

# The 2013 ESH-ESC Guidelines for the management of arterial hypertension: new targets, old policies

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## Abstract

### Introduction

The European Society of Hypertension–European Society of Cardiology Guidelines are the most comprehensive recommendations available. This review aims to discuss some new information and recurring problems in these guidelines.

### Discussion

The trend of the continuous lowering of treatment goals is finally reversed. New targets include the following: (1) hypertensive (adult) patients at low to moderate risk: blood pressure <140/90 mmHg; (2) elderly hypertensive patients: if fit and aged <80 years, systolic blood pressure <140 mmHg can be considered; in frail elderly patients, target should be adapted to individual tolerability. If aged >80 years, systolic blood pressure of 150 to 140 mmHg only should be considered if they are in good physical and mental condition (i.e. in frail elderly patients can be higher); (3) high-risk patients, with diabetes, cardiovascular disease or nephropathy: systolic blood pressure <140 mmHg because lower targets are not supported by valid evidence; and (4) high-normal blood pressure, even with organ damage and multiple risk factors: no drug treatment, only lifestyle changes.

Guidelines reaffirm that the main benefit of antihypertensive treatment is lowering of blood pressure and that the main drug classes are all suitable for the initiation and maintenance of treatment, either as monotherapy or in some combinations.

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The approach to initial monotherapy is 'liberal', as usual. This happens without establishing priorities and so justifies, the common strategies employing the most expensive drugs and combinations. A cornerstone of this strategy is not to recognise the important differences between the most used but less efficacious hydrochlorothiazide, and the thiazide-like diuretics such as chlorthalidone and indapamide, which more often do not require adding a second (or third or fourth) drug to reach the target. This is more evident in current practice.

### Conclusion

The new European Society of Hypertension–European Society of Cardiology Guidelines, after decades of increasingly aggressive target reductions, restore a unified target of <140/90 mmHg (and a much higher one for the elderly, but the guidelines continue to avoid a cost-effective approach in drug therapies, actually justifying the use of much more expensive strategies). One of the main mechanisms underlying this policy is to deny the superiority of thiazide-like diuretics.

## Introduction

### Background

In 1993, the Joint National Committee Report-5 (JNC-5) recommended a blood pressure (BP) treatment goal of <130/85 mmHg<sup>1</sup> for diabetic patients, relying on subgroup data from the diabetic patients enrolled in the Hypertension Optimal Treatment (HOT) trial<sup>2</sup>. This was later harshly criticised in a Cochrane review<sup>3</sup>.

Data from the UKPDS group<sup>4,5</sup> showed that diabetic and hypertensive patients with a tight BP goal had better macrovascular and microvascular

outcomes; however, the 'tight BP goal group' reached a mean systolic blood pressure (SBP) of 144 mmHg versus 155 mmHg in the usual care group.

In 2002 the American Diabetes Association recommended a treatment goal of <130/80 mmHg<sup>6</sup> for diabetic patients and stated, 'There is not a threshold value for BP; risk continues to decrease well into the normal range'<sup>7</sup>.

In 2003, the JNC-7<sup>8</sup>, and guidelines from many other international societies, confirmed the treatment goal of <130/80 mmHg for patients with diabetes and those with chronic kidney disease (CKD), and in 2007, an AHA Scientific Statement extended this goal to patients with coronary artery disease (CAD), myocardial infarction and angina.

The 2013 European Society of Hypertension–European Society of Cardiology (ESH-ESC) Guidelines<sup>9</sup>, without underlining the fact that for two decades an international consensus, with isolated discordant voices, pushed to treat to unrealistic and unproven targets, just admitted that 'The 2007 Guidelines, in common with other guidelines, recommended two distinct BP targets: <140/90 in (all) low-moderate risk hypertensives and <130/80 in high-risk hypertensives with diabetes, cerebrovascular, cardiovascular disease (CVD), or renal disease,' including very elderly people.

Since the National Heart, Lung, and Blood Institute stopped the publication of practice guidelines, the European Guidelines<sup>9</sup> provide the most comprehensive recommendations available.

This review does not intend to summarise and comment the ESH-ESC Guidelines (76 pages) but just discusses some new and/or recurring problems that are very relevant for public health.

## Discussion

### Treatment goals (r)evolution

#### When to initiate antihypertensive drug treatment?

With the accumulation of different evidences, in 2009 an ESH Task Force<sup>10</sup> began to distance itself from the previous recommendations. However, without an explicit and public questioning of the targets stressed for decades by propaganda pounding, the effects of ESH task force's 'reappraisal' on medical practice were minimal.

Now ESH-ESC Guidelines finally recognise that the evidence for drug treatment of Grade 1 hypertension (SBP 140–159 mmHg) is lacking because no randomised controlled trial (RCT) has specifically addressed this condition.

For the elderly in particular, the 2013 guidelines admit that all the demonstrated benefits in RCTs were for patients with SBP >160 mmHg. Notably, in the only RCT (Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly

Hypertensive Patients [JATOS]) that achieved SBP <140 mmHg, all-cause mortality was not significantly higher (hazard ratio = 1.28) in the strict treatment group (see Table 1).

SBP, systolic blood pressure; DBP, diastolic blood pressure; EWPHE, Working Party on High Blood Pressure in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; STOP-1, Stroke Prevention in Sickle Cell Anaemia; MRC, Medical Research Council; SYST-EUR, Systolic Hypertension in Europe; SYST-China, Systolic Hypertension in China; SCOPE, Study on Cognition and Prognosis in the Elderly; HYVET, Hypertension in the Very Elderly Trial; JATOS, Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients.

For high-normal BP, ESH reappraisal admitted that evidence for antihypertensive drugs is scanty at best. In addition, two large RCTs in which subjects with pre-diabetes or metabolic syndrome with high-normal BP had received ramipril (DREAM) or

valsartan (NAVIGATOR) showed no reduction in cardiovascular events. Finally, in large meta-analyses that show the benefits of antihypertensive drugs even in patients with SBP <140 mmHg, most of these patients were not truly normotensive but were already under the effect of hypertension therapies.

Summing up, in high-normal BP the intervention should be limited to lifestyle changes, and antihypertensive drugs are not recommended even for patients with CVD or CKD and diabetic patients with organ damage or multiple risk factors (in the absence of necessary evidence of benefit).

In Grade 1 hypertension BP drugs are recommended for patients with organ damage, CKD Grade ≥ 3, diabetes or symptomatic CVD, but targeting <140/90 mmHg.

Antihypertensive drug treatment should also be considered for patients with low to moderate risk, especially when BP remains within Grade 1 range despite modification of lifestyle for several weeks (or several months, in the absence of other risk factors).

In the elderly, hypertensive drug therapy is recommended for those having SBP ≥160 mmHg, and an SBP between 140 and 159 may be considered for those aged <80 years, provided it is well tolerated.

#### New unified BP target

Here are the new targets:

- Hypertensive (adult) patients at low to moderate risk: SBP <140 mmHg.
- Elderly hypertensive: if fit and aged <80 years, patients 'can be considered' for SBP <140 mmHg; in the frail elderly patients SBP should be 'adapted to individual tolerability' (i.e. *allow a higher BP!*). If patients are aged >80 years, then SBP should be maintained between 150 and 140 mmHg, but only if patients are in good physical and mental condition

**Table 1** Blood pressure at randomisation in antihypertensive trials in the elderly<sup>11</sup>

Trial acronym	Recruiting criteria			Mean baseline values		Achieved SBP	
	SBP (mmHG)		DBP (mmHG)	SBP (mmHG)	DBP (mmHG)	Active	Control
EWPHE	160–239	or	90–119	183	101	150	172
Coope/Warrender	>170	or	>105	196	99	162	180
SHEP	≥160	and	<90	170	77	143	155
STOP-1	≥180	or	≥105	195	94	167	186
MRC-elderly	160–209	and	<115	185	91	156	165
Syst-Eur	160–219	and	<95	174	85	151	161
Syst-China	160–219	and	<95	171	86	151	160
SCOPE (see Point a. in Notes section)	160–179	or	90–99	166	90	145	148
HYVET	160–179	and	<110	173	91	144	159
JATOS	≥160	and	<120	171	89	138	147

SBP, systolic blood pressure; DBP, diastolic blood pressure; EWPHE, Working Party on High Blood Pressure in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; STOP-1, Stroke Prevention in Sickle Cell Anaemia; MRC, Medical Research Council; SYST-EUR, Systolic Hypertension in Europe; SYST-China, Systolic Hypertension in China; SCOPE, Study on Cognition and Prognosis in the Elderly; HYVET, Hypertension in the Very Elderly Trial; JATOS, Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients.

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(i.e. in frail elderly patients, leave it higher. How many frail patients have been damaged by continued aggressive treatment recommendations covering many years?)

- High-risk patients: target SBP <140 mmHg; the previous recommendation of SBP <130/80 mmHg for patients with diabetes, CVD or CKD is not supported by valid evidence (notably, the large Action to Control Cardiovascular Risk in Diabetes [ACCORD] RCT overall did not find benefits and rather more serious adverse events in the group with SBP 119 vs. 134 mmHg).
- Patients with nephropathy: in ACCORD, for patients with estimated glomerular filtration rate (eGFR) within the normal range, the more aggressive therapy was associated with almost double the number of cases with eGFR <30 ml/min. Moreover, a systematic review of the three RCTs that compared different BP targets in non-diabetic CKD showed that, compared to a target  $\leq$ 140/90, a target <130/80 mmHg does not save lives or kidneys or reduce CV events, and various observations indeed show adverse effects from targets that are too low. The evidence is not conclusive, but in the analysed RCTs a few more deaths were always reported in the research arms with lower targets<sup>12</sup>.

A subgroup analysis of the African American Study of Kidney Disease and Hypertension (AASK) RCT shows a possible benefit for the minority of patients with high proteinuria and a trend to the opposite for the remaining two-thirds of patients with less proteinuria; however, it is only a hypothesis and needs to be tested.

*Target BP for organ damage studies: is there any evidence?*

It is very contradictory; for example, compared with those in placebo in Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial, diabetic patients more intensively treated with olmesartan showed not only a statistically significant (though clinically minimal) reduction in new onset microalbuminuria but also a higher incidence of cardiovascular mortality, and – as a trend – of total mortality<sup>13</sup>.

In Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) the BP obtained from the ramipril-telmisartan combination reduced proteinuria but without cardiovascular benefits and with increased risk of acute renal failure and dialysis (and 60 more deaths)<sup>14</sup>. In Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial patients with CVD or diabetes without macroalbuminuria received telmisartan or placebo. With telmisartan, rate of increase in albuminuria came down, but decreases in eGFR were greater, and the composite renal outcome and the number of deaths were higher, though not significantly<sup>15</sup>.

### Pharmacological therapy

Guidelines conclude that ‘the main benefits of antihypertensive treatment are due to lowering of BP and largely independent of the drugs employed. Therefore they reconfirm that diuretics (including thiazides, and thiazide-like chlorthalidone and indapamide), beta-blockers, calcium-channel blockers (CCB), ACE inhibitors and angiotensin receptor blockers (ARBs) are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations’.

This ‘liberal approach to initial monotherapy, without any intention

of establishing priorities,’ hides the usual bad habit to justify the use of more expensive drugs with equal effectiveness, in contrast with the Code of Conduct that all doctors should follow.

### Critical therapeutic issues

A very important question in relation to public health issues is: which diuretic a practitioner should choose? This review will address this question and somewhat less obvious issue.

#### Diuretics

The guidelines remember that diuretics are ‘still classified as the only first-choice drug by which to start with, in both the JNC-7<sup>8</sup> and the WHO/International Society of Hypertension Guidelines’<sup>16</sup>.

However, the ESH-ESC Guidelines seem to give greater importance to the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial<sup>17</sup>, in which the benazepril-amlodipine combination achieved significantly better results compared to the benazepril-hydrochlorothiazide (HCTZ) combination; however, guidelines state that ‘the evidence provided by ACCOMPLISH does not appear to bear sufficient weight to exclude diuretics from first-line choice(s)’.

In fact, ACCOMPLISH trial seems conceived to ‘revive in combination’ off-patent drugs, and, above all, like the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) study<sup>18</sup>, further justifies the use of drugs more profitable instead of diuretics. This is further dealt with in paragraph “Why choose chlorthalidone or indapamide and not HCTZ?”.

#### ACCOMPLISH: a commercial operation

It is stated that in ACCOMPLISH<sup>17</sup> amlodipine-benazepril combination has overcome the HCTZ-benazepril combination. Does this prove that amlodipine is better than thiazide or

thiazide-like diuretics in general (see Point b. in Notes section)?

No, because the conclusion of ACCOMPLISH is seriously biased, as would be evident from the following observations:

1. In the largest comparative RCT ever made, the thiazide-like diuretic chlorthalidone had already been demonstrated to be equivalent to amlodipine in the primary outcome and to be clearly superior in reducing heart failure (HF)<sup>19</sup>, and the superiority of diuretics over CCBs to prevent HF is confirmed in all meta-analyses<sup>20</sup>.
2. In the experimental group of Multiple Risk Factor Intervention Trial (MRFIT)<sup>21</sup> some centres used HCTZ and others used chlorthalidone. An interim analysis showed more cardiovascular events with HCTZ, and when the Safety Board decided to use only chlorthalidone this unfavourable trend was reversed (P = 0.04, comparing the two time periods).

Why, then, in ACCOMPLISH did the control group not use chlorthalidone–benazepril combination, instead of HCTZ–benazepril combination? Even though this was already held as unacceptable when ACCOMPLISH was designed, it is totally intolerable today, since the meta-analysis<sup>22</sup> shows with certainty the inferiority of HCTZ. Even the National Institute for Health and Clinic Excellence (NICE) Hypertension Guidelines<sup>23</sup> recommend to use as a diuretic chlorthalidone or indapamide and not HCTZ or bendrofluzide.

3. In two comparative studies indapamide SR had already demonstrated antihypertensive efficacy at least equal<sup>24</sup> or superior<sup>25</sup> to amlodipine, while HCTZ was slightly

less effective. Why has ACCOMPLISH not chosen chlorthalidone or indapamide SR to combine it with the ACE inhibitor?

4. The once-a-day use added a handicap to HCTZ because its shorter half-life leaves half a day without adequate coverage, not well covered even by benazepril, whose half-life is 10 to 11 hours. Instead amlodipine, or chlorthalidone, has a half-life of 40 to 60 hours, and both could compete on equal terms.
5. Furthermore, HCTZ was used at a starting dose of 12.5 mg (1/2 defined daily dose [DDD]) and achieved 19.3 mg as a daily average in ACCOMPLISH (76% of its DDD). Amlodipine has been used in full dose immediately and reached 7.7 mg as a daily average (154% of its DDD). In practice, amlodipine was always used at double dose compared with HCTZ.

So, whoever conceived ACCOMPLISH not only chose a *comparator of convenience* but also made impossible for HCTZ to compete fairly.

Unfortunately, given the lack of attention of regulators, ACCOMPLISH has served well its purpose of discrediting diuretics, since they were too inexpensive to see their role acknowledged in the treatment of hypertension.

#### *Why choose chlorthalidone or indapamide and not HCTZ?*

The current US guidelines for hypertension<sup>8</sup> recommend a thiazide or thiazide-like diuretic as initial drug, without showing any preference between HCTZ and chlorthalidone. HCTZ is available in various doses, from 12.5 mg onwards, and the more powerful chlorthalidone is available only in a 25-mg tablet, a dose that is excessive for most patients. Chlorthalidone is available in very few

combinations, which do not include the most popular ones with ACE inhibitors or ARBs. The consumption of HCTZ is far greater. However, the following shortcomings in the use of HCTZ need attention:

- In equal mg, chlorthalidone reduced SBP better than HCTZ, with similar<sup>26</sup> or higher effects on the levels of potassium (see Point c. in Notes section) and less changes in cholesterol.
- Compared to HCTZ 50 mg, chlorthalidone 25 mg gives a greater 24-hour BP reduction, especially at night (13 vs. 6 mm Hg)<sup>27</sup>, probably due to its 5-times longer half-life compared to HCTZ.
- HCTZ showed less reduction in BP compared with other antihypertensive drugs in a meta-analysis including 19 RCTs.<sup>28</sup>
- Reanalysis of RCT MRFIT showed that chlorthalidone is superior to HCTZ in reducing<sup>19</sup> cardiovascular events (hazard ratio = 0.79)
- Left ventricular hypertrophy (LVH)<sup>29</sup>: in a head-to-head trial, chlorthalidone reduced LVH more than the four antihypertensive comparators, ACE inhibitor included<sup>30</sup>.
- There is no strong evidence to support the efficacy of HCTZ. Chlorthalidone and indapamide have reduced cardiovascular outcomes in large RCTs: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), Systolic Hypertension in the Elderly Program (SHEP) and Post-stroke Antihypertensive Treatment Study (PATS), Perindopril Protection Against Recurrent Stroke Study (PROGRESS), Action in Diabetes and Vascular Disease: Preterax and

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Diamicron MR Controlled Evaluation (ADVANCE), Hypertension in the Very Elderly Trial (HYVET) and so on. Indapamide also achieves metabolic neutrality on glycaemia and lipaemia, less reduction in kaliemia and less increase in uricaemia.

*The best evidence comes from a network meta-analysis*

Without an RCT directly comparing head-to-head outcomes between chlorthalidone and HCTZ, the best solution is a network meta-analysis<sup>22</sup> of the nine RCTs (almost

all high-quality) indirectly comparing chlorthalidone or HCTZ with a common comparator—placebo or active drugs such as amlodipine or ACE inhibitors. The meta-analysis included almost 80,000 patients, and all the results are very consistent, even when adjusted for type of comparator, level of achieved BP and retrospective comparison inside the MRFIT RCT (Figure 1, Table 2). The rate of reduction in cardiovascular events achieved by chlorthalidone is always close to 20% (see Point d. in Notes section).

NICE Hypertension Guidelines<sup>23</sup> recognise clearly the inferiority of HCTZ and bendrofluazide compared to chlorthalidone or

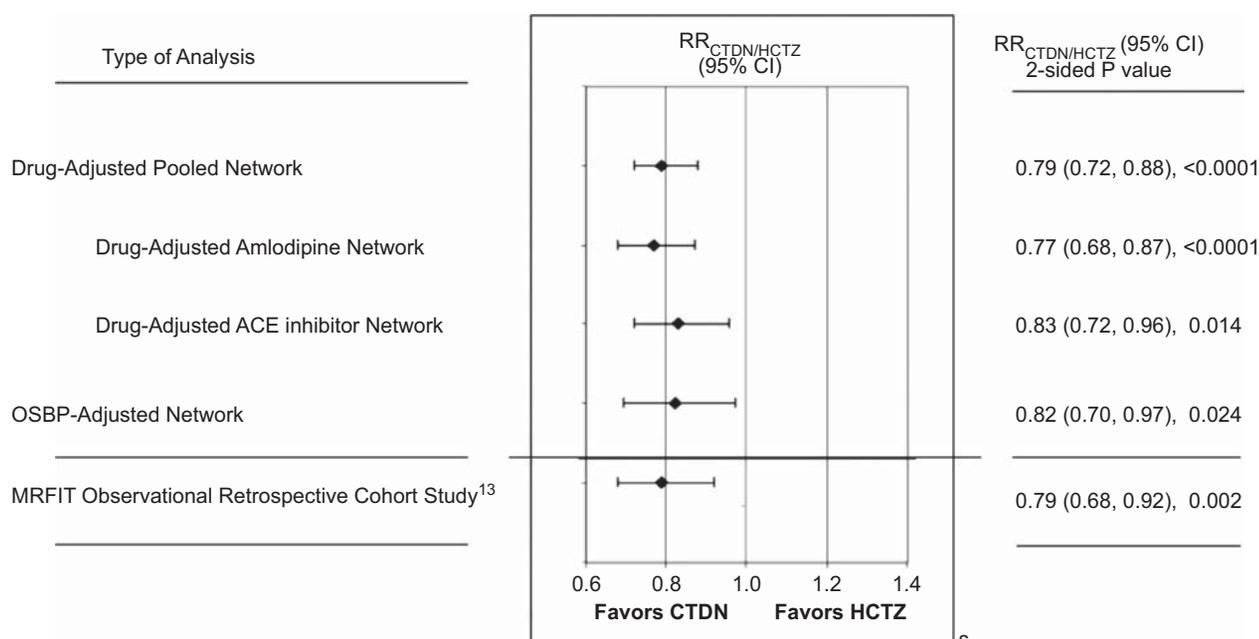
indapamide. Why, then, do ESH-ESC Guidelines insist that ‘no recommendation can be given to favour a particular diuretic agent’?

Here are two possible reasons. Refusing HCTZ would

1. challenge the habit, built on purpose with ASCOT and ACCOMPLISH, to give priority to a CCB (combined with ARBs or ACE inhibitors) rather than to ‘diuretics’. In fact, the greater efficacy of chlorthalidone compared to HCTZ (–21% cardiovascular events) is identical to that shown by amlodipine in ACCOMPLISH (–20% CV events vs. HCTZ), and the match between amlodipine and chlorthalidone would play on the risks of *laboratory-defined* diabetes (–18% with amlodipine<sup>23</sup>), HF (+38% with amlodipine<sup>23</sup>), tolerability (in trend about 13% better with the low-dose diuretic<sup>23</sup>) and price (moderate in Italy for generic amlodipine, 5 mg at 48€/year;

Condition	Pooled risk rate (95% confidence interval)	Test for heterogeneity
All-cause mortality	0.94 (0.82–1.09)	ns
Stroke	0.96 (0.76–1.21)	ns
Congestive heart failure	0.77 (0.61–0.98)	ns
Cardiovascular events	0.79 (0.72–0.88)	ns

ns, non-significant.



**Figure 1:** Risk rate: chlorthalidone versus hydrochlorothiazide for cardiovascular events by type of analysis (by courtesy of *Hypertension*<sup>22</sup>).

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negligible for chlorthalidone, 12.5 mg at 14.5€/year; see Point e. in Notes section).

2. most important, the market for more expensive drugs would be reduced because chlorthalidone alone (or with a second drug) is more likely than HCTZ to reach the target (even more so as now revised), reducing the space to add a second (or third or fourth) drug.

### Critical appraisal of the validity of relevant articles

Currently, there exists a large body of high quality scientific evidence that could allow an effective and cost-effective management of arterial hypertension, largely based on well conducted double blind RCTs, and whenever possible on *pragmatic* RCTs<sup>19</sup>, and on their systematic reviews. Unfortunately, many clinical guidelines do not reflect this kind of evidence, and seem to give greater importance to studies that, starting from their design, are better suited to satisfy the sponsor's needs. A paradigmatic example of such biases is the reluctance of ESH-ESC Guidelines to accept the evidence, strong and consistent though indirect, of the superiority of chlorthalidone and indapamide over HCTZ.

### Conclusion

The new ESH-ESC Guidelines, after decades of increasingly aggressive target reductions, finally restore a unified target of <140/90 mmHg, and higher for the elderly, but continue to avoid a cost-effective approach in drug therapies, and in fact, justify the use of much more expensive strategies. One of the main mechanisms underlying this policy is to deny the superiority of thiazide-like diuretics.

### Clinical applicability

From a strictly clinical perspective, the applicability of the best evidence

from the set of the RCTs is very good. However, this is unlikely to occur in practice, if the incentives and incomes of physicians and of their opinion leaders will continue (being equal to the effectiveness) to be aligned to the more costly therapeutic strategies, rather to the more cost-effective ones.

- a. The only drug that has reduced total mortality (not just stroke) in elderly aged >80 years is low-dose indapamide (plus an ACE inhibitor as needed) in HYVET trial.
- b. In ASCOT-BPLA<sup>18</sup>, similar arguments were supported with various artifices, comparing amlodipine (plus perindopril as required) with the less efficacious atenolol<sup>31</sup> (plus, as required, bendrofluzide, underdosed and with shorter half-life). Similar biases occurred in the open-label RCT ACCOMPLISH, also interrupted 'for obvious benefits' (although the primary outcome was not achieved). A critical analysis<sup>32</sup> of ASCOT-BPLA was sent to the NICE, and harsh critics have called it 'commercial speech'<sup>33</sup>. But ASCOT-BPLA, as ACCOMPLISH, achieved its purpose anyway.
- c. However, in large trials (SHEP, ALLHAT) also the minority of chlorthalidone-treated patients who developed hypokalemia had cardiovascular benefits<sup>34</sup>.
- d. A recent observational study<sup>35</sup> shows a non-significant reduction in the primary endpoint in comparisons made between chlorthalidone and HCTZ. But its serious flaws are discussed in Roush et al.<sup>36</sup>
- e. The difference in price between the two drugs is modest, but not irrelevant:

3.5 million €/year for each 100,000 patients.

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### *Supplementary information*

The doctor who chooses to operate in the Regional Health Service must follow its rules, and may deviate from them, for using prescription drugs, only if he or she is convinced that the most expensive drug is the only one able to cope with the disease, and he or she must be ready to account for his or her choice.

Medical morals are violated if a more expensive drug is prescribed instead of another one that is equally effective but less expensive, so damaging the whole community who support and share the pharmaceutical expenditure.

(freely translated from the Judgment No. 2238/2011 of the Administrative Tribunal of Rome-Lazio, with jurisdiction over the Italian territory)