Effects of Major Antihypertensive Drug Classes on Erectile Function: a Network Meta-analysis

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Abstract

Purpose To determine the effect of major antihypertensive classes on erectile function (EF) in patients with or at high risk of cardiovascular disease.

Methods We performed a systematic review and frequentist network meta-analysis of randomized controlled trials assessing the effect of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, and thiazide diuretics on EF compared to each other and to placebo (PROSPERO: CRD42020189529). Similarly, we performed a network meta-analysis to explore the effect of different β-blockers on erectile function (nebivolol, other vasodilating and non-vasodilating β-blockers, placebo). Records were identified through search of PubMed, Cochrane Library, and Scopus databases and sources of grey literature until September 2020.

Results We included 25 studies (7784 patients) in the qualitative and 16 studies in the quantitative synthesis. The risk of bias was concerning or high in the majority of studies, and inconsistency was also high. No significant differences in EF were demonstrated in the pairwise comparisons between major antihypertensive classes. Similarly, when placebo was set as the reference treatment group, no treatment strategy yielded significant effects on EF. In the β-blockers analysis, nebivolol contributed a beneficial effect on EF only when compared to non-vasodilatory β-blockers (OR 2.92, 95%CI 1.3–6.5) and not when compared to placebo (OR 2.87, 95%CI 0.75–11.04) or to other vasodilatory β-blockers (OR 2.15, 95%CI 0.6–7.77).

Conclusion All antihypertensive medication classes seem to exert neutral or insignificant effects on EF. Further high-quality studies are needed to better explore the effects of antihypertensive medication on EF.

Keywords Erectile dysfunction · Arterial hypertension · Antihypertensive medication · β-Blockers · Network meta-analysis

Introduction

Erectile dysfunction (ED) is a disease, highly prevalent in the general population, and its prevalence increases with age [1, 2]. ED not only exerts a negative influence on the patients’ quality of life, but it is also considered a marker of increased incidence of cardiovascular events [3, 4]. Furthermore, ED clusters with other cardiovascular risk factors, a finding indicating that ED is a manifestation of a systemic vascular disorder [5]. In particular, ED is twice as prevalent and more severe in the hypertensive compared to the general population [6].

To complicate things further, accumulated evidence suggests that antihypertensive agents often exert unfavourable outcomes on erectile function, thus compromising medication adherence, a factor crucial for hypertension management [7, 8]. Hypertension societies have issued recommendations and consensus papers on ED and its association with...
antihypertensive medications [6, 9]. Based on existing data, such documents suggest that among major antihypertensive classes, thiazide diuretics and β-blockers possess the worst profile regarding erectile function, while angiotensin receptor blockers (ARBs) the most favourable [6, 7, 10]. Still, recommendations do not comprehensively address this matter as they are mostly based on scarce data or evidence from expert opinions [11]. The latter is also reflected in the insufficient knowledge of the effects of cardiovascular medication on sexual function among physicians [12]. Of importance, contrary to other antihypertensive classes, β-blockers display substantial within-class heterogeneity in terms of effectiveness and adverse cardiac and metabolic profile [13]. In particular, experimental and clinical studies suggest that, unlike other β-blockers, nebivolol is beneficial in terms of erectile function preservation [13].

Within this framework, we aimed to systematically synthesize the available evidence and generate a network meta-analysis, aiming to determine the comparative effects of major classes of antihypertensive medications on erectile function. Due to within-class heterogeneity among β-blockers, we also generated a network meta-analysis exploring the effects of different β-blockers on erectile function.

Methods

Search Strategy

The aims and methods of this systematic review and network meta-analysis were documented in a protocol registered at PROSPERO (ID: CRD42020189529). We reported this study according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement for Network Meta-analyses (PRISMA-NMA) [14].

Two independent authors (IF, NP) systematically searched PubMed, Cochrane Library and Scopus databases for RCTs exploring the effects of antihypertensive agents on erectile function from database inception to September 2020. We conducted a targeted search of the grey literature, including abstracts from conferences organized by relevant scientific associations, published in international journals. EudraCT and Clinicaltrials.gov were also perused for ongoing relevant studies. We also scanned the reference lists of all identified studies for additional eligible trials. The detailed search syntax is available in Data Supplement 1.

Search Eligibility Criteria

We included RCTs on adult male subjects with or at high-risk of cardiovascular disease, studying the effects of orally administered major antihypertensive agents [angiotensin-converting enzyme inhibitors (ACE-i), ARBs, β-blockers, calcium channel blockers (CCBs) and thiazide diuretics]. We considered studies published in any language that assessed erectile function with validated questionnaires or questionnaires developed by the authors of each study. All included trials evaluated erectile function both before and after antihypertensive treatment. Moreover, we encompassed RCTs that compared the effects of an antihypertensive agent belonging in a major antihypertensive class with another or placebo.

On the contrary, we excluded single-arm, phase I and non-randomized or observational studies. When multiple records with potential overlapping populations were identified, the most recent study was included.

Data Extraction and Quality Assessment

Two authors (IF, NP) screened for eligibility all identified records. Any disagreements or discrepancies were resolved by consensus. Data extraction was performed independently in Microsoft Excel spreadsheets, based on relevant templates from the Cochrane Handbook for Systematic Reviews of Interventions. For each included record, we retrieved information about study and participant characteristics, interventions and outcomes. To ensure coherence between the reviewers, we conducted a pilot test. Established methods, recommended by the Cochrane Collaboration, were also used to extract data from full-text articles, summary tables and figures [15]. In trials assessing erectile function at multiple time points, only data concerning the baseline and last evaluation were extracted. In case of missing data, study authors were directly contacted for further information.

The quality of included studies was assessed by two authors independently. We estimated the risk of bias in each study with the revised Cochrane risk-of-bias tool for randomized studies (RoB2), examining sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias [16]. Any discrepancies were resolved by consensus. Accordingly, we evaluated the risk of bias across studies (publication bias) via visual assessment of funnel plot asymmetry and the Egger’s test [17].

Data Synthesis and Statistical Analysis

We performed a network meta-analysis estimating the effect of major antihypertensive classes (ACE-i, ARBs, β-blockers, CCBs and thiazide diuretics) on erectile function compared to each other and to placebo. Since β-blockers are considered a heterogeneous antihypertensive medication class [13], we performed a network meta-analysis to explore the result of different β-blockers on erectile function, by dividing them into vasodilatory (carvedilol and nebivolol) and non-vasodilatory (acebutolol, atenolol, bisoprolol and metoprolol). Moreover, given that nebivolol may exert a favourable effect on erectile
Results

Search Results and Quality Assessment

The literature search yielded 4997 relevant records, resulting in 78 eligible articles after screening all titles and abstracts. Ultimately, 25 trials were included in the qualitative synthesis [23–47], twelve in the quantitative synthesis of the major antihypertensive classes [23–34] and eight in the quantitative synthesis of the β-blockers [31–38]. Three studies were excluded from the quantitative analysis because they were involving only combination antihypertensive treatment [39–41] and six studies because they reported insufficient data [42–47]. The selection process is illustrated in Fig. 1 and Data Supplement 2.

Employing the RoB2 tool, the risk of bias was considered low in 9, with some concerns in 6 and high in 11 studies (Data Supplement 3).

Study Characteristics

A total of 7784 participants with a mean age of 56.2 ± 9.6 years were included in our study. The duration of treatment and follow-up ranged from 8 weeks to 5.8 years. Across trials reporting relevant data, 2456 patients reported ED at baseline, and the prevalence of ED was 37.5%. Similarly, 15.9% of participants had concomitant diabetes mellitus type 2, and 38.3 were smokers. Overall, we included 5 studies with at least one ACE-i arm [23, 25, 26, 29, 33], 8 studies with at least one ARB arm [23, 24, 27, 30, 32, 39–41], 19 studies with at least one b-blocker arm [25–27, 29–38, 41, 42, 44–47], 5 studies with at least one CCB arm [29, 33, 40, 41, 46], 9 studies with at least one thiazide arm [25, 28, 29, 33, 34, 39, 42, 43, 47] and 12 studies with at least one placebo arm [23, 27, 28, 31–34, 39, 43–45, 47]. Six trials compared β-blockers with each other [35–38, 42, 47], and six studies included at least one arm where a combination of antihypertensive treatment was administered [23, 25, 39–42]. Overall, four studies included patients with coronary artery disease or heart failure [23, 35, 37, 44]. Characteristics of all individual studies are depicted in Table 1.

Network Meta-analysis of Major Antihypertensive Agents Compared to Each Other and to Placebo

A total of twelve studies contributed to the erectile function assessment outcome (33 treatment arms and 2957 total patients analysed). The network graph of interventions is presented in Fig. 2. When placebo was set as the reference treatment group, none of the major antihypertensive agents significantly deteriorated erectile function (Fig. 3). Heterogeneity and inconsistency were deemed high in the model (Q-statistic p value=0.004, I²=55.8%, τ²=0.81).

Grading of Evidence

We determined the overall strength of evidence for the effect of major antihypertensive agents as well as different β-blockers on erectile function using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [21] and implementing the Confidence in Network Meta-Analysis (CINeMA) web application as proposed by Salanti and colleagues [22]. Two reviewers (IF, NP) graded risk of bias, inconsistency, indirectness, imprecision and publication bias among included trials.

We undertook an additional analysis comparing the role of nebivolol versus other vasodilating and non-vasodilating β-blockers, as well as placebo.

We used the frequentist approach with a random-effects model to produce direct and indirect effect estimates for patients with ED at baseline and at the end of each trial’s follow-up using odds ratios (ORs) throughout all analyses. For all analyses, higher ORs indicated higher odds for improved erectile function after treatment. The included trials assessed erectile function with different tools such as the IIEF-5, KEED and SSDDI or miscellaneous questionnaires developed by study authors [18–20]. Accordingly, some studies reported the number of participants with ED before and after antihypertensive treatment in a dichotomous (yes/no) way, based on the responses of each questionnaire, while others reported the degree of ED in a continuous way, based on the total score of each questionnaire. To account for these discrepancies in the estimation of erectile function, in studies reporting outcomes in a continuous way, we calculated the mean difference of the ED score before and after the intervention for each treatment arm. Subsequently, we estimated the standardized mean difference (SMD) and converted it to OR using the “smd2or” function of the “meta” package (R software, version 3.6.3). This transformation was imperative in order to incorporate in the same quantifying analysis studies that reported ED in a continuous way and studies that reported ED in a categorical way. Moreover, to classify the major antihypertensive classes in terms of erectile function deterioration, we used the P-score metric, which ranges from 0 to 1, to rank treatments. Overall, the closer a treatment was ranked to 1, the more harmful to erectile function it was considered, while the opposite applied for values close to 0.

To assess for inconsistency, we used both global approaches, e.g. computed the I² statistic (a value >50% was considered high) and local approaches, e.g. we assessed for consistency between direct and indirect sources of evidence with the node-splitting method. For all estimations, 95% confidence intervals (CIs) which did not include the unit value were considered statistically significant. All analyses were performed with R software (version 3.6.3) using the “meta” and “netmeta” packages.
With regard to pairwise comparisons of the five major antihypertensive classes, no significant differences were evident (Table 2). Of note, there was no direct comparison of the ARB group versus the CCB group and the ARB group versus the thiazide group.

Node splitting method detected significant disagreement between direct and indirect evidence for the CCB group versus the thiazide group, while no other significant disagreements were detected (Data supplement 4). Egger’s regression test did not demonstrate any publication bias (Data supplement 5).

**Grading of Evidence**

Overall, the level of evidence was deemed low or very low, due to the high risk of bias of the majority of included trials, as well as to the substantial level of heterogeneity across studies. The grading of the pairwise comparisons is illustrated in Table 2.

**Effects of β-Blocker Agents on Erectile Function**

We included a total of eight studies (1046 patients) in the quantitative synthesis of β-blockers. Relevant outcomes were available for vasodilatory (nebivolol, carvedilol) and non-vasodilatory β-blockers (acebutolol, atenolol, bisoprolol, metoprolol) as described in the “Methods” section. The network graph of β-blockers, generated by the studies which included at least two arms of different β-blockers or placebo, can be seen in Data supplement 6. Compared to placebo, neither vasodilatory (OR 2.07, 95% CI –0.6–7.1) nor non-vasodilatory β-blockers (OR 0.96, 95% CI 0.33–2.82) significantly improved or deteriorated erectile function. Across the pairwise comparisons, vasodilatory β-blockers seemed to have a significant beneficial effect on erectile function.

**Ranking of Antihypertensive Drug Classes with Regard to their Effect on Erectile Function**

The thiazide group ranked as the most detrimental antihypertensive medication class for erectile function (P-score=0.91), followed by the β-blocker group (P-score=0.60) and the CCB group (P-score=0.58). On the other hand, ARBs (P-score=0.27) were ranked as the least detrimental antihypertensive agent for erectile function followed by ACE-i (P-score=0.37).
| First author and year of publication | Design | Duration of treatment and follow-up | Population | Number of patients randomized | Questionnaire for ED assessment | Treatment arms | Primary outcome | Included in the quantitative synthesis |
|-------------------------------------|--------|-----------------------------------|------------|-------------------------------|-------------------------------|----------------|----------------|-----------------------------------------|
| Aldemir et al. 2015 [35]            | Parallel group | 14 weeks | Patients undergoing CABG | 60 | IIEF-5 | 1. Nebivolol 5mg 2. Metoprolol succinate 50mg | Difference in EF as assessed by IIEF-5 | β-Blockers |
| Bohm et al. 2010 (ONTARGET trial) [23] | Parallel group | Median 48 months | CAD or high CV risk patients | 1176 | IIEF-5 and KEED | 1. Ramipril 2. Telmisartan 3. Ramipril + telmisartan 4. Placebo | Composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure | Major antihypertensive agents |
| Bohm et al. 2010 (TRANSCEND trial) [23] | Parallel group | Median 48 months | CAD or high CV risk patients | 373 | IIEF-5 and KEED | 1. Telmisartan 2. Placebo | Composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure | Major antihypertensive agents |
| Boydak et al. 2005 [42]             | Parallel group | 12 weeks | Hypertensive without erectile dysfunction | 142 | Measurement of Quality of Life in Hypertensive Patients Questionnaire by Bulpitt and Fletcher (Br J Clin Pharmacol 1990) | 1. Nebivolol 5 mg 2. Atenolol 50 mg 3. Atenolol 50 mg + chlorthalidone 12.5 mg | Change in the mean number of episodes of satisfactory sexual intercourse per month | No |
| Brixius et al. 2007 [36]            | Cross-over | 26 weeks | Hypertensive without erectile dysfunction | 48 | IIEF-5 | 1. Nebivolol 5mg 2. Metoprolol succinate 95 mg | Difference in EF as assessed by IIEF | β-Blockers |
| Broekman et al. 1992 [31]           | Cross-over | 12 weeks | Hypertensive | 26 | Questionnaire by Slob et al (J Urol 1990) | Group 1: 1. Bisoprolol 2. Placebo Group 2: 1. Bisoprolol 2. Own medication 3. HCTZ 50 mg + potassium 3. HCTZ 50 mg + magnesium 4. HCTZ 50 mg + triamterene 100 mg 5. chlorthalidone 50 mg 6. Placebo (10 mg of thiamine) | Data on blood pressure. Qualitative and quantitative data on sexuality through questionnaires, including personal and sexual history, sexual functioning, sexual satisfaction and erectile difficulties | Both |
| Chang et al. 1991 [43]              | Parallel group | 8 weeks | Hypertensive with abnormal baseline ECG | 219 | SSDI | 1. Control (no placebo) 2. Tadalafil 5 mg 3. Losartan 50 mg 4. Tadalafil 5 mg + Losartan 50 mg | Difference in EF as assessed by SSDI | No |
| Chen et al. 2012 [24]               | Parallel group | 24 weeks | DM patients with erectile dysfunction | 124 | IIEF-5 | 1. Captopril 100 mg 2. Methylodopa 500 mg 3. Propranolol 160 mg 4. Captopril 100mg + hydrochlorothiazide 50 mg 5. Methylodopa 500 mg + hydrochlorothiazide 50 mg | Difference in EF as assessed by IIEF-5 | Major antihypertensive agents |
| Croog et al. 1988 [25]              | Parallel group | 24 weeks | Hypertensive | 761 | SSDI | 1. Captopril 100 mg 2. Methylodopa 500 mg 3. Propranolol 160 mg 4. Captopril 100mg + hydrochlorothiazide 50 mg 5. Methylodopa 500 mg + hydrochlorothiazide 50 mg | Difference in EF as assessed by SSDI | Major antihypertensive agents |
| First author and year of publication | Design | Duration of treatment and follow-up | Population | Number of patients randomized | Questionnaire for ED assessment | Treatment arms | Primary outcome | Included in the quantitative synthesis |
|-------------------------------------|--------|------------------------------------|------------|-------------------------------|--------------------------------|----------------|----------------|-----------------------------------|
| Fogari et al. 1998 [26]            | Cross-over | 40 weeks | Hypertensive without erectile dysfunction | 94 | SSDI | 1. Lisinopril 20 mg + hydrochlorothiazide 50 mg | Mean number of sexual intercourses per month and the number of patients complaining about sexual dysfunction symptoms | Major antihypertensive agents |
| Fogari et al. 2001 [32]            | Cross-over | 40 weeks | Hypertensive without erectile dysfunction | 160 | SSDI | 1. Carvedilol 50 mg + Valsartan 80 mg + Placebo | Mean number of sexual intercourses per month and the number of patients complaining about sexual dysfunction symptoms | Both |
| Fogari et al. 2002 [27]            | Parallel group | 16 weeks | Hypertensive without erectile dysfunction | 110 | SSDI | 1. Valsartan 80 mg + Atenolol 50 mg | Mean number of sexual intercourses per month and the number of patients complaining about sexual dysfunction symptoms | Major antihypertensive agents |
| Franzen et al. 2001 [44]           | Parallel group | 16 weeks | CAD patients | 192 | KEED | 1. Metoprolol succinate 95 mg + Placebo | Difference in EF as assessed by KEED | No |
| Grimm et al. 1997 [33]             | Parallel group | 48 months | Hypertensive | 557 | Miscellaneous questionnaire | 1. Beta-blockers | Difference in EF as assessed by specific questions | Both |
| Gür et al. 2017 [37]               | Parallel group | 12 weeks | Patients undergoing CABG | 119 | IIEF-5 | 1. Nebivolol 5 mg + Metoprolol succinate 50 mg | Difference in EF as assessed by IIEF-5 | β-Blockers |
| Joseph et al. 2018 [39]            | 2x2 factorial | 5.8 years | Intermediate CV risk | 2153 | IIEF-5 | 1. Candesartan 25 mg + HTZC 12.5 mg + Rosuvastatin 10 mg + Placebo | Difference in EF as assessed by IIEF-5 | No |
| Kostis et al. 1992 [45]            | Parallel group | 12 weeks | Hypertensive | 92 | Questionnaire by Reynolds et al. (Psychiatr Res 1998) | 1. Beta-blockers | Multi-outcome measures including sexual function | No |
| Martsevich et al. 2012 [38]        | Parallel group | 23 weeks | Hypertensive and overweight | 98 | IIEF-5 | 1. Carvedilol 25 mg + Bisoprolol 5 mg | Antihypertensive efficacy, metabolic effects and influence on EF as assessed by IIEF-5 | β-Blockers |
| Morrisette et al. 1983 [46]        | Cross-over | 20–36 weeks | Hypertensive with age 60–75 | 16 | Self-report (daily logs and visual analogue scales) on 13 measures of sexuality | 1. Beta-blockers | Effect of the antihypertensive medication on a range of sexual function components | No |
| Rosen et al. 1994 [47]             | Cross-over | NA | Hypertensive and sexual dysfunction | 21 | 12-item sexual function questionnaire by Rosen et al. (Psychiatr Res 1988) | 1. Beta-blockers | Sleep laboratory assessment (EEG, EMG, NO, ECG, penile tumescence), sexual function and hormonal measures (total and free testosterone, cortisol) | No |
| Cross-over                         |        | 24–32 weeks | | 12 | Miscellaneous questionnaire | 1. Beta-blockers | | |
| First author and year of publication | Design       | Duration of treatment and follow-up | Population                | Number of patients randomized | Questionnaire for ED assessment | Treatment arms | Primary outcome                                                                 | Included in the quantitative synthesis |
|-------------------------------------|--------------|-------------------------------------|---------------------------|--------------------------------|---------------------------------|----------------|--------------------------------------------------------------------------------|----------------------------------------|
| Scharf et al. 1989                  | Parallel group | 24 weeks                           | Hypertensive without erectile dysfunction | 156                            | SSDI                            | 1. Trichloromethiazide 2–4 mg 2. Atenolol 50–100 mg 3. Captopril 37.5–75 mg 4. Slow-release nifedipine 40–80 mg | Effect of medication on BP, sleep measures (including penile tumescence) and sexual function | Major antihypertensive agents |
| Suzuki et al. 1988                  | Parallel group | 24 weeks                           | Hypertensive              | 156                            | SSDI                            | 1. Trichloromethiazide 2–4 mg 2. Atenolol 50–100 mg 3. Captopril 37.5–75 mg 4. Slow-release nifedipine 40–80 mg | Difference in EF as assessed by SSDI | Major antihypertensive agents |
| VanBortel et al. 2005 [30]          | Parallel group | 12 weeks                           | Hypertensive              | 186                            | Questionnaire by Bulpitt and Fletcher (Br J Clin Pharmacol 1990) | 1. Nebivolol 5 mg 2. Losartan 50 mg | Difference in QoL as assessed by questionnaire | Major antihypertensive agents |
| Wassertheil et al. 1991 [34]        | 3x3 factorial | 6 months                           | Hypertensive and overweight | 390                            | Miscellaneous questionnaires    | 1. Placebo 2. Chlorothalidone 25 mg 3. Atenolol 50 mg | Change in BP after 6 months | Both |
| Xiaoma et al. 2014                  | Parallel group | 48 weeks                           | Hypertensive              | 240                            | IIEF-5                          | 1. Felodipine 5 mg + irbesartan 150 mg 2. Felodipine 5 mg | Difference in BP and EF as assessed by IIEF-5 | No |
| Yang et al. 2013                    | Parallel group | 48 weeks                           | Hypertensive              | 259                            | IIEF-5                          | 1. Felodipine 5 mg + irbesartan 150 mg 2. Felodipine 5 mg + metoprolol 47.5 mg | Difference in BP and EF as assessed by IIEF-5 | No |

BP blood pressure, CABG coronary artery bypass grafting, EEG electroencephalogram, ECG electrocardiogram, EMG electromyogram, EOG electrooculogram, KEED Cologne erectile inventory, CV cardiovascular, ED erectile dysfunction, IIEF International index of erectile function, NA not available, SSDI sexual symptom distress index, QoL quality of life.
compared to non-vasodilatory β-blockers (OR 2.17, 95% CI 1.15–4) (Data supplement 6).

When nebivolol was assessed separately from the rest of vasodilatory β-blockers group (essentially carvedilol), it did not show any significant beneficial effect on erectile function compared to placebo (OR 2.87, 95% CI 0.75–11.04) or to carvedilol (OR 2.15, 95% CI 0.6–7.77) (Fig. 4). However, nebivolol contributed a significant beneficial effect on erectile function compared to non-vasodilatory β-blockers (OR 2.92, 95% CI 1.3–6.5), while no difference between carvedilol and non-vasodilatory β-blockers was demonstrated (OR 1.36, 95% CI 0.5–3.69) (Data supplement 7). In terms of treatment raking, nebivolol ranked as the least detrimental β-blocker for erectile function (P-score=0.06), followed by vasodilatory β-blockers (P-score=0.5) and placebo (P-score=0.69). On the contrary, non-vasodilatory β-blockers ranked as the most detrimental β-blocker for erectile function (P-score=0.74). Still, in the GRADE assessment, evidence on the matter was rated as low or very low (Table 3).

**Discussion**

This systematic review and network meta-analysis suggests that there is insufficient evidence to support that any of the main antihypertensive classes exert significant detrimental or beneficial effects on erectile function when compared to each other or to placebo. On the comparative leg of the analysis, on a low strength of evidence, all major antihypertensive classes seem to exert a neutral effect on erectile function. Focusing on β-blockers, nebivolol may provide some beneficial effects on erectile function compared to non-vasodilatory β-blockers, on a low strength of evidence. However, compared to placebo or to other vasodilatory β-blockers, nebivolol did not show any significant beneficial effect on erectile function.

The guidelines for the management of arterial hypertension from the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) state that sexual dysfunction in men may be induced or aggravated by thiazide diuretics and β-blockers, while ACE-i, ARBs, CCBs and vasodilating β-blockers may present neutral or even beneficial effects on erectile function [9]. These recommendations mostly derive from systematic reviews of observational or interventional studies and from expert opinions [7, 8, 10, 48]. A brief meta-analysis of RCTs for the role of ARBs on ED demonstrated that ARBs exert beneficial effects on erectile function when compared with other treatment modalities [49]. However, this effect was almost exclusively driven by a non-randomized study of ARB-treated patients (n=1899) versus control (n=27) [50]. Based on our network meta-analysis of RCTs, there is no such evidence that ARBs exert a beneficial effect on erectile function as none of the major antihypertensive classes may aggravate or improve erectile function. Accordingly, the ESH Working Group on erectile function implies that nebivolol diverges from other β-blockers in terms of erectile function impairment [6]. This recommendation derives predominantly from translational data suggesting that nebivolol facilitates penile artery dilatation by enhancing nitric oxide signalling of the corpora cavernosa [51, 52]. Still, based on our analysis, no such beneficial effect of nebivolol on erectile function was proven in humans. Only a tendency for the beneficial effects of nebivolol compared to placebo on EF is being observed; however, the confidence interval of the comparison is too wide, thus implying that deriving such a conclusion from our results is imprecise, and our analysis may be underpowered to detect such a difference.

Patients’ perception on the adverse events related potential of drugs is important for medication adherence in the setting of arterial hypertension [53]. It has been postulated that being prejudiced for potential adverse events causes the so-called Hawthorne effect that further inhibits sexual function [54, 55]. Upon adverse events development, like ED, which cannot be objectively and extensively assessed by physicians, the presence of such side effects is often exaggerated [56].
Therefore, healthcare providers should promptly offer concise advice and information on the interplay of antihypertensive treatment and ED and must ensure proper medication adherence. Still, in patients reporting ED deterioration, phosphodiesterase type-5 inhibitors may not only be beneficial in treating ED, but they also have additive effects on the lowering of blood pressure and improved medication adherence [57, 58].

**Perspectives**

In a field of research, where review articles and expert commentary far exceed hard data [59], future prospective studies are needed to thoroughly address the role of major antihypertensive classes on erectile function. Ideally, a carefully designed, large, multi-arm RCT with standardized interventions and erectile function outcomes is necessary to better understand the effects of antihypertensive medications on erectile function and make recommendations for this common encounter. Last but not least, given that combination therapy is now recommended for the achievement of the blood pressure target and that dozens of different combinations exist, there is a paucity of data regarding potential interactions between antihypertensive agents and effectiveness of combinational therapies in erectile function. Without this level of evidence, it should not be stated that an antihypertensive drug class improves or deteriorates erectile function.

**Strengths and Limitations**

Our systematic review and network meta-analysis presents important strengths. To our knowledge, this is the first study to assess, in a holistic approach, the effects of antihypertensive medication on erectile function by including specifically RCTs and using data synthesis and meta-analysis techniques. In this scope, we generated a network meta-analysis to assess for direct and indirect estimates. Since β-blockers are considered a high heterogeneous drug class in terms of erectile function exacerbation, we provided a separate analysis exploring the within-class different effects of β-blockers. Furthermore, our results

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**Table 2** Pairwise comparison in network meta-analysis of major antihypertensive medication classes and grading of evidence

| Pairwise comparison | Participants | Network meta-analysis estimate | Confidence | Downgrading due to |
|--------------------|--------------|--------------------------------|------------|-------------------|
| **Mixed evidence. Odds ratio (95% confidence interval)** | | | | |
| ACE-i vs ARB | 707 vs 856 | 0.83 (0.23–3.02) | Low | Imprecision^a |
| ACE-i vs B-blocker | 707 vs 753 | 1.48 (0.47–4.71) | Low | Imprecision^a, heterogeneity^b |
| ACE-i vs CCB | 707 vs 116 | 1.59 (0.27–9.28) | Low | Within-study bias^a, imprecision^a |
| ACE-i vs thiazide | 707 vs 259 | 3.65 (0.72–18.38) | Very low | Within-study bias^a, imprecision^a, heterogeneity^b |
| ACE-i vs placebo | 707 vs 517 | 0.82 (0.19–3.49) | Low | Imprecision^a |
| ARB vs B-blocker | 856 vs 753 | 1.78 (0.53–6.00) | Low | Imprecision^a, heterogeneity^b |
| ARB vs placebo | 856 vs 517 | 0.99 (0.31–3.15) | Low | Imprecision^a |
| B-blocker vs CCB | 753 vs 116 | 1.07 (0.20–5.67) | Very low | Within-study bias^a, imprecision^a |
| B-blocker vs thiazide | 753 vs 259 | 2.46 (0.55–11.03) | Very low | Within-study bias^a, imprecision^a, heterogeneity^b |
| B-blocker vs placebo | 753 vs 517 | 0.56 (0.16–1.97) | Low | Imprecision^a, heterogeneity^b |
| CCB vs thiazide | 116 vs 259 | 2.29 (0.39–13.61) | Very low | Within-study bias^a, imprecision^a, heterogeneity^b, incoherence^d |
| CCB vs placebo | 116 vs 517 | 0.52 (0.08–3.44) | Low | Imprecision^a |
| Thiazide vs placebo | 259 vs 517 | 0.23 (0.04–1.28) | Low | Imprecision^a, heterogeneity^b |
| **Indirect evidence only. Odds ratio (95% confidence interval)** | | | | |
| ARB vs CCB | 856 vs 116 | 1.91 (0.29–12.75) | Low | Imprecision^a |
| ARB vs thiazide | 856 vs 259 | 4.39 (0.76–25.23) | Low | Imprecision^a, heterogeneity^b |
| **Ranking of treatments** | | | | |

Treatment effect is reported as odds ratio (95% confidence interval)  
ACE-i angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor blocker, CCB calcium channel blocker  
^a Confidence intervals include values favouring either treatment.  
^b Variability in the magnitude of effects across studies within the same comparison.  
^c Dominated by evidence at high or moderate risk of bias.  
^d Disagreement between direct and indirect estimates.  
^e 54% of the information is from studies at high risk of bias  
^f Substantial level of heterogeneity (I^2 = 55.8%)
contest previously published qualitative analyses and highlight the need for higher quality of evidence to suggest that any antihypertensive treatment exerts beneficial or detrimental effects on erectile function.

The findings of our study should be interpreted in the context of limitations relevant to the significant heterogeneity among the included trials. Across studies, important differences in design, population and sample size were observed. Indeed, our synthesis comprised individuals with normal erectile function or ED, participants with hypertension and/or concomitant cardiovascular comorbidities, patients previously treated for hypertension as well as treatment-naive males. Based on the previous notion, we could not adjust for important moderators of ED such as age, diabetes and smoking. Of note, none of the included trials standardized the effect of different antihypertensive agents on erectile function by assessing in the form of a subgroup analysis the degree of blood pressure lowering leading to erectile function deterioration. Additionally, most included trials were relatively old and raised methodological concerns as they did not strictly abide to the consolidated standards of reporting and performing RCTs. Accordingly, due to inadequacy or lack of relevant data, more than half of the included trials were excluded from the quantitative analysis. Therefore, the network meta-analysis of both major antihypertensive agents and β-blockers was performed with a relatively small number of patients, raising issues of power in terms of its ability to detect any differences among antihypertensive medication classes, if they exist. It should also be stressed that estimates of erectile function displayed significant variety among available trials, as study authors employed different validated and non-validated questionnaires to assess erectile function. To account for such discrepancies, we calculated SMDs and converted continuously reported outcomes to ORs to achieve a uniform effect measure for analysis. Still, this transformation, although described in the Cochrane Collaboration Handbook, may be regarded as an approximation and should be interpreted with caution. All in all, the plethora of limitations of the available body of literature demonstrated that there is insufficient evidence to support that any of the main antihypertensive classes exerts significant detrimental or beneficial effects on erectile function.

### Conclusion

Our systematic review and network meta-analysis suggests that all antihypertensive drugs seem to exert a neutral or insignificant effect on erectile function compared to each other or to placebo. Given that evidence is still weak on the matter, our analysis does not support the current ESC/ESH guidelines statement that ED may be induced or aggravated by thiazide diuretics and β-blockers, while ACE-i, ARBs, CCBs, and vasodilating β-blockers may present neutral or even beneficial effects on erectile function. Therefore, carefully designed, large RCTs with standardized interventions and outcomes

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**Table 3**  Pairwise comparison in network meta-analysis of β-blockers and grading of evidence

| Pairwise comparison                                      | Participants | Network meta-analysis estimate | Confidence | Downgrading due to |
|-----------------------------------------------------------|--------------|--------------------------------|------------|-------------------|
| Mixed evidence. Odds ratio (95% confidence interval)      |              |                                |            |                   |
| Nebivolol vs non-vasodilatory                             | 140 vs 431   | 2.92 (1.3–6.54)                | Low        | Heterogeneitya    |
| Non-vasodilatory vs Placebo                              | 431 vs 307   | 0.98 (0.33–2.89)               | Low        | Imprecisionb      |
| Non-vasodilatory vs Vasodilatory                         | 431 vs 308   | 0.73 (0.27–2)                  | Very low   | Within study biasc, imprecisionb |
| Vasodilatory vs Placebo                                  | 308 vs 307   | 1.33 (0.32–5.6)                | Very low   | Within study biasc, imprecisionb |
| Indirect evidence only. Odds ratio (95% confidence interval) |              |                                |            |                   |
| Nebivolol vs vasodilatory                                | 140 vs 168   | 2.15 (0.6–7.77)                | Low        | Within study biasc, imprecisionb |
| Nebivolol vs placebo                                     | 140 vs 307   | 2.87 (0.75–11.04)              | Very low   | Within study biasc, imprecisionb |
| Ranking of treatments                                    |              | Moderate                       |            | Inconsistencyd    |

Treatment effect is reported as odds ratio (95% confidence interval). Bold font indicates significant effect

a Variability in the magnitude of effects across studies within the same comparison

b Confidence intervals include values favouring either treatment

c Dominated by evidence at high or moderate risk of bias

d Evidence of inconsistency in the network (wide variance estimates)

**Fig. 4** Forest plot of the effect of nebivolol versus other vasodilatory versus non-vasodilatory β-blockers on erectile function
are needed to better explore the effects of antihypertensive medication on erectile function.

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Data Availability All data are available upon request.

Declarations

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent No humans were involved in this study.

Conflict of Interest The authors declare no competing interests.

References

1. Impotence: NIH Consensus Development Panel on Impotence. JAMA. 1993;270:83–90.
2. Shamloul R, Ghanem H. Erectile dysfunction. Lancet. 2013;381:153–65.
3. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol. 1994;151:54–61.
4. Vlachopoulos C, Jackson G, Stefanidis C, Montorsi P. Erectile dysfunction in the cardiovascular patient. n.d.;34:2034–46.
5. Gandaglia G, Briganti A, Jackson G, Kloner RA, Montorsi F, Montorsi P, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol. 2014;65:968–78.
6. Viijimaa M, Vlachopoulos C, Doumas M, Wolf J, Impriaios K, Terentes-Printzios D, et al. Update of the position paper on arterial hypertension and erectile dysfunction. J Hypertens. 2020;38:1220–34.
7. Nicolai MPJ, Liem SS, Both S, Pelger RCM, Putter H, Schalij MJ, et al. A review of the positive and negative effects of cardiovascular drugs on sexual function: a proposed table for use in clinical practice. Neth Heart J. 2014;22:11–9.
8. La Torre A, Giupponi G, Duffy D, Conca A, Cai T, Scardigli A. Sexual dysfunction related to drugs: a critical review part V: α-blocker and 5-ARI drugs. Pharmacoepidemiol. 2015;49:3–13.
9. Williams B, Mancia G, Spiering W, Rosei E, Burnier M, et al. 2018 ESC/EAS Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104.
10. Baumhökel M, Schlimmer N, Kritz M, Hacket G, Jackson G, Böhm M. Cardiovascular risk, drugs and erectile function - a systematic analysis. Int J Clin Pract. 2011;65:289–98.
11. Al Khaja KAJ, Sequeira RP, Alkhaja AK, Damanhori AHH. Antihypertensive drugs and male sexual dysfunction: a review of adult hypertension guideline recommendations. J Cardiovasc Pharmacol Ther. 2016;21:233–44.
31. Broekman CP, Haensel SM, Van de Ven LL, Slob AK, Matthijs Broekman CP, Haensel SM, et al. Bisoprolol and hypertension: effects on sexual functioning in men. TGO - Tijdschr Voor Ther Geneesm En Onderz. 1992;17:79–82±83.

32. Fogari R, Zoppa A, Poletti L, Marasi G, Mugellini A, Corradi L. Sexual activity in hypertensive men treated with valsartan or carvedilol: a crossover study. Am J Hypertens. 2001;14:27–31.

33. Grimm RH, Grandits GA, Prineas RJ, McDonald RH, Lewis CE, Şİ

34. Wassertheil-Smoller S, Blaufox MD, Oberman A, Davis BR, Swencionis C, Knerr MO, et al. Effect of antihypertensives on sexual function and quality of life: The TAIM study. Ann Intern Med. 1991;114:613–20.

35. Aldemir M, Keleşi I, Karalar M, Tecer E, Adali F, Pektaş MB, et al. Nebivolol compared with metoprolol for erectile function in males undergoing coronary artery bypass graft. Anatol J Cardiol. 2016;16:131–6.

36. Brixtius K, Middrecke M, Lichtenhal A, Jahn E, Schwinger RHG. Nitric oxide, erectile dysfunction and beta-blocker treatment (MR NOED study): benefit of nebivolol versus metoprolol in hypertensive men. Clin Exp Pharmacol Physiol. 2007;34:327–31.

37. Gür Ö, Gurkan S, Yumun G, Turker P, Gur O, Gurkan S, et al. The comparison of the effects of nebivolol and metoprolol on erectile dysfunction in the cases with coronary artery bypass surgery. Ann Thorac Cardiovasc Surg. 2017;23:91–5.

38. Martsevich SY, Tolpigina SN, Galiavich AS, Volkova EG, Malishevsky MV, Matushvin GV, et al. Comparison of the influence of long-term treatment based on carvedilol or bisoprolol on metabolic parameters and erectile function in hypertensive patients with overweight or obesity. Results of the randomized open-label parallel-groups stepped trial CABR. Ration Pharmacother Cardiol. 2012;8:626–35.

39. Joseph P, Lonn E, Bosch J, Lopez P, Zhu J, Keltui M, et al. Long-term effects of statins, blood pressure-lowering, and both on erectile function in persons at intermediate risk for cardiovascular disease: a substudy of the Heart Outcomes Prevention Evaluation-3 (HOPE-3) Randomized controlled trial. Can J Cardiol. 2018;34:38–44.

40. Xiaoma D, Jianli C, Xin S. Study on the effects of felodipine sustained release tablets joint irbesartan tablets on erectile function of male patients with hypertension. Chin J Androl. 2014;28:43–6.

41. Yang L, Yu J, Ma R, Zhao F, Lin X, Liu P, et al. The effect of combined antihypertensive treatment (felodipine with either irbesartan or metoprolol) on erectile function: a randomized controlled trial. Cardiol Switz. 2013;125:235–41.

42. Boydak B, Nalbantgil S, Fici F, Nalbantgil I, Zoghi M, Oberkan F, et al. A randomised comparison of the effects of nebivolol and atenolol with and without chlortalidone on the sexual function of hypertensive men. Clin Drug Investig. 2005;25:409–16.

43. Chang SW, Fine R, Siegel D, Chesney M, Black D, Hulley SB. The impact of diuretic therapy on reported sexual function. Arch Intern Med. 1991;151:2402–8.

44. Franzen D, Metha A, Seifert N, Braun M, Höpp HW. Effects of beta-blockers on sexual performance in men with coronary heart disease: A prospective, randomized and double blinded study. Int J Impot Res. 2001;13:348–51.

45. Kostis JB, Rosen RC, Bronoldo E, Taska L, Smith DE, Wilson AC. Superiority of nonpharmacologic therapy compared to propranolol and placebo in men with mild hypertension: a randomized, prospective trial. Am Heart J. 1992;123:466–74.

46. Morrissette DL, Skinner MH, Hoffman BB, Levine RE, Davidson JM. Effects of antihypertensive drugs atenolol and nifedipine on sexual function in older men: a placebo-controlled, crossover study. Arch Sex Behav. 1993;22:99–109.

47. Rosen RC, Kostis JB, Jekelis A, Taska LS. Sexual sequelae of antihypertensive drugs: treatment effects on self-report and physiological measures in middle-aged male hypertensives. Arch Sex Behav. 1994;23:135–52.

48. Douras M, Doura S. The effect of antihypertensive drugs on erectile function: a proposed management algorithm. J Clin Hypertens Greenwich Conn. 2006;8:359–64.

49. Ismail SB, Noor NM, Hussain HN, Sulaiman Z, Shamsudin MA, Irfan M. Angiotensin receptor blockers for erectile dysfunction in hypertensive men: a brief meta-analysis of randomized control trials. Am J Mens Health. 2019;13:15579831989273.

50. Della Chiesa A, Pfiffner D, Meier B, Hess OM. Sexual activity in hypertensive men. J Hum Hypertens. 2003;17:515–21.

51. Tobili JE, Cao G, Casas G, Mazza ON. In vivo and in vitro effects of nebivolol on penile structures in hypertensive rats. Am J Hypertens. 2006;19:1226–32.

52. Angulo J, Wright HM, Cuevas P, González-Corochano R, Fernández A, Cuevas B, et al. Nebivolol dilates human penile arteries and reverses erectile dysfunction in diabetic rats through enhancement of nitric oxide signaling. J Sex Med. 2010;7:6281–97.

53. Grégoire JP, Moisan J, Guibert R, Ciampi A, Milot A, Gaudet M, et al. Determinants of discontinuation of new courses of antihypertensive medications. J Clin Epidemiol. 2002;55:728–35.

54. Silvestri A. Report of erectile dysfunction after therapy with beta-blockers is related to patient knowledge of side effects and is reversed by placebo. Eur Heart J. 2003;24:1928–32.

55. Cocco G. Erectile dysfunction after therapy with metoprolol: the Hawthorne effect. Cardiology. 2009;112:174–7.

56. Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. ß-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. J Am Coll Cardiol. 2002;38:351–7.

57. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, et al. National guidelines in published maps and institutional affiliations. JAMA. 2002;288:351–7.

58. McLaughlin T, Harnett J, Burhani S, Scott B. Evaluation of erectile dysfunction after therapy with metoprolol. J Sex Med. 2006;3:216–23.