Beta-blocker bashing and downgrading in hypertension management: a fashionable trend representing a matter of concern

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In their commentary, Shantsila *et al*. [1] while discussing some relevant issues of the 2023 Guidelines for the Management of Hypertension of the European Society of Hypertension (ESH) [2], for example, the length of the text and the involvement of only a few primary care physicians, they largely focus on the discussion on beta-blockers. The authors conclude that 'the 2023 ESH Guidelines still argue in favour of beta-blockers that their clinical inferiority was simply to lesser blood pressure (BP) reduction rather than class effect'. However, this is an oversimplification that does not reflect the numerous arguments and facts that support the overall rationale of the 2023 ESH Guidelines for the recommended use of beta-blockers in the management of hypertension [2]. Taken together with other similar comments [3], it appears that it has become fashionable to down-grade beta-blockers and to dismiss the points already put forward in the 2023 ESH guidelines [2] and in previous publications revisiting beta-blocker benefits in detail [4,5]. Against this background, we use this opportunity to emphasize on key aspects of the beta-blocker discussion in brief. For a more comprehensive review of the literature, we refer to a very recent publication by us regarding the role of beta-blocker in hypertension [6].

1. **Beta-blockers reduce office SBP and DBP as effectively as the other major antihypertensive drugs.** This is of major importance because BP lowering per se accounts for a substantial proportion of the protective effect of antihypertensive treatment. Evidence is also available that BP-lowering effectiveness of beta-blockers extends to out-of-office BP values and use in combination treatment.
2. **Beta-blockers are protective in placebo-controlled BP-lowering randomized controlled trials (RCTs).** Beta-blockers have been tested in several BP-lowering RCTs, in which patients were randomized to a beta-blocker (mainly but not exclusively atenolol) vs. placebo or an untreated group. Use of beta-blockers was associated with significant reductions of major cardiovascular outcomes and mortality in most RCTs, an observation that has been confirmed by meta-analyses of these trials.
3. **Beta-blockers are protective in RCTs in comparison to other BP-lowering drugs.** Beta-blockers have been compared with other major antihypertensive drugs in multiple RCTs with somewhat discrepant results, that is, less protection by beta-blockers in LIFE and ASCOT but similar or even greater protection in several other RCTs. The discrepancies between individual trials are also reflected by the heterogeneous results of trial meta-analyses, which in some cases showed a similar but in others a lesser overall protective effect of beta-blockers vs. the comparison treatment, albeit usually with a difference of limited size. Although a modest increase (6%) of all-cause mortality in patients treated with beta-blockers was observed in one analysis, the risk of cardiovascular mortality was never increased and similar effects on cardiovascular outcomes were observed when only hypertension trials were analysed.
4. **Beta-blockers are protective in combination therapy with other blood pressure-lowering drugs.** No specifically designed RCT has compared the protective effect of combination treatment vs. placebo or

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an untreated patient group. This said, in virtually all placebo-controlled trials showing a reduction of cardiovascular outcomes, most patients randomized to the active treatment group were given a second and even three or more antihypertensive drugs after the initial monotherapy, leaving no doubt as to the protective effect of the combination treatment strategy. This applies also to beta-blockers for which a marked reduction of cardiovascular outcomes and stroke has been reported in three trials comparing a beta-blocker-diuretic combination with placebo. Furthermore, in many other trials, a similar protective effect has been shown for beta-blockers together with any other major antihypertensive agent compared with non-beta-blocker combinations.

5. **Beta-blockers reduce the risk of stroke.** Beta-blockers reduce the risk of stroke compared with placebo in RCTs. The 2023 ESH Guidelines acknowledged that meta-analyses of RCTs comparing beta-blockers with other antihypertensive drugs found a lesser reduction in stroke risk in response to beta-blocker treatment compared with other antihypertensive agents. However, stroke incidence is sensitive to small BP changes and a smaller BP reduction in beta-blocker-treated patients than in patients treated with the comparison drugs might explain these observations [6]. The BP difference was small in LIFE (average 0.3 mmHg SBP and 1.3 mmHg SBP at the last visit) in which all patients had left ventricular hypertrophy and a beta-blocker was chosen as comparator with an angiotensin receptor blocker to secure effective prevention of cardiac death. In ASCOT, the BP difference was large (average 5 mmHg SBP during the first year, and 2.9 mmHg SBP throughout the trial) and the 23% difference in stroke risk between the two treatment arms (beta-blocker treatment and CCB treatment) can thus be fully attributed to the SBP difference. This is supported by its fitting on the meta-regression analysis associating the overall effect of SBP reduction on the reduction of stroke events [7].

An important point made by the 2023 ESH Guidelines [2,6] is that the selection of BP-lowering drug classes, including beta-blockers, in the management of hypertension needs to be guided by the overall protective effect of drugs against outcomes rather than a potential negative impact on specific outcomes, which is common to all major antihypertensive drugs and specific outcomes [2,6]. The latter seems questionable, because if a lower protection against a specific outcome, for example, stroke reduction by beta-blockers, coexists with a similar overall cardiovascular protection, it is obvious that reduced protection against one specific outcome is compensated by an increased protection against other outcomes. Furthermore, physicians do not know which outcome a hypertensive patient will experience in the future, which renders the selection of drug classes based on their potential effects on specific clinical outcomes meaningless particularly when used in combination therapy. In the view of the ESH 2023 Guidelines Committee, abandoning beta-blockers as a first-line therapy option in the treatment of high BP is neither justified nor sensible. This would deprive treating physicians of an important therapeutic option.

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Conflicts of interest

The conflict of interest declaration of the authors as members of the Task Force members of the 2023 ESH Guidelines were compiled into one file that can be found on the ESH website: https://www.eshonline.org/guidelines/2023-guidelines/

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