



Antidepressant use and risk of cardiovascular outcomes in people aged 20 to 64: cohort study using a primary care database

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8 **REVISED PAPER FOR RESUBMISSION TO BMJ**
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Abstract**Objective**

To assess associations between different antidepressant treatments and the rates of three cardiovascular outcomes (myocardial infarction, stroke or transient ischaemic attack, arrhythmia) in people with depression.

Design

Cohort study.

Setting

Practices across the UK contributing to the QResearch® primary care database.

Participants

238 963 patients aged 20 to 64 years with a first diagnosis of depression between 1 January 2000 and 31 July 2011, followed up until 1 August 2012.

Exposures

Antidepressant class (tricyclic and related antidepressants, selective serotonin reuptake inhibitors, other antidepressants), dose, and duration of use, and commonly prescribed individual antidepressant drugs.

Main outcomes

Outcomes were first diagnoses of myocardial infarction, stroke or transient ischaemic attack and arrhythmia during five years follow-up. Cox proportional hazards models were used to estimate hazard ratios adjusting for potential confounding variables.

Results

During five years of follow-up 772 patients had a myocardial infarction, 1106 had a stroke or transient ischaemic attack and 1452 were diagnosed with arrhythmias.

There were no significant associations between antidepressant class and myocardial infarction over five years follow-up. In the first year of follow-up patients prescribed selective serotonin reuptake inhibitors had a significantly reduced risk (adjusted hazard ratio 0.58, 95% CI 0.42 to 0.79) and among individual drugs fluoxetine was associated with a significantly reduced risk (0.44, 95% CI 0.59 to 0.92) and lofepramine was associated with a significantly increased risk (3.07, 95% CI 1.50 to 6.26).

There were no significant associations between antidepressant class or individual drugs and risk of stroke or transient ischaemic attack.

Antidepressant class was not significantly associated with arrhythmia risk over five years follow-up although the risk was significantly increased during the first 28 days of treatment with tricyclic and related antidepressants (adjusted hazard ratio 1.99, 95% CI 1.27 to 3.13). Fluoxetine was associated with a significantly reduced risk of arrhythmia (0.74, 95% CI 0.59 to 0.92) over five years but citalopram was not significantly associated with arrhythmia risk even at high doses (1.11, 95%CI 0.72 to 1.71 for doses \geq 40 mg/day).

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Conclusions

This study has found no evidence that selective serotonin reuptake inhibitors as a class are associated with an increased risk of arrhythmia or stroke or transient ischaemic attack in people diagnosed with depression between the ages of 20 to 64. There was no evidence that citalopram is associated with a significantly increased risk of arrhythmia. There was some indication of a reduced risk of myocardial infarction for selective serotonin reuptake inhibitors, particularly fluoxetine and of an increased risk for lofepramine.

Confidential: For Review Only

What is already known on this topic

Depression is a common condition, and antidepressants particularly selective serotonin reuptake inhibitors are increasingly used in its treatment

Rates of cardiovascular disease are higher in people with depression but it is unclear whether different antidepressant treatments increase or reduce these rates.

High doses of certain antidepressants including citalopram can cause QT prolongation which may increase the risk of arrhythmia but this is not established.

What this study adds

This study found no evidence that selective serotonin reuptake inhibitors as a class are associated with an increased risk of arrhythmia and stroke or transient ischaemic attack in people with depression aged 20 to 64.

There was no evidence that citalopram is associated with a significantly increased risk of arrhythmia even at high doses.

There was some indication of a reduced risk of myocardial infarction for selective serotonin reuptake inhibitors, particularly fluoxetine and of an increased risk for lofepramine.

Introduction

Depression is a common and debilitating condition, which is frequently treated with antidepressants. It is established that depression increases the risk of cardiovascular outcomes but there is controversy as to whether use of antidepressants, particularly selective serotonin reuptake inhibitors, increases or reduces the risk of cardiovascular outcomes.^{1,2} This is important since antidepressants are one of the most commonly prescribed medications worldwide, and their use is increasing.³⁻⁵ In the United States antidepressants were the third most commonly used prescription drug in 2005 to 2008, and their use had increased by nearly 400% compared with 1988 to 1994,⁶ and in England more than 53 million antidepressant prescriptions were issued in 2013,⁷ nearly a twofold increase compared with a decade earlier.⁸ The majority (54%) of the prescriptions in England in 2013 were for selective serotonin reuptake inhibitors, including nearly 14 million prescriptions for the most commonly prescribed antidepressant citalopram.

Theoretically antidepressants such as selective serotonin reuptake inhibitors may have effects on coagulation and there are some studies exploring their cardioprotective effect. These studies have tended to be underpowered and explored outcomes in secondary care or other selected populations. Randomised controlled trials of antidepressants tend to be short term and underpowered to detect effects on cardiovascular outcomes whilst observational studies of cardiovascular outcomes show conflicting results and many have not accounted for depression and so are susceptible to indication biases. The observational studies have either been restricted to or predominantly included older people, so there is uncertainty about associations in a younger age group, although antidepressants are frequently prescribed for depression in adults of working age. There may be differential effects of antidepressants on cardiovascular outcomes according to age, since a meta-analysis of 13 observational studies found that selective serotonin reuptake inhibitor use was associated with a 40% increased risk of stroke, but this was only significant in studies restricted to older age groups and there was no significantly increased risk in studies with no age restriction although none of the studies specifically focussed on a younger age group.⁹ For myocardial infarction similarly there is uncertainty about an association with selective serotonin reuptake inhibitors. A large observational study in people aged 65 and over with depression found an increased risk of myocardial infarction for selective serotonin reuptake inhibitors¹⁰ whilst others in broader age groups have found no association^{11,12} or reduced risks¹³ which could be due to differing age ranges or indication biases.

The US Food and Drug Administration (FDA) issued a drug safety communication in 2011, stating that citalopram should not be prescribed at doses greater than 40 mg per day, based on findings of QT interval prolongation in a study of 119 subjects who received different doses of citalopram.¹⁴ A similar safety warning was issued by the European Medicines Agency in 2011. Further studies have reported QT interval prolongation with citalopram, and also with some other antidepressants such as escitalopram and

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amitriptyline.^{15 16} QT interval prolongation can lead to arrhythmias including potentially fatal torsades de pointes,¹⁷ but few studies have specifically assessed arrhythmia risk for different antidepressant drugs. A cohort study in predominantly older men of two different selective serotonin reuptake inhibitor antidepressants found significantly lower risks of arrhythmia for doses of citalopram over 40 mg/day compared with doses of 1–20 mg/day, with similar findings for sertraline.¹⁸ A cohort study in the US based on claims data found no significant differences in risk of ventricular arrhythmia/sudden death for 20 types of antidepressant drug compared with paroxetine except for a higher risk in mirtazapine users.¹⁹

Few observational studies of cardiovascular effects have examined associations with individual drugs, so there is a lack of evidence for specific commonly prescribed antidepressants and also in relation to duration and dose and especially there is a lack of evidence about the cardiovascular risks in younger people. We therefore carried out a cohort study in people aged 20 to 64 in order to investigate the associations between different individual antidepressant drugs and the risk of myocardial infarction, arrhythmia, and stroke/transient ischaemic attack and also examined both dose and duration of use.

Methods

The cohort study was designed to estimate associations between antidepressant treatment and a number of different adverse outcomes including arrhythmia, myocardial infarction, and stroke or transient ischaemic attack. Full details of the study design, the study outcomes and methods can be found in the study protocol.²⁰ Results relating to the epilepsy, suicide and self-harm outcomes have been published previously.^{21 22}

Study cohort

The study cohort was selected from a large primary care database (QResearch®, version 34). At the time of the study, the QResearch® database contained the anonymised longitudinal health records of over 12 million patients from more than 600 general practices across the United Kingdom which record data using the Egton Medical Information Systems (EMIS) medical records computer system. Recorded information includes patient characteristics, clinical diagnoses, symptoms and prescribed medications.

The cohort included patients with a first computer recorded diagnosis of depression between the ages of 20 to 64 at the time of diagnosis and diagnosed between 1st January 2000 to 31st July 2011. Patients with a diagnosis of depression were identified using diagnostic Read codes used in previous studies.^{10 23 24} Read codes are the clinical codes used in general practice in the United Kingdom. Patients were eligible for inclusion if their diagnosis of depression occurred at least 12 months after their registration with a study practice and the installation date of their practice's EMIS computer system.

Patients with a previous recorded diagnosis of depression, a diagnosis of schizophrenia, bipolar disorder or another type of psychosis or who had been prescribed lithium or antimanic drugs were excluded from the

1 cohort. Patients were also excluded if they had received prescriptions for an antidepressant either before
2 the study start date (1st January 2000), before their registration date, before they were aged 20, or more
3 than 36 months before their first recorded diagnosis of depression. Temporary residents were also
4 excluded.
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9 The earliest of the date of the first recorded diagnosis of depression, or the date of the first prescription for
10 an antidepressant was used as the patient's study entry date. Participants in the cohort were followed up
11 until the earliest of: date of death, date of leaving the practice, or the end of the follow-up period (1st
12 August 2012).
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15 16 **Outcomes**

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18 The three outcomes for these analyses were arrhythmia, myocardial infarction and stroke or transient
19 ischaemic attack. Patients with these outcomes were identified if they were recorded either on the
20 patients' general practice record using the relevant Read codes or on their linked Office of National
21 Statistics cause of death record using International Classification of Diseases (ICD) diagnostic codes, based
22 on codes used in previous studies²⁵⁻²⁷ as listed in appendix 1. For the analysis of each separate outcome we
23 only considered the first event, and excluded patients with a previous diagnosis of the outcome recorded at
24 baseline.
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30 31 **Exposures**

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33 Information was extracted on all antidepressant prescriptions during follow-up. The duration of each
34 prescription was calculated by dividing the number of tablets prescribed by number to be taken each day.
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37 For the main analyses antidepressant drugs were grouped according to the four main classes in the British
38 National Formulary (BNF): tricyclic and related antidepressants, selective serotonin reuptake inhibitors,
39 monoamine oxidase inhibitors and other antidepressants. Prescriptions for different antidepressant drugs
40 on the same date were classified as combined prescriptions.
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44 We calculated the daily dose of each prescription by multiplying the number of tablets to be taken each day
45 by the dose of each tablet, and converted this to a defined daily dose to enable comparison of doses
46 between antidepressant classes, using values assigned by the World Health Organisation's Collaborating
47 Centre for Drug Statistics Methodology (www.whocc.no/atc_ddd_index). For some prescriptions the dosing
48 instructions were missing or not sufficiently detailed to allow calculation of a daily dose (<5% of total
49 prescriptions).
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55 The eleven most frequently prescribed individual antidepressant drugs were also assessed.^{10,19}
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Confounding variables

Data were extracted on variables considered to be potential risk factors for the cardiovascular outcomes, or associated with the likelihood of receiving a particular antidepressant treatment, based on our previous study of antidepressants in people aged 65 or more.¹⁰ These were: age at study entry (continuous); sex; year of diagnosis of depression (continuous); severity of index diagnosis of depression (categorised as mild, moderate or severe, using the classification of Read codes for depression published by Martinez and colleagues²³ and additional classification by a member of the study team (RM) of some Read codes for depression used in our study²¹ but not included in the study by Martinez); deprivation (Townsend deprivation score corresponding to the patients postcode, in fifths); smoking status (non-smoker, ex-smoker, light smoker: 1–9 cigarettes/day, moderate smoker: 10–19 cigarettes/day, heavy smoker: ≥20 cigarettes/day, not recorded); alcohol intake (none, trivial: <1 unit/day, light: 1–2 units/day, medium: 3–6 units/day, heavy: 7–9 units/day, very heavy: >9 units/day, not recorded); ethnic group (categorised into a binary variable of white/not recorded or non-white (comprising Indian, Pakistani, Bangladeshi, other Asian, black African, black Caribbean, Chinese, other including mixed)); comorbidities at baseline (individual binary variables for each of coronary heart disease, , diabetes, hypertension, cancer, epilepsy/seizures, hypothyroidism, osteoarthritis, rheumatoid arthritis, asthma/chronic obstructive airways disease, osteoporosis, liver disease, renal disease, obsessive-compulsive disorder); use of other drugs at baseline (individual binary variables for each of antihypertensive drugs, aspirin, statins, anticoagulants, non-steroidal anti-inflammatory drugs, anticonvulsants, hypnotics/anxiolytics, anti-psychotics, bisphosphonates, oral contraceptives, hormone replacement therapy). In addition for the arrhythmia and myocardial infarction outcomes we adjusted for a diagnosis of stroke or transient ischaemic attack at baseline.

Statistical analysis

Cox's proportional hazards models were used to estimate associations between the three outcomes and antidepressant drug exposure, treating antidepressant exposure as a time-varying exposure to allow for patients starting and stopping and also changing between treatments during follow-up. We used robust standard errors to allow for clustering of patients within practices. Patients were excluded from the analysis of each outcome if they had the outcome recorded at baseline. Patients were classified as exposed to an antidepressant if there were no gaps of more than 90 days between the end of one prescription and the start of the next. If there were gaps of more than 90 days they counted as exposed for the first 90 days and then unexposed for the remaining period. When patients stopped an antidepressant they were classified as exposed for the first 90 days after the estimated date of stopping, so that outcomes occurring during withdrawal periods would be attributed to the antidepressant. The main analyses were based on the first five years of follow-up after study entry, and patients were censored at the earliest date of: five years

1 after study entry, date of death, date of leaving the practice, or the end of the follow-up period in these
2 analyses.
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5 The analysis calculated unadjusted and adjusted analysis hazard ratios for each antidepressant class
6 (tricyclic and related antidepressants, selective serotonin reuptake inhibitors, other antidepressants,
7 combined treatment) compared with periods of no antidepressant treatment. Patients prescribed
8 monoamine oxidase inhibitors at any time were excluded from these analyses as the number in this
9 category was small. Patients with missing deprivation scores were excluded from the adjusted analyses.
10 Analyses were carried out for time-varying exposures of prescribed daily dose (categorised as ≤ 0.5 , >0.5
11 and ≤ 1.0 , and >1.0 defined daily doses) and tests for trend within each drug class were calculated using
12 dose as a continuous variable. Periods of exposure time where daily dose was missing were excluded from
13 the analysis of dose. Additional analyses were carried out for time since starting treatment (categorised as:
14 no use; treatment duration of 1-28 days; 29-84 days; 85 or more days) and time since stopping treatment
15 (1-28 days, 29 to 84 days and 85 to 182 days after the estimated date of stopping treatment), and for the
16 11 most commonly prescribed individual antidepressants, as in a previous study.¹⁰ Individual
17 antidepressants were further categorised by dose (≤ 1 or >1 defined daily doses) and citalopram was also
18 categorised as ≤ 20 mg/day, 20- 39 mg/day and ≥ 40 mg/day for an analysis of the arrhythmia outcome, in
19 light of the FDA drug safety communication.²⁸
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22 Wald's significance tests were used to identify significant differences between antidepressant classes and
23 between individual antidepressant drugs. We tested for interactions between class of antidepressant and
24 age and sex. We assessed the proportional hazards assumption using log minus log plots.
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27 As sensitivity analysis we repeated the analyses including the entire follow-up period, and carried out an
28 analysis excluding patients who received no antidepressant prescriptions during follow-up. We repeated
29 our main analyses using selective serotonin reuptake inhibitors as the comparison group for drug class, the
30 middle dose category of selective serotonin reuptake inhibitors as the comparison group for drug dose, and
31 citalopram (the most commonly prescribed antidepressant) as the comparison group for individual
32 antidepressants.
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35 We also carried out an analysis restricted to the first year of follow-up, this was done since there was some
36 evidence of non-proportional hazards over five years of follow-up, and also this time period more closely
37 reflected the average duration of treatment. As a post-hoc analysis we also estimated adjusted hazard
38 ratios separately using interaction terms for the 0-1 years, 1-3 years and 3-5 years after the start of follow-
39 up to further investigate changes in hazard ratios over time. These analyses were carried out for drug class,
40 and only the five most frequently prescribed antidepressants due to the smaller numbers of events in the
41 later time periods. To examine the effect of adjusting for different confounding variables we carried out
42 additional analyses entering the variables in blocks. As a post-hoc analysis we used a stratified Cox model,
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2 with stratification by general practice to compare with our main models using robust standard errors to
3 account for clustering by practice.
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6 We calculated absolute risks of the three outcomes over one year, accounting for the confounding
7 variables using the adjusted hazard ratios from the analyses based on one year of follow-up based on the
8 method described by Altman et al.²⁹
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11 We included all eligible patients in the database in our analyses to maximise power. We used a P value of
12 <0.01 (two tailed) to determine statistical significance. We used Stata (v12.1) for all analyses.
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15 16 17 **Results**

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19 There were 327,235 patients with a first diagnosis of depression made between the ages of 20 and 64,
20 between 1st January 2000 and 31st July 2011. A total of 88,272 (27.0%) patients were excluded because they
21 had schizophrenia, bipolar disorder or other psychoses, had been prescribed lithium or antimanic drugs or
22 had been prescribed an antidepressant either before the study entry date, before age 20 or more than 36
23 months before their date of diagnosis of depression. This left 238,963 patients from 687 practices in the
24 final study cohort.
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28 The total length of follow-up was 1,307,326 person-years. 51.5% of patients in the cohort had at least 5
29 years of follow-up with a median of 5.2 years overall (interquartile range 2.5–8.2) . The mean age of
30 patients in the study cohort was 39.5 years (SD 11.1), and 61% were women (Table 1). There were 8201
31 (3.4%) of patients with a missing Townsend deprivation score.
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40 **Antidepressant treatment during follow-up**

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42 During follow-up 209,476 patients (87.7%) received a total of 3,337,336 antidepressant prescriptions. There
43 were 2,379,668 (71.3%) prescriptions for selective serotonin reuptake inhibitors, 533,798 (16.0%) for
44 tricyclic and related antidepressants, and 422,079 (12.7%) for the group of other antidepressants. In
45 addition 156 patients had received a total of 1,791 (0.05%) prescriptions for monoamine oxidase inhibitors.
46 There were 83,784 combined prescriptions where two or more different antidepressant drugs were
47 prescribed on the same day. The median duration of treatment during follow-up was 221 days
48 (interquartile range 79-590).
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54 Citalopram was the most commonly prescribed antidepressant (1,023,255 prescriptions, 31.5% of total)
55 followed by fluoxetine (778,285 prescriptions, 23.9%) then amitriptyline (236,416 prescriptions, 7.3%).
56 Supplementary Table 1s shows numbers of prescriptions for the 11 most commonly prescribed
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1 antidepressants, with information on prescribed daily doses. Distributions of baseline characteristics
2 according to the first antidepressant prescribed for these 11 drugs have been presented in a previous
3 paper.²²
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6 7 **Associations with arrhythmia**

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9 At baseline 2,373 patients had an existing diagnosis of arrhythmia. These patients were excluded from
10 analysis of the arrhythmia outcome along with the patients prescribed monoamine oxidase inhibitors,
11 leaving 236,434 patients in the analysis cohort. During the first five years of follow-up there were 1452 new
12 diagnoses of arrhythmia giving an incidence rate of 16.2 per 10,000 person-years (20.1 per 10,000 in men
13 and 13.8 per 10,000 in women).
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17 There were no significant associations with arrhythmia (at $P < 0.01$) for any of the drug classes over five
18 years compared with periods of no antidepressant treatment as shown in Table 2, although there was some
19 indication of a reduced hazard ratio for selective serotonin reuptake inhibitors (adjusted hazard ratio 0.84,
20 95% CI 0.73 to 0.97, $P = 0.02$) compared with no current use of antidepressants. In a direct comparison with
21 selective serotonin reuptake inhibitors (Table 2s in supplement) there was a significantly increased rate for
22 the group of other antidepressants (adjusted hazard ratio 1.44, 95% CI 1.12 to 1.85).
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26 There were no significant trends with dose in the three drug classes (Table 2). There was a significant
27 increase in the rate of arrhythmia in the first 28 days after starting tricyclic and related antidepressants
28 (adjusted hazard ratio= 1.99, 95% CI 1.27 to 3.13, $P = 0.003$), and a significant reduction from 84 days after
29 starting selective serotonin reuptake inhibitors (adjusted hazard ratio= 0.78, 95% CI 0.66 to 0.92, $P = 0.004$).
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33 In the analysis of the 11 most commonly prescribed drugs there were significant differences between the
34 drugs overall ($P = 0.004$) but no significant difference between the four tricyclic and related antidepressants
35 ($P = 0.22$) or the five selective serotonin reuptake inhibitors ($P = 0.39$), although there was a significantly
36 decreased risk for fluoxetine (adjusted hazard ratio 0.74, 95% CI 0.59 to 0.92, $P = 0.008$), and some
37 indication of an increased risk for lofepramine (adjusted hazard ratio 1.67, 95% CI 1.01 to 2.76, $P = 0.05$)
38 compared with periods of no antidepressant treatment (Figure 1a).
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42 In an analysis of dose for individual antidepressants (Table 3) arrhythmia rates were not significantly
43 increased for higher doses of citalopram (adjusted hazard ratio= 1.08, 95% CI 0.74 to 1.57, for doses >20
44 mg/day) or escitalopram (adjusted hazard ratio= 1.06, 95% CI 0.52 to 2.16, for doses >10 mg/day), but
45 there was a significant increase for lower doses of lofepramine (adjusted hazard ratio= 3.89, 95% CI 1.92 to
46 7.90, for doses ≤ 105 mg/day) and a significantly reduced risk for lower doses of fluoxetine (adjusted hazard
47 ratio=0.72, 95% CI 0.56 to 0.91, for doses ≤ 20 mg/day). Even for doses of citalopram ≥ 40 mg/day there
48 was no significantly increased risk (adjusted hazard ratio=1.11, 95% CI 0.72 to 1.71) although the number of
49 events was small ($n = 28$) (Table 3s in supplement).
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1 Adjusted hazard ratios were similar when patients who had not received any prescriptions for
2 antidepressants during follow-up were removed from the analysis (Table 4s in supplement) and when the
3 entire follow-up period was used (Table 5s in supplement) although there were more significant
4 associations due to larger numbers. When just the first year of follow-up was used (Table 4) results were
5 similar to the five year analysis although there was a higher hazard ratio for combined antidepressant use
6 (adjusted hazard ratio=3.45, 95%CI 1.24 to 9.57, P=0.017) and the association with fluoxetine was no longer
7 statistically significant (adjusted hazard ratio= 0.79, 95% CI 0.55 to 1.13, P=0.19). There was no indication of
8 non-proportional hazards for the arrhythmia outcome; separate results for years 0-1, 1-3 and 3-5 of follow-
9 up are shown in supplementary tables 6s and 7s.

17 **Associations with myocardial infarction**

19 At baseline 1,790 patients had a previous diagnosis of myocardial infarction recorded. These patients were
20 excluded from analysis of the myocardial infarction outcome along with the patients prescribed
21 monoamine oxidase inhibitors, leaving 237,017 patients in the analysis cohort. During the first five years of
22 follow-up there were 772 new diagnoses of myocardial infarction giving an incidence rate of 8.6 per 10,000
23 person-years (16.2 per 10,000 in men and 3.9 per 10,000 in women).

28 There was no significant association between antidepressant class and myocardial infarction over five years
29 in the adjusted analysis (Table 5) and no significant trends with dose. There was no clear pattern in risk
30 according to different periods of time after starting or stopping antidepressant drugs, although rates were
31 increased from 28 days after stopping tricyclic and related antidepressants.

35 There were no significant associations (at $P < 0.01$) for individual drugs in the adjusted analyses (Figure 1b)
36 and no significant difference between the five selective serotonin reuptake inhibitors ($P = 0.27$) or the four
37 tricyclic and related antidepressants ($P = 0.26$), although fluoxetine had an adjusted hazard ratio of 0.73
38 (95% CI 0.54 to 0.98, $P = 0.04$) and lofepramine had an adjusted hazard ratio of 2.02 (95% CI 1.14 to 3.59,
39 $P = 0.02$) both compared with periods of no antidepressant treatment .

44 Adjusted hazard ratios were similar when patients who had not received any antidepressant prescriptions
45 during follow-up were removed from the analysis (Table 8s in supplement) and when the entire follow-up
46 period was used (Table 9s in supplement). There was some indication that hazard rates were not
47 proportional over the 5 years of follow up and there were some differences in the hazard ratios when the
48 analysis was restricted to the first year of follow-up compared with values over 5 years. In this one year
49 analysis (Table 4) there was a significantly reduced risk for selective serotonin reuptake inhibitors
50 compared with no use of antidepressants (adjusted hazard ratio 0.58, 95% CI 0.42 to 0.79, $P = 0.001$), and
51 although overall there was no significant difference (at $P < 0.01$) between the five selective serotonin
52 reuptake inhibitors ($P = 0.11$) or the four tricyclic and related antidepressants ($P = 0.03$) there was a
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1 significant reduction with fluoxetine (adjusted hazard ratio 0.44, 95% CI 0.27 to 0.72, P=0.001) and a
2 significant increase with lofepramine (adjusted hazard ratio 3.07, 95% CI 1.50 to 6.26, P=0.002). There were
3 no significant associations with selective serotonin reuptake inhibitors in years 1-3 and 3-5 of follow-up
4 (Table 6s in supplement) nor with fluoxetine (Table 7s in supplement).
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11 **Associations with stroke/transient ischaemic attack**

12 At baseline 1,741 patients had a diagnosis of stroke or transient ischaemic attack recorded. These patients
13 were excluded from analysis of the stroke/ transient ischaemic attack outcome along with the patients
14 prescribed monoamine oxidase inhibitors, leaving 237,067 patients in the analysis cohort. During the first
15 five years of follow-up there were 1106 new diagnoses of stroke or transient ischaemic attack, giving an
16 incidence rate of 12.3 per 10,000 person-years (17.3 per 10,000 in men and 9.3 per 10,000 in women).
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23 There were no significant associations between antidepressant class and stroke/transient ischaemic attack
24 over five years and no significant trends (at P<0.01) with dose (Table 6). There was a significant increase in
25 risk during the first 28 days after starting other antidepressants (adjusted hazard ratio= 2.72, 95% CI 1.45 to
26 5.08, P=0.002), and from 85 to 182 days after stopping tricyclic and related antidepressants (adjusted
27 hazard ratio= 1.82, 95% CI 1.21 to 2.74, P=0.004). Rates were also increased in the first 84 days after
28 starting tricyclic and related antidepressants, although not significantly (at P<0.01).
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33 In the adjusted analysis of individual antidepressant drugs there were no significant associations for any of
34 the drugs (Figure 1c).
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37 Adjusted hazard ratios were similar when patients who had not received any prescriptions for
38 antidepressants during follow-up were removed (supplementary table 10s), and when either the entire
39 follow-up period (Table 11s in supplement), but they tended to be lower when just the first year of follow-
40 up was used in the analysis (Table 4). There was some indication that hazard rates were not proportional
41 over the 5 years of follow- up, with higher hazard ratios in the later periods of follow-up for tricyclic and
42 related antidepressants and selective serotonin reuptake inhibitors (supplementary tables 6s and 7s).
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48 **Additional analyses**

49 The results of analyses including confounding variables in blocks are shown in supplementary tables 12s to
50 14s, and show that adjustment for age, sex, deprivation, ethnic group and year of diagnosis had a marked
51 effect on hazard ratios, but additional adjustment for further blocks of variables had a relatively small
52 effect.
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2 Results were similar to those of our main models which used robust standard errors when the Cox models
3 were stratified by general practice.
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5 6 **Absolute risks**

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8 Table 7 shows absolute risks of the three outcomes over one year by antidepressant class and for the
9 individual drugs. Absolute risks of arrhythmia and myocardial infarction were highest for lofepramine (30
10 per 10,000 and 31 per 10,000 respectively), and for stroke/transient ischaemic attack were highest for
11 mirtazapine (24 per 10,000) but the 95% confidence intervals for these values were wide and mainly
12 overlapped with the other drugs.
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16 17 **Discussion**

18
19 The main findings of this large population-based cohort study were that selective serotonin reuptake
20 inhibitors were not associated with an increased risk of arrhythmia, myocardial infarction, or stroke or
21 transient ischaemic attack in a general population cohort of people with depression aged 20 to 64, and that
22 arrhythmia risk was not significantly increased in patients prescribed citalopram even at high doses (40
23 mg/day and over). There was some evidence that selective serotonin reuptake inhibitors were associated
24 with a reduced risk of arrhythmia and myocardial infarction. Fluoxetine was associated with the lowest risks
25 of these two outcomes but overall there were no significant differences between the selective serotonin
26 reuptake inhibitors. The risk of arrhythmia was significantly increased in the first 4 weeks of starting
27 tricyclic and related antidepressants, and the tricyclic drug lofepramine was associated with a significantly
28 increased risk of myocardial infarction in the first year of follow-up.
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36 37 **Strengths and limitations**

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39 This study included a large representative sample of people aged 20 to 64 diagnosed with depression in the
40 general UK population and had a long follow-up period. All eligible patients were included, so there is no
41 bias due to non-response and no recall bias since data on prescriptions and confounding variables were
42 recorded prospectively before the outcomes occurred. We reduced indication bias by restricting our cohort
43 to only include patients with a diagnosis of depression, since depression itself is an established risk factor
44 for cardiovascular outcomes,^{30 31} and otherwise it would be difficult to separate the effects of
45 antidepressant treatment from those of depression. This means that our findings can only be generalised to
46 people diagnosed with depression.
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53 Some bias may remain in comparisons between antidepressant drugs if the selection of a particular
54 antidepressant was influenced by risk factors for the outcome, but we accounted for a large number of
55 potential confounding variables in the analysis to reduce differences between comparison groups. The
56 increased risk in some analyses for lofepramine may nevertheless reflect preferential selection of this drug
57 in patients considered more prone to arrhythmias or heart disease, since this drug is viewed as being safer
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1 in overdose and less cardiotoxic than other tricyclic and related antidepressants.^{32 33} The increased risk of
2 arrhythmia for low doses of lofepramine but not higher doses supports this, whereby patients at highest
3 risk are prescribed lower doses, although numbers of events were small in both dose categories. However
4 in a comparison of baseline characteristics of patients prescribed different antidepressants there was no
5 indication that lofepramine was prescribed more frequently than other tricyclic antidepressants to patients
6 with cardiovascular risk factors,²² for example among patients whose first antidepressant prescription was
7 for lofepramine 1.1% had coronary heart disease compared with 2.1% for amitriptyline, and 0.8% had a
8 prior stroke recorded compared with 1.0% for amitriptyline. Similarly there was no indication that
9 fluoxetine was prescribed more frequently than other selective serotonin reuptake inhibitors to younger
10 patients or patients with fewer cardiovascular risk factors, for example the mean age of patients when first
11 prescribed fluoxetine was 38.8 years, compared with 39.8 for citalopram and 38.3 for paroxetine, and the
12 proportion of patients with hypertension when first prescribed fluoxetine was 6.7%, whereas for
13 paroxetine it was 5.3%.²²

23
24 There may still be some residual confounding due to variables which were either not recorded on the
25 database such as dietary factors and physical activity or were not recorded in sufficient detail for their
26 confounding effect to be completely removed by analysis. Whilst we adjusted for depression severity, this
27 was based on a basic classification of diagnostic Read codes for depression, since depression severity scores
28 are not routinely recorded in general practice. Numbers of patients in the different non-white ethnic
29 groups were small so these were combined for inclusion in the analysis which may contribute to residual
30 confounding. There will be some misclassification of the antidepressant exposure variables, as some
31 patients may not have taken their prescribed antidepressant, or may not have taken it at the prescribed
32 dose. This misclassification could underestimate associations with drug use. Furthermore although the
33 cohort was large, the number of events was small for some of the antidepressant exposure categories. In
34 particular there were relatively few prescriptions for citalopram at doses of 40 mg/day or more (19% of
35 citalopram prescriptions), and only 28 diagnoses of arrhythmia in this category, so the 95% confidence
36 interval for arrhythmia risk with high doses of citalopram arrhythmia is wide and increases in risk of up to
37 71% cannot be excluded.

38
39 The outcomes were not formally adjudicated in this study, but validation studies in other UK primary care
40 databases have shown high levels of validity across a range of diseases, and we would expect levels of
41 validity to be similar in QResearch®.^{34 35} For example, Khan reported high positive predictive values in
42 validation studies of acute myocardial infarction and cerebrovascular disease.³⁵ A study validating
43 diagnostic codes for ventricular arrhythmia and sudden cardiac death reported a positive predictive value
44 of 93%.³⁶ We included information from death certificates to identify additional patients with the
45 outcomes, which will have increased ascertainment and reduced misclassification.

Comparison with other studies

Our results for arrhythmia are consistent with those of two other large cohort studies^{18 19} in finding no increased risk for citalopram, even at high doses and our rates of arrhythmia are of the same order of magnitude. Our study adds new information on risks associated with other antidepressant drugs and on effects of duration. Our findings contrast to some extent with studies which have found QT interval prolongation in patients prescribed citalopram.¹⁴⁻¹⁶ One cross-sectional study¹⁵ which included 38,397 patients aged 18 and over with an electrocardiogram recorded after prescription of antidepressant or methadone found that QT prolongation was associated with dose for citalopram, escitalopram and amitriptyline but not for other antidepressants examined. A study of psychiatric in-patients aged 18 and over found that the majority of people with QT prolongation had two or more risk factors for QT prolongation, such as hypokalaemia, HIV infection, abnormal T wave morphology and alcohol or drug use disorders, and that citalopram (including escitalopram) were significantly associated with QT prolongation after adjusting for these factors.¹⁶ This lack of coherence may reflect the smaller numbers of arrhythmia outcomes in the cohort studies when split by antidepressant drug and dose. Thus power to detect an increased risk among higher antidepressant dose categories is low in comparison to studies which measure QT interval in adults receiving different doses of antidepressants and treat it as a continuous outcome variable in the analyses.^{14 15} Torsades de pointes which is the type of arrhythmia most closely related to QT interval prolongation is extremely rare, so the cohort studies including ours cannot rule out an association for this particular type of arrhythmia. Furthermore a surrogate measure such as QT interval may not necessarily translate into an effect on a clinically important outcome such as arrhythmia. Our findings of an increased risk of arrhythmia in the first 4 weeks of starting a tricyclic antidepressant days is consistent with a number of potential arrhythmias that can occur in tricyclic overdose in people with previously unsuspected cardiac abnormalities such as bundle branch block;^{37 38} our findings are important as few studies have examined this for prescribed doses of tricyclic antidepressants.

In our previous study of antidepressants in people aged 65 and over with depression^{10 25} we found a significantly increased risk of myocardial infarction for selective serotonin reuptake inhibitors but not for tricyclic or other antidepressants. Other observational studies have found similar results for selective serotonin reuptake inhibitors,^{39 40} whilst several have found no association^{11 12 41 42} or a reduced risk;^{13 43 44} few studies have assessed risks for individual antidepressants. A meta-analysis of 16 observational studies concluded that neither selective serotonin reuptake inhibitor nor tricyclic antidepressant use is associated with an increased risk of coronary heart disease,⁴⁵ but only two studies were restricted to patients with depression. These contradictory findings are likely to be due to differences between studies since they vary considerably in their sizes and inclusion criteria: several¹¹⁻¹³ either did not restrict their study sample to patients with depression or did not account for depression in the analysis and so are highly susceptible to indication bias since depression is a strong risk factor for cardiovascular disease; some are only in older or

1 postmenopausal populations^{10 39 42}; whilst one⁴⁴ was an interview-based case-control study prone to recall
2 bias. It is unclear why our results differ from our previous study in older people which had a very similar
3 study design,¹⁰ but it could be due to the larger number of myocardial infarction events (n=2350) in the
4 older cohort, or increased susceptibility to side effects in older people due to age-related pharmacokinetic
5 changes,⁴⁶ or the high prevalence of multimorbidity and use of concomitant medications in older people
6 may result in interactions giving different patterns of risk with antidepressant use.
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12 Observational studies of antidepressants and stroke have shown a more consistent pattern, with several
13 studies finding an increased risk of stroke with selective serotonin reuptake inhibitor use.^{10 42 47-49} A
14 systematic review and meta-analysis of 13 observational studies of selective serotonin reuptake inhibitors
15 and stroke⁹ reported that selective serotonin reuptake inhibitors were associated with an increased risk of
16 all types of stroke (overall adjusted odds ratio 1.40; 95 % confidence interval 1.09 to 1.80), and that the risk
17 was still significantly increased when the analysis was restricted to the studies in which potential
18 confounding by depression was considered. In a subgroup analysis by age group the combined odds ratio
19 for all types of stroke associated with selective serotonin reuptake inhibitor use was only significant in the
20 four studies^{10 42 50 51} restricted to people aged at least 50 years (overall adjusted odds ratio 1.58, 95% CI 1.06
21 to 2.36), and there was no significantly increased risk in studies with no age restriction (overall adjusted
22 odds ratio 1.13, 95% CI 0.91 to 1.39). This concurs with our findings in the current study of no association
23 between selective serotonin reuptake inhibitors and stroke in people aged 20 to 64 and of an increased risk
24 in our previous study¹⁰ in people aged 65 and over.
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34 **Clinical implications and future research**

35
36 Prescription of antidepressants is a complex process, involving balancing of risks and benefits for different
37 antidepressants and doses, accounting for severity of depression, patient risk factors, comorbidities and
38 preferences. The results of this study in adults aged 20 to 64 are reassuring in light of recent concerns
39 about citalopram and potential risk of arrhythmia, but as only small numbers of patients were prescribed
40 high doses of citalopram we cannot rule out the possibility of an increased risk so suggest that high doses of
41 citalopram should not be prescribed without a strong indication particularly where there are any risk
42 factors for an increased QT interval. There was also no evidence that selective serotonin reuptake inhibitors
43 are associated with an increased risk of myocardial infarction or stroke/transient ischaemic attack in this
44 age group; they may even be associated with a reduced risk of myocardial infarction and arrhythmia
45 particularly for fluoxetine. The potential cardio-protective effects of selective serotonin reuptake inhibitors,
46 particularly fluoxetine, warrant further investigation.
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55 The risk of arrhythmia was increased during the first 28 days of taking tricyclic and related antidepressants
56 and among the antidepressants studied lofepramine had the highest risks of arrhythmia, myocardial
57 infarction, and stroke/transient ischaemic attack. This finding may reflect selective prescribing of
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2 lofepramine since it is generally considered to be safer than other tricyclic and related antidepressants in
3 overdose, but could also indicate increased risks when taken at doses typically prescribed in primary care.
4 Further research using other designs such as the self-controlled case series approach may help to elucidate
5 this association.
6
7

8 9 **Conclusions**

10 This large observational study has found no evidence that selective serotonin reuptake inhibitors are
11 associated with an increased risk of arrhythmia, myocardial infarction, or stroke/transient ischaemic attack
12 in people with depression aged 20 to 64, but some indication that they are associated with a reduced risk
13 of myocardial infarction and arrhythmia particularly for fluoxetine. Citalopram was not significantly
14 associated with an increased risk of arrhythmia even at higher doses although the confidence interval was
15 wide. These findings are reassuring in light of recent safety concerns about selective serotonin reuptake
16 inhibitors.
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Approvals

The project has been independently peer reviewed and accepted by the QResearch Scientific board and has been approved in accordance with the agreed procedure with the Trent Research Ethics Committee (reference number: MREC/03/4/021).

Contributorship

CC, JHC, RM, AA, and MM contributed to the overall conception and design of the study. CC wrote the first draft of this manuscript. JHC undertook the data extraction. TH and CC carried out the statistical analyses of the study. All authors contributed to interpretation of results and drafting of this manuscript. All authors read and approved the final manuscript.

CC is the guarantor.

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Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: financial support from NIHR for the submitted work; Julia Hippisley-Cox is director of QResearch which is a not for profit venture between the University of Nottingham and EMIS (commercial supplier of GP clinical systems); no financial relationships with any organisations that might have an interest in the

1 submitted work in the previous three years; no other relationships or activities that could appear to have
2 influenced the submitted work.
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16 The lead author (Carol Coupland) affirms that this manuscript is an honest, accurate, and transparent
17 account of the study being reported; that no important aspects of the study have been omitted; and that
18 any discrepancies from the study as planned have been explained.
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23 **Data Sharing statement**

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25 The patient level data from the QResearch are specifically licensed according to its governance framework.
26 See www.qresearch.org for further details.
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Table 1: Characteristics of the study cohort (n= 238,963) at baseline. Values are numbers (column percentages unless stated otherwise).

Characteristic	n	%
Male	92,935	(38.9)
Female	146,028	(61.1)
Mean age (SD)	39.5	(11.1)
Ethnic group:		
Recorded	136,624	(57.2)
White/not recorded	227,451	(95.2)
Non-white	11,512	(4.8)
Depression severity (index diagnosis):		
Mild	171,208	(71.7)
Moderate	59,140	(24.8)
Severe	8,615	(3.6)
Smoking status†:		
Non smoker	110,849	(47.5)
Ex-smoker	35,132	(15.1)
Current light smoker	24,104	(10.3)
Current moderate smoker	40,546	(17.4)
Current heavy smoker	22,659	(9.7)
Not recorded	5,673	
Alcohol consumption†:		
Non drinker	55,253	(27.2)
Trivial (less than 1 unit per day)	77,579	(38.2)
Light (1-2 units per day)	51,310	(25.3)
Moderate (3 to 6 units per day)	14,482	(7.1)
Heavy (7 to 9 units per day)	2,174	(1.1)
Very heavy (over 9 units per day)	2,391	(1.2)
Not recorded	35,774	
Townsend deprivation score in fifths†:		
1 (Least deprived)	45,021	(19.5)
2	46,207	(20.0)
3	48,293	(20.9)
4	47,063	(20.4)
5 (Most deprived)	44,178	(19.1)
Not recorded	8,201	
Comorbidities at baseline:		
Coronary heart disease	4,109	(1.7)
Diabetes	7,371	(3.1)
Hypertension	17,217	(7.2)
Stroke/transient ischaemic attack	1,741	(0.7)
Arrhythmia	2,373	(1.0)
Any cancer	3,810	(1.6)
Asthma/chronic obstructive airways disease	31,816	(13.3)
Epilepsy/seizures	3,325	(1.4)
Hypothyroidism	5,267	(2.2)
Obsessive-compulsive disorder	494	(0.2)
Osteoarthritis	7,228	(3.0)
Osteoporosis	867	(0.4)
Liver disease	698	(0.3)
Renal disease	549	(0.2)
Rheumatoid arthritis	1,301	(0.5)
Medications at baseline:		
Anticonvulsants	2,672	(1.1)
Antihypertensive drugs	25,344	(10.6)

Antipsychotics	836	(0.4)
Anticoagulants	1,073	(0.5)
Aspirin	7,159	(3.0)
Bisphosphonates	854	(0.4)
Hypnotics/anxiolytics	11,354	(4.8)
Non-steroidal anti-inflammatory drugs	12,725	(5.3)
Statins	10,823	(4.5)
Oral contraceptives*	27,396	(18.8)
Hormone replacement therapy*	7,207	(4.9)

* Percentage is for females only.

†For smoking status, alcohol and deprivation categories percentages are out of total with recorded values.

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Table 2 Unadjusted and adjusted hazard ratios for arrhythmia by antidepressant class, dose, and duration over 5 years follow-up.

	No of events*	Person-years*	Unadjusted analysis		Adjusted analysis ¹		P
			Hazard ratio	95% CI	Hazard ratio	95% CI	
Antidepressant class							
No current use	887	568,365	1.00		1.00		
TCA's	102	41,208	1.59	(1.29 to 1.96)	1.09	(0.88 to 1.35)	0.46
SSRIs	352	224,985	1.02	(0.89 to 1.18)	0.84	(0.73 to 0.97)	0.02
Other antidepressants	68	28,048	1.55	(1.23 to 1.95)	1.21	(0.96 to 1.54)	0.11
Combined antidepressants	10	4,233	1.47	(0.75 to 2.89)	1.07	(0.54 to 2.09)	0.85
Antidepressant class and dose categories†							
No current use	887	568,365	1.00		1.00		
<i>TCA's:</i>							
≤ 0.5 DDD	51	23,506	1.37	(1.03 to 1.82)	0.89	(0.67 to 1.19)	0.44
>0.5 DDD/≤ 1.0 DDD	26	8,400	2.03	(1.39 to 2.96)	1.35	(0.91 to 1.99)	0.14
> 1.0 DDD	14	5,306	1.66	(0.98 to 2.81)	1.32	(0.77 to 2.26)	0.31
Test for trend ²							0.15
<i>SSRIs:</i>							
≤ 0.5 DDD	30	15,995	1.19	(0.82 to 1.71)	0.93	(0.64 to 1.35)	0.71
>0.5 DDD/≤ 1.0 DDD	236	157,668	0.97	(0.82 to 1.14)	0.79	(0.67 to 0.94)	0.007
> 1.0 DDD	75	42,566	1.16	(0.91 to 1.49)	0.98	(0.76 to 1.26)	0.88
Test for trend ²							0.55
<i>Others:</i>							
≤ 0.5 DDD	9	4,026	1.40	(0.74 to 2.64)	0.98	(0.52 to 1.86)	0.95
>0.5 DDD/≤ 1.0 DDD	31	13,199	1.52	(1.08 to 2.15)	1.16	(0.81 to 1.65)	0.41
> 1.0 DDD	20	8,411	1.49	(0.97 to 2.29)	1.28	(0.84 to 1.97)	0.25
Test for trend ²							0.69
Antidepressant class by time since starting and stopping treatment							
No current or recent use	804	510,266	1.00		1.00		
<i>TCA's:</i>							
first 28 days	23	5,482	2.56	(1.64 to 4.02)	1.99	(1.27 to 3.13)	0.003
29-84 days after starting	12	5,400	1.36	(0.77 to 2.43)	1.04	(0.58 to 1.87)	0.89
≥85 days after starting	44	18,941	1.52	(1.11 to 2.07)	0.91	(0.67 to 1.25)	0.57
1-28 days after stopping	11	3,614	2.04	(1.15 to 3.62)	1.57	(0.86 to 2.86)	0.14
29-84 days after stopping	11	7,030	1.02	(0.56 to 1.88)	0.85	(0.46 to 1.56)	0.60
85-182 days after stopping	15	10,711	1.00	(0.60 to 1.66)	0.79	(0.46 to 1.35)	0.39
<i>SSRIs:</i>							
first 28 days	44	20,639	1.31	(0.90 to 1.89)	1.23	(0.85 to 1.79)	0.28
29-84 days after starting	44	27,863	0.95	(0.66 to 1.37)	0.91	(0.63 to 1.32)	0.63
≥85 days after starting	198	127,197	1.04	(0.88 to 1.23)	0.78	(0.66 to 0.92)	0.004
1-28 days after stopping	22	15,685	0.88	(0.58 to 1.36)	0.94	(0.61 to 1.44)	0.76
29-84 days after stopping	41	30,405	0.94	(0.70 to 1.26)	0.94	(0.69 to 1.27)	0.69
85-182 days after stopping	66	46,815	0.97	(0.75 to 1.27)	1.01	(0.77 to 1.33)	0.92
<i>Others:</i>							
first 28 days	7	2,776	1.56	(0.75 to 3.23)	1.35	(0.65 to 2.80)	0.42
29-84 days after starting	7	3,504	1.44	(0.71 to 2.91)	1.07	(0.50 to 2.30)	0.85
≥85 days after starting	41	16,854	1.52	(1.13 to 2.04)	1.14	(0.85 to 1.54)	0.38
1-28 days after stopping	5	1,573	2.00	(0.83 to 4.79)	1.86	(0.78 to 4.46)	0.16
29-84 days after stopping	6	3,023	1.29	(0.58 to 2.88)	1.19	(0.54 to 2.65)	0.66
85-182 days after stopping	8	4,537	1.16	(0.58 to 2.34)	1.09	(0.54 to 2.21)	0.80

* Based on numbers in adjusted analysis

† Daily doses could not be evaluated for some prescriptions

SSRIs=selective serotonin reuptake inhibitors; TCAs=tricyclic and related antidepressants.

1 DDD= defined daily dose

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3 ¹ Adjusted for age, sex, year of diagnosis of depression, severity of depression, deprivation, smoking status, alcohol intake, ethnic
4 group (white/not recorded or non-white), coronary heart disease, diabetes, hypertension, cancer, epilepsy/seizures,
5 hypothyroidism, osteoarthritis, asthma/chronic obstructive airways disease, stroke/TIA, rheumatoid arthritis, osteoporosis, liver
6 disease, renal disease, obsessive-compulsive disorder, statins, NSAIDS, aspirin, antihypertensive drugs, anticonvulsants,
7 hypnotics/anxiolytics, oral contraceptives, hormone replacement therapy, antipsychotics, bisphosphonates, anticoagulants.

8 ² Test for trend uses continuous values of dose

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Table 3. Unadjusted and adjusted hazard ratios for arrhythmia by individual drug categorised according to dose for 5 years follow-up†

	No of events*	Person-years*	Unadjusted		Adjusted analysis ¹		P
			Hazard ratio	95% CI	Hazard ratio	95% CI	
Antidepressant drug							
No current use	887	568,365	1.00		1.00		
<i>TCAs:</i>							
Amitriptyline:≤ 1 DDD	41	16,040					
Amitriptyline:>1 DDD	4	1,442					
Dosulepin:≤ 1 DDD	23	10,967					
Dosulepin:>1 DDD	1	205					
Lofepramine:≤ 1 DDD	8	961	5.19	(2.55 to 10.54)	3.89	(1.92 to 7.90)	<0.001
Lofepramine:>1 DDD	8	3,394	1.49	(0.74 to 2.99)	1.17	(0.58 to 2.39)	0.66
Trazodone:≤ 1 DDD	2	2,139					
Trazodone:>1 DDD	1	19					
<i>SSRIs:</i>							
Citalopram:≤ 1 DDD	115	72,340	1.04	(0.85 to 1.28)	0.82	(0.66 to 1.01)	0.06
Citalopram:>1 DDD	34	17,854	1.27	(0.88 to 1.83)	1.08	(0.74 to 1.57)	0.70
Escitalopram:≤ 1 DDD	18	9,068	1.31	(0.81 to 2.12)	1.04	(0.63 to 1.72)	0.88
Escitalopram:>1 DDD	7	3,758	1.35	(0.69 to 2.64)	1.06	(0.52 to 2.16)	0.88
Fluoxetine:≤ 1 DDD	91	68,345	0.84	(0.66 to 1.07)	0.72	(0.56 to 0.91)	0.007
Fluoxetine:>1 DDD	16	11,072	0.92	(0.56 to 1.53)	0.78	(0.48 to 1.27)	0.32
Paroxetine:≤ 1 DDD	19	12,216	0.98	(0.62 to 1.57)	0.84	(0.53 to 1.34)	0.46
Paroxetine:>1 DDD	9	3,398	1.72	(0.90 to 3.27)	1.47	(0.77 to 2.84)	0.25
Sertraline:≤ 1 DDD	23	11,539	1.31	(0.86 to 2.01)	1.09	(0.70 to 1.68)	0.71
Sertraline:>1 DDD	9	6,448	0.89	(0.47 to 1.7)	0.78	(0.41 to 1.49)	0.45
<i>Others:</i>							
Mirtazapine:≤ 1 DDD	20	7,533	1.74	(1.13 to 2.70)	1.17	(0.75 to 1.84)	0.49
Mirtazapine:>1 DDD	6	1,933	1.94	(0.89 to 4.23)	1.48	(0.67 to 3.26)	0.33
Venlafaxine:≤ 1 DDD	18	8,432	1.35	(0.86 to 2.12)	1.14	(0.72 to 1.81)	0.57
Venlafaxine:>1 DDD	14	6,369	1.38	(0.82 to 2.32)	1.24	(0.74 to 2.08)	0.42

† Results only shown for drugs where there were at least 5 events in both dose categories

* Based on numbers in adjusted analysis

DDD = defined daily dose

DDD values are: amitriptyline 75 mg/day; dosulepin 150 mg/day; lofepramine 105 mg/day; trazodone 300 mg/day; citalopram 20 mg/day; escitalopram 10 mg/day; fluoxetine 20 mg/day; paroxetine 20 mg/day; sertraline 50 mg/day; mirtazapine 30 mg/day; venlafaxine 100 mg/day

¹ Adjusted for age, sex, year of diagnosis of depression, severity of depression, deprivation, smoking status, alcohol intake, ethnic group (white/not recorded or non-white), coronary heart disease, diabetes, hypertension, cancer, epilepsy/seizures, hypothyroidism, osteoarthritis, asthma/chronic obstructive airways disease, stroke/TIA, rheumatoid arthritis, osteoporosis, liver disease, renal disease, obsessive-compulsive disorder, statins, NSAIDs, aspirin, antihypertensive drugs, anticonvulsants, hypnotics/anxiolytics, oral contraceptives, hormone replacement therapy, antipsychotics, bisphosphonates, anticoagulants.

Table 4 Adjusted hazard ratios for arrhythmia, myocardial infarction and stroke or transient ischaemic attack by antidepressant class, dose, and individual drug over the first year of follow-up.

	Arrhythmia				Myocardial infarction				Stroke/TIA			
	No of events*	Adjusted hazard ratio ¹	95% CI	P	No of events*	Adjusted hazard ratio ¹	95% CI	P	No of events*	Adjusted hazard ratio ¹	95% CI	P
Antidepressant class												
No current use	127	1.00			90	1.00			113	1.00		
TCA	39	1.16	(0.81 to 1.67)	0.42	25	1.09	(0.72 to 1.66)	0.68	33	1.01	(0.69 to 1.49)	0.94
SSRI	141	0.86	(0.66 to 1.11)	0.24	63	0.58	(0.42 to 0.79)	0.001	118	0.83	(0.63 to 1.09)	0.18
Other antidepressants	20	1.33	(0.84 to 2.12)	0.23	9	0.81	(0.42 to 1.58)	0.54	16	1.15	(0.69 to 1.90)	0.59
Combined antidepressants	5	3.45	(1.24 to 9.57)	0.02	2	1.68	(0.43 to 6.65)	0.46	1	0.69	(0.10 to 4.96)	0.72
Antidepressant class and dose categories												
No current use	127	1.00			90	1.00			113	1.00		
<i>TCA</i> :												
≤ 0.5 DDD	21	0.98	(0.62 to 1.55)	0.92	12	0.86	(0.47 to 1.56)	0.62	18	0.87	(0.54 to 1.41)	0.58
>0.5 DDD/≤ 1.0 DDD	10	1.76	(0.92 to 3.35)	0.09	4	0.93	(0.35 to 2.50)	0.89	8	1.36	(0.66 to 2.78)	0.41
> 1.0 DDD	4	1.22	(0.46 to 3.24)	0.69	3	1.29	(0.41 to 4.04)	0.66	4	1.26	(0.47 to 3.38)	0.65
Test for trend ²				0.83				0.47				0.23
<i>SSRI</i> :												
≤ 0.5 DDD	11	0.95	(0.52 to 1.72)	0.85	5	0.76	(0.30 to 1.92)	0.56	7	0.73	(0.34 to 1.56)	0.42
>0.5 DDD/≤ 1.0 DDD	105	0.81	(0.62 to 1.08)	0.15	43	0.52	(0.37 to 0.73)	<0.001	90	0.81	(0.61 to 1.09)	0.16
> 1.0 DDD	21	1.07	(0.65 to 1.76)	0.79	11	0.75	(0.41 to 1.36)	0.34	17	0.99	(0.59 to 1.67)	0.98
Test for trend ²		0.57						0.42				0.47
<i>Others</i> :												
≤ 0.5 DDD	3	1.06	(0.34 to 3.32)	0.93	2	0.95	(0.23 to 3.96)	0.95	4	1.58	(0.57 to 4.35)	0.38
>0.5 DDD/≤ 1.0 DDD	13	1.65	(0.91 to 2.98)	0.10	3	0.53	(0.17 to 1.60)	0.26	7	0.95	(0.45 to 1.98)	0.88
> 1.0 DDD	2	0.80	(0.20 to 3.20)	0.76	2	1.04	(0.26 to 4.17)	0.95	4	1.76	(0.66 to 4.73)	0.26
Test for trend ²				0.51				0.40				0.72
Antidepressant drug												
No current use	130	1.00			90	1.00			113	1.00		
<i>TCA</i> :												
Amitriptyline	18	1.15	(0.69 to 1.94)	0.59	8	0.75	(0.37 to 1.55)	0.44	15	1.00	(0.59 to 1.70)	1.00
Dosulepin	8	0.73	(0.35 to 1.50)	0.39	8	1.07	(0.53 to 2.18)	0.85	12	1.12	(0.63 to 1.98)	0.70

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3													
4	Lofepramine	8	2.13	(1.05 to 4.33)	0.04	8	3.07	(1.50 to 6.26)	0.002	4	1.15	(0.43 to 3.11)	0.78
5	Trazodone	3	1.72	(0.53 to 5.56)	0.36	1	0.73	(0.10 to 5.19)	0.76	1	0.56	(0.08 to 3.72)	0.55
6	<i>SSRIs:</i>												
7	Citalopram	56	0.79	(0.57 to 1.10)	0.17	27	0.59	(0.39 to 0.91)	0.017	43	0.73	(0.51 to 1.05)	0.09
8	Escitalopram	9	1.01	(0.47 to 2.16)	0.99	4	0.67	(0.25 to 1.82)	0.43	5	0.63	(0.26 to 1.53)	0.31
9	Fluoxetine	48	0.79	(0.55 to 1.13)	0.19	18	0.44	(0.27 to 0.72)	0.001	56	1.06	(0.76 to 1.50)	0.72
10	Paroxetine	13	1.10	(0.61 to 1.99)	0.74	3	0.38	(0.12 to 1.22)	0.10	7	0.63	(0.28 to 1.38)	0.25
11	Sertraline	15	1.21	(0.71 to 2.07)	0.48	10	1.18	(0.64 to 2.20)	0.59	7	0.63	(0.30 to 1.35)	0.24
12	<i>Others:</i>												
13	Mirtazapine	8	1.20	(0.57 to 2.53)	0.62	5	0.91	(0.37 to 2.24)	0.84	12	1.85	(1.01 to 3.37)	0.04
14	Venlafaxine	11	1.64	(0.88 to 3.08)	0.12	4	0.89	(0.33 to 2.39)	0.81	3	0.51	(0.16 to 1.57)	0.24
15	All other antidepressants	3	0.90	(0.30 to 2.69)	0.85	1	0.46	(0.06 to 3.35)	0.44	2	0.64	(0.15 to 2.63)	0.53
16	Combined antidepressants	5	3.44	(1.24 to 9.55)	0.02	2	1.68	(0.43 to 6.64)	0.46	1	0.70	(0.10 to 4.97)	0.72

SSRIs=selective serotonin reuptake inhibitors; TCAs=tricyclic and related antidepressants.

* Based on numbers in adjusted analysis

¹ Adjusted for age, sex, year of diagnosis of depression, severity of depression, deprivation, smoking status, alcohol intake, ethnic group (white/not recorded or non-white), coronary heart disease, diabetes, hypertension, cancer, epilepsy/seizures, hypothyroidism, osteoarthritis, asthma/chronic obstructive airways disease, stroke/TIA (except for the stroke/TIA outcome), rheumatoid arthritis, osteoporosis, liver disease, renal disease, obsessive-compulsive disorder, statins, NSAIDs, aspirin, antihypertensive drugs, anticonvulsants, hypnotics/anxiolytics, oral contraceptives, hormone replacement therapy, antipsychotics, bisphosphonates, anticoagulants.

² Test for trend uses continuous values of dose

Table 5 Unadjusted and adjusted hazard ratios for myocardial infarction by antidepressant class, dose, and duration over 5 years follow-up.

	No of events*	Person years*	Unadjusted analysis		Adjusted analysis ¹		P
			Hazard ratio	95% CI	Hazard ratio	95% CI	
Antidepressant class							
No current use	469	570,843	1.00		1.00		
TCAs	63	41,295	1.83	(1.44 to 2.33)	1.20	(0.94 to 1.52)	0.14
SSRIs	182	225,863	1.02	(0.86 to 1.22)	0.85	(0.71 to 1.00)	0.06
Other antidepressants	33	28,144	1.39	(0.98 to 1.98)	1.00	(0.70 to 1.42)	0.98
Combined antidepressants	3	4,224	0.84	(0.27 to 2.59)	0.57	(0.18 to 1.75)	0.32
Antidepressant class and dose categories†							
No current use	469	570,843	1.00		1.00		
<i>TCAs:</i>							
≤ 0.5 DDD	31	23,555	1.59	(1.11 to 2.26)	1.02	(0.72 to 1.45)	0.89
>0.5 DDD/≤ 1.0 DDD	15	8,412	2.15	(1.31 to 3.53)	1.29	(0.78 to 2.13)	0.32
> 1.0 DDD	10	5,318	2.24	(1.21 to 4.16)	1.59	(0.86 to 2.97)	0.14
Test for trend ²							0.35
<i>SSRIs:</i>							
≤ 0.5 DDD	14	16,132	1.12	(0.68 to 1.86)	0.97	(0.57 to 1.63)	0.90
>0.5 DDD/≤ 1.0 DDD	110	158,252	0.89	(0.72 to 1.11)	0.73	(0.59 to 0.91)	0.005
> 1.0 DDD	50	42,683	1.46	(1.11 to 1.92)	1.16	(0.88 to 1.54)	0.30
Test for trend ²							0.03
<i>Others:</i>							
≤ 0.5 DDD	9	4,041	2.65	(1.38 to 5.10)	1.80	(0.94 to 3.45)	0.08
>0.5 DDD/≤ 1.0 DDD	8	13,236	0.72	(0.36 to 1.43)	0.51	(0.26 to 1.02)	0.06
> 1.0 DDD	11	8,440	1.54	(0.86 to 2.78)	1.11	(0.61 to 2.00)	0.74
Test for trend ²							0.79
Antidepressant class by time since starting and stopping treatment							
No current or recent use	416	512,509	1.00		1.00		
<i>TCAs:</i>							
first 28 days	6	5,499	1.08	(0.48 to 2.44)	0.83	(0.37 to 1.86)	0.65
29-84 days after starting	5	5,414	1.05	(0.44 to 2.51)	0.77	(0.32 to 1.83)	0.55
≥85 days after starting	33	18,957	2.17	(1.56 to 3.00)	1.23	(0.89 to 1.71)	0.21
1-28 days after stopping	5	3,627	1.60	(0.66 to 3.86)	1.30	(0.54 to 3.12)	0.56
29-84 days after stopping	13	7,056	2.32	(1.32 to 4.06)	1.85	(1.05 to 3.23)	0.03
85-182 days after stopping	20	10,753	2.36	(1.47 to 3.78)	1.89	(1.18 to 3.02)	0.008
<i>SSRIs:</i>							
first 28 days	14	20,710	0.66	(0.35 to 1.25)	0.63	(0.32 to 1.22)	0.17
29-84 days after starting	14	27,967	0.59	(0.34 to 1.02)	0.56	(0.31 to 0.99)	0.05
≥85 days after starting	109	127,711	1.12	(0.91 to 1.38)	0.84	(0.68 to 1.03)	0.10
1-28 days after stopping	20	15,744	1.64	(1.04 to 2.60)	1.66	(1.05 to 2.63)	0.03
29-84 days after stopping	22	30,521	0.96	(0.61 to 1.49)	1.00	(0.64 to 1.58)	0.98
85-182 days after stopping	33	47,004	0.95	(0.65 to 1.38)	0.99	(0.67 to 1.45)	0.95
<i>Others:</i>							
first 28 days	5	2,788	1.91	(0.76 to 4.84)	1.52	(0.60 to 3.82)	0.37
29-84 days after starting	2	3,514	0.67	(0.17 to 2.66)	0.53	(0.13 to 2.08)	0.36
≥85 days after starting	20	16,908	1.44	(0.90 to 2.29)	0.96	(0.60 to 1.53)	0.87
1-28 days after stopping	1	1,580	0.75	(0.11 to 5.35)	0.64	(0.09 to 4.54)	0.65
29-84 days after stopping	4	3,036	1.64	(0.62 to 4.37)	1.38	(0.52 to 3.67)	0.52
85-182 days after stopping	5	4,557	1.37	(0.56 to 3.33)	1.17	(0.48 to 2.85)	0.72

* Based on numbers in adjusted analysis

† Daily doses could not be evaluated for some prescriptions

1 SSRIs=selective serotonin reuptake inhibitors; TCAs=tricyclic and related antidepressants.

2 DDD= defined daily dose

3 ¹ Adjusted for age, sex, year of diagnosis of depression, severity of depression, deprivation, smoking status, alcohol intake, ethnic
4 group (white/not recorded or non-white), coronary heart disease, diabetes, hypertension, cancer, epilepsy/seizures,
5 hypothyroidism, osteoarthritis, asthma/chronic obstructive airways disease, stroke/TIA, rheumatoid arthritis, osteoporosis, liver
6 disease, renal disease, obsessive-compulsive disorder, statins, NSAIDs, aspirin, antihypertensive drugs, anticonvulsants,
7 hypnotics/anxiolytics, oral contraceptives, hormone replacement therapy, antipsychotics, bisphosphonates, anticoagulants
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9 ² Test for trend uses continuous values of dose

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Table 6 Unadjusted and adjusted hazard ratios for stroke or transient ischaemic attack by antidepressant class, dose, and duration over 5 years follow-up.

	No of events*	Person-years*	Unadjusted analysis		Adjusted analysis		P
			Hazard ratio	95% CI	Hazard ratio	95% CI	
Antidepressant class							
No current use	610	570,879	1.00		1.00		
TCA's	90	41,109	1.98	(1.56 to 2.52)	1.24	(0.98 to 1.58)	0.08
SSRIs	313	225,600	1.30	(1.12 to 1.51)	1.09	(0.93 to 1.27)	0.28
Other antidepressants	50	28,056	1.71	(1.30 to 2.25)	1.20	(0.91 to 1.60)	0.20
Combined antidepressants	11	4,196	2.59	(1.47 to 4.55)	1.54	(0.86 to 2.78)	0.15
Antidepressant class and dose categories†							
No current use	610	570,879	1.00		1.00		
<i>TCA's:</i>							
≤ 0.5 DDD	48	23,489	1.85	(1.36 to 2.50)	1.10	(0.81 to 1.49)	0.54
>0.5 DDD/≤ 1.0 DDD	24	8,362	2.62	(1.76 to 3.88)	1.59	(1.06 to 2.37)	0.02
> 1.0 DDD	12	5,265	2.06	(1.13 to 3.76)	1.52	(0.84 to 2.76)	0.17
Test for trend ²							0.27
<i>SSRIs:</i>							
≤ 0.5 DDD	24	16,083	1.37	(0.88 to 2.11)	1.12	(0.72 to 1.73)	0.61
>0.5 DDD/≤ 1.0 DDD	216	158,042	1.28	(1.09 to 1.52)	1.06	(0.90 to 1.26)	0.47
> 1.0 DDD	66	42,676	1.44	(1.12 to 1.87)	1.22	(0.94 to 1.59)	0.14
Test for trend ²							0.57
<i>Others:</i>							
≤ 0.5 DDD	10	4,017	2.25	(1.21 to 4.17)	1.54	(0.83 to 2.86)	0.17
>0.5 DDD/≤ 1.0 DDD	20	13,197	1.51	(0.99 to 2.29)	1.01	(0.65 to 1.57)	0.95
> 1.0 DDD	13	8,418	1.40	(0.82 to 2.38)	1.10	(0.65 to 1.87)	0.72
Test for trend ²							0.25
Antidepressant class by time since starting and stopping treatment							
No current or recent use	528	512,603	1.00		1.00		
<i>TCA's:</i>							
first 28 days	14	5,474	2.42	(1.35 to 4.37)	1.72	(0.95 to 3.10)	0.07
29-84 days after starting	16	5,393	2.58	(1.56 to 4.26)	1.79	(1.08 to 2.97)	0.02
≥85 days after starting	43	18,843	2.23	(1.64 to 3.02)	1.22	(0.90 to 1.67)	0.20
1-28 days after stopping	7	3,619	1.78	(0.85 to 3.72)	1.37	(0.65 to 2.89)	0.40
29-84 days after stopping	10	7,040	1.35	(0.72 to 2.53)	1.04	(0.56 to 1.95)	0.90
85-182 days after stopping	24	10,726	2.31	(1.54 to 3.47)	1.82	(1.21 to 2.74)	0.004
<i>SSRIs:</i>							
first 28 days	32	20,688	1.50	(0.96 to 2.36)	1.41	(0.89 to 2.23)	0.14
29-84 days after starting	34	27,938	1.04	(0.70 to 1.54)	1.00	(0.67 to 1.50)	0.99
≥85 days after starting	183	127,522	1.46	(1.22 to 1.74)	1.10	(0.92 to 1.32)	0.30
1-28 days after stopping	22	15,737	1.36	(0.87 to 2.11)	1.43	(0.91 to 2.24)	0.12
29-84 days after stopping	38	30,508	1.21	(0.87 to 1.68)	1.32	(0.95 to 1.85)	0.10
85-182 days after stopping	55	46,983	1.30	(0.98 to 1.74)	1.35	(1.01 to 1.81)	0.04
<i>Others:</i>							
first 28 days	10	2,781	3.71	(2.04 to 6.75)	2.72	(1.45 to 5.08)	0.002
29-84 days after starting	7	3,505	1.84	(0.88 to 3.84)	1.48	(0.70 to 3.10)	0.30
≥85 days after starting	27	16,854	1.64	(1.13 to 2.39)	1.07	(0.72 to 1.58)	0.74
1-28 days after stopping	4	1,574	2.40	(0.90 to 6.37)	2.15	(0.81 to 5.70)	0.13
29-84 days after stopping	2	3,024	0.64	(0.16 to 2.53)	0.58	(0.15 to 2.28)	0.43
85-182 days after stopping	7	4,542	1.76	(0.88 to 3.52)	1.43	(0.68 to 3.00)	0.35

* Based on numbers in adjusted analysis

† Daily doses could not be evaluated for some prescriptions

SSRIs=selective serotonin reuptake inhibitors; TCAs=tricyclic and related antidepressants.

1 DDD = defined daily dose

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3 ¹ Adjusted for age, sex, year of diagnosis of depression, severity of depression, deprivation, smoking status, alcohol intake, ethnic
4 group (white/not recorded or non-white), coronary heart disease, diabetes, hypertension, cancer, epilepsy/seizures,
5 hypothyroidism, osteoarthritis, asthma/chronic obstructive airways disease, rheumatoid arthritis, osteoporosis, liver disease, renal
6 disease, obsessive-compulsive disorder, statins, NSAIDs, aspirin, antihypertensive drugs, anticonvulsants, hypnotics/anxiolytics, oral
7 contraceptives, hormone replacement therapy, antipsychotics, bisphosphonates, anticoagulants.

8 ² Test for trend uses continuous values of dose
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Table 7 Absolute risks of arrhythmia, myocardial infarction and stroke or transient ischaemic attack over one year by antidepressant class and for individual drugs.

	Absolute risks over one year (per 10,000)					
	Arrhythmia ¹		Myocardial infarction ²		Stroke/TIA ³	
	Risk per 10,000	95% CI	Risk per 10,000	95% CI	Risk per 10,000	95% CI
No treatment	14	(11 to 17)	10	(8 to 12)	13	(11 to 16)
Antidepressant class						
TCAs	16	(11 to 23)	11	(7 to 17)	13	(9 to 19)
SSRIs	12	(9 to 16)	6	(4 to 8)	11	(8 to 14)
Other antidepressants	19	(12 to 30)	8	(4 to 16)	15	(9 to 25)
Combined antidepressants	48	(17 to 133)	17	(4 to 66)	9	(1 to 64)
Antidepressant drug						
<i>TCAs:</i>						
Amitriptyline	16	(10 to 27)	8	(4 to 16)	13	(8 to 22)
Dosulepin	10	(5 to 21)	11	(5 to 22)	15	(8 to 26)
Lofepamine	30	(15 to 60)	31	(15 to 62)	15	(6 to 40)
Trazodone	24	(7 to 78)	7	(1 to 52)	7	(1 to 48)
<i>SSRIs:</i>						
Citalopram	11	(8 to 15)	6	(4 to 9)	10	(7 to 14)
Escitalopram	14	(7 to 30)	7	(2 to 18)	8	(3 to 20)
Fluoxetine	11	(8 to 16)	4	(3 to 7)	14	(10 to 19)
Paroxetine	15	(9 to 28)	4	(1 to 12)	8	(4 to 18)
Sertraline	17	(10 to 29)	12	(6 to 22)	8	(4 to 18)
<i>Others:</i>						
Mirtazapine	17	(8 to 35)	9	(4 to 22)	24	(13 to 44)
Venlafaxine	23	(12 to 43)	9	(3 to 24)	7	(2 to 20)
All other antidepressants	13	(4 to 38)	5	(1 to 33)	8	(2 to 34)

SSRIs=selective serotonin reuptake inhibitors; TCAs=tricyclic and related antidepressants.

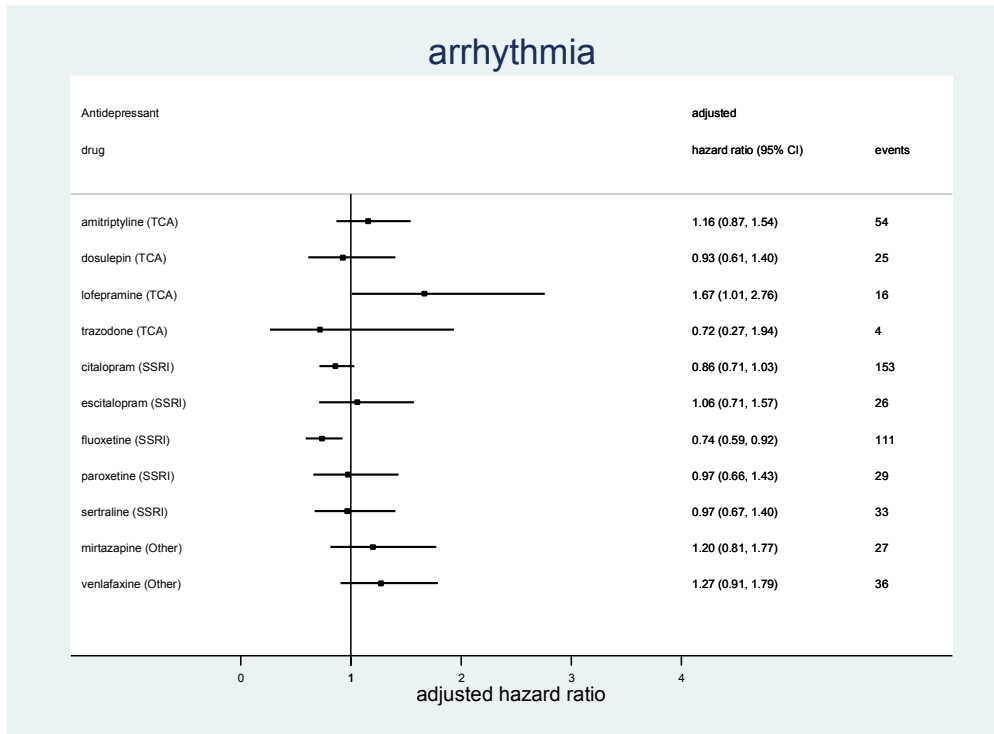
¹ Absolute risks are adjusted for confounders listed in table 2.

² Absolute risks are adjusted for confounders listed in table 5.

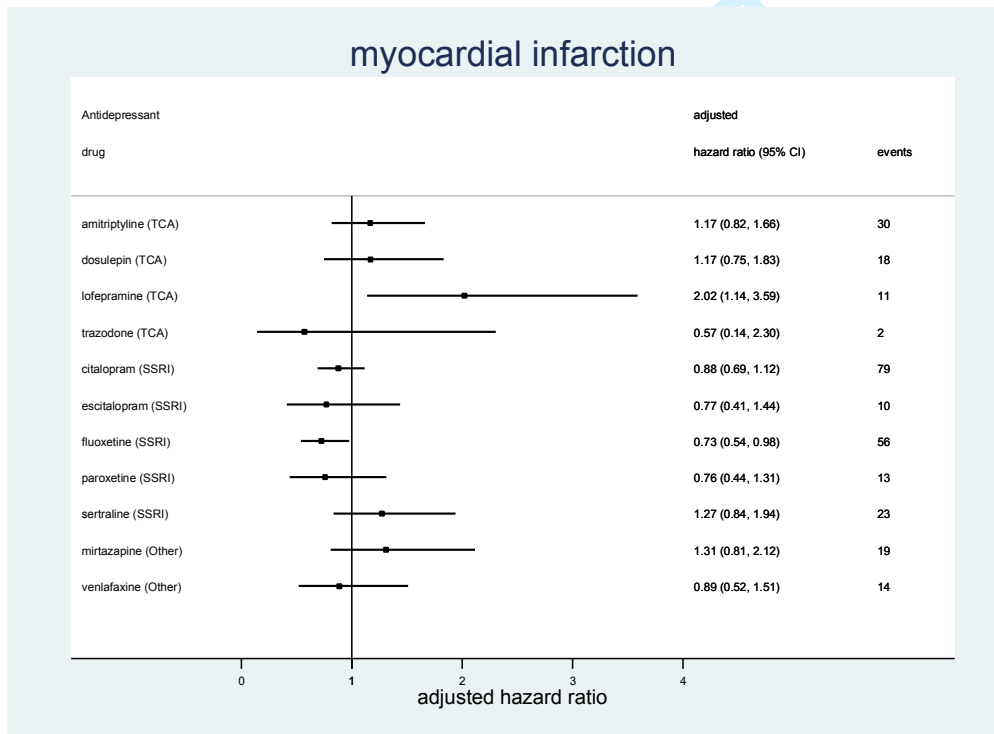
³ Absolute risks are adjusted for confounders listed in table 6.

Figure 1 Adjusted hazard ratios for (a) arrhythmia, (b) myocardial infarction, and (c) stroke or transient ischaemic attack for individual antidepressant drugs over 5 years follow-up.

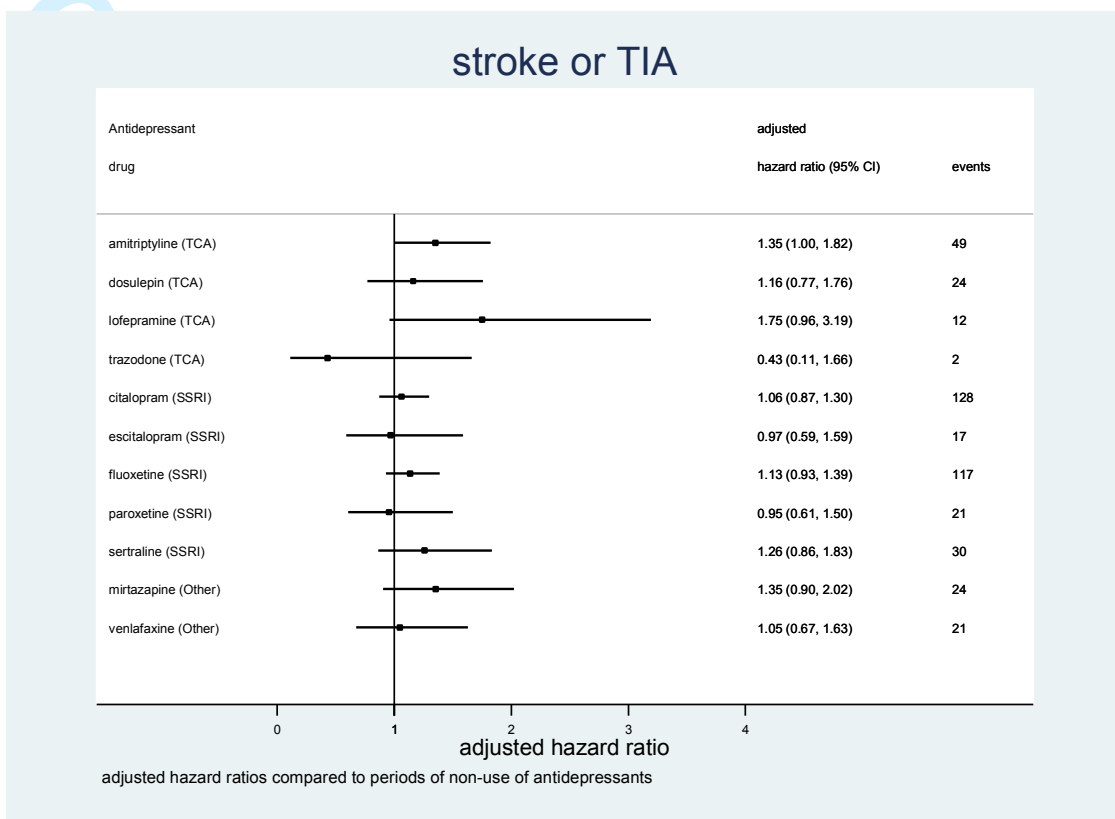
(a)



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(c)



Adjusted hazard ratios compared to periods of non-use of antidepressants

TCA = tricyclic and related antidepressant

SSRI = selective serotonin reuptake inhibitor

Review Only

Antidepressant use and risk of cardiovascular outcomes in people aged 20 to 64: cohort study using a primary care database

SUPPLEMENTARY TABLES

Table 1s	Numbers of prescriptions for different antidepressants by dose category
Table 2s	Adjusted hazard ratios for arrhythmia, myocardial infarction and stroke or transient ischaemic attack by antidepressant class, dose, and individual drug over 5 years follow-up with SSRIs as reference category for analysis of antidepressant class, mid-dose SSRIs as reference category for analysis of antidepressant dose and citalopram as reference category for analysis of individual drugs.
Table 3s	Unadjusted and adjusted hazard ratios for arrhythmia by citalopram split into 3 dose categories for 5 years follow-up.
Table 4s	Unadjusted and adjusted hazard ratios for arrhythmia by antidepressant class, dose and individual drug for 5 years follow-up, excluding untreated patients.
Table 5s	Unadjusted and adjusted hazard ratios for arrhythmia by antidepressant class, dose and individual drug for total follow-up.
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Table 7s	Adjusted hazard ratios for arrhythmia, myocardial infarction and stroke or transient ischaemic attack by individual antidepressant drug with separate hazard ratios for 0-1, 1-3 and 3-5 years of follow-up
Table 8s	Unadjusted and adjusted hazard ratios for myocardial infarction by antidepressant class, dose and individual drug for 5 years follow-up, excluding untreated patients.
Table 9s	Unadjusted and adjusted hazard ratios for myocardial infarction by antidepressant class, dose and individual drug for total follow-up.
Table 10s	Unadjusted and adjusted hazard ratios for stroke/ transient ischaemic attack by antidepressant class, dose and individual drug for 5 years follow-up, excluding untreated patients.
Table 11s	Unadjusted and adjusted hazard ratios for stroke/ transient ischaemic attack by antidepressant class, dose and individual drug for total follow-up.
Table 12s	Adjusted hazard ratios for arrhythmia by antidepressant class, and individual drug over 5 years adjusting for different subsets of confounders in blocks
Table 13s	Adjusted hazard ratios for myocardial infarction by antidepressant class, and individual drug over 5 years adjusting for different subsets of confounders in blocks
Table 14s	Adjusted hazard ratios for stroke/ transient ischaemic attack by antidepressant class, and individual drug over 5 years adjusting for different subsets of confounders in blocks

Table 1s Numbers of prescriptions for different antidepressant drugs by dose category

Antidepressant drug	n ¹	% ²	DDD value (mg/day)	Actual dose prescribed (mg/day) ³	
				Median	IQR
<i>Tricyclic and related antidepressants (TCA)</i>					
Amitriptyline	236,416	7.3	75	25	15 to 50
Dosulepin	125,302	3.9	150	75	50 to 150
Lofepamine	47,414	1.5	105	140	140 to 210
Trazodone	30,912	1.0	300	125	75 to 150
<i>Selective serotonin reuptake inhibitors (SSRI)</i>					
Citalopram	1,023,255	31.5	20	20	20 to 20
Escitalopram	139,190	4.3	10	10	10 to 20
Fluoxetine	778,285	23.9	20	20	20 to 20
Paroxetine	159,389	4.9	20	20	20 to 30
Sertraline	213,749	6.6	50	50	50 to 100
<i>Other antidepressants</i>					
Mirtazapine	142,400	4.4	30	30	15 to 45
Venlafaxine	205,984	6.3	100	112.5	75 to 150
All other antidepressants	66,553	2.0	-		
Combined antidepressants ⁴	83,784	2.6	-		
Total prescriptions	3,252,633				

¹ Number of prescriptions, where prescriptions for the same drug issued on the same day count as a single prescription and the doses have been summed.

² Percentage out of total number of prescriptions= 3,252,633

³ 5.0% of prescriptions had missing information on dosage.

⁴ Combined prescriptions for different antidepressant drugs are considered as a single prescription in this table.

DDD = defined daily dose value for the antidepressant drug

Table 2s Adjusted hazard ratios for arrhythmia, myocardial infarction and stroke or transient ischaemic attack by antidepressant class, dose, and individual drug over 5 years follow-up with SSRIs as reference category for analysis of antidepressant class, mid-dose SSRIs as reference category for analysis of antidepressant dose and citalopram as reference category for analysis of individual drugs

	Arrhythmia			Myocardial infarction			Stroke/TIA		
	Adjusted hazard ratio ¹	95% CI	P value	Adjusted hazard ratio ¹	95% CI	P value	Adjusted hazard ratio ¹	95% CI	P value
Antidepressant class									
SSRIs	1.00			1.00			1.00		
TCAs	1.29	(1.03 to 1.61)	0.03	1.42	(1.08 to 1.86)	0.012	1.14	(0.89 to 1.46)	0.28
Other antidepressants	1.44	(1.12 to 1.85)	0.005	1.18	(0.81 to 1.71)	0.39	1.11	(0.82 to 1.49)	0.51
Combined antidepressants	1.26	(0.64 to 2.51)	0.51	0.67	(0.21 to 2.11)	0.49	1.42	(0.78 to 2.59)	0.25
No current use	1.18	(1.03 to 1.37)	0.02	1.18	(1.00 to 1.41)	0.06	0.92	(0.79 to 1.07)	0.28
Antidepressant class and dose categories									
<i>SSRIs:</i>									
≤ 0.5 DDD	1.17	(0.80 to 1.73)	0.42	1.32	(0.76 to 2.29)	0.32	1.05	(0.68 to 1.63)	0.81
>0.5 DDD/≤ 1.0 DDD	1.00			1.00			1.00		
> 1.0 DDD	1.24	(0.93 to 1.64)	0.14	1.59	(1.13 to 2.22)	0.008	1.15	(0.87 to 1.51)	0.32
<i>TCAs:</i>									
≤ 0.5 DDD	1.13	(0.83 to 1.53)	0.46	1.40	(0.95 to 2.07)	0.09	1.04	(0.76 to 1.42)	0.83
>0.5 DDD/≤ 1.0 DDD	1.70	(1.13 to 2.54)	0.010	1.76	(1.05 to 2.94)	0.03	1.49	(1.00 to 2.24)	0.05
> 1.0 DDD	1.66	(0.97 to 2.86)	0.07	2.18	(1.15 to 4.14)	0.02	1.43	(0.78 to 2.62)	0.25
<i>Others:</i>									
≤ 0.5 DDD	1.23	(0.65 to 2.35)	0.52	2.46	(1.24 to 4.87)	0.010	1.45	(0.77 to 2.72)	0.25
>0.5 DDD/≤ 1.0 DDD	1.46	(1.01 to 2.12)	0.04	0.70	(0.34 to 1.43)	0.33	0.95	(0.61 to 1.50)	0.84
> 1.0 DDD	1.62	(1.04 to 2.52)	0.03	1.51	(0.83 to 2.76)	0.18	1.04	(0.60 to 1.78)	0.90
No current use	1.26	(1.06 to 1.49)	0.007	1.37	(1.10 to 1.69)	0.005	0.94	(0.80 to 1.11)	0.47
Antidepressant drug									
<i>SSRIs:</i>									
Citalopram	1.00			1.00			1.00		
Escitalopram	1.23	(0.80 to 1.89)	0.34	0.88	(0.46 to 1.69)	0.69	0.91	(0.55 to 1.50)	0.71
Fluoxetine	0.86	(0.67 to 1.11)	0.25	0.83	(0.58 to 1.17)	0.29	1.07	(0.84 to 1.35)	0.59
Paroxetine	1.13	(0.74 to 1.73)	0.56	0.86	(0.48 to 1.55)	0.62	0.90	(0.55 to 1.46)	0.66

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4	Sertraline	1.13	(0.77 to 1.66)	0.53	1.45	(0.89 to 2.37)	0.14	1.18	(0.80 to 1.75)	0.41
5	TCA:									
6	Amitriptyline	1.35	(0.99 to 1.84)	0.06	1.33	(0.88 to 2.00)	0.17	1.27	(0.91 to 1.77)	0.16
7	Dosulepin	1.08	(0.70 to 1.68)	0.73	1.33	(0.79 to 2.24)	0.28	1.09	(0.71 to 1.69)	0.69
8	Lofepamine	1.94	(1.16 to 3.27)	0.012	2.30	(1.24 to 4.25)	0.008	1.65	(0.88 to 3.09)	0.12
9	Trazodone	0.84	(0.30 to 2.30)	0.73	0.65	(0.16 to 2.73)	0.56	0.40	(0.10 to 1.57)	0.19
10	Others:									
11	Mirtazapine	1.40	(0.92 to 2.12)	0.11	1.49	(0.90 to 2.48)	0.12	1.27	(0.81 to 1.99)	0.29
12	Venlafaxine	1.48	(1.03 to 2.13)	0.03	1.01	(0.57 to 1.79)	0.98	0.99	(0.61 to 1.59)	0.95
13										
14	All other antidepressants	0.85	(0.41 to 1.76)	0.67	0.59	(0.19 to 1.89)	0.38	0.94	(0.46 to 1.94)	0.88
15	Combined antidepressants	1.24	(0.62 to 2.48)	0.54	0.64	(0.20 to 2.06)	0.46	1.45	(0.79 to 2.66)	0.23
16	No current use	1.17	(0.97 to 1.40)	0.11	1.14	(0.9 to 1.45)	0.29	0.94	(0.77 to 1.15)	0.55

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SSRIs=selective serotonin reuptake inhibitors; TCAs=tricyclic and related antidepressants.

¹ Adjusted for age, sex, year of diagnosis of depression, severity of depression, deprivation, smoking status, alcohol intake, ethnic group (white/not recorded or non-white), coronary heart disease, diabetes, hypertension, cancer, epilepsy/seizures, hypothyroidism, osteoarthritis, asthma/chronic obstructive airways disease, stroke/TIA (except for the stroke/TIA outcome), rheumatoid arthritis, osteoporosis, liver disease, renal disease, obsessive-compulsive disorder, statins, NSAIDs, aspirin, antihypertensive drugs, anticonvulsants, hypnotics/anxiolytics, oral contraceptives, hormone replacement therapy, antipsychotics, bisphosphonates, anticoagulants.

Table 3s. Unadjusted and adjusted hazard ratios for arrhythmia over 5 years follow-up with citalopram dose categorised into three categories

Daily dose of citalopram	No of events*	Person years*	Unadjusted			Adjusted analysis ¹		
			HR	95% CI	P	HR	95% CI	P
No current use	887	568,365	1.00			1.00		
Citalopram: ≤20 mg/day	115	72,340	1.05	(0.86 to 1.28)	0.65	0.82	(0.67 to 1.01)	0.07
Citalopram: 20-39 mg/day	6	3,947	0.99	(0.45 to 2.19)	0.99	0.93	(0.42 to 2.06)	0.87
Citalopram: ≥40 mg/day	28	13,907	1.35	(0.89 to 2.05)	0.16	1.11	(0.72 to 1.71)	0.62

* Based on numbers in adjusted analysis

¹ Adjusted for age, sex, year of diagnosis of depression, severity of depression, deprivation, smoking status, alcohol intake, ethnic group (white/not recorded; non-white), coronary heart disease, diabetes, hypertension, cancer, epilepsy/seizures, hypothyroidism, osteoarthritis, asthma/chronic obstructive airways disease, stroke/TIA, rheumatoid arthritis, osteoporosis, liver disease, renal disease, obsessive-compulsive disorder, statins, NSAIDs, aspirin, antihypertensive drugs, anticonvulsants, hypnotics/anxiolytics, oral contraceptives, hormone replacement therapy, antipsychotics, bisphosphonates, anticoagulants.

Table 4s Unadjusted and adjusted hazard ratios for arrhythmia by antidepressant class, dose and individual drug for 5 years follow-up, excluding untreated patients

	Unadjusted analysis				Adjusted analysis ¹		
	No of events*	HR	95% CI	P	HR	95% CI	P
Antidepressant class							
No current use	731	1.00			1.00		
TCAs	102	1.59	(1.28 to 1.97)	<0.001	1.08	(0.86 to 1.34)	0.52
SSRIs	352	1.02	(0.88 to 1.18)	0.80	0.83	(0.71 to 0.96)	0.012
Other antidepressants	68	1.55	(1.23 to 1.96)	<0.001	1.21	(0.95 to 1.53)	0.12
Combined antidepressants	10	1.49	(0.76 to 2.91)	0.25	1.07	(0.55 to 2.08)	0.85
Antidepressant class and dose categories							
No current use	731	1.00			1.00		
<i>TCAs:</i>							
≤ 0.5 DDD	51	1.36	(1.02 to 1.82)	0.04	0.88	(0.66 to 1.18)	0.39
>0.5 DDD/≤ 1.0 DDD	26	2.03	(1.38 to 2.97)	<0.001	1.34	(0.90 to 1.99)	0.15
> 1.0 DDD	14	1.66	(0.98 to 2.81)	0.06	1.31	(0.76 to 2.25)	0.33
<i>SSRIs:</i>							
≤ 0.5 DDD	30	1.18	(0.81 to 1.71)	0.38	0.91	(0.62 to 1.32)	0.62
>0.5 DDD/≤ 1.0 DDD	236	0.96	(0.8 to 1.14)	0.63	0.77	(0.65 to 0.92)	0.004
> 1.0 DDD	75	1.17	(0.91 to 1.5)	0.22	0.97	(0.75 to 1.25)	0.80
<i>Others:</i>							
≤ 0.5 DDD	9	1.40	(0.74 to 2.64)	0.31	0.96	(0.51 to 1.82)	0.90
>0.5 DDD/≤ 1.0 DDD	31	1.52	(1.08 to 2.15)	0.02	1.15	(0.81 to 1.64)	0.44
> 1.0 DDD	20	1.50	(0.98 to 2.31)	0.06	1.28	(0.84 to 1.97)	0.25
Antidepressant drug							
No current use	731	1.00			1.00		
<i>TCAs:</i>							
Amitriptyline	54	1.75	(1.32 to 2.33)	<0.001	1.15	(0.86 to 1.53)	0.35
Dosulepin	25	1.31	(0.86 to 1.98)	0.21	0.92	(0.60 to 1.39)	0.68
Lofepramine	16	2.09	(1.27 to 3.45)	0.004	1.65	(0.99 to 2.74)	0.053
Trazodone	4	1.33	(0.55 to 3.21)	0.53	0.71	(0.26 to 1.93)	0.50
<i>SSRIs:</i>							
Citalopram	153	1.07	(0.89 to 1.29)	0.47	0.84	(0.69 to 1.01)	0.07
Escitalopram	26	1.33	(0.91 to 1.94)	0.15	1.04	(0.69 to 1.55)	0.86
Fluoxetine	111	0.86	(0.68 to 1.08)	0.20	0.72	(0.57 to 0.91)	0.005
Paroxetine	29	1.12	(0.76 to 1.65)	0.56	0.96	(0.65 to 1.42)	0.84
Sertraline	33	1.15	(0.8 to 1.66)	0.45	0.95	(0.65 to 1.38)	0.79
<i>Others:</i>							
Mirtazapine	27	1.74	(1.19 to 2.53)	0.004	1.19	(0.81 to 1.76)	0.37
Venlafaxine	36	1.46	(1.04 to 2.05)	0.03	1.27	(0.90 to 1.78)	0.18
All other antidepressants	8	1.02	(0.51 to 2.03)	0.96	0.72	(0.36 to 1.44)	0.36
Combined antidepressants	10	1.49	(0.76 to 2.9)	0.25	1.06	(0.54 to 2.08)	0.85

* Based on numbers in adjusted analysis

DDD= defined daily dose

¹ Adjusted for age, sex, year of diagnosis of depression, severity of depression, deprivation, smoking status, alcohol intake, ethnic group (white/not recorded or non-white), coronary heart disease, diabetes, hypertension, cancer, epilepsy/seizures, hypothyroidism, osteoarthritis, asthma/chronic obstructive airways disease, stroke/TIA, rheumatoid arthritis, osteoporosis, liver disease, renal disease, obsessive-compulsive disorder, statins, NSAIDs, aspirin, antihypertensive drugs, anticonvulsants, hypnotics/anxiolytics, oral contraceptives, hormone replacement therapy, antipsychotics, bisphosphonates, anticoagulants.

Table 5s Unadjusted and adjusted hazard ratios for arrhythmia by antidepressant class, dose and individual drug for total follow-up period

	No of events*	Unadjusted analysis			Adjusted analysis ¹		
		HR	95% CI	P	HR	95% CI	P
Antidepressant class							
No current use	1517	1.00			1.00		
TCA's	165	1.60	(1.37 to 1.88)	<0.001	1.10	(0.93 to 1.30)	0.25
SSRIs	462	0.93	(0.83 to 1.05)	0.24	0.79	(0.71 to 0.89)	<0.001
Other antidepressants	104	1.48	(1.23 to 1.79)	<0.001	1.21	(1.00 to 1.46)	0.052
Combined antidepressants	17	1.26	(0.77 to 2.05)	0.35	0.94	(0.58 to 1.54)	0.82
Antidepressant class and dose categories							
No current use	1517	1.00			1.00		
<i>TCA's:</i>							
≤ 0.5 DDD	85	1.40	(1.12 to 1.73)	0.003	0.92	(0.74 to 1.15)	0.48
>0.5 DDD/≤ 1.0 DDD	42	2.03	(1.51 to 2.73)	<0.001	1.37	(1.01 to 1.85)	0.045
> 1.0 DDD	22	1.79	(1.18 to 2.71)	0.006	1.43	(0.93 to 2.20)	0.11
<i>SSRIs:</i>							
≤ 0.5 DDD	41	1.11	(0.82 to 1.5)	0.52	0.88	(0.65 to 1.19)	0.41
>0.5 DDD/≤ 1.0 DDD	297	0.88	(0.77 to 1.01)	0.07	0.74	(0.64 to 0.85)	<0.001
> 1.0 DDD	107	1.02	(0.83 to 1.25)	0.87	0.90	(0.73 to 1.11)	0.33
<i>Others:</i>							
≤ 0.5 DDD	11	1.03	(0.58 to 1.82)	0.92	0.77	(0.44 to 1.37)	0.38
>0.5 DDD/≤ 1.0 DDD	47	1.50	(1.12 to 2.00)	0.006	1.18	(0.87 to 1.59)	0.28
> 1.0 DDD	36	1.57	(1.14 to 2.18)	0.006	1.40	(1.02 to 1.93)	0.037
Antidepressant drug							
No current use	1517	1.00			1.00		
<i>TCA's:</i>							
Amitriptyline	92	1.67	(1.35 to 2.05)	<0.001	1.14	(0.92 to 1.41)	0.24
Dosulepin	33	1.28	(0.90 to 1.82)	0.17	0.89	(0.63 to 1.27)	0.53
Lofepramine	24	2.42	(1.62 to 3.61)	<0.001	1.95	(1.31 to 2.88)	0.001
Trazodone	10	1.74	(0.95 to 3.18)	0.07	1.11	(0.59 to 2.08)	0.74
<i>SSRIs:</i>							
Citalopram	204	0.96	(0.82 to 1.13)	0.65	0.80	(0.68 to 0.94)	0.008
Escitalopram	32	1.13	(0.79 to 1.62)	0.49	0.92	(0.63 to 1.32)	0.64
Fluoxetine	143	0.82	(0.68 to 0.98)	0.03	0.72	(0.60 to 0.86)	<0.001
Paroxetine	36	1.02	(0.72 to 1.45)	0.90	0.87	(0.61 to 1.24)	0.44
Sertraline	47	1.05	(0.78 to 1.41)	0.74	0.91	(0.67 to 1.23)	0.54
<i>Others:</i>							
Mirtazapine	42	1.61	(1.20 to 2.15)	0.001	1.20	(0.89 to 1.62)	0.23
Venlafaxine	53	1.40	(1.07 to 1.83)	0.013	1.24	(0.95 to 1.62)	0.12
All other antidepressants	15	1.14	(0.69 to 1.87)	0.60	0.74	(0.43 to 1.26)	0.27
Combined antidepressants	17	1.26	(0.77 to 2.05)	0.35	0.94	(0.58 to 1.54)	0.81

* Based on numbers in adjusted analysis

DDD= defined daily dose

¹ Adjusted for age, sex, year of diagnosis of depression, severity of depression, deprivation, smoking status, alcohol intake, ethnic group (white/not recorded or non-white), coronary heart disease, diabetes, hypertension, cancer, epilepsy/seizures, hypothyroidism, osteoarthritis, asthma/chronic obstructive airways disease, stroke/TIA, rheumatoid arthritis, osteoporosis, liver disease, renal disease, obsessive-compulsive disorder, statins, NSAIDs, aspirin, antihypertensive drugs, anticonvulsants, hypnotics/anxiolytics, oral contraceptives, hormone replacement therapy, antipsychotics, bisphosphonates, anticoagulants.

Table 6s Adjusted hazard ratios for arrhythmia, myocardial infarction and stroke or transient ischaemic attack by antidepressant class split over years 0-1, 1-3, and 3-5 years of follow-up

Drug class by year of follow-up	Arrhythmia			Myocardial infarction			Stroke/TIA		
	Adjusted hazard ratio ¹	95% CI	P	Adjusted hazard ratio ¹	95% CI	P	Adjusted hazard ratio ¹	95% CI	P
<i>TCAs:</i>									
0-1 years	1.16	(0.81 to 1.66)	0.42	1.07	(0.71 to 1.62)	0.73	1.03	(0.70 to 1.51)	0.90
1-3 years	1.23	(0.89 to 1.70)	0.21	1.24	(0.82 to 1.88)	0.30	1.08	(0.72 to 1.62)	0.70
3-5 years	0.85	(0.56 to 1.27)	0.42	1.12	(0.68 to 1.85)	0.64	1.62	(1.10 to 2.37)	0.014
<i>SSRIs:</i>									
0-1 years	0.85	(0.66 to 1.10)	0.21	0.59	(0.43 to 0.81)	0.001	0.84	(0.64 to 1.10)	0.21
1-3 years	0.90	(0.73 to 1.10)	0.31	0.88	(0.68 to 1.15)	0.36	1.09	(0.87 to 1.37)	0.45
3-5 years	0.79	(0.62 to 1.00)	0.052	1.14	(0.83 to 1.57)	0.41	1.37	(1.06 to 1.75)	0.014
<i>Others:</i>									
0-1 years	1.36	(0.86 to 2.15)	0.19	0.82	(0.43 to 1.58)	0.55	1.18	(0.71 to 1.95)	0.53
1-3 years	1.09	(0.73 to 1.61)	0.68	0.97	(0.56 to 1.69)	0.91	1.37	(0.90 to 2.08)	0.15
3-5 years	1.28	(0.83 to 1.98)	0.27	1.14	(0.62 to 2.10)	0.68	0.90	(0.50 to 1.62)	0.72

SSRIs=selective serotonin reuptake inhibitors; TCAs=tricyclic and related antidepressants.

¹ Adjusted for age, sex, year of diagnosis of depression, severity of depression, deprivation, smoking status, alcohol intake, ethnic group (white/not recorded or non-white), coronary heart disease, diabetes, hypertension, cancer, epilepsy/seizures, hypothyroidism, osteoarthritis, asthma/chronic obstructive airways disease, stroke/TIA (except for the stroke/TIA outcome), rheumatoid arthritis, osteoporosis, liver disease, renal disease, obsessive-compulsive disorder, statins, NSAIDs, aspirin, antihypertensive drugs, anticonvulsants, hypnotics/anxiolytics, oral contraceptives, hormone replacement therapy, antipsychotics, bisphosphonates, anticoagulants. Model also included terms for combined antidepressant treatment.

Reference group is no current use of antidepressants in each specific time interval.

Table 7s Adjusted hazard ratios for arrhythmia, myocardial infarction and stroke or transient ischaemic attack for five antidepressant drugs split over years 0-1, 1-3, and 3-5 years of follow-up

Drug by year of follow-up	Arrhythmia			Myocardial infarction			Stroke/TIA		
	Adjusted hazard ratio ¹	95% CI	P	Adjusted hazard ratio ¹	95% CI	P	Adjusted hazard ratio ¹	95% CI	P
<i>Amitriptyline</i>									
0-1 years	1.19	(0.71 to 2.00)	0.50	0.77	(0.37 to 1.56)	0.46	1.02	(0.59 to 1.74)	0.95
1-3 years	1.31	(0.85 to 2.02)	0.22	1.90	(1.18 to 3.06)	0.009	1.29	(0.78 to 2.13)	0.31
3-5 years	0.98	(0.59 to 1.62)	0.94	0.68	(0.29 to 1.60)	0.38	1.70	(1.03 to 2.80)	0.037
<i>Citalopram</i>									
0-1 years	0.81	(0.58 to 1.12)	0.20	0.62	(0.40 to 0.96)	0.030	0.75	(0.52 to 1.07)	0.12
1-3 years	1.07	(0.83 to 1.39)	0.60	0.78	(0.52 to 1.18)	0.24	1.00	(0.73 to 1.37)	0.98
3-5 years	0.66	(0.46 to 0.97)	0.032	1.37	(0.91 to 2.04)	0.13	1.57	(1.14 to 2.17)	0.006
<i>Fluoxetine</i>									
0-1 years	0.77	(0.54 to 1.09)	0.14	0.44	(0.27 to 0.73)	0.001	1.06	(0.75 to 1.48)	0.75
1-3 years	0.70	(0.50 to 0.99)	0.046	0.98	(0.66 to 1.48)	0.94	1.09	(0.79 to 1.50)	0.61
3-5 years	0.78	(0.53 to 1.16)	0.22	0.79	(0.43 to 1.46)	0.46	1.08	(0.69 to 1.69)	0.75
<i>Sertraline</i>									
0-1 years	1.23	(0.72 to 2.08)	0.45	1.22	(0.66 to 2.25)	0.54	0.65	(0.31 to 1.39)	0.27
1-3 years	0.80	(0.43 to 1.49)	0.49	0.90	(0.41 to 1.98)	0.80	1.60	(0.94 to 2.73)	0.08
3-5 years	0.89	(0.44 to 1.80)	0.74	1.70	(0.79 to 3.65)	0.17	1.61	(0.84 to 3.11)	0.15
<i>Venlafaxine</i>									
0-1 years	1.61	(0.87 to 2.98)	0.13	0.84	(0.32 to 2.23)	0.73	0.50	(0.16 to 1.55)	0.23
1-3 years	1.06	(0.63 to 1.81)	0.82	0.59	(0.22 to 1.61)	0.31	1.29	(0.72 to 2.33)	0.39
3-5 years	1.32	(0.76 to 2.31)	0.32	1.30	(0.57 to 2.93)	0.53	1.18	(0.57 to 2.47)	0.66
<i>All others (including combined)</i>									
0-1 years	1.16	(0.85 to 1.57)	0.35	0.92	(0.62 to 1.35)	0.66	0.97	(0.68 to 1.38)	0.86
1-3 years	1.00	(0.75 to 1.34)	0.98	0.89	(0.59 to 1.32)	0.56	1.18	(0.84 to 1.64)	0.34
3-5 years	0.98	(0.69 to 1.39)	0.90	1.08	(0.68 to 1.72)	0.75	1.17	(0.79 to 1.74)	0.42

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4 ¹ Adjusted for age, sex, year of diagnosis of depression, severity of depression, deprivation, smoking status, alcohol intake, ethnic group (white/not recorded or non-white), coronary heart disease,
5 diabetes, hypertension, cancer, epilepsy/seizures, hypothyroidism, osteoarthritis, asthma/chronic obstructive airways disease, stroke/TIA (except for the stroke/TIA outcome), rheumatoid arthritis,
6 osteoporosis, liver disease, renal disease, obsessive-compulsive disorder, statins, NSAIDs, aspirin, antihypertensive drugs, anticonvulsants, hypnotics/anxiolytics, oral contraceptives, hormone
7 replacement therapy, antipsychotics, bisphosphonates, anticoagulants.

8 Reference group is no current use of antidepressants in each specific time interval.
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Table 8s Unadjusted and adjusted hazard ratios for myocardial infarction by antidepressant class, dose and individual drug for 5 years follow-up, excluding untreated patients

	No of events*	Unadjusted analysis			Adjusted analysis ¹		
		HR	95% CI	P	HR	95% CI	P
Antidepressant class							
No current use	397	1.00			1.00		
TCAs	63	1.83	(1.43 to 2.35)	<0.001	1.19	(0.93 to 1.52)	0.16
SSRIs	182	1.02	(0.86 to 1.23)	0.79	0.84	(0.70 to 1.00)	0.051
Other antidepressants	33	1.38	(0.97 to 1.98)	0.08	0.98	(0.68 to 1.40)	0.89
Combined antidepressants	3	0.83	(0.27 to 2.55)	0.75	0.56	(0.18 to 1.72)	0.31
Antidepressant class and dose categories							
No current use	397	1.00			1.00		
<i>TCAs:</i>							
≤ 0.5 DDD	31	1.60	(1.12 to 2.28)	0.010	1.02	(0.72 to 1.46)	0.89
>0.5 DDD/≤ 1.0 DDD	15	2.14	(1.3 to 3.52)	0.003	1.28	(0.77 to 2.11)	0.34
> 1.0 DDD	10	2.24	(1.2 to 4.17)	0.011	1.57	(0.84 to 2.94)	0.15
<i>SSRIs:</i>							
≤ 0.5 DDD	14	1.13	(0.68 to 1.86)	0.64	0.96	(0.57 to 1.61)	0.87
>0.5 DDD/≤ 1.0 DDD	110	0.90	(0.72 to 1.12)	0.34	0.73	(0.58 to 0.91)	0.005
> 1.0 DDD	50	1.45	(1.09 to 1.91)	0.010	1.14	(0.85 to 1.52)	0.39
<i>Others:</i>							
≤ 0.5 DDD	9	2.64	(1.37 to 5.1)	0.004	1.77	(0.91 to 3.43)	0.09
>0.5 DDD/≤ 1.0 DDD	8	0.71	(0.36 to 1.42)	0.34	0.50	(0.25 to 1.01)	0.052
> 1.0 DDD	11	1.52	(0.84 to 2.76)	0.17	1.08	(0.59 to 1.96)	0.81
Antidepressant drug							
No current use	397				1.00		
<i>TCAs:</i>							
Amitriptyline	30	1.84	(1.28 to 2.63)	0.001	1.16	(0.81 to 1.66)	0.41
Dosulepin	18	1.80	(1.14 to 2.83)	0.011	1.16	(0.74 to 1.83)	0.51
Lofepamine	11	2.74	(1.54 to 4.86)	0.001	2.00	(1.13 to 3.56)	0.018
Trazodone	2	1.01	(0.25 to 4.05)	0.99	0.57	(0.14 to 2.29)	0.43
<i>SSRIs:</i>							
Citalopram	79	1.05	(0.82 to 1.34)	0.69	0.87	(0.68 to 1.12)	0.27
Escitalopram	10	0.89	(0.48 to 1.67)	0.72	0.76	(0.40 to 1.42)	0.38
Fluoxetine	56	0.89	(0.67 to 1.19)	0.43	0.72	(0.53 to 0.97)	0.031
Paroxetine	13	1.02	(0.60 to 1.73)	0.94	0.75	(0.43 to 1.29)	0.29
Sertraline	23	1.52	(1.00 to 2.31)	0.048	1.25	(0.82 to 1.91)	0.31
<i>Others:</i>							
Mirtazapine	19	2.20	(1.36 to 3.54)	0.001	1.29	(0.79 to 2.10)	0.30
Venlafaxine	14	1.05	(0.62 to 1.79)	0.85	0.86	(0.51 to 1.47)	0.59
All other antidepressants	3	0.72	(0.24 to 2.20)	0.57	0.51	(0.17 to 1.56)	0.24
Combined antidepressants	3	0.83	(0.27 to 2.55)	0.75	0.56	(0.18 to 1.72)	0.31

* Based on numbers in adjusted analysis

DDD= defined daily dose

¹ Adjusted for age, sex, year of diagnosis of depression, severity of depression, deprivation, smoking status, alcohol intake, ethnic group (white/not recorded or non-white), coronary heart disease, diabetes, hypertension, cancer, epilepsy/seizures, hypothyroidism, osteoarthritis, asthma/chronic obstructive airways disease, stroke/TIA, rheumatoid arthritis, osteoporosis, liver disease, renal disease, obsessive-compulsive disorder, statins, NSAIDs, aspirin, antihypertensive drugs, anticonvulsants, hypnotics/anxiolytics, oral contraceptives, hormone replacement therapy, antipsychotics, bisphosphonates, anticoagulants.

Table 9s Unadjusted and adjusted hazard ratios for myocardial infarction by antidepressant class, dose and individual drug for total follow-up period

	No of events*	Unadjusted analysis			Adjusted analysis ¹		
		HR	95% CI	P	HR	95% CI	P
Antidepressant class							
No current use	783	1.00			1.00		
TCA's	93	1.78	(1.44 to 2.19)	<0.001	1.18	(0.96 to 1.45)	0.12
SSRIs	260	1.02	(0.89 to 1.18)	0.75	0.88	(0.76 to 1.02)	0.080
Other antidepressants	60	1.66	(1.28 to 2.17)	<0.001	1.22	(0.93 to 1.60)	0.16
Combined antidepressants	8	1.17	(0.60 to 2.30)	0.65	0.81	(0.41 to 1.60)	0.55
Antidepressant class and dose categories							
No current use	783	1.00			1.00		
<i>TCA's:</i>							
≤ 0.5 DDD	46	1.51	(1.11 to 2.04)	0.008	0.98	(0.73 to 1.33)	0.90
>0.5 DDD/≤ 1.0 DDD	25	2.38	(1.61 to 3.53)	<0.001	1.44	(0.97 to 2.15)	0.072
> 1.0 DDD	14	2.23	(1.32 to 3.75)	0.003	1.62	(0.97 to 2.71)	0.065
<i>SSRIs:</i>							
≤ 0.5 DDD	21	1.11	(0.73 to 1.69)	0.63	0.97	(0.63 to 1.48)	0.87
>0.5 DDD/≤ 1.0 DDD	160	0.94	(0.79 to 1.12)	0.52	0.80	(0.67 to 0.96)	0.015
> 1.0 DDD	71	1.31	(1.03 to 1.67)	0.030	1.11	(0.87 to 1.43)	0.41
<i>Others:</i>							
≤ 0.5 DDD	13	2.39	(1.39 to 4.11)	0.002	1.76	(1.02 to 3.04)	0.041
>0.5 DDD/≤ 1.0 DDD	16	1.00	(0.62 to 1.61)	1.00	0.71	(0.44 to 1.15)	0.17
> 1.0 DDD	25	2.13	(1.4 to 3.23)	<0.001	1.56	(1.02 to 2.40)	0.040
Antidepressant drug							
No current use	783	1.00			1.00		
<i>TCA's:</i>							
Amitriptyline	49	1.75	(1.33 to 2.31)	<0.001	1.14	(0.86 to 1.51)	0.36
Dosulepin	25	1.90	(1.29 to 2.79)	0.001	1.27	(0.86 to 1.87)	0.22
Lofepamine	13	2.55	(1.51 to 4.30)	<0.001	1.90	(1.15 to 3.12)	0.012
Trazodone	2	0.68	(0.17 to 2.70)	0.58	0.38	(0.09 to 1.52)	0.17
<i>SSRIs:</i>							
Citalopram	113	1.04	(0.85 to 1.27)	0.70	0.91	(0.74 to 1.12)	0.36
Escitalopram	13	0.89	(0.52 to 1.53)	0.67	0.79	(0.46 to 1.35)	0.38
Fluoxetine	78	0.87	(0.69 to 1.10)	0.25	0.74	(0.58 to 0.95)	0.019
Paroxetine	21	1.16	(0.75 to 1.78)	0.51	0.87	(0.56 to 1.35)	0.53
Sertraline	33	1.44	(1.02 to 2.04)	0.039	1.27	(0.9 to 1.81)	0.18
<i>Others:</i>							
Mirtazapine	32	2.38	(1.67 to 3.40)	<0.001	1.48	(1.03 to 2.14)	0.036
Venlafaxine	27	1.39	(0.95 to 2.04)	0.093	1.15	(0.78 to 1.70)	0.48
All other antidepressants	7	1.04	(0.46 to 2.38)	0.92	0.80	(0.35 to 1.84)	0.60
Combined antidepressants	8	1.17	(0.60 to 2.30)	0.65	0.81	(0.41 to 1.60)	0.55

* Based on numbers in adjusted analysis

DDD= defined daily dose

¹ Adjusted for age, sex, year of diagnosis of depression, severity of depression, deprivation, smoking status, alcohol intake, ethnic group (white/not recorded or non-white), coronary heart disease, diabetes, hypertension, cancer, epilepsy/seizures, hypothyroidism, osteoarthritis, asthma/chronic obstructive airways disease, stroke/TIA, rheumatoid arthritis, osteoporosis, liver disease, renal disease, obsessive-compulsive disorder, statins, NSAIDs, aspirin, antihypertensive drugs, anticonvulsants, hypnotics/anxiolytics, oral contraceptives, hormone replacement therapy, antipsychotics, bisphosphonates, anticoagulants.

Table 10s Unadjusted and adjusted hazard ratios for stroke/TIA by antidepressant class, dose and individual drug for 5 years follow-up, excluding untreated patients

	No of events*	Unadjusted analysis			Adjusted analysis ¹		
		HR	95% CI	P	HR	95% CI	P
Antidepressant class							
No current use	525	1.00			1.00		
TCA's	90	1.93	(1.52 to 2.46)	<0.001	1.19	(0.93 to 1.51)	0.17
SSRIs	313	1.26	(1.08 to 1.48)	0.003	1.04	(0.89 to 1.21)	0.65
Other antidepressants	50	1.66	(1.25 to 2.20)	<0.001	1.15	(0.86 to 1.53)	0.36
Combined antidepressants	11	2.51	(1.42 to 4.43)	0.001	1.47	(0.81 to 2.65)	0.20
Antidepressant class and dose categories							
No current use	525	1.00			1.00		
<i>TCA's:</i>							
≤ 0.5 DDD	48	1.80	(1.32 to 2.45)	<0.001	1.05	(0.77 to 1.43)	0.75
>0.5 DDD/≤ 1.0 DDD	24	2.54	(1.72 to 3.77)	<0.001	1.51	(1.02 to 2.26)	0.042
> 1.0 DDD	12	2.00	(1.10 to 3.66)	0.024	1.44	(0.79 to 2.62)	0.24
<i>SSRIs:</i>							
≤ 0.5 DDD	24	1.33	(0.86 to 2.06)	0.20	1.07	(0.69 to 1.66)	0.76
>0.5 DDD/≤ 1.0 DDD	216	1.25	(1.05 to 1.49)	0.011	1.01	(0.85 to 1.20)	0.88
> 1.0 DDD	66	1.40	(1.08 to 1.81)	0.012	1.16	(0.89 to 1.51)	0.28
<i>Others:</i>							
≤ 0.5 DDD	10	2.18	(1.17 to 4.07)	0.014	1.47	(0.78 to 2.76)	0.23
>0.5 DDD/≤ 1.0 DDD	20	1.46	(0.96 to 2.24)	0.08	0.97	(0.62 to 1.51)	0.88
> 1.0 DDD	13	1.36	(0.80 to 2.31)	0.26	1.05	(0.61 to 1.79)	0.87
Antidepressant drug							
No current use	525	1.00			1.00		
<i>TCA's:</i>							
Amitriptyline	49	2.21	(1.64 to 2.99)	<0.001	1.29	(0.95 to 1.75)	0.10
Dosulepin	24	1.76	(1.17 to 2.66)	0.007	1.11	(0.74 to 1.68)	0.62
Lofepamine	12	2.21	(1.21 to 4.05)	0.010	1.66	(0.91 to 3.04)	0.10
Trazodone	2	0.75	(0.19 to 2.97)	0.68	0.41	(0.11 to 1.58)	0.20
<i>SSRIs:</i>							
Citalopram	128	1.21	(0.99 to 1.48)	0.06	1.01	(0.83 to 1.24)	0.89
Escitalopram	17	1.12	(0.68 to 1.84)	0.65	0.92	(0.56 to 1.52)	0.75
Fluoxetine	117	1.32	(1.07 to 1.62)	0.009	1.08	(0.88 to 1.33)	0.47
Paroxetine	21	1.18	(0.76 to 1.84)	0.46	0.91	(0.58 to 1.43)	0.68
Sertraline	30	1.50	(1.03 to 2.18)	0.032	1.20	(0.82 to 1.74)	0.35
<i>Others:</i>							
Mirtazapine	24	2.16	(1.46 to 3.20)	<0.001	1.29	(0.86 to 1.94)	0.22
Venlafaxine	21	1.30	(0.85 to 1.98)	0.23	1.00	(0.64 to 1.56)	1.00
All other antidepressants	8	1.43	(0.71 to 2.88)	0.32	0.96	(0.48 to 1.93)	0.90
Combined antidepressants	11	2.51	(1.42 to 4.43)	0.001	1.47	(0.81 to 2.65)	0.20

* Based on numbers in adjusted analysis

DDD= defined daily dose

¹ Adjusted for age, sex, year of diagnosis of depression, severity of depression, deprivation, smoking status, alcohol intake, ethnic group (white/not recorded or non-white), coronary heart disease, diabetes, hypertension, cancer, epilepsy/seizures, hypothyroidism, osteoarthritis, asthma/chronic obstructive airways disease, rheumatoid arthritis, osteoporosis, liver disease, renal disease, obsessive-compulsive disorder, statins, NSAIDs, aspirin, antihypertensive drugs, anticonvulsants, hypnotics/anxiolytics, oral contraceptives, hormone replacement therapy, antipsychotics, bisphosphonates, anticoagulants.

Table 11s Unadjusted and adjusted hazard ratios for stroke/TIA by antidepressant class, dose and individual drug for total follow-up period

	No of events*	Unadjusted analysis			Adjusted analysis ¹		
		HR	95% CI	P	HR	95% CI	P
Antidepressant class							
No current use	1082	1.00			1.00		
TCA's	138	1.92	(1.59 to 2.31)	<0.001	1.23	(1.01 to 1.49)	0.036
SSRIs	447	1.28	(1.14 to 1.44)	<0.001	1.10	(0.98 to 1.24)	0.12
Other antidepressants	81	1.63	(1.31 to 2.04)	<0.001	1.20	(0.96 to 1.5)	0.11
Combined antidepressants	21	2.22	(1.47 to 3.35)	<0.001	1.44	(0.94 to 2.2)	0.09
Antidepressant class and dose categories							
No current use	1082	1.00			1.00		
<i>TCA's:</i>							
≤ 0.5 DDD	80	1.89	(1.49 to 2.38)	<0.001	1.17	(0.92 to 1.48)	0.20
>0.5 DDD/≤ 1.0 DDD	31	2.14	(1.53 to 3.01)	<0.001	1.32	(0.93 to 1.86)	0.12
> 1.0 DDD	16	1.86	(1.12 to 3.09)	0.017	1.33	(0.78 to 2.26)	0.29
<i>SSRIs:</i>							
≤ 0.5 DDD	32	1.22	(0.83 to 1.80)	0.30	1.02	(0.69 to 1.49)	0.94
>0.5 DDD/≤ 1.0 DDD	293	1.25	(1.08 to 1.44)	0.002	1.05	(0.92 to 1.21)	0.46
> 1.0 DDD	112	1.50	(1.24 to 1.82)	<0.001	1.32	(1.08 to 1.61)	0.006
<i>Others:</i>							
≤ 0.5 DDD	14	1.86	(1.11 to 3.12)	0.018	1.37	(0.81 to 2.29)	0.24
>0.5 DDD/≤ 1.0 DDD	32	1.45	(1.03 to 2.05)	0.033	1.02	(0.72 to 1.46)	0.90
> 1.0 DDD	26	1.60	(1.07 to 2.42)	0.024	1.27	(0.85 to 1.90)	0.25
Antidepressant drug							
No current use	1082	1.00			1.00		
<i>TCA's:</i>							
Amitriptyline	79	2.05	(1.63 to 2.58)	<0.001	1.28	(1.01 to 1.62)	0.039
Dosulepin	31	1.72	(1.19 to 2.47)	0.004	1.10	(0.76 to 1.59)	0.62
Lofepramine	16	2.32	(1.40 to 3.86)	0.001	1.82	(1.09 to 3.04)	0.022
Trazodone	6	1.48	(0.66 to 3.29)	0.34	0.83	(0.37 to 1.83)	0.64
<i>SSRIs:</i>							
Citalopram	189	1.27	(1.08 to 1.49)	0.004	1.11	(0.95 to 1.30)	0.20
Escitalopram	28	1.40	(0.95 to 2.06)	0.089	1.16	(0.78 to 1.72)	0.47
Fluoxetine	154	1.25	(1.05 to 1.48)	0.011	1.08	(0.91 to 1.29)	0.38
Paroxetine	31	1.25	(0.88 to 1.79)	0.22	0.99	(0.68 to 1.42)	0.94
Sertraline	44	1.40	(1.03 to 1.9)	0.034	1.17	(0.85 to 1.61)	0.33
<i>Others:</i>							
Mirtazapine	35	1.90	(1.36 to 2.64)	<0.001	1.25	(0.90 to 1.75)	0.19
Venlafaxine	39	1.46	(1.05 to 2.01)	0.022	1.17	(0.84 to 1.63)	0.36
All other antidepressants	14	1.51	(0.90 to 2.55)	0.12	1.08	(0.65 to 1.81)	0.77
Combined antidepressants	21	2.22	(1.47 to 3.35)	<0.001	1.44	(0.94 to 2.20)	0.092

* Based on numbers in adjusted analysis

DDD= defined daily dose

¹ Adjusted for age, sex, year of diagnosis of depression, severity of depression, deprivation, smoking status, alcohol intake, ethnic group (white/not recorded or non-white), coronary heart disease, diabetes, hypertension, cancer, epilepsy/seizures, hypothyroidism, osteoarthritis, asthma/chronic obstructive airways disease, rheumatoid arthritis, osteoporosis, liver disease, renal disease, obsessive-compulsive disorder, statins, NSAIDs, aspirin, antihypertensive drugs, anticonvulsants, hypnotics/anxiolytics, oral contraceptives, hormone replacement therapy, antipsychotics, bisphosphonates, anticoagulants.

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Table 12s Adjusted hazard ratios for arrhythmia by antidepressant class, and individual drug over 5 years follow-up adjusted for different subsets of confounding variables

	Unadjusted		Model A ¹		Model B ²		Model C ³		Full model ⁴	
	Hazard ratio	95% CI	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
Antidepressant class										
No current use	1.00		1.00		1.00		1.00		1.00	
TCA's	1.59	(1.29 to 1.96)	1.20	(0.97 to 1.49)	1.19	(0.96 to 1.48)	1.11	(0.89 to 1.38)	1.09	(0.88 to 1.35)
SSRIs	1.02	(0.89 to 1.18)	0.92	(0.80 to 1.06)	0.91	(0.79 to 1.05)	0.85	(0.74 to 0.98)	0.84	(0.73 to 0.97)
Other antidepressants	1.55	(1.23 to 1.95)	1.32	(1.04 to 1.67)	1.31	(1.04 to 1.66)	1.24	(0.98 to 1.57)	1.21	(0.96 to 1.54)
Combined antidepressants	1.47	(0.75 to 2.89)	1.20	(0.61 to 2.36)	1.20	(0.61 to 2.35)	1.10	(0.57 to 2.15)	1.07	(0.54 to 2.09)
Antidepressant drug										
No current use	1.00		1.00		1.00		1.00		1.00	
<i>TCA's:</i>										
Amitriptyline	1.75	(1.32 to 2.33)	1.32	(0.99 to 1.75)	1.30	(0.98 to 1.73)	1.19	(0.89 to 1.59)	1.16	(0.87 to 1.54)
Doxepin	1.31	(0.87 to 1.98)	0.97	(0.64 to 1.47)	0.96	(0.64 to 1.46)	0.94	(0.62 to 1.42)	0.93	(0.61 to 1.40)
Lofepamine	2.10	(1.28 to 3.46)	1.92	(1.17 to 3.15)	1.90	(1.15 to 3.12)	1.71	(1.03 to 2.82)	1.67	(1.01 to 2.76)
Trazodone	1.33	(0.55 to 3.21)	0.80	(0.30 to 2.16)	0.81	(0.30 to 2.18)	0.73	(0.27 to 1.96)	0.72	(0.27 to 1.94)
<i>SSRIs:</i>										
Citalopram	1.07	(0.90 to 1.28)	0.93	(0.77 to 1.12)	0.92	(0.76 to 1.1)	0.86	(0.72 to 1.04)	0.86	(0.71 to 1.03)
Escitalopram	1.33	(0.91 to 1.93)	1.11	(0.75 to 1.64)	1.10	(0.75 to 1.63)	1.07	(0.72 to 1.59)	1.06	(0.71 to 1.57)
Fluoxetine	0.86	(0.69 to 1.08)	0.82	(0.65 to 1.02)	0.81	(0.65 to 1.01)	0.75	(0.60 to 0.93)	0.74	(0.59 to 0.92)
Paroxetine	1.13	(0.77 to 1.66)	1.02	(0.69 to 1.50)	1.02	(0.69 to 1.50)	0.97	(0.66 to 1.43)	0.97	(0.66 to 1.43)
Sertraline	1.15	(0.80 to 1.65)	1.06	(0.73 to 1.53)	1.05	(0.72 to 1.51)	0.98	(0.68 to 1.42)	0.97	(0.67 to 1.40)
<i>Others:</i>										
Mirtazapine	1.73	(1.19 to 2.52)	1.34	(0.91 to 1.97)	1.34	(0.91 to 1.97)	1.25	(0.85 to 1.83)	1.20	(0.81 to 1.77)
Venlafaxine	1.45	(1.04 to 2.03)	1.34	(0.95 to 1.87)	1.33	(0.95 to 1.86)	1.28	(0.91 to 1.80)	1.27	(0.91 to 1.79)
All other antidepressants	1.02	(0.51 to 2.03)	0.82	(0.41 to 1.63)	0.81	(0.41 to 1.62)	0.75	(0.38 to 1.51)	0.73	(0.37 to 1.46)
Combined antidepressants	1.47	(0.75 to 2.89)	1.20	(0.61 to 2.36)	1.20	(0.61 to 2.35)	1.10	(0.56 to 2.14)	1.06	(0.54 to 2.08)

¹ Model A: adjusted only for age, sex, deprivation, ethnicity, year of diagnosis

² Model B: adjusted for age, sex, deprivation, ethnicity, year of diagnosis plus depression severity, smoking, alcohol

³ Model C: adjusted for variables in model B plus coronary heart disease, diabetes, hypertension, stroke/TIA, rheumatoid arthritis, renal disease, statins, aspirin, antihypertensives, anticoagulants

⁴ Full model: adjusted for confounders listed in footnote to Table 2

Table 13s Adjusted hazard ratios for myocardial infarction by antidepressant class, and individual drug over 5 years follow-up adjusted for different subsets of confounding variables.

	Unadjusted		Model A ¹		Model B ²		Model C ³		Full model ⁴	
	Hazard ratio	95% CI	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
Antidepressant class										
No current use	1.00		1.00		1.00		1.00		1.00	
TCA's	1.83	(1.44 to 2.33)	1.33	(1.04 to 1.69)	1.27	(1.00 to 1.61)	1.23	(0.97 to 1.57)	1.20	(0.94 to 1.52)
SSRIs	1.02	(0.86 to 1.22)	0.91	(0.77 to 1.08)	0.90	(0.76 to 1.07)	0.85	(0.72 to 1.01)	0.85	(0.71 to 1.00)
Other antidepressants	1.39	(0.98 to 1.98)	1.07	(0.75 to 1.53)	1.01	(0.71 to 1.45)	1.00	(0.70 to 1.43)	1.00	(0.70 to 1.42)
Combined antidepressants	0.84	(0.27 to 2.59)	0.63	(0.20 to 1.92)	0.59	(0.19 to 1.82)	0.58	(0.19 to 1.78)	0.57	(0.18 to 1.75)
Antidepressant drug										
No current use	1.00		1.00		1.00		1.00		1.00	
<i>TCA's:</i>										
Amitriptyline	1.84	(1.28 to 2.62)	1.31	(0.92 to 1.86)	1.26	(0.88 to 1.79)	1.21	(0.85 to 1.72)	1.17	(0.82 to 1.66)
Doxepin	1.79	(1.14 to 2.81)	1.27	(0.81 to 1.99)	1.21	(0.77 to 1.90)	1.20	(0.76 to 1.88)	1.17	(0.75 to 1.83)
Lofepamine	2.73	(1.54 to 4.84)	2.31	(1.30 to 4.11)	2.20	(1.24 to 3.91)	2.05	(1.16 to 3.64)	2.02	(1.14 to 3.59)
Trazodone	1.01	(0.25 to 4.06)	0.64	(0.16 to 2.56)	0.60	(0.15 to 2.40)	0.58	(0.14 to 2.33)	0.57	(0.14 to 2.30)
<i>SSRIs:</i>										
Citalopram	1.05	(0.83 to 1.33)	0.93	(0.73 to 1.18)	0.92	(0.73 to 1.18)	0.88	(0.69 to 1.12)	0.88	(0.69 to 1.12)
Escitalopram	0.89	(0.48 to 1.67)	0.83	(0.44 to 1.55)	0.83	(0.44 to 1.54)	0.79	(0.42 to 1.47)	0.77	(0.41 to 1.44)
Fluoxetine	0.89	(0.67 to 1.18)	0.80	(0.60 to 1.08)	0.79	(0.59 to 1.06)	0.73	(0.54 to 0.99)	0.73	(0.54 to 0.98)
Paroxetine	1.02	(0.60 to 1.73)	0.82	(0.47 to 1.41)	0.81	(0.47 to 1.41)	0.77	(0.44 to 1.33)	0.76	(0.44 to 1.31)
Sertraline	1.53	(1.01 to 2.31)	1.37	(0.90 to 2.09)	1.34	(0.88 to 2.04)	1.27	(0.84 to 1.94)	1.27	(0.84 to 1.94)
<i>Others:</i>										
Mirtazapine	2.21	(1.37 to 3.55)	1.43	(0.89 to 2.32)	1.31	(0.81 to 2.12)	1.32	(0.81 to 2.13)	1.31	(0.81 to 2.12)
Venlafaxine	1.06	(0.63 to 1.80)	0.93	(0.54 to 1.58)	0.90	(0.53 to 1.54)	0.89	(0.52 to 1.52)	0.89	(0.52 to 1.51)
All other antidepressants	0.72	(0.24 to 2.21)	0.55	(0.18 to 1.68)	0.54	(0.18 to 1.66)	0.53	(0.17 to 1.61)	0.52	(0.17 to 1.60)
Combined antidepressants	0.84	(0.27 to 2.59)	0.63	(0.20 to 1.93)	0.59	(0.19 to 1.82)	0.58	(0.19 to 1.78)	0.57	(0.18 to 1.75)

¹ Model A: adjusted only for age, sex, deprivation, ethnicity, year of diagnosis

² Model B: adjusted for age, sex, deprivation, ethnicity, year of diagnosis plus depression severity, smoking, alcohol

³ Model C: adjusted for variables in model B plus coronary heart disease, diabetes, hypertension, stroke/TIA, rheumatoid arthritis, renal disease, statins, aspirin, antihypertensives, anticoagulants

⁴ Full model: adjusted for confounders listed in footnote to Table 5

Table 14s Adjusted hazard ratios for stroke/TIA by antidepressant class, and individual drug over 5 years follow-up adjusted for different subsets of confounding variables.

	Unadjusted		Model A ¹		Model B ²		Model C ³		Full model ⁴	
	Hazard ratio	95% CI	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
Antidepressant class										
No current use	1.00		1.00		1.00		1.00		1.00	
TCA's	1.98	(1.56 to 2.52)	1.40	(1.10 to 1.77)	1.35	(1.06 to 1.72)	1.31	(1.03 to 1.67)	1.24	(0.98 to 1.58)
SSRIs	1.30	(1.12 to 1.51)	1.18	(1.01 to 1.37)	1.16	(1.00 to 1.36)	1.11	(0.96 to 1.29)	1.09	(0.93 to 1.27)
Other antidepressants	1.71	(1.30 to 2.25)	1.33	(1.01 to 1.77)	1.29	(0.97 to 1.71)	1.27	(0.96 to 1.68)	1.20	(0.91 to 1.60)
Combined antidepressants	2.59	(1.47 to 4.55)	1.84	(1.02 to 3.31)	1.77	(0.98 to 3.21)	1.71	(0.95 to 3.08)	1.54	(0.86 to 2.78)
Antidepressant drug										
No current use	1.00		1.00		1.00		1.00		1.00	
<i>TCA's:</i>										
Amitriptyline	2.27	(1.69 to 3.06)	1.56	(1.16 to 2.11)	1.51	(1.12 to 2.04)	1.44	(1.07 to 1.94)	1.35	(1.00 to 1.82)
Doxepin	1.81	(1.20 to 2.72)	1.23	(0.81 to 1.85)	1.19	(0.79 to 1.80)	1.20	(0.79 to 1.80)	1.16	(0.77 to 1.76)
Lofepamine	2.27	(1.24 to 4.15)	1.94	(1.07 to 3.53)	1.90	(1.04 to 3.44)	1.85	(1.01 to 3.36)	1.75	(0.96 to 3.19)
Trazodone	0.77	(0.19 to 3.06)	0.52	(0.13 to 2.00)	0.49	(0.13 to 1.89)	0.46	(0.12 to 1.76)	0.43	(0.11 to 1.66)
<i>SSRIs:</i>										
Citalopram	1.24	(1.02 to 1.52)	1.14	(0.93 to 1.39)	1.12	(0.92 to 1.37)	1.08	(0.89 to 1.32)	1.06	(0.87 to 1.30)
Escitalopram	1.15	(0.70 to 1.88)	1.04	(0.64 to 1.71)	1.03	(0.63 to 1.68)	1.00	(0.61 to 1.64)	0.97	(0.59 to 1.59)
Fluoxetine	1.36	(1.11 to 1.65)	1.26	(1.03 to 1.54)	1.24	(1.01 to 1.52)	1.16	(0.95 to 1.42)	1.13	(0.93 to 1.39)
Paroxetine	1.21	(0.78 to 1.88)	1.00	(0.64 to 1.57)	0.99	(0.63 to 1.56)	0.97	(0.62 to 1.53)	0.95	(0.61 to 1.50)
Sertraline	1.55	(1.06 to 2.25)	1.37	(0.94 to 1.99)	1.35	(0.93 to 1.96)	1.29	(0.89 to 1.88)	1.26	(0.86 to 1.83)
<i>Others:</i>										
Mirtazapine	2.23	(1.51 to 3.28)	1.56	(1.05 to 2.33)	1.48	(0.99 to 2.20)	1.44	(0.96 to 2.15)	1.35	(0.90 to 2.02)
Venlafaxine	1.33	(0.88 to 2.03)	1.11	(0.72 to 1.73)	1.09	(0.70 to 1.69)	1.09	(0.71 to 1.70)	1.05	(0.67 to 1.63)
All other antidepressants	1.47	(0.73 to 2.96)	1.13	(0.56 to 2.26)	1.11	(0.55 to 2.21)	1.09	(0.54 to 2.19)	1.00	(0.50 to 2.02)
Combined antidepressants	2.59	(1.47 to 4.55)	1.84	(1.02 to 3.31)	1.78	(0.98 to 3.21)	1.71	(0.95 to 3.09)	1.55	(0.86 to 2.78)

¹ Model A: adjusted only for age, sex, deprivation, ethnicity, year of diagnosis

² Model B: adjusted for age, sex, deprivation, ethnicity, year of diagnosis plus depression severity, smoking, alcohol

³ Model C: adjusted for variables in model B plus coronary heart disease, diabetes, hypertension, rheumatoid arthritis, renal disease, statins, aspirin, antihypertensives, anticoagulants

⁴ Full model: adjusted for confounders listed in footnote to Table 6

	Outcome	Code type	Code	Code Description
1				
2				
3	Arrhythmia	Read code	327Z	ECG: supraventric. arryth. NOS
4	Arrhythmia	Read code	328Z	ECG: ventricular arrhythmia NOS
5	Arrhythmia	Read code	EMISNQAS1	Asystolic vasovagal syncope
6	Arrhythmia	Read code	F2560	Hypsarrhythmia
7	Arrhythmia	Read code	G57-1	Cardiac arrhythmias
8	Arrhythmia	Read code	G570	Paroxysmal supraventricular tachycardia
9	Arrhythmia	Read code	G570-99	Parox. supravent. tachycardia
10	Arrhythmia	Read code	G5700	Paroxysmal atrial tachycardia
11	Arrhythmia	Read code	G5701	Paroxysmal atrioventricular tachycardia
12	Arrhythmia	Read code	G5702	Paroxysmal junctional tachycardia
13	Arrhythmia	Read code	G5703	Paroxysmal nodal tachycardia
14	Arrhythmia	Read code	G570z	Paroxysmal supraventricular tachycardia NOS
15	Arrhythmia	Read code	G571	Paroxysmal ventricular tachycardia
16	Arrhythmia	Read code	G571-1	Ventricular tachycardia
17	Arrhythmia	Read code	G571-99	Paroxysmal ventric. tachyc.
18	Arrhythmia	Read code	G572	Paroxysmal tachycardia unspecified
19	Arrhythmia	Read code	G5720	Essential paroxysmal tachycardia
20	Arrhythmia	Read code	G5721	Bouveret-Hoffmann syndrome
21	Arrhythmia	Read code	G572z	Paroxysmal tachycardia NOS
22	Arrhythmia	Read code	G573	Atrial fibrillation and flutter
23	Arrhythmia	Read code	G5730	Atrial fibrillation
24	Arrhythmia	Read code	G5731	Atrial flutter
25	Arrhythmia	Read code	G5732	Paroxysmal atrial fibrillation
26	Arrhythmia	Read code	G5733	Non-rheumatic atrial fibrillation
27	Arrhythmia	Read code	G573z	Atrial fibrillation and flutter NOS
28	Arrhythmia	Read code	G574	Ventricular fibrillation and flutter
29	Arrhythmia	Read code	G5740	Ventricular fibrillation
30	Arrhythmia	Read code	G5740-1	Cardiac arrest-ventricular fibrillation
31	Arrhythmia	Read code	G5741	Ventricular flutter
32	Arrhythmia	Read code	G574z	Ventricular fibrillation and flutter NOS
33	Arrhythmia	Read code	G576-1	Premature beats
34	Arrhythmia	Read code	G5760	Ectopic beats unspecified
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Outcome	Code type	Code	Code Description
Arrhythmia	Read code	G5760-1	Extrasystoles
Arrhythmia	Read code	G5761	Supraventricular ectopic beats
Arrhythmia	Read code	G5762	Ventricular ectopic beats
Arrhythmia	Read code	G5763	Atrial premature depolarization
Arrhythmia	Read code	G5764	Junctional premature depolarization
Arrhythmia	Read code	G5765	Ventricular premature depolarization
Arrhythmia	Read code	G576z	Ectopic beats NOS
Arrhythmia	Read code	G577	Sinus arrhythmia
Arrhythmia	Read code	G57y	Other cardiac dysrhythmias
Arrhythmia	Read code	G57y-99	Cardiac dysrhythmias NOS
Arrhythmia	Read code	G57y0	Persistent sinus bradycardia
Arrhythmia	Read code	G57y1	Severe sinus bradycardia
Arrhythmia	Read code	G57y3	Sick sinus syndrome
Arrhythmia	Read code	G57y4	Sinoatrial node dysfunction NOS
Arrhythmia	Read code	G57y5	Wandering atrial pacemaker
Arrhythmia	Read code	G57y6	Nodal rhythm disorder
Arrhythmia	Read code	G57y7	Sinus tachycardia
Arrhythmia	Read code	G57y8	Bigeminal pulse
Arrhythmia	Read code	G57y9	Supraventricular tachycardia NOS
Arrhythmia	Read code	G57yA	Re-entry ventricular arrhythmia
Arrhythmia	Read code	G57yz	Other cardiac dysrhythmia NOS
Arrhythmia	Read code	G57z	Cardiac dysrhythmia NOS
Arrhythmia	Read code	G57z-99	Cardiac dysrhythmias NOS
Arrhythmia	Read code	Gyu5a	[X]Other specified cardiac arrhythmias
Arrhythmia	ICD9	427	Cardiac dysrhythmias
Arrhythmia	ICD9	427	Paroxysmal supraventricular tachycardia
Arrhythmia	ICD9	427.1	Paroxysmal ventricular tachycardia
Arrhythmia	ICD9	427.2	Paroxysmal tachycardia, unspecified
Arrhythmia	ICD9	427.3	Atrial fibrillation and flutter
Arrhythmia	ICD9	427.31	Atrial fibrillation
Arrhythmia	ICD9	427.32	Atrial flutter

	Outcome	Code type	Code	Code Description
1				
2				
3	Arrhythmia	ICD9	427.4	Ventricular fibrillation and flutter
4	Arrhythmia	ICD9	427.41	Ventricular fibrillation
5	Arrhythmia	ICD9	427.42	Ventricular flutter
6	Arrhythmia	ICD9	427.6	Premature beats
7	Arrhythmia	ICD9	427.6	Premature beats, unspecified
8	Arrhythmia	ICD9	427.61	Supraventricular premature beats
9	Arrhythmia	ICD9	427.69	Other
10	Arrhythmia	ICD9	427.8	Other specified cardiac dysrhythmias
11	Arrhythmia	ICD9	427.81	Sinoatrial node dysfunction
12	Arrhythmia	ICD9	427.89	Other
13	Arrhythmia	ICD9	427.9	Cardiac dysrhythmia, unspecified
14	Arrhythmia	ICD9	427.9	Cardiac dysrhythmia, unspecified
15	Arrhythmia	ICD9	427.9	Cardiac dysrhythmia, unspecified
16	Arrhythmia	ICD9	427.9	Cardiac dysrhythmia, unspecified
17	Arrhythmia	ICD9	427.9	Cardiac dysrhythmia, unspecified
18	Arrhythmia	ICD10	I47	Paroxysmal tachycardia
19	Arrhythmia	ICD10	I47.0	Re-entry ventricular arrhythmia
20	Arrhythmia	ICD10	I47.1	Supraventricular tachycardia
21	Arrhythmia	ICD10	I47.1	Supraventricular tachycardia
22	Arrhythmia	ICD10	I47.2	Ventricular tachycardia
23	Arrhythmia	ICD10	I47.9	Paroxysmal tachycardia, unspecified
24	Arrhythmia	ICD10	I48	Atrial fibrillation and flutter
25	Arrhythmia	ICD10	I48	Atrial fibrillation and flutter
26	Arrhythmia	ICD10	I49	Other cardiac arrhythmias
27	Arrhythmia	ICD10	I49.0	Ventricular fibrillation and flutter
28	Arrhythmia	ICD10	I49.1	Atrial premature depolarization
29	Arrhythmia	ICD10	I49.2	Junctional premature depolarization
30	Arrhythmia	ICD10	I49.3	Ventricular premature depolarization
31	Arrhythmia	ICD10	I49.3	Ventricular premature depolarization
32	Arrhythmia	ICD10	I49.4	Other and unspecified premature depolarization
33	Arrhythmia	ICD10	I49.5	Sick sinus syndrome
34	Arrhythmia	ICD10	I49.8	Other specified cardiac arrhythmias
35	Arrhythmia	ICD10	I49.9	Cardiac arrhythmia, unspecified
36	Arrhythmia	ICD10	I49.9	Cardiac arrhythmia, unspecified
37	Arrhythmia	ICD10	I49.9	Cardiac arrhythmia, unspecified
38	Myocardial infarction	Read code	EMISR4QF11	First myocardial infarction
39	Myocardial infarction	Read code	G30	Acute myocardial infarction
40	Myocardial infarction	Read code	G30-1	Attack - heart
41	Myocardial infarction	Read code	G30-1	Attack - heart
42	Myocardial infarction	Read code	G30-2	Coronary thrombosis
43				
44				
45				
46				
47				

Outcome	Code type	Code	Code Description
Myocardial infarction	Read code	G30-3	Cardiac rupture following myocardial infarction (MI)
Myocardial infarction	Read code	G30-4	Heart attack
Myocardial infarction	Read code	G30-5	MI - acute myocardial infarction
Myocardial infarction	Read code	G30-6	Thrombosis - coronary
Myocardial infarction	Read code	G30-7	Silent myocardial infarction
Myocardial infarction	Read code	G30-98	Coronary thrombosis
Myocardial infarction	Read code	G30-99	Myocardial Infarction
Myocardial infarction	Read code	G300	Acute anterolateral infarction
Myocardial infarction	Read code	G301	Other specified anterior myocardial infarction
Myocardial infarction	Read code	G3010	Acute anteroapical infarction
Myocardial infarction	Read code	G3011	Acute anteroseptal infarction
Myocardial infarction	Read code	G301z	Anterior myocardial infarction NOS
Myocardial infarction	Read code	G302	Acute inferolateral infarction
Myocardial infarction	Read code	G303	Acute inferoposterior infarction
Myocardial infarction	Read code	G304	Posterior myocardial infarction NOS
Myocardial infarction	Read code	G305	Lateral myocardial infarction NOS
Myocardial infarction	Read code	G306	True posterior myocardial infarction
Myocardial infarction	Read code	G307	Acute subendocardial infarction
Myocardial infarction	Read code	G3070	Acute non-Q wave infarction
Myocardial infarction	Read code	G3071	Acute non-ST segment elevation myocardial infarction
Myocardial infarction	Read code	G308	Inferior myocardial infarction NOS
Myocardial infarction	Read code	G309	Acute Q-wave infarct
Myocardial infarction	Read code	G30A	Mural thrombosis
Myocardial infarction	Read code	G30B	Acute posterolateral myocardial infarction
Myocardial infarction	Read code	G30X	Acute transmural myocardial infarction of unspecif site
Myocardial infarction	Read code	G30X0	Acute ST segment elevation myocardial infarction
Myocardial infarction	Read code	G30y	Other acute myocardial infarction
Myocardial infarction	Read code	G30y0	Acute atrial infarction
Myocardial infarction	Read code	G30y1	Acute papillary muscle infarction
Myocardial infarction	Read code	G30y2	Acute septal infarction
Myocardial infarction	Read code	G30yz	Other acute myocardial infarction NOS
Myocardial infarction	Read code	G30z	Acute myocardial infarction NOS

	Outcome	Code type	Code	Code Description
1				
2				
3	Myocardial infarction	Read code	G310-1	Dressler's syndrome
4	Myocardial infarction	Read code	G31y1	Microinfarction of heart
5	Myocardial infarction	Read code	G35	Subsequent myocardial infarction
6	Myocardial infarction	Read code	G350	Subsequent myocardial infarction of anterior wall
7	Myocardial infarction	Read code	G351	Subsequent myocardial infarction of inferior wall
8	Myocardial infarction	Read code	G353	Subsequent myocardial infarction of other sites
9	Myocardial infarction	Read code	G353	Subsequent myocardial infarction of other sites
10	Myocardial infarction	Read code	G35X	Subsequent myocardial infarction of unspecified site
11	Myocardial infarction	Read code	G360	Haemopericardium/current comp folow acut myocard infarct
12	Myocardial infarction	Read code	G361	Atrial septal defect/curr comp folow acut myocardal infarct
13	Myocardial infarction	Read code	G362	Ventric septal defect/curr comp fol acut myocardal infarctn
14	Myocardial infarction	Read code	G363	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
15	Myocardial infarction	Read code	G363	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
16	Myocardial infarction	Read code	G364	Ruptur chordae tendinae/curr comp fol acute myocard infarct
17	Myocardial infarction	Read code	G365	Rupture papillary muscle/curr comp fol acute myocard infarct
18	Myocardial infarction	Read code	G365	Rupture papillary muscle/curr comp fol acute myocard infarct
19	Myocardial infarction	Read code	G366	Thrombosis atrium,auric append&vent/curr comp foll acute MI
20	Myocardial infarction	Read code	G366	Thrombosis atrium,auric append&vent/curr comp foll acute MI
21	Myocardial infarction	Read code	G38	Postoperative myocardial infarction
22	Myocardial infarction	Read code	G380	Postoperative transmural myocardial infarction anterior wall
23	Myocardial infarction	Read code	G381	Postoperative transmural myocardial infarction inferior wall
24	Myocardial infarction	Read code	G382	Postoperative transmural myocardial infarction other sites
25	Myocardial infarction	Read code	G382	Postoperative transmural myocardial infarction other sites
26	Myocardial infarction	Read code	G383	Postoperative transmural myocardial infarction unspec site
27	Myocardial infarction	Read code	G384	Postoperative subendocardial myocardial infarction
28	Myocardial infarction	Read code	G38z	Postoperative myocardial infarction, unspecified
29	Myocardial infarction	Read code	G501	Post infarction pericarditis
30	Myocardial infarction	Read code	G501	Post infarction pericarditis
31	Myocardial infarction	Read code	Gyu34	[X]Acute transmural myocardial infarction of unspecif site
32				
33	Myocardial infarction	ICD9	410	Acute myocardial infarction
34	Myocardial infarction	ICD9	410	Of anterolateral wall
35	Myocardial infarction	ICD9	410.1	Of other anterior wall
36	Myocardial infarction	ICD9	410.1	Of other anterior wall
37	Myocardial infarction	ICD9	410.2	Of inferolateral wall
38	Myocardial infarction	ICD9	410.3	Of inferoposterior wall
39	Myocardial infarction	ICD9	410.4	Of other inferior wall
40	Myocardial infarction	ICD9	410.5	Of other lateral wall
41	Myocardial infarction	ICD9	410.5	Of other lateral wall
42	Myocardial infarction	ICD9	410.6	True posterior wall infarction
43				
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Outcome	Code type	Code	Code Description
Myocardial infarction	ICD9	410.7	Subendocardial infarction
Myocardial infarction	ICD9	410.8	Of other specified sites
Myocardial infarction	ICD9	410.9	Unspecified site
Myocardial infarction	ICD10	I21	Acute myocardial infarction
Myocardial infarction	ICD10	I21.0	Acute transmural myocardial infarction of anterior wall
Myocardial infarction	ICD10	I21.1	Acute transmural myocardial infarction of inferior wall
Myocardial infarction	ICD10	I21.2	Acute transmural myocardial infarction of other sites
Myocardial infarction	ICD10	I21.3	Acute transmural myocardial infarction of unspecified site
Myocardial infarction	ICD10	I21.4	Acute subendocardial myocardial infarction
Myocardial infarction	ICD10	I21.9	Acute myocardial infarction, unspecified
Myocardial infarction	ICD10	I22	Subsequent myocardial infarction
Myocardial infarction	ICD10	I22.0	Subsequent myocardial infarction of anterior wall
Myocardial infarction	ICD10	I22.1	Subsequent myocardial infarction of inferior wall
Myocardial infarction	ICD10	I22.8	Subsequent myocardial infarction of other sites
Myocardial infarction	ICD10	I22.9	Subsequent myocardial infarction of unspecified site
Stroke or TIA	Read code	F4236	Amaurosis fugax
Stroke or TIA	Read code	Fyu55	[X]Other transnt cerebral ischaemic attacks+related syndroms
Stroke or TIA	Read code	G61	Intracerebral haemorrhage
Stroke or TIA	Read code	G61-1	CVA - cerebrovascular accid due to intracerebral haemorrhage
Stroke or TIA	Read code	G61-2	Stroke due to intracerebral haemorrhage
Stroke or TIA	Read code	G61-98	Cerebral haemorrhage NOS
Stroke or TIA	Read code	G61-99	Cerebral haemorrhage
Stroke or TIA	Read code	G610	Cortical haemorrhage
Stroke or TIA	Read code	G611	Internal capsule haemorrhage
Stroke or TIA	Read code	G612	Basal nucleus haemorrhage
Stroke or TIA	Read code	G613	Cerebellar haemorrhage
Stroke or TIA	Read code	G614	Pontine haemorrhage
Stroke or TIA	Read code	G615	Bulbar haemorrhage
Stroke or TIA	Read code	G616	External capsule haemorrhage
Stroke or TIA	Read code	G618	Intracerebral haemorrhage, multiple localized

	Outcome	Code type	Code	Code Description
1				
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3	Stroke or TIA	Read code	G61X	Intracerebral haemorrhage in hemisphere, unspecified
4	Stroke or TIA	Read code	G61X0	Left sided intracerebral haemorrhage, unspecified
5	Stroke or TIA	Read code	G61X1	Right sided intracerebral haemorrhage, unspecified
6	Stroke or TIA	Read code	G61z	Intracerebral haemorrhage NOS
7	Stroke or TIA	Read code	G63y0	Cerebral infarct due to thrombosis of precerebral arteries
8	Stroke or TIA	Read code	G63y1	Cerebral infarction due to embolism of precerebral arteries
9	Stroke or TIA	Read code	G64	Cerebral arterial occlusion
10	Stroke or TIA	Read code	G64-1	CVA - cerebral artery occlusion
11	Stroke or TIA	Read code	G64-2	Infarction - cerebral
12	Stroke or TIA	Read code	G64-3	Stroke due to cerebral arterial occlusion
13	Stroke or TIA	Read code	G640	Cerebral thrombosis
14	Stroke or TIA	Read code	G6400	Cerebral infarction due to thrombosis of cerebral arteries
15	Stroke or TIA	Read code	G641	Cerebral embolism
16	Stroke or TIA	Read code	G641-1	Cerebral embolus
17	Stroke or TIA	Read code	G6410	Cerebral infarction due to embolism of cerebral arteries
18	Stroke or TIA	Read code	G64z	Cerebral infarction NOS
19	Stroke or TIA	Read code	G64z-1	Brainstem infarction NOS
20	Stroke or TIA	Read code	G64z-2	Cerebellar infarction
21	Stroke or TIA	Read code	G64z-99	Cerebral A. occlusion NOS
22	Stroke or TIA	Read code	G64z0	Brainstem infarction
23	Stroke or TIA	Read code	G64z1	Wallenberg syndrome
24	Stroke or TIA	Read code	G64z1-1	Lateral medullary syndrome
25	Stroke or TIA	Read code	G64z2	Left sided cerebral infarction
26	Stroke or TIA	Read code	G64z3	Right sided cerebral infarction
27	Stroke or TIA	Read code	G64z4	Infarction of basal ganglia
28	Stroke or TIA	Read code	G65	Transient cerebral ischaemia
29	Stroke or TIA	Read code	G65-1	Drop attack
30	Stroke or TIA	Read code	G65-2	Transient ischaemic attack
31	Stroke or TIA	Read code	G65-3	Vertebro-basilar insufficiency
32	Stroke or TIA	Read code	G65-99	Transient Ischaemic Attacks
33	Stroke or TIA	Read code	G650	Basilar artery syndrome
34	Stroke or TIA	Read code	G650-1	Insufficiency - basilar artery
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Outcome	Code type	Code	Code Description
Stroke or TIA	Read code	G651	Vertebral artery syndrome
Stroke or TIA	Read code	G6510	Vertebro-basilar artery syndrome
Stroke or TIA	Read code	G652	Subclavian steal syndrome
Stroke or TIA	Read code	G653	Carotid artery syndrome hemispheric
Stroke or TIA	Read code	G654	Multiple and bilateral precerebral artery syndromes
Stroke or TIA	Read code	G656	Vertebrobasilar insufficiency
Stroke or TIA	Read code	G65y	Other transient cerebral ischaemia
Stroke or TIA	Read code	G65z	Transient cerebral ischaemia NOS
Stroke or TIA	Read code	G65z-99	Transient Ischaemic Attacks
Stroke or TIA	Read code	G65z0	Impending cerebral ischaemia
Stroke or TIA	Read code	G65z1	Intermittent cerebral ischaemia
Stroke or TIA	Read code	G65zz	Transient cerebral ischaemia NOS
Stroke or TIA	Read code	G66	Stroke and cerebrovascular accident unspecified
Stroke or TIA	Read code	G66-1	CVA unspecified
Stroke or TIA	Read code	G66-2	Stroke unspecified
Stroke or TIA	Read code	G66-3	CVA - Cerebrovascular accident unspecified
Stroke or TIA	Read code	G66-98	Stroke/CVA - undefined
Stroke or TIA	Read code	G66-99	Stroke
Stroke or TIA	Read code	G660	Middle cerebral artery syndrome
Stroke or TIA	Read code	G661	Anterior cerebral artery syndrome
Stroke or TIA	Read code	G662	Posterior cerebral artery syndrome
Stroke or TIA	Read code	G663	Brain stem stroke syndrome
Stroke or TIA	Read code	G664	Cerebellar stroke syndrome
Stroke or TIA	Read code	G665	Pure motor lacunar syndrome
Stroke or TIA	Read code	G666	Pure sensory lacunar syndrome
Stroke or TIA	Read code	G667	Left sided CVA
Stroke or TIA	Read code	G668	Right sided CVA
Stroke or TIA	Read code	G6760	Cereb infarct due cerebral venous thrombosis, nonpyogenic
Stroke or TIA	Read code	G6W	Cereb infarct due unsp occlus/stenosis precerebr arteries
Stroke or TIA	Read code	G6X	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artr
Stroke or TIA	Read code	Gyu62	[X]Other intracerebral haemorrhage
Stroke or TIA	Read code	Gyu63	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artr

	Outcome	Code type	Code	Code Description
1				
2				
3	Stroke or TIA	Read code	Gyu64	[X]Other cerebral infarction
4	Stroke or TIA	Read code	Gyu65	[X]Occlusion and stenosis of other precerebral arteries
5	Stroke or TIA	Read code	Gyu66	[X]Occlusion and stenosis of other cerebral arteries
6	Stroke or TIA	Read code	Gyu6F	[X]Intracerebral haemorrhage in hemisphere, unspecified
7	Stroke or TIA	Read code	Gyu6G	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
8	Stroke or TIA	Read code	ZV12D	[V]Personal history of transient ischaemic attack
9				
10				
11				
12	Stroke or TIA	ICD9	430	Subarachnoid hemorrhage
13	Stroke or TIA	ICD9	431	Intracerebral hemorrhage
14	Stroke or TIA	ICD9	432	Other and unspecified intracranial hemorrhage
15	Stroke or TIA	ICD9	432	Nontraumatic extradural hemorrhage
16	Stroke or TIA	ICD9	432.1	Subdural hemorrhage
17	Stroke or TIA	ICD9	432.9	Hemorrhage, intracranial, NOS
18	Stroke or TIA	ICD9	433	Occlusion and stenosis of precerebral arteries
19	Stroke or TIA	ICD9	433	Occlusion and stenosis of basilar artery
20	Stroke or TIA	ICD9	433	Occlusion and stenosis of basilar artery without cerebral infarction
21	Stroke or TIA	ICD9	433.01	Occlusion and stenosis of basilar artery with cerebral infarction
22	Stroke or TIA	ICD9	433.1	Occlusion and stenosis of carotid artery
23	Stroke or TIA	ICD9	433.1	Occlusion and stenosis of carotid artery without cerebral infarction
24	Stroke or TIA	ICD9	433.11	Occlusion and stenosis of carotid artery with cerebral infarction
25	Stroke or TIA	ICD9	433.2	Occlusion and stenosis of vertebral artery
26	Stroke or TIA	ICD9	433.2	Occlusion and stenosis of vertebral artery without cerebral infarction
27	Stroke or TIA	ICD9	433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
28	Stroke or TIA	ICD9	433.3	Occlusion and stenosis of multiple and bilateral precerebral arteries
29	Stroke or TIA	ICD9	433.3	Occlusion and stenosis of multiple and bilateral precerebral arteries without cerebral infarction
30	Stroke or TIA	ICD9	433.8	Occlusion and stenosis of other specified precerebral artery
31	Stroke or TIA	ICD9	433.8	Occlusion and stenosis of other specified precerebral artery without cerebral infarction
32	Stroke or TIA	ICD9	433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
33	Stroke or TIA	ICD9	433.9	Occlusion and stenosis of unspecified precerebral artery
34	Stroke or TIA	ICD9	433.9	Occlusion and stenosis of unspecified precerebral artery without cerebral infarction
35	Stroke or TIA	ICD9	433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
36	Stroke or TIA	ICD9	434	Occlusion of cerebral arteries
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Outcome	Code type	Code	Code Description
Stroke or TIA	ICD9	434	Cerebral thrombosis
Stroke or TIA	ICD9	434	Cerebral thrombosis without cerebral infarction
Stroke or TIA	ICD9	434.01	Cerebral thrombosis with cerebral infarction
Stroke or TIA	ICD9	434.1	Cerebral embolism
Stroke or TIA	ICD9	434.1	Cerebral embolism without cerebral infarction
Stroke or TIA	ICD9	434.11	Cerebral embolism with cerebral infarction
Stroke or TIA	ICD9	434.9	Cerebral artery occlusion unspecified
Stroke or TIA	ICD9	434.9	Cerebral artery occlusion unspecified without cerebral infarction
Stroke or TIA	ICD9	434.91	Cerebral artery occlusion unspecified with cerebral infarction
Stroke or TIA	ICD9	435	Transient cerebral ischemia
Stroke or TIA	ICD9	435	Basilar artery syndrome
Stroke or TIA	ICD9	435.1	Vertebral artery syndrome
Stroke or TIA	ICD9	435.2	Subclavian steal syndrome
Stroke or TIA	ICD9	435.3	Vertebrobasilar artery syndrome
Stroke or TIA	ICD9	435.9	Transient ischemic attack, unspec.
Stroke or TIA	ICD9	436	Acute but ill-defined cerebrovascular disease
Stroke or TIA	ICD9	437	Other and ill-defined cerebrovascular disease
Stroke or TIA	ICD9	437	Cerebral atherosclerosis
Stroke or TIA	ICD9	437.1	Other generalized ischemic cerebrovascular disease
Stroke or TIA	ICD9	437.3	Cerebral aneurysm nonruptured
Stroke or TIA	ICD9	437.4	Cerebral arteritis
Stroke or TIA	ICD9	437.5	Moyamoya disease
Stroke or TIA	ICD9	437.6	Nonpyogenic thrombosis of intracranial venous sinus
Stroke or TIA	ICD9	437.7	Transient global amnesia
Stroke or TIA	ICD9	437.8	Other ill-defined cerebrovascular disease
Stroke or TIA	ICD9	437.9	Unspecified cerebrovascular disease
Stroke or TIA	ICD10	G46*	Vascular syndromes of brain in cerebrovascular diseases (I60-I67+)
Stroke or TIA	ICD10	G46.0*	Middle cerebral artery syndrome (I66.0+)
Stroke or TIA	ICD10	G46.1*	Anterior cerebral artery syndrome (I66.1+)
Stroke or TIA	ICD10	G46.2*	Posterior cerebral artery syndrome (I66.2+)
Stroke or TIA	ICD10	G46.3*	Brain stem stroke syndrome (I60 - I67+)

	Outcome	Code type	Code	Code Description
1				
2				
3	Stroke or TIA	ICD10	G46.4*	Cerebellar stroke syndrome (I60 - I67+)
4	Stroke or TIA	ICD10	G46.5*	Pure motor lacunar syndrome (I60 - I67+)
5	Stroke or TIA	ICD10	G46.6*	Pure sensory lacunar syndrome (I60 - I67+)
6	Stroke or TIA	ICD10	G46.7*	Other lacunar syndromes (I60 - I67+)
7	Stroke or TIA	ICD10	G46.8*	Other vascular syndromes of brain in cerebrovascular diseases (I60 - I67+)
8	Stroke or TIA	ICD10	I60	Subarachnoid haemorrhage
9	Stroke or TIA	ICD10	I60	Subarachnoid haemorrhage
10	Stroke or TIA	ICD10	I60.0	Subarachnoid haemorrhage from carotid siphon and bifurcation
11	Stroke or TIA	ICD10	I60.1	Subarachnoid haemorrhage from middle cerebral artery
12	Stroke or TIA	ICD10	I60.2	Subarachnoid haemorrhage from anterior communicating artery
13	Stroke or TIA	ICD10	I60.3	Subarachnoid haemorrhage from posterior communicating artery
14	Stroke or TIA	ICD10	I60.4	Subarachnoid haemorrhage from basilar artery
15	Stroke or TIA	ICD10	I60.5	Subarachnoid haemorrhage from vertebral artery
16	Stroke or TIA	ICD10	I60.6	Subarachnoid haemorrhage from other intracranial arteries
17	Stroke or TIA	ICD10	I60.7	Subarachnoid haemorrhage from intracranial artery, unspecified
18	Stroke or TIA	ICD10	I60.8	Other subarachnoid haemorrhage
19	Stroke or TIA	ICD10	I60.9	Subarachnoid haemorrhage, unspecified
20	Stroke or TIA	ICD10	I60.9	Subarachnoid haemorrhage, unspecified
21	Stroke or TIA	ICD10	I61	Intracerebral haemorrhage
22	Stroke or TIA	ICD10	I61.0	Intracerebral haemorrhage in hemisphere, subcortical
23	Stroke or TIA	ICD10	I61.1	Intracerebral haemorrhage in hemisphere, cortical
24	Stroke or TIA	ICD10	I61.2	Intracerebral haemorrhage in hemisphere, unspecified
25	Stroke or TIA	ICD10	I61.2	Intracerebral haemorrhage in hemisphere, unspecified
26	Stroke or TIA	ICD10	I61.3	Intracerebral haemorrhage in brain stem
27	Stroke or TIA	ICD10	I61.3	Intracerebral haemorrhage in brain stem
28	Stroke or TIA	ICD10	I61.4	Intracerebral haemorrhage in cerebellum
29	Stroke or TIA	ICD10	I61.4	Intracerebral haemorrhage in cerebellum
30	Stroke or TIA	ICD10	I61.5	Intracerebral haemorrhage, intraventricular
31	Stroke or TIA	ICD10	I61.6	Intracerebral haemorrhage, multiple localized
32	Stroke or TIA	ICD10	I61.6	Intracerebral haemorrhage, multiple localized
33	Stroke or TIA	ICD10	I61.8	Other intracerebral haemorrhage
34	Stroke or TIA	ICD10	I61.9	Intracerebral haemorrhage, unspecified
35	Stroke or TIA	ICD10	I62	Other nontraumatic intracranial haemorrhage
36	Stroke or TIA	ICD10	I62	Other nontraumatic intracranial haemorrhage
37	Stroke or TIA	ICD10	I62.0	Subdural haemorrhage (acute)(nontraumatic)
38	Stroke or TIA	ICD10	I62.1	Nontraumatic extradural haemorrhage
39	Stroke or TIA	ICD10	I62.9	Intracranial haemorrhage (nontraumatic), unspecified
40	Stroke or TIA	ICD10	I63	Cerebral infarction
41	Stroke or TIA	ICD10	I63	Cerebral infarction
42	Stroke or TIA	ICD10	I63.0	Cerebral infarction due to thrombosis of precerebral arteries
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Outcome	Code type	Code	Code Description
Stroke or TIA	ICD10	I63.1	Cerebral infarction due to embolism of precerebral arteries
Stroke or TIA	ICD10	I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
Stroke or TIA	ICD10	I63.3	Cerebral infarction due to thrombosis of cerebral arteries
Stroke or TIA	ICD10	I63.4	Cerebral infarction due to embolism of cerebral arteries
Stroke or TIA	ICD10	I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
Stroke or TIA	ICD10	I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
Stroke or TIA	ICD10	I63.8	Other cerebral infarction
Stroke or TIA	ICD10	I63.9	Cerebral infarction, unspecified
Stroke or TIA	ICD10	I64	Stroke, not specified as haemorrhage or infarction
Stroke or TIA	ICD10	I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
Stroke or TIA	ICD10	I65.0	Occlusion and stenosis of vertebral artery
Stroke or TIA	ICD10	I65.1	Occlusion and stenosis of basilar artery
Stroke or TIA	ICD10	I65.2	Occlusion and stenosis of carotid artery
Stroke or TIA	ICD10	I65.3	Occlusion and stenosis of multiple and bilateral precerebral arteries
Stroke or TIA	ICD10	I65.8	Occlusion and stenosis of other precerebral artery
Stroke or TIA	ICD10	I65.9	Occlusion and stenosis of unspecified precerebral artery
Stroke or TIA	ICD10	I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
Stroke or TIA	ICD10	I66.0	Occlusion and stenosis of middle cerebral artery
Stroke or TIA	ICD10	I66.1	Occlusion and stenosis of anterior cerebral artery
Stroke or TIA	ICD10	I66.2	Occlusion and stenosis of posterior cerebral artery
Stroke or TIA	ICD10	I66.3	Occlusion and stenosis of cerebellar arteries
Stroke or TIA	ICD10	I66.4	Occlusion and stenosis of multiple and bilateral cerebral arteries
Stroke or TIA	ICD10	I66.8	Occlusion and stenosis of other cerebral artery
Stroke or TIA	ICD10	I66.9	Occlusion and stenosis of unspecified cerebral artery
Stroke or TIA	ICD10	I67	Other cerebrovascular diseases
Stroke or TIA	ICD10	I67.8	Other specified cerebrovascular diseases
Stroke or TIA	ICD10	I67.9	Cerebrovascular disease, unspecified
Stroke or TIA	ICD10	I68*	Cerebrovascular disorders in diseases classified elsewhere
Stroke or TIA	ICD10	I68.8*	Other cerebrovascular disorders in diseases classified elsewhere
Stroke or TIA	ICD10	I69	Sequelae of cerebrovascular disease
Stroke or TIA	ICD10	I69.0	Sequelae of subarachnoid haemorrhage
Stroke or TIA	ICD10	I69.1	Sequelae of intracerebral haemorrhage

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Outcome	Code type	Code	Code Description
Stroke or TIA	ICD10	I69.2	Sequelae of other nontraumatic intracranial haemorrhage
Stroke or TIA	ICD10	I69.3	Sequelae of cerebral infarction
Stroke or TIA	ICD10	I69.4	Sequelae of stroke, not specified as haemorrhage or infarction
Stroke or TIA	ICD10	I69.8	Sequelae of other and unspecified cerebrovascular diseases

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