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

Journal:	*BMJ*
Manuscript ID:	BMJ.2015.027737
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	24-Jun-2015
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Keywords:	antidepressants, depression, myocardial infarction, stroke, arrhythmia, cardiovascular

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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 ≥40 mg/day).

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 with depression aged 25 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.

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

Antidepressants are one of the most commonly prescribed medications worldwide, and their use is increasing.[1-3] 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,[4] and in England more than 53 million antidepressant prescriptions were issued in 2013[5], nearly a twofold increase compared with a decade earlier.[6] 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.

Whilst it is established that depression increases the risk of cardiovascular outcomes there is controversy as to whether use of antidepressants , particularly selective serotonin reuptake inhibitors, increases or reduces the risk of cardiovascular outcomes.[7 8] Randomised controlled trials of antidepressants tend to be short term and underpowered to detect effects on cardiovascular outcomes. Observational studies have found both increased[9 10] and reduced risks[11] of myocardial infarction associated with selective serotonin reuptake inhibitors. A meta-analysis of 13 observational studies found that selective serotonin reuptake inhibitor use was associated with a 40% increased risk of all types of stroke (adjusted odds ratio 1.4; 95% CI 1.1 to 1.8), but this was only significant in studies in older age groups.[12]

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.[13] 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 amitriptyline.[14 15] QT interval prolongation can lead to arrhythmias including potentially fatal torsades de pointes,[16] 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.[17] A cohort study in a younger population 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.[18]

Most observational studies of cardiovascular effects have examined classes of antidepressants rather than individual drugs and have not assessed dose or duration of use; they have also mainly been in older people and 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 several different adverse outcomes including arrhythmia, myocardial infarction, and stroke or transient ischaemic attack. Full details of the study design and methods can be found in the study protocol.[19]

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 and from 1st January 2000 until 31st July 2011. Patients with a diagnosis of depression were identified using diagnostic Read codes used in previous studies.[10 20 21] 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 cohort. Patients were also excluded if they had received prescriptions for an antidepressant either before the study start date (1st January 2000), before their registration date, before they were aged 20, or more than 36 months before their first recorded diagnosis of depression. Temporary residents were also excluded.

The earliest of the date of the first recorded diagnosis of depression, or the date of the first prescription for an antidepressant was used as the patient's study entry date. Participants in the cohort were followed up until the earliest of: date of death, date of leaving the practice, or the end of the follow-up period (1st August 2012).

Outcomes

The three outcomes for these analyses were arrhythmia, myocardial infarction and stroke or transient ischaemic attack. Patients with these outcomes were identified if they were recorded either on the patients' general practice record using the relevant Read codes or on their linked Office of National

Statistics cause of death record using International Classification of Diseases (ICD) diagnostic codes, based on codes used in previous studies[22-24] as listed in appendix 1.

Exposures

Information was extracted on all antidepressant prescriptions during follow-up. The duration of each prescription was calculated by dividing the number of tablets prescribed by number to be taken each day.

For the main analyses antidepressant drugs were grouped according to the four main classes in the British National Formulary (BNF): tricyclic and related antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and other antidepressants. Prescriptions for different antidepressant drugs on the same date were classified as combined prescriptions.

We calculated the daily dose of each prescription by multiplying the number of tablets to be taken each day by the dose of each tablet, and converted this to a defined daily dose to enable comparison of doses between antidepressant classes, using values assigned by the World Health Organisation's Collaborating Centre for Drug Statistics Methodology (www.whocc.no/atc_ddd_index).

The eleven most frequently prescribed individual antidepressant drugs were also assessed.[10 19]

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; sex; year of diagnosis of depression; severity of index diagnosis of depression (categorised as mild, moderate or severe, using codes published by Martinez and colleagues[20] and some additional classification by a member of the study team); 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); 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); ethnic group (categorised as white/not recorded or non-white (Indian, Pakistani, Bangladeshi, other Asian, black African, black Caribbean, Chinese, other including mixed)); comorbidities at baseline (coronary heart disease, stroke/transient ischaemic attack (except when stroke/transient ischaemic attack was the outcome), 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 (antihypertensive drugs, aspirin, statins, anticoagulants, non-steroidal anti-inflammatory drugs, anticonvulsants, hypnotics/anxiolytics, anti-psychotics, bisphosphonates, oral contraceptives, hormone replacement therapy).

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. The main analyses were based on the first five years of follow-up after study entry.

The analysis calculated unadjusted and adjusted analysis hazard ratios for each antidepressant class (tricyclic and related antidepressants, selective serotonin reuptake inhibitors, other antidepressants) compared with periods of no antidepressant treatment. Patients prescribed monoamine oxidase inhibitors at any time were excluded from these analyses as the number in this category was small. Analyses were carried out for time-varying exposures of prescribed daily dose (categorised as ≤0.5, >0.5 and ≤1.0, and >1.0 defined daily doses) and tests for trend within each class were calculated using dose as a continuous variable. Additional analyses were carried out for time since starting treatment (categorised as: no use; 1-28 days; 29-84 days; 85 or more days) and time since stopping (1-28 days, 29 to 84 days and 85 to 182 days after stopping treatment) and for the 11 most commonly prescribed individual antidepressants, as in a previous study.[10] Individual antidepressants were further categorised by dose (≤ 1 or >1 defined daily doses) and citalopram was also categorised as ≤20 mg/day, 20- 39 mg/day and ≥40 mg/day for an analysis of the arrhythmia outcome, in light of the FDA drug safety communication.[25]

Wald's significance tests were used to identify significant differences between antidepressant classes and between individual antidepressant drugs. We tested for interactions between class of antidepressant and age and sex. We assessed the proportional hazards assumption using log minus log plots.

As sensitivity analyses we repeated the analyses firstly restricted to the first year of follow-up, then including the entire follow-up period. We carried out a further analysis excluding patients who received no antidepressant prescriptions during follow-up.

We calculated absolute risks of the three outcomes over one year, accounting for the confounding variables using the adjusted hazard ratios from the analyses based on one year of follow-up based on the method described by Altman et al.[26]

We included all eligible patients in the database in our analyses to maximise power. We used a P value of <0.01 (two tailed) to determine statistical significance. We used Stata (v12.1) for all analyses.

Results

There were 327,235 patients with a first diagnosis of depression made between the ages of 20 and 64, between 1st January 2000 and 31st July 2011. A total of 88,272 (27.0%) patients were excluded because they had schizophrenia, bipolar disorder or other psychoses, had been prescribed lithium or antimanic drugs or had been prescribed an antidepressant either before the study entry date, before age 20 or more than 36 months before their date of diagnosis of depression. This left 238,963 patients from 687 practices in the final study cohort.

The median length of follow-up was 5.2 years (interquartile range 2.5–8.2) with a total of 1,307,326 person-years of follow-up. The mean age of patients in the study cohort was 39.5 years (SD 11.1), and 61% were women (Table 1).

Antidepressant treatment during follow-up

During follow-up 209,476 patients (87.7%) received a total of 3,337,336 antidepressant prescriptions. There were 2,379,668 (71.3%) prescriptions for selective serotonin reuptake inhibitors, 533,798 (16.0%) for tricyclic and related antidepressants, 1,791 (0.05%) for monoamine oxidase inhibitors and 422,079 (12.7%) for the group of other antidepressants. There were 83,784 combined prescriptions where two or more different antidepressant drugs were prescribed on the same day. The median duration of treatment during follow-up was 221 days (interquartile range 79-590).

Citalopram was the most commonly prescribed antidepressant (1,023,255 prescriptions, 31.5% of total) followed by fluoxetine (778,285 prescriptions, 23.9%). Supplementary Table 1 shows numbers of prescriptions for the 11 most commonly prescribed antidepressants, with information on prescribed daily doses.

Incidence rates

At baseline 2,373 patients had an existing diagnosis of arrhythmia, 1,790 of myocardial infarction and 1,741 of stroke or transient ischaemic attack. These patients were excluded from analyses of each respective outcome along with patients prescribed monoamine oxidase inhibitors. During the first five years of follow-up there were 1452 new diagnoses of arrhythmia, 772 patients had a myocardial infarction and 1106 patient had a stroke or transient ischaemic attack. The incidence rate of arrhythmia was 16.2 per 10,000 person-years (20.1 per 10,000 in men and 13.8 per 10,000 in women), the incidence rate of myocardial infarction was 8.6 per 10,000 person-years (16.2 per 10,000 in men and 3.9 per 10,000 in women) and for stroke or transient ischaemic attack it was 12.3 per 10,000 person-years (17.3 per 10,000 in men and 9.3 per 10,000 in women).

Associations with arrhythmia

There were no significant associations with arrhythmia (at P<0.01) for any of the drug classes over five years compared with periods of no antidepressant treatment as shown in Table 2, although there was some indication of a reduced hazard ratio for selective serotonin reuptake inhibitors (adjusted hazard ratio 0.84, 95% CI 0.73 to 0.97, P=0.02). There were no significant trends for dose in the three drug classes.

There was a significant increase in the rate of arrhythmia in the first 28 days after starting tricyclic and related antidepressants (adjusted hazard ratio= 1.99, 95% CI 1.27 to 3.13, P=0.003), and a significant reduction from 84 days after starting selective serotonin reuptake inhibitors (adjusted hazard ratio= 0.78, 95% CI 0.66 to 0.92, P=0.004).

In the analysis of the 11 most commonly prescribed drugs there was a significant decrease in risk for fluoxetine (adjusted hazard ratio 0.74, 95% CI 0.59 to 0.92, P=0.008), and some indication of an increased risk for lofepramine (adjusted hazard ratio 1.67, 95% CI 1.01 to 2.76, P=0.05), but overall there was no significant difference between the five selective serotonin reuptake inhibitors (P=0.39) or the four tricyclic and related antidepressants (P=0.22) (figure 1a).

In an analysis of dose for individual antidepressants (table 3) risks were not significantly increased for higher doses of citalopram (adjusted hazard ratio= 1.08, 95% CI 0.74 to 1.57, for doses >20 mg/day) or escitalopram (adjusted hazard ratio= 1.06, 95% CI 0.52 to 2.16, for doses >10 mg/day), but there was a significant increase for lower doses of lofepramine (≤ 105 mg/day) and a significantly reduced risk for lower doses of fluoxetine (adjusted hazard ratio=0.72, 95% CI 0.56 to 0.91, for doses ≤ 20 mg/day). Even for doses of citalopram ≥ 40 mg/day there was no significantly increased risk (adjusted hazard ratio=1.11, 95% CI 0.72 to 1.71) (supplementary table 2).

Adjusted hazard ratios were similar when patients who had not received any prescriptions for antidepressants during follow-up were removed from the analysis (supplementary table 3) and when the entire follow-up period was used (supplementary table 4) although there were more significant associations due to larger numbers. When just the first year of follow-up was used (supplementary table 5) results were similar to the five year analysis although there was a higher hazard ratio for combined antidepressant use (adjusted hazard ratio=3.45, 95%CI 1.24 to 9.57, P=0.017) and the association with fluoxetine was no longer statistically significant (adjusted hazard ratio= 0.79, 95% CI 0.55 to 1.13, P=0.19).

Associations with myocardial infarction

There was no significant association between antidepressant class and myocardial infarction over five years in the adjusted analysis (Table 4) and no significant trends with dose. There was no clear pattern in risk

according to different periods of time after starting or stopping antidepressant drugs, although rates were increased from 28 days after stopping tricyclic and related antidepressants.

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

Adjusted hazard ratios were similar when patients who had not received any antidepressant prescriptions during follow-up were removed from the analysis (supplementary table 6) and when the entire follow-up period was used (supplementary table 7), but there were some differences when the analysis was restricted to the first year of follow-up (supplementary table 8). In this analysis there was a significantly reduced risk for selective serotonin reuptake inhibitors compared with no use of antidepressants (adjusted hazard ratio 0.58, 95% CI 0.42 to 0.79, P=0.001), a significant reduction with fluoxetine (adjusted hazard ratio 0.44, 95% CI 0.27 to 0.72, P=0.001) and a significant increase with lofepramine (adjusted hazard ratio 3.07, 95% CI 1.50 to 6.26, P=0.002). Overall there was no significant difference (at P<0.01) between the five selective serotonin reuptake inhibitors (P=0.11) or the four tricyclic and related antidepressants (P=0.03).

Associations with stroke/transient ischaemic attack

There were no significant associations between antidepressant class and stroke/transient ischaemic attack over five years and no significant trends (at P<0.01) with dose (Table 5). There was a significant increase in risk during the first 28 days after starting other antidepressants (adjusted hazard ratio= 2.72, 95% CI 1.45 to 5.08, P=0.002), and from 85 to 182 days after stopping tricyclic and related antidepressants (adjusted hazard ratio= 1.82, 95% CI 1.21 to 2.74, P=0.004). Rates were also increased in the first 84 days after starting tricyclic and related antidepressants, although not significantly (at P<0.01).

In the adjusted analysis of individual antidepressant drugs there were no significant associations for any of the drugs (figure 1c).

Adjusted hazard ratios were similar when patients who had not received any prescriptions for antidepressants during follow-up were removed (supplementary table 9), and when either the entire follow-up period (supplementary table 10) or just the first year of follow-up was used in the analysis (supplementary table 11).

Absolute risks

Table 6 shows absolute risks of the three outcomes over one year by antidepressant class and for the individual drugs. Absolute risks of arrhythmia and myocardial infarction were highest for lofepramine (30

per 10,000 and 31 per 10,000 respectively), these equate to numbers needed to harm of 631 (95% CI 215 to 13662) and 484 (95% CI 191 to 1986) respectively compared with no treatment.

Discussion

The main findings of this large population-based cohort study were that selective serotonin reuptake inhibitors were not associated with an increased risk of arrhythmia, myocardial infarction, or stroke or transient ischaemic attack in a general population cohort of people with depression aged 20 to 64, and that arrhythmia risk was not significantly increased in patients prescribed citalopram even at high doses (40 mg/day and over). There was some evidence that selective serotonin reuptake inhibitors were associated with a reduced risk of arrhythmia and myocardial infarction. These risks were lowest for fluoxetine, although there were no significant differences overall between the selective serotonin reuptake inhibitors. The risk of arrhythmia was significantly increased in the first 4 weeks of starting tricyclic and related antidepressants, and the tricyclic drug lofepramine was associated with an increased risk of myocardial infarction over one year.

Strengths and limitations

This study included a large representative sample of people with depression in the general UK population and had a long follow-up period. All eligible patients were included, so there is no bias due to non-response and no recall bias since data on prescriptions and confounding variables were recorded prospectively before the outcomes occurred. We reduced indication bias by restricting our cohort to only include patients with a diagnosis of depression, since depression itself is an established risk factor for cardiovascular outcomes,[27 28] and otherwise it would be difficult to separate the effects of antidepressant treatment from those of depression.

Some bias may remain in comparisons between antidepressant drugs if the selection of a particular antidepressant was influenced by risk factors for the outcome, but we accounted for a large number of potential confounding variables in the analysis to reduce differences between comparison groups. The increased risk in some analyses for lofepramine may nevertheless reflect preferential selection of this drug in patients considered more prone to arrhythmias or heart disease, since this drug is viewed as being safer in overdose and less cardiotoxic than other tricyclic and related antidepressants.[29 30] The increased risk of arrhythmia for low doses of lofepramine but not higher doses supports this, whereby patients at highest risk are prescribed lower doses, although numbers of events were small in both dose categories. However in a comparison of baseline characteristics of patients prescribed different antidepressants there was no indication that lofepramine was prescribed more frequently than other tricyclic antidepressants to patients with cardiovascular risk factors,[31] for example among patients whose first antidepressant prescription was for lofepramine 1.1% had coronary heart disease compared with 2.1% for amitriptyline, and 0.8% had a

prior stroke recorded compared with 1.0% for amitriptyline. Similarly there was no indication that fluoxetine was prescribed less frequently than other selective serotonin reuptake inhibitors to patients with cardiovascular risk factors.

There may still be some residual confounding due to variables which were either not recorded on the database such as dietary factors and physical activity or were not recorded in sufficient detail for their confounding effect to be completely removed by analysis. Numbers of patients in the different non-white ethnic groups were small so these were combined for inclusion in the analysis which may contribute to residual confounding. There will be some misclassification of the antidepressant exposure variables, as some patients may not have taken their prescribed antidepressant, or may not have taken it at the prescribed dose. This misclassification could underestimate associations with drug use. Furthermore although the cohort was large, the number of events was small for some of the antidepressant exposure categories. In particular there were relatively few prescriptions for citalopram at doses of 40 mg/day or more (19% of citalopram prescriptions), and only 28 diagnoses of arrhythmia in this category, so the 95% confidence interval for arrhythmia risk with high doses of citalopram arrhythmia is wide and increases in risk of up to 71% cannot be excluded.

The outcomes were not formally adjudicated in this study, but validation studies in other UK primary care databases have shown high levels of validity across a range of diseases, and we would expect levels of validity to be similar in QResearch®.[32 33] For example, Khan reported high positive predictive values in validation studies of acute myocardial infarction and cerebrovascular disease.[33] A study validating diagnostic codes for ventricular arrhythmia and sudden cardiac death reported a positive predictive value of 93%.[34] We included information from death certificates to identify additional patients with the 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 [17 18] 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. [13-15] This lack of coherence may reflect the smaller numbers of arrhythmia outcomes in the cohort studies when split by antidepressant drug and dose. Torsades de pointes which is the type of arrhythmia most closely related to QT interval prolongation is extremely rare, so the cohort studies cannot rule out an association for this particular type of arrhythmia.[35] A recent study of psychiatric in-patients found only people with two or more risk factors for QT prolongation, such as hypokalaemia, HIV infection and alcohol or drug use disorders, in addition to higher doses of citalopram and escitalopram developed either QT prolongation or a complication such as arrhythmia or sudden

death.[15] Even in a large cohort study, the presence of two or more such risk factors is likely to be rare. 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.[13 14] 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;[36 37] our findings are important as few studies have examined this for prescribed doses of tricyclic antidepressants.

In our previous study of antidepressants in older people with depression[10 22] we found a significantly increased risk of myocardial infarction for selective serotonin reuptake inhibitors but not for other antidepressants. Other observational studies have found similar results,[9 38] whilst several have found no association with selective serotonin reuptake inhibitors[39-42] or a reduced risk;[11 41 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: several are not restricted to patients with depression and so are highly susceptible to indication bias since depression is a strong risk factor for cardiovascular disease; some are only in elderly populations; whilst others are interview-based case-control studies prone to recall bias. It is unclear why our results differ from our previous study in older people which had a very similar study design,[10] but it could be due to the larger number of events in the older cohort, or increased susceptibility to side effects in older people due to age-related pharmacokinetic changes,[46] or the high prevalence of multimorbidity and use of concomitant medications in older people may result in interactions giving different patterns of risk with antidepressant use.

Observational studies of antidepressants and stroke have shown a more consistent pattern, with several studies finding an increased risk of stroke with selective serotonin reuptake inhibitor use.[10 42 47-49] A systematic review and meta-analysis of 13 observational studies of selective serotonin reuptake inhibitors and stroke[12] reported that selective serotonin reuptake inhibitors were associated with an increased risk of all types of stroke (adjusted odds ratio 1.40; 95 % confidence interval (CI), 1.09–1.80), and that risks were even higher when the analysis was restricted to the studies in which potential confounding by depression was considered. In a subgroup analysis by age group the odds ratios for stroke associated with selective serotonin reuptake inhibitor use were higher in studies restricted to older people, and were only significant in this group. This concurs with our findings in the current study of no association between selective serotonin reuptake inhibitors and stroke in people aged 20 to 64.

Clinical implications and future research

Prescription of antidepressants is a complex process, involving balancing of risks and benefits for different antidepressants and doses, accounting for severity of depression, patient risk factors, comorbidities and preferences. The results of this study in adults aged 20 to 64 are reassuring in light of recent concerns about citalopram and potential risk of arrhythmia, but as only small numbers of patients were prescribed high doses of citalopram we cannot rule out the possibility of an increased risk so suggest that high doses of citalopram should not be prescribed without a strong indication particularly where there are any risk factors for an increased QT interval. There was also no evidence that selective serotonin reuptake inhibitors are associated with an increased risk of myocardial infarction or stroke/transient ischaemic attack in this age group; they may even be associated with a reduced risk of myocardial infarction and arrhythmia particularly for fluoxetine. The potential cardioprotective effects of selective serotonin reuptake inhibitors, particularly fluoxetine, warrant further investigation including a randomised controlled trial.

The risk of arrhythmia was increased during the first 28 days of taking tricyclic and related antidepressants and among the antidepressants studied lofepramine had the highest risks of arrhythmia, myocardial infarction, and stroke/transient ischaemic attack. This finding may reflect selective prescribing of lofepramine since it is generally considered to be safer than other tricyclic and related antidepressants in overdose, but could also indicate increased risks when taken at doses typically prescribed in primary care. Further research using other designs such as the self-controlled case series approach may help to elucidate this association.

Conclusions

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

Acknowledgements

We acknowledge the contribution of practices who contribute to the QResearch® and to Egton Medical Information Systems (EMIS) and the University of Nottingham for expertise in establishing, developing and supporting the database. RM's contribution to the study has been funded through the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care East Midlands (CLAHRC EM).

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.

Funding

The project was funded by the National Institute for Health Research (NIHR) School for Primary Care Research (project number 81). The funding body did not play a role in the study design, writing of the manuscript or in the decision to submit the manuscript for publication.

Disclaimer

This paper presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

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

submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Transparency declaration

The lead author (Carol Coupland) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data Sharing statement

The patient level data from the QResearch are specifically licensed according to its governance framework. See www.qresearch.org for further details.

References

1. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. *Arch Gen Psychiatry* 2009;66(8):848-56.
2. Lockhart P, Guthrie B. Trends in primary care antidepressant prescribing 1995–2007: a longitudinal population database analysis. *Br J Gen Pract* 2011;61:e565-e72.
3. Stephenson CP, Karanges E, McGregor IS. Trends in the utilisation of psychotropic medications in Australia from 2000 to 2011. *Australian and New Zealand Journal of Psychiatry* 2013;47(1):74-87.
4. Pratt LA BD, Gu Q. . Antidepressant use in persons aged 12 and over: United States, 2005–2008. *NCHS data brief, no 76. Hyattsville, MD: National Center for Health Statistics*, 2011.
5. Health and Social Care Information Centre, Prescribing and Primary Care. Prescription Cost Analysis England 2013. 2014.
6. The NHS Information Centre PSU. Prescription cost analysis: England 2003. 2004.
7. Hatcher S, Arroll B. Newer antidepressants for the treatment of depression in adults. *BMJ* 2012;344.
8. Jolly K, Langman MJS. Psychotropic medication: curing illness or creating problems? *Heart* 2009;95(23):1893-94.
9. Blanchette CM, Simoni-Wastila L, Stuart B. Cardiovascular risk of antidepressant use in elderly medicare beneficiaries: Comparison by therapeutic class. *Ann Epidemiol* 2005;15(8):643-44.
10. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ* 2011;343:d4551
11. Schlienger RG, Fischer LM, Jick H, Meier CR. Current use of selective serotonin reuptake inhibitors and risk of acute myocardial infarction. *Drug Safety* 2004;27(14):1157-65.
12. Shin D, Oh Y, Eom C-S, Park S. Use of selective serotonin reuptake inhibitors and risk of stroke: a systematic review and meta-analysis. *J Neurol* 2014;261(4):686-95.
13. FDA Drug Safety Communication. FDA Drug Safety Communication: Abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide). *MedWatch, 2011.*
14. Castro VM, Clements CC, Murphy SN, Gainer VS, Fava M, Weilburg JB, et al. QT interval and antidepressant use: a cross sectional study of electronic health records. *BMJ* 2013;346:f288.
15. Girardin FR, Gex-Fabry M, Berney P, Shah D, Gaspoz J-M, Dayer P. Drug-Induced Long QT in adult psychiatric inpatients: The 5-year cross-sectional ECG Screening Outcome in Psychiatry Study. *Am. J. Psychiatry* 2013;170(12):1468-76.
16. El-Sherif N, Turitto G. Torsade de pointes. *Curr. Opin. Cardiol.* 2003;18(1):6-13.
17. Zivin K, Pfeiffer PN, Bohnert AS, Ganoczy D, Blow FC, Nallamothu BK, et al. Evaluation of the FDA warning against prescribing citalopram at doses exceeding 40 mg. *Am. J. Psychiatry* 2013;170(6):642-50.

18. Leonard CE, Bilker WB, Newcomb C, Kimmel SE, Hennessy S. Antidepressants and the risk of sudden cardiac death and ventricular arrhythmia. *Pharmacoepidemiology and Drug Safety* 2011;20(9):903-13.

19. Coupland C, Morriss R, Arthur A, Moore M, Hill T, Hippisley-Cox J. Safety of antidepressants in adults aged under 65: protocol for a cohort study using a large primary care database. *BMC Psychiatry* 2013;13(1):135.

20. Martinez C, Rietbrock S, Wise L, Ashby D, Chick J, Moseley J, et al. Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. *BMJ* 2005;330(7488):389.

21. Hippisley-Cox J, Pringle M, Hammersley V, Crown N, Wynn A, Meal A, et al. Antidepressants as risk factor for ischaemic heart disease: case-control study in primary care. *BMJ* 2001;323(7314):666-9.

22. Coupland C, Dhiman P, Barton G, Morriss R, Arthur A, Sach T, et al. A study of the safety and harms of antidepressant drugs for older people: a cohort study analysis using a large primary care database. *Health Technol Assess* 2011;15(28).

23. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients on Cox 2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case control analysis. *BMJ* 2005;366:1366-74.

24. Hippisley-Cox J, Coupland C, Brindle P. Derivation and validation of QStroke score for predicting risk of ischaemic stroke in primary care and comparison with other risk scores: a prospective open cohort study. *BMJ* 2013;346.

25. FDA Drug Safety Communication. FDA Drug Safety Communication: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. *Medwatch 2012*.

26. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999;319(7223):1492-95.

27. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur. Heart J.* 2006;27(23):2763-74.

28. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and Risk of Stroke Morbidity and Mortality. *JAMA* 2011;306(11):1241-49.

29. Taylor D. Antidepressant drugs and cardiovascular pathology: a clinical overview of effectiveness and safety. *Acta Psychiatrica Scandinavica* 2008;118(6):434-42.

30. NICE. Depression: the treatment and management of depression in adults (update). *National Clinical Practice Guideline 90*, 2009.

31. Coupland C, Hill T, Morriss R, Arthur A, Moore M, Hippisley-Cox J. Antidepressant use and risk of suicide and attempted suicide or self harm in people aged 20 to 64: cohort study using a primary care database. *BMJ* 2015;350:h517.
32. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br. J. Clin. Pharmacol.* 2010;69(1):4-14.
33. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br. J. Gen. Pract.* 2010;60:e128-e36.
34. Hennessy S, Leonard CE, Palumbo CM, Bilker WB, Newcomb C, Kimmel SE. Diagnostic codes for sudden cardiac death and ventricular arrhythmia functioned poorly to identify outpatient events in EPIC's General Practice Research Database. *Pharmacoepidemiology and Drug Safety* 2008;17(12):1131-36.
35. Bird ST, Crentsil V, Temple R, Pinheiro S, Demczar D, Stone M. Cardiac Safety Concerns Remain for Citalopram at Dosages Above 40 mg/Day. *Am. J. Psychiatry* 2014;171(1):17-19.
36. Thanacoody HKR, Thomas SL. Tricyclic Antidepressant Poisoning. *Toxicol. Rev.* 2005;24(3):205-14.
37. Roose SP, Glassman AH, Giardina EV, Walsh B, Woodring S, Bigger J. Tricyclic antidepressants in depressed patients with cardiac conduction disease. *Arch. Gen. Psychiatry* 1987;44(3):273-75.
38. Tata LJ, West J, Smith C, Farrington P, Card T, Smeeth L, et al. General population based study of the impact of tricyclic and selective serotonin reuptake inhibitor antidepressants on the risk of acute myocardial infarction. *Heart* 2005;91(4):465-71.
39. Hamer M, Batty GD, Seldenrijk A, Kivimaki M. Antidepressant medication use and future risk of cardiovascular disease: the Scottish Health Survey. *Eur. Heart J.* 2011;32(4):437-42.
40. Meier CR, Schlienger RG, Jick H. Use of selective serotonin reuptake inhibitors and risk of developing first-time acute myocardial infarction. *Br. J. Clin. Pharmacol.* 2001;52(2):179-84.
41. Monster TBM, Johnsen SP, Olsen ML, McLaughlin JK, Sorensen HT. Antidepressants and risk of first-time hospitalization for myocardial infarction: a population-based case-control study. *Am. J. Med.* 2004;117(10):732-7.
42. Smoller JW, Allison M, Cochrane BB, Curb JD, Perlis RH, Robinson JG, et al. Antidepressant Use and Risk of Incident Cardiovascular Morbidity and Mortality Among Postmenopausal Women in the Women's Health Initiative Study. *Arch. Intern. Med.* 2009;169(22):2128-39.
43. Kimmel SE, Schelleman H, Berlin JA, Oslin DW, Weinstein RB, Kinman JL, et al. The effect of selective serotonin re-uptake inhibitors on the risk of myocardial infarction in a cohort of patients with depression. *Br. J. Clin. Pharmacol.* 2011;72(3):514-17.
44. Sauer WH, Berlin JA, Kimmel SE. Selective Serotonin Reuptake Inhibitors and Myocardial Infarction. *Circulation* 2001;104(16):1894-98.
45. Oh S-W, Kim J, Myung S-K, Hwang S-S, Yoon D-H. Antidepressant Use and Risk of Coronary Heart Disease: Meta-Analysis of Observational Studies. *Br. J. Clin. Pharmacol.* 2014:727-37.

46. Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. *Exp. Gerontol.* 2003;38(8):843-53.

47. Castro VM, Gallagher PJ, Clements CC, Murphy SN, Gainer VS, Fava M, et al. Incident user cohort study of risk for gastrointestinal bleed and stroke in individuals with major depressive disorder treated with antidepressants. *BMJ Open* 2012;2(2).

48. Chen Y, Guo JJ, Li H, Wulsin L, Patel NC. Risk of cerebrovascular events associated with antidepressant use in patients with depression: A population-based, nested case-control study. *Ann. Pharmacother.* 2008;42(2):177-84.

49. Trifiro G, Dieleman J, Sen EF, Gambassi G, Sturkenboom M. Risk of Ischemic Stroke Associated With Antidepressant Drug Use in Elderly Persons. *J. Clin. Psychopharmacol.* 2010;30(3):252-58.

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:		
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)
HRT*	7,207	(4.9)

* Percentage is for females only.

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

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

			Unadjusted analysis		Adjusted analysis		
	No of events*	Person-years*	Hazard ratio	95% CI	Hazard ratio	95% CI	P
Antidepressant class							
No current use	887	568,365	1.00		1.00		
TCAs	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		
TCAs:							
≤ 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
SSRIs:							
≤ 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
Others:							
≤ 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		
TCAs:							
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
SSRIs:							
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
Others:							
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.

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.

[2] Test for trend uses continuous values of dose

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

			Unadjusted		Adjusted analysis[1]		
	No of events*	Person-years*	Hazard ratio	95% CI	Hazard ratio	95% CI	P
Antidepressant drug							
No current use	887	568,365	1.00		1.00		
TCAs:							
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					
SSRIs:							
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:>1DDD	9	6,448	0.89	(0.47 to 1.7)	0.78	(0.41 to 1.49)	0.45
Others:							
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 **Unadjusted and adjusted hazard ratios for myocardial infarction by antidepressant class, dose, and duration over 5 years follow-up.**

			Unadjusted analysis		Adjusted analysis[1]		
	No of events*	Person years*	Hazard ratio	95% CI	Hazard ratio	95% CI	P
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		
TCAs:							
≤ 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
SSRIs:							
≤ 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
Others:							
≤ 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		
TCAs:							
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
SSRIs:							
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
Others:							
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

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

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

[2] Test for trend uses continuous values of dose

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

			Unadjusted analysis		Adjusted analysis		
	No of events*	Person-years*	Hazard ratio	95% CI	Hazard ratio	95% CI	P
Antidepressant class							
No current use	610	570,879	1.00		1.00		
TCAs	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		
TCAs:							
≤ 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
SSRIs:							
≤ 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
Others:							
≤ 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		
TCAs:							
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
SSRIs:							
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
Others:							
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.

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.

[2] Test for trend uses continuous values of dose

Table 6 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						
TCAs:						
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)
Lofepramine	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)
SSRIs:						
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)
Others:						
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.

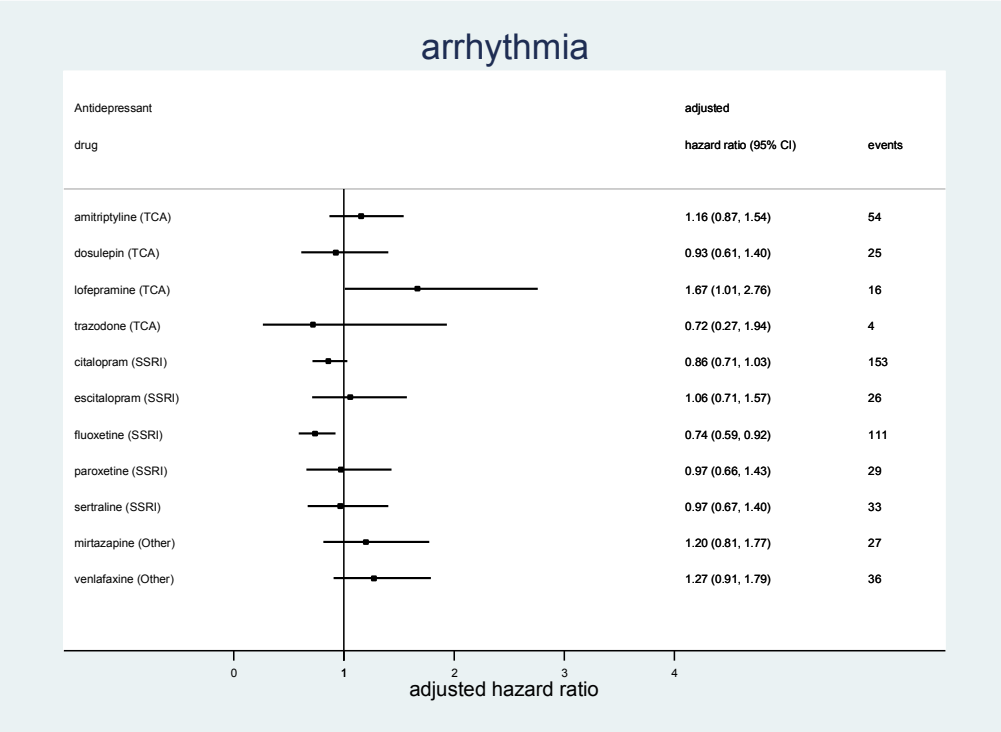
[1] Absolute risks are adjusted for confounders listed in table 2.

[2] Absolute risks are adjusted for confounders listed in table 3.

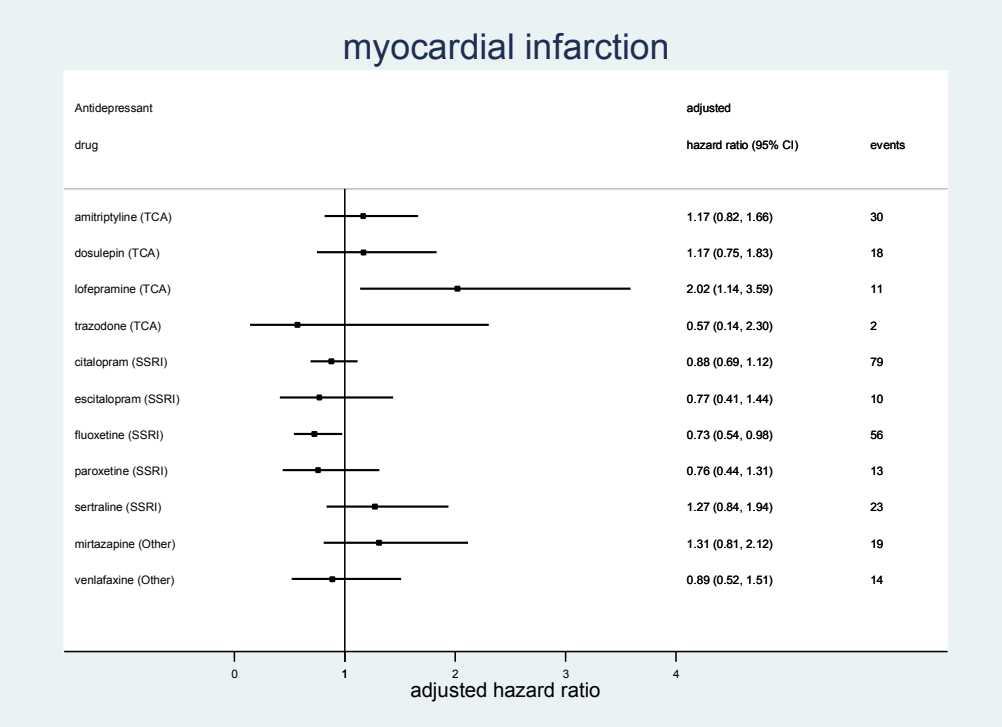
[3] Absolute risks are adjusted for confounders listed in table 4.

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.**

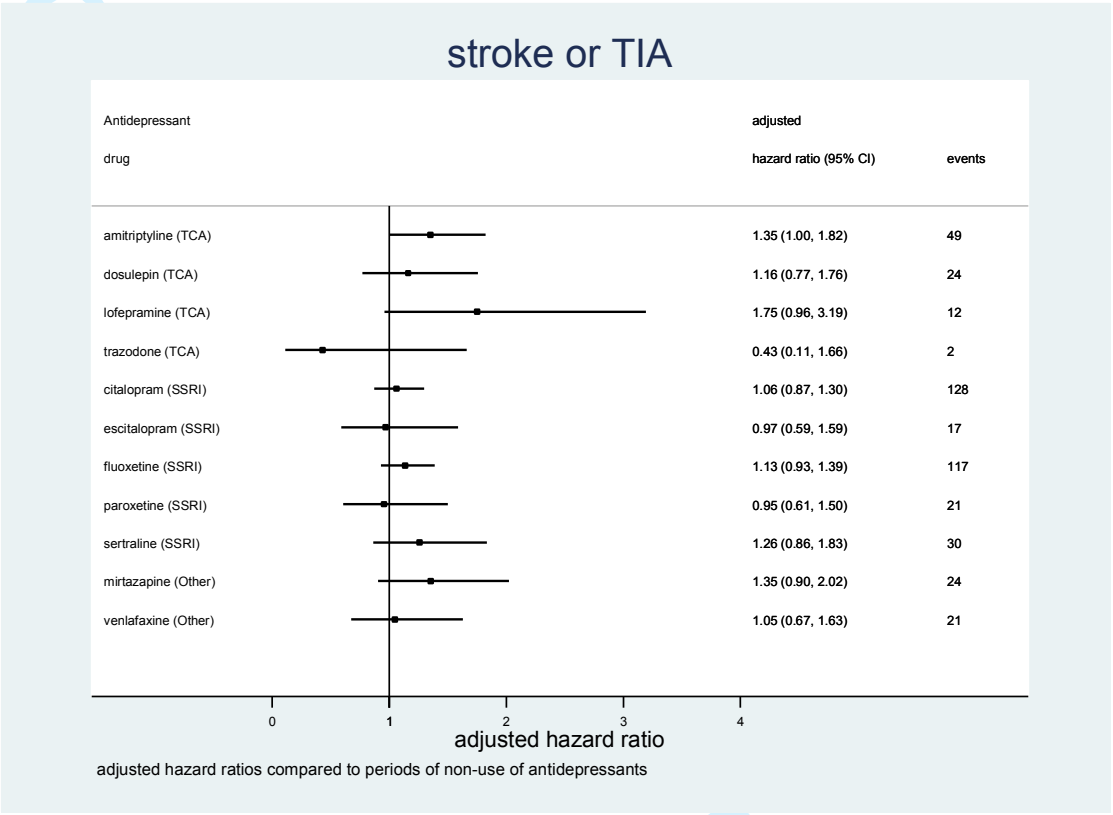
(a)



(b)



(c)



Adjusted hazard ratios compared to periods of non-use of antidepressants
TCA = tricyclic and related antidepressant
SSRI = selective serotonin reuptake inhibitor

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	Unadjusted and adjusted hazard ratios for arrhythmia by citalopram split into 3 dose categories for 5 years follow-up.
Table 3s	Unadjusted and adjusted hazard ratios for arrhythmia by antidepressant class, dose and individual drug for 5 years follow-up, excluding untreated patients.
Table 4s	Unadjusted and adjusted hazard ratios for arrhythmia by antidepressant class, dose and individual drug for total follow-up.
Table 5s	Unadjusted and adjusted hazard ratios for arrhythmia by antidepressant class, dose and individual drug for 1 year follow-up.
Table 6s	Unadjusted and adjusted hazard ratios for myocardial infarction by antidepressant class, dose and individual drug for 5 years follow-up, excluding untreated patients.
Table 7s	Unadjusted and adjusted hazard ratios for myocardial infarction by antidepressant class, dose and individual drug for total follow-up.
Table 8s	Unadjusted and adjusted hazard ratios for myocardial infarction by antidepressant class, dose and individual drug for 1 year follow-up.
Table 9s	Unadjusted and adjusted hazard ratios for stroke/TIA by antidepressant class, dose and individual drug for 5 years follow-up, excluding untreated patients.
Table 10s	Unadjusted and adjusted hazard ratios for stroke/TIA by antidepressant class, dose and individual drug for total follow-up.
Table 11s	Unadjusted and adjusted hazard ratios for stroke/TIA by antidepressant class, dose and individual drug for 1 year follow-up.

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

Antidepressant drug	n[1]	%[2]	Actual dose prescribed (mg/day)[3]		
			DDD value (mg/day)	Median	IQR
Tricyclic and related antidepressants (TCA)					
Amitriptyline	236,416	7.3	75	25	15 to 50
Dosulepin	125,302	3.9	150	75	50 to 150
Lofepramine	47,414	1.5	105	140	140 to 210
Trazodone	30,912	1.0	300	125	75 to 150
Selective serotonin reuptake inhibitors (SSRI)					
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
Other antidepressants					
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	3,252,633				

[1] Numbers 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. Unadjusted and adjusted hazard ratios for arrhythmia over 5 years follow-up with citalopram categorised into three dose categories

			Unadjusted			Adjusted analysis[1]		
	No of events*	Person years*	HR	95% CI	P	HR	95% CI	P
Antidepressant drug								
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 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 3s. 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)	0.517
SSRIs	352	1.02	(0.88 to 1.18)	0.803	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)	0.124
Combined antidepressants	10	1.49	(0.76 to 2.91)	0.248	1.07	(0.55 to 2.08)	0.852
Antidepressant class and dose categories							
No current use	731	1.00			1.00		
TCAs:							
≤ 0.5 DDD	51	1.36	(1.02 to 1.82)	0.035	0.88	(0.66 to 1.18)	0.386
>0.5 DDD/≤ 1.0 DDD	26	2.03	(1.38 to 2.97)	<0.001	1.34	(0.90 to 1.99)	0.147
> 1.0 DDD	14	1.66	(0.98 to 2.81)	0.062	1.31	(0.76 to 2.25)	0.326
SSRIs:							
≤ 0.5 DDD	30	1.18	(0.81 to 1.71)	0.381	0.91	(0.62 to 1.32)	0.617
>0.5 DDD/≤ 1.0 DDD	236	0.96	(0.8 to 1.14)	0.633	0.77	(0.65 to 0.92)	0.004
> 1.0 DDD	75	1.17	(0.91 to 1.5)	0.218	0.97	(0.75 to 1.25)	0.802
Others:							
≤ 0.5 DDD	9	1.40	(0.74 to 2.64)	0.306	0.96	(0.51 to 1.82)	0.900
>0.5 DDD/≤ 1.0 DDD	31	1.52	(1.08 to 2.15)	0.017	1.15	(0.81 to 1.64)	0.438
> 1.0 DDD	20	1.50	(0.98 to 2.31)	0.062	1.28	(0.84 to 1.97)	0.253
Antidepressant drug							
No current use	731	1.00			1.00		
TCAs:							
Amitriptyline	54	1.75	(1.32 to 2.33)	<0.001	1.15	(0.86 to 1.53)	0.347
Dosulepin	25	1.31	(0.86 to 1.98)	0.206	0.92	(0.60 to 1.39)	0.680
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)	0.533	0.71	(0.26 to 1.93)	0.504
SSRIs:							
Citalopram	153	1.07	(0.89 to 1.29)	0.469	0.84	(0.69 to 1.01)	0.068
Escitalopram	26	1.33	(0.91 to 1.94)	0.146	1.04	(0.69 to 1.55)	0.860
Fluoxetine	111	0.86	(0.68 to 1.08)	0.197	0.72	(0.57 to 0.91)	0.005
Paroxetine	29	1.12	(0.76 to 1.65)	0.560	0.96	(0.65 to 1.42)	0.843
Sertraline	33	1.15	(0.8 to 1.66)	0.452	0.95	(0.65 to 1.38)	0.787
Others:							
Mirtazapine	27	1.74	(1.19 to 2.53)	0.004	1.19	(0.81 to 1.76)	0.371
Venlafaxine	36	1.46	(1.04 to 2.05)	0.028	1.27	(0.90 to 1.78)	0.175
All other antidepressants	8	1.02	(0.51 to 2.03)	0.964	0.72	(0.36 to 1.44)	0.356
Combined antidepressants	10	1.49	(0.76 to 2.9)	0.248	1.06	(0.54 to 2.08)	0.854

* 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 4s. Unadjusted and adjusted hazard ratios for arrhythmia by antidepressant class, dose and individual drug for total follow-up period.

		Unadjusted analysis			Adjusted analysis[1]		
	No of events*	HR	95% CI	P	HR	95% CI	P
Antidepressant class							
No current use	1517	1.00			1.00		
TCAs	165	1.60	(1.37 to 1.88)	<0.001	1.10	(0.93 to 1.30)	0.251
SSRIs	462	0.93	(0.83 to 1.05)	0.238	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)	0.354	0.94	(0.58 to 1.54)	0.815
Antidepressant class and dose categories							
No current use	1517	1.00			1.00		
TCAs:							
≤ 0.5 DDD	85	1.40	(1.12 to 1.73)	0.003	0.92	(0.74 to 1.15)	0.477
>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)	0.105
SSRIs:							
≤ 0.5 DDD	41	1.11	(0.82 to 1.5)	0.516	0.88	(0.65 to 1.19)	0.414
>0.5 DDD/≤ 1.0 DDD	297	0.88	(0.77 to 1.01)	0.071	0.74	(0.64 to 0.85)	<0.001
> 1.0 DDD	107	1.02	(0.83 to 1.25)	0.865	0.90	(0.73 to 1.11)	0.328
Others:							
≤ 0.5 DDD	11	1.03	(0.58 to 1.82)	0.916	0.77	(0.44 to 1.37)	0.377
>0.5 DDD/≤ 1.0 DDD	47	1.50	(1.12 to 2.00)	0.006	1.18	(0.87 to 1.59)	0.284
> 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		
TCAs:							
Amitriptyline	92	1.67	(1.35 to 2.05)	<0.001	1.14	(0.92 to 1.41)	0.244
Dosulepin	33	1.28	(0.90 to 1.82)	0.172	0.89	(0.63 to 1.27)	0.531
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)	0.072	1.11	(0.59 to 2.08)	0.738
SSRIs:							
Citalopram	204	0.96	(0.82 to 1.13)	0.646	0.80	(0.68 to 0.94)	0.008
Escitalopram	32	1.13	(0.79 to 1.62)	0.489	0.92	(0.63 to 1.32)	0.640
Fluoxetine	143	0.82	(0.68 to 0.98)	0.030	0.72	(0.60 to 0.86)	<0.001
Paroxetine	36	1.02	(0.72 to 1.45)	0.903	0.87	(0.61 to 1.24)	0.438
Sertraline	47	1.05	(0.78 to 1.41)	0.736	0.91	(0.67 to 1.23)	0.541
Others:							
Mirtazapine	42	1.61	(1.20 to 2.15)	0.001	1.20	(0.89 to 1.62)	0.231
Venlafaxine	53	1.40	(1.07 to 1.83)	0.013	1.24	(0.95 to 1.62)	0.115
All other antidepressants	15	1.14	(0.69 to 1.87)	0.604	0.74	(0.43 to 1.26)	0.267
Combined antidepressants	17	1.26	(0.77 to 2.05)	0.354	0.94	(0.58 to 1.54)	0.812

* 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 1 year follow-up period.

		Unadjusted analysis			Adjusted analysis[1]		
	No of events*	HR	95% CI	P	HR	95% CI	P
Antidepressant class							
No current use	127	1.00			1.00		
TCAs	39	1.56	(1.09 to 2.23)	0.016	1.16	(0.81 to 1.67)	0.422
SSRIs	141	0.92	(0.71 to 1.19)	0.529	0.86	(0.66 to 1.11)	0.244
Other antidepressants	20	1.72	(1.10 to 2.69)	0.018	1.33	(0.84 to 2.12)	0.226
Combined antidepressants	5	4.05	(1.46 to 11.22)	0.007	3.45	(1.24 to 9.57)	0.017
Antidepressant class and dose categories							
No current use	127	1.00			1.00		
TCAs:							
≤ 0.5 DDD	21	1.37	(0.87 to 2.17)	0.173	0.98	(0.62 to 1.55)	0.921
>0.5 DDD/≤ 1.0 DDD	10	2.37	(1.28 to 4.36)	0.006	1.76	(0.92 to 3.35)	0.088
> 1.0 DDD	4	1.30	(0.48 to 3.52)	0.608	1.22	(0.46 to 3.24)	0.693
Test for trend				0.719			0.825
SSRIs:							
≤ 0.5 DDD	11	1.16	(0.64 to 2.11)	0.620	0.95	(0.52 to 1.72)	0.855
>0.5 DDD/≤ 1.0 DDD	105	0.86	(0.65 to 1.15)	0.311	0.81	(0.62 to 1.08)	0.151
> 1.0 DDD	21	1.16	(0.71 to 1.88)	0.551	1.07	(0.65 to 1.76)	0.787
Test for trend				0.632			0.568
Others:							
≤ 0.5 DDD	3	1.54	(0.49 to 4.80)	0.459	1.06	(0.34 to 3.32)	0.925
>0.5 DDD/≤ 1.0 DDD	13	2.12	(1.22 to 3.69)	0.008	1.65	(0.91 to 2.98)	0.098
> 1.0 DDD	2	0.89	(0.22 to 3.53)	0.866	0.80	(0.20 to 3.20)	0.757
Test for trend				0.425			0.514
Antidepressant drug							
No current use	130	1.00			1.00		
TCAs:							
Amitriptyline	18	1.73	(1.04 to 2.87)	0.034	1.15	(0.69 to 1.94)	0.587
Dosulepin	8	0.93	(0.45 to 1.91)	0.844	0.73	(0.35 to 1.50)	0.394
Lofepramine	8	2.20	(1.08 to 4.49)	0.029	2.13	(1.05 to 4.33)	0.036
Trazodone	3	2.34	(0.72 to 7.58)	0.156	1.72	(0.53 to 5.56)	0.365
SSRIs:							
Citalopram	56	0.90	(0.65 to 1.24)	0.508	0.79	(0.57 to 1.10)	0.169
Escitalopram	9	1.10	(0.52 to 2.33)	0.798	1.01	(0.47 to 2.16)	0.986
Fluoxetine	48	0.80	(0.56 to 1.15)	0.222	0.79	(0.55 to 1.13)	0.191
Paroxetine	13	1.08	(0.60 to 1.93)	0.807	1.10	(0.61 to 1.99)	0.740
Sertraline	15	1.39	(0.83 to 2.31)	0.207	1.21	(0.71 to 2.07)	0.477
Others:							
Mirtazapine	8	1.86	(0.94 to 3.68)	0.077	1.20	(0.57 to 2.53)	0.625
Venlafaxine	11	1.76	(0.95 to 3.26)	0.075	1.64	(0.88 to 3.08)	0.121
All other antidepressants	3	1.19	(0.39 to 3.60)	0.756	0.90	(0.30 to 2.69)	0.845
Combined antidepressants	5	4.05	(1.46 to 11.21)	0.007	3.44	(1.24 to 9.55)	0.018

* 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. Unadjusted and adjusted hazard ratios for myocardial infarction 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	397	1.00			1.00		
TCAs	63	1.83	(1.43 to 2.35)	<0.001	1.19	(0.93 to 1.52)	0.156
SSRIs	182	1.02	(0.86 to 1.23)	0.791	0.84	(0.70 to 1.00)	0.051
Other antidepressants	33	1.38	(0.97 to 1.98)	0.076	0.98	(0.68 to 1.40)	0.892
Combined antidepressants	3	0.83	(0.27 to 2.55)	0.749	0.56	(0.18 to 1.72)	0.308
Antidepressant class and dose categories							
No current use	397	1.00			1.00		
TCAs:							
≤ 0.5 DDD	31	1.60	(1.12 to 2.28)	0.010	1.02	(0.72 to 1.46)	0.890
>0.5 DDD/≤ 1.0 DDD	15	2.14	(1.3 to 3.52)	0.003	1.28	(0.77 to 2.11)	0.337
> 1.0 DDD	10	2.24	(1.2 to 4.17)	0.011	1.57	(0.84 to 2.94)	0.154
SSRIs:							
≤ 0.5 DDD		1.13	(0.68 to 1.86)	0.643	0.96	(0.57 to 1.61)	0.866
>0.5 DDD/≤ 1.0 DDD	14	0.90	(0.72 to 1.12)	0.340	0.73	(0.58 to 0.91)	0.005
> 1.0 DDD	110	1.45	(1.09 to 1.91)	0.010	1.14	(0.85 to 1.52)	0.388
Others:	50						
≤ 0.5 DDD		2.64	(1.37 to 5.1)	0.004	1.77	(0.91 to 3.43)	0.090
>0.5 DDD/≤ 1.0 DDD		0.71	(0.36 to 1.42)	0.338	0.50	(0.25 to 1.01)	0.052
> 1.0 DDD	9	1.52	(0.84 to 2.76)	0.165	1.08	(0.59 to 1.96)	0.806
Antidepressant drug							
No current use	397				1.00		
TCAs:							
Amitriptyline	30	1.84	(1.28 to 2.63)	0.001	1.16	(0.81 to 1.66)	0.406
Dosulepin	18	1.80	(1.14 to 2.83)	0.011	1.16	(0.74 to 1.83)	0.513
Lofepramine	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)	0.991	0.57	(0.14 to 2.29)	0.428
SSRIs:							
Citalopram	79	1.05	(0.82 to 1.34)	0.691	0.87	(0.68 to 1.12)	0.272
Escitalopram	10	0.89	(0.48 to 1.67)	0.720	0.76	(0.40 to 1.42)	0.384
Fluoxetine	56	0.89	(0.67 to 1.19)	0.434	0.72	(0.53 to 0.97)	0.031
Paroxetine	13	1.02	(0.60 to 1.73)	0.939	0.75	(0.43 to 1.29)	0.292
Sertraline	23	1.52	(1.00 to 2.31)	0.048	1.25	(0.82 to 1.91)	0.305
Others:							
Mirtazapine	19	2.20	(1.36 to 3.54)	0.001	1.29	(0.79 to 2.10)	0.303
Venlafaxine	14	1.05	(0.62 to 1.79)	0.850	0.86	(0.51 to 1.47)	0.592
All other antidepressants	3	0.72	(0.24 to 2.20)	0.567	0.51	(0.17 to 1.56)	0.240
Combined antidepressants	3	0.83	(0.27 to 2.55)	0.749	0.56	(0.18 to 1.72)	0.310

* 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 7s. Unadjusted and adjusted hazard ratios for myocardial infarction by antidepressant class, dose and individual drug for total follow-up period.

		Unadjusted analysis			Adjusted analysis[1]		
	No of events*	HR	95% CI	P	HR	95% CI	P
Antidepressant class							
No current use	783	1.00			1.00		
TCAs	93	1.78	(1.44 to 2.19)	<0.001	1.18	(0.96 to 1.45)	0.119
SSRIs	260	1.02	(0.89 to 1.18)	0.749	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)	0.160
Combined antidepressants	8	1.17	(0.60 to 2.30)	0.646	0.81	(0.41 to 1.60)	0.549
Antidepressant class and dose categories							
No current use	783	1.00			1.00		
TCAs:							
≤ 0.5 DDD	46	1.51	(1.11 to 2.04)	0.008	0.98	(0.73 to 1.33)	0.902
>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
SSRIs:							
≤ 0.5 DDD	21	1.11	(0.73 to 1.69)	0.634	0.97	(0.63 to 1.48)	0.872
>0.5 DDD/≤ 1.0 DDD	160	0.94	(0.79 to 1.12)	0.516	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)	0.405
Others:							
≤ 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)	0.997	0.71	(0.44 to 1.15)	0.169
> 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		
TCAs:							
Amitriptyline	49	1.75	(1.33 to 2.31)	<0.001	1.14	(0.86 to 1.51)	0.361
Dosulepin	25	1.90	(1.29 to 2.79)	0.001	1.27	(0.86 to 1.87)	0.222
Lofepramine	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)	0.579	0.38	(0.09 to 1.52)	0.170
SSRIs:							
Citalopram	113	1.04	(0.85 to 1.27)	0.696	0.91	(0.74 to 1.12)	0.364
Escitalopram	13	0.89	(0.52 to 1.53)	0.674	0.79	(0.46 to 1.35)	0.383
Fluoxetine	78	0.87	(0.69 to 1.10)	0.252	0.74	(0.58 to 0.95)	0.019
Paroxetine	21	1.16	(0.75 to 1.78)	0.505	0.87	(0.56 to 1.35)	0.533
Sertraline	33	1.44	(1.02 to 2.04)	0.039	1.27	(0.9 to 1.81)	0.177
Others:							
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)	0.478
All other antidepressants	7	1.04	(0.46 to 2.38)	0.919	0.80	(0.35 to 1.84)	0.598
Combined antidepressants	8	1.17	(0.60 to 2.30)	0.646	0.81	(0.41 to 1.60)	0.548

* 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 8s. Unadjusted and adjusted hazard ratios for myocardial infarction by antidepressant class, dose and individual drug for 1 year follow-up period.

		Unadjusted analysis			Adjusted analysis[1]		
	No of events*	HR	95% CI	P	HR	95% CI	P
Antidepressant class							
No current use	90	1.00			1.00		
TCAs	25	1.50	(0.99 to 2.27)	0.057	1.09	(0.72 to 1.66)	0.682
SSRIs	63	0.66	(0.48 to 0.91)	0.011	0.58	(0.42 to 0.79)	0.001
Other antidepressants	9	1.09	(0.57 to 2.10)	0.794	0.81	(0.42 to 1.58)	0.541
Combined antidepressants	2	2.37	(0.59 to 9.53)	0.223	1.68	(0.43 to 6.65)	0.458
Antidepressant class and dose categories							
No current use	90	1.00			1.00		
TCAs:							
≤ 0.5 DDD	12	1.24	(0.68 to 2.25)	0.481	0.86	(0.47 to 1.56)	0.620
>0.5 DDD/≤ 1.0 DDD	4	1.31	(0.49 to 3.47)	0.591	0.93	(0.35 to 2.50)	0.891
> 1.0 DDD	3	1.47	(0.47 to 4.58)	0.505	1.29	(0.41 to 4.04)	0.660
Test for trend				0.665			0.470
SSRIs:							
≤ 0.5 DDD	5	0.81	(0.33 to 2.03)	0.659	0.76	(0.30 to 1.92)	0.565
>0.5 DDD/≤ 1.0 DDD	43	0.58	(0.41 to 0.83)	0.003	0.52	(0.37 to 0.73)	<0.001
> 1.0 DDD	11	0.95	(0.53 to 1.71)	0.861	0.75	(0.41 to 1.36)	0.343
Test for trend				0.457			0.424
Others:							
≤ 0.5 DDD	2	1.56	(0.38 to 6.33)	0.536	0.95	(0.23 to 3.96)	0.948
>0.5 DDD/≤ 1.0 DDD	3	0.68	(0.22 to 2.08)	0.500	0.53	(0.17 to 1.60)	0.258
> 1.0 DDD	2	1.26	(0.32 to 4.92)	0.744	1.04	(0.26 to 4.17)	0.953
Test for trend				0.600			0.397
Antidepressant drug							
No current use	90	1.00			1.00		
TCAs:							
Amitriptyline	8	1.13	(0.55 to 2.31)	0.747	0.75	(0.37 to 1.55)	0.442
Dosulepin	8	1.43	(0.71 to 2.86)	0.317	1.07	(0.53 to 2.18)	0.847
Lofepramine	8	3.36	(1.67 to 6.79)	0.001	3.07	(1.50 to 6.26)	0.002
Trazodone	1	1.19	(0.17 to 8.56)	0.862	0.73	(0.10 to 5.19)	0.755
SSRIs:							
Citalopram	27	0.68	(0.44 to 1.04)	0.074	0.59	(0.39 to 0.91)	0.017
Escitalopram	4	0.74	(0.27 to 2.05)	0.565	0.67	(0.25 to 1.82)	0.431
Fluoxetine	18	0.48	(0.29 to 0.79)	0.004	0.44	(0.27 to 0.72)	0.001
Paroxetine	3	0.50	(0.18 to 1.38)	0.182	0.38	(0.12 to 1.22)	0.104
Sertraline	10	1.44	(0.79 to 2.61)	0.230	1.18	(0.64 to 2.20)	0.593
Others:							
Mirtazapine	5	1.53	(0.64 to 3.68)	0.338	0.91	(0.37 to 2.24)	0.837
Venlafaxine	4	0.94	(0.36 to 2.48)	0.897	0.89	(0.33 to 2.39)	0.813
All other antidepressants	1	0.60	(0.08 to 4.34)	0.616	0.46	(0.06 to 3.35)	0.443
Combined antidepressants	2	2.37	(0.59 to 9.52)	0.224	1.68	(0.43 to 6.64)	0.459

* 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 stroke/TIA 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	525	1.00			1.00		
TCAs	90	1.93	(1.52 to 2.46)	<0.001	1.19	(0.93 to 1.51)	0.165
SSRIs	313	1.26	(1.08 to 1.48)	0.003	1.04	(0.89 to 1.21)	0.652
Other antidepressants	50	1.66	(1.25 to 2.2)	<0.001	1.15	(0.86 to 1.53)	0.357
Combined antidepressants	11	2.51	(1.42 to 4.43)	0.001	1.47	(0.81 to 2.65)	0.203
Antidepressant class and dose categories							
No current use	525	1.00			1.00		
TCAs:							
≤ 0.5 DDD	48	1.80	(1.32 to 2.45)	<0.001	1.05	(0.77 to 1.43)	0.750
>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)	0.237
SSRIs:							
≤ 0.5 DDD	24	1.33	(0.86 to 2.06)	0.203	1.07	(0.69 to 1.66)	0.761
>0.5 DDD/≤ 1.0 DDD	216	1.25	(1.05 to 1.49)	0.011	1.01	(0.85 to 1.20)	0.877
> 1.0 DDD	66	1.40	(1.08 to 1.81)	0.012	1.16	(0.89 to 1.51)	0.278
Others:							
≤ 0.5 DDD	10	2.18	(1.17 to 4.07)	0.014	1.47	(0.78 to 2.76)	0.229
>0.5 DDD/≤ 1.0 DDD	20	1.46	(0.96 to 2.24)	0.078	0.97	(0.62 to 1.51)	0.883
> 1.0 DDD	13	1.36	(0.80 to 2.31)	0.263	1.05	(0.61 to 1.79)	0.869
Antidepressant drug							
No current use	525	1.00			1.00		
TCAs:							
Amitriptyline	49	2.21	(1.64 to 2.99)	<0.001	1.29	(0.95 to 1.75)	0.099
Dosulepin	24	1.76	(1.17 to 2.66)	0.007	1.11	(0.74 to 1.68)	0.615
Lofepramine	12	2.21	(1.21 to 4.05)	0.010	1.66	(0.91 to 3.04)	0.099
Trazodone	2	0.75	(0.19 to 2.97)	0.678	0.41	(0.11 to 1.58)	0.195
SSRIs:							
Citalopram	128	1.21	(0.99 to 1.48)	0.061	1.01	(0.83 to 1.24)	0.886
Escitalopram	17	1.12	(0.68 to 1.84)	0.654	0.92	(0.56 to 1.52)	0.750
Fluoxetine	117	1.32	(1.07 to 1.62)	0.009	1.08	(0.88 to 1.33)	0.469
Paroxetine	21	1.18	(0.76 to 1.84)	0.458	0.91	(0.58 to 1.43)	0.683
Sertraline	30	1.50	(1.03 to 2.18)	0.032	1.20	(0.82 to 1.74)	0.351
Others:							
Mirtazapine	24	2.16	(1.46 to 3.20)	<0.001	1.29	(0.86 to 1.94)	0.219
Venlafaxine	21	1.30	(0.85 to 1.98)	0.232	1.00	(0.64 to 1.56)	0.998
All other antidepressants	8	1.43	(0.71 to 2.88)	0.315	0.96	(0.48 to 1.93)	0.903
Combined antidepressants	11	2.51	(1.42 to 4.43)	0.001	1.47	(0.81 to 2.65)	0.201

* 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 10s. Unadjusted and adjusted hazard ratios for stroke/TIA by antidepressant class, dose and individual drug for total follow-up period.

		Unadjusted analysis			Adjusted analysis[1]		
	No of events*	HR	95% CI	P	HR	95% CI	P
Antidepressant class							
No current use	1082	1.00			1.00		
TCAs	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)	0.118
Other antidepressants	81	1.63	(1.31 to 2.04)	<0.001	1.20	(0.96 to 1.5)	0.111
Combined antidepressants	21	2.22	(1.47 to 3.35)	<0.001	1.44	(0.94 to 2.2)	0.093
Antidepressant class and dose categories							
No current use	1082	1.00			1.00		
TCAs:							
≤ 0.5 DDD	80	1.89	(1.49 to 2.38)	<0.001	1.17	(0.92 to 1.48)	0.196
>0.5 DDD/≤ 1.0 DDD	31	2.14	(1.53 to 3.01)	<0.001	1.32	(0.93 to 1.86)	0.117
> 1.0 DDD	16	1.86	(1.12 to 3.09)	0.017	1.33	(0.78 to 2.26)	0.293
SSRIs:							
≤ 0.5 DDD	32	1.22	(0.83 to 1.80)	0.304	1.02	(0.69 to 1.49)	0.936
>0.5 DDD/≤ 1.0 DDD	293	1.25	(1.08 to 1.44)	0.002	1.05	(0.92 to 1.21)	0.460
> 1.0 DDD	112	1.50	(1.24 to 1.82)	<0.001	1.32	(1.08 to 1.61)	0.006
Others:							
≤ 0.5 DDD	14	1.86	(1.11 to 3.12)	0.018	1.37	(0.81 to 2.29)	0.237
>0.5 DDD/≤ 1.0 DDD	32	1.45	(1.03 to 2.05)	0.033	1.02	(0.72 to 1.46)	0.898
> 1.0 DDD	26	1.60	(1.07 to 2.42)	0.024	1.27	(0.85 to 1.90)	0.253
Antidepressant drug							
No current use	1082	1.00			1.00		
TCAs:							
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)	0.616
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)	0.342	0.83	(0.37 to 1.83)	0.642
SSRIs:							
Citalopram	189	1.27	(1.08 to 1.49)	0.004	1.11	(0.95 to 1.30)	0.202
Escitalopram	28	1.40	(0.95 to 2.06)	0.089	1.16	(0.78 to 1.72)	0.469
Fluoxetine	154	1.25	(1.05 to 1.48)	0.011	1.08	(0.91 to 1.29)	0.377
Paroxetine	31	1.25	(0.88 to 1.79)	0.218	0.99	(0.68 to 1.42)	0.943
Sertraline	44	1.40	(1.03 to 1.9)	0.034	1.17	(0.85 to 1.61)	0.328
Others:							
Mirtazapine	35	1.90	(1.36 to 2.64)	<0.001	1.25	(0.90 to 1.75)	0.187
Venlafaxine	39	1.46	(1.05 to 2.01)	0.022	1.17	(0.84 to 1.63)	0.364
All other antidepressants	14	1.51	(0.90 to 2.55)	0.120	1.08	(0.65 to 1.81)	0.765
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.

Table 11s. Unadjusted and adjusted hazard ratios for stroke/TIA by antidepressant class, dose and individual drug for 1 year follow-up period.

		Unadjusted analysis			Adjusted analysis[1]		
	No of events*	HR	95% CI	P	HR	95% CI	P
Antidepressant class							
No current use	113	1.00			1.00		
TCAs	33	1.44	(0.98 to 2.12)	0.065	1.01	(0.69 to 1.49)	0.944
SSRIs	118	0.88	(0.67 to 1.15)	0.340	0.83	(0.63 to 1.09)	0.181
Other antidepressants	16	1.54	(0.95 to 2.50)	0.083	1.15	(0.69 to 1.90)	0.593
Combined antidepressants	1	0.89	(0.13 to 6.34)	0.911	0.69	(0.10 to 4.96)	0.715
Antidepressant class and dose categories							
No current use	113	1.00			1.00		
TCAs:							
≤ 0.5 DDD	18	1.34	(0.82 to 2.18)	0.245	0.87	(0.54 to 1.41)	0.583
>0.5 DDD/≤ 1.0 DDD	8	1.93	(0.95 to 3.92)	0.069	1.36	(0.66 to 2.78)	0.407
> 1.0 DDD	4	1.45	(0.54 to 3.92)	0.463	1.26	(0.47 to 3.38)	0.649
Test for trend				0.598			0.228
SSRIs:							
≤ 0.5 DDD	7	0.84	(0.39 to 1.78)	0.642	0.73	(0.34 to 1.56)	0.419
>0.5 DDD/≤ 1.0 DDD	90	0.86	(0.65 to 1.14)	0.294	0.81	(0.61 to 1.09)	0.161
> 1.0 DDD	17	1.02	(0.61 to 1.70)	0.934	0.99	(0.59 to 1.67)	0.977
Test for trend				0.572			0.470
Others:							
≤ 0.5 DDD	4	2.30	(0.84 to 6.31)	0.105	1.58	(0.57 to 4.35)	0.379
>0.5 DDD/≤ 1.0 DDD	7	1.35	(0.68 to 2.67)	0.390	0.95	(0.45 to 1.98)	0.883
> 1.0 DDD	4	1.93	(0.72 to 5.20)	0.193	1.76	(0.66 to 4.73)	0.260
Test for trend				0.962			0.718
Antidepressant drug							
No current use	113	1.00			1.00		
TCAs:							
Amitriptyline	15	1.54	(0.90 to 2.64)	0.115	1.00	(0.59 to 1.70)	0.996
Dosulepin	12	1.58	(0.89 to 2.80)	0.122	1.12	(0.63 to 1.98)	0.702
Lofepramine	4	1.24	(0.46 to 3.38)	0.671	1.15	(0.43 to 3.11)	0.784
Trazodone	1	0.88	(0.12 to 6.28)	0.896	0.56	(0.08 to 3.72)	0.548
SSRIs:							
Citalopram	43	0.77	(0.54 to 1.10)	0.153	0.73	(0.51 to 1.05)	0.089
Escitalopram	5	0.69	(0.28 to 1.67)	0.407	0.63	(0.26 to 1.53)	0.305
Fluoxetine	56	1.07	(0.76 to 1.49)	0.704	1.06	(0.76 to 1.50)	0.724
Paroxetine	7	0.65	(0.30 to 1.40)	0.268	0.63	(0.28 to 1.38)	0.247
Sertraline	7	0.87	(0.45 to 1.71)	0.692	0.63	(0.30 to 1.35)	0.239
Others:							
Mirtazapine	12	2.75	(1.53 to 4.93)	0.001	1.85	(1.01 to 3.37)	0.045
Venlafaxine	3	0.71	(0.27 to 1.88)	0.487	0.51	(0.16 to 1.57)	0.239
All other antidepressants	2	0.89	(0.22 to 3.62)	0.874	0.64	(0.15 to 2.63)	0.534
Combined antidepressants	1	0.90	(0.13 to 6.34)	0.913	0.70	(0.10 to 4.97)	0.717

* 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.

Outcome	Code type	Code	Code Description
Arrhythmia	Read code	327Z	ECG: supraventric. arryth. NOS
Arrhythmia	Read code	328Z	ECG: ventricular arrhythmia NOS
Arrhythmia	Read code	EMISNQAS1	Asystolic vasovagal syncope
Arrhythmia	Read code	F2560	Hypsarrhythmia
Arrhythmia	Read code	G57-1	Cardiac arrhythmias
Arrhythmia	Read code	G570	Paroxysmal supraventricular tachycardia
Arrhythmia	Read code	G570-99	Parox. supravent. tachycardia
Arrhythmia	Read code	G5700	Paroxysmal atrial tachycardia
Arrhythmia	Read code	G5701	Paroxysmal atrioventricular tachycardia
Arrhythmia	Read code	G5702	Paroxysmal junctional tachycardia
Arrhythmia	Read code	G5703	Paroxysmal nodal tachycardia
Arrhythmia	Read code	G570z	Paroxysmal supraventricular tachycardia NOS
Arrhythmia	Read code	G571	Paroxysmal ventricular tachycardia
Arrhythmia	Read code	G571-1	Ventricular tachycardia
Arrhythmia	Read code	G571-99	Paroxysmal ventric. tachyc.
Arrhythmia	Read code	G572	Paroxysmal tachycardia unspecified
Arrhythmia	Read code	G5720	Essential paroxysmal tachycardia
Arrhythmia	Read code	G5721	Bouveret-Hoffmann syndrome
Arrhythmia	Read code	G572z	Paroxysmal tachycardia NOS
Arrhythmia	Read code	G573	Atrial fibrillation and flutter
Arrhythmia	Read code	G5730	Atrial fibrillation
Arrhythmia	Read code	G5731	Atrial flutter
Arrhythmia	Read code	G5732	Paroxysmal atrial fibrillation
Arrhythmia	Read code	G5733	Non-rheumatic atrial fibrillation
Arrhythmia	Read code	G573z	Atrial fibrillation and flutter NOS
Arrhythmia	Read code	G574	Ventricular fibrillation and flutter
Arrhythmia	Read code	G5740	Ventricular fibrillation
Arrhythmia	Read code	G5740-1	Cardiac arrest-ventricular fibrillation
Arrhythmia	Read code	G5741	Ventricular flutter
Arrhythmia	Read code	G574z	Ventricular fibrillation and flutter NOS
Arrhythmia	Read code	G576-1	Premature beats
Arrhythmia	Read code	G5760	Ectopic beats unspecified

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
Arrhythmia	ICD9	427.4	Ventricular fibrillation and flutter
Arrhythmia	ICD9	427.41	Ventricular fibrillation
Arrhythmia	ICD9	427.42	Ventricular flutter
Arrhythmia	ICD9	427.6	Premature beats
Arrhythmia	ICD9	427.6	Premature beats, unspecified
Arrhythmia	ICD9	427.61	Supraventricular premature beats
Arrhythmia	ICD9	427.69	Other
Arrhythmia	ICD9	427.8	Other specified cardiac dysrhythmias
Arrhythmia	ICD9	427.81	Sinoatrial node dysfunction
Arrhythmia	ICD9	427.89	Other
Arrhythmia	ICD9	427.9	Cardiac dysrhythmia, unspecified
Arrhythmia	ICD10	I47	Paroxysmal tachycardia
Arrhythmia	ICD10	I47.0	Re-entry ventricular arrhythmia
Arrhythmia	ICD10	I47.1	Supraventricular tachycardia
Arrhythmia	ICD10	I47.2	Ventricular tachycardia
Arrhythmia	ICD10	I47.9	Paroxysmal tachycardia, unspecified
Arrhythmia	ICD10	I48	Atrial fibrillation and flutter
Arrhythmia	ICD10	I49	Other cardiac arrhythmias
Arrhythmia	ICD10	I49.0	Ventricular fibrillation and flutter
Arrhythmia	ICD10	I49.1	Atrial premature depolarization
Arrhythmia	ICD10	I49.2	Junctional premature depolarization
Arrhythmia	ICD10	I49.3	Ventricular premature depolarization
Arrhythmia	ICD10	I49.4	Other and unspecified premature depolarization
Arrhythmia	ICD10	I49.5	Sick sinus syndrome
Arrhythmia	ICD10	I49.8	Other specified cardiac arrhythmias
Arrhythmia	ICD10	I49.9	Cardiac arrhythmia, unspecified
Myocardial infarction	Read code	EMISR4QFI1	First myocardial infarction
Myocardial infarction	Read code	G30	Acute myocardial infarction
Myocardial infarction	Read code	G30-1	Attack - heart
Myocardial infarction	Read code	G30-2	Coronary thrombosis

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
Myocardial infarction	Read code	G310-1	Dressler's syndrome
Myocardial infarction	Read code	G31y1	Microinfarction of heart
Myocardial infarction	Read code	G35	Subsequent myocardial infarction
Myocardial infarction	Read code	G350	Subsequent myocardial infarction of anterior wall
Myocardial infarction	Read code	G351	Subsequent myocardial infarction of inferior wall
Myocardial infarction	Read code	G353	Subsequent myocardial infarction of other sites
Myocardial infarction	Read code	G35X	Subsequent myocardial infarction of unspecified site
Myocardial infarction	Read code	G360	Haemopericardium/current comp folow acut myocard infarct
Myocardial infarction	Read code	G361	Atrial septal defect/curr comp folow acut myocardal infarct
Myocardial infarction	Read code	G362	Ventric septal defect/curr comp fol acut myocardal infarctn
Myocardial infarction	Read code	G363	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
Myocardial infarction	Read code	G364	Ruptur chordae tendinae/curr comp fol acute myocard infarct
Myocardial infarction	Read code	G365	Rupture papillary muscle/curr comp fol acute myocard infarct
Myocardial infarction	Read code	G366	Thrombosis atrium,auric append&vent/curr comp foll acute MI
Myocardial infarction	Read code	G38	Postoperative myocardial infarction
Myocardial infarction	Read code	G380	Postoperative transmural myocardial infarction anterior wall
Myocardial infarction	Read code	G381	Postoperative transmural myocardial infarction inferior wall
Myocardial infarction	Read code	G382	Postoperative transmural myocardial infarction other sites
Myocardial infarction	Read code	G383	Postoperative transmural myocardial infarction unspec site
Myocardial infarction	Read code	G384	Postoperative subendocardial myocardial infarction
Myocardial infarction	Read code	G38z	Postoperative myocardial infarction, unspecified
Myocardial infarction	Read code	G501	Post infarction pericarditis
Myocardial infarction	Read code	Gyu34	[X]Acute transmural myocardial infarction of unspecif site
Myocardial infarction	ICD9	410	Acute myocardial infarction
Myocardial infarction	ICD9	410	Of anterolateral wall
Myocardial infarction	ICD9	410.1	Of other anterior wall
Myocardial infarction	ICD9	410.2	Of inferolateral wall
Myocardial infarction	ICD9	410.3	Of inferoposterior wall
Myocardial infarction	ICD9	410.4	Of other inferior wall
Myocardial infarction	ICD9	410.5	Of other lateral wall
Myocardial infarction	ICD9	410.6	True posterior wall infarction

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
Stroke or TIA	Read code	G61X	Intracerebral haemorrhage in hemisphere, unspecified
Stroke or TIA	Read code	G61X0	Left sided intracerebral haemorrhage, unspecified
Stroke or TIA	Read code	G61X1	Right sided intracerebral haemorrhage, unspecified
Stroke or TIA	Read code	G61z	Intracerebral haemorrhage NOS
Stroke or TIA	Read code	G63y0	Cerebral infarct due to thrombosis of precerebral arteries
Stroke or TIA	Read code	G63y1	Cerebral infarction due to embolism of precerebral arteries
Stroke or TIA	Read code	G64	Cerebral arterial occlusion
Stroke or TIA	Read code	G64-1	CVA - cerebral artery occlusion
Stroke or TIA	Read code	G64-2	Infarction - cerebral
Stroke or TIA	Read code	G64-3	Stroke due to cerebral arterial occlusion
Stroke or TIA	Read code	G640	Cerebral thrombosis
Stroke or TIA	Read code	G6400	Cerebral infarction due to thrombosis of cerebral arteries
Stroke or TIA	Read code	G641	Cerebral embolism
Stroke or TIA	Read code	G641-1	Cerebral embolus
Stroke or TIA	Read code	G6410	Cerebral infarction due to embolism of cerebral arteries
Stroke or TIA	Read code	G64z	Cerebral infarction NOS
Stroke or TIA	Read code	G64z-1	Brainstem infarction NOS
Stroke or TIA	Read code	G64z-2	Cerebellar infarction
Stroke or TIA	Read code	G64z-99	Cerebral A. occlusion NOS
Stroke or TIA	Read code	G64z0	Brainstem infarction
Stroke or TIA	Read code	G64z1	Wallenberg syndrome
Stroke or TIA	Read code	G64z1-1	Lateral medullary syndrome
Stroke or TIA	Read code	G64z2	Left sided cerebral infarction
Stroke or TIA	Read code	G64z3	Right sided cerebral infarction
Stroke or TIA	Read code	G64z4	Infarction of basal ganglia
Stroke or TIA	Read code	G65	Transient cerebral ischaemia
Stroke or TIA	Read code	G65-1	Drop attack
Stroke or TIA	Read code	G65-2	Transient ischaemic attack
Stroke or TIA	Read code	G65-3	Vertebro-basilar insufficiency
Stroke or TIA	Read code	G65-99	Transient Ischaemic Attacks
Stroke or TIA	Read code	G650	Basilar artery syndrome
Stroke or TIA	Read code	G650-1	Insufficiency - basilar artery

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/stenos precerebr arteries
Stroke or TIA	Read code	G6X	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
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 artrs

Outcome	Code type	Code	Code Description
Stroke or TIA	Read code	Gyu64	[X]Other cerebral infarction
Stroke or TIA	Read code	Gyu65	[X]Occlusion and stenosis of other precerebral arteries
Stroke or TIA	Read code	Gyu66	[X]Occlusion and stenosis of other cerebral arteries
Stroke or TIA	Read code	Gyu6F	[X]Intracerebral haemorrhage in hemisphere, unspecified
Stroke or TIA	Read code	Gyu6G	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
Stroke or TIA	Read code	ZV12D	[V]Personal history of transient ischaemic attack
Stroke or TIA	ICD9	430	Subarachnoid hemorrhage
Stroke or TIA	ICD9	431	Intracerebral hemorrhage
Stroke or TIA	ICD9	432	Other and unspecified intracranial hemorrhage
Stroke or TIA	ICD9	432	Nontraumatic extradural hemorrhage
Stroke or TIA	ICD9	432.1	Subdural hemorrhage
Stroke or TIA	ICD9	432.9	Hemorrhage, intracranial, NOS
Stroke or TIA	ICD9	433	Occlusion and stenosis of precerebral arteries
Stroke or TIA	ICD9	433	Occlusion and stenosis of basilar artery
Stroke or TIA	ICD9	433	Occlusion and stenosis of basilar artery without cerebral infarction
Stroke or TIA	ICD9	433.01	Occlusion and stenosis of basilar artery with cerebral infarction
Stroke or TIA	ICD9	433.1	Occlusion and stenosis of carotid artery
Stroke or TIA	ICD9	433.1	Occlusion and stenosis of carotid artery without cerebral infarction
Stroke or TIA	ICD9	433.11	Occlusion and stenosis of carotid artery with cerebral infarction
Stroke or TIA	ICD9	433.2	Occlusion and stenosis of vertebral artery
Stroke or TIA	ICD9	433.2	Occlusion and stenosis of vertebral artery without cerebral infarction
Stroke or TIA	ICD9	433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
Stroke or TIA	ICD9	433.3	Occlusion and stenosis of multiple and bilateral precerebral arteries
Stroke or TIA	ICD9	433.3	Occlusion and stenosis of multiple and bilateral precerebral arteries without cerebral infarction
Stroke or TIA	ICD9	433.8	Occlusion and stenosis of other specified precerebral artery
Stroke or TIA	ICD9	433.8	Occlusion and stenosis of other specified precerebral artery without cerebral infarction
Stroke or TIA	ICD9	433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
Stroke or TIA	ICD9	433.9	Occlusion and stenosis of unspecified precerebral artery
Stroke or TIA	ICD9	433.9	Occlusion and stenosis of unspecified precerebral artery without cerebral infarction
Stroke or TIA	ICD9	433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
Stroke or TIA	ICD9	434	Occlusion of cerebral arteries

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
Stroke or TIA	ICD10	G46.4*	Cerebellar stroke syndrome (I60 - I67+)
Stroke or TIA	ICD10	G46.5*	Pure motor lacunar syndrome (I60 - I67+)
Stroke or TIA	ICD10	G46.6*	Pure sensory lacunar syndrome (I60 - I67+)
Stroke or TIA	ICD10	G46.7*	Other lacunar syndromes (I60 - I67+)
Stroke or TIA	ICD10	G46.8*	Other vascular syndromes of brain in cerebrovascular diseases (I60 - I67+)
Stroke or TIA	ICD10	I60	Subarachnoid haemorrhage
Stroke or TIA	ICD10	I60.0	Subarachnoid haemorrhage from carotid siphon and bifurcation
Stroke or TIA	ICD10	I60.1	Subarachnoid haemorrhage from middle cerebral artery
Stroke or TIA	ICD10	I60.2	Subarachnoid haemorrhage from anterior communicating artery
Stroke or TIA	ICD10	I60.3	Subarachnoid haemorrhage from posterior communicating artery
Stroke or TIA	ICD10	I60.4	Subarachnoid haemorrhage from basilar artery
Stroke or TIA	ICD10	I60.5	Subarachnoid haemorrhage from vertebral artery
Stroke or TIA	ICD10	I60.6	Subarachnoid haemorrhage from other intracranial arteries
Stroke or TIA	ICD10	I60.7	Subarachnoid haemorrhage from intracranial artery, unspecified
Stroke or TIA	ICD10	I60.8	Other subarachnoid haemorrhage
Stroke or TIA	ICD10	I60.9	Subarachnoid haemorrhage, unspecified
Stroke or TIA	ICD10	I61	Intracerebral haemorrhage
Stroke or TIA	ICD10	I61.0	Intracerebral haemorrhage in hemisphere, subcortical
Stroke or TIA	ICD10	I61.1	Intracerebral haemorrhage in hemisphere, cortical
Stroke or TIA	ICD10	I61.2	Intracerebral haemorrhage in hemisphere, unspecified
Stroke or TIA	ICD10	I61.3	Intracerebral haemorrhage in brain stem
Stroke or TIA	ICD10	I61.4	Intracerebral haemorrhage in cerebellum
Stroke or TIA	ICD10	I61.5	Intracerebral haemorrhage, intraventricular
Stroke or TIA	ICD10	I61.6	Intracerebral haemorrhage, multiple localized
Stroke or TIA	ICD10	I61.8	Other intracerebral haemorrhage
Stroke or TIA	ICD10	I61.9	Intracerebral haemorrhage, unspecified
Stroke or TIA	ICD10	I62	Other nontraumatic intracranial haemorrhage
Stroke or TIA	ICD10	I62.0	Subdural haemorrhage (acute)(nontraumatic)
Stroke or TIA	ICD10	I62.1	Nontraumatic extradural haemorrhage
Stroke or TIA	ICD10	I62.9	Intracranial haemorrhage (nontraumatic), unspecified
Stroke or TIA	ICD10	I63	Cerebral infarction
Stroke or TIA	ICD10	I63.0	Cerebral infarction due to thrombosis of precerebral arteries

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

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