Controversy in Angiotensin Receptor Blockers - Myocardial Infarction Paradox

고려대 구로병원 순환기내과

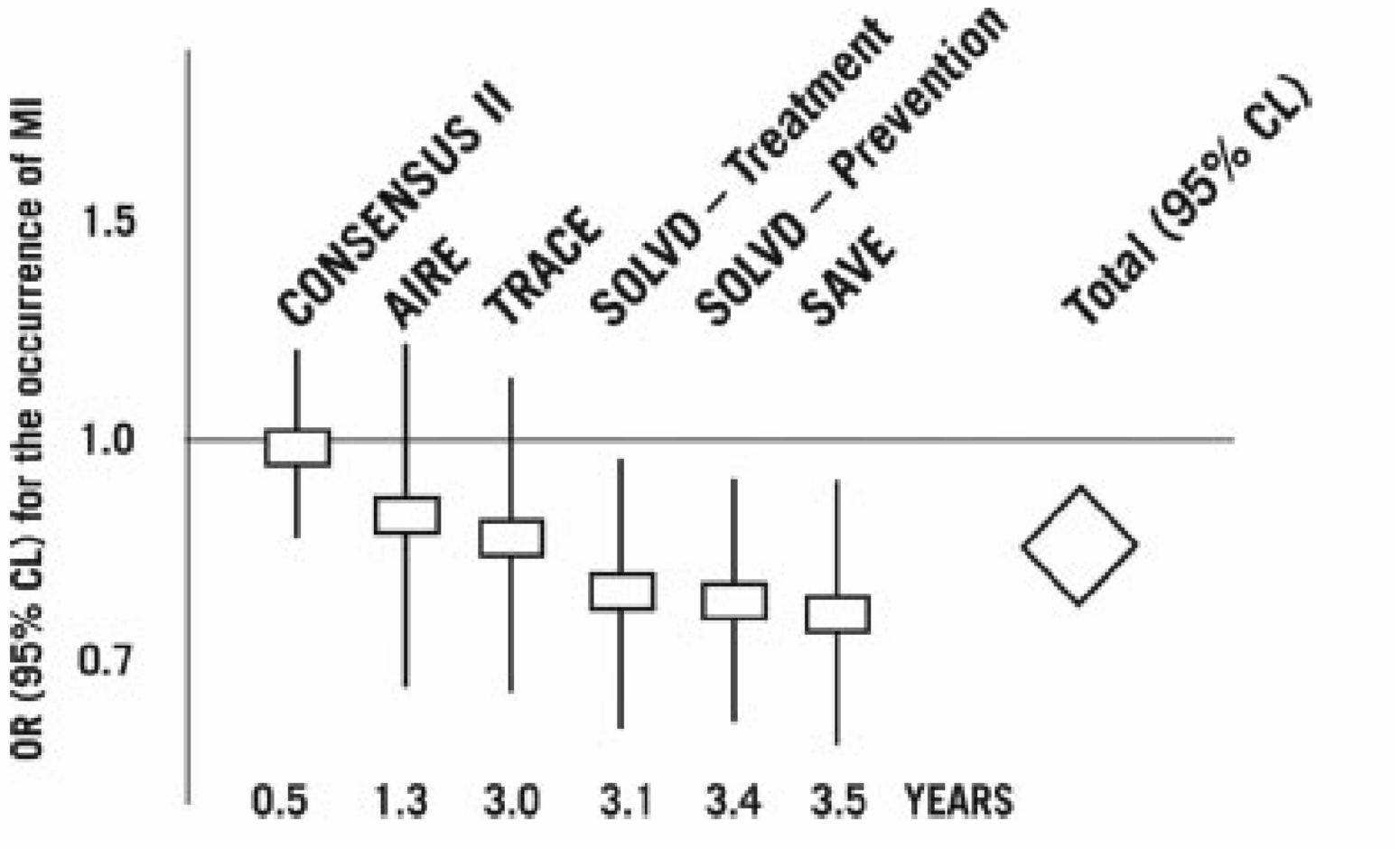
박 창 규

"To know that we know what we know, and to know that we do not know what we do not know, that is true knowledge."

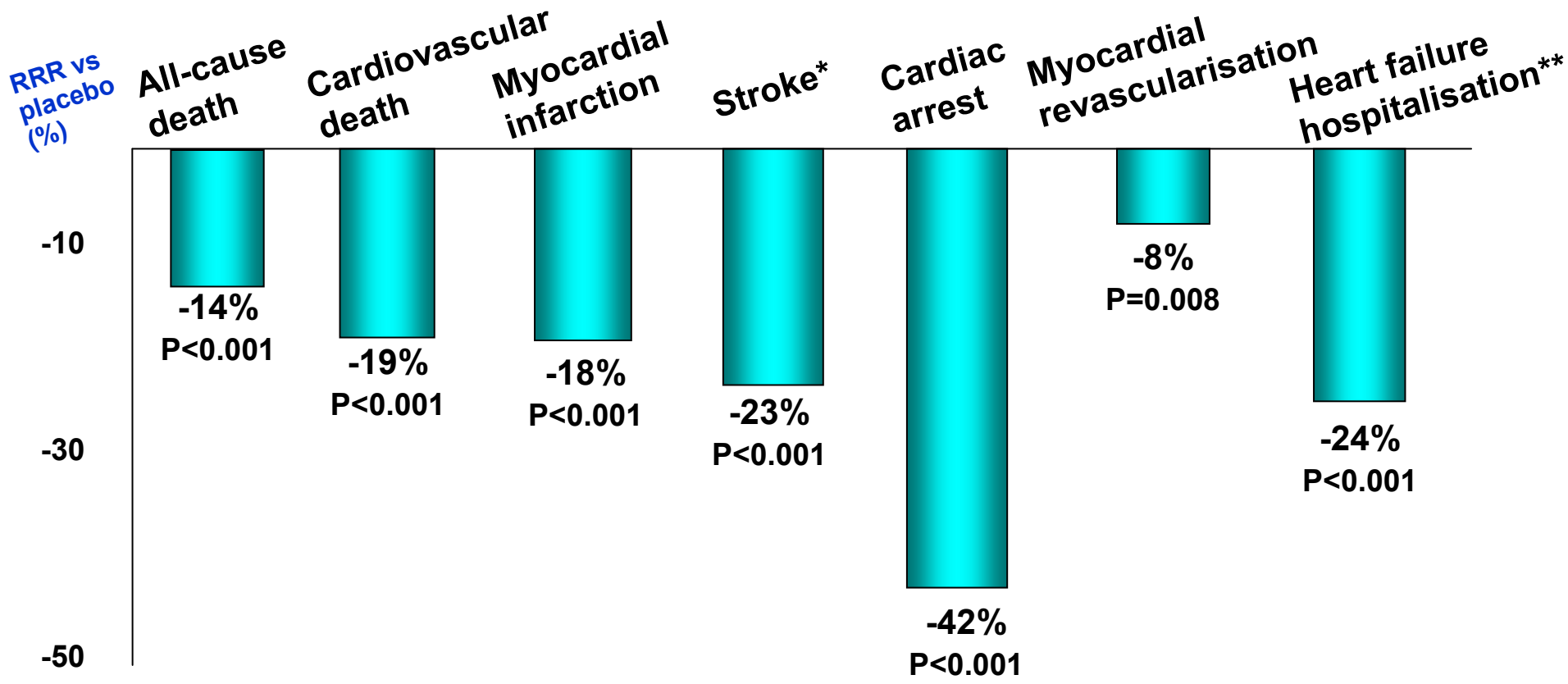
—Copernicus (1473–1543)

ACEi v. placebo

Effect on MI by trial duration



Summary:Meta-analysis of ACE inhibitor trials in CAD patients *without* HF or LV dysfunction



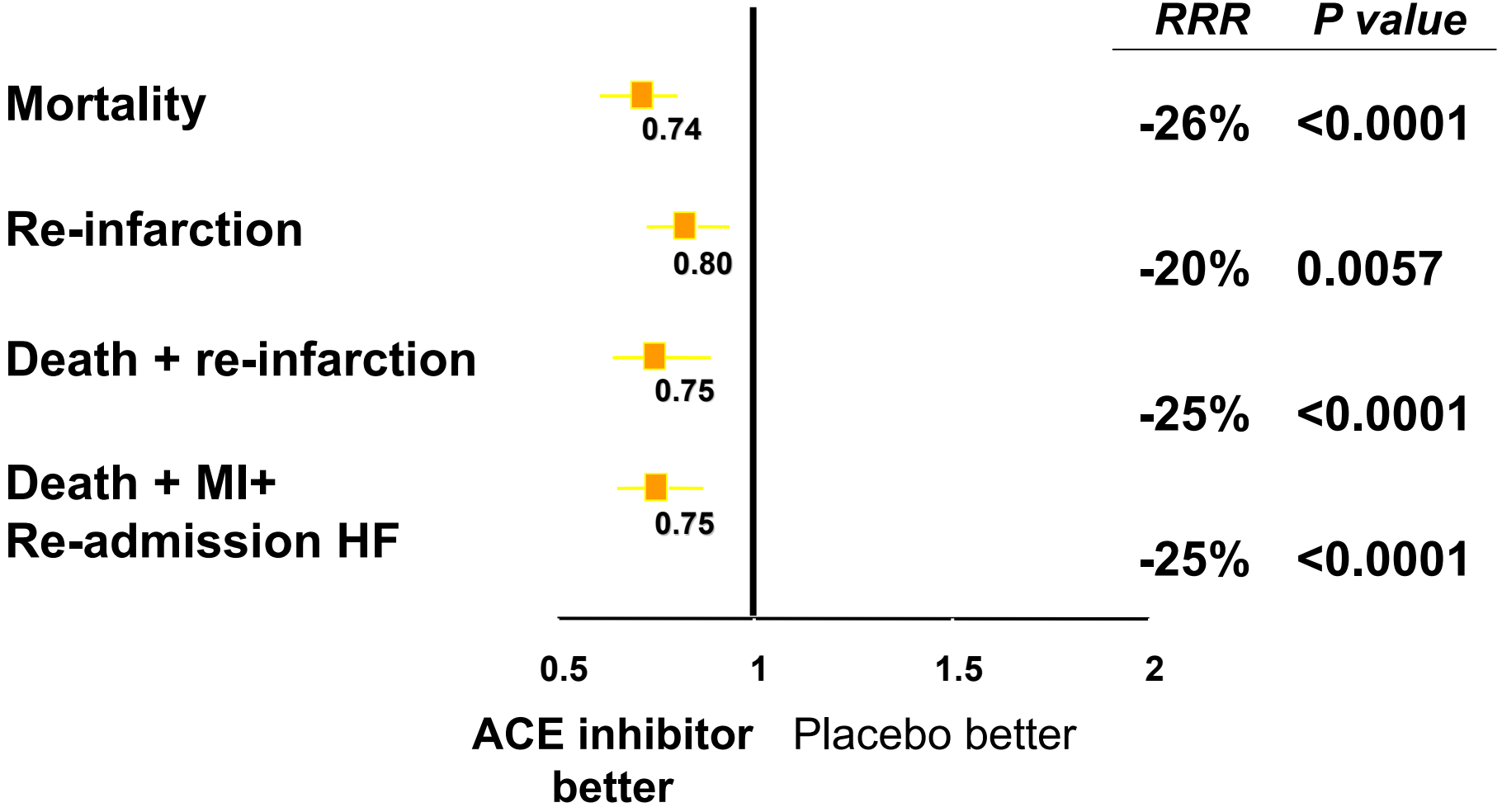
* End point not reported in QUIET

** End point not reported in PEACE and CAMELOT

Danchin N et al. *Arch Int Med*. 2006;166:787-796.

Long-term benefits of ACE inhibitors after AMI

Overview of SAVE - AIRE - TRACE (n=5 966)



Flather MD et al. *Lancet* 2000;355:1575-81

CONTROVERSIES IN CARDIOVASCULAR MEDICINE

Do angiotensin receptor blockers increase the risk of myocardial infarction?

Angiotensin Receptor Blockers May Increase Risk of Myocardial Infarction

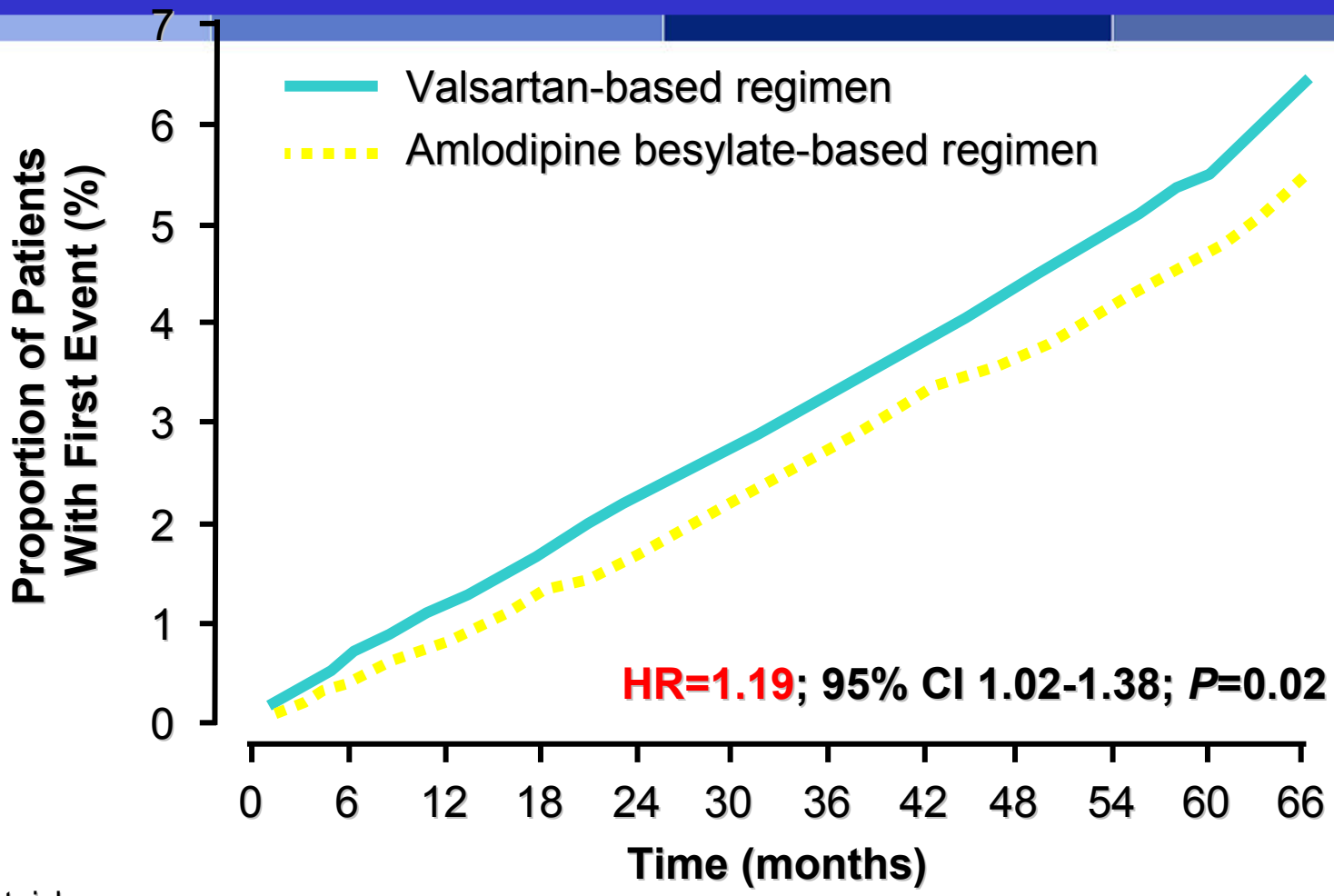
Unraveling the ARB-MI Paradox

Martin H. Strauss, MD, FRCPC; Alistair S. Hall, MB ChB, PhD, FRCP(UK)

Circulation 2006;114;838-854

Defining the ARB-MI Paradox

VALUE: Fatal and Non-Fatal Myocardial Infarction



Number at risk

Valsartan	7649	7499	7458	7319	7177	7016	6853	6680	6504	6078	3864	1520
Amlodipine besylate	7596	7497	7458	7332	7205	7065	6905	6727	6562	6141	3840	1532

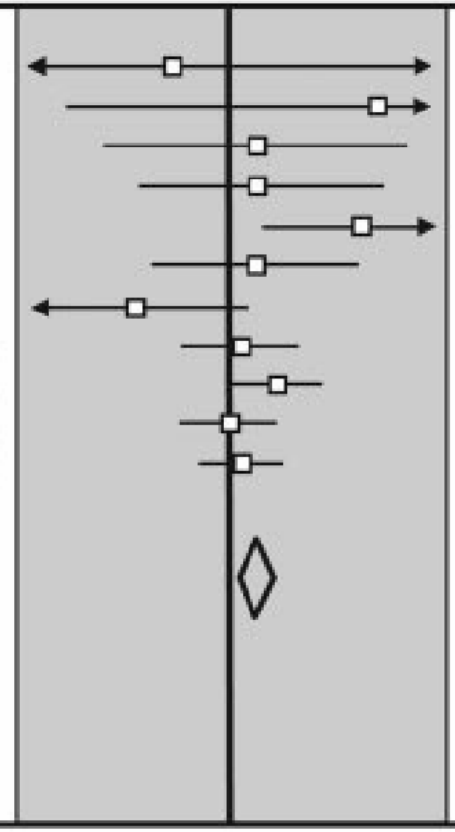
Julius S et al. *Lancet*. June 2004;363.

ARB v. Comparator

IDNT, CHARM-Alternative, SCOPE, RENAAL, LIFE, VALUE, ELITE I, ELITE II, DETAIL, OPTIMAAL, and VALIANT

Trial	ARB n/N (MI)	Control n/N (MI)	Odds Ratio 95% CI	Weight %	Odds Ratio 95% CI
ELITE	3 / 352	4 / 370		0.25	0.79 (0.17 to 3.54)
DETAIL	9 / 120	6 / 130		0.34	1.68 (0.58 to 4.86)
ELITE II	31 / 1,578	28 / 1,574		1.78	1.11 (0.66 to 1.85)
IDNT	39 / 579	66 / 1,136		2.69	1.17 (0.78 to 1.76)
CHARM-Alt	75 / 1013	48/ 1,015		2.87	1.61 (1.11 to 2.34)
SCOPE	70 / 2,477	63 / 2,460		3.97	1.11 (0.78 to 1.56)
RENAAL	50 / 751	68 / 762		4.08	0.73 (0.50 to 1.06)
LIFE	198 / 4,605	188 / 4,588		11.66	1.05 (0.86 to 1.29)
VALUE	369 / 7,649	313 / 7,596		19.34	1.18 (1.01 to 1.38)
OPTIMAAL	384 / 2,744	379 / 2,733		21.13	1.01 (0.87 to 1.18)
VALIANT	587 / 4,909	559 / 4,909		31.84	1.06 (0.93 to 1.20)
TOTAL	**26,777**	**27,273**		**1.08**	*(1.01 to 1.16)*

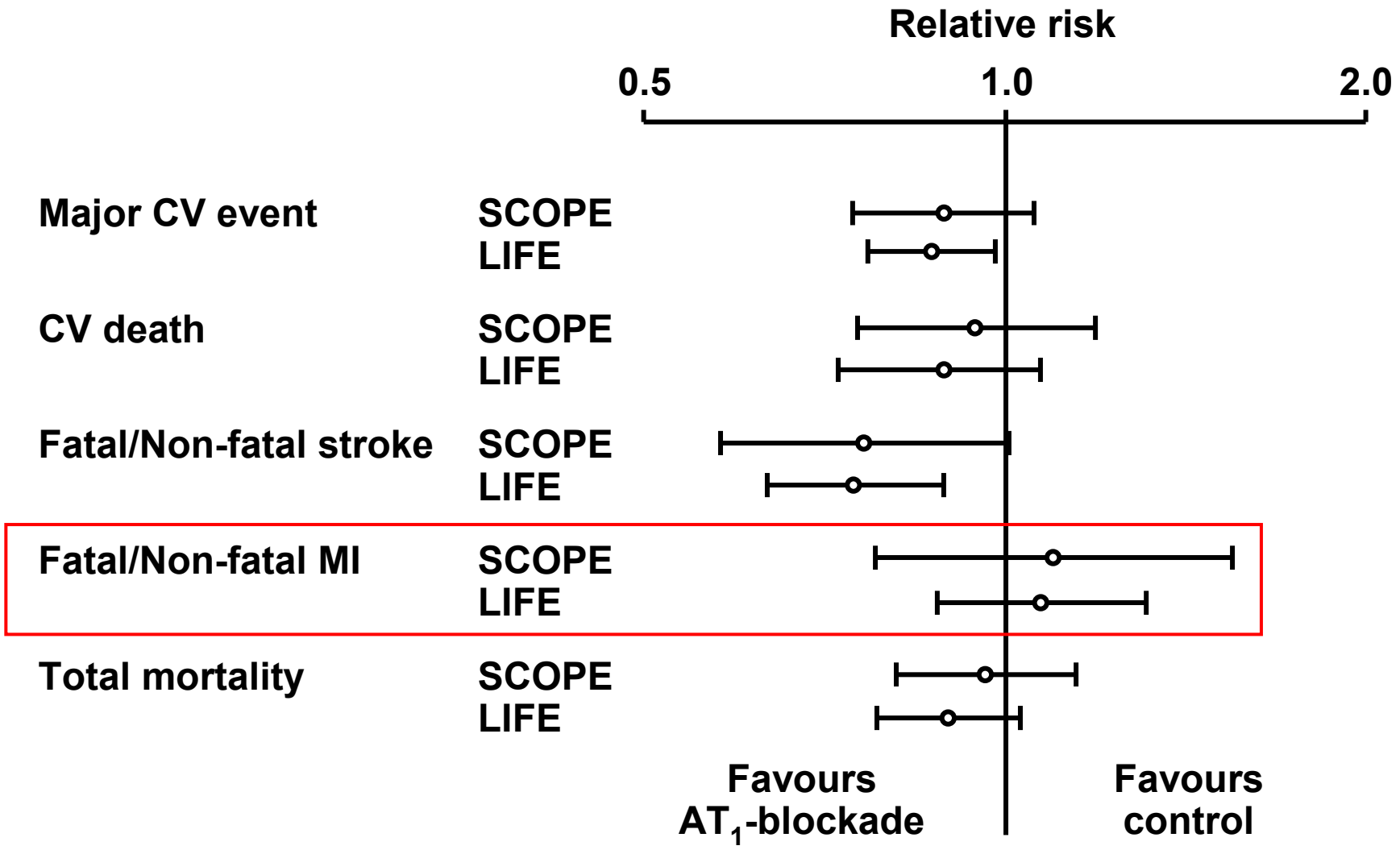
Total (95% CI)
Total Events: 1,826 (ARB), 1,722 (Control)
Test for heterogeneity. Chi^2 = 11.7
df=10 (p=0.32), I^2 = 14.6%
Test for overall effect: Z = 2.18 (p=0.03)



0.5 0.7 1.0 1.5 2.0

Favors ARB **Favors Control**

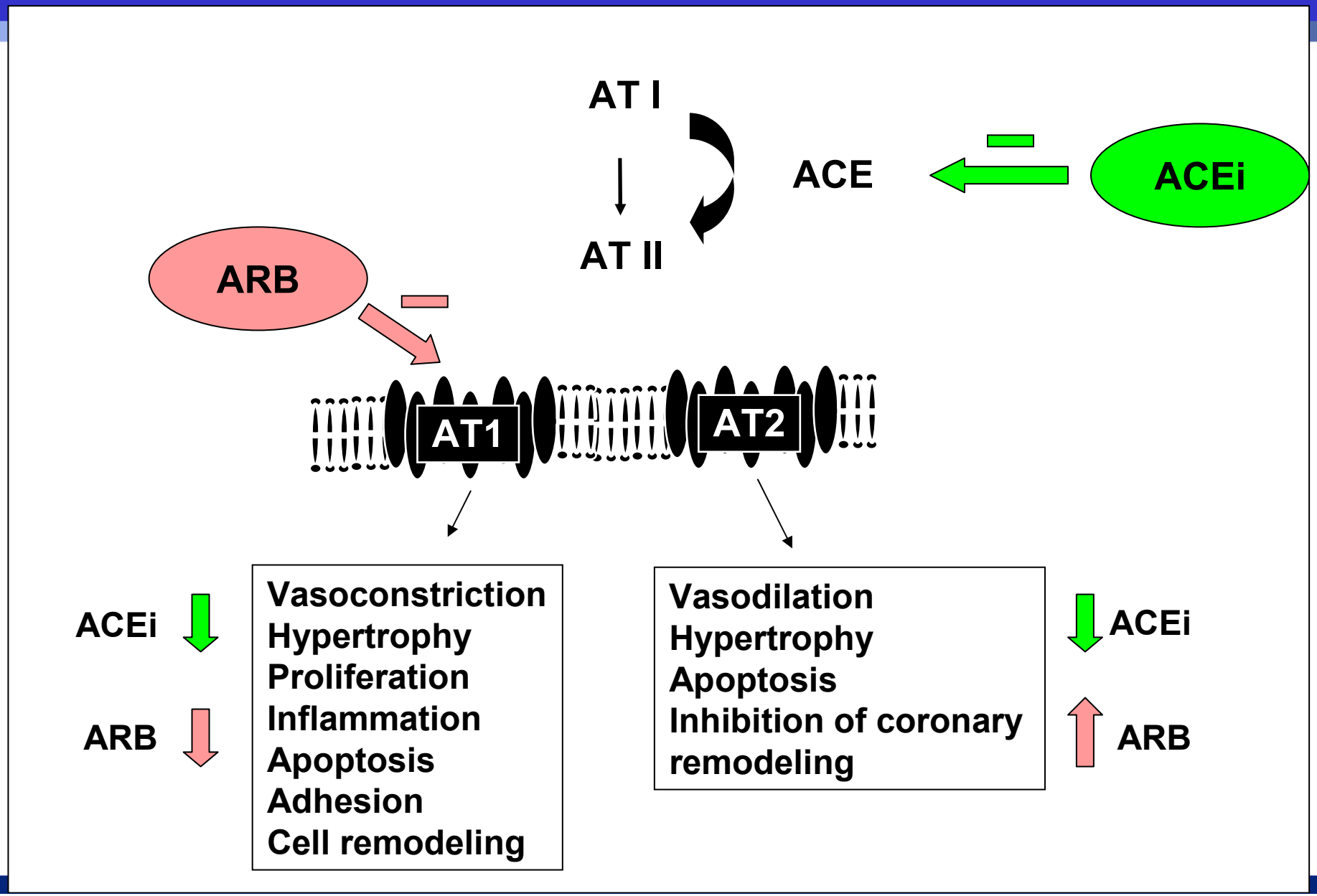
Relative risk, AT_1-receptor blocker vs control



Lithell et al, J Hypertens in press

Do ARBs Increase the Risk of MI?

Differential effects of ACEis and ARBs on AT_2 receptors



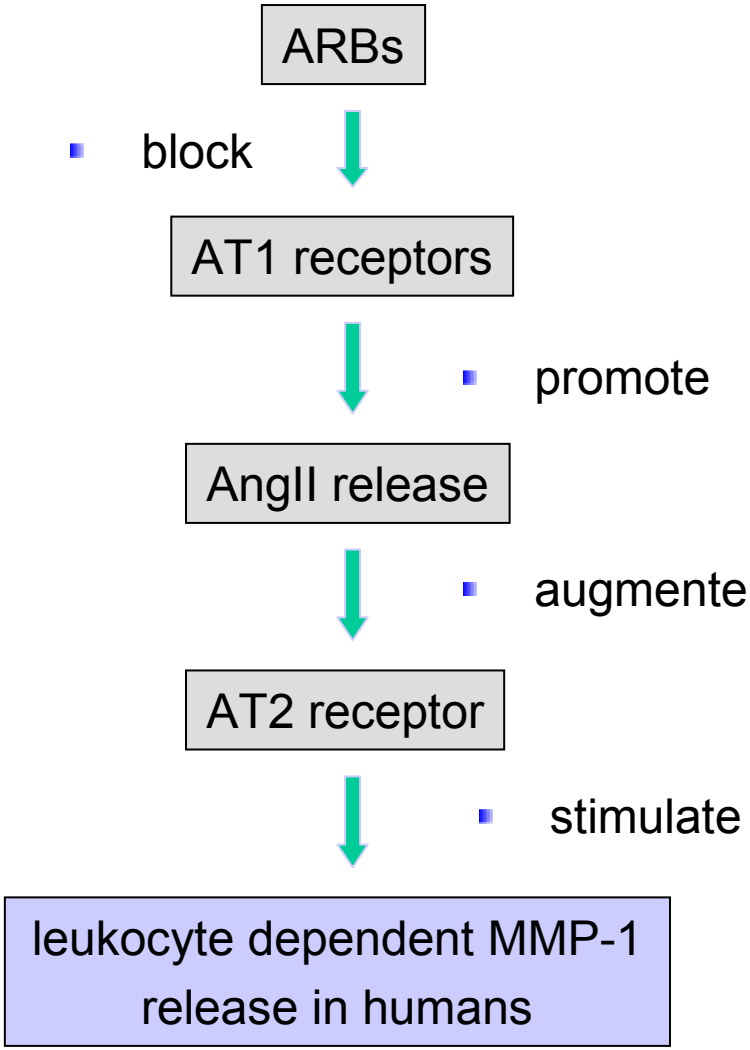
ARBs May Increase MI: Biological Plausibility

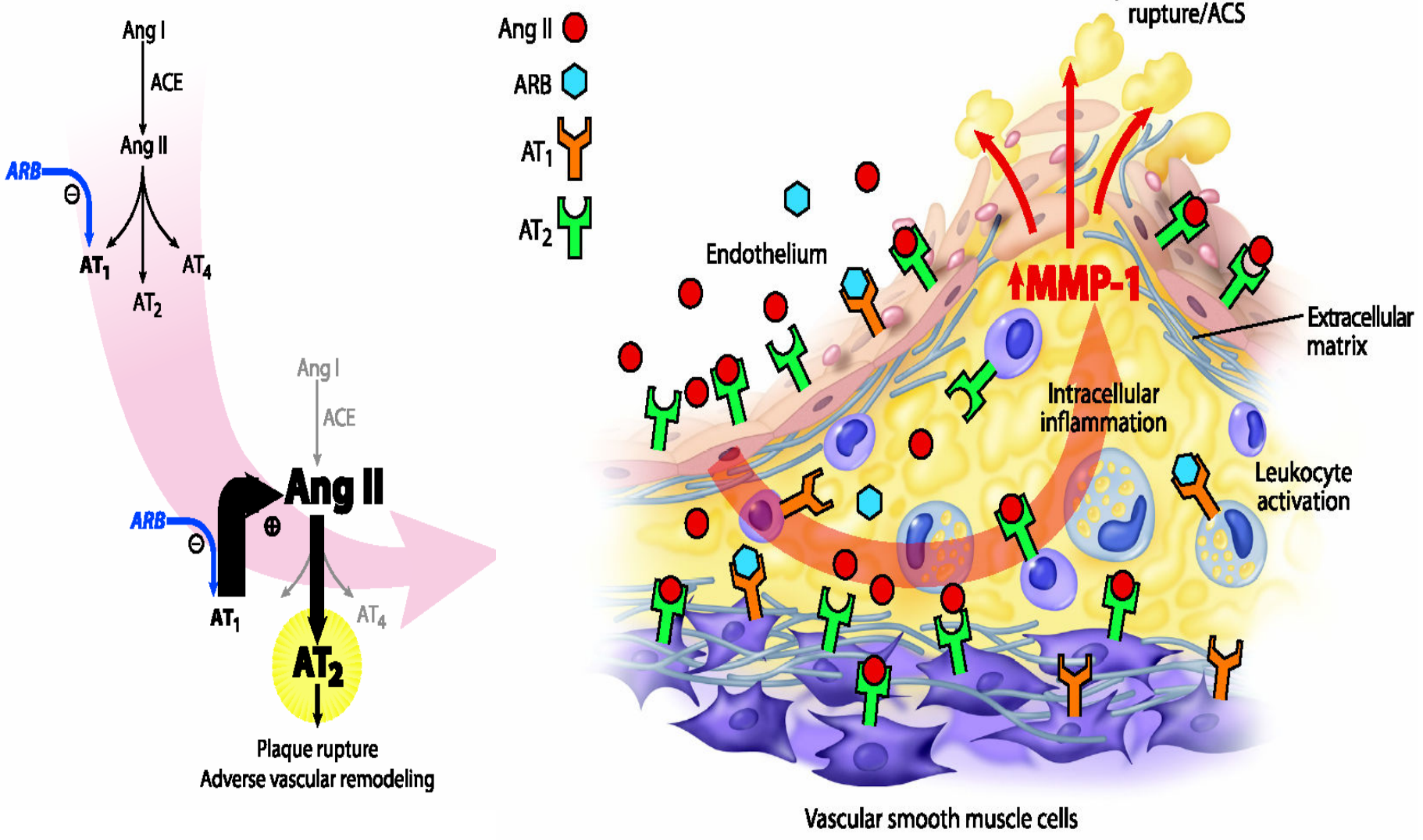
- ARBs increase Ang II levels several-fold above baseline
- AT2 receptor stimulation may even be harmful

  → growth promotion, fibrosis, and hypertrophy

  → proatherogenic and proinflammatory effects
- Overexpression of AT2 in human cardiac myocytes is associated with increased cardiac hypertrophy
- AT2 receptors inhibit vascular endothelial growth factor–induced angiogenesis in endothelial cells.
- AT2 stimulation inhibit hypoxia-induced neovascularization

AT_2 Impact on MMP-1 Dependent Plaque Rupture





Circulation
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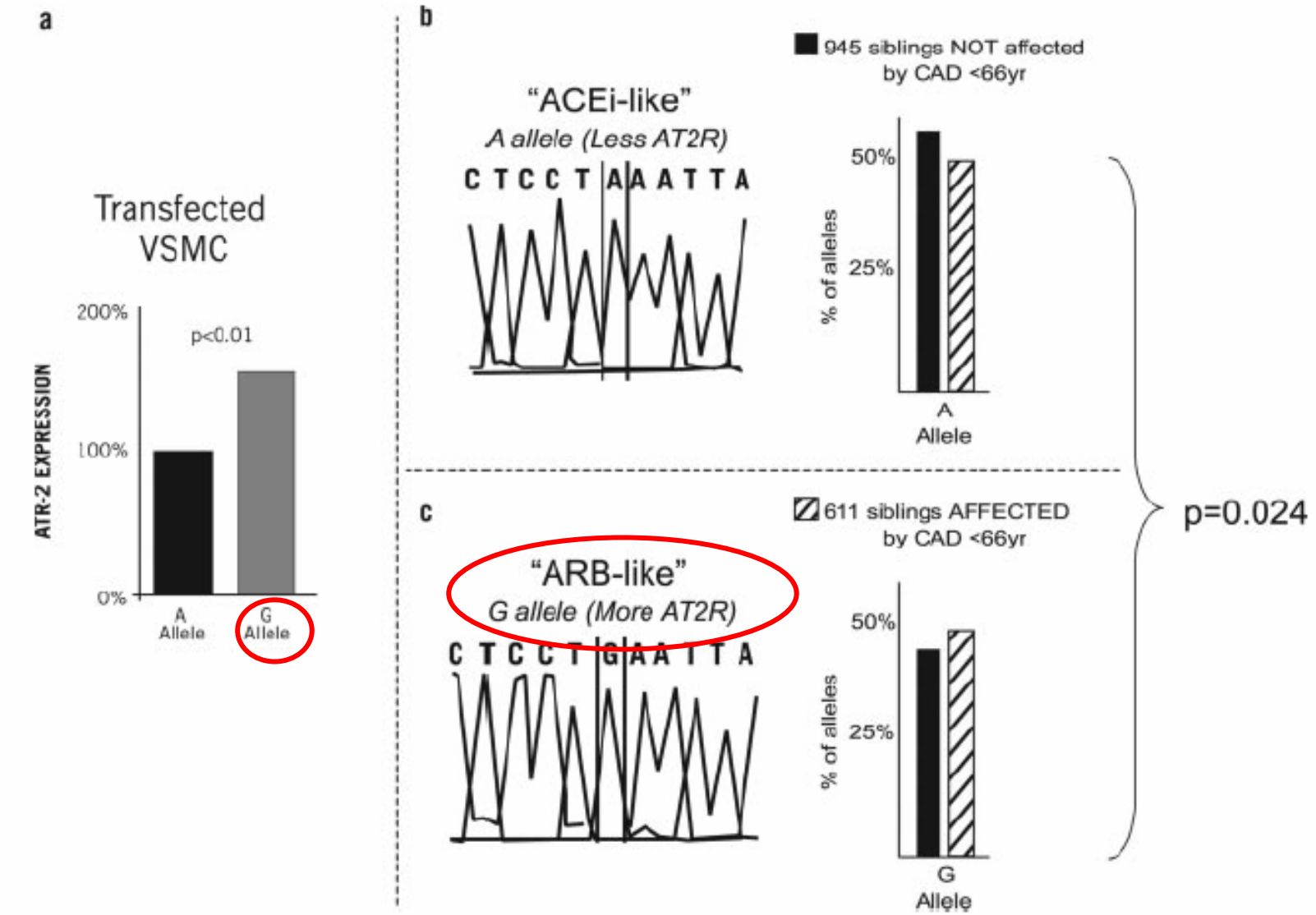
American Heart Association
Learn and Live
2006;114:838-854

ACEi Better than ARB ?

X-linked AT2 receptor gene polymorphism (1332 G/A)



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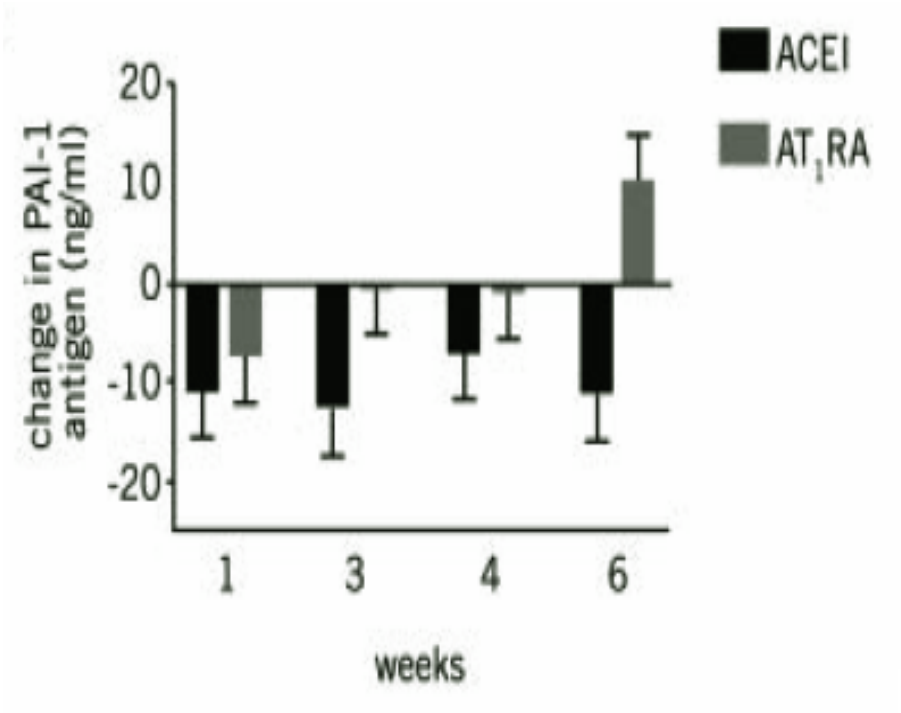
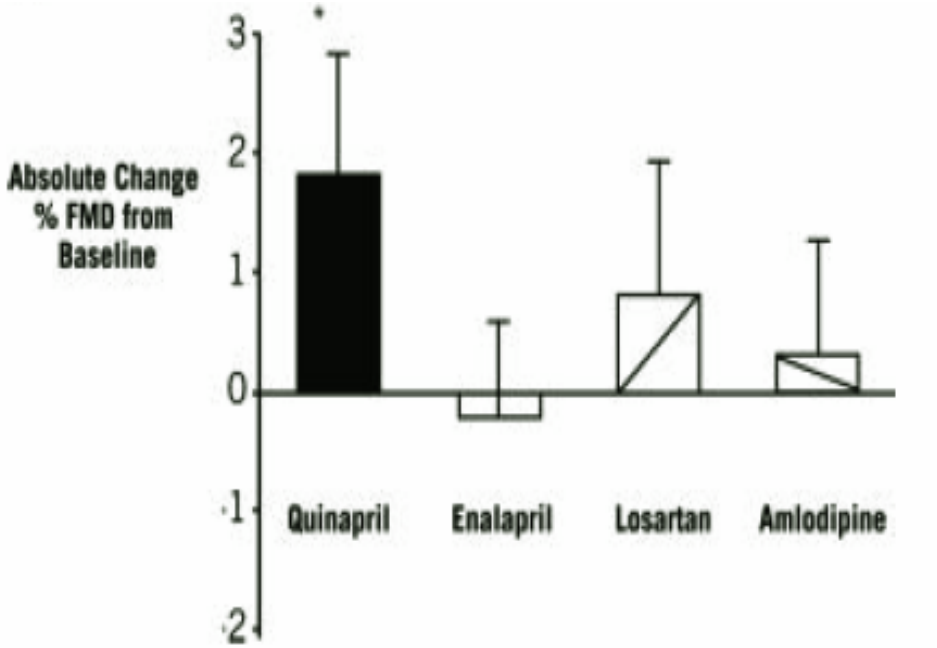
Change in PAI-1 and FMD with ACEi or ARB

Change in PAI-1 [1]



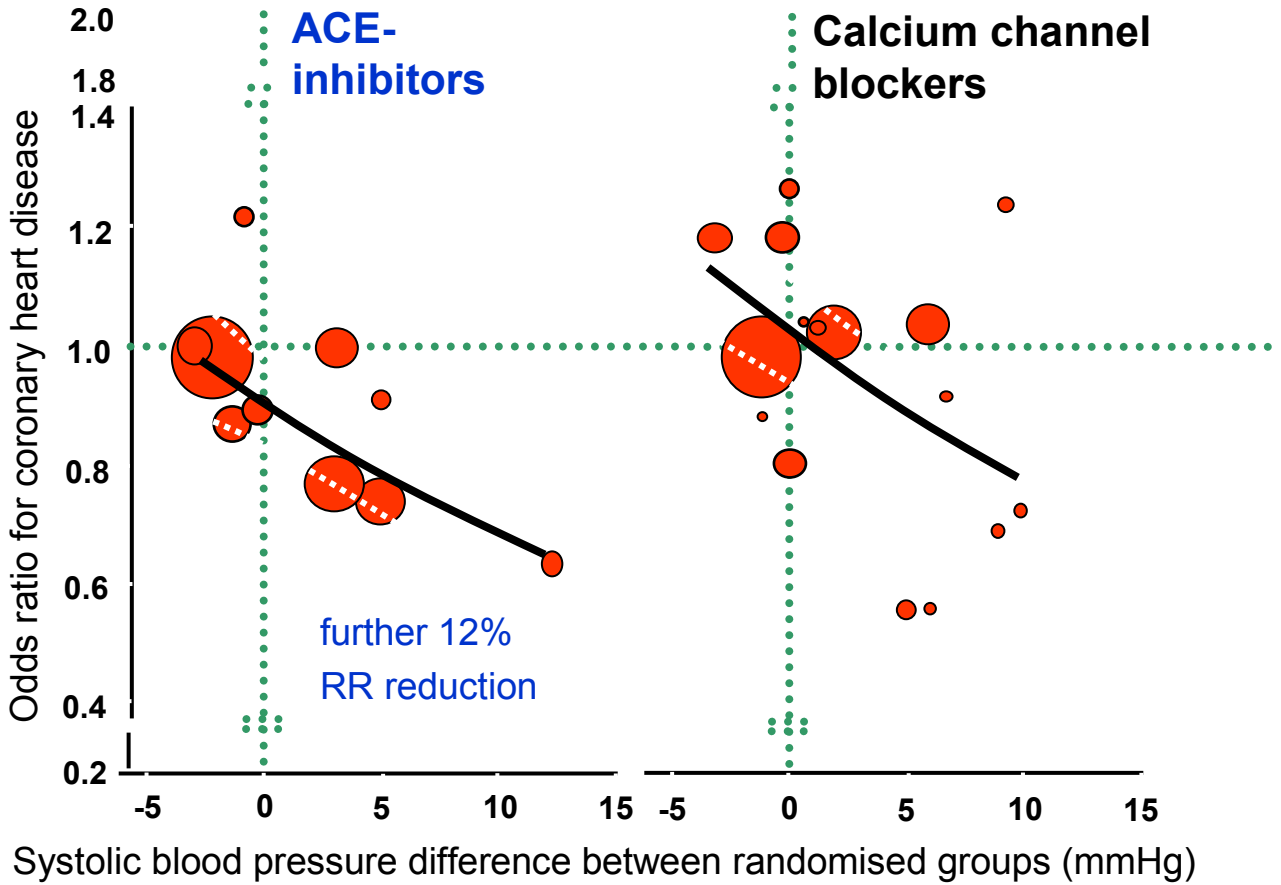
Absolute change in FMD after therapy [2]



1. Brown NJ et al. Hypertension. 2002;40:961-966
2. Anderson TJ et al. J Am Coll Cardiol. 2000;35:60-66

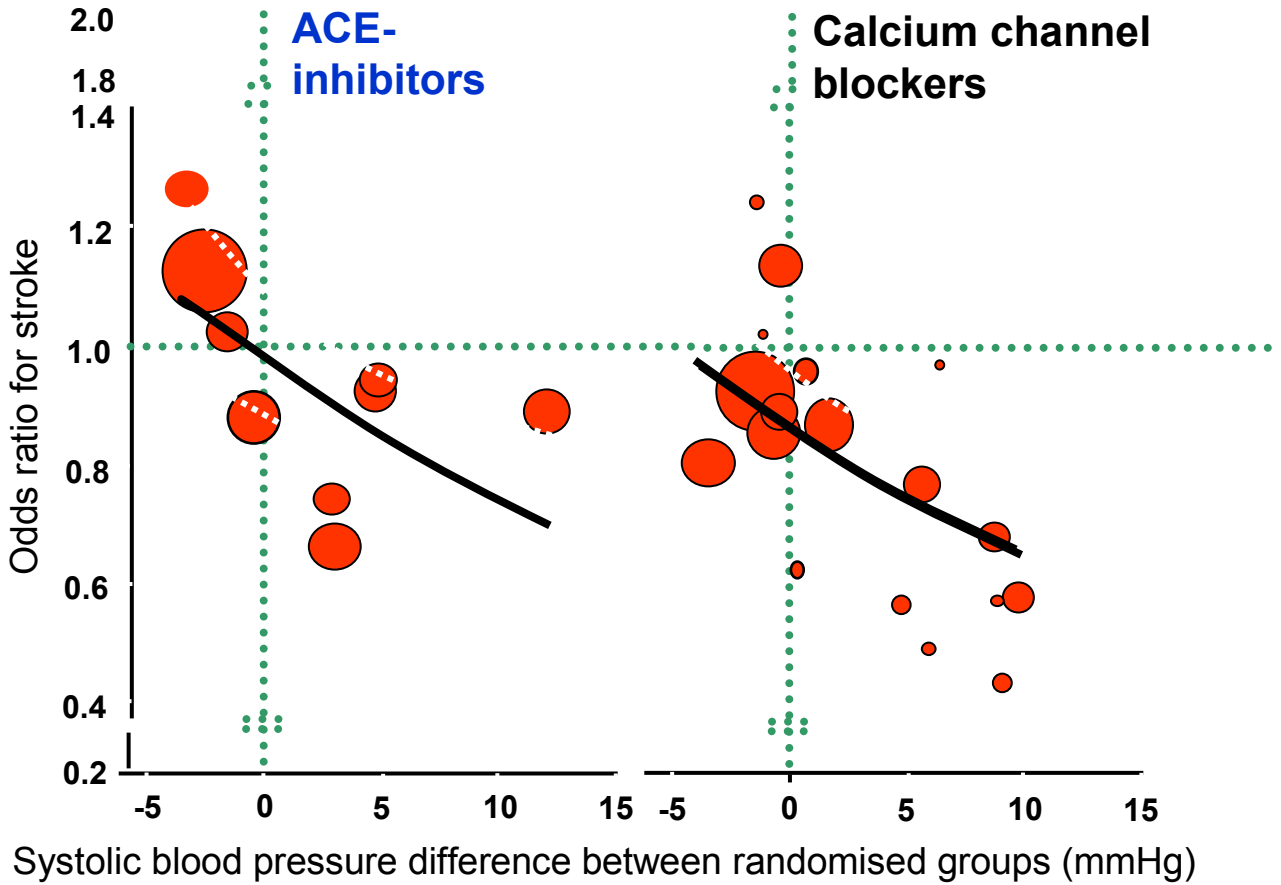
Blood Pressure– Independent Effects of ACEIs v. ARBs

Relationship between ORs for CHD and differences in achieved SBP between randomised groups



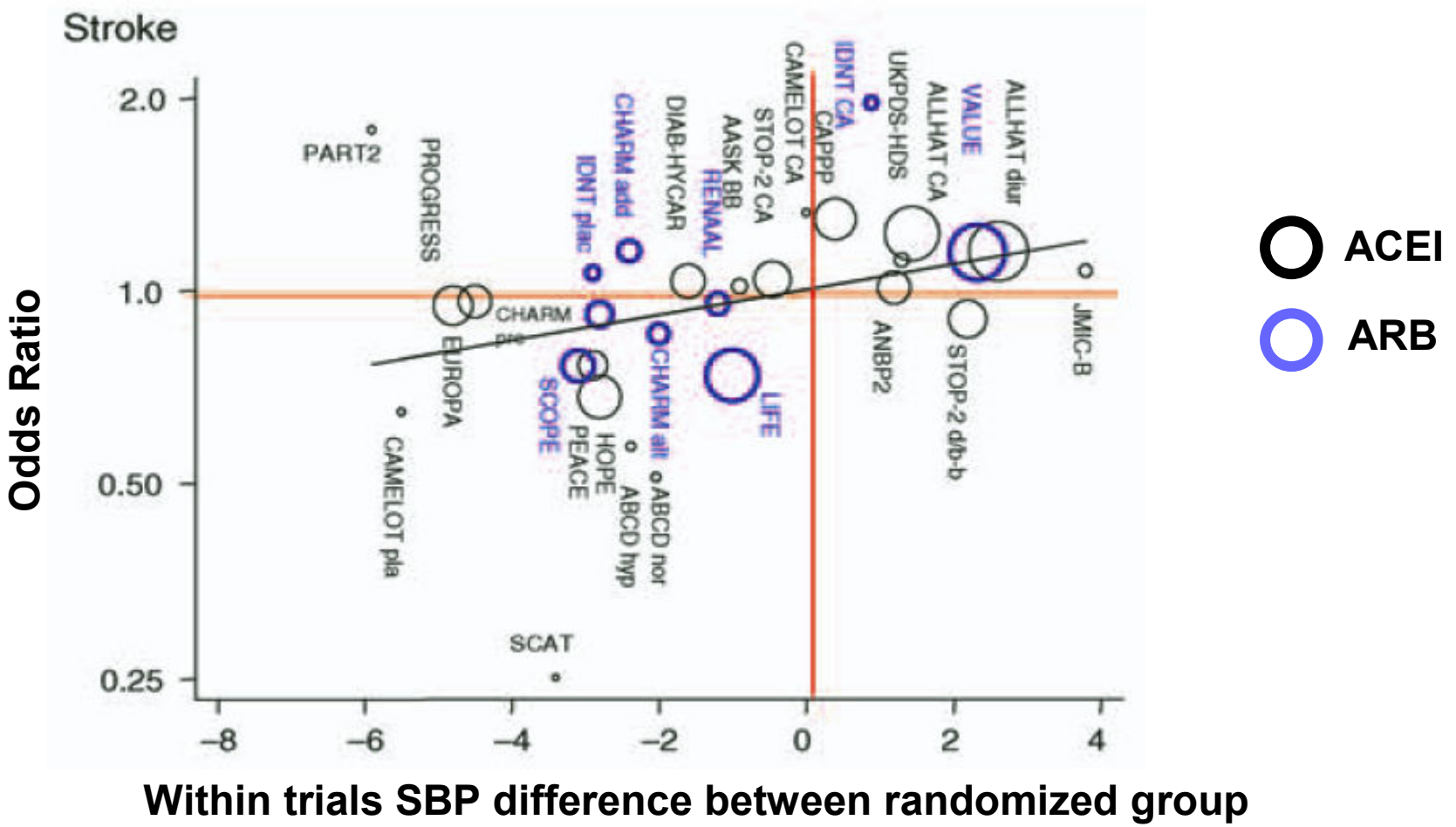
Verdecchia *et al* 2005

Relationship between ORs for Stroke and differences in achieved SBP between randomised groups



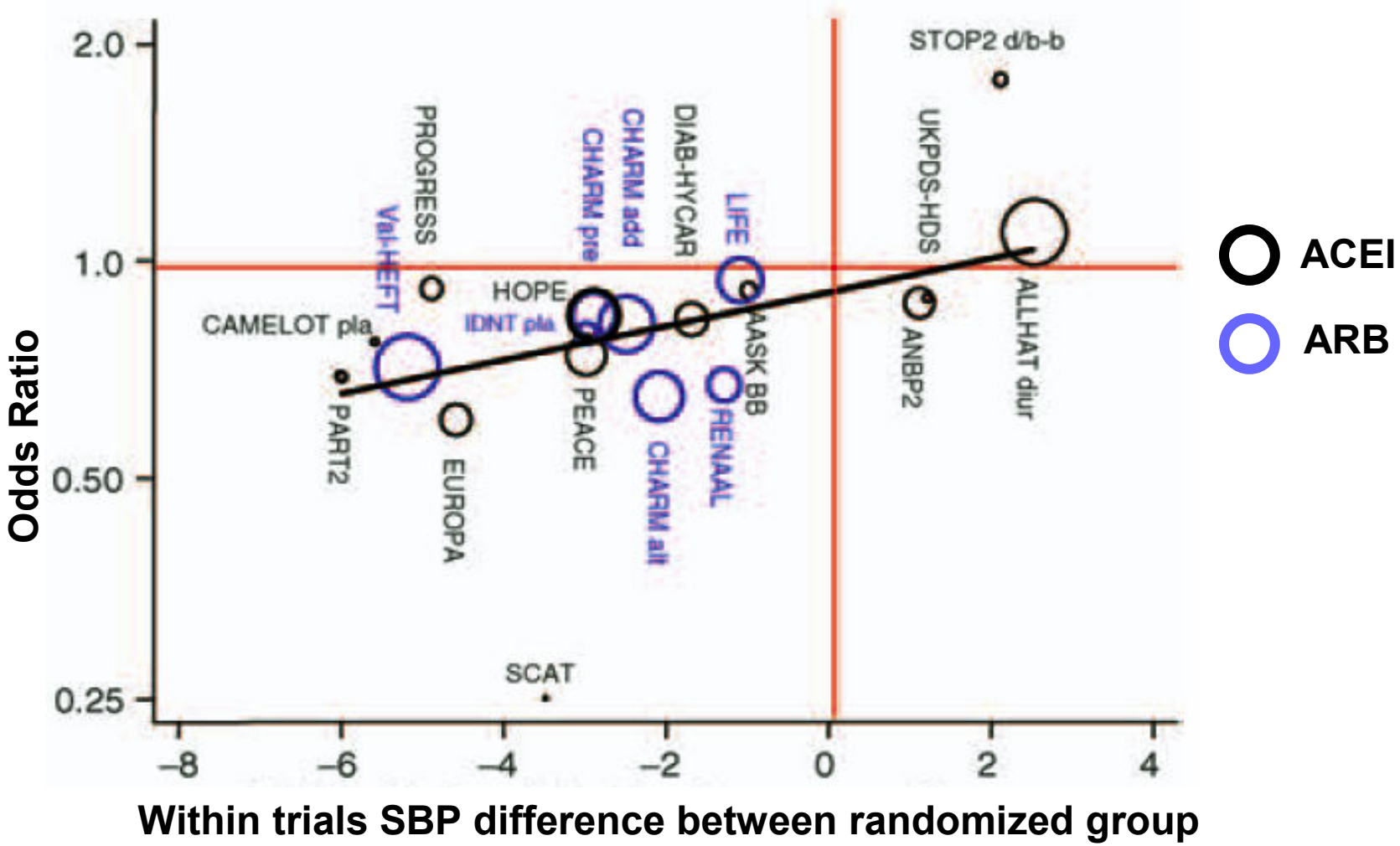
Verdecchia *et al* 2005

Associations of BP reduction with RR for stroke in trials of ACEI and ARB



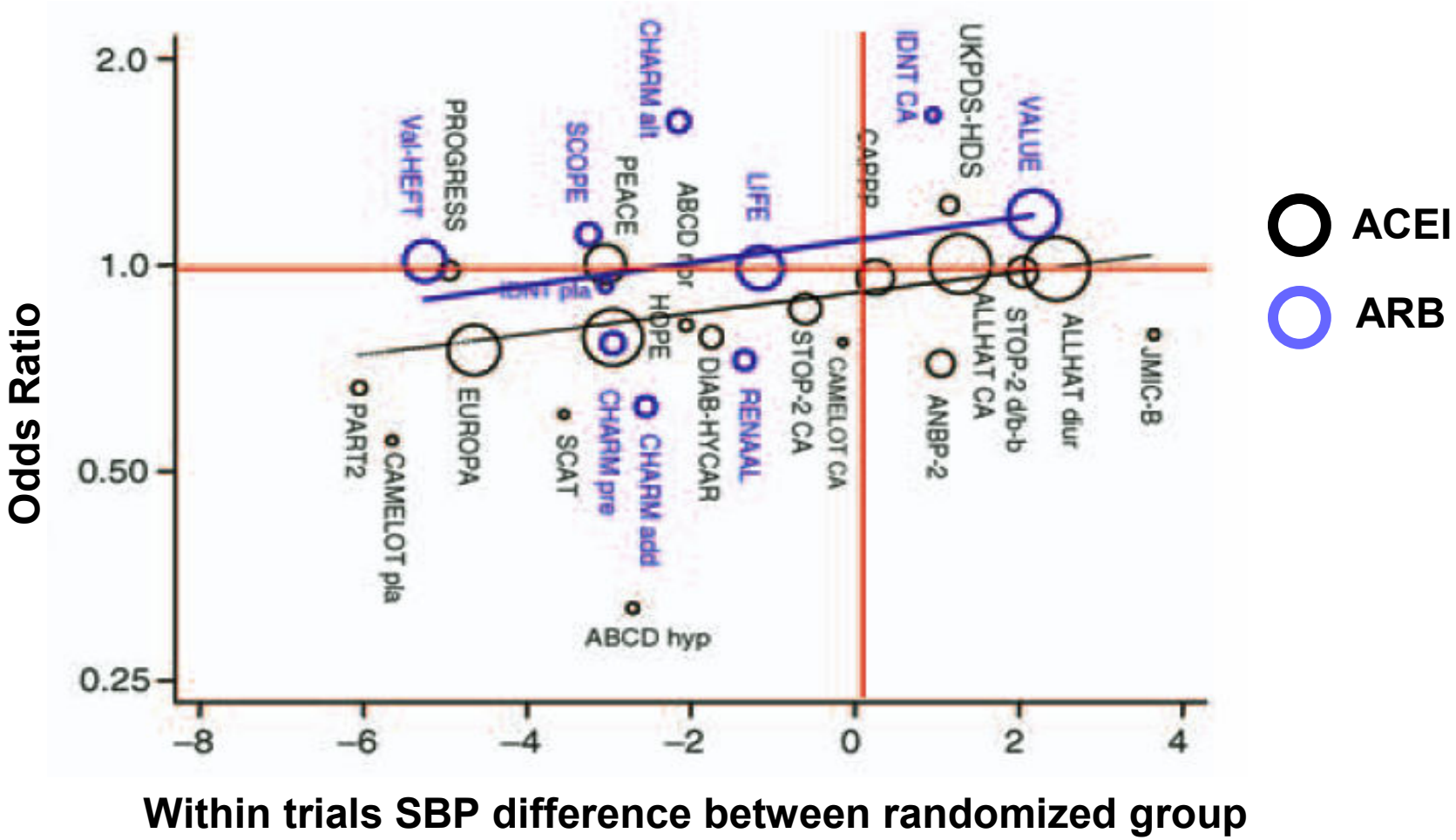
Journal of Hypertension 2007, 25:951–958

Associations of BP reduction with RR for heart failure in trials of ACEI and ARB



Journal of Hypertension 2007, 25:951–958

Associations of BP reduction with RR for CHD in trials of ACEI and ARB

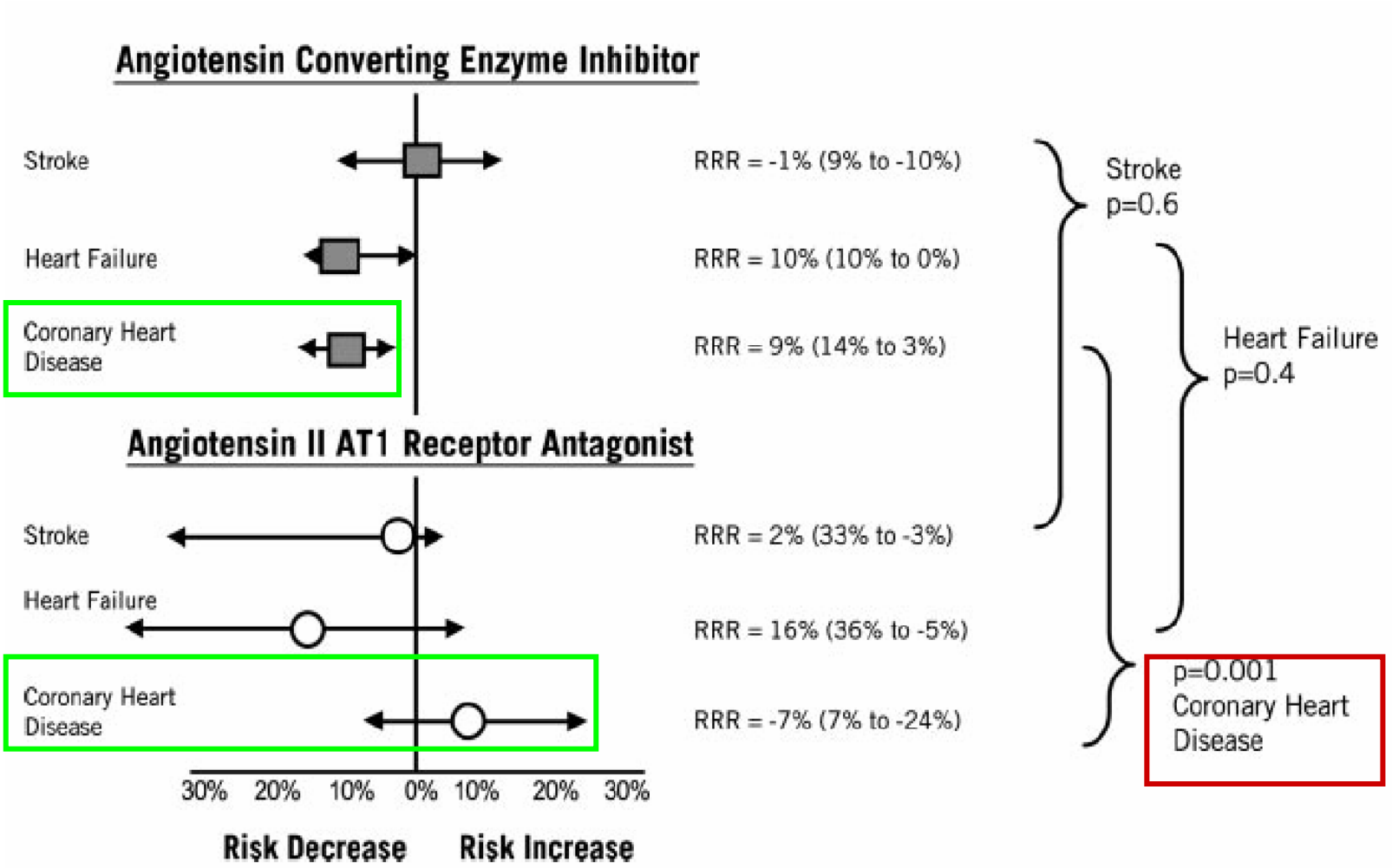


Journal of Hypertension 2007, 25:951–958

BPLTTC Regression Meta-analysis

ACEis or comparators - AASK, ABCD(H), ABCD(N), ALLHAT, ANBP2, CAPPP, DIAB-HYCAR, EUROPA,, HOPE, JMIC-B, PART-2, PEACE, PROGRESS, SCAT, STOP-2, and UKPDSHDS

ARBs or comparators - IDNT, LIFE, RENAAL, SCOPE, and VALUE.



Do ARBs Surely Increase the Risk of MI?

- **However, ARB v. ACEi**

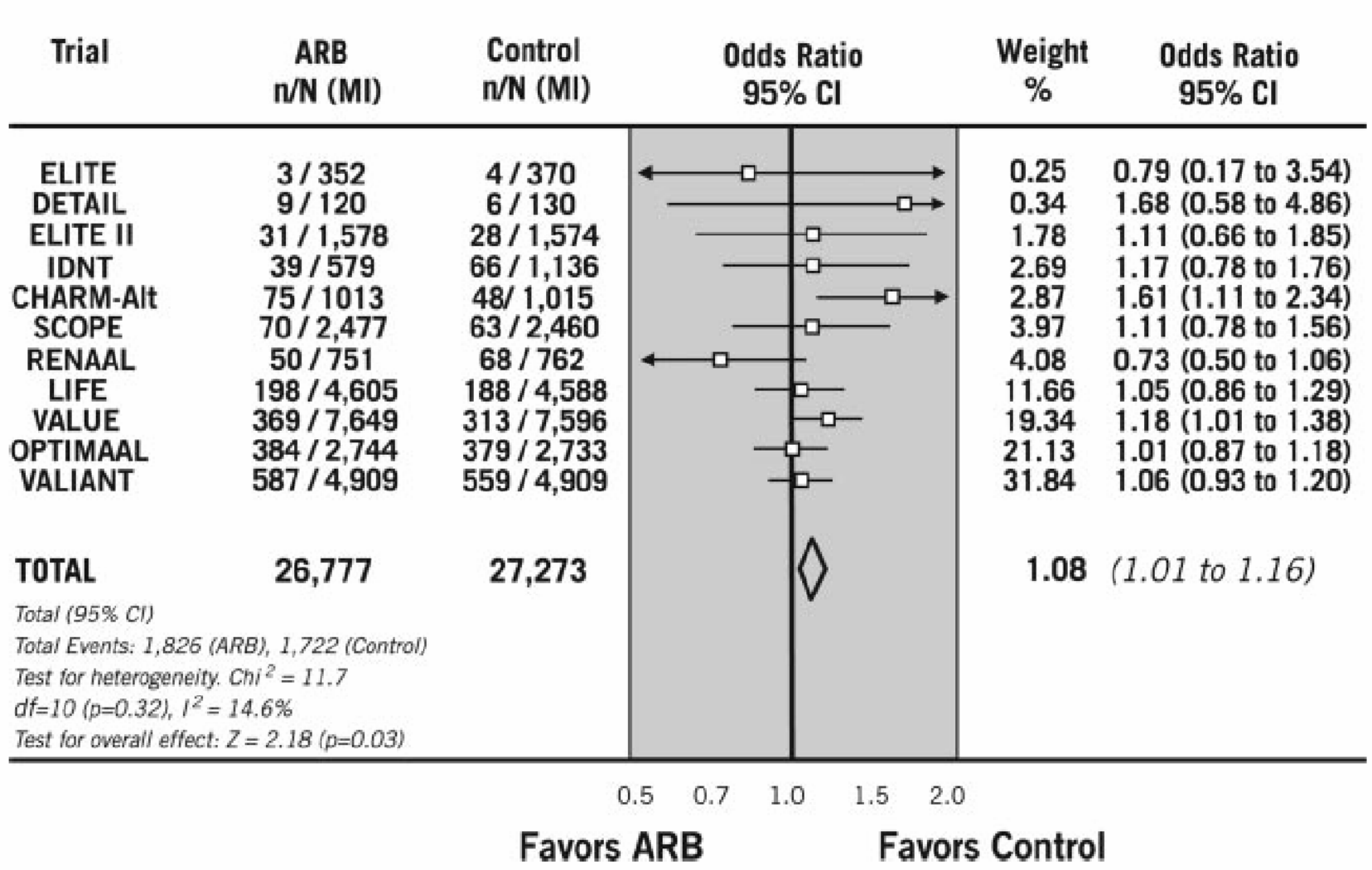
ELITE I, ELITE II, DETAIL, OPTIMAAL, and VALIANT

	Number at Risk	Number of Events	Control Event Rate	Odds Ratio (95% CL)	P Value Overall Effect
ARB versus ACEi					
Global Death	19,419	3,474	17.42%	1.06 (0.99-1.14)	0.10*
CV Death	19,419	2,910	14.59%	1.06 (0.98-1.15)	0.14
Non CV Death	19,419	564	2.8%	1.05 (0.89-1.25)	0.55
Stroke	18,697	704	3.9%	0.91 (0.79-1.06)	0.25
MI	19,419	1,990	10.05%	1.04 (0.95-1.15)	0.37

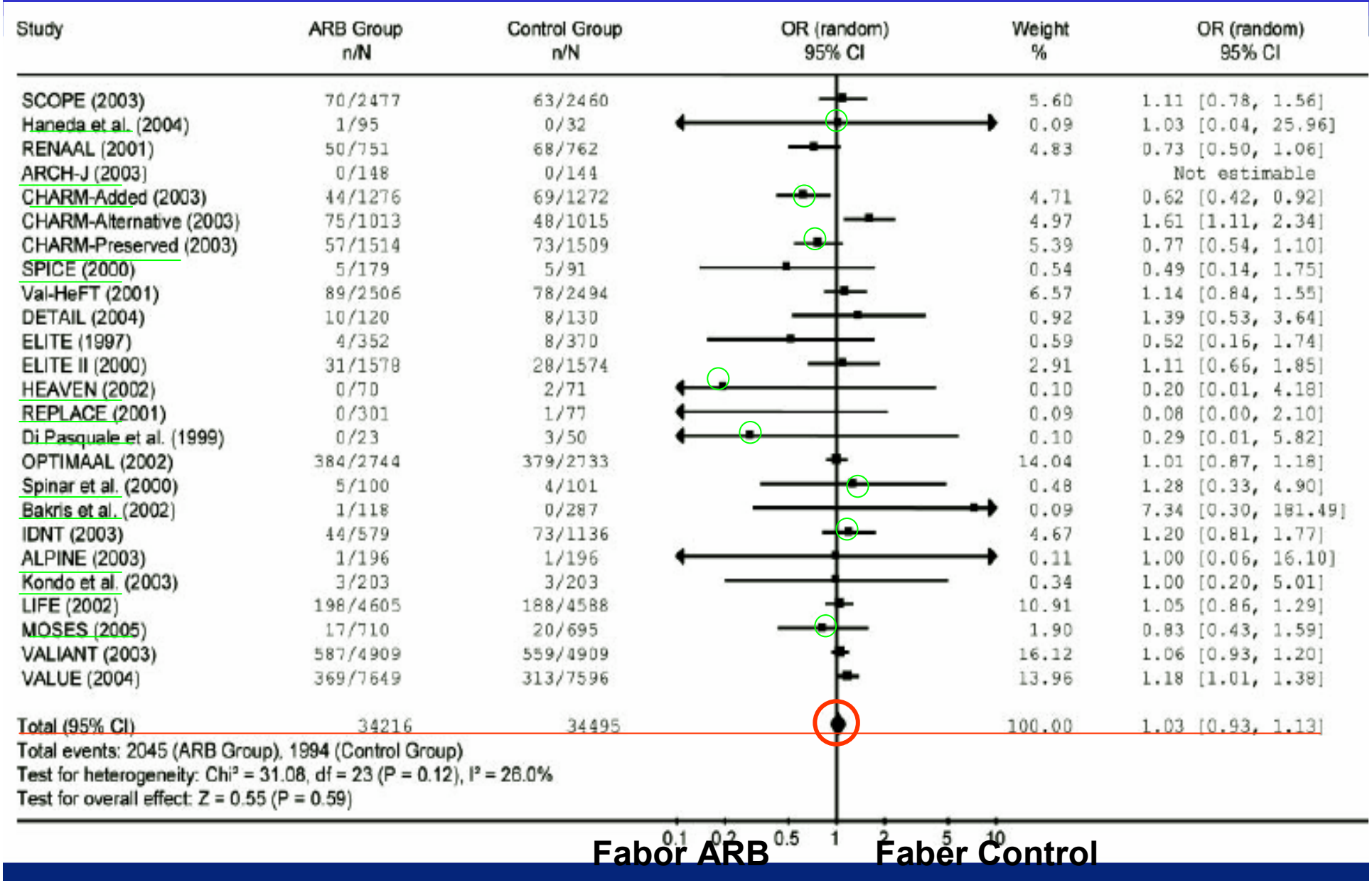
(* p<0.10;** p<0.05;*** p<0.01;**** p<0.001)

ARB v. Comparator

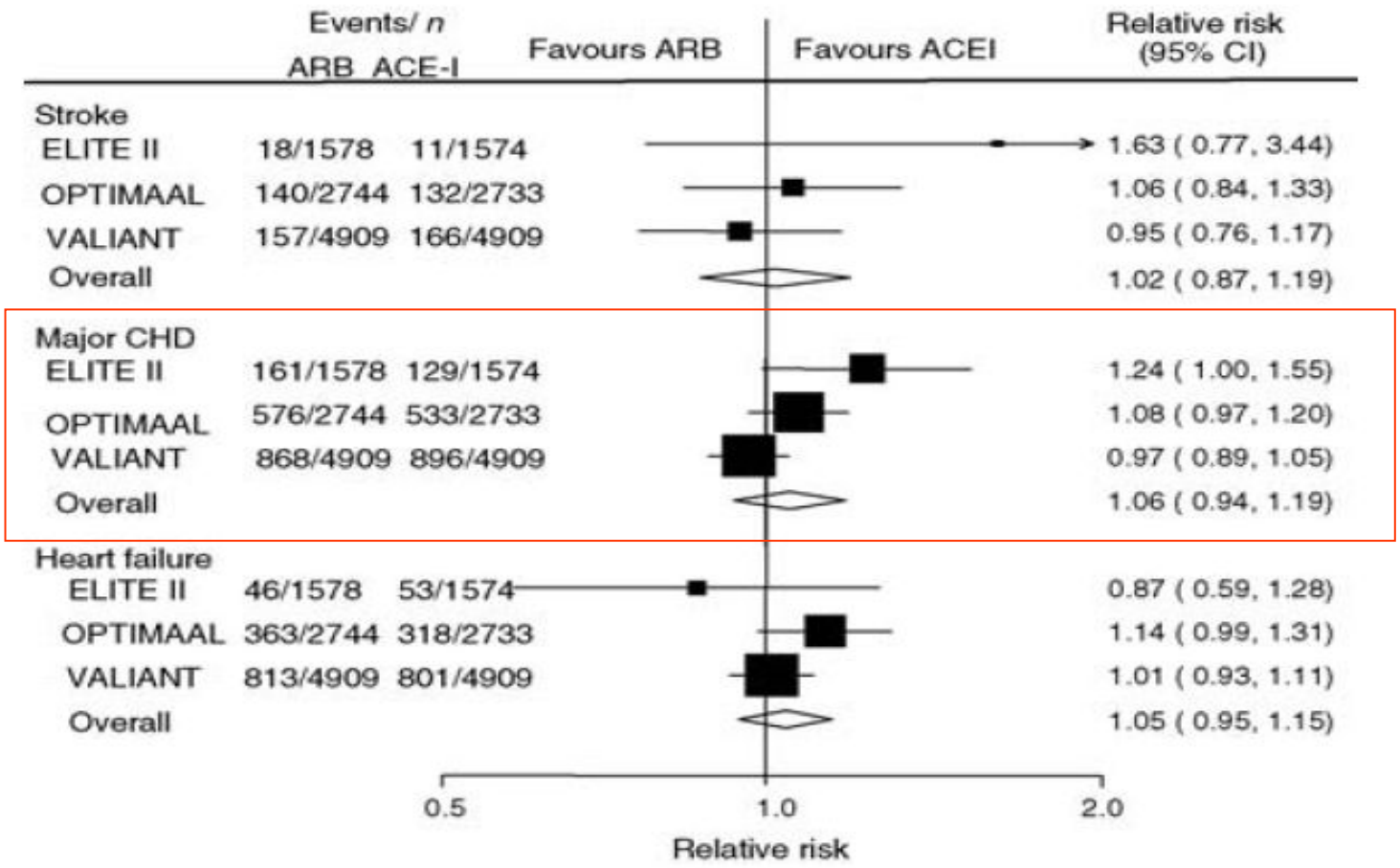
IDNT, CHARM-Alternative, SCOPE, RENAAL, LIFE, VALUE, ELITE I, ELITE II, DETAIL, OPTIMAAL, and VALIANT



Overall effect of ARBs on risk of MI



Meta-analysis of trials directly comparing ACEI with ARB-based regimens for the outcomes of stroke, CHD and heart failure



CONCLUSION

“ARBs might be inferior to ACEis with respect to prevention of MI and CV death”

Biological plausibility
Clinical evidence
Meta-analyses

STILL REMAIN

“ACEis is the preferred choice as initial therapy (or an ARB if an ACEi is not tolerated) at present hypertension treatment recommendation”

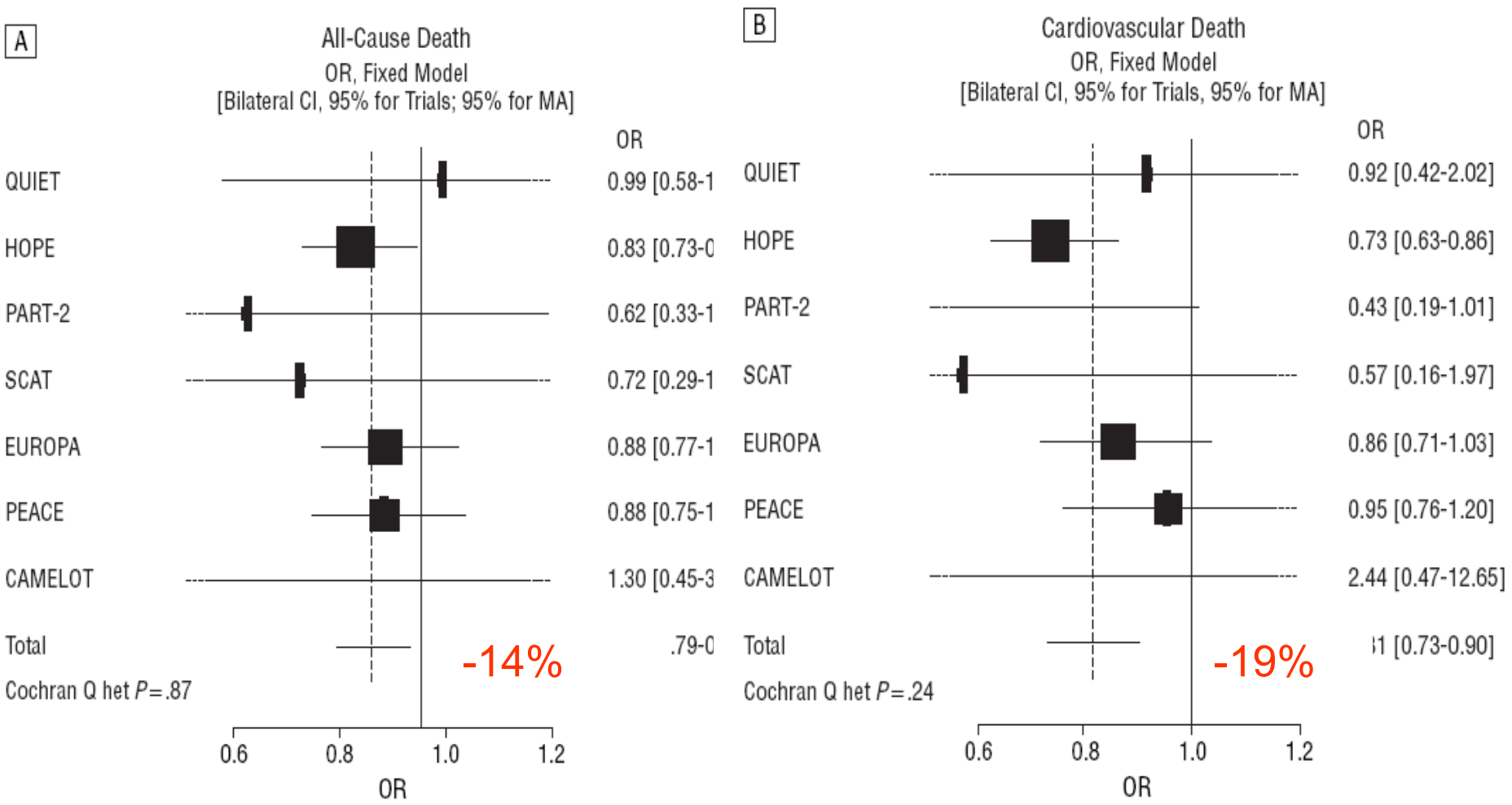
.

WE NEED MORE EVIDENCE FOR THE CONTROVERSY OF ARB-MI PARADOX

- Results from the prospective ONTARGET and TRANSCEND trials are eagerly awaited to better define the role of ARBs in protecting patients at risk for MI and other atherosclerotic heart disease–related events.

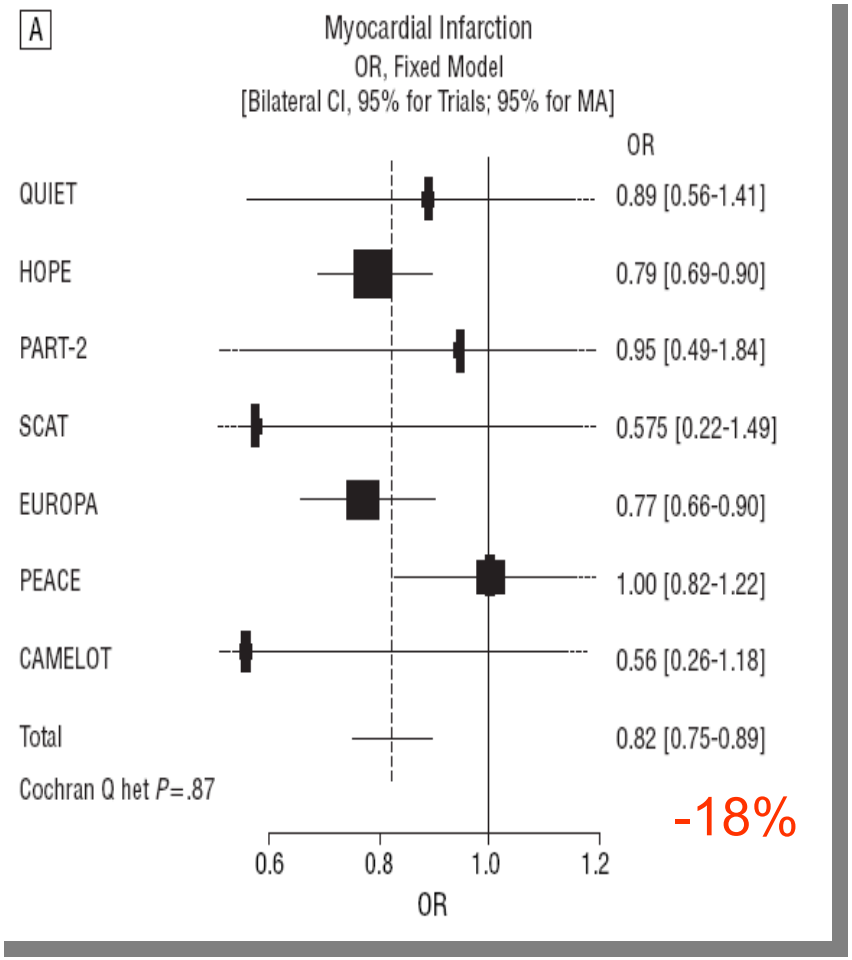
경청하여 주셔서 감사합니다.

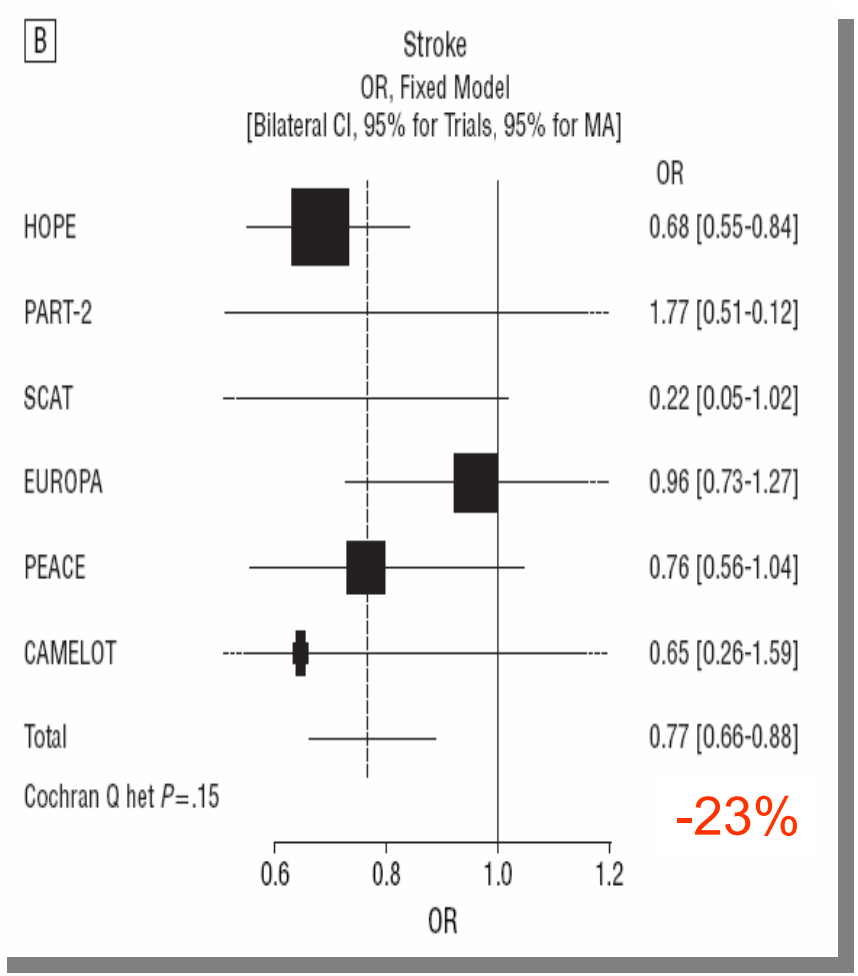
Meta-analysis of RCTs of ACE-I in patients with CAD and no heart failure or LV dysfunction



Danchin et al. Arch Intern Med 2006; 166: 787-96

Meta-analysis of RCTs of ACE-I in patients with CAD and no heart failure or LV dysfunction





Danchin et al. Arch Intern Med 2006; 166: 787-96

Summary of meta-analyses for treatment with an ARB vs placebo; placebo or non-ACEI comparator

	Number at Risk	Number of Events	Control Event Rate	Odds Ratio (95% CL)	P Value Overall Effect
ARB versus placebo					
Global Death	9,626	1,579	16.9%	0.94 (0.66-1.24)	0.24
CV Death	9,626	1,035	11.0%	0.95 (0.83-1.08)	0.43
Non CV Death	9,626	529	5.6%	0.98 (0.82-1.17)	0.81
Stroke	9,626	421	4.7%	0.84 (0.69-1.02)	0.09 *
MI	9,626	454	4.90%	1.05 (0.76-1.47)	0.76
ARB versus placebo / non ACEi comparator					
Global Death	34,631	4,127	12.2%	0.96 (0.90-1.03)	0.26
CV Death	34,631	2,118	6.3%	0.95 (0.87-1.04)	0.27
Non CV Death	34,631	1,998	5.8%	0.99 (0.91-1.09)	0.87
Stroke	34,631	1,581	4.7%	0.94 (0.75-1.19)	0.61
MI	34,631	1,547	4.4%	1.13 (1.02-1.25)	0.02 **
ARB versus placebo / non ACEi comparator / ACEi					
Global Death	55,050	7,601	14.0%	1.01 (0.96-1.06)	0.80
CV Death	54,050	5,028	9.2%	1.01 (0.95-1.07)	0.71
Non CV Death	54,050	2,562	4.7%	1.00 (0.93-1.09)	0.89
Stroke	53,318	2,285	4.4%	0.92 (0.79-1.08)	0.32
MI	54,050	3,537	6.3%	1.08 (1.01-1.16)	0.03 **

Trials included IDNT, CHARM Alternative, SCOPE, RENAAL, LIFE, VALUE, ELITE, ELITE-2, DETAIL, OPTIMAAL, and VALIANT.

ARB v. Comparator

IDNT, CHARM-Alternative, SCOPE, RENAAL, LIFE, VALUE, ELITE I, ELITE II, DETAIL, OPTIMAAL, and VALIANT

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(* p<0.10; ** p<0.05; *** p<0.01; **** p<0.001)

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Hypothesis

Attenuation of both AT_1 and AT_2 receptor–mediated effects (with ACEis) is preferable to isolated AT_1 receptor antagonism but with additional AT_2 receptor stimulation (ARB therapy)

Included

Randomized, controlled trials
At least 100 patients in each group
Treatment for at least 6 months
Published in the English language
From 1980 to March 2005
Jadad score of at least 3

Excluded

CHARM-Added

CHARM-Preserved
Val-HEFT

Major clinical end points

Global death
Cardiovascular death
Non-cardiovascular death
Stroke
Myocardial infarction

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ACEi v. Comparator

CAMELOT, DIABHYCAR, Collaborative Study, BENEDICT, PROGRESS, CONSENSUS, SAVE, AIRE, TRACE, SOLVD Prevention, SOLVD Treatment, FOSINOPRIL, MARCATOR, MERCATOR, SCAT, PART-2, QUIET, HOPE, EUROPA, PEACE, CONSENSUS II, PREVEND IT, ALLHAT, ANBP-2, HYVET Pilot, ABCD, FACET, CAPP, STOP-2, UKPDS 39, J-MIND, CARMEN, ESTIC FLOSEQUINAN VeHFT-2, ELITE, ELITE-2, DETAIL, OPTIMAAL, and VALIANT

	Number at Risk	Number of Events	Control Event Rate	Odds Ratio (95% CL)	P Value Overall Effect
ACEi versus placebo					
Global Death	68,631	7,840	12.2%	0.88 (0.84-0.92)	<0.00001 ****
CV Death	65,497	5,661	9.3%	0.84 (0.76-0.92)	0.0001 ****
Non CV Death	64,487	2,138	3.3%	0.98 (0.90-1.07)	0.70
Stroke	56,373	1,948	3.8%	0.83 (0.71-0.98)	0.03 **
MI	66,986	4,655	7.6%	0.82 (0.77-0.87)	<0.00001 ****
ACEi versus placebo / non ARB comparator					
Global Death	131,524	15,169	12.2%	0.90 (0.85-0.95)	0.0002 ****
CV Death	124,244	8,937	7.4%	0.87 (0.80-0.94)	0.0008 ****
Non CV Death	123,234	5,620	5.0%	0.99 (0.93-1.05)	0.69
Stroke	117,106	4,781	4.3%	0.93 (0.81-1.07)	0.29
MI	128,523	6,440	5.1%	0.84 (0.79-0.88)	<0.00001 ****
ACEi versus placebo / non ARB comparator / ARB					
Global Death	150,943	18,643	13.0%	0.91 (0.86-0.95)	<0.00001 ****
CV Death	143,663	11,847	8.4%	0.88 (0.82-0.95)	0.0005 ****
Non CV Death	142,653	6,184	4.7%	0.98 (0.93-1.04)	0.56
Stroke	135,803	5,485	4.2%	0.94 (0.83-1.06)	0.31
MI	144,790	8,377	5.8%	0.86 (0.82-0.90)	<0.00001 ****

(* p<0.10; ** p<0.05; *** p<0.01; **** p<0.001)

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EUROPA: results