Update sulla terapia antiipertensiva e antiaggregante nel paziente cardiometabolico

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Antiplatelet therapy

Aspirin

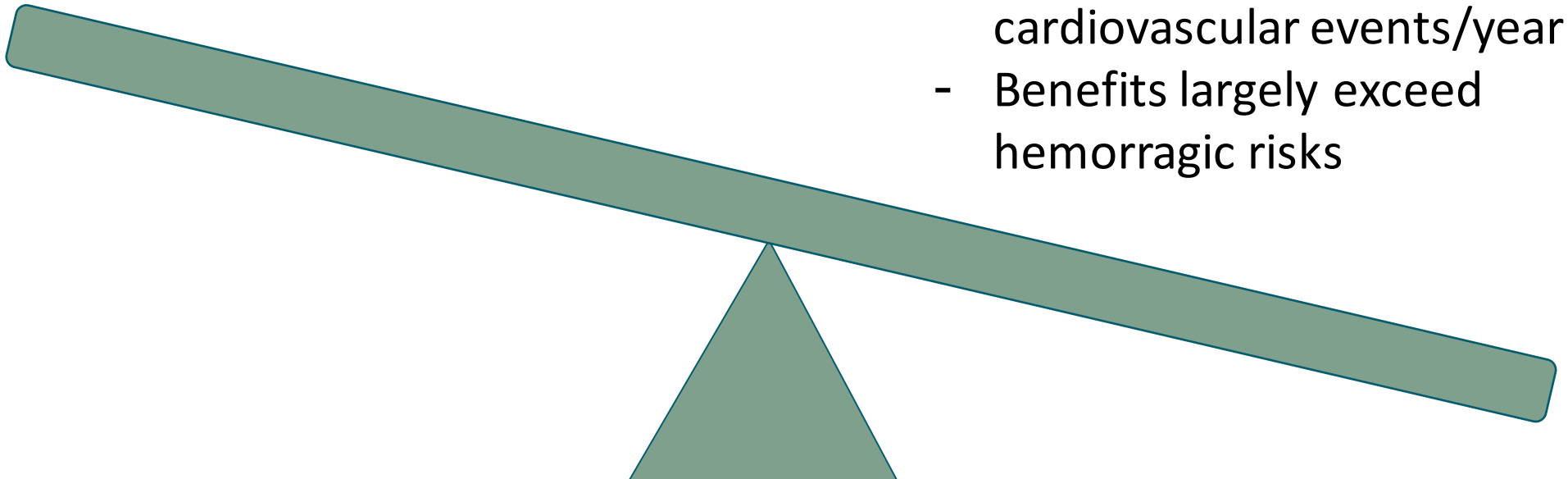
Aspirin: settings

Primary prevention

- No clear evidences
- Uncertain balance between vascular prevention and risk of bleeds

Secondary prevention

- Prevention of 1/5 of atherothrombotic vascular complications
- ↓ 10-20/1000 non fatal cardiovascular events/year
- Benefits largely exceed hemorragic risks



Randomized trials in primary prevention

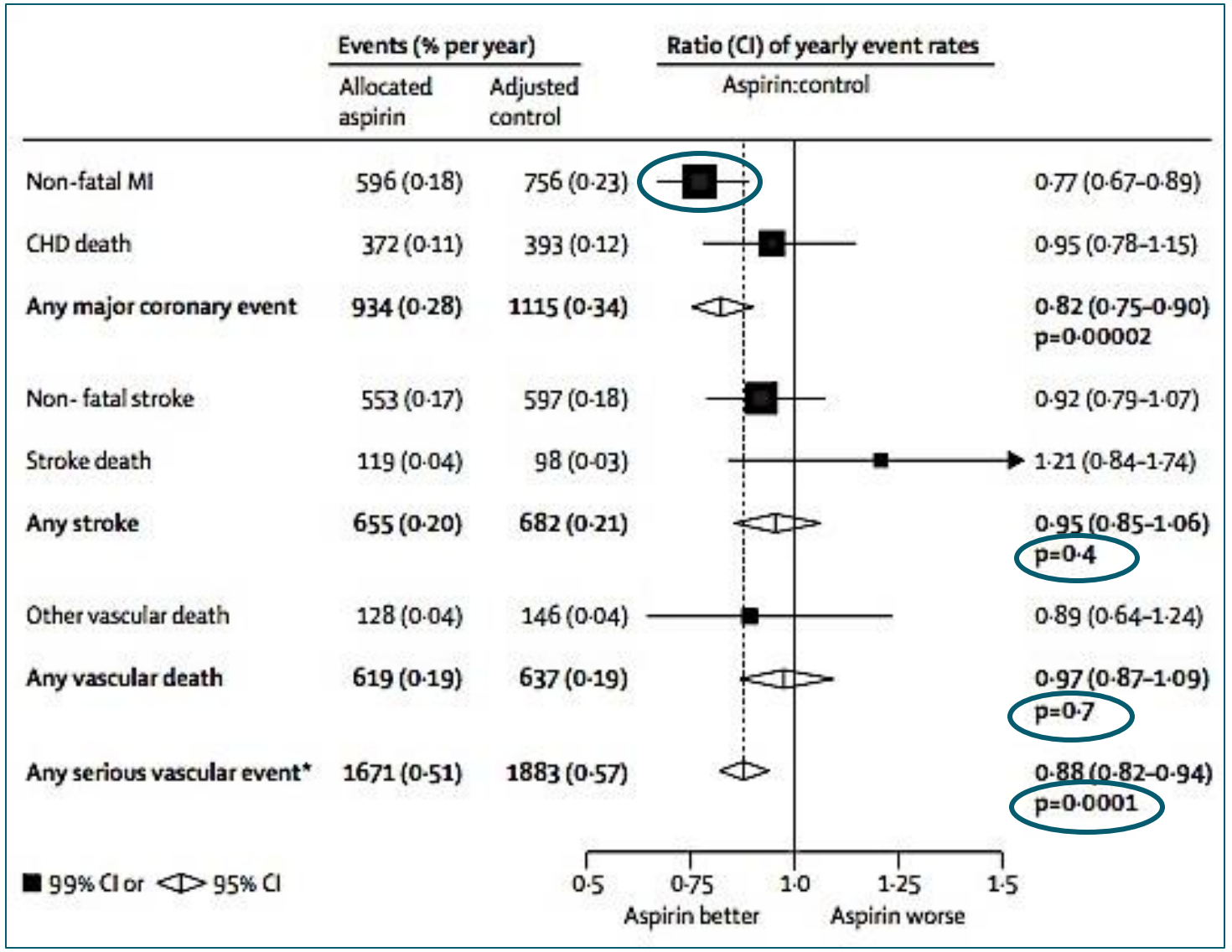
	Year	N° of partecipants	Mean FU	Aspirin regimen	Primary endpoint	NNT	NNH
British Doctors' Study	1988	5139	5.6	500 mg/die	MI, stroke, CV death	3266	1260
US Physicians' Health Study	1988	22071	5.0	325 mg on	MI, stroke, CV death	875	2760
Thrombosis Preventio Trial					s	501	2335
Hypertension Optima Treatment Trial						956	650
Primary Prevention Project						451	442
Women's Health Study				alternate daily		4495	4372
POPADAD	2008	1276	6.7	100 mg/die	MI, stroke, CV death or amputation	1425	-1069
JPAD	2008	2539	4.1	81 or 100 mg daily	Any atherothrombotic event	325	547
AAA	2010	3350	8.2	100 mg/die	Coronary events, stroke or revascularization	- 2747	981

More than 100.000 patients

Mean duration of follow up: 6 years.

More than 4000 serious vascular events ranging from 0.25% to 2.4%.

Aspirin in primary prevention in general population

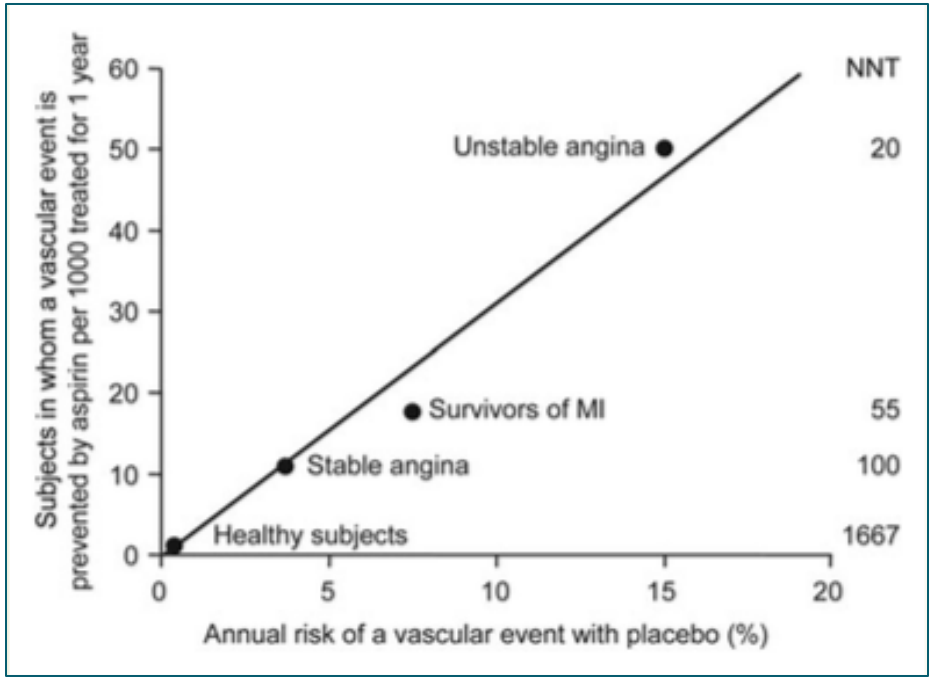


Antithrombotic Trialists' (ATT) Collaboration; Lancet 2009; 373: 1849–60

Individual partecipant data of 6 primary prevention trials
→ 95000 individuals

- Reduction serious vascular events, due mainly to a reduction in non-fatal myocardial infarction
- No differences in vascular, non vascular and all cause mortality
- Marginally significant increase in haemorragic strokes
- Significant increase in major gastrointestinal and other extracranial bleeds, mostly due to non fatal bleeds

Aspirin in primary prevention in general population



Absolute decrease in events depending on the underlying CVD risk

Relationship between risk of coronary events and haemorragic events

	Major coronary event	Probably ischaemic stroke	Haemorrhagic stroke	Major extracranial bleed
Age (per decade)	1·84 (1·74–1·95)	2·46 (2·27–2·65)	1·59 (1·33–1·90)	2·15 (1·93–2·39)
Male sex*	2·43 (1·94–3·04)	1·44 (1·14–1·82)	1·11 (0·52–2·34)	1·99 (1·45–2·73)
Diabetes mellitus	2·66 (2·28–3·12)	2·06 (1·67–2·54)	1·74 (0·95–3·17)	1·55 (1·13–2·14)
Current smoker	2·05 (1·85–2·28)	2·00 (1·72–2·31)	2·18 (1·57–3·02)	1·56 (1·25–1·94)
Mean blood pressure (per 20 mm Hg)†	1·73 (1·59–1·89)	2·00 (1·77–2·26)	2·18 (1·65–2·87)	1·32 (1·09–1·58)
Cholesterol (per 1 mmol/L)	1·18 (1·12–1·24)	1·02 (0·95–1·09)	0·90 (0·77–1·07)	0·99 (0·90–1·08)
Body-mass index (per 5 kg/m²)	1·09 (1·03–1·15)	1·06 (0·98–1·14)	0·85 (0·71–1·02)	1·24 (1·13–1·35)

Antithrombotic Trialists' (ATT) Collaboration; Lancet 2009; 373: 1849–60
Patrono C. European Heart Journal (2013) 34, 3403–3411

Aspirin in primary prevention in general population

Earlier 6 trial of ASA in primary prevention

All 9 trial of ASA in primary prevention

Table 2 Meta-analyses of primary prevention aspirin trials

Meta-analysis	Major vascular events	Major coronary events	Any stroke	Vascular death	Any death
ATT Collaboration:[1] rate ratio (95% CI)	0.88 (0.82–0.94)	0.82 (0.75–0.90)	0.95 (0.85–1.06)	0.97 (0.87–1.09)	0.95 (0.88–1.02)
Raju *et al.*:[30] relative risk (95% CI)	0.88 (0.83–0.94)	0.83 (0.69–1.00)	0.93 (0.82–1.05)	0.96 (0.84–1.09)	0.94 (0.88–1.00)
Bartolucci *et al.*:[31] odds ratio (95% CI)	0.87 (0.80–0.93)	0.85 (0.69–1.02)	0.92 (0.83–1.02)	0.96 (0.80–1.14)	0.93 (0.87–1.00)

- More recent trials do not materially change picture from ATT (< 10% of overall population)
- Aspirin → 12% proportional reduction in major vascular events (driven mainly by reduction in non-fatal myocardial infarction)
- Benefits must be weighed against the increased risk of bleedings (trials excluded people at high risk of bleeding complications)

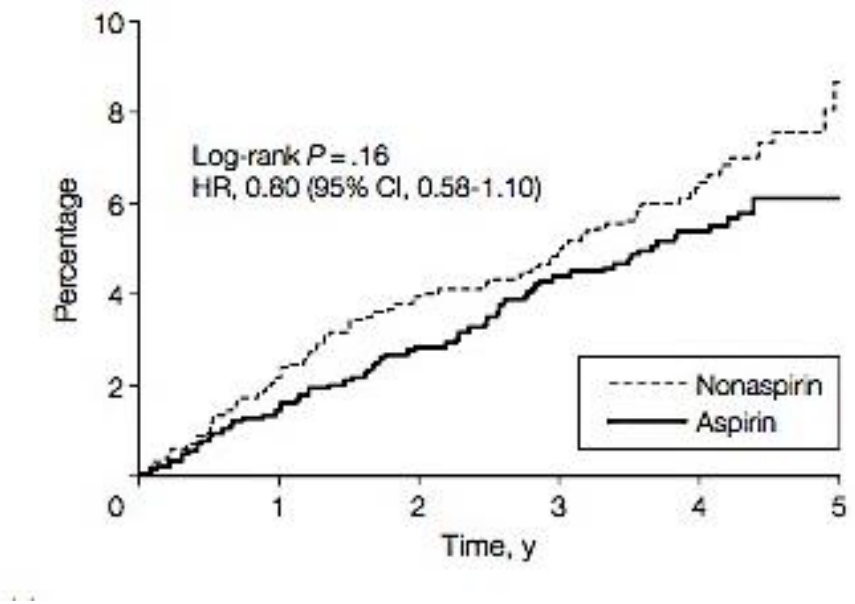
Unconclusive evidences and heterogeneous recommendations

Patrono C. European Heart Journal (2013) 34, 3403–3411

Aspirin in primary prevention in diabetics

JPAD

No differences in total percentage of atherosclerotic events (primary endpoint)

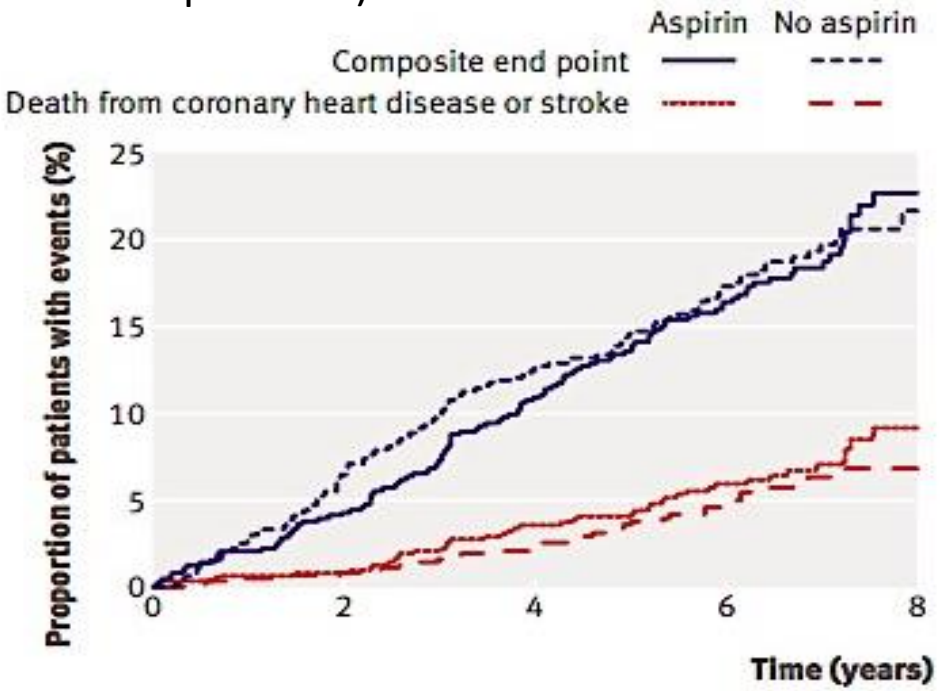


No differences in cerebrovascular disease, coronary arteries disease events, death for any cause

Significant reduction of coronary + cerebrovascular mortality in aspirin arm

POPADAD

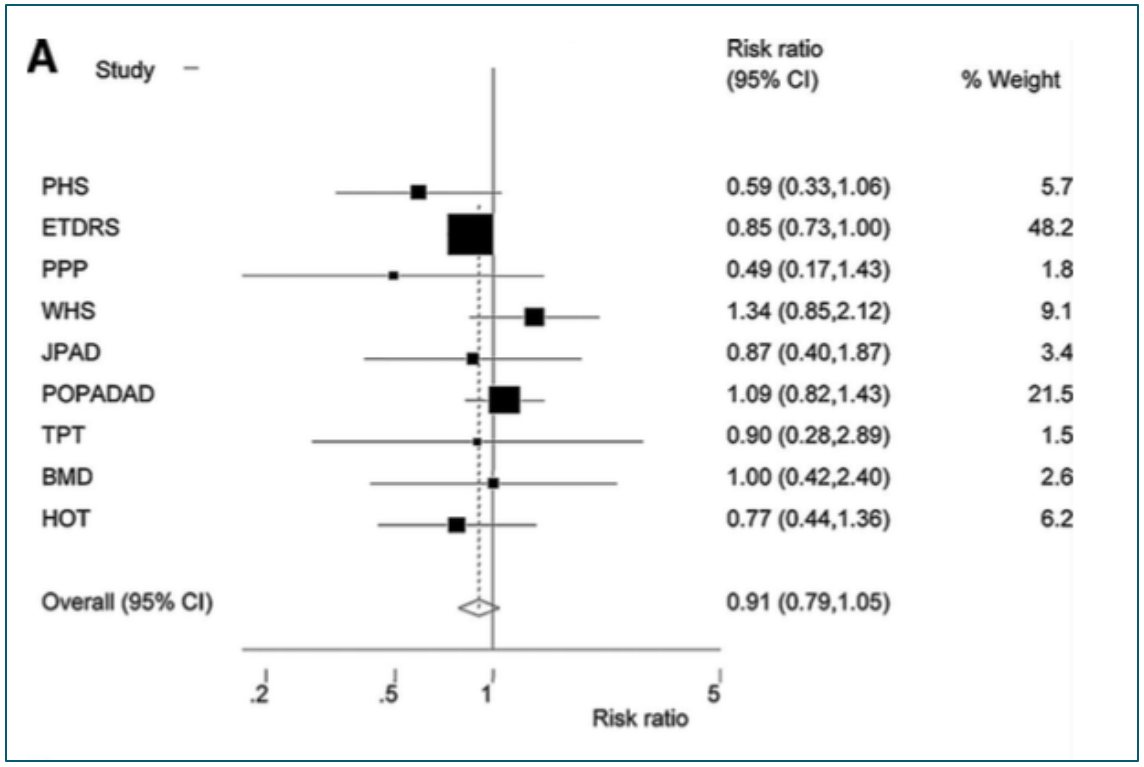
No differences in primary endpoint (death from coronary heart disease, stroke, non fatal MI, above ankle amputation)



No differences in secondary endpoints and in safety events

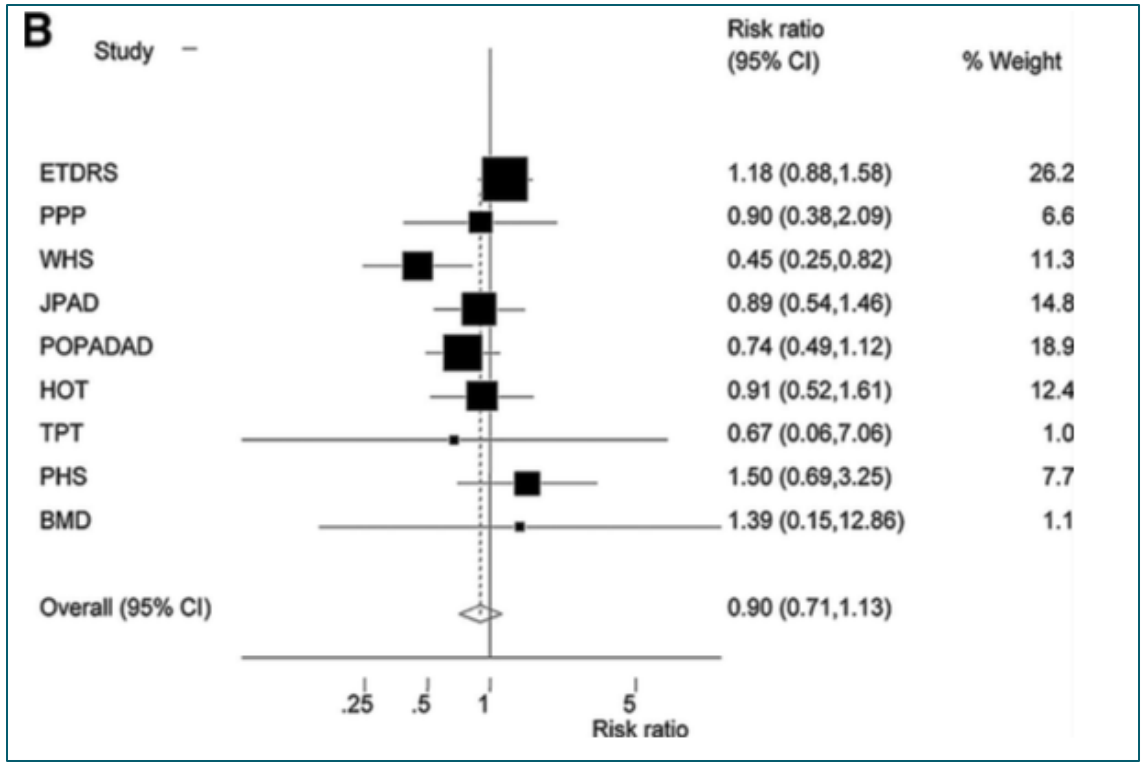
Aspirin in primary prevention in diabetics

Effect of aspirin on coronary artery disease
(non fatal and fatal myocardial infarction)



9% reduction in CAD → not statistically significant

Effect of aspirin on stroke



10% reduction in stroke → not statistically significant

Pignone M. et al. Diabetes Care. 2010 Jun; 33(6): 1395–1402.

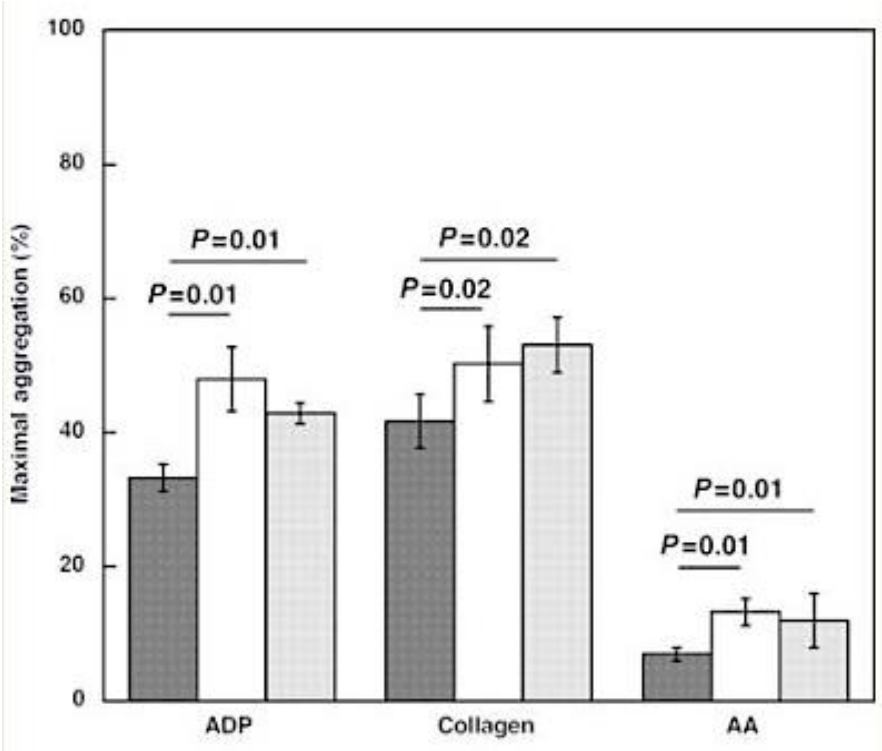
Antiplatelet therapy in people with diabetes

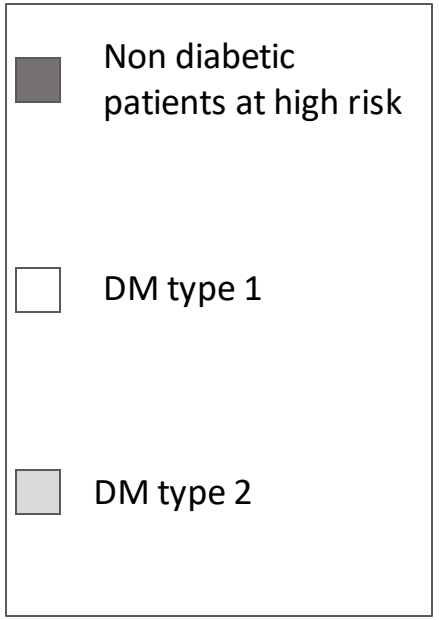
Recommendations	Class	Level
Antiplatelet therapy with aspirin in DM-patients at low CVD risk is not recommended.	III	A
Antiplatelet therapy for primary prevention may be considered in high risk patients with DM on an individual basis.	IIb	C
Aspirin at a dose of 75-160 mg/day is recommended as secondary prevention in DM.	I	A
A $P2Y_{12}$ receptor blocker is recommended in patients with DM and ACS for 1 year and in those subjected to PCI (duration depending on stent type). In patients with PCI for ACS preferably prasugrel or ticagrelor should be given.	I	A
Clopidogrel is recommended as an alternative antiplatelet therapy in case of aspirin intolerance.	I	B

Rydèn L. et al European Heart Journal (2013) 34, 3035–3087

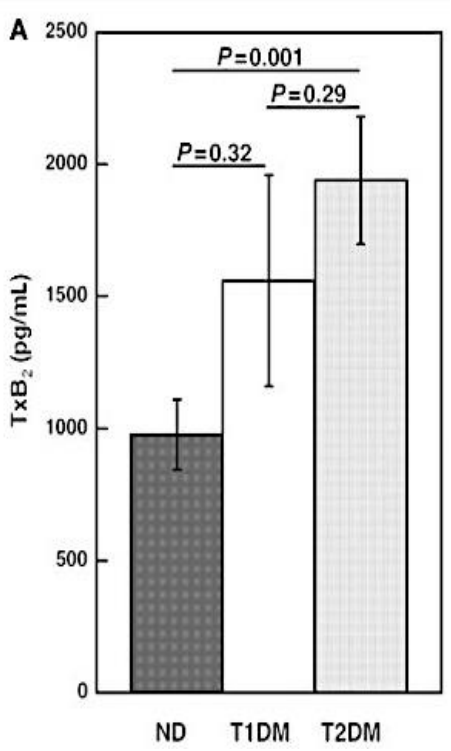
Aspirin in diabetes: high on-treatment platelet reactivity

Maximal percentage of platelat aggregation following attivation by ADP, collagen and arachidonic acid





Serum tromboxane concentrations and collagen induced tromboxane B2 production by platelets



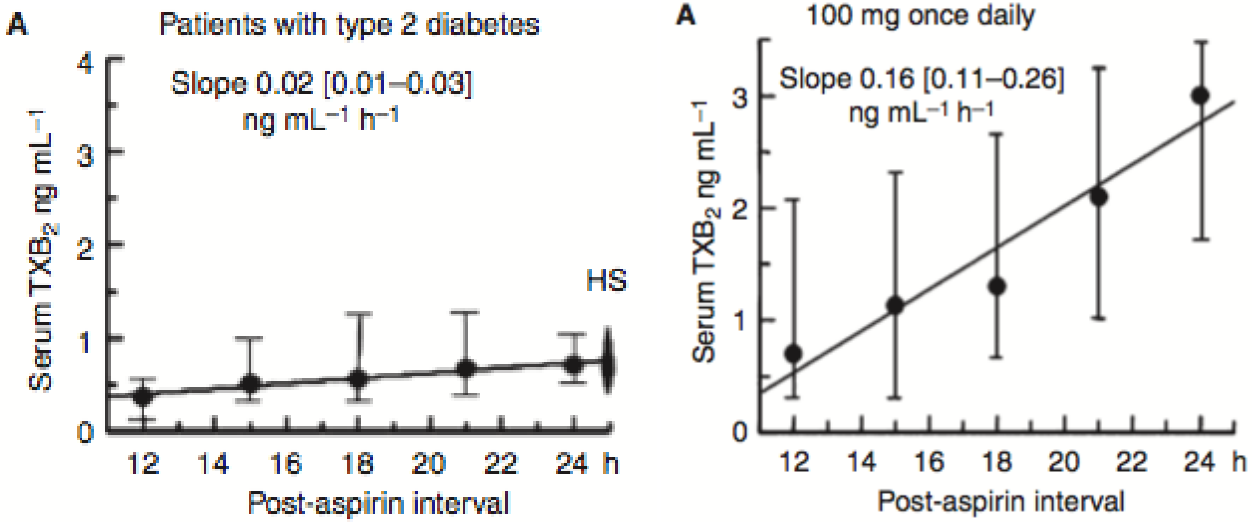
Reduced platelet sensitivity to the inhibitory action of aspirin on COX-1 in diabetic patients

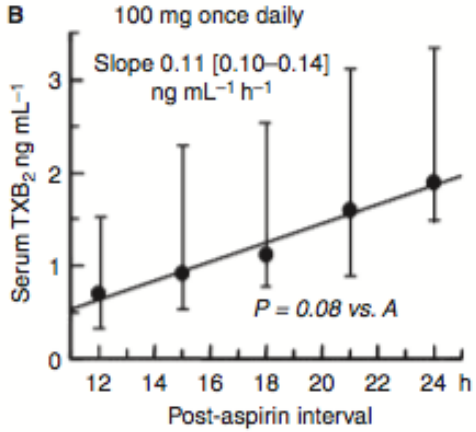
Pulcinelli M. et al. European Heart Journal (2009) 30, 1279–1286

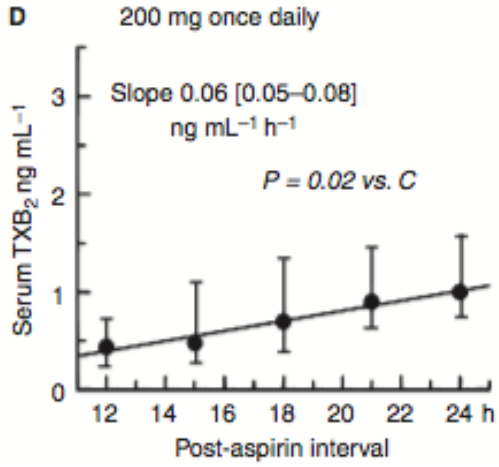
Aspirin in diabetes: high on-treatment platelet reactivity

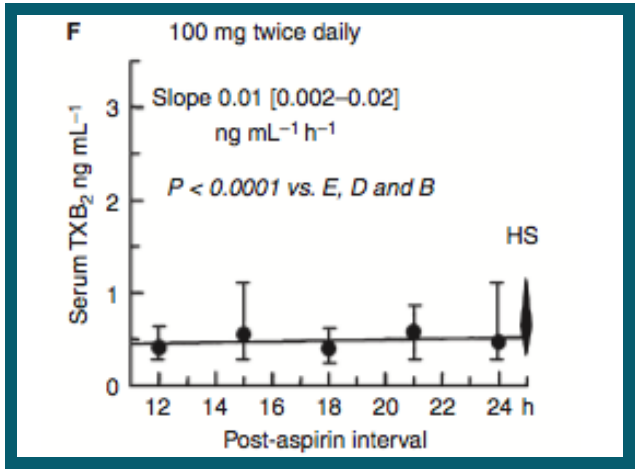
Potential mechanisms

- Faster recovery of the drug target expression or activity due to modified platelet turnover
- Co-morbidities (eg obesity), altering the pharmacokinetics of lipophilic drugs
- High intra-platelet protein translation due to low-grade inflammation
- Modification of the drug target (COX-1, P2Y12) due to hyper-glycation
- Variable pharmacokinetic and biotransformation (thienopyridines)









Variable Rate of Platelet Thromboxane Recovery in aspirin-treated Type 2 Diabetes Patients

Rocca B. et al Journal of Thrombosis and Haemostasis, 10: 1220–1230

Conclusion -1-

- Net clinical benefit of giving aspirin in primary prevention is difficult to assess by the imprecision of estimates of benefits and risks either in general population and in diabetic patients

- According to ESC guidelines aspirin in primary prevention may be considered in individual patient with high cardiovascular risk and low hemorragic risk.

- Aspirin from patients with type 2 diabetes (DM2) are characterized by increased volume, persistently enhanced TXA2 biosynthesis and platelet hyper-reactivity

- The conventional once daily dosing of aspirin may be sub-optimal in at least a fraction of patients with DM2.

- Trials specifically addressed to diabetic patients and testing a personalized antiplatelet regimen (e.g. bid) are needed.

Blood pressure control

Treatment target in diabetic patients

Guidelines recommendations

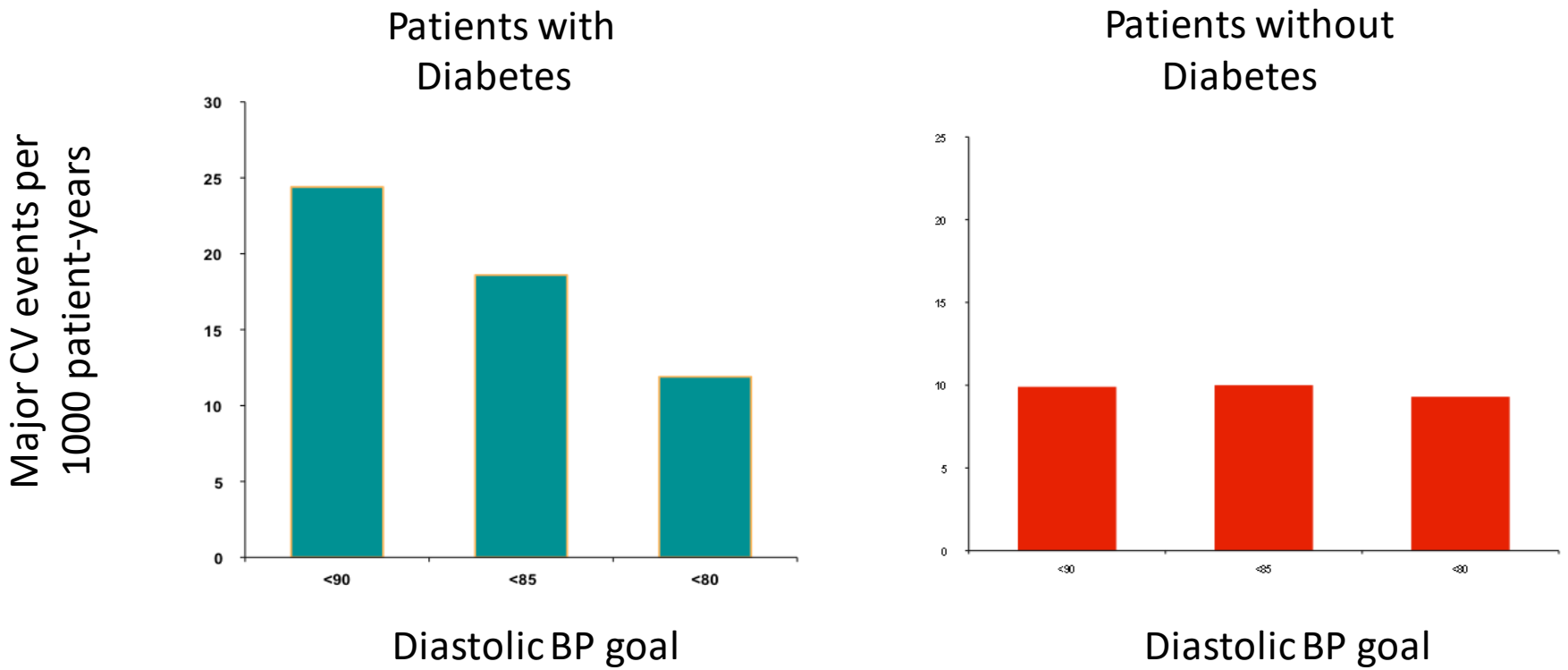
A SBP goal <140 mmHg:		
a) is recommended in patients at low–moderate CV risk;	I	B
b) is recommended in patients with diabetes;	I	A
c) should be considered in patients with previous stroke or TIA;	IIa	B
d) should be considered in patients with CHD;	IIa	B
e) should be considered in patients with diabetic or non-diabetic CKD.	IIa	B
In elderly hypertensives less than 80 years old with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg.	I	A
In fit elderly patients less than 80 years old SBP values <140 mmHg may be considered, whereas in the fragile elderly population SBP goals should be adapted to individual tolerability.	IIb	C
In individuals older than 80 years and with initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg provided they are in good physical and mental conditions.	I	B
A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated.	I	A

BP targets in type 2 DM are generally recommended to be <140/85 mmHg, but a lower target of <130/80 mmHg is recommended in selected patients (e.g. younger patients at elevated risk for specific complications) for additional gains on stroke, retinopathy and albuminuria risk. Renin-angiotensin-aldosterone system blocker is recommended in the treatment of hypertension in DM, particularly in the presence of proteinuria or micro- albuminuria. Recommended BP target in patients with type 1 DM is <130/80 mmHg.	I	B

Mancia G. et al. European Heart Journal (2013) 34, 2159–2219
Piepoli M.F. et al. European Heart Journal (2016) 37, 2315–2381

HOT trial

18,790 patients with a baseline diastolic BP of 100-115 mm Hg randomized to a target diastolic BP of ≤90 mm Hg, ≤85 mm Hg, or ≤80 mm Hg



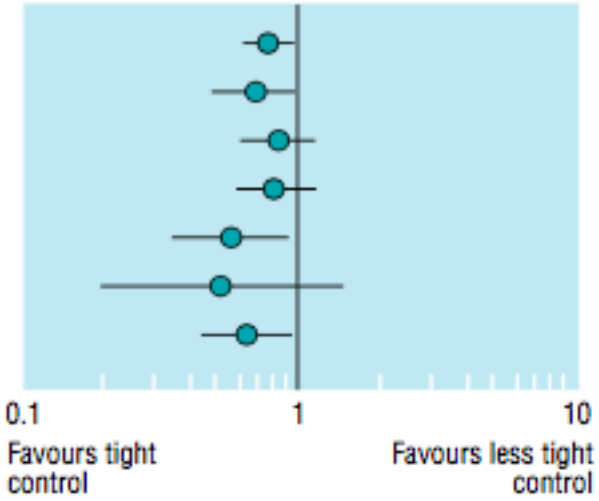
More intensive blood pressure control provides greater benefit in diabetics

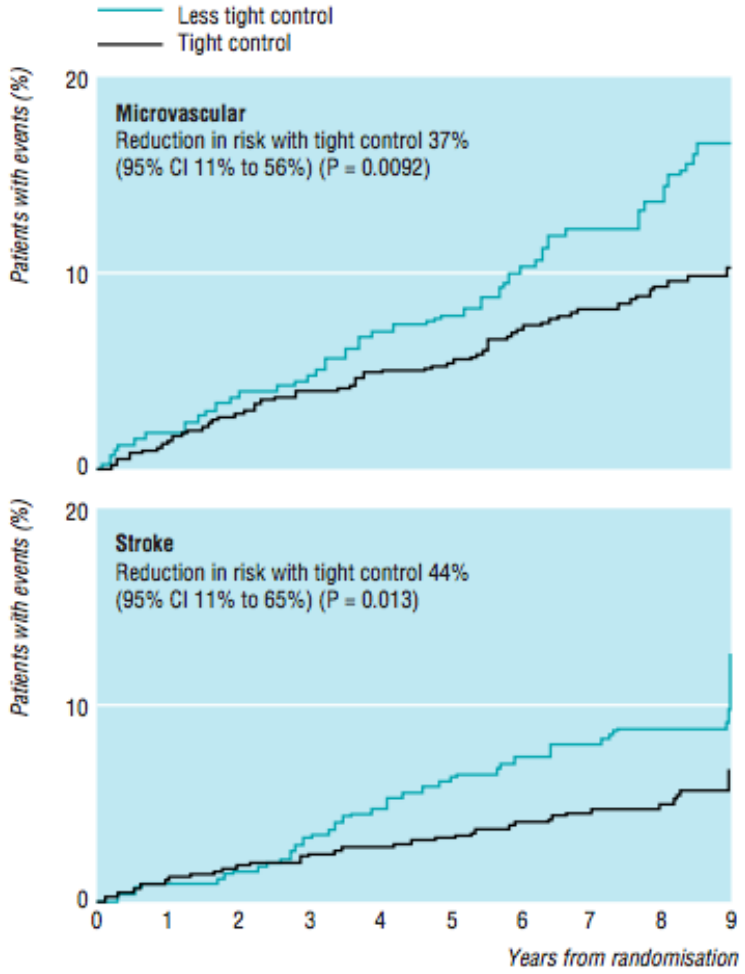
Hansson L et al. Lancet 1998;351:1755-1762

UKPDS 38 trial

1148 patients with type 2 diabetes randomized to a tight blood pressure control (PA < 150/85 mmHg) with the use of captopril/atenolol or to a less tight control (PA < 180/105 mmHg)

Clinical end point	P value
Any diabetes related end point	0.0046
Deaths related to diabetes	0.019
All cause mortality	0.17
Myocardial infarction	0.13
Stroke	0.013
Peripheral vascular disease	0.17
Microvascular disease	0.0092



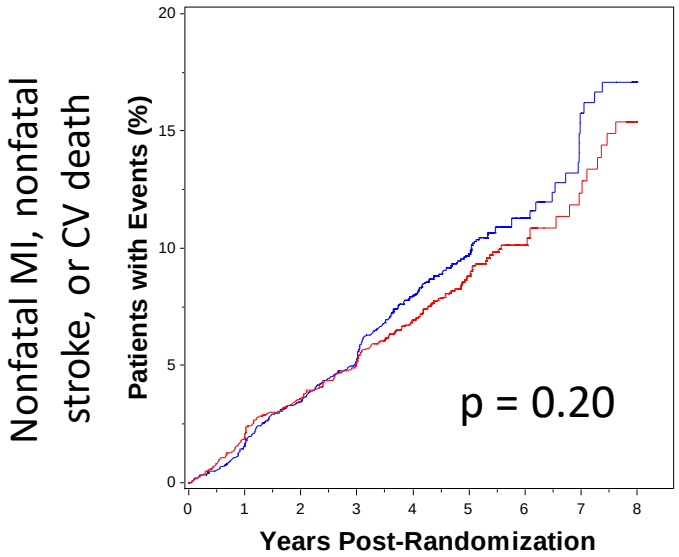


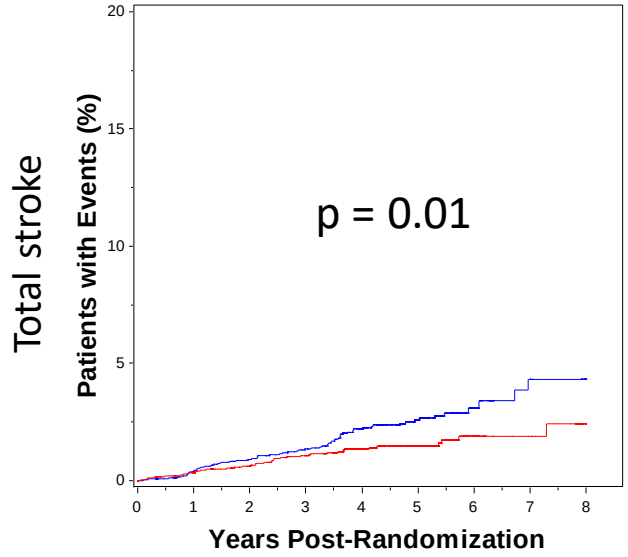
More intensive blood pressure control (mean 144/82 mmHg) provides significant reduction in macrovascular and microvascular endpoint

UK Prospective Diabetes Study Group; BMJ 1998;317:703–13

ACCORD-BP trial

4,733 diabetic patients randomized to intensive BP control (target SBP <120 mm Hg) or standard BP control (target SBP <140 mm Hg) for 4.7 years





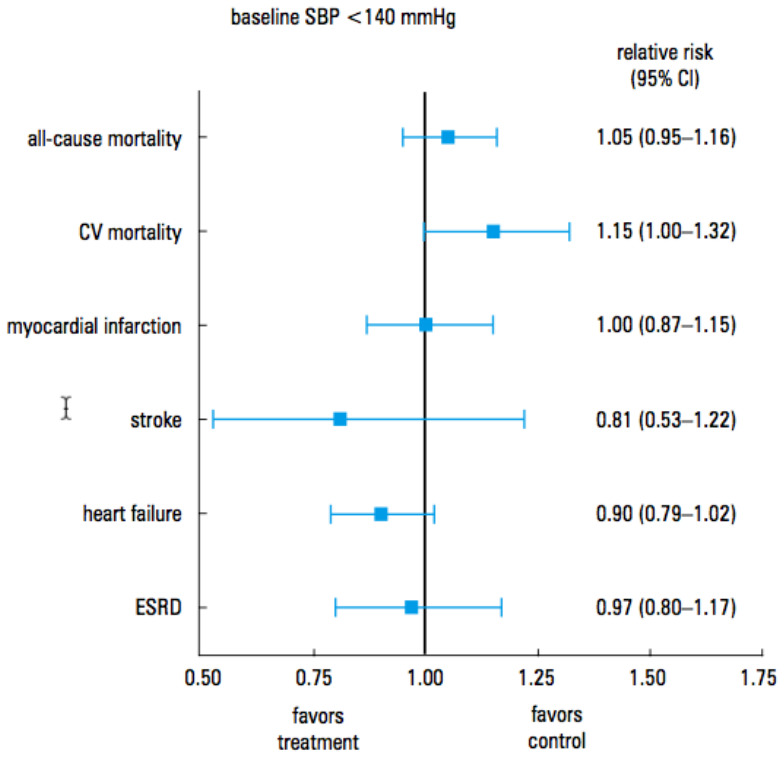
Intensive BP control in DM does not reduce a composite of adverse CV events, but does reduce the rate of stroke and of macroalbuminuria

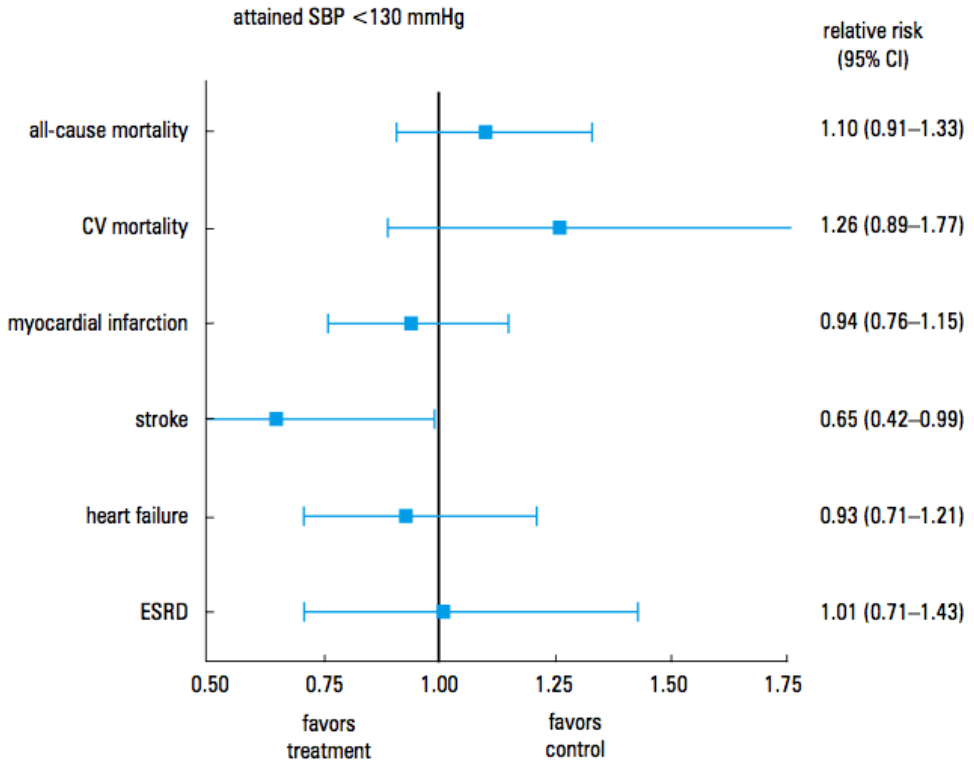
Signals of possible harm in the intensive BP control with more syncope, hypotension and hyperkalemia

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

Treatment target in diabetic patients

49 trials corresponding to 73738 participants





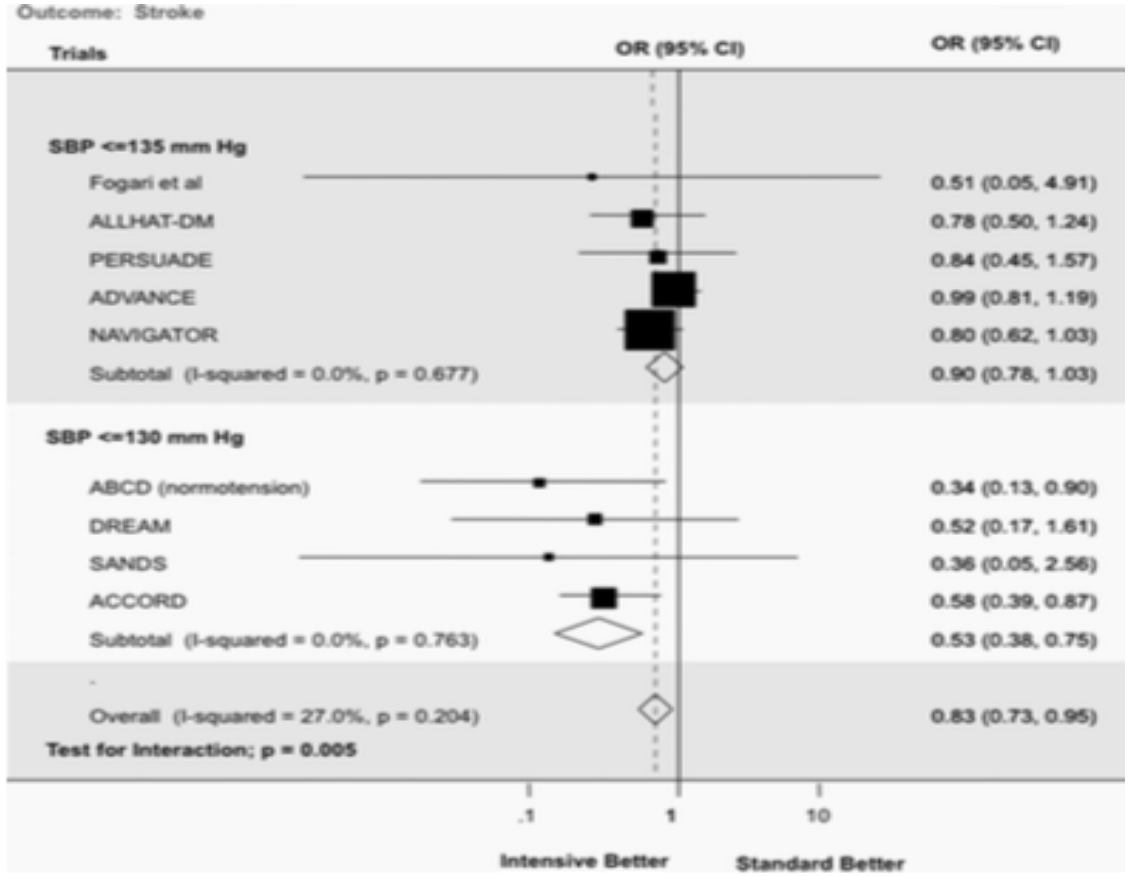
Baseline SBP < 140 mm Hg → increased risk of cardiovascular death and trend towards an increased risk of all cause mortality; significant reduction in stroke

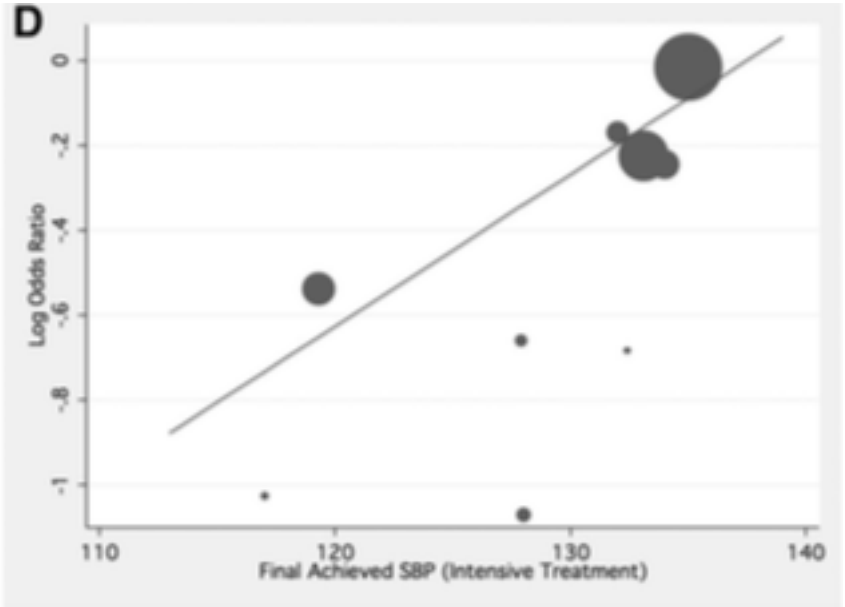
Attained SBP < 130 mmHg → non-significant increase in all cause and cardiovascular mortality

Brimble K.S. Pol Arch Med Wewn. 2016; 126 (6): 411-418

Treatment target in diabetic patients

13 randomized control studies including 37,736 diabetic hypertensive patients





Intensive BP control was associated with a 17% reduction in the stroke odds ratio, with a greater magnitude of benefit in trials in which the systolic BP was ≤ 130 mm Hg (p = 0.005)

Bangalore S et al. Circulation. 2011;123(24):2799–810.

Gaps in evidence

- Few, often underpowered, randomized trials addressed to PA target in diabetics (ACCORD, SPS3, UKPDS…)
- No individual patients meta-analysis
- Meta-analysis are pooling studies with different selection criteria and methodological approach

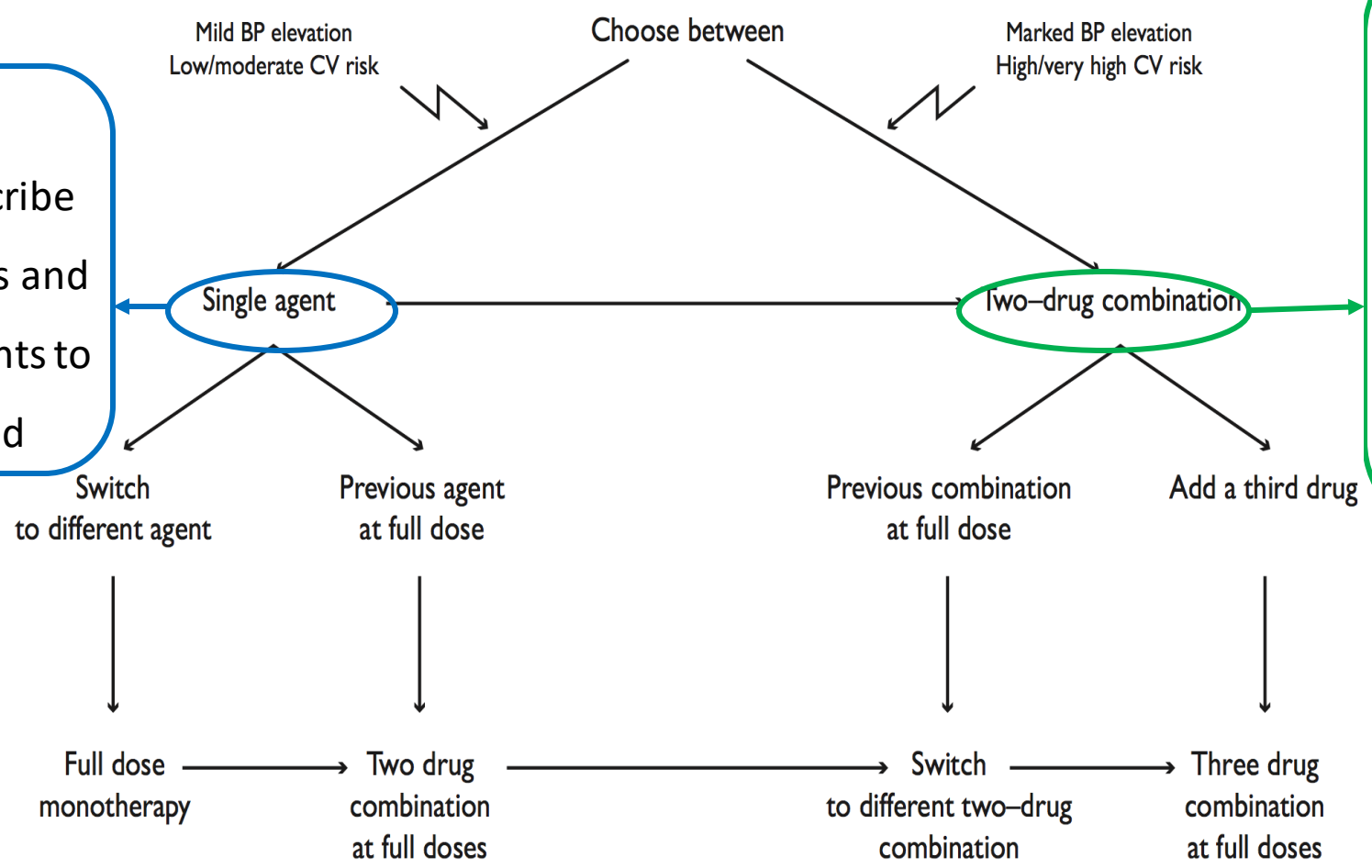
Blood pressure control

Optimal therapy in diabetic patients

Monotherapy versus drug combination strategies

Advantages:

- Ability to ascribe effectiveness and adverse events to the drug used

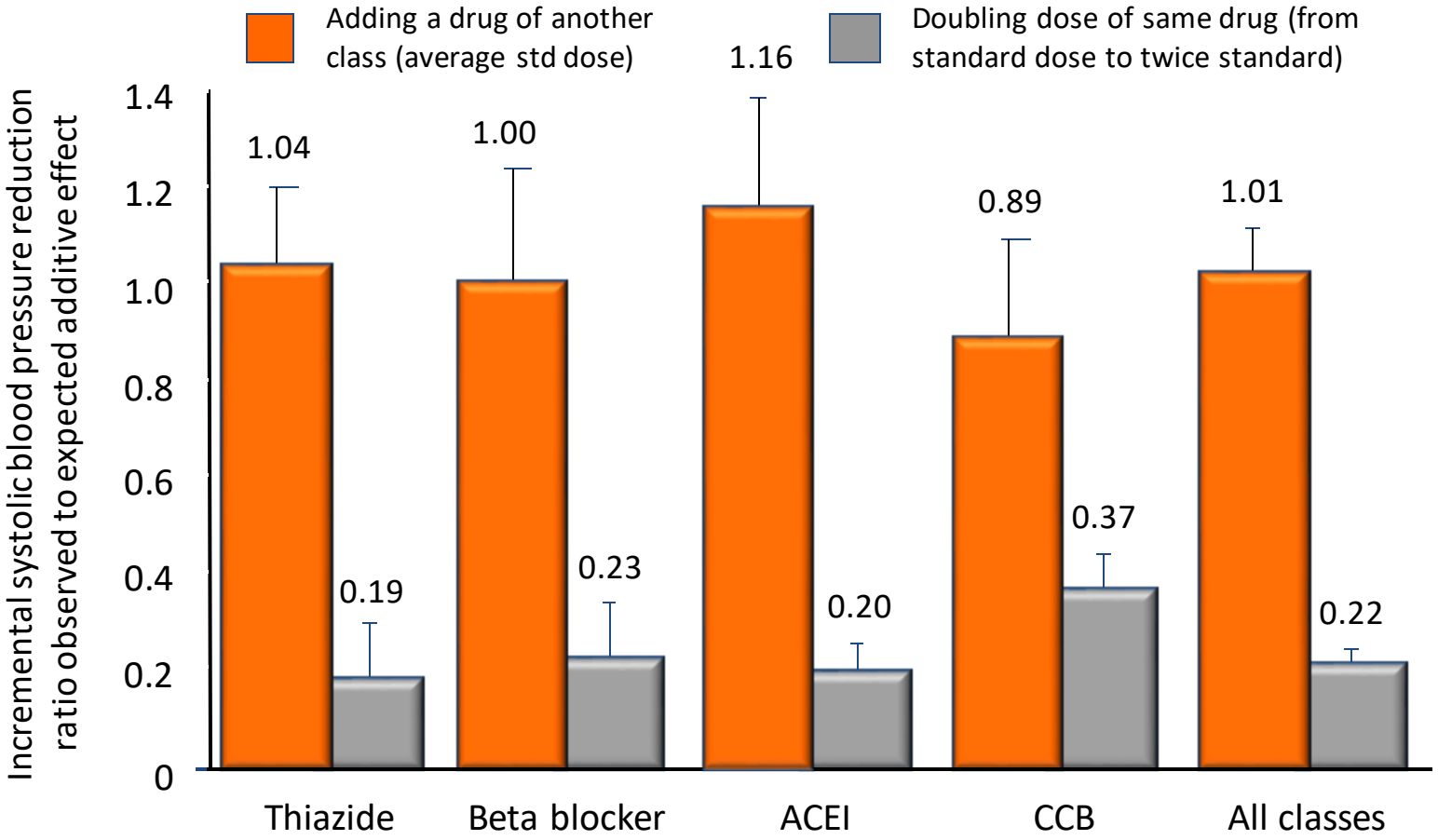


Advantages:

- prompter response
- greater probability to achieve the target
- better adherence
- synergies between different classes of agents

ESH – ESC Guidelines Committee. European Heart Journal (2013) 34, 2159–2219

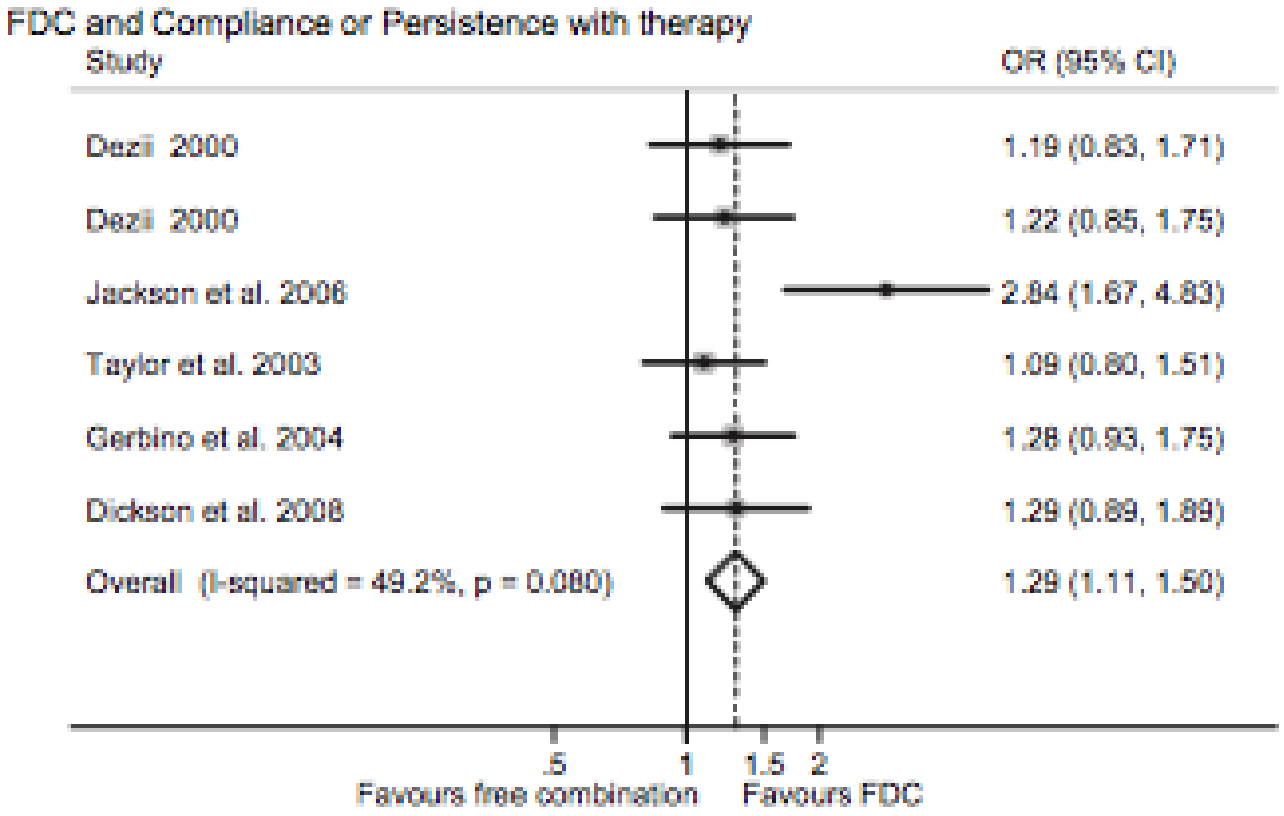
Monotherapy versus drug combination strategies



Combining blood pressure-lowering drugs from different classes is more effective than doubling the dose of one drug

Wald et al. Am J Med 2009;122:290-300

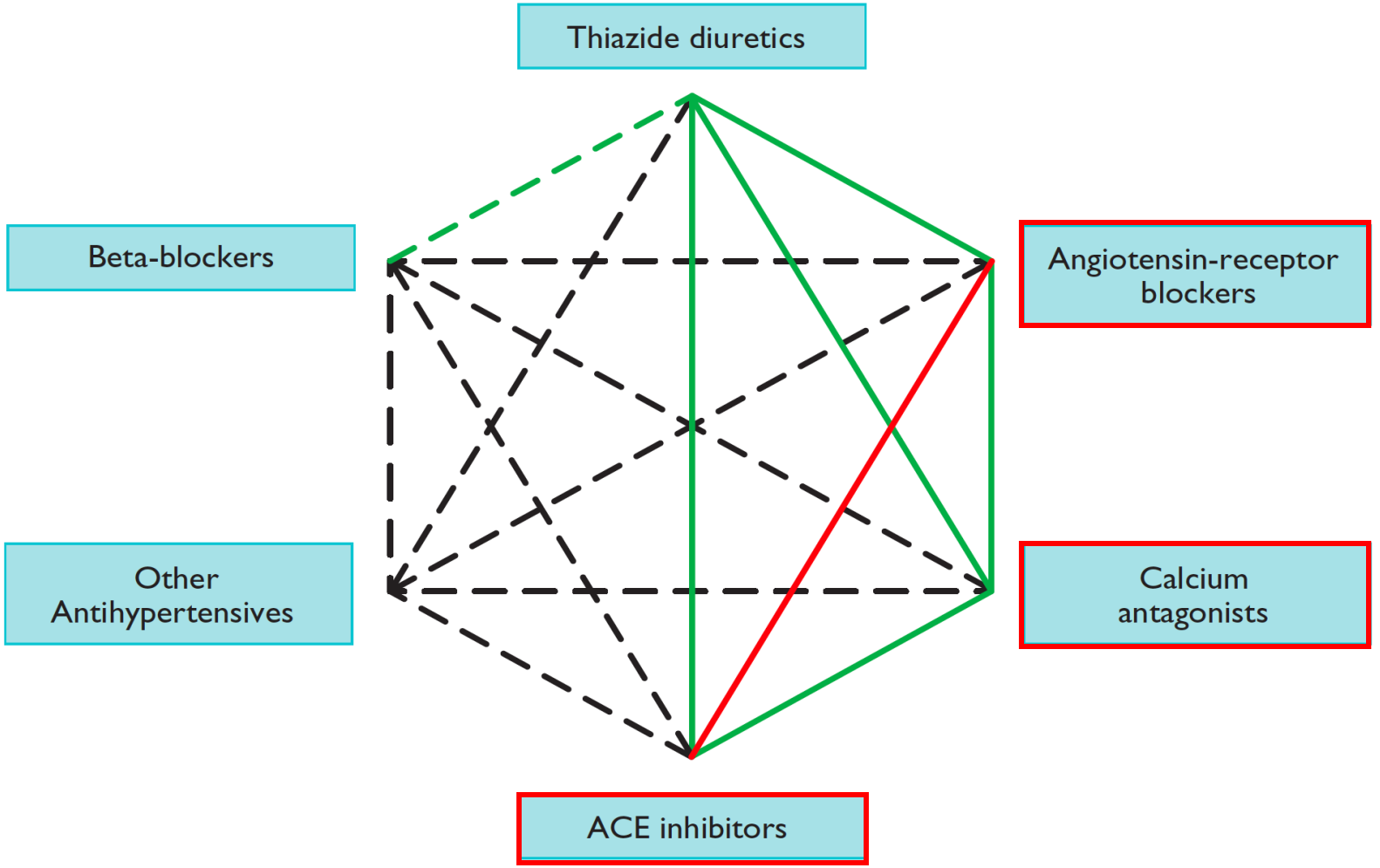
Fixed-dose combination



The use of an FDC as compared with the free-drug combination was associated with a 29% significant increase in compliance and persistence with therapy

Gupta AK et al. Hypertension 2010;55:399 – 407.

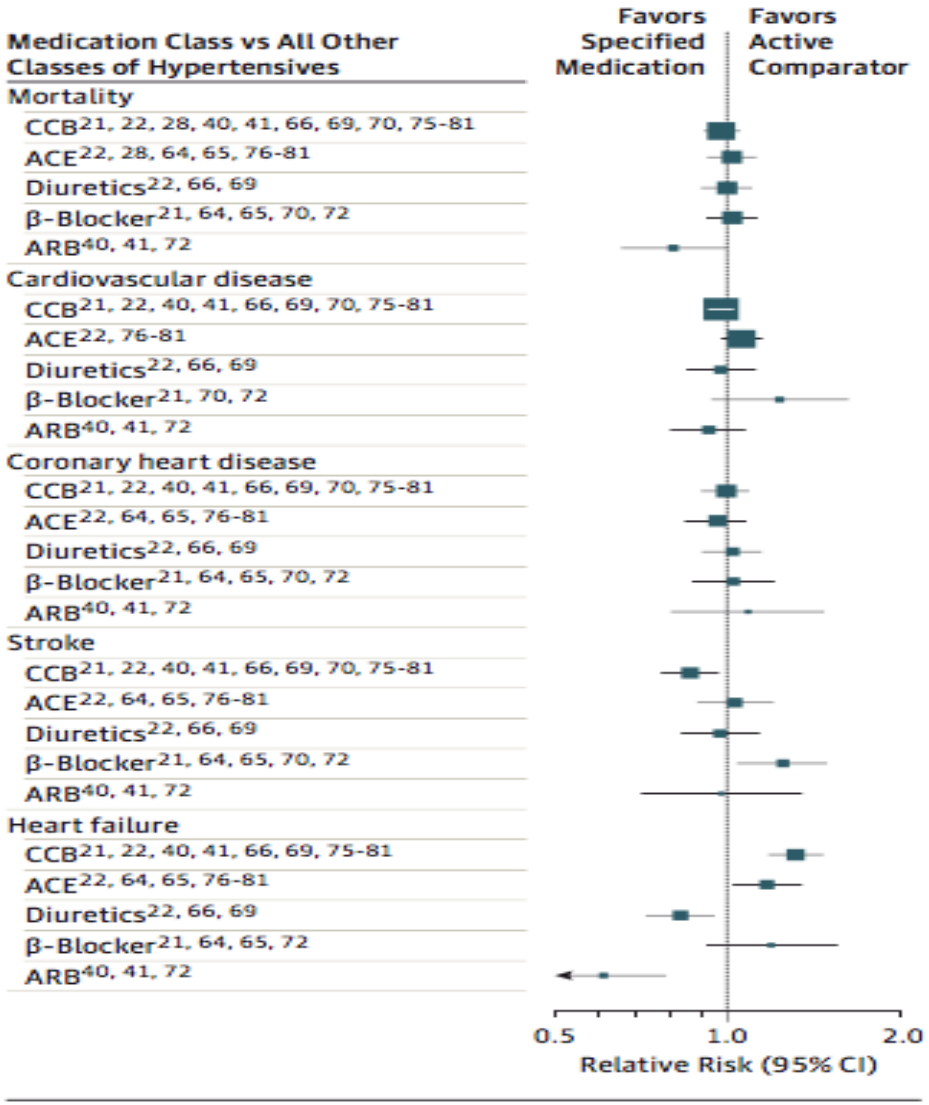
Combinations of classes of antihypertensive drugs



ACE = angiotensin-converting enzyme.

ESH – ESC Guidelines Committee. European Heart Journal (2013) 34, 2159–2219

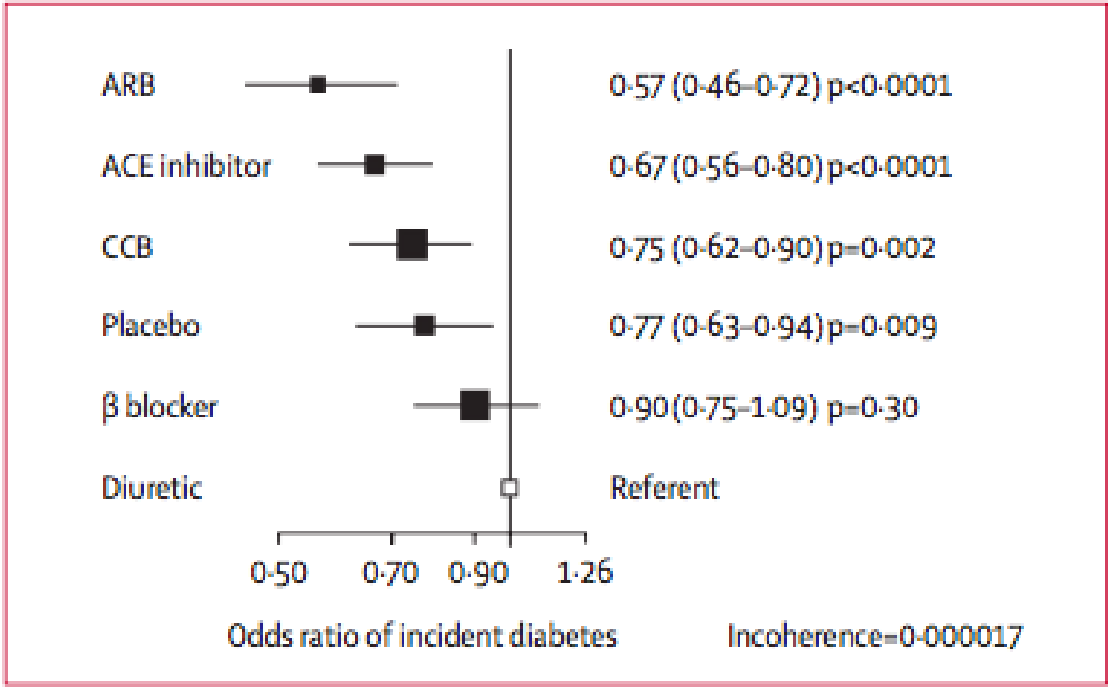
Different class of antihypertensives



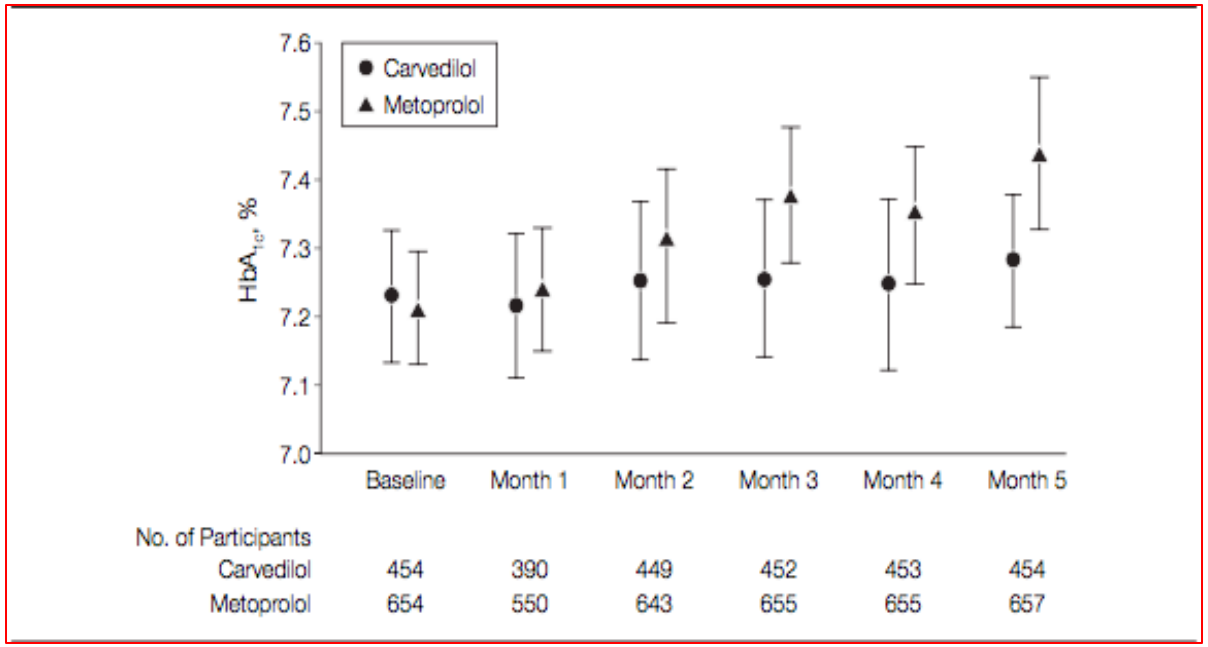
Few differences in the associations between BP-lowering treatment and outcomes based on different classes of medication used

Emdin C.A. JAMA. 2015;313(6):603-615

Different class of antihypertensives



Network meta-analysis of 22 clinical trials with 143 153 participants who did not have diabetes at randomization. ARB and ACE inhibitors are the antihypertensive agents least associated with incident diabetes followed by CCB and placebo, β blockers, and diuretics



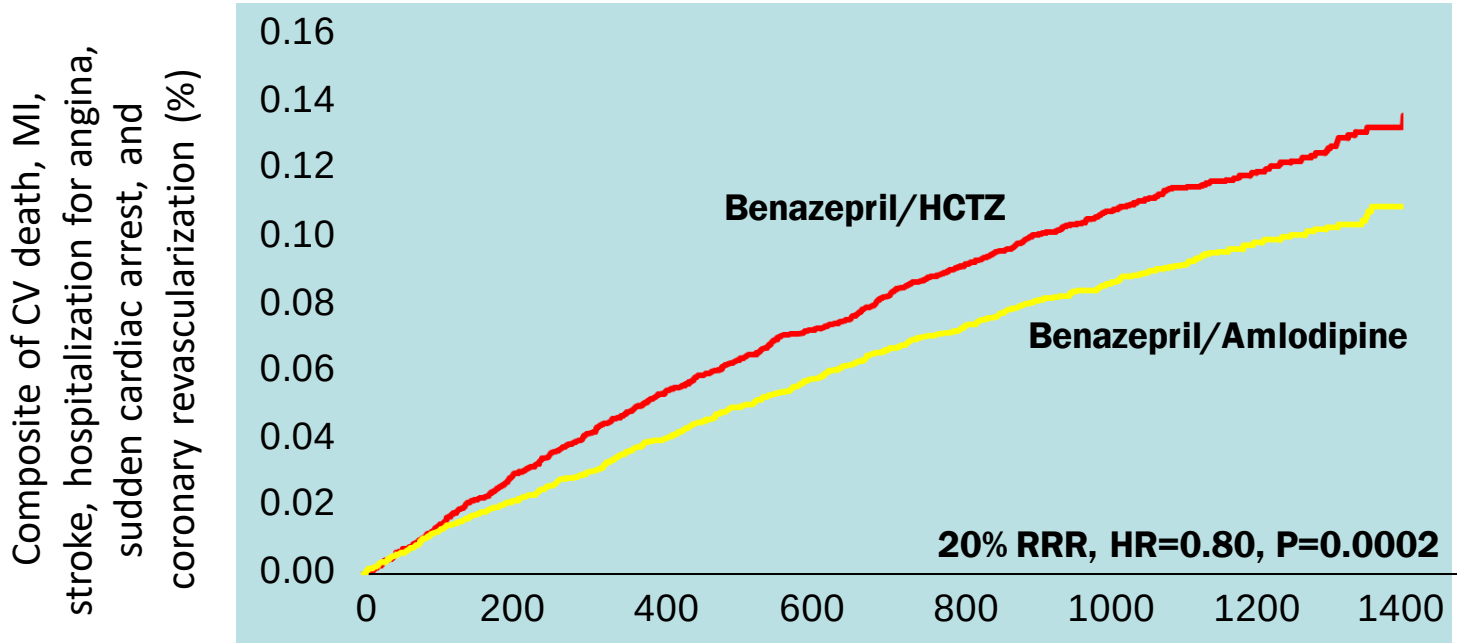
Randomized double blind trial comparing effects of carvedilol and metoprolol tartrate on glycemic control on 1235 patients with type 2 DM. Use of carvedilol in the presence of RAS blockade did not affect glycemic control.

Elliott W. et al.Lancet 2007; 369: 201–07
Bakris G.L. JAMA. 2004;292(18):2227-2236

ACCOMPLISH trial

11,506 high-risk hypertensive patients randomized to benazepril (40 mg) and amlodipine (10 mg) or benazepril (40 mg) and HCTZ (25 mg) for 36 months.

60.4% of the patients had diabetes



Combination treatment with benazepril/amlodipine is superior to treatment with benazepril/hydrochlorothiazide in reducing the risk of cardiovascular events and of death. Similar benefit in the pre-specified sub analysis of diabetic patients (low and high risk)

Jamerson K et al. NEJM 2008;359:2417-2428

Conclusion -2-

- Systolic blood pressure target in diabetic patients is < 140 mmHg but there are still controversial about diastolic blood pressure target and target in high risk patients with microvascular complications

- Combination therapy is often required in diabetic patients and is more effective in reducing blood pressure than monotherapy: fixed-dose combination therapy increase compliance

- Incomplete evidence that the cardiovascular benefits of specific classes of antihypertensive drugs extend beyond lowering blood pressure

- RAS blockers may be preferred especially in presence of proteinuria or microalbuminuria.