# Correspondence

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## Antihypertensive efficacy of spironolactone: what about sex?

**Francesca Pizzolo and Oliviero Olivieri**

Department of Medicine, University of Verona, Verona, Italy

Correspondence to Francesca Pizzolo, MD, PhD, Department of Medicine, University of Verona, Piazzale Scuro, 37134 Verona, Italy
Tel: +39 45 8126490/8124401; fax: +39 45 8027473;
e-mail: francesca.pizzolo@univr.it

We read with interest the paper of Parthasarathy *et al.* [1], investigating the blood pressure (BP) response to two different diuretics [a mineralocorticoid receptor antagonist (MRA) and a thiazide diuretic] in patients subdivided, according to aldosterone-to-renin ratio (ARR) value, in high and low ARR group, respectively. Given the high incidence of primary aldosteronism and the widely recognized adverse effects of aldosterone on cardiovascular system, further research on MRA use in hypertensive patients is warranted.

Parthasarathy and colleagues found that spironolactone is equally effective in the two groups of patients and, importantly, it is highly powerful (with a mean global reduction of about 15 mmHg in mean 24-h systolic ambulatory BP after 12 weeks of treatment).

However, we would like to have some additional information, which was not included in the text, about the sex-related response to spironolactone. In our study published in 2008 [2] on primary-care hypertensive patients treated with potassium kanrenoate (the active metabolite of spironolactone), we reported that the drug was two-fold more effective in reducing SBP in women than in men (after 2 months of treatment −16.4 versus −8.2 mmHg). Moreover, a subanalysis of the results showed that the larger effect was obtained in postmenopausal women suggesting a role of aldosterone in this particular form of hypertension. In contrast and consistently with Parthasarathy *et al.*'s data, patients previously identified by a raised ARR did not have a response to MRA treatment statistically different from patients with normal ratio. Even taking into account the differences in the study design (intervention study with a single drug, analyzing office BP measurements versus a randomized, cross-over trial, analyzing ambulatory BP monitoring), it should be interesting to verify this aspect in Parthasarathy *et al.*'s patients both for the mean 24-h systolic ambulatory BP and for office SBP.

A confirmation of our previous data could be important not only for practical purposes but also for the possible pathogenetic implications that could be drawn.

Finally, we underline that in both studies MRA treatment was very effective and well tolerated, suggesting the opportunity to reconsider the role of this type of drugs in hypertension management.

## References

1 Parthasarathy HK, Alhashmi K, McMahon AD, Struthers AD, McInnes GT, Ford I, *et al.* Does the ratio of serum aldosterone to plasma renin activity predict the efficacy of diuretics in hypertension? Results of RENALDO. *J Hypertens* 2010; **28**:170–177.

2 Olivieri O, Pizzolo F, Ciacciarelli A, Corrocher R, Signorelli D, Falcone S, Blengio GS. Menopause not aldosterone-to-renin ratio predicts blood pressure response to a mineralocorticoid receptor antagonist in primary care hypertensive patients. *Am J Hypertens* 2008; **21**:976–982.

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## Blood pressure lowering in the oldest old: a step toward abandoning arbitrary blood pressure targets

**Francois Gueyffier[a,b,c], Marco I. Perez[d], James M. Wright[d], Ivanny Marchant[b,e,f], Vijaya M. Musini[d] and Theodora Bejan-Angoulvant[a,b,c]**

[a]Department of Clinical Pharmacology, Hospices Civils de Lyon, Lyon, [b]UMR 5558, CNRS, Villeurbanne, [c]Université Claude Bernard Lyon 1, Lyon, France, [d]Departments of Anesthesiology, Pharmacology & Therapeutics and Medicine, University of British Columbia, Vancouver, British Columbia, Canada, [e]IMTh – Institute for Theoretical Medicine, Lyon, France and [f]Escuela de Medicina, Departamento de Pre-clínica. Universidad de Valparaíso, Valparaíso, Chile

Correspondence to Theodora Bejan-Angoulvant, MD, Hospices Civils de Lyon, 28 Av Doyen Lepine, Lyon, France
Tel: +33 4 7235 7231; fax: +33 4 7212 9419;
e-mail: theodora.bejan-angoulvant@chu-lyon.fr

The clear benefit of treatment in hypertensive individuals above 80 years of age on nonfatal outcomes, in particular stroke and heart failure, contrasts with the remaining uncertainties regarding the fact that treatment may increase total mortality. The suspicion of deleterious treatment effects evolved as the evidence accumulated over time: it was first estimated as a marginally significant increase of 14% of total mortality in a 1999 systematic review of limited subgroups from randomized controlled trials done in larger populations [1] [$P = 0.05$; 95% confidence interval (CI) 0–31; no significant heterogeneity]. In 2003, the results from the Hypertension in the Very Elderly Trial (HYVET) pilot trial [2], reinforced that suspicion, with a relative increase in risk of 23% in total mortality (both results combined: $P = 0.03$; 95% CI 1–31; no significant heterogeneity). Recently, the HYVET trial [3] offered the unexpected and apparently reassuring result: a statistically significant reduction in both stroke and total mortality was observed at the second interim analysis after 2 years of follow-up, which led the investigators to prematurely interrupt the trial.

The completion of data collection to the final date of trial follow-up modified somewhat the results of this interim analysis: the primary outcome, stroke, displayed a risk reduction of 30% (95% CI −1 to 51; $P = 0.06$), and the risk reduction of death from any cause was a 21% reduction (95% CI 4–35; $P = 0.02$); unfortunately, these results were no longer significant when measured against the a-priori decided [4] threshold of $P$ less than 0.01 for statistical significance. The most likely interpretation for this quick evolution of results between the time of decision and the final completed analysis is that the initial results were an overestimation of reality, as has been proven to be the case with early truncation of trials [5]. Whatever the interpretation of this result, it dramatically weakens the level of evidence of HYVET, which has to be considered as an inconclusive trial, when considered alone.

As expected from the pooling of two results, both statistically significant but in opposite directions, the updated meta-analysis was significantly heterogeneous, both in terms of statistical significance and clinical relevance. The probability that the difference between HYVET results and those from previous synthesis of evidence was due to chance alone was estimated to be less than 0.003, that is, a rather unusual level for heterogeneity tests, known to be underpowered. This discrepancy led us to update our 1999 meta-analysis focusing on total mortality, exploring possible causes through meta-regression and eventually concluding that a high intensity of therapy was to be avoided [6]. In their editorial commentary, Reboldi *et al.* [7] have provided interesting points of discussion about our updated systematic review.

They introduced the debate by suggesting that the disappointing scenario of a high prevalence of uncontrolled hypertension after 80 years of age may be related to the promotion of negative results. They suggested that the lack of evidence in this age group may have influenced physicians, making them reluctant to adequately treat the oldest old with hypertension. They build their reasoning on a mix of HYVET results, those from a subgroup meta-analysis and the recently published update of the European Society of Hypertension (ESH) guidelines [8], stating that 'even in the very elderly stratum of the population, antihypertensive treatment does not only prevent cardiovascular morbid events but also translates into prolongation of life', and that 'an evidence-based general recommendation can now be given to prescribe antihypertensive treatment to octogenarians with SBP above 160 mmHg with the target to lower it below 150 mmHg'. First, we do not share their feeling of knowing *a priori* what adequate treatment is, before critically appraising the results from the best evidence. Second, their statement that blood pressure (BP) in the oldest old is not adequately controlled is based on a BP target defined as SBP less than 140 and DBP less than 90 mmHg, in contradiction with the targets they promote later on in their commentary. In such discussions, hypertension definition has to be clearly distinguished from BP target under treatment, even if both have always been arbitrary. In addition, differences of 10 or 20 mmHg can make huge differences in terms of hypertension prevalence, or deleterious consequences of treatment. We think it important to emphasize a particular aspect of the HYVET protocol: the rules for treatment escalation were based on a conservative BP target of 150 mmHg, and no additional treatment was mandated after two drugs in modest dosage was attained, explaining why 50% of randomized patients did not achieve the target. Third, Reboldi *et al.* [7] did not acknowledge two clear limitations of their rationale: they used the results from HYVET, which are not statistically significant (see above) and cited a subgroup meta-analysis concerned with a population of hypertensive individuals above 65 years of age, which is not relevant for addressing questions for patients 80 years of age or above.

Then, Reboldi *et al.* [7] focused their discussion on two methodological issues, putting into question the reality of the heterogeneity regarding mortality results on one hand and possible explanations through meta-regression for the heterogeneity of mortality results on the other hand.

They correctly stated that the analyzed trials were not powerful enough to demonstrate a small significant effect on mortality. In order to illustrate their statement, Reboldi *et al.* computed the size of a trial to be powerful enough to demonstrate a statistically significant 6% increase of mortality (that observed in our meta-analysis). This computation is questionable. First, they used an unusual 0.01 threshold for statistical significance of bilateral test, as did the authors of the HYVET trial, without justifying it. Second, they based their computation on the 6% increase corresponding to the average point estimate of a meta-analysis with significant heterogeneity. The basic principle to deal with a significant heterogeneity in meta-analysis is to avoid direct interpretation and *a fortiori* any prediction based on this point estimate. If alternatively, we had to compute the sample size for a trial aiming at testing the hypothesis that overtreatment would result in a mortality increase, we would use the point estimate of a meta-analysis that did not display heterogeneity, that is, that from trials available before the results of HYVET were published, with usual statistical significant threshold. We then would have to decide between the point estimate observed at 3 years, that is, 35% increase, or that observed after 5 years, that is, 17% increase. The resulting sample size would be suitable for a future clinical trial.

The weakness of the available evidence regarding the impact of antihypertensive treatment on mortality in the very old comes mainly from the fact that no trial adopted mortality as the primary outcome. Importantly, we have to accept that the most powerful clinical trial available to date is inconclusive. Dealing with this uncomfortable

situation, we must try to explain the heterogeneity and to inform patients as clearly and honestly as possible using the best available evidence.

Reboldi *et al.* [7] stated that we should have used random effect model to perform the meta-regression, because 'fixed-effect meta-regression is likely to produce misleading results in the presence of heterogeneity'. We agree with their statement and take the liberty to present the results using their suggestion: the results of the meta-regression using a random effect model remain significant and, thus, our conclusions do not change. Most of all, we observe that their reasoning contradicts their former claim that the heterogeneity is attributable to unreliable underpowered data.

The conclusion of our meta-analysis, that a high intensity of therapy is to be avoided, is based on secondary post-hoc analyses. However, it is in line with the trend observed in the meta-regression of observed BP under treatment, and most of all, it is also in agreement with the common sense approach of being cautious not to lower the BP too much in a frail elderly population.

## References


1 Gueyffier F, Bulpitt C, Boissel JP, Schron E, Ekbom T, Fagard R, *et al.* Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. INDANA Group. *Lancet* 1999; **353**:793–796.

2 Bulpitt CJ, Beckett NS, Cooke J, Dumitrascu DL, Gil-Extremera B, Nachev C, *et al.* Hypertension in the Very Elderly Trial Working Group. Results of the pilot trial for the Hypertension in the Very Elderly Trial. *J Hypertens* 2003; **21**:2409–2417.

3 Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, *et al.* Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008; **358**:1887–1898.

4 Bulpitt C, Fletcher A, Beckett N, Coope J, Gil-Extremera B, Forette F, *et al.* Hypertension in the Very Elderly Trial (HYVET): protocol for the main trial. *Drugs Aging* 2001; **18**:151–164.

5 Bassler D, Montori VM, Briel M, Glasziou P, Guyatt G. Early stopping of randomized clinical trials for overt efficacy is problematic. *J Clin Epidemiol* 2008; **61**:241–246.

6 Bejan-Angoulvant T, Saadatian-Elahi M, Wright J, Schron E, Lindholm LH, Fagard R, *et al.* Treatment of hypertension in patients 80 years and older: the lower the better? A meta-analysis of randomized controlled trials. *J Hypertension* 2010; **28**:1366–1372.

7 Reboldi G, Gentile G, Angeli F, Verdecchia P. Blood pressure lowering in the oldest old. *J Hypertens* 2010; **28**:1373–1376.

8 Mancia G, Laurent SP, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, *et al.* Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens* 2009; **27**:2121–2158.


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## Reply


**Gianpaolo Reboldi[a], Giorgio Gentile[a], Fabio Angeli[b] and Paolo Verdecchia[c]**

[a]Department of Internal Medicine, University of Perugia, [b]Department of Cardiology, Hospital 'S. Maria della Misericordia', Perugia and [c]Department of Medicine, Assisi Hospital, Assisi, Italy

Correspondence to Gianpaolo Reboldi, MD, PhD, MSc, Department of Internal Medicine, University of Perugia, Italy
E-mail: paolo@unipg.it


We thank the authors for their interest in our Commentary [1] and the issues they raised. Our aim in commenting the updated meta-analysis was to promote the discussion in an area in which important clinical decisions are frequently made in the absence of conclusive evidence.

It is beyond question that Gueyffier *et al.* in their letter highlighted important issues concerning the treatment of hypertension in the very elderly. However, it seems that they have somewhat misinterpreted our position and we apologize if our reasoning was not clear. Our position in this area is in line with the aphorism of Sir Francis Bacon, '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' [2]. We do not know, and hence actually we never stated, either '*a priori*' or '*a posteriori*', what 'adequate treatment' is for octogenarians. Being far from certainty, we openly stated that 'the optimal goals of antihypertensive therapy in the oldest old have always been the object of debate' [1]. Thus, in commenting the data reported by Bejan-Angoulvant *et al.* [3], we tried to delineate the scenario, through a chronologic reconstruction of available evidence from observational studies, intervention trials, systematic reviews, and clinical practice guidelines. Our aim was threefold: define what we know, what we do not know yet, and highlight the 'grey areas' of uncertainty. We believe that our chronologic reconstruction of available evidence emphasizes the limits of current knowledge rather than formally endorsing whatsoever position.

We agree with Gueyffier *et al.* that, as a general rule, differences of 10 or 20 mmHg can make huge differences in terms of hypertension prevalence, even if data from Framingham [4] underscore that more than 60% of individuals aged 80 or older had blood pressure (BP) values at least 160/100 mmHg or were receiving treatment. However, it is also evident that previous studies, cited at the beginning of our commentary [1], used BP targets reported in previous guidelines [5,6], whereas only the recently updated European Society of Hypertension (ESH) guidelines [7] highlighted the issue of specific targets in the oldest old. Secondly, we never endorsed the BP target of 140/90 mmHg. The 140/90 mmHg target was cited using quotation marks, so there is no contradiction with the target later reported in our commentary. We interpret the systolic blood pressure (SBP) target of 150 mmHg, recommended by the updated ESH guidelines and not arbitrarily promoted by us, as a cautionary step which may represents a wise approach at the present time, until further substantial evidence will become available. Moreover, the true point of concern is that, as Hajjar *et al.* [8] reported 35% of physicians consider that the increase in BP with age is a normal process of aging, and 25% consider treating hypertension in an 85-year-old patient to have more risks than benefits. Therefore, it may appear pointless, if not purely

academic, to discuss about the different thresholds for the diagnosis and the treatment of hypertension in the oldest old, when a large number of physicians are reluctant to treat an 80-year-old man. It may be more important to adequately acknowledge that elderly people may actually benefit from antihypertensive treatment.

## Methodological aspects

Contrary to the perspective of Gueyffier *et al.*, we did not 'compute the size of a trial to be powerful enough to demonstrate a statistically significant 6% increase of mortality'. We concur with them that a realistic interpretation of predictions from a random-effects model can indeed be difficult in the presence of heterogeneity, but our concern was the conclusiveness of their meta-analysis and the potential implication of their relevant findings, not the predicted effect treatment in a future study. Consequently, we calculated the optimum information size (OIS) [9] for this meta-analysis and not the sample size requirement for a future trial. This unfortunate misunderstanding makes a huge difference. OIS is the minimum amount of information required in the collective literature for reliable conclusions about an intervention to be reached before conducting a new study, that is whether the results of a series of trials are so extremely clear that further studies are not needed. With this in mind, one may wish to set the type I error rate (alpha level) at least at 0.01 (instead of the commonly used 0.05) and set power at 90 or 95% [10].

Optimum information size provides a first approximation of the minimum sample size required, and our illustrative calculations (assuming a clinically relevant 6% relative risk increase and a 14% incidence in controls) showed that using a moderately conservative alpha of 0.01 and lower-than-recommended power (80%) the required information size should be at least 159 694. Increasing power to 90 or 95% (as recommended) would further increase OIS to 203 272 or 243 232, respectively, whereas the meta-analysis included only 6701 patients. On this ground, we concluded that the evidence cumulated so far was unlikely to be conclusive. Even excluding HYVET results from the meta-analysis, OIS calculation with alpha 0.01 and power 80, 90 or 95% (assuming a 17% relative risk increase at 5 years and a 17% mortality in controls, i.e. the ratios and rates observed excluding HYVET data) would yield a minimum required information size OIS of 8550, 10 854 and 12 966, respectively, still well above the 2856 patients studied before HYVET. As noted, inclusion of HYVET introduces a statistically significant heterogeneity and OIS calculation does not take this into account explicitly [10]. Heterogeneity indeed affects the information size and, as recently demonstrated by Wetterslev *et al.* [11] the required information size in a random-effects model is a monotone increasing function of the degree of heterogeneity. These authors derived an adjusting factor for the required information size under random-effects model meta-analysis using the inconsistency ($I^2$) statistic. To preserve $\alpha$ and $\beta$, the correction factor increases the information size according to the impact that heterogeneity has on the meta-analysis. Accordingly, our illustrative estimate ($n = 159\,694$), for an 'unadjusted' information size requirements (assuming near-null inconsistency) would rise to 275 334 when adjusted using the heterogeneity correction factor based on 42% inconsistency statistic (i.e. the $I^2$ statistic for this meta-analysis) [3,11]. Even with a less conservative alpha set to 0.05 and 80% power, the heterogeneity-adjusted information size for this meta-analysis would be 95 489, still well above 6701. Given these figures, we reluctantly have to accept that this meta-analysis is not conclusive. In dealing with this uncomfortable situation, we must, however, carefully balance between significant benefits and possible, yet unproven, harms.

Gueyffier *et al.* substantially accepted our suggestion and came to a conclusion that we already presented in our commentary: 'we obtained the same point-estimate (22% increase) but with much wider 95% confidence intervals (CIs), spanning from 2 to 45%, and a lower level of statistical significance ($P = 0.033$ vs. $<0.001$)' [1]. Rather than questioning the level of statistical significance achieved, our suggestion had to be interpreted as a word of caution before drawing conclusions about causal relationships, because a fixed-effects model might be overoptimistic [12]. Apart from this, the relationship described by a meta-regression is an observational association across trials, and even though the original studies are randomized trials, the meta-regression is across trials and does not have the benefit of randomization to underpin a causal interpretation [12].

As correctly stated by Gueyffier *et al.* the conclusion of this meta-analysis, that a high intensity of therapy is to be avoided, is based on secondary post-hoc analyses conducted on a limited number of studies, none of them originally designed to evaluate mortality as the primary end-point. Thus, the findings of this meta-analysis have to be considered as hypothesis-generating rather than hypothesis-testing. Apart from this, the associations derived from meta-regressions are observational in nature, and have a weaker interpretation than the causal relationships derived from randomized comparisons.

In conclusion, we agree with Gueyffier *et al.* on being cautious and not lower the BP too much in a frail elderly patient, and, as we stated, physicians should pursue 'wise' rather than 'arbitrary' targets, tailor therapy to the individual patient, and carefully balance between clinically significant benefits and possible, yet unproven, harmful effects.

## References

1 Reboldi G, Gentile G, Angeli F, Verdecchia P. Blood pressure lowering in the oldest old. *J Hypertens* 2010; **28**:1373–1376.

2 Bacon F. (1605) The advancement learning. In Spedding J, Ellis R, Heath D, editors. *The works of Francis Bacon,* vol. 3. London: Longman; 1857–1861. pp. 293.
3 Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, Schron EB, Lindholm LH, Fagard R, *et al.* Treatment of hypertension in patients 80 years and older: the lower the better? A meta-analysis of randomized controlled trials. *J Hypertens* 2010; **28**:1366–1372.
4 Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. *JAMA* 2005; **294**:466–472.
5 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, *et al.* 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25**:1105–1187.
6 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, *et al.* The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**:2560–2572.
7 Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, *et al.* Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens* 2009; **27**:2121–2158.
8 Hajjar I, Miller K, Hirth V. Age-related bias in the management of hypertension: a national survey of physicians' opinions on hypertension in elderly adults. *J Gerontol A Biol Sci Med Sci* 2002; **57**:M487–M491.
9 Pogue J, Yusuf S. Overcoming the limitations of current meta-analysis of randomised controlled trials. *Lancet* 1998; **351**:47–52.
10 Pogue JM, Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for cumulative meta-analysis. *Control Clin Trials* 1997; **18**:580–593; discussion 661–6.
11 Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 2008; **61**:64–75.
12 Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002; **21**:1559–1573.

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