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Cardiovascular Risk, Drugs and Erectile Function –A Systematic Analysis

Baumhäkel: CV-DrugED

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Disclosures

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Abstract

Aims

Erectile dysfunction is a major problem with an increasing prevalence in cardiovascular high-risk patients due to the association with cardiovascular risk factors. Drugs used for evidenced based treatment of cardiovascular diseases have been reported to decrease erectile function, but possible mechanisms are poorly characterized.

Methods

MEDLINE, EMBASE and Cochrane Registry search was performed including manuscripts until January 2010. Searching terms are: “erectile dysfunction or impotence” in combination with “ACE-inhibitors”, “angiotensin”, “beta-blockers”, “calcium antagonist” and “diuretics”. Animal studies, letters, reviews, case-reports and manuscripts other than English language and trials dealing with combination treatment are excluded.

Results

Analysis of literature revealed five epidemiological trials evaluating the effect of different cardiovascular drugs on erectile function. There were eight trials evaluating the effect of beta-blockers, five trials evaluating the effect of ace-inhibitors or angiotensin-receptor-blockers and one trial evaluating the effect of diuretics on erectile function. Results of these trials demonstrate that only thiazide diuretics and beta-blockers except nebivolol may adversely influence erectile function. ACE-inhibitors, angiotensin-receptor-blockers and calcium-channel-blockers are reported to have no relevant or even a positive effect on erectile function.

Conclusion

Inappropriate patients’ concerns about adverse effects of cardiovascular drugs on erectile function might limit the use of important medications in cardiovascular high-risk patients. Knowledge about the effects of drug-treatments on erectile function and about the major role

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3 of the endothelium in penile function might improve patients' adherence to evidence based
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5 treatment of cardiovascular diseases.
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10 11 12 **What's known?**

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15 Erectile dysfunction is known to be related to endothelial dysfunction and therefore,
16
17 cardiovascular risk factors and diseases are closely associated. Those cardiovascular risk
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19 patients have to be treated with cardiovascular drugs according to evidence based guidelines.
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21 These drugs were often accused to impair erectile function as a major adverse effect, likely to
22
23 influence treatment adherence of patients.
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29 30 **What's new?**

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32 Only thiazide diuretics and beta-blockers except nebivolol may adversely influence erectile
33
34 function. ACE-inhibitors, angiotensin-receptor-blockers, and calcium-channel-blockers are
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36 reported to have no relevant or even a positive effect on erectile function. Knowledge about
37
38 these effects of drug-treatments on erectile function and about the major role of the
39
40 endothelium in penile function might improve patients' adherence to evidence based
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42 treatment of cardiovascular diseases.
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Introduction

Erectile dysfunction is defined as the inability to attain or maintain a penile erection sufficient for satisfactory sexual performance (1). Prevalence of erectile dysfunction in the Western industrialized countries amounts to 20-30% in the general male population and probably higher, about 75% in cardiovascular high-risk (2). This imposes an enormous economical and psychological impact on affected individuals and society (3-6).

Physiology of erectile function is dependent on a balanced vascular, neurologic, hormonal, and psychological system. Sexual stimuli are processed within the central nervous system and relayed to the spinal cord by neural signals. Neural impulses initiate blood flow to the pelvic vascular bed via the non-adrenergic/non-cholinergic nerves by a consecutive release of nitric oxide (7). Initiation and maintenance of penile erection is primarily dependent on the function of the vascular system within an appropriate hormonal milieu. Initial blood flow into the corpora cavernosa and the corpus spongiosum starts an erection. Pressure within the intracavernosal spaces increases to prevent penile venous outflow, allowing a firm erection. High levels of nitric oxide in the corpora cavernosa maximize blood flow and penile engorgement (8). Appropriate testosterone levels have been demonstrated to be necessary for maintenance of intrapenile nitric oxide synthase levels (9).

Previously, psychological factors have been suggested to be the major cause of erectile dysfunction, but in the last two decades, it has been recognized that endothelial dysfunction and subsequent cardiovascular diseases account for erectile problems more often than not (10, 11). The Massachusetts Male Aging Study as well as the Cologne Male Survey demonstrated a correlation between age and incidence of erectile dysfunction with an increase in erectile dysfunction in patients with cardiovascular risk factors or diseases (3, 12). The prevalence of erectile dysfunction amounts to 75% in cardiovascular high-risk patients reinforcing the

1
2
3 strong association of erectile dysfunction with cardiovascular risk factors and diseases (13,
4
5 14) with impairment of endothelial function by cardiovascular risk factors such as
6
7 hypertension being the common pathophysiological link. (figure 1) (15).
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11
12 Erectile dysfunction, as a symptom of impairment of the endothelial monolayer of the corpus
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14 cavernosum and the penile arteries is recognised to become clinically relevant prior to
15
16 cardiovascular events due to the extensive network (surface area) of endothelium in the penis
17
18 (16). Erectile dysfunction therefore represents an early sign and symptom of generalized
19
20 endothelial dysfunction and atherosclerosis, providing a means for the early detection of high-
21
22 risk individuals with the opportunity to prevent cardiovascular events (17).
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30 Within the last four decades the medical press and the lay media have reported on an
31
32 association of impaired erectile function with drugs used for treatment of cardiovascular
33
34 diseases and hypertension in particular. The publicity surrounding these reports has caused
35
36 concerns among patients, thereby potentially impairing adherence to important cardiovascular
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38 medical regimens. Results from small trials suggested that the treatment of hypertension with
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40 ACE-inhibitors, AT1-antagonists, beta-blockers, diuretics or calcium-channel blockers rather
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42 than hypertension itself could be associated with vascular and organ damage, contributing to
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44 erectile dysfunction (18). This manuscript presents and evaluates data from clinical trials, but
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46 also preclinical studies and possible mechanisms of action of drugs commonly used for the
47
48 treatment of cardiovascular diseases regarding adverse or beneficial effects on erectile
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50 function.
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57 **Methods**

58 *Data Sources and Searches*

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3 A systematic search of the literature was conducted by two independent reviewers considering
4 manuscripts published until January 2010. Target databases were MEDLINE, EMBASE and
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A systematic search of the literature was conducted by two independent reviewers considering manuscripts published until January 2010. Target databases were MEDLINE, EMBASE and Cochrane Clinical Trials Registry. The following terms were used for research: “erectile dysfunction or impotence” in combination with “ACE-inhibitors”, “angiotensin”, “beta-blockers”, “calcium antagonist”, and “diuretics”.

Study Selection

Selection of references was performed in three steps (figure 2). Studies were first excluded if they were nonhuman data, letters, reviews, case-reports or manuscripts in a language other than English. Secondly, trials dealing with combined treatment with PDE-5 inhibitors or combination treatment with more than one substance were excluded. Finally, clinical trials, which did not explore the effects of single cardiovascular drugs were excluded, e.g. the Massachusetts Male Aging Study (4). These trials are demonstrated in a separate table, including epidemiological trials with more than 500 patients (table). Additionally, trials evaluating erectile function with a validated questionnaire or direct assessment of penile rigidity were extracted. Both reviewers conducted the complete selection process independently. Effects of cardiovascular drugs on erectile function and possible mechanisms are described in detail in the discussion section.

Results

Systematic analysis of literature revealed eight trials evaluating the effects of beta-blockers, five trials evaluating the effect of treatment with ace-inhibitors or angiotensin-receptor-blockers and one trial evaluating the effect of treatment with diuretics on erectile function (table). There was no trial evaluating the effect of calcium-channel-blockers on erectile function. Most of these trials were performed in patients with hypertension. Moreover, five epidemiological trials with more than 500 patients studied the effects of different

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3 cardiovascular drugs on erectile function (ace-inhibitors, angiotensin-receptor-blockers, beta-
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5 blockers, diuretics, and calcium-channel-blockers; table).
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10 Results of these trials demonstrate that only thiazide diuretics and beta-blockers, except
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12 Nebivolol, may influence erectile function. ACE-inhibitors, angiotensin-receptor-blockers and
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14 calcium-channel-blockers are reported to have no relevant or even a positive effect on erectile
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16 function.
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22 **Discussion**

23 *Beta-Blockers*

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25 Beta-blockers were frequently suggested to be associated with impairment of sexual desire,
26
27 libido and especially erectile dysfunction. Several trials from the 1980s in patients with
28
29 hypertension treated with different beta-blockers revealed conflicting results regarding
30
31 influence on erectile function, but these data were limited. In most trials, erectile dysfunction
32
33 was not the primary objective and was assessed by patient-reports, instead of evaluation with
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35 a questionnaire or measurement of penile rigidity (19-22).
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43 In the late 1990s, trials compared the beta-blockers carvedilol and atenolol to the ACE-
44
45 inhibitor lisinopril and the AT1-antagonist losartan (table). Treatment with carvedilol and
46
47 atenolol decreased the frequency of sexual contacts in men with newly diagnosed
48
49 hypertension compared to lisinopril or losartan (23, 24). However, these trials were limited to
50
51 the surrogate of sexual contacts, which is not equivalent to erectile function. Carvedilol is a
52
53 lipophilic, non-selective adrenergic blocker with multiple cationic channel blocking
54
55 properties. Various data and underlying mechanisms are difficult to interpret, especially in
56
57 comparison to different beta-blockers. Furthermore, a meta-analysis of the later beta-blocker
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59 trials in the 90s including 35.000 patients indicated a small, but significant increase in the
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3 annual risk of developing sexual dysfunction in patients treated with a beta-blocker compared
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5 to placebo (5 of 1000 patients, 95% CI 2-8). This analysis however, concerned sexual
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7 behaviour and not specifically erectile dysfunction (25).
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12 Recent randomized, prospective trials have failed to confirm any negative effects of beta-
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14 blockers on erectile function. In 65 patients with coronary heart disease treatment with
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16 metoprolol (95mg) for four months did not influence erectile function, which was assessed
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18 with a standardized and validated questionnaire (26). Increase of erectile dysfunction in
19
20 connection with beta-blockers might be biased by psychological effects derived from the
21
22 awareness of being treated with a certain substance. Patients who were informed about
23
24 potential adverse effects of beta-blockers on erectile function more frequently reported
25
26 erectile dysfunction compared to patients without knowledge about the drug used, but
27
28 nevertheless, this trial evaluated erectile dysfunction without a standardized questionnaire
29
30 (figure 3) (27). In those patients with impaired erectile function, treatment with sildenafil and
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32 placebo was similarly effective showing a psychological impact on the provenance of this
33
34 adverse effect. These results were confirmed in a recent trial with hypertensive patients
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36 treated with metoprolol (28).
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46 Recent clinical trials reported beneficial effects of nebivolol, a third generation beta-blocker
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48 with nitric-oxide-mediated vasodilatory properties (29). In hypertensive patients treated with
49
50 atenolol, metoprolol or bisoprolol, switching treatment to nebivolol improved erectile
51
52 function in 69% of patients (30). Another trial demonstrated no effects of nebivolol on
53
54 erectile function in patients with hypertension, whereas atenolol decreased erectile function
55
56 (31). Similar effects were demonstrated in a cross-over trial in hypertensive men treated with
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58 metoprolol and nebivolol. Metoprolol decreased sexual function, whereas nebivolol improved
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60 sexual activity and erectile dysfunction subscores even though both drugs showed similar

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3 antihypertensive effectiveness (29). This advantage to erectile function has been supposed to
4 be related to nitric-oxide-release and direct vasodilation by nebivolol (26). A recent
5 observational trial confirmed these results. In univariate analysis, treatment with carvedilol
6 was associated with decreased erectile function, whereas nebivolol improved erectile function
7 in multivariate analysis (32).
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17 *Mechanisms*

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19 Several reports on varying frequencies of sexual dysfunction depending on structure and
20 lipophilicity of beta-blockers were published, but only a few studies addressed possible
21 mechanisms (33). Direct effects on penile and vascular smooth muscle cells with a decreased
22 perfusion pressure due to unopposed alpha-receptor stimulation were suggested, but not
23 experimentally proven or clinically investigated (34). Decreased levels of testosterone and, in
24 part, of the follicle-stimulating hormone by metoprolol, pindolol, atenolol and propranolol
25 have been suggested to be involved in reduction of sexual function and desire (33).
26 Depression of Leydig cell activity involves beta-2 type receptors (31). Hence, particularly
27 non-selective beta-blockers such as propranolol were suggested to influence sexual function
28 (35). Moreover, propranolol was demonstrated to increase latency to initial erection and to
29 inhibit erectile reflexes, which may affect erectile function (34). These effects were dependent
30 on stereo-selectivity of propranolol with (-)-propranolol showing the most pronounced effects
31 and were supposed to be, at least in part, independent of beta-adrenoceptor blockade (36).
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53 Nebivolol was investigated in an atherosclerotic animal model. Nebivolol, but not metoprolol
54 improved endothelial function of the aorta and the corpus cavernosum with a significant
55 reduction in penile oxidative stress and collagen content (37). Nebivolol protected cavernosal
56 tissue against structural changes and increased expression of eNOS, whereas the calcium-
57 channel blocker amlodipine did not (38). As selective beta-blockers might impair erectile
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3 function, in contrast, considering the strong correlation and pathophysiological link between
4
5 endothelial and erectile function, beta-blockers with beneficial effects on nitric oxide synthase
6
7 and oxidative stress have been suggested to improve erectile function.
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10 11 12 *Diuretics*

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15 Data about the effect of single use of diuretics on erectile function are sparse. A small number
16
17 of patients and inadequate evaluation of erectile function limits the results of the trials.
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19 Compared to placebo, chlorthalidone was demonstrated to impair erectile function (table)
20
21 (39). There is a multiplicity of trials with thiazides in combination treatment. These were not
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23 considered for analysis, because of the difficulty of interpretation of interaction of
24
25 combination treatments with ACE-inhibitors, AT1-antagonists or calcium-channel blockers.
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32 Results from trials evaluating the influence of multiple drugs on erectile function vary, but
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34 even these trials suggest a negative effect of thiazides on erectile function (table). A
35
36 prospective trial in a general population assessed erectile function with two questions at
37
38 baseline and after five years in men free from moderate or severe erectile dysfunction at
39
40 baseline (34). In multivariate analysis, use of diuretics was associated with an increased risk
41
42 of developing erectile dysfunction (RR=1.3, CI 0.7-2.4). Similar results were obtained in
43
44 patients with hypertension (40, 41). The recent ONTARGET/TRANSCEND-erectile
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46 dysfunction substudy, a randomized, controlled, blinded trial using multivariate analysis, did
47
48 not demonstrate a significant association of pre-treatment with diuretics with erectile function
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50 in cardiovascular high-risk patients (14). In summary, thiazide diuretics may have a negative
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52 influence on erectile function, but clear data are missing.
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60 There are only insufficient data about the effects of non-thiazide diuretics on erectile function.
The Massachusetts Male Aging Study revealed an association of increased prevalence of

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3 erectile dysfunction with the use of diuretics in univariate analysis, but only non-thiazides
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5 such as loop-diuretics and aldosterone-antagonists remained significant after adjustment for
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7 co-morbidities (table) (41). Randomized, prospective trials providing data on treatment with
8
9 aldosterone-antagonists such as spironolactone or eplerenone are lacking.
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12 13 14 15 *Mechanisms*

16
17 The underlying mechanisms of negative effects of thiazides on erectile function are unknown.
18
19 It has been suggested that sodium depletion leads to increased central alpha 2 adrenergic
20
21 function, which may depress erectile performance (39). However, an influence of thiazides on
22
23 sex related hormones is not likely, because there was no effect on testosterone, estradiol or
24
25 prolactin levels in humans (39).
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32 Even though there are no data about aldosterone-antagonists on erectile dysfunction from
33
34 clinical trials, animal studies revealed information about possible mechanisms. Aldosterone
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36 has been demonstrated to enhance norepinephrine-induced contraction of isolated human
37
38 corpora-cavernosal smooth muscle cells, hence decreasing erectile function (42). Pretreatment
39
40 with spironolactone abolished these negative effects completely. On the other hand,
41
42 spironolactone is supposed to decrease erectile function and sexual desire due to androgen
43
44 suppression by competing with testosterone and dihydrotestosterone for peripheral androgen
45
46 binding sites (43). Additionally, spironolactone seems to be a weak inhibitor of testosterone
47
48 synthesis. In summary, use of aldosterone-antagonists could be associated with a negative
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50 influence on erectile function, but clinical trials are missing. There are no data about possible
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52 mechanism of loop-diuretics on erectile function, but speculation about sodium-depletion may
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54 also apply for loop-diuretics.
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Calcium-channel blockers

There is no clinical trial evaluating the effect of calcium-channel-blockers on erectile function with adequate assessment of erectile dysfunction. Patients with hypertension or coronary artery disease reported a decrease of erectile function with nifedipine compared to placebo (44, 45). In contrast, trials evaluating effects of multi-drug treatment did not reveal negative effects of treatment with calcium-channel-blockers on erectile function, except a prospective trial in a general population (14, 34, 40, 41, 46). Although relaxation of vascular and cavernosal smooth muscle cells is crucial in the physiology of erectile function, there is no clinical evidence for beneficial effects of calcium-channel blockers. Calcium-channel-antagonists are reported to have no relevant effect on erectile function in men regarding quality of trials demonstrating negative effects on erectile function.

Mechanisms

Increase of heart rate after treatment with short acting dihydropyridines might be a reasonable speculation to explain the negative effects of calcium-channel-antagonists on erectile function as it is known to impair endothelial and likely erectile function, but experimental data are lacking (47). In contrast, “in vitro” experiments indicated a reduction of norepinephrine induced contraction of corpora cavernosal smooth muscle cells by nifedipine, diltiazem and verapamil (48). Further studies confirmed these data and provided information on recovery of impaired neurogenic relaxation of corpora cavernosa in hypertensive rats treated with amlodipine (49, 50).

ACE-inhibitors

Data about the influence of ACE-inhibitors on erectile function are limited due to quality of assessment of ED. Currently, there is only one trial evaluating the effects of treatment with an ACE-inhibitor in patients with ED compared to placebo (51). Treatment with ACE-inhibitors

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3 improved erectile function assessed with a standardized questionnaire. Cavernosal blood-flow
4
5 was determined using ultrasound, but there was no significant difference between the ACE-
6
7 inhibitor and placebo. Consistently, there was no influence of treatment with ACE-inhibitors
8
9 on erectile function in several trials, evaluating the effects of different kinds of cardiovascular
10
11 drugs (table) (14, 34, 40, 41, 46).
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15 16 17 *Angiotensin-Receptor-Blockers*

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19 Comparable to the effects of ACE-inhibitors, the angiotensin receptor blocker valsartan was
20
21 shown to increase frequency of sexual contacts, compared to the beta-blocker carvedilol (18).
22
23 These preliminary results could be confirmed in 82 patients with hypertension and erectile
24
25 dysfunction. Treatment with losartan for twelve weeks significantly improved erectile
26
27 function, satisfaction, and sexual activity significantly (52). Moreover, a recent open-label
28
29 study in 3502 hypertensive patients, of whom 952 were newly diagnosed, with erectile
30
31 dysfunction treated with valsartan revealed an improvement of erectile function even in
32
33 patients, in whom drug treatment had been switched from another class of antihypertensive
34
35 drugs (figure 4) (53). Moreover, in patients with the metabolic syndrome, irbesartan improved
36
37 erectile function in parallel to a decline of blood pressure and independent of concomitant
38
39 treatment with diuretics (54). These results were limited by absence of a control group, but
40
41 were confirmed in recent trials in patients with hypertension and high cardiovascular risk.
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43 There was no negative effect of treatment with an angiotensin-receptor-blocker on erectile
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45 function, except in one trial in a general population (14, 34, 40, 41, 46).
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55 *Mechanisms*

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57 Penile blood flow as well as contractility of cavernosal smooth muscle cells depends on a
58
59 complex balance between various paracrine regulators including angiotensin II and nitric
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oxide (55). Angiotensin II is synthesized in endothelial and smooth muscle cells of penile

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3 arteries and the corpus cavernosum (56, 57). Hence, ACE regulates cavernosal smooth muscle
4
5 tone in a paracrine fashion by local angiotensin II production with tissue concentrations of
6
7 angiotensin II being one and two orders of magnitude higher compared to the aorta or plasma
8
9 levels respectively (56). In patients with organic erectile dysfunction, plasma and cavernosal
10
11 levels of angiotensin II are elevated in the phase of penile detumescence compared to healthy
12
13 men (57). Consequently, local intracavernosal injection of angiotensin II was demonstrated to
14
15 spontaneously terminate drug induced erection in anesthetized dogs, while losartan increased
16
17 intracavernosal pressure in a dose dependent manner resulting in an improvement of erection
18
19 (56). Moreover, angiotensin II is was demonstrated to upregulate the PDE-V with consecutive
20
21 detrimental effects on erectile function, which might be abolished by angiotensin-receptor-
22
23 blockers (58).
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31 Beneficial effects of angiotensin-receptor-blockers in clinical trials were confirmed in several
32
33 disease models in rodents. In hypertensive rats, blood pressure related structural changes of
34
35 penile vessels and the corpus cavernosum were significantly decreased in animals treated with
36
37 losartan compared to amlodipine (59). Similar effects were demonstrated in hypertensive rats
38
39 treated with a combination of the PDE-V-inhibitor sildenafil and the angiotensin-receptor-
40
41 blocker losartan. Functional and structural modifications in cavernosal tissue were
42
43 significantly reduced in animals treated with the combination compared to monotherapy with
44
45 losartan or even sildenafil (60). Moreover, in ApoE-knockout mice, a rodent model for
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47 atherosclerosis, treatment with irbesartan improved endothelial function of the aorta as well as
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49 the corpus cavernosum to the same extent (37). These effects were demonstrated to be
50
51 independent of blood pressure reduction. Moreover, effects were related to a reduction of
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53 oxidative stress in the corpus cavernosum. Angiotensin II increases production of reactive
54
55 oxygen species via stimulation of the AT1-receptor and consecutively NADPH oxidase with
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3 increased radical load on vascular endothelium (61, 62). Thus, angiotensin receptor blockade
4 improves endothelial and erectile function via identical mechanisms.
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10 Angiotensin receptor blockers improved endothelial and erectile function in several clinical
11 trials, which were in line with experimental studies. While angiotensin II impairs erectile
12 function by contraction of vascular and cavernosal smooth muscle cells, bradykinin was
13 recently shown to balance these negative effects. In isolated human corpora cavernosa,
14 bradykinin increased relaxation of smooth muscle cells in parallel to the increase of
15 intracellular levels of cAMP and cGMP (63). A head to head trial is missing so far, but data of
16 the recent ONTARGET/TRANSCEND-erectile dysfunction substudy provided information
17 on whether ACE-inhibitors, angiotensin-receptor-blockers, or a combination thereof are able
18 to improve erectile function and whether inhibition of bradykinin-degradation via ACE-
19 inhibition will exert any further beneficial effects beyond AT1-antagonism (14). In 1549
20 cardiovascular high-risk patients included, there was neither a beneficial effect of the ACE-
21 inhibitor ramipril, the angiotensin-receptor blocker telmisartan, nor of the combination of both
22 on erectile function (64). In ACE-intolerant patients in the TRANSCEND-trial, telmisartan
23 was not superior to placebo.
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45 **Conclusion**

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48 Erectile dysfunction is a major problem, increasing with age, with a prevalence of 20-30% in
49 the general population (3). In cardiovascular high-risk patients, prevalence increases to 50-
50 70% with a significant impact of cardiovascular risk factors and diseases on erectile function
51 (14). Drugs used for treatment of cardiovascular diseases have often been accused of
52 influencing erectile function. Analysis of the literature demonstrates that evidence at best is
53 firm only for thiazide diuretics and beta-blockers having a negative effect whereas nebivolol
54 may have a positive influence on erectile function. ACE-inhibitors, angiotensin-receptor-
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3 blockers, and calcium-channel-blockers are reported to have no relevant or, in the case of
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5 ARBs, even a positive effect on erectile function respectively. Comparison and valuation of
6
7 the trials included in this analysis is limited by the different study-designs. Erectile
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9 dysfunction was not the primary objective in all trials and evaluation of erectile dysfunction
10
11 was not standardized. Furthermore, physicians should be aware of the physiological and even
12
13 psychological impact of cardiovascular events on erectile function. Importantly, patients'
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15 concerns about the adverse effects of drugs on erectile function might limit the use of
16
17 important medications in cardiovascular high-risk patients. Worsening of erectile dysfunction
18
19 after identifying a patient at risk is more likely to be due to atherosclerosis and cardiovascular
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21 risk factors rather than the intake of drugs. We recommend explaining the effects of drug-
22
23 treatments and the role of atherosclerosis in erectile dysfunction to the patients in order to
24
25 improve patients' adherence to evidence based treatment of cardiovascular diseases. This
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27 analysis clearly demonstrates the importance of a validated evaluation of drug effects on
28
29 erectile function in future trials on cardiovascular disease.
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Legends:**Figure 1: Physiology of penile erection.**

Mechanism involved in regulation of smooth muscle tone of the corpus cavernosum. NANC-nerves were stimulated via spinal nerves subsequent to a sexual stimulus built in the central nervous system. ET: endothelin, IP₃: inositol trisphosphate NA: noradrenaline, NANC: non adrenergic-non-cholinergic nerves, NO: nitric oxide, PGE: prostaglandine, PLC: phospholipase C.

Figure 2: Reference selection**Figure 3: Beta-blocker and erectile dysfunction, a psychological issue.**

Patients were treated with atenolol (50mg) for 90 days (n=32 per group). Incidence of erectile dysfunction increases significantly dependent on knowledge of treatment or treatment and side-effects (upper panel). Patients with new erectile dysfunction (n=16) were treated either with sildenafil or placebo for two weeks in a cross-over-design. Despite one patient, erectile function improved regardless of treatment (lower panel).

Figure 4: Treatment with valsartan improves erectile function.

Treatment with valsartan for 6 months decreases prevalence of erectile dysfunction in hypertensive male patients. Pre-specified subgroups were patients with or without previous antihypertensive treatment and patients receiving valsartan as part of a combination therapy. Erectile dysfunction was assessed using the International Index of Erectile Function (IIEF). Differences were significant in all groups (p<0.0001).

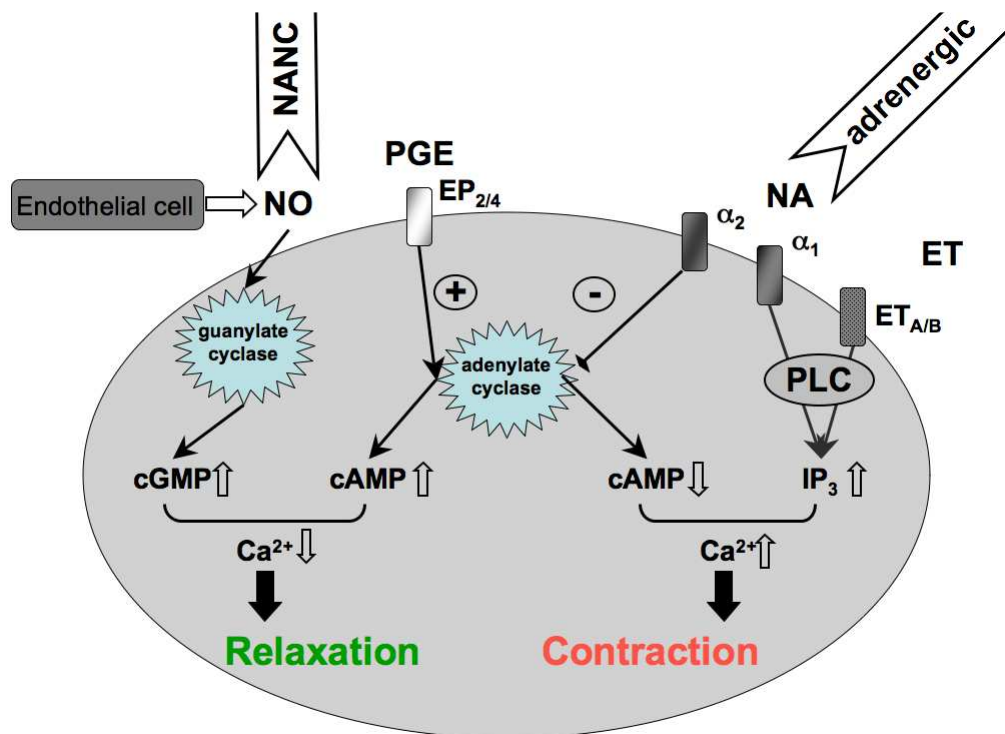
Table: Clinical trials evaluating the association of cardiovascular drugs and erectile function

Epidemiological Trials											
Year	Disease	n	Trial design	Measurement ED	Anal. multiv.	Result					Ref
						ACE-I	ARB	Beta-Blocker	Diuretic	CCB	
2001	General Population	922	Prospective Observation	Questionnaire	Yes	(+/-)	n.a.	(+/-)	- (only non-thiazides)	(+/-)	(41)
2003	Diabetes /Hypertension	1412	Open survey	Questionnaire	only for ACE-I	+	n.a.	(+/-)	(+/-)	(+/-)	(46)
2006	Hypertension	634	Observation	Questionnaire	No	(+/-)	(+/-)	-	-	(+/-)	(40)
2007	General Population	1665	Prospective observation	Questionnaire	Yes	(+/-)	-	- non-selective (+/-) selective	-	-	(34)
2007	CV-risk	1357	RCT	Questionnaire	Yes	(+/-)	(+/-)	(+/-)	(+/-)	(+/-)	(14)
Beta-Blockers											
Year	compound	Disease	n	Trial design	Control	Measurement ED	Anal. multiv.	Result			Ref
1998	Atenolol	Hypertension	90	RCT	Lisinopril	Questionnaire	No	Decrease of sexual intercourse in patients treated with atenolol			(23)
2001	Carvedilol	Hypertension	160	RCT	Valsartan	Questionnaire	No	Decrease of sexual intercourse in patients treated with carvedilol			(24)
2001	Metoprolol	CAD	65	RCT	Placebo	Questionnaire	No	No difference of ED-score			(26)
2005	Nebivolol	Hypertension	131	RCT	Comparison	Questionnaire	No	Decrease of sexual intercourse in atenolol, but not nebivolol group			(31)
2006	Nebivolol	Hypertension	44	CT	Switch from other beta-blockers	Questionnaire	No	Improvement of erectile function after switching to nebivolol			(30)
2007	Nebivolol	Hypertension	50	RCT		Questionnaire	No	Increase of ED in metoprolol compared to nebivolol			(29)
2008	Metoprolol	Hypertension	114	RCT	No	Questionnaire	No	Decrease of erectile function dependent on knowledge of treatment with metoprolol			(28)
2010	Any Beta-Blocker	Hypertension	1007	Cross-sectional, observation	No	Questionnaire	Yes	Increase of erectile function in patients treated with nebivolol			(32)
Diuretics											
Year	Compound	Disease	n	Trial design	Control	Measurement ED	Anal. multiv.	Result			Ref
1990	Chlorthalidone	ED	79	RCT	Placebo	Questionnaire	No	Decrease of erectile function in patients treated with chlorthalidone			(39)
Calcium-Channel-Blockers											
Year	Compound	Disease	n	Trial design	Control	Measurement ED	Anal. multiv.	Result			Ref
No trials											
ACE-Inhibitors											
Year	Compound	Disease	n	Trial design	Control	Measurement ED	Anal. multiv.	Result			Ref
2005	ACE-inhibitor	ED	59	RCT	Placebo	Questionnaire	No	Improvement of ED			(51)
Angiotensin Receptor Blockers											

Year	Compound	Disease	n	Trial design	Control	Measurement ED	Anal. multiv.	Result	Ref
2001	Valsartan	Hypertension	160	RCT	Carvedilol	Questionnaire	No	Decrease of sexual intercourse in patients treated with carvedilol	(24)
2001	Losartan	Hypertension	164	Observation	No	Questionnaire	No	Improvement of sexual function in 11.8% patients with sexual dysfunction No effect in patients without sexual dysfunction	(52)
2003	Valsartan	Hypertension	3502	Open, prosp.	No	Questionnaire	No	Decrease of prevalence of ED from 75.4% to 53.0%, p<0.0001	(53)
2008	Irbesartan	Metabolic syndrome	1069	Open, prosp.	No	Questionnaire	No	Decrease of prevalence of ED from 78.5% to 63.7%, p<0.001	(54)

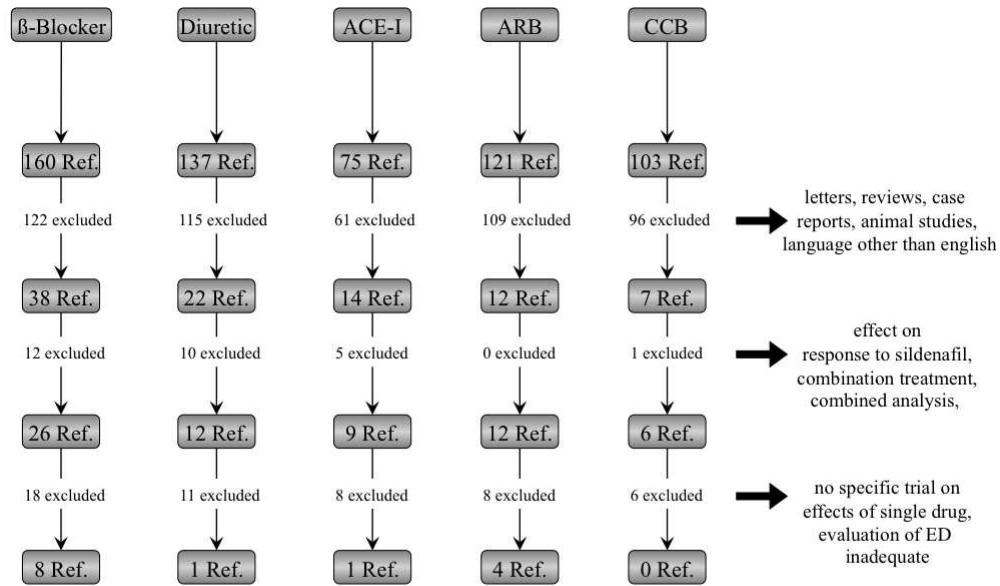
The table depicts epidemiological trials with more than 500 patients evaluating the effects of different cardiovascular drugs on erectile function (above). Trials evaluating the effect of beta-blockers, diuretics, calcium-channel-blockers, ACE-inhibitors, and angiotensin-receptor-blockers are presented below. (+/-): no effect on erectile function; -: decrease of erectile function; +: increase of erectile function; n.a.: information not available

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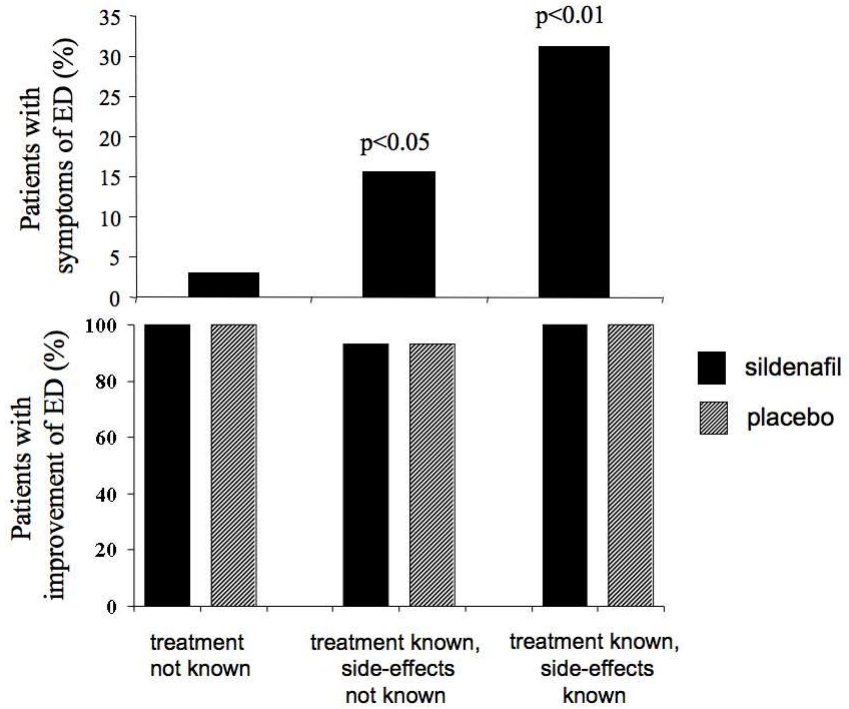
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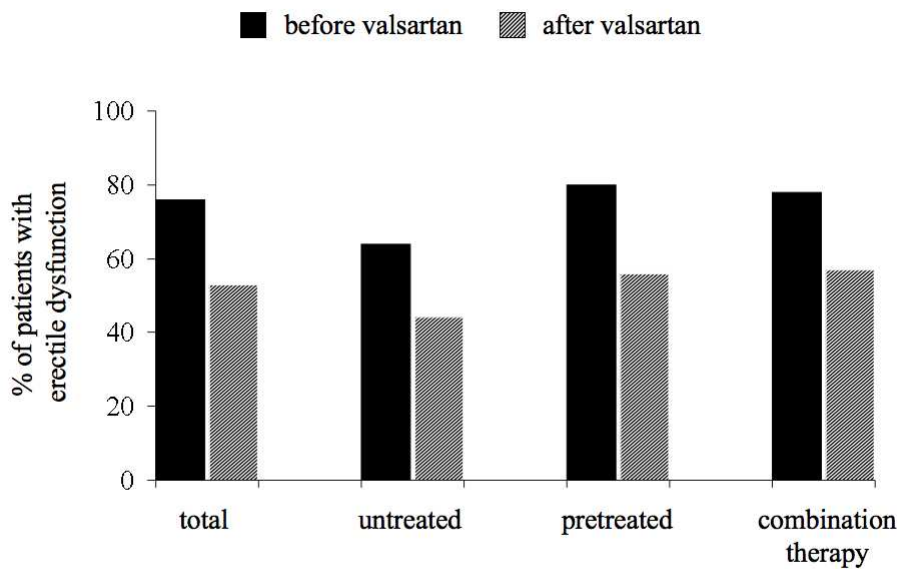
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Table: Clinical trials evaluating the association of cardiovascular drugs and erectile function

Epidemiological Trials											
Year	Disease	n	Trial design	Measurement ED	Anal. multiv.	Result					Ref
						ACE-I	ARB	Beta-Blocker	Diuretic	CCB	
2001	General Population	922	Prospective Observation	Questionnaire	Yes	(+/-)	n.a.	(+/-)	- (only non-thiazides)	(+/-)	(41)
2003	Diabetes /Hypertension	1412	Open survey	Questionnaire	only for ACE-I	+	n.a.	(+/-)	(+/-)	(+/-)	(46)
2006	Hypertension	634	Observation	Questionnaire	No	(+/-)	(+/-)	-	-	(+/-)	(40)
2007	General Population	1665	Prospective observation	Questionnaire	Yes	(+/-)	-	- non-selective (+/-) selective	-	-	(34)
2007	CV-risk	1357	RCT	Questionnaire	Yes	(+/-)	(+/-)	(+/-)	(+/-)	(+/-)	(14)
Beta-Blockers											
Year	compound	Disease	n	Trial design	Control	Measurement ED	Anal. multiv.	Result			Ref
1998	Atenolol	Hypertension	90	RCT	Lisinopril	Questionnaire	No	Decrease of sexual intercourse in patients treated with atenolol			(23)
2001	Carvedilol	Hypertension	160	RCT	Valsartan	Questionnaire	No	Decrease of sexual intercourse in patients treated with carvedilol			(24)
2001	Metoprolol	CAD	65	RCT	Placebo	Questionnaire	No	No difference of ED-score			(26)
2005	Nebivolol	Hypertension	131	RCT	Comparison	Questionnaire	No	Decrease of sexual intercourse in atenolol, but not nebivolol group			(31)
2006	Nebivolol	Hypertension	44	CT	Switch from other beta-blockers	Questionnaire	No	Improvement of erectile function after switching to nebivolol			(30)
2007	Nebivolol	Hypertension	50	RCT		Questionnaire	No	Increase of ED in metoprolol compared to nebivolol			(29)
2008	Metoprolol	Hypertension	114	RCT	No	Questionnaire	No	Decrease of erectile function dependent on knowledge of treatment with metoprolol			(28)
2010	Any Beta-Blocker	Hypertension	1007	Cross-sectional, observation	No	Questionnaire	Yes	Increase of erectile function in patients treated with nebivolol			(32)
Diuretics											
Year	Compound	Disease	n	Trial design	Control	Measurement ED	Anal. multiv.	Result			Ref
1990	Chlorthalidone	ED	79	RCT	Placebo	Questionnaire	No	Decrease of erectile function in patients treated with chlorthalidone			(39)
Calcium-Channel-Blockers											
Year	Compound	Disease	n	Trial design	Control	Measurement ED	Anal. multiv.	Result			Ref
No trials											
ACE-Inhibitors											
Year	Compound	Disease	n	Trial design	Control	Measurement ED	Anal. multiv.	Result			Ref
2005	ACE-inhibitor	ED	59	RCT	Placebo	Questionnaire	No	Improvement of ED			(51)
Angiotensin Receptor Blockers											

Year	Compound	Disease	n	Trial design	Control	Measurement ED	Anal. multiv.	Result	Ref
2001	Valsartan	Hypertension	160	RCT	Carvedilol	Questionnaire	No	Decrease of sexual intercourse in patients treated with carvedilol	(24)
2001	Losartan	Hypertension	164	Observation	No	Questionnaire	No	Improvement of sexual function in 11.8% patients with sexual dysfunction No effect in patients without sexual dysfunction	(52)
2003	Valsartan	Hypertension	3502	Open, prosp.	No	Questionnaire	No	Decrease of prevalence of ED from 75.4% to 53.0%, p<0.0001	(53)
2008	Irbesartan	Metabolic syndrome	1069	Open, prosp.	No	Questionnaire	No	Decrease of prevalence of ED from 78.5% to 63.7%, p<0.001	(54)

The table depicts epidemiological trials mit more than 500 patients evaluating the effects of different cardiovascular drugs on erectile function (above). Trials evaluating the effect of beta-blockers, diuretics, calcium-channel-blockers, ACE-inhibitors, and angiotensin-receptor-blockers are presented below. (+/-): no effect on erectile function; -: decrease of erectile function; +: increase of erectile function; n.a.: information not available