Adverse Cardiac Events in Older Patients Receiving Venlafaxine: A Population-Based Study

Joanne M. Ho, MD; Tara Gomes, MHSc; Sharon E. Straus, MD, MSc; Peter C. Austin, PhD; Muhammad Mamdani, PharmD, MA, MPH; and David N. Juurlink, MD, PhD

ABSTRACT

Objective: Venlafaxine is a commonly prescribed antidepressant, but whether its noradrenergic effects impart increased cardiovascular risk is unknown. We sought to examine the cardiac safety of venlafaxine relative to sertraline in older patients.

Method: We conducted a population-based retrospective cohort study using administrative health care databases in Ontario, Canada. We included all patients aged 66 years or older who commenced treatment with either venlafaxine or sertraline between April 1, 2000, and March 31, 2009. We used inverse probability of treatment weighting with the propensity score to account for observed systematic differences in baseline characteristics between the 2 treatment groups. The primary outcome was a composite of death or hospitalization for acute myocardial infarction or congestive heart failure (as defined by codes from the *International Classification of Diseases, Ninth* and *Tenth Revisions*) within the first year of therapy. In secondary analyses, each outcome was examined separately.

Results: We studied 48,876 patients initiated on venlafaxine and 41,238 patients initiated on sertraline. Of these, 3,966 (8.1%) and 3,707 (9.0%) experienced the primary outcome, respectively. We found no significant difference in the risk of adverse cardiac events with venlafaxine relative to sertraline (hazard ratio = 0.97; 95% CI, 0.93–1.02). Secondary analyses revealed no differences in the risk of death or acute myocardial infarction between the 2 drugs, but the risk of heart failure was unexpectedly lower among patients treated with venlafaxine (hazard ratio = 0.87; 95% CI, 0.80–0.95). We found consistent results after stratification according to preexisting cardiovascular disease.

Conclusions: As compared with sertraline, low to moderate dose venlafaxine is not associated with an increased risk of adverse cardiac events in older patients. The lower risk of heart failure among venlafaxine patients warrants further study.

J Clin Psychiatry 2014;75(6):e552–e558

Submitted: *April 1, 2013; accepted November 11, 2013 (doi:10.4088/JCP.13m08508).*
Corresponding author: *Joanne M. Ho, MD, Sunnybrook Health Sciences Centre, G Wing 106, 2075 Bayview Ave, Toronto, Ontario M4N 3M5, Canada (jm.ho@mail.utoronto.ca).*

Depression is common, with a lifetime prevalence of 12%–16% in North America. Among patients with cardiovascular disease, the prevalence may be as high as 30%,[1–3] and depression is independently associated with morbidity and mortality.[4,5] Although nonpharmacologic treatments are available, medication remains a common element of therapy for many patients. With a prescription rate exceeding 1 prescription for every 10 persons in the United States between 2005 and 2008, antidepressants are used by tens of millions of people every day.[6,7]

Among the various drug treatment options for depression, second-generation antidepressants are the most widely prescribed.[6] These include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and other drugs such as bupropion, mirtazapine, and trazodone. Comparative effectiveness studies have found no difference in efficacy among classes in the treatment of depression, but the safety profiles of these drugs may differ, particularly with regard to cardiovascular safety.[8] Given the high prevalence of depression among older patients, and particularly those with cardiovascular disease, any safety differences would be important to establish.

Venlafaxine, the most commonly prescribed SNRI, is thought to alleviate depression by inhibiting serotonin and norepinephrine reuptake.[9–12] At lower doses, it acts like an SSRI, and, unlike tricyclic antidepressants, its lack of anticholinergic effects[13] may make it a favorable agent for older patients.[14–16] However, these patients may be vulnerable to its noradrenergic effects, which are more pronounced at higher doses.[14,15,17–19] These effects can lead to tachycardia and hypertension,[17,20–22] and some case reports implicate venlafaxine as a possible contributor to acute myocardial infarction and heart failure.[23,24] A small randomized controlled trial (n = 52) of long-term care patients demonstrated an increase in adverse events necessitating drug cessation with venlafaxine compared to sertraline.[25] Although not sufficiently powered to explore cardiac safety, venlafaxine-treated patients exhibited an increased heart rate and more cases of heart failure.[25]

We speculated that, by virtue of its noradrenergic effects, venlafaxine might be associated with an increased risk of adverse cardiac events among older patients relative to other antidepressants that do not prevent norepinephrine reuptake.

METHOD

Setting

We conducted a population-based retrospective cohort study of all residents aged 66 years or older who commenced treatment with either venlafaxine or sertraline between April 1, 2000, and March 31, 2009, in the province of Ontario, Canada. These patients have universal coverage for hospital care, physician services, and prescription medications.

Clinical Points

- We found no difference in adverse cardiac events among older patients newly started on low to moderate doses of venlafaxine relative to sertraline, 2 first-line pharmacotherapies for depression. This observation persisted in patients with and without preexisting cardiovascular disease.
- In our study, the majority of patients taking venlafaxine were on low to moderate doses. Therefore, clinicians should still monitor patients on high venlafaxine doses (exceeding 200 mg/d) for noradrenergic effects, such as hypertension and tachycardia, which may precipitate adverse cardiac events.

Data Sources

We linked administrative databases using an encrypted version of each subject's unique health insurance number.[26,27] We identified dispensed prescriptions using the Ontario Drug Benefit database, which contains records of all medications covered under the provincial insurance program filled in outpatient pharmacies for individuals aged 65 years and older. We used the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) and National Ambulatory Care Reporting System to identify hospitalizations and emergency department visits, respectively. These databases have been validated for data completeness and accuracy.[28,29] We identified physician claims with the Ontario Health Insurance Plan Database and obtained demographic information from the Registered Persons Database. These governmental administrative databases are not publicly available, but are routinely linked to study drug safety at the Institute for Clinical Evaluative Sciences.[30,31]

Study Design

We identified all patients aged 66 years or older who were new users of venlafaxine or sertraline during the study period. We defined *new users* as patients who had not filled a prescription for any antidepressant in the preceding year. We did not study patients during their first year of eligibility for prescription drug coverage (age 65) in order to avoid incomplete records when ascertaining new-user status. Sertraline-treated patients served as the comparison group because it is similar to venlafaxine in serotonergic activity,[32] efficacy,[8] and popularity in Canada[33] but does not potentiate norepinephrine. Patients were followed until they experienced the primary outcome, switched or discontinued antidepressant therapy (defined as the absence of another prescription filled within 1.5 times the day supply of the previous prescription), reached the end of the study period (March 31, 2010), or completed 1 year of therapy, since drug-specific adverse cardiac events are most likely to manifest early in the course of treatment.[20,23,24,34] We excluded patients concomitantly taking other antidepressants or who started venlafaxine and sertraline on the same day. Patients on tamoxifen were excluded because SSRIs and SNRIs may differentially modulate the response to tamoxifen.[35]

The primary outcome was defined a priori as a composite of death from any cause or incident hospital admission for acute myocardial infarction or heart failure. In a secondary analysis, each component of the composite outcome was analyzed separately. We identified death using the Registered Persons Database, and hospitalization for acute myocardial infarction or congestive heart failure with codes from the *International Classification of Diseases, Ninth* and *Tenth Revisions* (*ICD-9* and *ICD-10*) from the CIHI-DAD. We defined *acute myocardial infarction* as any of *ICD-9* code 410, or *ICD-10* codes I21 and I22, and I20 (unstable angina); and congestive heart failure using *ICD-9* code 428 and *ICD-10* code I50. In order to exclude patients with nonischemic chest pain, we limited our definition of myocardial infarction to patients hospitalized for at least 3 days.[36] The date of death or hospital admission was used as the outcome date for all analyses. These outcome definitions have been validated previously, with positive predictive values of approximately 90%.[37–39]

As a sensitivity analysis to assess the robustness of our findings to potentially unmeasured confounding variables, we conducted a "tracer analysis," in which we replicated our analyses using gastrointestinal hemorrhage as the outcome of interest, because we expected no differential risk of hemorrhage between the 2 patient groups.[40–42] Finally, to explore the role of dose, we performed an exploratory time-varying analysis in which we examined the effect of dose using 3 dose categories: low (initial titrating doses venlafaxine ≤ 37.5 mg/d and sertraline ≤ 25 mg/d), moderate (venlafaxine 37.6–200 mg/d and sertraline 26–150 mg/d), and high (venlafaxine > 200 mg/d and sertraline > 150 mg/d).[18,19,43,44] This study was approved by the research ethics boards of Sunnybrook Health Sciences Centre and the University of Toronto.

Data Analysis

We compared the baseline characteristics of patients in the 2 groups using standardized differences, which are less sensitive to sample size than conventional *P* values.[45] To control for baseline differences between the 2 treatment groups, we used inverse probability of treatment weighting using the propensity score.[46] The propensity score was estimated using a logistic regression model that included all the potential confounders listed in Table 1. We then performed a balance assessment,[46,47] comparing the distribution of measured baseline covariates between the treatment groups in the weighted sample using standardized differences. We also visually inspected the weights using box plots.

Using the weighted sample, we performed time-to-event analyses with sertraline as the reference group. We estimated hazard ratios in the weighted sample using Cox proportional hazards regression and obtained a robust variance estimate. From the fitted model, we derived survival curves for each treatment group. Supplementary analyses included stratification for preexisting cardiovascular disease and replication of all analyses with trimmed and stabilized weights.[48] Because conventional inverse probability of treatment weighting using the propensity score is designed for use with exposures that are fixed at baseline, the exploratory

Table 1. Baseline Characteristics of Older Patients Taking Venlafaxine Compared to Sertraline

Characteristic	Sertraline (N = 41,238)	Venlafaxine (N = 48,876)	Standardized Difference Crude	Standardized Difference Weighted
Demographics				
Age at start of cohort drug, median (IQR)	77 (71–82)	75 (70–81)	.17	< .001
Age, n (%)				
66–75, y	18,090 (43.9)	25,197 (51.6)	.15	< .001
76–85, y	17,095 (41.5)	17,828 (36.5)	.1	< .001
≥ 86, y	6,053 (14.7)	5,851 (12.0)	.08	< .001
Male, n (%)	14,538 (35.3)	17,373 (35.5)	.01	.007
No. of medications (past 12 months), median (IQR)	8 (5–13)	9 (5–13)	.02	.001
Long-term care facility resident, n (%)	4,742 (11.5)	6,067 (12.4)	.03	< .001
Hospitalization (past 12 mo), n (%)	12,406 (30.1)	12,769 (26.1)	.09	< .001
Comorbidities (past 36 mo), n (%)				
Heart failure	6,815 (16.5)	6,538 (13.4)	.09	.001
Cardiovascular disease	22,725 (55.1)	23,938 (49.0)	.12	< .001
Stroke	7,838 (19.0)	7,844 (16.0)	.08	< .001
Valvular heart disease	1,367 (3.3)	1,203 (2.5)	.05	< .001
Coronary artery disease	15,174 (36.8)	16,416 (33.6)	.07	< .001
Conduction disorder	4,931 (12.0)	4,782 (9.8)	.07	< .001
Renal disease	5,228 (12.7)	5,750 (11.8)	.03	< .001
Anxiety	30,214 (73.3)	37,027 (75.8)	.06	< .001
Dementia	7,115 (17.3)	8,730 (17.9)	.02	< .001
Medications to treat cardiac disease (past 12 mo), n (%)				
Loop diuretics	7,797 (18.9)	8,075 (16.5)	.06	.001
ACE inhibitors/ARBs	18,299 (44.4)	22,376 (45.8)	.03	< .001
Negative chronotropic drugs[a]	16,499 (40.0)	18,151 (37.1)	.06	< .001
Statins	12,411 (30.1)	17,422 (35.6)	.12	.001
Antiarrhythmic drugs	1,133 (2.7)	1,109 (2.3)	.03	< .001
Antiplatelet drugs	8,913 (21.6)	8,232 (16.8)	.12	< .001
Warfarin	4,489 (10.9)	5,050 (10.3)	.02	< .001
Aldosterone antagonists	1,749 (4.2)	1,677 (3.4)	.04	< .001
Medications that might trigger cardiac disease (past 12 mo), n (%)				
Thiazolidinediones	232 (0.6)	484 (1.0)	.05	.002
Systemic steroids	3,648 (8.8)	4,317 (8.8)	< .001	< .001
Nonsteroidal antiinflammatory drug	12,555 (30.4)	14,886 (30.5)	< .001	< .001
Medications associated with pain (past 12 mo), n (%)				
Opioids	11,917 (28.9)	13,792 (28.2)	.02	< .001
Gabapentin	200 (0.5)	388 (0.8)	.04	< .001
Medications associated with mortality (past 12 mo), n (%)				
Cholinesterase inhibitors	2,105 (5.1)	3,233 (6.6)	.06	.003
Antipsychotic drugs	3,499 (8.5)	5,097 (10.4)	.07	.002

[a]Negative chronotropic drugs include β-blockers and nondihydropyridine calcium channel blockers.
Abbreviations: ACE = angiotensin converting enzyme, ARB = angiotension II receptor blocker, IQR = interquartile range.

secondary analyses that incorporated time-varying doses were conducted in the original, unweighted sample. A Cox proportional hazards model was fit to estimate the effect of dose on the hazard of the composite outcome. In this set of exploratory analyses, dose was treated as a time-varying covariate, and we adjusted for type of SSRI (venlafaxine vs sertraline) and all measured confounding variables that achieved clinical and statistical significance (Table 1, eAppendix 1). All analyses were conducted using SAS version 9.3 (SAS Institute; Cary, North Carolina).

Table 2. Dose Categories of Older Patients on Venlafaxine Compared to Sertraline (N = 90,114)

Dose Category	Sertraline (%)[a]	Venlafaxine (%)[a]
Low[b]	38	35
Moderate[c]	60	62
High[d]	2	3

[a]Percentage of prescriptions.
[b]Low: sertraline ≤ 25 mg/d, venlafaxine ≤ 37.5 mg/d.
[c]Moderate: sertraline 26–150 mg/d, venlafaxine 37.6–200 mg/d.
[d]High: sertraline > 150 mg/d, venlafaxine > 200 mg/d.

RESULTS

During the 10-year study period, we identified 48,876 patients who commenced treatment with venlafaxine and 41,238 patients who commenced treatment with sertraline; these patients were followed for a median of 105 (interquartile range [IQR], 45 to 365) and 90 (IQR, 45 to 317) days, respectively. Subjects treated with venlafaxine and sertraline exhibited similar baseline demographics and comorbidities, although minor differences were found with regard to age and history of cardiovascular and psychiatric disease (Table 1, eAppendix 1). We successfully adjusted for these differences by weighting with the propensity score (Table 1, eAppendix 1). In the weighted sample, all of the standardized differences were less than or equal to .007, indicating that all meaningful differences in means and prevalence estimates of measured baseline covariates had been eliminated by weighting. Approximately half of the study population had preexisting cardiovascular disease at the outset of antidepressant therapy. Only 2.9% of all prescriptions were for venlafaxine doses > 200 mg per day, indicating that the majority of patients did not receive high-dose venlafaxine (Table 2). During the

Table 3. Adverse Cardiac Events in Older Patients on Venlafaxine Compared to Sertraline (N = 90,114)

Outcome	Events in Venlafaxine Patients, n (%)	Events in Sertraline Patients, n (%)	Crude Hazard Ratio (95% CI)	Weighted Events in Venlafaxine, n (%)	Weighted Events in Sertraline, n (%)	Weighted Hazard Ratio (95% CI)
Composite[a]	3,966 (8.1)	3,707 (9.0)	0.74 (0.71–0.77)	4,259 (8.7)	3,459 (8.4)	0.97 (0.93–1.02)
Acute myocardial infarction	430 (0.9)	404 (1.0)	0.71 (0.62–0.82)	447 (0.9)	385 (0.9)	0.91 (0.80–1.05)
Congestive heart failure	986 (2.0)	1,109 (2.7)	0.60 (0.55–0.66)	1,094 (2.2)	995 (2.4)	0.87 (0.80–0.95)
Death	3,098 (6.3)	2,770 (6.7)	0.77 (0.73–0.81)	3,325(6.8)	2,602 (6.3)	1.01 (0.96–1.06)
Gastrointestinal hemorrhage	333 (0.7)	298 (0.7)	0.88 (0.75–1.03)	353 (0.7)	282 (0.7)	0.99 (0.84–1.16)

[a]Composite outcome of all-cause mortality, and hospitalization for acute myocardial infarction and congestive heart failure.

1 year of follow-up, 8.5% of patients experienced the primary composite outcome, 1.4% switched antidepressants, 63.7% discontinued their antidepressant, and 26.3% completed the full year of follow-up without experiencing the primary outcome.

In the primary analysis, 3,966 (8.1%) of venlafaxine-treated patients and 3,707 (9.0%) of sertraline-treated patients experienced the composite outcome of death or hospital admission for acute myocardial infarction or heart failure (Table 3) at an overall rate of 5.2 events per 10,000 patient days of drug exposure. After weighting with the propensity score, we found no significant difference in the risk of adverse cardiac events in patients started on venlafaxine compared to sertraline (hazard ratio = 0.97; 95% CI, 0.93–1.02; Table 3). We also found no significant difference in the secondary outcomes of death or acute myocardial infarction (Table 3). However, we unexpectedly found that venlafaxine use was associated with a lower incidence of heart failure (hazard ratio = 0.87; 95% CI, 0.80–0.95).

These trends persisted in a secondary analysis in which we stratified according to baseline history of cardiac disease (Figure 1). The propensity score–generated weights for venlafaxine and sertraline groups were similar, and supplementary analyses using stabilized and trimmed inverse probability of treatment weights yielded similar results. As expected, we found no significant difference in the risk of gastrointestinal hemorrhage (hazard ratio = 0.99; 95% CI, 0.84–1.16).

In our set of exploratory analyses examining dose, our time-varying dose analyses found no difference in the primary outcome between venlafaxine and sertraline (Table 4). There was an increased risk for adverse cardiac events among patients on high-dose antidepressants compared to low doses (Table 4). This is not unexpected since high-dose antidepressants are often used in patients with more severe depression, a known risk factor for adverse cardiac events.[5,49,50]

DISCUSSION

Using the health records of more than 90,000 older patients, we found no increased risk of adverse cardiac events among patients treated with venlafaxine as compared with sertraline, regardless of baseline cardiovascular disease. This finding is important in light of limited evidence that venlafaxine's noradrenergic effects might confer increased cardiovascular risk. The lower risk of heart failure among venlafaxine patients was an unexpected finding, and further studies are necessary to explore the basis of this association.

Our findings complement those of other recent population-based studies[51–53] that found no increased risk of death or cardiac arrhythmia among patients on venlafaxine, although these studies did not examine the risk of myocardial infarction or heart failure, which might be particularly important given the drug's noradrenergic effects. Cardiac safety has been the focus of a number of clinical trials[54,55] of second-generation antidepressants, which found no increased risk in adverse cardiac events among patients on sertraline or venlafaxine. With small numbers of older patients, however, the results from these clinical trials could not be generalized to an older population.[54,55] A small study comparing paroxetine, sertraline, and venlafaxine among patients suffering from posttraumatic stress disorder found a higher rate of side effects and subsequent dropouts among those on venlafaxine.[56] Although this study did not specifically study cardiac outcomes nor did it include older patients, more venlafaxine patients suffered from palpitations, which may be a noradrenergic-mediated symptom.[56] A case-control study[57] using telephone surveys investigated the risk of myocardial infarction among users of high serotonin transporter affinity antidepressants compared to those antidepressants with low and moderate serotonin transporter affinities and to patients not receiving antidepressants. The researchers found a decreased risk of myocardial infarction among patients on antidepressants with high serotonin transporter affinity, which included sertraline; however, their study participants were younger, had no history of cardiovascular disease, and were not necessarily new users of their antidepressants.[57] Furthermore, instead of performing a head-to-head comparison of sertraline and venlafaxine, this study compared groups of antidepressants with different serotonin transporter affinities.[57] Venlafaxine was grouped among other non-SSRI antidepressants, along with tricyclic antidepressants, trazodone, bupropion, and mirtazapine, which, aside from their serotonin transporter affinity properties, are pharmacologically different. Although Johnson et al[20] found an increase in adverse cardiac effects, such as increased heart rate and blood pressure among older community-dwelling patients with depression on venlafaxine, there were no cases of myocardial infarction or heart failure. This study, however, had a smaller sample size, thereby limiting its statistical power to detect such cardiac events.[20] Our study is the first population-based study to specifically compare the cardiac toxicity of the commonly

Figure 1. Adverse Cardiac Events in Older Patients Without and With Cardiovascular Disease Taking Venlafaxine Compared to Sertraline

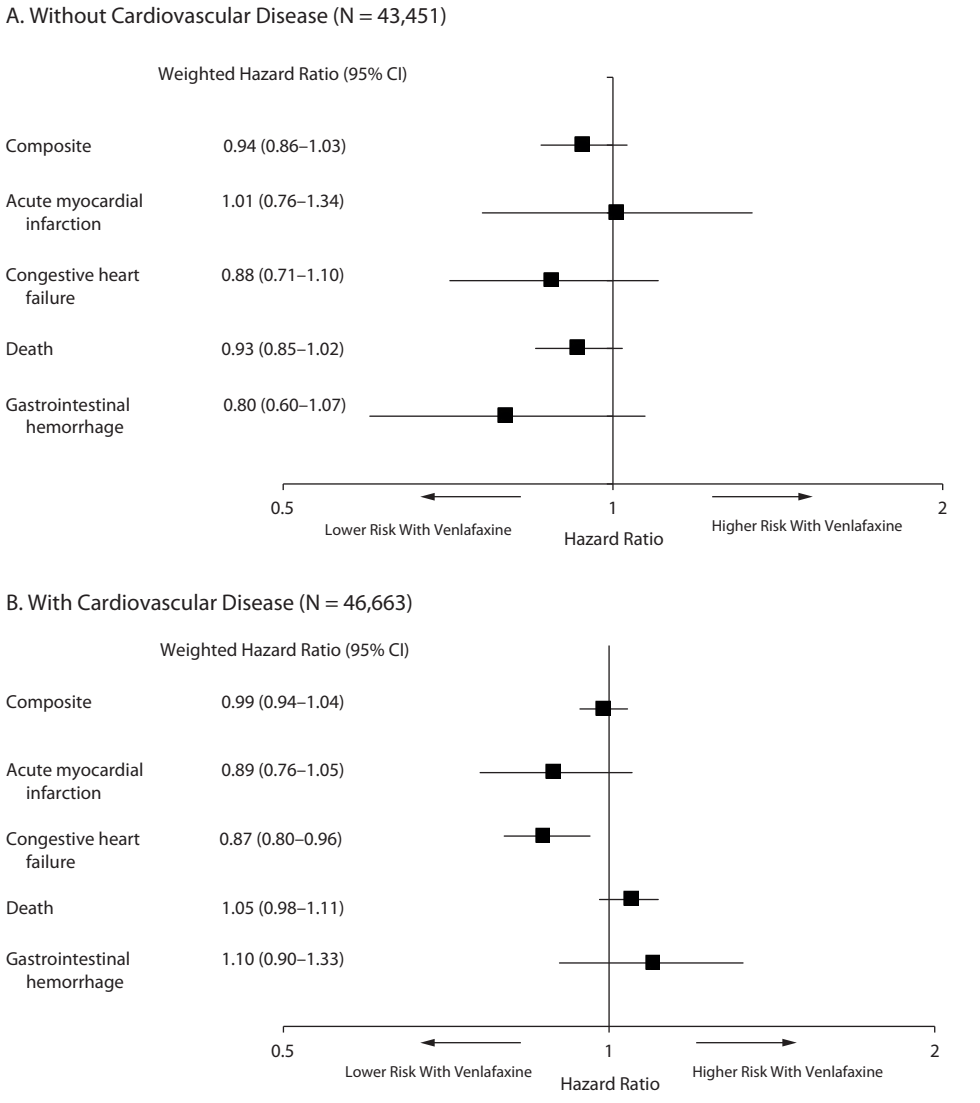

Table 4. Time-Varying Dose Analysis of Venlafaxine and the Risk for Adverse Cardiac Events

Variable	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio[a] (95% CI)	*P* Value
Venlafaxine[b]	0.84 (0.80–0.87)	1.00 (0.96–1.05)	.89
Moderate dose[c]	0.90 (0.85–0.94)	1.06 (1.01–1.12)	.01
High dose[c]	0.98 (0.94–1.06)	1.41 (1.25–1.59)	< .001

[a]Adjusted for age, female sex, hospitalization in the past year, stroke, heart failure, cardiovascular disease, use of statins and antiplatelets, and the aggregated diagnosis groups, limited minor and stable but persistent psychosocial disease.
[b]Sertraline is reference.
[c]Low dose is reference.

prescribed antidepressants venlafaxine and sertraline, and it provides further insight into the safety of these drugs among older patients with cardiovascular disease.[58] Overall, our results provide a measure of reassurance to physicians treating depression among older patients, particularly those with cardiovascular disease.

Some limitations of our study merit discussion. The results derive from older patients, and the generalizability to younger patients is unknown. However, our study addresses venlafaxine's risk in an understudied population in a real-world setting; this is relevant because most real-world patients treated for depression are excluded from randomized controlled trials.[59] A recent meta-analysis and meta-regression[60] of randomized trials of the effect of antidepressants and late-life depression found a small number of clinical trials that included older individuals; however, none included safety as an outcome in this growing vulnerable population. Although we utilized a propensity score incorporating variables that might relate to both exposures and outcomes, our administrative databases had no information on important factors such as body weight, alcohol and smoking status, or cytochrome P450 2D6 phenotype.[61,62] However, there is no apparent reason why these factors might differ between the 2 antidepressant groups.

Nevertheless, our cohorts were generally similar even before weighting, and we found no significant difference in our tracer outcome. Because some clinicians concerned about the hemodynamic effects of venlafaxine might have avoided this drug in those with cardiovascular or hypertensive disease, there is a risk of channeling bias. Although this mild difference in baseline cardiovascular disease between groups was successfully balanced with inverse probability of treatment weighting, this potential bias deserves mention. Our validated primary outcome allowed us to identify adverse cardiac events severe enough to result in death or hospitalization. It did not, however, allow us to capture less severe cardiac events and effects, such as mild heart failure, exacerbated hypertension, or tachycardia, that might have been induced by venlafaxine.[20] If these mild conditions prompted timely outpatient interventions, hospitalization could be prevented, therefore resulting in the decreased risk of hospitalization for heart failure. Although outpatient diagnosis codes for hypertension, tachycardia, and heart failure exist, we did not include them in our outcomes because they are not well validated in isolation.[63] Finally, we could not reliably explore the association between high-dose venlafaxine and adverse cardiac outcomes. Whether high-dose venlafaxine is associated with increased cardiac risk remains unknown.

In summary, in this population-based study, we found no significant difference in the cardiovascular safety profiles of low to moderate doses of venlafaxine compared to sertraline. Our results offer a measure of reassurance about the drug's cardiac safety; however, physicians should still exercise caution in patients on higher doses or those who manifest overt noradrenergic effects.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), gabapentin (Neurontin, Gralise and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), tamoxifen (Soltamox and others), trazodone (Oleptro and others), venlafaxine (Effexor and others), warfarin (Coumadin, Jantoven, and others).

Author affiliations: Department of Medicine (Drs Ho and Juurlink); The Leslie Dan Faculty of Pharmacy (Dr Mamdani and Ms Gomes); Institute of Health Policy, Management and Evaluation (Drs Straus, Austin, Mamdani, and Juurlink), and Department of Pediatrics (Dr Juurlink), University of Toronto; The Institute for Clinical Evaluative Sciences (Drs Austin, Mamdani, and Juurlink and Ms Gomes); Li Ka Shing Knowledge Institute, St. Michael's Hospital (Drs Straus and Mamdani and Ms Gomes); and The Sunnybrook Research Institute (Dr Juurlink), Toronto, Ontario, Canada.

Potential conflicts of interest: **Dr Ho** is a trainee with the University of Toronto Department of Medicine Clinician Scientist Training Program. **Dr Straus** is funded by a Tier 1 Canada Research Chair in Knowledge Translation and Quality of Care. **Dr Mamdani** has served as an advisory board member for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Hoffman La Roche, Novartis, Novo Nordisk, and Pfizer and has sat on 1–2 advisory boards for Pfizer for which he received honoraria valued at less than $5,000. **Drs Austin** and **Juurlink** and **Ms Gomes** report no financial relationships or other relationship relevant to the subject of this article.

Funding/support: This study was supported by a grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Drug Innovation Fund and the Institute for Clinical Evaluative Sciences (ICES), a nonprofit research institute sponsored by the Ontario MOHLTC (Canada). At the time of this study, Dr Ho was supported by the Canadian Institute for Health Research Drug Safety and Effectiveness Cross-disciplinary Training (DSECT) program. Dr Austin is supported by a Career Investigator award from the Heart and Stroke Foundation.

Role of sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Disclaimer: The opinions, results and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred.

Acknowledgments: The authors thank Ashif Kachra, CHIM, for administrative support, and Chelsea Hellings, MSc, for project coordination. Mr Kachra and Ms Hellings are employed by ICES. The authors also thank Brogan Inc (Ottawa, Canada) for use of their Drug Product and Therapeutic Class Database.

Additional information: This study was conducted at the Institute for Clinical Evaluative Sciences, University of Toronto, Toronto, Ontario, Canada.

Supplementary material: See accompanying pages.

REFERENCES

1. Patten SB, Wang JL, Williams JVA, et al. Descriptive epidemiology of major depression in Canada. *Can J Psychiatry*. 2006;51(2):84–90.
2. Thombs BD, Bass EB, Ford DE, et al. Prevalence of depression in survivors of acute myocardial infarction. *J Gen Intern Med*. 2006;21(1):30–38.
3. Kessler RC, Berglund P, Demler O, et al; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003;289(23):3095–3105.
4. Hamer M, Bates CJ, Mishra GD. Depression, physical function, and risk of mortality: National Diet and Nutrition Survey in adults older than 65 years. *Am J Geriatr Psychiatry*. 2011;19(1):72–78.
5. Frasure-Smith N, Lespérance F, Talajic M. Depression following myocardial infarction: impact on 6-month survival. *JAMA*. 1993;270(15):1819–1825.
6. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. *Arch Gen Psychiatry*. 2009;66(8):848–856.
7. Pratt LA, Brody DJ, Gu Q. *Antidepressant Use in Persons Aged 12 and Over*. Washington, DC: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2011:2005–2008.
8. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. *Ann Intern Med*. 2011;155(11):772–785.
9. Melichar JK, Haida A, Rhodes C, et al. Venlafaxine occupation at the noradrenaline reuptake site: in-vivo determination in healthy volunteers. *J Psychopharmacol*. 2001;15(1):9–12.
10. Abdelmawla AH, Langley RW, Szabadi E, et al. Comparison of the effects of venlafaxine, desipramine, and paroxetine on noradrenaline- and methoxamine-evoked constriction of the dorsal hand vein. *Br J Clin Pharmacol*. 1999;48(3):345–354.
11. Siepmann T, Ziemssen T, Mueck-Weymann M, et al. The effects of venlafaxine on autonomic functions in healthy volunteers. *J Clin Psychopharmacol*. 2007;27(6):687–691.
12. Harvey AT, Rudolph RL, Preskorn SH. Evidence of the dual mechanisms of action of venlafaxine. *Arch Gen Psychiatry*. 2000;57(5):503–509.
13. Holliday SM, Benfield P. Venlafaxine: a review of its pharmacology and therapeutic potential in depression. *Drugs*. 1995;49(2):280–294.
14. Effexor XR (venlafaxine) [package insert]. Kirkland**,** Canada: Wyeth Pfizer Canada Inc.
15. Debonnel G, Saint-André É, Hébert C, et al. Differential physiological effects of a low dose and high doses of venlafaxine in major depression. *Int J Neuropsychopharmacol*. 2007;10(1):51–61.
16. Feighner JP. The role of venlafaxine in rational antidepressant therapy. *J Clin Psychiatry*. 1994;55(suppl A):62–68, discussion 69–70, 98–100.
17. Feighner JP. Cardiovascular safety in depressed patients: focus on venlafaxine. *J Clin Psychiatry*. 1995;56(12):574–579.
18. Preskorn S. Two in one: the venlafaxine story. *J Pract Psychiatry Behav Health*. 1999;5(6):346–350.
19. Blier P, Saint-André E, Hébert C, et al. Effects of different doses of venlafaxine on serotonin and norepinephrine reuptake in healthy volunteers. *Int J Neuropsychopharmacol*. 2007;10(1):41–50.
20. Johnson EM, Whyte E, Mulsant BH, et al. Cardiovascular changes associated with venlafaxine in the treatment of late-life depression. *Am J Geriatr Psychiatry*. 2006;14(9):796–802.
21. Kok R, Nolen W, Heeren T. Cardiovascular changes associated with venlafaxine in the treatment of late-life depression. *Am J Geriatr Psychiatry*. 2007;15(8):725, author reply 726.
22. Danjou P, Hackett D. Safety and tolerance profile of venlafaxine. *Int Clin Psychopharmacol*. 1995;10(suppl 2):15–20.

23. Charniot JC, Vignat N, Monsuez JJ, et al. Cardiogenic shock associated with reversible dilated cardiomyopathy during therapy with regular doses of venlafaxine. *Am J Emerg Med*. 2010;28(2):256. e1–e5.
24. Colucci VJ, Berry BD. Heart failure worsening and exacerbation after venlafaxine and duloxetine therapy. *Ann Pharmacother*. 2008;42(6):882–887.
25. Oslin DW, Ten Have TR, Streim JE, et al. Probing the safety of medications in the frail elderly: evidence from a randomized clinical trial of sertraline and venlafaxine in depressed nursing home residents. *J Clin Psychiatry*. 2003;64(8):875–882.
26. Juurlink DN, Institute for Clinical Evaluative Sciences in Ontario. *Canadian Institute for Health Information Discharge Abstract Database: A Validation Study*. Toronto, Ontario: Institute for Clinical Evaluative Sciences; 2006.
27. Williams J, Young W. *A Summary of Studies on the Quality of Health Care Administrative Databases in Canada. Patterns of Health Care in Ontario: The ICES Practice Atlas*.2nd ed. Ottawa, Ontario: Canadian Medical Association; 1996:339:45.
28. CIHI. CIHI Data Quality Study of the 2009–2010 Discharge Abstract Database. https://secure.cihi.ca/free_products/Reabstraction_june19revised_09_10_en.pdf. Updated June 2012. Accessed November 18, 2013.
29. The data quality study of the Canadian discharge abstract database. Proceedings of Statistics Canada Symposium 2001. http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.196.805&rep=rep1&type=pdf. Accessed November 18, 2013.
30. Gill SS, Rochon PA, Herrmann N, et al. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. *BMJ*. 2005;330(7489):445.
31. Juurlink DN, Mamdani M, Kopp A, et al. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA*. 2003;289(13):1652–1658.
32. Tatsumi M, Groshan K, Blakely RD, et al. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *Eur J Pharmacol*. 1997;340(2–3):249–258.
33. Lam RW, Kennedy SH, Grigoriadis S, et al; Canadian Network for Mood and Anxiety Treatments (CANMAT). Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults, 3: pharmacotherapy. *J Affect Disord*. 2009;117(suppl 1):S26–S43.
34. Ripple MG, Pestaner JP, Levine BS, et al. Lethal combination of tramadol and multiple drugs affecting serotonin. *Am J Forensic Med Pathol*. 2000;21(4):370–374.
35. Carver JR, Shapiro CL, Ng A, et al; ASCO Cancer Survivorship Expert Panel. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. *J Clin Oncol*. 2007;25(25):3991–4008.
36. Tu JV, Austin PC, Filate WA, et al; Canadian Cardiovascular Outcomes Research Team. Outcomes of acute myocardial infarction in Canada. *Can J Cardiol*. 2003;19(8):893–901.
37. Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. *Am Heart J*. 2002;144(2):290–296.
38. So L, Evans D, Quan H. ICD-10 coding algorithms for defining comorbidities of acute myocardial infarction. *BMC Health Serv Res*. 2006;6(1):161.
39. Varas-Lorenzo C, Castellsague J, Stang MR, et al. Positive predictive value of ICD-9 codes 410 and 411 in the identification of cases of acute coronary syndromes in the Saskatchewan Hospital automated database. *Pharmacoepidemiol Drug Saf*. 2008;17(8):842–852.
40. van Walraven C, Mamdani MM, Wells PS, et al. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. *BMJ*. 2001;323(7314):655–658.
41. de Abajo FJ, García-Rodríguez LA. Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy: interaction with nonsteroidal anti-inflammatory drugs and effect of acid-suppressing agents. *Arch Gen Psychiatry*. 2008;65(7):795–803.
42. de Abajo FJ, Rodríguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *BMJ*. 1999;319(7217):1106–1109.
43. Khan A, Upton GV, Rudolph RL, et al; Venlafaxine Investigator Study Group. The use of venlafaxine in the treatment of major depression and major depression associated with anxiety: a dose-response study. *J Clin Psychopharmacol*. 1998;18(1):19–25.
44. Lalit V, Appaya PM, Hegde RP, et al. Escitalopram versus citalopram and sertraline: a double-blind controlled, multi-centric trial in Indian patients with unipolar major depression. *Indian J Psychiatry*. 2004;46(4):333–341.
45. Mamdani M, Sykora K, Li P, et al. Reader's guide to critical appraisal of cohort studies, 2: assessing potential for confounding. *BMJ*. 2005;330(7497):960–962.
46. Austin PC. A tutorial and case study in propensity score analysis: an application to estimating the effect of in-hospital smoking cessation counseling on mortality. *Multivariate Behav Res*. 2011;46(1):119–151.
47. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083–3107.
48. Lee BK, Lessler J, Stuart EA. Weight trimming and propensity score weighting. *PLoS ONE*. 2011;6(3):e18174.
49. Lauzon C, Beck CA, Huynh T, et al. Depression and prognosis following hospital admission because of acute myocardial infarction. *CMAJ*. 2003;168(5):547–552.
50. Frasure-Smith N, Lespérance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. *Circulation*. 1995;91(4):999–1005.
51. Martinez C, Assimes TL, Mines D, et al. Use of venlafaxine compared with other antidepressants and the risk of sudden cardiac death or near death: a nested case-control study. *BMJ*. 2010;340:c249.
52. Leonard CE, Bilker WB, Newcomb C, et al. Antidepressants and the risk of sudden cardiac death and ventricular arrhythmia. *Pharmacoepidemiol Drug Saf*. 2011;20(9):903–913.
53. Weeke P, Jensen A, Folke F, et al. Antidepressant use and risk of out-of-hospital cardiac arrest: a nationwide case-time-control study. *Clin Pharmacol Ther*. 2012;92(1):72–79.
54. Davidson J, Watkins L, Owens M, et al. Effects of paroxetine and venlafaxine XR on heart rate variability in depression. *J Clin Psychopharmacol*. 2005;25(5):480–484.
55. Glassman AH, O'Connor CM, Califf RM, et al; Sertraline Antidepressant Heart Attack Randomized Trial (SADHEART) Group. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*. 2002;288(6):701–709.
56. Smajkic A, Weine S, Djuric-Bijedic Z, et al. Sertraline, paroxetine, and venlafaxine in refugee posttraumatic stress disorder with depression symptoms. *J Trauma Stress*. 2001;14(3):445–452.
57. Sauer WH, Berlin JA, Kimmel SE. Effect of antidepressants and their relative affinity for the serotonin transporter on the risk of myocardial infarction. *Circulation*. 2003;108(1):32–36.
58. Coupland C, Dhiman P, Morriss R, et al. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ*. 2011;343:d4551.
59. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?" *Lancet*. 2005;365(9453):82–93.
60. Tedeschini E, Levkovitz Y, Iovieno N, et al. Efficacy of antidepressants for late-life depression: a meta-analysis and meta-regression of placebo-controlled randomized trials. *J Clin Psychiatry*. 2011;72(12):1660–1668.
61. Lobello KW, Preskorn SH, Guico-Pabia CJ, et al. Cytochrome P450 2D6 phenotype predicts antidepressant efficacy of venlafaxine: a secondary analysis of 4 studies in major depressive disorder. *J Clin Psychiatry*. 2010;71(11):1482–1487.
62. Whyte EM, Romkes M, Mulsant BH, et al. CYP2D6 genotype and venlafaxine-XR concentrations in depressed elderly. *Int J Geriatr Psychiatry*. 2006;21(6):542–549.
63. Schultz SE, Rothwell DM, Chen Z, et al. Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records. *Chronic Dis Inj Can*. 2013;33(3):160–166.

Supplementary material follows this article.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Adverse Cardiac Events in Older Patients Receiving Venlafaxine: A Population-Based Study

Author(s): Joanne M. Ho, MD; Tara Gomes, MHSc; Sharon E. Straus, MD, MSc; Peter C. Austin, PhD; Muhammad Mamdani, PharmD, MA, MPH; and David N. Juurlink, MD, PhD

DOI Number: 10.4088/JCP.13m08508

List of Supplementary Material for the article

1. eAppendix 1 Aggregated Diagnosis Groups of Older Individuals on Venlafaxine Compared to Sertraline

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

eAppendix 1. Aggregated Diagnosis Groups of Older Individuals on Venlafaxine Compared to Sertraline

Characteristic	Sertraline	Venlafaxine	Standardized Difference	
	N=41,238	N=48,876	Crude	Weighted
Aggregated Diagnosis Groups				
Time Limited				
Minor	18,315 (44.4%)	22,435 (45.9%)	0.03	0.001
Minor-Primary Infections	28,361 (68.8%)	33,464 (68.5%)	0.01	<0.001
Major	10,191 (24.7%)	11,094 (22.7%)	0.05	<0.001
Major-Primary Infections	7,710 (18.7%)	8,677 (17.8%)	0.02	0.001
Allergies	4,017 (9.7%)	4,713 (9.6%)	0.001	0.001
Asthma	4,826 (11.7%)	5,393 (11.0%)	0.02	<0.001
Likely to Recur				
Discrete	25,095 (60.9%)	29,848 (61.1%)	0.001	<0.001
Discrete-Infections	15,601 (37.8%)	18,381 (37.6%)	0.001	<0.001
Progressive	9,931 (24.1%)	10,003 (20.5%)	0.09	<0.001
Chronic Medical				
Stable	36,730 (89.1%)	43,573 (89.2%)	0.001	0.001
Unstable	28,371 (68.8%)	32,026 (65.5%)	0.07	<0.001
Chronic Specialty				
Stable-Orthopedic	2,053 (5.0%)	2,272 (4.6%)	0.02	<0.001
Stable-Ear,Nose,Throat	4,052 (9.8%)	4,558 (9.3%)	0.02	0.001
Stable-Eye	15,148 (36.7%)	16,721 (34.2%)	0.05	<0.001
Unstable-Orthopedic	2,921 (7.1%)	3,644 (7.5%)	0.01	<0.001
Unstable-Ear,Nose,Throat	1,112 (2.7%)	1,165 (2.4%)	0.02	<0.001
Unstable-Eye	8,005 (19.4%)	9,171 (18.8%)	0.02	<0.001
Dermatologic	9,659 (23.4%)	11,902 (24.4%)	0.02	<0.001
Injuries or Adverse Effects				
Minor	14,103 (34.2%)	16,694 (34.2%)	0.001	<0.001
Major	14,939 (36.2%)	17,518 (35.8%)	0.01	<0.001
Psychosocial				
Time Limited, Minor	4,354 (10.6%)	4,890 (10.0%)	0.02	<0.001
Stable, Recurrent or Persistent	25,155 (61.0%)	32,589 (66.7%)	0.12	0.001
Unstable, Recurrent or Persistent	9,327 (22.6%)	11,486 (23.5%)	0.02	0.001
Signs or Symptoms				
Minor	27,612 (67.0%)	32,471 (66.4%)	0.01	<0.001
Uncertain	34,365 (83.3%)	40,700 (83.3%)	0.001	<0.001
Major	24,808 (60.2%)	28,952 (59.2%)	0.02	0.001
Discretionary	14,760 (35.8%)	17,376 (35.6%)	0.01	0.001
See and Reassure	1,300 (3.2%)	1,343 (2.7%)	0.02	<0.001
Prevention or Administrative	20,534 (49.8%)	24,515 (50.2%)	0.01	0.001
Malignancy	10,128 (24.6%)	12,527 (25.6%)	0.02	0.001
Pregnancy	213 (0.5%)	210 (0.4%)	0.01	0.001
Dental	891 (2.2%)	1,049 (2.1%)	0.001	<0.001