Myocardial Infarction, Antidepressants and Mortality*

Mattias Öhman†

November 3, 2016

Abstract

I estimate the effect of SSRI antidepressants on the risk of mortality for myocardial infarction (MI) patients using Propensity Score Matching on individual health variables such as pharmaceutical drug prescription, patient history and severity of the MI. The effect of antidepressants on mortality is a heavily debated topic. MI patients have an elevated risk of developing depression, and antidepressants are among the most common treatments for depression and anxiety. However, there are indications that some classes of antidepressants may have drug-induced cardiovascular effects and could be harmful for individuals with heart problems, but there is a lack of large-scale studies using credible identification strategies. My findings indicate no increased risk of two-year mortality for MI patients using SSRI. The results are stable for several specifications and robustness checks.

Keywords: Myocardial infarction, antidepressants, SSRI, Propensity Score Matching, mortality
JEL Codes: I10, I18, I31

*I would like to thank Claes Held, Erik Olsson, Ingeborg Waernbaum, Ulrika Wikman, Claudia Lissåker, Ronnie Pingel, Erik Grönqvist, Matz Dahlberg, Bodil Svennblad and Linuz Aggeborn for helpful discussions, comments and suggestions. I also thank Nikolaj Siersbæk and the participants at the NHESG 2015 conference in Uppsala who commented on an early version of this paper.
†U-CARE and Department of Economics, Uppsala University; Box 513, 751 20 Uppsala, Sweden. E-mail: mattias.ohman@nek.uu.se.

1 Introduction

Myocardial infarction (MI), more commonly known as heart attack, occurs when the blood cannot flow to a part of the heart muscle. MI patients have an increased risk of developing depression, and individuals who have experienced a MI have a higher mortality rate than the general population (e.g. Taylor et al. 2005; Thombs et al. 2006; Aso et al. 2011). Between 11-25 percent of the outpatients and as many as 35-70 percent of the inpatients with a heart failure meet the criteria for depression (Thomas et al. 2001; Joynt, Whellan, et al. 2004). Depression is associated with an increased risk of cardiac morbidity and mortality for individuals with an established coronary heart disease. Thus it is important to treat patients with a depression after an MI to alleviate the risk of a subsequent MI (Joynt, Whellan, et al. 2004). Antidepressants are a very common treatment for depression and anxiety today (Olfson and Marcus 2009).

However, studies suggest that treatment of depression has not decreased the risk of mortality (ENRICHD 2003; Joynt and O'Connor 2005). Some studies find that antidepressants lower the risk of mortality, while other studies find that both the old tricyclic antidepressants (TCA) and the newer Selective serotonin reuptake inhibitor (SSRI) antidepressants may increase the risk (Tata et al. 2005; Hamer et al. 2010; Noordam et al. 2016). The current consensus is that TCA should be avoided and that SSRI is relatively safe, but there is a need for large-scale studies using credible identification strategies.

In this study I estimate the effect of SSRI antidepressants on the risk of two-year mortality after the first MI, for patients who were prescribed SSRI within six months of the infarction. The identification strategy relies on nearest-neighbor matching on the propensity score on a rich set of covariates, such as patient history and MI severity. By matching on these variables, the aim is to create statistical twins who differs only in treatment status. The main contribution of this study is the use of a large and rich dataset of almost the complete population of MI patients in Sweden, which to my knowledge has not been utilized before, together with an identification strategy that allows for a causal interpretation of the results.

I use data from several Swedish population wide registers. The Swedish quality register for cardiac intensive care (RIKS-HIA and SEPHIA) from Swedeheart, the National Patient Register (in- and outpatient care), the prescribed drug register and the cause of death registry from The National Board of Health and Welfare. Individuals included in the data had their first MI between 2007 and 2011.

Results indicate no increased risk of mortality. The results are robust for various specifications. There are, however, no indication of a protective effect of using antidepressants.

The paper is organized as follows. In the next section I shortly discuss the medical background. Section 3 describes the data, followed by a discussion of the empirical strategy and methodological considerations in section 4. Descriptive statistics is presented in section 5, and the main results in section 6. I discuss the results in section 7, and section 8 concludes the paper. Additional results, descriptive statistics, and covariate balance are presented in the appendix.

2 Medical background

As depression has been on the rise during the last decades in the western world, so has the use of antidepressants (Olfson and Marcus 2009; Reid and Barbui 2010). Depression is a mental disorder characterized by a persistent low mood. The individual often have low self-esteem, feelings of worthlessness, and have lost of interest in activities that he or she normally enjoys. Individuals who are depressed often have unusual loss or gain of weight and experience insomnia (American Psychiatric Association 2013). Estimates suggest that about nine out of ten individuals who commit suicide suffered from depression (Hawton et al. 2013). Antidepressants are, together with psychological therapy, the most common treatment for depression (Olfson and Marcus 2009). According to statistics from The National Board of Health and Welfare (Socialstyrelsen), almost 10 percent of the population in Sweden in 2015 was prescribed some kind of antidepressant.[1] However, the effects of antidepressants are a heavily debated topic. For example, some studies find that antidepressants lower the risk of mortality, while others find the opposite, or no effect at all (Dahlberg and Lundin 2005; Cipriani et al. 2005; Ludwig et al. 2009; Ghassemi et al. 2014).

Myocardial infarction occurs when the blood cannot flow to a part of the heart muscle. Common symptoms are chest pain, sweating, and dizziness (National Institutes of Health 2015). The mortality rate for MI patients is high (Aso et al. 2011). Depression and anxiety is common among patients recovering from a myocardial infarction (Ziegelstein 2001; Thombs et al. 2006; Williams 2011). 11-25 percent of the outpatients and 35-70 percent of the inpatients with heart failure meet the criteria for depression (Thomas et al. 2001; Joynt, Whellan, et al. 2004). It is well-known from the literature that

[1] Note that antidepressants are not exclusively prescribed to individuals diagnosed with depression or anxiety.

depressed patients are at higher risk of mortality after a myocardial infarction, both through direct and indirect pathways (e.g. Frasure-Smith et al. 1995, Barth et al. 2004, Hare et al. 2013), as illustrated in Figure 1. Depression is associated with poor health behavior in general, including risk factors such as smoking and a poor diet. Joynt, Whellan, et al. (2004) concludes that it is important to treat patients with a depression after an MI to alleviate the risk of a subsequent MI.

However, some studies suggest that treatment of depression has not succeeded to decrease the risk of mortality (ENRICHD 2003; Joynt and O'Connor 2005). The effects of treating depression with antidepressants for MI patients are not clear. There is an ongoing discussion whether antidepressants increase or decrease cardiovascular mortality (Narayan and Stein 2009). Melle et al. (2007) does not find an improvement of post-MI long-term depression, or an improvement of the cardiac prognosis. There is a consensus in the literature that the earlier tricyclic antidepressants have cardiac effects, and is contraindicated for MI patients (Cohen et al. 2000; Joynt, Whellan, et al. 2004; Hamer et al. 2010). SSRI antidepressants are considered more safe, and Taylor et al. (2005) find that SSRI decrease mortality. However, Tata et al. (2005) suggest that both TCA and SSRI might increase the risk, whilst Noordam et al. (2016) find that the current use of antidepressants, regarding both TCA and SSRI, are associated with a lower risk of recurrent MI.

In a meta-analysis by Pizzi et al. (2011), the researchers find that the estimated effects differ between RCT:s and observational studies. In RCT:s they find no difference in mortality risk, while the observational studies indicate a decreased risk. The problem with RCT:s are that they often have small samples, short follow-up time, and it is not always clear if the results are externally valid. On the other hand, most observational studies do not use a credible identification strategy, and can only show associations. Thus, there is a need for more studies on SSRI use for MI patients that can utilize the population of MI patients while at the same time allow for a causal interpretation of the results.

3 Data

In this section I will describe the data available. Descriptives are shown later in section 5 and in the appendix.

The data consists of several Swedish population wide registers between the years 2006 and 2013. The Swedeheart registers (RIKS-HIA and SEPHIA) include almost all myocardial infarction patients in Sweden. RIKS-HIA is nationwide and an almost

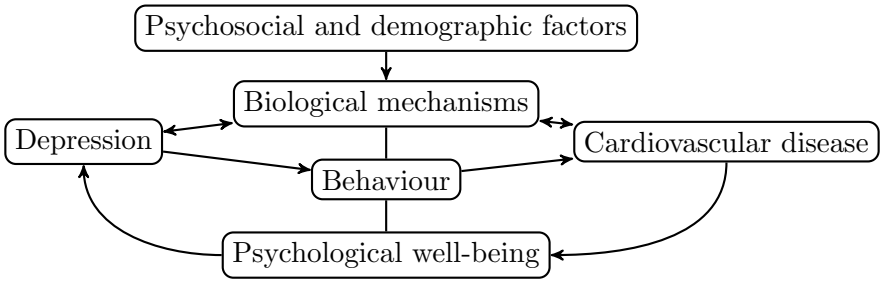

FIGURE 1. Relationship between cardiovascular disease and depression. Simplified and adapted from Hare et al. (2013).

complete register of all myocardial infarction patients in Sweden. About 90 percent of the hospitals are included. SEPHIA includes follow-up data for patients below 75 years age. The registers from The National Board of Health and Welfare include all prescribed drugs to the individuals, the in- and outpatient diagnoses, and the cause of death.[2]

To create a credible matching on health history, the year before the first MI is used as a measure of pre-MI health history (365 days). Therefore, I exclude all individuals with their first MI in 2006. I exclude individuals with their first MI in 2012 or 2013, to be able to have a follow-up period for individuals experiencing an MI in 2010 or 2011. Additionally, I exclude all patients who had an earlier MI, i.e., I only include patients experiencing their first MI during the years between 2007 and 2011. Some patients experience several MI:s during these years, but I focus only on the first MI. If an individual received antidepressants (of any kind) during the year before the MI he or she is excluded.[3] Individuals receiving antidepressants other than SSRI:s are excluded, as well as observations with missing values on the variables included in the most comprehensive specification.[4] After exclusions the sample consists of in total 38,319 patients.

The pre-MI health history is determined by using the prescribed drug register and the hospital in- and outpatient registers. Second level ATC is used for prescribed drugs,

[2]Primary care is not included in the in- and outpatient data, so only diagnoses a patient receives after visiting for example a hospital are included. The in- and outpatient registries include chapters F, I, J and N.

[3]2,036 individuals receive antidepressants within two years of the MI (the follow-up period) but not within six months (the treatment period). They are kept in the sample, in the control group, but the conclusions are no different if they are excluded. See section A.2 in the appendix.

[4]There are 8,389 missing values for Left Ventricular Ejection Fraction. Instead of dropping these observations, I have created a missing value indicator which is included in the propensity score estimation.

and first chapter level ICD for the diagnoses.[5] I use dummies indicating if the individual has received at least one drug or diagnosis within these classes.[6]

In addition to the pre-MI health variables, the individuals are matched on a large set of variables measuring the severity of the MI and other potential confounders. Variables include year of the MI, sex, employment status, diabetes, Killip class etc. All variables are presented in section A.1, and the specifications in Table A1 in the appendix.

The outcome is measured as all-cause two-year mortality. The treatment is SSRI antidepressants (ATC code: N06AB), which is the most common class of antidepressants today, for individuals receiving SSRI within six months of the MI (183 days). As I discuss in the next section, the follow-up time differs between the treatment group and the control group. The treated group is followed two years (730 days) from the day of first treatment of SSRI. The untreated group is followed two years from a random day within the first six months of the MI.

4 Empirical strategy

In a randomized controlled trial (RCT) we randomize individuals to a treatment group and a control group. The randomization ensures that the treatment is independent of individual characteristics and self-selection, and the two groups are (in theory) balanced in both observable and unobservable covariates. The causal effect can be estimated by simply running the following regression:

$$Y_i = \alpha + \tau T_i + u_i, \tag{1}$$

where Y is the outcome and T is the treatment for individual i. τ is the estimated coefficient of interest. Without randomization, equation (1) is likely biased due to selection into treatment, i.e., T is correlated with the error term u.

With observational data it is not possible to *ex post* randomize individuals. In the case of antidepressant treatment we know that a selection into treatment exist; depression is included in the error term in equation (1), and the probability of receiving

[5] ATC stands for the Anatomical Therapeutic Chemical Classification System. There are 14 main categories, for example code C with include drugs for cardiovascular system and code J for antiinfectives for systemic use. The inpatient and outpatient registers are classified according to the International Classification of Diseases (ICD) codes in the corresponding way using the ICD-10 classification. ICD-10 consists of 22 main categories, for example E which includes endocrine, nutritional and metabolic diseases, and M which includes diseases of the musculoskeletal system and connective tissue. Both the ATC and ICD classifications are maintained by the World Health Organization (WHO).

[6] Which ATC and ICD chapters to include was decided after discussions with medical expertise. See Table A5.

antidepressants is, obviously, higher for individuals who are depressed. Depression is correlated with worse general health, and therefore it is not possible to interpret the estimated coefficient as the causal effect of receiving antidepressants.

Regression Discontinuity Design (RDD), Instrumental Variables (IV) and Difference-in-Difference (DiD) are common methods and designs described in the econometric literature. Another approach to estimate causal effects is matching. Matching has an intuitive appeal: If we only compare individuals who are identical in all covariates, the only difference between them is the treatment status. One problem is that exact matching usually requires very large samples when we have many covariates. However, Rosenbaum and Rubin (1983) show that we do not need to have identical covariates to estimate a causal effect. It suffices with identical (or near-identical) *propensity score*. That is, what is important is that the likelihood of treatment for any given individual is identical.

Two fundamental assumptions are required for propensity score matching: Unconfoundedness and overlap.

Assumption 1. *Unconfoundedness:* $Y(0), Y(1) \perp\!\!\!\perp T|X$

The unconfoundedness assumption tells us that the potential outcomes are independent of the treatment assignment, conditional on a set of covariates X. Obviously, this is a strong assumption on the available data, and does not allow that any unobservable characteristics influence the treatment assignment and potential outcomes simultaneously.

Assumption 2. *Overlap:* $0 < P(T = 1|X) < 1$

The overlap assumption requires that all individuals with the same propensity score has a positive probability of being in either the treatment or control group. The combination of these two assumptions is called *strong ignorabililty*. If the assumptions are fulfilled, we are able to estimate a causal effect.[7]

Unfortunately it is not possible to test if the unconfoundeness assumption holds. We can never know if we have all relevant covariates in our model. Whether matching is a reasonable strategy is a question that must be answered on a case-by-case basis. If we have good knowledge of relevant covariates, matching can be used if we have the data. Myocardial infarction is such a case. The Swedish national quality registers RIKS-HIA and SEPHIA have information on more or less all relevant characteristics regarding the MI for almost the full population of patients. In addition to these variables, there is

[7]See Imbens (2015) for a more technical discussion on the assumptions.

information on earlier health history, as well as age, sex, employment status etc. I argue that matching on these characteristics fulfills the unconfoundedness assumption.

In contrast, the overlap assumption can be tested. The large dataset of MI patients makes the overlap assumption fulfilled. I discard observations without an overlap using a caliper of 0.2 of the normalized SD of the propensity score, following the advice from Austin (2011) and others.

How can the individuals treatment status differ if strong ignorability is fulfilled? One reason is treatment cultures. After matching, the main source of variation likely stems from cultural practice; between counties and between individual doctors (see Table 2). For example, each county in Sweden has a Läkemedelskommitté (a pharmaceutical committee), which give recommendations of treatment for different diseases and patient groups. These recommendations are supposed to follow the best medical practice, but there are some differences in the recommendations between the committees. These differences can create a variation in the prescription of antidepressants, i.e., in one county a depressed patient will receive antidepressants but had not in another county.

I estimate the average treatment effect of the treated (ATT),

$$\begin{aligned} \tau_{ATT} &= E(\tau|T=1) = E[Y(1)|T=1] - E[Y(0)|T=1] \\ &= \frac{1}{N_t}\sum_{i=1}^{N_t}\Big(Y_i(1) - Y_i(0)|T_i=1\Big). \end{aligned} \tag{2}$$

The ATT focus on the outcomes for whom the treatment is intended, i.e., the individuals that are eligible for antidepressant treatment, and estimates the average difference in outcome for those who received treatment compared with the counterfactual if they had not received treatment. Since the number of controls is large relative to the number of treated, the main specification use four neighbors for each treated individual, which will utilize more of the data and decrease the variance.[8]

Two-year all-cause mortality is used as the outcome. The follow-up time begins the day of treatment initiation for patients who receive SSRI within six months of their first MI. For untreated (i.e., individuals who do not receive SSRI within six months of the MI), the follow-up time starts from a random day within the six first months after the MI. This is a way of avoiding survival and immortal time bias which arises because treatment is not fixed at one point in time. Zhou et al. (2005), Suissa (2007) and Lévesque et al. (2010) discusses this problem. The bias arises because an individual could die before the treatment status is fixed, since I allow for a window of six months.

[8]Specifications using one-to-one matching are presented in the appendix.

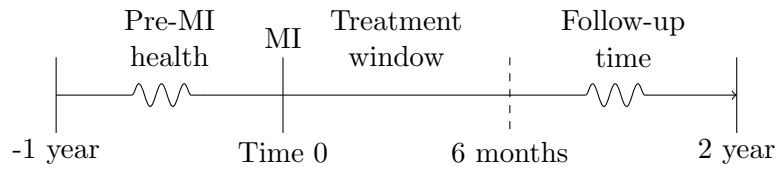

FIGURE 2. Measurement timeline of covariates, treatment and outcome.

The reason to allow for a treatment window is that developing depression, and receive medication, often take some time. Individuals who feel depressed after the MI may not yet identify the mood status as depression, but rather as a direct consequence of the MI, and will not search for help.[9] However, the strategy I use make the follow-up time shorter for some individuals who experience an MI in 2011. There are no reason to believe that this in itself bias the results, however. Figure 2 presents a measurement timeline of the variables.

The individuals are matched on several classes of variables, divided into year, SES, general health, patient history and MI measures. The patient history is measured within the year before the MI. The variables used is presented in section A.1 in the appendix. Figure 3 illustrate the identification problem and the reasoning behind the choice of variables to match on. The general health and socioeconomic status (SES) possibly affect the likelihood of treatment, the mediators and the outcome. Thus, a credible matching must in some way control for the health of the individual (this includes sex, age, and, for example, smoking). In the same way, the severity of the MI is likely affecting depression, the likelihood of receiving antidepressants and, obviously, mortality, and must also be controlled for in the matching. Depression affects both the likelihood of receiving treatment and the outcome. Matching on these classes of variables creates statistical twins who differs only in one important aspect, the treatment with SSRI antidepressants.

5 Descriptive statistics

In this section I present general descriptive statistics. Due to the many variables in the data most tables are presented in the appendix.

Table 1 show the share of individuals who received a depression or anxiety diagnosis, and whether they were treated with SSRI antidepressants within six months of

[9]Very few individuals receive antidepressants within the first month of the MI, although the literature suggest that depression is common among MI patients. 2,672 individuals die within six months of the MI, compared with 4,769 individuals within two years, about 56 percent of the deaths.

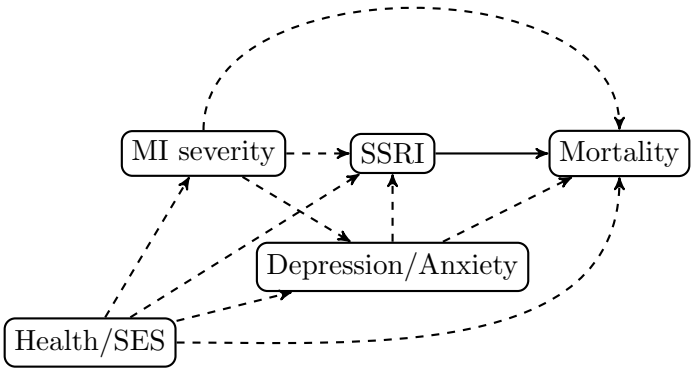

FIGURE 3. Health and MI affects both the treatment and the outcome. The solid line is the causal effect of interest.

the MI. The table also presents the two-year mortality in the sample. It stands clear that relatively few individuals received a diagnosis. About 3 percent received SSRI antidepressants, which is three times the share of those who received a diagnosis. These findings stand somewhat in contrast to the claims in the literature that more than 10 percent of the patients with heart failure are depressed (Joynt, Whellan, et al. 2004). Some of those who are prescribed SSRI antidepressants may receive SSRI for non-obvious reasons, or, possibly, are prescribed SSRI due to a mild depression that is not recorded in the registers.[10] As can be seen in the table, 13 percent of the sample died within two years, but of the treated patients, the two-year mortality was about 17 percent.

One of the sources to the random component in antidepressant prescription is differences in prescription cultures between counties. Table 2 presents the percent of SSRI, depression/antiety, mortality, and the mean value of the answer to the anxiety question in the EQ-5D questionnaire (a value between 1 and 3, where 3 is the worst health), divided on county.[11] For example, we can see that Värmland has a low share of depression and anxiety, but a relatively high prescription of SSRI. If we compare Värmland and Dalarna, the difference in SSRI prescriptions and depression/anxiety diagnoses does not seem to be reflected in the EQ-5D questionnaire. Assuming that the patients are more or less the same between the counties, this reflects differences in the prescription culture, which is exploited by the matching method.

[10] Note that the individuals may have received a diagnosis in the primary care which is not included in the data.

[11] About 40 percent of the sample have answered the EQ-5D questionnaire. The questionnaire is answered by patients below age 75 about two months after the MI.

TABLE 1
Diagnosis, antidepressants, and mortality

	All	Treated	Untreated	Diff
Diagnosis:				
Depression/anxiety	0.01	0.18	0.00	0.18***
	(0.10)	(0.38)	(0.07)	(0.01)
Outcome:				
Mortality	0.13	0.17	0.13	0.04***
	(0.34)	(0.38)	(0.34)	(0.01)
Treatment:				
SSRI	0.03			
	(0.17)			
Observations	38,319	1,101	37,218	38,319

Notes: Diagnosis and treatment are measured within six months of the MI. Outcome is measured as two-year mortality from SSRI treatment for the treated group, and from a random point in day for the untreated group.

TABLE 2
SSRI, depression and mortality by county

	SSRI	Depressed/anxiety	Mortality	EQ-5D: Anxiety
Gotland	4.23	0.47	8.92	1.32
Jämtland	4.04	1.10	14.86	1.39
Västmanland	3.41	1.03	11.58	1.21
Södermanland	3.52	1.52	12.02	1.32
Blekinge	3.27	1.57	14.25	1.32
Gävleborg	3.31	0.52	12.03	1.40
Västra Götaland	3.31	1.03	14.09	1.41
Skåne	3.02	1.16	11.65	1.35
Värmland	3.09	0.50	12.46	1.32
Kronoberg	3.00	1.61	15.34	1.33
Östergötland	2.87	1.37	13.04	1.39
Uppsala	2.81	0.70	8.70	1.40
Örebro	2.94	0.52	12.28	1.34
Jönköping	2.58	0.53	12.62	1.35
Stockholm	2.42	1.15	12.41	1.44
Kalmar	2.70	0.82	13.32	1.40
Norrbotten	2.24	0.58	13.34	1.22
Dalarna	2.23	0.86	10.82	1.33
Västerbotten	2.59	0.81	8.33	1.27
Halland	1.94	0.90	13.15	1.25
Västernorrland	1.64	0.52	12.52	1.27

Notes: Percent of individuals who receive SSRI, depression/anxiety diagnosis and dies within two years of MI, by county. Sorted by SSRI prescription.

Table 3
Cause of death

	ICD	Share	Frequency	Description
1	I219	36.43	1,847	Acute myocardial infarction, unspecified
2	I258	6.67	338	Other forms of chronic ischaemic heart disease
3	I259	5.21	264	Chronic ischaemic heart disease, unspecified
4	I251	3.23	164	Atherosclerotic heart disease
5	C349	2.70	137	Malignant neoplasm of bronchus and lung
Other	...	45.76	2,320	522 different codes
Total			5,070	

Notes: ICD-10.

Table 3 presents the five most common causes of death in the sample. The four most common causes are problems with the heart, and not causes directly connected to psychological ill-being.

As a back-on-the-envelope calculation, the average time on SSRI for the treated group is about 50 months for those who experienced an MI in 2008, and about 23 months for those with an MI in 2011.[12] Thus, SSRI treatment is in general a longtime treatment.

6 Results

In this section I present the results from the propensity score matching. I estimate four different specifications. In the first column, I match on year of MI, SES and general health variables. In the second column, I include medical variables from the prescribed drugs registry and in- and outpatient history. The third column instead match on variables related to the MI. The last column include all variables, and is the preferred specification. The variables included in each specification can be seen in Table A1 in the appendix, and the propensity scores are estimated by logistic regression models shown in Table A11. The appendix also include results for ordinary OLS regressions using the same specifications, in section A.2.

Table 4 presents the main results. I estimate the ATT using the four nearest neighbors with a caliper of 0.2 of the normalized SD of the PS.[13] There is a clear pattern in the results, and the estimate shrinks for each specification.

[12] Calculated by simply taking the difference between the first and last occurrence in the data.

[13] I first estimate the PS using logistic regression, then trim the sample according to the preferred caliper, and run nearest-neighbor matching on the estimated PS. The difference in sample size is due to the trimming, i.e., lack of overlap in the PS. The trimming is shown in section A.3. In the appendix I also show the estimates for matching on only one neighbor in Table A7.

TABLE 4
Antidepressants and mortality

	(1)	(2)	(3)	(4)
SSRI	0.024*	0.022	0.020	0.009
	(0.013)	(0.013)	(0.014)	(0.014)
Year/SES/Health	Yes	Yes	Yes	Yes
Medical	No	Yes	No	Yes
MI measures	No	No	Yes	Yes
Observations	38,307	38,291	38,307	38,291
Treated	1,099	1,101	1,099	1,096

Notes: Standard errors in parenthesis. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$. Treatment model: logit. 4 Nearest-neighbor matching on propensity score. Caliper: ± 0.2 normalized sd(PS). Matching with replacement. ATT. Dependent variable: Mortality within two years of treatment start for the treated group, and two year from a random day within six months of MI for the control group. Treatment: SSRI antidepressants within six months of first MI.

In terms of balance, the third specification is much better than the two first specifications (see the diagnostics section in appendix A.4). However, the preferred specification is the fourth, which includes all variables available (which should result in the best prediction on the individuals health status), and have a good balance in the covariates. All point estimates are positive, but only the first specification is statistically significant (at the 10 percent level). The three first specifications all have omitted variables, which is likely to bias the estimates upwards, since individuals who receive SSRI have worse health than individuals who do not. However, it might be the case that the most depressed individuals do not receive SSRI, which would attenuate the bias downwards (see the discussion in section 7).

7 Discussion

The results in Table 4 suggest that there is no increase in the risk of two-year mortality for individuals who has experienced a myocardial infarction and receive SSRI. The preferred specification indicate an increase of 0.9 percentage points, but is far from statistically significant. Since the literature suggest that depression and anxiety is common worldwide among patients with cardiovascular disease, this is a positive finding, as many of those patients receive SSRI antidepressants. This study does, however, not address the question whether antidepressants are effective means against depression, and there is

no indication of a *lower* mortality rate due to the treatment. Whether antidepressants should be prescribed for MI patients must therefore depend on their effectiveness on treating depression and anxiety and potential side effects.

Is the chosen empirical strategy applicable in this case? Could the results depend on the choice of method? As with all matching methods the strategy used in this paper relies on observable characteristics. Economists are often worried that there are important unobservable characteristics, which is why methods such as IV, DiD and RDD exploiting exogenous variation are commonly used. While these methods might be the "gold standard" in economics, the method of choice must be judged on a case-by-case basis. Matching methods can be used if we have good knowledge of the possible confounding factors, and have access to a rich dataset. I argue that it is the case here.

There are some important limitations in this study. Relatively few individuals in the sample actually receive a depression or anxiety diagnosis, and since data from the primary care is lacking it is likely that some individuals have a diagnosis which is not seen in the data. Of 38,319 patients, only 371 individuals receive a diagnosis within six months of the MI. During the same period, 1,101 patients are prescribed SSRI antidepressants. Only 18 percent of the individuals receiving treatment have a diagnosis corresponding to the prescription.[14] The most likely reason is the lack of data from the primary care, but other explanations could be off-label prescription[15], or that the general practitioner does not think that it is necessary to do an ordinary examination before prescribing the drug. Since myocardial infarction is linked to depression, some general practitioners perhaps intervene on early signs of depression. There is evidence that such prescription is becoming more common (Mojtabai and Olfson 2011).

The possibility of omitted variables creates problems for the matching. Ideally, all patients should be identical except for the treatment status. The propensity score matching reduces the many-dimensional problem to a one-dimensional problem, but it cannot solve the problem with unobservable characteristics. In this specific case we can be worried that patients receiving SSRI:s without a diagnosis have worse general health than patients without SSRI:s and no diagnosis, a problem the matching cannot solve. This would create an upward bias, and result in significant positive effects on mortality of SSRI:s. A second problem is that not all depressed individuals receive SSRI:s, as the worst cases are likely to not go to a general practitioner, which could create a bias downwards. Thus, the bias may go in both directions. On the other hand, it is not obvious what this worse health could be; the data is rich on health variables, and since mortality

[14] The share of SSRI among patients with depression/anxiety is about 54 percent.
[15] Prescribing a pharmaceutical drug for an unapproved indication or patient group.

is such a severe outcome it is not unreasonable to assume that the variables used in the matching can take this into account.

8 Conclusions

Using a rich dataset on 38,319 first time myocardial infarction patients in Sweden during 2007-2011, I estimate the causal effect of the use of SSRI antidepressants on mortality using a propensity score matching. I find no evidence that use of SSRI increase the likelihood of mortality within two years.

The individuals are matched on several categories of variables, such as socioeconomic status, earlier health history and the severity of the MI. The most common cause of death is another myocardial infarction or other heart failures.

Matching can only be done on observable characteristics, and there may be unobservable characteristics which could bias the results. Individuals who are depressed or having anxiety are likely to have worse health than individuals who do not. The worst cases, however, may not use SSRI, since it is possible that they do not receive care. The balance tests indicate that the matching is able to create "statistical twins" on the observed characteristics, and it is not obvious in which direction the potential bias of omitted variables may go. While SSRI does not seem to increase the likelihood of mortality, this study cannot answer the question whether SSRI antidepressants are effective means against depression for these patients.

References

American Psychiatric Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5).* American Psychiatric Publishing.

Aso, Shin-ichi, Hiroshi Imamura, Yukio Sekiguchi, Tomomi Iwashita, Ryosuke Hirano, Uichi Ikeda, and Kazufumi Okamoto. 2011. "Incidence and mortality of acute myocardial infarction. A population-based study including patients with out-of-hospital cardiac arrest." *International Heart Journal* 52 (4): 197–202.

Austin, Peter C. 2011. "Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies." *Pharmaceutical Statistics* 10 (2): 150–161.

B, Rubin Donald, and Neal Thomas. 1996. "Matching using estimated propensity scores: Relating theory to practice." *Biometrics* 52 (1): 249–264.

Barth, Jurgen, Martina Schumacher, and Christoph Herrmann-Lingen. 2004. "Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis." *Psychosomatic Medicine* 66 (6): 802–813.

Caliendo, Marco, and Sabine Kopeinig. 2008. "Some practical guidance for the implementation of propensity score matching." *Journal of Economic Surveys* 22 (1): 31–72.

Cipriani, Andrea, Corrado Barbui, and John R Geddes. 2005. "Suicide, depression, and antidepressants." *British Medical Journal* 330 (7488): 373–374.

Cohen, Hillel W, Geoffrey Gibson, and Michael H Alderman. 2000. "Excess risk of myocardial infarction in patients treated with antidepressant medications: Association with use of tricyclic agents." *The American Journal of Medicine* 108 (1): 2–8.

Dahlberg, Matz, and Douglas Lundin. 2005. "Antidepressants and the suicide rate: Is there really a connection?" In *Substance Use: Individual Behaviour, Social Interactions, Markets and Politics,* edited by Björn Lindgren and Michael Grossman, 16:121–141. Emerald Group Publishing Limited.

ENRICHD. 2003. "Effects of treating depression and low perceived social support on clinical events after myocardial infarction: The enhancing recovery in coronary heart disease patients (ENRICHD) randomized trial." *JAMA* 289 (23): 3106–3116.

Frasure-Smith, Nancy, Francois Lesperance, and Mario Talajic. 1995. "The impact of negative emotions on prognosis following myocardial infarction: Is it more than depression?" *Health Psychology* 14 (5): 388–398.

Ghassemi, Marzyeh, John Marshall, Nakul Singh, David J Stone, and Leo Anthony Celi. 2014. "Leveraging a critical care database: Selective serotonin reuptake inhibitor use prior to ICU admission is associated with increased hospital mortality." *Chest* 145 (4): 745–752.

Hamer, Mark, G David Batty, Adrie Seldenrijk, and Mika Kivimaki. 2010. "Antidepressant medication use and future risk of cardiovascular disease: The Scottish health survey." *European Heart Journal* 32.

Hare, David L, Samia R Toukhsati, Peter Johansson, and Tiny Jaarsma. 2013. "Depression and cardiovascular disease: A clinical review." *European Heart Journal* 35:1365–1372.

Hawton, Keith, Carolina Casañas i Comabella, Camilla Haw, and Kate Saunders. 2013. "Risk factors for suicide in individuals with depression: A systematic review." *Journal of Affective Disorders* 147 (1–3): 17–28.

Imbens, Guido W. 2015. "Matching methods in practice: Three examples." *Journal of Human Resources* 50 (2): 373–419.

Joynt, Karen E, and Christopher M O'Connor. 2005. "Lessons from SADHART, ENRICHD, and other trials." *Psychosomatic Medicine* 67 (Suppl 1): S63–S66.

Joynt, Karen E, David J Whellan, and Christopher M O'connor. 2004. "Why is depression bad for the failing heart? A review of the mechanistic relationship between depression and heart failure." *Journal of Cardiac Failure* 10 (3): 258–271.

Lévesque, Linda E, James A Hanley, Abbas Kezouh, and Samy Suissa. 2010. "Problem of immortal time bias in cohort studies: Example using statins for preventing progression of diabetes." *British Medical Journal* 340:b5087.

Ludwig, Jens, Dave E Marcotte, and Karen Norberg. 2009. "Anti-depressants and suicide." *Journal of Health Economics* 28 (3): 659–676.

Melle, Joost P van, Peter De Jonge, Adriaan Honig, Aart H Schene, Astrid M G Kuyper, Harry J G M Crijns, Annique Schins, Dorien Tulner, Maarten P van den Berg, and Johan Ormel. 2007. "Effects of antidepressant treatment following myocardial infarction." *The British Journal of Psychiatry* 190 (6): 460–466.

Mojtabai, Ramin, and Mark Olfson. 2011. "Proportion of antidepressants prescribed without a psychiatric diagnosis is growing." *Health Affairs* 30 (8): 1434–1442.

Narayan, Sanjiv M, and Murray B Stein. 2009. "Do depression or antidepressants increase cardiovascular mortality? The absence of proof might be more important than the proof of absence." *Journal of the American College of Cardiology* 53 (11): 959–961".

National Institutes of Health. 2015. "What is a heart attack?" Accessed September 16, 2016. `http://www.nhlbi.nih.gov/health/health-topics/topics/heartattack` .

Noordam, Raymond, Nikkie Aarts, Maarten J G Leening, Henning Tiemeier, Oscar H Franco, Albert Hofman, Bruno H Stricker, and Loes E Visser. 2016. "Use of antidepressants and the risk of myocardial infarction in middle-aged and older adults: A matched case-control study." *European Journal of Clinical Pharmacology* 72 (2): 211–218.

Olfson, Mark, and Steven C Marcus. 2009. "National patterns in antidepressant medication treatment." *Archives of General Psychiatry* 66 (8): 848–856.

Pizzi, Carmine, Anne Wilhelmina Saskia Rutjes, Grazia Maria Costa, Fiorella Fontana, Andrea Mezzetti, and Lamberto Manzoli. 2011. "Meta-analysis of selective serotonin reuptake inhibitors in patients with depression and coronary heart disease." *The American Journal of Cardiology* 107 (7): 972–979.

Reid, Steven, and Corrado Barbui. 2010. "Long term treatment of depression with selective serotonin reuptake inhibitors and newer antidepressants." *British Medical Journal* 340.

Rosenbaum, Paul R, and Donald B Rubin. 1983. "The central role of the propensity score in observational studies for causal effects." *Biometrika* 70 (1): 41–55.

Suissa, Samy. 2007. "Immortal time bias in observational studies of drug effects." *Pharmacoepidemiology and Drug Safety* 16 (3): 241–249.

Tata, LJ, J West, C Smith, P Farrington, T Card, L Smeeth, and R Hubbard. 2005. "General population based study of the impact of tricyclic and selective serotonin reuptake inhibitor antidepressants on the risk of acute myocardial infarction." *Heart* 91 (4): 465–471.

Taylor, C Barr, Marston E Youngblood, Diane Catellier, Richard C Veith, Robert M Carney, Matthew M Burg, Peter G Kaufmann, John Shuster, Thomas Mellman, James A Blumenthal, et al. 2005. "Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction." *Archives of General Psychiatry* 62 (7): 792–798.

Thomas, P, G Kavan Michael, N Elasser Gary, D Pharm, and J Barone Eugene. 2001. "Assessment and treatment of depression following myocardial infarction." *American Family Physician* 64 (4): 641–648.

Thombs, Brett D, Eric B Bass, Daniel E Ford, Kerry J Stewart, Konstantinos K Tsilidis, Udita Patel, James A Fauerbach, David E Bush, and Roy C Ziegelstein. 2006. "Prevalence of depression in survivors of acute myocardial infarction." *Journal of General Internal Medicine* 21 (1): 30–38.

Williams, Redford B. 2011. "Depression after heart attack." *Circulation* 123 (25): e639–e640.

Zhou, Zheng, Elham Rahme, Michal Abrahamowicz, and Louise Pilote. 2005. "Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: A comparison of methods." *American Journal of Epidemiology* 162 (10): 1016–1023.

Ziegelstein, Roy C. 2001. "Depression in patients recovering from a myocardial infarction." *JAMA* 286 (13): 1621–1627.

A Appendix

The appendix includes a more detailed description of the variables included the specifications, the propensity score estimations, additional results, and several descriptive tables showing the balance before and after trimming and matching of the sample. I also present figures showing the common support, and love plots showing the balance before and after matching.

A.1 Variable selection

There are different traditions regarding how to select variables to include in matching models. In general, there are two different strains: One focus on selection based on theoretical arguments, the other is more data-driven. Since the goal of the propensity score is to find good balance between the treated and untreated groups, it is not obvious that one is better than another. In fact, as long as the researcher does not see how the variables included affect the outcome, there is no (or very little) danger that he or she selects variables that give the "preferred" outcome.

Another result in the literature is that the bias of including "too many" variables or variables that are unrelated to the treatment and outcome is less than the bias of omitting variables that are important. Thus, in matching it is quite common to include many variables. Only variables measured after treatment or that we know are only related to the treatment and not the outcome should unambiguously be avoided. More variables can, however, make the estimations less precise (B and Thomas 1996; Caliendo and Kopeinig 2008).

My approach has been mostly theoretically driven, and the variables are selected after discussions with medical and statistical expertise. I run four separate specifications. Each specification include and/or remove a class of variables, as shown in Table A1. The first specification includes the year of MI, SES and general health variables. The second specification include earlier health history in the form of prescribed drugs and in- and outpatient data the year before the MI. The third specification removes the

health history variables, but instead include variables related to the MI. The fourth, and preferred, specification includes all variables.

Most variables are dummy variables. Age, heart rate and systolic blood pressure at admission are discrete. The ATC and ICD variables take the value 1 if the individual received a diagnosis (ICD) or pharmaceutical drug (ATC) at least once during the year before the MI. See Table A5 for the specific ATC and ICD codes included.

I also present four tables (Table A2-A5) with descriptives of all variables included in the specifications, before trimming and matching.

A.2 Additional results

This subsection contains a discussion on additional results, such as OLS regressions and matching results using only one nearest-neighbor. I use the same specifications as in the main results.

The point estimates for the OLS regressions in Table A6 are in statistical terms not different from the estimates in the main results. In fact, the standard errors are smaller, and, except for the last specification, the estimates smaller. The OLS is able to use the full sample, compared with the matching that only use the number of treated individuals plus one or four controls. OLS, however, does not ensure that the treated and untreated individuals are comparable (i.e., common support) and may overweight observations with no overlap in the data. In addition, OLS requires a functional form to be specified, which matching does not. However, these potential sources of bias does not seem to matter much for the conclusions in this case.

Table A7 show the results using only one nearest-neighbor. In comparison to the main results, the standard errors are somewhat larger, and both the first and third specification have statistically significant results. However, even though the estimates are some what larger, the conclusion is not different for the preferred fourth specification.

In the main specifications individuals who receive antidepressants (not only SSRI) after the treatment window of six months, but within the two year follow-up, are kept (in total 2,036 observations) and remains in the control group. One could be worried that keeping these individuals in the sample would attenuate the estimates. In Table A8 the observations are dropped, and all specifications are run again. As can be seen in the table the estimates are actually smaller compared with the main specifications, with no statistically significant result.

Table A9 show specifications with two other outcomes. The first row simply use the two year follow-up time from the day of the MI for both the treated and the untreated

TABLE A1
Variables in specifications

	(1)	(2)	(3)	(4)
Sex	x	x	x	x
Age	x	x	x	x
Employment status	x	x	x	x
Year	x	x	x	x
Smoking status	x	x	x	x
Diabetes	x	x	x	x
Hypertension	x	x	x	x
History of stroke	x	x	x	x
Previous PCI	x	x	x	x
Depression/anxiety	x	x	x	x
ATC		x		x
ICD		x		x
ECG rhythm			x	x
Systolic blood pressure at admission			x	x
Heart rate at admission			x	x
History of CHF			x	x
ECG QRS			x	x
Killip class			x	x
Reperfusion treatment			x	x
Bleeding under care			x	x
CPR or defib			x	x
Mechanical complication			x	x
New atrial fibriliation			x	x
Reinfarct during care			x	x
Left Ventricular Ejection Fraction			x	x
AV block			x	x
Beta blockers at discharge			x	x
Statins at discharge			x	x
Nitrates at discharge			x	x
ACE inhibitors or Angiotensin II at discharge			x	x
Other lipid lowering agents at discharge			x	x
Other antiplatelet at discharge			x	x

Notes: Included ATC codes: B01, C01, C02, C05, C07, C09, C10, N05, N06, N07. Included ICD codes: F, I, J, N. Killip class is constructed using pulmonary rales status and cardiogenic shock.

TABLE A2
Descriptives: SES and year covariates

General covariates	All	Treated	Untreated	Diff
Female	0.32	0.44	0.32	0.12***
	(0.47)	(0.50)	(0.47)	(0.02)
Age				
<50 years	0.06	0.07	0.06	0.01
	(0.24)	(0.26)	(0.24)	(0.01)
50-75 years	0.60	0.54	0.60	-0.06***
	(0.49)	(0.50)	(0.49)	(0.02)
>75 years	0.34	0.39	0.34	0.05***
	(0.47)	(0.49)	(0.47)	(0.01)
Employment status				
Other	0.02	0.02	0.02	0.00
	(0.14)	(0.15)	(0.14)	(0.00)
Employed	0.30	0.28	0.30	-0.02
	(0.46)	(0.45)	(0.46)	(0.01)
Retired	0.68	0.69	0.68	0.02
	(0.47)	(0.46)	(0.47)	(0.01)
Year				
2007	0.20	0.23	0.20	0.02*
	(0.40)	(0.42)	(0.40)	(0.01)
2008	0.19	0.21	0.19	0.02
	(0.40)	(0.41)	(0.39)	(0.01)
2009	0.19	0.19	0.19	-0.00
	(0.39)	(0.39)	(0.39)	(0.01)
2010	0.20	0.18	0.20	-0.02*
	(0.40)	(0.39)	(0.40)	(0.01)
2011	0.21	0.19	0.21	-0.02
	(0.41)	(0.40)	(0.41)	(0.01)
Observations	38,319	1,101	37,218	38,319

Notes: Age is included as a discrete variable when estimating the propensity score.

TABLE A3
Descriptives: Health variables measured at MI

General health	All	Treated	Untreated	Diff
Smoking status				
Never smoker	0.44	0.42	0.44	-0.02
	(0.50)	(0.49)	(0.50)	(0.02)
Former smoker	0.33	0.26	0.33	-0.07***
	(0.47)	(0.44)	(0.47)	(0.01)
Current smoker	0.23	0.32	0.23	0.09***
	(0.42)	(0.47)	(0.42)	(0.01)
Diabetes	0.15	0.17	0.15	0.02*
	(0.36)	(0.38)	(0.36)	(0.01)
Hypertension	0.44	0.47	0.44	0.03*
	(0.50)	(0.50)	(0.50)	(0.02)
History of stroke	0.94	0.91	0.94	-0.03***
	(0.24)	(0.29)	(0.24)	(0.01)
Previous PCI	0.03	0.02	0.03	-0.00
	(0.16)	(0.15)	(0.16)	(0.00)
Depression				
Within year before	0.00	0.01	0.00	0.01***
	(0.04)	(0.09)	(0.04)	(0.00)
Within six months after	0.01	0.18	0.00	0.18***
	(0.10)	(0.38)	(0.07)	(0.01)
Observations	38,319	1,101	37,218	38,319

Notes: Both "Depression within year before" and "Depression within six months after" [the MI] are included as covariates when estimating the propensity score.

TABLE A4
Descriptives: MI severity measures

MI measures	All	Treated	Untreated	Diff
ECG rhythm				
Other	0.02	0.03	0.02	0.01
	(0.15)	(0.17)	(0.15)	(0.01)
Atrial fibrillation	0.09	0.09	0.09	0.01
	(0.28)	(0.29)	(0.28)	(0.01)
Sinus	0.89	0.88	0.89	-0.02
	(0.31)	(0.33)	(0.31)	(0.01)
Systolic blood pressure at admission	148.60	148.35	148.60	-0.25
	(28.87)	(29.26)	(28.86)	(0.89)
Heart rate at admission	79.78	82.32	79.71	2.61***
	(22.09)	(22.16)	(22.09)	(0.68)
History of CHF	0.04	0.04	0.04	0.01
	(0.19)	(0.21)	(0.19)	(0.01)
ECG QRS	0.31	0.35	0.31	0.04**
	(0.46)	(0.48)	(0.46)	(0.01)
Killip class	0.10	0.11	0.10	0.01
	(0.30)	(0.31)	(0.30)	(0.01)
Reperfusion treatment	0.34	0.33	0.35	-0.01
	(0.48)	(0.47)	(0.48)	(0.01)
Bleeding under care	0.01	0.02	0.01	0.01**
	(0.11)	(0.15)	(0.11)	(0.00)
CPR or defib	0.03	0.02	0.03	-0.01
	(0.16)	(0.14)	(0.16)	(0.00)
Mechanical complication	0.00	0.00	0.00	-0.00
	(0.06)	(0.05)	(0.06)	(0.00)
New atrial fibriliation	0.04	0.04	0.04	-0.00
	(0.20)	(0.20)	(0.20)	(0.01)
Reinfarct during care	0.01	0.01	0.01	0.00
	(0.09)	(0.09)	(0.09)	(0.00)
Left Ventricular Ejection Fraction	0.32	0.34	0.32	0.03*
	(0.46)	(0.47)	(0.46)	(0.01)
(LVEF: Missing)	0.22	0.23	0.22	0.01
	(0.41)	(0.42)	(0.41)	(0.01)
AV block	0.02	0.01	0.02	-0.00
	(0.13)	(0.12)	(0.13)	(0.00)
Beta blockers at discharge	0.89	0.89	0.88	0.01
	(0.32)	(0.31)	(0.32)	(0.01)
Statins at discharge	0.87	0.86	0.87	-0.02
	(0.33)	(0.35)	(0.33)	(0.01)
Nitrates at discharge	0.10	0.12	0.10	0.02**
	(0.30)	(0.32)	(0.30)	(0.01)
ACE inhibitors or Angiotensin II at discharge	0.73	0.73	0.73	-0.00
	(0.44)	(0.44)	(0.44)	(0.01)
Other lipid lowering agents at discharge	0.01	0.01	0.01	-0.00
	(0.10)	(0.09)	(0.10)	(0.00)
Other antiplatelet at discharge	0.81	0.76	0.81	-0.05***
	(0.39)	(0.43)	(0.39)	(0.01)
Observations	38,319	1,101	37,218	38,319

Notes: Systolic blood pressure and heart rate at admission are discrete variables. 22 percent of the sample have missing values for Left Ventricular Ejection Fraction, so a missing value indicator are included when estimating the propensity score.

TABLE A5
Descriptives: Patient history

Medical covariates	All	Treated	Untreated	Diff
ATC				
B01	0.31	0.35	0.30	0.05***
	(0.46)	(0.48)	(0.46)	(0.01)
C01	0.15	0.17	0.15	0.02
	(0.36)	(0.37)	(0.36)	(0.01)
C02	0.01	0.01	0.01	0.00
	(0.10)	(0.11)	(0.10)	(0.00)
C05	0.02	0.02	0.02	0.00
	(0.14)	(0.15)	(0.14)	(0.00)
C07	0.30	0.33	0.30	0.04***
	(0.46)	(0.47)	(0.46)	(0.01)
C09	0.31	0.35	0.31	0.05***
	(0.46)	(0.48)	(0.46)	(0.01)
C10	0.21	0.23	0.21	0.02
	(0.41)	(0.42)	(0.41)	(0.01)
N05	0.17	0.33	0.16	0.16***
	(0.37)	(0.47)	(0.37)	(0.01)
N06	0.00	0.00	0.00	0.00
	(0.02)	(0.03)	(0.02)	(0.00)
N07	0.01	0.02	0.01	0.01**
	(0.10)	(0.13)	(0.10)	(0.00)
ICD				
F	0.01	0.03	0.01	0.02***
	(0.09)	(0.16)	(0.09)	(0.00)
I	0.05	0.06	0.05	0.01
	(0.21)	(0.23)	(0.21)	(0.01)
J	0.00	0.00	0.00	0.00
	(0.06)	(0.06)	(0.06)	(0.00)
N	0.00	0.00	0.00	0.00
	(0.05)	(0.06)	(0.05)	(0.00)
Observations	38,319	1,101	37,218	38,319

Notes: Pharmaceutical drug history and in- and outpatient history (excluding primary care) the year before MI. Dummy variables taking the value 1 if the individual received a drug or diagnosis within the category at least once during this time period.

TABLE A6
OLS: Antidepressants and mortality

	(1)	(2)	(3)	(4)
SSRI	0.020*	0.012	0.015	0.011
	(0.011)	(0.011)	(0.011)	(0.011)
Year/SES/Health	Yes	Yes	Yes	Yes
Medical	No	Yes	No	Yes
MI measures	No	No	Yes	Yes
Observations	38,307	38,291	38,307	38,291

Notes: Robust standard errors in parenthesis. *** p < 0.01, ** p < 0.05, * p < 0.1. OLS. Dependent variable: Mortality within two years of treatment start for the treated group, and two year from a random day within six months of MI for the control group. Treatment: SSRI antidepressants within six months of first MI.

TABLE A7
Antidepressants and mortality (1 NN)

	(1)	(2)	(3)	(4)
SSRI	0.030**	0.027	0.030*	0.012
	(0.014)	(0.016)	(0.016)	(0.017)
Year/SES/Health	Yes	Yes	Yes	Yes
Medical	No	Yes	No	Yes
MI measures	No	No	Yes	Yes
Observations	38,307	38,291	38,307	38,291
Treated	1,099	1,101	1,099	1,096

Notes: Standard errors in parenthesis. *** p < 0.01, ** p < 0.05, * p < 0.1. Treatment model: logit. 1 Nearest-neighbor matching on propensity score. Caliper: ±0.2 sd(PS). Matching with replacement. ATT. Dependent variable: Mortality within two years of treatment start for the treated group, and two year from a random day within six months of MI for the control group. Treatment: SSRI antidepressants within six months of first MI.

TABLE A8
Antidepressants and mortality (subsample)

	(1)	(2)	(3)	(4)
SSRI	0.021	0.010	0.013	0.006
	(0.013)	(0.014)	(0.014)	(0.014)
Year/SES/Health	Yes	Yes	Yes	Yes
Medical	No	Yes	No	Yes
MI measures	No	No	Yes	Yes
Observations	36,272	36,262	36,268	36,259
Treated	1,098	1,101	1,096	1,097

Notes: Standard errors in parenthesis. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$. Treatment model: logit. 4 Nearest-neighbor matching on propensity score. Caliper: ±0.2 sd(PS). Matching with replacement. ATT. Dependent variable: Mortality within two years of treatment start for the treated group, and two year from a random day within six months of MI for the control group. Treatment: SSRI antidepressants within six months of first MI.

group, and the second row use the day of SSRI initiation for the treated group, but the day of the MI for the untreated group. The second row have three statistically significant estimates. However, the fourth specification is not significant.

In addition to these tests, I have run each specification without using a caliper and not trimming the data. The estimates and standard errors are only insignificantly different from the main results. I have also run the specifications without replacement with one nearest neighbor. The estimates are in general somewhat smaller than in the main specifications. These results are available upon request.

Overall, these robustness checks confirm the results in the main section, and we can conclude that there is no evidence of an increased risk of two-year mortality for MI patients receiving SSRI.

A.2.1 Individuals with depression or anxiety

Table A10 presents descriptive statistics of the number of individuals with a depression or anxiety diagnosis in the in- and outpatient care, conditional on whether they receive SSRI within two or six months of the MI.

While a significantly larger share of the patients with a diagnosis received SSRI compared with patients without a diagnosis, in absolute numbers there are more patients who receive SSRI without a diagnosis. This can be explained by at least two things. Only diagnoses from the in- and outpatient registry is included, excluding primary care.

TABLE A9
Antidepressants and mortality (other outcomes)

Outcome: Within two years	(1)	(2)	(3)	(4)
... of MI	0.020	0.017	0.015	0.004
	(0.013)	(0.013)	(0.013)	(0.013)
... of SSRI treatment	0.032**	0.029**	0.027**	0.017
	(0.013)	(0.013)	(0.013)	(0.014)
Year/SES/Health	Yes	Yes	Yes	Yes
Medical	No	Yes	No	Yes
MI measures	No	No	Yes	Yes
Observations	38,307	38,291	38,307	38,291
Treated	1,099	1,101	1,099	1,096

Notes: Standard errors in parenthesis. *** p < 0.01, ** p < 0.05, * p < 0.1. Treatment model: logit. 4 Nearest-neighbor matching on propensity score. Caliper: ±0.2 sd(PS). Matching with replacement. ATT. Dependent variable: The first row use a two year follow-up from MI for both the treatment and control group. The second row use a two year follow-up from treatment start for the treated group, and two year from MI for the control group. Treatment: SSRI antidepressants within six months of first MI.

Thus, it is likely that there are some individuals in the sample with a diagnosis than can be seen here. Second, especially for psychiatric drugs, it is not uncommon that individuals receive medication without a corresponding diagnosis (Mojtabai and Olfson 2011). It should be noted that only about than half of the patients with a (confirmed) diagnosis receive SSRI.

TABLE A10
Receiving SSRI conditional on depression/anxiety diagnosis

Diagnosis within six months	All	Yes	No	Diff
SSRI				
Within two months	0.01	0.24	0.01	0.23***
	(0.10)	(0.43)	(0.09)	(0.02)
Within six months	0.03	0.54	0.02	0.51***
	(0.17)	(0.50)	(0.15)	(0.03)
Observations	38,319	371	37,948	38,319

Notes: Depression or anxiety ICD codes F32, F33, F41. ATC code N06AB.

A.3 Propensity score and trimming

Table A11 show the estimations of the propensity score, using logistic regression with treatment status as outcome. The propensity score is predicted and used as a matching variable using nearest-neighbor matching.

Table A12 show the number of observations which lack overlap, i.e., no neighbor within 0.2 of the normalized SD of the PS, in the data for each respective specification. Observations without overlap is trimmed (dropped in the sample).

A.4 Diagnostics

A.4.1 Covariate balance after matching

Tables A13-A16 presents the covariate balance of the variables after trimming, before and after matching. It is ideal that the standard difference of the matched variables is 0, and the matched ratio is 1. The matching is not very successful in the first two specifications. It is, however, much better in the third and fourth specifications. See also the love plots in section A.4.3.

A.4.2 Common support

Figure A1 show the common support before trimming the data. It is clear from the figures that the propensity score, or the likelihood of treatment, is relatively low for both treated and untreated individuals. There are, however, some individuals with quite high propensity scores. The figures show the density of individuals with the corresponding propensity score. Since there are so many more untreated individuals the figures hide the fact that there are almost the same amount of individuals with a propensity score above 0.3 in the both groups (173 individuals in the untreated group, and 199 individuals in the treated group, irrespective of specification).

A.4.3 Love plots

Figure A2-A5 show love plots for the respective specification. The love plots can be compared with the standardized difference in the raw and matched samples in Tables A13-A16. It is clear from these figures that the first two specifications do not succeed to create comparable groups, but the third and fourth specifications are successful.

TABLE A11
Estimating the propensity score: Logistic regression

	(1)	(2)	(3)	(4)
Year				
2008	-0.0758 (0.0983)	-0.0813 (0.0986)	-0.0631 (0.0984)	-0.0696 (0.0987)
2009	-0.0942 (0.100)	-0.0938 (0.101)	-0.0764 (0.101)	-0.0791 (0.101)
2010	-0.207** (0.101)	-0.217** (0.102)	-0.189* (0.102)	-0.204** (0.102)
2011	-0.199** (0.0997)	-0.202** (0.100)	-0.171* (0.101)	-0.178* (0.101)
Female	0.436*** (0.0685)	0.354*** (0.0700)	0.442*** (0.0693)	0.361*** (0.0707)
Age	0.00579 (0.00408)	0.00168 (0.00424)	0.00256 (0.00439)	0.0000441 (0.00447)
Employment status				
Employed	-0.00745 (0.230)	0.0442 (0.231)	0.00895 (0.230)	0.0566 (0.231)
Retired	-0.0360 (0.239)	-0.0386 (0.240)	-0.0195 (0.240)	-0.0302 (0.240)
Smoking status				
Former smoker	-0.0562 (0.0808)	-0.0818 (0.0812)	-0.0563 (0.0811)	-0.0816 (0.0814)
Current smoker	0.412*** (0.0833)	0.377*** (0.0844)	0.416*** (0.0839)	0.375*** (0.0850)
Diabetes	0.136 (0.0879)	0.0569 (0.0920)	0.0903 (0.0892)	0.0366 (0.0928)
Hypertension	0.0711 (0.0679)	-0.0647 (0.0806)	0.0525 (0.0695)	-0.0630 (0.0813)
History of stroke	-0.422*** (0.116)	-0.321*** (0.122)	-0.409*** (0.116)	-0.328*** (0.123)
Previous PCI	0.0280 (0.207)	-0.0908 (0.219)	0.00277 (0.210)	-0.0632 (0.220)
Depression				
Within year before	1.972*** (0.349)	1.412*** (0.417)	1.988*** (0.350)	1.449*** (0.417)
Within six months after	3.837*** (0.112)	3.748*** (0.113)	3.832*** (0.112)	3.746*** (0.114)
ATC				
B01		0.146 (0.0898)		0.136 (0.0908)
C01		-0.0791 (0.102)		-0.121 (0.107)
C02		0.130 (0.290)		0.114 (0.291)
C05		-0.183 (0.225)		-0.181 (0.226)
C07		-0.00147 (0.0816)		-0.00283 (0.0834)
C09		0.193** (0.0840)		0.170* (0.0872)
C10		0.0330 (0.0886)		0.0233 (0.0908)
N05		0.657*** (0.0759)		0.653*** (0.0762)
N06		-0.126 (1.183)		-0.0954 (1.177)
N07		0.324 (0.259)		0.319 (0.258)
ICD				
F		0.366 (0.269)		0.352 (0.266)
I		-0.0555 (0.154)		-0.0709 (0.155)
J		-0.0579 (0.514)		-0.0935 (0.516)
N		0.00112 (0.552)		-0.0713 (0.562)
ECG rhythm				
Atrial fibrillation			-0.311 (0.219)	-0.310 (0.220)
Sinus			-0.300 (0.196)	-0.277 (0.196)
Systolic blood pressure at admission			0.000335 (0.00115)	0.000643 (0.00116)
Heart rate at admission			0.00254 (0.00155)	0.00228 (0.00157)
History of CHF			0.0108 (0.164)	-0.0772 (0.167)
ECG QRS			0.140** (0.0709)	0.132* (0.0711)
Killip class			-0.118 (0.110)	-0.114 (0.110)
Reperfusion treatment			0.0268 (0.0761)	0.0528 (0.0767)
Bleeding under care			0.310 (0.228)	0.297 (0.227)
CPR or defib			-0.323 (0.231)	-0.310 (0.230)
Mechanical complication			-0.116 (0.603)	-0.0462 (0.602)
New atrial fibriliation			-0.158 (0.166)	-0.141 (0.166)
Reinfarct during care			0.172 (0.329)	0.185 (0.329)
Left Ventricular Ejection Fraction			0.0650 (0.0794)	0.0774 (0.0796)
(LVEF: Missing)			0.0808 (0.0872)	0.0747 (0.0876)
AV block			-0.302 (0.290)	-0.295 (0.290)
Beta blockers at discharge			0.0864 (0.109)	0.0839 (0.110)
Statins at discharge			0.0944 (0.108)	0.137 (0.110)
Nitrates at discharge			0.193* (0.104)	0.173 (0.109)
ACE inhibitors or Angiotensin II at discharge			0.0685 (0.0791)	0.0401 (0.0817)
Other lipid lowering agents at discharge			-0.154 (0.340)	-0.158 (0.339)
Other antiplatelet at discharge			-0.285*** (0.0863)	-0.268*** (0.0866)
Observations	38,319	38,319	38,319	38,319
Pseudo R2	.1078406	.1170926	.1115441	.1202518
Log lik.	-4,454.8	-4,408.6	-4,436.31	-4,392.83

Notes: Standard errors in parenthesis. *** p < 0.01, ** p < 0.05, * p < 0.1. Dependent variable: SSRI antidepressants within six months of the first MI.

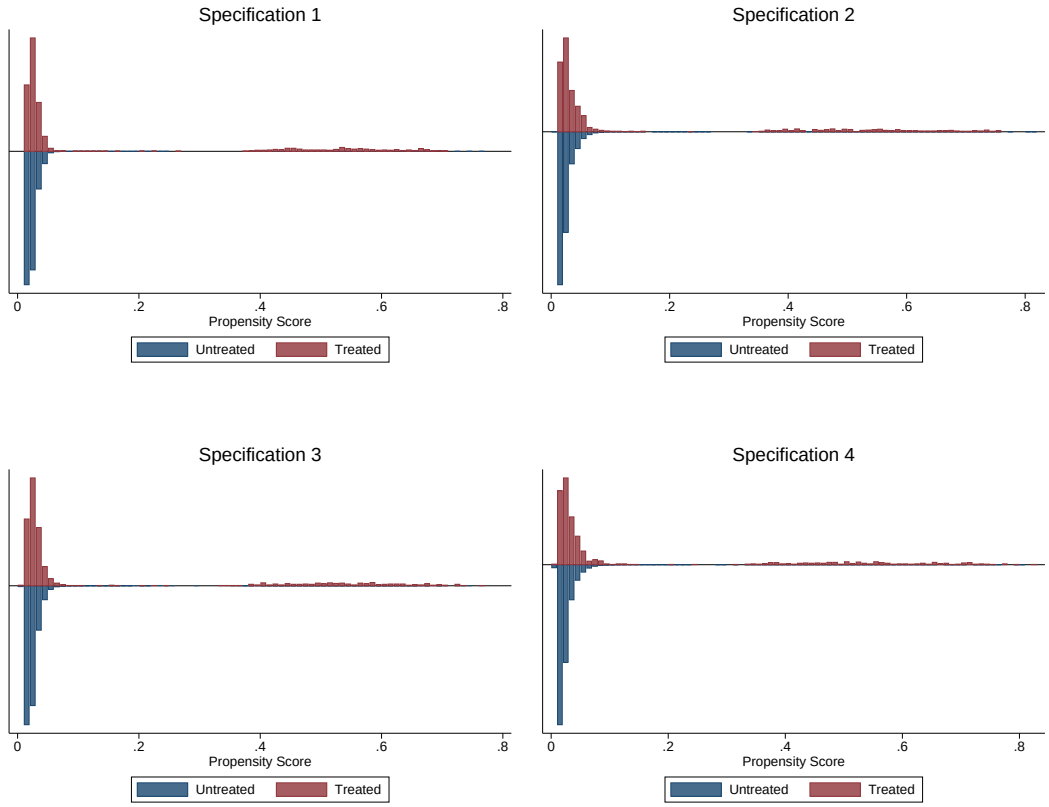

FIGURE A1. Common support.

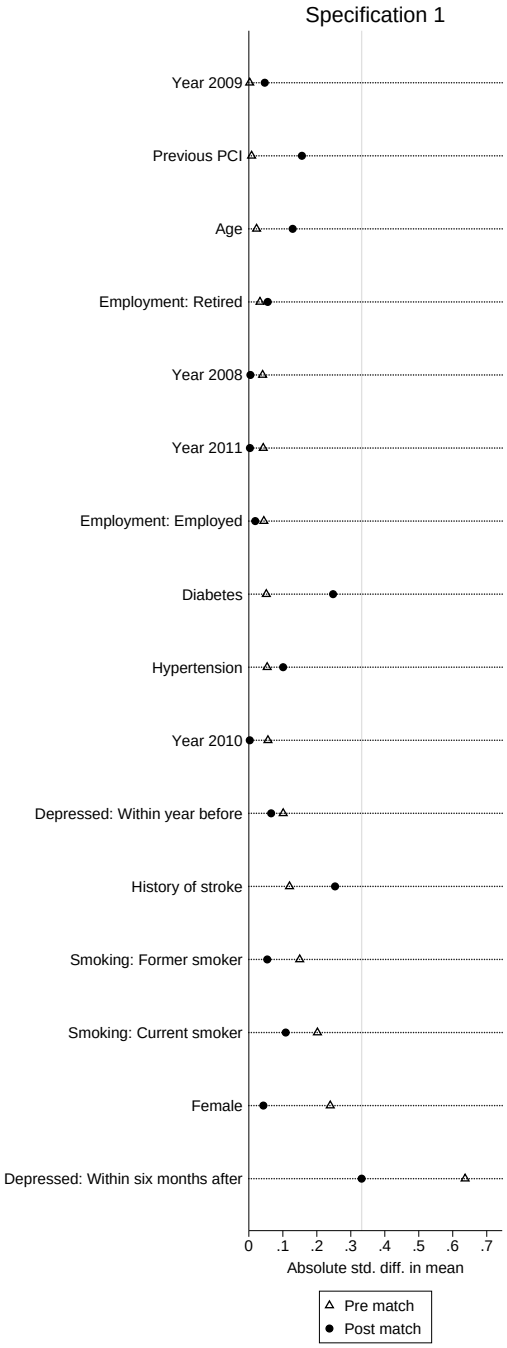

FIGURE A2. Specification 1. ATT, 4 NN.

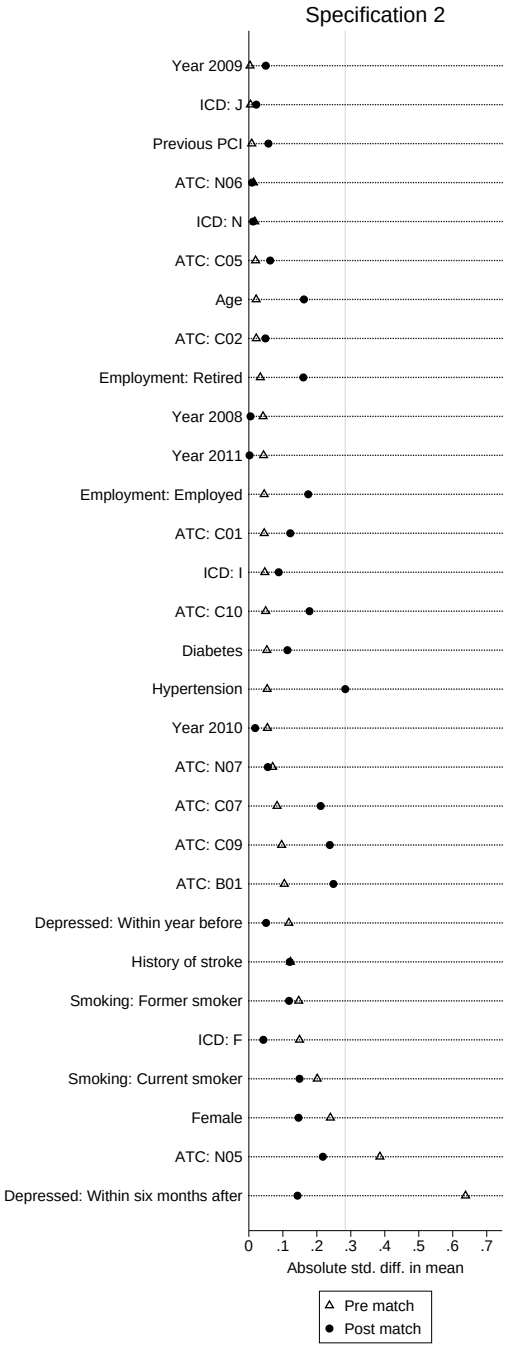

FIGURE A3. Specification 2. ATT, 4 NN.

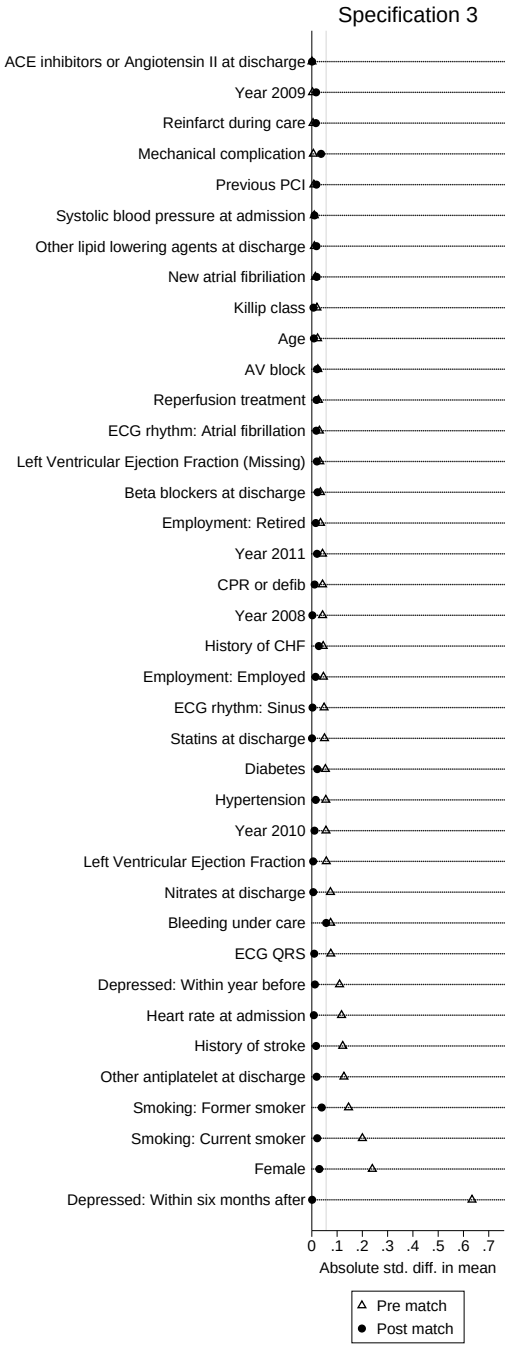

FIGURE A4. Specification 3. ATT, 4 NN.

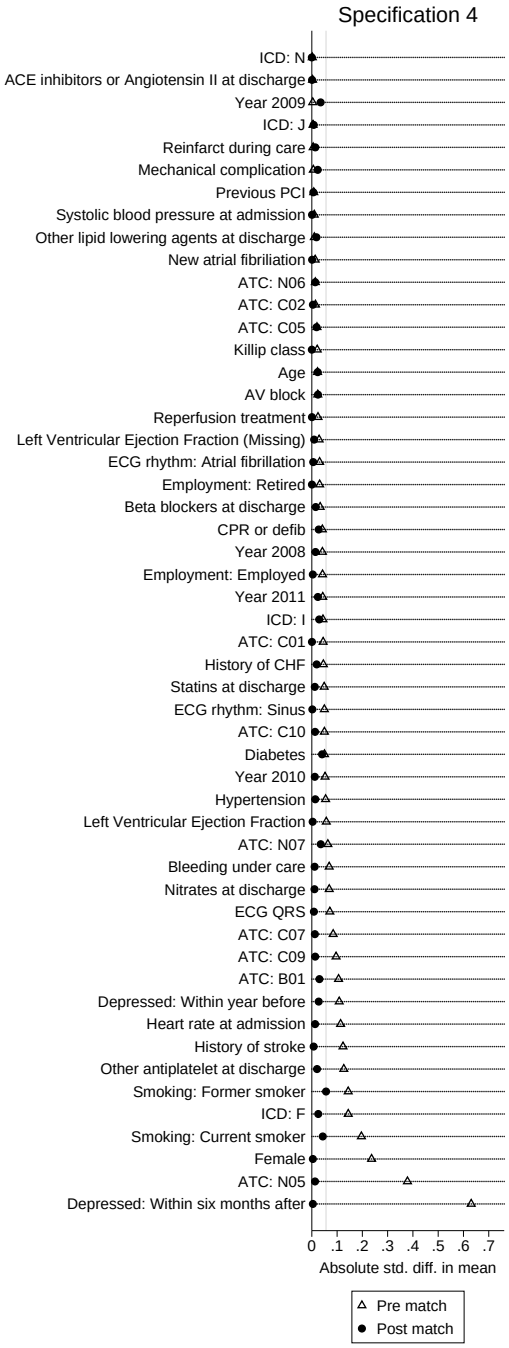

FIGURE A5. Specification 4. ATT, 4 NN.

TABLE A12
Trimming of the data

Overlap ±.01036	Treatment 0	1	Total
0	10	2	12
1	37208	1099	38307
Total	37218	1101	38319

Notes: Specification 1.

Overlap ±.0106	Treatment 0	1	Total
0	28	0	28
1	37190	1101	38291
Total	37218	1101	38319

Notes: Specification 2.

Overlap ±.01044	Treatment 0	1	Total
0	10	2	12
1	37208	1099	38307
Total	37218	1101	38319

Notes: Specification 3.

Overlap ±.01066	Treatment 0	1	Total
0	23	5	28
1	37195	1096	38291
Total	37218	1101	38319

Notes: Specification 4.

TABLE A13
Covariate balance: Specification 1

	Std. diff.		Ratio	
	Raw	Matched	Raw	Matched
Year				
2008	0.040	0.017	1.063	1.025
2009	-0.003	0.035	0.997	1.060
2010	-0.056	0.012	0.917	1.021
2011	-0.042	-0.023	0.940	0.966
Female	0.240	-0.035	1.130	0.992
Age	0.023	-0.034	1.103	1.046
Employment status				
Employed	-0.044	0.017	0.962	1.017
Retired	0.033	-0.034	0.975	1.030
Smoking status				
Former smoker	-0.150	0.017	0.875	1.019
Current smoker	0.202	-0.002	1.231	0.999
Diabetes	0.051	0.015	1.101	1.026
Hypertension	0.054	0.011	1.010	1.001
History of stroke	-0.120	-0.085	1.484	1.308
Previous PCI	-0.008	0.100	0.953	2.138
Depression				
Within year before	0.101	0.000	6.444	1.000
Within six months after	0.636	0.000	32.697	1.000

Notes: ATT, 4 NN.

TABLE A14
Covariate balance: Specification 2

	Std. diff.		Ratio	
	Raw	Matched	Raw	Matched
Year				
2008	0.042	-0.015	1.065	0.979
2009	-0.003	0.035	0.995	1.061
2010	-0.055	0.039	0.920	1.070
2011	-0.043	-0.001	0.939	0.998
Female	0.240	-0.032	1.130	0.993
Age	0.021	0.031	1.104	0.991
Employment status				
Employed	-0.045	-0.004	0.961	0.996
Retired	0.034	0.005	0.974	0.996
Smoking status				
Former smoker	-0.147	0.069	0.877	1.084
Current smoker	0.201	-0.058	1.230	0.959
Diabetes	0.053	-0.016	1.104	0.973
Hypertension	0.054	0.058	1.010	1.010
History of stroke	-0.122	-0.033	1.495	1.103
Previous PCI	-0.008	0.022	0.951	1.149
Depression				
Within year before	0.118	0.026	10.816	1.330
Within six months after	0.638	0.001	32.957	1.001
ATC				
B01	0.104	0.062	1.080	1.043
C01	0.045	-0.003	1.090	0.995
C02	0.022	0.018	1.223	1.182
C05	0.020	0.023	1.142	1.162
C07	0.083	0.032	1.069	1.024
C09	0.096	0.053	1.074	1.037
C10	0.049	0.037	1.070	1.051
N05	0.385	0.027	1.606	1.021
N06	0.014	0.000	1.690	1.000
N07	0.070	0.020	1.852	1.163
ICD				
F	0.149	-0.009	3.715	0.950
I	0.047	0.023	1.208	1.093
J	0.005	0.005	1.082	1.081
N	0.017	-0.007	1.365	0.889

Notes: ATT, 4 NN.

TABLE A15
Covariate balance: Specification 3

	Std. diff.		Ratio	
	Raw	Matched	Raw	Matched
Year				
2008	0.043	0.002	1.066	1.003
2009	-0.003	0.017	0.997	1.028
2010	-0.056	0.011	0.917	1.018
2011	-0.042	-0.021	0.940	0.969
Female	0.239	-0.030	1.130	0.993
Age	0.023	0.008	1.105	1.026
Employment status				
Employed	-0.046	0.015	0.960	1.015
Retired	0.034	-0.016	0.974	1.014
Smoking status				
Former smoker	-0.145	0.039	0.878	1.045
Current smoker	0.200	-0.021	1.229	0.984
Diabetes	0.054	-0.022	1.105	0.964
Hypertension	0.055	0.015	1.010	1.002
History of stroke	-0.122	-0.017	1.495	1.050
Previous PCI	-0.008	0.018	0.953	1.122
Depression				
Within year before	0.110	0.012	7.309	1.142
Within six months after	0.634	0.001	32.189	1.002
ECG rhythm				
Atrial fibrillation	0.030	-0.018	1.090	0.953
Sinus	-0.049	0.003	1.124	0.994
Systolic blood pressure at admission	-0.010	0.011	1.027	0.960
Heart rate at admission	0.118	-0.008	1.000	0.909
History of CHF	0.045	-0.028	1.237	0.888
ECG QRS	0.075	0.010	1.057	1.006
Killip class	0.020	-0.007	1.054	0.984
Reperfusion treatment	-0.026	0.019	0.983	1.014
Bleeding under care	0.074	0.057	1.747	1.503
CPR or defib	-0.043	-0.011	0.763	0.928
Mechanical complication	-0.006	-0.037	0.892	0.547
New atrial fibriliation	-0.014	-0.019	0.939	0.917
Reinfarct during care	0.005	-0.016	1.052	0.852
Left Ventricular Ejection Fraction	0.057	-0.005	1.044	0.997
(LVEF: Missing)	0.032	0.020	1.043	1.026
AV block	-0.024	-0.021	0.828	0.847
Beta blockers at discharge	0.034	0.023	0.919	0.944
Statins at discharge	-0.050	-0.001	1.114	1.001
Nitrates at discharge	0.074	0.006	1.207	1.013
ACE inhibitors or Angiotensin II at discharge	0.001	-0.001	1.000	1.001
Other lipid lowering agents at discharge	-0.010	-0.018	0.902	0.835
Other antiplatelet at discharge	-0.127	0.019	1.195	0.978

Notes: ATT, 4 NN.

TABLE A16
Covariate balance: Specification 4

	Std. diff.		Ratio	
	Raw	Matched	Raw	Matched
Year				
2008	0.042	-0.014	1.066	0.980
2009	-0.004	0.035	0.995	1.060
2010	-0.052	0.012	0.923	1.020
2011	-0.043	-0.024	0.939	0.964
Female	0.236	-0.004	1.129	0.999
Age	0.023	0.023	1.108	1.008
Employment status				
Employed	-0.042	0.004	0.963	1.004
Retired	0.031	-0.000	0.976	1.000
Smoking status				
Former smoker	-0.144	0.056	0.880	1.067
Current smoker	0.196	-0.043	1.226	0.968
Diabetes	0.050	-0.041	1.098	0.934
Hypertension	0.055	0.014	1.010	1.002
History of stroke	-0.123	-0.007	1.500	1.021
Previous PCI	-0.008	0.006	0.956	1.037
Depression				
Within year before	0.108	0.027	8.926	1.381
Within six months after	0.631	0.004	31.805	1.007
ATC				
B01	0.106	0.030	1.081	1.020
C01	0.045	-0.001	1.089	0.999
C02	0.014	0.004	1.145	1.040
C05	0.020	0.019	1.146	1.133
C07	0.084	0.012	1.071	1.009
C09	0.096	0.013	1.074	1.009
C10	0.050	-0.013	1.071	0.984
N05	0.378	0.013	1.598	1.010
N06	0.014	-0.014	1.698	0.667
N07	0.063	-0.035	1.759	0.778
ICD				
F	0.144	-0.025	3.588	0.861
I	0.044	0.029	1.196	1.122
J	0.005	-0.007	1.087	0.889
N	0.002	0.000	1.040	1.000
ECG rhythm				
Atrial fibrillation	0.031	0.005	1.093	1.015
Sinus	-0.050	-0.002	1.127	1.005
Systolic blood pressure at admission	-0.010	0.001	1.026	0.935
Heart rate at admission	0.114	-0.013	1.000	0.918
History of CHF	0.046	0.019	1.241	1.091
ECG QRS	0.071	0.008	1.055	1.005
Killip class	0.021	0.000	1.057	1.000
Reperfusion treatment	-0.024	0.000	0.984	1.000
Bleeding under care	0.069	0.011	1.683	1.077
CPR or defib	-0.042	0.027	0.767	1.218
Mechanical complication	-0.006	-0.023	0.894	0.668
New atrial fibriliation	-0.013	0.001	0.942	1.005
Reinfarct during care	0.006	-0.014	1.061	0.871
Left Ventricular Ejection Fraction	0.057	0.003	1.044	1.002
(LVEF: Missing)	0.029	0.009	1.040	1.012
AV block	-0.024	-0.024	0.830	0.824
Beta blockers at discharge	0.033	0.015	0.922	0.961
Statins at discharge	-0.049	-0.012	1.111	1.025
Nitrates at discharge	0.069	0.011	1.193	1.026
ACE inhibitors or Angiotensin II at discharge	0.003	-0.001	0.998	1.001
Other lipid lowering agents at discharge	-0.010	-0.018	0.904	0.835
Other antiplatelet at discharge	-0.126	0.021	1.194	0.976

Notes: ATT, 4 NN.