Effects of major antihypertensive drug classes on erectile function: a network meta-analysis

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Abstract

Aims

Major antihypertensive medication classes are suggested to exert diverse effects on erectile function (EF). Guideline recommendations suggest that thiazide diuretics and β-blockers possess the worst profile regarding erectile function (EF), while angiotensin receptor blockers and nebivolol the best profile. We aimed to determine the comparative effect of major antihypertensive classes on 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 antihypertensive agents on EF (PROSPERO: CRD42020189529). 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.

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) (Data Supplement I) [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 II.

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 heterogenous 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 favorable effect on erectile function [6], 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 SSDI 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 I^2 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 and p-values lower than 0.05 were considered statistically significant. All analyses were performed with R software (version 3.6.3) using the "meta" and "netmeta" packages.

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.

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 Data Supplement III and IV.

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 V).

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 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%. 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]. Characteristics of all individual studies are depicted in Table 1.

Table 1
Characteristics of included studies in the systematic review.

First author and year of publication	Design	Follow-up duration	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	Patients on high CV risk	1176	IIEF-5 and KEED	1. Ramipril 2. Telmisartan 3. Ramipril + Telmisartan	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	Patients on high CV risk	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 5mg 2. Atenolol 50mg 3. Atenolol 50mg + Chlorthalidone 12,5mg	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 95mg	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	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. HCTZ 50mg 2. HCTZ 50mg + Potassium 3. HCTZ 50mg + magnesium 4. HCTZ 50mg + triamterene 100 mg 5. chlorthalidone 50mg 6. Placebo (10mg of thiamine)	Various aspects of quality of life including social performance, physiologic and emotional states and general well-being	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.

First author and year of publication	Design	Follow-up duration	Population	Number of patients randomized	Questionnaire for ED assessment	Treatment arms	Primary outcome	Included in the quantitative synthesis
Chen et al. 2012 [24]	Parallel group	24 weeks	DM patients with erectile dysfunction	124	IIEF-5	1. Control (no placebo) 2. Tadalafil 5mg 3. Losartan 50mg 4. Tadalafil 5 mg + Losartan 50mg	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 100mg 2. Methyldopa 500mg 3. Propranolol 160mg 4. Captopril 100mg + Hydrochlorothiazide 50mg 5. Methyldopa 500mg + Hydrochlorothiazide 50mg 6. Propranolol 160mg + Hydrochlorothiazide 50mg	Difference in EF as assessed by SSDI	Major antihypertensive agents
Fogari et al. 1998 [26]	Cross-over	40 weeks	Hypertensive without erectile dysfunction	94	SSDI	1. Lisinopril 20mg 2. Atenolol 100mg	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 50mg 2. Valsartan 80mg 3. 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 80mg 2. Atenolol 50mg	Mean number of sexual intercourses per month and the number of patients complaining about sexual dysfunction symptoms	Major antihypertensive agents

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.

First author and year of publication	Design	Follow-up duration	Population	Number of patients randomized	Questionnaire for ED assessment	Treatment arms	Primary outcome	Included in the quantitative synthesis
Franzen et al. 2001 [44]	Parallel group	16 weeks	CAD patients	192	KEED	1. Metoprolol succinate 95mg 2. Placebo	Difference in EF as assessed by KEED	No
Grimm et al. 1997 [33]	Parallel group	48 months	Hypertensive	557	Miscellaneous questionnaire	1. Acebutolol 400mg 2. Amlodipine 5mg 3. Chlorthalidone 15mg 4. Doxazosin 2mg 5. Enalapril 5mg 6. Placebo ALL: Diet	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 5mg 2. Metoprolol succinate 50mg	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 25mg + HTCZ 12.5mg 2. Rosuvastatin 10mg 3. 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 1988)	1. Propranolol 2. Non-drug group 3. Placebo	Multi-outcome measures including sexual function	No
Martsevich et al. 2012 [38]	Parallel group	23 weeks	Hypertensive and overweight	98	IIEF-5	1. Carvedilol 25mg 2. Bisoprolol 5mg	Antihypertensive efficacy, metabolic effects and influence on EF as assessed by IIEF-5	β-blockers
Morrissette et al. 1993 [46]	Cross-over	20–36 weeks	Hypertensive with age 60–75	16	Self-reports (daily logs and visual analog scales) on 13 measures of sexuality	1. Atenolol 2. Slow-release nifedipine	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. 1988)	1. Methyldopa 500mg 2. Propranolol 160mg 3. Atenolol 100mg 4. HCTZ/triamterene 100/50mg 5. Placebo	Sleep laboratory assessment (EEG, EMG, EOG, ECG, penile tumescence), sexual function and hormonal measures (total and free testosterone, cortisol)	No
Scharf et al. 1989 [28]	Cross-over	24–32 weeks	Hypertensive without erectile dysfunction	12	Miscellaneous questionnaire	1. Prazosin 2. HCTZ	Effect of medication on BP, sleep measures (including penile tumescence) and sexual function	Major antihypertensive agents

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.

First author and year of publication	Design	Follow-up duration	Population	Number of patients randomized	Questionnaire for ED assessment	Treatment arms	Primary outcome	Included in the quantitative synthesis
Suzuki et al. 1988 [29]	Parallel group	24 weeks	Hypertensive	156	SSDI	1. Trichloromethiazide 2-4mg 2. Atenolol 50–100 mg 3. Captopril 37.5-75mg 4. Slow-release nifedipine 40-80mg	Difference in EF as assessed by SSDI	Major antihypertensive agents
VanBortel et al. 2005 [30]	Parallel group	12 weeks	Hypertensive	186	Measurement of Quality of Life in Hypertensive Patients Questionnaire by Bulpitt and Fletcher (Br J Clin Pharmacol 1990)	1. Nebivolol 5mg 2. Losartan 50mg	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. Chlorthalidone 25mg 3. Atenolol 50mg	Change in BP after 6 months	Both
Xiaoma et al. 2014 [40]	Parallel group	48 weeks	Hypertensive	240	IIEF-5	1. Felodipine 5mg + Irbesartan 150mg 2. Felodipine 5mg	Difference in BP and EF as assessed by IIEF-5	No
Yang et al. 2013 [41]	Parallel group	48 weeks	Hypertensive	259	IIEF-5	1. Felodipine 5mg + Irbesartan 150mg 2. Felodipine 5mg + metoprolol 47.5mg	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.

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 analyzed). The network graph of interventions is presented in Fig. 1. When placebo was set as the reference treatment group, none of the major antihypertensive agents significantly deteriorated erectile function (Fig. 2). Heterogeneity and inconsistency were deemed high in the model (Q-statistic p-value = 0.004, I^2 = 55.8%, tau^2 = 0.81).

With regards 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.

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[1]
ACE-i vs B-blocker	707 vs 753	1.48 (0.47–4.71)	Low	Imprecision[1], heterogeneity[2]
ACE-i vs CCB	707 vs 116	1.59 (0.27–9.28)	Low	Within-study bias[3], imprecision[1]
ACE-i vs Thiazide	707 vs 259	3.65 (0.72–18.38)	Very low	Within-study bias[3], imprecision[1], heterogeneity[2]
ACE-i vs Placebo	707 vs 517	0.82 (0.19–3.49)	Low	Imprecision[1]
ARB vs B-blocker	856 vs 753	1.78 (0.53-6.00)	Low	Imprecision[1], heterogeneity[2]
ARB vs Placebo	856 vs 517	0.99 (0.31–3.15)	Low	Imprecision[1]
B-blocker vs CCB	753 vs 116	1.07 (0.20–5.67)	Very low	Within-study bias[3], imprecision[1]
B-blocker vs Thiazide	753 vs 259	2.46 (0.55–11.03)	Very low	Within-study bias[3], imprecision[1], heterogeneity[2]
B-blocker vs Placebo	753 vs 517	0.56 (0.16–1.97)	Low	Imprecision[1], heterogeneity[2]
CCB vs Thiazide	116 vs 259	2.29 (0.39–13.61)	Very low	Within-study bias[3], imprecision[1], heterogeneity[2], incoherence[4]
CCB vs Placebo	116 vs 517	0.52 (0.08–3.44)	Low	Imprecision[1]
Thiazide vs Placebo	259 vs 517	0.23 (0.04–1.28)	Low	Imprecision[1], heterogeneity[2]
Indirect evidence only. Odds Ratio (95% Confidence Interval)				
ARB vs CCB	856 vs 116	1.91 (0.29–12.75)	Low	Imprecision[1]
ARB vs Thiazide	856 vs 259	4.39 (0.76–25.23)	Low	Imprecision[1], heterogeneity[2]
Ranking of treatments			Low	Within-study bias[5], heterogeneity[6]

[1]Confidence intervals include values favoring either treatment.

[2]Variability in the magnitude of effects across studies within the same comparison.

[3]Dominated by evidence at high or moderate risk of bias.

[4]Disagreement between direct and indirect estimates.

[5]54% of the information is from studies at high risk of bias

[6]Substantial level of heterogeneity (I^2 = 55.8%)

**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*

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 VI). Egger's regression test did not demonstrate any publication bias (Data supplement VII).

Ranking of antihypertensive drug classes with regards to their effect on ED

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).

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 VIII. 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 compared to non-vasodilatory β-blockers (OR 2.17, 95% CI 1.15-4) (Data supplement VIII).

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. 3). 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 IX). In terms of treatment raking, nebivolol ranked as the least detrimental β-blocker for erectile function (non-vasodilatory β-blockers P-score = 0.74, placebo P-score = 0.69, vasodilatory β-blockers P-score = 0.5), nebivolol P-score = 0.06). In the GRADE assessment, evidence on the matter was rated as low or very low (Table 3).

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	Heterogeneity[1]
Non-vasodilatory vs Placebo	431 vs 307	0.98 (0.33–2.89)	Low	Imprecision[2]
Non-vasodilatory vs Vasodilatory	431 vs 308	0.73 (0.27-2)	Very low	Within study bias[3], imprecision[2]
Vasodilatory vs Placebo	308 vs 307	1.33 (0.32–5.6)	Very low	Within study bias[3], imprecision[2]
Indirect evidence only. Odds Ratio (95% Confidence Interval)				
Nebivolol vs Vasodilatory	140 vs 168	2.15 (0.6–7.77)	Low	Within study bias[3], imprecision[2]
Nebivolol vs Placebo	140 vs 307	2.87 (0.75–11.04)	Very low	Within study bias[3], imprecision[2]
Ranking of treatments			Moderate	Inconsistency[4]
[1]Variability in the magnitude of effects across studies within the same comparison.				
[2]Confidence intervals include values favoring either treatment.				
[3]Dominated by evidence at high or moderate risk of bias.				
[4]Evidence of inconsistency in the network (wide variance estimates).				
**treatment effect is reported as odds ratio (95% confidence interval).*				
***bold font indicates significant effect.*				

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 signaling 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 sources of evidence in a field of research that is alive with multiple interventions and heterogeneously designed studies. 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 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-naïve males. 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 are needed to better explore the effects of antihypertensive medication on erectile function.

Declarations

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Compliance with ethical standards

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Conflict of interest

The authors declare no conflict of interest.

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.

Availability of data and material

All data are available upon request.

Authors' contributions

IF, NP, ID, IM and GG contributed to the conception or design of the work. IF, NP and EA contributed to the acquisition, analysis, or interpretation of data for the work. IF and NP drafted the manuscript. ID, IM, EA and GG critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Figures

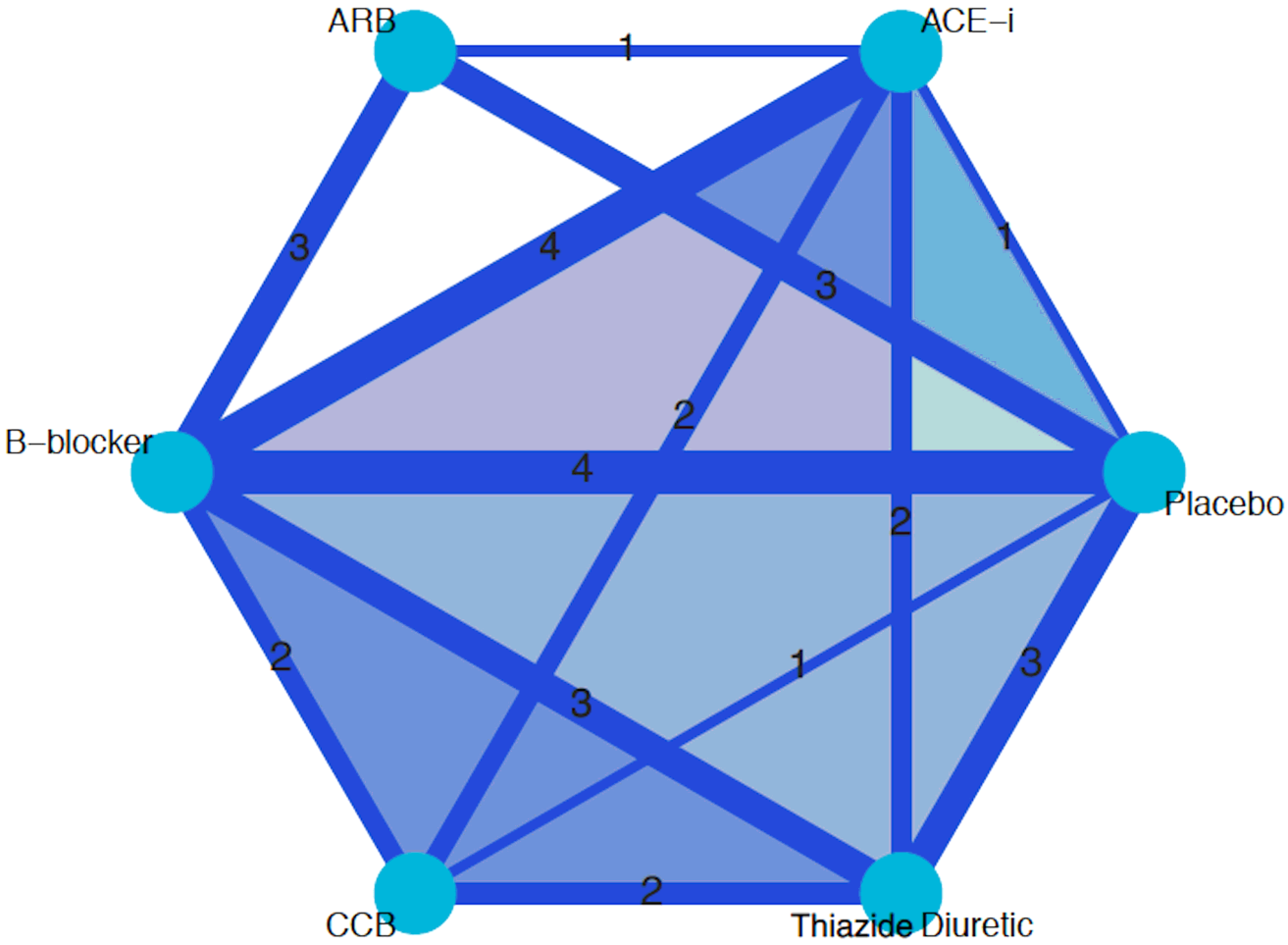

Figure 1

Network graph of interventions *ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker

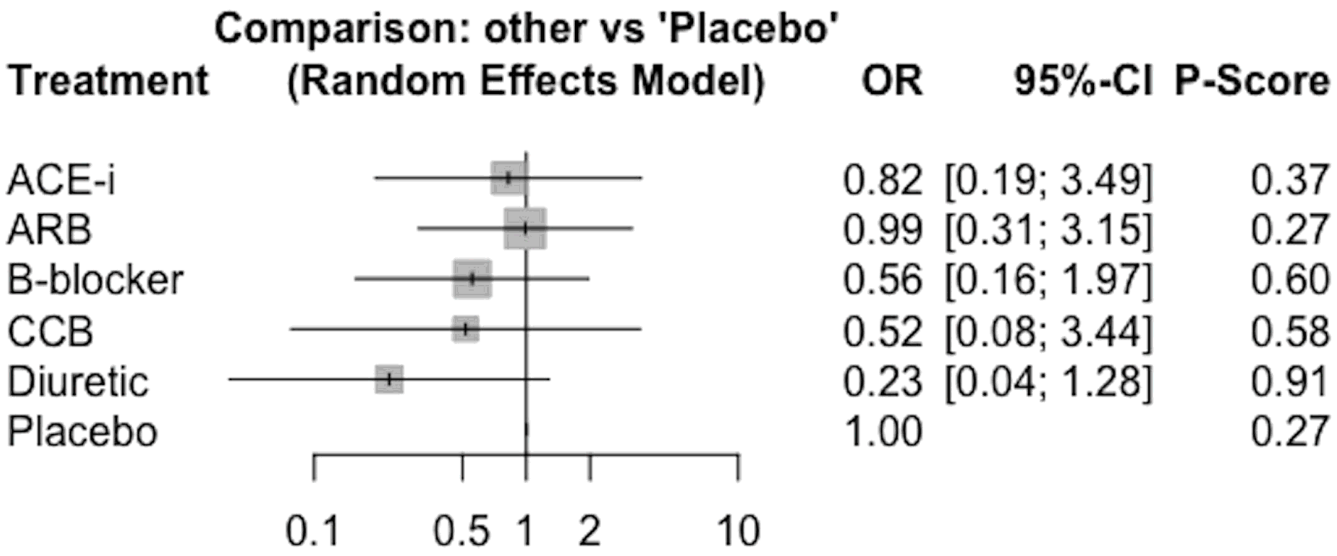

Figure 2

Forest plot of comparison between major antihypertensive medication classes and placebo concerning the effect on erectile function. *ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker

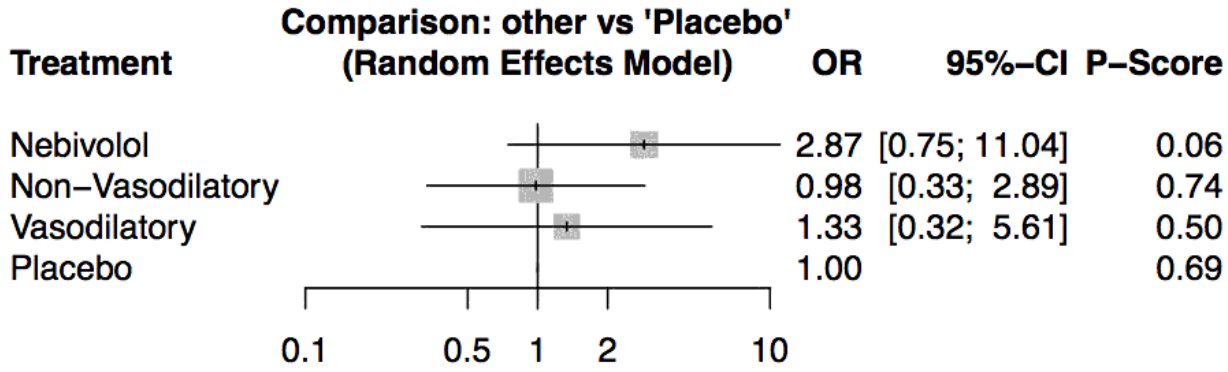

Figure 3

Forest plot of the effect of nebivolol versus other vasodilatory versus non-vasodilatory b-blockers on erectile function.

Supplementary Files

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