



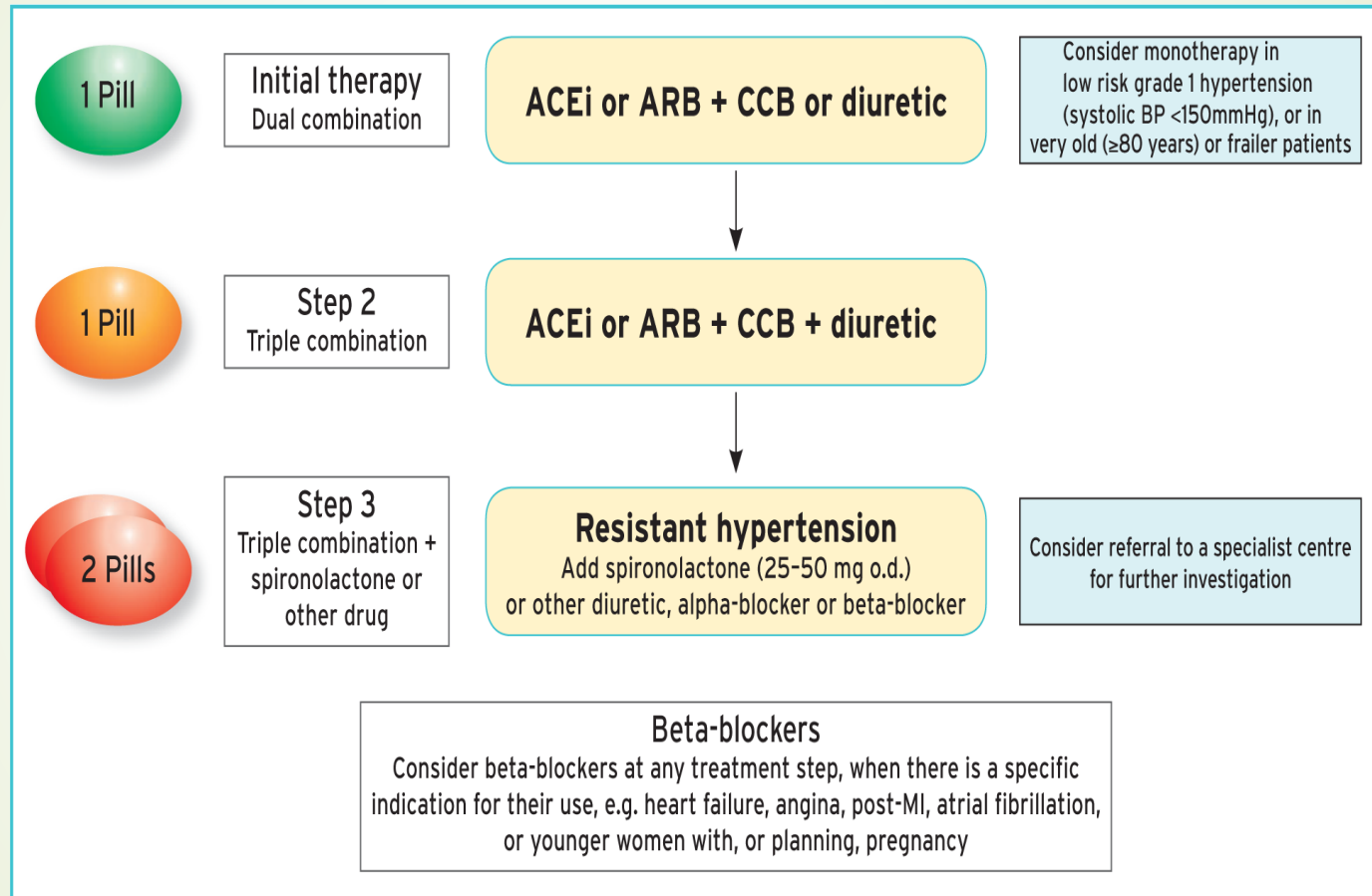
Does the choice of ACEi & ARB really matter in the initiation and Management of Hypertension?

DR.W.S.SANTHARAJ MD FACC FCCP FRCP(Edin)

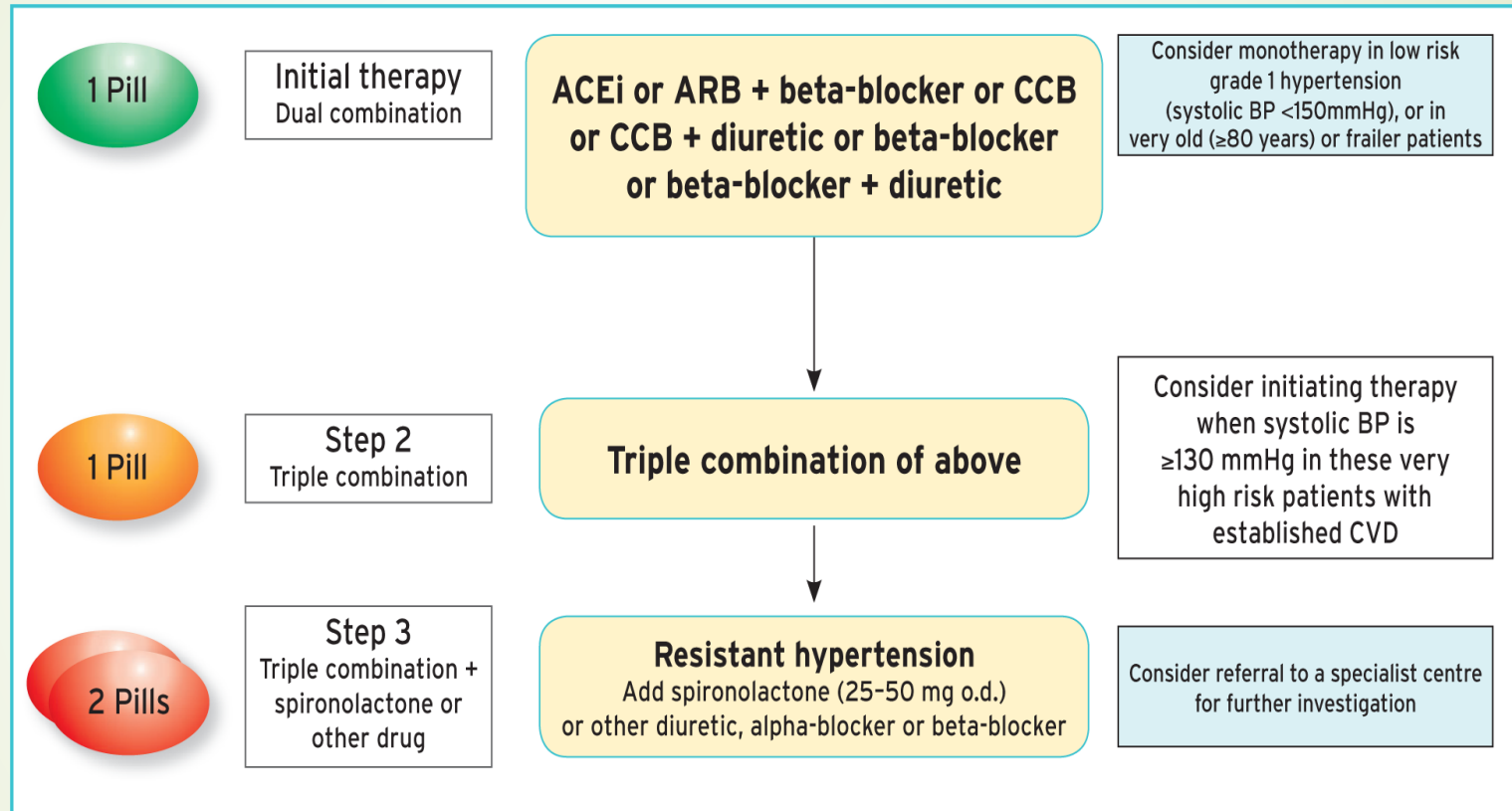
CONSULTANT CARDIOLOGIST

COLOMBO SRI LANKA

Core drug treatment strategy for **uncomplicated hypertension**. The core algorithm is also appropriate for most ...

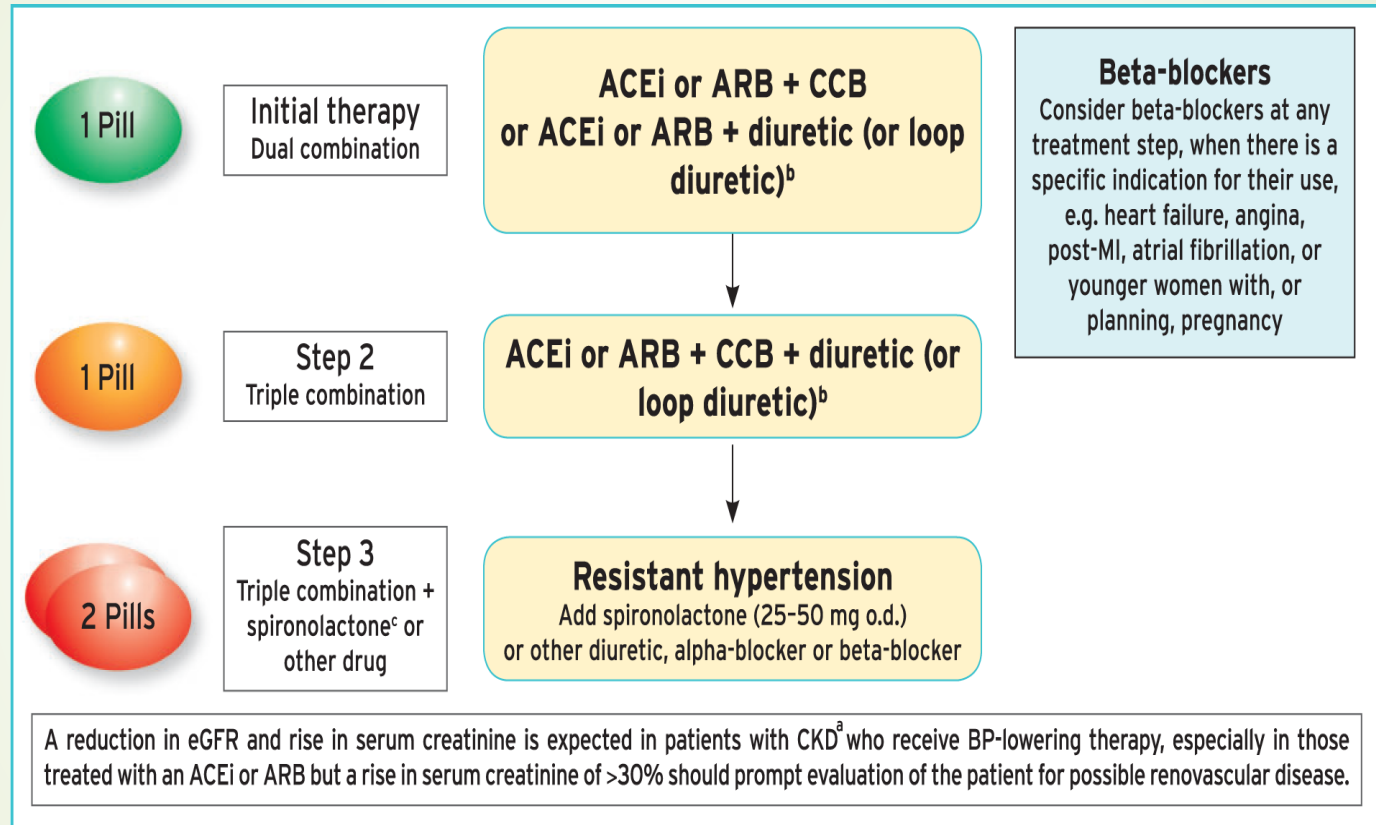


Drug treatment strategy for hypertension and coronary artery disease. ACEi = angiotensin-converting enzyme ...



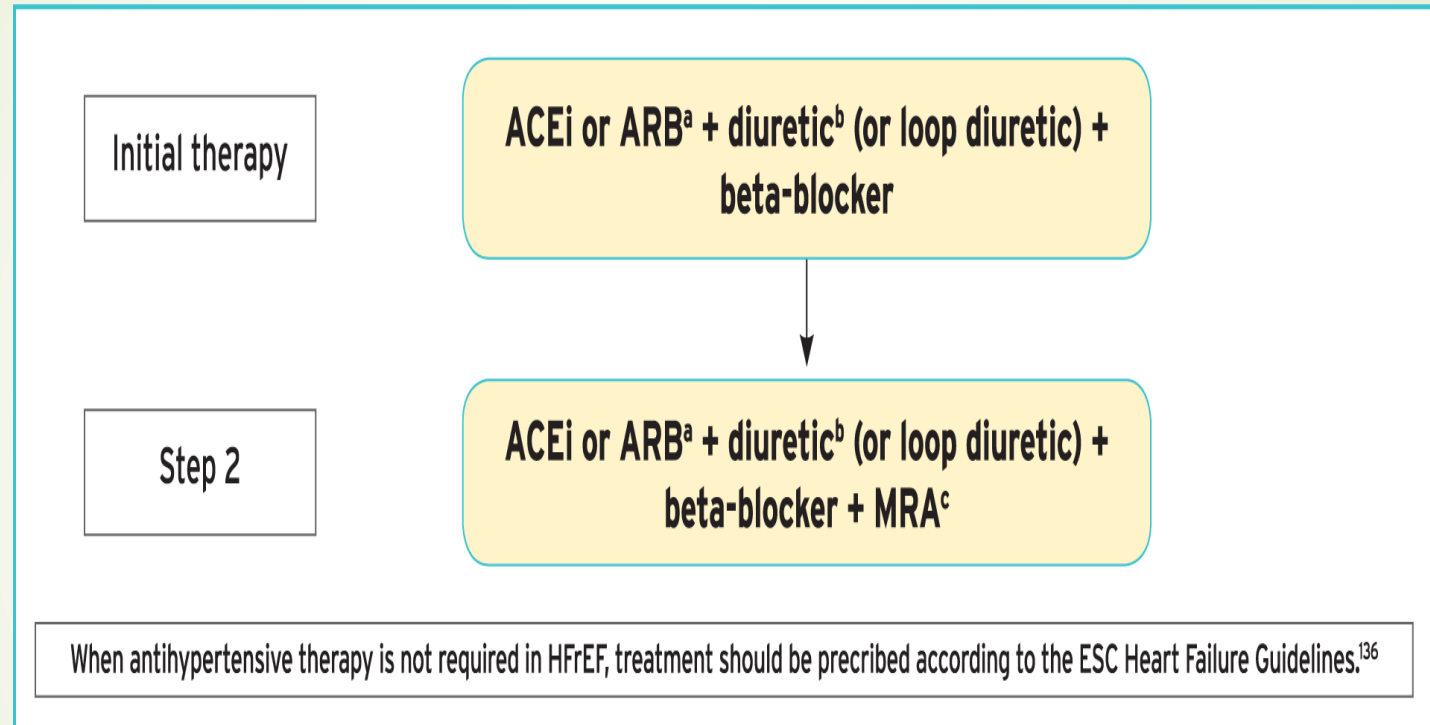
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Drug treatment strategy for hypertension and **chronic kidney** disease. ACEi = angiotensin-converting enzyme ...



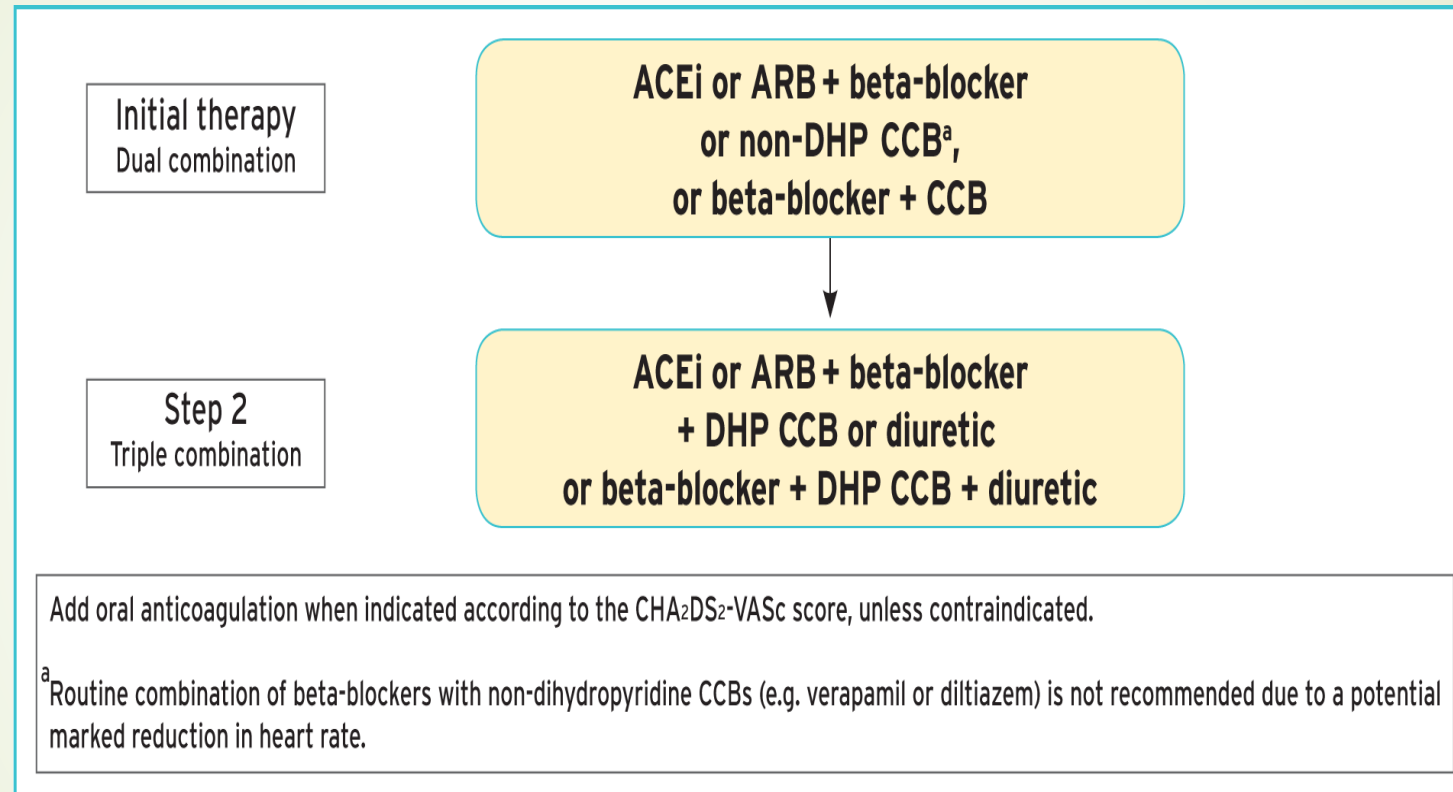
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Drug treatment strategy for hypertension and **hear failure with reduced ejection fraction. Do not use ...**



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Drug treatment strategy for hypertension and atrial fibrillation. ACEi = angiotensin-converting enzyme ...



Natural history of coronary atherosclerosis

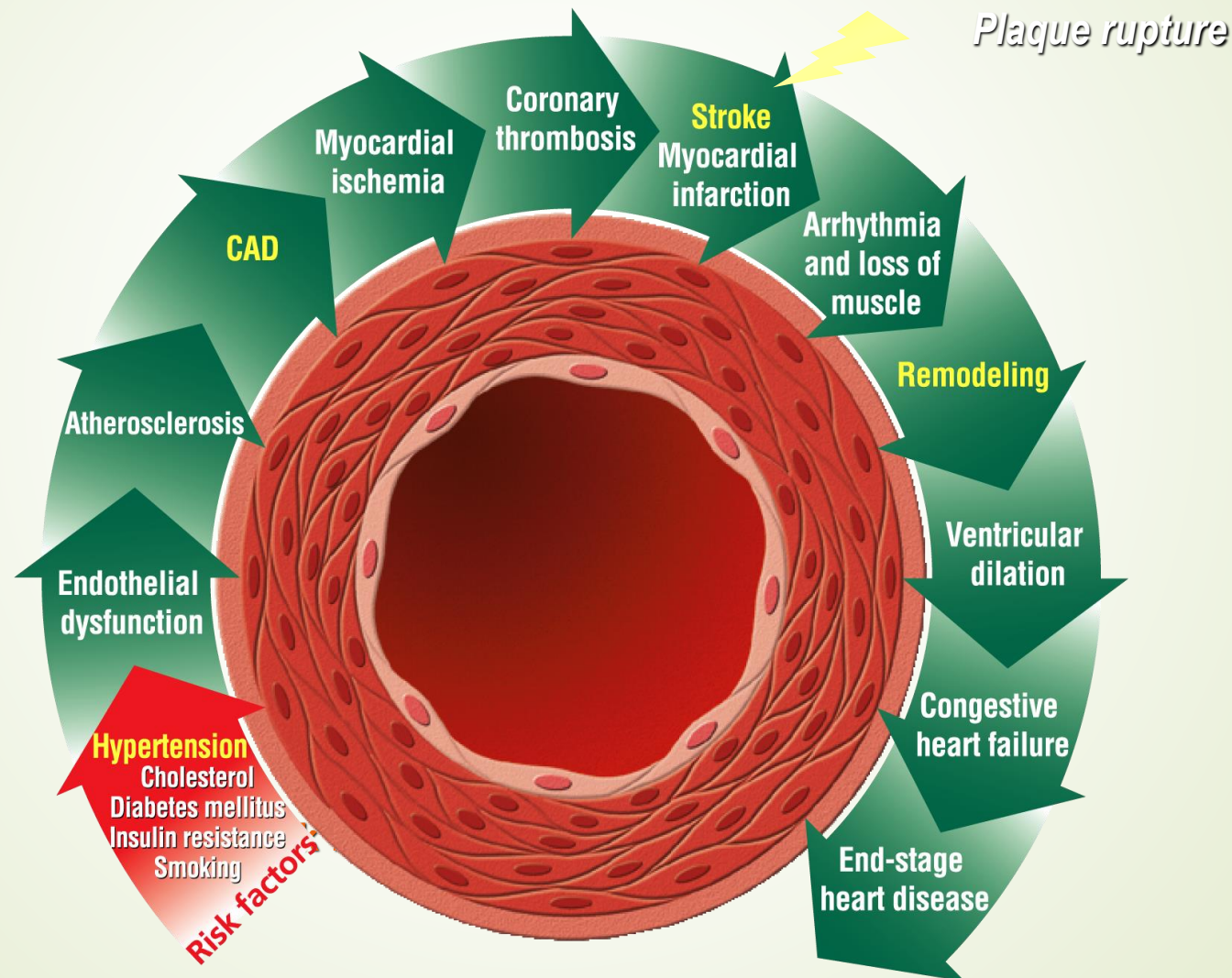


Table 5 Ten year cardiovascular risk categories (Systematic COronary Risk Evaluation system)

Very high risk	People with any of the following:
	<p>Documented CVD, either clinical or unequivocal on imaging</p> <ul style="list-style-type: none"> ● Clinical CVD includes acute myocardial infarction, acute coronary syndrome, coronary or other arterial revascularization, stroke, TIA, aortic aneurysm, and PAD ● Unequivocal documented CVD on imaging includes significant plaque (i.e. $\geq 50\%$ stenosis) on angiography or ultrasound; it does not include increase in carotid intima-media thickness ● Diabetes mellitus with target organ damage, e.g. proteinuria or a with a major risk factor such as grade 3 hypertension or hypercholesterolaemia ● Severe CKD (eGFR < 30 mL/min/1.73 m²) ● A calculated 10 year SCORE of $\geq 10\%$
High risk	People with any of the following:
	<ul style="list-style-type: none"> ● Marked elevation of a single risk factor, particularly cholesterol > 8 mmol/L (> 310 mg/dL), e.g. familial hypercholesterolaemia or grade 3 hypertension (BP $\geq 180/110$ mmHg) ● Most other people with diabetes mellitus (except some young people with type 1 diabetes mellitus and without major risk factors, who may be at moderate-risk)
	Hypertensive LVH
	Moderate CKD eGFR 30-59 mL/min/1.73 m²
	A calculated 10 year SCORE of 5-10%
Moderate risk	<p>People with:</p> <ul style="list-style-type: none"> ● A calculated 10 year SCORE of ≥ 1 to $< 5\%$ ● Grade 2 hypertension ● Many middle-aged people belong to this category
Low risk	<p>People with:</p> <ul style="list-style-type: none"> ● A calculated 10 year SCORE of $< 1\%$

Table 7 Correction factors for the Systemic COronary Risk Evaluation (SCORE) cardiovascular risk estimates in first-generation immigrants to Europe³⁵

Region of origin	Multiplication factor
Southern Asia	1.4
Sub-Saharan Africa	1.3
Caribbean	1.3
Western Asia	1.2
Northern Africa	0.9
Eastern Asia	0.7
Southern America	0.7

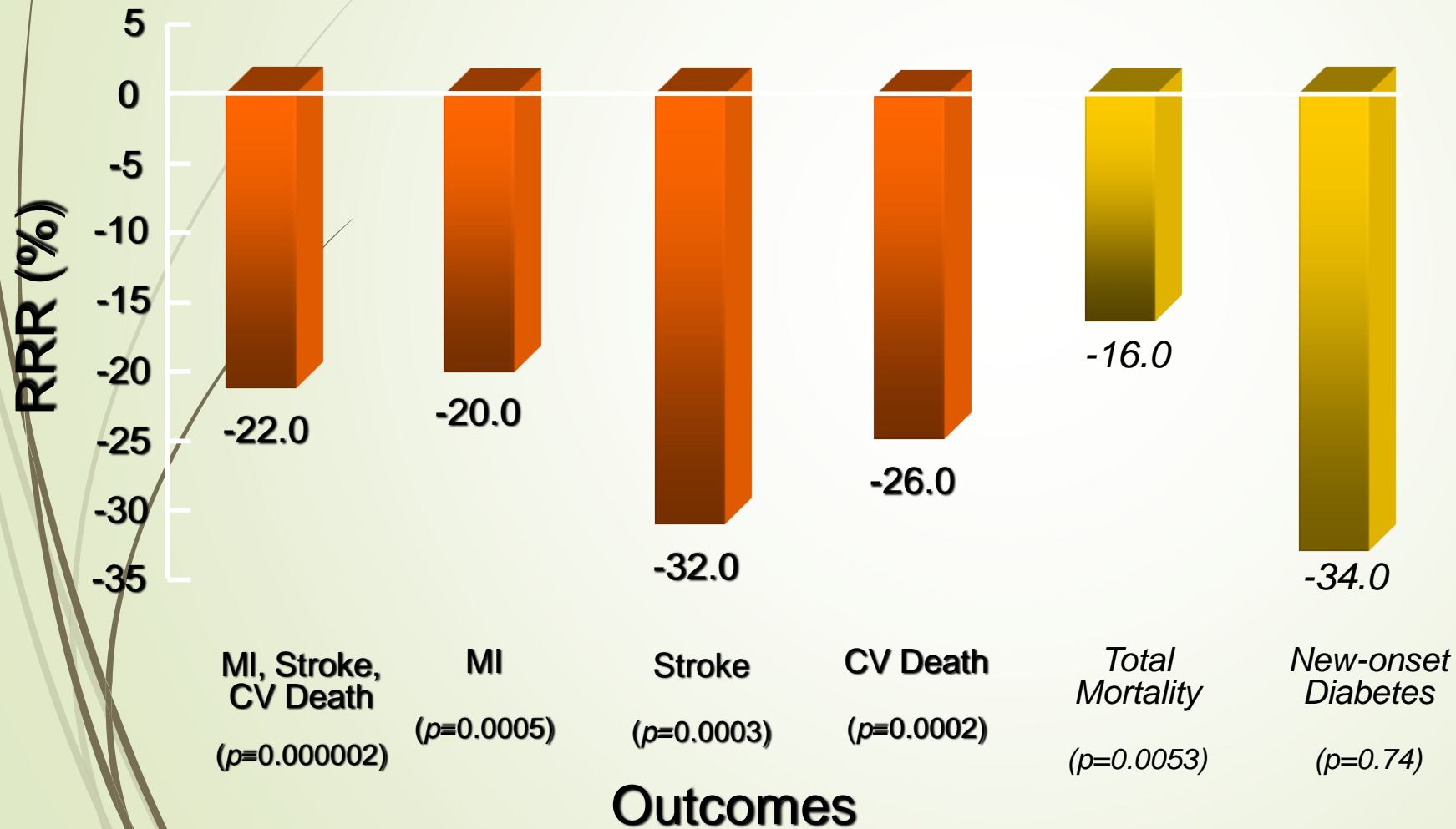


HOPE STUDY

- ▶ The HOPE study, which involved 9,297 high-risk patients with vascular disease or diabetes plus one other cardiovascular risk factor without a history of HF or left ventricular dysfunction, showed that ramipril was associated with significant reductions in all-cause mortality, MI and stroke in these patients.
- ▶ The findings of the HOPE study support the prescription of an ACE inhibitor for prevention of cardiovascular complications in all high-risk patients, which therefore includes those with stable angina .

Hope. Ramipril vs Placebo

CV Benefits of Ramipril in High Risk Patients



HOPE - Secondary and Other Endpoint Results

Endpoint	Ramipril (n=4645)	Placebo (n=46532)	RR	P value
Secondary Outcomes - %				
Revascularization	16.0	18.6	0.84	<0.001
Hospitalization for UA	12.2	12.4	0.98	0.68
Complications/DM	6.2	7.4	0.84	<0.03
Hospitalization for HF	3.3	3.8	0.87	0.19
Other Outcomes - %				
Heart failure	9.2	11.7	0.77	<0.001
Cardiac arrest	0.8	1.2	0.63	0.03
Worsening angina	23.8	26.2	0.89	0.003
New diagnosis of DM	3.7	5.3	0.68	0.002
Unstable angina with ECG changes	3.9	4.0	0.96	0.72

UA = unstable angina; DM = diabetes mellitus; HF = heart failure

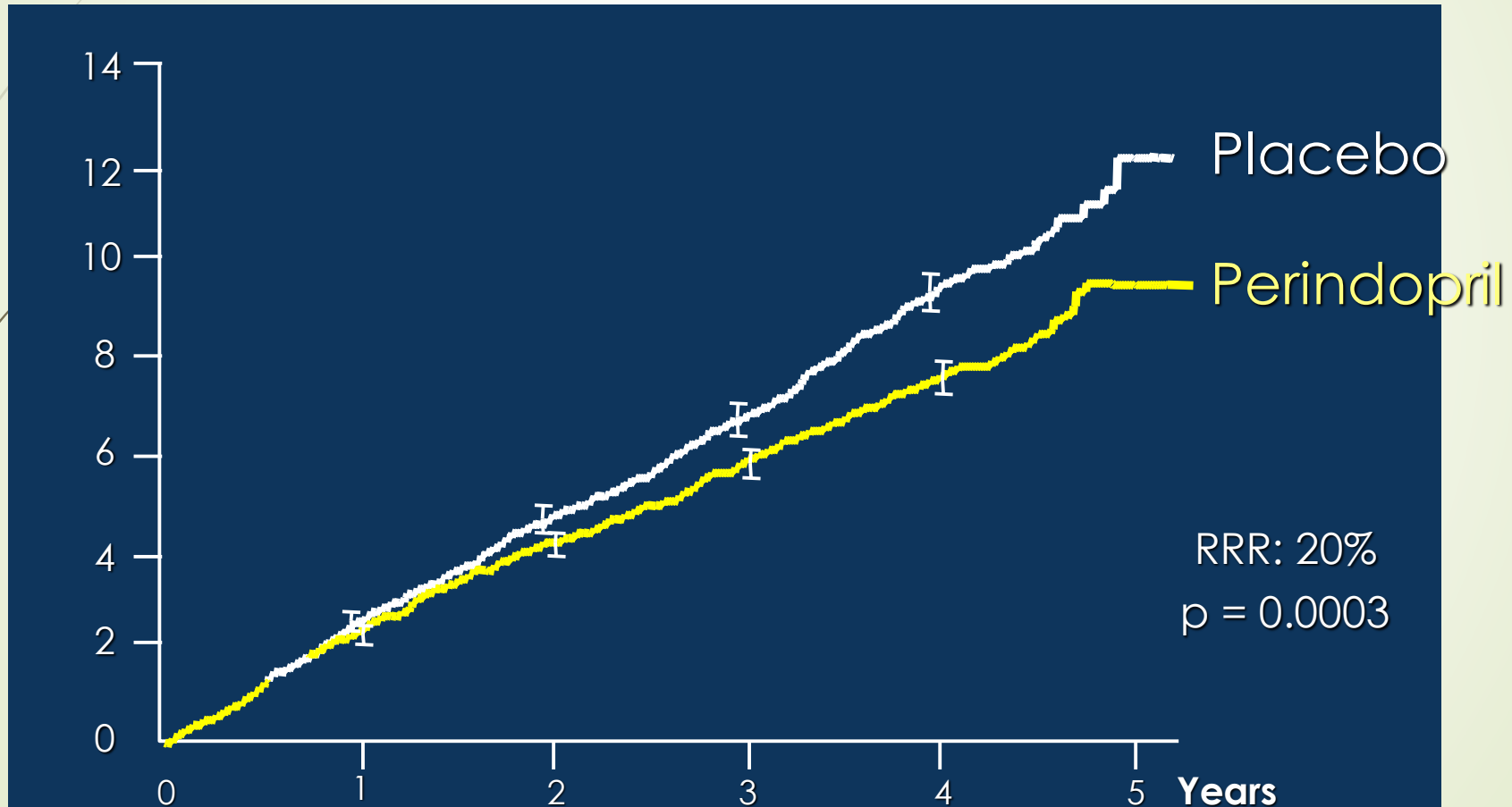


EUROPA STUDY

- ▶ The use of perindopril in the EUROPA study, involving 13,655 patients with stable coronary disease and no clinical evidence of HF, reduced the risk of cardiovascular death, MI or cardiac arrest.
- ▶ The results of the EUROPA study further demonstrated that these ACE inhibitors should be considered in all patients with CAD

Primary End Point

% CV death, MI or cardiac arrest



Placebo annual event rate: 2.4%

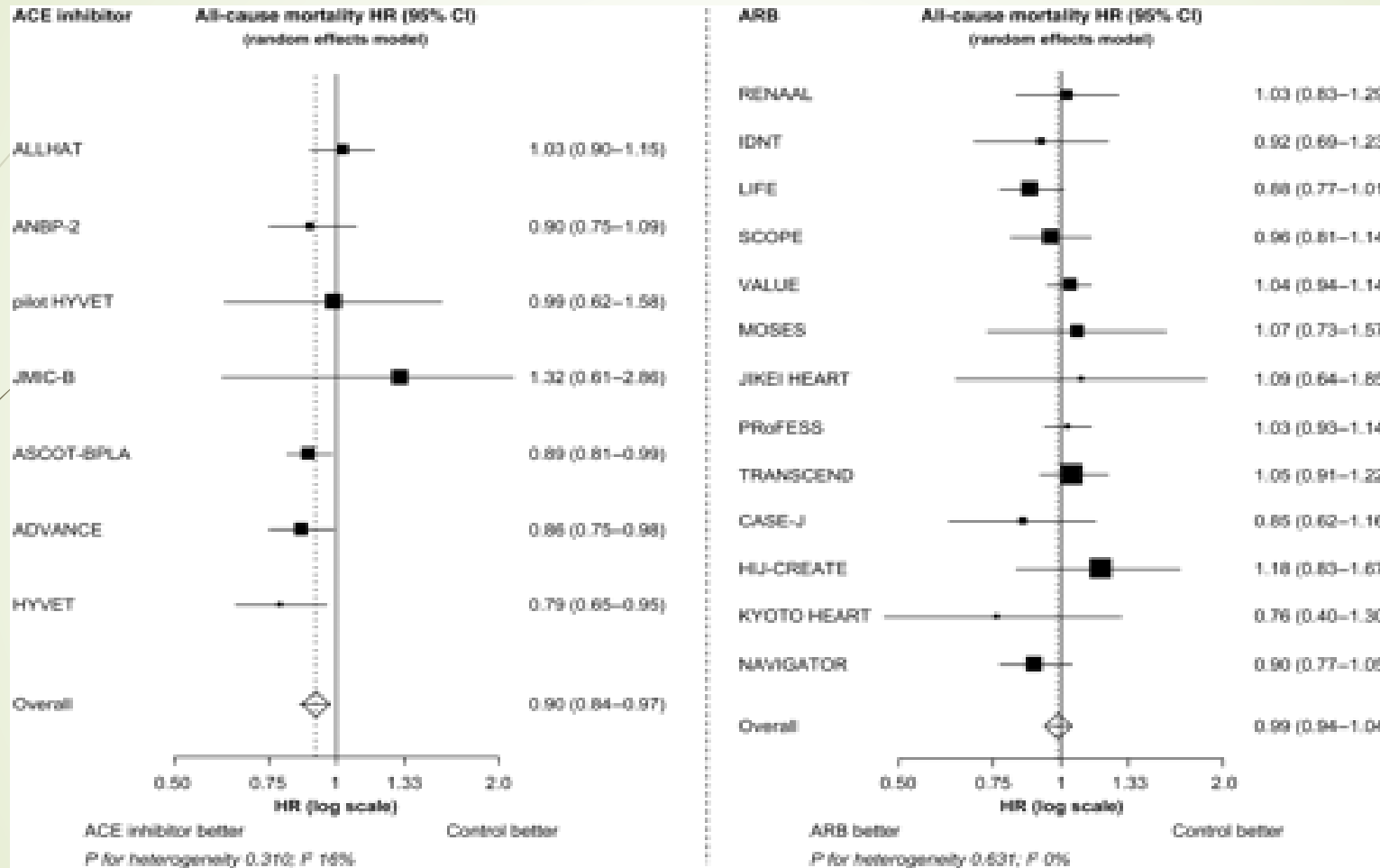
Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin–angiotensin–aldosterone system inhibitors involving 158 998 patients

Laura C. van Vark^{1*}, Michel Bertrand², K. Martijn Akkerhuis¹, Jasper J. Brugts¹, Kim Fox³, Jean-Jacques Mourad⁴, and Eric Boersma¹

¹Department of Cardiology, Thoraxcenter, Erasmus MC, 's Gravendijkwal 230, 3015 GE Rotterdam, The Netherlands; ²Lille Heart Institute, Lille, France; ³Royal Brompton and National Heart Hospital, London, UK; and ⁴Avicenne University Hospital, Bobigny and Paris 13 University, Paris, France

Received 24 August 2011; revised 15 February 2012; accepted 5 March 2012; online publish-ahead-of-print 17 April 2012

The all-cause mortality treatment effect of ACE inhibitor and ARB trials.





CONCLUSION

- **The overall reduction in all-cause mortality resulted almost completely from the class of ACE inhibitors, which were associated with a statistically significant 10% relative reduction in all-cause mortality, whereas no mortality reduction was observed with the ARBs**
- **BP-dependent beneficial effects in the prevention of stroke and heart failure are similar for ACE inhibitors and ARBs**
- **ACE inhibitors and ARBs have also been shown to be equally effective in preventing atrial fibrillation and new-onset diabetes**
- **In view of the high prevalence of hypertension in the general population, widespread use of ACE inhibitors may therefore result in a considerable gain in lives saved**



Original Investigation

May 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

Jun Cheng, MD¹; Wen Zhang, MMed²; Xiaohui Zhang, MMed¹; [et al](#)

[» Author Affiliations](#) | [Article Information](#)

JAMA Intern Med. 2014;174(5):773-785. doi:10.1001/jamainternmed.2014.348

From: **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**

JAMA Intern Med. 2014;174(5):773-785. doi:10.1001/jamainternmed.2014.348

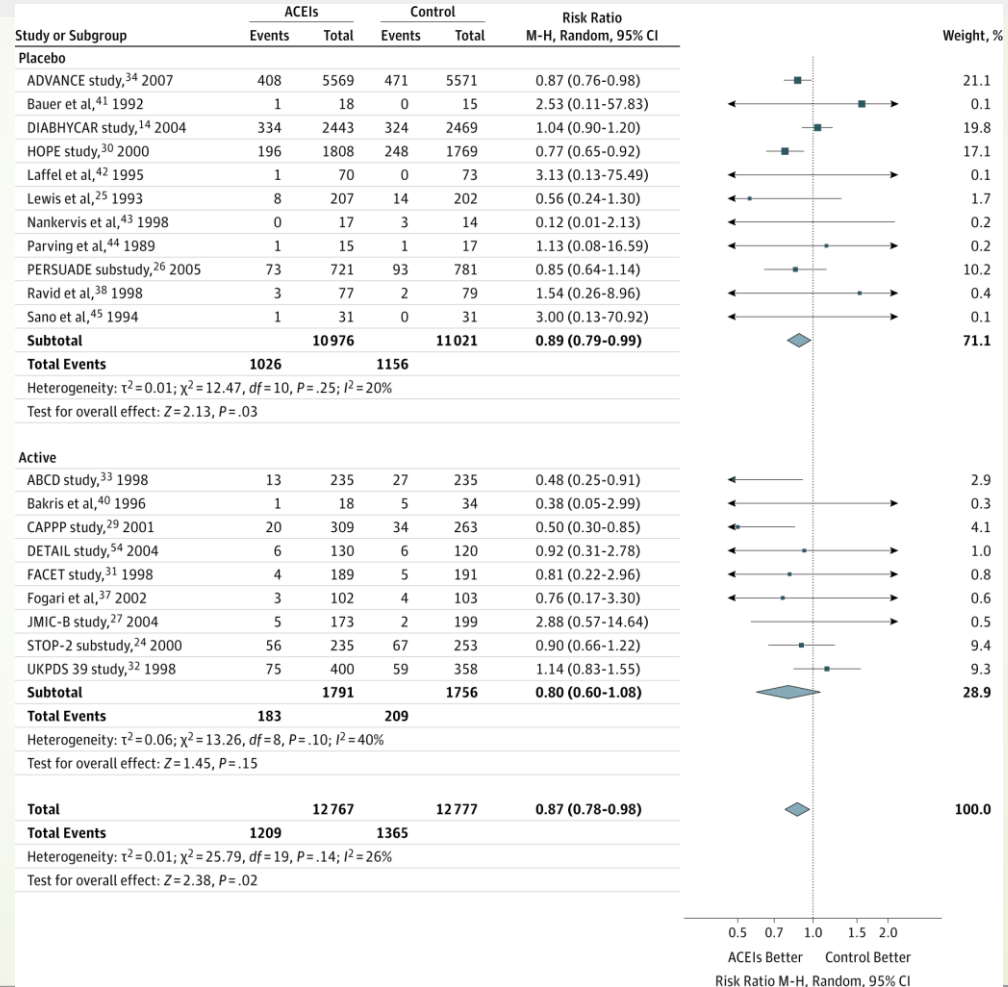
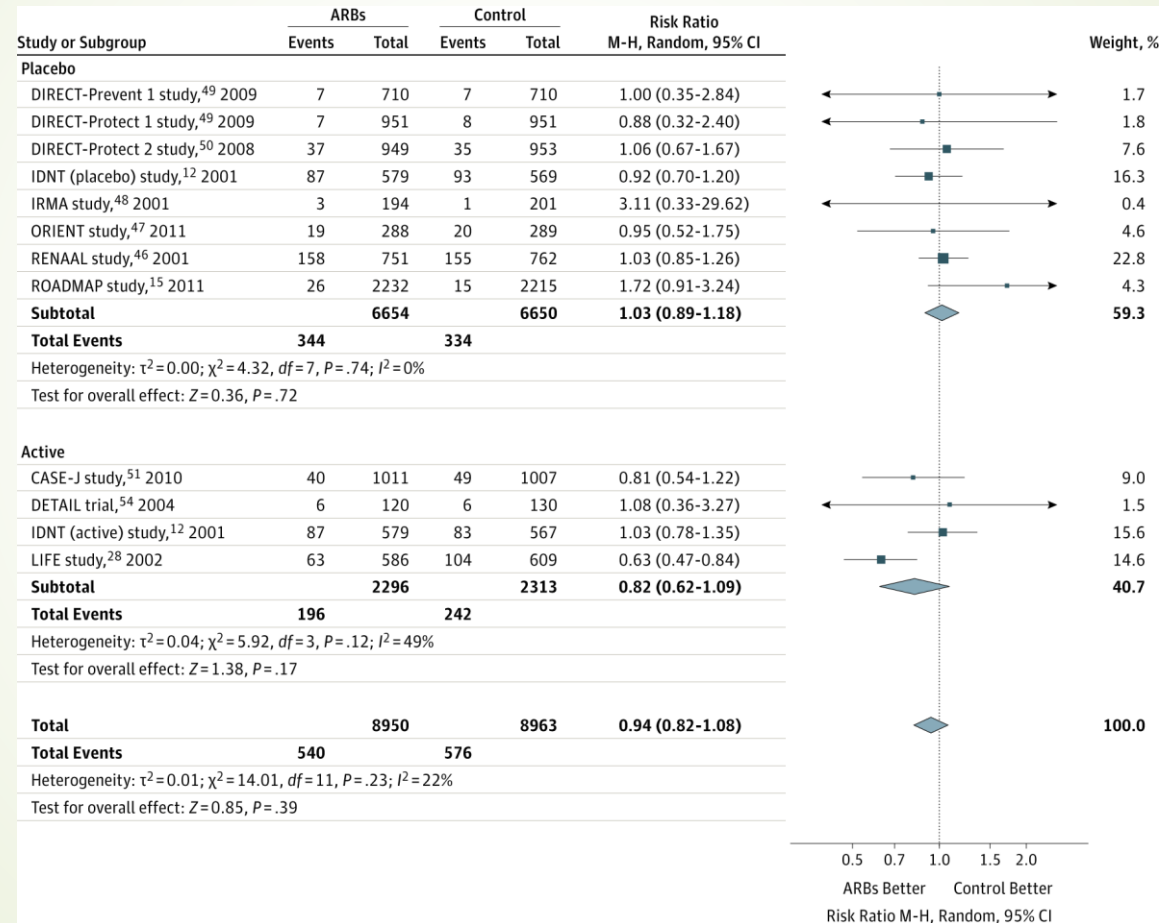



Figure Legend:

From: **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**


JAMA Intern Med. 2014;174(5):773-785. doi:10.1001/jamainternmed.2014.348





Twenty-three of 35 identified trials compared **ACEIs** with placebo or active drugs (32 827 patients)

Thirteen compared **ARBs** with no therapy (controls) (23 867 patients).



When compared with controls
(placebo/active treatment), ACEIs
significantly reduced the

Risk of **all-cause mortality** by 13%
(RR, 0.87; 95% CI, 0.78-0.98),

CV deaths by 17% (0.83; 0.70-0.99),

Major CV events by 14% (0.86; 0.77-
0.95), **including myocardial infarction** by
21% (0.79; 0.65-0.95)

Heart failure by 19% (0.81; 0.71-0.93).



Treatment with ARBs did not significantly affect


All-cause mortality

(RR, 0.94; 95% CI, 0.82-1.08)

CV death rate (1.21; 0.81-1.80),

Major CV events (0.94; 0.85-1.01)

**with the exception of heart failure
(0.70; 0.59-0.82)**



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.

European Journal of Preventive Cardiology



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Angiotensin-converting enzyme inhibitors reduce mortality compared to angiotensin receptor blockers: Systematic review and meta-analysis

[Gabriel LO Salvador](#), [Vinicius M Marmentini](#), [Willian R Cosmo](#), more...

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First Published September 1, 2017 | Research Article |



<https://doi.org/10.1177/2047487317728766>

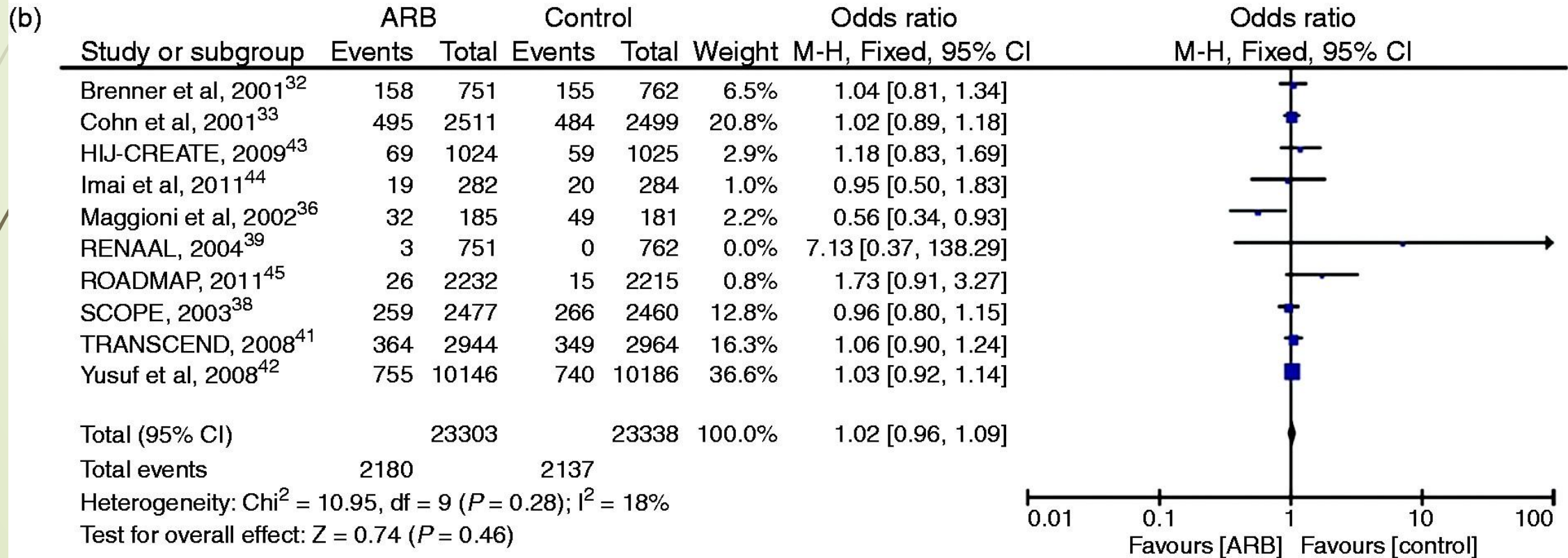
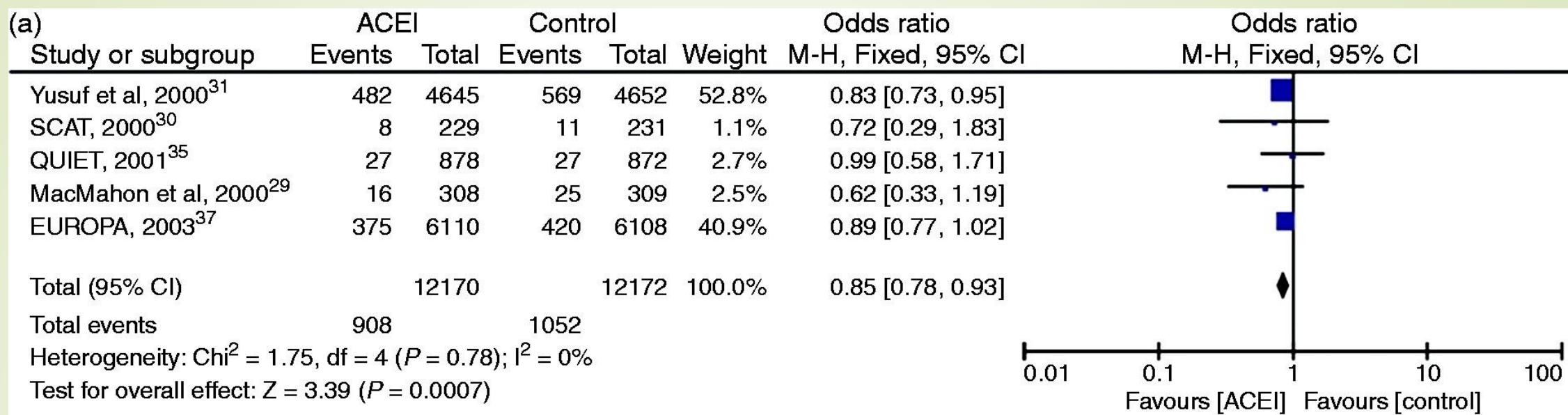
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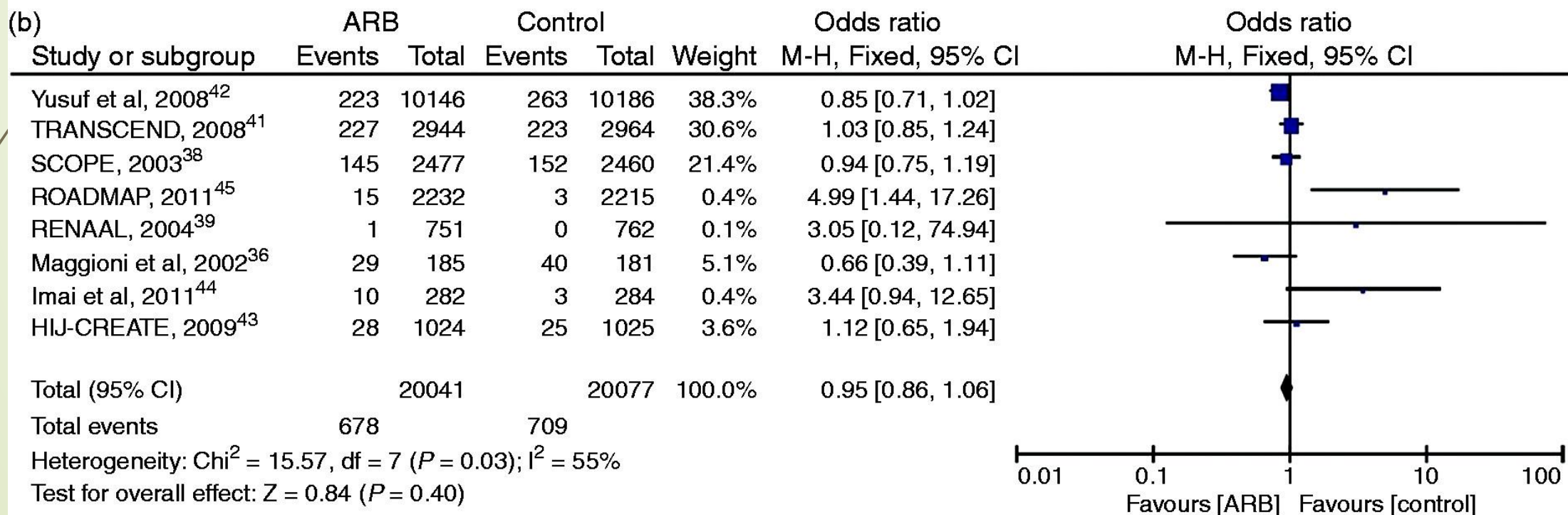
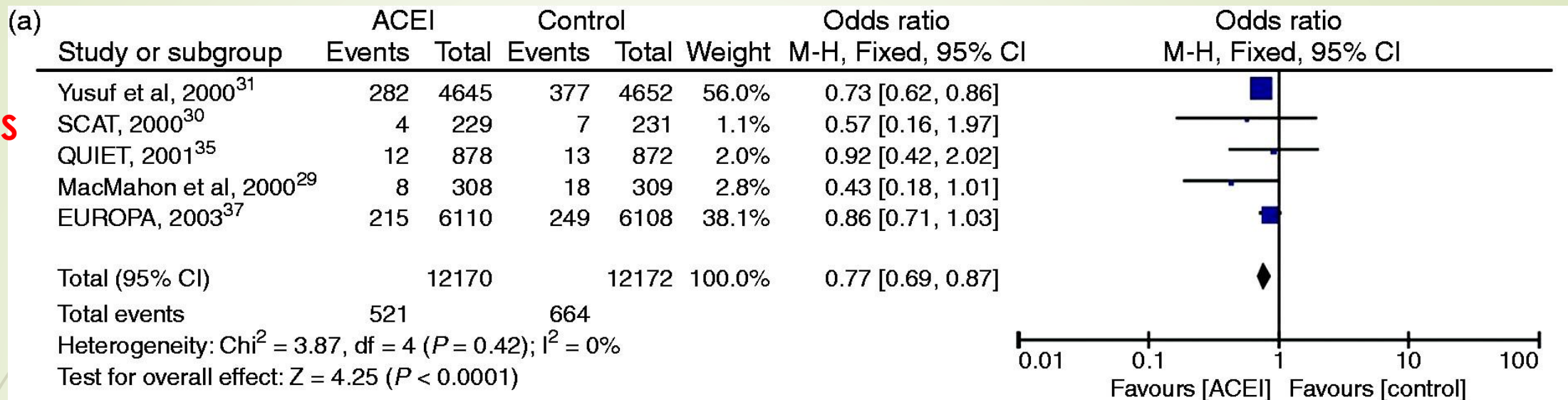
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TOTAL DEATHS



**TOTAL
CVS DEATHS**





Conclusion

Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use is similar in preventing major cardiovascular outcomes regarding acute myocardial infarction, stroke and heart failure/hospitalisation. However, the use of angiotensin-converting enzyme inhibitors is more effective in reducing total deaths and cardiovascular deaths than angiotensin II receptor blockers.



Journal of the American College of Cardiology

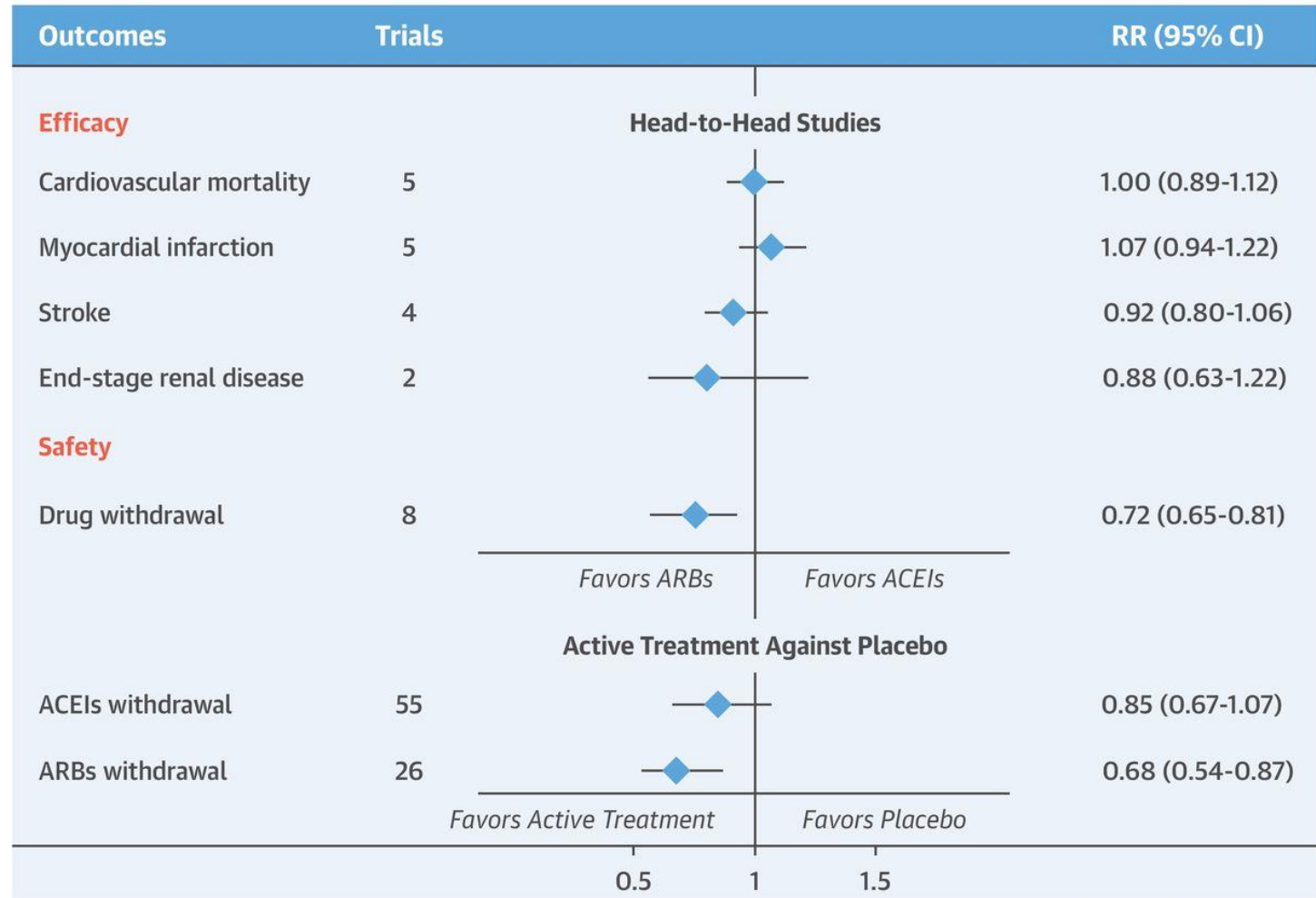
Volume 71, Issue 13, April 2018

DOI: [10.1016/j.jacc.2018.01.058](https://doi.org/10.1016/j.jacc.2018.01.058)

Angiotensin-Converting Enzyme Inhibitors in Hypertension To Use or Not to Use?

Franz H. Messerli, Sripal Bangalore, Chirag Bavishi and Stefano F. Rimoldi

CENTRAL ILLUSTRATION: Efficacy and Safety of ACE Inhibitors and ARBs From Head-to-Head Studies and Compared With Placebo Trials



Messerli, F.H. et al. *J Am Coll Cardiol.* 2018;71(13):1474-82.

Franz H. Messerli et al. *JACC* 2018;71:1474-1482

Cardio-protection from ACE Inhibitors in At Risk Patients: Evidences from recent meta-analyses

	ACEI vs Placebo				ARB vs Placebo			
	Myocardial Infarction	Cardiovascular Death	All-Cause Death	N	Myocardial Infarction	Cardiovascular Death	All-Cause Death	N
High risk, Bangalore et al ³	0.83 (0.78–0.9)	0.83 (0.7–0.99)	0.89 (0.80–1.0)	62 398	0.93 (0.85–1.03)	1.02 (0.92–1.14)	1.01 (0.96–1.06)	66 282
High risk, Savarese ⁴	0.81 (0.75–0.88)	0.9 (0.78–1.03)	0.91 (0.85–0.98)	53 791	0.9 (0.8–1.02)	1.03 (0.85–1.26)	1.01 (0.94–1.08)	54 421
Diabetes mellitus, Cheng ⁵	NA	0.83 (0.70–0.99)	0.89 (0.79–0.99)	21 997	NA	1.21 (0.81–1.8)	1.03 (0.89–1.18)	13 304
Hypertension, Thomopoulos et al ⁶	NA	0.87 (0.78–0.98)	0.91 (0.85–0.98)	49 440	NA	1.03 (0.94–1.13)	1.01 (0.97–1.06)	65 256

Values indicate hazard ratio (95% confidence interval). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Risk of MI, CV Mortality, and All-Cause Mortality in Parallel Meta-Analyses of Placebo-Controlled Trials of ACEI & ARBs

Overall results demonstrated

- 9% to 11% risk reduction in all-cause mortality (P<0.05)
- 10% to 17% risk reduction in cardiovascular mortality (P<0.05)
- 17% to 19% risk reduction in MI (P<0.05)

Do ARBs Increase the Risk of MI?

Evidence from ONTARGET Study

ARB achieved a lower BP than ACEI (0.9/0.6 mmHg) but paradoxically had a Non significant 7% excess of MI²

Table 3. Incidence of the Primary Outcome, Its Components, and Death from Any Cause.

Outcome	Ramipril (N= 8576)	Telmisartan (N= 8542)	Combination Therapy (N=8502)	Telmisartan vs. Ramipril	Combination Therapy vs. Ramipril
		<i>number (percent)</i>		<i>risk ratio (95% CI)</i>	
Death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure*	1412 (16.5)	1423 (16.7)	1386 (16.3)	1.01 (0.94–1.09)	0.99 (0.92–1.07)
Death from cardiovascular causes, myocardial infarction, or stroke†	1210 (14.1)	1190 (13.9)	1200 (14.1)	0.99 (0.91–1.07)	1.00 (0.93–1.09)
Myocardial infarction‡	413 (4.8)	440 (5.2)	438 (5.2)	1.07 (0.94–1.22)	1.08 (0.94–1.23)
Stroke‡	405 (4.7)	369 (4.3)	373 (4.4)	0.91 (0.79–1.05)	0.93 (0.81–1.07)
Hospitalization for heart failure‡	354 (4.1)	394 (4.6)	332 (3.9)	1.12 (0.97–1.29)	0.95 (0.82–1.10)
Death from cardiovascular causes	603 (7.0)	598 (7.0)	620 (7.3)	1.00 (0.89–1.12)	1.04 (0.93–1.17)
Death from noncardiovascular causes	411 (4.8)	391 (4.6)	445 (5.2)	0.96 (0.83–1.10)	1.10 (0.96–1.26)
Death from any cause	1014 (11.8)	989 (11.6)	1065 (12.5)	0.98 (0.90–1.07)	1.07 (0.98–1.16)

ARB (Telmisartan) was not inferior to the ACEI (Ramipril) for reducing the risk of major CV events overall, including CV death¹

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 10, 2008 VOL. 358 NO. 15

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

The ONTARGET Investigators*

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*

Different Mechanisms of ACE Inhibitors and ARBs

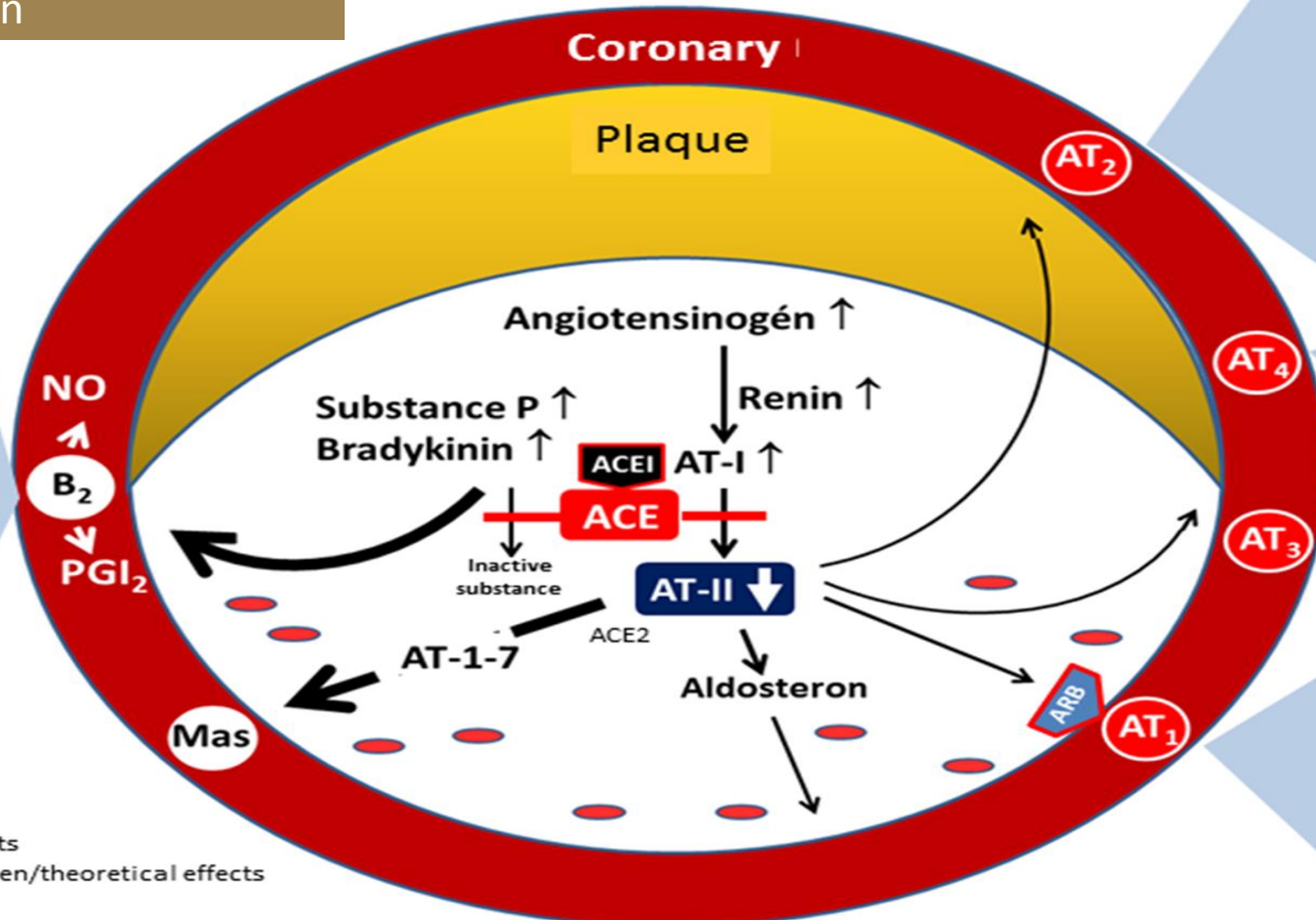
ACEIs

Suppress Ang II and prevent the breakdown of Bradykinin

ARBs

Selective antagonist of AT1
Increase Ang II Levels by 200% to 300%

- Vasodilation
- Antiaggregation
- Antiproliferation
- Stimulate t-PA synthesis
- Cytoprotection
- Endothelfunction
- Plaque stabilization



- Vasodilation
- Antiproliferation (?)
- Antioxidant effect
- Neuroprotection
- Apoptosis (?)
- Hypertrophy (?)
- Remodelling (?)
- Plaque instabilisation (?)
- Inflammation (?)

Increased expression of PAI-1 (?)

- Endotheldysfunction
- Prothrombotic (?)

- Vasodilation
- Antiinflammatory
- Improved endothelfunction
- Reduced hypertrophy
- Antiproliferation

Blue: Beneficial/proven effects
Red: Non-beneficial /unproven/theoretical effects



CONCLUSIONS

- **Ace inhibitors have the strongest evidence in treatment and prevention of cardiovascular disease.**
- **Clinical trials comparing ACE and ARB blockers are rare.**
- **Most meta analysis studies have shown that ACE inhibitors reduce cardiovascular mortality in high risk patients when comparing with ARB blockers.**
- **In lower risk patients both ACE and ARB blockers has equal effect on CVS Mortality.**
- **Withdrawal of medication due to side effects are higher in ACE inhibitors than ARB Blockers.**



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”