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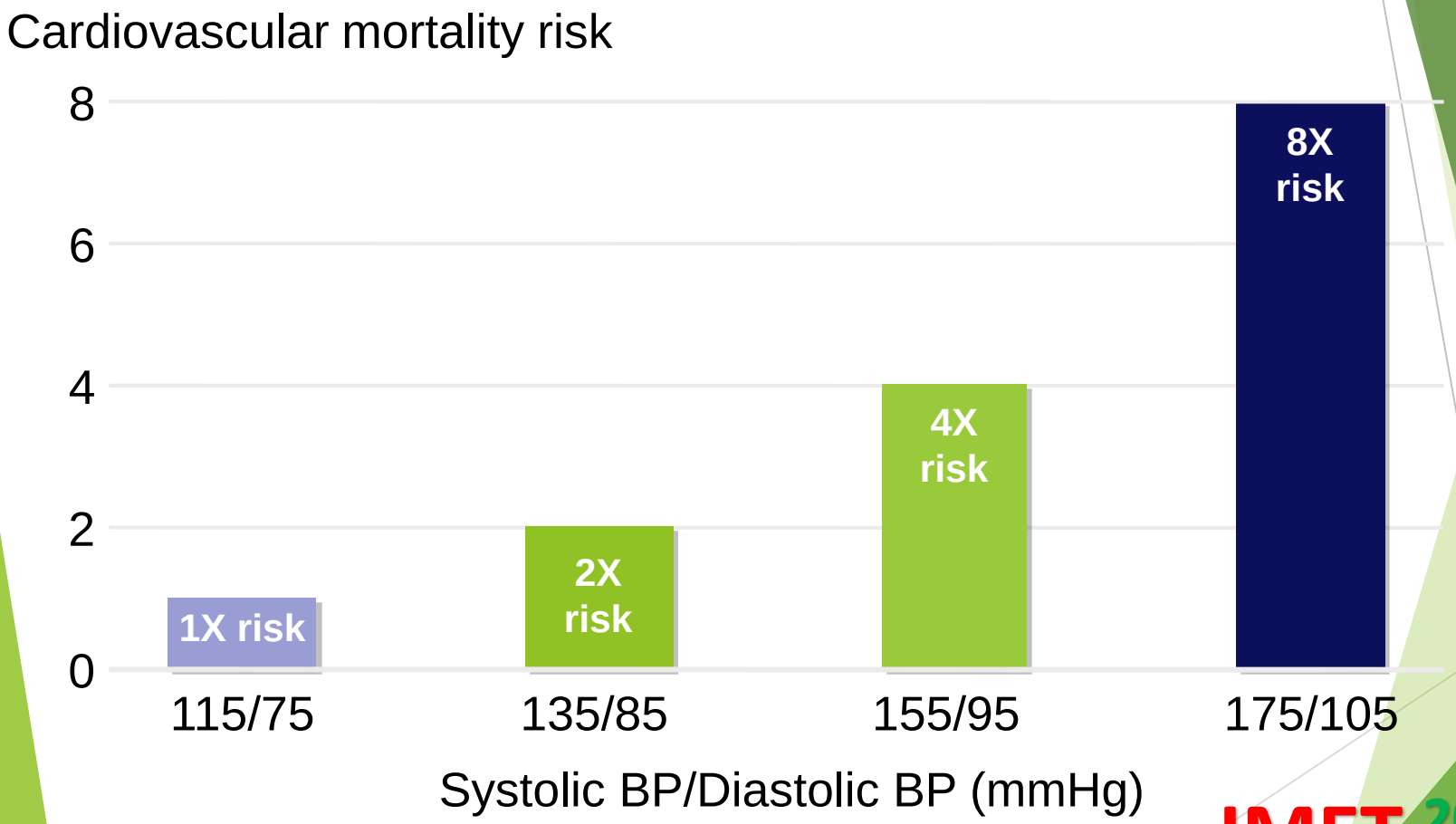
Hypertension Update

Raed A. H. Abu Sham'a, MD

Internist & Cardiologist

Cardiac Pacing and Electrophysiology

Cardiovascular Mortality Risk Doubles with Each 20/10 mmHg Increment in Systolic/Diastolic BP*

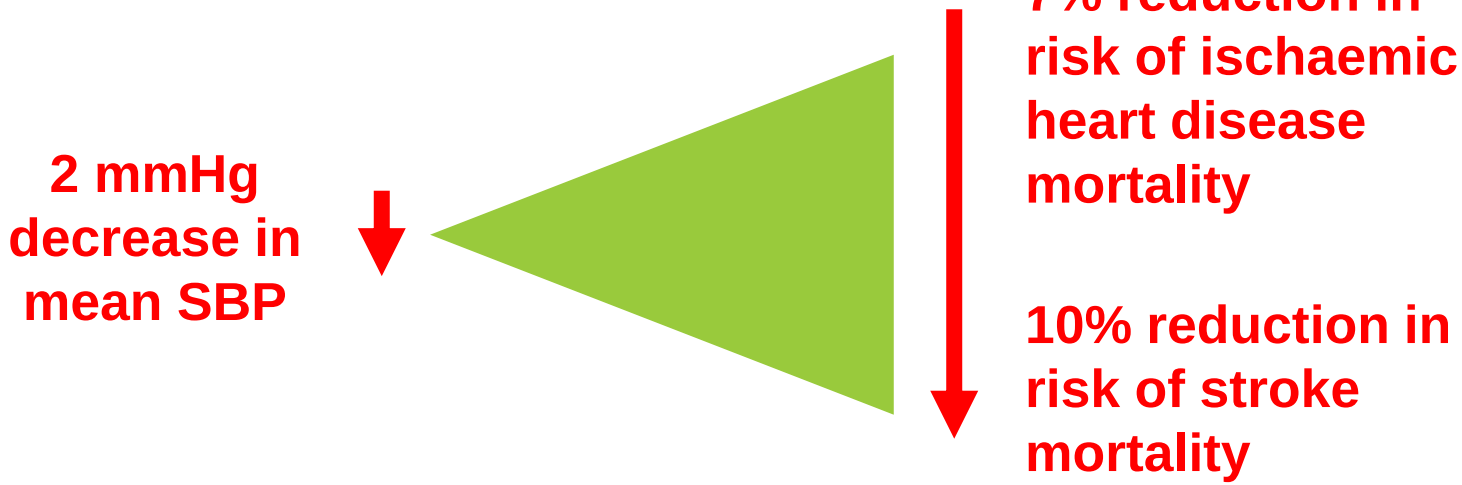


*Individuals aged 40–69 years

Lewington et al. Lancet 2002;360:1903–13

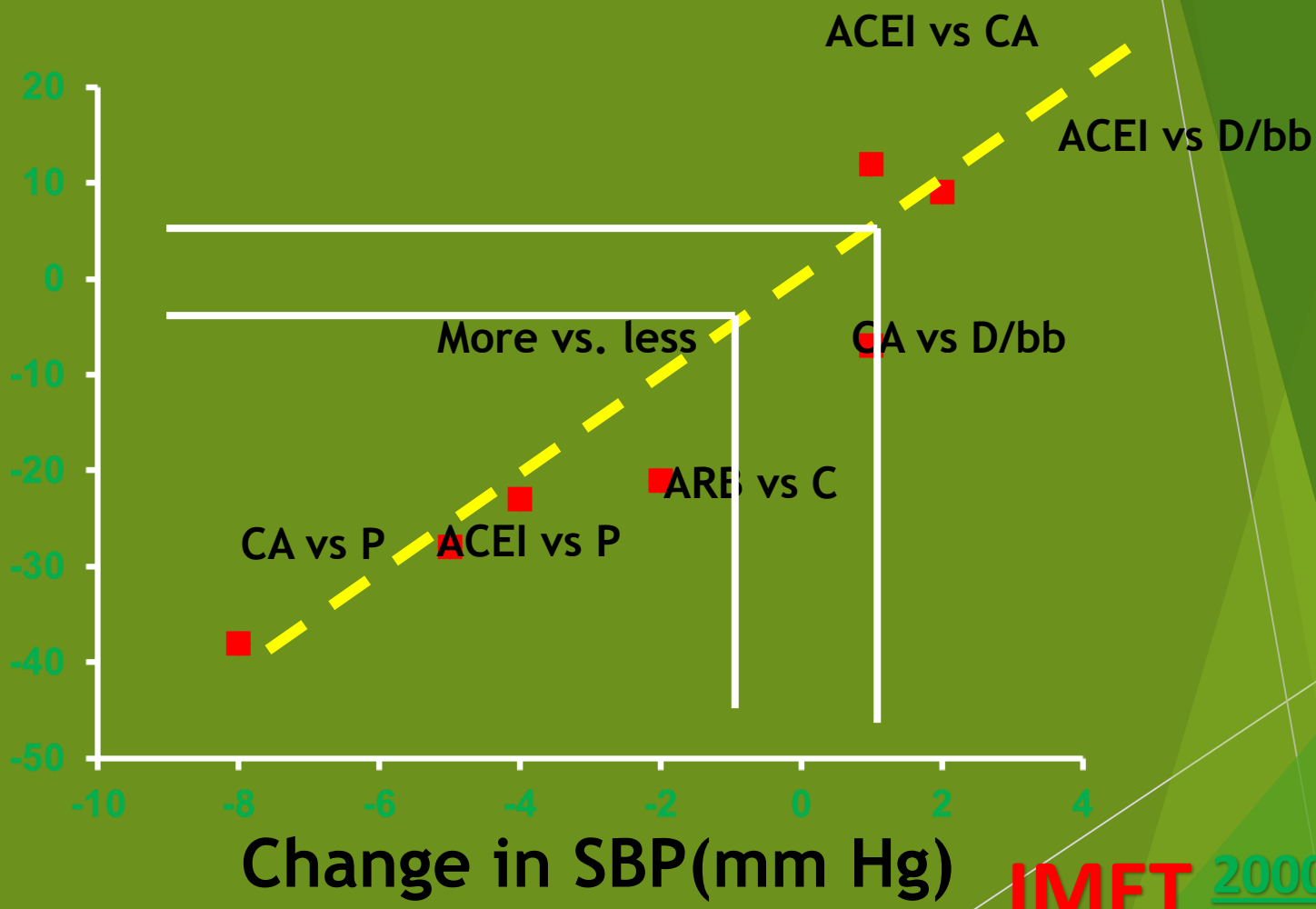
Blood Pressure Reduction of 2 mmHg Decreases the Risk of Cardiovascular Events by 7–10%

- Meta-analysis of 61 prospective, observational studies
- 1 million adults
- 12.7 million person-years



Lewington et al. Lancet 2002;360:1903–13

Change in the rate of stroke (%)



The Lancet 2003;362:1527-35

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Reduction of 1 mmHg of SBP reduce the risk of STROKE by %5

Reduction of BP is the GOAL of treatment

Is there any importance for treatment how to reach BP target?

JNC 5 (1993)

"Because **diuretics and beta-blockers** have been shown to reduce CV morbidity and mortality in controlled clinical trials, these two classes of drugs are preferred for initial drug therapy"

JNC 6 (1997)

"When the decision has been made to begin antihypertensive therapy, and if there are no indications for another type of drug, **a diuretic or beta-blocker** should be chosen because numerous randomized controlled trials have shown a reduction in morbidity and mortality with these agents"

What have we learned from Beta Blockers?

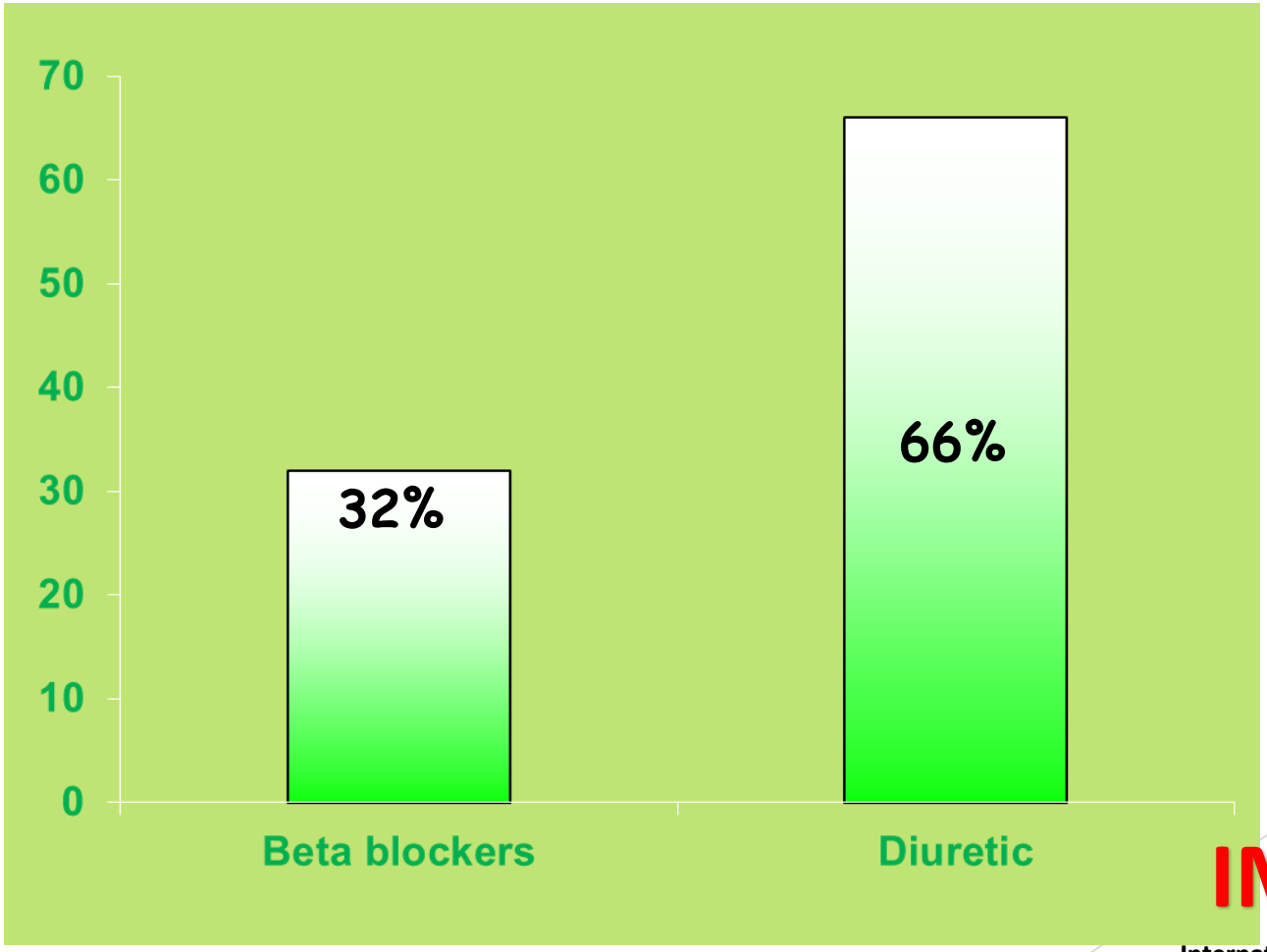
Are β-Blockers Efficacious as First-line Therapy for Hypertension in the Elderly?

A Systematic Review

Franz H. Messerli, MD; Ehud Grossman, MD; Uri Goldbourt, PhD

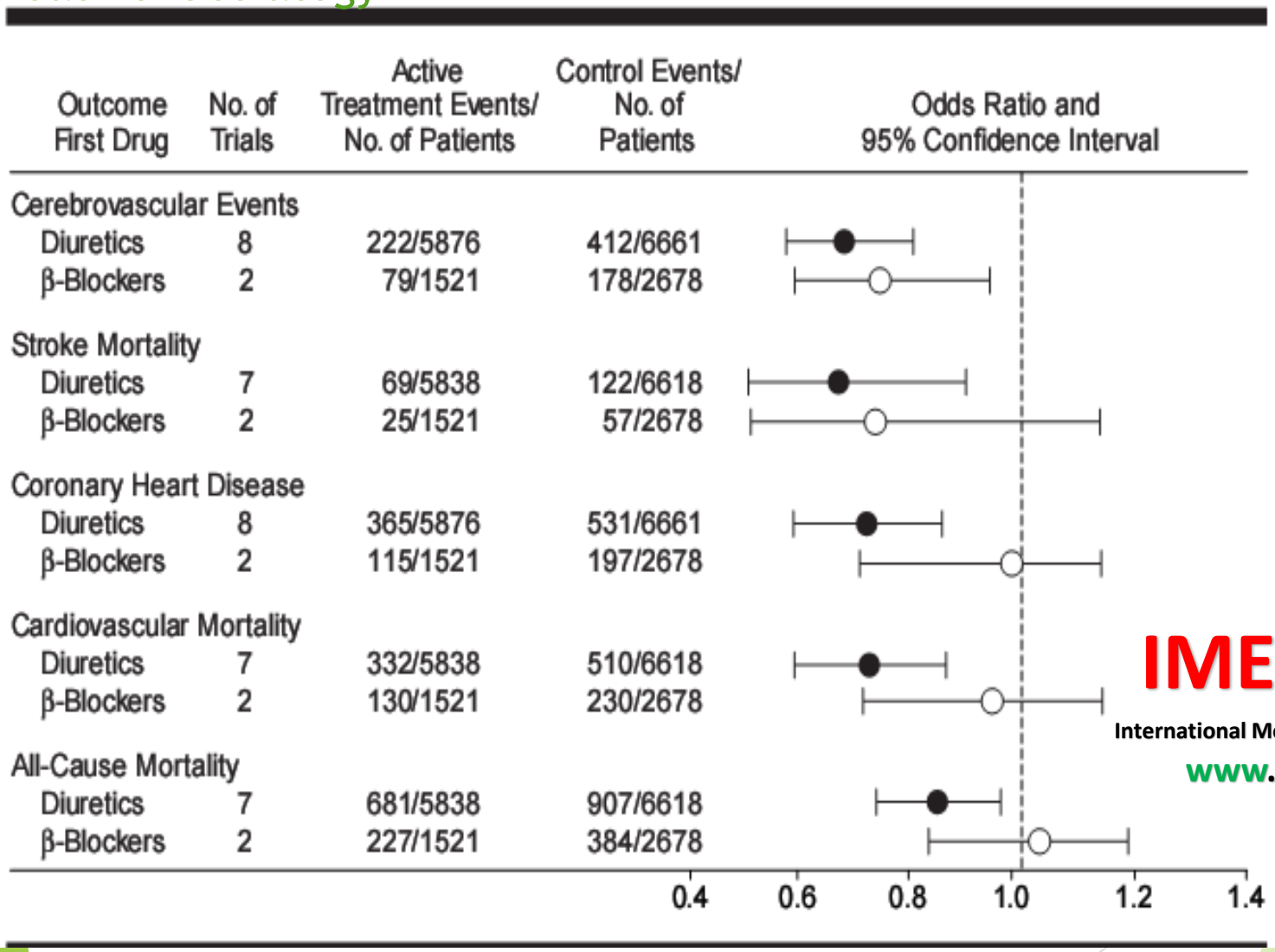
JAMA 1998;279:1903-7

Response Rate to Treatment in Elderly Hypertensives



Messerli, Grossman, Goldbourt JAMA 1998;279:1903-7

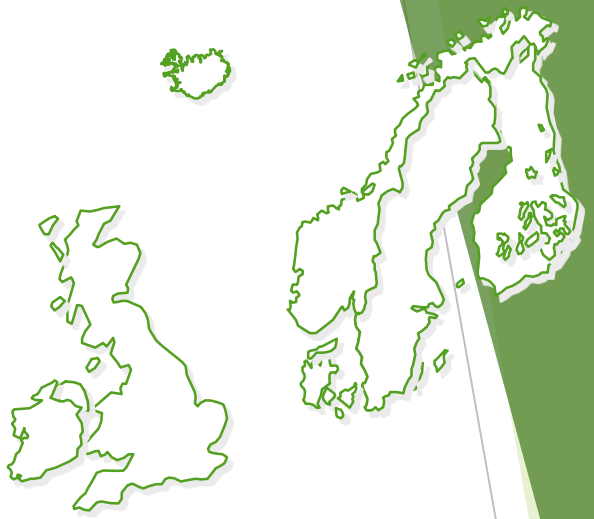
Meta-analysis of prospective clinical trials in elderly hypertensive patients according to first-line treatment strategy



Anglo-Scandinavian

ascot

Cardiac Outcomes Trial

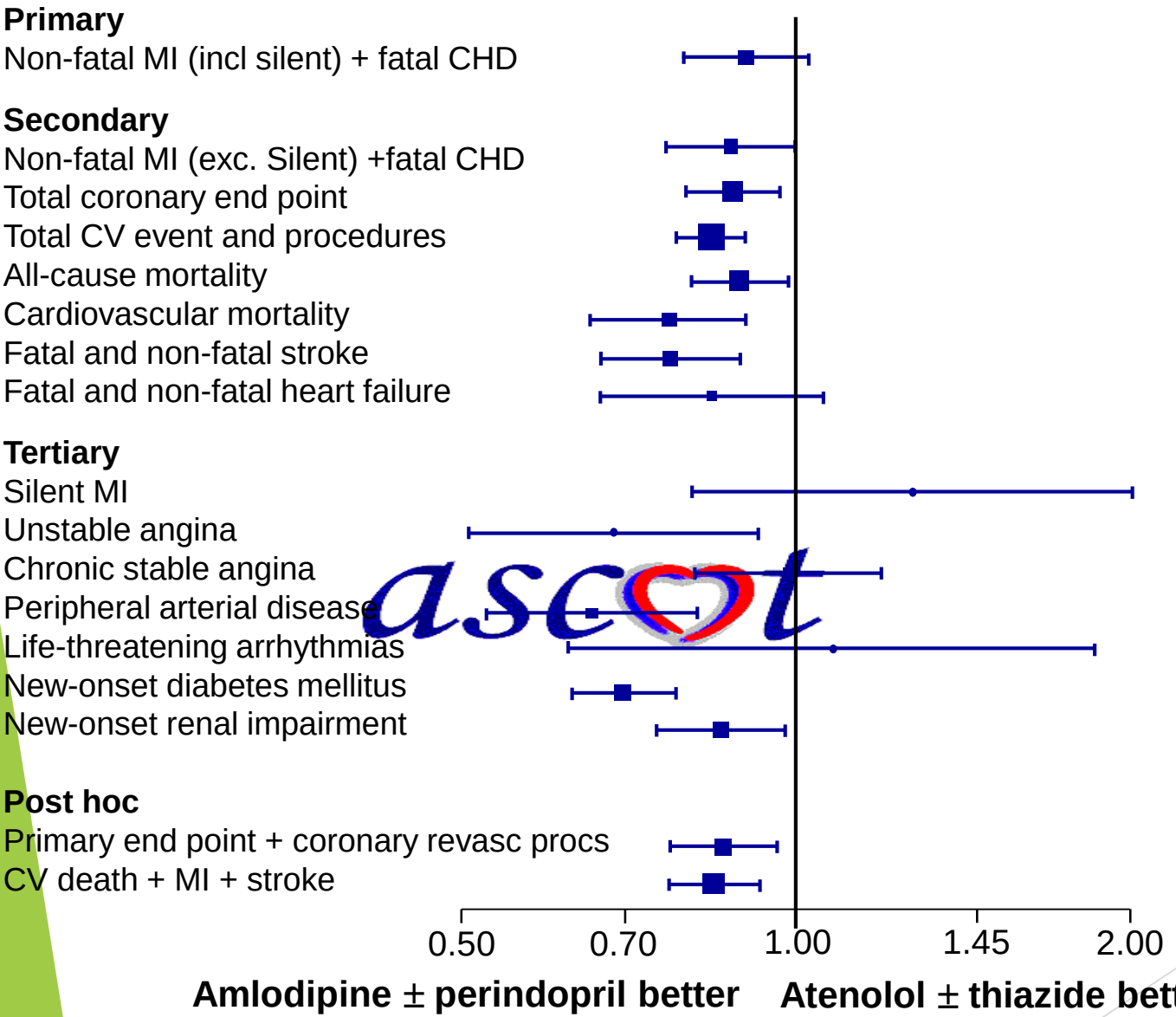


A randomised controlled trial of the prevention of CHD and other vascular events by BP and cholesterol lowering in a factorial study design

B.Dahlof (Co-chair), P.Sever (Co-chair), N. Poulter (Secretary)
H. Wedel (Statistician), G. Beevers, M. Caulfield, R. Collins
S. Kjeldsen, A. Kristinsson, J. Mehlsen, G. McInnes, M. Nieminen
E. O'Brien, J. Östergren, on behalf of the ASCOT Investigators

Lancet, September 2005; 386:895-906

Summary of all end points



Unadjusted Hazard ratio (95% CI)

0.90 (0.79-1.02)

0.87 (0.76-1.00)
0.87 (0.79-0.96)
0.84 (0.78-0.90)
0.89 (0.81-0.99)
0.76 (0.65-0.90)
0.77 (0.66-0.89)
0.84 (0.66-1.05)

1.27 (0.80-2.00)
0.68 (0.51-0.92)
0.98 (0.81-1.19)
0.65 (0.52-0.81)
1.07 (0.62-1.85)
0.70 (0.63-.078)
0.85 (0.75-0.97)

0.86 (0.77-0.96)
0.84 (0.76-0.92)

he area of the blue square is proportional to the amount of statistical information

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Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis

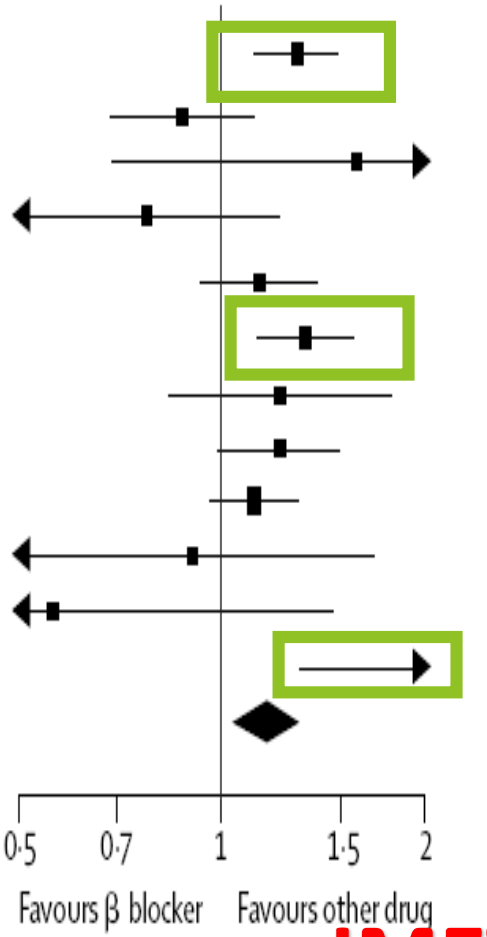
Lars Hjalmar Lindholm, Bo Carlberg, Ola Samuelsson

The Lancet October 18, 2005

Stroke for all BB versus other antihypertensives

Stroke	β blocker n/N	Other drug n/N	RR 95% CI	RR 95% CI
ASCOT-BPLA	422/9618	327/9639		1·29 (1·12–1·49)
CONVINCE	118/8297	133/8179		0·87 (0·68–1·12)
ELSA	14/1157	9/1177		1·58 (0·69–3·64)
HAPPHY	32/3297	41/3272		0·77 (0·49–1·23)
INVEST	201/11309	176/11267		1·14 (0·93–1·39)
LIFE	309/4588	232/4605		1·34 (1·13–1·58)
MRC Old	56/1102	45/1081		1·22 (0·83–1·79)
NORDIL	196/5471	159/5410		1·22 (0·99–1·50)
STOP-2	237/2213	422/4401		1·12 (0·96–1·30)
UKPDS	17/358	21/400		0·90 (0·48–1·69)
Yurenev	6/150	11/154		0·56 (0·21–1·48)
MRC	42/4403	18/4297		2·28 (1·31–3·95)
Total events	1650/51963	1594/53882		1·16 (1·04–1·30)

Test for heterogeneity: χ^2=22·39 (p=0·02)



Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis

Lars Hjalmar Lindholm, Bo Carlberg, Ola Samuelsson

Lancet 2005; 366: 1545–53

Interpretation: In comparison with other antihypertensive drugs, the effect of β blockers is less than optimum, with a raised risk of stroke. Hence, we believe that β blockers should not remain first choice in the treatment of primary hypertension and should not be used as reference drugs in future randomised controlled trials of hypertension.

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doi:10.1016/j.jacc.2009.04.087

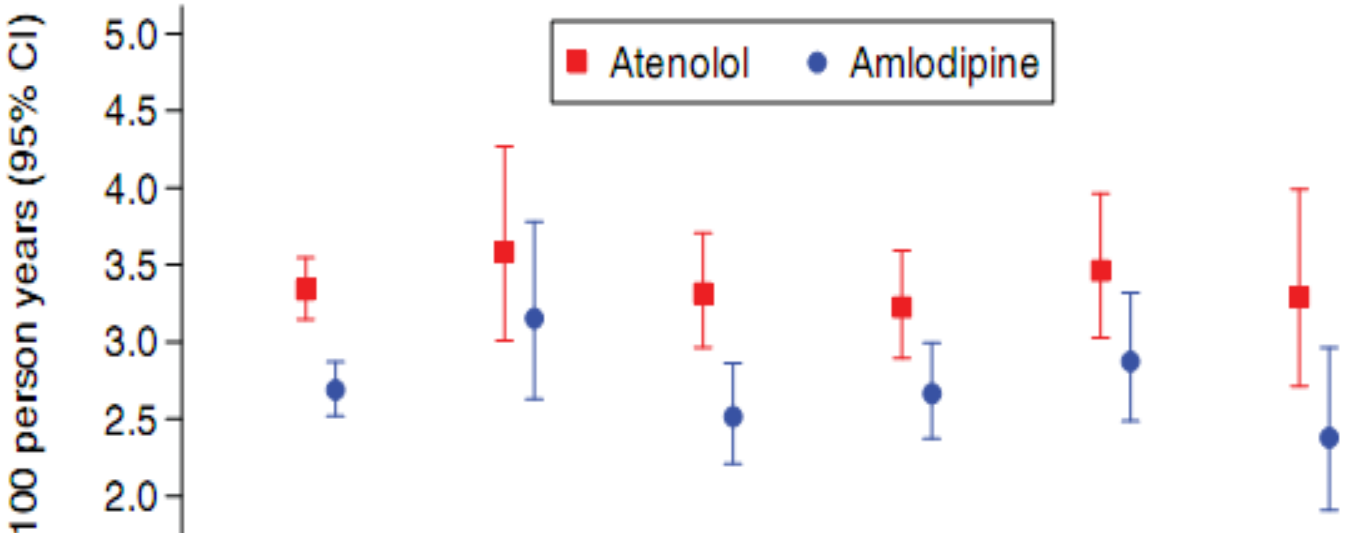
Hypertension

Baseline Heart Rate, Antihypertensive Treatment, and Prevention of Cardiovascular Outcomes in ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial)

Neil R. Poulter, MB, MSc,* Joanna E. Dobson, MSc,* Peter S. Sever, PhD,* Björn Dahlöf, MD, PhD,† Hans Wedel, PhD,‡ Norm R. C. Campbell, MD,§ on behalf of the ASCOT Investigators

London, United Kingdom; Göteborg, Sweden; and Calgary, Alberta, Canada

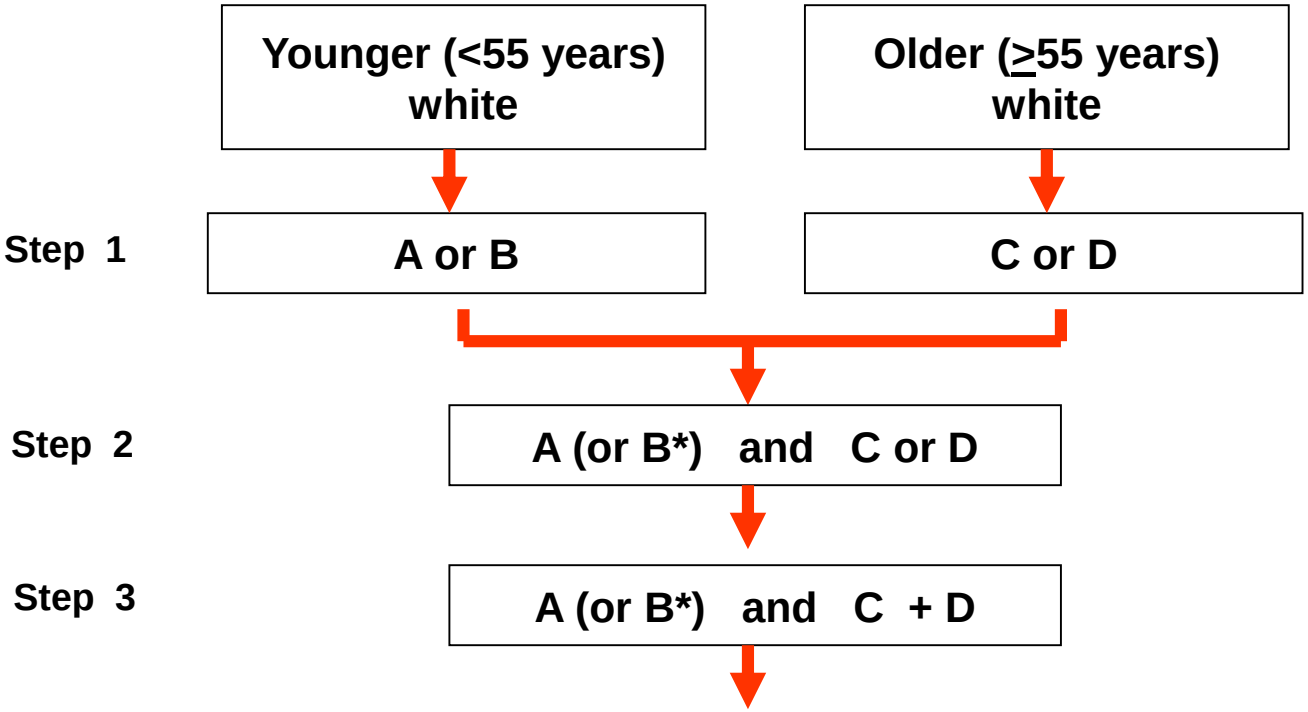
A



Conclusions There was no evidence that the superiority of amlodipine-based over atenolol-based therapy for patients with hypertension uncomplicated by coronary heart disease was attenuated with higher baseline heart rate. These data suggest that, in similar hypertensive populations without previous or current coronary artery disease, higher baseline heart rate is not an indication for preferential use of beta-blocker–based therapy. (J Am Coll Cardiol 2009;54:1154–61) © 2009 by the American College of Cardiology Foundation

Aten	1075	125	308	329	210	103
Amlod	891	116	230	283	183	79

BHS March 2004

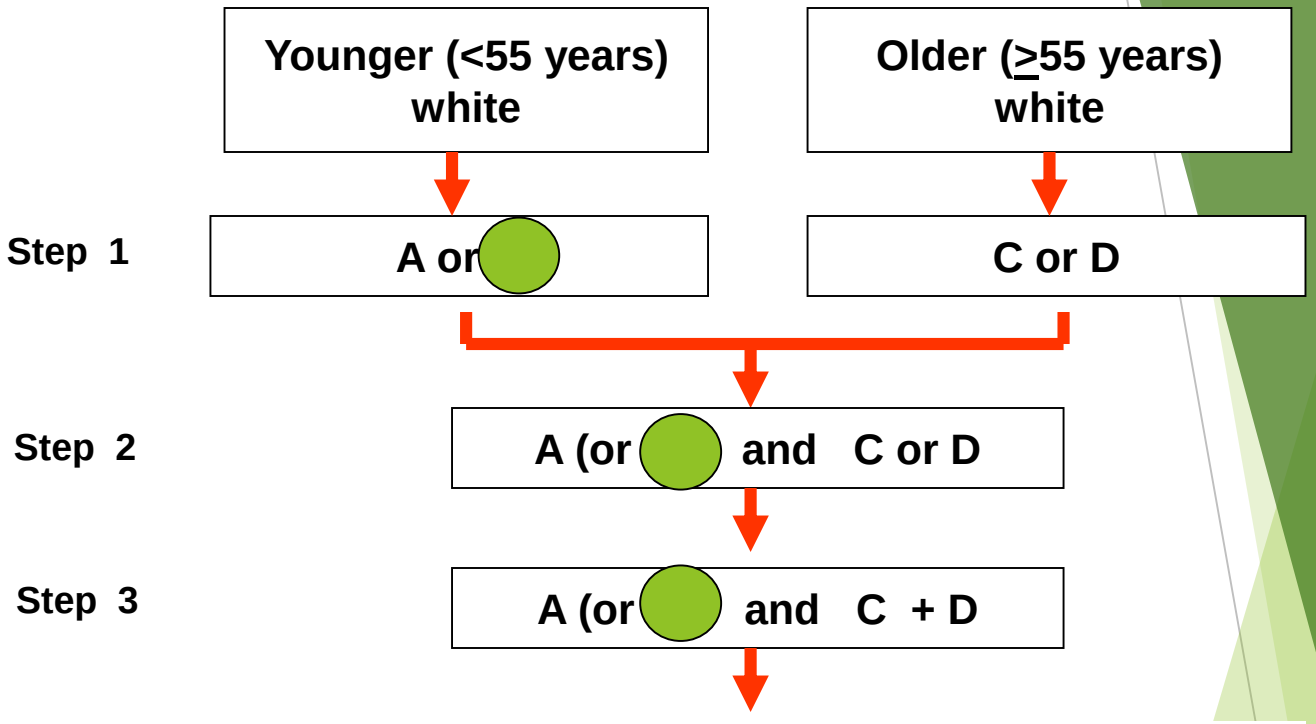


A : ACEI or ARB
C: CCB

B: β blockers
D: Diuretic

*Coadministration of B and D may increase the risk of new onset diabetes

BHS March 2006

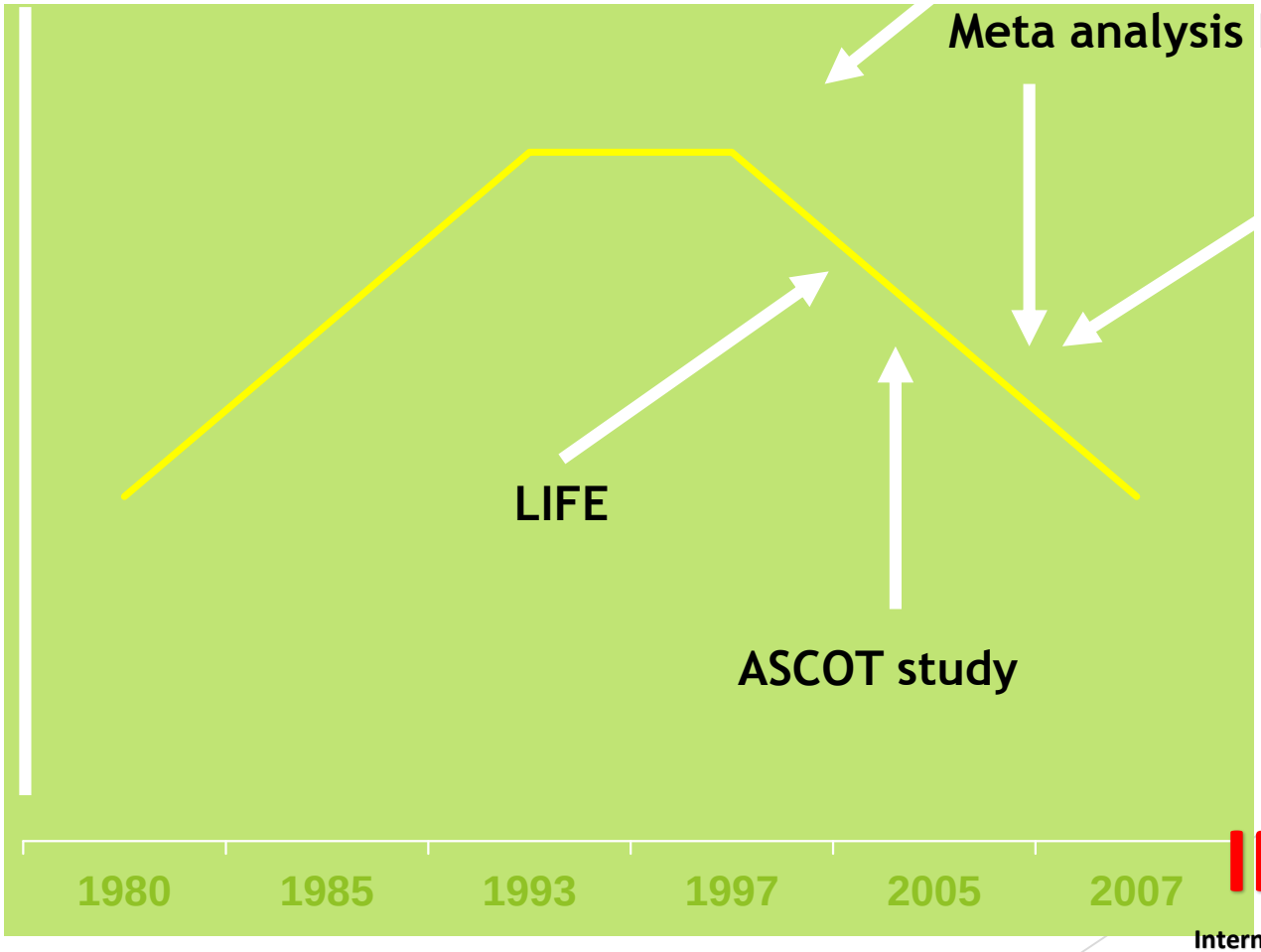


A : ACEI or ARB
C: CCB

B: β blockers
D: Diuretic

*Coadministration of B and D may increase the risk of new onset diabetes

Beta Blockers During the Years



What have we learned from ARBs?

PRoFESS Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Telmisartan to Prevent Recurrent Stroke and Cardiovascular Events

N Engl J Med 2008;359:1225-37.

Telmisartan to Prevent Recurrent Stroke and Cardiovascular Events

N Engl J Med 2008;359:1225-37.

20332 pts with Ischemic stroke

Follow-up 2.5 years

10146 Telmisartan

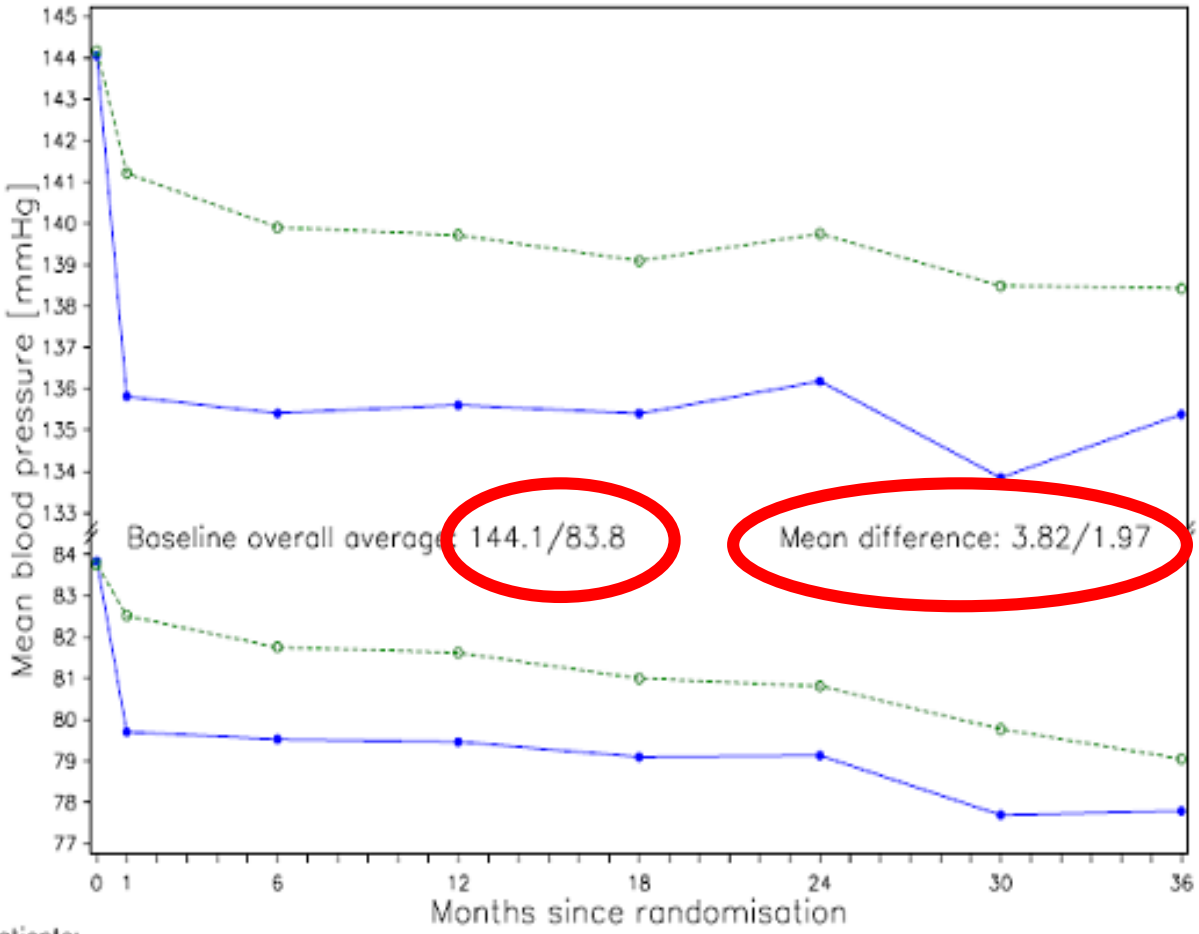
10186 Placebo

The primary outcome was recurrent stroke.

Secondary outcomes were major cardiovascular events (death from cardiovascular causes, recurrent stroke, myocardial infarction, or new or worsening heart failure) and new-onset diabetes

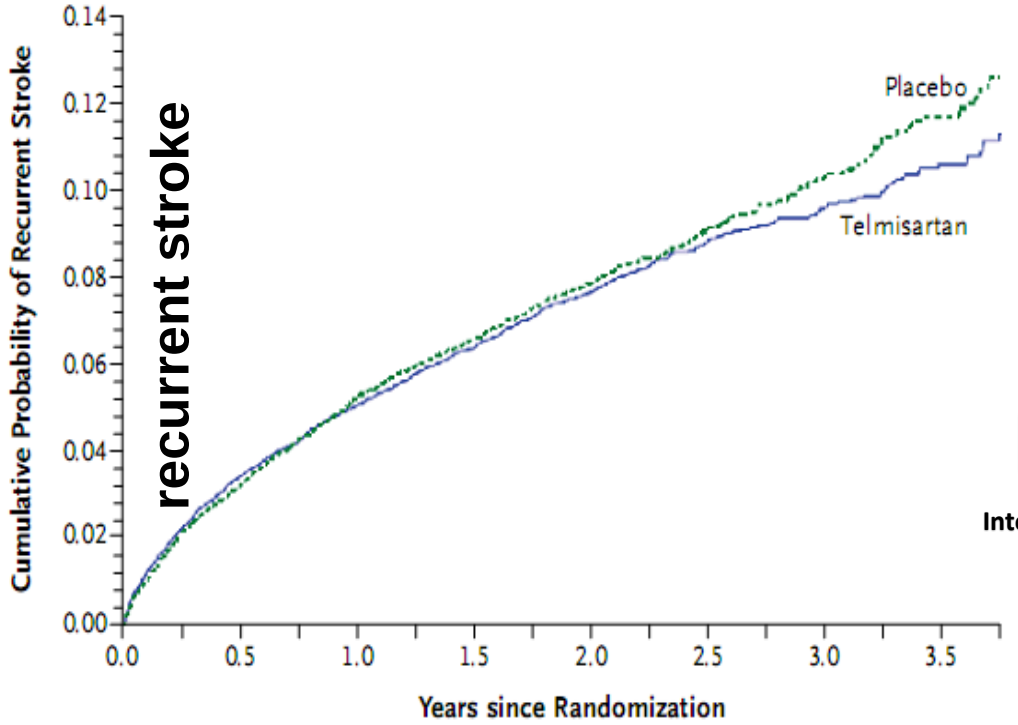
Telmisartan to Prevent Recurrent Stroke and Cardiovascular Events

N Engl J Med 2008;359:1225-37.



Telmisartan to Prevent Recurrent Stroke and Cardiovascular Events

N Engl J Med 2008;359:1225-37.



No. at Risk								
Telmisartan	10,146	9667	9400	9135	6947	4457	2337	1052
Placebo	10,186	9725	9402	9148	6957	4404	2326	1045

Figure 1. Kaplan–Meier Curves of the Cumulative Probability of Recurrent Stroke (Primary Outcome).

During a mean follow-up of 2.5 years, 880 patients (8.7%) in the telmisartan group and 934 patients (9.2%) in the placebo group had a subsequent stroke (hazard ratio in the telmisartan group, 0.95; 95% CI, 0.86 to 1.04; P=0.23). Hazard ratios were calculated with the use of the Cox model, which was adjusted for baseline age, use of angiotensin-converting–enzyme inhibitors, diabetes status, and modified Rankin Scale score.

TRANSCEND Study

Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial

*The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators**

Lancet 2008; 372: 1174–83

TRANSCEND Study

Lancet 2008; 372: 1174–83

5926 pts intolerant to ACEI
With CVD or DM and TOD

Follow-up 56 months

2954
Telmisartan

2972
Placebo

The primary outcome was the composite of cardiovascular death, myocardial infarction, stroke, or hospitalisation for heart failure . Mean blood pressure was lower in the telmisartan group than in the placebo group throughout the study (weighted mean difference between groups 4.0/2.2 [SD 19.6/12.0] mm Hg).

TRANSCEND Study

Lancet 2008; 372: 1174–83

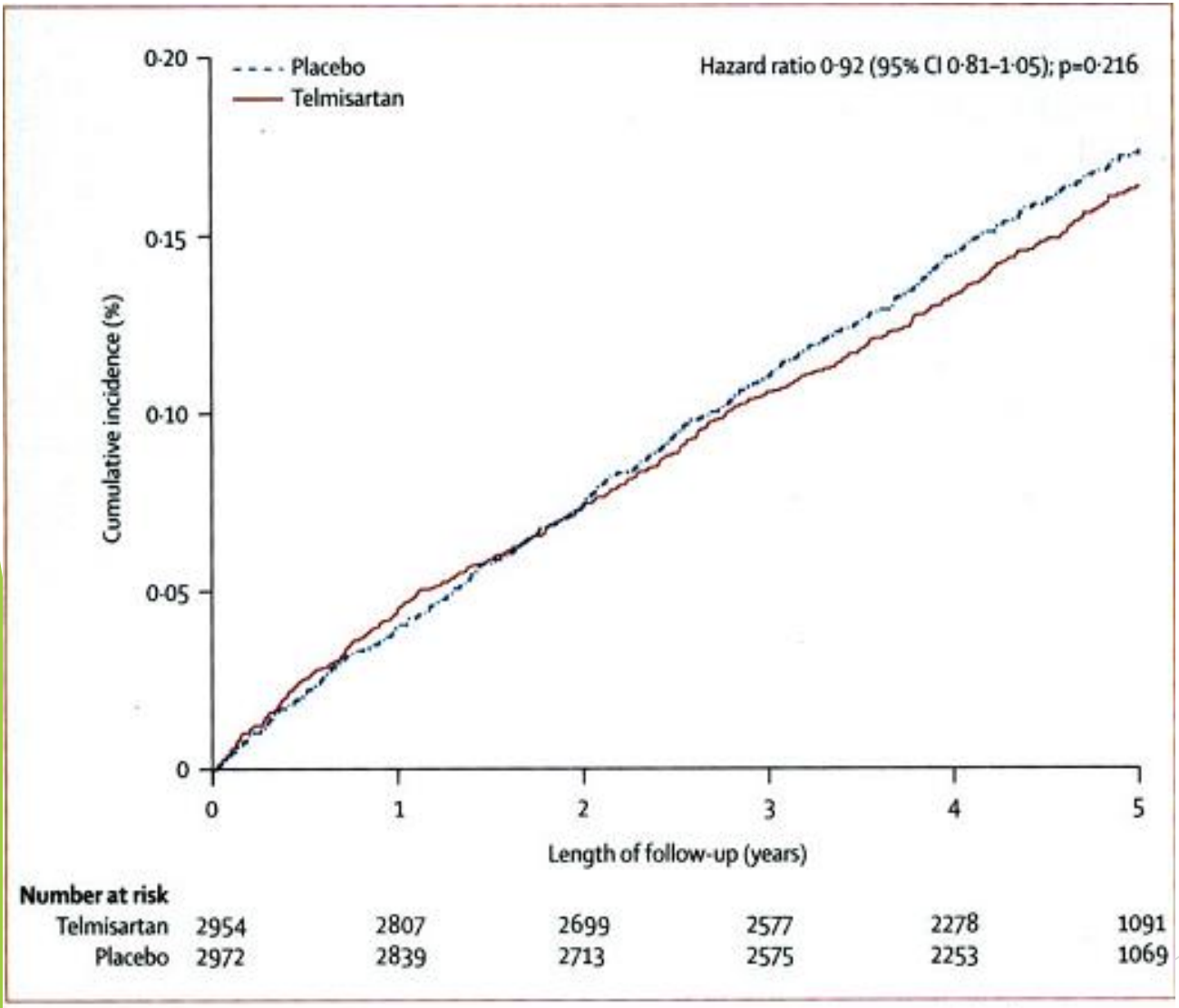


Figure 2: Kaplan–Meier curves for the primary outcome of cardiovascular death, myocardial infarction, stroke, or heart failure hospitalisation

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Dual Blockade of the RAAS

ACEI + ARB

ONTARGET trial

Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events

The ONTARGET Investigators*

N Engl J Med 2008;358:1547-59.

Renal outcomes with Telmisartan, Ramipril, or both, in people at high vascular risk

(the ONTARGET study)

a multicentre, randomised, double-blind, controlled trial.

Lancet 2008; 372: 547-53

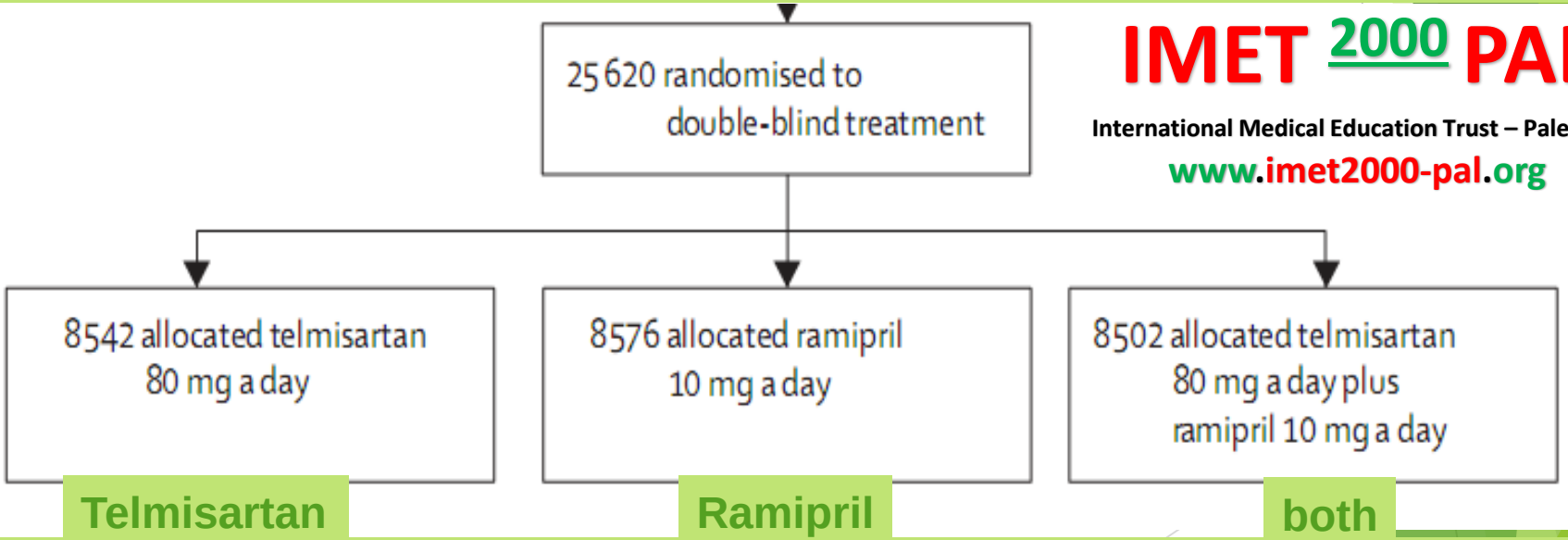
ONTARGET trial

Study population

Age: 55 years or older

with established vascular disease or

with diabetes with target organ damage.



Primary composite outcome

Death from CV causes, MI, Stroke or Hospitalization for heart failure

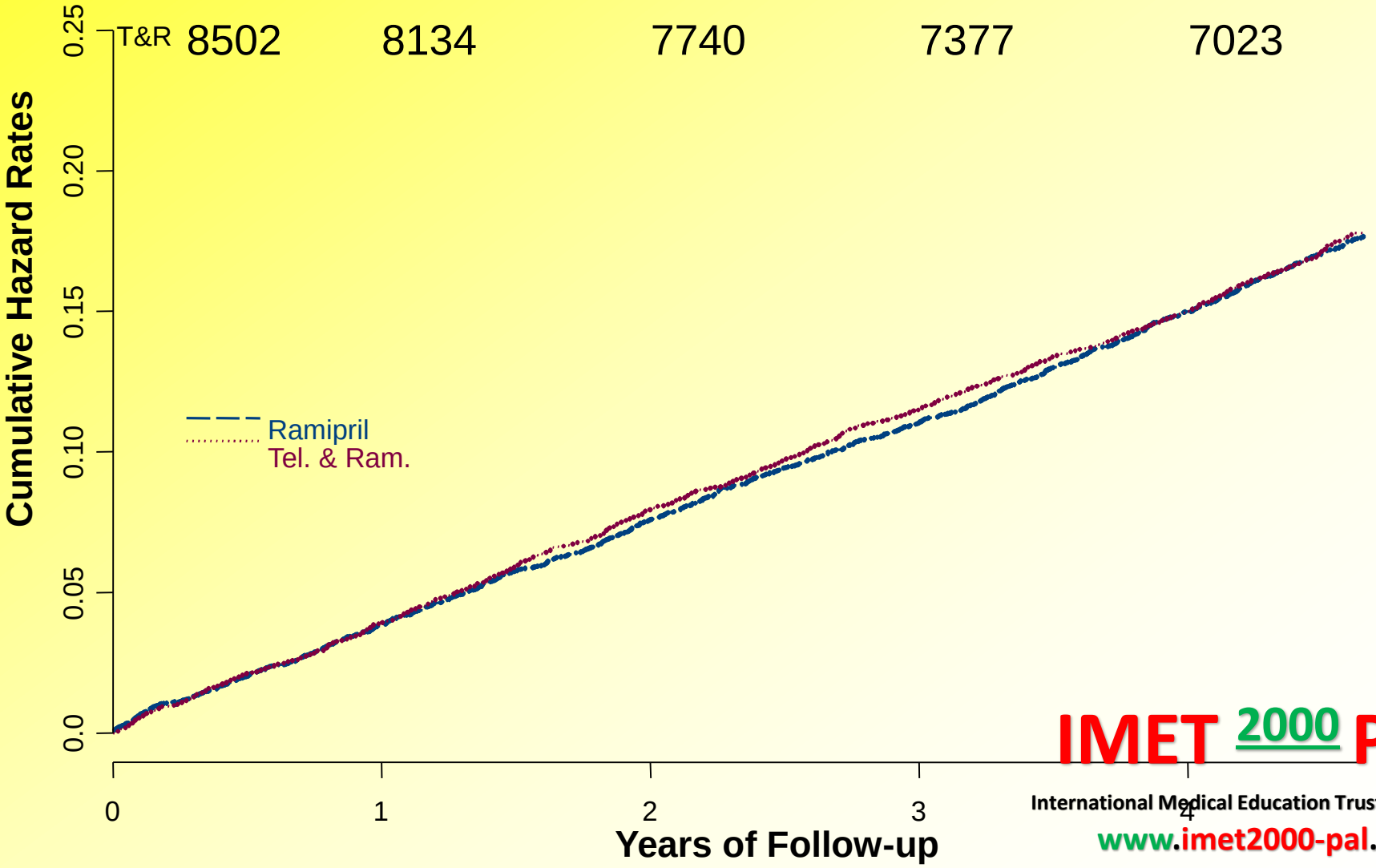
Change in BP (mmHg)

	Ramipril	Telmisartan	Combination
Systolic	-6.0	-6.9	-8.4
Diastolic	-4.6	-5.2	-6.0

Combination vs Ramipril

Time to Primary Outcome

	# at Risk	Yr 1	Yr 2	Yr 3	Yr 4
R	8576	8214	7832	7473	7095
T&R	8502	8134	7740	7377	7023



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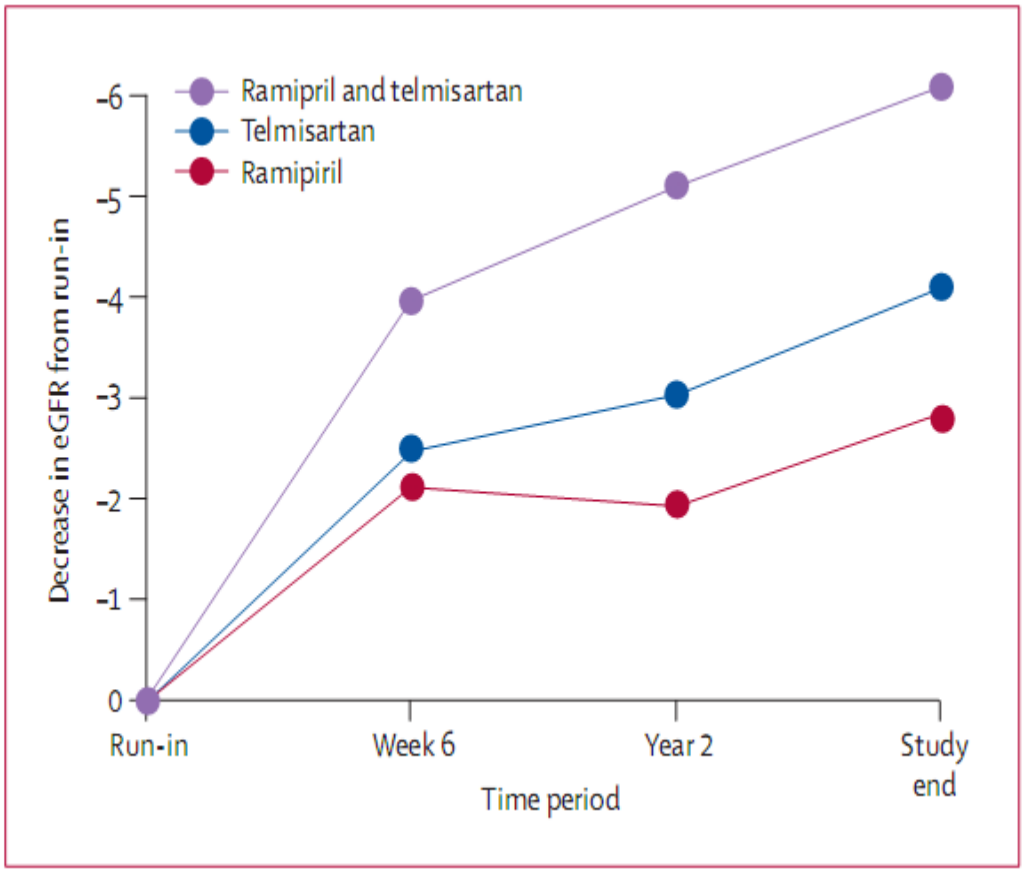
Reasons for Permanently Stopping Study Medications

	Ram N=8576	Ram + Tel N=8502	Ram + Tel vs. Ram RR	P
Hypotension	149	406	2.75	<0.0001
Syncope	15	29	1.95	0.032
Cough	360	392	1.10	0.1885
Diarrhea	12	39	3.28	0.0001
Angioedema	25	18	0.73	0.30
Renal Impairment	60	94	1.58	0.0050
Any Discontinuation	2099	2495	1.20	<0.0001

Renal outcomes with Telmisartan, Ramipril, or both, in people at high vascular risk (the ONTARGET study)

a multicentre, randomised, double-blind, controlled trial



Lancet 2008; 372: 547-53

Renal outcomes with Telmisartan, Ramipril, or both, in people at high vascular risk (the ONTARGET study)

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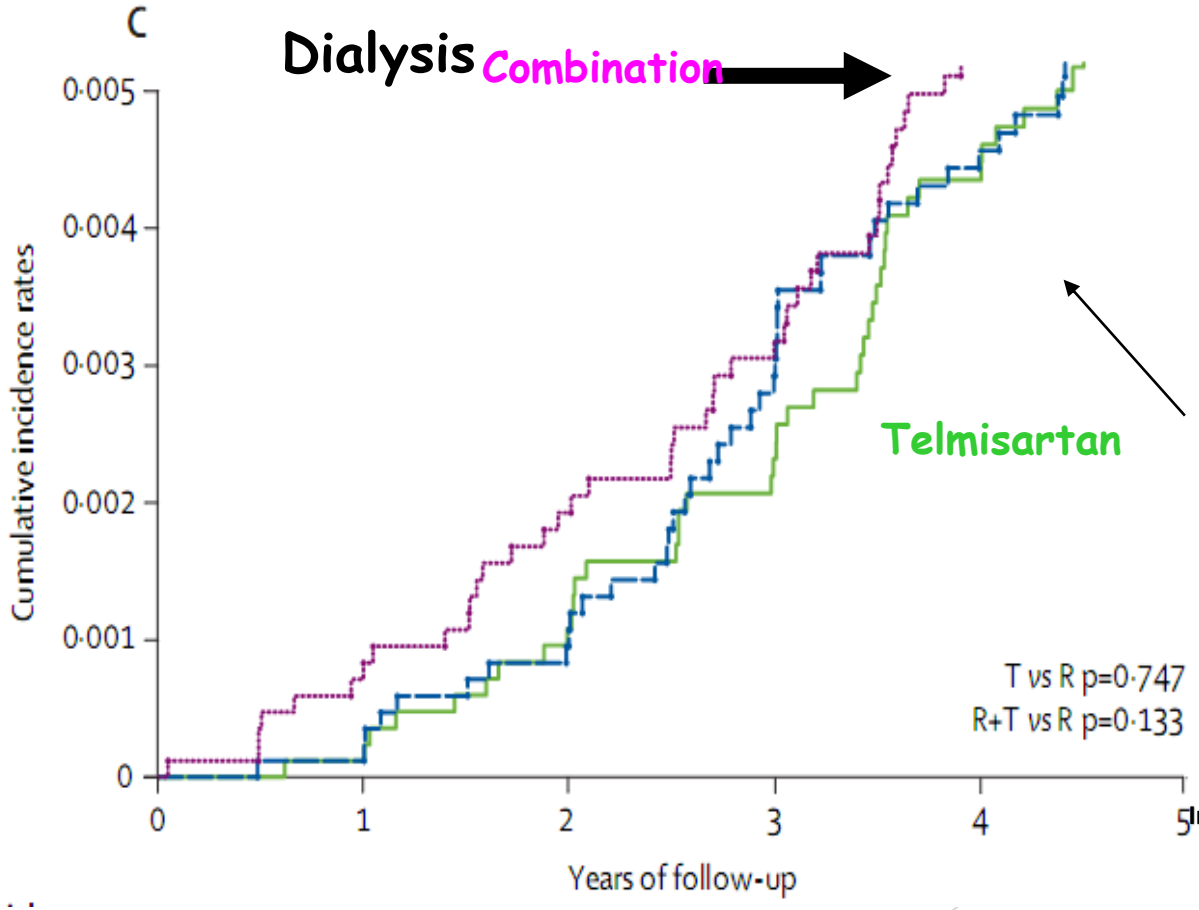
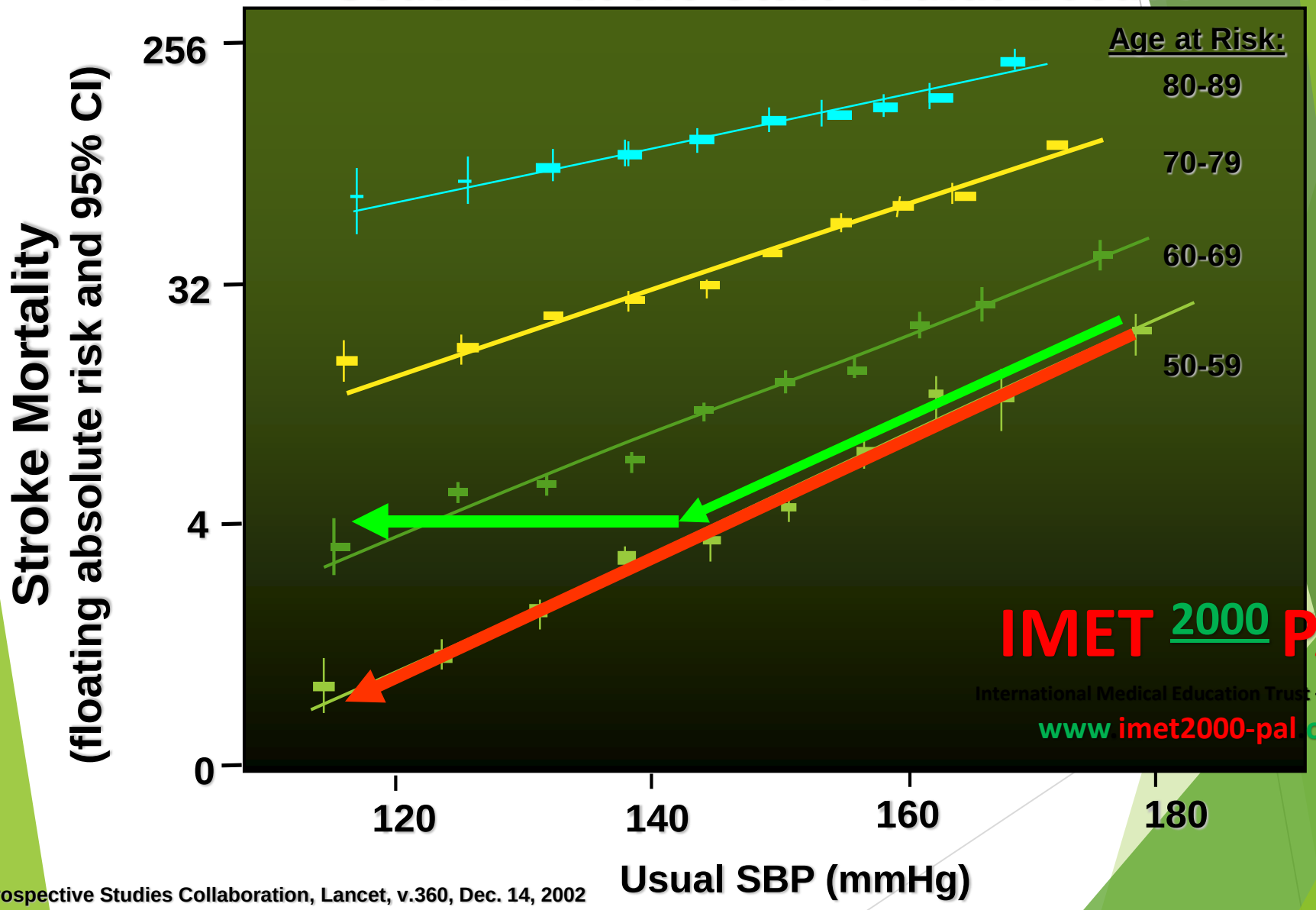


Conclusions of Combination therapy

Despite the better control of BP

- It does not reduce the primary outcome to a greater extent compared to Ramipril alone.
- It has higher adverse events.
- It attenuates the increase in urinary albumin excretion but has a deleterious effect on renal function

Stroke Mortality Rate in Each Decade of Age vs Usual BP at the Start of that Decade



Prospective Studies Collaboration, Lancet, v.360, Dec. 14, 2002

THE COCHRANE COLLABORATION®

[Intervention Review]

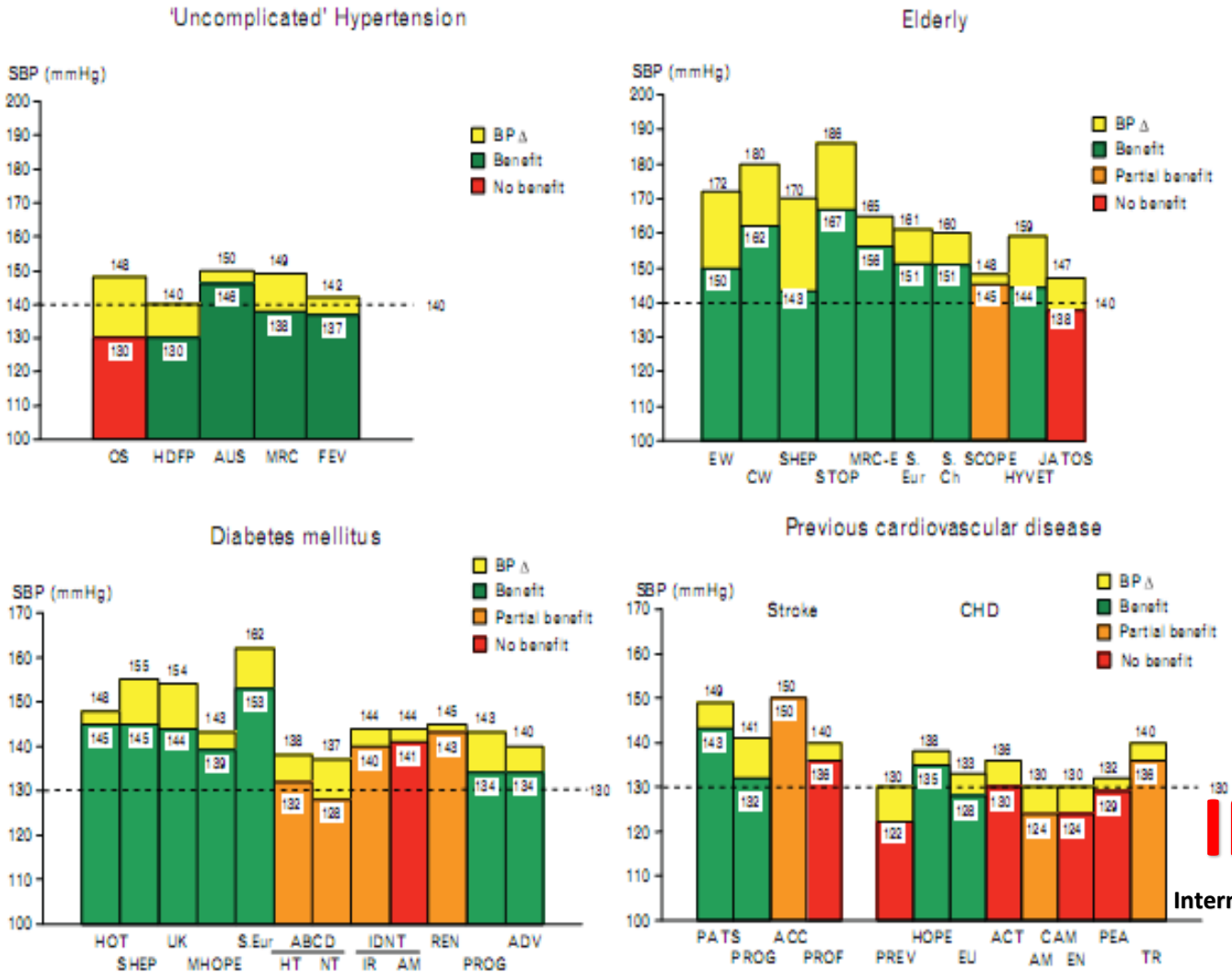
Treatment blood pressure targets for hypertension

Jose Agustin Arguedas[1], Marco I Perez[2], James M Wright[2]

This version published online: 8 July 2009 in Issue 3, 2009.

There is no proof to suggest that reduction of BP below 140- 160 / 90–100 mmHg is associated with reduction on morbidity and mortality

Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document J Hypertension (in press)



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Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document

J Hypertension (in press)

Box 4. Blood pressure goals of treatment

(1) On the whole, there is sufficient evidence to recommend that SBP be lowered below 140 mmHg (and DBP below 90 mmHg) in all hypertensive patients, both those at low moderate risk and those at high risk. Evidence is only missing in the elderly hypertensive patients, in whom the benefit of lowering SBP below 140 mmHg has never been tested in randomized trials.

(2) The recommendation of previous guidelines to aim at a lower goal SBP (<130 mmHg) in diabetic patients and in patients at very high cardiovascular risk (previous cardiovascular events) may be wise, but it is not consistently supported by trial evidence. In no randomized trial in diabetic patients has SBP been brought down to below 130 mmHg with proven benefits, and trials in which SBP was lowered to below 130 mmHg in patients with previous cardiovascular events have given controversial results.

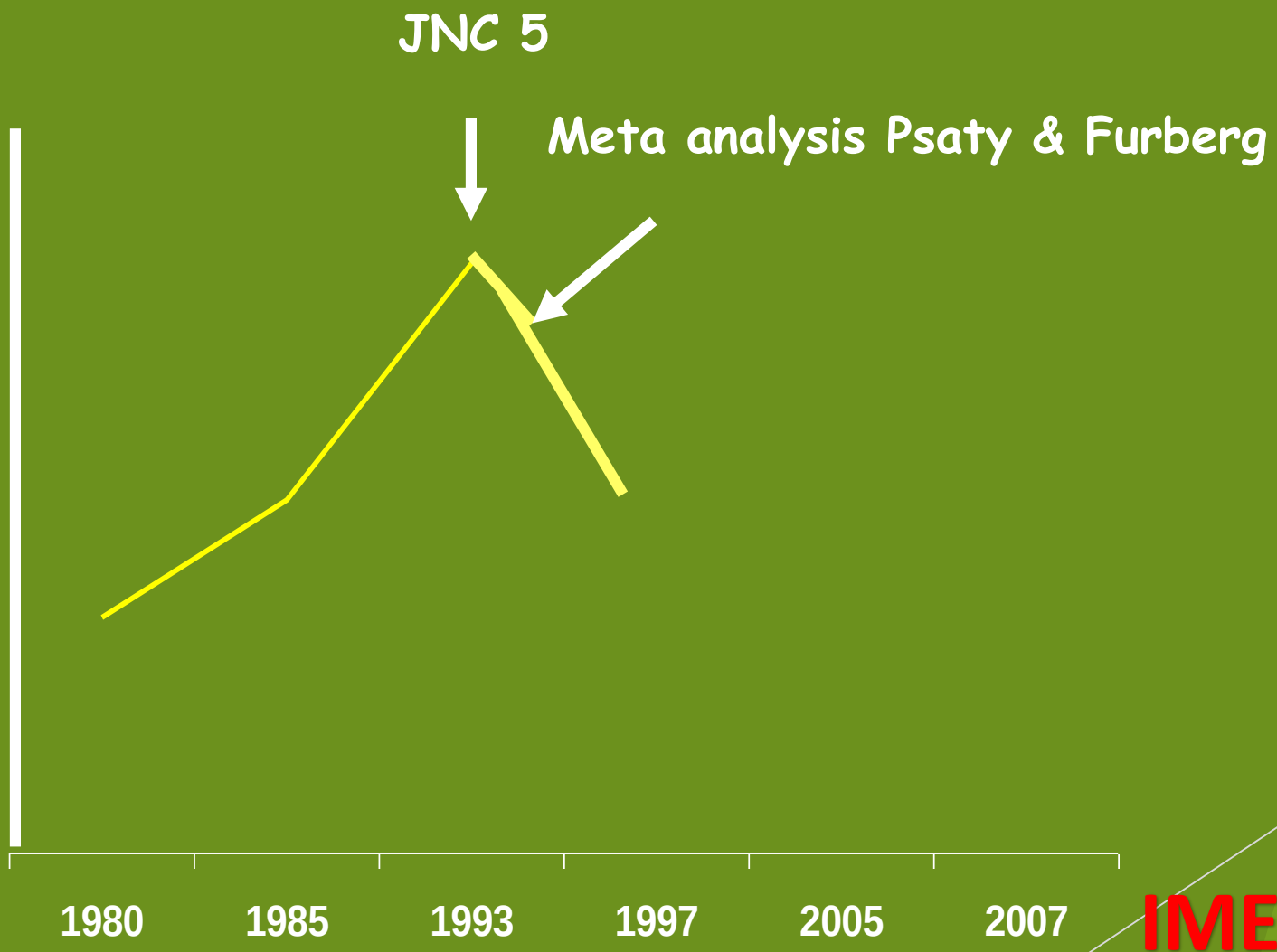
(3) Despite their obvious limitations and a lower strength of evidence, *post hoc* analyses of trial data indicate a progressive reduction of cardiovascular events incidence with progressive lowering of SBP down to about 120 mmHg and DBP down to about 75 mmHg, although the additional benefit at low BP values becomes rather small. A J-curve phenomenon is unlikely to occur until lower values are reached, except perhaps in patients with advanced atherosclerotic artery diseases.

(4) On the basis of current data, it may be prudent to recommend lowering SBP/DBP to values within the range 130–139/80–85 mmHg, and possibly close to lower values in this range, in all hypertensive patients. More critical evidence from specific randomized trials is desirable, however.

On the basis of current data, it may be prudent to recommend lowering SBP/DBP to values within the range 130–139/80–85mmHg, and possibly close to lower values in this range, in all hypertensive patients.

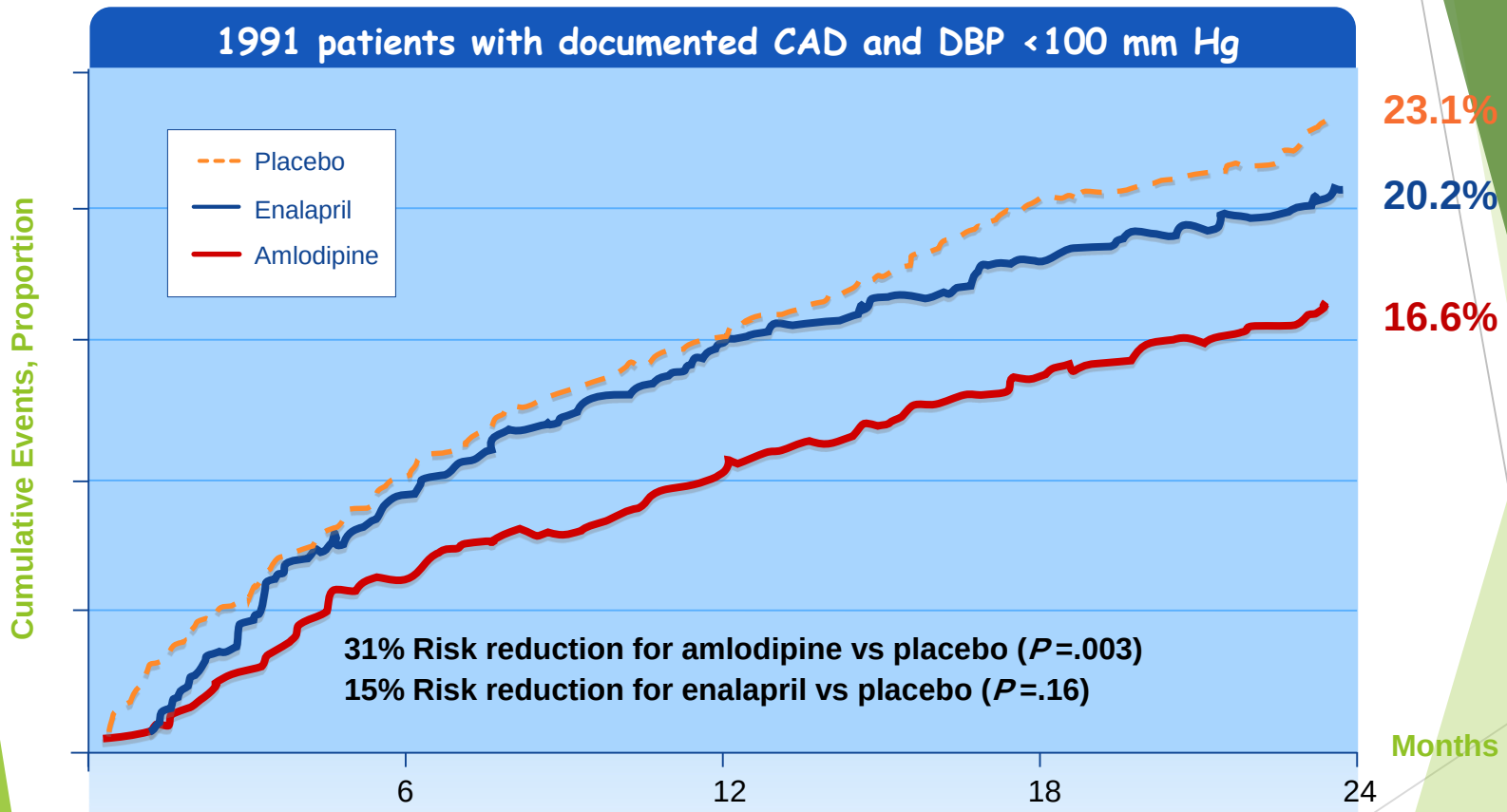
What have we learned from CCBs?

CCB during the years



CAMELOT:

Primary Composite End Point Adverse CV Events



- No support the view that ACEi prevents CVS events beyond the benefits of BP lowering

JAMA; 2004; 292: 2217-226

Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension

The ACCOMPLISH Trial

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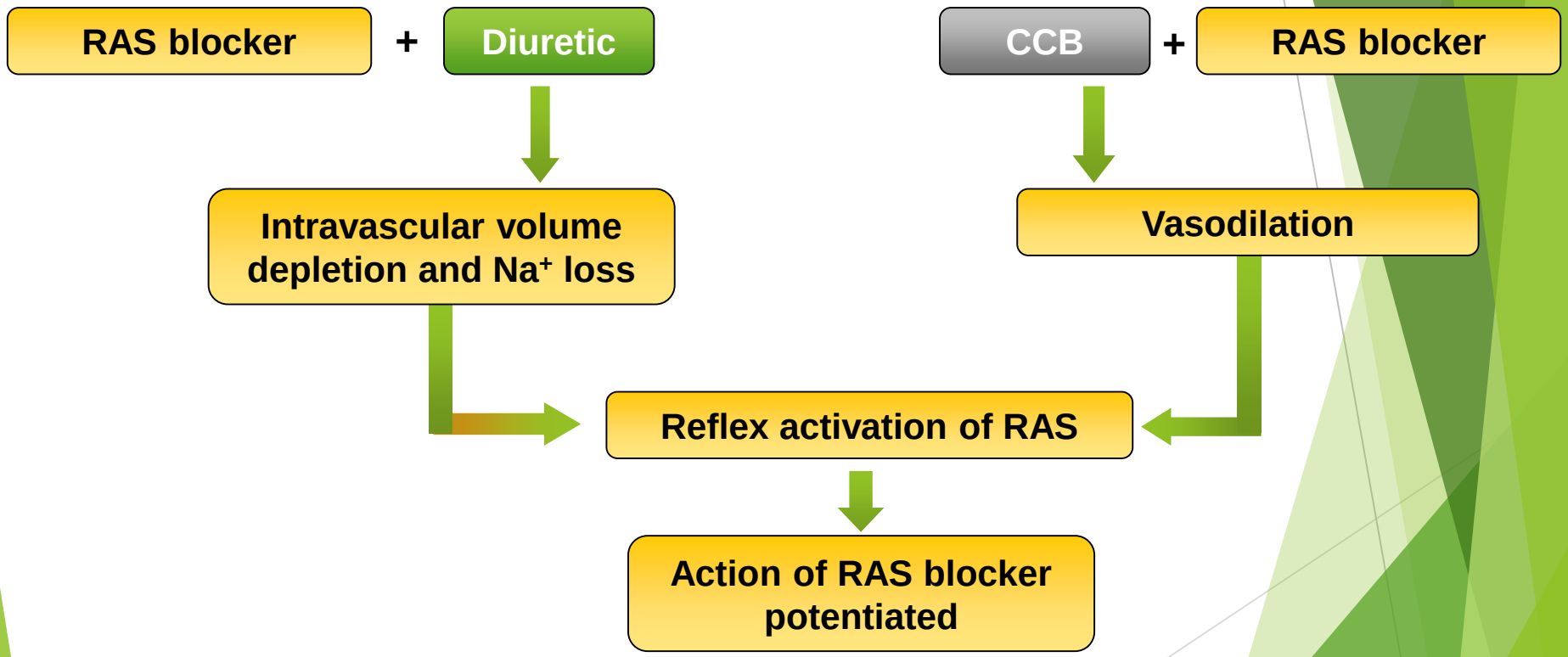
Rationale of Common Combinations

Rationale for combination of RAS blocker with diuretic or a CCB



CCB = calcium channel blocker; RAS = renin-angiotensin system

Stanton T, et al. *J Hum Hypertens* 2002;16:75–8
Jamerson K, et al. *Am J Hypertens* 2004;17:793–801

Trial Objectives

- To compare the clinical benefits of two **single pill-combination** therapies on CV mortality and morbidity in high-risk hypertensive patients

Primary Objective

To measure the time to first event of composite CV morbidity and mortality in the two treatment groups

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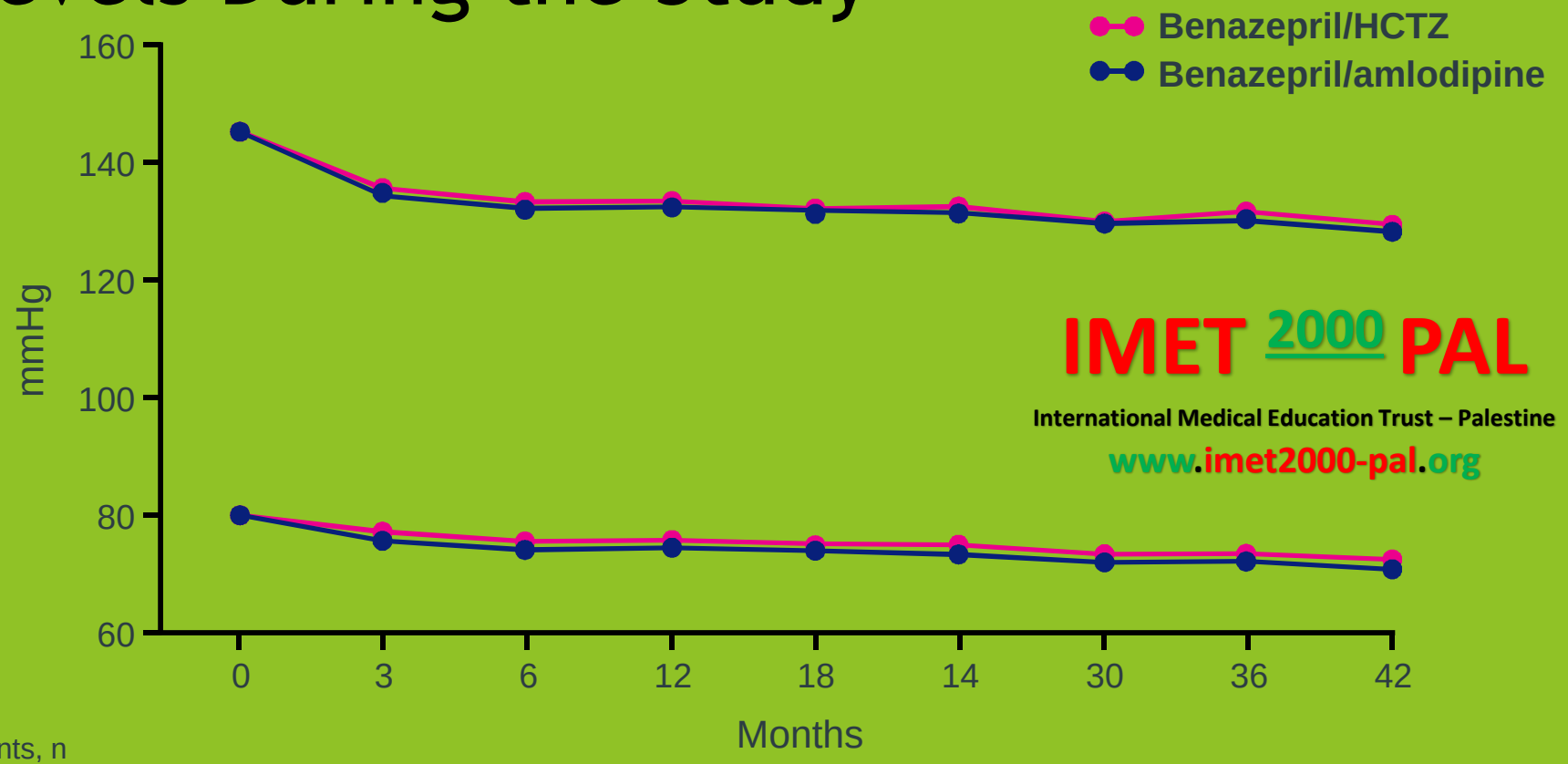
Jamerson K, et al. *Am J Hypertens* 2004;17:793–801

RESULTS

ACCOMPLISH: Blood Pressure (BP) Levels During the Study

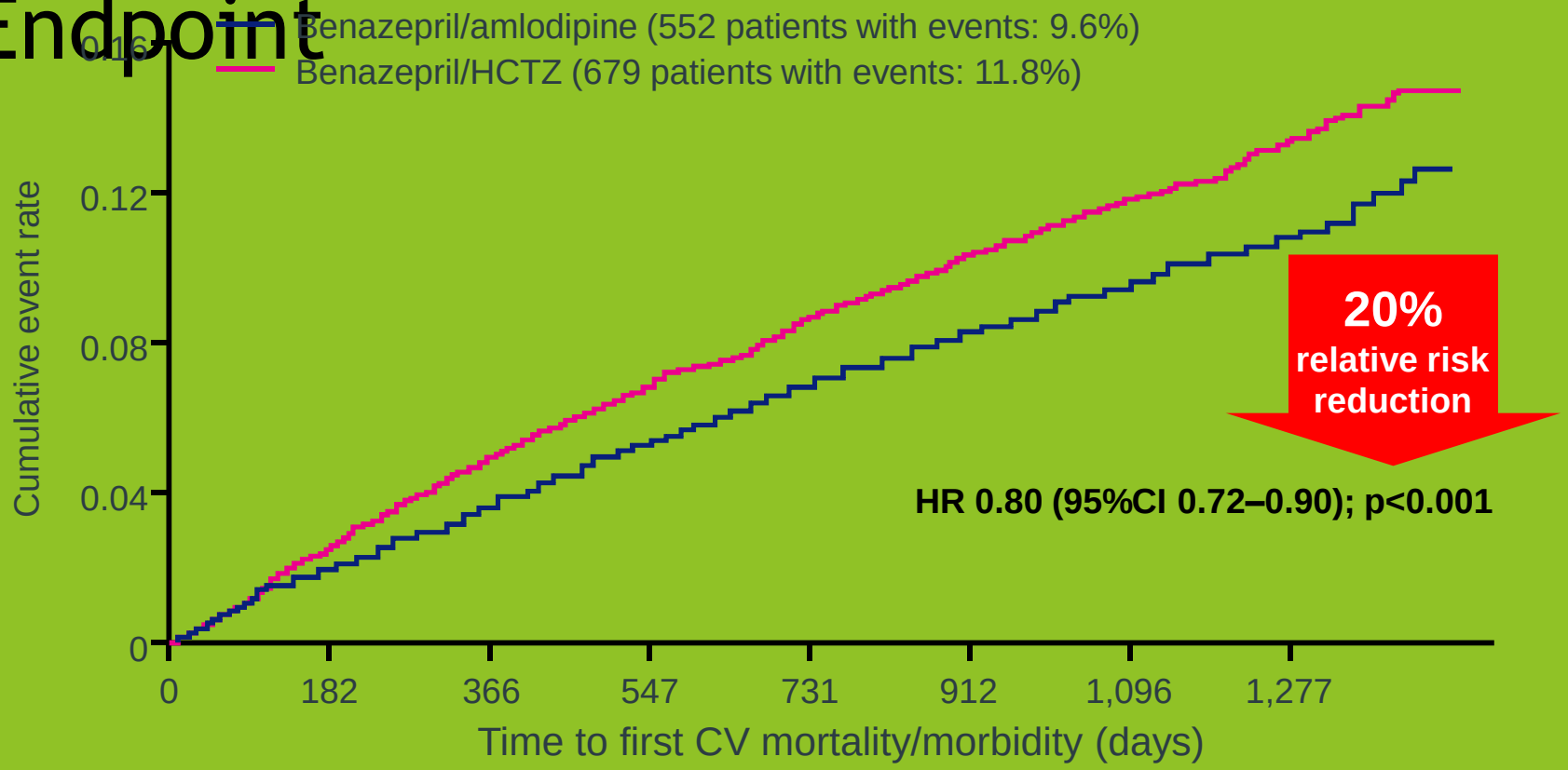


Patients, n									
Benazepril/amlodipine	5,740	5,517	5,404	5,178	5,010	4,866	4,298	2,804	1,074
Benazepril/HCTZ	5,757	5,537	5,408	5,222	5,033	4,825	4,299	2,529	1,042

The mean SBP/DBP following titration was 131.6/73.3 mm Hg in the benazepril/amlodipine group and 132.5/74.4 mm Hg in the benazepril/HCTZ group. The mean difference in SBP/DBP between the 2 groups was 0.9/1.1 mmHg ($p<0.001$)

Jamerson K, et al. *N Engl J Med* 2008;359:2417–28

ACCOMPLISH: Primary Endpoint

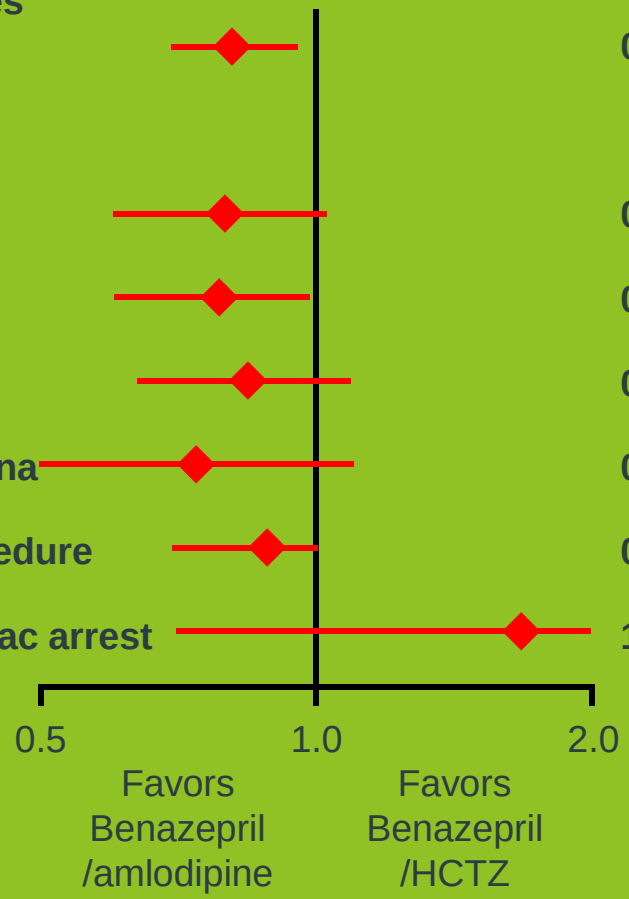


Months	0	6	12	18	24	30	36	42
Patients at risk (N)								
Benazepril/amlodipine	5,512	5,317	5,141	4,959	4,739	2,826	1,447	
Benazepril/HCTZ	5,483	5,274	5,082	4,892	4,655	2,749	1,390	

Jamerson K, et al. *N Engl J Med* 2008;359:2417–28

ACCOMPLISH: Components of the Primary Endpoint*

	HR (95%CI)	p-value
Composite of death from CV causes and CV events:	**0.80 (0.72–0.90)**	**<0.001**
Component:		
Death from CV causes	**0.80 (0.62–1.03)**	**0.08**
MI (fatal/non-fatal)	**0.78 (0.62–0.99)**	**0.04**
Stroke (fatal/non-fatal)	**0.84 (0.65–1.08)**	**0.17**
Hospitalization for unstable angina	**0.75 (0.50–1.10)**	**0.14**
Coronary revascularization procedure	**0.86 (0.74–1.00)**	**0.05**
Resuscitation after sudden cardiac arrest	**1.75 (0.73–4.17)**	**0.20**



*Only the first event in an individual patient was counted in the analysis of the primary end point

Jamerson K, et al. *N Engl J Med* 2008;359:2417–28

ACCOMPLISH: Summary

- Excellent BP control rates of between 72–75% were achieved with single-pill combinations in the ACCOMPLISH trial

- BP levels were similar between treatment groups

- The benazepril + amlodipine single-pill combination reduced the relative risk of CV morbidity and mortality by 20% compared with benazepril + HCTZ single-pill combination (HR 0.80; p<0.001)

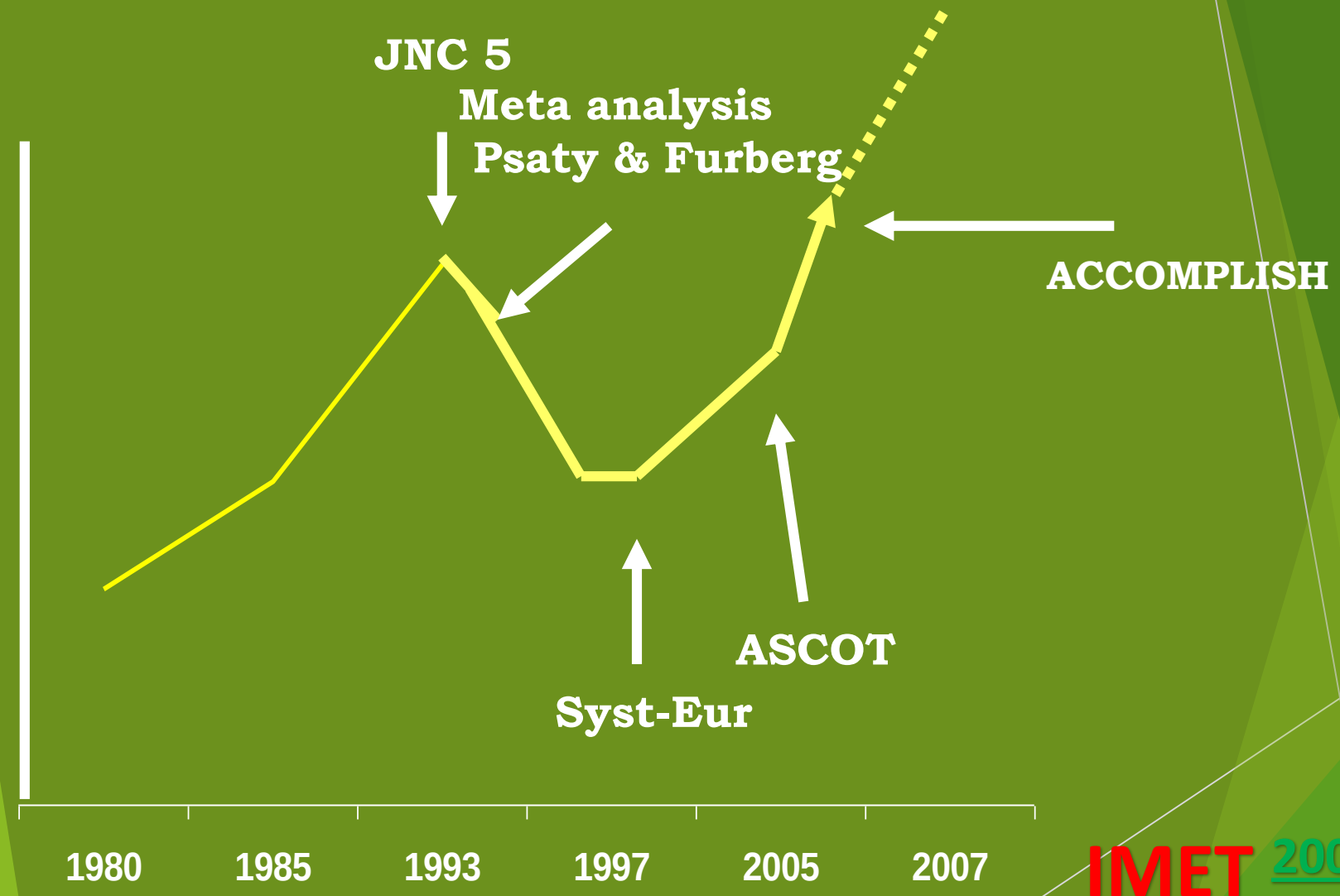
Jamerson K, et al. *N Engl J Med* 2008;359:2417–28

ACCOMPLISH: Conclusion

These findings support the justefied use of a ACEi + CCB single-pill combination when combination therapy is required

Jamerson K, et al. *N Engl J Med* 2008;359:2417–28

CCB During the Years



Calcium Antagonists (DHP)

- Very effective in lowering BP.
- Anti-anginal effect.
- Anti atherosclerotic effect
- Do not impair glucose and lipid metabolism.
- Reduce left ventricular mass.
- No interaction with NSAID

Conclusions

1. **Beta Blockers** are less effective in reducing morbidity and mortality especially among elderly.
2. **ACEIs, CCBs** and **ARBs** are effective in reducing morbidity and mortality
3. **Monotherapy** is not enough for controlling most patients with HTN
4. **CCBs** are more effective than diuretics if combined with ACEIs or ARBs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