Published in final edited form as:

J Clin Psychiatry. 2017 February ; 78(2): 190–195. doi:10.4088/JCP.15m10324.

High-Dose Citalopram and Escitalopram and the Risk of Out-of-Hospital Death

Wayne A. Ray, Ph.D., Cecilia P. Chung, M.D., MPH, Katherine T. Murray, M.D., Kathi Hall, B.S., and C. Michael Stein, MB, ChB

Vanderbilt University School of Medicine: Department of Health Policy (WAR, KH); Departments of Medicine and Pharmacology, Divisions of Cardiology (KTM), Rheumatology (CMS, CPC) and Clinical Pharmacology (KTM, CMS)

Abstract

Objective—Studies demonstrating higher doses of citalopram (>40mg) and escitalopram (>20mg) prolong the QTc interval prompted regulatory agency warnings, which are controversial, given the absence of confirmatory clinical outcome studies. We compared the risk of potential arrhythmia-related deaths for high doses of these SSRIs to that for equivalent doses of fluoxetine, paroxetine, and sertraline.

Method—The Tennessee Medicaid retrospective cohort study included 54,220 persons 30–74 years of age without cancer or other life-threatening illness prescribed high-dose SSRIs. The mean age was 47 years and 76% were female. Demographic characteristics and comorbidity for individual SSRIs were comparable. Because arrhythmia-related deaths are typically sudden and occur outside the hospital, we analyzed out-of-hospital sudden unexpected death as well as sudden cardiac deaths, a more specific indicator of pro-arrhythmic effects.

Results—The adjusted risk of sudden unexpected death for citalopram did not differ significantly from that for the other SSRIs. The respective hazard ratios (HRs) for citalopram versus escitalopram, fluoxetine, paroxetine, and sertraline were 0.84 (95% confidence interval [CI], 0.40–1.75), 1.24 (0.75–2.05), 0.75 (0.45–1.24), and 1.53 (0.91–2.55). There were no significant differences for sudden cardiac death or all study deaths, nor were there significant differences among high-risk patients (>60 years of age, upper quartile baseline cardiovascular risk). Escitalopram users had no significantly increased risk for any study endpoint.

Conclusions—We found no evidence that risk of sudden unexpected death, sudden cardiac death, or total mortality for high-dose citalopram and escitalopram differed significantly from that for comparable doses of fluoxetine, paroxetine, and sertraline.

There are questions regarding the relative cardiac safety of certain selective serotonin reuptake inhibitor (SSRI) antidepressants, the mainstay of antidepressant therapy for more than 25 years.¹ A thorough QT interval study of citalopram demonstrated a dose-related increase in the QTc interval, with an increase of 18.5 ms for a 60 mg daily dose.²

Furthermore, prior to the FDA warning, there were multiple case reports of QTc prolongation and torsade de pointes for this SSRI, both in overdose and in the usual clinical doses.³ These data, coupled with lack of evidence from fixed-dose studies of greater efficacy for the 60 mg dose, led the FDA to warn against citalopram use in doses >40 mg.

The FDA warning has been controversial,⁴ in part because of negative findings from controlled studies of clinical outcomes.⁵ A Veterans Administration (VA) retrospective cohort study found no evidence that the risk of either diagnosed ventricular arrhythmias or cardiac mortality for higher doses of citalopram differed from that for either lower doses of citalopram or equivalent doses of sertraline.⁶ A multi-state Medicaid retrospective cohort study found no significant difference in diagnosed ventricular arrhythmia/sudden cardiac death between citalopram doses of 20 mg and >40 mg (hazard ratio [HR] of 1.31 [95% confidence interval, 0.88–1.95]).⁷

The FDA asserted that these epidemiologic studies could not be relied upon to detect the adverse cardiac effects of high-dose citalopram.^{8,9} One concern was the study endpoints. Because torsade de pointes and other related arrhythmias often are rapidly fatal, patients may not survive long enough to receive a diagnosis. Overall cardiac mortality includes numerous deaths unlikely to be related to pro-arrhythmic medication effects, which would bias toward the null. The FDA also questioned comparison of low- versus high-dose citalopram, as patients with greater cardiovascular morbidity could be “channeled” to receive lower doses. Such confounding, if incompletely controlled for, would mask an adverse effect of higher doses. Furthermore, the comparison between low and high doses is less clinically relevant, as patients typically start with lower doses that are titrated upward when response is inadequate.¹⁰

A thorough QT interval study of escitalopram, the S-enantiomer of citalopram, also found a dose-related increase in QTc.² The prolongation of 10.7 ms for the 30 mg daily dose was comparable to that for moxifloxacin, known to have pro-arrhythmic effects.¹¹ Although the relation between moderate QTc increases and risk of arrhythmias is complex, these data suggest that high-dose escitalopram also might have adverse cardiac effects, particularly given case reports of serious ventricular arrhythmias.³ Indeed, the European Medicines and Healthcare products Regulatory Agency (MHRA) issued an advisory for escitalopram recommending a maximum daily dose of 20 mg.¹²

We thus conducted a cohort study to assess the cardiovascular safety of high doses of citalopram and escitalopram relative to other SSRIs. Our study differed in two ways from previous investigations. First, to better identify deaths related to medication effects, we focused on those outside the hospital in a cohort of patients for whom such deaths should otherwise be infrequent. Deaths were classified to identify those most likely to be related to pro-arrhythmic medication effects. Second, we directly compared high doses of citalopram and escitalopram with comparable doses of other SSRIs.

Methods

Cohort and Followup

We conducted a retrospective cohort study of Tennessee Medicaid enrollees (Appendix) with prescriptions for high doses of SSRIs filled from 1998 through 2011. The cohort included patients for whom deaths outside the hospital, absent pro-arrhythmic medication effects, should be relatively infrequent. To reduce the occurrence of deaths related to terminal illness, we excluded patients 75 years of age or older, with cancer and other life-threatening diseases, or residing in a nursing home (Appendix Table 1). The cohort also excluded persons less than 30 years of age because cardiac deaths in children and young adults are very rare.¹³ Patients in the hospital could not enter the cohort until 30 days after discharge, because deaths during this period may be related to the reasons for the hospitalization. For patients who met these eligibility criteria, there were no further restrictions on psychiatric diagnoses.

The study SSRIs were citalopram, escitalopram, fluoxetine, paroxetine, and sertraline. We did not consider fluvoxamine, given its limited use in the study population. *High dose* SSRI use was defined as >40 mg/day for citalopram, fluoxetine, and paroxetine; >20 mg for escitalopram, and >150 mg for sertraline. These cutpoints were based both on clinical guidelines¹⁰ and the cohort dose distribution.

Patients entered the cohort on the date they filled the first SSRI prescription on which they met the study inclusion/exclusion criteria (Appendix Tables 1 and 2). Patients remained in the cohort until the end of the study, death, failure to meet inclusion/exclusion criteria, or the cessation of study SSRI use. Those who left the cohort could reenter if they subsequently became eligible.

Given that the ventricular arrhythmias of concern are acute drug effects,^{14;15} cohort followup consisted of current use of study SSRIs (Appendix Figure 1). We excluded person-time during and in the 30 days following hospitalization, which led to exclusion of deaths for patients admitted to the hospital. This should reduce potential confounding and improve capacity to detect adverse SSRI effects, given that many inpatient deaths are unlikely to be related to the cardiac effects of SSRIs. Bias could be introduced if the study groups differed with regard to the proportions of patients with an SSRI-related arrhythmia who survived until hospital admission but ultimately died in the hospital. However, this scenario seems unlikely, given that medication-related ventricular arrhythmias are rapidly lethal, most frequently leading to death before the patient can seek medical care.^{16–18}

Endpoints

The primary endpoint was *sudden unexpected deaths*, the composite of sudden cardiac deaths, other cardiovascular deaths, and unintentional medication overdose deaths. These deaths were considered most likely to be related to serious ventricular arrhythmias.

Sudden cardiac deaths were defined as an ultimately fatal sudden pulseless condition consistent with a ventricular tachyarrhythmia occurring in the absence of a known noncardiac condition as the proximate cause of the death.¹⁹ Because sudden cardiac deaths

frequently are due to serious ventricular arrhythmias, they have been considered an indicator of pro-arrhythmic medication effects.^{15;20–22} We identified these deaths from a previously validated computerized definition that utilized multiple sources of data, including computerized death certificates, hospital discharge files, and Medicaid files with terminal outpatient medical care encounters (Appendix).¹⁵ In the validation studies, this definition had positive predictive values of 87%–90%.^{15;21}

Some sudden cardiac deaths could be misclassified as due to other cardiovascular causes. Thus, the primary endpoint included *other cardiovascular deaths*; cardiovascular deaths that did not meet the definition for sudden cardiac death (Appendix Table 3).

Although SSRI overdose is infrequently fatal,²³ pro-arrhythmic effects could increase the risk of death from other medications commonly taken by antidepressant users, including opioids and cyclic antidepressants. Because such deaths can be difficult to distinguish post-mortem from those due to arrhythmias^{24;25} the sudden unexpected death category also included *unintentional medication overdose deaths* (Appendix Table 4).

Other deaths included all other deaths during followup. *All study deaths* were the total of sudden unexpected deaths and other deaths.

Statistical Analysis

For each of the study endpoints, we compared the risk among current users of citalopram to that for each of escitalopram, fluoxetine, paroxetine, and sertraline. The comparisons were to individual SSRIs because it is possible that each has different cardiac effects.¹ We performed a similar comparison for escitalopram.

The relative risk of death, adjusted for patient characteristics, was estimated with the hazard ratio (HR) from a proportional hazards regression model, with SSRI use as a time-dependent covariate. HRs were adjusted for potential differences between users of different SSRIs, as described by 111 covariates (Appendix Table 5). These included calendar time, demographic factors, nonstudy antidepressants, diagnoses and medications related to psychiatric, neurologic, musculoskeletal, cardiovascular and respiratory conditions, indicators of frailty, other pro-arrhythmic medications, other comorbidity, and recent medical care utilization. Because patient comorbidity could vary during followup, all covariates were time-dependent.

We controlled for the large number of study covariates by stratifying the regression analysis by 20 quantiles of a time-dependent disease risk score (Appendix).^{26–28} The disease risk score, the risk of death as a function of the study covariates, facilitates analyses for multiple exposure categories, given that propensity scores are less suited to non-binary comparisons.^{26–28} Because the disease risk score models the probability of the outcome, a separate score was calculated for each study endpoint.

All analyses were done with SAS version 9.4. All p-values are two-sided.

The study was funded by a grant from the National Heart, Lung and Blood Institute. The funder had no role in the conduct of the study or publication of the manuscript.

Results

The cohort included 54,220 persons with 557,519 qualifying prescriptions for high doses of the study SSRIs (Table 1). The mean age was 47 years, 76% were female, and 10% were 60 years of age or older. There were 45% with a diagnosis of major depression, 16% with bipolar disorders, and 10% with schizophrenia or a related psychosis. Co-prescribing of other psychiatric medications was common; in the past year 42% had filled a prescription for an antipsychotic, 58% for a benzodiazepine and 23% for a mood stabilizer. Cohort members frequently used analgesics; in the past year 71% had filled an opioid prescription, and 39% a skeletal muscle relaxant prescription. The covariates distributions for the individual SSRIs were comparable. The summary measures of the risk for study endpoints, the disease risk scores, for the specific SSRIs were comparable.

There were 245 deaths during 38,061 person-years of study followup, or 64.4 deaths per 10,000 person-years (Figure 1). These consisted of 145 sudden unexpected deaths (38.1 per 10,000) and 100 (26.3 per 10,000) other deaths. The sudden unexpected deaths included 95 (25.0 per 10,000) sudden cardiac deaths, 24 (6.3 per 10,000) other cardiovascular deaths, and 26 (6.8 per 10,000) unintentional overdose deaths.

There was some variation in the unadjusted incidence of study endpoints among the individual SSRIs (Table 2). The incidence of sudden unexpected death ranged from 27.2 per 10,000 person-years for sertraline to 58.8 per 10,000 person-years for escitalopram. The incidence of all deaths ranged from 50.3 per 10,000 person-years for sertraline to 84.9 per 10,000 person-years for paroxetine.

However, when the adjusted risk of sudden unexpected death for citalopram was compared to that for the other SSRIs (Table 3), none of the resulting HRs were statistically significant. The HRs for citalopram versus escitalopram, fluoxetine, paroxetine, and sertraline were 0.84 (95% confidence interval [CI] 0.40–1.75), 1.24 (0.75–2.05), 0.75 (0.45–1.24), and 1.53 (0.91–2.55), respectively. There also were no significant differences for sudden cardiac death, other deaths, and all study deaths. Similarly, there were no statistically significant differences for any of the study endpoints when escitalopram was compared to fluoxetine, paroxetine, and sertraline (Table 3). We also compared both citalopram and escitalopram versus a pooled comparison group consisting of all of the other three SSRIs. The respective HRs for sudden unexpected death were 1.16 (0.75–1.78) and 1.37 (0.71–2.64), those for sudden cardiac death were 0.96 (0.55–1.68) and 1.31 (0.60–2.87), and those for all study deaths were 0.93 (0.66–1.31) and 0.91 (0.50–1.63).

We conducted sensitivity analyses for patients thought to be at greatest risk for the adverse effects of QT prolongation.²⁹ For patients 60 years of age or older the HRs for sudden unexpected death for citalopram versus fluoxetine, paroxetine and sertraline were 1.28 (0.36–4.59), 0.72 (0.21–2.46), and 1.71 (0.46–6.44), respectively (escitalopram numbers inadequate). For patients in the upper quartile for risk of sudden cardiac death, the HRs for citalopram versus escitalopram, fluoxetine, paroxetine, and sertraline were 0.87 (0.34–2.25), 1.04 (0.55–1.99), 0.64 (0.34–1.23), and 1.17 (0.61–2.22), respectively.

Discussion

In this cohort study of high-dose users of SSRIs, we found no evidence that the risk of sudden unexpected death for citalopram differed from that for comparable users of other SSRIs. Although the incidence of death varied among the users of the different medications, there was no consistent pattern indicating greater risk for citalopram and, when citalopram was compared with each of the other SSRIs, none of the differences were statistically significant. Furthermore, there was no evidence of increased risk for citalopram in groups thought to be at particular risk for pro-arrhythmic medication effects: persons 60 years of age or older or in the upper quartile with regard to baseline cardiovascular risk factors. A similar finding was present for high doses of escitalopram.

One study limitation is the sudden unexpected death endpoint's potential lack of specificity for arrhythmia-related deaths, a criticism of the mortality endpoint of the VA cohort study.⁸ We chose the broader endpoint because of concerns that in a population with frequent use of medications with high overdose risk, arrhythmia-related deaths might be misclassified. To limit the bias inherent in increasing sensitivity at the potential expense of specificity, we restricted the cohort to non-hospitalized patients for whom deaths unrelated to adverse medication effects should be relatively infrequent. We also did not consider in-hospital cardiovascular deaths (e.g., heart failure, stroke), which are unlikely to be related to pro-arrhythmic effects of outpatient medications. Furthermore, we also performed all study analyses for sudden cardiac death, a more specific indicator of pro-arrhythmic medication effects.^{15;20–22} Findings were essentially unchanged.

Confounding could affect study findings if higher-risk patients were selectively prescribed SSRIs other than citalopram. The FDA warning published in late 2011, the last year of our study, is unlikely to have affected our findings. However, prior case reports of QTc prolongation³ could have led to avoidance of high-dose citalopram in patients with elevated cardiac risk. The minor differences between SSRI users in demographic characteristics and comorbidity did not support such channeling, as indicated by the comparable summary disease risk scores for the study SSRIs. Furthermore, these factors were accounted for in the statistical analysis. Nevertheless, because we relied upon medical care encounters to define comorbidity, we thus could not control for several potential confounders such as smoking, family history of cardiac disease or measures of depression severity and other psychiatric comorbidity.

Study power was limited for some of the individual drug comparisons. When citalopram was compared to sertraline, the upper bound of the 95% confidence limit for the sudden unexpected death HR was 2.55, indicating that clinically important risks might not have been detected. However, for paroxetine, thought to have good cardiac safety,¹ the upper bound was 1.24. Thus, it seems unlikely that a large, consistent difference between citalopram and other SSRIs would have been missed.

Our study findings must be interpreted in the context of limited information on the cardiac safety of high doses of fluoxetine, paroxetine, and sertraline, given the absence of thorough QT studies for these drugs. There are reported cases of increased QT and/or ventricular

arrhythmias for all of the study SSRIs,^{3,30} although these are infrequent.³ The SADHART study,³¹ a placebo-controlled randomized controlled trial in patients with recent myocardial infarction/unstable angina and major depression, found that sertraline patients had no significant changes in QTc or other measures of cardiac function, although data were not reported for high doses. Further study of the cardiac effects of high doses of the other SSRIs would be useful.

Conclusion

In this cohort study of high-dose SSRI users, we found no evidence that the risk of sudden unexpected death, sudden cardiac death, or total out-of-hospital mortality for citalopram and escitalopram differed significantly from that for fluoxetine, paroxetine, or sertraline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by a grant from the NHLBI (# HL081707), the NIAMS (#K23AR064768) and a Vanderbilt Physician Scientist Development award. We gratefully acknowledge the Tennessee Bureau of TennCare and the Tennessee Department of Health, which provided study data.

References

1. Beach SR, Kostis WJ, Celano CM, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. *J Clin Psychiatry*. 2014; 75:e441–e449. [PubMed: 24922496]
2. Temple R, Laughren T, Stockbridge N. Removal from labeling of 60-mg citalopram dose. *Pharmaco Drug Safety*. 2012; 21:784–786.
3. Beach SR, Celano CM, Noseworthy PA, Januzzi JL, Huffman JC. QTc prolongation, torsades de pointes, and psychotropic medications. *Psychosomat*. 2013; 54:1–13.
4. Vieweg WVR, Hasnain M, Howland RH, et al. Citalopram, QTc interval prolongation, and torsade de pointes. How should we apply the recent FDA ruling? *Am J Med*. 2012; 125:859–868. [PubMed: 22748401]
5. Howland RH. A critical evaluation of the cardiac toxicity of citalopram: part 2. *J Psychosoc Nurs Ment Health Serv*. 2011; 49:13–16.
6. Zivin K, Pfeiffer PN, Bohnert ASB, et al. Evaluation of the FDA warning against prescribing citalopram at doses exceeding 40 mg. *Am J Psychiatry*. 2013; 170:642–650. [PubMed: 23640689]
7. Leonard CE, Bilker WB, Newcomb C, Kimmel SE, Hennessy S. Additional data on citalopram and the risk of sudden cardiac death and ventricular arrhythmia. *Pharmaco Drug Safety*. 2012; 21:331–332.
8. Bird ST, Crensil 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; 171:17–19. [PubMed: 24399423]
9. Zivin K, Pfeiffer PN, Bohnert AS, et al. Safety of high-dosage citalopram. *Am J Psychiatry*. 2014; 171:20–22. [PubMed: 24399424]
10. Lam RW, Kennedy SH, Grigoriadis S, et al. Canadian network for mood and anxiety treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy. *J Affective Disord*. 2009; 117:S26–S43.
11. Falagas ME, Rafailidis PI, Rosmarakis ES. Arrhythmias associated with fluoroquinolone therapy. *International Journal of Antimicrobial Agents*. 2007; 29:374–379. [PubMed: 17241772]
12. Citalopram and escitalopram: QT interval prolongation - new maximum daily dose restrictions (including in elderly patients), contraindications, and warnings. *Drug Safety Update*. 2001; 5:A1.

13. Liberthson RR. Sudden death from cardiac causes in children and young adults. *N Engl J Med.* 1996; 334:1039–1044. [PubMed: 8598843]
14. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose. *Ann Intern Med.* 2010; 152:85–92. [PubMed: 20083827]
15. Chung CP, Murray KT, Stein CM, Hall K, Ray WA. A computer case definition for sudden cardiac death. *Pharmacoepidemiol Drug Saf.* 2010; 19:563–572. [PubMed: 20029823]
16. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med.* 2001; 345:1473–1482. [PubMed: 11794197]
17. Marcus FI, Cobb LA, Edwards JE, et al. Mechanism of death and prevalence of myocardial ischemic symptoms in the terminal event after acute myocardial infarction. *Am J Cardiol.* 1988; 61:8–15. [PubMed: 3337021]
18. Hinkle LE, Thaler HT. Clinical classification of cardiac deaths. *Circulation.* 1982; 65:457–464. [PubMed: 7055867]
19. Siscovick DS, Raghunathan TE, Psaty BM, et al. Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med.* 1994; 330:1852–1857. [PubMed: 8196728]
20. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MCP. QTc interval screening in methadone treatment. *Ann Intern Med.* 2009; 150:387–395. [PubMed: 19153406]
21. Kawai VK, Murray KT, Stein CM, et al. Validation of a computer case definition for sudden cardiac death in opioid users. *BMC Research Notes.* 2012; 5:473. [PubMed: 22938531]
22. Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry.* 2001; 58:1161–1167. [PubMed: 11735845]
23. Barbey JT, Roose SP. SSRI safety in overdose. *J Clin Psychiatry.* 1998; 59:42–48.
24. Kao D, Bartelson BB, Khatri V, et al. Trends in reporting methadone-associated cardiac arrhythmia, 1997–2011. An analysis of registry data. *Ann Intern Med.* 2013; 158:735–740. [PubMed: 23689766]
25. Stringer J, Welsh C, Tommasello A. Methadone-associated Q-T interval prolongation and torsades de pointes. *Am J Health-Syst Pharm.* 2009; 66:825–833. [PubMed: 19386945]
26. Arbogast PG, Kaltenbach L, Ding H, Ray WA. Adjustment of multiple cardiovascular risk factors with a summary risk score. *Epidemiol.* 2008; 19:30–37.
27. Arbogast PG, Ray WA. Use of disease risk scores in pharmacoepidemiologic studies. *Statistical Meth Med Res.* 2009; 18:67–80.
28. Arbogast PG, Ray WA. Performance of disease risk scores, propensity scores, and traditional multivariable outcome regression in the presence of multiple confounders. *Am J Epi.* 2011; 174:613–620.
29. FDA. FDA drug safety communication: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. Safety Announcement. 2011
30. Erfurth A, Loew m, Dobmeier P, Wendler G. EKG-Veränderungen nach Paroxetin. *Nervenarzt.* 1998; 69:629–631. [PubMed: 9715482]
31. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA.* 2002; 288:701–709. [PubMed: 12169073]

Clinical Points

- FDA-mandated studies of 60mg citalopram and 30mg escitalopram reported QT prolongation suggestive of increased risk for serious arrhythmias.
- We compared high-dose citalopram and escitalopram to comparable doses of other SSRIs and found no increased risk for sudden unexpected, sudden cardiac, or total out-of-hospital death.
- In the study population, there was no evidence these drugs increased risk of arrhythmia-related deaths.

Figure 1.
Study deaths, number (N) and incidence (I) per 10,000 person-years of study followup.

Table 1

Cohort characteristics at the time of filling of study SSRI prescriptions. All values are proportions unless otherwise noted. Unless otherwise stated, medication and diagnosis variables reflect the year preceding the prescription fill date.

	Citalopram	Escitalopram	Fluoxetine	Paroxetine	Sertraline
Persons in cohort, N	9,860	4,185	13,692	11,080	15,403
Study SSRI prescriptions, N	88,243	27,850	160,144	99,630	181,652
Age, years, mean	46.6	46.2	47.2	47.0	46.9
Age 65 years or older	2.4%	2.5%	2.6%	3.3%	3.2%
Female	76.5%	75.1%	78.9%	74.7%	75.1%
<i>Other antidepressants</i>					
TCA: Any past year	16.1%	14.8%	20.6%	20.5%	17.3%
Trazodone: Any past year	26.2%	23.2%	26.1%	26.2%	26.0%
Other antidepressant: Any past year	30.9%	40.3%	24.6%	25.0%	28.6%
<i>Psychiatric diagnoses and health care</i>					
Schizophrenia/psychosis	11.4%	10.6%	9.8%	10.3%	10.1%
Bipolar disorder	18.4%	21.3%	15.7%	14.0%	15.5%
Major depression	46.0%	50.0%	46.2%	43.3%	44.1%
Other mood disorder	37.1%	40.0%	36.8%	36.5%	36.5%
Panic disorder	11.5%	11.4%	9.7%	17.0%	11.0%
Psychiatric hospitalization past year	5.3%	7.5%	3.9%	4.0%	4.7%
<i>Psychiatric and analgesic medications</i>					
Antipsychotic: Any past year	44.2%	54.1%	37.9%	41.1%	42.6%
Benzodiazepine: Any past year	54.3%	67.9%	57.8%	62.4%	57.1%
Mood stabilizer: Any past year	25.6%	31.9%	22.2%	20.8%	23.2%
Opioid: Any past year	72.5%	76.4%	70.8%	67.9%	70.6%
Musculoskeletal relaxant: Any past year	40.1%	45.2%	39.6%	37.2%	39.3%
<i>Cardiovascular diagnoses and health care</i>					
Coronary heart disease	9.7%	10.7%	9.4%	9.5%	9.9%

	Citalopram	Escitalopram	Fluoxetine	Paroxetine	Sertraline
Arrhythmia	4.6%	4.7%	3.8%	4.2%	4.3%
Congestive heart failure	3.8%	4.3%	4.0%	3.9%	3.8%
Cerebrovascular disease	4.1%	4.8%	4.1%	4.2%	4.4%
Diabetes	21.7%	21.7%	20.8%	22.3%	21.1%
Cardiovascular hospitalization past year	1.6%	2.0%	1.7%	1.9%	1.8%
Other hospitalization past year	9.5%	10.8%	9.9%	9.8%	9.6%
<i>Cardiovascular medications</i>					
ACE inhibitor/Angiotensin receptor blocker	31.9%	32.1%	30.4%	30.8%	31.4%
Beta blocker	22.1%	22.7%	20.8%	21.8%	21.2%
Calcium channel blocker	16.7%	16.9%	18.0%	18.2%	17.5%
Digoxin	1.3%	1.3%	1.4%	1.4%	1.4%
Loop diuretic	16.1%	18.6%	18.8%	16.7%	16.0%
Insulin or other injectable hypoglycemic	6.8%	6.6%	7.5%	7.6%	7.2%
Statin	30.3%	31.9%	29.5%	28.5%	32.5%
<i>Summary measures of disease risk</i>					
Disease risk score quantile, mean ^a					
Sudden unexpected death	9.6	9.8	9.5	9.4	9.4
Other death	9.8	9.5	9.5	9.4	9.4
All study deaths	9.8	9.8	9.5	9.4	9.4

^aRanges from 0 to 19, where 0 is the lowest and 19 the highest risk quantile. Because the values represent 20 quantiles, by definition the mean for the entire population is 9.5.

Table 2

Unadjusted incidence of study endpoints according to current use of individual SSRIs. Rates are per 10,000 person-years of followup.

	Citalopram (6,011 person-years)		Escitalopram (1,700 person-years)		Fluoxetine (11,117 person-years)		Paroxetine (6,714 person-years)		Sertraline (12,518 person-years)	
	Deaths	Rate	Deaths	Rate	Deaths	Rate	Deaths	Rate	Deaths	Rate
Sudden Unexpected Death	26	43.3	10	58.8	38	34.2	37	55.1	34	27.2
Sudden Cardiac Death	15	25.0	7	41.2	23	20.7	27	40.2	23	18.4
Other Deaths	13	21.6	2	11.8	36	32.4	20	29.8	29	23.2
All Deaths	39	64.9	12	70.6	74	66.6	57	84.9	63	50.3

Study endpoint hazard ratios (HRs) for citalopram and escitalopram compared to other study SSRIs. CI denotes confidence interval.

Table 3

	SSRI Comparator			
	Escitalopram	Fluoxetine	Paroxetine	Sertraline
	HR (95% CI)			
Citalopram vs Comparator				
Sudden unexpected death	0.84 (0.40 – 1.75)	1.24 (0.75 – 2.05)	0.75 (0.45 – 1.24)	1.53 (0.91 – 2.55)
Sudden cardiac death	0.73 (0.30 – 1.80)	1.12 (0.58 – 2.16)	0.56 (0.30 – 1.05)	1.28 (0.67 – 2.47)
Other deaths	1.80 (0.41 – 7.98)	0.59 (0.31 – 1.11)	0.64 (0.32 – 1.29)	0.81 (0.42 – 1.57)
All Deaths	1.02 (0.53 – 1.96)	0.89 (0.60 – 1.31)	0.70 (0.47 – 1.06)	1.18 (0.79 – 1.77)
Escitalopram vs Comparator				
Sudden unexpected death		1.47 (0.73 – 2.98)	0.89 (0.44 – 1.80)	1.82 (0.89 – 3.70)
Sudden cardiac death		1.54 (0.65 – 3.63)	0.76 (0.33 – 1.77)	1.76 (0.75 – 4.14)
Other deaths		0.33 (0.08 – 1.36)	0.36 (0.08 – 1.52)	0.45 (0.11 – 1.90)
All Deaths		0.87 (0.47 – 1.61)	0.69 (0.37 – 1.29)	1.16 (0.62 – 2.15)