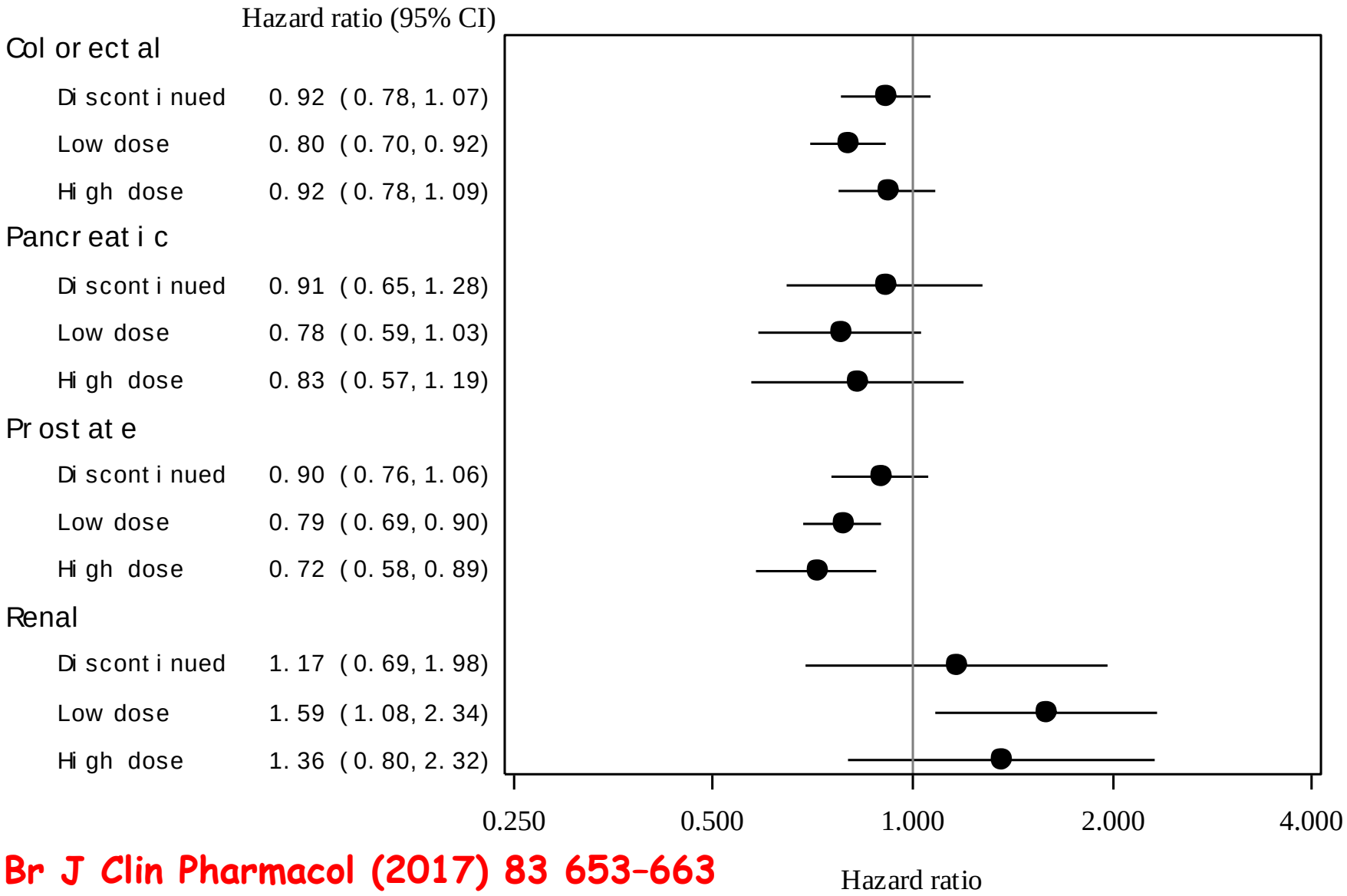
Br J Clin Pharmacol (2017) **83** 653–663

PHARMACOEPIDEMIOLOGY

Spironolactone use and risk of incident cancers: a retrospective, matched cohort study

Correspondence Dr Isla S Mackenzie, Clinical Reader in Clinical Pharmacology, Medicines Monitoring Unit (MEMO), Division of Molecular and Clinical Medicine, Level 7, Mailbox 2, University of Dundee, Dundee, DD1 9SY, UK. Tel.: +44 1382 383119; Fax: +44 1382 740209; E-mail: i.s.mackenzie@dundee.ac.uk

Hazard ratios in 4 types of cancer for low and high dose spironolactone exposure versus matched controls



Br J Clin Pharmacol (2017) 83 653–663

Conclusions

- Spironolactone not associated with increased cancer incidence
- Spironolactone was associated with reduced prostate cancer
- Dose-dependent reduced PSA and biological plausibility suggests a causal association with reduced prostate cancer

Br J Clin Pharmacol (2017) 83 653–663

A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism

Hari K. Parthasarathy[a], Joel Ménard[b], William B. White[c], William F. Young Jr[d], Gordon H. Williams[e], Bryan Williams[f], Luis Miguel Ruilope[g], Gordon T. McInnes[h], John M. Connell[i] and Thomas M. MacDonald[i]

Spironolactone more potent than eplerenone

Journal of Hypertension 2011;29:980–990

Effect of amiloride, or amiloride plus hydrochlorothiazide, versus hydrochlorothiazide on glucose tolerance and blood pressure (PATHWAY-3): a parallel-group, double-blind randomised phase 4 trial

*Morris J Brown, Bryan Williams, Steve V Morant, David J Webb, Mark J Caulfield, J Kennedy Cruickshank, Ian Ford, Gordon McInnes, Peter Sever, Jackie Salsbury, Isla S Mackenzie, Sandosh Padmanabhan, Thomas M MacDonald, for the British Hypertension Society's Prevention and Treatment of Hypertension with Algorithm-based Therapy (PATHWAY) Studies Group**

Interpretation The combination of amiloride with hydrochlorothiazide, at doses equipotent on blood pressure, prevents glucose intolerance and improves control of blood pressure compared with montherapy with either drug. These findings, together with previous data about morbidity and mortality for the combination, support first-line use of amiloride plus hydrochlorothiazide in hypertensive patients who need treatment with a diuretic.

Lancet Diabetes Endocrinol. 2016;4:136-47

Hypotheses

- Amiloride will have the opposite effect to hydrochlorothiazide (HCTZ) on K^+ and glucose, but same effect on blood pressure.
- *Combination* of diuretics with different sites of action in the nephron will be synergistic for Na^+ loss and hence BP reduction
- Consequently, the combination of half-maximal doses of amiloride and HCTZ will:
  - Neutralise the undesired effects of HCTZ, on glucose and K^+
  - Potentiate the desired effect of HCTZ, on blood pressure

Study Methods and Design

PATHWAY 3
Clinical Trials in Hypertension

Screening

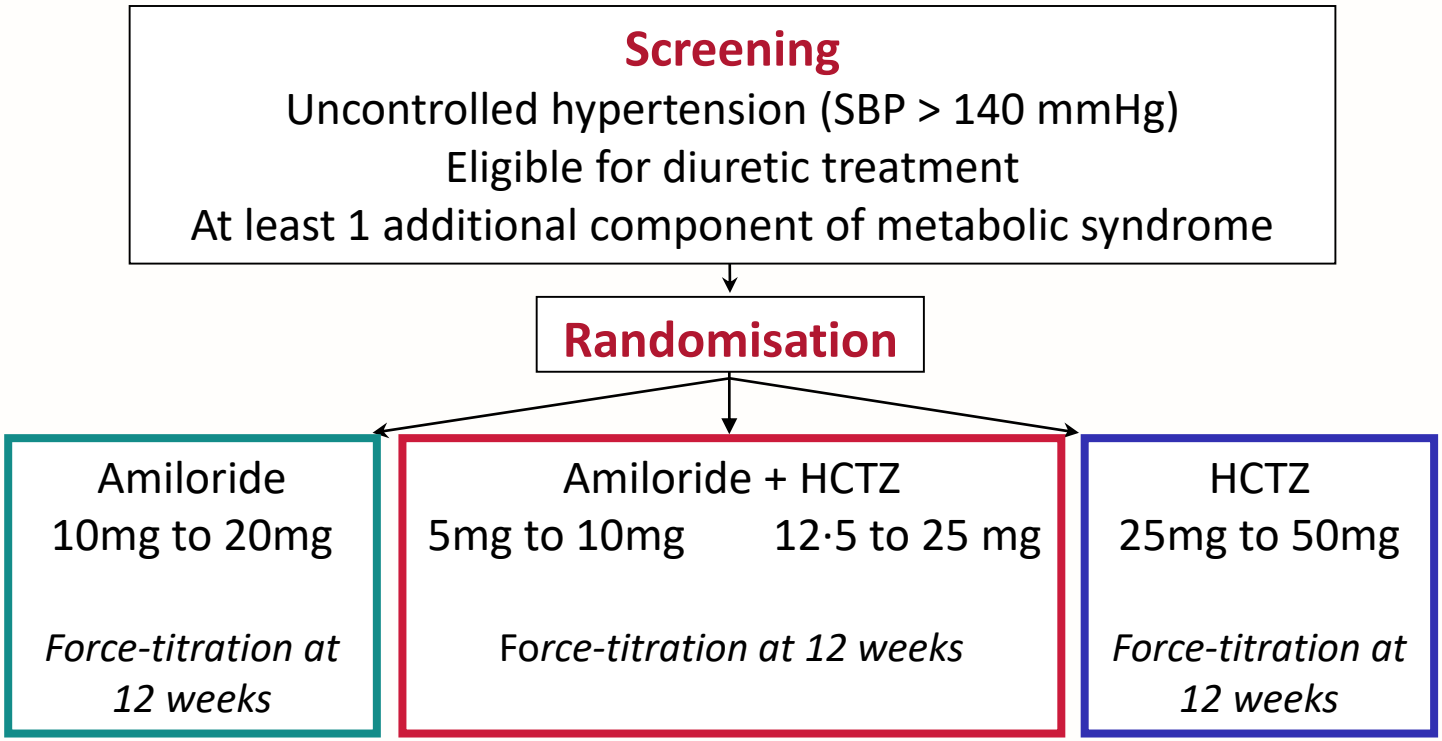
Uncontrolled hypertension (SBP > 140 mmHg)

Eligible for diuretic treatment

At least 1 additional component of metabolic syndrome

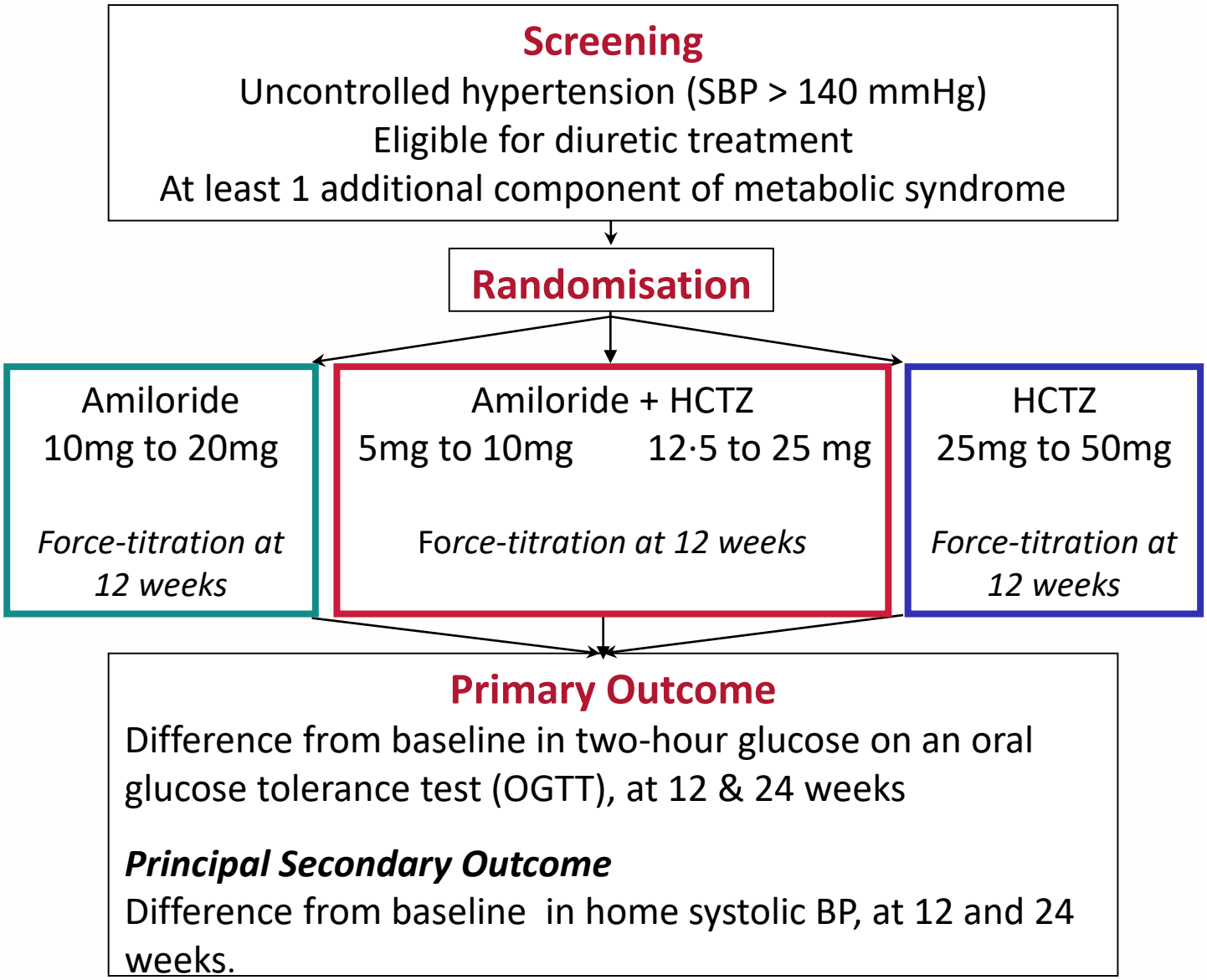
Study Methods and Design

PATHWAY 3
Clinical Trials in Hypertension



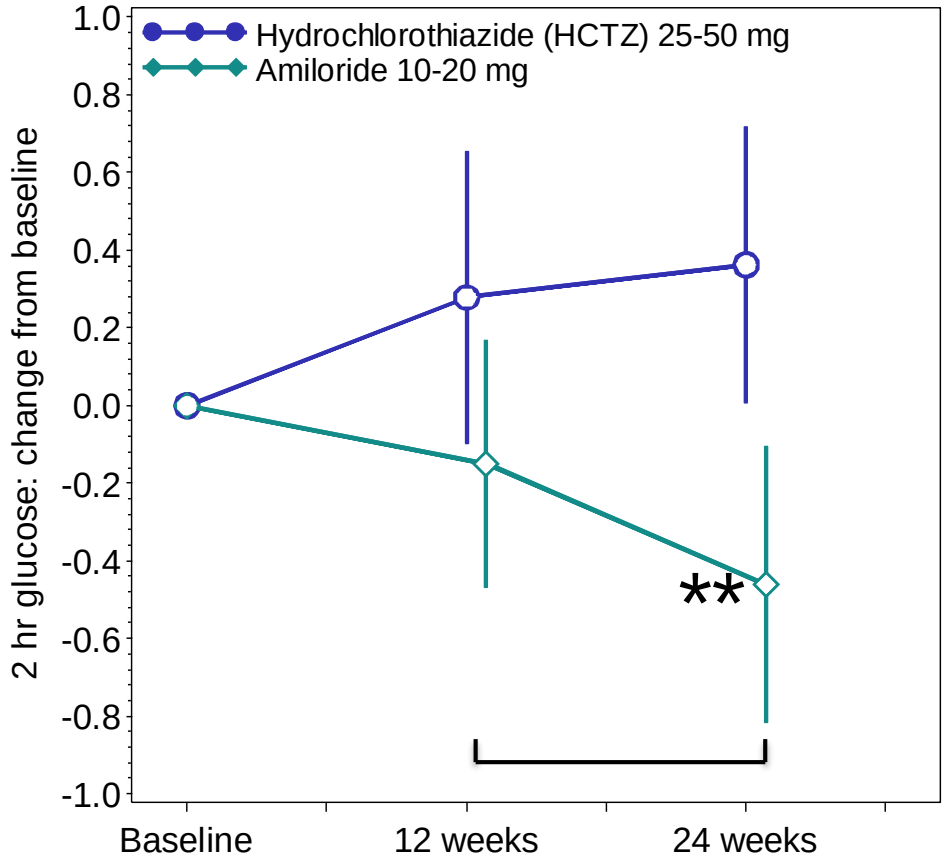
Study Methods and Design

PATHWAY 3
Clinical Trials in Hypertension



Hierarchical primary endpoints

Difference in change from baseline in OGTT 2 hr glucose for [i] amiloride vs HCTZ



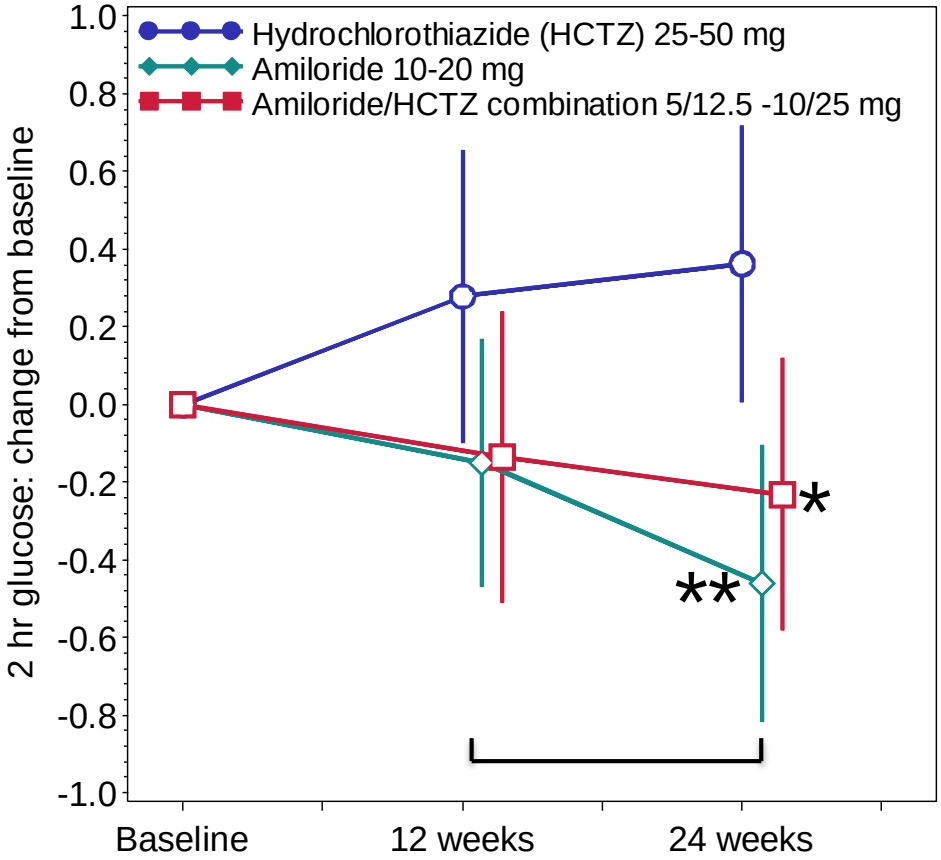
Average difference from HCTZ (mmol/L) (12 & 24 weeks)

Amiloride n=132
-0.55 (-0.96,-0.14)
P=0.009

Adjusted means (95% CI) for change from baseline in 2 hr glucose during OGTT. Doses were doubled at 12 weeks. **=p<0.01 vs HCTZ

Hierarchical primary endpoints

Difference in change from baseline in OGTT 2 hr glucose for [i] amiloride vs HCTZ, [ii] combination vs HCTZ



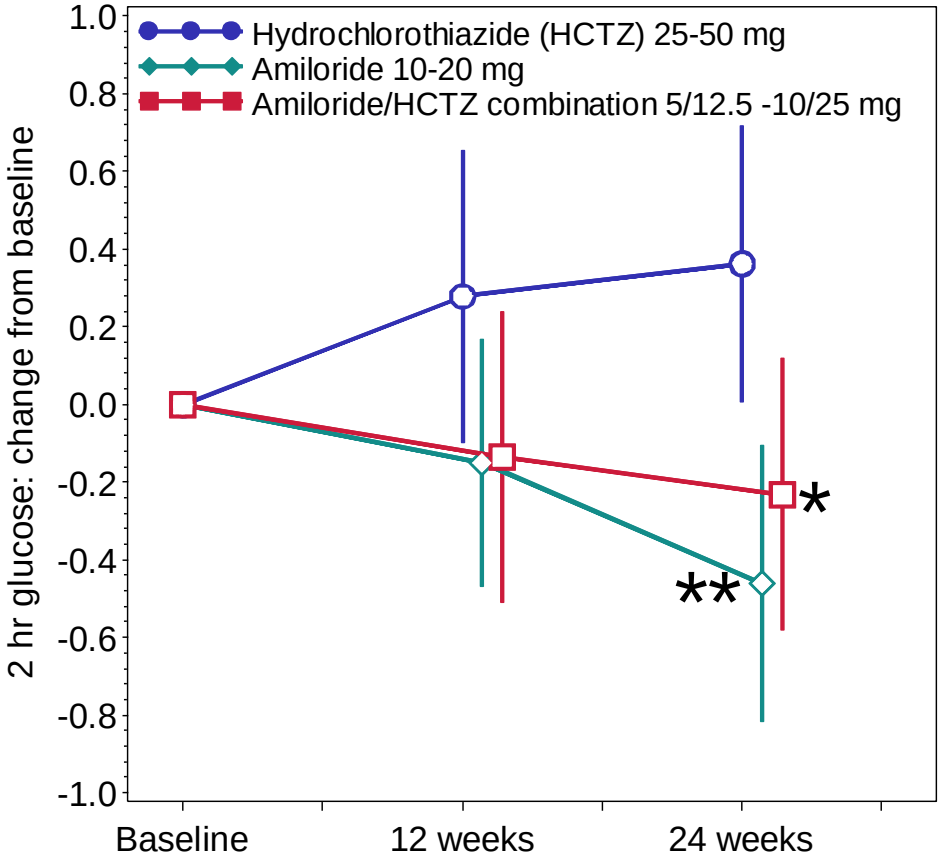
Average difference from HCTZ (mmol/L) (12 & 24 weeks)

Amiloride n=132
-0.55 (-0.96,-0.14)
P=0.009

Adjusted means (95% CI) for change from baseline in 2 hr glucose during OGTT. Doses were doubled at 12 weeks. **=p<0.01 vs HCTZ; *=p<0.05 vs HCTZ

Hierarchical primary endpoints

Difference in change from baseline in OGTT 2 hr glucose for [i] amiloride vs HCTZ, [ii] combination vs HCTZ



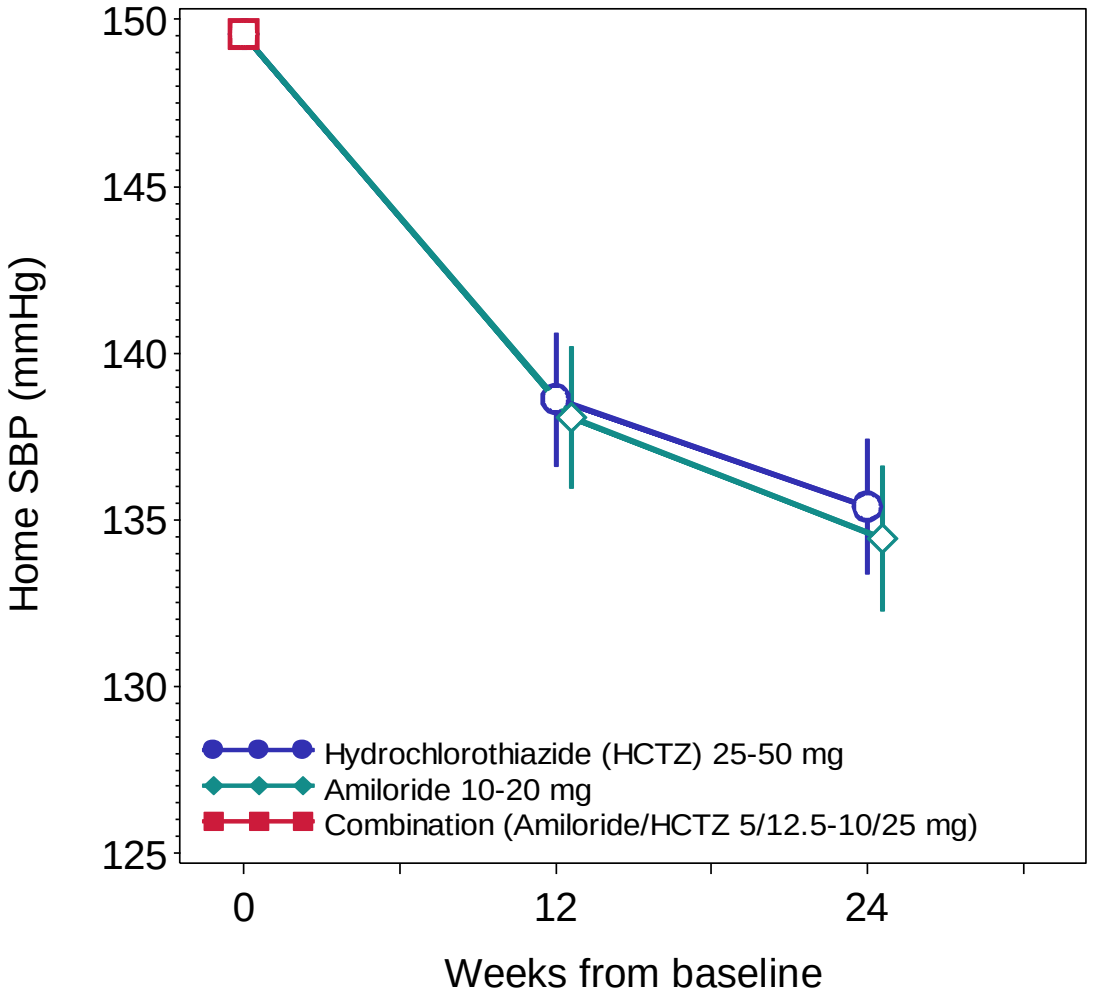
High-dose difference from HCTZ (mmol/L) (24 weeks)

Amiloride n=132	Amiloride/HCTZ n=133
-0.73 (-1.20,-0.25)	**-0.50** (-0.98, -0.025)
P=0.005	**P=0.024**

Adjusted means (95% CI) for change from baseline in 2 hr glucose during OGTT. Doses were doubled at 12 weeks. **=p<0.01 vs HCTZ; *=p<0.05 vs HCTZ

Secondary endpoints

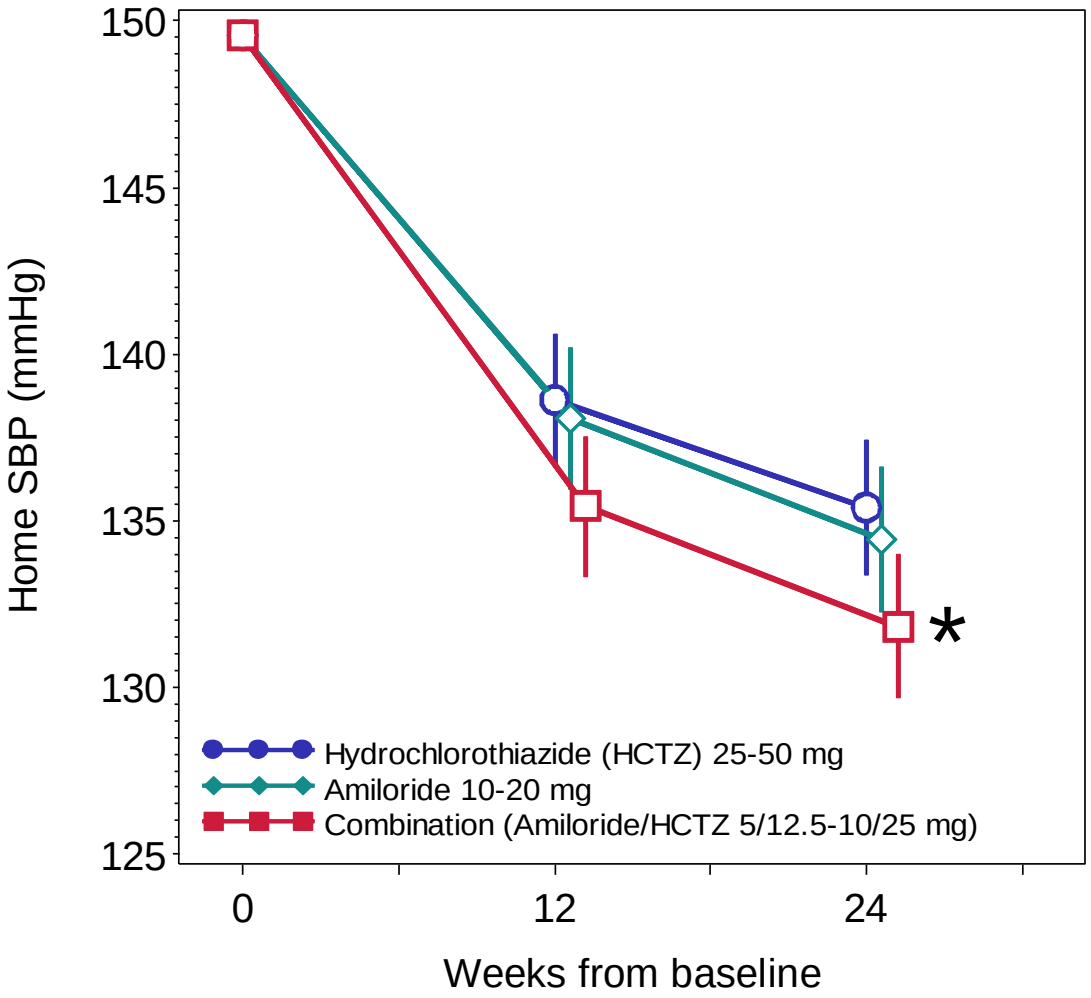
Blood Pressure reduction



Home SBP (mean, 95% CI) adjusting for baseline covariates

Secondary endpoints

Blood Pressure reduction



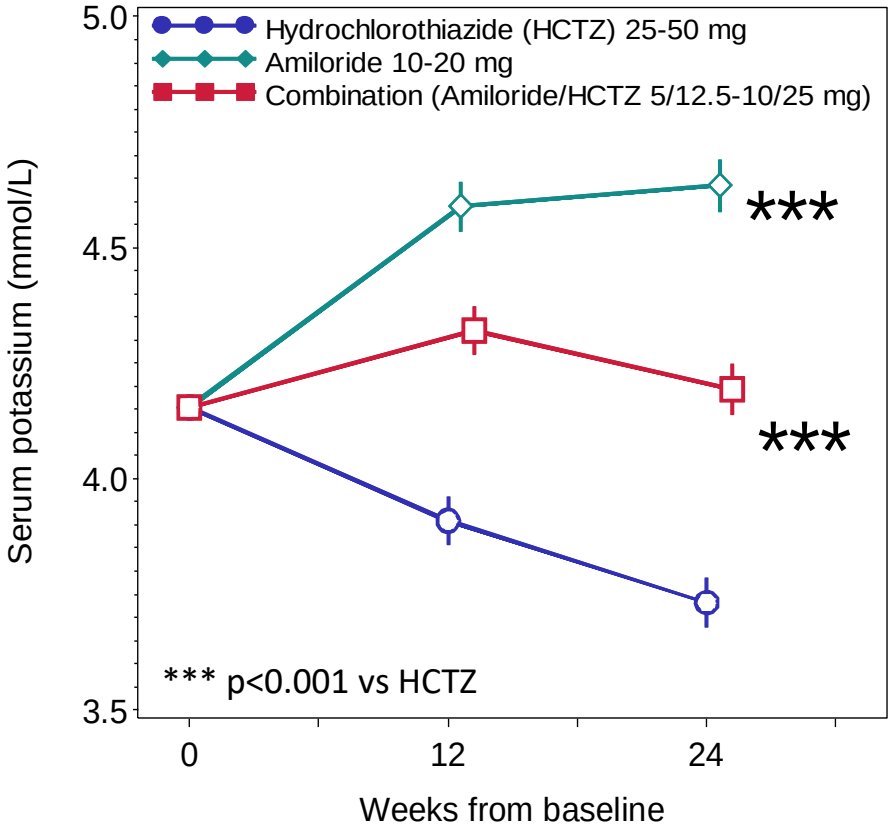
Home SBP (mean, 95% CI) adjusting for baseline covariates

* p=0.02 for combination vs HCTZ at week 24.

Across weeks 12 (low-dose) and 24 (high-dose), BP fall on combination of amiloride and HCTZ was 3·4 (0·9, 5·8) mmHg greater than on HCTZ (p=0·007)

Secondary Outcomes

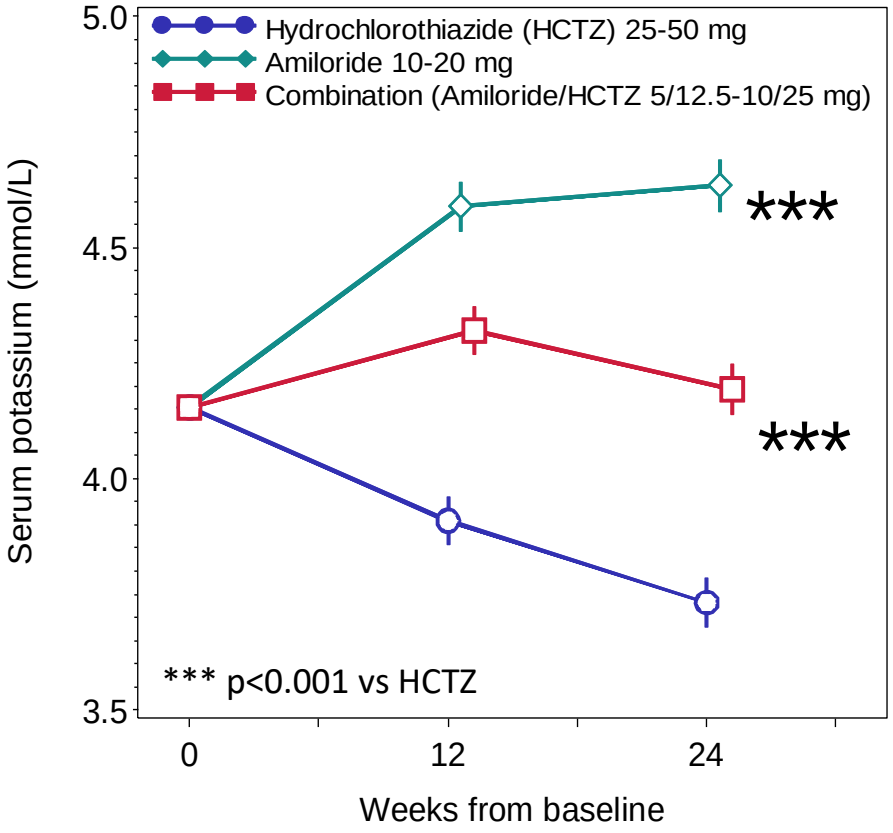
Potassium

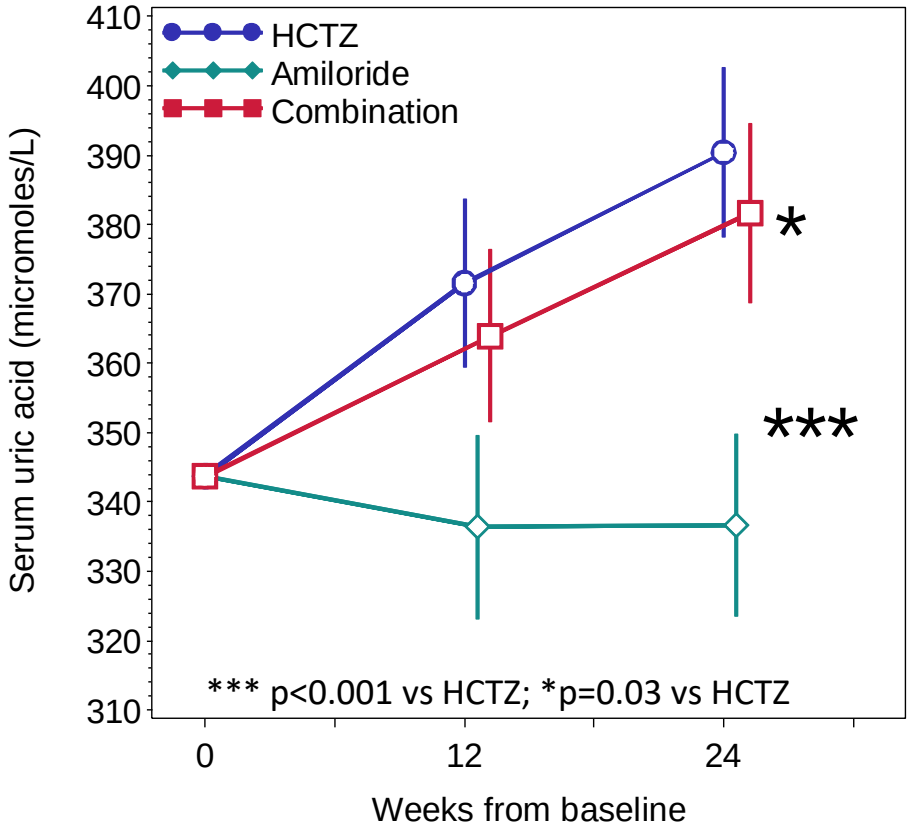


Mean (95% CI) serum potassium, on a model adjusting for baseline covariaties

Secondary Outcomes

Potassium and Uric Acid





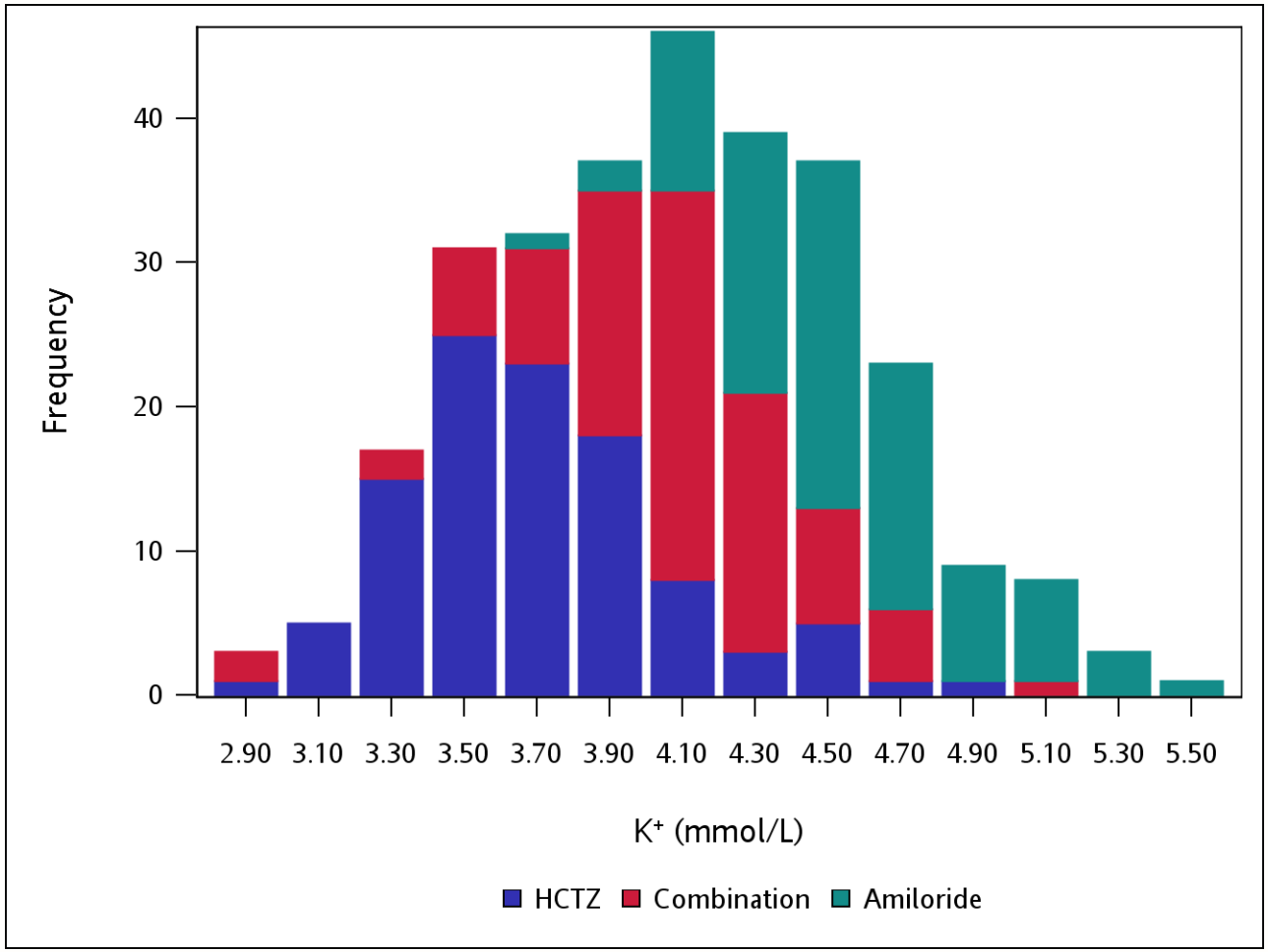
Mean (95% CI) uric acid, from a model adjusting for baseline covariates

Safety Data

	Amiloride (N=132)		Combination (N=133)		HCTZ (N=134)		
	n	%	n	%	n	%	p value
Withdrawals (due to AE's)	17	11.7	16	10.7	10	6.8	
Serious Adverse Events	2	1.4	7	4.8	4	2.7	
Any adverse event	97	66.4	95	65.1	92	61.3	
Selected adverse events							
Dizziness	9	6.2	15	10.0	16	11.0	
Muscle spasms	12	8.2	14	9.3	10	6.8	
Hyperkalaemia	7	4.8	3	2.0	0	0	0.017
Diabetes	11	11.6	9	8.6	13	11.4	

Safety data

Incidence/severity of hypo/hyperkalaemia



Implications of findings

- The combination of amiloride and HCTZ is a 'win-win' which at equipotent doses
  - amplifies the desirable effects of each drug on BP,
  - neutralizes the undesirable changes in blood glucose and potassium
- Amiloride-HCTZ is the only diuretic with superiority in outcome trials (vs CCB[1] and beta-blockade[2])
- In summary, PATHWAY-2 and PATHWAY-3 show that K^+-sparing diuretics are effective and safe, and can be preferred choices for the treatment of hypertension
- Comination better than monotherapy

[1]Brown et al. Lancet, **356**:366- 372, 2000; [2]MRC Working Party. *BMJ* 1992; **304**: 405-12

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 26, 2015 VOL. 373 NO. 22

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

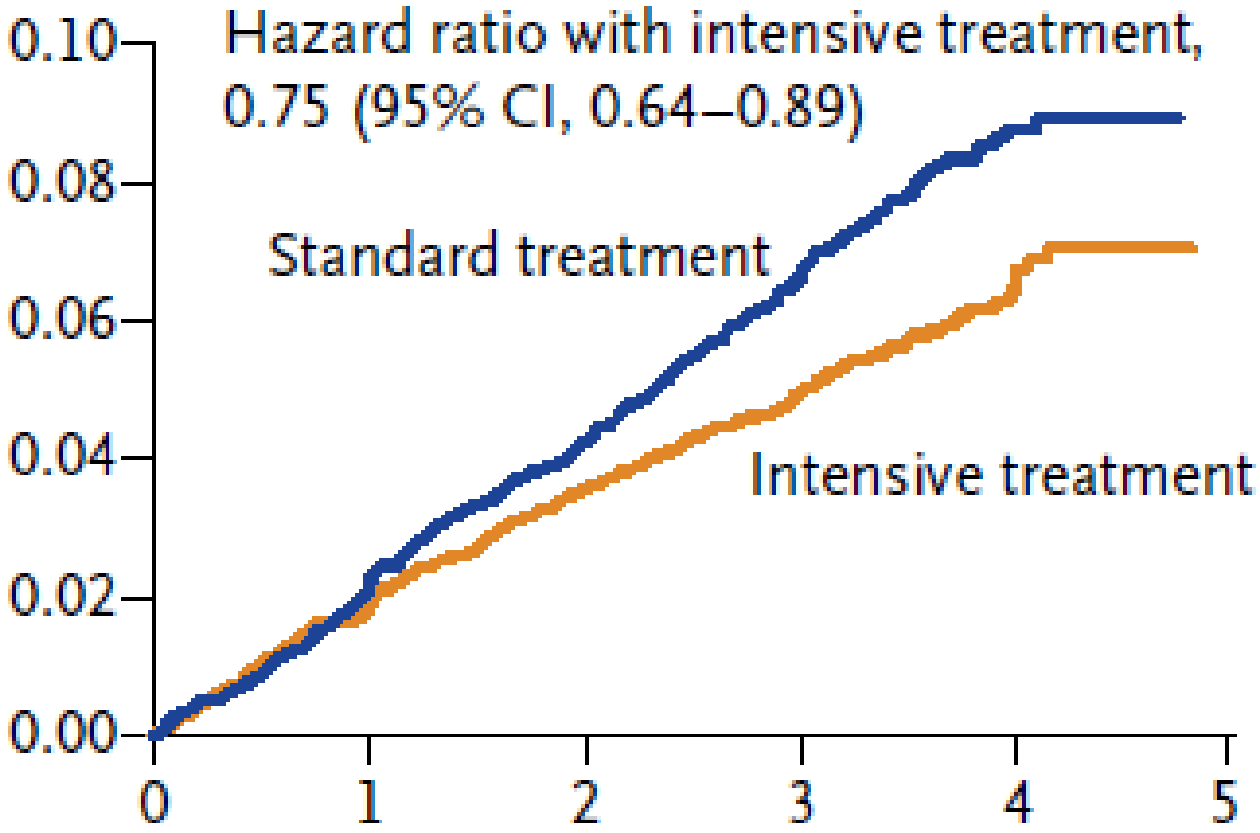
The SPRINT Research Group*

9361 persons with SBP of 130mmHg or higher and increased CV risk,

but without diabetes

N Engl J Med 2015;373:2103-16

SPRINT Benefits after 1 year



N Engl J Med 2015;373:2103-16

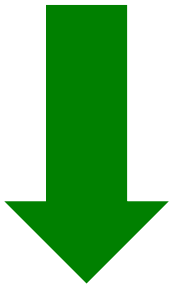
Sprint Inclusion

- Age 50 +
  - SBP: 130 – 180 mmHg on 0 or 1 medication
  - SBP: 130 – 170 mmHg on up to 2 medications
  - SBP: 130 – 160 mmHg on up to 3 medications
  - SBP: 130 – 150 mmHg on up to 4 medications
- Framingham Risk > 15%
- GFR 20 to 59ml/min
- PVD
- Clinical or subclinical CV disease other than stroke
- Standing BP ≥ 110mmHg

N Engl J Med 2015;373:2103-16

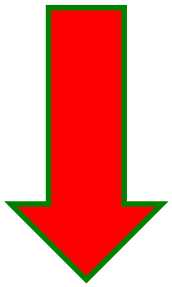
Screening SBP = 130 mmHg

Intensive Rx



More Rx to 120mmHg

Standard Rx



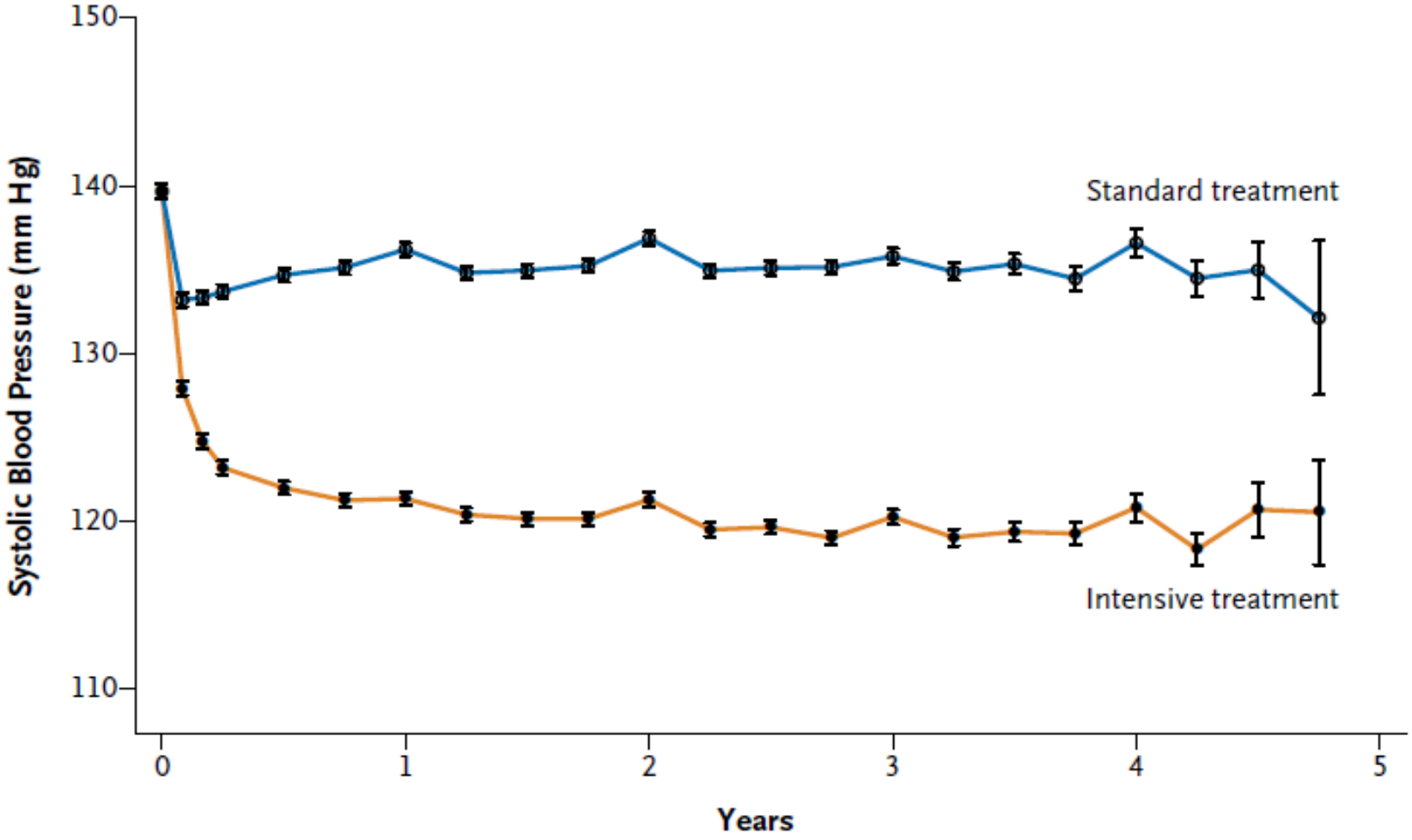
Rx withdrawn to 140mmHg

Mean of 3 Office BPs

NICE Guidelines

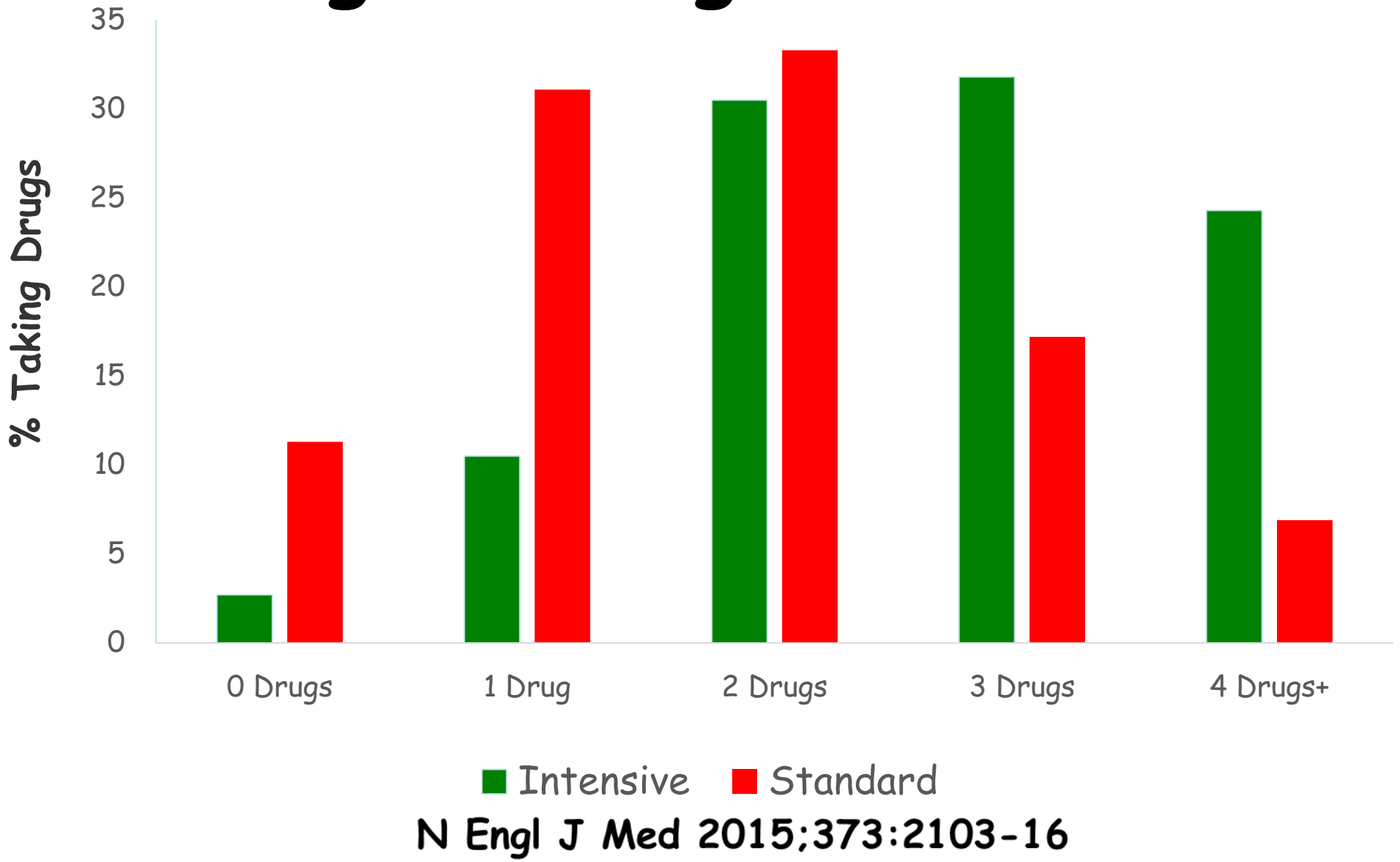
Hypertension must be diagnosed using ABPM

Achieved BP 122 v 135 mmHg



N Engl J Med 2015;373:2103-16

Drugs Average 2.8 v 1.8



N Engl J Med 2015;373:2103-16

Which Drugs?
% of each

• ACE	lisinopril	37 v 28
• ARB	azilsartan	40 v 27
• Diuretics	chlortalidone	55 v 33
• Aldo antag	spironolactone	9 v 4
• Alpha B	doxazosin	10 v 6
• Beta B	metop/atenolol	41 v 31
• Calcium B	diltiaz/amlodipine	57 v 35

N Engl J Med 2015;373:2103-16

Can we do this?

- chlortalidone 12.5-25mg
  - Only available at 50mg
  - £88 per month!
- azilsartan 40-80mg
  - Not approved by SMC
  - £16.80 to £19.95 per month!
- azilsartan / chlorthalidone combination
  - Not licensed in EU

http://www.bnf.org/

Primary End Point: Time to…

- Composite
  - MI
  - ACS without MI
  - Stroke
  - CHF
  - CV death

N Engl J Med 2015;373:2103-16

Study stopped early due to benefit of intensive Rx

3.3 years of the planned 5 years

N Engl J Med 2015;373:2103-16

Primary End Point: Time to…

- Composite 243 v 319 p<0.001
  - MI 97 v 116 ns
  - ACS 40 v 40 ns
  - Stroke 62 v 70 ns
  - CHF 62 v 100 p<0.002
  - CV death 37 v 65 p<0.005

N Engl J Med 2015;373:2103-16

CV Deaths

- CHD 18 v 32
- Sudden CV 2 v 11
- Stroke 8 v 9
- CHF 8 v 9
- Other 1 v 4

N Engl J Med 2015;373:2103-16

Sprint Downsides

- Intensive Rx had more:
  - Hypotension
  - Syncope
  - Electrolyte abnormalities
  - AKI
- But less:
  - Orthostatic hypotension

N Engl J Med 2015;373:2103-16

Sprint Summary

Patients at high CV risk but without diabetes a SBP of <120 mm Hg v <140 mm Hg resulted in lower rates of fatal and nonfatal major CV events and death from any cause

N Engl J Med 2015;373:2103-16

Original Investigation

Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years
A Randomized Clinical Trial

Jeff D. Williamson, MD, MHS; Mark A. Supiano, MD; William B. Applegate, MD, MPH; Dan R. Berlowitz, MD; Ruth C. Campbell, MD, MSPH; Glenn M. Chertow, MD; Larry J. Fine, MD; William E. Haley, MD; Amret T. Hawfield, MD; Joachim H. Ix, MD, MAS; Dalane W. Kitzman, MD; John B. Kostis, MD; Marie A. Krousel-Wood, MD; Lenore J. Launer, PhD; Suzanne Oparil, MD; Carlos J. Rodriguez, MD, MPH; Christianne L. Roumie, MD, MPH; Ronald I. Shorr, MD, MS; Kaycee M. Sink, MD, MAS; Virginia G. Wadley, PhD; Paul K. Whelton, MD; Jeffrey Whittle, MD; Nancy F. Woolard; Jackson T. Wright Jr, MD, PhD; Nicholas M. Pajewski, PhD; for the SPRINT Research Group

- 34% reduction primary EP
- 33% reduction mortality
- No increase SAEs
- Hypotension 2.4% v 1.4%

JAMA doi:10.1001/jama.2016.7050
Published online May 19, 2016.

SPRINT Generalizable to Older Patients

120mmHg target better than 140mmHg

(Achieved BP 123.4mmHg v 134.8mmHg)

JAMA doi:10.1001/jama.2016.7050
Published online May 19, 2016

Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis

Dena Ettehad, Connor A Emdin, Amit Kiran, Simon G Anderson, Thomas Callender, Jonathan Emberson, John Chalmers, Anthony Rodgers, Kazem Rahimi

Our results provide strong support for lowering SBP to less than 130 mmHg

Lancet 2016; 387: 957–67

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 26, 2016 VOL. 374 NO. 21

Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease

Eva M. Lonn, M.D., Jackie Bosch, Ph.D., Patricio López-Jaramillo, M.D., Ph.D., Jun Zhu, M.D., Lisheng Liu, M.D., Prem Pais, M.D., Rafael Diaz, M.D., Denis Xavier, M.D., Karen Sliwa, M.D., Ph.D., Antonio Dans, M.D., Alvaro Avezum, M.D., Ph.D., Leopoldo S. Piegas, M.D., Ph.D., Katalin Keltai, M.D., Ph.D., Matyas Keltai, M.D., Ph.D., Irina Chazova, M.D., Ph.D., Ron J.G. Peters, M.D., Ph.D., Claes Held, M.D., Ph.D., Khalid Yusoff, M.D., Basil S. Lewis, M.D., Petr Jansky, M.D., Alexander Parkhomenko, M.D., Ph.D., Kamlesh Khunti, M.D., Ph.D., William D. Toff, M.D., Christopher M. Reid, Ph.D., John Varigos, B.Sc., Lawrence A. Leiter, M.D., Dora I. Molina, M.D., Robert McKelvie, M.D., Ph.D., Janice Pogue, Ph.D.,* Joanne Wilkinson, B.A., Hyejung Jung, M.Sc., Gilles Dagenais, M.D., and Salim Yusuf, M.B., B.S., D.Phil., for the HOPE-3 Investigators†

Candesartan 16mg + HCTZ 12.5mg v placebo did not reduce CV events over 5.6y

NEJM 2016:374;2009-20

HOPE 3 v SPRINT

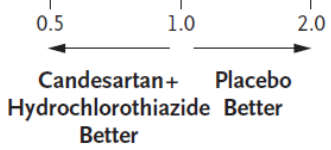
- Δ BP 6mmHg v 14.8mmHg (at 1 year)
- Less potent v more potent drugs
- Lower CV risk v High CV risk
  - Event rate <1%/y v 2.2%/y

- Not a high BP trial v a high BP trial!
  - Baseline BP in HOPE 3 138/82 mmHg

Highest BP Tertile: Significant Benefit

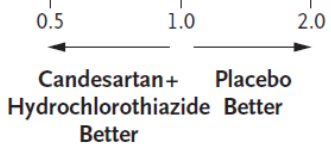
A First Coprimary Outcome

Subgroup	Mean Systolic Blood Pressure	Difference in Blood Pressure	Candesartan+ Hydrochlorothiazide	Placebo	Hazard Ratio (95% CI)	P Value for Trend
	mm Hg		*no. of events/total no. of participants (%)*			
Overall	138.1	6.0/3.0	260/6356 (4.1)	279/6349 (4.4)	0.93 (0.79–1.10)	—
Systolic blood pressure						0.02
≤131.5 mm Hg	122.2	6.1/3.1	70/2080 (3.4)	62/2122 (2.9)	1.16 (0.82–1.63)	
131.6–143.5 mm Hg	137.6	5.6/2.7	87/2120 (4.1)	81/2141 (3.8)	1.08 (0.80–1.46)	
>143.5 mm Hg	154.1	5.8/3.0	103/2156 (4.8)	136/2084 (6.5)	0.73 (0.56–0.94)	



B Second Coprimary Outcome

Subgroup	Mean Systolic Blood Pressure	Difference in Blood Pressure	Candesartan+ Hydrochlorothiazide	Placebo	Hazard Ratio (95% CI)	P Value for Trend
	mm Hg		*no. of events/total no. of participants (%)*			
Overall	138.1	6.0/3.0	312/6356 (4.9)	328/6349 (5.2)	0.95 (0.81–1.11)	—
Systolic blood pressure						0.009
≤131.5 mm Hg	122.2	6.1/3.1	90/2080 (4.3)	74/2122 (3.5)	1.25 (0.92–1.70)	
131.6–143.5 mm Hg	137.6	5.6/2.7	99/2120 (4.7)	98/2141 (4.6)	1.02 (0.77–1.34)	
>143.5 mm Hg	154.1	5.8/3.0	123/2156 (5.7)	156/2084 (7.5)	0.76 (0.60–0.96)	



NEJM 2016:374;2009-20

HOPE 3 Summary

Low risk normotensives who took less effective medication got no detectable benefit in HOPE 3

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

14mmHg Lower BP:

No benefit on MACE

Reduced stroke

N Engl J Med 2010;362:1575-85.

SPRINT v ACCORD

- SPRINT no diabetes
- SPRINT 2x size of ACCORD
- SPRINT Older subjects
- SPRINT Renal disease allowed
- SPRINT Excluded stroke
- ACCORD CHF not a primary EP
- ACCORD: Factorial design
  - Not inconsistent with SPRINT?

SPRINT v ACCORD-BP

- N = 9,361 v 4,733
- Primary EP: 562 v 445
- Age: 68y v 62y
- CKD: 28% v excluded
- SPRINT better powered

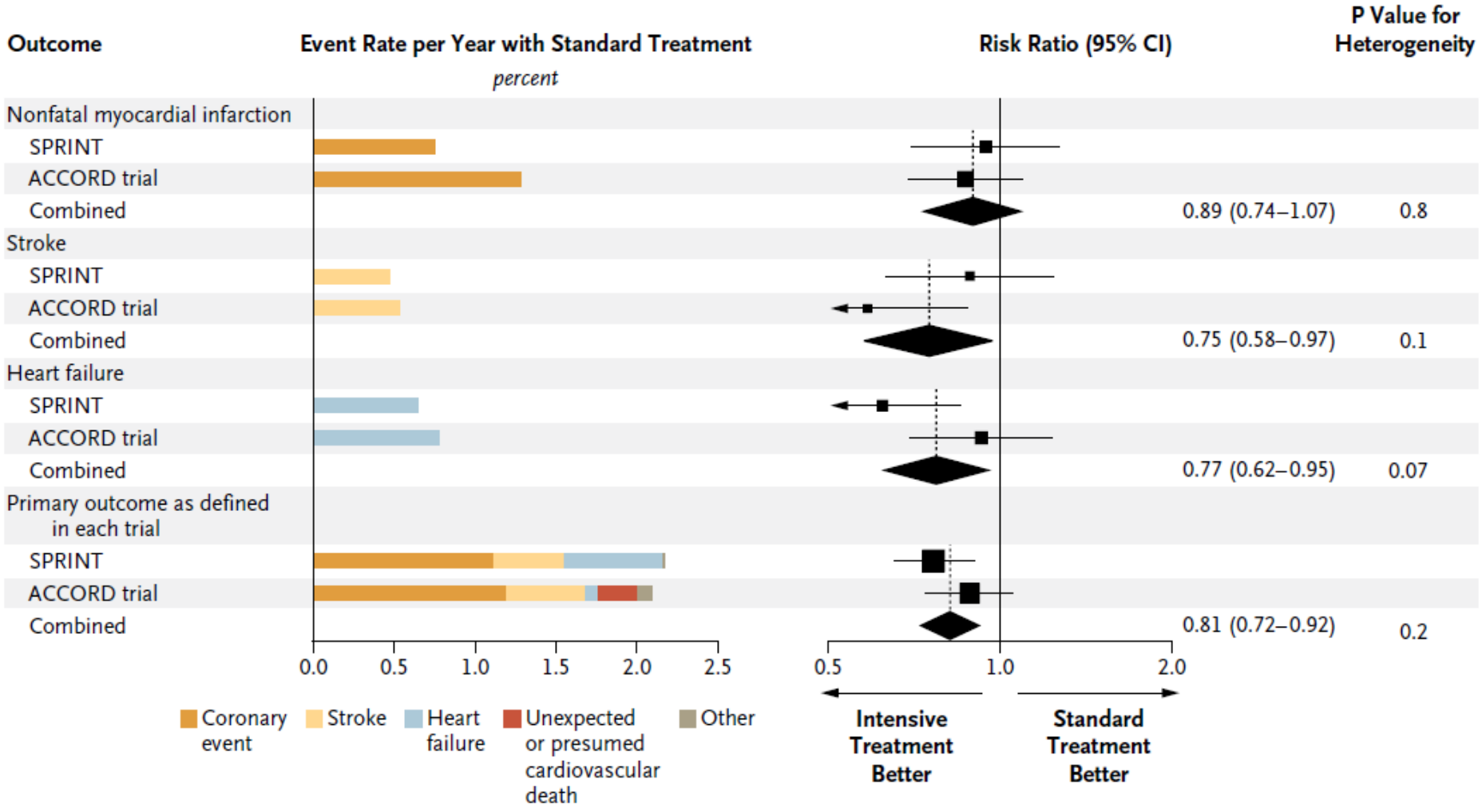
ACCORD

Primary End Point: Time to…

- Composite
  - MI
  - Stroke
  - CV death
    - Note: 81 events unexpected death presumed to be due to ischaemic CV disease" and "presumed CV death"

N Engl J Med 2015;373:2103-16

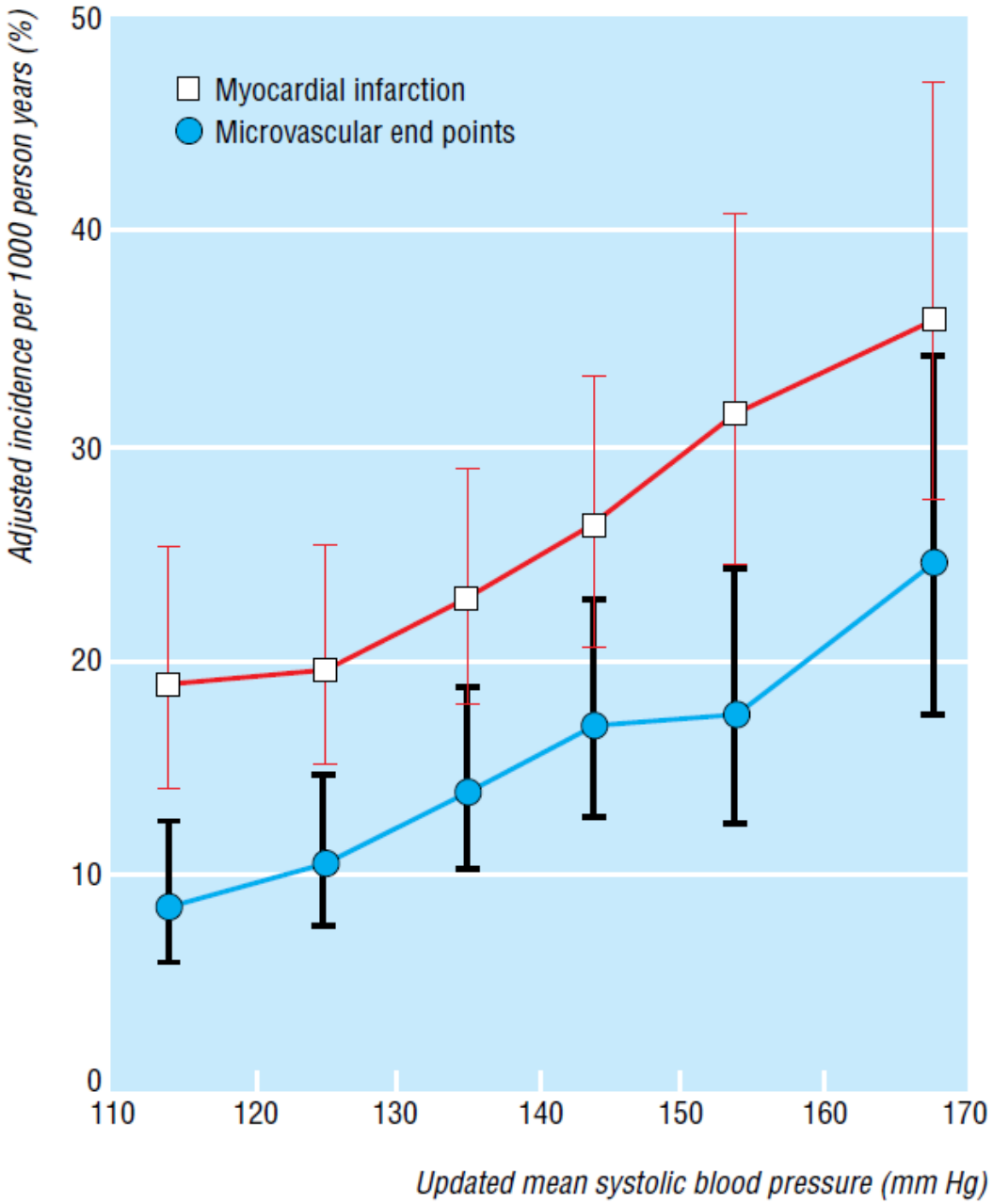
SPRINT v ACCORD



NEJM 2015:373;2175-8

BP Lower v Higher in Diabetes

	End Point	Intensive BP	Conventional BP	HR EP	HR Mortality
UKPDS	Composite	144/82	154/87	**0.72** (0.62-0.92)	**0.82** (0.63-1.08)
HOT	APTC	140/81	144/85	**0.48** (0.29-0.81)	0.56 (0.31-1.02)
ABCD	Cr Cl	132/78	138/86	NS	0.51 P=0.037
ACCORD BP	APTC	119/64	133/71	0.88 (0.73-1.06)	**1.07** (0.85-1.35)



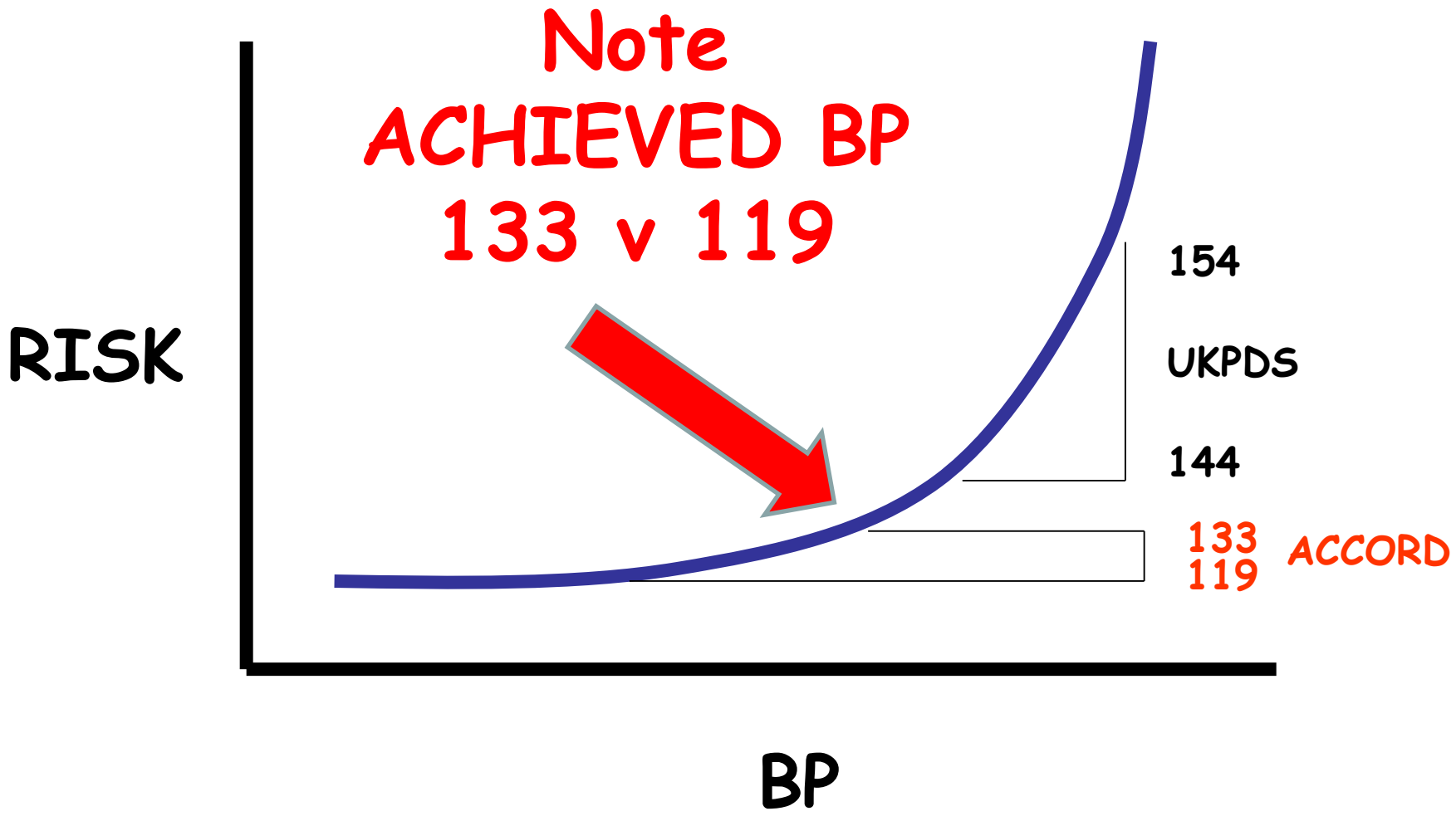
UKPDS BMJ 2000;321:412–9

Older & comorbid

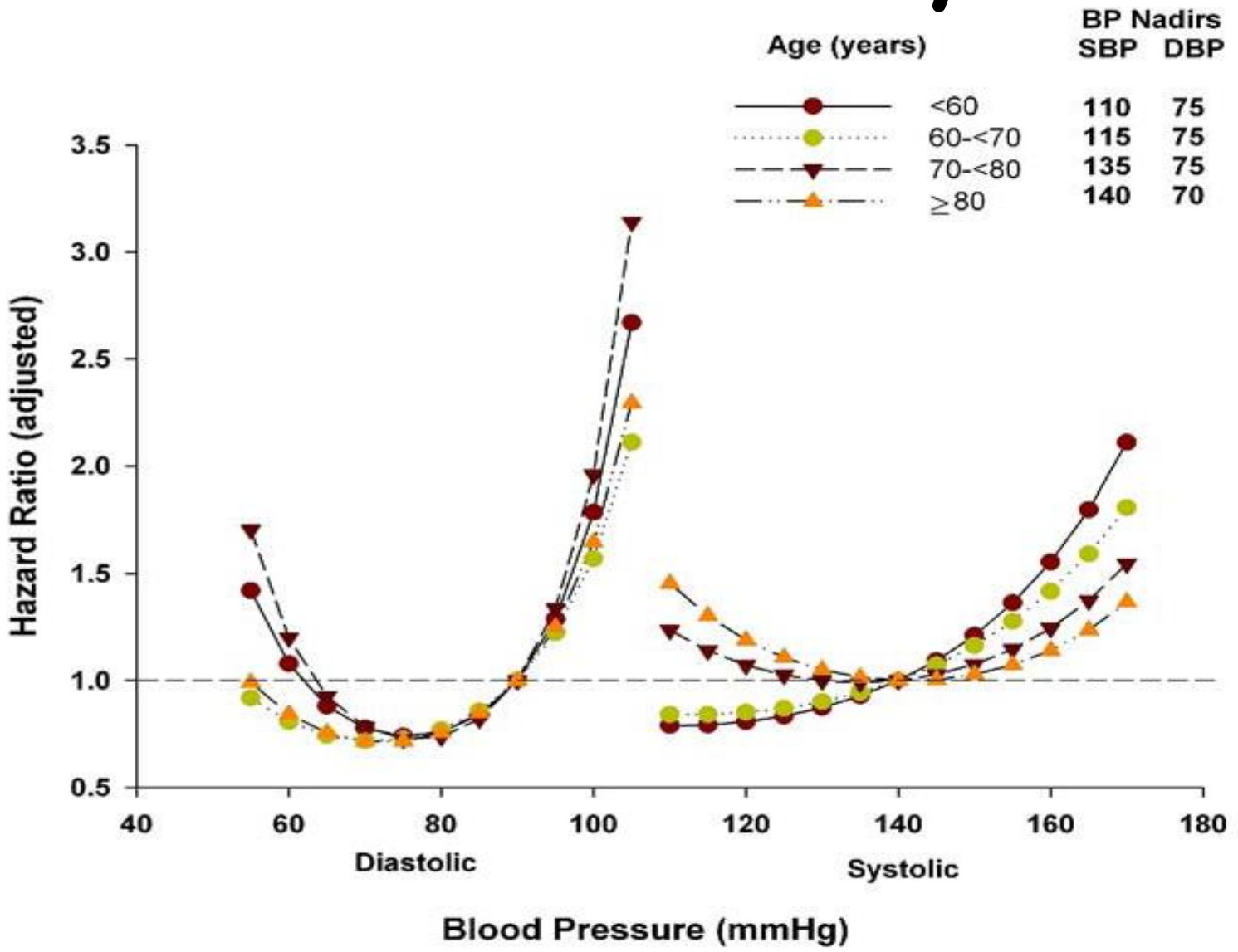
Young & Fit

	ACCORD	UKPDS
Age	62	53
Diabetes Duration	10y	0
CVD	1/3	0
BMI	32	28
Other Rx	Statin, ACE, aspirin	Nil
HBA1c	8.3	7.1
LDL	2.7	3.5

ACCORD-BP: Not a Mysterious Result

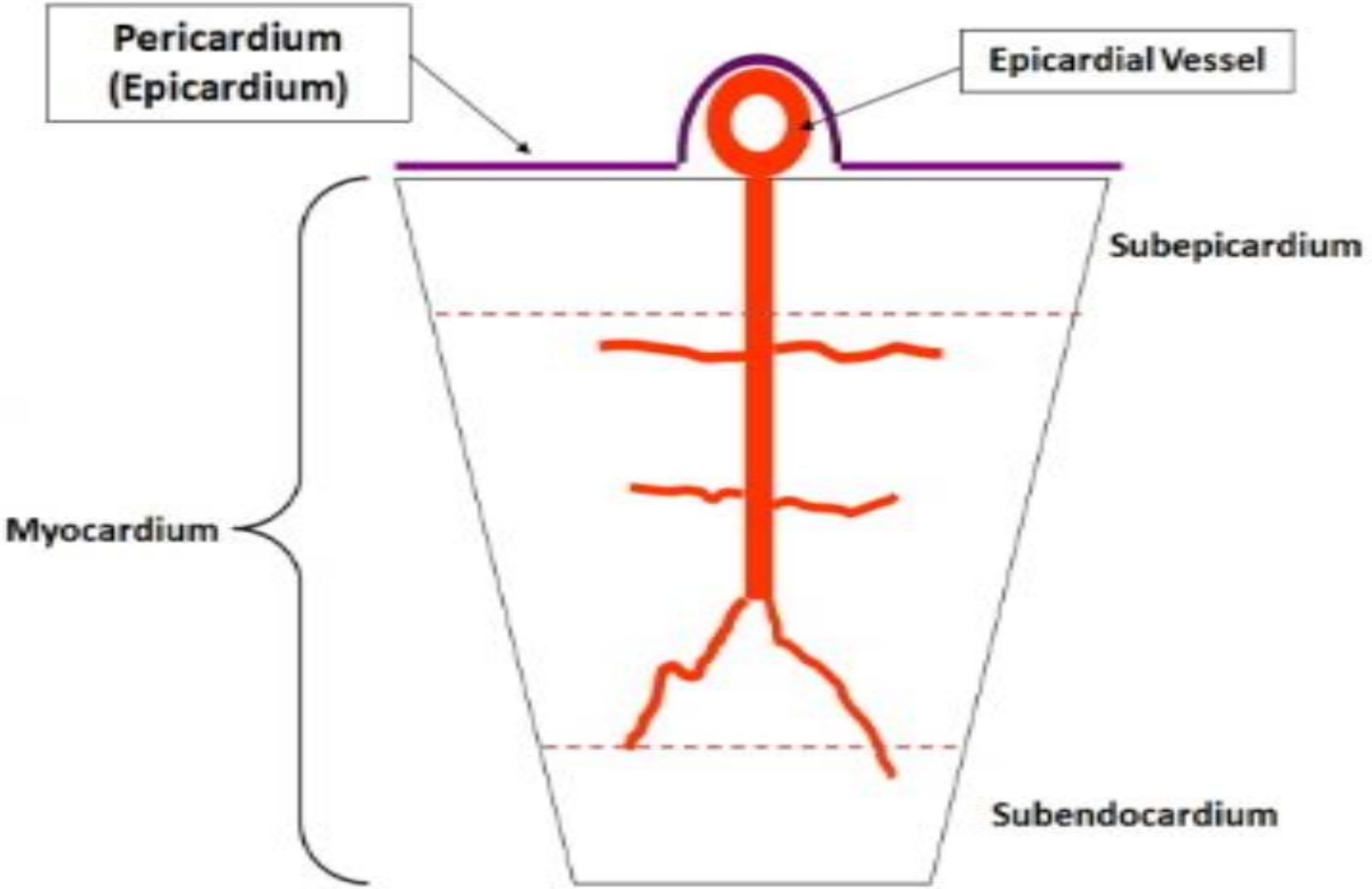


INVEST Elderly



Am J Med 2010;123:719-726

Coronary Flow in Diastole



Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial

ADVANCE Collaborative Group*

Perindopril/indapami cebo

4.3

135/7 7mmHg

reduction events

Not really a BP trial

Lancet 2007;370:829–40

ORIGINAL ARTICLE

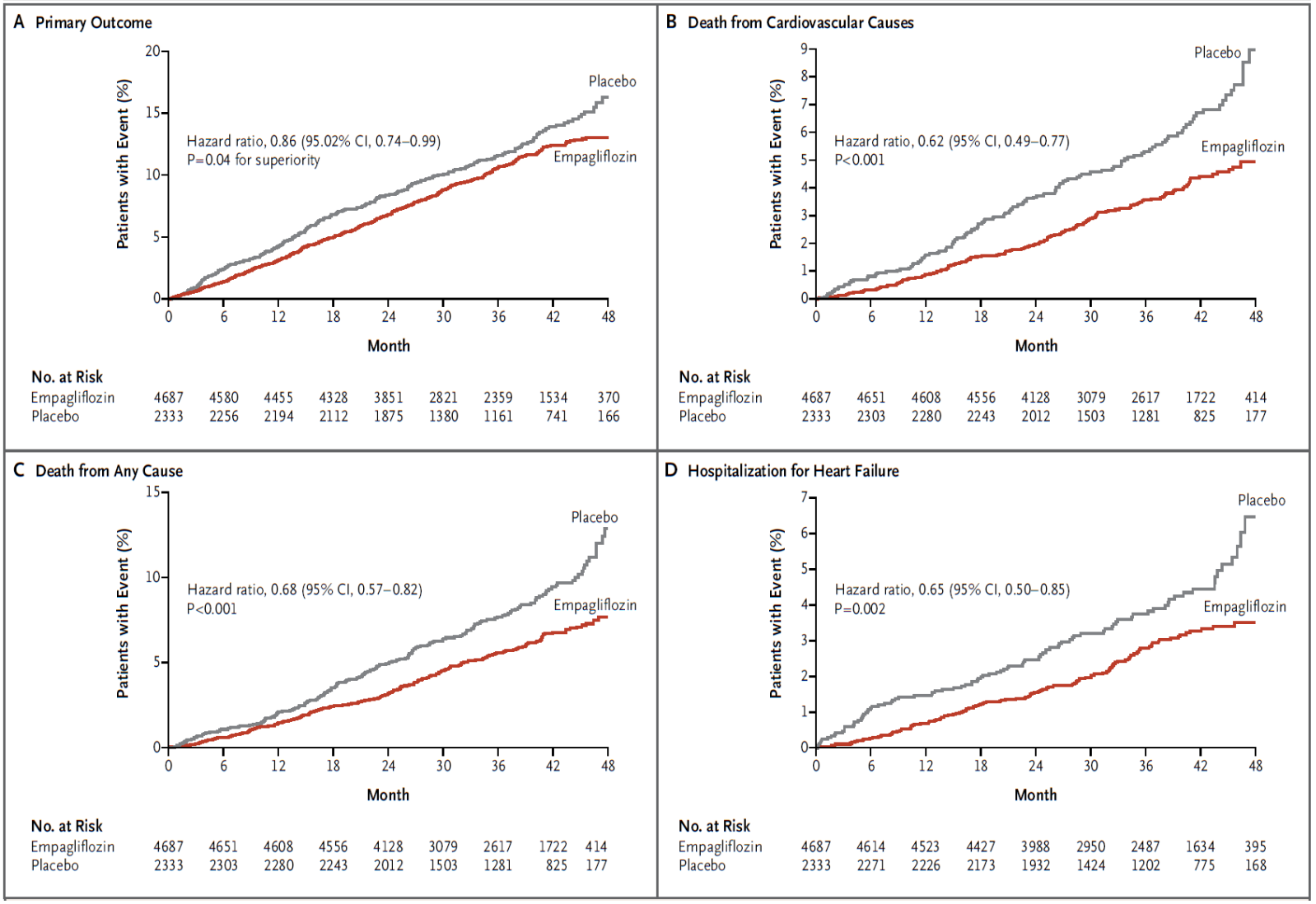
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

- **Reduced BP (4/2mmHg) and ABPM**
  - **Fewer BP drugs**
- **BP 131.3/75.1 mmHg at study end**
- **Less MI, CV death, CHF, renal EPs**

N Engl J Med 2015;373:2117-28

EMPA-REG Outcomes Rapid



N Engl J Med 2015;373:2117-28

Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses

Mattias Brunström, Bo Carlberg

SBP below 140 mm Hg, is associated with an increased risk of CV death, with no observed benefit.

BMJ 2016;352:i717

BP Guideline Targets

NICE	ESH/ ESC	ADA	AHA	JSB2	IDF	JNC8
130-140 /80	140 /85	130 /80	130 /80	130 /80	130 /80	140 /90

Spectrum

Young, few co-morbidities, no IHD

BP as low as you like

Old, many co-morbidities, high probability IHD

Do not push too low

My View

- 120mmHg at least as good as 133mmHg (ACCORD achieved BP)
- EMPA-REG achieved close to 130mmHg with great outcome
- 140mmHg target makes no sense
- The over-riding conclusion is:

LOWER BP TO PREVENT CV DISEASE IN DIABETES

You know it makes sense

Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials

*Blood Pressure Lowering Treatment Trialists' Collaboration**

Treatment with any commonly-used regimen reduces the risk of total major cardiovascular events

Lancet 2003;362:1527–35

NICE: Similar Efficacy….?