

Supplementary material to:

Serious arrhythmia in initiators of citalopram, escitalopram, and other selective serotonin reuptake inhibitors: A population-based cohort study in older adults

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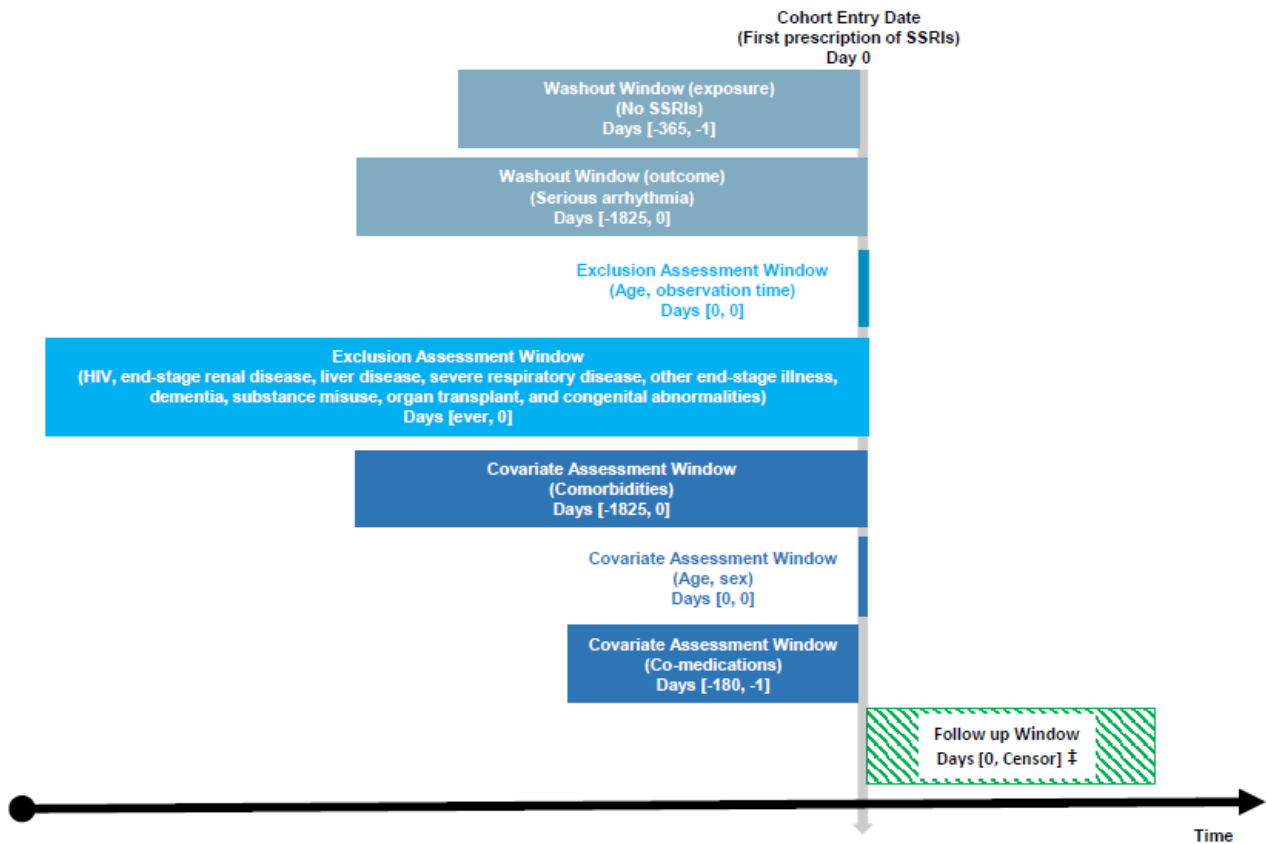


Figure S1 Depiction of study design. Figure based on Schneeweiss *et al.*(1) Licensed under CC BY, can be found at <https://presc.sdu.dk/repeat-diagrams/>.

‡ Earliest of outcome of interest (serious arrhythmia), death, emigration, exclusion criterion, six months of follow-up, or end of study period.

HIV, human immunodeficiency virus; SSRIs, selective serotonin reuptake inhibitors

Table S1 The emulated trial design compared to the hypothetical clinical trial

Protocol component	A hypothetical clinical trial	Target trial emulation (observational data)
Eligibility criteria	Participants aged 65 and above who did not meet the exclusion criteria. Enrollment continues until required sample size is achieved.	Individuals aged 65 and above who filled a prescription of a SSRI (a record in the Danish National Prescription Registry), who did not meet the exclusion criteria.
Washout window for the exposure	No use of SSRIs one year before enrollment.	At least one year with no prescription of SSRIs before the index date.
Exclusion criteria	Previous diagnosis of serious arrhythmia 5 years before the index date, history of HIV, end-stage renal diseases, liver diseases, severe respiratory diseases, other end-stage diseases, organ transplants, congenital abnormalities, or substance misuse.	Less than one year of observation time prior to the index date, more than one SSRI on the index date, previous diagnosis of serious arrhythmia 5 years before the index date, history of HIV, end-stage renal diseases, liver diseases, severe respiratory diseases, other end-stage diseases, organ transplants, congenital abnormalities, substance misuse at any time before the index date.
Treatment assignment/Exposure and comparator groups	Eligible participants are assigned randomly to either of the exposure groups or the comparator group and receive a defined daily dose until the end of the trial.	Eligible individuals are divided into three groups: two exposure groups and one active comparator group. The exposure groups were citalopram and escitalopram and the comparator group comprised of other SSRIs.
Outcome	Serious arrhythmia	Serious arrhythmia
Follow-up	Intention-to-treat	Intention-to-treat
Censoring	Participants are followed until the occurrence of the outcome (serious arrhythmia), loss to follow-up, death, end of follow-up, or end of study period, whatever happens first.	Individuals are followed from the index date (fill of prescription) until the occurrence of the outcome (serious arrhythmia), emigration, death, end of follow-up, or end of study period, whatever happens first.

HIV, human immunodeficiency virus; SSRIs, selective serotonin reuptake inhibitors

Table S2 Definitions and time windows for exposures, outcomes, exclusion criteria, and covariates

Variable	Code	Time window (before index)
Exposures		
Citalopram	ATC: N06AB04	Index date
Escitalopram	ATC: N06AB10	Index date
Comparators		
Other SSRIs	ATC: N06AB03, N06AB08, N06AB05, N06AB06	Index date
Outcomes		
Serious arrhythmia	ICD-10: I47.2 (Ventricular tachycardia), I49.0 (Ventricular fibrillation & flutter), I49.3 (Ventricular premature depolarization), I46 (Cardiac arrest)	6 months follow-up with a 5 year event free washout
Serious arrhythmia, sensitivity	ICD-10: I47.2 (Ventricular tachycardia), I49.0 (Ventricular fibrillation and flutter)	6 months follow-up with a 5 year event free washout
Exclusion criteria		
HIV	ICD-10: B21-B24	Ever
End-stage renal disease	ICD-10: Z21, Z49, N18.5	Ever
Liver disease	ICD-10: K70-K74, K76.2-K76.7	Ever
Severe respiratory disease	ICD-10: E66.2, I27, J84, J96.1, J96.9, R09.2, Z99.1	Ever
Other end-stage illness	ICD-10: E40-E43, I70.2, R02, R40.2, R64	Ever
Dementia and drugs to treat dementia	ICD-10: F00-F03, G30, N06D	Ever
Substance misuse and drugs to treat misuse	ICD-10: F11-F19, R78.1-R78.5, T40 ATC: N07BC	Ever

Organ transplant	NCSP: KAS, FQA, FQB, JJC, GDG, JLE	Ever
Congenital abnormalities/childhood conditions	ICD-10: E84, F71-F73, F78, F79, G51, G80, Q01-Q03, Q05, Q20-Q26, Q90	Ever
Comorbidities		
Cancer	ICD-10: C (excl. C44)	5 years
Serious neurologic disease	ICD-10: G10-G14, G35-37, G71, G82	5 years
Acute coronary syndrome	ICD-10: I20.0, I21.0, I22.0	5 years
Other ischemic heart disease	ICD-10: I11 (excl. I11.0), I20 (excl. I20.0), I24, I25	5 years
Heart failure/cardiomyopathy	ICD-10: I11.0, I13.0, I13.2, I42, I43, I50, J81	5 years
Valve disorders	ICD-10: I34-I37	5 years
Cardiac surgery/invasive cardiac procedure	NCSP: F	5 years
Thyroid disturbances	ICD-10: E00-E06, O90.5 ATC: H03AA01, H03BB01, H03BB02, H03BA02	5 years 6 months
Cerebrovascular disease	ICD-10: G45, G46, I60, I69	5 years
Arterial disease	ICD-10: I65, I70-I74, I77, K55.0, K55.1	5 years
Arrhythmia and antiarrhythmic drugs (class I and III)	ICD-10: I44, I45, I47 (excl. I47.2), I48, I49 (excl. I49.0, I49.3) ATC: C01B	5 years 6 months
Venous thromboembolism	ICD-10: I26, I80 (excl. I80.0), I81	5 years
Renal disease	ICD-10: I12, I13, N00-N08, N17-N19, N25, Z49, Z94.0, Z99.2	5 years
Respiratory disease	ICD-10: J40-J47, J60-J69, J70, J92, J96, J98.2, J98.3	5 years
Rheumatic disease	ICD-10: M05-M09, M30-M34, M35.1, M35.3, M45	5 years
Psychiatric disease and antipsychotics	ICD-10: F20-F25, F28-F34, F38-F45, F48, F50-F55, F59-F66, F68-F73, F78-F84, F88-F95, F98-F99 ATC: N05A	5 years 6 months
Alcohol-related diseases and drugs to treat alcohol misuse	ICD-10: F10 ATC: N07BB, N07BC	5 years 6 months
Smoking-related diseases and drugs to treat smoking dependence	ICD-10: J40-J44, J47, C34 ATC: R03BA, R03AC, R03BB, R03CC	5 years 6 months
Obesity and drugs to treat obesity	ICD-10: E66 ATC: A08A	5 years 6 months
Co-medications		
ACE inhibitors and angiotensin receptor blockers	ATC: C09A, C09B, C09C, C09D	6 months
Calcium channel blockers	ATC: C08C, C08D	6 months
Loop diuretics	ATC: C03C, C03EB	6 months
Other diuretics	ATC: C03A, C03B	6 months
Beta-blockers	ATC: C07	6 months
Digoxin	ATC: C01AA05	6 months
Nitrates	ATC: C01DA	6 months
Platelet inhibitors	ATC: B01AC	6 months
Anticoagulants	ATC: B01AA	6 months
Lipid-lowering drugs	ATC: C10	6 months
Oral antidiabetic drugs	ATC: A10B	6 months
Insulin	ATC: A10A	6 months
Antidepressants	ATC: N06A (excl. N06AB)	6 months
Anxiolytics	ATC: N05B, N05C	6 months
Corticosteroids, inhalants	ATC: R03AK	6 months
Oral corticosteroids	ATC: H02AB	6 months
Xantines	ATC: R03DA	6 months
NSAIDs	ATC: M01A	6 months
Opioids	ATC: N02A	6 months
Antiepileptic drugs	ATC: N03	6 months
Antiparkinsons drugs	ATC: N04B	6 months
Hormone replacement therapy	ATC: G03CA03, G03CA04, G03CA535, G03CA57, G03FA, G03FB, G03HB01, G03XC01	6 months

ACE, angiotensin-converting enzyme; ATC, anatomic therapeutic chemical (2); HIV, human immunodeficiency virus; excl., excluding; ICD-10, International Classification of Diseases (3); NCSP, NOMESCO Classification of Surgical Procedures (4); NSAIDs, non-steroid anti-inflammatory drugs

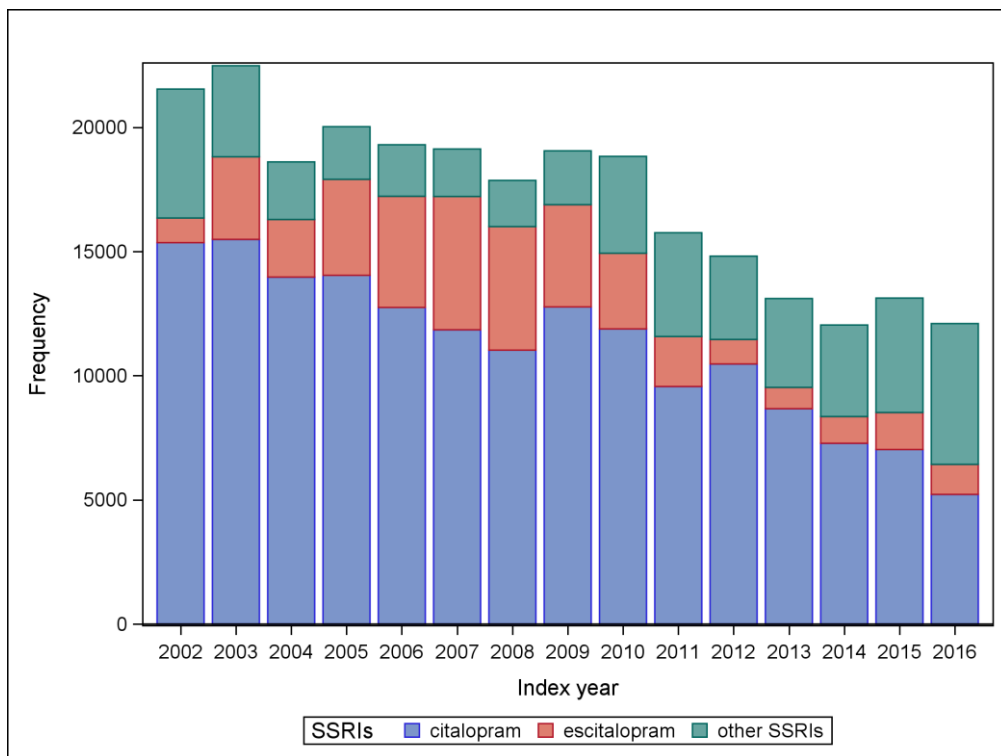


Figure S3 Distribution of initiators of selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors during the study period from 2002 to 2016

Table S3 Main and sensitivity analyses of the relative risk of serious arrhythmia with citalopram and escitalopram compared to other SSRIs. Sensitivity analyses using 1 and 6 months gap in the period after the EMA's recommendation and a final sensitivity analysis using ICD-10 I47.2 (ventricular tachycardia) and I49.0 (ventricular fibrillation and flutter) in the definition of serious arrhythmia. Estimates are provided both as crude, age and sex, and propensity score adjusted and matched.

RR (95% CIs)	Crude	Age and sex adjusted	Propensity score adjusted	Propensity score matched
Whole study period				
Citalopram	0.96 (0.69-1.34)	0.90 (0.64-1.26)	0.87 (0.62-1.22)	1.13 (0.76-1.70)
Escitalopram	0.87 (0.56-1.37)	0.81 (0.51-1.28)	0.86 (0.53-1.40)	0.96 (0.52-1.72)
Period before				
Citalopram	1.34 (0.84-2.15)	1.26 (0.77-2.03)	1.18 (0.72-1.96)	1.52 (0.86-2.67)
Escitalopram	1.19 (0.67-2.11)	1.06 (0.59-1.90)	0.94 (0.51-1.72)	1.06 (0.55-2.06)
Period after				
Citalopram	0.59 (0.35-1.00)	0.55 (0.32-0.94)	0.54 (0.31-0.93)	0.83 (0.46-1.48)
Escitalopram	0.57 (0.20-1.62)	0.55 (0.19-1.59)	0.58 (0.20-1.63)	0.67 (0.19-2.36)
Period after, 1 month gap				

Citalopram	0.57 (0.34-0.98)	0.53 (0.31-0.91)	0.52 (0.30-0.90)	0.79 (0.44-1.42)
Escitalopram	0.57 (0.20-1.64)	0.56 (0.20-1.60)	0.57 (0.20-1.60)	0.67 (0.19-2.36)
Period after, 6 months gap				
Citalopram	0.57 (0.33-0.98)	0.53 (0.31-0.91)	0.51 (0.29-0.90)	0.77 (0.43-1.40)
Escitalopram	0.58 (0.20-1.68)	0.57 (0.20-1.64)	0.58 (0.20-1.64)	0.68 (0.19-2.40)
Change in outcome definition				
Citalopram	1.17 (0.56-2.43)	1.14 (0.55-2.38)	1.05 (0.51-2.14)	1.04 (0.70-1.56)
Escitalopram	0.84 (0.30-2.35)	0.85 (0.30-2.42)	NA	0.83 (0.46-1.51)

References

1. Schneeweiss S, Rassen JA, Brown JS, Rothman KJ, Happe L, Arlett P, et al. Graphical Depiction of Longitudinal Study Designs in Health Care Databases. *Ann Intern Med.* 2019 19;170(6):398–406.
2. WHOCC - ATC/DDD Index [Internet]. [cited 2020 Sep 22]. Available from: https://www.whooc.no/atc_ddd_index/
3. ICD-10 Version:2016 [Internet]. [cited 2022 Jan 5]. Available from: <https://icd.who.int/browse10/2016/en>
4. Nordic Medico-Statistical Committee. NOMESCO classification of surgical procedures. Copenhagen: Nordic Medico-Statistical Committee; 2010.