

Preoperative central nervous system stimulant exposure and atrial fibrillation after coronary artery bypass grafting: a propensity-matched federated cohort study

Justin Lum

University of Rochester Medicine

Andrew Jordan

University of Rochester Medicine

Kazuhiro Hisamoto

Kazuhiro_Hisamoto@urmc.rochester.edu

University of Rochester Medicine

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Abstract

Background

Postoperative atrial fibrillation is a common complication of coronary artery bypass grafting (CABG), and prescription stimulant use is increasing among adults. We evaluated the association between recorded preoperative stimulant exposure and atrial fibrillation or flutter after CABG.

Methods

Using the TriNetX Research Network, we compared patients with an order for 1 of 6 stimulants within 3 months before or on the date of CABG with patients without a recorded order. Patients with atrial fibrillation or flutter documented at least 1 day before CABG were excluded before matching. Cohorts were matched 1:1 on 43 characteristics. The primary outcome occurred during postoperative days 1 through 30.

Results

Among 1082 matched patients per group, atrial fibrillation or flutter occurred in 147 exposed patients (13.6%) and 115 controls (10.6%; risk ratio [RR] 1.28, 95% confidence interval [CI] 1.02–1.61; $P = 0.035$). The risk difference was 3.0 percentage points (95% CI 0.2–5.7) and the hazard ratio was 1.29 (95% CI 1.01–1.65). Sensitivity analyses remained above the null but varied in magnitude (RR range 1.28–2.47).

Conclusions

Recorded preoperative stimulant exposure was associated with a modestly higher rate of atrial fibrillation or flutter after CABG. The direction of association was consistent across sensitivity analyses, although the magnitude varied with cohort and outcome definitions. These observational data do not establish causality or support a specific perioperative medication strategy.

Background

Postoperative atrial fibrillation is one of the most common complications after CABG and is associated with longer hospitalisation, stroke, readmission and mortality [1–3]. Prescription stimulant use has increased among adults, making perioperative exposure increasingly relevant to cardiac surgical practice [4, 5].

Amphetamine- and methylphenidate-class medications increase sympathetic tone, heart rate and blood pressure. Observational studies of longer-term cardiovascular risk have been mixed, although an early

increase in cardiovascular events after stimulant initiation has been reported in older adults [6–9]. CABG-specific evidence is sparse.

We evaluated whether a recorded stimulant medication order shortly before CABG was associated with atrial fibrillation or flutter during the first 30 postoperative days. To define the population at risk before matching, patients with preoperative atrial fibrillation were excluded during cohort construction. Sensitivity analyses evaluated alternative outcome handling, drug-class restriction and longer follow-up.

Methods

Data source and study design

This retrospective cohort study used the TriNetX Research Network, a federated network of deidentified electronic health record (EHR) data from 117 participating health care organisations [10]. TriNetX maps diagnoses, procedures, medications, laboratory values and demographic data to standard terminologies and performs cohort matching and outcome analyses without releasing patient-level data to investigators. The platform limited eligible index events to the 20 years preceding the analysis, which was generated on 2 September 2026.

Cohort and exposure definitions

Patients were required to have a qualifying CABG procedure code (CPT 1006217, 1006207, 1006216 or 1006199, or ICD-10-PCS 0210). The exposed cohort additionally required an order for amphetamine, dextroamphetamine, lisdexamfetamine, methylphenidate, dexamethylphenidate or serdexmethylphenidate within 3 months before or on the date of CABG. The comparator cohort required no recorded order for any of these agents at any time in the available record.

For the primary analysis, both cohorts excluded patients with ICD-10-CM I48 recorded at least 1 day before CABG. The index date was the first qualifying CABG date on which the cohort criteria were met. Outcomes were assessed from postoperative day 1 through day 30.

Outcomes

The primary outcome was atrial fibrillation or flutter (ICD-10-CM I48). Heart failure (ICD-10-CM I50) and all-cause mortality were exploratory outcomes in the primary matched cohorts. The atrial fibrillation analysis retained all matched patients. For heart failure and mortality, TriNetX applied outcome-specific prior-history exclusions where configured; the resulting denominators are reported explicitly.

Propensity score matching

For each analysis, TriNetX independently performed 1:1 greedy nearest-neighbour propensity score matching without replacement using a caliper of 0.1 pooled standard deviations of the logit of the propensity score. The model included 43 demographic, diagnostic, procedural, medication, laboratory and oncology characteristics (Additional file 1: Table S1). Balance was assessed with standardised mean differences (SMDs), with an absolute SMD below 0.10 considered acceptable [11, 12]. Because the platform rematches each analysis, matched patients may differ across specifications even when sample sizes are identical.

Sensitivity analyses

Sensitivity analyses included: (1) a 1- to 90-day analysis using the same preoperative atrial fibrillation restriction and full matched denominators; (2) an alternative 1- to 30-day incident-outcome specification that excluded patients with preoperative atrial fibrillation at the outcome-analysis stage; (3) a 1- to 30-day analysis restricted to amphetamine-class agents; and (4) 30- to 180-day and 1- to 180-day analyses using the 6-agent exposure definition. Dorsalgia (ICD-10-CM M54) was included as a negative-control outcome in the extended-window analyses [13].

Statistical analysis

TriNetX calculated risks, risk differences, risk ratios (RRs), odds ratios and 95% confidence intervals (CIs). Kaplan–Meier analyses used daily intervals and censored patients after the last recorded fact; log-rank tests and Cox hazard ratios were also generated. No multiplicity adjustment was performed, and secondary outcomes were considered exploratory.

Results

Primary matched cohort

The cohort queries identified 1130 stimulant-exposed patients and 224,249 comparators. After application of analysis eligibility criteria, 1116 exposed patients and 220,446 comparators were available for matching; 1082 patients were retained in each matched cohort (Table 1). Most characteristics were well balanced (Table 2 and Additional file 1: Table S1). Beta-blocker use remained slightly more common in the stimulant cohort (77.0% vs 72.6%; SMD 0.102), and the largest residual SMD was 0.137 for the sparse binge-eating-disorder variable (0.9% vs 0%).

Table 1
Analytic specifications for atrial fibrillation or flutter

Analysis	Cohort and outcome handling	Window	Matched N/arm
Primary	Six agents; pre-CABG I48 excluded before matching; all matched patients retained for AF analysis	Days 1–30	1082
Sensitivity	Same cohort restriction and AF handling as the primary analysis	Days 1–90	1082
Sensitivity	Six agents; preoperative I48 excluded at outcome-analysis stage	Days 1–30	1243
Sensitivity	Amphetamine-class only; preoperative I48 excluded at outcome-analysis stage	Days 1–30	880
Sensitivity	Six agents; preoperative I48 excluded at outcome-analysis stage	Days 30–180	1243
Sensitivity	Six agents; preoperative I48 excluded at outcome-analysis stage	Days 1–180	1243
AF atrial fibrillation or flutter, CABG coronary artery bypass grafting, I48 ICD-10-CM code I48. TriNetX independently repeated propensity score matching for every analysis; identical sample sizes do not imply identical matched pairs.			

Table 2
Selected characteristics of the primary matched cohorts

Characteristic	Stimulant	No stimulant	SMD
Age at index, years	58.6 ± 15.7	57.8 ± 15.8	0.048
Female sex	31.8%	31.3%	0.010
White race	83.1%	82.3%	0.020
Black race	9.7%	10.9%	0.040
ADHD	29.0%	28.5%	0.012
Depressive episode	26.2%	25.8%	0.008
Heart failure	26.2%	25.8%	0.011
Type 2 diabetes mellitus	35.3%	35.0%	0.006
Tobacco use	10.1%	10.3%	0.006
Opioid-related disorder	4.1%	3.4%	0.034
Anticoagulant use	75.1%	72.9%	0.051
Beta-blocker use	77.0%	72.6%	0.102
Serum creatinine, mg/dL	1.2 ± 1.3	1.2 ± 1.2	0.037
Binge-eating disorder	0.9%	0%	0.137
Values are mean ± standard deviation or percentage. Matching included 43 characteristics; selected characteristics and the 2 variables with SMD greater than 0.10 are shown. ADHD attention-deficit/hyperactivity disorder, SMD standardised mean difference.			

Atrial fibrillation or flutter

Atrial fibrillation or flutter occurred in 147 of 1082 stimulant-exposed patients (13.6%) and 115 of 1082 controls (10.6%). The absolute risk difference was 3.0 percentage points (95% CI 0.2–5.7) and the RR was 1.28 (95% CI 1.02–1.61; $P = 0.035$). Kaplan–Meier analysis produced a hazard ratio of 1.29 (95% CI 1.01–1.65; log-rank $P = 0.039$); the proportional-hazards test was not significant ($P = 0.299$; Table 3 and Fig. 1).

Table 3
Primary 1- to 30-day postoperative outcomes

Outcome	Stimulant, n/N (%)	No stimulant, n/N (%)	Risk difference (95% CI)	Risk ratio (95% CI)	Hazard ratio (95% CI)
Atrial fibrillation or flutter	147/1082 (13.6)	115/1082 (10.6)	3.0% (0.2–5.7)	1.278 (1.017–1.607)	1.292 (1.012–1.649)
Heart failure	50/743 (6.7)	25/745 (3.4)	3.4% (1.2–5.6)	2.005 (1.254–3.206)	2.040 (1.262–3.297)
All-cause mortality	26/1075 (2.4)	18/1080 (1.7)	0.8% (– 0.4 to 1.9)	1.451 (0.800–2.631)	1.451 (0.795–2.646)
Atrial fibrillation or flutter retained all matched patients; heart failure and mortality used outcome-specific prior-history exclusions. Secondary outcomes were exploratory and not adjusted for multiple comparisons. CI confidence interval.					

Exploratory outcomes

Heart failure was recorded in 50 of 743 stimulant-exposed patients (6.7%) and 25 of 745 controls (3.4%; RR 2.01, 95% CI 1.25–3.21; $P = 0.003$). Mortality occurred in 26 of 1075 exposed patients (2.4%) and 18 of 1080 controls (1.7%; RR 1.45, 95% CI 0.80–2.63; $P = 0.217$). These analyses used outcome-specific prior-history exclusions and were not adjusted for multiple comparisons.

Sensitivity analyses

The 1- to 90-day analysis using the same preoperative atrial fibrillation restriction found atrial fibrillation or flutter in 16.5% of exposed patients and 12.6% of controls (RR 1.32, 95% CI 1.07–1.62). Estimates were larger when preoperative atrial fibrillation was excluded at the outcome-analysis stage: RR 2.08 (95% CI 1.48–2.92) for the alternative 1- to 30-day specification; RR 2.47 (95% CI 1.66–3.66) for the amphetamine-class analysis; and RRs of 2.02 to 2.32 for the extended-window analyses (Table 4). Dorsalgia remained near the null in the 30- to 180-day and 1- to 180-day analyses (RR 1.02 and 1.11, respectively). The direction of association was consistent, but the magnitude varied materially with cohort and outcome handling.

Table 4
Sensitivity analyses of atrial fibrillation or flutter

Analysis	Window	Stimulant, n/N (%)	No stimulant, n/N (%)	Risk ratio (95% CI)
Pre-CABG AF restriction; full matched denominator	Days 1–90	179/1082 (16.5)	136/1082 (12.6)	1.316 (1.071–1.618)
Outcome-stage preoperative-AF exclusion	Days 1–30	102/904 (11.3)	45/830 (5.4)	2.08 (1.48–2.92)
Amphetamine-class only	Days 1–30	87/669 (13.0)	31/588 (5.3)	2.47 (1.66–3.66)
Delayed postoperative window	Days 30–180	28/802 (3.5)	12/797 (1.5)	2.32 (1.19–4.53)
Extended postoperative window	Days 1–180	130/904 (14.4)	59/830 (7.1)	2.02 (1.51–2.71)
Each analysis was independently propensity matched. Dorsalgia, the negative-control outcome, remained near the null in the 30- to 180-day and 1- to 180-day analyses (risk ratios 1.02 and 1.11, respectively). AF atrial fibrillation or flutter, CABG coronary artery bypass grafting, CI confidence interval.				

Discussion

In this federated propensity-matched study, a recorded stimulant order within 3 months of CABG was associated with a modest increase in atrial fibrillation or flutter during postoperative days 1 through 30. The primary estimate corresponded to a 3.0-percentage-point absolute difference and a 28% relative increase. Sensitivity analyses remained above the null but produced larger estimates, emphasising that effect magnitude depended on cohort and outcome definitions.

The result is biologically plausible in a cardiac surgical population. Sympathetic activation, atrial inflammation, volume shifts and electrolyte disturbances converge after CABG, and stimulant-related catecholaminergic effects could add to this substrate. Nevertheless, the study does not identify whether medications were continued, withheld or recently discontinued, and it cannot distinguish medication effects from the conditions and behaviours associated with stimulant use. The findings therefore support careful medication reconciliation and prospective study, not a specific recommendation to stop stimulants or alter the timing of surgery.

The difference between the primary and alternative incident-outcome specifications is clinically and methodologically important. Excluding preoperative atrial fibrillation during cohort construction defines the population at risk before matching and preserves equal matched denominators. Excluding preoperative outcomes after matching can alter denominators unequally between cohorts and yielded larger estimates here. We therefore consider the cohort-restriction analysis the most conservative and clinically interpretable estimate.

The absolute atrial fibrillation rates were lower than the approximately 20% to 30% incidence commonly reported in surgical cohorts using systematic inpatient surveillance [1–3]. Diagnosis-code ascertainment may miss brief, self-limited episodes observed only on telemetry. Although nondifferential under-ascertainment would not necessarily bias the RR, differential documentation cannot be excluded. The null dorsalgia analysis argues against gross nonspecific ascertainment differences but does not address cardiovascular-specific confounding.

The heart-failure association is exploratory. It was based on outcome-specific denominators and was not adjusted for multiple testing; it should not be interpreted as an established perioperative effect. The absence of a statistically significant early mortality association is reassuring but imprecise.

Limitations

Residual confounding is likely because urgency, ventricular function, atrial size, bypass and cross-clamp times, graft strategy, perioperative beta-blocker or amiodarone use, electrolytes and surveillance practices were unavailable; beta-blocker use also remained slightly imbalanced. Medication orders do not establish dispensing, adherence or perioperative ingestion, and stimulant indication may mark unmeasured behavioural or cardiovascular risk. Diagnosis codes may miss telemetry-only arrhythmias, and patient-level data were unavailable for event adjudication or independent model diagnostics. Sensitivity and secondary analyses were not adjusted for multiplicity, and network composition and coding practices may change over time. Accordingly, confidence intervals are more informative than nominal *P* values.

Conclusions

Preoperative stimulant exposure was associated with a modestly higher rate of atrial fibrillation or flutter after CABG. The direction persisted across sensitivity analyses, although the magnitude varied substantially. Prospective studies incorporating medication administration, operative characteristics and systematic rhythm surveillance are needed before these findings should influence perioperative stimulant management.

Abbreviations

ADHD
Attention-deficit/hyperactivity disorder
CABG
Coronary artery bypass grafting
CI
Confidence interval
EHR
Electronic health record

HR
Hazard ratio
ICD-10-CM
International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-10-PCS
International Classification of Diseases, Tenth Revision, Procedure Coding System
RR
Risk ratio
SMD
Standardised mean difference

Declarations

Ethics approval and consent to participate

The study used aggregated, deidentified data and met exempt criteria under 45 CFR 46.104(d)(4); institutional review board approval and informed consent were not required.

Consent for publication

Not applicable.

Availability of data and materials

The data underlying this study were accessed through the TriNetX Research Network. Only aggregate results generated within the TriNetX platform were available to the investigators, and the authors are not permitted to redistribute patient-level data. Access to the network is available to qualified researchers through TriNetX (<https://trinetx.com>). All aggregate data supporting the conclusions of this article are included within the article and Additional file 1.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

JL contributed to the conception and design of the study, designed and executed the network queries, analyzed and interpreted the data, and drafted the manuscript. AJ revised the manuscript. KH supervised the study, interpreted the data and revised the manuscript. All authors read and approved of the final manuscript.

Acknowledgements

Not applicable.

Data Availability

TriNetX data were used under license and are not publicly available. Cohort definitions, terminology codes, covariate specifications, and analytic methods are provided in the Supplemental Appendix for investigators with TriNetX access.

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Figures

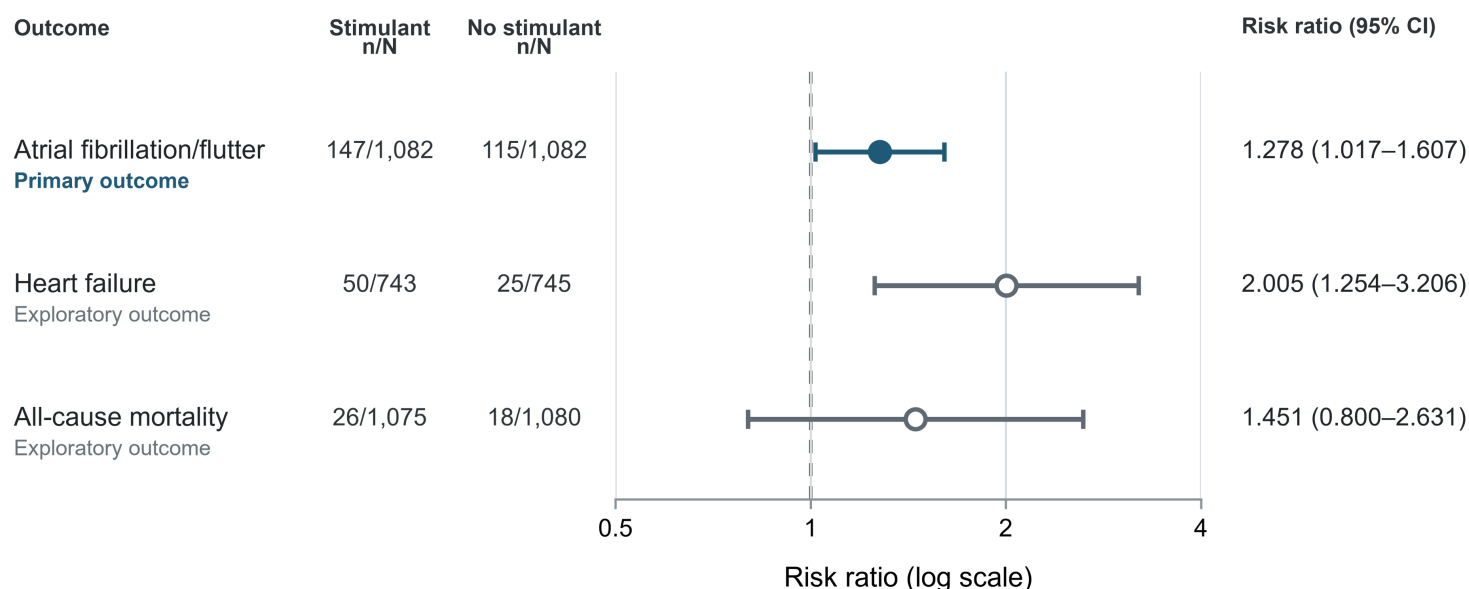


Figure 1

Risk ratios for 1- to 30-day postoperative outcomes

Points indicate risk ratios; horizontal lines indicate 95% confidence intervals. Atrial fibrillation or flutter was the primary outcome. Heart failure and mortality were exploratory outcomes and used outcome-

specific prior-history exclusions.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CABGStimulantAdditionalfile1.docx](#)