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Cardiovascular drugs and erectile dysfunction – a symmetry analysis

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Erectile dysfunction is a problem frequently reported among patients being treated with cardiovascular drugs.
- Use of thiazide diuretics and β-adrenoceptor blockers has previously been correlated with erectile dysfunction.

WHAT THIS STUDY ADDS

- Use of cardiovascular drugs is not associated with a high risk of erectile dysfunction when using prescribing of 5-phosphodiesterase inhibitors as a proxy for erectile dysfunction.

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AIM

Erectile dysfunction is a common problem among patients with cardiovascular diseases and the influence of cardiovascular drugs is much debated. The aim of this study was to evaluate the short term potential for different cardiovascular drugs to affect the risk of being prescribed a drug against erectile dysfunction.

METHODS

We employed a symmetry analysis design and included all Danish male individuals born before 1950 who filled their first ever prescription for a cardiovascular drug and a 5-phosphodiesterase inhibitor within a 6 month interval during 2002–2012. If the cardiovascular drug induces erectile dysfunction, this would manifest as a non-symmetrical distribution of subjects being prescribed the cardiovascular drug first *vs.* persons following the opposite pattern. Furthermore, we calculated the number of patients needed to treat for one additional patient to be treated for erectile dysfunction (NNTH).

RESULTS

We identified 20 072 males with a median age of 64 years (IQR 60–70) who initiated a cardiovascular drug and a 5-phosphodiesterase inhibitor within a 6 month interval. Sequence ratios showed minor asymmetry in prescription orders after adjustment for trends in prescribing. This asymmetry was most profound for thiazides (1.28, 95% CI 1.20, 1.38), calcium channel blockers (1.29, 95% CI 1.21, 1.38) and ACE inhibitors (1.29, 95% CI 1.21, 1.37), suggesting a small liability of these drugs to provoke erectile dysfunction. NNTH values were generally large, in the range of 330–6400, corresponding to small absolute effects.

CONCLUSION

Our study does not suggest that cardiovascular drugs strongly affect the risk of being prescribed a drug against erectile dysfunction on a short term basis.

Introduction

Erectile dysfunction (ED) is a problem that is frequently reported as an adverse reaction to pharmacotherapy, particularly with cardiovascular drugs such as antihypertensive medications [1, 2]. Many of these alleged adverse reactions have previously been studied in randomized controlled trials and in epidemiological studies [3, 4].

Results point toward thiazide diuretics and β-adrenoceptor blockers, so-called older antihypertensive drugs, as having a possible negative impact on erectile function. On the other hand, results seem to suggest that newer cardiovascular drugs, especially angiotensin II receptor antagonists, may have no or even beneficial effects on erectile function [3, 4].

However, differences in study designs and in the evaluation of ED [3] make comparison of cardiovascular drugs complex. Comparative analyses do exist [3, 5, 6], but the evaluation of ED is often based on unstandardized questionnaires [3]. In addition, the association between ED and use of cardiovascular drugs may be confounded by the underlying diseases, which cause prescribing of the drugs in question [3]. Consequently, it is difficult to arrive at definite conclusions regarding the effect of cardiovascular drugs on erectile function. To our knowledge, no comparative study has examined the association between ED and cardiovascular drugs solely by the use of prescription data.

We undertook this controlled study to evaluate the short term potential for different cardiovascular drugs to affect the risk of being prescribed a drug against erectile dysfunction. We did so using the Danish nationwide prescription registry and employing a symmetry analysis approach, i.e. evaluating asymmetries in prescription orders between incident users of 5-phosphodiesterase inhibitors and cardiovascular drugs.

Methods

The design employed was the symmetry analysis, originally described by Hallas [7].

In brief, we used prescribing of a 5-phosphodiesterase inhibitor (PDI: Anatomical Therapeutic Classification (ATC) code G04BE) as proxy for development of ED. During the study period, PDIs were available by prescription only and with partial co-payment. We included cardiovascular drugs classified under the following ATC codes: B01AA (vitamin K antagonists), B01AC (platelet inhibitors), C01AA (digitalis glycosides), C03A (thiazides), C03C (loop diuretics), C03CDA01 (spironolactone), C07 (β-adrenoceptor blockers), C08 (calcium channel blockers), C09A (ACE inhibitors, plain), C09C (angiotensin II receptor antagonists, plain) and C10AA (statins). We then identified all men who within a predefined time window of 6 months started a cardiovascular drug and a PDI for the first time (i.e. were incident users of both drugs). Within this particular group of men, we would expect an equal number starting either drug first, i.e. a symmetrical distribution of prescription orders if there was no association [7]. If, however, the cardiovascular drug causes ED, we would expect more subjects starting the cardiovascular drug before the PDI, i.e. an asymmetrical order. It can be shown that the sequence ratio, i.e. the ratio of counts of men who starts cardiovascular drugs first *vs.* men who starts PDIs first, is an estimate of the incidence rate ratio of PDI prescribing in follow-up exposed *vs*. non-exposed to cardiovascular drugs, possibly with a small conservative bias [8].

We used the variant of the symmetry analysis, where the index drug is anchored in time and the rate of PDI initiation is estimated in a symmetrical time window before and after the first prescription of the index drug [9]. The width of the interval was set to 6 months and sensitivity analysis was performed extending the width of the interval to 12 months. The trend effects of index drugs and PDI were adjusted by the method described by Tsiropoulos *et al.* [9].

For all cardiovascular drugs we calculated the number of patients needed to treat for one additional patient to be treated for ED (NNTH: exposure needed for one additional patient to be harmed [10]). The methods employed were based on the 'naturalistic' NNTH measure [10] and the approach described by Altman [11] and are detailed in Appendix A (Supplementary material). Any effect estimate suggesting a lowered risk of ED was designated an infinitely high NNTH. We refrained from calculating the NNTH when the point estimate and confidence interval limits all implied a protective effect against ED.

We calculated the median age with interquartile range (IQR) of the study population and performed sensitivity analyses stratifying the study population by age below and above the median age. This was done in order to test for potential differences across different age groups.

The data source used was the Danish National Prescription Registry, as hosted by Statistics Denmark [12]. We restricted the analysis to all Danish males born before 1950, and analyzed all first prescriptions of cardiovascular drugs initiated during the period 2002 through 2012 within this cohort.

All calculations were performed using STATA Release 13.0 (StataCorp, College Station, Texas, USA). The study was approved by the Danish Data Protection Agency. According to Danish law, ethical approval is not required for purely registry-based studies [13].

Results

We identified 20 072 male subjects with a median age of 64 years (IQR 60–70) who initiated a cardiovascular drug and a PDI within a 6 month interval. During the study period there was an increase in the prescribing of PDIs among Danish males above 50 years i.e. in 2002 the annual consumption was 916 defined daily doses (DDD) per 1000 inhabitants and in 2012 the annual consumption was 2577 DDD per 1000 inhabitants [14, 15].

The distribution of first cardiovascular drug prescriptions and their respective ordering relative to the first

prescriptions of a PDI is shown in Table 1. Except for digitalis glycosides, all cardiovascular drugs had estimates of crude sequence ratios above or equal to unity. The highest crude sequence ratios were seen for thiazides (1.32, 95% CI 1.23, 1.41), calcium channel blockers (1.34, 95% CI 1.25, 1.44) and ACE inhibitors (1.33, 95% CI 1.25, 1.41) (Table 1). The increase in the prescribing of PDIs relative to the prescribing of cardiovascular drugs [14] explained some of the observed asymmetry. After trend adjustment, the highest sequence ratios were observed for thiazides (1.28, 95% CI 1.20, 1.38), calcium channel blockers (1.29, 95% CI 1.21, 1.38) and ACE inhibitors (1.29, 95% CI 1.21, 1.37) with statistical significance (Table 1). Vitamin K antagonists, platelet inhibitors, loop diuretics, spironolactone and statins showed trend adjusted sequence ratios equalling unity (Table 1). However, it must be noted that there was only a limited number of male subjects who started a PDI and a vitamin K antagonist, digitalis glycoside and spironolactone, limiting the statistical power of these analyses.

The NNTH is shown in Table 1. The lowest NNTH values, corresponding to the largest absolute effect, were seen for thiazides (370, 95% CI 300, 500), calcium channel blockers (330, 95% CI 270, 440) and ACE inhibitors (350, 95% CI 290, 440).

When we extended the width of the interval to 12 months we observed small reductions in sequence ratios compared with the main analysis. However, the patterns in sequence ratios remained the same with ACE inhibitors having the lowest NNTH value (240, 95% CI 200, 310) (data not shown in full).

Sensitivity analyses stratifying the study population by age below or above the median age did not yield results materially different from the main analysis (data not shown in full).

Discussion

For most drug classes we found no associations between use of cardiovascular drugs and the short term risk of being prescribed a PDI. The estimated NNTHs were generally high, implying a low attributable risk of the outcome.

Our study has several strengths. First, data from the national prescription registry have been shown to have a high validity [12]. Secondly, we were able to include all first time users of PDIs and cardiovascular drugs with a drug free run in period of up to 17 years. As such, there is no selection bias in our study. The symmetry analysis can be regarded as a self-controlled design [16] due to the comparison of the follow-up post-exposure with that of the pre-exposure follow-up. Accordingly, this self-controlled design enabled us to control for confounders that are stable over time [16], e.g. unmeasured life style risk factors, which could confound our results such as smoking [7], age, diabetes [17] or hypertension [18]. Lastly, our study design enabled us to compare different cardiovascular drugs within the same analytical setting.

Some limitations need to be discussed. First, prescribing of a PDI is not a perfect proxy for ED and the timing of the PDI prescription may not accurately reflect the onset of ED. This will mainly confer a conservative bias. Secondly, some physicians would respond to a drug-induced ED by discontinuing the cardiovascular drug rather than prescribe a PDI, whereby these patients would not contribute to our study. Thirdly, some physicians might avoid prescribing drugs with a suspected adverse effect on erectile function, if the patient is known to have ED. For these latter two reasons, symmetry analyses work best with adverse drug reactions that are interpreted as spontaneous, non-drug related events. However, other studies have demonstrated that fairly well known drug-related problems are often handled

Table 1

Sequence ratios for cardiovascular drugs and 5-phosphodiesterase inhibitors (ATC, G04BE: sildenafil, vardenafil, tadalafil) and NNTH

Cardiovascular drugs (ATC)	Cardiovascular drug prescribed first/last	Crude sequence ratio (CI)	Trend adjusted sequence ratio (CI)	Number of subjects treated with a cardiovascular drug (*n*)	NNTH (CI)
Vitamin K antagonists (B01AA)	516/477	1.08 (0.96, 1.23)	1.05 (0.93, 1.19)	64 743	2600 (780, ∞)
Platelet inhibitors (B01AC)	1847/1773	1.04 (0.98, 1.11)	1.02 (0.95, 1.09)	199 105	6400 (1400, ∞)
Digitalis glycosides (C01AA)	203/220	0.92 (0.77, 1.12)	0.90 (0.75, 1.09)	35 643	∞ (2100, ∞)
Thiazides (C03A)	1772/1346	1.32 (1.23, 1.41)	1.28 (1.20, 1.38)	145 927	370 (300, 500)
Loop diuretics (C03C)	787/775	1.02 (0.92, 1.12)	0.99 (0.90, 1.09)	129 331	∞ (1900, ∞)
Spironolactone (C03CDA01)	287/283	1.01 (0.86, 1.20)	0.99 (0.84, 1.17)	47 627	∞ (1200, ∞)
β-adrenoceptor blockers (C07)	1375/1136	1.21 (1.12, 1.31)	1.18 (1.09, 1.28)	142 242	680 (480, 1200)
Calcium channel blockers (C08)	1935/1444	1.34 (1.25, 1.44)	1.29 (1.21, 1.38)	144 385	330 (270, 440)
ACE inhibitors, plain (C09A)	2385/1797	1.33 (1.25, 1.41)	1.29 (1.21, 1.37)	184 053	350 (290, 440)
Angiotensin II receptor antagonists, plain (C09C)	1133/949	1.19 (1.10, 1.30)	1.16 (1.06, 1.26)	84 259	540 (360, 1200)
Statins (C10AA)	2550/2561	1.00 (0.94, 1.05)	0.97 (0.91, 1.02)	234 545	∞ (4700, ∞)

NNTH number of patients needed to treat for one additional patient to be treated for ED; ATC Anatomical Therapeutic Chemical classification; CI 95% confidence interval

by prescribing second drugs, rather than discontinuing the index drug [19, 20].

Associations between the use of certain antihypertensives and the risk of ED have been shown in previous studies, especially for β-adrenoceptor blockers [3, 21] and thiazides [21–23]. We found no associations with use of spironolactone despite the established anti-androgen effect [24]. The observed association with use of ACE inhibitors, although minor, contradicts that of a previous clinical trial [25] and observational studies [3, 5, 6]. The majority of studies on angiotensin receptor antagonists have suggested a beneficial effect towards ED [3], which is not in accordance with our finding. Lastly, our finding of a negative association with the use of calcium channel blockers is confirmed by one study [6], but contradicts another [5]. The differences in study results may be caused by differences in composition of the study populations and differences in study designs e.g. methods for evaluating ED.

In conclusion, we found only weak associations between the use of cardiovascular drugs and the risk of being prescribed a PDI. Therefore, our study does not suggest an association of major clinical relevance between use of these drugs and the risk of developing erectile dysfunction.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). All authors declare no support from any organization for the submitted work. JH had financial relationships with Pfizer in the previous 3 years. The remaining authors declare no financial relationship with any organizations that might have an interest in the submitted work in the previous 3 years. All authors declare no other relationships or activities that could appear to have influenced the submitted work.

Contributors

All authors contributed in planning the study. JH performed data analysis and data management. LR and AP drafted the first manuscript and interpreted the data. All authors contributed in finalizing the manuscript. All authors have read and agreed the final manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix A
Calculation of the NNTH