Effect of Antidepressant on Coronary Artery Disease in Patients with Posttraumatic Stress Disorder: Results from Korean National Health Insurance Database

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ABSTRACT

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Introduction

There had been several studies which had tried to assess the association between antidepressant medication and cardiovascular disease (CVD), but the direction and the magnitude of association suggested in previous literature are inconsistent and

inconclusive. In PTSD, which is a result of neurobiological and psychological reaction to traumatic events, there is a paucity of evidence to understand the association between antidepressants and CVD, and existing evidence conflict with each other. Diversity in prescription patterns of antidepressants further complicates the analysis, rendering it difficult to assess the cardiovascular effect. As a result, only limited and conflicting evidence on CVD effect of antidepressants in PTSD exist and the association is not well understood. The objective of this study is to analyze the prescription patterns of antidepressants in Korean PTSD patients and assess the cardiovascular effect of antidepressant in PTSD.

Methods

This study utilized Korean National Health Insurance Database (NHID), which is a nationally representative database constructed by Korean National Health Insurance Service (NHIS) that consists of administrative data for medical service utilization in South Korea. A total of 74,168 adult patients diagnosed with PTSD in 2004 – 2018 were identified from NHID. Participants were excluded from the final analysis if information on insurance eligibility was missing (N = 5), received antidepressant medication prior to PTSD diagnosis (N = 20,977), diagnosed with coronary artery disease prior to PTSD diagnosis (N = 1,719), or followed up for less than a month (N = 949), leaving 50,518 participants for final analyses.

Insurance claim records for antidepressant medication were obtained from the database. Antidepressant medications were classified into 4 types in accordance with active ingredient codes: selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressant (TCA) and other antidepressant medication. Participants were categorized into 'no antidepressant, 'single class', and 'multiple classes' groups by number of antidepressant class they had been prescribed during the follow-up. Information on antidepressant prescription patterns including duration of prescription, medication possession ratio (MPR), and combination of antidepressant classes were collected from the database. Coronary artery disease (CAD) with revascularization was selected as an outcome variable. Age, sex, insurance premium, Charlson comorbidity index, history of hypertension, history of dyslipidemia, psychiatric comorbidities, and admission due to psychiatric disorders were selected as covariates.

Descriptive analysis by prescription group was conducted to evaluate the characteristics of participants by prescription pattern. Marginal structural model (MSM) was constructed to control confounding by indication due to psychiatric comorbidities, medical comorbidities, and socioeconomic status. Hazard ratios were estimated from MSM with application of time-dependent inverse probability weights. Results from MSM were compared to those from conventional time-dependent Cox regression. Dose-response analysis was conducted to estimate the

effect of prescription duration and MPR. For sensitivity analyses, lag-time analysis with lag time of 6 and 12 months was conducted to assess the effect of protopathic bias. Additionally, to test the possible bias by violation of positivity assumption, sensitivity analysis by progressive truncation of the stabilized IP weights was conducted: 1 – 99%, 5 – 95%, and 10 – 90%. The analysis was repeated on subpopulation who received health checkup to assess the confounding effects of lifestyle factors and biomedical indicators. Finally, bounding factors were estimated in accordance with the theory of Ding & Vanderweele to assume the potential impact of unmeasured confounders on the estimand.

Results

The number of participants in 'no antidepressant', 'single class', and 'multiple classes' were 21,340 (42.24%), 15,970 (31.61%), and 13,208 (26.15%) respectively. Mean age of participants at the initial PTSD diagnosis was 43.13 years (standard deviation [SD] = 15.46 years), and mean duration of follow-up was 6.86 years (SD = 4.26 years). Most prescribed antidepressant class was SSRI, followed by other antidepressants, TCA, and SNRI. Mean duration of prescription among treated was 23.89 months (SD = 39.30 months), and mean MPR among treated was 28.39%. (SD = 39.38%)

Participants ever prescribed with antidepressants had 1.31 times higher hazard of developing CAD with revascularization compared to those who were not. (95% confidence interval [CI] 1.18 – 1.46) Participants who received single class of antidepressants had 1.18 times higher hazard of CAD, (95% CI 1.04 – 1.33), while the hazard ratio of those who received multiple classes of antidepressants was 1.46. (95% CI 1.29 – 1.65) Dose-response between number of antidepressant classes and risk of CAD was detected, with the hazard ratio being the highest in '4 classes' subgroup. (HR = 1.97, 95% CI 1.40 – 2.76) Exposure to SSRI, SNRI, and other antidepressants increased the risk of CAD, while SNRI was not associated with CAD.

Patients with longer duration of antidepressant exposure had higher risk of incident CAD: the hazard ratio for developing CAD with revascularization increased along with the prescription duration, with HR of '6 months or shorter' group being 1.27 (95% CI 1.08 – 1.48) and HR of '24 months or longer' group being 1.64 (95% CI 1.42 – 1.91). Polynomial spline also showed dose-response pattern in duration – CAD association. Duration of SSRI, TCA, and other antidepressants was positively associated with CAD, while duration of SNRI did not show significant dose-response pattern. In comparison, dose-response pattern in MPR-CAD relationship was nonlinear, with HR of 'lower than 20%' group being 1.39 (1.21 – 1.60) and '80% or higher' group being 1.22. (95% CI 0.93 – 1.60)

Results from polynomial spline were also concurrent with stratified analysis, showing nonlinear dose-response pattern between MPR and CAD.

Results from lag-time analysis was not significantly different from those from main analysis, indicating that the possible protopathic bias has minute effect on the estimate. IP weight truncation did not significantly alter the estimated values, suggesting that the impact of possible bias by violation of positivity assumption is likely to be minimal. Results from subgroup analysis on those who received health checkup were mostly consistent with those from main analysis, suggesting that the confounding effects of biomedical indicators and lifestyle factors do not significantly alter the estimand. Estimated bounding factors suggest low probability of complete nullification by unmeasured confounding, indicating that the interpretation of the estimand is unlikely to be altered by residual confounding.

Conclusion

Positive association between antidepressant medication for PTSD and CAD was detected. The association was stronger in participants who received multiple classes of antidepressants and who were prescribed with antidepressants for longer period. Combination of TCAs and SSRIs increased the risk of CAD the most, while SNRI did not increase the risk of CAD. The results indicate that antidepressants for PTSD treatment increase CAD risk and suggests necessity of proper cardiovascular risk

assessment before administration of antidepressant medication. PTSD patients who receive antidepressants for an extended period should be carefully monitored to prevent major cardiovascular events, as CVD risk is higher is those with long exposure to antidepressants. Especially, for PTSD patients receiving both TCAs and SSRIs simultaneously, preventive measures against coronary artery disease such as therapeutic drug monitoring or medication switching could be considered.

Keywords: Post-Traumatic Stress Disorder (PTSD), Antidepressive Agents, Cardiovascular Disease, Coronary Artery Disease (CAD).

I. INTRODUCTION

1. Background

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that develops when individuals are exposed to traumatic events.[1,2] PTSD is a relatively common disorder with approximately 4-8% of estimated lifetime prevalence.[3-5] In Korea, estimated lifetime prevalence of PTSD ranged from 1.2 to 1.6%,[6,7] but the clinical importance of PTSD in Korea is gradually increasing, as the prevalence of PTSD has rapidly increased over the past 10 years.[7,8]

PTSD is a disorder that is a result of complex neurobiological reaction after exposure to traumatic events, including alterations in neurotransmitters such as serotonin,[9,10] gamma-aminobutyric acid[11,12], and norepinephrine,[13] dysregulations of hypothalamic–pituitary–adrenal (HPA) axis,[14,15] increased sympathetic tones,[16,17] and consequent inflammatory reaction.[17,18] The inflammatory and endocrine alterations in patients with PTSD is mainly driven by the re-experiencing symptom cluster of PTSD[17] and consequential neuronal alteration,[18] including increased activation of amygdala[19-21] and reduced volume of hippocampus.[22,23] Higher resolution imaging techniques have shown that reduction in *cornu ammonis 3* and dentate gyrus of hippocampus are associated with PTSD symptoms.[24]

From these neurobiological changes comes physical consequences and comorbidities. A large body of literature suggested that patients with PTSD have higher risk of developing cardiovascular disease (CVD) including coronary artery disease,[25,26] stroke, [27,28] and mortality due to cardiovascular diseases.[26,29] Although the specific mechanism is yet to be understood, it had been hypothesized that increased inflammatory activity[30,31] and alteration of HPA axis[32,33] increase the risk of CVD in patients with PTSD.

Patients with PTSD also suffer from psychiatric comorbidities, including mood disorder, [34,35] anxiety disorder,[36,37] and somatoform disorder, [38,39] and such comorbid psychiatric symptoms and disorders are also risk factors of CVD.[40,41] Mood disorders, for instance, which is one of the most common psychiatric comorbidities in PTSD, induces excessive sympathetic and/or diminished parasympathetic modulation and inflammatory reactions via inflammatory cytokines.[34,35] Anxiety disorder, which share a large portion of pathophysiology with PTSD, is also well known to be linked with CVD via both behavioral and physiologic changes, such as endothelial dysfunction[a11] and autonomic dysfunction.[36,37]

There are several treatment options for PTSD that can alleviate symptoms and prevent progression, including antidepressant medications[42] and several types of psychotherapeutic treatments.[43,44] Antidepressant medications such as selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRIs) and tricyclic antidepressant (TCA) are recommended as first-line

pharmacologic agents for PTSD and major depressive disorder (MDD),[45,46] but some studies have suggested that pharmacological agents have limited efficacy in establishing remission for both PTSD and depression in certain individuals.[47] For instance, results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D), which one of the largest and longest clinical trial for treatment of MDD, showed that remission rate from MDD after treatment with a first-line antidepressant medication was only 36.8%.[48]

As PTSD symptoms is associated with alteration in neurobiological and endocrine system, effects of antidepressant medication and psychotherapeutic treatment on CVD had been rigorously researched. However, pre-existing evidence on association between antidepressant medication and CVD is inconclusive: while some researchers had implied that antidepressant medication increases CVD risk,[49-52] there are several studies that had failed to detect any association between antidepressant medication and CVD[53,54] or had detected protective effect of antidepressant medications on CVD.[55,56] As such, current evidence is insufficient to provide any conclusive interpretation on how antidepressant medication affects CVD. This is due to difficulties in estimating cardiovascular effect of antidepressant medication. The mixed pattern of association between antidepressant medication and CVD also appears to individuals with PTSD: a recent analysis using data from 143,323 female veterans in the U.S. showed that selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are

associated with greater risk of ischemic heart disease. In contrast, in a study of 1,079 U.S. veterans, antidepressant use was not associated with incident CVD.[57] As it is, current evidence is insufficient for drawing out definitive conclusions for antidepressant-CVD associations in PTSD.

2. Study Objectives

The objective of this study is to understand the pattern of antidepressant medication prescription in individuals with PTSD, including antidepressant class, combination of medications, duration of prescription, and medication possession ratio (MPR). Additionally, this study aimed to assess the cardiovascular effects of patterns of antidepressant medication prescription in individuals with PTSD. Overall cardiovascular effects of antidepressant medication, as well as cardiovascular effect by medication type, will be evaluated in this study.

II. Theoretical background

1. Association between PTSD and Cardiovascular Disease

Post-traumatic stress disorder is a psychiatric disorder that is characterized by persistent maladaptive reactions after being exposed to psychological trauma.[33] After being exposed to severe psychological trauma such as natural disaster,[58] military conflict,[59] and assault,[60] some individuals are influenced by disruption in neural circuits such as activation in the bilateral amygdala and thalamus[61] and decrease in hippocampal volume,[62] as well as alteration in neuroendocrine reaction such as hypothalamus-pituitary-adrenal (HPA) axis[63,64] and sympathetic-adrenal-medullary (SAM) system.[17,64] This neurobiological alteration results in characteristic symptoms of PTSD such as hyperarousal, [65] re-experiencing[66,67] and avoidance.[68] People with PTSD also suffers from increased inflammatory cytokines[18] and dysregulation of metabolism, which results in metabolic disorders such as metabolic syndrome[69,70] and dyslipidemia.[71,72]

These alterations in metabolism and endocrine system, which are one of the probable mechanisms of symptom development in PTSD, also increase the risk of metabolic disruption and consequent cardiovascular disease development in individuals with PTSD. For instance, inflammatory cytokines such as interleukin-6, interleukin-1b, and tumor necrosis factor α (TNF- α), play major role in

atherosclerotic changes of artery.[73] Elevation of serum inflammatory cytokine level such as IL-1β,[74,75] IL-6,[76,77] interferon-γ (IFN- γ),[78] and TNF- α,[76] had been reported from several studies worldwide, and it is hypothesized that inflammatory reactions could attribute to increased CVD risk in PTSD.[79]

Endocrinological alteration is also a potential cause of CVD in PTSD. There had been constant reports of alterations in HPA axis and disrupted cortisol regulation,[63,64] which could be attributed to stress response in PTSD.[80] There had been several reports on increased sensitivity of glucocorticoid receptors and enhanced negative feedback of the HPA axis in PTSD, [81] but the inconsistency in the results exist.[82,83] As a result, individuals with PTSD and suffer from higher risk of cardiovascular diseases such as coronary heart disease[84] and stroke.[85,86] Although precise mechanism of cardiovascular comorbidity in PTSD is yet to be understood, it is postulated that biological reactions suggested above contributes to cardiovascular consequences in patients with PTSD.[81]

Another aspect that needs attention is common psychiatric symptoms and comorbidities of PTSD. Individuals with PTSD suffer from several comorbidities including depressive disorder,[87,88] anxiety-related disorders[89,90] and bipolar disorder.[91,92] PTSD and depressive disorder share similar symptoms including sleep disturbances, involvement in everyday activities, and difficulties in concentration.[93] It also shares certain pathophysiology of PTSD, including dysregulation in sympathetic tones,[94-96] platelet aggregation,[97,98] and increase in inflammatory

cytokines,[99-101] which are all related to increased CVD risk. However, the overlapping symptoms does not fully explain the comorbidity: research suggested a number of shared psychiatric pathophysiology between PTSD and depressive disorders, such as maladaptive cognitive alteration[102] and shared genetic influence for serotonin transporter polymorphism[103] are important explanatory factors of comorbidity.

Anxiety disorder is one of the most closely related psychiatric disorders to PTSD, and is also well known to be linked with CVD via both behavioral changes, such as smoking and decreased physical activity,[104-105] and physiologic changes, such as endothelial dysfunction[106] and autonomic dysfunction.[107,108] Research into the psychopathology of stress-related disorders revealed several genetic factors that are thought to be the common factor of anxiety disorders and PTSD.[134]

Traumatic events are also strongly associated with psychiatric symptom constructs that are associated with psychotic disorders[110] and somatoform disorder,[111] which are suggested to be associated with increased risk of CVD.[112-114] The existence of psychiatric comorbidities and their interaction with neurobiological system further complicates the link between PTSD and CVD.

2. Antidepressant Medications in PTSD

It is well known that antidepressants are effective in controlling psychiatric symptoms in PTSD. Current treatment guideline for PTSD highlights the importance of both psychotherapeutic treatment and antidepressant medication.[115] A meta-analysis showed that SSRIs and SNRIs are efficient for treating patients with severe symptoms.[116] A systematic review on 28 studies concluded that antidepressant discontinuation was associated with higher risk of relapse in anxiety-related disorders, including PTSD.[117]

There are several regimens that are being used for PTSD treatment, but SSRIs are considered to be the first-line treatment.[118,119] SSRIs increase serotonin levels in the brain by inhibiting reuptake of serotonin from the synapse, which is a neurotransmitter that is closely tied with anxiety.[120-122] Sertraline, paroxetine, and fluoxetine are commonly used,[119,123] but other SSRIs such as escitalopram are also beneficial for PTSD management.[123]

SNRIs block reuptake of both serotonin and norepinephrine, thereby stabilizing the norepinephrine and serotonin level in the brain and suppressing PTSD symptoms.[124] Venlafaxine is often prescribed as a first-line treatment agent for PTSD,[45,125] but evidence that supports efficacy of other SNRIs is limited. A network meta-analysis showed that while venlafaxine is effective in controlling PTSD symptoms, but not associated with treatment discontinuation,[126] indicating that

venlafaxine alone is insufficient as a first-line treatment agent of PTSD. As a result, SNRI is not as often prescribed as SSRI as a first-line antidepressant for PTSD treatment.[125]

TCAs are usually prescribed as second-line treatment for PTSD.[45] TCAs work primarily on the norepinephrine system and also have certain degree of anticholinergic effects as well.[127] Although imipramine and amitriptyline are one of the medications that had been used for PTSD earlier than paroxetine, their acceptance was lower than other treatment options.[128] Results from a network meta-analysis also showed that amitriptyline imipramine was associated with neither symptom relief nor treatment termination.[126] However, Puetz, Youngstedt & Herring suggested that SSRIs and TCAs showed greater effects on PTSD compared to other medications.[129]

Other antidepressants that are often used for PTSD treatment include monoamine oxidase inhibitors (MAOIs) such as selegiline, mirtazapine, and bupropion. MAOIs are also one of the early regimen that had been used for PTSD treatment alongside TCAs, and they inhibit the monoamine oxidase, which is an enzyme that breaks down monoamines, resulting in higher concentrations of serotonin, norepinephrine, and other monoamines.[130] Although MAOIs are often used for treating Parkinson's disease, a trial showed that moclobemide, one of the MAOIs, was effective in treating PTSD.[131] However, the evidence that supports the application of MAOIs for PTSD treatment is limited.

Mirtazapine is a more recent regimen compared to TCAs and MAOIs. It is classified as noradrenergic and specific serotonergic antidepressant, as it acts as an antagonist for both α2-adrenergic receptor and serotonergic receptors such as 5-HT_{2A} and 5-HT_{2C}.[132] A double-blind randomized clinical trial suggested that mirtazapine showed better performance in treating PTSD and general anxiety disorder compared to placebo.[133]

3. Effect of Antidepressant Medication on Cardiovascular Disease in PTSD

Previous research on association between antidepressant medication and CVD had provided conflicting results. Traditionally, antidepressant medications are thought to have cardiotoxicity and increase CVD risk.[49-52] For instance, result from a sub-analysis of the Depression Effects on Coronary Artery Disease Events (DECADE) study suggested that application of antidepressant medication decreases the risk of major cardiovascular event (MACE).[134] A meta-analysis on 22 observational studies on use of antidepressant and cardiovascular/cerebrovascular disease had concluded that use of selective serotonin reuptake inhibitor (SSRI) was associated with increased risk of cerebrovascular disease, while use of tricyclic antidepressant (TCA) increased the risk of acute heart disease.[135]

However, some researchers claim that antidepressant medication does not increase the risk of CVD and is, in some cases, even beneficial for prevention: an analysis

of data from Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study indicated that antidepressant medication is associated with increased risk of stroke, coronary heart disease and CVD death.[136] Several other studies had also reported that they did not detect any association between antidepressant medication and CVD[53] or had found protective effect of antidepressant medications on CVD.[55,56]

This complex association is due to ambivalent action of antidepressant medication. On one hand, antidepressant medications relieve depressive symptoms of patients, which are major risk factors of CVD development.[137-139] It had been suggested that depressive symptoms are related to reduced heart rate variability,[140,141] increased inflammatory cytokines,[142-144] and disrupted serum lipid profile.[145-147] By relieving symptoms, antidepressant medications can block metabolic disturbances consequential to depressive symptoms, decreasing the risk of cardiovascular diseases.[148,149] Additionally, a few protective biological mechanisms of antidepressant medications were also suggested. For instance, it had been suggested that SSRI inhibits collagen-induced platelet aggregation and activation, which result in decreased risk of atherosclerotic diseases.[150]

On the other hand, however, there are evidence that suggest cardiotoxicity of antidepressant medications. Common antidepressants such as SSRIs and TCAs are thought to exacerbate atherosclerosis in coronary and carotid artery.[151,152] Additionally, several previous research results presented that antidepressant

medication use is associated with higher risk of cardiac arrythmia such as atrial fibrilation[153,154] and QT interval prolongation,[155,156] which are risk factors of thrombotic cardiovascular events such as coronary artery disease and ischemic stroke.[130,131] Antidepressant medications are also known to be related to type 2 diabetes and impaired glucose regulation, further increasing CVD risk.[157]

The ambivalent association between antidepressant medication and CVD is further complicated by confounding by indication. Individuals with more severe psychiatric symptoms are more likely to receive antidepressant medication, and they are also at higher risk of developing CVD. As such, there is a high probability that association detected from observational studies had been confounded. (**Figure 1**)

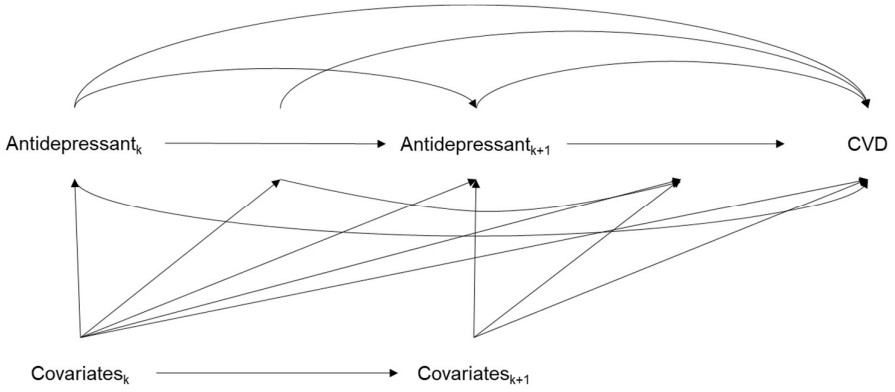


Figure 1. Directed acyclic graph illustrating time-varying confounding by indication. Association between antidepressant medication and CVD is likely to be confounded by confounding effect of psychiatric symptoms and comorbidities, which change throughout the course of follow-up. Conventional time-dependent Cox regression fails to adjust for time-dependent confounding effects by covariates.

Heterogeneities in antidepressant prescription pattern intensifies the difficulties in interpretation. SSRIs are considered first-line medications for PTSD, and they are the most frequently prescribed antidepressants for PTSD treatment.[158,159] Some researchers suggest that exposure to SSRIs are suggested to be associated with atherosclerosis in coronary and carotid artery,[151,152] which leads to coronary artery diseases and ischemic stroke.[160] In contrast, SSRIs might also provide beneficial effects to cardiovascular system, most likely resulting from its side effects on appetite and resulting

SNRIs and tricyclic antidepressants (TCAs) are also prescribed, but the frequency of prescription for PTSD treatment is relatively low compared to SSRI.[161] Other types of antidepressants including tetracyclic antidepressants[162] and monoamine oxidase inhibitors[161] have been suggested to be effective for PTSD treatment and are occasionally prescribed to patients. Cardiovascular effects of antidepressants are known to differ by medication types,[163] so understanding patterns of antidepressant prescription is an important part of assessing cardiovascular effects of it. However, most previous studies have reviewed the cardiovascular effects of antidepressants by class rather than combination, hindering the interpretation.

4. Overview of Marginal Structural Model (MSM)

Marginal structural model was first introduced to the field of epidemiology by a group of epidemiologists including Robins, Hernán, and Ángel in 2000.[66] The model was developed for effect estimation of time-dependent exposure on outcome in the presence of time-dependent confounders in the pathway of causation.[164]

In observation study, the propensity of participants being allocated to certain treatment group is different by confounder vectors, both measured and unmeasured. In observational study without time-varying confounders, either conventional regression model or inverse probability weighting is enough for randomization.[165] However, in existence of time-varying confounding effect, conventional regression is not capable of conditional randomization, as conditioning for confounder vectors partially conditions of the effect of interest A_{k+1}.[166,169] The main objective of marginal structural model in observational study is to properly address confounding by indication due to time-varying confounders and provide estimates that are approximate to those from randomized controlled trials.[167,169]

True weights for counterfactual analysis are unknown but could be estimated by applying logistic regression of exposure on the previous exposure vector and the confounding vector.[170] Probability of individuals being allocated to treatment is estimated, and its inverse value is set as IP weight for counterfactual analysis. After

multiplying overall probability of exposure in population for weight stabilization, stabilized IP weight for individuals could be estimated.

Although true probability cannot be obtained, the numerator and the denominator of the stabilized IP weight can be estimated from pooled logistic regression model.

Marginal structural model is most effective when applied to cohort study with research hypothesis where variables of interest are thoroughly investigated. However, several attempts on applying marginal structural model to the nationwide health service database to control time-varying confounding effects. For instance, a study on Taiwanese National Health Insurance Database utilized MSM to control time-varying confounding effects of socioeconomic status.[171] Lim et al. applied MSM to the second version of the National Health Insurance Service – National Sample Cohort of Korea to control time-varying confounding effects from comorbidities and socioeconomic status.[172] Although it is impossible to guarantee the absence of unmeasured confounding effect in observational study,[173] MSM is able to properly account for measured confounders to enhance comparability and provide less biased estimates in observational studies.[164,174]

In spite of its ability to marginalize the pathway between the confounding vector and exposure, estimand from MSM could still be affected by unmeasured confounder in observational studies. As they are not measured throughout the study, it is impossible to deduce the exact effect from a given observational dataset, and only indirect estimation of its effect on estimand could be done. Ding and

Vanderweele developed a method for sensitivity analysis to assess potential influence of unmeasured confounding without any assumption on association between variables.[175] The method applies 'joint bounding factor', which is a hypothetical factor calculated from maximum value of relative risk of exposure on unmeasured confounders and relative risk of unmeasured confounders on outcome. If observed relative risk is larger than the joint bounding factor, it could be said that true association will still be statistically significant after considering unmeasured confounding effect. Ding and Vanderweele provided a proof that this result is also applicable to survival analysis with rare outcome, making the sensitivity analysis applicable for this study.[176,177]

III. MATERIALS AND METHODS

1. Data and Study Participants

This study utilized the Korean National Health Insurance Database (NHID), which is a cohort of Korean citizens who utilized medical service covered by Korean National Health Insurance System (NHIS). Korean NHIS constructed NHID by collecting administrative records of medical service utilization since 2002. The database consists of information on insurance eligibility, diagnostic records, claim for medication, procedures, and operation, prescription records and health check-up results.

A washout period of 2 years was set and collected data from patients diagnosed with PTSD in 2004-2018. Adult participants with at least one F43.1 ICD-10 diagnostic code on administrative records were defined as 'patients with PTSD'. (N = 74,168) Patients without complete record for insurance eligibility (N = 5), received antidepressant medication prior to PTSD diagnosis (N = 20,935), followed up for shorter than 30 days (N = 949), and diagnosed with coronary artery disease prior to PTSD diagnosis (N = 228) were excluded, leaving 51,058 participants for the final analysis. (Figure 2)

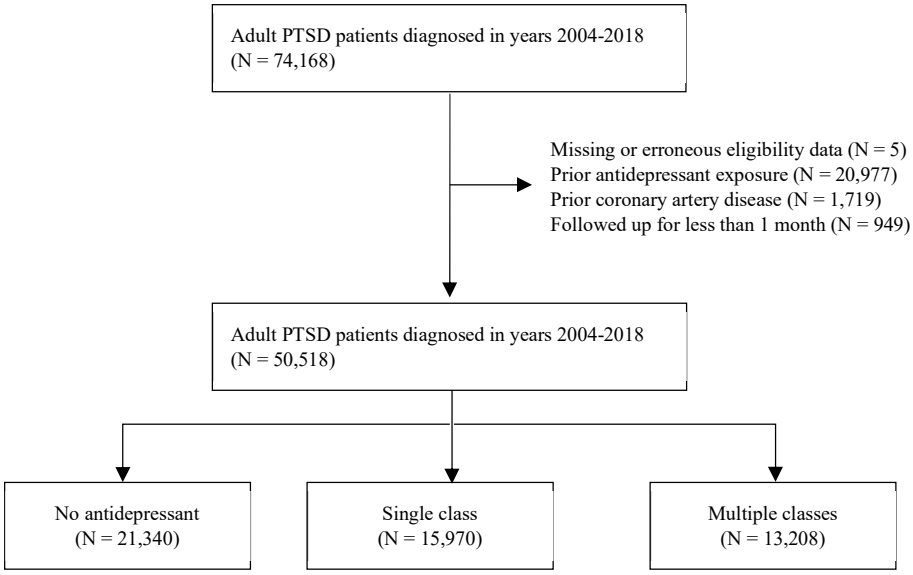


Figure 2. Flow diagram of inclusion and exclusion of participants

2. Measurement

1) Assessment of exposure: antidepressant medication

Insurance claim data for exposure to antidepressant was obtained from NHID. Information on pharmaceutical code of ingredients, frequency of intake, and total days of intake were obtained. Antidepressant medications were classified into 'selective serotonin reuptake inhibitor (SSRI)', 'serotonin-norepinephrine reuptake inhibitor (SNRI)', 'tricyclic antidepressants (TCA)' and 'other antidepressants' according to code of ingredients. Participants ever prescribed with antidepressants of each class was considered to be exposed to the corresponding antidepressant

class. List of pharmaceutical code of ingredients that indicate antidepressant medication included in this study is provided in Appendix 1.

The duration of medication possession after initial PTSD diagnosis were estimated by prescription record. Sum of duration covered by antidepressant prescription of each participant was defined as duration of prescription. Overall covered duration as well as class-specific duration were estimated from the database. The antidepressant class with the longest duration of prescription was defined as main treatment class. Participants were categorized into 4 groups in accordance with duration of medication possession: short-term (less than 6 months), short-intermediate (6 – 11 months), long-intermediate (12 – 18 months), and long-term (18 months or longer).

Medication possession ratio (MPR) was calculated as the proportion of durations of medication possession in follow-up duration. Overall MPR as well as class-specific MPR were estimated from the database. Participants were categorized into 4 groups in accordance with MPR: low (less than 20%), low-moderate (20 – 49%), high-moderate (50 – 79%), and high (80% or higher). Duration of medication possession and MPR of each antidepressant class were also estimated.

Participants were categorized into groups in accordance with prescription patterns. For main analysis, participants were categorized by initial treatment regimen. Those who never received antidepressants were classified as ‘no antidepressant’ group. Addition or switching of regimen did not trigger reclassification of participants. For

additional analysis, participants were classified in accordance with all medications they have ever received. Participants were categorized into 'no antidepressant', 'single class', and 'multiple classes' groups, and further classified into subgroups by combination of prescribed antidepressant medications.

2) Assessment of outcome: coronary artery disease with revascularization

Coronary artery disease (CAD) with revascularization was selected as an outcome variable to assess cardiovascular effects of antidepressant medication. To increase the validity of diagnosis, operational definition was applied to define cases. Participants were considered to be diagnosed with CAD with revascularization if all of the followings were true:

(1) Participants had at least one healthcare utilization record with ICD-10 diagnostic code for coronary artery disease. List of diagnostic codes used for operative definition provided in Appendix 2.

(2) Participants had undergone procedures and/or surgical interventions for coronary artery revascularization. List of procedures and surgical interventions is provided in Appendix 3.

(3) Participants was either hospitalized, deceased, or attended 4 or more outpatient sessions due to CAD.[178]

The index date of participant was defined as the date of first diagnosis for PTSD. For participants who were diagnosed with coronary artery disease with revascularization, the first date to be diagnosed was defined as the terminal point of follow-up. For participants who were not diagnosed with coronary artery disease with revascularization, the last date of medical service utilization or the date of expiration were defined as the terminal point.

3) Assessment of covariates

Monthly insurance premium was selected as a surrogate variable for socioeconomic status, as insurance premium of Korean NHIS increases in proportion to monthly income for employee-insured individuals and in proportion to income, property, vehicles, and other assets for self-employed insured individuals. Medical comorbidities were assessed by Charlson Comorbidity Index (CCI), which is a comprehensive index for evaluation of comorbid conditions.[179] History of hypertension and dyslipidemia, which are not included in CCI calculation, were separately reviewed. To adjust for psychiatric symptoms and comorbidities, diagnostic records of patients were reviewed and checked if patients were ever diagnosed with depressive symptoms/disorders, anxiety-related disorders, somatoform disorders, psychotic disorders, and manic episodes/bipolar disorders. These psychiatric symptoms and disorders are common comorbidities in PTSD and

are potentially associated with selection of treatment modality.[180-183] Participants with two or more records of medical service utilization with corresponding diagnostic codes were considered to be diagnosed with psychiatric comorbidities. Diagnostic codes for psychiatric comorbidities are presented in Appendix 4. History of psychiatric admission was reviewed and added as a covariate to indirectly evaluate the severity of psychiatric symptoms.

3. Statistical Analysis

Descriptive analysis was conducted to assess the participant characteristics by prescription pattern. For continuous variables, analysis of variance (ANOVA) was used for comparison. For categorical variables, χ^2 test was performed for comparison.

Marginal structural model was constructed for proper adjustment of time-varying confounding by indication that could be introduced by psychiatric and medical comorbidities. Inverse probability weights for antidepressant prescription were calculated by logistic regression for marginal randomization of population. Conditional probability of treatment allocation and censoring were estimated, and crude probability of treatment allocation was multiplied for standardization of weights.[164,184] Participants were considered to be exposed to antidepressant classes after the initial date of prescription. Time-dependent duration of antidepressant prescription and MPR of participants were estimated by each time interval. Detailed

statistical methods of IP weight estimation and MSM construction are provided in Appendix 5.

Effects of prescribed antidepressant class, as well as effects of prescription patterns, were estimated. Estimand from MSM was compared with that from conventional time-dependent Cox regression model. Dose response in duration-CAD association and MPR-CAD association was tested by stratified analysis and polynomial splining. Effects of total duration, as well as class-specific duration, were estimated.

Several sensitivity analyses were conducted to test the possible effects of biases and check consistency and stability of the estimand. First, lag times of 6, 12, and 24 months were set consecutively to assess the effect of protopathic bias.[185] Additionally, to test the effect of possible violation of positivity assumption, sensitivity analysis by progressive truncation of the stabilized IP weights was conducted: 1-99%, 5-95%, and 10-90%. Positivity assumption is one of the core assumptions for MSM, indicating that the conditional probability of exposure and outcome under certain covariate vector is a nonzero value.[164-165] As participants with extreme IP weight values have low probability of having counterparts with similar IP weight, it is possible that it could cause the violation of positivity assumption. By truncating extreme values, possible bias from violation of positivity assumption could be assessed.

NHID Health checkup database was not used in the main analysis to prevent excess exclusion of participants. A subgroup analysis on participants who had undergone health checkup was conducted to assess the possible confounding effects of lifestyle factors and metabolic profiles. In this subgroup analysis, additional covariates including body mass index (BMI), systolic blood pressure, diastolic blood pressure, fasting serum glucose level, and total serum cholesterol level were added to the covariate set.

Finally, to check the effect of residual confounders on the estiamnd, bounding factors based on Ding & Vanderweele's theory were calculated for statistically significant effect sizes. Large bounding factors suggest that nullification of estimand by unmeasured confounding effects are less likely to take place.

4. Ethics Statement

This study was approved by the Institutional Review Board of Yonsei University Health System (IRB number: 4-2021-0836). Informed consent for the present study was waived as this study used deidentified NHID data only without any information that could be used for identifying individual participants. The authors assert that all procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the 1975 Declaration of Helsinki, as revised in 2008.

IV. Results

1. Characteristics of Participants

Among 50,518 participants included in final analyses, 21,340 participants did not receive antidepressant, 15,970 participants received single class of antidepressants, and 13,208 participants received multiple classes of antidepressants. Mean age of participants who did not receive antidepressants was higher compared to those who received them. Proportion of female participants was the highest in 'single class' group and the lowest in 'no antidepressant' group, indicating that age and sex are predictors of treatment exposure. Participants who received multiple classes of antidepressants paid the least insurance premium, suggesting the association between low socioeconomic status and antidepressant prescription.

Psychiatric comorbidities were significantly associated with antidepressant exposure: all psychiatric comorbidities that were assessed in this study were most prevalent in participants who received two or more classes of antidepressants. Prevalence of admission due to psychiatric disorders was also the highest in 'multiple classes' group. Proportion of participants with history of hypertension and dyslipidemia was also higher in those who received antidepressants.

The numbers and proportion of participants whose main treatment regimen was SSRI, SNRI, TCA, and other antidepressants were 20,151 (39.89%), 1,410 (2.79%),

3,615 (7.16%), and 4,002 (7.92%) respectively. The numbers and proportion of participants who were ever prescribed with SSRI, SNRI, TCA, and other antidepressants were 23,495 (46.51%), 3,929 (7.78%), 8,025 (15.89%), and 11,837 (23.43%) respectively.

Mean duration of antidepressant prescription among treated was 23.89 months. (SD 39.30 months) Mean duration of prescription for SSRI, SNRI, TCA, and other antidepressants among those who received the corresponding antidepressant class were 17.98 months (SD 32.44 months), 11.68 months (SD 22.17 months), 15.89 months (SD 31.24 months), and 16.96 months (SD 31.18 months) respectively. Participants of 'multiple classes' group tended to receive antidepressants longer than 'single class' group. Mean MPR of antidepressants among treated was 28.39%. (SD 39.38%) Mean value of class-specific MPR for SSRI, SNRI, TCA, and other antidepressants among those who received the corresponding antidepressant class were 24.43% (SD 33.36%), 16.02% (SD 24.81%), 15.59% (SD 26.42%), and 21.22% (SD 30.59%) respectively. Participants of 'multiple classes' group tended to have higher MPRs than 'single class' group. (Table 1)

Table 1. Characteristics of participants by prescription pattern (N = 50,518)

	Full cohort (N = 50,518)	No antidepressant (N = 21,340)	Single class (N = 15,970)	Multiple classes (N = 13,208)	p-value
Age, mean (SD)	43.13 (15.46)	43.82 (15.76)	42.31 (15.45)	42.58 (14.94)	<0.001
Men, N (%)	19,170 (37.95)	8,506 (39.86)	5,724 (35.84)	4,940 (37.40)	<0.001
Years of follow-up, mean (SD)	6.86 (4.26)	6.76 (4.29)	6.56 (4.22)	7.42 (4.21)	<0.001
Monthly insurance premium, N (%)					<0.001
0 (Medicaid receiver)	2,838 (5.62)	746 (3.50)	882 (5.52)	1,210 (9.16)	
<25p	9,953 (19.70)	4,052 (18.99)	3,128 (19.59)	2,773 (20.99)	
25 – 49p	10,671 (21.12)	4,531 (21.23)	3,394 (21.25)	2,746 (20.79)	
50 – 74p	11,841 (23.44)	5,188 (24.31)	3,729 (23.35)	2,924 (22.14)	
≥75p	13,915 (27.54)	6,251 (29.29)	4,418 (27.66)	3,246 (24.58)	
N/A	1,300 (2.57)	572 (2.68)	419 (2.62)	309 (2.34)	
Charlson comorbidity index, N (%)					
0	11,128 (22.03)	4,834 (22.65)	3,613 (22.62)	2,681 (20.30)	
1	13,357 (26.44)	5,588 (26.19)	4,279 (26.79)	3,490 (26.42)	
2	9,152 (18.12)	3,701 (17.34)	2,880 (18.03)	2,571 (19.47)	
3	5,495 (10.88)	2,299 (10.77)	1,688 (10.57)	1,508 (11.42)	
≥4	11,386 (22.54)	4,918 (23.05)	3,510 (21.98)	2,958 (22.40)	
Hypertension, N (%)	9,380 (19.46)	4,290 (20.10)	2,913 (18.24)	2,627 (19.89)	<0.001
Dyslipidemia, N (%)	15,687 (31.05)	6,465 (30.30)	4,712 (29.51)	4,510 (34.15)	<0.001
Psychiatric comorbidities, N (%)[a]					
Psychotic disorders	2,716 (5.38)	694 (3.25)	743 (4.65)	1,279 (9.68)	<0.001
Manic episodes/bipolar disorders	4,586 (9.08)	961 (4.50)	1,151 (7.21)	2,474 (18.73)	<0.001
Depressive symptoms/disorders	25,709 (50.89)	7,115 (33.34)	8,445 (52.88)	10,149 (76.84)	<0.001
Anxiety-related disorders other than PTSD	25,250 (49.98)	8,488 (39.78)	7,970 (49.91)	8,792 (66.57)	<0.001
Somatoform disorders	6,581 (13.03)	2,311 (10.83)	1,953 (12.23)	2,317 (17.54)	<0.001
Admission due to psychiatric disorder, N (%)[a]	6,131 (12.14)	1,327 (6.22)	1,776 (11.12)	3,028 (20.93)	<0.001
CAD with revascularization, N (%)	1,543 (3.05)	593 (2.78)	449 (2.81)	501 (3.79)	<0.001
All-cause mortality, N (%)	1,375 (2.72)	560 (2.62)	363 (2.27)	452 (3.42)	<0.001
Class of main treatment regimen, N (%)[a]					<0.001
None	21,340 (42.24)	21,340 (100.00)	-	-	
SSRI	20,151 (39.89)	-	11,297 (70.74)	8,854 (67.04)	
SNRI	1,410 (2.79)	-	609 (3.81)	801 (6.06)	
TCA	3,615 (7.16)	-	2,187 (13.69)	1,428 (10.81)	
Other antidepressants	4,002 (7.92)	-	1,877 (11.75)	2,125 (16.09)	
Class of ever prescribed antidepressants, N (%)[a]					<0.001
None	21,340 (42.24)	21,340 (100.00)	-	-	
SSRI	23,495 (46.51)	-	11,297 (70.74)	12,198 (92.35)	
SNRI	3,929 (7.78)	-	609 (3.81)	3,320 (25.14)	
TCA	8,025 (15.89)	-	2,187 (13.69)	5,838 (44.20)	
Other antidepressants	11,837 (23.43)	-	1,877 (11.75)	9,960 (75.41)	

	Full cohort (N = 50,518)	No antidepressant (N = 21,340)	Single class (N = 15,970)	Multiple classes (N = 13,208)	p-value
Duration of antidepressant prescription, mean (SD)[a]	23.89 (39.30)	-	9.13 (22.82)	41.08 (46.92)	<0.001
None (0), N (%)	21,340 (42.24)	21,340 (100.00)	-	-	
Short-term (<6), N (%)	17,104 (33.86)	-	12,456 (78.00)	4,648 (35.19)	
Short intermediate (6 - 11), N (%)	2,186 (4.33)	-	1,005 (6.29)	1,181 (8.94)	
Long intermediate (12 - 23), N (%)	2,108 (4.17)	-	812 (5.08)	1,296 (9.81)	
Long-term (>=24), N (%)	7,780 (15.40)	-	1,697 (10.63)	6,083 (46.06)	
Duration by class, mean (SD)[a]					
SSRI (N = 23,495)	17.98 (32.44)	-	9.31 (22.25)	26.01 (37.89)	<0.001
SNRI (N = 3,929)	11.68 (22.17)	-	5.52 (14.73)	12.81 (23.11)	<0.001
TCA (N = 8,025)	15.89 (31.23)	-	8.40 (23.02)	18.70 (33.37)	<0.001
Other antidepressants (N = 11,837)	16.64 (30.57)	-	7.32 (19.50)	18.40 (31.93)	<0.001
Medication possession ratio, %, mean (SD)[a]	28.39 (39.30)	-	14.41 (50.84)	44.82 (38.89)	<0.001
None (0), N (%)	21,340 (42.24)	21,340 (100.00)	-	-	
Low (<20), N (%)	17,969 (35.57)	-	12,652 (79.22)	5,317 (40.26)	
Low intermediate (20 - 49), N (%)	3,615 (7.16)	-	1,411 (8.84)	2,204 (16.69)	
High intermediate (50 - 79), N (%)	2,825 (5.59)	-	790 (4.95)	2,035 (15.41)	
High (≥80), N (%)	4,769 (9.44)	-	1,117 (6.99)	3,652 (27.65)	
Medication possession ratio by class, %, mean (SD)[a]					
SSRI (N = 23,495)	24.43 (33.36)		16.79 (28.69)	31.50 (35.74)	<0.001
SNRI (N = 3,929)	16.02 (24.81)		10.73 (21.67)	16.99 (25.22)	<0.001
TCA (N = 8,025)	15.59 (26.42)		9.05 (20.94)	18.03 (27.81)	<0.001
Other antidepressants (N = 11,837)	21.22 (30.59)		11.54 (23.78)	23.05 (31.37)	<0.001

SD, standard deviation; p, percentile; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant medication.
[a] Measured at follow-up termination.

2. Estimation of Inverse Probability Weights

Factors associated with antidepressant prescription and their magnitudes of association are presented in Table 2. Female gender and low insurance premium were positively associated with antidepressant prescription. Participants with psychiatric comorbidities, except for psychotic disorders, had higher probability of receiving antidepressants. Charlson Comorbidity Index was also positively associated with antidepressant administration, while hypertension and dyslipidemia were negatively associated with antidepressant prescription. (Table 2) The mean value of the log-transformed value of the stabilized weights at baseline was -0.006 (SD 0.143), and the mean of the log-transformed value of the non-stabilized weights at baseline was 0.870. (SD 0.208) (Figure 3)

Factors associated with probability of allocation to treatment groups (‘no treatment’, ‘single class’, and ‘multiple classes’) and their magnitudes of association are presented in Table 3. Odds of being allocated to ‘no antidepressant’ group was set as a reference value. Odds ratio of female gender was 1.20 (95% confidence interval [CI] 1.19 – 1.21) for ‘single class’ group allocation and 1.09 (95% CI 1.08 – 1.10) for ‘multiple classes’ group allocation. Participants with lower insurance premium had higher odds of being allocated to either treatment groups, but the association for ‘multiple classes’ group was stronger. Individuals with higher CCI were more likely to receive antidepressants, whereas individuals with

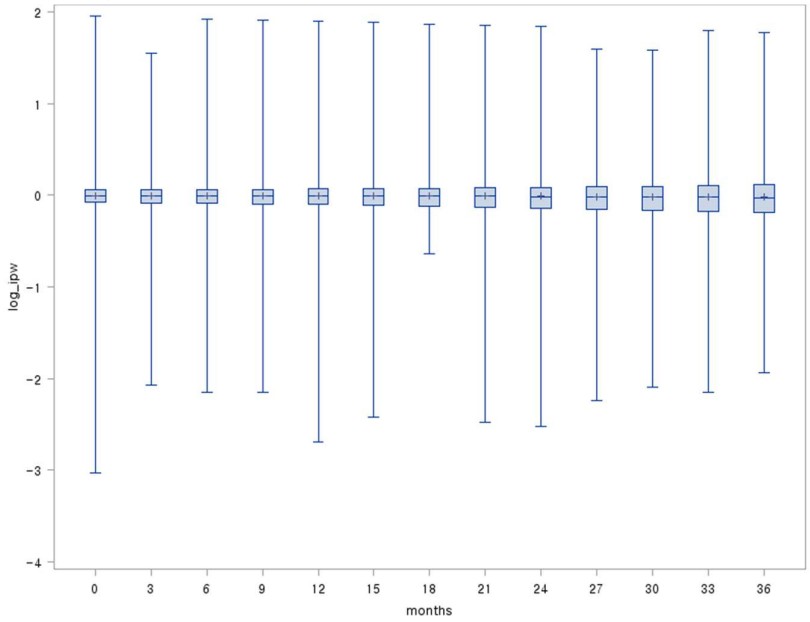
hypertension had lower probability of antidepressant prescription. For all psychiatric comorbidities except for psychotic disorders, odds ratio for being allocated to 'multiple classes' group was larger than odds ratio for being allocated to 'single class' group. Charlson Comorbidity Index and hypertension was also positively associated with antidepressant administration. The mean value of the log-transformed value of the stabilized weights was -0.006 (SD 0.143) at baseline and -0.009 (SD 0.156) at the fourth time interval. The mean of the log-transformed value of the non-stabilized weights was 0.870 (SD 0.208) at baseline and 0.871 (SD 0.239) at the fourth time interval (Figure 4).

Table 2. Association between confounding factors and antidepressant prescription.

	OR	95% CI
Age	**0.99**	**0.99 – 0.99**
Female	**1.15**	**1.14 – 1.16**
Monthly insurance premium		
0	**1.74**	**1.71 – 1.77**
≤25p	**1.13**	**1.12 – 1.14**
25 – 50p	**1.05**	**1.04 – 1.06**
50 – 75p	**1.01**	**1.00 – 1.02**
≥75p	ref	
Not applicable	**1.06**	**1.03 – 1.08**
Charlson Comorbidity Index		
0	ref	
1	**1.11**	**1.10 – 1.12**
2	**1.27**	**1.26 – 1.28**
3	**1.37**	**1.36 – 1.39**
≥4	**1.47**	**1.45 – 1.49**
Hypertension	**0.96**	**0.95 – 0.97**
Dyslipidemia	**0.92**	**0.90 – 0.04**
Psychiatric comorbidities		
Psychotic disorders	0.98	0.95 – 1.00
Manic episodes/bipolar disorders	**1.79**	**1.74 – 1.84**
Depressive symptoms/disorders	**2.31**	**2.29 – 2.33**
Anxiety-related disorders	**1.22**	**1.21 – 1.23**
Somatoform disorders	**1.13**	**1.12 – 1.15**
Admission due to psychiatric symptoms	**2.14**	**2.10 – 2.17**

OR, odds ratio; CI, confidence interval; SD, standard deviation.

A. Stabilized weight



B. Non-stabilized weight

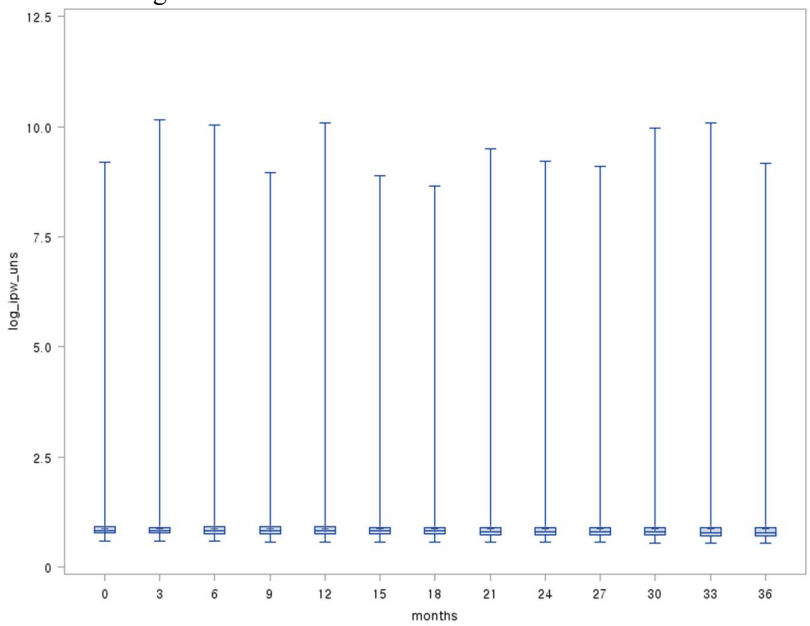


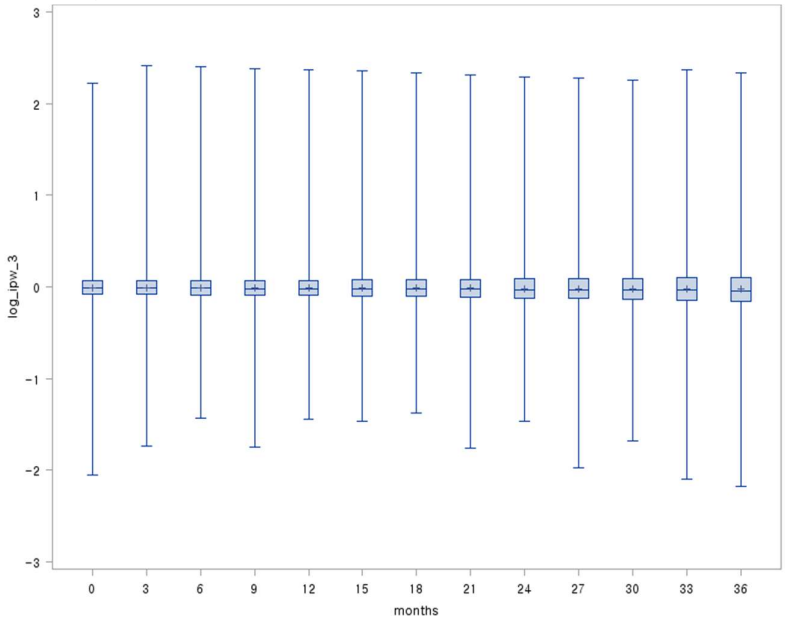
Figure 3. Box plot of log-transformed value of IP weights for antidepressant prescription. A: Stabilized weight; B: Non-stabilized weight

Table 3. Association between confounding factors and treatment group allocation.

	Single class		Multiple classes	
	OR	**95% CI**	**OR**	**95% CI**
Age	**0.99**	**0.99 – 0.99**	**0.99**	**0.99 – 0.99**
Female	**1.20**	**1.19 – 1.21**	**1.09**	**1.08 – 1.10**
Monthly insurance premium				
0	**1.28**	**1.26 – 1.31**	**2.30**	**2.25 – 2.34**
≤25p	**1.04**	**1.02 – 1.05**	**1.26**	**1.25 – 1.28**
25 – 50p	1.01	0.99 – 1.02	**1.10**	**1.09 – 1.11**
50 – 75p	**0.98**	**0.97 – 0.99**	**1.04**	**1.03 – 1.06**
≥75p		ref		ref
Not applicable	**1.08**	**1.06 – 1.11**	1.01	0.99 – 1.04
Charlson Comorbidity Index				
0		ref		ref
1	**1.07**	**1.06 – 1.08**	**1.17**	**1.16 – 1.18**
2	**1.18**	**1.16 – 1.19**	**1.40**	**1.38 – 1.42**
3	**1.25**	**1.23 – 1.27**	**1.55**	**1.52 – 1.57**
≥4	**1.37**	**1.34 – 1.39**	**1.62**	**1.60 – 1.65**
Hypertension	**0.93**	**0.92 – 0.94**	**0.99**	**0.98 – 0.99**
Psychotic disorders	1.00	0.98 – 1.03	**0.95**	**0.92 – 0.97**
Manic episodes/bipolar disorders	**1.35**	**1.31 – 1.40**	**2.17**	**2.11 – 2.23**
Depressive symptoms/disorders	**1.86**	**1.84 – 1.88**	**2.93**	**2.90 – 2.96**
Anxiety-related disorders	**1.09**	**1.07 – 1.10**	**1.40**	**1.38 – 1.41**
Somatoform disorders	**1.02**	**1.01 – 1.04**	**1.25**	**1.24 – 1.28**
Admission due to psychiatric symptoms	**1.66**	**1.63 – 1.70**	**2.61**	**2.56 – 2.66**

*'No antidepressant' group was used as a referent group.

A. Stabilized weight



B. Non-stabilized weight

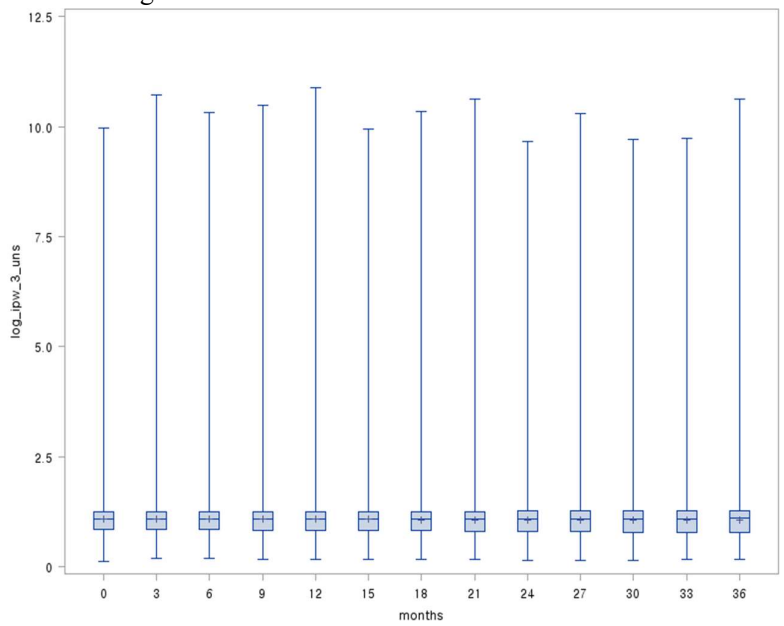


Figure 4. Box plot of log-transformed value of IP weights for treatment group allocation. A: Stabilized weight; B: Non-stabilized weight

3. Association between Antidepressant Class and CAD

Antidepressant prescription was positively associated with CAD with revascularization. (hazard ratio [HR] = 1.31, 95% confidence interval [CI] 1.18 – 1.46) Participants exposed to two or more classes of antidepressants had higher risk of developing CAD (HR = 1.46, 95% CI 1.29 – 1.65) compared to those prescribed with single class of antidepressants. (HR = 1.27, 95% CI 1.12 – 1.44) Hazard ratios and 95% CIs for CAD in participants who received 1, 2, 3, and 4 classes of antidepressants were 1.18 (1.04 – 1.33), 1.45 (1.26 – 1.67), 1.47 (1.21 – 1.80), and 1.97 (1.40 – 2.76) respectively. (Table 3, Figure 5)

Participants whose main treatment modality was SSRI had 1.43 times higher risk of developing CAD compared to 'no antidepressant' group. (95% CI 1.07 – 1.60) Participants whose main treatment modality was SNRI (HR = 0.94, 95% CI 0.77 – 1.15) did not present higher risk of CAD than 'no antidepressant' group. Participants whose main treatment modality was TCA had 1.20 times higher hazard of CAD, but the statistical significance was of marginal level. (95% CI 0.90 – 1.70) Participants who were prescribed with other antidepressants the longest had 1.24 times higher risk of CAD development compared to those who were not prescribed with any antidepressants. (95% CI 1.02 – 1.54; Table 3, Figure 5)

When analyzed by history of antidepressant prescription, exposure to all antidepressant classes except SNRI had statistically significant positive association

with CAD with revascularization: Hazard ratios and 95% CIs of ever exposure to SSRI, SNRI, TCA, and other antidepressants were 1.47 (1.32 – 1.64), 1.19 (0.98 – 1.44), 1.29 (1.14 – 1.46), and 1.21 (1.07 – 1.37) respectively. (Table 3, Figure 6)

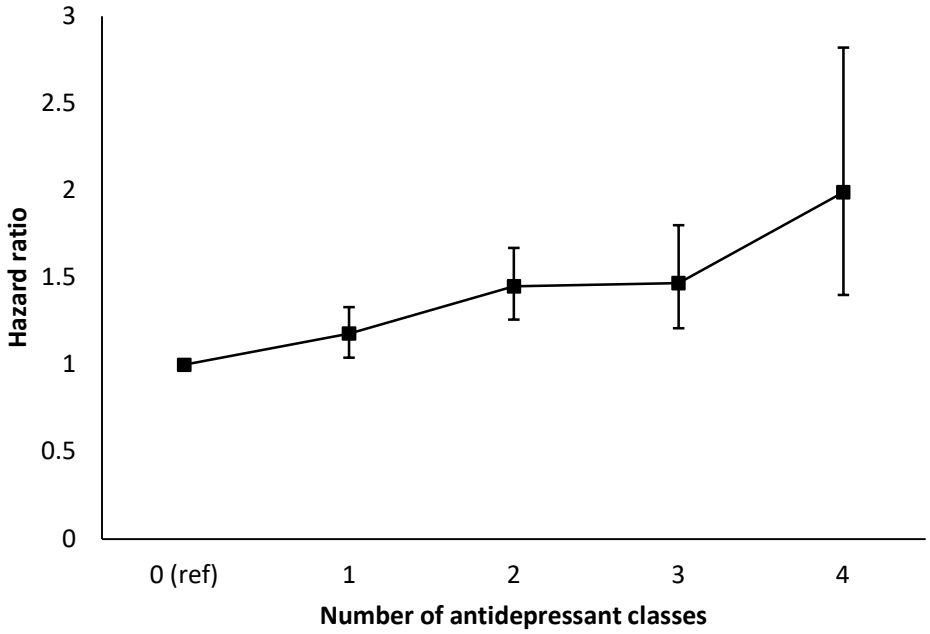


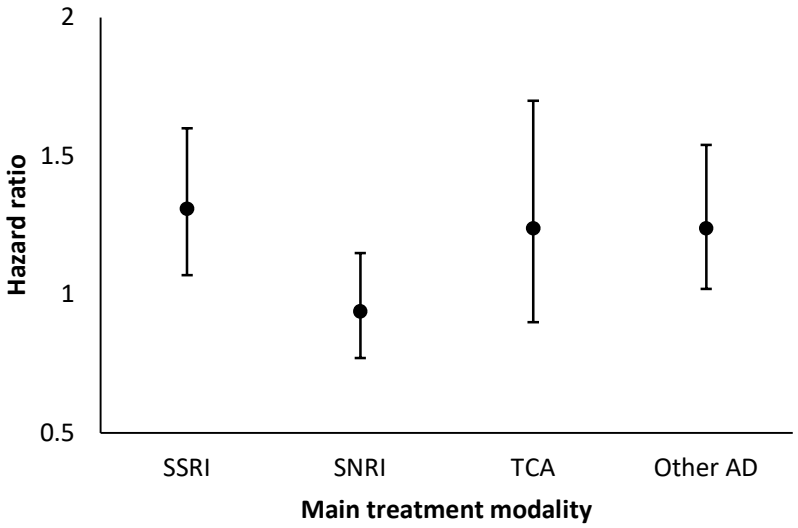
Figure 5. Hazard ratio for CAD with revascularization by number of antidepressant classes.

Table 4. Association between antidepressant classes and coronary artery disease (N = 50,518).

	Incidence rate of CAD per 1,000 person-years	Crude model, HR (95% CI)	Fully adjusted model with time-fixed covariates, HR (95% CI)	Fully adjusted model with time-fixed covariates, HR (95% CI)	Marginal structural model, HR (95% CI)
No antidepressants	4.12	ref	ref	ref	ref
Ever prescribed	4.68	**1.35 (1.12 – 1.39)**	**1.17 (1.01 – 1.36)**	1.13 (0.97 – 1.31)	**1.31 (1.18 – 1.46)**
Number of classes					
Single class	4.28	**1.31 (1.13 – 1.51)**	**1.16 (1.01 – 1.33)**	1.14 (0.99 – 1.31)	**1.18 (1.04 – 1.33)**
Multiple classes	5.11	**1.52 (1.32 – 1.75)**	**1.26 (1.08 – 1.47)**	**1.20 (1.02 – 1.41)**	**1.46 (1.29 – 1.65)**
2 classes	4.92	**1.50 (1.26 – 1.78)**	1.23 (0.95 – 1.59)	1.20 (0.92 – 1.55)	**1.45 (1.26 – 1.67)**
3 classes	5.20	**1.51 (1.18 – 1.93)**	**1.27 (1.06 – 1.53)**	1.19 (0.98 – 1.45)	**1.47 (1.21 – 1.80)**
4 classes	6.44	**1.71 (1.14 – 2.57)**	1.30 (0.86 – 1.97)	1.25 (0.84 – 1.86)	**1.97 (1.40 – 2.76)**
Main treatment regimen					
SSRI	4.51	**1.30 (1.13 – 1.49)**	**1.18 (1.02 – 1.36)**	**1.24 (1.08 – 1.42)**	**1.31 (1.07 – 1.60)**
SNRI	3.90	0.96 (0.86 – 1.07)	0.93 (0.61 – 1.41)	0.93 (0.62 – 1.27)	0.94 (0.77 – 1.15)
TCA	4.71	**1.71 (1.35 – 2.13)**	**1.40 (1.12 – 1.74)**	**1.40 (1.13 – 1.72)**	1.24 (0.90 – 1.70)
Other antidepressants	5.61	**1.65 (1.33 – 2.04)**	**1.25 (1.01 – 1.56)**	**1.27 (1.03 – 1.57)**	**1.24 (1.02 – 1.54)**
Ever prescribed					
SSRI	4.71	**1.47 (1.30 – 1.66)**	**1.26 (1.10 – 1.43)**	**1.18 (1.04 – 1.34)**	**1.47 (1.32 – 1.64)**
SNRI	4.67	0.90 (0.74 – 1.09)	0.97 (0.80 – 1.12)	0.84 (0.69 – 1.02)	1.19 (0.98 – 1.44)
TCA	5.12	**1.32 (1.17 - 1.50)**	**1.27 (1.12 - 1.44)**	**1.35 (1.17 – 1.56)**	**1.29 (1.14 – 1.46)**
Other antidepressants	5.22	1.11 (0.93 – 1.33)	1.12 (0.94 – 1.34)	1.09 (0.94 – 1.25)	**1.21 (1.07 – 1.37)**

For fully adjusted model, variables listed below were included as covariates: age, sex, monthly insurance premium, Charlson comorbidity index, psychiatric comorbidities, and history of psychiatric admission. For marginal structural model, inverse probability weight was estimated by multivariate logistic regression model adjusted by same set of variables listed above. HR, hazard ratio; CI, confidence interval; ref, reference.

A. By main treatment modality



B. By ever exposure

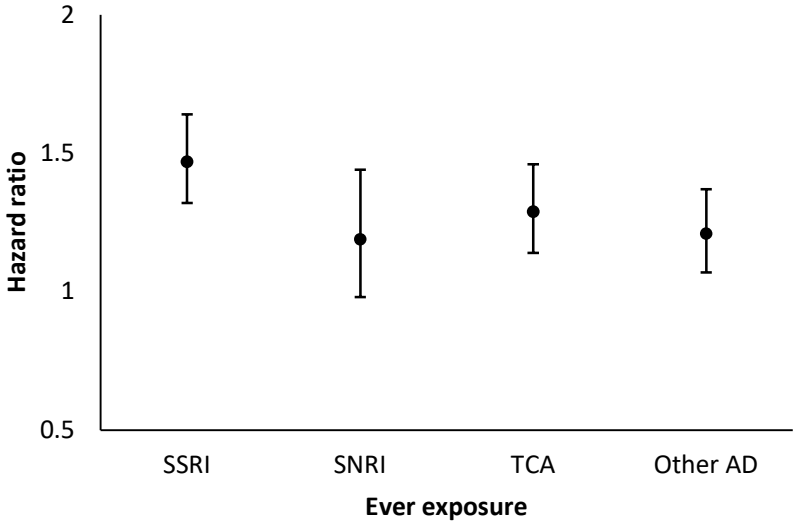


Figure 6. Hazard ratio for CAD with revascularization by antidepressant classes. A: By main treatment modality; B: By ever exposure.

Most common combination of antidepressant classes was 'SSRI only', (N = 11,297) followed by 'SSRI + other antidepressant' (N = 5,323) and 'TCA only'. (N = 2,187) Prevalence rate of CAD with revascularization was the highest in 'TCA + other antidepressant' group (6.54 per 1,000 person-year), followed by '4 classes' group (6.44 per 1,000 person-year) and 'SSRI + TCA + Other antidepressant' group (6.02 per 1,000 person-years). In general, combinations that include SSRI and other antidepressants showed higher prevalence rate of CAD with revascularization, while combinations that include SNRI showed lower prevalence rate.

Hazard ratio for CAD with revascularization was the highest in 'TCA + other antidepressant' group, (HR = 1.64, 95% CI 1.11 – 2.42) followed by 'SSRI + TCA + other AD' group (HR = 1.52, 95% CI 1.22 – 1.88) and '4 classes' group. (HR = HR = 1.45, 95% CI 1.06 – 2.00) In general, hazard ratio was higher in individuals who received SSRI and other antidepressants compared to SNRI. (Table 5)

Additional analysis on antidepressant combination was conducted with respect to main and adjuvant class of antidepressant. Highest hazard ratios were detected in 'SSRI + TCA + other antidepressant' combination, as it was in main analysis. Among the combination, the hazard ratio was the highest in 'main other antidepressants + adjuvant SSRI, TCA", (HR = 2.81, 95% CI 1.72 – 4.60) followed by 'main TCA + adjuvant SSRI, other antidepressants' (HR = 2.21, 95% CI 1.19 – 4.10) and 'main SSRI, adjuvant TCA + other antidepressants. (HR = 1.38, 95% CI 1.04 – 1.84) 'Main TCA + adjuvant SSRI' combination was strongly associated

with CAD (HR = 1.63, 95% CI 1.13 – 2.35), while 'main SSRI + adjuvant TCA' combination did not increase the risk of CAD. (HR = 1.06, 95% CI 0.65 – 1.70) When main treatment regimen was SNRI, no increase in hazard was detected regardless of adjuvant antidepressants. (Table 6)

Table 5. Hazard ratio for CAD with revascularization by antidepressant class combination.

Antidepressant combination	N (%)	Incidence rate of CAD per 1,000 person-years	HR (95% CI)
No antidepressant	21,340 (42.24)	4.12	ref
1 class			
SSRI only	11,297 (22.36)	4.22	0.90 (0.78 - 1.04)
SNRI only	609 (1.21)	4.14	0.90 (0.56 - 1.47)
TCA only	2,187 (4.33)	4.00	1.15 (0.91 - 1.45)
Other AD only	1,877 (3.72)	4.99	**1.38 (1.08 - 1.76)**
2 classes			
SSRI + SNRI	741 (1.47)	4.88	0.97 (0.64 – 1.47)
SSRI + TCA	2,120 (4.20)	4.84	**1.28 (1.02 - 1.61)**
SSRI + Other AD	5,323 (10.54)	4.85	0.99 (0.82 - 1.18)
SNRI + TCA	121 (0.24)	4.90	1.04 (0.39 - 2.77)
SNRI + Other AD	304 (0.60)	3.36	0.76 (0.35 - 1.65)
TCA + Other AD	483 (0.96)	6.58	**1.64 (1.11 - 2.42)**
3 classes			
SSRI + SNRI + TCA	266 (0.53)	3.01	0.76 (0.36 - 1.63)
SSRI + SNRI + Other AD	1,002 (1.98)	3.96	0.85 (0.57 - 1.24)
SSRI + TCA + Other AD	1,962 (3.88)	6.02	**1.52 (1.22 - 1.88)**
SNRI + TCA + Other AD	102 (0.20)	4.79	1.03 (0.38 - 2.83)
4 classes	784 (1.55)	6.44	**1.45 (1.06 - 2.00)**

CAD, coronary artery disease; HR, hazard ratio; CI, confidence interval.

Table 6. Hazard ratio for CAD with revascularization by main and adjuvant antidepressant class.

Antidepressant combination	N (%)	Incidence rate of CAD per 1,000 person-years	HR (95% CI)
No AD	21,340 (42.24)	4.12	ref
Main class: SSRI			
SSRI only	11,297 (22.36)	4.22	0.90 (0.78 – 1.04)
+SNRI	526 (1.04)	5.15	1.05 (0.65 – 1.70)
+TCA	1,578 (3.12)	4.49	1.15 (0.87 – 1.51)
+Other AD	4,362 (8.63)	4.72	0.91 (0.75 – 1.11)
+SNRI+TCA	164 (0.32)	4.16	1.03 (0.46 – 2.34)
+SNRI+Other AD	598 (1.18)	4.11	0.81 (0.49 – 1.34)
+TCA+Other AD	1,227 (2.43)	5.51	**1.38 (1.04 – 1.84)**
+SNRI+TCA+Other AD	399 (0.79)	5.56	1.30 (0.81 – 2.09)
Main class: SNRI			
SNRI only	609 (1.21)	4.14	0.90 (0.56 – 1.47)
+SSRI	215 (0.43)	4.25	1.03 (0.47 – 2.23)
+TCA	72 (0.14)	3.27	0.84 (0.20 – 3.56)
+Other AD	209 (0.41)	2.97	0.69 (0.25 – 1.87)
+SSRI+TCA	39 (0.08)	0.00	*
+SSRI+Other AD	142 (0.28)	4.24	0.96 (0.35 – 2.61)
+TCA+Other AD	45 (0.09)	3.07	0.61 (0.07 – 5.35)
+SSRI+TCA+Other AD	79 (0.16)	5.76	1.19 (0.41 – 3.48)
Main class: TCA			
TCA only	2,187 (4.33)	4.00	1.15 (0.91 – 1.45)
+SSRI	542 (1.07)	5.71	**1.63 (1.13 – 2.35)**
+SNRI	49 (0.10)	7.32	1.31 (0.35 – 4.89)
+Other AD	295 (0.58)	4.12	0.99 (0.54 – 1.84)
+SSRI+SNRI	63 (0.12)	1.71	0.42 (0.06 – 3.24)
+SSRI+Other AD	327 (0.65)	6.21	**1.71 (1.08 – 2.71)**
+SNRI+Other AD	26 (0.05)	8.16	1.64 (0.38 – 7.01)
+SSRI+SNRI+Other AD	126 (0.25)	9.04	**2.21 (1.19 – 4.10)**
Main class: Other AD			
Other AD only	1,877 (3.72)	4.99	**1.38 (1.08 – 1.76)**
+SSRI	961 (1.90)	5.35	1.35 (0.96 – 1.88)
+SNRI	95 (0.19)	4.10	0.90 (0.27 – 3.04)
+TCA	188 (0.37)	10.37	**2.81 (1.72 – 4.60)**
+SSRI+SNRI	262 (0.52)	3.51	0.87 (0.42 – 1.79)
+SSRI+TCA	408 (0.81)	7.30	**1.73 (1.15 – 2.62)**
+SNRI+TCA	31 (0.06)	3.77	0.94 (0.16 – 5.84)
+SSRI+SNRI+TCA	180 (0.36)	6.71	1.34 (0.70 – 2.57)

*: Unable to estimate due to complete separation.

4. Association Between Prescription Pattern and CAD

Dose-response of association by duration of prescription was detected: hazard ratio for CAD was the highest in participants prescribed with antidepressants for 24

months or longer, (HR = 1.64, 95% CI 1.42 – 1.91) while shorter duration of prescription increased the hazard less. (Table 5) Similar trend of association could be found when analyzed by antidepressant classes, except for SNRI which did not show linear dose-response. (Table 7) In contrast, the dose-response by MPR appeared to by nonlinear. The association was the strongest in 'high-intermediate' group and was the weakest in 'high' group, with their HR (95% CI) being 1.64 (1.28 – 2.16) and 1.22 (0.93 – 1.60) respectively. In general, the hazard of CAD with revascularization increased 4% by 10% increase in MPR. (Table 7) Results from polynomial spline was concurrent with stratified analysis: longer duration of prescription was positively associated with CAD with revascularization, while dose-response between MPR and CAD was nonlinear. (Figure 8)

Similar trends were detected in class-specific analysis apart from SNRI, where increased MPR was negatively associated with CAD. Stratified analysis and polynomial spline for prescription duration of each antidepressant class showed positive dose-response association between duration of SSRI, TCA, and other antidepressant prescription and risk of CAD. Among them, the positive dose-response pattern was most prominent in TCA. Duration of SNRI prescription did not show positive dose-response with CAD. (Table 8, Figure 9) Stratified analysis and polynomial spline for MPR of each antidepressant class showed non-linear dose-response pattern. (Table 9, Figure 10)

Table 7. Association between antidepressant prescription pattern and CAD with revascularization.

	Prevalence rate of CAD, per 1,000 person-years	Crude model, HR (95% CI)	Fully adjusted model with time-fixed covariates, HR (95% CI)	Fully adjusted model with time-fixed covariates, HR (95% CI)	Marginal structural model, HR (95% CI)
No antidepressants	4.12	ref	ref	ref	ref
Duration of prescription, months					
Short-term (<6)	4.05	**1.27 (1.08 – 1.48)**	**1.19 (1.02 – 1.39)**	**1.19 (1.01 – 1.39)**	**1.31 (1.12 – 1.53)**
Short-intermediate (6 – 11)	4.18	1.26 (0.86 – 1.85)	1.16 (0.79 – 1.70)	1.13 (0.78 – 1.65)	1.26 (0.85 – 1.86)
Long-intermediate (12 – 23)	5.29	1.21 (0.85 – 1.71)	0.99 (0.70 – 1.41)	0.95 (0.67 – 1.34)	1.17 (0.81 – 1.68)
Long (≥24)	5.62	**1.64 (1.42 – 1.91)**	**1.30 (1.11 – 1.54)**	**1.22 (1.04 – 1.42)**	**1.68 (1.44 – 1.96)**
By 1 year increase		**1.29 (1.06 – 1.57)**	1.17 (0.95 – 1.43)	1.14 (0.94 – 1.37)	**1.27 (1.04 – 1.57)**
Medication possession ratio, %					
Low (<20)	3.86	**1.36 (1.18 – 1.57)**	**1.24 (1.08 – 1.44)**	**1.26 (1.09 – 1.46)**	**1.39 (1.21 – 1.60)**
Low-intermediate (20 – 49)	5.72	**1.51 (1.20 – 1.89)**	1.20 (0.95 – 1.52)	1.25 (0.99 – 1.57)	**1.59 (1.27 – 1.97)**
High-intermediate (50 – 79)	6.59	**1.66 (1.32 – 2.10)**	**1.30 (1.02 – 1.66)**	**1.34 (1.05 – 1.70)**	**1.64 (1.28 – 2.16)**
High (≥80)	5.95	1.24 (0.96 – 1.60)	1.02 (0.78 – 1.34)	1.05 (0.81 – 1.37)	1.22 (0.93 – 1.60)
By 10% increase		**1.03 (1.01 – 1.05)**	1.01 (0.99 – 1.03)	1.02 (0.99 – 1.04)	**1.04 (1.02 – 1.05)**

For fully adjusted model, variables listed below were included as covariates: age, sex, monthly insurance premium, Charlson comorbidity index, psychiatric comorbidities, and history of psychiatric admission. For marginal structural model, inverse probability weight was estimated by multivariate logistic regression model adjusted by same set of variables listed above. HR, hazard ratio; CI, confidence interval; ref, reference.

Table 8. Association between duration of prescription and CAD with revascularization by antidepressant class.

Duration of prescription, months	Prevalence rate of CAD, per 1,000 person-years	Crude model, HR (95% CI)	Fully adjusted model with time-fixed covariates, HR (95% CI)	Fully adjusted model with time-varying covariates, HR (95% CI)	Marginal structural model, HR (95% CI)
SSRI					
None (0)	4.23	ref	ref	ref	ref
Short-term (<6)	4.29	**1.30 (1.11 – 1.51)**	**1.22 (1.04 – 1.43)**	**1.26 (1.08 – 1.47)**	**1.34 (1.15 – 1.57)**
Short-intermediate (6 – 11)	4.75	1.02 (0.68 – 1.54)	0.93 (0.61 – 1.41)	0.96 (0.64 – 1.46)	1.07 (0.70 – 1.64)
Long-intermediate (12 – 23)	5.58	**1.39 (1.00 – 1.94)**	1.17 (0.83 – 1.64)	1.22 (0.87 – 1.71)	1.28 (0.89 – 1.82)
Long (≥24)	5.62	**1.47 (1.24 – 1.75)**	**1.24 (1.03 – 1.49)**	**1.26 (1.05 – 1.52)**	**1.51 (1.26 – 1.80)**
By 1 year increase		**1.06 (1.03 – 1.08)**	**1.03 (1.01 – 1.06)**	**1.03 (1.01 – 1.06)**	**1.06 (1.03 – 1.08)**
SNRI					
None (0)	4.43	ref	ref	ref	ref
Short-term (<6)	4.72	0.99 (0.77 – 1.28)	0.88 (0.68 – 1.14)	1.00 (0.78 – 1.27)	1.00 (0.77 – 1.30)
Short-intermediate (6 – 11)	7.06	**1.69 (1.02 – 2.81)**	1.46 (0.88 – 2.44)	1.41 (0.89 – 2.25)	1.65 (0.96 – 2.84)
Long-intermediate (12 – 23)	4.50	0.87 (0.45 – 1.67)	0.76 (0.39 – 1.46)	0.82 (0.46 – 1.45)	0.94 (0.48 – 1.84)
Long (≥24)	3.45	0.88 (0.54 – 1.42)	0.69 (0.43 – 1.12)	0.57 (0.35 – 0.93)	0.85 (0.51 – 1.44)
By 1 year increase		0.98 (0.90 – 1.07)	0.94 (0.86 – 1.03)	0.94 (0.86 – 1.02)	0.98 (0.90 – 1.08)
TCA					
None (0)	4.28	ref	ref	ref	ref
Short-term (<6)	4.45	**1.47 (1.23 – 1.74)**	**1.34 (1.13 – 1.16)**	**1.34 (1.13 – 1.60)**	**1.39 (1.21 – 1.60)**
Short-intermediate (6 – 11)	6.91	**2.08 (1.59 – 2.72)**	**1.55 (1.20 – 2.08)**	**1.58 (1.20 – 2.07)**	**2.04 (1.55 – 2.69)**
Long-intermediate (12 – 23)	6.11	1.37 (0.87 – 2.15)	1.23 (0.78 – 1.94)	1.28 (0.81 – 2.02)	1.43 (0.89 – 2.27)
Long (≥24)	5.80	**1.67 (1.27 – 2.26)**	**1.42 (1.04 – 1.94)**	**1.39 (1.02 – 1.90)**	**1.62 (1.17 – 2.25)**
By 1 year increase		**1.10 (1.06 – 1.13)**	**1.07 (1.03 – 1.10)**	**1.06 (1.03 – 1.10)**	**1.09 (1.06 – 1.13)**
Other antidepressants					
None (0)	4.19	ref	ref	ref	ref
Short-term (<6)	4.82	**1.30 (1.10 – 1.53)**	1.17 (0.99 – 1.39)	**1.19 (1.01 – 1.42)**	**1.33 (1.13 – 1.58)**
Short-intermediate (6 – 11)	5.89	1.17 (0.79 – 1.72)	1.06 (0.72 – 1.58)	1.07 (0.72 – 1.58)	1.19 (0.80 – 1.78)
Long-intermediate (12 – 23)	4.18	0.94 (0.61 – 1.45)	0.82 (0.53 – 1.27)	0.85 (0.55 – 1.32)	0.87 (0.55 – 1.40)
Long (≥24)	6.23	**1.55 (1.27 – 1.89)**	**1.25 (1.01 – 1.55)**	**1.39 (1.02 – 1.90)**	**1.58 (1.28 – 1.95)**
By 1 year increase		**1.07 (1.04 – 1.10)**	**1.04 (1.01 – 1.07)**	**1.06 (1.03 – 1.10)**	**1.09 (1.06 – 1.13)**

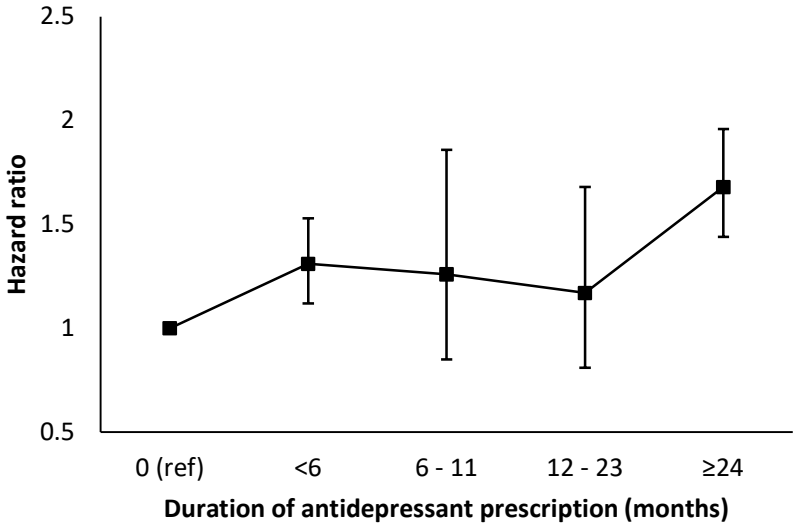
For fully adjusted model, variables listed below were included as covariates: age, sex, monthly insurance premium, Charlson comorbidity index, psychiatric comorbidities, and history of psychiatric admission. For marginal structural model, inverse probability weight was estimated by multivariate logistic regression model adjusted by same set of variables listed above. HR, hazard ratio; CI, confidence interval; ref, reference.

Table 9. Association between MPR and CAD with revascularization by antidepressant class.

Class-specific MPR, %	Prevalence rate of CAD, per 1,000 person-years	Crude model, HR (95% CI)	Fully adjusted model with time-fixed covariates, HR (95% CI)	Fully adjusted model with time-varying covariates, HR (95% CI)	Marginal structural model, HR (95% CI)
SSRI					
None (0)	4.23	ref	ref	ref	ref
Low (<20)	4.17	**1.39 (1.21 – 1.60)**	**1.27 (1.10 – 1.46)**	**1.30 (1.13 – 1.50)**	**1.42 (1.23 – 1.63)**
Low-intermediate (20 – 49)	5.52	**1.36 (1.06 – 1.73)**	1.15 (0.89 – 1.47)	1.18 (0.92 – 1.52)	**1.41 (1.10 – 1.81)**
High-intermediate (50 – 79)	6.06	1.26 (0.95 – 1.68)	1.05 (0.78 – 1.40)	1.08 (0.80 -1 .45)	1.27 (0.94 – 1.71)
High (≥80)	6.04	1.15 (0.83 – 1.59)	1.05 (0.76 – 1.46)	1.10 (0.79 – 1.53)	1.16 (0.83 – 1.63)
By 10% increase		**1.03 (1.00 – 1.06)**	1.01 (0.98 – 1.04)	1.01 (0.99 – 1.04)	**1.03 (1.00 – 1.06)**
SNRI					
None (0)	4.43	ref	ref	ref	ref
Low (<20)	4.74	1.14 (0.92 – 1.40)	1.02 (0.82 – 1.26)	0.99 (0.78 – 1.24)	1.18 (0.95 – 1.46)
Low-intermediate (20 – 49)	4.35	0.80 (0.48 – 1.33)	0.68 (0.41 – 1.13)	0.65 (0.37 – 1.15)	0.77 (0.45 – 1.34)
High-intermediate (50 – 79)	5.54	0.82 (0.39 – 1.74)	0.68 (0.32 – 1.44)	0.76 (0.34 – 1.70)	0.81 (0.36 – 1.82)
High (≥80)	3.06	0.40 (0.10 – 1.02)	0.40 (0.10 – 1.50)	0.34 (0.09 – 1.37)	0.45 (0.11 – 1.83)
By 10% increase		0.93 (0.86 – 1.01)	**0.91 (0.84 – 0.99)**	0.91 (0.84 – 1.00)	0.93 (0.86 – 1.02)
TCA					
None (0)	4.28	ref	ref	ref	ref
Low (<20)	4.52	**1.53 (1.31 – 1.79)**	**1.38 (1.18 – 1.62)**	**1.28 (1.11 – 1.48)**	**1.49 (1.27 – 1.75)**
Low-intermediate (20 – 49)	5.86	1.30 (0.91 – 1.84)	1.06 (0.74 – 1.51)	1.14 (0.81 – 1.61)	1.31 (0.91 – 1.89)
High-intermediate (50 – 79)	9.17	**2.75 (2.02 – 3.74)**	**2.17 (1.59 – 2.98)**	**1.94 (1.41 – 2.66)**	2.59 (1.85 – 3.64)
High (≥80)	6.20	1.27 (0.72 – 2.24)	1.07 (0.61 – 1.90)	0.92 (0.54 – 1.46)	1.24 (0.67 – 2.27)
By 10% increase		**1.09 (1.05 – 1.13)**	**1.06 (1.02 – 1.09)**	**1.06 (1.02 – 1.09)**	**1.09 (1.05 – 1.13)**
Other antidepressants					
None (0)	4.19	ref	ref	ref	ref
Low (<20)	4.70	**1.31 (1.13 – 1.53)**	**1.20 (1.02 – 1.40)**	**1.18 (1.01 – 1.37)**	**1.33 (1.14 – 1.56)**
Low-intermediate (20 – 49)	5.55	1.21 (0.92 – 1.62)	1.01 (0.74 – 1.38)	0.95 (0.68 – 1.33)	1.22 (0.90 – 1.66)
High-intermediate (50 – 79)	8.15	**1.72 (1.29 – 2.29)**	**1.47 (1.08 – 2.01)**	**1.53 (1.12 – 2.09)**	**1.74 (1.28 – 2.35)**
High (≥80)	6.19	1.14 (0.77 – 1.70)	0.99 (0.64 – 1.52)	0.93 (0.64 – 1.36)	1.15 (0.75 – 1.76)
By 10% increase		**1.07 (1.02 – 1.13)**	1.01 (0.98 – 1.04)	1.02 (0.99 – 1.05)	**1.07 (1.02 – 1.12)**

For fully adjusted model, variables listed below were included as covariates: age, sex, monthly insurance premium, Charlson comorbidity index, psychiatric comorbidities, and history of psychiatric admission. For marginal structural model, inverse probability weight was estimated by multivariate logistic regression model adjusted by same set of variables listed above. HR, hazard ratio; CI, confidence interval; ref, reference.

A. Duration of antidepressant prescription



B. MPR

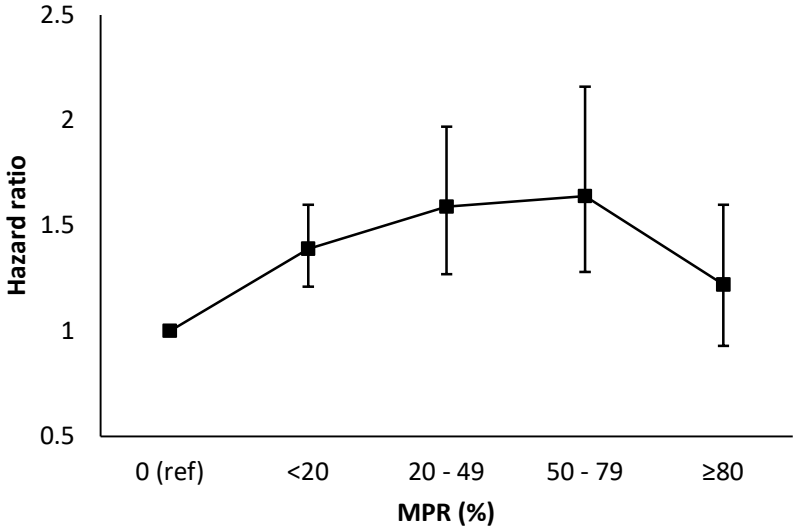
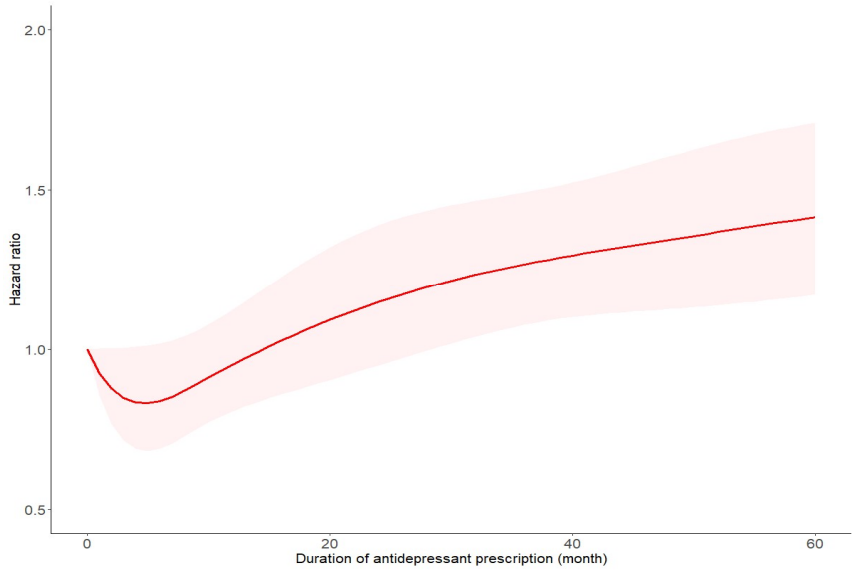


Figure 7. Association between prescription patterns and CAD with revascularization. A: duration of antidepressant prescription; B: MPR.

A. Duration of antidepressant prescription



B. MPR

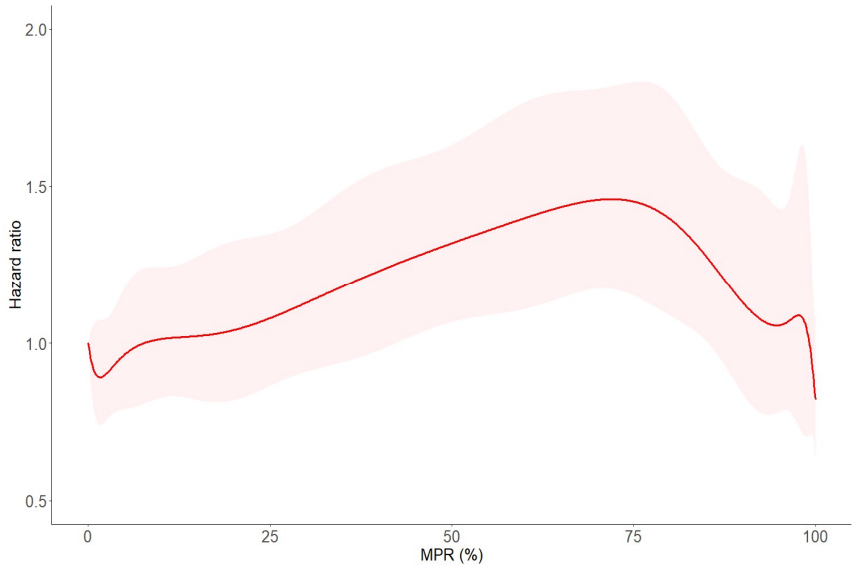
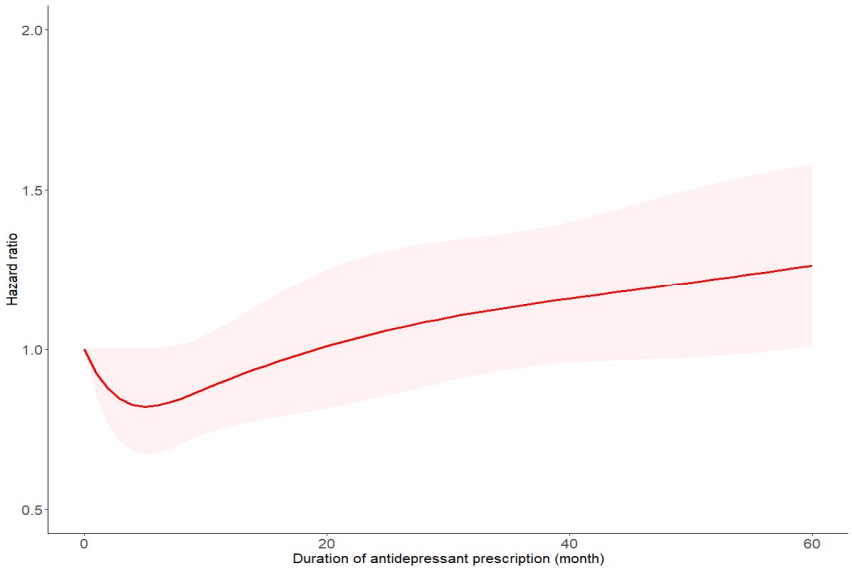
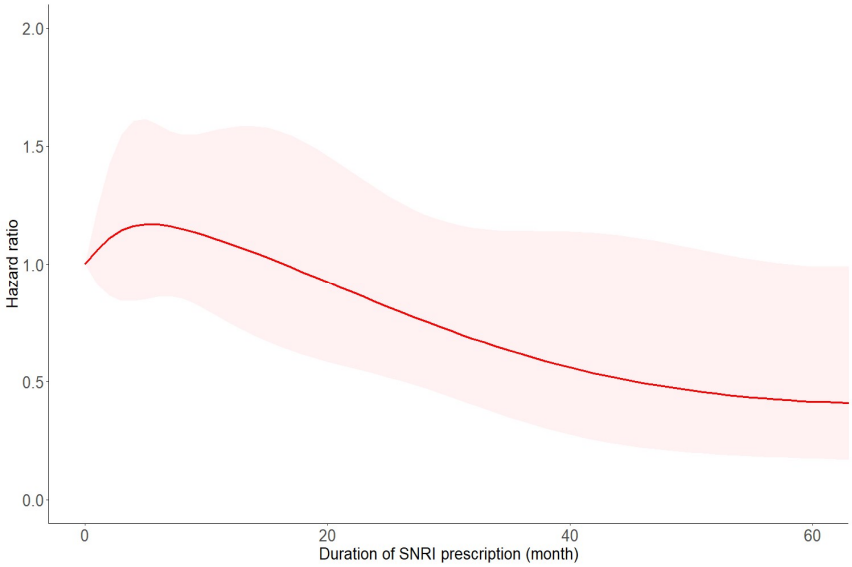


Figure 8. Polynomial spline for dose-response between prescription patterns and hazard ratio for CAD. A: duration of antidepressant prescription; B: MPR.

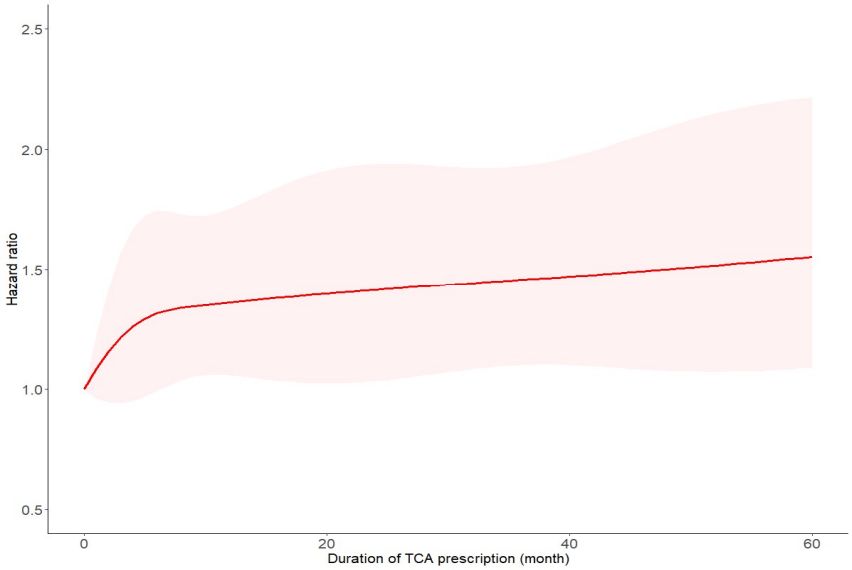
A. SSRI



B. SNRI



C. TCA



D. Other antidepressants prescription

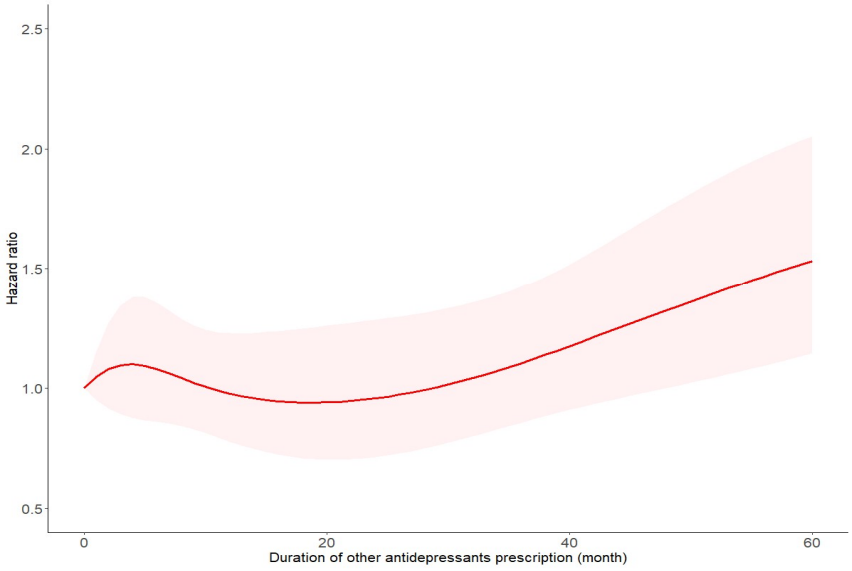
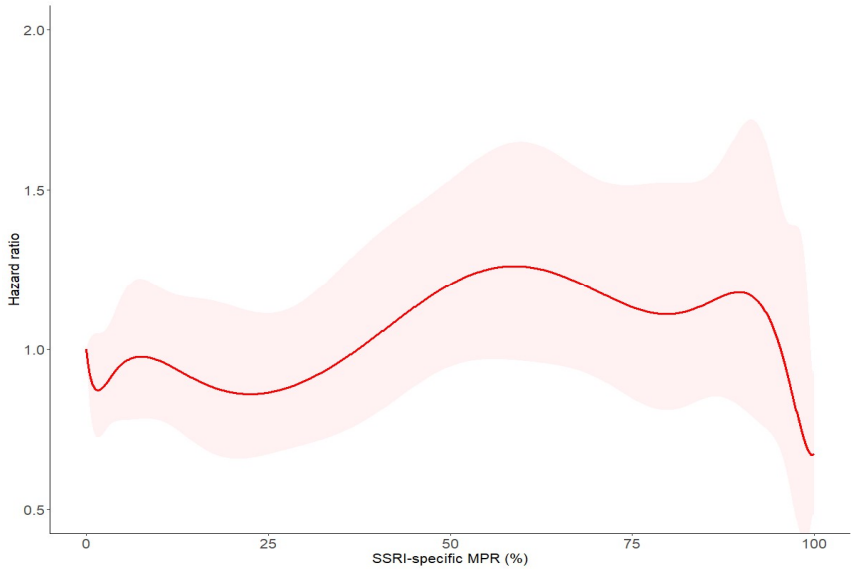
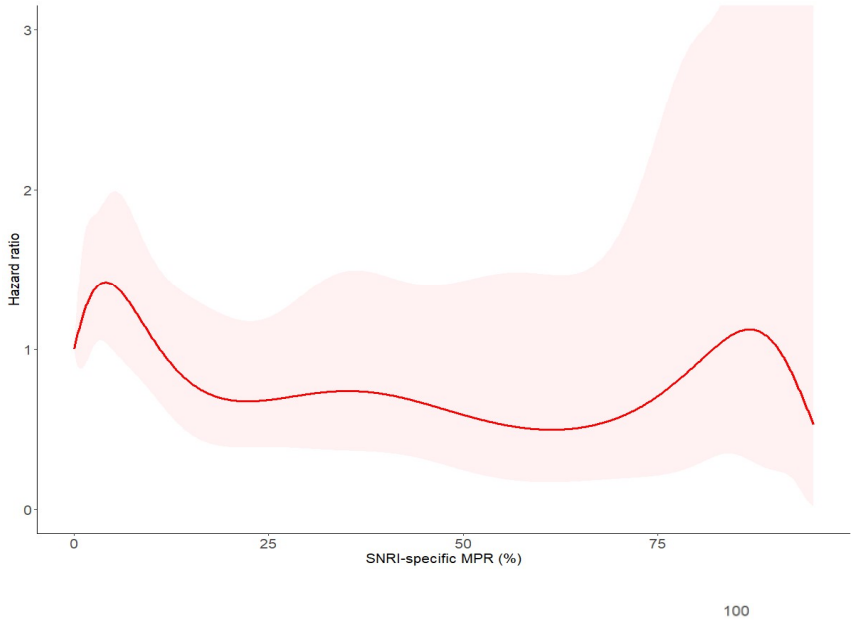


Figure 9. Dose response between class-specific duration of prescription and CAD with revascularization. A: SSRI; B: SNRI; C: TCA; D: Other antidepressants.

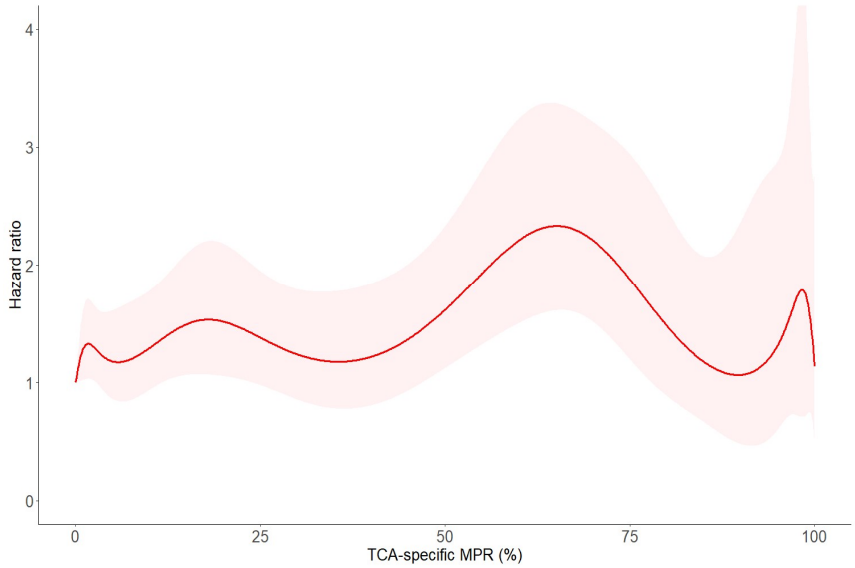
A. SSRI



B. SNRI



C. TCA



D. Other antidepressants

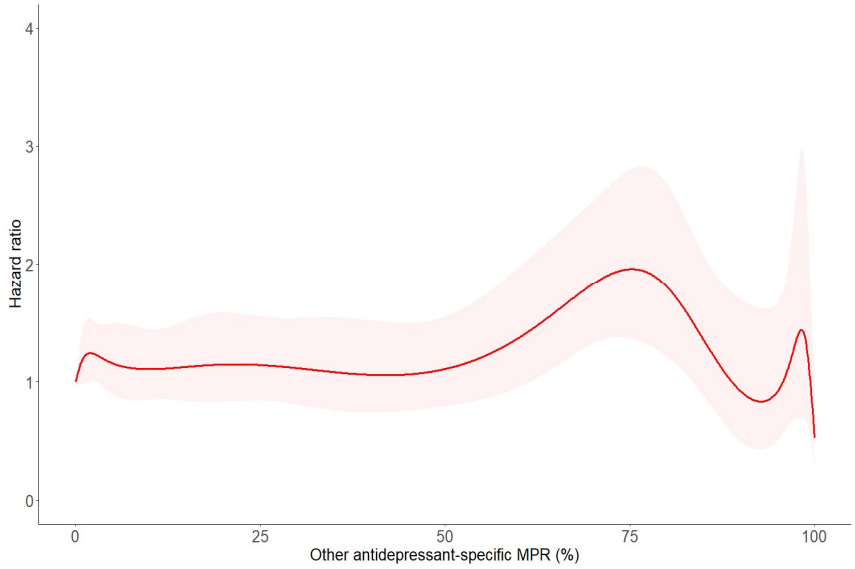


Figure 10. Dose response between class-specific MPR and CAD with revascularization.
A: SSRI; B: SNRI; C: TCA; D: Other antidepressants.

5. Sensitivity Analyses

Appendices 6 – 7 present the results from lag-time analysis with lag time of 6, 12, and 24 months, which was conducted to assess the magnitude of protopathic bias. In all assessments, the estimand did not significantly shift from the original estimand regardless of lag time, indicating that the impact of possible protopathic bias to the estimand is not likely to be significant.

Appendices 8 – 9 present the results from progressive IP weight truncation, which was conducted to assess the effect of possible violation of positivity assumption by removing extreme values. Results from truncations introduced no significant changes in estimand, both for antidepressant class assessment and prescription pattern assessment. The results from progressive IP weight truncation suggest that the probability of violation of positivity assumption is low in this analysis.

Appendix 10 – 11 shows characteristics of participant subgroup who had received health checkup. (N = 37,558) The mean age of the subgroup was 46.34 years, which was significantly higher than the mean age of the full cohort. Among 37,558 participants of the subgroup, 16,295 participants (43.39%) did not have any records of antidepressant prescription, 11,762 participants (31.32%) received single class of antidepressants, and 9,501 participants (25.30%) received multiple classes of antidepressants. Descriptive analysis on the subgroup showed that antidepressant prescription is positively associated with cigarette smoking and alcohol

consumption. In contrast, differences in laboratory test results such as systolic blood pressure, diastolic blood pressure, fasting blood glucose, and total serum cholesterol were minimal, albeit being statistically significant. (Appendix 10)

Individuals who did not receive health checkup paid less insurance premium and had more medical and psychiatric comorbidities. They were also more likely to be prescribed with antidepressant medication. The proportion of participants exposed to antidepressants was also higher in those who did not receive health checkup. However, the proportion of participants who were diagnosed with CAD with revascularization was higher in those who received health checkup. (Appendix 11)

Appendix 12 shows the comparison between the estimand from the subgroup analysis and it from the main analysis. The hazard ratio of antidepressant prescription on CAD with revascularization was 1.34 (95% CI 1.19 – 1.51) in subgroup analysis, which was not significantly different from the estimate of main analysis. (HR = 1.31, 95% CI 1.18 – 1.46) Positive dose-response between number of antidepressant classes and CAD with revascularization was also detected in this subgroup analysis, although the estimated hazard ratio of '4 classes' subgroup was relatively smaller (HR = 1.54, 95% CI 0.93 – 2.56) compared to that of main analysis. (HR = 1.97, 95% CI 1.40 – 2.76) In analysis by main treatment regimen, the hazard ratio of SSRI was larger in subgroup analysis (HR = 1.45, 95% CI 1.28 – 1.65) than in main analysis (HR = 1.31, 95% CI 1.07 – 1.60), but other estimates

did not differ significantly. In analysis by ever exposure, duration of prescription, and MPR, no significant difference was detected. (Appendix 13)

Appendix 13 present the bounding factors HR_{AU} and HR_{UY}, which are minimum amplitude of association between unmeasured confounder, exposure, and outcome to completely explain away the estimated effect size. For instance, to completely explain the hazard ratio of antidepressant exposure on CAD with revascularization, the joint bounding factor $\frac{RR_{AU} \times RR_{UY}}{RR_{AU}+RR_{UY}-1}$ should be larger than 1.31. One of the possible combinations of bounding factors (HR_{AU}, HR_{UY}) is (1.5, 3.5): in this scenario, the effect size of unmeasured confounder – exposure association is 1.5, and the effect size of unmeasured confounder – outcome association is 3.5. While hazard ratio of 1.5 is likely to be detected, hazard ratio of 4 is highly unlikely. Therefore, the estimated bounding factors suggest that unmeasured confounding effect is unlikely to nullify the estimated effect size. Other bounding factors for estimated effect sizes also suggested that total nullification by unmeasured confounding effects is implausible.

V. DISCUSSION

1. Discussion of the Study Methods

The objective of this study was to investigate prescription patterns of antidepressants after diagnosis of PTSD and evaluate the overall and class-specific cardiovascular effects of antidepressant prescription. This includes evaluation of duration of medication possession and MPR, testing the dose response in association, and conducting stratified analysis by antidepressant combinations.

As application of antidepressant is associated with both psychiatric symptoms and cardiovascular disease, there is a risk of confounding by indication embedded in the study design. The results showed that participants exposed to antidepressants have higher risk of experiencing CAD with revascularization during the follow-up. Antidepressant prescription was also associated with higher risk of psychiatric comorbidities and psychiatric hospitalization, suggesting higher symptom severity in those treated with antidepressants.

Confounding effects of time-varying confounders, the most important of which being medical and psychiatric comorbidities, is also a major source of bias when poorly controlled. It is not possible to control for the time-varying confounding effect by conventional regression, as its conditions on part of the effect of interest.[166] Application of baseline IP weight also does not provide adequate marginalization,

as past vectors for exposure and covariates affect both the future exposure and outcome.[167]

To overcome this and conduct proper marginalization, marginal structural model was applied. Calculation of inverse probability weight based on potential predictors of treatment allocation and constructing pseudo-population based on IP weights enable controlling for confounding by indication by emulating concept of randomized controlled trial.[164, 186] In this study, measured time-dependent confounders include socioeconomic status, psychiatric comorbidities, medical comorbidities, and history of psychiatric admission. Originally additional adjustment by variables from health checkup database was considered, but there was a probability of introducing additional selection bias due to low rate of participation to health checkup. As an alternative measure to medical condition, Charlson Comorbidity Index was calculated at each time interval.

There are several methodological limitations of this study. Similar to other MSM, the assumption of no unmeasured confounding is not empirically verifiable. The unmeasured confounders that could significantly affect the estimand include inflammatory cytokine level, serum cortisol and epinephrine level, serum leukocytes and lymphocytes level, and health behaviors. Most of the unmeasured confounding derives from the limitations of the NHID, which is an administrative database rather than a well-defined cohort. Although it is highly likely that a set of covariates that we have included in MSM is enough to achieve exchangeability, no

empirical methods can completely rule out the possibility of unmeasured confounding effect. To test the magnitude of possible bias by unmeasured confounding, sensitivity analysis method developed by Ding & Vanderweele was applied, and the result showed that unmeasured confounding with comparably large magnitude association between both exposure and outcome is needed to significantly bias the estimates. Also, as the main analysis

Misclassification and misdiagnosis are also potential threats to the accuracy of the estimand. Particularly, diagnostic accuracy of PTSD had been a subject of debate, but there is no consensus on the direction of misdiagnosis.[187] As previous investigation indicates, it is possible that misclassification or misdiagnosis in Korean NHID could introduce misclassification bias to the estimand.[188] To improve diagnostic accuracy, definitions of psychiatric disorders that had been formerly used by the Korean NHIS was applied to the study.[189-191]

Another important limitation of this study is that psychometric measures, such as scores from PTSD Checklist for DSM-5 (PCL-5) scale and Generalized Anxiety Disorder-7 item (GAD-7), are not provided in the database. Therefore, it is impossible to properly determine the severity and types of PTSD symptoms. For indirect assessment of psychiatric symptoms was done by reviewing diagnostic codes for psychiatric comorbidities and hospitalization record due to psychiatric disorders.

Finally, as NHID consists of healthcare utilization records that are covered by Korean NHIS, effects of antidepressant prescription that are not covered by Korean NHIS could not be estimated from this study, which might introduce misclassification bias to the results. However, it could be postulated that the effect of possible misclassification bias on the results is minimal, since according to Korean Ministry of Health and Welfare, 94.2% of total antidepressant consumption was covered by Korean NHIS in year 2018.[192]

2. Discussion of the Results

1) Summary of the results

Overall, exposure to antidepressant medication appeared to be a risk factor of incident CAD with revascularization in PTSD patients. Dose-response pattern by number of antidepressant classes was detected in the analysis, with patients who received all 4 classes presenting the highest hazard ratio for CAD with revascularization. While SNRI was not significantly associated with CAD, all other classes of antidepressants increased the risk of CAD.

Risk of incident CAD with revascularization was dependent of combination of antidepressants: combinations that included TCA and other antidepressants were strongly associated with CAD, while combinations with SNRI tended to have

weaker association with CAD. The association was the strongest in participants whose main treatment modality was TCA, and those treated mainly with SSRI showed the weakest significant association.

While exposure to antidepressant medication was an important predictor of CAD, total duration of prescription was a better predictor of incident CAD than MPR: while positive dose-response pattern was detected in duration-CAD association, the pattern was less definite in MPR-CAD association. Results from polynomial spline reaffirmed the dose-response pattern of the association, indicating that total duration of prescription rather than MPR better predicts the risk of CAD. When analyzed by antidepressant class, the association between duration of SNRI and CAD was unclear, while positive dose-response pattern was detected in other classes of antidepressants.

Results from lag-time analysis did not significantly differ from main analysis, suggesting that the effect of protopathic bias was well controlled by MSM. Progressive IP weight truncation did not significantly alter the results, indicating that violation of positivity assumption is not likely to affect the interpretation. Estimated bounding factors suggested that unmeasured confounding effect by itself could not explain the estimated effect away completely.

2) Interpretation of the results

As prevalence of psychiatric disorders increased and importance of proper management against psychiatric disorders grew, so did the interest of researchers in medical comorbidities of psychiatric disorders and adverse effects of treatment. Particularly, a large number of studies had been dedicated to understanding cardiovascular comorbidities in psychiatric disorders[25-28,193,194] and their association with antidepressant medication.[49-51,195,196] However, evidence from previous studies on cardiovascular effect of antidepressants was inconsistent and thus inconclusive on direction of cardiovascular effects of antidepressants.

PTSD is a psychiatric disorder that results from multiple neurobiological response to traumatic events,[9-18] and therefore comorbidities, both psychiatric and medical, are common in PTSD.[25-28,34-39] As a result, antidepressants in PTSD imposes wide spectrum of pharmacologic effects, ranging from symptom relief[148,149] to exacerbation of atherosclerosis,[151,152] which impose mixed impact on cardiovascular disease. The complexity of association is further increased by psychiatric comorbidities of PTSD, such as mood disorder,[34,35] anxiety disorder,[36,37] and somatoform disorder,[38,39] as they are both associated with antidepressant prescription pattern and CVD, introducing confounding by indication to the analysis model. These symptoms and disorders change over the course of treatment, thereby introducing time-dependent nature to the confounding effect. Additionally,

heterogeneity in antidepressant classes and medication possession also contributes to the difficulties in analyzing the cardiovascular effect of antidepressants in PTSD.

This study tried to account for probable confounding effects and biases, including confounding by indication, protopathic bias, and residual confounding, and to estimate cardiovascular effects of antidepressants in PTSD in Korean population. This study utilized Korean NHID, which is one of the Korean databases with the highest external validity, as it consists of all administrative records of medical service utilization that are covered by Korean NHIS. As a result, estimand of this study could be widely applied to Korean population. In addition, by controlling for time-dependent confounding by indication, this study tried to provide estimand which are closer to real-world effect compared to those from conventional analysis.

One of the important findings of this study could be found from class-specific and combination-specific analysis, where cardiovascular effects of different medication combinations have been tested. Results from this study indicate that antidepressant combinations that includes TCAs have strong association with CAD in PTSD, while combinations with SNRIs show less apparent association. This suggests that prescribing TCAs to PTSD patients with high CVD risk should be avoided and alternative treatment options should be considered. Previously several studies have reported cardiotoxicity of TCAs, including arrythmia,[197] QT prolongation,[198] and thromboembolism.[199] The cardiotoxic effects of TCAs were consistently detected in this study as well, indicating the cardiovascular risk of TCA application in PTSD.

SNRIs, on the other hand, appeared not to be associated with CAD in PTSD. A systematic review on cardiovascular effect of duloxetine showed that increase in heart rate and blood pressure due to duloxetine administration is subclinical.[200] Another cohort study had also reported that all classes of antidepressants except SNRIs increased the risk of major adverse cardiovascular events.[201] It could be postulated from these results, as well as evidence from this study, that SNRI is relatively safe in the perspective of cardiovascular disease. In this study, only 7.78% participants were ever prescribed with SNRIs, and only 2.79% of participants were mainly treated with SNRIs. Considering the lower cardiovascular burden of SNRIs, prescription of SNRIs to patients with higher CVD risk could be considered as an alternative option to TCAs.

It should be noted that SSRIs do not increase the CVD risk significantly when administered alone, but the combination of SSRIs with TCAs tend to show the strongest association with CVD. This might be attributed to pharmacokinetic interactions between TCAs and SSRIs: commonly used SSRIs inhibit the metabolism of CYP450 enzymes such as CYP2D6 (fluoxetine, paroxetine, and sertraline), CYP1A2, CYP2C19, and CYP3A4 (fluvoxamine), which are related to metabolism of TCAs and MAOIs.[202-203] Several practitioners and researchers have suggested that the combination of SSRI and TCA should not be recommended and, should they be administered simultaneously, they should be presceibed under caution.[204-205]

Therapeutic drug monitoring (TDM) for antidepressants could be a way to prevent adverse effects in the existence of certain interactions with each other. Although TDM use in antidepressant treatment is not considered to be a standard of care due to limited evidence on the assumptions,[206] a systematic review had successfully demonstrated that serum concentration of TCAs well predicted the response to the medication due to its cardiotoxic potentials.[207,208] As for SSRIs, a concentration-effect relationship is not as clear as in TCAs, but some reports suggest dose dependence of clinical improvement in SSRIs as well.[209,210] Further studies on adverse cardiovascular effects of antidepressants and role of TDM on CVD prevention in PTSD could help better understand the mechanisms of action and drug-drug interaction in commonly prescribed antidepressants for PTSD treatment.

3. Implications of the Study

There had been several studies that assessed cardiovascular effect of antidepressants in PTSD, but existing evidence was insufficient and conflicting, rendering it impossible to draw out definite conclusion. Results from this study suggest that PTSD patients under antidepressant medication have a higher risk of developing CAD, and the risk is positively associated with duration of prescription and number of antidepressant classes. This implication could be generalized to

Korean population, as the evidence is from Korean NHID, which covers around 98% of Korean citizens.

As it has been previously investigated in several studies, cardiovascular comorbidity is one of major comorbidities in PTSD, and importance of preventing cardiovascular disease in PTSD has been suggested. Results from this study emphasize the negative cardiovascular effects of antidepressant medication, which is an important treatment modality for PTSD, and suggest the importance of cardiovascular disease prevention in PTSD patients who receive long-term pharmacologic treatment, including TDM and surveillance for cardiovascular diseases. The results from this study also indicate difference in cardiovascular effect by combination of antidepressants and could help clinicians select antidepressant regimen for PTSD that would impose less toll on cardiovascular health of patients.

VI. Conclusion

Antidepressant medication for treating PTSD increases the risk of coronary artery disease. Cardiovascular effect of antidepressants in PTSD is proportional to duration of exposure to antidepressant and classes of prescribed antidepressants. Antidepressant combinations that include SNRI tend to be less related to coronary artery disease, while other classes of antidepressants increase the risk of developing incident coronary artery disease. It would be reasonable for clinicians to assess cardiovascular risk of PTSD patients who are receiving long-term antidepressant treatment and consider TDM, medication switching, or medication discontinuation for those with high risk of CAD development. Especially, for those receiving TCAs with SSRIs, therapeutic drug monitoring for serum TCA and SSRI level could be helpful in preventing CAD.

REFERENCES

1. Bryant RA. Post-traumatic stress disorder: a state-of-the-art review of evidence and challenges. World Psychiatry 2019;18:259-69.
2. Yehuda R. Post-traumatic stress disorder. New England journal of medicine 2002;346:108-14.
3. de Vries GJ, Olff M. The lifetime prevalence of traumatic events and posttraumatic stress disorder in the Netherlands. Journal of Traumatic Stress: Official Publication of The International Society for Traumatic Stress Studies 2009;22:259-67.
4. Merz J, Schwarzer G, Gerger H. Comparative Efficacy and Acceptability of Pharmacological, Psychotherapeutic, and Combination Treatments in Adults With Posttraumatic Stress Disorder: A Network Meta-analysis. JAMA Psychiatry 2019;76:904-13.
5. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Archives of general psychiatry 2005;62:593-602.
6. Kim H, Lee J, Chang SM, Hong JP, Lee D-W, Hahm B-J, et al. Prevalence of lifetime psychiatric disorders and suicidality in adults with subthreshold posttraumatic stress disorder: A population-based nationwide study in Korea. Psychological trauma: theory, research, practice, and policy 2021.
7. Kim S-Y, Yang K, Oh I-H, Park S, Cheong H-K, Hwang J-W. Incidence and Direct Medical Cost of Acute Stress Disorder and Post-traumatic Stress Disorder in Korea: Based on National Health Insurance Service Claims Data from 2011 to 2017. JKMS 2021;36:e125-0.
8. Kim K, Tsai AC, Lowe S, Stewart R, Jung SJ. Urbanicity, posttraumatic stress disorder, and effect modification by socioeconomic position: A nested case–control study of the Korean National Health Insurance Database. Acta Psychiatrica Scandinavica 2023;147(1):54-64.
9. Murrough JW, Huang Y, Hu J, Henry S, Williams W, Gallezot J-D, et al. Reduced Amygdala Serotonin Transporter Binding in Posttraumatic Stress Disorder. Biological Psychiatry 2011;70:1033-8.

10. Corchs F, Nutt DJ, Hood S, Bernik M. Serotonin and sensitivity to trauma-related exposure in selective serotonin reuptake inhibitors-recovered posttraumatic stress disorder. Biological Psychiatry 2009;66:17-24.
11. Trousselard M, Lefebvre B, Caillet L, Andruetan Y, de Montleau F, Denis J, et al. Is plasma GABA level a biomarker of Post-Traumatic Stress Disorder (PTSD) severity? A preliminary study. Psychiatry Research 2016;241:273-9.
12. Vaiva G, Thomas P, Ducrocq F, Fontaine M, Boss V, Devos P, et al. Low posttrauma GABA plasma levels as a predictive factor in the development of acute posttraumatic stress disorder. Biological Psychiatry 2004;55:250-4.
13. Southwick SM, Davis LL, Aikins DE, Rasmusson A, Barron J, Morgan III CA. Neurobiological alterations associated with PTSD. 2007.
14. Speer KE, Semple S, Naumovski N, D'Cunha NM, McKune AJ. HPA axis function and diurnal cortisol in post-traumatic stress disorder: A systematic review. Neurobiology of Stress 2019;11:100180.
15. Dunlop BW, Wong A. The hypothalamic-pituitary-adrenal axis in PTSD: Pathophysiology and treatment interventions. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2019;89:361-79.
16. Vaccarino V, Bremner JD. Behavioral, emotional and neurobiological determinants of coronary heart disease risk in women. Neuroscience & Biobehavioral Reviews 2017;74:297-309.
17. Lima BB, Hammadah M, Wilmot K, Pearce BD, Shah A, Levantsevych O, et al. Posttraumatic stress disorder is associated with enhanced interleukin-6 response to mental stress in subjects with a recent myocardial infarction. Brain, Behavior, and Immunity 2019;75:26-33.
18. Michopoulos V, Powers A, Gillespie CF, Ressler KJ, Jovanovic T. Inflammation in fear-and anxiety-based disorders: PTSD, GAD, and beyond. Neuropsychopharmacology 2017;42:254-70.
19. Hughes KC, Shin LM. Functional neuroimaging studies of post-traumatic stress disorder. Expert Rev Neurother 2011;11:275-85.
20. Protopopescu X, Pan H, Tuescher O, Cloitre M, Goldstein M, Engelien W, et al. Differential time courses and specificity of amygdala activity in posttraumatic

stress disorder subjects and normal control subjects. Biological Psychiatry 2005;57:464-73.

21. Stevens JS, Jovanovic T, Fani N, Ely TD, Glover EM, Bradley B, et al. Disrupted amygdala-prefrontal functional connectivity in civilian women with posttraumatic stress disorder. Journal of psychiatric research 2013;47:1469-78.
22. Bremner JD, Elzinga B, Schmahl C, Vermetten E. Structural and functional plasticity of the human brain in posttraumatic stress disorder. Progress in brain research 2007;167:171-86.
23. Admon R, Milad MR, Hendler T. A causal model of post-traumatic stress disorder: disentangling predisposed from acquired neural abnormalities. Trends in cognitive sciences 2013;17:337-47.
24. Neylan TC, Mueller SG, Wang Z, Metzler TJ, Lenoci M, Truran D, et al. Insomnia severity is associated with a decreased volume of the CA3/dentate gyrus hippocampal subfield. Biological psychiatry 2010;68:494-6.
25. Sumner JA, Kubzansky LD, Elkind MS, Roberts AL, Agnew-Blais J, Chen Q, et al. Trauma exposure and posttraumatic stress disorder symptoms predict onset of cardiovascular events in women. Circulation 2015;132:251-9.
26. Song H, Fang F, Arnberg FK, Mataix-Cols D, de la Cruz LF, Almqvist C, et al. Stress related disorders and risk of cardiovascular disease: population based, sibling controlled cohort study. bmj 2019;365.
27. Byers AL, Covinsky KE, Neylan TC, Yaffe K. Chronicity of posttraumatic stress disorder and risk of disability in older persons. JAMA psychiatry 2014;71:540-6.
28. Nelson CA, Bhutta ZA, Harris NB, Danese A, Samara M. Adversity in childhood is linked to mental and physical health throughout life. bmj 2020;371.
29. Ebrahimi R, Lynch K, VIernes B, Beckham J, Tseng C-H, Shroyer A, et al. Posttraumatic stress disorder and cardiovascular mortality-impact on age at death for women veterans. Journal of the American College of Cardiology 2021;77:1514-.
30. Kiecolt-Glaser JK, Gouin J-P, Weng N-p, Malarkey WB, Beversdorf DQ, Glaser R. Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation. Psychosomatic medicine 2011;73:16.

31. Fagundes CP, Glaser R, Kiecolt-Glaser JK. Stressful early life experiences and immune dysregulation across the lifespan. Brain, behavior, and immunity 2013;27:8-12.
32. Carpenter LL, Shattuck TT, Tyrka AR, Geracioti TD, Price LH. Effect of childhood physical abuse on cortisol stress response. Psychopharmacology 2011;214:367-75.
33. O'Donnell CJ, Schwartz Longacre L, Cohen BE, Fayad ZA, Gillespie CF, Liberzon I, et al. Posttraumatic Stress Disorder and Cardiovascular Disease: State of the Science, Knowledge Gaps, and Research Opportunities. JAMA Cardiology 2021;6:1207-16.
34. Dedert EA, Calhoun PS, Watkins LL, Sherwood A, Beckham JC. Posttraumatic stress disorder, cardiovascular, and metabolic disease: a review of the evidence. Annals of Behavioral Medicine 2010;39:61-78.
35. Breslau N, Davis GC, Peterson EL, Schultz LR. A second look at comorbidity in victims of trauma: the posttraumatic stress disorder–major depression connection. Biological Psychiatry 2000;48:902-9.
36. Goldstein-Piekarski AN, Williams LM, Humphreys K. A trans-diagnostic review of anxiety disorder comorbidity and the impact of multiple exclusion criteria on studying clinical outcomes in anxiety disorders. Translational Psychiatry 2016;6:e847-e.
37. Knowles KA, Sripada RK, Defever M, Rauch SA. Comorbid mood and anxiety disorders and severity of posttraumatic stress disorder symptoms in treatment-seeking veterans. Psychological Trauma: Theory, Research, Practice, and Policy 2019;11:451.
38. van Dijke A, Ford JD, van der Hart O, van Son M, van der Heijden P, Buhring M. Complex posttraumatic stress disorder in patients with borderline personality disorder and somatoform disorders. Psychological Trauma: Theory, Research, Practice, and Policy 2012;4:162.
39. Perkonigg A, Pfister H, Stein MB, Höfler M, Lieb R, Maercker A, et al. Longitudinal course of posttraumatic stress disorder and posttraumatic stress disorder symptoms in a community sample of adolescents and young adults. American Journal of Psychiatry 2005;162:1320-7.

40. Dao TK, Chu D, Springer J, Gopaldas RR, Menefee DS, Anderson T, et al. Clinical depression, posttraumatic stress disorder, and comorbid depression and posttraumatic stress disorder as risk factors for in-hospital mortality after coronary artery bypass grafting surgery. The Journal of Thoracic and Cardiovascular Surgery 2010;140:606-10.
41. Park CS, Choi E-K, Han K-D, Ahn H-J, Kwon S, Lee S-R, et al. Increased cardiovascular events in young patients with mental disorders: a nationwide cohort study. European Journal of Preventive Cardiology 2023;30:1582-92.
42. Watts BV, Schnurr PP, Mayo L, Young-Xu Y, Weeks WB, Friedman MJ. Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. The Journal of clinical psychiatry 2013;74:11710.
43. Gerger H, Munder T, Gemperli A, Nüesch E, Trelle S, Jüni P, et al. Integrating fragmented evidence by network meta-analysis: relative effectiveness of psychological interventions for adults with post-traumatic stress disorder. Psychological Medicine 2014;44:3151-64.
44. Frost ND, Laska KM, Wampold BE. The Evidence for Present-Centered Therapy as a Treatment for Posttraumatic Stress Disorder. Journal of Traumatic Stress 2014;27:1-8.
45. Friedman M, Lowry P, Ruzek J. VA/DoD clinical practice guidelines for the management of post-traumatic stress. The Management of Post-Traumatic Stress Working Group. Retrieved October 2010;22:2011.
46. Gelenberg AJ, Freeman M, Markowitz J, Rosenbaum J, Thase M, Trivedi M, et al. American Psychiatric Association practice guidelines for the treatment of patients with major depressive disorder. Am J Psychiatry 2010;167:9-118.
47. Albott CS, Lim KO, Forbes MK, Erbes C, Tye SJ, Grabowski JG, et al. Efficacy, safety, and durability of repeated ketamine infusions for comorbid posttraumatic stress disorder and treatment-resistant depression. The Journal of clinical psychiatry 2018;79:17462.
48. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or

several treatment steps: a STAR* D report. American Journal of Psychiatry 2006;163:1905-17.

49. Burgess C, Turner P. Cardiotoxicity of antidepressant drugs. Neuropharmacology 1980;19:1195-9.

50. Rubin RR, Peyrot M, Gaussoin SA, Espeland MA, Williamson D, Faulconbridge LF, et al. Four-Year Analysis of Cardiovascular Disease Risk Factors, Depression Symptoms, and Antidepressant Medicine Use in the Look AHEAD (Action for Health in Diabetes) Clinical Trial of Weight Loss in Diabetes. Diabetes Care 2013;36:1088-94.

51. Roose SP. Considerations for the use of antidepressants in patients with cardiovascular disease. American Heart Journal 2000;140:S84-S8.

52. Young JG, Hernán MA, Picciotto S, Robins JM. Relation between three classes of structural models for the effect of a time-varying exposure on survival. Lifetime data analysis 2010;16:71-84.

53. Kuehl LK, Muhtz C, Hinkelmann K, Dettenborn L, Wingenfeld K, Spitzer C, et al. Association between major depression and cardiovascular risk: the role of antidepressant medication. Psychopharmacology 2016;233:3289-95.

54. Almuwaqqat Z, Jokhadar M, Norby FL, Lutsey PL, O'Neal WT, Seyerle A, et al. Association of Antidepressant Medication Type With the Incidence of Cardiovascular Disease in the ARIC Study. Journal of the American Heart Association 2019;8:e012503.

55. Fernandes N, Prada L, Rosa MM, Ferreira JJ, Costa J, Pinto FJ, et al. The impact of SSRIs on mortality and cardiovascular events in patients with coronary artery disease and depression: systematic review and meta-analysis. Clinical Research in Cardiology 2021;110:183-93.

56. Monster TBM, Johnsen SP, Olsen ML, McLaughlin JK, Sørensen HT. Antidepressants and risk of first-time hospitalization for myocardial infarction: A population-based case-control study. The American Journal of Medicine 2004;117:732-7.

57. Scherrer JF, Salas J, Schneider FD, Friedman MJ, van den Berk-Clark C, Chard KM, et al. PTSD improvement and incident cardiovascular disease in more than 1000 veterans. Journal of psychosomatic research 2020;134:110128.
58. Galea S, Nandi A, Vlahov D. The epidemiology of post-traumatic stress disorder after disasters. Epidemiologic reviews 2005;27:78-91.
59. Yasan A, Saka G, Ozkan M, Ertem M. Trauma type, gender, and risk of PTSD in a region within an area of conflict. Journal of Traumatic Stress 2009;22:663-6.
60. Michael T, Ehlers A, Halligan SL, Clark DM. Unwanted memories of assault: what intrusion characteristics are associated with PTSD? Behaviour Research and Therapy 2005;43:613-28.
61. Jenness JL, Peverill M, Miller AB, Heleniak C, Robertson MM, Sambrook KA, et al. Alterations in neural circuits underlying emotion regulation following child maltreatment: a mechanism underlying trauma-related psychopathology. Psychological Medicine 2021;51:1880-9.
62. Karl A, Schaefer M, Malta LS, Dörfel D, Rohleder N, Werner A. A meta-analysis of structural brain abnormalities in PTSD. Neuroscience & Biobehavioral Reviews 2006;30:1004-31.
63. Sriram K, Rodriguez-Fernandez M, Doyle FJ, III. Modeling Cortisol Dynamics in the Neuro-endocrine Axis Distinguishes Normal, Depression, and Post-traumatic Stress Disorder (PTSD) in Humans. PLOS Computational Biology 2012;8:e1002379.
64. Bremner JD, Charney D, Stein D, Hollander E, Rothbaum B. Neural circuits in fear and anxiety. 2010.
65. Wessa M, Rohleder N, Kirschbaum C, Flor H. Altered cortisol awakening response in posttraumatic stress disorder. Psychoneuroendocrinology 2006;31:209-15.
66. Aerni A, Traber R, Hock C, Roozendaal B, Schelling G, Papassotiropoulos A, et al. Low-Dose Cortisol for Symptoms of Posttraumatic Stress Disorder. American Journal of Psychiatry 2004;161:1488-90.
67. Brewin CR. A cognitive neuroscience account of posttraumatic stress disorder and its treatment. Behaviour Research and Therapy 2001;39:373-93.

68. Alexandra Kredlow M, Fenster RJ, Laurent ES, Ressler KJ, Phelps EA. Prefrontal cortex, amygdala, and threat processing: implications for PTSD. Neuropsychopharmacology 2022;47:247-59.
69. Heppner PS, Crawford EF, Haji UA, Afari N, Hauger RL, Dashevsky BA, et al. The association of posttraumatic stress disorder and metabolic syndrome: a study of increased health risk in veterans. BMC medicine 2009;7:1-8.
70. Rosenbaum S, Stubbs B, Ward PB, Steel Z, Lederman O, Vancampfort D. The prevalence and risk of metabolic syndrome and its components among people with posttraumatic stress disorder: a systematic review and meta-analysis. Metabolism 2015;64:926-33.
71. van den Berk Clark C, Kansara V, Fedorova M, Ju T, Renirie T, Lee J, et al. How does PTSD treatment affect cardiovascular, diabetes and metabolic disease risk factors and outcomes? A systematic review. Journal of Psychosomatic Research 2022;157:110793.
72. Buckley TC, Green BL, Schnurr PP. Trauma, PTSD, and Physical Health: Clinical Issues. 2004.
73. Tousoulis D, Antoniades C, Stefanadis C. Assessing inflammatory status in cardiovascular disease. Heart 2007;93:1001.
74. von Känel R, Hepp U, Kraemer B, Traber R, Keel M, Mica L, et al. Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder. Journal of psychiatric research 2007;41:744-52.
75. Tucker P, Ruwe WD, Masters B, Parker DE, Hossain A, Trautman RP, et al. Neuroimmune and cortisol changes in selective serotonin reuptake inhibitor and placebo treatment of chronic posttraumatic stress disorder. Biological psychiatry 2004;56:121-8.
76. Bersani FS, Wolkowitz OM, Lindqvist D, Yehuda R, Flory J, Bierer LM, et al. Global arginine bioavailability, a marker of nitric oxide synthetic capacity, is decreased in PTSD and correlated with symptom severity and markers of inflammation. Brain, behavior, and immunity 2016;52:153-60.

77. Guo M, Liu T, Guo J-C, Jiang X-L, Chen F, Gao Y-S. Study on serum cytokine levels in posttraumatic stress disorder patients. Asian Pacific journal of tropical medicine 2012;5:323-5.
78. Hoge EA, Brandstetter K, Moshier S, Pollack MH, Wong KK, Simon NM. Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. Depression and Anxiety 2009;26:447-55.
79. Kim Y-K, Amidfar M, Won E. A review on inflammatory cytokine-induced alterations of the brain as potential neural biomarkers in post-traumatic stress disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2019;91:103-12.
80. Krantz DS, Shank LM, Goodie JL. Post-traumatic stress disorder (PTSD) as a systemic disorder: Pathways to cardiovascular disease. Health Psychology 2022;41:651-62.
81. Sumner JA, Cleveland S, Chen T, Gradus JL. Psychological and biological mechanisms linking trauma with cardiovascular disease risk. Translational Psychiatry 2023;13:25.
82. Yehuda R. Advances in understanding neuroendocrine alterations in PTSD and their therapeutic implications. Annals of the new York Academy of Sciences 2006;1071:137-66.
83. Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, et al. Biological studies of post-traumatic stress disorder. nature Reviews neuroscience 2012;13:769-87.
84. Akosile W, Young R, Lawford B, Voisey J, Colquhoun D. PTSD symptoms associated with myocardial infarction: practical clinical implications. Australasian Psychiatry 2017;26:60-4.
85. Perkins JD, Wilkins SS, Kamran S, Shuaib A. Post-traumatic stress disorder and its association with stroke and stroke risk factors: A literature review. Neurobiology of Stress 2021;14:100332.
86. Chen M-H, Pan T-L, Li C-T, Lin W-C, Chen Y-S, Lee Y-C, et al. Risk of stroke among patients with post-traumatic stress disorder: nationwide longitudinal study. British Journal of Psychiatry 2015;206:302-7.

87. Elhai JD, de Francisco Carvalho L, Miguel FK, Palmieri PA, Primi R, Christopher Frueh B. Testing whether posttraumatic stress disorder and major depressive disorder are similar or unique constructs. Journal of Anxiety Disorders 2011;25:404-10.
88. Frueh BC, Gold PB, Dammeyer M, Pellegrin KL, Hamner MB, Johnson MR, et al. Differentiation of depression and PTSD symptoms in combat veterans. Depression and Anxiety 2000;11:175-9.
89. Smoller JW. The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. Neuropsychopharmacology 2016;41:297-319.
90. McFarlane AC, Van Hooff M, Goodhew F. Anxiety disorders and PTSD. 2012.
91. Rakofsky JJ, Ressler KJ, Dunlop BW. BDNF function as a potential mediator of bipolar disorder and post-traumatic stress disorder comorbidity. Molecular Psychiatry 2012;17:22-35.
92. Goldberg JF, Garno JL. Development of posttraumatic stress disorder in adult bipolar patients with histories of severe childhood abuse. Journal of Psychiatric Research 2005;39:595-601.
93. Ford JD, Elhai JD, Ruggiero KJ, Frueh BC. Refining posttraumatic stress disorder diagnosis: evaluation of symptom criteria with the National Survey of Adolescents. Journal of Clinical Psychiatry 2009;70:748.
94. Bradley SM & Rumsfeld JS. Sympathetic nervous system activity in major depression. Trends in Cardiovascular Medicine 2015;25(7):614-22.
95. Veith RC, Lewis N, Linares OA, Barnes RF, Raskind MA, Villacres EC, et al. Sympathetic nervous system activity in major depression: basal and desipramine-Induced alterations in plasma norepinephrine kinetics. Archives of General Psychiatry 1994;51(5):411-22.
96. Otte C, Neylan TC, Pipkin SS, Browner WS, Whooler MA. Depressive symptoms and 24-hour urinary norepinephrine excretion levels in patients with coronary disease: findings from the Heart and Soul Study. American Journal of Psychiatry 2005;162:2139-45.

97. Tagliarini C, Carbone MG, Pagni G, Marazziti D, Pomara N. Is there a relationship between morphological and functional platelet changes and depressive disorder? CNS Spectrums 2022;27(2):157-90.

98. Lopes-Vilches I, Serra-Milas M, Navarro V, Hernandez MR, Vilata J, Diaz-Ricard M, et al. Prothrombotic platelet phenotype in major depression: downregulation by antidepressant treatment. Journal of Affective Disorders 2014;159:39-45.

99. Young JJ, Bruno D, Pomara N. A review of the relationship between proinflammatory cytokines and major depressive disorder. Journal of Affective Disorders 2014;169:15-20.

100. Postal M & Appenzeller S. The importance of cytokines and autoantibodies in depression. Autoimmunity Reviews 2015;14(1):30-45.

101. Liu JJ, Wei YB, Strawbridge R, Bao Y, Chang S, Shi L, et al. Peripheral cytokine levels and response to antidepressant treatment in depression: a systematic review and meta-analysis. Molecular Psychiatry 2020;25(2):339-50.

102. Ehlers A, Clark DM. A cognitive model of posttraumatic stress disorder. Behaviour Research and Therapy 2000;38:319-45.

103. Lee HJ, Lee MS, Kang RH, Kim H, Kim SD, Kee BS, et al. Influence of the serotonin transporter promoter gene polymorphism on susceptibility to posttraumatic stress disorder. Depress Anxiety 2005;21:135-9.

104. Gavrieli A, Farr OM, Davis CR, Crowell JA,Mantzoros CS. Early life adversity and/or posttraumatic stress disorder severity are associated with poor diet quality, including consumption of transfatty acids, and fewer hours of resting or sleeping in a US Middle-aged Population: a cross-sectional and prospective Study. Metabolism 2015;64(11):1597–610.

105. Celano CM, Daunis DJ, Lokko HN, Campbell KA, Huffman JC. Anxiety disorders and cardiovascular disease. Current Psychiatry Reports 2016;18:1-1.

106. Narita K, Murata T, Hamada T, Takahashi T, OmoriM, Suganuma N, et al. Interactions among higher trait anxiety, sympathetic activity, and endothelial function in the elderly. Journal of Psychiatric Research 2007;41(5):418–27.

107. Carnevali L, Mancini M, Koenig J, Makovac E, Watson DR, Meeten F, Critchley HD, Ottaviani C. Cortical morphometric predictors of autonomic dysfunction in generalized anxiety disorder. Autonomic Neuroscience. 2019 Mar 1;217:41-8.

108. Yeragani VK, Tancer M, Seema KP, Josyulab K, Desai N. Increased pulse-wave velocity in patients with anxiety: Implications for autonomic dysfunction. Journal of Psychosomatic Research 2006;61(1):25-31.

109. Smoller JW. The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. Neuropsychopharmacology 2016;41(1):297-319.

110. Gibson LE, Alloy LB, Ellman LM. Trauma and the psychosis spectrum: A review of symptom specificity and explanatory mechanisms. Clinical Psychology Review 2016;49:92-105.

111. Gupta MA. Review of somatic symptoms in post-traumatic stress disorder. International review of psychiatry 2013;25:86-99.

112. Goldstein BI, Carnethon MR, Matthews KA, McIntyre RS, Miller GE, Raghuveer G, et al. Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2015;132:965-86.

113. Huang KL, Su TP, Chen TJ, Chou YH, Bai YM. Comorbidity of cardiovascular diseases with mood and anxiety disorder: a population based 4-year study. Psychiatry and clinical neurosciences 2009;63:401-9.

114. Cohen BE, Edmondson D, Kronish IM. State of the art review: depression, stress, anxiety, and cardiovascular disease. American journal of hypertension 2015;28:1295-302.

115. Association AP. Clinical practice guideline for the treatment of posttraumatic stress disorder (PTSD) in adults. 2017.

116. Huang Z-D, Zhao Y-F, Li S, Gu H-Y, Lin L-L, Yang Z-Y, et al. Comparative efficacy and acceptability of pharmaceutical management for adults with post-traumatic stress disorder: a systematic review and meta-analysis. Frontiers in pharmacology 2020;11:559.

117. Batelaan NM, Bosman RC, Muntingh A, Scholten WD, Huijbregts KM, van Balkom AJ. Risk of relapse after antidepressant discontinuation in anxiety

disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials. bmj 2017;358.

118. Berger W, Mendlowicz MV, Marques-Portella C, Kinrys G, Fontenelle LF, Marmar CR, et al. Pharmacologic alternatives to antidepressants in posttraumatic stress disorder: A systematic review. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2009;33:169-80.

119. Bajor LA, Balsara C, Osser DN. An evidence-based approach to psychopharmacology for posttraumatic stress disorder (PTSD) - 2022 update. Psychiatry Research 2022;317:114840.

120. Mandrioli R, Mercolini L, A Saracino M, A Raggi M. Selective serotonin reuptake inhibitors (SSRIs): therapeutic drug monitoring and pharmacological interactions. Current Medicinal Chemistry 2012;19(12):1846-63.

121. Stein DJ & Stahl S. Serotonin and anxiety: current models. International Clinical Psychopharmacology. 2000 Aug 1;15:S1-6.

122. Karayol R, Medrihan L, Warner-Schmidt JL, Fait BW, Rao MN, Holzner EB, et al. Serotonin receptor 4 in the hippocampus modulates mood and anxiety. Molecular Psychiatry 2021;26(6):2334-49.

123. Raut SB, Marathe PA, van Eijk L, Eri R, Ravindran M, Benedek DM, et al. Diverse therapeutic developments for post-traumatic stress disorder (PTSD) indicate common mechanisms of memory modulation. Pharmacology & Therapeutics 2022;239:108195.

124. Bernardy NC, Friedman MJ. Pharmacological management of posttraumatic stress disorder. Current Opinion in Psychology 2017;14:116-21.

125. Forman-Hoffman V, Middleton JC, Feltner C, Gaynes BN, Weber RP, Bann C, et al. Psychological and pharmacological treatments for adults with posttraumatic stress disorder: a systematic review update. 2018.

126. Cipriani A, Williams T, Nikolakopoulou A, Salanti G, Chaimani A, Ipser J, et al. Comparative efficacy and acceptability of pharmacological treatments for post-traumatic stress disorder in adults: a network meta-analysis. Psychological Medicine 2018;48(12):1975-84.

127. Frazer A. Norepinephrine involvement in antidepressant action. Journal of Clinical Psychiatry. 2000 Jan 1;61:25-30.
128. Gu W, Wang C, Li Z, Wang Z, Zhang X. Pharmacotherapies for Posttraumatic Stress Disorder: A Meta-Analysis. The Journal of Nervous and Mental Disease 2016;204.
129. Puetz TW, Youngstedt SD, Herring MP. Effects of pharmacotherapy on combat-related PTSD, anxiety, and depression: a Systematic Review and Meta-Regression Analysis. PloS One 2015;10(5):e0126529.
130. Youdim MB, Edmondson D, Tipton KF. The therapeutic potential of monoamine oxidase inhibitors. Nature Reviews Neuroscience 2006;7(4):295-309.
131. Neal LA, Shapland W, Fox C. An Open trial of moclobemide in the treatment of post-traumatic stress disorder. International Clinical Psychopharmacolog. 1997;12(4):231.
132. Gorman JM. Mirtazapine: clinical overview. Journal of Clinical Psychiatry 1999;60:9-13.
133. Davidson JR, Weisler RH, Butterfield MI, Casat CD, Connor KM, Barnett S, et al. Mirtazapine vs. placebo in posttraumatic stress disorder: a pilot trial. Biological Psychiatry 2003;53(2):188-91.
134. Lavoie KL, Paine NJ, Pelletier R, Arsenault A, Diodati JG, Campbell TS, et al. Relationship between antidepressant therapy and risk for cardiovascular events in patients with and without cardiovascular disease. Health Psychology 2018;37:989.
135. Biffi A, Scotti L, Corrao G. Use of antidepressants and the risk of cardiovascular and cerebrovascular disease: a meta-analysis of observational studies. European Journal of Clinical Pharmacology 2017;73:487-97.
136. Hansen RA, Khodneva Y, Glasser SP, Qian J, Redmond N, Safford MM. Antidepressant Medication Use and Its Association With Cardiovascular Disease and All-Cause Mortality in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Annals of Pharmacotherapy 2016;50:253-61.
137. Elovainio M, Keltikangas-JÄRvinen L, Pulkki-RÅBack L, KivimÄKi M, Puttonen S, Viikari L, et al. Depressive symptoms and C-reactive protein: The

Cardiovascular Risk in Young Finns Study. Psychological Medicine 2006;36:797-805.

138. Whooley MA, de Jonge P, Vittinghoff E, Otte C, Moos R, Carney RM, et al. Depressive Symptoms, Health Behaviors, and Risk of Cardiovascular Events in Patients With Coronary Heart Disease. JAMA 2008;300:2379-88.

139. Harshfield EL, Pennells L, Schwartz JE, Willeit P, Kaptoge S, Bell S, et al. Association Between Depressive Symptoms and Incident Cardiovascular Diseases. JAMA 2020;324:2396-405.

140. Kim CK, McGorray SP, Bartholomew BA, Marsh M, Dicken T, Wassertheil-Smoller S, et al. Depressive Symptoms and Heart Rate Variability in Postmenopausal Women. Archives of Internal Medicine 2005;165:1239-44.

141. Vaccarino V, Lampert R, Bremner JD, Lee F, Su S, Maisano C, et al. Depressive symptoms and heart rate variability: evidence for a shared genetic substrate in a study of twins. Psychosomatic medicine 2008;70:628-36.

142. Ferketich AK, Ferguson JP, Binkley PF. Depressive symptoms and inflammation among heart failure patients. American heart journal 2005;150:132-6.

143. Fagundes CP, Glaser R, Hwang BS, Malarkey WB, Kiecolt-Glaser JK. Depressive symptoms enhance stress-induced inflammatory responses. Brain, behavior, and immunity 2013;31:172-6.

144. Johansson P, Lesman-Leegte I, Svensson E, Voors A, van Veldhuisen DJ, Jaarsma T. Depressive symptoms and inflammation in patients hospitalized for heart failure. American heart journal 2011;161:1053-9.

145. Horsten M, Wamala SP, Vingerhoets A, Orth-Gomer K. Depressive symptoms, social support, and lipid profile in healthy middle-aged women. Psychosomatic medicine 1997;59:521-8.

146. Rhee SJ, Kim EY, Kim SH, Lee HJ, Kim B, Ha K, et al. Subjective depressive symptoms and metabolic syndrome among the general population. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2014;54:223-30.

147. Olusi SO, Fido AA. Serum lipid concentrations in patients with major depressive disorder. Biological psychiatry 1996;40:1128-31.

148. Wong M-L, Dong C, Esposito K, Thakur S, Liu W, Elashoff RM, et al. Elevated Stress-Hemoconcentration in Major Depression Is Normalized by Antidepressant Treatment: Secondary Analysis from a Randomized, Double-Blind Clinical Trial and Relevance to Cardiovascular Disease Risk. PLOS ONE 2008;3:e2350.
149. Pizzi C, Rutjes AWS, Costa GM, Fontana F, Mezzetti A, Manzoli L. Meta-Analysis of Selective Serotonin Reuptake Inhibitors in Patients With Depression and Coronary Heart Disease. The American Journal of Cardiology 2011;107:972-9.
150. Tseng Y-L, Chiang M-L, Huang T-F, Su K-P, Lane H-Y, Lai Y-C. A selective serotonin reuptake inhibitor, citalopram, inhibits collagen-induced platelet aggregation and activation. Thrombosis Research 2010;126:517-23.
151. Shively CA, Silverstein-Metzler M, Justice J, Willard SL. The impact of treatment with selective serotonin reuptake inhibitors on primate cardiovascular disease, behavior, and neuroanatomy. Neuroscience & Biobehavioral Reviews 2017;74:433-43.
152. Lusetti M, Licata M, Silingardi E, Reggiani Bonetti L, Palmiere C. Cardiac Toxicity in Selective Serotonin Reuptake Inhibitor Users. The American Journal of Forensic Medicine and Pathology 2015;36.
153. Garg PK, Claxton JNS, Soliman EZ, Chen LY, Lewis TT, Mosley T, Jr., et al. Associations of anger, vital exhaustion, anti-depressant use, and poor social ties with incident atrial fibrillation: The Atherosclerosis Risk in Communities Study. European Journal of Preventive Cardiology 2021;28:633-40.
154. Fenger-Grøn M, Vestergaard M, Pedersen HS, Frost L, Parner ET, Ribe AR, et al. Depression, antidepressants, and the risk of non-valvular atrial fibrillation: a nationwide Danish matched cohort study. European journal of preventive cardiology 2019;26:187-95.
155. Castro VM, Clements CC, Murphy SN, Gainer VS, Fava M, Weilburg JB, et al. QT interval and antidepressant use: a cross sectional study of electronic health records. Bmj 2013;346:f288.
156. Davey P. QT interval and mortality from coronary artery disease. Progress in cardiovascular diseases 2000;42:359-84.

157. Barnard K, Peveler RC, Holt RIG. Antidepressant Medication as a Risk Factor for Type 2 Diabetes and Impaired Glucose Regulation: Systematic review. Diabetes Care 2013;36:3337-45.
158. Loeffler G, Coller R, Tracy L, Derderian BR. Prescribing trends in us active duty service members with posttraumatic stress disorder: a population-based study from 2007-2013. The Journal of Clinical Psychiatry 2018;79:15309.
159. Gasparyan A, Navarro D, Navarrete F, Manzanares J. Pharmacological strategies for post-traumatic stress disorder (PTSD): From animal to clinical studies. Neuropharmacology 2022;218:109211.
160. Kim K, Kang S, Nam CM, Stewart R, Tsai AC, Jung SJ. A marginal structural model to estimate the effect of antidepressant medication treatment on major cardiovascular events among people with post-traumatic stress disorder. Psychological Medicine 2023;53(16):7837-46.
161. Friedman MJ. PTSD: pharmacotherapeutic approaches. Focus 2013;11:315-20.
162. McGrane IR, Shuman MD. Mirtazapine therapy for posttraumatic stress disorder: implications of alpha-adrenergic pharmacology on the startle response. Harvard review of psychiatry 2018;26:36-41.
163. Behlke LM, Lenze EJ, Carney RM. The cardiovascular effects of newer antidepressants in older adults and those with or at high risk for cardiovascular diseases. CNS drugs 2020;34:1133-47.
164. Robins JM, Hernán MÁ, Brumback B. Marginal Structural Models and Causal Inference in Epidemiology. Epidemiology 2000;11.
165. Hernán MA, Robins JM. Causal inference. CRC Boca Raton, FL; 2010.
166. Tsai AC, Weiser SD, Petersen ML, Ragland K, Kushel MB, Bangsberg DR. A Marginal Structural Model to Estimate the Causal Effect of Antidepressant Medication Treatment on Viral Suppression Among Homeless and Marginally Housed Persons With HIV. Archives of General Psychiatry 2010;67:1282-90.
167. Hernán MÁ, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology 2000:561-70.

168. Hernán MA, Brumback B, Robins JM. Marginal Structural Models to Estimate the Joint Causal Effect of Nonrandomized Treatments. Journal of the American Statistical Association 2001;96:440-8.
169. Robins JM. Marginal structural models versus structural nested models as tools for causal inference. Statistical models in epidemiology, the environment, and clinical trials: Springer; 2000. p.95-133.
170. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. American journal of epidemiology 2008;168:656-64.
171. Cho HE, Wang L, Chen J-S, Liu M, Kuo C-F, Chung KC. Investigating the causal effect of socioeconomic status on quality of care under a universal health insurance system-a marginal structural model approach. BMC Health Services Research 2019;19:1-10.
172. Lim H, Kim YN, Chang TI, Kim JY. Association of systolic blood pressure with incident chronic kidney disease estimated by marginal structural model: a nationwide population-based study. Kidney Research and Clinical Practice 2023.
173. Hernán MA. A definition of causal effect for epidemiological research. Journal of Epidemiology & Community Health 2004;58:265-71.
174. Williamson T, Ravani P. Marginal structural models in clinical research: when and how to use them? Nephrology Dialysis Transplantation 2017;32:ii84-ii90.
175. Ding P, VanderWeele TJ. Sensitivity analysis without assumptions. Epidemiology (Cambridge, Mass.) 2016;27:368.
176. Suarez D, Haro JM, Novick D, Ochoa S. Marginal structural models might overcome confounding when analyzing multiple treatment effects in observational studies. Journal of Clinical Epidemiology 2008;61:525-30.
177. Spreeuwenberg MD, Bartak A, Croon MA, Hagenaars JA, Busschbach JJV, Andrea H, et al. The Multiple Propensity Score as Control for Bias in the Comparison of More Than Two Treatment Arms: An Introduction From a Case Study in Mental Health. Medical Care 2010;48:166-74.
178. Kim D-W, Lim H, Choi JK, Pak H-Y, Youk TM, Kang M, et al. A study on comparison of operational definitions of disease based on health insurance claims data. National Health Insurance Service Ilsan Hospital Research Center 2019.

179. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
180. Cerimele JM, Bauer AM, Fortney JC, Bauer MS. Patients with co-occurring bipolar disorder and posttraumatic stress disorder: a rapid review of the literature. The Journal of clinical psychiatry 2017;78:3747.
181. Sautter FJ, Brailey K, Uddo MM, Hamilton MF, Beard MG, Borges AH. PTSD and comorbid psychotic disorder: Comparison with veterans diagnosed with PTSD or psychotic disorder. Journal of Traumatic Stress 1999;12:73-88.
182. Compean E, Hamner M. Posttraumatic stress disorder with secondary psychotic features (PTSD-SP): Diagnostic and treatment challenges. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2019;88:265-75.
183. Price M, Legrand AC, Brier ZMF, Hébert-Dufresne L. The symptoms at the center: Examining the comorbidity of posttraumatic stress disorder, generalized anxiety disorder, and depression with network analysis. Journal of Psychiatric Research 2019;109:52-8.
184. Howe CJ, Cole SR, Mehta SH, Kirk GD. Estimating the effects of multiple time-varying exposures using joint marginal structural models: alcohol consumption, injection drug use, and HIV acquisition. Epidemiology 2012;23:574.
185. Suissa S, Dell'Aniello S. Time-related biases in pharmacoepidemiology. Pharmacoepidemiology and Drug Safety 2020;29(9):1101-10.
186. Allan V, Ramagopalan SV, Mardekian J, Jenkins A, Li X, Pan X, et al. Propensity score matching and inverse probability of treatment weighting to address confounding by indication in comparative effectiveness research of oral anticoagulants. Journal of comparative effectiveness research 2020;9:603-14.
187. Tully J, Bhugra D, Lewis SJ, Drennan G, Markham S. Is PTSD overdiagnosed? BMJ 2021;373:n787.
188. Park E-C. Evaluating the consistency of health insurance claim disease code and medical record and improvement plan. Health Insurance Review & Assessment Service 2017:1-287.

189. Korean National Health Insurance Service. Patients with “Posttraumatic Stress Disorder” Increased by 45.4% Over the Past Five Years. 2020.06.29. https://www.nhis.or.kr/nhis/together/wbhaea01600m01.do?mode=view&articleNo=137570&article.offset=920&articleLimit=10.

190. Park J, Choi W, Kim DW, Song J, Lee SB, Lee S, et al. Status of Treatment for Newly Incident Mental Illnesses and Neccesity for Coverage Expansion. National Health Insurance Service Ilsan Hospital Research Center 2017.

191. Choi W, Lee B-O, Kim DW, Lee S-K, Hong SJ, Kang JI, et al. Study on the Prevalence of Mental Illness and Characteristics of Psychiatric Diagnosis and Treatment in Korean Cancer Patients. National Health Insurance Service Ilsan Hospital Research Center 2014.

192. Kim D-S, Kim J, Lee D-H, Kim S, Kim B-Y. Pharmaceutical consumption and sales statistics 2018. Ministry of Health and Welfare & Health Insurance Review & Assessment Service 2018.

193. Goldstein BI, Korczak DJ. Links between child and adolescent psychiatric disorders and cardiovascular risk. Canadian Journal of Cardiology 2020;36:1394-405.

194. Pelletier R, Bacon SL, Arsenault A, Dupuis J, Laurin C, Blais L, et al. Relative associations between depression and anxiety on adverse cardiovascular events: does a history of coronary artery disease matter? A prospective observational study. BMJ Open 2015;5:e006582.

195. Coupland C, Hill T, Morriss R, Moore M, Arthur A, Hippisley-Cox J. Antidepressant use and risk of cardiovascular outcomes in people aged 20 to 64: cohort study using primary care database. BMJ 2016;352.

196. Huang C-J, Hsieh M-H, Hou W-H, Liu J-C, Jeng C, Tsai P-S. Depression, antidepressants, and the risk of coronary heart disease: A population-based cohort study. International Journal of Cardiology 2013;168:4711-6.

197. Whyte IM, Dawson AH, Buckley NA. Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. QJM 2003 May 1;96(5):369-74.

198. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart. 2003 Nov 1;89(11):1363-72.

199. Kunutsor SK, Seidu S, Khunti K. Depression, antidepressant use, and risk of venous thromboembolism: systematic review and meta-analysis of published observational evidence. Annals of Medicine 2018;50(6):529-37.

200. Park K, Kim S, Ko YJ, Park BJ. Duloxetine and cardiovascular adverse events: A systematic review and meta-analysis. Journal of Psychiatric Research 2020;124:109-14.

201. Grace SL, Medina-Inojosa JR, Thomas RJ, Krause H, Vickers-Douglas KS, Palmer BA, et al. Antidepressant use by class: association with major adverse cardiac events in patients with coronary artery disease. Psychotherapy and psychosomatics. 2018 Mar 13;87(2):85-94.

202. Biffi A, Scotti L, Corrao G. Use of Antidepressants and the Risk of Cardiovascular and Cerebrovascular Disease: a Meta-Analysis of Observational Studies. European Journal of Clinical Pharmacology 2017;73:487-97.

203. Gillman PK. Tricyclic Antidepressant Pharmacology and Therapeutic Drug Interactions Updated. British Journal of Pharmacology 2007;151(6):737-48.

204. Preskorn SH, Flockhart D. 2006 Guide to Psychiatric Drug Interactions. Primary Psychiatry 2006;13(4):35.

205. Gillman K. Drug Interactions and Fluoxetine: a Commentary From a Clinician's Perspective. Expert Opinion on Drug Safety 2005;4(6):965-8.

206. Aronson JK, Hardman M. ABC of Monitoring Drug Therapy. Measuring Plasma Drug Concentrations. BMJ 1992;305(6861):1078.

207. Funk CS, Hart XM, Gründer G, Hiemke C, Elsner B, Kreutz R, et al. Is Therapeutic Drug Monitoring Relevant for Antidepressant Drug Therapy? Implications From a Systematic Review and Meta-Analysis With Focus on Moderating Factors. Frontiers in Psychiatry 2022;13:826138.

208. Müller MJ, Eich FX, Regenbogen B, Sachse J, Härtter S, Hiemke C. Amisulpride doses and plasma levels in different age groups of patients with schizophrenia or schizoaffective disorder. Journal of psychopharmacology 2009;23(3):278-86.

209. Jakubovski E, Varigonda AL, Freemantle N, Taylor MJ, Bloch MH. Systematic review and meta-analysis: dose-response relationship of selective serotonin reuptake inhibitors in major depressive disorder. American Journal of Psychiatry 2016;173(2):174-83.

210. Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K, Eckermann G, Egberts K, Gerlach M, Greiner C, Gründer G. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry 2018;51:9-62.

APPENDICES

Appendix 1. List of pharmaceutical code of ingredients for antidepressant medications.

Appendix 2. List of ICD-10 diagnostic codes for major cardiovascular events and psychiatric comorbidities.

Appendix 3. Insurance claim codes for procedures and surgical interventions for revascularization.

Appendix 4. Insurance fee codes for psychotherapeutic treatment covered by Korean NHIS.

Appendix 5. Statistical methods for IP weight estimation and MSM construction.

Appendix 6. Association between antidepressant class and CAD with revascularization under lag-time analysis.

Appendix 7. Association between antidepressant prescription pattern and coronary artery disease under lag-time analysis.

Appendix 8. Association between antidepressant class and CAD with revascularization under progressive inverse probability weight truncation.

Appendix 9. Association between antidepressant prescription pattern and coronary artery disease under progressive inverse probability weight truncation.

Appendix 10. Characteristics of participants who have participated in health checkup. (N = 37,558)

Appendix 11. Difference in participant characteristics by health checkup participation.

Appendix 12. Comparison of estimand between full cohort and health checkup subgroup.

Appendix 13. Bounding factors for statistically significant hazard ratio.

Appendix 1. List of pharmaceutical code of ingredients for antidepressant medications.

Category	Active ingredients code	Pharmaceutical contents
SSRI	1615	Fluoxetine hydrochloride
	1625	Fluvoxamine maleate
	2093	Paroxetine hydrochloride
	2270	Sertraline hydrochloride
	4283	Citalopram hydrobromide
	4748	Escitalopram oxalate
SNRI	6285	Vortioxetine hydrobromide
	2475	Venlafaxine hydrochloride
	3558	Milnacipran hydrochloride
	4955	Duloxetine hydrochloride
	6264	Desvenlafaxine succinate monohydrate
TCA	1075	Amitriptyline hydrochloride
	1080	Amoxapine
	1363	Clomipramine hydrochloride
	1737	Imipramine hydrochloride
	2034	Nortriptyline hydrochloride
	2296	Sodium tianeptine
Other antidepressants	1499	St. John's Wort 50% ethanol extract
	1725	St. John's Wort 80% methanol extract
	1962	Mirtazapine
	1967	Moclobemide
	2264	Selegiline hydrochloride
	2429	Trazodone hydrochloride
	4281	Bupropion hydrochloride
	6131	Agomelatine

Appendix 2. List of ICD-10 diagnostic codes for coronary artery disease.

ICD-10 codes	Disease entity
Myocardial infarction	
I21	**Acute myocardial infarction**
I21.0	Acute transmural myocardial infarction of anterior wall
I21.1	Acute transmural myocardial infarction of inferior wall
I21.2	Acute transmural myocardial infarction of other sites
I21.3	Acute transmural myocardial infarction of unspecified site
I21.4	Acute subendocardial myocardial infarction
I21.9	Acute myocardial infarction, unspecified
I22	**Subsequent myocardial infarction**
I22.0	Subsequent myocardial infarction of anterior wall
I22.1	Subsequent myocardial infarction of inferior wall
I22.8	Subsequent myocardial infarction of other sites
I22.9	Subsequent myocardial infarction of unspecified site
Ischemic heart disease other than myocardial infarction	
I20	**Angina pectoris**
I20.0	Unstable angina
I20.1	Angina pectoris with documented spasm
I20.8	Other forms of angina pectoris
I20.9	Angina pectoris, unspecified
I24	**Other acute ischemic heart diseases**
I24.0	Coronary thrombosis not resulting in myocardial infarction
I24.8	Other forms of acute ischemic heart disease
I24.9	Acute ischemic heart disease, unspecified
I25	**Chronic ischemic heart disease**
I25.0	Atherosclerotic cardiovascular disease, so described
I25.1	Atherosclerotic heart disease
I25.2	Old myocardial infarction
I25.5	Ischemic cardiomyopathy
I25.6	Silent myocardial ischemia
I25.8	Other forms of chronic ischemic heart disease
I25.9	Chronic ischemic heart disease, unspecified

Appendix 3. Insurance claim codes for procedures and surgical interventions for revascularization.

Fee codes	Procedures and surgical interventions
M6551	Percutaneous transluminal coronary angioplasty, single vessel
M6552	Percutaneous transluminal coronary angioplasty, additional vessel
M6563	Percutaneous transluminal coronary angioplasty of culprit lesion in acute myocardial infarction
M6554	Percutaneous transluminal coronary angioplasty of chronic total occlusion
M6561	Percutaneous transcatheter placement of intracoronary stent, single vessel
M6562	Percutaneous transcatheter placement of intracoronary stent, additional vessel
M6563	Percutaneous transcatheter placement of intracoronary stent with percutaneous transluminal coronary atherectomy, single vessel
M6564	Percutaneous transcatheter placement of intracoronary stent with percutaneous transluminal coronary atherectomy, additional vessel
M6565	Percutaneous coronary intervention of culprit lesion in acute myocardial infarction
M6566	Percutaneous coronary intervention of chronic total occlusion
M6567	Percutaneous coronary intervention of chronic total occlusion with percutaneous transluminal coronary atherectomy
M6571	Percutaneous transluminal coronary atherectomy, single vessel
M6572	Percutaneous transluminal coronary atherectomy, additional vessel
M6634	Percutaneous thrombus removal, coronary artery
M6638	Mechanical thrombectomy, coronary artery
OA631	Angioplasty, end-to-end anastomosis, by thoracotomy
OA632	Angioplasty, end-to-end anastomosis, by laparotomy
OA633	Angioplasty, end-to-end anastomosis, others
OA634	Angioplasty, patch graft, by thoracotomy, artificial vessel
OA635	Angioplasty, patch graft, by thoracotomy, autologous vessel
OA636	Angioplasty, patch graft, by laparotomy, artificial vessel
OA637	Angioplasty, patch graft, by laparotomy, autologous vessel
OA638	Angioplasty, others, artificial vessel
OA639	Angioplasty, others, autologous vessel
OB631	Angioplasty, end-to-end anastomosis with cross-clamping, by thoracotomy
OB632	Angioplasty, end-to-end anastomosis with cross-clamping, by laparotomy
OB633	Angioplasty, end-to-end anastomosis with cross-clamping, others
OB634	Angioplasty, patch graft with cross-clamping, by thoracotomy, artificial vessel
OB635	Angioplasty, patch graft with cross-clamping, by thoracotomy, autologous vessel
OB636	Angioplasty, patch graft with cross-clamping, by laparotomy, artificial vessel
OB637	Angioplasty, patch graft with cross-clamping, by laparotomy, autologous vessel
OB638	Angioplasty, others with cross-clamping, artificial vessel
OB639	Angioplasty, others with cross-clamping, autologous vessel
O1641	Vascular bypass operation, aorta-coronary, simple, 1 site
O1640	Vascular bypass operation, aorta-coronary, simple, 2 sites

O1648	Vascular bypass operation, aorta-coronary, simple, 3 sites
O1649	Vascular bypass operation, aorta-coronary, simple, 4 or more sites
OA641	Vascular bypass operation with off pump coronary artery bypass graft, aorta-coronary, simple, 1 site
OA640	Vascular bypass operation with off pump coronary artery bypass graft, aorta-coronary, simple, 2 sites
OA648	Vascular bypass operation with off pump coronary artery bypass graft, aorta-coronary, simple, 3 sites
OA649	Vascular bypass operation with off pump coronary artery bypass graft, aorta-coronary, simple, 4 or more sites
O1647	Vascular bypass operation, aorta-coronary, complex
OA647	Vascular bypass operation with off pump coronary artery bypass graft, aorta-coronary, complex

Appendix 4. List of ICD-10 diagnostic codes for psychiatric disorders.

1) Psychotic disorders

ICD-10 codes	Disease entity
F20	**Schizophrenia**
F20.0	Paranoid schizophrenia
F20.1	Hebephrenic schizophrenia
F20.2	Catatonic schizophrenia
F20.3	Undifferentiated schizophrenia
F20.4	Post-schizophrenic depression
F20.5	Residual schizophrenia
F20.6	Simple schizophrenia
F20.8	Other schizophrenia
F20.9	Schizophrenia, unspecified
F21	**Schizotypal disorder**
F22	**Persistent delusional disorders**
F22.0	Delusional disorder
F22.8	Other persistent delusional disorders
F22.9	Persistent delusional disorder, unspecified
F23	**Acute and transient psychotic disorders**
F23.0	Acute polymorphic psychotic disorder without symptoms of schizophrenia
F23.1	Acute polymorphic psychotic disorder with symptoms of schizophrenia
F23.2	Acute schizophrenia-like psychotic disorder
F23.3	Other acute predominantly delusional psychotic disorders
F23.8	Other acute and transient psychotic disorders
F23.9	Acute and transient psychotic disorder, unspecified
F25	**Schizoaffective disorders**
F25.0	Schizoaffective disorder, manic type
F25.1	Schizoaffective disorder, depressive type
F25.2	Schizoaffective disorder, mixed type
F25.8	Other schizoaffective disorder
F25.9	Schizoaffective disorder, unspecified
F28	**Other nonorganic psychotic disorders**
F29	**Unspecified nonorganic psychosis**

2) Manic episodes/bipolar disorders

ICD-10 codes	Disease entity
F30	**Manic episode**
F30.0	Hypomania
F30.1	Mania without psychotic symptoms
F30.2	Mania with psychotic symptoms
F30.8	Other manic episodes
F30.9	Manic episode, unspecified
F31	**Bipolar affective disorder**
F31.0	Bipolar affective disorder, current episode hypomania
F31.1	Bipolar affective disorder, current episode manic without psychotic symptoms
F31.2	Bipolar affective disorder, current episode manic with psychotic symptoms
F31.3	Bipolar affective disorder, current episode mild or moderate depression
F31.4	Bipolar affective disorder, current episode severe depression without psychotic symptoms
F31.5	Bipolar affective disorder, current episode severe depression with psychotic symptoms
F31.6	Bipolar affective disorder, current episode mixed
F31.8	Other bipolar affective disorders
F31.9	Bipolar affective disorder, unspecified

3) Depressive symptoms/disorders

ICD-10 codes	Disease entity
F32	**Depressive episode**
F32.0	Mild depressive episode
F32.1	Moderate depressive episode
F32.2	Severe depressive episode without psychotic symptoms
F32.3	Severe depressive episode with psychotic symptoms
F32.8	Other depressive episodes
F32.9	Depressive episode, unspecified
F33	**Recurrent depressive disorder**
F33.0	Recurrent depressive disorder, current episode mild
F33.1	Recurrent depressive disorder, current episode moderate
F33.2	Recurrent depressive disorder, current episode severe without psychotic symptoms
F33.3	Recurrent depressive disorder, current episode severe with psychotic symptoms
F33.4	Recurrent depressive disorder, currently in remission
F33.8	Other recurrent depressive disorders
F33.9	Recurrent depressive disorder, unspecified
F34	**Persistent mood disorder**
F34.0	Cyclothymia
F34.1	Dysthymia
F34.8	Other persistent mood disorders
F34.9	Persistent mood disorder, unspecified

4) Anxiety-related disorders

F40	**Phobic anxiety disorders**
F40.0	Agoraphobia
F40.1	Social phobias
F40.2	Specific phobias
F40.8	Other phobic anxiety disorders
F40.9	Phobic anxiety disorder, unspecified
F41	**Other anxiety disorders**
F41.0	Panic disorder
F41.1	Generalized anxiety disorder
F41.2	Mixed anxiety and depressive disorder
F41.3	Other mixed anxiety disorders
F41.8	Other specified anxiety disorders
F41.9	Anxiety disorders, unspecified
F42	**Obsessive-compulsive disorder**
F42.0	Predominantly obsessional thoughts or ruminations
F42.1	Predominantly compulsive acts
F42.2	Mixed obsessional thoughts and acts
F42.8	Other obsessive-compulsive disorders
F42.9	Obsessive-compulsive disorder, unspecified

5) Somatoform disorders

Somatoform disorders	
F45	**Somatoform disorders**
F45.0	Somatization disorder
F45.1	Undifferentiated somatoform disorder
F45.2	Hypochondriacal disorder
F45.3	Somatoform autonomic dysfunction
F45.4	Persistent somatoform pain disorder
F45.8	Other somatoform disorders
F45.9	Somatoform disorder, unspecified

Appendix 5. Statistical methods for IP weight estimation and MSM construction.

Pooled logistic regression was used to estimate the associations between the covariate vector and the propensity of antidepressant exposure in 3-month-long time intervals:

$$logit\ pr\left[A_k\ = a_{ki} \middle| \overline{A_{k-1}} = \overline{a_{(k-1)\iota}}\right] = \beta_{0ki} + \overline{\beta_{1k\iota} A_{k-1}}$$

$$logit\ pr\left[A_k\ = a_{ki} \middle| \overline{A_{k-1}} = \overline{a_{(k-1)\iota}},\ \overline{L_k} = \overline{l_{k\iota}}\right] = \beta_{0ki} + \overline{\beta_{1k\iota}\, A_{k-1}} + \overline{\beta_{2k\iota}\, L_k}$$

(A_k: Exposure to antidepressant medication at time interval $I_k = [t_k, t_{k+1}]$;
$\overline{A_{(k-1)}}$: Column vector of treatment modality at time interval $I_1 \sim I_{k-1}$;
L_k: Covariates at time interval I_k; $\overline{L_{k-1}}$: Column vector of covariates at time interval $I_0 \sim I_{k-1}$;
β_{0ki}: Time-dependent intercept; $\overline{\beta_{1k\iota}}$: Column vector of regression coefficients for $\overline{A_{k-1}}$ on A_k;
$\overline{\beta_{2k\iota}}$: Column vector of regression coefficient for $\overline{L_k}$ on A_k)

The stabilized IP weight for antidepressant exposure was estimated as follows:

$$AW_i(t)\ = \prod_{k=0}^{t} \frac{pr(A(k) = a_i(k) | \bar{A}(k-1) = \bar{a}_\iota(k-1))}{pr(A(k) = a_i(k) | \bar{A}(k-1) = \bar{a}_\iota(k-1),\ \overline{L_k} = \overline{l_{k\iota}})}$$

For estimation of hazard ratio by number of antidepressant classes, the conditional probability of being allocated to a corresponding group by antidepressant number was used instead of the conditional probability of antidepressant exposure.

$$AW_i(t)\ = \prod_{k=0}^{t} \frac{pr(A'(k) = a_i'(k) | \bar{A}'(k-1) = \overline{a_\iota'}(k-1))}{pr(A'(k) = a_i'(k) | \overline{A'}(k-1) = \bar{a}_\iota(k-1),\ \overline{L_k} = \overline{l_{k\iota}})}$$

Probability of being censored by each time interval was estimated by pooled logistic regression:

$$logit\ pr\left[C_k = c_{ki} \middle| \overline{A_{k-1}} = \overline{a_{(k-1)\iota}},\ \overline{C_{k-1}} = \overline{c_{(k-1)\iota}}\ \right] = \gamma_{0ki} + \overline{\gamma_{1k\iota}}\overline{A_{k-1}} + \overline{\gamma_{2k\iota}}\overline{C_{k-1}}$$

$$logit\ pr\left[C_k = c_{ki} \middle| \overline{A_{k-1}} = \overline{a_{(k-1)\iota}},\ \overline{C_{k-1}} = \overline{c_{(k-1)\iota}},\ \overline{L_k} = \overline{l_{k\iota}}\right]$$
$$= \gamma_{0ki} + \overline{\gamma_{1k\iota}}\overline{A_{k-1}} + \overline{\gamma_{2k\iota}}\overline{C_{k-1}} + \overline{\gamma_{3k}}\overline{L_k}$$

(C_k: Censoring status at time interval I_k; γ_{0k} : Time-dependent intercept; $\overline{\gamma_{1k\iota}}$: Column vector of regression coefficients for $\overline{A_{k-1}}$ on C_k; $\overline{\gamma_{2k}}$: Column vector of regression coefficients for $\overline{C_{k-1}}$ on C_k; $\overline{\gamma_{3k\iota}}$: Column vector of regression coefficients for $\overline{L_k}$ on C_k)

The stabilized IP weight for censoring was estimated as follows:

$$CW_i(t) = \prod_{k=0}^{t} \frac{pr(C(k) = c_i(k) | \bar{C}(k-1) = \bar{c_\iota}(k-1), \bar{A}(k-1) = \bar{a_\iota}(k-1))}{pr(C(k) = c_i(k) | \bar{C}(k-1) = \bar{c_\iota}(k-1), \bar{A}(k-1) = \bar{a_\iota}(k-1), \overline{L_k} = \overline{l_{k\iota}})}$$

For estimation of hazard ratio by number of antidepressant classes, the conditional probability of being allocated to a corresponding group by antidepressant number was used instead of the conditional probability of antidepressant exposure.

$$CW_i'(t) = \prod_{k=0}^{t} \frac{pr(C(k) = c_i(k) | \bar{C}(k-1) = \bar{c_\iota}(k-1), \bar{A}'(k-1) = \overline{a_\iota'}(k-1))}{pr(C(k) = c_i(k) | \bar{C}(k-1) = \bar{c_\iota}(k-1), \bar{A}'(k-1) = \overline{a_\iota'}(k-1), \overline{L_k} = \overline{l_{k\iota}})}$$

The final IP weights for individuals at time interval t were estimated as the product of AW_i and CW_i. Discrete-time survival analysis model was constructed to estimate the hazard ratios and 95% confidence intervals. Results from MSM was compared to those from conventional time-varying Cox regression model.

Appendix 6. Association between antidepressant class and CAD with revascularization under lag-time analysis.

Lag time	Main analysis, HR (95% CI)	6 months, HR (95% CI)	12 months, HR (95% CI)	24 months, HR (95% CI)
No antidepressants	ref	ref	ref	ref
Ever prescribed	**1.31 (1.18 – 1.46)**	**1.31 (1.18 – 1.46)**	**1.30 (1.17 – 1.45)**	**1.28 (1.15 – 1.43)**
Number of antidepressant classes				
Single class	**1.18 (1.04 – 1.33)**	**1.18 (1.04 – 1.34)**	**1.15 (1.02 – 1.31)**	1.12 (0.98 – 1.27)
Multiple classes	**1.46 (1.29 – 1.65)**	**1.48 (1.31 – 1.68)**	**1.48 (1.30 – 1.68)**	**1.48 (1.30 – 1.68)**
2 classes	**1.45 (1.26 – 1.67)**	**1.44 (1.25 – 1.66)**	**1.45 (1.25 – 1.67)**	**1.45 (1.18 – 1.77)**
3 classes	**1.47 (1.20 – 1.80)**	**1.47 (1.20 – 1.79)**	**1.45 (1.18 – 1.77)**	**1.45 (1.18 – 1.77)**
4 classes	**1.97 (1.40 – 2.76)**	**1.97 (1.40 – 2.76)**	**1.97 (1.40 – 2.77)**	**1.97 (1.42 – 2.77)**
Main treatment regimen				
SSRI	**1.43 (1.07 – 1.60)**	**1.41 (1.26 – 1.58)**	**1.44 (1.28 – 1.61)**	**1.40 (1.24 – 1.58)**
SNRI	0.94 (0.77 – 1.15)	0.91 (0.74 – 1.10)	0.92 (0.75 – 1.12)	0.93 (0.76 – 1.13)
TCA	1.24 (0.90 – 1.70)	1.13 (0.81 – 1.57)	1.17 (0.84 – 1.62)	1.09 (0.77 – 1.54)
Other antidepressants	**1.24 (1.02 – 1.54)**	**1.24 (1.03 – 1.50)**	**1.24 (1.02 – 1.50)**	**1.26 (1.04 – 1.53)**
Ever prescribed				
SSRI	**1.47 (1.32 – 1.64)**	**1.46 (1.30 – 1.62)**	**1.48 (1.32 – 1.65)**	**1.44 (1.28 – 1.61)**
SNRI	1.19 (0.98 – 1.44)	1.16 (0.96 – 1.40)	1.18 (0.97 – 1.42)	1.17 (0.97 – 1.42)
TCA	**1.29 (1.14 – 1.46)**	**1.25 (1.10 – 1.42)**	**1.24 (1.10 – 1.40)**	**1.28 (1.13 – 1.45)**
Other antidepressants	**1.21 (1.07 – 1.37)**	1.10 (0.97 – 1.25)	1.10 (0.97 – 1.25)	1.13 (0.99 – 1.28)

Appendix 7. Association between antidepressant prescription pattern and coronary artery disease under lag-time analysis.

Lag time	Main analysis, HR (95% CI)	6 months, HR (95% CI)	12 months, HR (95% CI)	24 months, HR (95% CI)
No antidepressants	ref	ref	ref	ref
Duration of prescription, months				
Short-term (<6)	**1.31 (1.18 – 1.46)**	**1.36 (1.16 – 1.58)**	**1.38 (1.18 – 1.61)**	**1.39 (1.19 – 1.63)**
Short-intermediate (6 – 11)	1.26 (0.85 – 1.86)	1.26 (0.86 – 1.86)	1.28 (0.86 – 1.90)	1.45 (0.98 – 2.16)
Long-intermediate (12 – 23)	1.17 (0.81 – 1.68)	1.17 (0.82 – 1.68)	1.17 (0.82 – 1.68)	1.23 (0.85 – 1.78)
Long (≥24)	**1.68 (1.44 – 1.96)**	**1.68 (1.44 – 1.96)**	**1.69 (1.45 – 1.96)**	**1.69 (1.45 – 1.90)**
By 1 year increase	**1.06 (1.04 – 1.08)**	**1.06 (1.04 – 1.08)**	**1.06 (1.04 – 1.08)**	**1.06 (1.04 – 1.08)**
Medication possession ratio, %				
Low (<20)	**1.39 (1.21 – 1.60)**	**1.41 (1.22 – 1.62)**	**1.41 (1.23 – 1.63)**	**1.43 (1.24 – 1.65)**
Low-intermediate (20 – 49)	**1.59 (1.27 – 1.97)**	**1.60 (1.27 – 2.01)**	**1.63 (1.30 – 2.05)**	**1.67 (1.33 – 2.11)**
High-intermediate (50 – 79)	**1.64 (1.28 – 2.16)**	**1.68 (1.31 – 2.16)**	**1.72 (1.35 – 2.21)**	**1.78 (1.39 – 2.28)**
High (≥80)	1.22 (0.93 – 1.60)	1.28 (0.98 – 1.68)	1.29 (0.98 – 1.70)	**1.33 (1.01 – 1.76)**
By 10% increase	**1.04 (1.02 – 1.05)**	**1.05 (1.03 – 1.07)**	**1.05 (1.03 – 1.07)**	**1.05 (1.03 – 1.08)**

For fully adjusted model, variables listed below were included as covariates: age, sex, monthly insurance premium, Charlson comorbidity index, psychiatric comorbidities, and history of psychiatric admission. For marginal structural model, inverse probability weight was estimated by multivariate logistic regression model adjusted by same set of variables listed above. HR, hazard ratio; CI, confidence interval; ref, reference.

Appendix 8. Association between antidepressant class and CAD with revascularization under progressive inverse probability weight truncation.

IP weight truncation	Main analysis, HR (95% CI) (N = 50,518)	1 - 99p, HR (95% CI) (N = 49,508)	5 - 95p, HR (95% CI) (N = 45,467)	10 - 90p, HR (95% CI) (N = 40,416)
No antidepressants	ref	ref	ref	ref
Ever prescribed	**1.31 (1.18 – 1.46)**	**1.28 (1.15 – 1.42)**	**1.34 (1.20 – 1.50)**	**1.34 (1.19 – 1.51)**
Number of antidepressant classes				
Single class	**1.18 (1.04 – 1.33)**	**1.15 (1.02 – 1.30)**	**1.19 (1.04 – 1.35)**	**1.18 (1.03 – 1.34)**
Multiple classes	**1.46 (1.29 – 1.65)**	**1.44 (1.27 – 1.63)**	**1.54 (1.35 – 1.75)**	**1.54 (1.33 – 1.79)**
2 classes	**1.45 (1.26 – 1.67)**	**1.40 (1.27 – 1.63)**	**1.50 (1.29 – 1.75)**	**1.53 (1.29 – 1.81)**
3 classes	**1.47 (1.20 – 1.80)**	**1.45 (1.18 – 1.77)**	**1.49 (1.29 – 1.73)**	**1.57 (1.23 – 2.01)**
4 classes	**1.97 (1.40 – 2.76)**	**1.92 (1.36 – 2.71)**	**2.14 (1.49 – 3.08)**	**2.19 (1.49 – 3.21)**
Main treatment regimen				
SSRI	**1.43 (1.07 – 1.60)**	**1.41 (1.25 – 1.58)**	**1.48 (1.31 – 1.67)**	**1.47 (1.29 – 1.67)**
SNRI	0.94 (0.77 – 1.15)	0.89 (0.73 – 1.08)	0.92 (0.75 – 1.13)	0.88 (0.70 – 1.10)
TCA	1.24 (0.90 – 1.70)	1.22 (0.88 – 1.69)	1.20 (0.85 – 1.69)	1.37 (0.97 – 1.93)
Other antidepressants	**1.24 (1.02 – 1.54)**	**1.21 (1.00 – 1.47)**	**1.29 (1.05 – 1.57)**	**1.29 (1.04 – 1.60)**
Ever prescribed				
SSRI	**1.47 (1.32 – 1.64)**	**1.46 (1.31 – 1.63)**	**1.50 (1.34 – 1.68)**	**1.50 (1.33 – 1.69)**
SNRI	1.19 (0.98 – 1.44)	1.15 (0.95 – 1.39)	1.15 (0.94 – 1.41)	1.24 (1.01 – 1.53)
TCA	**1.29 (1.14 – 1.46)**	**1.24 (1.10 – 1.40)**	**1.28 (1.13 – 1.46)**	**1.25 (1.08 – 1.45)**
Other antidepressants	**1.21 (1.07 – 1.37)**	**1.26 (1.10 – 1.43)**	**1.26 (1.10 – 1.43)**	**1.29 (1.07 – 1.56)**

Appendix 9. Association between antidepressant prescription pattern and coronary artery disease under progressive inverse probability weight truncation.

HR (95% CI)	Main analysis (N = 50,518)	1 – 99p (N = 49,508)	5 – 95p (N = 45,467)	10 – 90p (N = 40,416)
No antidepressants	ref	ref	ref	ref
Duration of prescription, months				
Short-term (<6)	**1.31 (1.12 – 1.53)**	**1.33 (1.14 – 1.55)**	**1.32 (1.12 – 1.56)**	**1.34 (1.12 – 1.60)**
Short-intermediate (6 – 11)	1.26 (0.85 – 1.86)	1.26 (0.85 – 1.81)	1.27 (0.84 – 1.92)	1.25 (0.80 – 1.96)
Long-intermediate (12 – 23)	1.17 (0.81 – 1.68)	1.16 (0.80 – 1.68)	1.26 (0.86 – 1.83)	0.97 (0.61 – 1.54)
Long (≥24)	**1.68 (1.44 – 1.96)**	**1.69 (1.45 – 1.98)**	**1.72 (1.46 – 2.04)**	**1.76 (1.47 – 2.11)**
By 1 year increase	**1.06 (1.04 – 1.08)**	**1.06 (1.04 – 1.08)**	**1.06 (1.04 – 1.08)**	**1.06 (1.04 – 1.08)**
Medication possession ratio, %				
Low (<20)	**1.39 (1.21 – 1.60)**	**1.41 (1.22 – 1.62)**	1.41 (1.21 – 1.64)	1.42 (1.21 – 1.67)
Low-intermediate (20 – 49)	**1.59 (1.27 – 1.97)**	1.60 (1.27 – 2.01)	1.53 (1.19 – 1.97)	**1.51 (1.15 – 1.98)**
High-intermediate (50 – 79)	**1.64 (1.28 – 2.16)**	**1.66 (1.30 – 2.14)**	**1.82 (1.41 – 2.36)**	**1.71 (1.28 – 2.29)**
High (≥80)	1.22 (0.93 – 1.60)	1.20 (0.90 – 1.58)	1.21 (0.89 – 1.64)	1.25 (0.91 – 1.73)
By 10% increase	**1.04 (1.02 – 1.05)**	**1.04 (1.02 – 1.05)**	**1.05 (1.02 – 1.07)**	**1.04 (1.02 – 1.05)**

Appendix 10. Characteristics of participants who have participated in health checkup (N = 37,558)

	Full cohort (N = 37,558)	No antidepressant (N = 16,295)	Single class (N = 11,762)	Multiple classes (N = 9,501)	p-value
Age, mean (SD)	46.23 (14.14)	46.82 (14.44)	42.31 (15.45)	45.82 (14.20)	<0.001
Men, N (%)	14,136 (37.64)	6,386 (39.19)	4,197 (35.68)	3,553 (37.40)	<0.001
Years of follow-up, mean (SD)	7.29 (4.22)	7.16 (4.27)	7.00 (4.18)	7.85 (4.15)	<0.001
Monthly insurance premium, N (%)					<0.001
0 (Medicaid receiver)	1,551 (4.13)	389 (2.39)	474 (4.03)	688 (7.24)	
<25p	7,248 (19.30)	3,029 (18.59)	2,244 (19.08)	1,975 (20.79)	
25 – 49p	7,835 (20.86)	3,417 (20.97)	2,460 (20.91)	1,958 (20.61)	
50 – 74p	9,229 (24.57)	4,133 (25.36)	2,914 (24.77)	2,182 (22.97)	
≥75p	10,609 (28.25)	4,851 (29.77)	3,318 (28.21)	2,440 (25.68)	
N/A	1,086 (2.89)	476 (2.92)	352 (2.99)	258 (2.72)	
Charlson comorbidity index, N (%)					<0.001
0	6,787 (18.07)	3,116 (19.12)	2,127 (18.08)	1,544 (16.25)	
1	9,204 (24.51)	3,994 (24.51)	2,934 (24.94)	2,276 (23.96)	
2	6,928 (18.45)	2,874 (17.64)	2,171 (18.46)	1,883 (19.82)	
3	4,613 (12.28)	1,947 (11.95)	1,446 (12.29)	1,220 (12.84)	
≥4	10,026 (26.69)	4,364 (26.78)	3,084 (26.22)	2,578 (27.13)	
Hypertension, N (%)	8,512 (22.66)	3,737 (22.89)	2,541 (21.60)	2,241 (23.59)	<0.001
Dyslipidemia, N (%)	13,879 (36.95)	5,812 (35.67)	4,184 (35.57)	3,883 (40.87)	<0.001
Psychiatric comorbidities, N (%)[a]					
Psychotic disorders	1,659 (4.42)	412 (2.53)	437 (3.72)	810 (8.53)	<0.001
Manic episodes/bipolar disorders	2,823 (7.52)	567 (3.48)	709 (6.03)	1,547 (16.28)	<0.001
Depressive symptoms/disorders	18,765 (49.96)	5,329 (32.70)	6,173 (52.48)	7,263 (76.44)	<0.001
Anxiety-related disorders other than PTSD	19,273 (51.32)	6,775 (41.58)	6,080 (51.69)	6,418 (67.55)	<0.001
Somatoform disorders	5,508 (14.67)	1,973 (12.11)	1,643 (13.97)	1,892 (19.91)	<0.001
Admission due to psychiatric disorder, N (%)[a]	4,192 (11.16)	942 (5.78)	1,187 (10.09)	2,063 (21.71)	<0.001
CAD with revascularization, N (%)	1,278 (3.40)	501 (3.07)	378 (3.21)	399 (4.20)	<0.001
All-cause mortality, N (%)	922 (2.45)	375 (2.30)	239 (2.03)	308 (3.24)	<0.001
Class of main treatment regimen, N (%)[a]					<0.001
None	16,295 (43.39)	16,295 (100.00)	-	-	
SSRI	6,289 (66.16)	-	8,103 (68.89)	6,286 (66.16)	
SNRI	572 (6.02)	-	457 (3.89)	562 (6.02)	
TCA	1,085 (11.42)	-	1,789 (15.21)	1,085 (11.42)	
Other antidepressants	1,558 (16.40)	-	1,413 (12.01)	1,558 (16.40)	
Class of ever prescribed antidepressants, N (%)[a]					<0.001
None	16,295 (43.39)	16,295 (100.00)	-	-	
SSRI	16,853 (44.87)	-	8,103 (68.89)	8,750 (92.10)	
SNRI	2,827 (7.53)	-	457 (3.89)	2,370 (24.94)	
TCA	6,100 (16.24)	-	1,789 (15.21)	4,311 (45.37)	
Other antidepressants	8,505 (22.64)	-	1,413 (12.01)	7,092 (74.64)	

	Full cohort (N = 37,558)	No antidepressant (N = 16,295)	Single class (N = 11,762)	Multiple classes (N = 9,501)	p-value
Duration of antidepressant prescription, mean (SD)[a]	23.02 (38.31)	-	8.87 (22.21)	40.53 (46.04)	<0.001
None (0), N (%)	16,295 (43.39)	16,295 (100.00)	-	-	
Short-term (<6), N (%)	12,592 (33.53)	-	9,246 (78.61)	3,346 (35.22)	
Short intermediate (6 - 11), N (%)	1,494 (3.98)	-	694 (5.90)	800 (8.42)	
Long intermediate (12 - 23), N (%)	1,419 (3.78)	-	549 (4.67)	870 (9.16)	
Long-term (>=24), N (%)	5,758 (15.33)	-	1,273 (10.82)	4,485 (47.21)	
Duration by class, mean (SD)[a]					
SSRI (N = 16,853)	18.37 (33.23)	-	9.58 (22.93)	26.51 (38.76)	<0.001
SNRI (N = 2,827)	12.18 (23.16)	-	5.85 (16.16)	13.40 (24.09)	<0.001
TCA (N = 6,100)	15.70 (31.27)	-	8.24 (22.83)	18.80 (33.68)	<0.001
Other AD (N = 8,505)	16.95 (31.26)	-	6.82 (18.50)	18.98 (32.86)	<0.001
Medication possession ratio, %, mean (SD)[a]	26.47 (34.93)	-	13.34 (25.63)	42.72 (37.94)	<0.001
None (0), N (%)	16,295 (43.39)	16,295 (100.00)	-	-	
Low (<20), N (%)	13,505 (35.96)	-	9,547 (81.17)	3,958 (41.66)	
Low intermediate (20 - 49), N (%)	2,570 (6.84)	-	981 (8.34)	1,589 (16.72)	
High intermediate (50 - 79), N (%)	1,980 (5.27)	-	535 (4.55)	1,445 (15.21)	
High (≥80), N (%)	3,208 (8.54)	-	699 (5.94)	2,509 (26.41)	
Medication possession ratio by class, %, mean (SD)[a]					
SSRI (N = 16,853)	22.55 (32.31)	-	15.11 (27.16)	29.66 (35.02)	<0.001
SNRI (N = 2,827)	15.43 (24.29)	-	10.35 (21.31)	16.40 (24.70)	<0.001
TCA (N = 6,100)	14.77 (25.89)	-	8.48 (20.20)	17.38 (27.50)	<0.001
Other AD (N = 8,505)	20.03 (29.99)	-	10.44 (22.73)	21.94 (30.89)	<0.001
Systolic blood pressure, mmHg, mean (SD)	119.86 (15.79)	120.17 (15.93)	119.52 (15.59)	119.74 (15.80)	0.002
Diastolic blood pressure, mmHg, mean (SD)	75.19 (10.65)	75.33 (10.70)	74.95 (10.50)	75.26 (10.76)	0.010
Fasting blood glucose, mg/dL, mean (SD)	94.81 (26.18)	94.54 (25.10)	94.63 (28.13)	95.50 (25.46)	0.012
Total serum cholesterol, mg/dL, mean (SD)	192.09 (43.79)	192.03 (45.21)	191.60 (45.38)	192.80 (39.04)	0.136
Cigarette smoking, N (%)					<0.001
Nonsmoker	24,903 (66.31)	10,976 (67.36)	7,855 (66.78)	6,072 (63.91)	
Past smoker	3,067 (8.17)	1,355 (8.32)	966 (8.21)	746 (7.85)	
Current smoker	8,464 (22.54)	3,454 (21.20)	3,454 (21.20)	2,418 (25.45)	
Frequency of alcohol consumption, N (%)					0.001
Nondrinker	20,330 (54.13)	8,854 (54.34)	6,363 (54.10)	5,113 (53.82)	
Twice per week or less	12,437 (33.11)	5,414 (33.22)	3,955 (33.63)	3,068 (32.29)	
Three times per week or more	3,821 (10.17)	1,588 (9.75)	1,153 (9.80)	1,080 (11.37)	

SD, standard deviation; p, percentile; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant medication.
[a] Measured at follow-up termination

Appendix 11. Difference in participant characteristics by health checkup participation.

Health checkup participation	No (N = 12,960)	Yes (N = 37,558)	p-value
Age, mean (SD)	33.41 (15.12)	46.34 (14.14)	<0.001
Men, N (%)	7,926 (61.16)	23,422 (62.36)	0.015
Years of follow-up, mean (SD)	5.66 (4.14)	7.29 (4.22)	<0.001
Monthly insurance premium, N (%)			<0.001
0 (Medicaid receiver)	1,287 (9.93)	1,551 (4.13)	
<25p	2,705 (20.87)	7,248 (19.30)	
25 – 49p	2,836 (21.88)	7,835 (20.86)	
50 – 74p	2,612 (20.15)	9,229 (24.57)	
≥75p	3,306 (25.51)	10,609 (28.25)	
N/A	214 (1.65)	1,086 (2.89)	
Charlson comorbidity index, N (%)			<0.001
0	4,341 (33.50)	6,787 (18.07)	
1	4,153 (32.04)	9,204 (24.51)	
2	2,224 (17.16)	6,928 (18.45)	
3	882 (6.81)	4,613 (12.28)	
≥4	1,360 (10.49)	10,026 (26.69)	
Hypertension, N (%)	1,318 (10.17)	8,512 (22.66)	<0.001
Dyslipidemia, N (%)	1,808 (13.95)	13,879 (36.95)	<0.001
Psychiatric comorbidities, N (%)[a]			
Psychotic disorders	1,057 (8.16)	1,659 (4.42)	<0.001
Manic episodes/bipolar disorders	1,763 (13.60)	2,823 (7.52)	<0.001
Depressive symptoms/disorders	6,944 (53.58)	18,765 (49.66)	<0.001
Anxiety-related disorders other than PTSD	5,977 (46.12)	19,273 (51.32)	<0.001
Somatoform disorders	1,073 (8.28)	5,508 (14.67)	<0.001
Admission due to psychiatric disorder, N (%)[a]	1,939 (14.96)	4,192 (11.16)	<0.001
CAD with revascularization, N (%)	265 (2.04)	1,278 (3.40)	<0.001
All-cause mortality, N (%)	453 (3.50)	922 (2.45)	<0.001
Antidepressant treatment group, N (%)			<0.001
No antidepressant	5,045 (38.93)	16,295 (43.39)	
Single class	4,208 (32.47)	11,762 (31.32)	
Multiple classes	3,707 (28.60)	9,501 (25.30)	
Class of main treatment regimen, N (%)[a]			<0.001
None	5,045 (38.93)	16,295 (43.39)	
SSRI	5,762 (44.46)	14,389 (38.31)	
SNRI	381 (2.94)	1,029 (2.74)	
TCA	741 (5.72)	2,874 (7.65)	
Other antidepressants	1,031 (7.96)	2,971 (7.91)	
Class of ever prescribed antidepressants, N (%)[a]			
None	5,045 (38.93)	16,295 (43.39)	<0.001
SSRI	6,642 (51.25)	16,853 (44.87)	<0.001
SNRI	1,102 (8.50)	2,827 (7.53)	<0.001
TCA	1,925 (14.85)	6,100 (16.24)	<0.001
Other antidepressants	3,332 (25.71)	8,505 (22.64)	<0.001
Duration of antidepressant prescription, mean (SD)[a]	20.98 (34.90)	23.02 (38.31)	<0.001
None (0), N (%)	5,045 (38.93)	16,295 (43.39)	
Short-term (<6), N (%)	4,512 (34.81)	12,592 (33.53)	
Short intermediate (6 - 11), N (%)	692 (5.34)	1,494 (3.98)	
Long intermediate (12 - 23), N (%)	689 (5.32)	1,419 (3.78)	
Long-term (>=24), N (%)	2,022 (15.60)	5,758 (15.33)	
Duration by class, mean (SD)[a]			
SSRI (N = 23,495)	17.02 (30.34)	18.37 (33.23)	0.004
SNRI (N = 3,929)	10.39 (19.39)	12.18 (23.16)	0.023
TCA (N = 8,025)	116.49 (31.13)	15.70 (31.27)	0.332
Other antidepressants (N = 11,837)	15.87 (28.70)	16.96 (31.26)	0.079
Medication possession ratio, %, mean (SD)[a]	32.49 (37.28)	26.47 (34.93)	<0.001
None (0), N (%)	5,045 (38.93)	16,295 (43.39)	
Low (<20), N (%)	4,464 (34.44)	13,505 (35.96)	
Low intermediate (20 - 49), N (%)	1,045 (8.06)	2,570 (6.84)	
High intermediate (50 - 79), N (%)	845 (6.52)	1,980 (5.27)	
High (≥80), N (%)	1,561 (12.04)	3,208 (8.54)	
Medication possession ratio by class, %, mean (SD)[a]			
SSRI (N = 23,495)	28.91 (35.51)	22.66 (32.31)	<0.001
SNRI (N = 3,929)	17.55 (26.05)	15.43 (24.28)	0.016
TCA (N = 8,025)	18.17 (27.87)	14.77 (25.89)	<0.001
Other antidepressants (N = 11,837)	24.27 (31.84)	20.03 (29.99)	<0.001

SD, standard deviation; p, percentile; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant medication.

[a] Measured at follow-up termination.

Appendix 12. Comparison of estimand between full cohort and health checkup subgroup.

	Full cohort (N = 50,518)	Health checkup subgroup (N = 37,558)
No antidepressants	ref	ref
Ever prescribed	**1.31 (1.18 – 1.46)**	**1.34 (1.19 – 1.51)**
Number of classes		
Single class	**1.18 (1.04 – 1.33)**	**1.30 (1.11 – 1.52)**
Multiple classes	**1.46 (1.29 – 1.65)**	**1.40 (1.18 – 1.65)**
2 classes	**1.45 (1.26 – 1.67)**	**1.31 (1.06 – 1.61)**
3 classes	**1.47 (1.21 – 1.80)**	**1.55 (1.17 – 2.05)**
4 classes	**1.97 (1.40 – 2.76)**	1.54 (0.93 – 2.56)
Main treatment regimen		
SSRI	**1.31 (1.07 – 1.60)**	**1.45 (1.28 – 1.65)**
SNRI	0.94 (0.77 – 1.15)	0.89 (0.72 – 1.11)
TCA	1.24 (0.90 – 1.70)	1.29 (0.92 – 1.83)
Other antidepressants	**1.24 (1.02 – 1.54)**	**1.29 (1.05 – 1.58)**
Ever prescribed		
SSRI	**1.47 (1.32 – 1.64)**	**1.50 (1.33 – 1.69)**
SNRI	1.19 (0.98 – 1.44)	1.17 (0.97 – 1.40)
TCA	**1.29 (1.14 – 1.46)**	**1.32 (1.11 – 1.58)**
Other antidepressants	**1.21 (1.07 – 1.37)**	**1.23 (1.00 – 1.51)**
Duration of prescription, months		
Short-term (<6)	**1.31 (1.12 – 1.53)**	**1.29 (1.08 – 1.53)**
Short-intermediate (6 – 11)	1.26 (0.85 – 1.86)	1.30 (0.94 – 1.78)
Long-intermediate (12 – 23)	1.17 (0.81 – 1.68)	1.28 (0.93 – 1.77)
Long (≥24)	**1.68 (1.44 – 1.96)**	**1.49 (1.24 – 1.81)**
By 1 year increase	**1.27 (1.04 – 1.57)**	**1.26 (1.02 – 1.55)**
Medication possession ratio, %		
Low (<20)	**1.39 (1.21 – 1.60)**	**1.25 (1.07 – 1.47)**
Low-intermediate (20 – 49)	**1.59 (1.27 – 1.97)**	**1.42 (1.07 – 1.89)**
High-intermediate (50 – 79)	**1.64 (1.28 – 2.16)**	**1.44 (1.06 – 1.97)**
High (≥80)	1.22 (0.93 – 1.60)	1.07 (0.75 – 1.52)
By 10% increase	**1.04 (1.02 – 1.05)**	**1.03 (1.00 – 1.06)**

In full cohort analysis, variables listed below were included as covariates for IP weight estimation: age, sex, monthly insurance premium, Charlson comorbidity index, psychiatric comorbidities, and history of psychiatric admission. In health checkup subgroup analysis, variables listed below were added to a covariate set for IP weight estimation: ln(systolic blood pressure), ln(diastolic blood pressure), ln(fasting blood glucose), ln(serum total cholesterol), cigarette use, and alcohol consumption. HR, hazard ratio; CI, confidence interval; ref, reference.

Appendix 13. Bounding factors for statistically significant hazard ratios.

IP weight truncation	HR (95% CI)	Bounding factors HR_{AU}, HR_{UY}
No antidepressants	ref	ref
Ever prescribed	**1.31 (1.18 – 1.46)**	1.5, 3.5
Number of antidepressant classes		
Single class	**1.18 (1.04 – 1.33)**	1.3, 3
Multiple classes	**1.46 (1.29 – 1.65)**	1.8, 3.5
2 classes	**1.45 (1.26 – 1.67)**	1.8, 3.4
3 classes	**1.47 (1.21 – 1.80)**	1.8, 3.5
4 classes	**1.97 (1.40 – 2.76)**	2.5, 5.8
Main treatment regimen		
SSRI	**1.43 (1.07 – 1.60)**	1.5, 10
SNRI	0.94 (0.77 – 1.15)	-
TCA	1.24 (0.90 – 1.70)	-
Other antidepressants	**1.24 (1.02 – 1.54)**	1.3, 6
Ever prescribed		
SSRI	**1.47 (1.32 – 1.64)**	1.8, 3.5
SNRI	1.19 (0.98 – 1.44)	-
TCA	**1.29 (1.14 – 1.46)**	1.5, 3
Other antidepressants	**1.21 (1.07 – 1.37)**	1.3, 4
Covered duration, months		
Short-term (<6)	**1.31 (1.12 – 1.53)**	1.5, 3.5
Short-intermediate (6 – 11)	1.26 (0.85 – 1.86)	-
Long-intermediate (12 – 23)	1.17 (0.81 – 1.68)	-
Long (≥24)	**1.68 (1.44 – 1.96)**	2, 5.3
Medication possession ratio, %		
Low (<20)	**1.27 (1.04 – 1.57)**	1.5, 2.8
Low-intermediate (20 – 49)	**1.39 (1.21 – 1.60)**	1.5, 6.3
High-intermediate (50 – 79)	**1.59 (1.27 – 1.97)**	2, 3.9
High (≥80)	**1.64 (1.28 – 2.16)**	2, 4.6

국문요약

외상후스트레스장애 환자에서 항우울제가 관상동맥질환에 미치는 영향: 국민건강보험공단 청구자료 분석 결과

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김광현

서론: 과거 많은 연구에서 항우울제와 심뇌혈관질환 사이의 상관관계를 평가하였으나, 선행 연구에서 관측되는 상관관계의 방향성과 크기는 일관되지 않아 이로부터 결론을 도출하기 어렵다. 심리적 트라우마에 대한 복잡한 신경생물학적 및 심리학적 반응의 결과인 PTSD에서 항우울제와 심혈관질환 사이의 상관관계에 대한 연구 결과는 부족한 실정이며, 존재하는 근거들은 상호 상충한다. 처방 패턴의 다양성은 항우울제의 심혈관질환에 대한 영향을 평가하는 것을 더욱 어렵게 한다.

그 결과로, PTSD에서 항우울제와 심혈관질환 사이의 상관관계에 대한 근거 자료는 제한적이며 상호 상충된다. 본 연구는 한국의 PTSD 환자에서 항우울제가 처방되는 패턴을 파악하고 항우울제의 심혈관질환에 대한 영향을 평가하는 것을 목적으로 한다.

연구방법: 본 연구에서는 대한민국 국민의 의료서비스 이용 관련 행정 자료로 구성된 국민건강보험공단 데이터베이스를 활용하였다. 2004년에서 2018년 사이에 PTSD를 진단받은 74,168명의 성인 PTSD 환자가 국민건강보험공단 데이터베이스에서 확인되었다. 건강보험 자격득실 정보에 결측치가 있는 경우 (N = 5), PTSD 진단 이전 항우울제에 노출된 기록이 존재하는 경우 (N = 20,977), PTSD 진단 이전 관상동맥질환을 진단받은 과거력이 존재하는 경우 (N = 1,719) 및 추적관찰 기간이 1개월 미만인 경우 (N = 949) 분석 대상에서 제외하여 총 50,518명의 대상자가 최종 분석에 포함되었다. 항우울제 및 심리치료에 대한 보험 청구 기록은 해당 데이터베이스에서 추출하였다. 항우울제는 약제 성분에 따라 선택적 세로토닌 재흡수 억제제(SSRI), 세로토닌-노르에피네프린 재흡수 억제제(SNRI), 삼환계 항우울제(TCA) 및 기타 항우울제로 분류하였다. 항우울제 처방 패턴에 따라 '항우울제 처방 없음', '단일 약제유형', '복합 유형'으로 대상자를 분류하였다. 처방 기간, 약물소지율(MPR), 약제유형의 조합을 비롯한 항우울제 처방

패턴을 평가하였다. 종속변인은 '혈관재개통술이 필요한 관상동맥질환'으로 설정하였다. 연령, 성별, 건강보험료, Charlson Comorbidity Index, 고혈압 병력, 이상지질혈증 병력, 정신질환 동반이환 및 정신과적 입원력을 공변량으로 선택하였다.

대상자의 약제 처방 패턴에 따른 특성을 파악하기 위하여 기술통계량 분석을 수행하였다. 정신질환 동반이환, 내과적 동반이환 및 사회경제적 지위에 의한 시간의존적 교란효과를 통제하기 위하여 marginal structural model (MSM)을 구축하였으며 시간의존적 역확률 가중치를 산출하여 위험비를 산출하였다. 모형의 안정성을 평가하기 위하여 MSM에서의 결과치를 전통적 시간의존 Cox 회귀분석에서의 결과와 비교하였다. 누적 처방기간 및 전체 추적관찰 기간 중 MPR 대한 용량반응 분석을 수행하였다. 민감도 분석으로 불멸자 바이어스를 평가하기 위하여 6개월과 12개월의 지연시간을 설정하여 지연시간 분석을 수행하였다. 추가로, 양수성 가정의 위배로 인하여 도입될 수 있는 바이어스를 평가하기 위하여 안정화 역확률가중치의 1-99%, 5-95%, 10-90%에 해당하는 대상자에 대해서 민감도 분석을 수행하였다. 생활습관과 생의학적 지표의 교란효과를 평가하기 위해 건강검진을 받은 대상자를 대상으로 분석을 반복하였다. 마지막으로, Ding과 Vanderweele에 이론에 따른 bounding factor를 산출하여 측정되지

않은 교란효과의 영향을 평가하였다. 안정화 역확률가중치 절단은 추정치를 유의한 수준으로 변화하지 않았으며, 이는 양수성 가정 위배에 따른 영향은 미미함을 암시한다.

연구결과: '항우울제 처방 없음', '단일 약제유형', '복합 유형'에 속하는 대상자의 수는 각각 21,340명 (42.24%), 15,970명 (31.61%), 13,208명 (26.14%)이었다. PTSD 첫 진단 시의 대상자의 평균 연령은 43.13세였고, (표준편차 15.46년) 평균 추적관찰 기간은 6.86년이었다. (표준편차 4.26년) 가장 흔하게 처방된 항우울제 유형은 SSRI였으며, 이후 기타 항우울제, TCA, SNRI 순이었다. 평균 항우울제 처방 기간은 23.89개월이었으며 (표준편차 39.30개월) 평균 약물소지율은 28.39%였다. (표준편차 39.38%)

항우울제를 한 번이라도 처방받은 대상자는 그렇지 않은 대상자에 비해 혈관 재형성이 필요한 관상동맥질환이 발생할 위험도가 1.34배 높았다. (95% 신뢰구간 1.20 – 1.49) 단일 항우울제 유형만을 처방받은 대상자는 관상동맥질환의 위험도비가 1.17배였으며, (95% 신뢰구간 1.03 – 1.32) 반면 복수 유형의 항우울제를 처방받은 대상자의 위험비는 1.46이었다. (95% 신뢰구간 1.29 – 1.65) 모든 유형의 항우울제를 처방받은 대상자는 1.99의 위험비를 보여 (95% 신뢰구간 1.40 – 2.82) 처방받은 항우울제 유형의 수와 관상동맥질환의 상관관계에서 용량-

반응 관계를 확인할 수 있었다. SSRI, TCA 및 기타 항우울제는 관상동맥질환의 위험을 증가시킨 반면, SNRI 노출 여부와 관상동맥질환 사이의 상관관계는 확인되지 않았다.

항우울제 처방기간은 관상동맥질환과 양의 상관관계를 보였다: 24개월 이상 항우울제를 처방받은 대상자는 혈관 재형성이 필요한 관상동맥질환이 발생할 위험비가 1.46배였으나 (95% 신뢰구간 1.20 – 1.76) 그보다 짧은 기간 동안 노출된 경우 '처방내역 없음' 군과 비교하여 관상동맥질환 발생의 위험이 높지 않았다. 다항 스플라인 결과에서 역시 노출기간 – 관상동맥질환 관계에서의 용량-반응 관계를 확인할 수 있었다. SSRI, TCA 및 기타 항우울제의 처방 기간은 관상동맥질환과 양의 상관관계를 보였으나, SNRI의 처방 기간은 관상동맥질환과 상관관계를 보이지 않았다. 이에 반해, MPR에 대한 층화 분석 및 다항 스플라인의 결과에 의하면 MPR은 관상동맥질환과 직접적인 관련성을 보이지 않았다.

지연시간 분석에서의 결과는 본 분석에서와 유의한 차이를 보이지 않아 불멸시간 바이어스가 추정치에 미칠 수 있는 영향은 유의하지 않음을 알 수 있었다. 안정화 역확률가중치 절단 결과 예측치가 유의한 수준으로 변하지 않았으며, 이는 양수성 가정의 위배로 인하여 도입될 수 있는 바이어스는 미미함을 시사한다. 건강검진 대상자를 대상으로

한 하위그룹 분석 결과는 본 분석 결과와 대부분 큰 차이가 없어 생의학적 지표와 생활습관 요인의 교란효과가 추정치를 크게 변화시키지 않는 것으로 나타났다. 추정된 bounding factor는 측정되지 않은 교란효과로 인해 추정치가 온전히 무효화할 가능성이 낮음을 시사하며, 이는 잔류 교란효과가 분석 결과의 해석을 변경할 가능성이 낮음을 의미한다.

결론: PTSD 치료를 위한 항우울제와 관상동맥질환 사이의 양의 상관관계가 관찰되었으며, 복수의 유형의 항우울제를 처방받은 대상자 및 장기간 처방받은 대상자에서 그 연관성이 더 강하게 확인되었다. TCA와 SSRI를 동시에 처방받은 군에서 관상동맥질환 위험도가 가장 크게 증가한 반면, SNRI는 관상동맥질환 위험도를 증가시키지 않았다. 본 연구의 결과는 PTSD 치료를 위한 항우울제가 심혈관질환의 위험을 증가시킨다는 것을 보여 주며, 항우울제 처방 이전 심혈관질환 위험 평가의 필요성을 시사한다. 장기간 항우울제에 노출될 경우 관상동맥질환 위험이 더 크게 상승하므로 장기간 항우울제를 처방받는 PTSD 환자에서는 심혈관질환 예방을 위한 주의 깊은 감시가 필요할 것이다. 특히, TCA와 SSRI를 같이 처방받는 PTSD 환자에서는 치료적 약물농도 모니터링과 약물 교체를 비롯하여 관상동맥질환을 예방하기 위한 개입 방안을 고려해야 할 것이다.