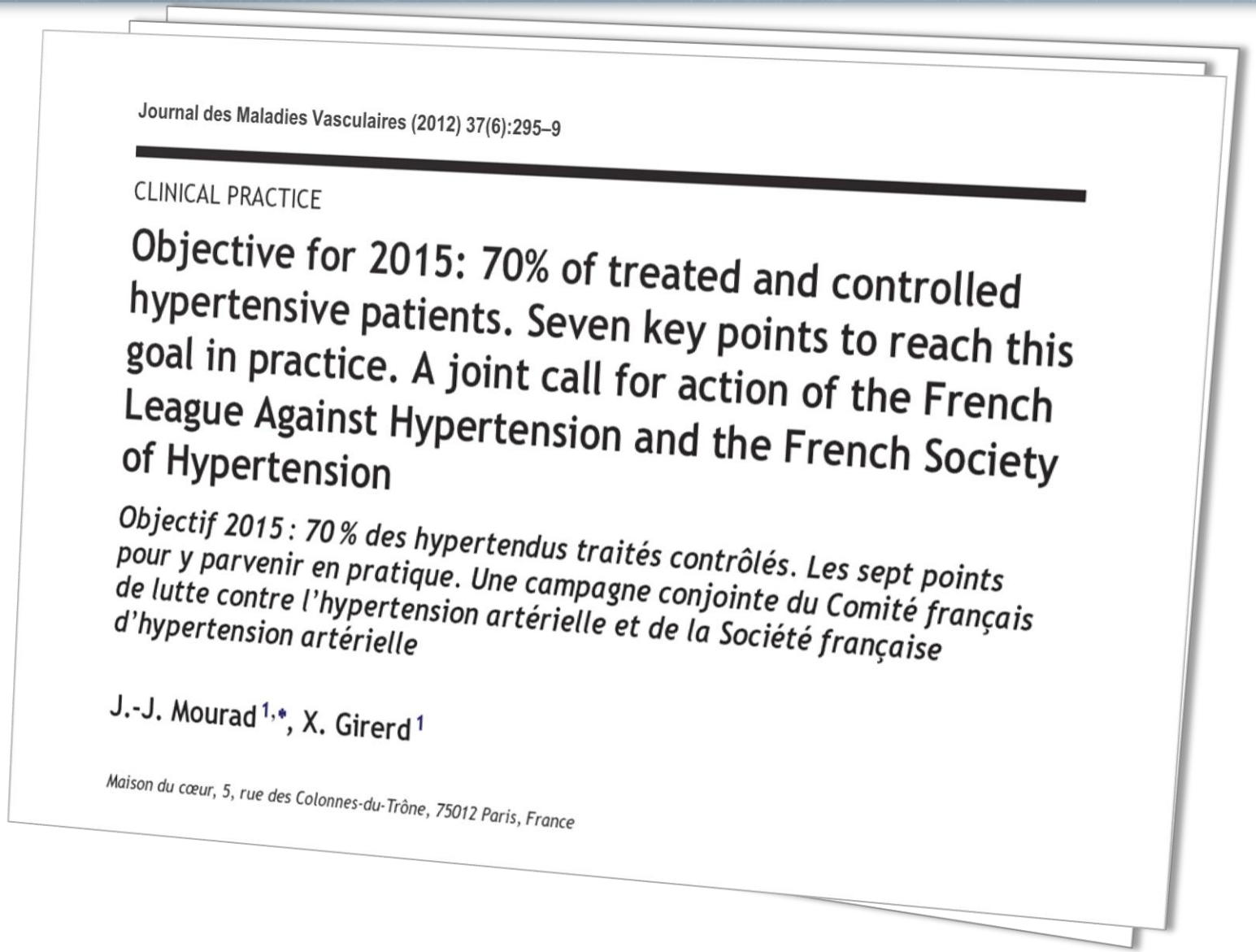
Value of fixed combination treatments in hypertensive patients.

Jean-Jacques Mourad
(France)

Davos, Feb 2015

Objective for 2015: improving BP control in treated hypertensive patients in France



Journal des Maladies Vasculaires (2012) 37(6):295–9

CLINICAL PRACTICE

Objective for 2015: 70% of treated and controlled hypertensive patients. Seven key points to reach this goal in practice. A joint call for action of the French League Against Hypertension and the French Society of Hypertension

Objectif 2015 : 70 % des hypertendus traités contrôlés. Les sept points pour y parvenir en pratique. Une campagne conjointe du Comité français de lutte contre l'hypertension artérielle et de la Société française d'hypertension artérielle

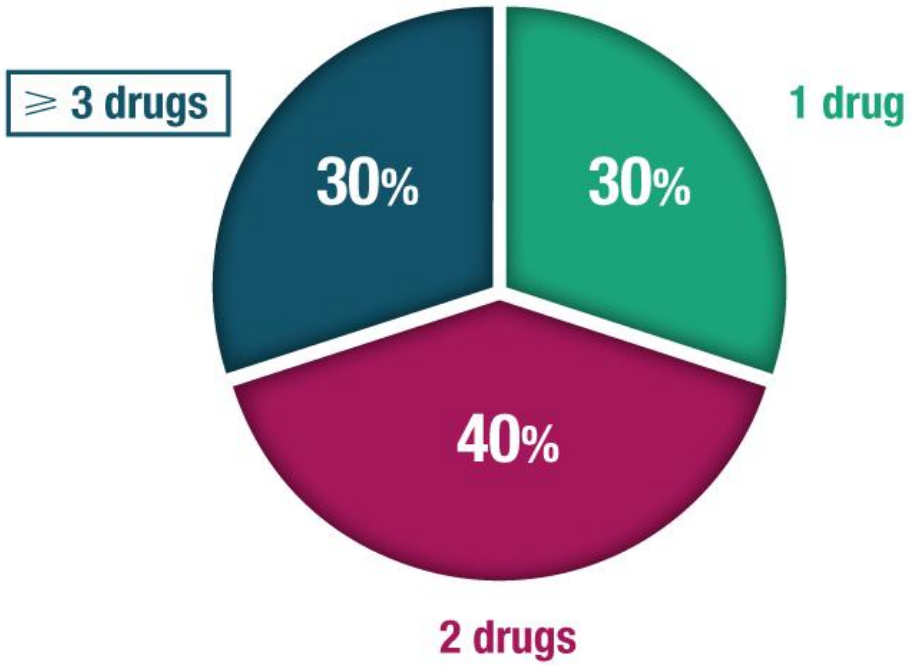
J.-J. Mourad [1,*], X. Girerd [1]

Maison du cœur, 5, rue des Colonnes-du-Trône, 75012 Paris, France

Mourad & Girerd. *J Mal Vasc* 2012;37:295–9

A true need

- 1 hypertensive patient out of 3 already treated by 3 antihypertensive drugs or more

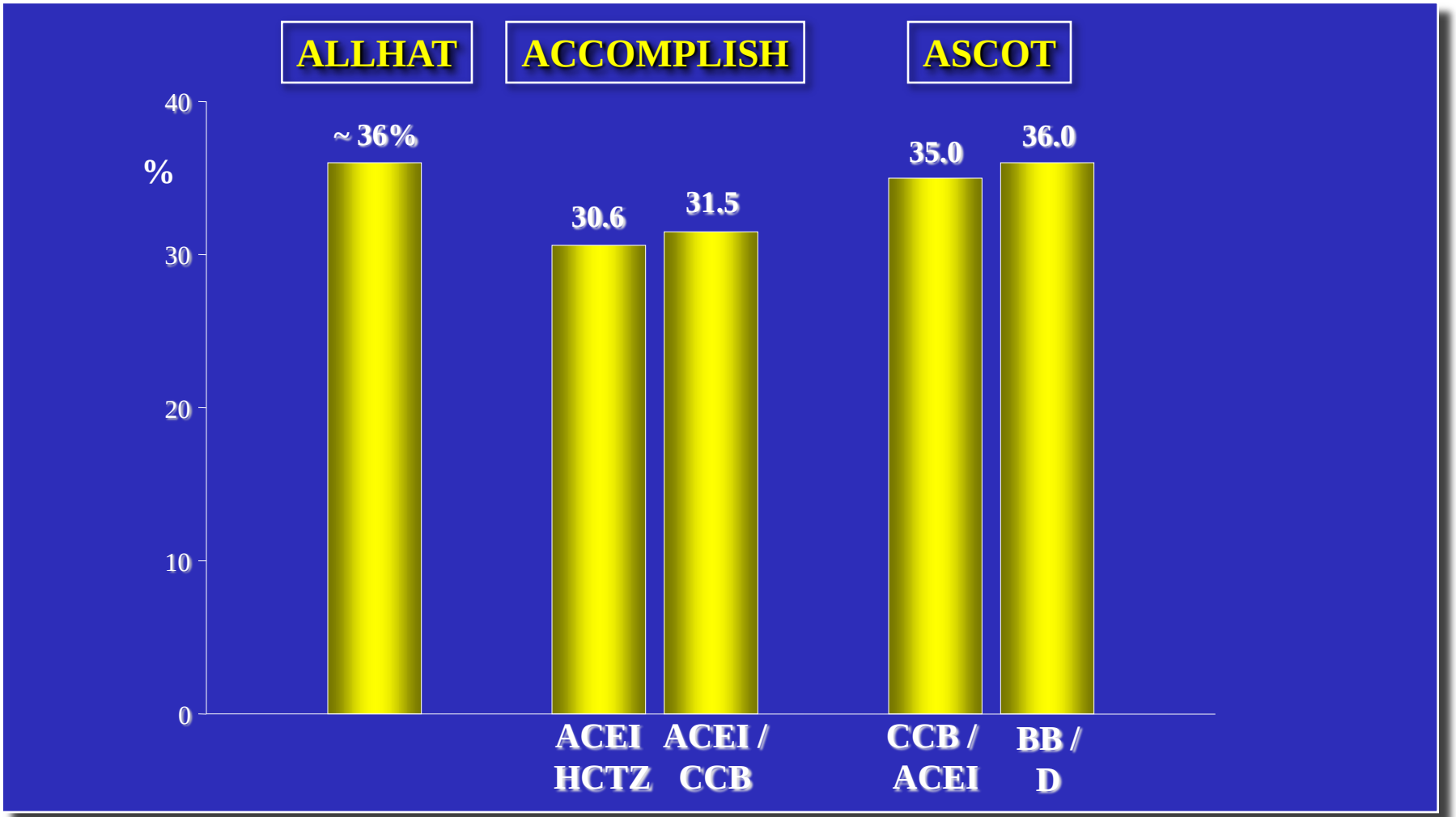


18 652 patients

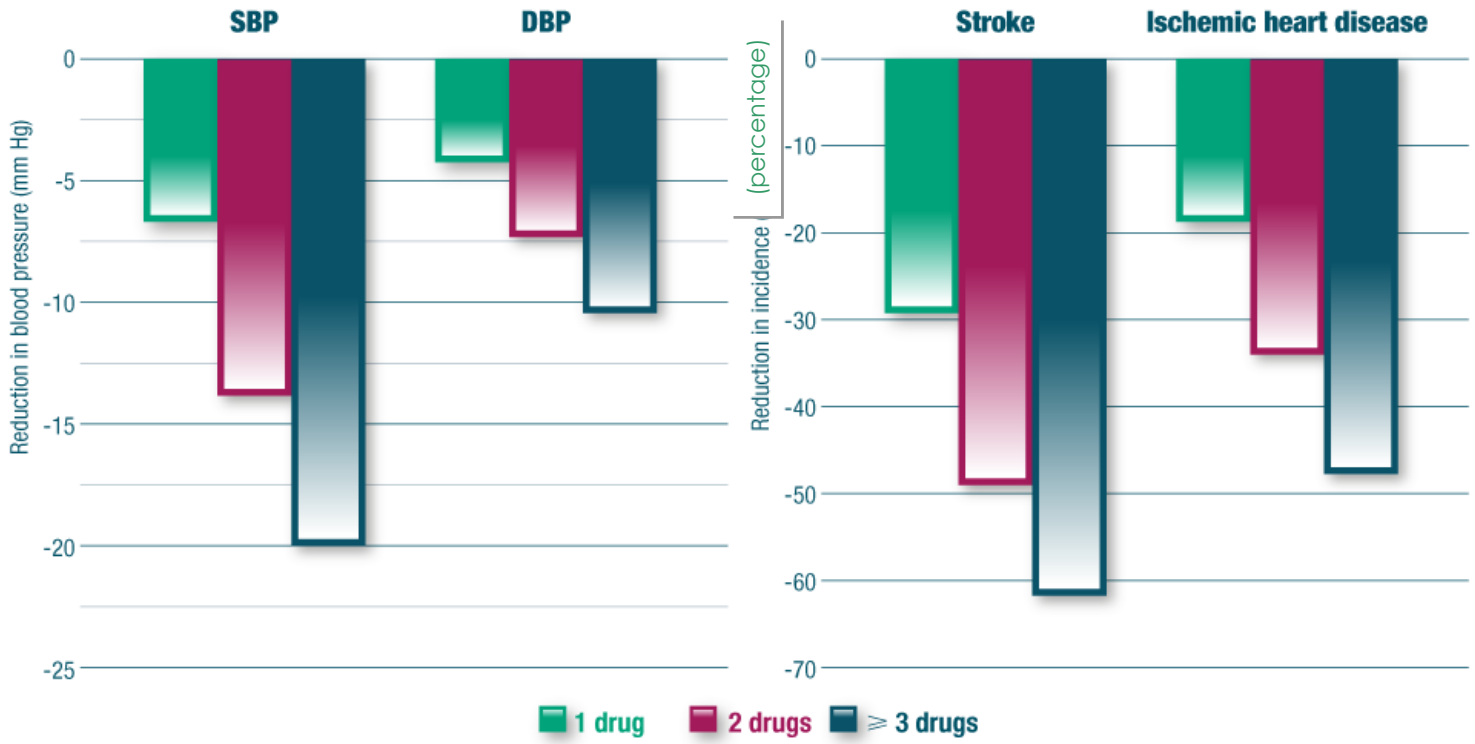
Northern Europe (Belgium, Germany, Sweden, Switzerland), **Southern Europe** (Greece, Italy, Spain, Turkey), **North Amerida** (Canada), **Latin America** (Columbia, Mexico, Peru), **Middle East** (Kuwait, Lebanon, Qatar, Saudi Arabia, UAE), **Asia** (Hong Kong, Indonesia, Korea, Singapore, Taiwan, Thailand, Vietnam, Australia)

Thomas M, Neuberger HR, Volpe M, et al. *J Hum Hypertens*. 2010;24:336-344.

Use of ≥ 3 Drugs in Some Major Antihypertensive Treatment Trials



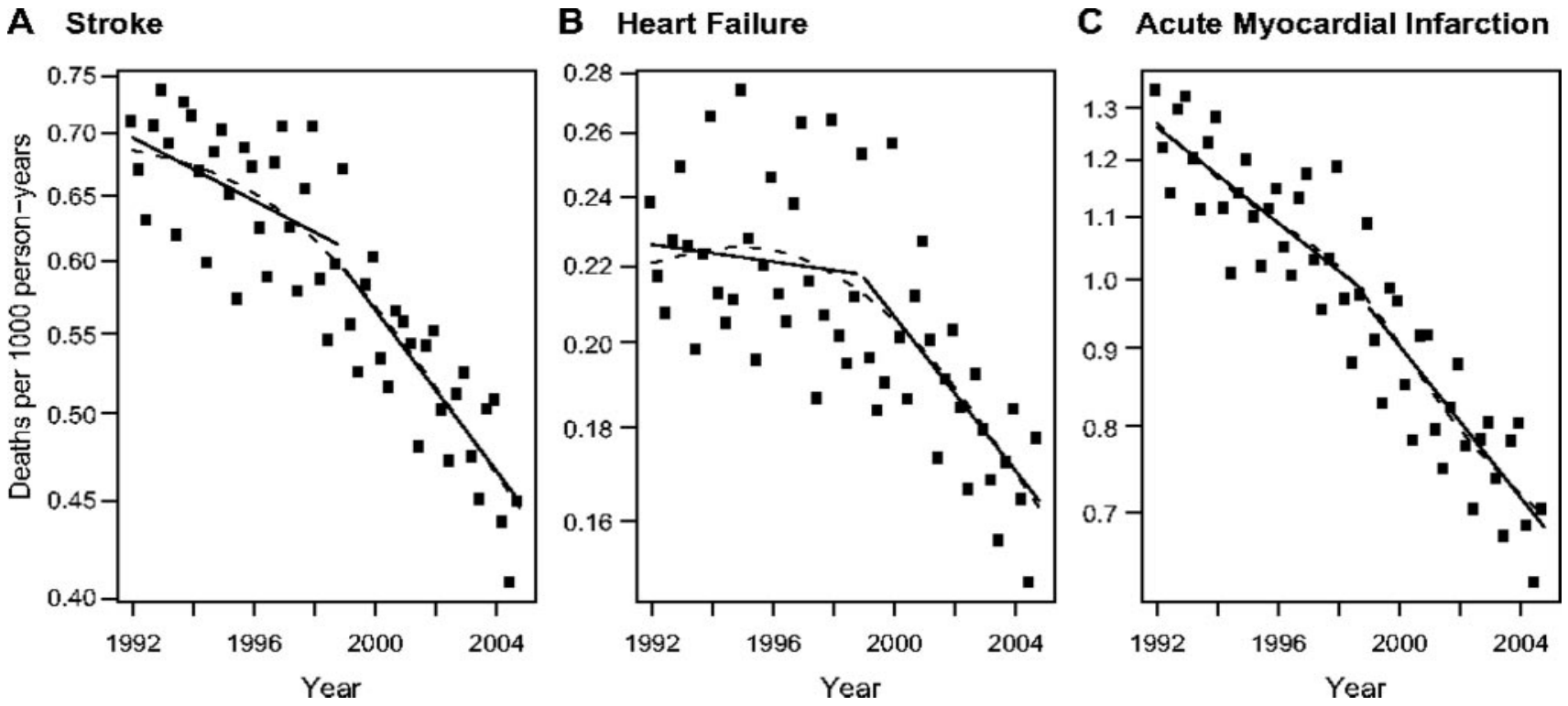
Triple-drug therapy goes further



Law M R, Wald N J, Morris J K, Jordan R E. *BMJ*. 2003;326:1427-1434

Increases in Antihypertensive Prescriptions and Reductions in Cardiovascular Events in Canada

Norm R.C. Campbell, Rollin Brant, Helen Johansen, Robin L. Walker, Andreas Wielgosz, Jay Onysko,Ru-Nie Gao, Christie Sambell, Stephen Phillips, Finlay A. McAlister; for the Canadian HypertensionEducation Program Outcomes Research Task Force



Hypertension. 2009;53:128-134

Increases in Antihypertensive Prescriptions and Reductions in Cardiovascular Events in Canada

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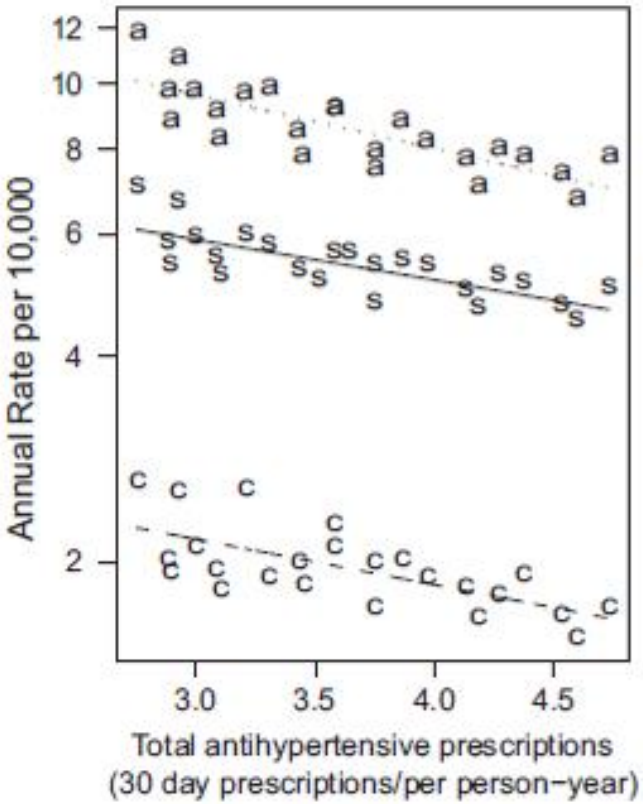
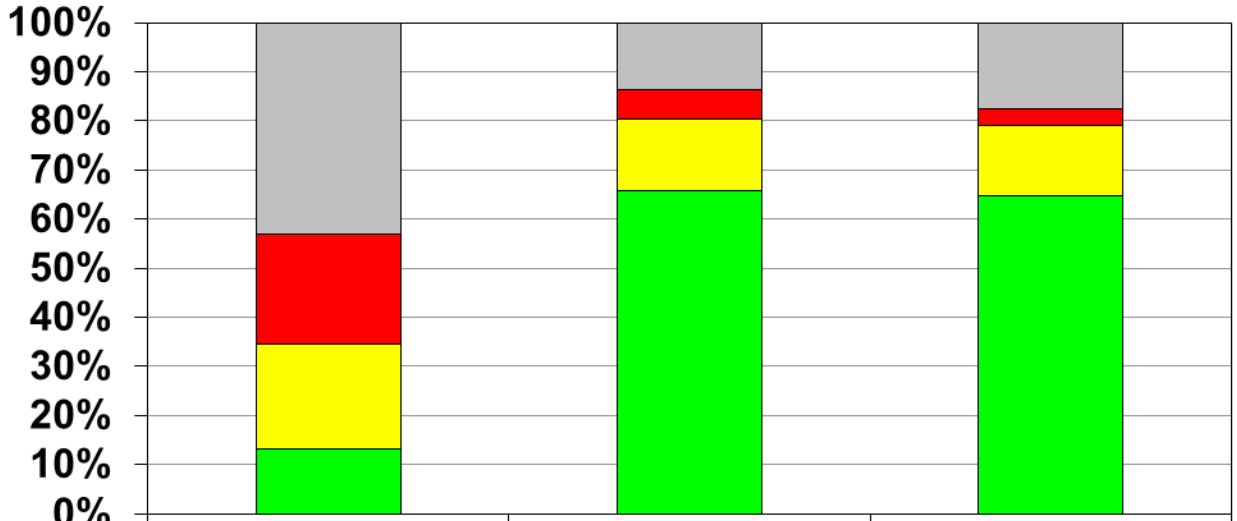


Figure 3. Age- and sex-adjusted mortality rates from stroke (s), HF (c), and AMI (a) in relationship to total antihypertensive prescriptions in Canada between 1996 and 2003. Antihypertensive prescriptions were expressed in 30-day prescriptions per person per year.

Hypertension. 2009;53:128-134

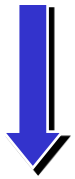
Improvements in BP control in Canada



	CHHS (1992)	ON-BP (2006)	CHMS (2009)
Unaware	43	13.7	17.4
Aware, Not Treated	22.4	5.8	3.5
Treated, Not Controlled	21.4	14.7	14.4
Treated and Controlled	13.2	65.7	64.6

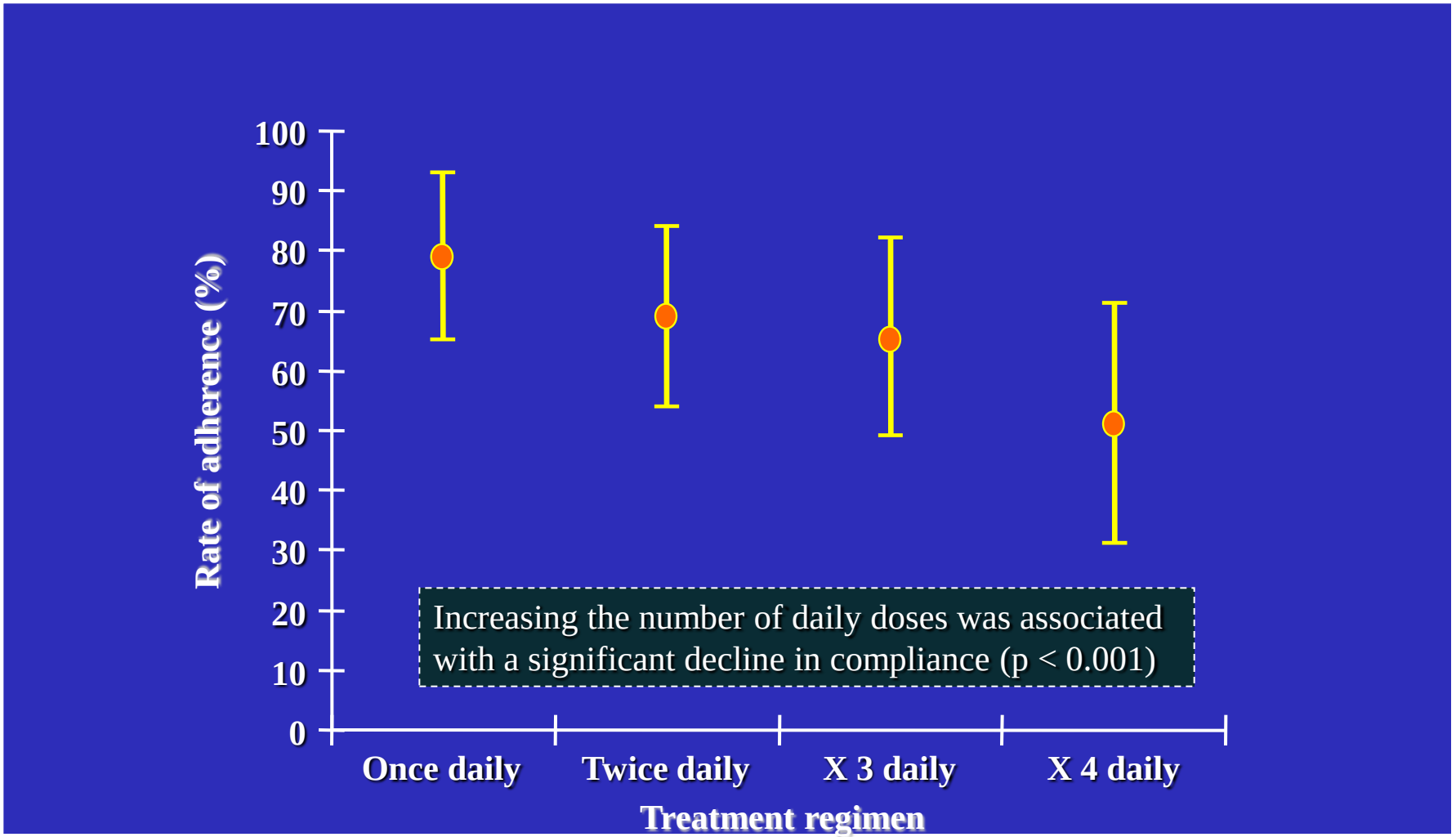
2013 ESH/ESC GUIDELINES
NICE GUIDELINES
FRENCH GUIDELINES

“ … three … drugs may be required in many cases”



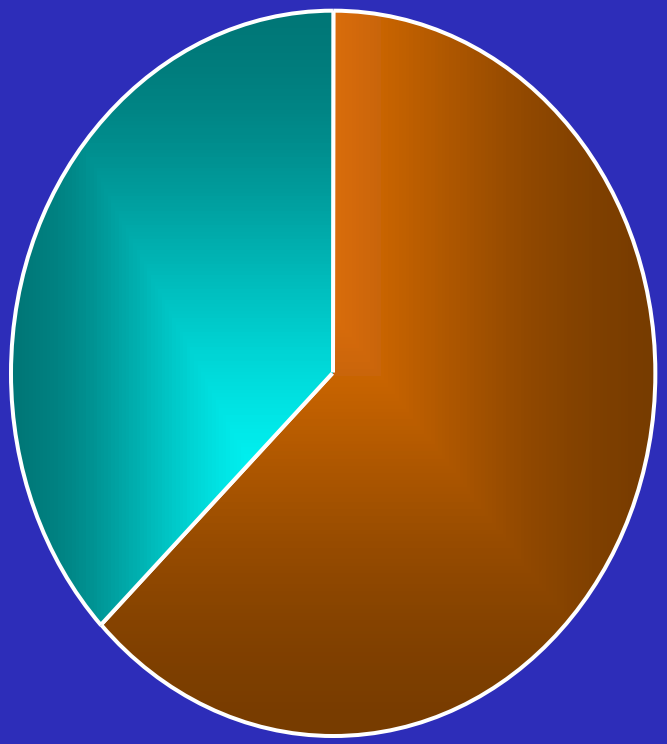
RAS-blocker + CCB + Diuretic

Compliance Usually Decreases as Pill Burden Increases



Claxton et al., Clin Ther 2001; 23: 1296-1310

Discontinuation of Antihypertensive Treatment in Lombardy (793000 patients with initially prescribed monotherapy*)



Discontinuers
62.8%

*** Discontinuation defined as no prescription renewal for ≥ 90 days**

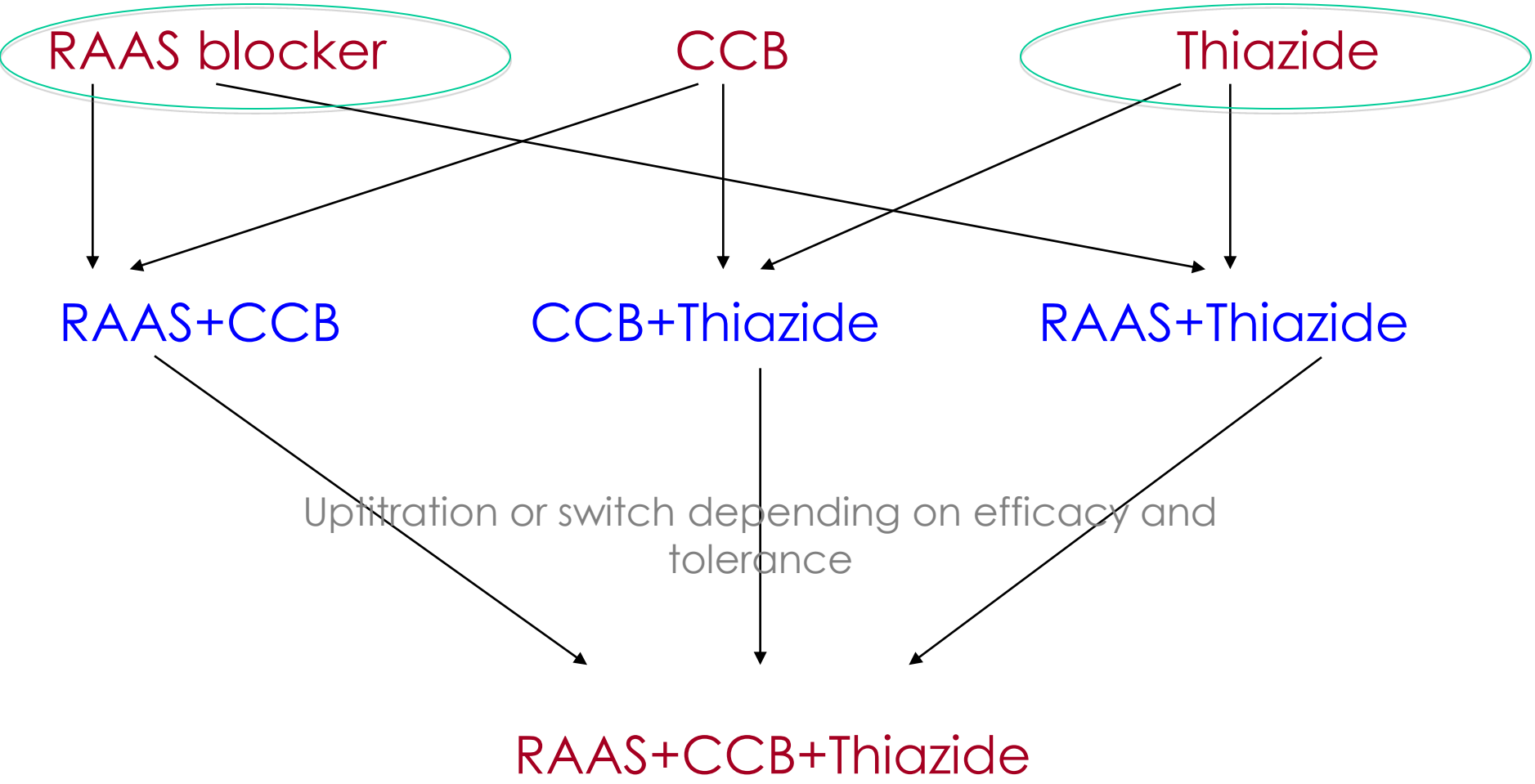
Corrao et al., Am J Hypertens 2012; 25: 549 - J Hypertens 2008; 26: 819

Adherence and CV risk

In patients (n=249504) continuing treatment the risk of coronary/cerebrovascular events (n=12016) was 37% less than in patients stopping treatment

Corrao J Hypertens 2011,29,610-618

Simple model of Uptitration



Choice of the cornerstones in HT treatment

Evidence versus Common opinions

Which class?
Which molecule?

Choice of the cornerstones in HT treatment

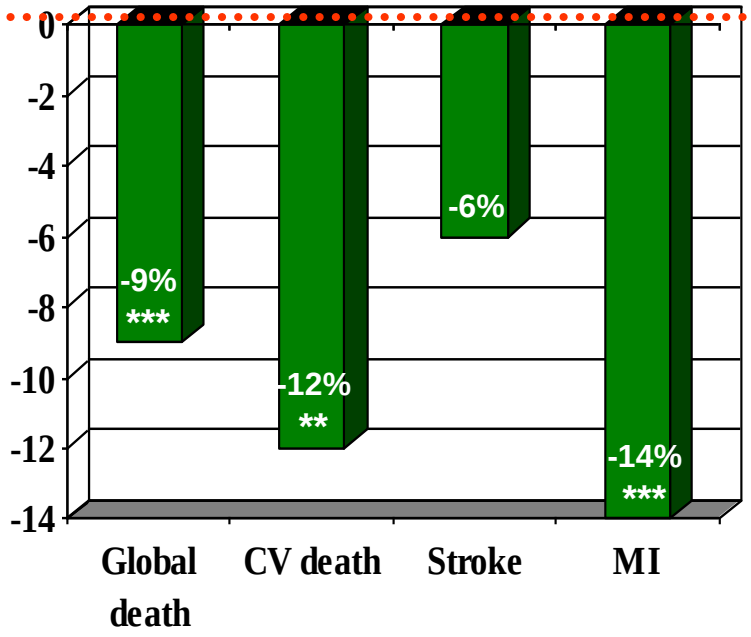
Evidence versus Common opinions

Which class?

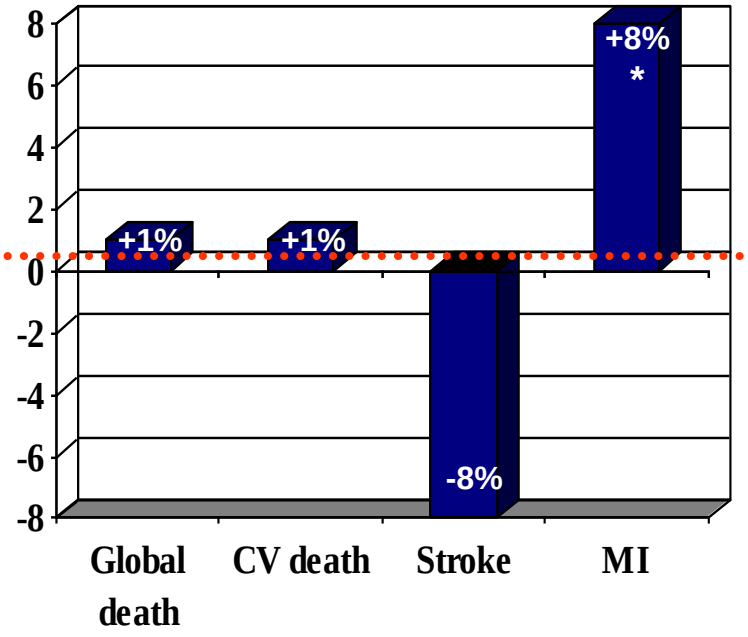
Which molecule?

ACE inhibitors or ARBs ?

ACE inhibitors vs comparators
(39 trials, n=150 943)



ARBs vs comparators
(11 trials, n=55 050)



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live

Strauss MH, Hall AS. Circulation. 2006;114:838-854.

Differential effects of ACE inhibitors and ARBs on the RAS

	ACE inhibitor	ARB	Effects
Renin	↑↑	↑↑↑	converts angiotensinogen to angiotensin I
Angiotensin II	↓↓	↑↑↑	AT_1 and AT_2 agonist
AT_1	↓↓	↓↓↓	vasoconstriction; increased norepinephrine, aldosterone, and vasopressin release; renal tubular sodium reabsorption; left ventricular hypertrophy; endothelial dysfunction; cardiac arrhythmias; cellular proliferation
AT_2	↓↓	↑↑	vasodilation, endothelial stabilization, reverse remodeling, antiproliferative effects, neuronal regeneration, cell differentiation (emerging data suggest activation might be deleterious)
Bradykinin	↑↑↑	↔	vasodilation augments renal plasma flow, increases nitric oxide and prostacyclin, ischemic preconditioning, stabilizes vascular permeability, cough, angioedema

Epstein BJ, Gums JG. *Ann Pharmacother* 2005.

Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147 020 patients from randomised trials

Sripal Bangalore, director of research,[1] assistant professor of medicine,[2] Sunil Kumar, fellow in cardiovascular medicine,[3] Jørn Wetterslev, chief physician,[4] Franz H Messerli, director, hypertension program; professor of clinical me

Trial	Events ARBs	Events Control	Relative risk (95% CI)	Weight (%)	Relative risk (95% CI)
Placebo					
CHARM-alternative[22]	75/1013	48/1015		3	1.57 (1.10 to 2.23)
CHARM-preserved[23]	57/1514	73/1509		4	0.78 (0.55 to 1.09)

WHAT IS ALREADY KNOWN ON THIS TOPIC

Angiotensin receptor blockers are important in the treatment of cardiovascular conditions

Previous studies have shown an increased risk of myocardial infarction with these drugs and have raised concern among physicians and patients

WHAT THIS STUDY ADDS

There is firm evidence to refute the hypothesis of angiotensin receptor blockers increasing the risk of myocardial infarction (ruling out even a 0.3% absolute increase)

Compared with controls (active treatment or placebo), angiotensin receptor blockers reduce the risk of stroke, heart failure, and new onset diabetes.

Despite lower blood pressure with angiotensin receptor blockers when compared with placebo, there also was no detectable beneficial effect for the outcome of myocardial infarction or cardiovascular mortality

Random effects overall: I^2=30.7%, P=0.055	2834/67 892	2088/67 659	100	0.99 (0.92 to 1.07)
Fixed effects overall				1.01 (0.96 to 1.06)
P=0.15 for interaction				

0.1 1 10

ARBs better Control better

Fig 2 |Angiotensin receptor blockers (ARBs) and myocardial infarction, stratified by comparison group (placebo *v* active treatment)

BMJ 2011;342:d2234

	Strauss (Circulation 2006)		Baker (Ann Intern Med 2009)		Bangalore (BMJ 2011)		van Vark (Eur Heart J 2012)		Savarese (JACC 2012)	
No studies/ N patients	34 / 123 681		8 / 37 148		37 / 147 020		20 / 158 998		26 / 108 212	
Main Inclusion criteria	RCTs comparing RAAS with placebo		RCTs comparing ACE inhibitor or ARB therapy with placebo or active control in patients with stable ischemic heart disease with preserved left ventricular function		RCTs, until August 2010, of ARBs compared with controls (placebo/active treatment)		>66% of the patients hypertensive. RAAS inhibitors vs other strategies Published between 2000-2011		double-blind RCTS comparing either an ARB or an ACE-I with placebo, excluding patients with HF	
Total Mortality	-12%	-6%	-13%	+5%	ND	0%	-10%	-1%	-9%	0%
CV Mortality	-16%	-5%	-17%	+2%	ND	-1%	-12% (p=0.051)	-4%	-10% (p=0.11)	+3% NS
Stroke	-17%	-16%	-22%	-17%	ND	-10%	ND	ND	-20%	-10%
MI	-18%	+5%	-17%	No data	ND	0%	ND	ND	-19%	-9.5% (p=0.09)
Heart Failure	ND	ND	ND	ND	ND	-13%	ND	ND	-21%	-10% NS
New onset diabetes	ND	ND	ND	ND	ND	-15%	ND	ND	-14%	-11%

First column: ACE results; Second Column ARBs results; **green** significant benefit; **white** : favorable trend; **red** : neutral or non favorable trend

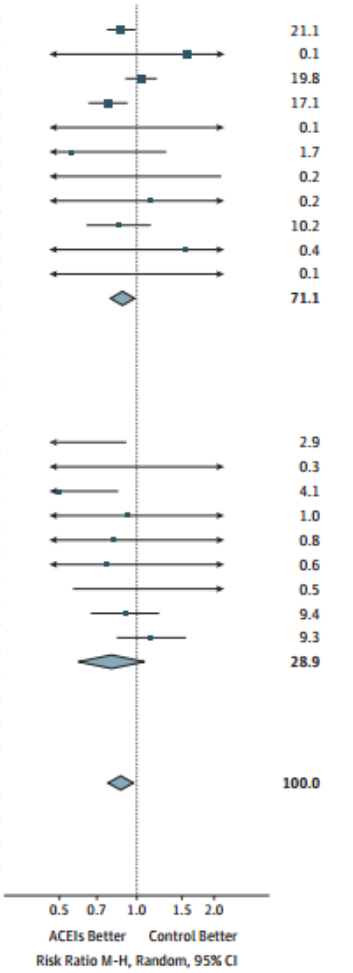
Effect of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on All-Cause Mortality, Cardiovascular Deaths, and Cardiovascular Events in Patients With Diabetes Mellitus

A Meta-analysis

Jun Cheng, MD; Wen Zhang, MMed; Xiaohui Zhang, MMed; Fei Han, MD; Xiayu Li, MD; Xuelin He, MD; Qun Li, MMed; Jianghua Chen, MMed

Figure 2. Angiotensin-Converting Enzyme Inhibitors (ACEIs) and All-Cause Mortality Stratified by Comparison Group (Placebo vs Active)

Study or Subgroup	ACEIs Events	ACEIs Total	Control Events	Control Total	Risk Ratio M-H, Random, 95% CI	Weight, %
Placebo						
ADVANCE study,[34] 2007	408	5569	471	5571	0.87 (0.76-0.98)	21.1
Bauer et al,[41] 1992	1	18	0	15	2.53 (0.11-57.83)	0.1
DIABHYCAR study,[14] 2004	334	2443	324	2469	1.04 (0.90-1.20)	19.8
HOPE study,[30] 2000	196	1808	248	1769	0.77 (0.65-0.92)	17.1
Laffel et al,[42] 1995	1	70	0	73	3.13 (0.13-75.49)	0.1
Lewis et al,[25] 1993	8	207	14	202	0.56 (0.24-1.30)	1.7
Nankervis et al,[43] 1998	0	17	3	14	0.12 (0.01-2.13)	0.2
Parving et al,[44] 1989	1	15	1	17	1.13 (0.08-16.59)	0.2
PERSUADE substudy,[26] 2005	73	721	93	781	0.85 (0.64-1.14)	10.2
Ravid et al,[38] 1998	3	77	2	79	1.54 (0.26-8.96)	0.4
Sano et al,[45] 1994	1	31	0	31	3.00 (0.13-70.92)	0.1
Subtotal		**10976**		**11021**	**0.89 (0.79-0.99)**	**71.1**
Total Events	**1026**		**1156**			
Heterogeneity: $\tau^2=0.01$; $\chi^2=12.47$, $df=10$, $P=.25$; $I^2=20\%$						
Test for overall effect: $Z=2.13$, $P=.03$						
Active						
ABCD study,[33] 1998	13	235	27	235	0.48 (0.25-0.91)	2.9
Bakris et al,[40] 1996	1	18	5	34	0.38 (0.05-2.99)	0.3
CAPPP study,[29] 2001	20	309	34	263	0.50 (0.30-0.85)	4.1
DETAIL study,[54] 2004	6	130	6	120	0.92 (0.31-2.78)	1.0
FACET study,[31] 1998	4	189	5	191	0.81 (0.22-2.96)	0.8
Fogari et al,[37] 2002	3	102	4	103	0.76 (0.17-3.30)	0.6
JMIC-B study,[27] 2004	5	173	2	199	2.88 (0.57-14.64)	0.5
STOP-2 substudy,[24] 2000	56	235	67	253	0.90 (0.66-1.22)	9.4
UKPDS 39 study,[32] 1998	75	400	59	358	1.14 (0.83-1.55)	9.3
Subtotal		**1791**		**1756**	**0.80 (0.60-1.08)**	**28.9**
Total Events	**183**		**209**			
Heterogeneity: $\tau^2=0.06$; $\chi^2=13.26$, $df=8$, $P=.10$; $I^2=40\%$						
Test for overall effect: $Z=1.45$, $P=.15$						
Total		**12767**		**12777**	**0.87 (0.78-0.98)**	**100.0**
Total Events	**1209**		**1365**			
Heterogeneity: $\tau^2=0.01$; $\chi^2=25.79$, $df=19$, $P=.14$; $I^2=26\%$						
Test for overall effect: $Z=2.38$, $P=.02$						



-13%

JAMA 2014

Effect of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on All-Cause Mortality, Cardiovascular Deaths, and Cardiovascular Events in Patients With Diabetes Mellitus

A Meta-analysis

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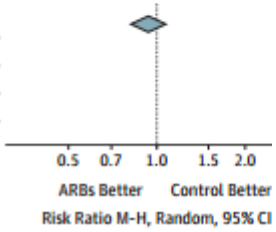
Figure 3. Angiotensin II Receptor Blockers (ARBs) and All-Cause Mortality Stratified by Comparison Group (Placebo vs Active)

Conclusions

Our meta-analysis shows that ACEIs reduce all-cause mortality, CV mortality, and major CV events in patients with DM, whereas ARBs have no beneficial effects on these outcomes. Thus, ACEIs should be considered as first-line therapy to limit the excess mortality and morbidity in this population.

Total		**8950**	**8963**	**0.94 (0.82-1.08)**
Total Events	**540**	**576**		
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 14.01$, $df = 11$, $P = .23$; $I^2 = 22\%$				
Test for overall effect: $Z = 0.85$, $P = .39$				



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Conclusions

Our meta-analysis shows that ACEIs reduce all-cause mortality, CV mortality, and major CV events in patients with DM, whereas ARBs have no beneficial effects on these outcomes. Thus, ACEIs should be considered as first-line therapy to limit the excess mortality and morbidity in this population.

Impact of renin–angiotensin system inhibitors on mortality and major cardiovascular endpoints in hypertension: A number-needed-to-treat analysis

Jasper J. Brugts [a], Laura van Vark [a], Martijn Akkerhuis [a], Michel Bertrand [b], Kim Fox [c,d], Jean-Jacques Mourad [e,f,1], Eric Boersma [a,*,1]

Effect of renin angiotensin aldosterone system (RAAS) inhibition on all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, and a composite of myocardial infarction and stroke over 4.3 years.

	Incidence rate (events/patient-year)		HR (95% CI)	NNT (2.5th to 97.5th percentile)
	Control	Active		
All-cause mortality				
RAAS inhibitor	0.0252	0.0233	0.954 (0.91 to 0.99)	113 (85 to 168)
ACE inhibitor	0.0255	0.022	0.905 (0.84 to 0.97)	67 (53 to 92)
ARB	0.0249	0.0246	0.991 (0.94 to 1.04)	335 (−4341 to 5076)
Cardiovascular mortality				
RAAS inhibitor	0.0117	0.0104	0.934 (0.87 to 1.00)	170 (126 to 259)
ACE inhibitor	0.012	0.0103	0.884 (0.78 to 1.01)	116 (88 to 172)
ARB	0.0111	0.0104	0.969 (0.90 to 1.05)	409 (−3034 to 4431)
Myocardial infarction				
RAAS inhibitor	0.013	0.0107	0.956 (0.89 to 1.02)	117 (95 to 154)
ACE inhibitor	0.0148	0.012	0.921 (0.86 to 0.99)	80 (65 to 105)
ARB	0.0094	0.0092	1.004 (0.91 to 1.11)	338 (−4184 to 5427)
Stroke				
RAAS inhibitor	0.0137	0.0125	0.912 (0.83 to 1.00)	203 (136 to 404)
ACE inhibitor	0.0092	0.009	0.923 (0.78 to 1.09)	337 (165 to 1752)
ARB	0.0196	0.0179	0.902 (0.80 to 1.01)	131 (83 to 308)
Composite of myocardial infarction and stroke				
RAAS inhibitor	0.0246	0.0227	0.927 (0.87 to 0.99)	136 (96 to 235)
ACE inhibitor	0.0233	0.0204	0.896 (0.80 to 1.01)	86 (64 to 131)
ARB	0.0267	0.025	0.947 (0.86 to 1.04)	157 (89 to 567)

International Journal of Cardiology 181 (2015) 425–429

Choice of the cornerstones in HT treatment

Evidence versus Common opinions

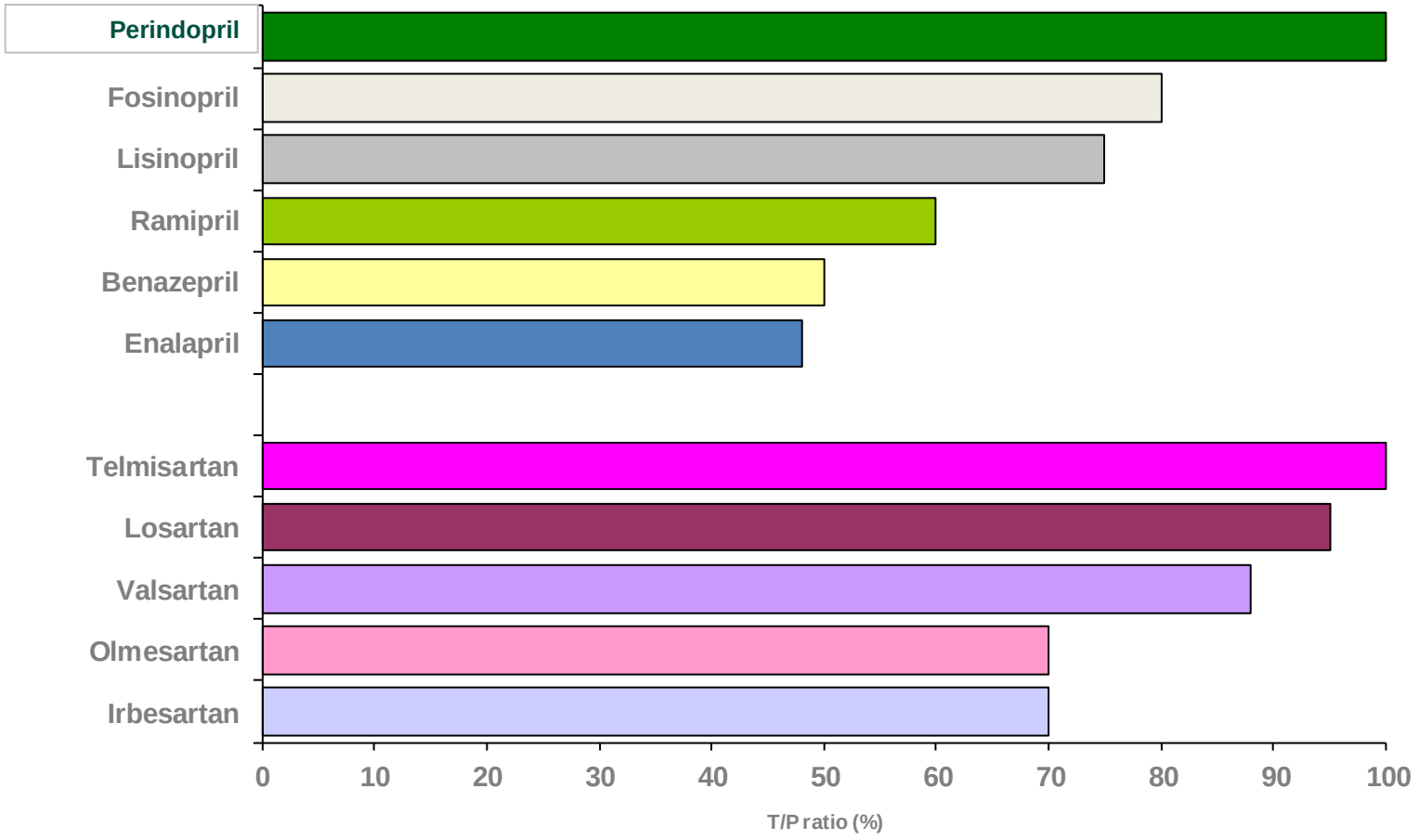
Which class?

Which molecule?

Evidence versus conventional opinion is the vision of a mean effect adapted to the antihypertensive treatment?

- Antihypertensive drugs are so different
- Even in the same drug class, there are huge differences
  - In terms of duration of action
  - In terms of dosages

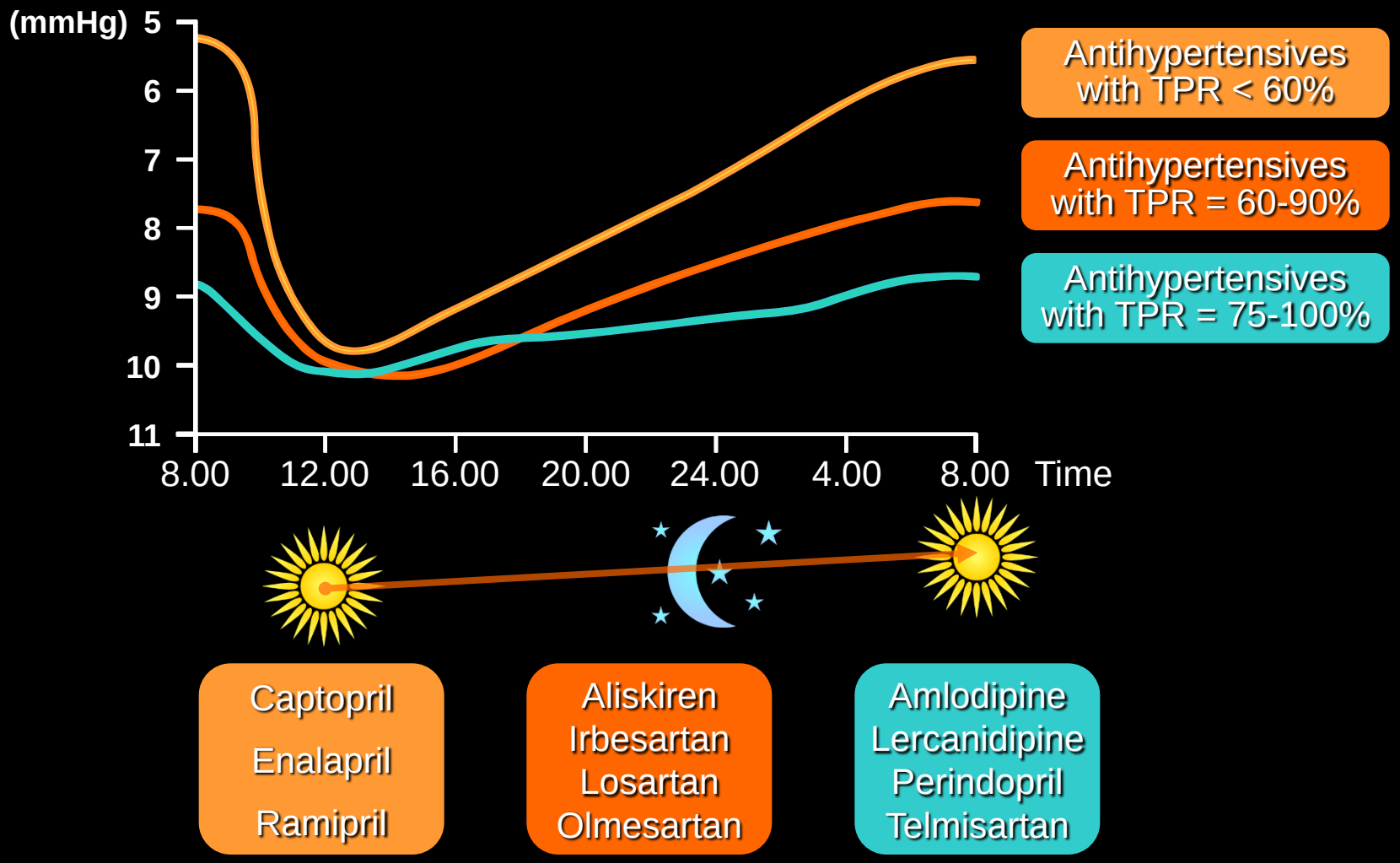
24 hour antihypertensive efficacy: trough-to-peak ratio



1. Physicians Desk Reference. NJ: Medical Economics Company; 2008. 2. Diamant H and Vincent HH. Lisinopril versus enalapril: evaluation of trough:peak ratio by ambulatory blood pressure monitoring. *J Hum Hypertens*. 1999;13:405-412. 3. Martell M, Gill B, Marin R, et al. Trough to peak ratio of once-daily lisinoprol and twice-daily captopril in patients with essential hypertension. *J Hum Hypertens*. 1998;12:69-72. 4. Hermida RC, Calvo C, Ayala DE, et al. Administration time-dependent effects of valsartan on ambulatory blood pressure in hypertensive subjects. *Hypertension*. 2000;42:282-290.

Importance of trough/peak ratio > 75%

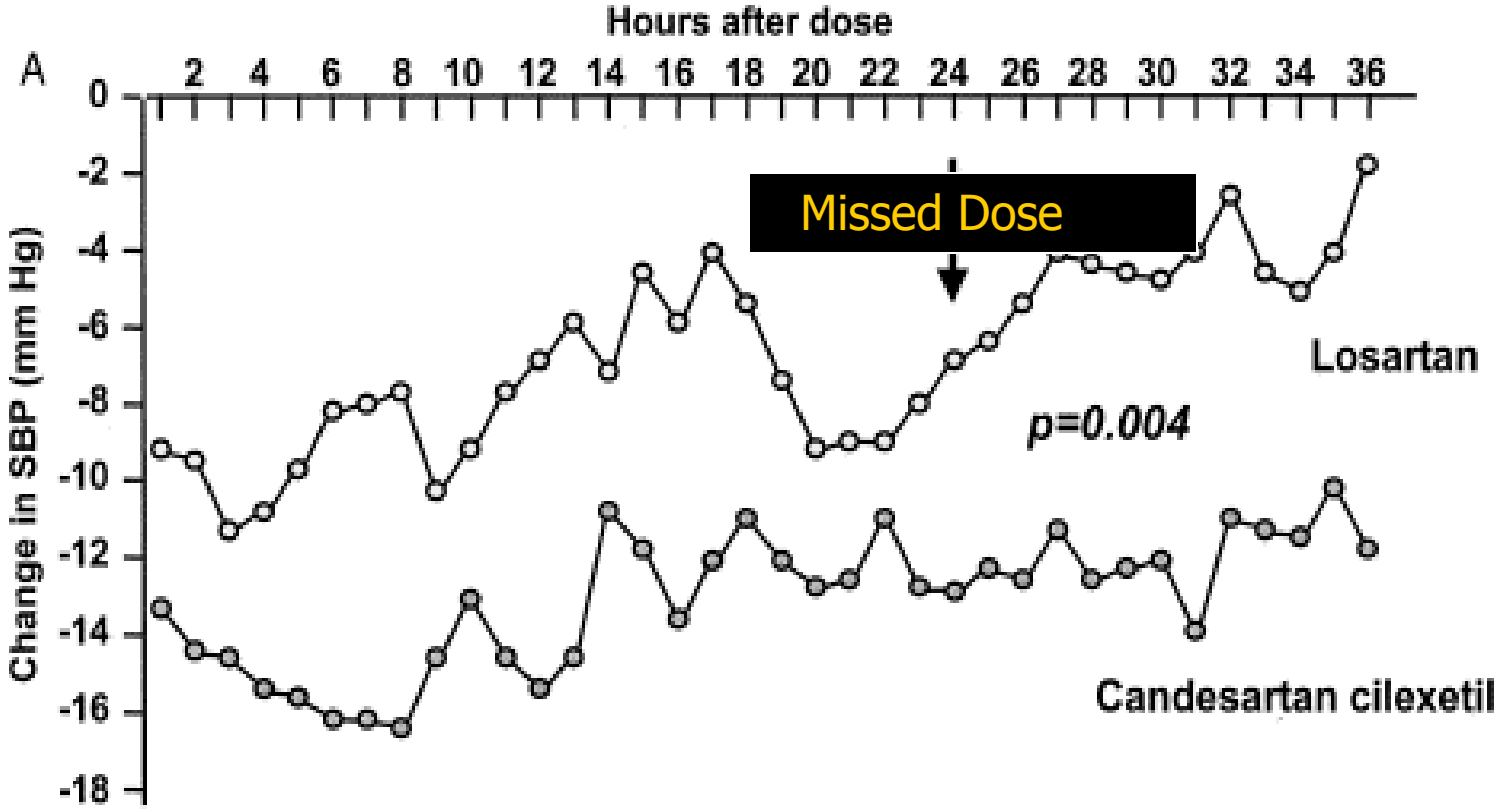
24 h blood pressure reduction after administration



Montvale NJ. Physicians Desk Reference. Medical Economics Company 2008.

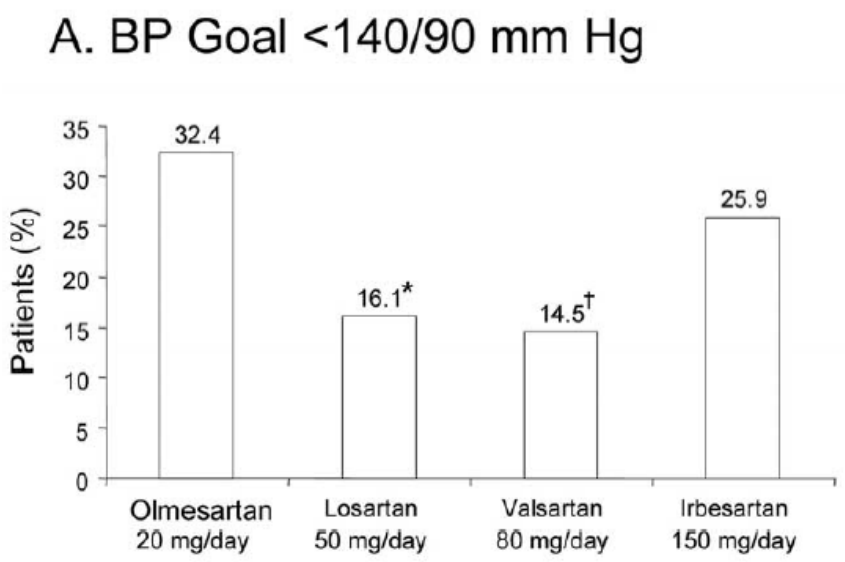
Effects of Two ARBs Approved for Once Daily Dosing on 24 Hour Blood Pressure

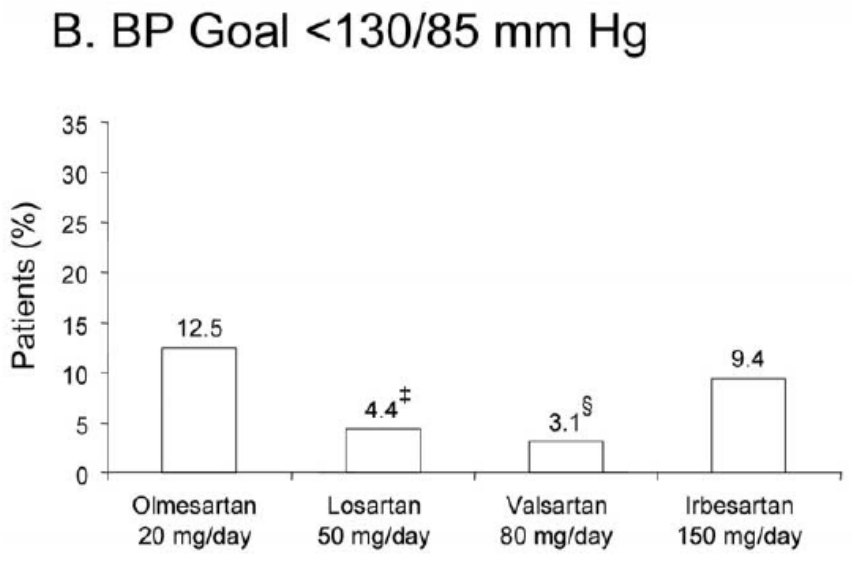
(Mancia et al AJC 1999: 84; 28S)



Role of Angiotensin Receptor Blockers as Monotherapy in Reaching Blood Pressure Goals

Suzanne Oparil, Tonous N. Silfani, and J. Findlay Walker





Am J Hypertens 2005

Differences between diuretics ?

Use of Diuretics in Patients with Hypertension

Michael E. Ernst and Marvin Moser.

Table 1. Pharmacokinetic Characteristics of the Thiazide Diuretics Approved for Use in the United States.*

Diuretic†	Relative Carbonic Anhydrase Inhibition‡	Oral Bioavailability	Volume of Distribution	Protein Binding	Route of Elimination	Elimination Half-Life
		percent	*liters per kilogram*	*percent*		*hr*
Thiazide-type						
Chlorothiazide	++	15–30	1	70	100% Renal	1.5–2.5
Hydrochlorothiazide	+	60–70	2.5	40	95% Renal	9–10
Methychlothiazide	—	—	—	—	Hepatically metabolized	—
Polythiazide	+	—	—	—	25% Renal	26
Bendroflumethiazide	0	90	1.0–1.5	94	30% Renal	9
Thiazide-like						
Chlorthalidone	+++	65	3–13	99	65% Renal	50–60
Metolazone	+	65	113 (total)§	95	80% Renal	8–14
Indapamide	++	93	25 (total)§	75	Hepatically metabolized	14

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Are all diuretics the same?

Tableau 1. Baisse de la pression artérielle systolique (PAS, intervalle de confiance 95%, mmHg) et diastolique (PAD) induite par l'hydrochlorothiazide (HCTZ) ou l'indapamide SR administrés en monothérapie[15]

*Nombre de malades.

	n*	PAS	PAD
HCTZ (mg/jour)			
• ≤25	317	-18,88 (-20,84, -16,92)	-11,01 (-11,89, -10,13)
• 50	56	-19,3 (-22,6-16,00)	-14,00 (-15,96,-12,04)
Indapamide SR	265	-22,23 (-23,88,-20,58)	-11,72 (-12,75,-10,69)

TABLEAU 1
Diurétiques : durée d'action selon la dose

Diurétiques	Dose (mg)	Durée d'action (heures)
Thiazidique		
Chlortalidone	12,5-50	24-72
HCTZ	12,5-50	8-15
Indapamide	1,25-5	18-24
Chlorothiazide	125-500	6-12
De l'anse		
Furosémide	20-80	6-8
Epargneur potassique		
Triamtérène	50-100	7-9
Amiloride	5-10	24

Are diuretics similar ?

Consequently, the GDG recommended that when thiazide-type diuretics are used for the treatment for primary hypertension, thiazide-like diuretics, e.g. chlortalidone (12.5mg -25mg od) or indapamide (1.5mg SR or 2.5mg o.d.) should be preferred to conventional thiazide diuretics, e.g. bendroflumethiazide or hydrochlorthiazide. The GDG did not consider it necessary to recommend that those people already treated with low dose BFZ and in whom blood pressure is controlled, should be switched to CTD or IND. However, when new diuretic therapy was to be initiated, then CTD or IND should be preferred.

Conclusions

Combination treatment is a true need in many patients even in primary prevention.

Concept of therapeutic debt in many countries

FDCs should allow a vast majority of hypertensive patients to be treated by a single pill

The choice of the RAAS inhibitor should be based on proven evidence instead of powerful promotion

Some datas support differences between thiazides that could influence prognosis