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A meta-analysis of randomized controlled trials assessing the impact of beta-blockers on arterial stiffness, peripheral blood pressure and heart rate

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ABSTRACT

Background: The recognition of beta-blockers as a preferred initial therapy for hypertension has been a hot topic of debate recently. This meta-analysis was aimed to assess the impact of different beta-blockers on arterial stiffness as indexed by pulse wave velocity (PWV), peripheral blood pressure (BP) and heart rate, relative to the placebo, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).
Methods: Two authors independently searched articles, appraised eligibility and abstracted information, and the data were analyzed using STATA.
Results: Twenty-four articles involving 27 independent trials were eligible. Relative to the placebo, treatment with beta-blockers led to remarkable improvement in PWV (WMD, 95% CI, *P*: −1.115 m/s, −1.561 to −0.669, <0.001), systolic BP (−12.355 mmHg, −14.330 to −10.380, <0.001), diastolic BP (−8.619 mmHg, −10.357 to −6.880, <0.001), mean BP (−9.683 mmHg, −11.172 to −8.194, <0.001), pulse pressure (−4.448 mmHg, −7.386 to −1.510, 0.003) and heart rate (−12.335, −22.739 to −1.932, 0.020). Beta-blockers were remarkably superior to ACEIs in DBP (−2.540 mmHg, −4.463 to −0.617, 0.010) and heart rate (−9.859 bpm, −11.752 to −7.969, <0.001). In contrast to ARBs, beta-blocker treatment increased systolic BP (2.042 mmHg, 0.639 to 3.444, 0.004) but reduced heart rate (−8.814 bpm, −9.756 to −7.873, <0.001) significantly. No publication bias was observed.
Conclusions: Beta-blockers exerted more favorable impact than the placebo on arterial stiffness, peripheral BP and heart rate, but less favorable impact than ACEIs or ARBs on all, except heart rate, characters, especially in trials with longer duration of treatment and higher baseline PWV.

1. Introduction

A wealth of evidence supports that increased stiffening of the arterial circulation is a primary cause of hypertension, and importantly is a powerful predictor for adverse cardiovascular outcomes [1,2]. National and international guidelines have recommended five classes of drugs for the first-line treatment of hypertension; however some antihypertensive agents exert varied impact on arterial stiffness [3]. A highly debatable point of view surrounds the recognition of beta-blockers as first-line drugs in uncomplicated hypertension [4,5]. Beta-blockers are recognized as a heterogeneous class of drugs with different pharmacologic and physiologic properties, and they can selectively or non-selectively block the activation of beta-adrenergic receptors [6]. Atenolol, developed in 1976, is one of the most widely prescribed beta-blockers worldwide [7]. However, a majority of comparative trials in hypertension have found that atenolol, a selective $beta_1$-receptor antagonist, is less effective than agents of different classes such as nebivolol and the renin-angiotensin system (RAS) inhibitors in improving vascular function and central hemodynamic indices, despite comparable changes in peripheral blood pressure [8–10]. Nebivolol and carvedilol are the third-generation beta-blockers bearing vasodilating properties, and their superior efficacy on arterial compliance and elasticity relative to atenolol was reported by several trials [8,11]. As recommended by the UK National Institute for Clinical Excellence (NICE) (http://www.nice.org.uk/guidance/cg127/chapter/1-recommendations), beta-blockers are not a preferred initial therapy for hypertension. In view of the fact that beta-blockers are not a homogeneous group, it seems premature to extrapolate the findings gathered from atenolol to all beta-blockers for the treatment of hypertension. With the accumulation of more comparative data over time, we sought to systematically assess the impact of different beta-blockers on arterial stiffness as indexed by pulse

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wave velocity (PWV), peripheral blood pressure and heart rate in separate comparisons with the placebo, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) via a meta-analysis of randomized controlled trials (RCTs) from the English language literature. Meanwhile, possible sources for the presence of heterogeneity across trials were extensively explored.

The conduct of this systematic meta-analysis of RCTs adhered to the protocols outlined in the Quality of Reports of Meta-Analyses (QUOROM) statement [12].

2. Methods

2.1. Literature search

We searched Medline (PubMed), Embase, Cochrane Central Register of Controlled Trials and Google-Scholar databases for potentially eligible articles using key terms "beta-blocker", "β-blocker", "pulse wave velocity" and "PWV" as of February 4, 2016. Beta-blockers of all available classes included propranolol, pindolol, atenolol, metoprolol, bisoprolol, arotinolol, nebivolol, labetalol and carvedilol. Only published articles in English language and human beings were retrieved. The reference lists of some major reviews and original contributions were also scanned by hand for additional missing hits.

2.2. Eligibility criteria

All included articles must satisfy the predefined criteria, including: (i) randomized clinical trial with either a cross-over or parallel design; (ii) mean follow-up time of at least 1 month; (iii) comparison of any beta-blocker agent with the placebo or ACEIs or ARBs, or vice versa; and (iv) available data on any type of PWV before and after treatment or the corresponding change values. Conference abstracts and posters were not considered in this meta-analysis as they contained inadequate information for a complete comparison.

2.3. Article selection

With aforementioned eligibility criteria in mind, two authors (Wenquan Niu and Yue Qi) independently reviewed the title or abstract of each retrieved article, and when necessary, the full text was tracked for further evaluation. For each clinical trial, we recorded its registered or adopted name if available, the country where study participants were enrolled, and acquisition time, seeking to remove duplicate publications from the same group. In case of more than one publication from the same trial, the trial with the largest sample size and complete data of interest was retained in final analysis. Any uncertainty over eligibility appraisal was settled by a discussion.

2.4. Information extraction

A standardized information collection table was formulated, and the extraction process was completed by two authors (Wenquan Niu and Yue Qi). Relevant information extracted included the first author's name, year of publication, the country where study participants were enrolled, baseline hypertension status, study design, sample size in each arm, PWV subtype, wash-out period, duration of clinical trial, the beta-blocker and its dosage used in treatment group, the placebo or ACEIs or ARBs used in control group, the mean values and standard deviations of PWV, peripheral systolic and diastolic blood pressure (SBP and DBP), peripheral mean blood pressure (MBP), peripheral pulse pressure (PP) and heart rate or the corresponding changes before and after treatment in both arms, as well as some baseline characteristics of study participants, including age, gender, body weight and height, and body mass index (BMI) if available. At last, the two independent tables were compared for divergences, and there was no disagreement after a consensus discussion.

2.5. Statistical analysis

For each clinical trial, the changes in PWV, SBP, DBP, MBP, PP and heart rate from baseline to follow-up were expressed as weighted mean difference (WMD) and its 95% confidence interval (95% CI), and these effect-size estimates were pooled in a random-effects meta-analysis model based on the DerSimonian & Laird method [13]. The validity of pooled estimates was assessed by heterogeneity and publication bias. The magnitude of heterogeneity was quantified by I^2 statistic, a percentage reflecting the proportion of the observed variability across trials that results from heterogeneity rather than chance. The probability of publication bias was statistically evaluated using Egger regression asymmetry test and the trim-and-fill method. The trim-and-fill method can estimate the number of theoretically missing trials due to publication bias to make the Filled funnel plot symmetrical.

Heterogeneity was explored by both subgroup analysis and meta-regression analysis. Subgroup analysis was based on the differences in continent, study design, baseline hypertension status, PWV subtype, wash-out period, duration of clinical trial, beta-blocker subtype and active drug in control group, respectively. As an extension of subgroup analysis, meta-regression analysis can account for the effect of both continuous and categorical characteristics under investigation individually or simultaneously.

All statistical analyses were carried out by Stata software version 13.0 (StataCorp LP, College Station, Texas).

3. Results

3.1. Qualified trials

Using per-defined key terms, the initial search of four databases generated a total of 404 unduplicated articles, and only 24 articles met the pre-determined eligibility requirements [9,10,14–35]. All qualified articles were published in English language from the year 1991 [14] to 2015 [35]. Two articles summarized data by PWV subtypes [14,29] and one article by different beta-blocker agents [21], leading to a total of 27 independent clinical trials with 1145/1144 study participants in the treatment/control group. In addition, given that one article provided data according to two follow-up time points (6 months and 12 months) [19], we treated them separately only in follow-up time-specific subgroup analysis, and in other cases the trial with longer follow-up time was retained.

3.2. Characteristics

Tables 1A, 1B, 1C show the baseline characteristics of study participants in this meta-analysis. Of 27 independent trials, 20 were performed with a parallel design, and 7 with a cross-over design. The majority of clinical trials adopted carotid-femoral PWV (cfPWV) as a measure of arterial stiffness ($n = 17$), 6 trials using brachial-ankle PWV (baPWV), 2 trials using carotid-radial PWV (crPWV) and 2 trials using brachial-radial PWV (brPWV). Twenty-three trials involved study participants with essential hypertension at baseline, and 6 of them had untreated essential hypertension. Nine trials reported wash-out period of over 2 weeks, and 12 trials of $\leq$2 weeks. Follow-up time ranged from 4 weeks to 12 months, with 15 trials lasting more than 3 months and 12 trials lasting $\leq$3 months. Of 27 trials studied, 14 used atenolol with the rest 13 trials using non-atenolol, 22 used selective beta-blockers with the rest 5 trials using non-selective beta-blockers with vasodilating properties. As for the drugs used in control group, the placebo was reported in 5 trials, ACEI in 10 trials and ARB in 12 trials. No statistically significant differences were found for age, male percentage, body weight, height and BMI between treatment and control groups ($P > 0.05$).