Citalopram and EKG Monitoring

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Title: EKG monitoring after the FDA warnings for citalopram: Unheeded alerts?

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Impact Statement: 1) We certify that this research is novel. 2) This study evaluates rates of EKG monitoring following the 2011-2012 Food and Drug Administration (FDA) warnings regarding concerns of QT prolongation associated with high dose citalopram use. Among VA patients prescribed high dose citalopram, after an initial period of responsiveness following the first FDA warning, rates of EKG monitoring largely returned to pre-warning levels. Among older Veterans maintained on high dose citalopram with previous cardiac risk factors—those who would be at highest risk of the negative cardiac outcomes outlined by the FDA warning—we did not observe an increase from pre-warning EKG monitoring levels following the drug safety warnings. Lack of responsiveness to the FDA warnings may be due to many factors including lack of clarity surrounding which patients should receive EKG monitoring, conflicting evidence regarding the risk for adverse cardiac events related to high dose citalopram use, provider substitution of other antidepressant medications for citalopram, and lack of provider knowledge regarding the warnings. This work highlights the need for future studies aimed at understanding how health systems can best help providers and patients make decisions regarding medication use following FDA warnings, balancing the potential risks of the medication with the risks and benefits of complying with the drug safety warnings.

Citalopram and EKG Monitoring

Abstract:

Objective: The 2011-2012 FDA warnings for citalopram recommended providers perform EKG monitoring for patients at risk of QT prolongation. We evaluated national trends in EKG monitoring among Veteran's Affairs (VA) patients prescribed high dose citalopram before and after the drug safety announcements.

Design: Interrupted time-series analyses estimated the effects of the warnings on EKG monitoring among patients prescribed high dose citalopram, or a comparison antidepressant, sertraline, not subject to the FDA warnings.

Setting: National VA healthcare system data linked to Medicare data for Veterans dually eligible for VA and Medicare services.

Participants: Adult VA outpatients prescribed citalopram or sertraline from 2/2010 to 9/2013 (N=1,068,816).

Measurements: EKG monitoring for VA outpatients prescribed high dose citalopram (>40 mg or >20 mg daily in adults >60 years old) or sertraline across study periods.

Results: Among patients prescribed high dose citalopram, EKG monitoring increased from 9.0% before the start of first FDA warning, to a peak of 12.6% among patients 18-60 years old, and from 14.0% to 19.4% for patients 61-100 years old, respectively. However, following the second FDA warning in 2012, EKG monitoring declined, returning to pre-warning levels across both age groups. Among patients with a history of previous cardiac risk factors, EKG monitoring did not increase among patients prescribed high dose citalopram in either age group.

Conclusions: Among patients with previous cardiac risk factors, EKG frequency did not significantly change in patients at greatest potential risk for QT prolongation. Lack of

responsiveness to the FDA warnings may be due to many factors including lack of clarity surrounding which patients should receive EKG monitoring, provider substitution of citalopram to alternative antidepressants, conflicting evidence regarding the risk for adverse cardiac events with high dose citalopram use, and lack of provider knowledge regarding the warnings.

Key Words: Citalopram, FDA warning, EKG

Introduction:

In 2011, the US Food and Drug Administration (FDA) issued a drug safety warning for citalopram, cautioning providers against using doses above 40 mg per day, given concerns for potential QT prolongation.[1] The FDA issued a revised warning in 2012, recommending against using doses above 20 mg per day in those age 60 or older.[2] The FDA based these recommendations on post-marking reports of QT interval prolongation and concerns for development of Torsades de Pointes (TdP) associated with high dose citalopram use.[3,4] The FDA concluded that there was no evidence for additional effectiveness of citalopram doses >40 mg/day to justify the potential increased cardiac risk.[2,5] For patients for whom citalopram use was not recommended but considered essential, the FDA recommended more frequent electrolyte and/or electrocardiogram (EKG) monitoring.[2]

Following the 2011-2012 FDA warnings, prescribers needed to determine how to appropriately monitor and weigh the potential cardiac risk associated with high dose citalopram use against the risk of psychiatric destabilization among patients previously on therapeutic doses of citalopram.[6] Additionally, the 2011-2012 FDA recommendations

left room for interpretation regarding which patients should receive EKG monitoring, therefore, prescribers need to decide whether to order EKGs for: 1) patients who might have an increased risk for adverse cardiac outcomes; 2) those newly prescribed citalopram; 3) those on any dose of citalopram; or 4) patients prescribed higher than-recommended doses. While a randomized clinical trial evaluating use of citalopram for treatment of agitation in dementia (Citalopram for Agitation in Alzheimer Disease Study [CitAD]), found use of high dose citalopram prolonged the QT interval,[7] several studies have called into question whether the actual risk for adverse cardiac events related to citalopram justifies the FDA warning.[4,8] Previous research has found no increase in cardiac mortality or ventricular arrhythmia for patients on high doses of citalopram[8] with studies finding that the QT prolongation with citalopram and other antidepressants has been modest.[9,10] In our previous work, we found low rates of EKG monitoring (8.5%) within a university-based outpatient primary care clinic among patients (N=199) maintained on higher than recommended doses of citalopram following the FDA warnings.[11] This low rate of EKG monitoring occurred despite a pharmacist intervention to alert prescribing providers to the warning.[11] To our knowledge, no other studies have been performed evaluating EKG monitoring after the citalopram drug safety warnings.

In the current study, we evaluated national trends in EKG monitoring among patients on high dose citalopram following the 2011-2012 FDA drug safety warnings within the Veteran's Affairs (VA) healthcare system compared to an alternative antidepressant, sertraline, not subject to the drug safety warnings. We sought to determine whether trends in EKG monitoring observed in our previous work in a single health system[11] reflected national prescribing practices, given that the VA engaged in

several systematic efforts to ensure broad communication of the citalopram drug safety warnings and to monitor subsequent prescribing.[12,13] We anticipated that the drug safety warnings would be associated with an increase in EKG monitoring among patients on high dose citalopram, as well as in patients with a history of previous cardiovascular risk factors that would place them at greater potential risk for negative cardiac outcomes associated with citalopram use.

Methods:

Study Cohort:

We assembled a rolling cohort of VA patients aged 18-100 from 2/2010 to 9/2013. The cohort included patients with citalopram prescriptions from at least 12 months prior to the first FDA warning (8/2011) and 12 months after the last warning (3/2012). The VA Ann Arbor Healthcare System Institutional Review Board approved this study.

Measures of Citalopram and Sertraline Use:

We compiled quarterly citalopram and sertraline prescribing rates for VA users. To be included in the denominator for each three-month period, we required patients to have at least one VA outpatient appointment during the observation period. We linked Pharmacy Benefits Management (PBM) data to patient demographic data from the Corporate Data Warehouse (CDW) to construct the study cohort. We defined the index dispense date as the date of the first citalopram prescription fill. Citalopram use data included both new (no prescription claims in the 180 days prior to the index dispense

date) and continuing citalopram prescriptions during each three-month period. We calculated daily dose of citalopram by calculating the quantity of tablets dispensed divided by the number of days supplied, multiplied by the dosage per tablet. For each quarter, we calculated the proportion of patients with high dose and any dose citalopram prescription fills. As the definition of high dose citalopram varied by age (high dose >40 mg age 18-60, >20 mg age >60), we created a younger (18-60) and an older (61-100) cohort.

Rates of EKG Monitoring:

To determine the rate of EKG monitoring, we evaluated the number of EKGs performed (CPT codes 93000, 93005, 93010, 93040, 93041, and 93042) during the quarter observed, divided by the number of patients with fills for either citalopram or sertraline during that quarter. We determined quarterly proportion of EKG monitoring in patients newly prescribed citalopram, maintained on any dose citalopram, and prescribed above recommended doses of citalopram compared to an alternative antidepressant not subject to the FDA warning (sertraline). For Veterans dually eligible for VA and Medicare services, we linked VA administrative data to Centers for Medicare and Medicaid Services (CMS) data, to account for Veterans who received medical care and EKG monitoring outside of the VA healthcare system.

Among patients with previous cardiac risk factors, we assessed whether an EKG was completed within the past three months among patients maintained on high dose citalopram, as compared to any dose citalopram and sertraline. Prior cardiac risk factors included a diagnosis of myocardial infarction, congestive heart failure, arrhythmia, or

angina within the past 12 months of the antidepressant medication fill (see **Supplemental Table 1** for International Classification of Diseases, Ninth Revision codes).

Statistical Analysis:

In order to understand changes in EKG monitoring among patients maintained on citalopram and sertraline following the FDA warnings, we calculated the proportion of patients who had an EKG performed within the past three months among patients prescribed citalopram and compared findings across three study periods: 1) Starting in 2/2010 prior to the FDA warning in 8/2011 [pre-warning period]; 2) post-2011 FDA warning until the second warning in 3/2012 [warning 1 period]; and 3) post-2012 FDA warning until 9/2013 [warning 2 period]. To examine the effect of the FDA warnings on the proportion of patients who received EKG monitoring, we fit separate interrupted time series regression (ITS) models [14,15] with first-order autoregressive errors among: 1) high dose citalopram users based on age (>40 mg, or >20 mg daily in adults >60 years old after the second warning), 2) citalopram users of any dose, and 3) any dose use of sertraline (a comparison antidepressant not subject to the FDA warning). We used a three-phase ITS model to describe the changes in both the level (intercept) and trend over time (slope) of change in EKG monitoring during the study period across age groups (18-60, 61-100). Based on the ITS model, we tested for the statistical significance of the difference in the levels in the quarter prior to warning 1 to the end of the study period in 9/2013, controlling for pre-warning level and trend. Lastly, we conducted analyses to assess EKG monitoring in only those patients diagnosed with

previous cardiac risk factors (myocardial infarction, congestive heart failure, arrhythmia, and angina) within the past year. We conducted all statistical analyses using the SAS 9.4 statistical software package (SAS Institute Inc., Cary NC).

Results:

Sample Characteristics:

The study sample included 1,068,816 VA outpatient service users aged 18-100 prescribed an antidepressant of interest (citalopram or sertraline) of which 602,388 were dually eligible for Medicare. Of VA service users, 58.3% (N=623,498) were prescribed citalopram. Of patients prescribed citalopram, the majority were male (N=561,485, 90.1%), white (N=452,844, 72.6%), and of non-Hispanic ethnicity (N=554,522, 88.9%); 48.8% (N=304,332) were between ages 61-100. At the start of the study, 21.8% of younger (age 18-60) and 17.3% of older (age 61-100) citalopram users were prescribed higher than recommended doses.

EKG Monitoring Among Patients on High Dose Citalopram:

At the start of the study period in 2/2010, 8.4% of younger and 9.7% of older high dose citalopram users received EKG monitoring. Among patients prescribed high dose citalopram, EKG monitoring increased from 9.2% just prior to the first FDA warning in 8/2011, to a peak of 12.6% in users 18-60. Among users 61-100, EKG monitoring increased from 10.6% just prior to the first FDA warning, to a peak of 14.9%. However, by the time of the second FDA warning in 3/2012, the rates of EKG monitoring began to decline among both age groups. At the end of the study period in 9/2013 among the

younger cohort, 10.6% received EKG monitoring, unchanged from pre-warning monitoring levels (p=0.18). Among the older cohort, 9.8% receiving EKG monitoring at the end of the study, unchanged from pre-warning monitoring (p=0.89). Overall rates of EKG monitoring did not change significantly following the drug safety warnings among patients prescribed any dose citalopram or sertraline.

For Veterans dually eligible for Medicare services, we linked VA and CMS data to account for additional EKG monitoring that may occur outside of the VA healthcare system. When accounting for CMS data, trends and patterns in EKG utilization remained unchanged from EKG monitoring rates seen within the VA healthcare system alone. **Figure 1** demonstrates the quarterly proportion of citalopram users who received EKG monitoring throughout the study periods. **Supplemental Table 2** depicts changes in level and trend of EKG monitoring during the three study periods for patients prescribed high dose citalopram, any dose of citalopram, or sertraline. The inclusion of CMS data resulted in an additional observed increase in EKG monitoring among patients prescribed high dose citalopram of 1.4% (total increase from 12.6% in VA healthcare system alone to 14.0% in combined VA and CMS data) in patients 18-60, and 4.5% (increase from 14.9% to 19.4%) in patients 61-100. Similarly, trends in EKG monitoring for any dose citalopram and sertraline remained unchanged when accounting for CMS data.

EKG Monitoring Among Patients Newly Prescribed Citalopram:

Among patients newly prescribed citalopram (no previous prescription within the past 180 days), for high dose citalopram users, EKG monitoring increased after the first

FDA warning among both younger (increase in EKG monitoring from 7.8% in 8/2011 to a peak of 14.0%) and older cohorts (12.4% to 15.5%) (**Supplemental Figure 1**). For the younger cohort, after an initial decline following the second FDA warning, rates of EKG monitoring for patients newly prescribed high dose citalopram increased to 14.5% at the end of the study period, significantly increased from pre-warning monitoring levels ($p<0.001$). However, for older adults, following the initial increase, rates in EKG monitoring then decreased and returned to near baseline levels (12.3% at end of study period) and were unchanged from pre-warning monitoring levels ($p=0.09$). Rates of EKG monitoring did not change significantly among patients newly prescribed any dose citalopram or sertraline among either the younger or older cohorts.

EKG Monitoring Among Patients with Previous Cardiac Risk Factors:

We examined EKG monitoring among patients prescribed citalopram and sertraline who had a history of cardiac risk factors within the past year. **Supplemental Figure 2** demonstrates the quarterly proportion of citalopram users with previous cardiac risk factors who received EKG monitoring within the past three months. EKG monitoring rates did not change within the past three months for patients with previous cardiac risk factors among patients prescribed high dose citalopram, any dose citalopram, or sertraline.

Discussion:

Among patients prescribed higher than recommended doses of citalopram, following the first FDA warning there was an initial increase in the rates of EKG

monitoring for both younger and older Veterans receiving services through the VA and Medicare. However, after this initial period of responsiveness, rates of EKG monitoring largely declined back to baseline levels by the end of the study period in 2013. For patients with previous cardiac risk factors for whom the FDA recommended more frequent monitoring, we found no change in rates of EKG monitoring among patients on high dose citalopram for both younger and older adults. Older adults with prior cardiac comorbidities that can predispose to poor cardiac outcomes would be at highest risk for the concerns for QT prolongation highlighted by the FDA warnings. Among this highest risk group—who could potentially benefit most from cardiac monitoring—EKG monitoring did not change. However, these results are similar to previous work outside of the VA healthcare system, demonstrating low overall rates of EKG monitoring (8.5%) following the FDA warnings and no increase in monitoring among patients with previous cardiac risk factors at greatest risk for negative cardiac outcomes.[11]

Studies evaluating the implementation and responsiveness to FDA drug safety warnings have found the warnings often have variable, and at times, limited impact in influencing changes in prescribing practices[16,17]—with one study finding that in reviewing 200 black box warnings, over 40% of patients still received a potentially inappropriate medication following the black box warning.[18] Many factors may influence the decision of an individual provider to order an EKG following the citalopram safety warnings, including lack of clarity surrounding which patients should receive EKG monitoring, lack of health system incentives to comply with the FDA warnings, provider knowledge regarding the drug safety warnings, and how concerned a provider is regarding a particular FDA warning. Following the FDA warnings, several large-scale

observational studies have demonstrated conflicting results regarding the impact of citalopram on QT prolongation and risk for subsequent ventricular arrhythmia, calling into question whether the risk of adverse cardiac events associated with citalopram use justifies the FDA warning.[8,9,19] Perhaps another explanation for the low rate of EKGs monitoring we observed in this study may have occurred if a majority of patients switched to a new antidepressant or reduced their citalopram dose. We previously found that rates of high dose, any dose, and new citalopram prescribing declined significantly and remained low following the 2011 and 2012 drug safety warnings throughout the VA healthcare system—with citalopram falling from previously being the most widely prescribed antidepressant within the VA prior to the FDA warnings to third, below sertraline and bupropion at one year following the second FDA warning.[11,20] Additionally, we observed concomitant increases in other antidepressant use during the same time periods, suggesting that providers substituted alternative antidepressants for citalopram.[20] Given the uncertainty surrounding whether, when, and how often patients should receive EKG monitoring, providers may have found it less burdensome to make medication adjustments than perform periodic cardiac monitoring and the associated medical documentation as recommended by the FDA warning.

There are several limitations to our current study. The VA represents the largest integrated healthcare system in the United States,[21] therefore, our sample included a high proportion of male patients, and our results may not be fully generalizable to other clinical populations and healthcare systems. However, this study is the first analysis of EKG monitoring following the citalopram warnings among a national sample. For patients with previous cardiac risk factors we only assessed EKG monitoring within the

past three months. It is possible that providers may have elected not to repeat such monitoring if a patient had an EKG within a longer time frame than we evaluated in this study (e.g., within the past 6 or 12 months). Lastly, while we were able to determine if an individual had an EKG performed, we were not able to see the results of the EKG to understand the proportion of patients with a prolonged QT interval on high dose citalopram, or determine why an EKG was ordered (e.g., directly related to the drug safety warning or for monitoring of another condition).

This study demonstrated that for patients prescribed high dose citalopram, following an initial increase in EKG monitoring after the first FDA warning, cardiac monitoring returned largely to pre-warning levels. This limited responsiveness to the FDA warnings occurred despite several VA PBM activities[22] directed to reduce inappropriate prescribing including three National PBM Bulletins related to the citalopram use[13]—suggesting that rates of EKG monitoring may be even lower in health systems without such interventions. Lack of responsiveness to the citalopram drug safety warnings may in part be due lack of clarity surrounding which patients should receive EKG monitoring, provider substitution of other antidepressants for citalopram, and lack of provider knowledge regarding the warnings. Although there are frequent FDA drug safety warnings, and concerns for QT prolongation among the most common reason for drug safety warnings,[23] there have been limited rigorous studies evaluating the impact of these warnings[16,17]—with previous studies suffering from methodologic limitations such as lack of a control group. Given the paucity of previous studies evaluating health systems responses to drug safety warnings, as well as the large number of patients maintained on citalopram within the VA and elsewhere at the time of

the drug safety warning, this study adds to the limited studies evaluating drug safety warnings, demonstrating a small and temporary response to the warnings.[18] Lastly, in light of this low responsiveness to drug safety warnings, it is crucial for health systems to evaluate and understand what the barriers and facilitators are to adhere to the drug safety warnings, in order to help health systems best determine how to communicate and monitor drug safety warnings. In another part of the current study, we will be identifying and interviewing VA facilities with low and high responsiveness to the citalopram drug safety warnings to evaluate the ways in which the drug safety warnings were directly communicated across VA facilities and determine if specific strategies were more effect in improving adherence to the citalopram warnings. This work highlights the need for future studies aimed at understanding how health systems can best help providers and patients make decisions regarding medication use, considering both the risk of the medication as well as potential risks and benefits of complying with the drug safety warnings themselves.

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Figure Legend:

Figure 1. A. Quarterly proportion of patients aged 18-60 receiving cardiac monitoring in VA or CMS among citalopram or sertraline users. **B.** Quarterly proportion of patients 61-100 receiving cardiac monitoring receiving healthcare services through the VA and Medicare.

Supplemental Material:

Supplemental Table 1. List of International Classification of Diseases (ICD9), Ninth Revision codes for cardiac risk factors.

Supplemental Table 2. Rates and trends of quarterly EKG monitoring among citalopram or sertraline users ages 18-60 and 61-100 among Veterans receiving healthcare services through the VA and Medicare.

Supplemental Figure 1. Quarterly proportion of patients receiving EKG monitoring newly prescribed citalopram among **A.** patients aged 18-60 and **B.** patients 61-100 as compared to sertraline.

Supplemental Figure 2. Quarterly proportion of patients receiving EKG monitoring among patients with previous cardiac risk factors among **A.** patients aged 18-60 and **B.** patients 61-100 as compared to sertraline.

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Conflict of Interest Disclosures: The authors have no conflicts of interest

Elements of Financial/ Personal Conflicts	LBG	HMK	MY	HCK	JH	KZ
	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Employment or Affiliation	No	No	No	No	No	No
Grants/Funds	No	No	No	No	No	No
Honoraria	No	No	No	No	No	No
Speaker Forum	No	No	No	No	No	No
Consultant	No	No	No	No	No	No
Stocks	No	No	No	No	No	No
Royalties	No	No	No	No	No	No
Expert Testimony	No	No	No	No	No	No
Board Member	No	No	No	No	No	No
Patents	No	No	No	No	No	No
Personal Relationship	No	No	No	No	No	No

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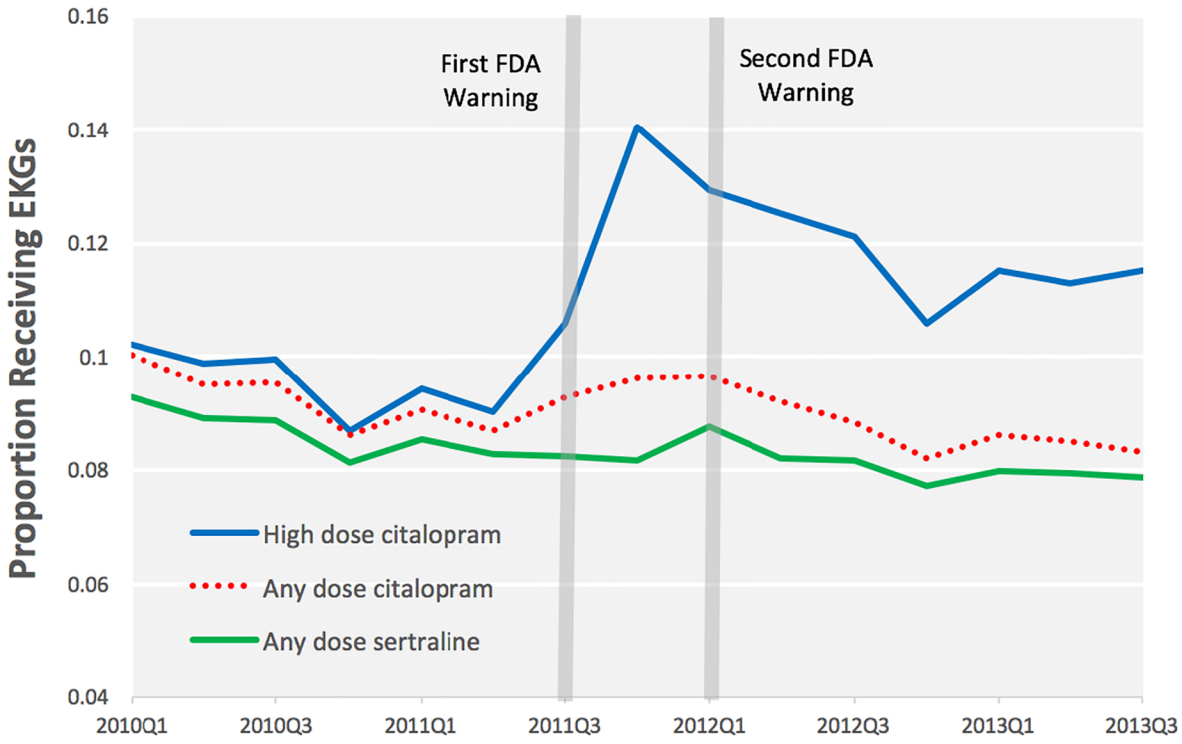

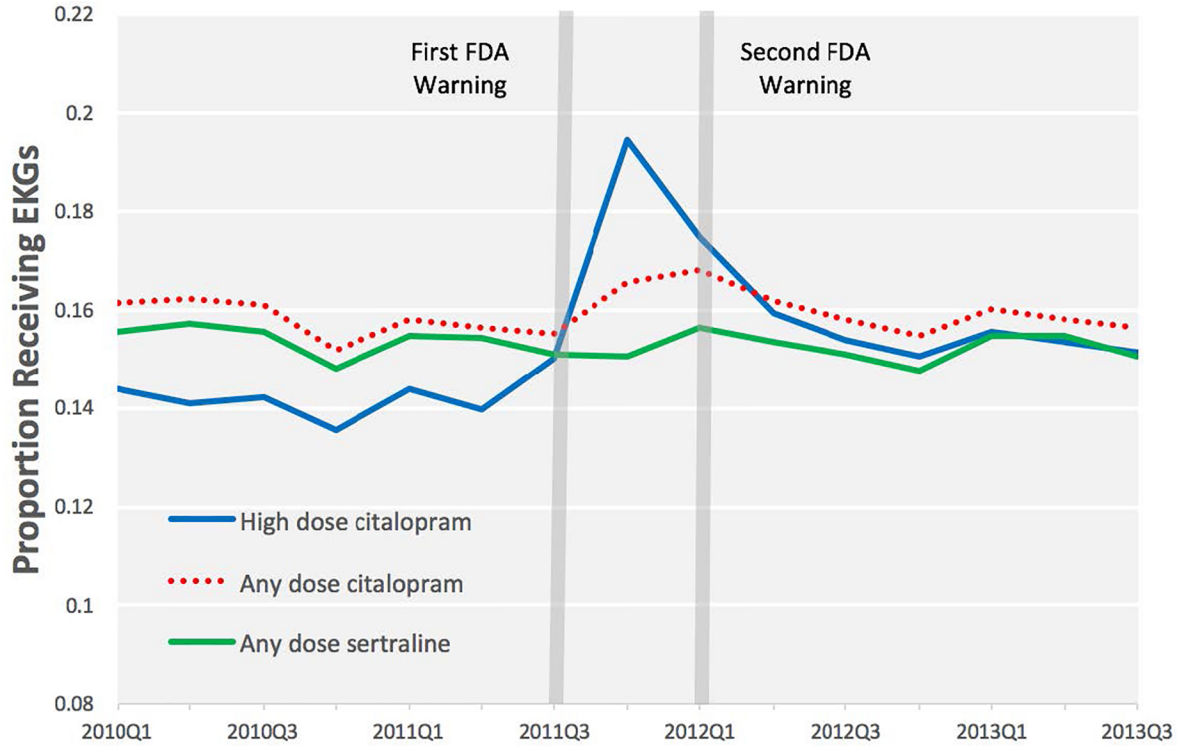

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Supplemental Tables and Figures:

Supplemental Table 1. List of International Classification of Diseases (ICD9), Ninth Revision codes for cardiac risk factors.

Cardiac Risk Factor	ICD9 codes
Angina	411.1, 413, 413.0, 413.1, 413.9
Arrhythmia	427, 427.0, 427.1, 427.2, 427.3, 427.31, 427.32, 427.4, 427.41, 427.42, 427.5, 427.8, 427.81, 427.89, 427.9, 429.4, 997.1, V12.53
Congestive Heart Failure (CHF)	428.9, 429.1, 402, 402.0, 402.00, 402.02, 402.1, 402.10, 402.11, 402.9, 402.90, 402.91, 404, 414.19, 425.4, 428, 428.0, 428.1, 428.2, 428.20, 428.21, 428.22, 428.23, 428.3, 428.30, 428.31, 428.32, 428.33, 428.4, 428.40, 428.41, 428.42, 428.43, 428.9, 424, 997.1
Myocardial Infarction (MI)	410, 411.0, 411.1, 411.81, 412., 414.2, 414.8, 429.7, 429.71, 429.79

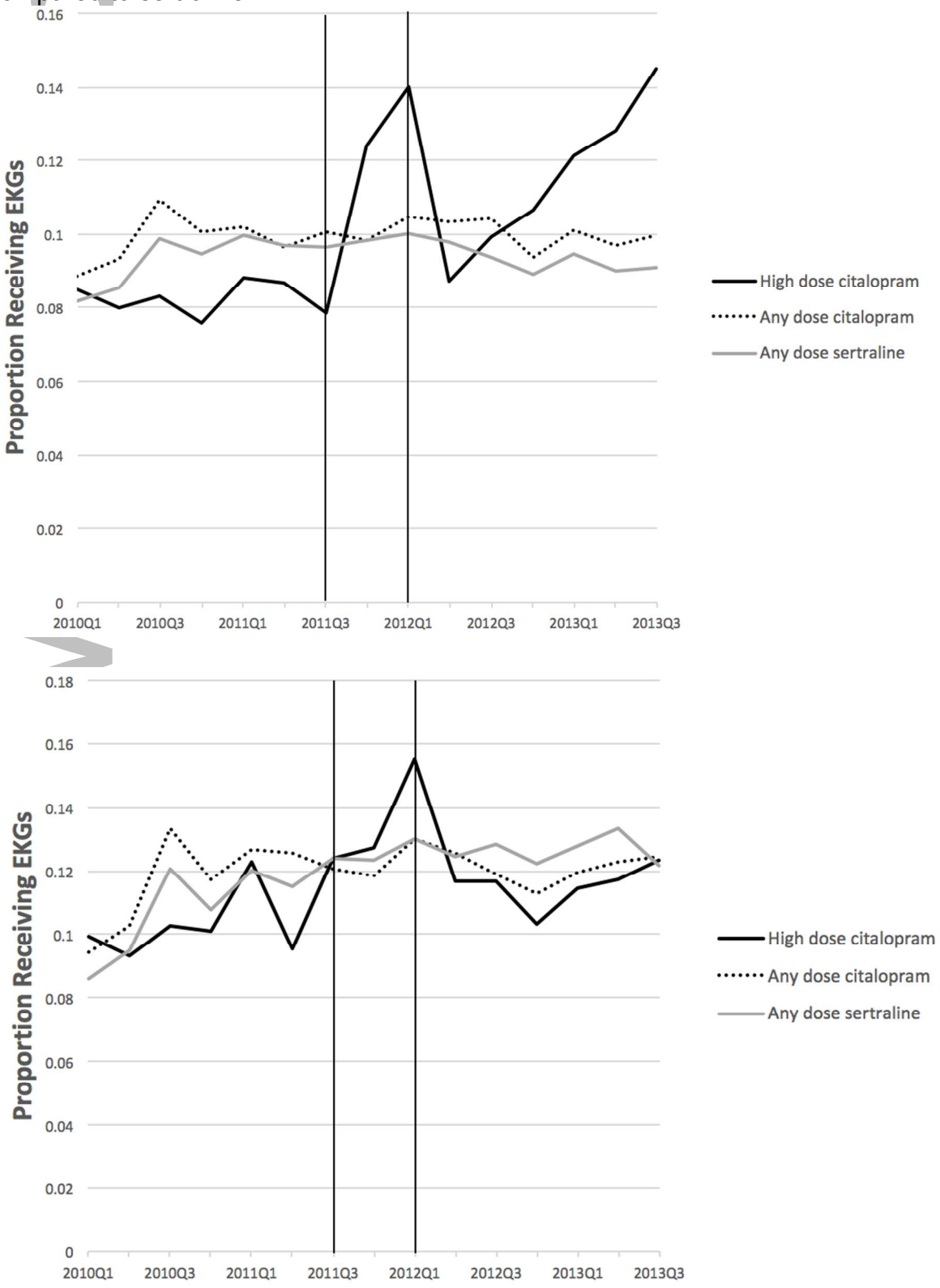
Supplemental Table 2. Rates and trends of quarterly EKG monitoring among citalopram or sertraline users ages 18-60 and 61-100 among Veterans receiving healthcare services through the VA and Medicare.

	18-60 years old			61-100 years old		
	High dose citalopram	**Any dose citalopram**	**Sertraline**	**High dose citalopram**	**Any dose citalopram**	**Sertraline**
Pre-Warning Period						
Level	9.88[c]	9.87[c]	9.28[c]	14.00[c]	16.3[c]	15.70[c]
SE	0.53	0.26	0.15	0.26	0.22	0.23
Slope	-0.06	-0.16[a]	-0.17[b]	0.05	-0.12[a]	-0.07
SE	0.12	0.06	0.03	0.06	0.05	0.05
Warning Period 1						
Warning 1 Level	6.09[a]	1.06	-0.49	7.47[c]	0.78	-0.80
SE	1.86	0.95	0.57	1.07	0.79	0.82
Slope	-1.22	0.12	0.76	-2.21[b]	0.45	0.75
SE	1.13	0.58	0.35	0.65	0.48	0.50
Warning Period 2						
Warning 2 Level	-0.78	-0.63	-0.62	-1.82[a]	-0.89	-0.61
SE	1.00	0.50	0.30	0.54	0.42	0.44
Slope	1.09	-0.10	-0.64	2.07[a]	-0.38	-0.65
SE	1.13	0.58	0.35	0.65	0.48	0.50

All values represent percentages
SE = standard error
$p < 0.05^{a}$ $p < 0.01^{b}$ $p < 0.001^{c}$

Citalopram and EKG Monitoring

Supplemental Figure 1. Quarterly proportion of patients receiving EKG monitoring newly prescribed citalopram among **A.** patients aged 18-60 and **B.** patients 61-100 as compared to sertraline.



Citalopram and EKG Monitoring

Supplemental Figure 2. Quarterly proportion of patients receiving EKG monitoring among patients with previous cardiac risk factors among **A.** patients aged 18-60 and **B.** patients 61-100 as compared to sertraline.