CARDIOVASCULAR AND NEUROPSYCHIATRIC EVENTS FOLLOWING VARENICLINE USE FOR SMOKING CESSATION

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At a Glance Commentary (Word count: 136)

Varenicline has been shown to improve smoking cessation rates more effectively than bupropion, single forms of nicotine replacement, non-pharmacological methods, and placebo in randomized clinical trials but its evidence regarding its real world cardiovascular and neuropsychiatric safety has been inconsistent.

We found new varenicline users had a statistically significant 34% increased incidence of cardiovascular hospitalizations and emergency department visits while taking the medication. This finding was consistent in numerous subgroup and sensitivity analyses with different types of patients, different outcome definitions and different risk and control intervals. We also observed a 6% increase in the incidence of neuropsychiatric hospitalizations and emergency department visits of questionable robustness and clinical significance.

The risks of cardiovascular due to varenicline should be considered by patients and physicians when weighing the risks and benefits of its use.

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Dr. Gershon and Mr. Campitelli had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Abstract

Background

Varenicline aids in smoking cessation but has also been associated with serious adverse events. The aim of this study was to determine the risks of cardiovascular and neuropsychiatric events following varenicline receipt in a real-world setting.

Methods

A population-based, self-controlled risk interval study using linked universal health administrative data from the diverse, multicultural population of Ontario, Canada was conducted. In two separate analyses, new varenicline users between September 1, 2011 and February 15, 2014 were observed from one year before to one year after varenicline receipt. The relative incidences of cardiovascular and neuropsychiatric hospitalizations and emergency department visits in the 12 weeks following varenicline receipt (the risk interval) compared with the remaining observation period (the control interval) were estimated in two separate fixed-effect conditional Poisson regressions. Sensitivity analyses tested the robustness of the results.

Measurement and Main Results

Among 56,851 new users of varenicline, 6317 cardiovascular and 10,041 neuropsychiatric hospitalizations and emergency department visits occurred from one year before to one year after receipt. The incidence of cardiovascular events was 34% higher in the risk compared to the control interval (Relative Incidence [RI] 1·34; 95% CI 1·25-1·44). Findings were consistent in sensitivity analyses, most notably in those without any history of previous cardiovascular disease. The relative incidence of neuropsychiatric events was marginally significant in the primary (Relative Incidence 1·06; 95% CI 1·00-1·13) but not all sensitivity analyses.

Conclusions

Varenicline appears to be associated with an increased risk of cardiovascular but not neuropsychiatric events.

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Introduction

The health benefits of quitting smoking are numerous.[1] Varenicline (Chantix in the United States; Champix in Canada, Europe, and other countries) is a commonly used medication that has been shown to improve smoking cessation rates more effectively than bupropion, nicotine replacement, non-pharmacological methods, and placebo in randomized clinical trials (RCT).[2-5] Safety advisories, however, warn of its possible association with serious adverse cardiovascular and neuropsychiatric events.[6;7]

Meta-analyses of RCTs have examined the risk of cardiovascular events following varenicline use compared with placebo hypothesized to occur because of its action on the α4β2, α3β4 and α7 nicotine acetylcholine receptors.[8;9] Varenicline was associated with a significant increased risk of events (Odds Ratio [OR] 1·72; 95% confidence interval [95% CI] 1·09-2·71) in one conducted by Singh *et al.*,[6] non-significant increased risks in two conducted by Prochaska *et al*. (Relative Risk [RR] 1·40; 95% CI 0·82-2·39) and Mills *et al*. (RR 1·30; 95% CI 0·79-2·23) and no increased risk in one conducted by Sterling, *et al*. (RR 1·03, 95% CI 0·72 – 1·49),[9-11] all which used different trial inclusion criteria, summary statistics, and cardiovascular outcome definitions. Thus, lack of statistical power precludes a definitive conclusion about risk. In addition, many of the RCTs in the meta-analyses included patients who were mostly white and male and excluded those with a history of cardiovascular disease.[11] Therefore, their results are not generalizable to many real-world varenicline users.

With respect to neuropsychiatric adverse events, a large RCT and two meta-analyses of RCT failed to find a significant increased risk of varenicline over placebo.[5;7;12] A recent observational

study using within person analyses to reduce time invariant confounding found no association between varenicline and suicidal behavior (Hazard Ratio [HR] 1·00; 95% CI 0·72-1·37), but found a significant association with the incidence of new psychiatric diagnoses (HR 1·18; 95% CI 1·05-1·31).[13] Thus, it is possible but less likely that varenicline is associated with adverse neuropsychiatric events.

We conducted the current study to examine the risk of cardiovascular and neuropsychiatric adverse events after varenicline initiation in a real world setting. We used a self-controlled design to analyze post-marketing data from patients who received varenicline while minimizing potential confounding and maintaining power.

Methods

Study design

We used a self-controlled risk interval study design to assess the association between varenicline use and cardiovascular and neuropsychiatric outcomes. This design anchors patient observation time to the date of a given exposure (index date), and then examines the timing of events in relation to that exposure within a defined observation period.[14-16] Analyses are conditioned on exposed patients having an event at some point during the observation period.[14] Its main advantage over case-control and cohort studies is that it estimates within-subject relative incidence of events for exposed patients only. Hence, each patient serves as his or her own control, eliminating time-invariant confounding that can arise from comparing patients from different exposure groups.

Ethics approval was obtained from the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Canada.

Study setting and data sources

Ontario, Canada has a diverse, multicultural population (13·3 million persons as of 2011) and virtually all residents have access to universal, publicly-funded physician services and hospital care. We used the following population-based health administrative databases between September 1, 2010 and March 31, 2015. The Ontario Drug Benefit database, which has previously been validated and used extensively in research,[17-19] captures outpatient prescription medication claims for all residents covered under the provincial drug program, including seniors over the age of 65; those receiving social assistance and those in long-term care. The Canadian Institute for Health Information Discharge Abstract Database, the Ontario Mental Health Reporting System, and the Canadian Institute for Health Information National Ambulatory Care Reporting System contain detailed administrative, demographic, clinical, and diagnostic information for, respectively, all hospitalizations to regular beds, hospitalizations to designated psychiatric beds, and emergency department visits in Ontario. The Ontario Registered Persons Database contains basic demographic information including, as appropriate, date of death. The Ontario Health Insurance Plan physician claims database captures outpatient services provided by the majority of physicians within the province and shadow billing for those paid from alternative payment plans. We also used several validated disease algorithms to identify the presence of asthma, chronic obstructive pulmonary disease, diabetes, and hypertension.[20-23] These datasets were individually linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences.

Study population and exposure

The Ontario Drug Benefit program database was used to identify new users of varenicline between September 1, 2011 (the date varenicline became an eligible benefit) and February 15, 2014. The exposure was varenicline use and the date each patient filled their first prescription was their index date.

Cardiovascular and neuropsychiatric outcomes

The primary outcomes were cardiovascular and neuropsychiatric hospitalizations and emergency department visits. Cardiovascular events included acute myocardial infarction, unstable angina, other ischemic heart disease, ischemic stroke, heart failure, cardiac dysrhythmias, and peripheral vascular disease. Neuropsychiatric events included intentional self-harm, depressive or bipolar episodes, psychotic, anxiety, neurotic or stress-related disorders, insomnia, hallucinations, and signs/symptoms of hostility and/or agitation. Please see **Table 1** for list of diagnosis codes used to define the above conditions. To prevent double-counting of adverse events, we excluded hospital transfers and emergency department visits that led to hospitalization.

Statistical analysis

Risk of cardiovascular and neuropsychiatric adverse events were analyzed separately. Each patients' observation period was from one year before to one year after their index date (the date they received varenicline). This period was purposely kept short, and in sensitivity analyses truncated further to be focused only on pre- or post-exposure time, to minimize time varying confounding due to factors such as increasing age or body mass index which are associated with

increased cardiovascular events.[15] By design, analyses were restricted to varenicline users who had an outcome of interest at some point during the observation period.

The observation period was segmented into risk, induction, and control intervals. We defined the risk interval as the first 12 weeks following varenicline use since this is the standard varenicline treatment duration.[24] When using pre-exposure observation time, an assumption of the self-controlled risk interval design is that the occurrence of an outcome does not alter the probability of subsequent exposure.[25] Outcomes which smoking contributes to, like myocardial infarction, might increase motivation for someone to quit smoking and subsequently the probability they are started on varenicline. Therefore to avoid violating the assumption, we did not analyze events that occurred in the six weeks immediately preceding varenicline use, as they were not reflective of the actual baseline event rate of the study population. We designated this time period the induction interval. The control interval comprised all time in the observation period that was not in the other intervals. As mentioned, it did not include the induction period because events in this period would have artificially elevated the baseline risk. A fixed-effects conditional Poisson regression model was used to estimate the relative incidence of cardiovascular and neuropsychiatric adverse events, separately, in the risk interval compared with the control interval. To test the robustness of our findings, sensitivity analyses were conducted to determine the impact of having longer or shorter risk intervals (4 weeks to 16 weeks) or induction intervals (0 to 8 weeks).

Pre-specified subgroup analyses examined patients by age, sex, and previous history of an event. The latter were defined as acute-care hospitalizations or emergency department visits in the five years prior to the observation period.

As additional sensitivity analyses, we analyzed only hospitalizations, as they are usually more serious and likely more objective than emergency department visits.[26] We also analyzed only ischemic-related cardiovascular events, only heart failure events and only neuropsychiatric events with an intentional self-harm diagnosis. To assess if the competing risk of death or time varying confounding due to time of year were influencing our results, we repeated the analyses excluding those who had died during the observation period and adjusting for month, respectively.

To address the possibility that people who had events prior to the risk interval were at higher risk of a subsequent event because of that previous event and not due to varenicline use, we conducted four sensitivity analyses: first retaining only patients' first event during the study period (ie. no patient had more than one event); second examining just events that occurred after varenicline initiation so that the control period consisted of post exposure events only; third, stratifying this last analysis by a history of events prior to the index date; and fourth, excluding events that occurred within four months of a previous event.

The entire analysis was replicated using hospitalizations or emergency department visits for lower-body injuries, an outcome with no known association with varenicline (see **Table 1** for diagnosis codes).

We used the total number of initial varenicline users in the Ontario Drug Benefit database —the whole study population-- to consider attributable risks of adverse events. This was expressed as

the number of excess outcomes per 1,000 varenicline users that were attributable to varenicline during the 12 week risk interval.[27]

All statistical tests were two-tailed and we defined $p < 0{\cdot}05$ as the level of statistical significance. Analyses were performed using SAS Enterprise Guide, version 6·1 (SAS Institute Inc.).

Role of the funding source

The study sponsor did not play any role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Results

There were a total of 56,851 new users of varenicline between September 1, 2011 and February 15, 2014. Of those, 4,185 and 4,720 had one or more cardiovascular and neuropsychiatric adverse events, respectively, (**Tables 2 and 3**) for a total of 6,317 cardiovascular and 10,041 neuropsychiatric events during the observation period. The weekly distribution of these events from the start of the observation period can be seen in **Figures 1 and 2**. Of these, 748 (11·9%) and 581 (5·8%) cardiovascular and neuropsychiatric adverse events that were in the induction period, respectively, were removed from the control period.

The incidence of cardiovascular events was 34% higher in the risk compared to the control interval (Relative Incidence [RI] 1·34; 95% CI 1·25-1·44) (**Table 4**). This remained relatively

unchanged when longer or shorter risk intervals were used or when the induction interval was extended up to 8 weeks. The increased risk of cardiovascular adverse events was observed among those less than and older than 65 years (p= 0.002 for the interaction), males and females (p = 0.075 for the interaction), and among those with and without a history of cardiovascular events (p = 0.250 for the interaction). There were only small differences in the relative incidence, which remained significant, when only hospitalizations, when only ischemic-related events or only heart failure events were examined; when those who died during the observation period were excluded; and adjusting for month.

When just patients' first events during the study period were analyzed (ie. no patient had more than one event) and when only patients who did not have a cardiovascular event within four months of a previous cardiovascular event were analyzed, the RI did not notably change. When only events after varenicline initiation were considered (post-exposure as control only) and when this analysis was repeated in only those without a history of a cardiovascular event, the RI was lower but still significant. (**Table 4**)

The relative incidence of neuropsychiatric events was significantly increased (RI 1·06; 95% CI 1·00-1·13) in the risk compared to the control interval (**Table 5**). However, the significance was not robust in sensitivity analyses. Individuals aged 65 or older, who constituted 7·5% of all patients with a neuropsychiatric outcome during the observation period, had a significantly increased risk of neuropsychiatric events (RI 1·44; 95% CI 1·15-1·80), while younger patients did not (p=0.007 for the interaction). RI estimates were not significant when examining only hospitalizations or only intentional self-harm events and when those who died were excluded.

RI estimates did not vary notably in sensitivity analyses.

There was no significant association between varenicline use and lower-body injuries (RI 0·95; 95% CI 0·87-1·03).

We estimated that 3·95 cardiovascular adverse events (95% CI 3·12-4·76) per 1,000 varenicline users were attributable to varenicline during the 12 week risk interval.

Discussion

We conducted an observational, self-controlled analysis of new varenicline users and observed a 34% increased incidence of cardiovascular hospitalizations and emergency department visits in all people prescribed varenicline, and a 12% increased incidence in patients without a history of a cardiovascular event within the 12 weeks following initiation. Thus, the true cardiovascular risk of varenicline likely lies between these two estimates. We also observed a small 6% increase in the incidence of neuropsychiatric hospitalizations and emergency department visits that was not robust to sensitivity analyses. These results can be used by patients and physicians when weighing the risks and benefits of varenicline use. This increased risk is not likely due to other smoking cessation agents nor smoking cessation itself.[10]

We conducted several sensitivity analyses to test if a peak in cardiovascular events that occurred prior to varenicline initiation contributed to events not related to varenicline use in the risk period, and biased the results. However, results were consistent when we examined only patients' first events, considered post-exposure as control time and performed other such

analyses. Of note, risk of a cardiovascular events was no greater in those with compared to those without a cardiovascular history.

Self-controlled risk interval study designs can be limited because the incident risk ratio does not consider those who do not have an outcome; however, we were able to estimate that 3·95 cardiovascular adverse events (95% CI 3·12-4·76) per 1,000 varenicline users were attributable to varenicline during the 12 week risk interval using previously described methods. This is a value that physicians can quote to their patients.[27]

There is conflicting evidence on the cardiovascular risk of varenicline from different meta-analyses of RCTs. The magnitude of our findings are consistent with those of Prochaska *et al.* and Mills *et al.*, except that our results reached statistical significance, likely because we captured more events from more varenicline users. Our study further extends these previous studies by evaluating varenicline safety in a likely older and frailer real-world population with a higher baseline cardiovascular event rate. Our risk estimate is lower in magnitude and measured with a greater amount of precision than that observed by Singh *et al.*, however, those results have been questioned due to several methodological issues.[11] Our study is not consistent with the results of the meta-analysis by Sterling, *et al.*, however, that study had a very low event rate with 14 of the 38 included studies reporting no cardiovascular events—suggesting again that our real world study population was likely older and frailer in comparison.[9] Our study is also not consistent with a retrospective cohort study by Kotz, *et al.*, which found reduced associations of various cardiovascular events with significant hazard ratios ranging from 0·58 to 0·95.[8] However, this study associated varenicline with greater reductions in cardiovascular outcomes

than targeted cardiovascular medications, suggesting that unmeasured confounding may have played a role.

Patients and physicians should consider the potential cardiovascular risks of varenicline in context with its potential benefits. Varenicline has been shown to increase the odds of quitting smoking by almost 3 times and quitting smoking significantly reduces the risk of having a cardiovascular event—especially among those with a history of cardiovascular disease.[28;29]

With respect to neuropsychiatric outcomes, the small increased relative incidence we observed was not robust to sensitivity analyses and of questionable clinical significance. Thus, it is consistent with previous studies that did not find varenicline to be associated with neuropsychiatric events.[5;7;12]

We found a significantly increased risk of neuropsychiatric adverse events among those 65 years or older--of which 83% were for mood or anxiety disorders (data not shown). This finding might be due to older people being more sensitive to varenicline's effects. Alternatively, it could be due to those over 65 being more representative of the general population than those under 65 years, who were only eligible for varenicline coverage if they had characteristics associated with higher rates of baseline psychiatric disease that could have led to a relative incremental neuropsychiatric impact being missed. More research on the real-world association of varenicline with neuropsychiatric outcomes in older populations would be of value.

There are limitations of our study that merit emphasis. First, our prescription database can

indicate that a medication was dispensed, but not when it was taken or that it was taken or taken as prescribed. However, any non-adherence would have biased our risk estimates towards the null. Second, we relied on international classification of disease diagnosis codes (ICD) from hospital and emergency department records to ascertain events and, while ICD coding for cardiovascular conditions such as acute myocardial infarction,[30] ischemic stroke,[31] and congestive heart failure,[32] has been shown to have reasonable validity, the accuracy of neuropsychiatric coding is less certain. Our neuropsychiatric codes, however, were similar to those used in previous studies.[13;33] Third, we did not have information about individual smoking habits. Success in quitting smoking could have theoretically led to a lower cardiovascular event rate in the post-exposure control interval, making the event rate in the risk interval appear relatively high. However, given low cessation rates—even with smoking cessation therapy—and their impact, this would not likely have accounted for results observed.[3;34] This is evident by the fact that repeating the analysis using the post-exposure observation time for the control interval still produced notable results. Also, when we repeated the analysis omitting post exposure time (using only pre-exposure observation time for our control interval), we obtained results similar to our primary analysis. Fourth, nicotine withdrawal could have contributed to neuropsychiatric events that were mis-attributed to varenicline, although it seems that their severity (leading to emergency department visit or hospitalization) is more than would normally be expected. Fifth, we did not have information on other smoking medications, such as nicotine replacement therapy, however, as none of these have been found to be associated with an increased risk of cardiovascular events, they are unlikely to have confounded the results. Sixth, time dependent changes in variables that we could not measure could have contributed to outcomes, but this was likely minimal due to the short observation period, the control period including time before and

after the risk period and consistent results in sensitivity analyses that considered post-exposure time and that adjusted for seasonality. Seventh, we cannot be sure of causality using an observational study design. Eighth, increased awareness of neuropsychiatric adverse events due to Food and Drug Administration warnings during the time of this study may have led physicians and patients to increase monitoring for these complications thus preventing them from progressing to adverse events.[35] This might mean our findings are only generalizable to people who receive such monitoring and the risk of varenicline is greater in those who do not.

Conclusions

Using self-controlled analyses, we assessed the safety of real world varenicline use in a large population while minimizing confounding. Varenicline use was associated with a significant increased risk of cardiovascular adverse events--even in people with no cardiovascular disease history--and no clear increase in neuropsychiatric adverse events. These results can be used by patients and physicians when weighing the risks and benefits of varenicline use.

Declaration of interests

All authors report no conflict of interests.

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Figure Titles and Legends

Figure 1. Weekly distribution of cardiovascular events before and after initiation of varenicline.

Caption: The bar graph depicts the distribution in the number of cardiovascular events per week each week from one year prior to one year after the date of varenicline initiation. The relative incidences of events and their 95% confidence intervals were determined by comparing the risk interval with the control intervals

Figure 2. Weekly distribution of neuropsychiatric events before and after initiation of varenicline.

Caption: The bar graph depicts the distribution in the number of neuropsychiatric events per week each week from one year prior to one year after the date of varenicline initiation. The relative incidences of events and their 95% confidence intervals were determined by comparing the risk interval with the control intervals

Tables

Table 1. List of diagnosis codes used to define cardiovascular events, neuropsychiatric events and lower body injuries.

Outcome	International Classification of Diseases, 10th revision (ICD-10)	Diagnostic and Statistical Manual of Mental Disorders, 4th revision (DSM-IV)
Cardiovascular events		not applicable
Acute myocardial infarction	I21, I22, I25.2	not applicable
Unstable Angina	I20.0	not applicable
Other ischemic heart diseases	I20.1-I20.9, I24.0, I24.8 I24.9, I25 (excluding I25.2), I70.0	not applicable
Ischemic stroke	I63, I64, G45 (excluding G45.4)	not applicable
Heart failure	I11.0, I13.0, I13.2, I50, J81	not applicable
Cardiac dysrhythmias	I45.6-I459, I46.0 I46.9, I47, I48, I49	not applicable
Peripheral vascular disease	I65, I70 (excluding I70.0), I73.9, I74.2-I74.9, K55.0, K55.1	not applicable
Neuropsychiatric events		
Intentional self-harm	X60-X84	not applicable*
Depressive or bipolar episodes	F30-F39	296, 311, 300.4, 301.13, 293.83
Psychotic, anxiety, neurotic, or stress-related disorders	F20-F29, F40-F49	295, 301.22, 297.1, 298.8, 292.11, 291.5, 297.3, 293.81, 293.82, 298.9, 300 (excluding 3004), 308.3, 3098
Insomnia	F51	307.4
Hallucinations	R44	not applicable
Signs/symptoms of hostility and/or agitation	R45	not applicable
Lower-body Injuries		
Injury to the hip and thigh	S70-S79	not applicable
Injury to the knee and lower leg	S80-S89	not applicable
Injury to the ankle and foot	S90-S99	not applicable

*In the Ontario Mental Health Reporting System (OMHRS), which captures all Ontario hospitalizations occurring to designated psychiatric beds, intentional self-harm events are captured in separate, specific data fields that do not use DSM-IV codes.

Table 2. Characteristics of new varenicline users who had a cardiovascular event during the observation period

Characteristic	Varenicline users with an cardiovascular event during the observation period
Total number	4185
Number of cardiovascular events during observation period	6317
Number who died in the year following varenicline use, n (%)	401 (9.6)
Demographic characteristics	
Age (years), mean ± SD	61.6 ± 10.8
Age group, n (%)	
<65 years	2489 (59.5)
≥65 years	1696 (40.5)
Sex, n (%)	
Male	2544 (60.8)
Female	1641 (39.2)
Neighbourhood income quintile, n (%)	
1 (lowest income)	1572 (37.6)
2	945 (22.7)
3	694 (16.7)
4	565 (13.6)
5 (highest income)	409 (9.8)
Rural residence, n (%)	808 (19.3)
Comorbidities, n (%)	
History of cardiovascular disease	
History	1306 (31.2)
No history	2879 (68.8)
Diabetes	1610 (38.5)
Hypertension	2968 (70.9)
Asthma	1037 (24.8)
Chronic obstructive pulmonary disease (COPD)	2645 (63.2)
Health Services Use	
Number of primary care visits in year prior to index date, mean ± SD	8.2 ± 8.1
Documented primary care smoking cessation counselling in year prior to index date, n (%)	1094 (26.1)
Cardiologist visit in year prior to index date, n (%)	2468 (59.0)

Table 3. Characteristics of new varenicline users who had a neuropsychiatric event during the observation period

Characteristic[a]	Varenicline users with an neuropsychiatric event during the observation period
Total number	4720
Number of neuropsychiatric events during observation period	10041
Number who died in the year following varenicline use, n (%)	131 (2.8)
Demographic characteristics	
Age (years), mean ± SD	44.5 ± 14.0
Age group, n (%)	
<65 years	4368 (92.5)
≥65 years	352 (7.5)
Sex, n (%)	
Male	2227 (47.2)
Female	2493 (52.8)
Neighbourhood income quintile, n (%)	
1 (lowest income)	2073 (43.9)
2	1095 (23.3)
3	681 (14.5)
4	507 (10.8)
5 (highest income)	364 (7.8)
Rural residence, n (%)	686 (14.5)
Comorbidities, n (%)	
History of neuropsychiatric event	
History	2489 (52.7)
No history	2231 (47.3)
Diabetes	946 (20.0)
Hypertension	1419 (30.1)
Asthma	1610 (34.1)
Chronic obstructive pulmonary disease (COPD)	1689 (35.8)
Health Services Use	
Number of primary care visits in year prior to index date, mean ± SD	9.7 ± 10.5
Documented primary care smoking cessation counselling in year prior to index date, n (%)	1143 (24.2)
Psychiatrist visit in year prior to index date, n (%)	2273 (48.2)

Table 4. Relative incidence of cardiovascular events following varenicline initiation

Analysis	Relative Incidence of cardiovascular events (95% confidence interval)	*P*-value
Primary analysis (risk interval was 12 weeks following varenicline initiation; induction interval was 6 weeks preceding varenicline initiation)	1.34 (1.25-1.44)	<0.001
Varying risk intervals		
4 weeks following varenicline initiation	1.30 (1.15-1.46)	<0.001
8 weeks following varenicline initiation	1.42 (1.31-1.55)	<0.001
16 weeks following varenicline initiation	1.30 (1.22-1.39)	<0.001
Varying induction intervals		
1 weeks preceding varenicline initiation	1.27 (1.19-1.37)	<0.001
2 weeks preceding varenicline initiation	1.30 (1.21-1.40)	<0.001
4 weeks preceding varenicline initiation	1.33 (1.24-1.43)	<0.001
8 weeks preceding varenicline initiation	1.36 (1.27-1.46)	<0.001
No induction interval	1.24 (1.15-1.33)	<0.001
Varying control intervals +/- history of cardiovascular disease		
Pre-exposure only	1.54 (1.43-1.67)	<0.001
Post-exposure only	1.17 (1.08-1.26)	<0.001
Post-exposure only, history of cardiovascular event prior to exposure	1.22 (1.09-1.36)	<0.001
Post-exposure only, no history of cardiovascular event prior to exposure	1.12 (1.01-1.25)	0.033
Subgroup analyses		
Age <65 years[a]	1.22 (1.10-1.34)	<0.001
Age ≥65 years[a]	1.53 (1.38-1.70)	<0.001
Male[b]	1.28 (1.16-1.40)	<0.001
Female[b]	1.46 (1.30-1.63)	<0.001
History of event prior to observation window[c]	1.27 (1.13-1.43)	<0.001
No history of event prior to observation window[c]	1.39 (1.27-1.52)	<0.001
Sensitivity analyses		
Only hospitalization events	1.36 (1.25-1.48)	<0.001
Only ischemic-related cardiovascular events	1.35 (1.21-1.51)	<0.001
Only heart failure cardiovascular events	1.31 (1.13-1.51)	<0.001
Excluding those who died in the observation period	1.27 (1.17-1.37)	<0.001
Only considering patients' first event	1.27 (1.16-1.40)	<0.001
Including only patients who did not have a cardiovascular event within four months of a previous cardiovascular event	1.26 (1.16-1.38)	<0.001
Primary analysis with adjustment for calendar month	1.34 (1.24-1.44)	<0.001

[a] p = 0.002 for the interaction
[b] p = 0.075 for the interaction
[c] p = 0.250 for the interaction

Table 5. Relative incidence of neuropsychiatric events following varenicline initiation

Type of Analysis	Relative Incidence of neuropsychiatric events (95% confidence interval)	*P*-value
Primary analysis (risk interval was 12 weeks following varenicline initiation; induction interval was 6 weeks preceding varenicline initiation)	1.06 (1.00-1.13)	0.042
Varying different risk intervals		
4 weeks following varenicline initiation	1.04 (0.95-1.15)	0.389
8 weeks following varenicline initiation	1.05 (0.98-1.13)	0.163
16 weeks following varenicline initiation	1.06 (1.01-1.12)	0.025
Varying different induction intervals		
1 weeks preceding varenicline initiation	1.06 (1.00-1.13)	0.045
2 weeks preceding varenicline initiation	1.06 (1.00-1.13)	0.047
4 weeks preceding varenicline initiation	1.06 (1.00-1.13)	0.046
8 weeks preceding varenicline initiation	1.06 (1.00-1.12)	0.050
No induction interval	1.06 (1.00-1.13)	0.045
Observation time in control interval		
Pre-exposure only	1.07 (1.01-1.14)	0.029
Post-exposure only	1.05 (0.99-1.12)	0.108
Post-exposure only, history of neuropsychiatric event prior to exposure	1.08 (1.00-1.17)	0.045
Post-exposure only, no history of neuropsychiatric event prior to exposure	1.00 (0.88-1.12)	0.913
Subgroup analyses		
Age <65 years[a]	1.04 (0.98-1.11)	0.192
Age ≥65 years[a]	1.44 (1.15-1.80)	0.002
Male[b]	1.06 (0.97-1.16)	0.177
Female[b]	1.07 (0.98-1.16)	0.128
History of event prior to observation window[c]	1.03 (0.95-1.10)	0.511
No history of event prior to observation window[c]	1.14 (1.03-1.27)	0.010
Sensitivity analyses		
Only hospitalization events analyzed	1.06 (0.96-1.17)	0.280
Only intentional self-harm neuropsychiatric events analyzed	1.05 (0.91-1.20)	0.525
Excluding those who died in the observation period	1.05 (0.99-1.12)	0.086
Only considering patients' first event	0.98 (0.90-1.07)	0.649
Including only patients who did not have a cardiovascular event within four months of a previous cardiovascular event	1.04 (0.96-1.12)	0.336
Primary analysis with adjustment for calendar month	1.07 (1.00-1.13)	0.037

[a] p = 0.007 for the interaction
[b] p = 0.923 for the interaction
[c] p = 0.081 for the interaction