



The right therapy for the blood pressure control





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Conflict of interest disclosure

Speakers' bureau and Scientific Boards:

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Servier

Category	 Whelton PK et al. JACC 2018;71:e127-e248 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA			 Williams B et al. Eur Heart J 2018;39(33):3021-3104 2018 ESC-ESH		
	Systolic BP (mmHg)		Diastolic BP (mmHg)	Systolic BP (mmHg)		Diastolic BP (mmHg)
Optimal	-	-		<120	and	<80
Normal	<120	and	<80	120-129	and/or	80-84
High-normal	-	-	-	130-139	and/or	85-89
Elevated	120-129	and	<80	-	-	-
Hypertension Stage/Grade*						
1	130-139	or	80-89	140-159	and/or	90-99
2	≥140	or	≥90	160-179	and/or	100-109
3	-	-	-	≥ 180	and/or	≥ 110
ISH	-	-	-	≥ 140	and	< 90

* 'Stage' for ACC/AHA/etc; 'Grade' for ESC-ESH; ISH=Isolated systolic hypertension



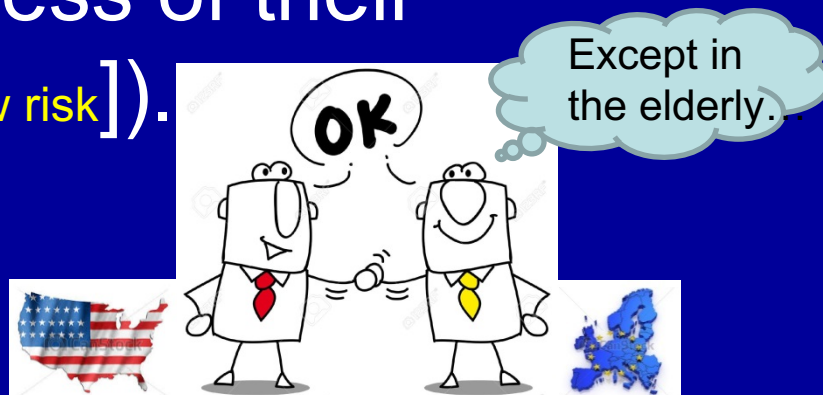
2018 ACC/AHA/AAPA/ABC/ACPM/
AGS/APhA/ASH/ASPC/NMA/PCNA

Whelton PK et al. JACC 2018;71:e127-e248

Drug treatment is recommended in **all patients whose BP is $\geq 140/90$ mmHg** under lifestyle measures, regardless of their absolute CV risk (**IA** [**IC**_{in low risk}]).



2018 ESC/ESH
Williams B et al. Eur Heart J
2018;39(33):3021-3104



Drug treatment is recommended in **all patients whose BP is $\geq 140/90$ mmHg ($\geq 160/90$ mmHg if age > 80) (IA)** under lifestyle measures, regardless of their absolute CV risk.

SPECIAL FOCUS ISSUE: BLOOD PRESSURE

EDITORIAL COMMENT

What to Do When Blood Pressure Is Between 130/80 and 139/89 mm Hg?*



Paolo Verdecchia, MD,^a Fabio Angeli, MD,^b Gianpaolo Reboldi, MD, PhD, MSc^c



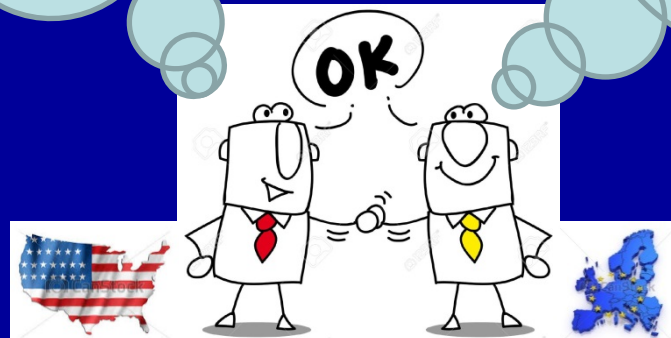
To use or not to use antihypertensive drugs in those patients whose BP is in the range 130-139/80-89 mmHg despite lifestyle measures?

Drug treatment in patients with BP 130-139/80-89 mmHg?

In general: **YES**, if the **CV risk is high....**

Clinical CV disease
(CAD, CHF, stroke), **or**
10-year CV risk $\geq 10\%$,
diabetes, chronic
renal disease,
age ≥ 65 years

Established CV/Renal disease (TIA,
stroke, cerebral hemorrhage,
angina, MI, heart failure, coronary
revascularization, atherosclerotic
plaques, peripheral artery disease,
chronic kidney disease, Afib), **or**
whether BP approaches
140/90 mmHg (but NOT in
case of diabetes..)



Blood Pressure Targets



**2018 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/
ASPC/ NMA/PCNA**

Whelton PK et al.
JACC 2018;71:e127-e248

< 130/80 mmHg in almost all patients

✓ **IB** for SBP, **IC** for DBP
in pts with high CV risk

✓ **IIbB** for SBP, **IIbC** for DBP
in pts with low CV risk



2018 ESC/ESH

Williams B et al. Eur Heart J
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< 140/90 mmHg in almost all patients (IA). Peculiarities:

- Hypertension -/+ (Diabetes, or CAD, or prior stroke/TIA)
 - Age < 65 yrs (**120*-129** mmHg if well tolerated) **(IA)**
 - Age ≥ 65 yrs (**130*-139** mmHg if well tolerated) **(IA)**
- Hypertension + (Chronic kidney disease)
 - All ages (**130*-139** mmHg if well tolerated) **(IA)**

*** Not below these 'safety boundaries' (fear of the J curve) !!!!**

Keep Blood Pressure Low, but Not Too Much...

Does Evidence Support the Recommendation of Rigid ‘Safety Boundaries’?

Paolo Verdecchia, Fabio Angeli, Claudio Cavallini, Gianpaolo Reboldi

If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties.

—Francis Bacon, *The Advancement of Learning*.
Holborne. 1605

To what extent should blood pressure (BP) be lowered in hypertensive patients? Should ≥ 1 BP targets be strictly defined? Or should we tailor the goal to individual patients, considering factors such as age, comorbidities, and balancing efficacy and tolerability of treatment?

The recently released 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) Guidelines state that BP should be lowered to levels $<140/90$ mmHg in all patients (I A recommendation) and to $\leq 130/80$ mmHg in most patients provided that the treatment is well tolerated (I A recommendation).¹

Thus, the take-home message of the 2018 ESC/ESH Guidelines is that a BP target $<140/90$ mmHg is the first objective of treatment and that a more ambitious BP goal ($\leq 130/80$ mmHg) should be pursued in most patients at condition that the treatment is well tolerated at levels $<140/90$ mmHg.¹

Unfortunately, to quote an aphorism attributed to Voltaire, “the perfect is enemy of the good.” Indeed, a few lines below, the European Guidelines¹ complicate the message by adding

Such recommendation contrasts with the 2017 American College of Cardiology/American Heart Association Hypertension Guidelines, approved by other 9 US Scientific Societies, which recommend a systolic BP target <130 mmHg in almost all hypertensive patients.²

In plain words, hypertensive patients aged ≥ 65 years should not have their systolic BP lowered <130 mmHg in Europe, whereas it is recommended to lower their systolic BP <130 mmHg in the United States. Ironically, one could argue that, on one side of the Ocean, someone may have misinterpreted the evidence supporting the Hypertension Guidelines.

When looking at younger patients, that is, those aged <65 years, the 2018 European Guidelines state that systolic BP should be lowered to <130 mmHg in most patients, but not <120 mmHg (I A recommendation).¹

Specifically, the guidelines first recommend of being more aggressive with judicio (ie, taking patient’s tolerability, as assessed during the clinical visit, into account). Subsequently, however, the guidelines introduce a sort of formal own judicio consisting of precise safety boundaries not to be exceeded (120 mmHg in patients aged <65 years, 130 mmHg in patients aged ≥ 65 years).¹ Thus, 31 years after the first report by Cruickshank et al,³ the 2018 ESC/ESH Guidelines seem to fully endorse, with the strength of a I A recommendation, the implication of the J-curve hypothesis. Namely, an exces-

In our opinion, the 2018 European Guidelines I A recommendation that systolic BP should not be lowered below pre-defined safety boundaries (120 mmHg in patients aged <65 , 130 mmHg in patients aged ≥ 65 years) is unsupported by sound evidence and should be reconsidered.





ESC/ESH 2018

Williams B et al. Eur Heart J
2018;39(33):3021-3104



Initial therapy
Dual combination

ACEi or ARB + CCB or diuretic

Consider monotherapy in low-risk
grade 1 hypertension or in very old
(≥ 80 years) or frailer patients



Step 2
Triple combination

ACEi or ARB + CCB + diuretic



Step 3
Triple combination +
spironolactone or
other drug

Resistant hypertension
Add spironolactone (25–50 mg o.d.)
or other diuretic, alpha-blocker or beta-blocker

Consider referral to a specialist
centre for further investigation



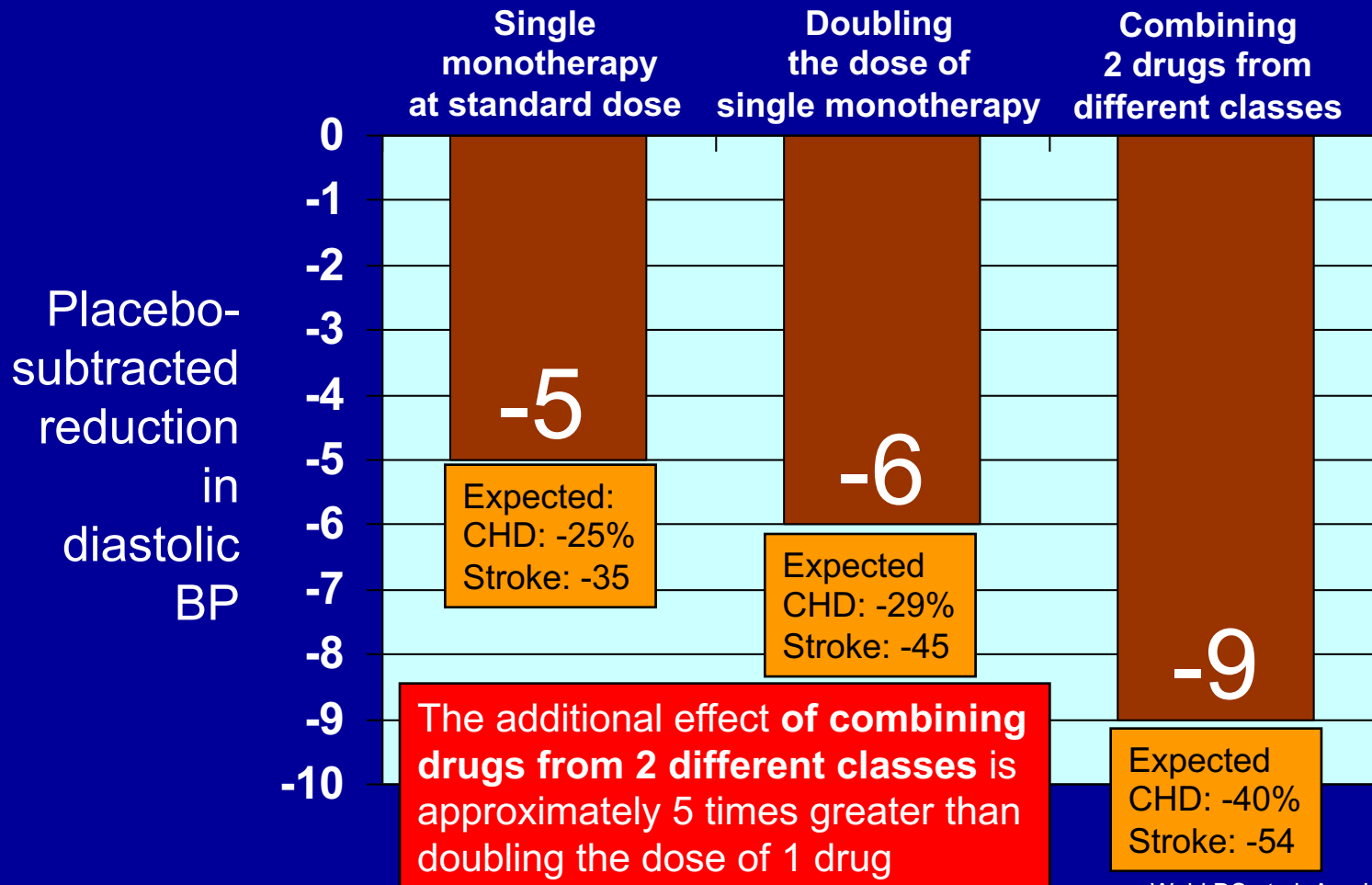
Beta-blockers

Consider beta-blockers at any treatment step, when there is a specific
indication for their use, e.g. heart failure, angina, post-MI, atrial fibrillation, or
younger women with, or planning, pregnancy

- 1) **Step 1.** ACEIs, or ARBs associated with CCBs or diuretics as initial therapy (with some exceptions in which monotherapy remains indicated)
- 2) **Step 2.** Triple combination with either an ACEis/ARBs plus CCBs plus diuretics
- 3) **Step 3.** Triple combination plus spironolactone/α-blocker/β-blocker, in patients with resistant hypertension.

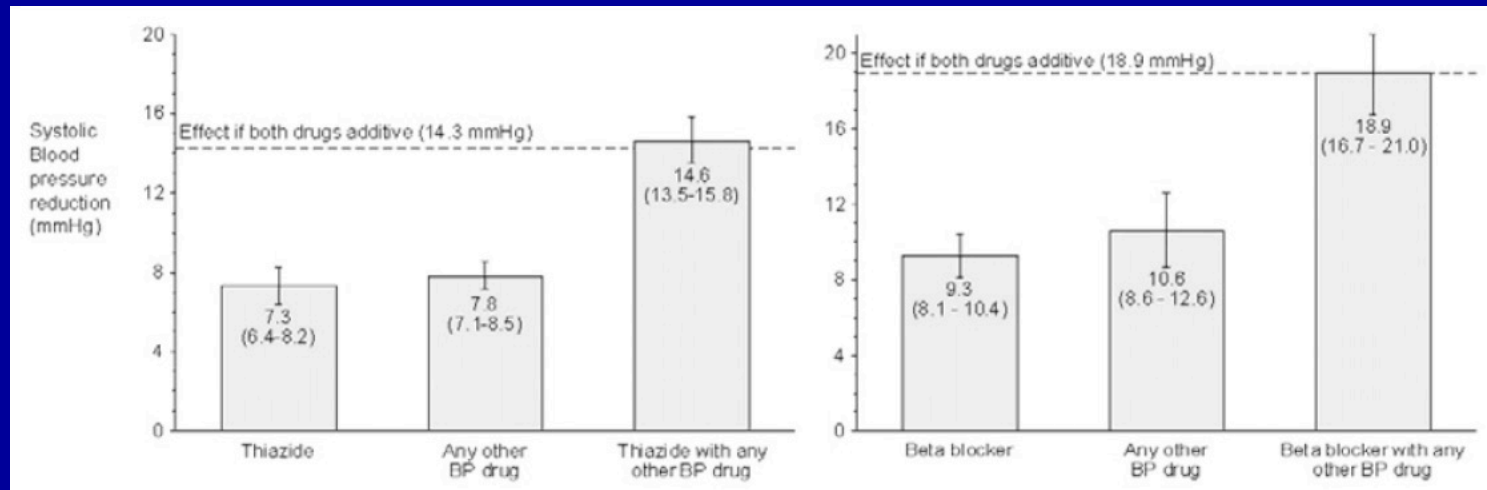
Combination Therapy Versus Monotherapy in Reducing Blood Pressure: Meta-analysis on 11,000 Participants from 42 Trials

David S. Wald, MD, Malcolm Law, FRCP, Joan K. Morris, PhD, Jonathan P. Bestwick, MSc, Nicholas J. Wald, FRS
Wolfson Institute of Preventive Medicine at Barts and The London Queen Mary's School of Medicine and Dentistry, Charterhouse Square, London, United Kingdom.

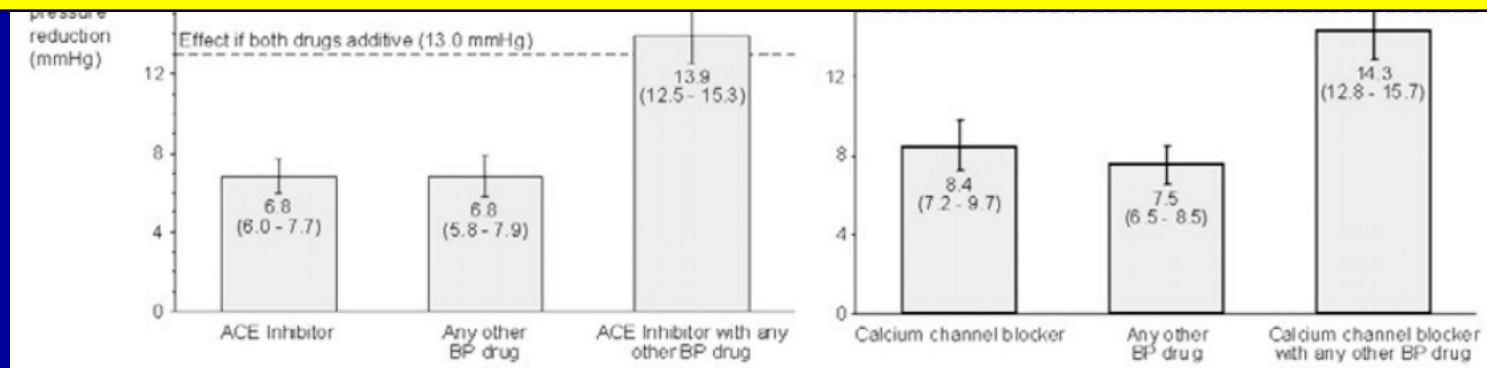


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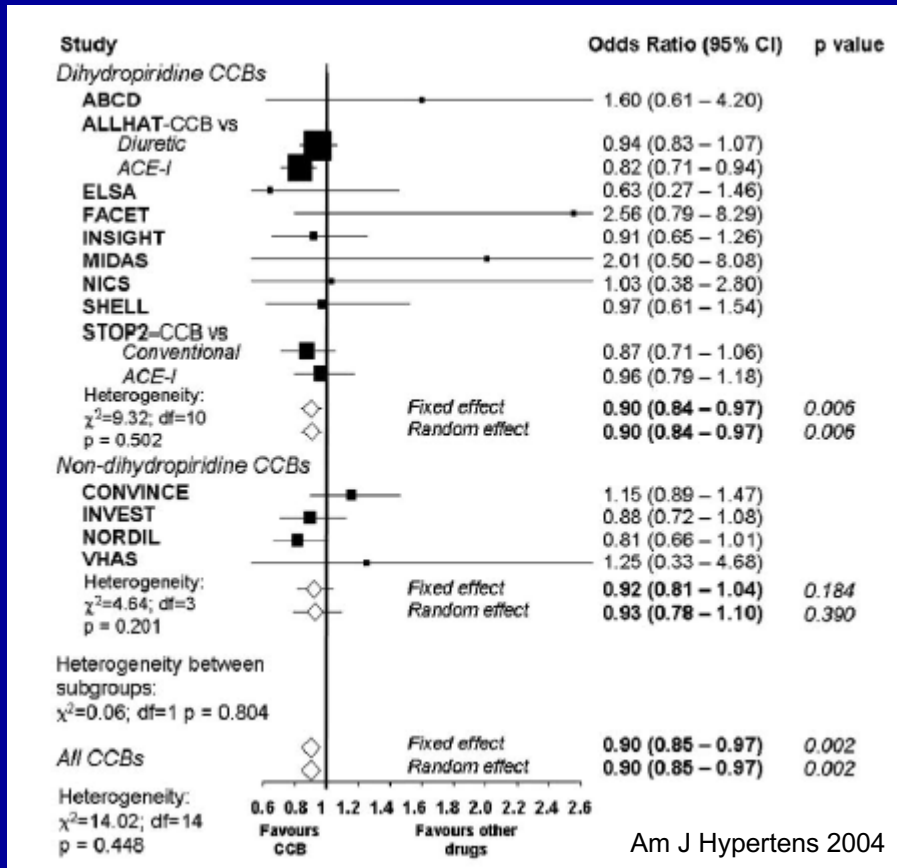
The greater antihypertensive effect of the initial combination, compared to the initial monotherapy, was the same across the different classes of drugs.



Calcium Channel Blockade to Prevent Stroke in Hypertension

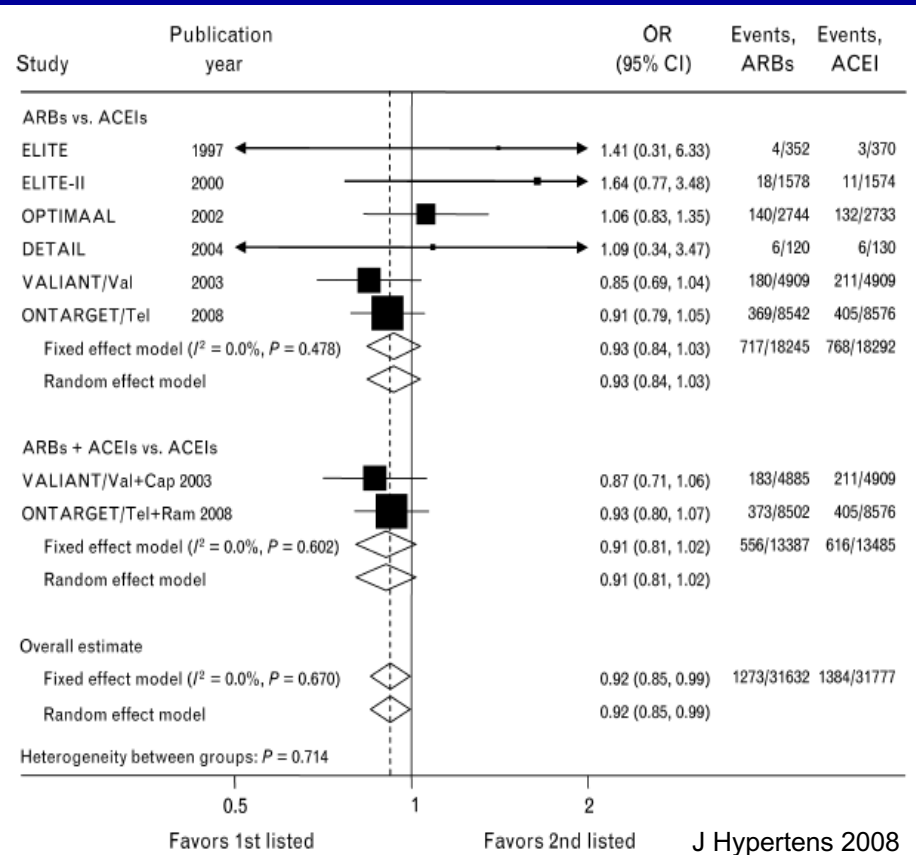
A Meta-Analysis of 13 Studies With 103,793 Subjects

Fabio Angeli, Paolo Verdecchia, Gian Paolo Reboldi, Roberto Gattobigio, Maurizio Bentivoglio, Jan A. Staessen, and Carlo Porcellati



Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction, stroke and death: a meta-analysis

Gianpaolo Reboldi^a, Fabio Angeli^b, Claudio Cavallini^b, Giorgio Gentile^a, Giuseppe Mancia^c and Paolo Verdecchia^b



The combination between calcium channel blockers and angiotensin receptor blockers is a reasonable option in patients at high risk of stroke

Quale diuretico
preferire nelle
combinazioni ?

Head-to-Head Comparisons of Hydrochlorothiazide With Indapamide and Chlorthalidone Antihypertensive and Metabolic Effects

George C. Roush, Michael E. Ernst, John B. Kostis, Suraj Tandon, Domenic A. Sica

Abstract—Hydrochlorothiazide (HCTZ) has often been contrasted with chlorthalidone, but relatively little is known about HCTZ versus indapamide (INDAP). This systematic review retrieved 9765 publications, and from these, it identified 14 randomized trials with 883 patients comparing HCTZ with INDAP and chlorthalidone on antihypertensive potency or metabolic effects. To make fair comparisons, the dose of the diuretic in each arm was assigned 1 of 3 dose levels. In random effects meta-analysis, INDAP and chlorthalidone lowered systolic blood pressure more than HCTZ: -5.1 mmHg (95% confidence interval, -8.7 to -1.6); $P=0.004$ and -3.6 mmHg (95% confidence interval, -7.3 to 0.0); $P=0.052$, respectively. For both comparisons, there was minimal heterogeneity in effect across trials and no evidence for publication bias. The HCTZ–INDAP contrast was biased in favor of greater HCTZ potency because of a much greater contribution to the overall effect from trials in which the HCTZ arm had a higher dose level than the INDAP arm. For the HCTZ–INDAP comparison, no single trial was responsible for the overall result nor was it possible to detect significant modifications of this comparison by duration of follow-up, high- versus low-bias trials, or the presence or absence of background medications. There were no detectable differences between HCTZ and INDAP in metabolic adverse effects, including effects on serum potassium. In conclusion, these head-to-head comparisons demonstrate that, like chlorthalidone, INDAP is more potent than HCTZ at commonly prescribed doses without evidence for greater adverse metabolic effects. (*Hypertension*. 2015;65:00-00. DOI: 10.1161/HYPERTENSIONAHA.114.05021.) • [Online Data Supplement](#)

Key Words: blood pressure ■ chlorthalidone ■ hydrochlorothiazide ■ hypokalemia ■ indapamide

Long-acting diuretics (chlorthalidone, indapamide) are better than short-acting diuretics (hydrochlorothiazide, furosemide, etc) for the treatment of hypertension

Two-drug combinations as initial treatment



Cons

- Excessive BP reduction?
- One of the two or more drugs might be ineffective: it is difficult to identify it (or them).
- In case of side effects: which is the guilty drug?



Pros

- Prompter, and more sustained, BP response (conclusive and unequivocal evidence).
- Lower drop-out rate (conclusive and unequivocal evidence).
- Outcome benefits (as strongly suggested by several studies).

**Thank you
for your attention**

