Impact of Preoperative Varenicline on Postoperative Outcomes in Cardiac Surgery: Comparison with Nicotine Replacement Therapy and Active Smoking

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INTRODUCTION

- The Clinical Problem: Tobacco smoking is a critical modifiable risk factor in cardiac surgery, linked to increased myocardial infarction (MI), pulmonary complications, and prolonged ICU stays.
- The Knowledge Gap: While smoking cessation ≥4 weeks preoperatively is recommended, there are no established studies directly comparing the postoperative effects of varenicline versus Nicotine Replacement Therapy (NRT) or no pharmacotherapy in cardiac surgery patients.
- Objective: To evaluate the 3-, 6-, and 12-month postoperative cardiovascular and safety outcomes of preoperative varenicline use compared to NRT and active smoking in nicotine-dependent patients undergoing cardiac surgery.

METHODS

- Study Design: Retrospective cohort study using the TriNetX US Collaborative Network (Nov 2005 – Nov 2025).
- Study Population: Adults with documented nicotine dependence (ICD-10 F17) undergoing cardiac surgery.
- Comparison Groups:
  - Cohort A: Preoperative Varenicline vs. Preoperative NRT
    - Cohort B: Preoperative Varenicline vs. Active Smokers
- Statistical Analysis: 1:1 Propensity Score Matching (PSM) adjusting for age, race, BMI, comorbidities, baseline labs, medications, and specific cardiac procedure types. Post-Match Cohorts: Varenicline (n=323), NRT (n=323), Active Smokers (n=323).
- Outcomes (at 3, 6, and 12 months):
  - Primary: Major Adverse Cardiovascular Events (MACE: cerebral infarction, all-cause mortality, or acute MI).
  - Secondary: Emergency Department (ED) visits, arrhythmias, pneumonia, mechanical ventilation, and postoperative infections.

RESULTS

Outcome	Varenicline (n=316)	NRT (n=316)	Risk Ratio (95% CI)	p-value
3-months Outcome				
ED Visit	31 (9.81%)	49 (15.51%)	0.633 (0.415–0.965)	0.03
Myocardial Infarction	36 (11.39%)	79 (25.00%)	0.456 (0.317–0.654)	< 0.01
MACE	50 (15.82%)	95 (30.06%)	0.526 (0.388–0.714)	< 0.01
Arrhythmias	110 (34.81%)	124 (39.24%)	0.887 (0.723–1.088)	0.25
Pneumonia	20 (6.33%)	23 (7.28%)	0.870 (0.488–1.551)	0.64
Acute Respiratory Failure / ARDS	35 (11.08%)	45 (14.24%)	0.778 (0.514–1.176)	0.24
Antipsychotic Use	56 (17.72%)	54 (17.09%)	1.037 (0.738–1.457)	0.84
Mechanical Ventilation	71 (22.47%)	70 (22.15%)	1.014 (0.758–1.357)	0.92
Post-operative Infection	15 (4.75%)	23 (7.28%)	0.652 (0.347–1.226)	0.18
All-Cause Mortality	Not reported	Not reported	—	—
6-months Outcome				
ED Visit	42 (13.29%)	62 (19.62%)	0.677 (0.473–0.970)	0.03
Myocardial Infarction	39 (12.34%)	85 (26.90%)	0.459 (0.325–0.648)	< 0.01
MACE	57 (18.04%)	105 (33.23%)	0.543 (0.409–0.720)	< 0.01
Arrhythmias	117 (37.03%)	128 (40.51%)	0.914 (0.751–1.112)	0.37
Pneumonia	24 (7.60%)	26 (8.23%)	0.923 (0.542–1.572)	0.77
Acute Respiratory Failure / ARDS	38 (12.03%)	50 (15.82%)	0.760 (0.514–1.125)	0.17
Antipsychotic Use	59 (18.67%)	60 (18.99%)	0.983 (0.711–1.359)	0.92
Mechanical Ventilation	72 (22.79%)	74 (23.42%)	0.973 (0.732–1.293)	0.85
Post-operative Infection	15 (4.75%)	29 (9.18%)	0.517 (0.283–0.946)	0.03
All-Cause Mortality	12 (3.80%)	11 (3.48%)	1.091 (0.489–2.436)	0.83
1-year Outcome				
ED Visit	57 (18.04%)	81 (25.63%)	0.704 (0.521–0.951)	0.02
Myocardial Infarction	43 (13.61%)	89 (28.17%)	0.483 (0.348–0.671)	< 0.01
MACE	63 (19.94%)	118 (37.34%)	0.534 (0.410–0.695)	< 0.01
Arrhythmias	123 (38.92%)	133 (42.09%)	0.925 (0.765–1.117)	0.42
Pneumonia	26 (8.23%)	31 (9.81%)	0.839 (0.510–1.379)	0.49
Acute Respiratory Failure / ARDS	41 (12.98%)	55 (17.41%)	0.745 (0.513–1.083)	0.12
Antipsychotic Use	64 (20.25%)	65 (20.57%)	0.985 (0.724–1.340)	0.92
Mechanical Ventilation	72 (22.79%)	76 (24.05%)	0.947 (0.714–1.256)	0.71

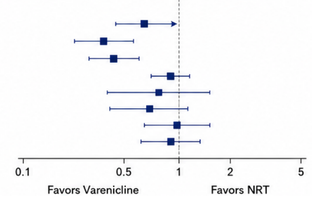

Figure 1. Varenicline vs. Nicotine Replacement Therapy (NRT)

Outcome	Varenicline (n=323)	Smoker (n=323)	Risk Ratio (95% CI)	p-value
3-months Outcome				
ED Visit	31 (9.60%)	34 (10.53%)	0.912 (0.575–1.447)	0.69
Myocardial Infarction	37 (11.46%)	71 (21.98%)	0.521 (0.361–0.752)	<0.01
MACE	51 (15.79%)	87 (26.94%)	0.586 (0.430–0.799)	<0.01
Arrhythmias	113 (34.99%)	111 (34.37%)	1.018 (0.824–1.258)	0.87
Pneumonia	21 (6.50%)	18 (5.57%)	1.167 (0.634–2.148)	0.62
Acute Respiratory Failure / ARDS	35 (10.84%)	29 (8.98%)	1.207 (0.756–1.926)	0.43
Antipsychotic Use	56 (17.34%)	54 (16.72%)	1.037 (0.738–1.458)	0.83
Mechanical Ventilation	72 (22.29%)	72 (22.29%)	1.000 (0.750–1.334)	1
Post-operative Infection	16 (4.95%)	15 (4.64%)	1.067 (0.536–2.121)	0.85
All-Cause Mortality	Not reported	Not reported	—	—
6-months Outcome				
ED Visit	43 (13.3%)	42 (13.0%)	1.024 (0.689–1.522)	0.91
Myocardial Infarction	40 (12.4%)	75 (23.2%)	0.533 (0.375–0.758)	<0.01
MACE	58 (17.96%)	91 (28.17%)	0.637 (0.476–0.853)	<0.01
Arrhythmias	120 (37.15%)	118 (36.53%)	1.017 (0.831–1.245)	0.87
Pneumonia	25 (7.74%)	20 (6.19%)	1.250 (0.709–2.205)	0.44
Acute Respiratory Failure / ARDS	38 (11.77%)	30 (9.29%)	1.267 (0.805–1.993)	0.31
Antipsychotic Use	59 (18.27%)	56 (17.34%)	1.054 (0.756–1.468)	0.76
Mechanical Ventilation	73 (22.60%)	72 (22.29%)	1.014 (0.761–1.351)	0.92
Post-operative Infection	16 (4.95%)	17 (5.26%)	0.941 (0.484–1.830)	0.86
All-Cause Mortality	12 (3.72%)	≤10 (3.10%)	1.200 (0.526–2.738)	0.66
1-year Outcome				
ED Visit	58 (17.96%)	62 (19.20%)	0.935 (0.677–1.292)	0.69
Myocardial Infarction	44 (13.62%)	79 (24.46%)	0.557 (0.398–0.779)	<0.01
MACE	64 (19.81%)	98 (30.34%)	0.653 (0.496–0.859)	<0.01
Arrhythmias	126 (39.01%)	124 (38.39%)	1.016 (0.837–1.234)	0.87
Pneumonia	27 (8.36%)	22 (6.81%)	1.227 (0.714–2.109)	0.46
Acute Respiratory Failure / ARDS	41 (12.69%)	30 (9.29%)	1.367 (0.876–2.133)	0.17
Antipsychotic Use	64 (19.81%)	62 (19.20%)	1.032 (0.755–1.412)	0.84
Mechanical Ventilation	73 (22.60%)	74 (22.91%)	0.986 (0.742–1.311)	0.93
Post-operative Infection	19 (5.88%)	18 (5.57%)	1.056 (0.564–1.974)	0.87
All-Cause Mortality	13 (4.03%)	13 (4.03%)	1.000 (0.471–2.124)	1

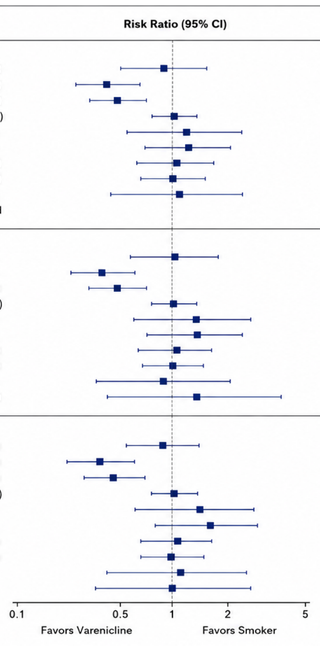

Figure 2. Varenicline vs. Active Smokers

CONCLUSION

- Varenicline demonstrated a statistically significant reduction in cardiovascular complications across all timepoints:
  - **MACE:** Reduced by nearly half at 12 months (**19.9% vs. 37.3%**; RR 0.53, p < 0.01).
  - **Myocardial Infarction:** Significantly lower at 12 months (**13.6% vs. 28.2%**; RR 0.48, p < 0.01).
  - **ED Visits:** Consistently lower, reaching significance at 12 months (**18.0% vs. 25.6%**; RR 0.70, p = 0.02).
  - **Postoperative Infection:** Halved at 6 months (**4.8% vs. 9.2%**; p = 0.03).Varenicline vs. Active Smokers
- Patients treated with varenicline experienced significantly fewer cardiovascular events compared to those who continued smoking:
  - **MACE:** Significantly reduced at 12 months (**19.8% vs. 30.3%**; RR 0.65, p < 0.01).
  - **Myocardial Infarction:** Significantly lower at 12 months (**13.6% vs. 24.5%**; RR 0.56, p < 0.01).

DISCUSSION

- **Cardiovascular Benefit:** The early and sustained reduction in MACE and MI suggests a cardiovascular advantage of varenicline over NRT in the perioperative setting. This may be due to NRT delivering external nicotine, which maintains sympathetic activation and endothelial stress during a highly vulnerable postoperative window.
- **Broader Recovery:** Lower ED utilization and postoperative infection rates point to greater overall postoperative stability.

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