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Impact of the Black Triangle Label on Prescribing of New Drugs in the United Kingdom: Lessons for the United States at a Time of Deregulation

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Abstract

Purpose—Newly approved novel drugs in Europe receive a black triangle label to promote pharmacovigilance. With growing momentum for earlier drug approvals and reliance on real-world evidence, we studied if the black triangle label promotes more judicious prescribing.

Methods—We examined whether general practitioners prescribed escitalopram, tadalafil, and vardenafil with a black triangle more cautiously than the same or similar drugs without a black triangle in The Health Improvement Network (UK). We performed interrupted time-series analyses to estimate changes in new prescription rates and nested case-control studies to compare characteristics of new users before and after removal of a black triangle.

Results—Prescribing rates to the 33,441 new-users of these new drugs were highest shortly after initial approval and declined subsequently; there were no increases in rates of new prescriptions after a black triangle's removal (new prescriptions/million/month post-label: escitalopram −1.5 [95% CI −1.9, −1.2]; tadalafil and vardenafil: −0.1 [95% CI −0.6, 0.4]). Among drugs in the same

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class, loss of a patent had more impact on prescribing rates than loss of a black triangle. People who began taking black triangle drugs were less likely to be young or to have multiple comorbidities or recent hospitalization compared with those starting the same drugs after the label's removal. However, these differences generally reflected secular trends seen also in similar, unlabeled medicines.

Conclusions—Accelerated drug approvals could cause more uncertainty about drug effectiveness and safety, but specific labeling of newly approved medicines is unlikely to promote more judicious prescribing.

Keywords

black triangle; physicians' practice patterns; drug labeling; interrupted time series analysis

Introduction

Newly marketed novel drugs have been labeled with a black triangle in the United Kingdom (UK) for decades and throughout the European Union (EU) since 2013.^{1,2} The black triangle symbol (▼) can be found at the top of product labeling for patients and healthcare professionals, often accompanied by text such as, "This medicinal product is subject to additional monitoring."³ This label is designed to promote more intensive monitoring of drugs in the years after approval.³ Labeled drugs include new active substances, biologics, and drugs granted conditional approval pending post-marketing studies.⁴ Of the studies examining the black triangle's effectiveness, most have focused on spontaneous reporting of adverse drug events (ADEs).^{5,6}

With increases in black box warnings and marketing withdrawals of drugs, there remains an important societal need for well-informed, deliberate prescribing of recently approved drugs.⁷ While the express purpose of the black triangle in Europe is not to influence prescribing, theoretically such labeling could help those in greatest need access new drugs while limiting more widespread exposure until completion of more conclusive post-marketing studies.⁸ Indeed, the Institute of Medicine (IOM) recommended use of a black triangle-like label to promote greater safety of new medications in the US.⁹ The recent passage of the US 21st Century Cures Act increases reliance on real-world evidence and could lead to earlier drug approvals based on less rigorous evidence.¹⁰ Such a situation would make it even more critical to communicate to prescribers and patients alike the incompleteness of safety information for newly approved medicines. One prior study investigated the impact of risk evaluation and mitigation strategies on off-label prescribing patterns of new drugs for a rare disease.¹¹ To our knowledge, no study has evaluated the impact of a more generic and broadly used label for new medication, including the black triangle, on prescribing rates and behaviors.

We studied whether presence of a black triangle could make prescribers more cautious, hypothesizing that prescribing rates would increase after a label's removal. We expected new drugs in well-established drug classes would preferentially be prescribed to patients in greatest need. Thus, we hypothesized that patients newly prescribed selective serotonin reuptake inhibitors (SSRIs) with a black triangle would be older and sicker (e.g., with more

severe, refractory disease) than patients starting the same SSRIs after a black triangle's removal. Furthermore, for newer, less established drug classes, and particularly lifestyle drugs such as phosphodiesterase type 5 inhibitors (PDE5Is), we expected a different form of caution with early prescribing, favoring patients at lower risk of complications. We therefore hypothesized that men newly prescribed PDE5Is with a black triangle would be older but less sick than men who began these drugs after the label's removal.

Methods

Study Design

To estimate the effects of removal of a black triangle on prescribing practices, we used an interrupted time-series (ITS) approach paired with a case-control design (Figure S1). ITS is a robust quasi-experimental design that evaluates the effects of time-limited interventions longitudinally.¹² ITS compares levels and trends of outcomes across successive time periods before and after interventions; in this study, the intervention was removal of a black triangle. The case-control design enabled comparison of individuals newly prescribed labeled drugs (cases) with first-time users of the same drug after the label's removal (controls). Secondly, to understand influences of secular trends on prescribing, we compared people who started comparable, unlabeled drugs across the same two periods. Another secondary analysis compared people who began taking labeled drugs with contemporary new users of unlabeled comparator drugs (Figure S1).

This study was approved by The Health Improvement Network (THIN) Scientific Review Committee (16THIN006) and deemed exempt for institutional review board review (#824432, University of Pennsylvania; Pro20160000100, Rutgers).

Data Source

The study used anonymized data from 1998 through 2014 in THIN, a population-representative database with electronic health records from approximately 6% of the UK population (>12 million individuals).¹³ THIN contains practice- and patient-level data collected through routine clinical care from > 600 general practices across the UK. Data include demographics, diagnoses, outpatient prescriptions, referrals, and laboratory results. THIN is a valid source for pharmacoepidemiologic research¹⁴ and has been used to study policy interventions using ITS.¹⁵

Subject Selection

Eligible subjects were registered in THIN practices with Vision software and had 183 days of baseline data. We focused on individuals who received first-ever prescriptions for escitalopram, tadalafil, vardenafil (drugs of interest), or comparable drugs from the same class—SSRIs or PDE5Is, respectively (Table S1). Drugs of interest were selected from medicines marketed in the UK whose black triangles were added or removed between 2000 and 2010 (Supplementary Methods). Analyses of PDE5Is excluded females, children, and people diagnosed with pulmonary hypertension to focus on the use of PDE5Is to treat erectile dysfunction.

The pre-selected primary comparators for escitalopram were citalopram and fluoxetine. These were longstanding SSRIs, one a structurally similar medication from the same manufacturer (citalopram) and both available in generic form when escitalopram was approved. Secondarily, we examined a comparator, sertraline, that went off patent during the study period. The pre-selected primary comparator for tadalafil and vardenafil was sildenafil, the only other approved PDE5I, whose black triangle had been removed over 1 year before tadalafil and vardenafil were approved.

Independent Variables

The primary independent variable for ITS analysis was presence of a black triangle. The primary independent variables for case-control studies were person-level characteristics (age, sex, prior medical conditions, number of comorbidities, number of concomitant medications, prior SSRI use [SSRI analyses only], recent hospitalization, and local deprivation) and practice-level covariates (country and practice size) (Supplementary Methods).

Outcomes

The primary outcomes were the levels and changes of monthly new prescription rates of drugs of interest or comparators per million eligible individuals in THIN. Changes in monthly rates were calculated based on the slope of trend lines from ITS analyses. Changes in prescription levels were calculated based on the distance between trend lines before and after label removal. ITS analyses excluded the first six months after initial drug approval to account for delayed adoption of new prescribing habits. For the case-control study, cases and controls received new prescriptions for drugs of interest or comparators during year-long intervals during or after the black triangle period (Supplementary Methods, Figure S1, Table S1).

Statistical Analysis

We used descriptive statistics to summarize the rates of new drug prescribing during the black triangle period studied and a corresponding interval after a black triangle's removal. To estimate changes in levels and trends of first-time prescribing between periods during and after a black triangle, ITS data were analyzed using ordinary least-squares segmented regression adjusted for autocorrelation.¹⁶ Other analyses studied additional periods after patents for comparators expired (e.g., sertraline, sildenafil) (Table S1). Single-group analyses for drugs of interest compared prescription trends before and after removal of a black triangle. Multiple-group analyses evaluated effects of removal of a black triangle on prescribing levels and trends relative to contemporary comparators. Secondary and sensitivity analyses modeled additional and alternative time periods relative to the date of black triangle removal (Supplementary Methods).

For case-control studies we compared characteristics of paired groups of new users using logistic regression as implemented using generalized estimating equations (GEE) with an exchangeable correlation structure and robust standard errors to account for clustering by practice. Multivariable models incorporated person- and practice-level variables presumed to be associated with new use of labeled drugs or to confound the relationship between labeling

and age (see Independent Variables). Missing Townsend deprivation scores (<5% in most samples) were multiply imputed with 20 imputed datasets. To account for clustering from individuals who began multiple drugs in a single analysis, we performed sensitivity analyses including participants only once for their first drug. All models within each drug class included the same covariate set to directly compare coefficients and 95% confidence intervals (CIs) across models.

All hypothesis tests used a two-sided type I error rate of 0.05. Analyses were performed using Stata 12.1 and 14.1 (StataCorp).

Results

Population-wide impact of black triangle on prescribing

There were 797,077 eligible new users of SSRIs during the study period, of whom 76,285 (9.6%) individuals received new escitalopram prescriptions (Figure S2). Over the 3-year study period that escitalopram had a black triangle, GPs wrote a median of 312 new prescriptions (interquartile range [IQR] 288, 326) per million patients per month. Over three years after removal of the label, the median rate of new escitalopram prescriptions dropped to 126 (IQR 96, 183)/million/month. During the label period, rates of new prescriptions did not significantly change (-1.2 [95% CI $-2.8, 0.4$]/million/month) (Table 1). Following removal of the black triangle, rates of new prescribing declined modestly (-1.5 [95% CI $-1.9, -1.2$]/million/month). Compared with two longstanding SSRI comparators, citalopram and fluoxetine, trends of new escitalopram prescribing did not differ either before or after removal of the black triangle (Table 1, Figure 1A). However, the level of first-time prescribing of citalopram and fluoxetine increased relative to escitalopram after escitalopram's black triangle was removed. Compared with sertraline, GPs newly prescribed escitalopram to more patients each month before removal of the black triangle and to similar numbers in the months afterward the label's removal (Table 1, Figure 1B). Notably, when generic sertraline subsequently became available, rates of new prescribing of sertraline steadily increased while relative monthly prescribing of escitalopram declined further (-8.8 [95% CI $-9.5, -8.0$]/million/month).

There were 173,866 eligible new PDE5I users, of whom 75,224 (43.3%) received new prescriptions of tadalafil or vardenafil; 9,799 (5.6%) started both medications. When both tadalafil and vardenafil had black triangles in the study period, GPs prescribed them to a median of 460 new users (IQR 443, 500)/million/month. Over the same interval after the labels' removal, GPs wrote fewer new prescriptions (377 [IQR 351, 407]/million/month). Rates of new prescribing of labeled tadalafil and vardenafil were highest in the months after initial approval and declined in the years before removal of the label (-3.4 [95% CI $-5.5, -1.3$]) (Table 2). After removal of the black triangles, monthly rates of new prescribing of tadalafil and vardenafil did not change. Both before and after removal of their labels, trends in prescribing of tadalafil and vardenafil closely followed sildenafil's (Table 2, Figure 1C). After the label's removal, however, sildenafil was prescribed at slightly higher levels. When generic sildenafil became available, GPs prescribed sildenafil at high and increasing rates while new prescribing of tadalafil and vardenafil declined sharply (Figure 1D).

In secondary analyses, new prescribing declined more within two years after removal of black triangles than in subsequent years (Tables S2 and S3). In sensitivity analyses that assumed premature removal of labels or excluded six months after label removal, results were similar (Tables S4 and S5).

Characteristics of individuals prescribed drugs with and without a black triangle label

When we compared patients newly prescribed escitalopram before and after removal of the black triangle, individuals prescribed labeled escitalopram were less likely to be children or elderly or to have multiple comorbidities or recent hospitalization (Table 3, Table S6). There were similar differences across time periods among those newly prescribed citalopram and fluoxetine. In comparing contemporary new users of labeled escitalopram and unlabeled citalopram or fluoxetine, we found those starting escitalopram were less likely to be children, more likely to take multiple other medications, and more likely to have a previously diagnosed mood disorder and receive prior SSRIs. People who began labeled or unlabeled SSRIs did not significantly differ in number of comorbidities.

Compared with new users of tadalafil or vardenafil after removal of the black triangle, men prescribed labeled PDE5Is were less likely to be under age 40 or to have multiple comorbidities or recent hospital admission (Table 4, Table S7). Men who started taking labeled tadalafil or vardenafil were also more likely to have diabetes mellitus (related comorbidity) and cardiovascular disease (relative contraindication) than new users in the post-label era. As we found with SSRIs, there were similar differences between new users of sildenafil across the same eras, with overlapping confidence intervals for all variables (Table 4). Similar differences were also seen between new users of sildenafil before and after removal of its own black triangle, except that men who started labeled sildenafil were less likely to take multiple other medications or have previously diagnosed erectile dysfunction. When we compared individuals starting labeled tadalafil or vardenafil with those beginning unlabeled sildenafil in the same era, men who began labeled drugs were less likely to be under age 40 and take multiple medications, and more likely to have diabetes and prior erectile dysfunction. As with SSRIs, we saw no significant differences in comorbidity burden between men who began labeled or unlabeled PDE5Is.

In sensitivity analyses that included new users of multiple drugs only once, the findings did not substantially change (Figures S3 and S4).

Discussion

In contrast to our expectations, we found that newly approved drugs labeled with a black triangle were not prescribed at lower rates that increased over time. In fact, GPs prescribed new drugs from two drug classes at the highest levels shortly after their initial approval and at lower rates in subsequent years. The removal of a black triangle was not associated with an increased rate of prescribing but rather with no changes (PDE5Is) or declines (escitalopram) in the rates of new prescriptions. Furthermore, new generic availability of comparable drugs corresponded with more dramatic differences in prescribing than removal of black triangle labels. These findings suggest that market forces play a larger role in prescribing rates than black triangle labeling. When comparing characteristics of individuals

newly prescribed drugs over time, we expected to find numerous differences, depending on whether medicines had a change in labeling (i.e., removal of a black triangle) and on clinicians' familiarity with drug classes (i.e., well-established SSRIs versus newer PDE5Is). However, our findings were similar for drugs in these two disparate drug classes irrespective of the black triangle label. We did find some modest clinical differences between individuals starting older drugs and those starting recently approved drugs with a black triangle. Nonetheless, it remains unclear whether these differences in prescribing reflected drugs' relative "newness" or presence of a black triangle.

The black triangle has been used in the UK Yellow Card Scheme and subsequently in the EU to promote pharmacovigilance and ADE reporting for new medical products.⁴ Earlier studies showed that systematic implementation and notification of these schemes increased ADE reporting.^{17,18} However, subsequent studies suggested somewhat limited impact of a black triangle label on new drug monitoring. In surveys, only half to two-thirds of physicians recognized the black triangle as a label for new medications.^{19,20} Furthermore, general practitioners consistently underreported ADEs associated with black triangle medications, including up to 90% of minor events and one-quarter to one-half of serious events.^{5,6} One study identified several factors associated with lower rates of ADE reporting among GPs, including higher numbers of patients seen and prescriptions written.²¹ At one time, approximately one-quarter of drugs assigned with a black triangle label lacked the symbol in official product information.²²

The 21st Century Cures Act could lead to broad, accelerated drug approvals in the US based on less substantive levels of evidence of efficacy or safety.¹⁰ With such a shift in regulation and increasing reliance on real-world evidence, it would be increasingly critical for clinicians and the public to recognize which novel drugs were recently approved and had incomplete safety information. Even before the passage of this new legislation, we and others have advocated for the use of labeling schemes similar to the black triangle for newly approved medicines in the US.^{8,23} Such labeling for recently approved drugs in the US might not only raise awareness about the uncertainty of their safety but also promote more judicious prescribing channeled to patients with the greatest need and, thus, the highest benefit-risk ratio.⁸ Indeed, the IOM recommended use of a black triangle-like label to promote greater safety of new medications.⁹ Notably, the FDA declined this recommendation because of concerns that such a label could be confusing to and misinterpreted by prescribers and patients, and that adequate systems were already in place to communicate the "newness" of recently approved drugs and devices.²⁴ Our findings support the conclusion that a black triangle-type label may not substantially limit prescribing in practice. These results contrast with other studies showing that changes in drug labeling in *response* to new safety information can affect prescribing behavior.^{25,26} Other studies have also shown the relatively greater impact of market forces compared with drug regulation alone.²⁷

Our study has several strengths. We leveraged routinely collected population-representative healthcare data to evaluate the impact of a longstanding label for new drugs on utilization and prescribing. ITS analyses with unexposed comparators have strong internal validity by controlling for confounding and secular trends, making them particularly useful in studying

the impact of policies on drug utilization.^{28,29} Furthermore, the case-control studies permitted understanding of a black triangle's impact on prescribing at the individual level. Sensitivity analyses suggested that our findings were robust to various assumptions. Finally, this study is novel and has important implications for policy makers in the US, Europe, and elsewhere.

This study also has certain limitations. We focused on effects of black triangle labeling on drug prescribing from two classes first approved over a decade ago. Our findings may not apply to more recent approvals across the EU or to prescribing of other types of medication (e.g., chemotherapies, biologics, vaccines). Furthermore, because we found some minor clinical differences between people prescribed drugs with a black triangle and similar drugs without a black triangle, we cannot rule out the possibility that the label affects prescribing behaviors at least to some degree.

Labeling of newly approved drugs with a black triangle is not associated with more limited prescribing among general practitioners. Economics (e.g., drug marketing and cost) appears to have a larger impact on prescribing trends than a black triangle label. With the passage of the 21st Century Cures Act, accelerated drug approvals could lead to more uncertainty about the effectiveness and safety of new drugs in the future. However, labeling of newly approved medicines in the fashion of the black triangle is unlikely to promote more judicious prescribing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

1. The black triangle label for newly approved drugs does not appear to promote judicious prescribing.
2. Market forces have more impact on prescribing than the black triangle.
3. People who initiate black triangle drugs are different from new users of the same drugs after the label's removal, but these differences reflect secular trends.

Figure 1. Interrupted time-series analysis of new prescriptions for drugs with a black triangle and comparators

Monthly rates and trends of new prescriptions for drugs with a black triangle (blue)—escitalopram (A, B) and tadalafil or vardenafil (C, D)—and same-class comparators (purple)—fluoxetine or citalopram (A), sertraline (B), and sildenafil (D)—before and after removal of a black triangle (black vertical dashed line) and, where applicable, patent protection for comparators (purple vertical solid line)—sertraline (B) and sildenafil (D).

Table 1

Changes in prescription levels and rates of escitalopram over time and compared with other SSRIs

	Change in level (new prescriptions per 1 million individuals per month [95% CI])		Change in rate (new prescriptions per 1 million individuals per month [95% CI])	
	Before removal of escitalopram ▼	After removal of escitalopram ▼	Before removal of escitalopram ▼	After removal of escitalopram ▼
Single group analysis				
Escitalopram over time	–	–118 (–164, –72)	–1.2 (–2.8, 0.4)	–1.5 (–1.9, –1.2)
Multiple group analyses, escitalopram vs. comparators below				
vs. citalopram and fluoxetine	–324 (–372, –276)	–274 (–421, –126)	0.6 (–2.2, 3.5)	0.01 (–1.9, 2.0)
vs. sertraline	65 (28, 101)	–78 (–115, –41) [‡]	2.1 (0.3, 3.8)	–6.0 (–6.9, –5.1) [‡]

▼ black triangle; CI, confidence interval; SSRIs, selective serotonin reuptake inhibitors.

[‡] Before expiration of sertraline patent (see Figure 1). After sertraline became available in generic form, the change in rates of prescribing of escitalopram versus sertraline was –8.8 (–9.5, –8.0)/million/month.

Changes in prescription levels and rates of tadalafil and vardenafil over time and compared with sildenafil

Table 2

	Change in level (new prescriptions per 1 million individuals per month [95% CI])			Change in rate (new prescriptions per 1 million individuals per month [95% CI])		
	Before removal of tadalafil's and vardenafil's	After removal of tadalafil's and vardenafil's	After expiration of sildenafil's patent	Before removal of tadalafil's and vardenafil's	After removal of tadalafil's and vardenafil's	After expiration of sildenafil's patent
Single group analysis, tadalafil and vardenafil over time	–	–19 (–67, 30)	–38 (–63, –12)	–3.4 (–5.5, –1.3)	–0.1 (–0.6, 0.4)	–10.6 (–11.2, –10.0)
Multiple group analysis, tadalafil and vardenafil vs. sildenafil	8 (–36, 53)	–70 (–127, –14)	–265 (–376, –155)	–0.02 (–2.5, 2.5)	0.2 (–0.5, 0.9)	–14.4 (–22.3, –6.5)

black triangle; CI, confidence interval

Table 3

Multivariable models from case-control studies comparing new users of escitalopram and comparators before and after removal of escitalopram's black triangle

Variable	Adjusted odds ratio (95% confidence interval) [†]		
	esci during vs. after ▼	cita/fluoxetine during vs. after esci ▼	esci vs. cita/fluoxetine during esci ▼
Ages under 20	−0.27 (−0.43, −0.12)	−0.17 (−0.23, −0.10)	−0.29 (−0.40, −0.18)
Ages 20–39 (reference)	–	–	–
Ages 40–59	0.01 (−0.06, 0.07)	−0.00 (−0.03, 0.02)	0.03 (−0.02, 0.07)
Ages 60–79	−0.01 (−0.10, 0.09)	0.03 (−0.01, 0.07)	−0.02 (−0.09, 0.05)
Ages 80	−0.15 (−0.29, −0.01)	0.05 (−0.01, 0.11)	−0.07 (−0.18, 0.03)
Female sex	0.08 (0.02, 0.15)	0.02 (−0.00, 0.05)	0.01 (−0.04, 0.05)
0–1 medications [‡] (reference)	–	–	–
2–4 medications [‡]	−0.03 (−0.11, 0.04)	0.03 (−0.00, 0.06)	0.07 (0.02, 0.11)
5 medications [‡]	−0.05 (−0.14, 0.04)	0.02 (−0.02, 0.06)	0.09 (0.03, 0.15)
0–1 comorbidities (reference)	–	–	–
2 comorbidities	−0.10 (−0.17, −0.03)	−0.10 (−0.14, −0.07)	−0.02 (−0.07, 0.02)
3 comorbidities	−0.20 (−0.29, −0.11)	−0.27 (−0.31, −0.23)	−0.02 (−0.08, 0.04)
Recent hospitalization [‡]	−0.36 (−0.58, −0.13)	−0.26 (−0.39, −0.14)	−0.12 (−0.22, −0.01)
Prior use of SSRI	−0.06 (−0.14, 0.02)	0.04 (0.00, 0.07)	0.55 (0.49, 0.62)
Prior diagnosis of mood disorder	−0.06 (−0.15, 0.03)	−0.16 (−0.22, −0.10)	0.11 (0.06, 0.16)

▼ black triangle; cita, citalopram; esci, escitalopram; fluo, fluoxetine; SSRI, selective serotonin reuptake inhibitor.

[†] ORs were generated using generalized estimating equations with the same prespecified covariate set consisting of the variables shown, local measures of deprivation (Townsend scores), and the size and country of the general practice.

[‡] Measured 1–183 days before the respective case/control period.

Table 4

Multivariable models from case-control studies comparing new users of tadalafil, vardenafil, and sildenafil before and after removal of tadalafil's/vardenafil's black triangle

Variable	Adjusted odds ratio (95% confidence interval) [†]			
	tada/vard during vs. after ▼	sild during vs. after tada/vard ▼	sild during vs. after sild ▼	tada/vard vs. sild during tada/vard ▼
Ages 18–39	−0.15 (−0.27, −0.02)	0.01 (−0.10, 0.12)	−0.14 (−0.27, −0.01)	−0.25 (−0.36, −0.14)
Ages 40–59 (reference)	–	–	–	–
Ages 60–79	0.07 (−0.00, 0.14)	0.02 (−0.05, 0.09)	0.14 (0.07, 0.21)	0.10 (0.04, 0.17)
Ages 80	0.10 (−0.20, 0.40)	−0.09 (−0.35, 0.18)	−0.02 (−0.33, 0.29)	0.04 (−0.21, 0.30)
0–2 medications [‡] (reference)	–	–	–	–
3–5 medications [‡]	0.09 (0.01, 0.17)	−0.00 (−0.08, 0.07)	−0.10 (−0.19, −0.01)	0.20 (0.12, 0.28)
6 medications [‡]	0.06 (−0.04, 0.16)	−0.00 (−0.11, 0.10)	−0.25 (−0.36, −0.13)	0.34 (0.24, 0.44)
0–1 comorbidities (reference)	–	–	–	–
2 comorbidities	−0.10 (−0.19, −0.01)	−0.07 (−0.15, 0.01)	−0.09 (−0.18, 0.01)	−0.04 (−0.12, 0.04)
3 comorbidities	−0.30 (−0.39, −0.21)	−0.23 (−0.33, −0.14)	−0.20 (−0.31, −0.09)	−0.04 (−0.13, 0.05)
Recent hospitalization [‡]	−0.57 (−0.88, −0.25)	−0.39 (−0.63, −0.15)	−0.12 (−0.42, 0.17)	−0.15 (−0.39, 0.09)
Prior diabetes mellitus	0.14 (0.05, 0.23)	0.02 (−0.07, 0.11)	0.20 (0.11, 0.30)	0.25 (0.16, 0.34)
Prior cardiovascular disease	0.24 (0.14, 0.34)	0.11 (0.01, 0.20)	0.12 (−0.00, 0.25)	−0.05 (−0.14, 0.05)
Prior erectile dysfunction	−0.07 (−0.18, 0.04)	−0.03 (−0.13, 0.07)	−0.29 (−0.41, −0.18)	0.25 (0.15, 0.36)

▼ black triangle; sild, sildenafil; tada, tadalafil; vard, vardenafil.

[†] ORs were generated using generalized estimating equations with the same prespecified covariate set consisting of the variables shown, local measures of deprivation (Townsend scores), and the size and country of the general practice.

[‡] Measured 1–183 days before the respective case/control period.