Therapeutic vs. Subtherapeutic Doses of SSRIs on MACE Outcomes

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INTRODUCTION

The most common type of heart disease in the United States is Coronary Artery Disease (CAD). The prevalence of depression among patients with CAD is 3 times higher than the general population. Treatment of depression is crucial for a better outcome in such cases, including the avoidance of heart failure, another episode of MI, cardiac arrhythmia, and cardiac death as defined by the 4-point Major Adverse Cardiovascular Event (MACE) scale (1).

Previous studies suggest that the incidence of 4-point MACE is significantly less in patients treated with Selective Serotonin Reuptake Inhibitors (SSRIs) (2). However, more recent studies are contradicting these reports, indicating that further study is needed. We would like to present preliminary results of our study, the effect of subtherapeutic vs therapeutic doses of SSRIs and MACE outcomes. Though it is a small sample size, our study showed a higher incidence of MACE outcomes with subtheraputic SSRI dosage.

OBJECTIVES

1. To identify the 4-point MACE and all-cause mortality rate in CAD patients (MI, NSTEMI, or unstable angina) with depression who were treated with long-term SSRIs (at least 3 months) compared to those with CAD and depression who were not treated with SSRIs or those were treated with an alternative psychopharmacologic agent other than SSRI.
2. Exploratory analyses of the efficacy of long-term SSRI use in CAD patients (MI, NSTEMI, or unstable angina) with depression in terms of improving depression symptoms and preventing further episodes of depression by use of PHQ-2 and PHQ-9 Scores.
3. To explore the major side-effects of long-term use of SSRIs in CAD patients (MI, NSTEMI, or unstable angina) with depression.

	Optimal Dose for Depression (mg)	Max Approved Dose in Depression (mg)
Bupropion[1]	150–300	450
Citalopram[2]	20–40	60
Escitalopram[2]	10–20	20
Fluoxetine[2]	20–40	80
Fluvoxamine[1]	100–150	300 (in OCD)
Mirtazapine[2]	15–30	45
Paroxetine[2]	20–30	50
Sertraline[2]	50–100	200
Venlafaxine[2]	75–150	225

The SSRIs Ranked		
First line	Escitalopram	Doesn't cause CYP drug interactions but can fall victim to them. Approved in children down to age 12.
	Fluoxetine	Relatively low risk of withdrawal symptoms and weight gain. Only SSRI with approval in bulimia. Best-studied SSRI in children. High risk of drug interactions.
	Sertraline	Favored in cardiac disease and pregnancy. Few drug interactions below 150 mg/day.
Second line	Citalopram	Highest risk of QTc prolongation. Low risk of CYP drug interactions. Dose capped to 20 mg/day in patients over age 60.
	Fluvoxamine	Indicated only in OCD (in children and adults). High risk of drug interactions. Second worst for withdrawal problems.
	Paroxetine	Highest risk of withdrawal problems, fatigue, sexual dysfunction, weight gain, cognitive impairment, suicidality in children, and birth defects. Strong CYP2D6 drug interactions.

METHODOLOGY

This is a retrospective chart review of CAD patients from August 2011 to December 2019.

Inclusion criteria

1. Patients presented in our primary care and cardiology outpatient clinics with CAD (MI, NSTEMI, or unstable angina) and 4-point MACE, between August 2011 and December 2019.
2. ICD-10 code confirms depression diagnosis.
3. Patients admitted to the outpatient clinic for at least 1 month. Followed at least one encounter status post index admission > 30 days.
4. Patient age range of 18 to 75 years.

Exclusion criteria

1. Patients who discontinued therapy before 3 months time.
2. History of bipolar disorders, schizophrenia spectrum disorders, and neurocognitive disorders.
3. Patients who are on psychotropic medications other than benzodiazepines and zolpidem, zaleplon, or eszopiclone.
4. History of substance use in a dependent fashion within the last year.
5. Other acute or chronic health conditions known to affect cardiac outcomes.
6. History of primary bleeding disorders.

RESULTS

Of the 142 patients included in the sample, 72% were prescribed SSRIs for > 3 months, and 33% experienced a MACE event following initiation of treatment with SSRI. Among the 32% (n=38) of patients prescribed SSRI following CAD diagnosis, 16% (n=7) were initially placed on subtherapeutic doses.

Patients initially placed on subtherapeutic doses of SSRI were significantly more likely than patients initially on therapeutic doses to experience MACE 1 (p=0.02), MACE 3 (p=0.01), any MACE-related outcome (p=0.04), and to experience a higher number of MACE-related outcomes (p=0.01). Overall, patients placed on sub-therapeutic regimens has a median of 4 lifetime MACE events, compared to a median of 1.5 MACE events among patients placed on therapeutic regimens (p=0.02).

Additional analyses did not show any significant differences by age, obesity or other demographic between patients on subtherapeutic vs. therapeutic doses. However patients on therapeutic doses of SSRI had significantly higher incidence of diabetes (p=0.03). No other differences were found across clinical characteristics.

Although not shown, comparisons between those on subtherapeutic dosages of medication and those not on medication were also examined, with significantly higher rates of MACE-related outcomes found in the subtherapeutic group.

DISCUSSION

The current study examined potential relations between the intensity of the SSRI dosing regimen and MACE events. All patients who received sub-therapeutic doses experienced at least one MACE event during their lifetime, with half experiencing at least 4 such events.

The results indicated a higher incidence of lifetime MACE among patients with subtherapeutic SSRI treatment vs therapeutic SSRI treatment (median of 4 lifetime events vs 1.5 lifetime events).

Given the small sample size, these results should be interpreted with caution and considered preliminary.

CONCLUSION

Although limited by a correlational design and small sample size, the current findings may serve to motivate further research on relations between CAD, SSRI use, and MACE events. Further studies can focus on additional factors such as patient geographic location, ethnicity, between antidepressants and gender; among others.

Future studies may also want to consider sensitivity analyses which examine potential differences in SSRI dosing at a more granular level.

REFERENCES

1. Jang HY, Kim JH, Song YK, Shin JY, Lee HY, Ahn YM, Oh JM, Kim IW. Antidepressant Use and the Risk of Major Adverse Cardiovascular Events in Patients Without Known Cardiovascular Disease: A Retrospective Cohort Study. Front Pharmacol. 2020 Dec 10;11:594474. doi: 10.3389/fphar.2020.594474. PMID: 33362548; PMCID: PMC7758770.

2. Piña IL, Di Palo KE, Ventura HO. Psychopharmacology and Cardiovascular Disease. J Am Coll Cardiol. 2018 May 22;71(20):2346-2359. doi: 10.1016/j.jacc.2018.03.458. PMID: 29773162.

3. Aziz, R. (2022, April 5). *Antidepressants: When Dosage Matters*. CARLAT PUBLISHING RSS. https://www.thecarlatreport.com/articles/3687-antidepressants-when-dosage-matters

4. Aiken, C. (2020, November 12). *How to select an SSRI*. CARLAT PUBLISHING RSS. https://www.thecarlatreport.com/articles/3324-how-to-select-an-ssri