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Supplementary Material

Article Title: Long-Term Antipsychotic Use and Major Cardiovascular Events: A Retrospective Cohort Study

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List of Supplementary Material for the article

Disclaimer

Long term antipsychotic use and major cardiovascular events: a retrospective cohort study

Supplementary appendix

Supplementary eTable 1. Side effect profile of selected antipsychotic medication

Medication	Weight gain	Lipids	Glucose	Other
High risk				
Olanzapine	+++	+++	+++	Sedation Hypotension CYP 1A2
Clozapine	+++	+++	+++	Agranulocitosis Myocarditis Lens opacities Sedation Hypotension CYP 1A2, 3A4, 2D6
Thioridazine	+++	++	++	QT prolongation Sedation Hypotension CYP 1A2, 2D6
Intermediate risk				
Quetiapine	++	+	+/-	Sedation CYP 3A4
Risperidone	++	+	+/-	Extrapiramidal effects CYP 2D6, 3A4
Low risk				
Haloperidol	+	-	-	QT prolongation Extrapiramidal effects CYP 3A4
Aripiprazole	+	-	-	CYP 2D6, 3A4
Ziprasidone	+	-	-	QT prolongation CYP 3A4
Trifluoperazine	+	-	-	Extrapiramidal effects
Levomepromazine	+	-	-	Sedation

Supplementary eTable 2. Participant follow-up and treatment information

	Low-Risk metabolic side effects (N=223)	Intermediate-risk metabolic side effects (N= 465)	High-risk metabolic side effects (N = 320)
Follow up information for primary outcome			
Median follow up time, months	39.0	33.0	41.5
Median survival time, months	NA	85	90
Incidence rate (events / 1000 person-year)	18.2	49.3	58.1

Supplementary eTable 3. Crude cumulative incidence of outcome measures in low, intermediate and high risk groups during study follow up.

Outcome - no. (%)	Low-risk group (N=223)	Intermediate-risk group (N= 465)	High-risk group (N = 320)	p value[1]
Myocardial infarction	4 (1.8)	14 (3.01)	16 (5.0)	0.11
Stroke	9 (4.0)	49 (10.5)	55 (17.2)	< 0.01
Peripheral artery disease	1 (0.5)	13 (2.8)	6 (1.9)	0.12
N-STEMI	6 (2.7)	11 (2.4)	15 (4.7)	0.17
CABG	0 (0.0)	1 (0.2)	4 (1.25)	0.06
All cause mortality	48 (21.5)	119 (25.6)	84 (26.3)	0.41
Diabetes	13 (5.8)	31 (6.7)	51 (15.9)	< 0.01
Weight gain*, BMI > 25 Kg/m^2	5 (2.4)	21 (4.9)	42 (14.8)	< 0.01

BMI: body mass index, N-STEMI: non ST elevation myocardial infarction, CABG: coronary artery bypass grafting.

1. Two sided p value, Chi squared test.

* N: low risk = 210, intermediate risk= 428, high risk = 284.

Supplementary eTable 4. Incidence rate ratios of suicide attempts and psychiatric hospitalizations during follow-up for high-, intermediate- and low-risk groups.

Main exposure	Incidence rate ratio (95% CI)[1]	p value[1]
Suicide attempts		
High risk of metabolic side effect antipsychotics	0.79 (0.38 - 1.81)	0.53
Intermediate risk of metabolic side effect antipsychotics	0.83 (0.38 - 1.81)	0.64
Psychiatric hospitalization		
High risk of metabolic side effect antipsychotics	1.07 (0.57 - 2.02)	0.83
Intermediate risk of metabolic side effect antipsychotics	1.36 (0.73 - 2.55)	0.33

1. P value based on Poisson regression with robust standard errors. Exposure modeled using low-risk group as baseline category.

Supplementary eTable 5. Crude and propensity score adjusted hazard ratios of primary composite outcome for main exposure

Main exposure	Crude HR (95% CI)[1]	Adjusted HR (95% CI)[2]		
		Overall	< 2 years from baseline	< 5 years from baseline
High risk of metabolic side effect antipsychotics	3.08 (1.85 - 5.11)	3.14 (1.87 - 5.26)	2.87 (1.06 - 7.78)	2.55 (1.43 - 4.56)
Intermediate risk of metabolic side effect antipsychotics	3.17 (1.90 - 5.29)	2.75 (1.62 - 4.65)	2.38 (0.89 - 6.35)	2.13 (1.20 - 3.78)

Abbreviations: HR: Hazard ratio, 95% CI: 95% confidence interval.
Primary composite outcome: myocardial infarction, stroke, peripheral artery disease, acute coronary syndrome or new revascularization procedure.
1. Univariate Cox proportional hazards model with exact method for ties. Exposure was modeled using low-risk medications as the reference group
2. Multivariate Cox proportional hazards model including main exposure and propensity score as regression splines. Exposure was modeled using low-risk medications as the reference group

Supplementary eTable 6. Crude and propensity score adjusted hazard ratios of secondary outcomes for main exposure

Main exposure	Crude HR (95% CI)	p value[1]	Adjusted HR (95% CI)	p value[2]
Composite secondary outcome				
High risk of metabolic side effects	1.48 (1.10 - 1.99)	0.01	1.41 (1.04 - 1.92)	0.03
Intermediate risk of side effects	1.91 (1.42 - 2.57)	< 0.01	1.55 (1.14 - 2.11)	< 0.01
All cause mortality				
High risk of metabolic side effects	1.04 (0.73 - 1.49)	0.81	0.95 (0.66 - 1.37)	0.78
Intermediate risk of side effects	1.72 (1.22 - 2.41)	< 0.01	1.32 (0.93 - 1.89)	0.13
Incident type 2 diabetes				
High risk of metabolic side effects	2.85 (1.55 - 5.24)	< 0.01	2.76 (1.45 - 5.25)	< 0.01
Intermediate risk of side effects	1.44 (0.75 - 2.76)	0.27	1.33 (0.67 - 2.66)	0.41

Abbreviations: HR: Hazard ratio, 95% CI: 95% confidence interval.
Composite secondary outcome: myocardial infarction, stroke, peripheral artery disease, acute coronary syndrome, new revascularization procedure and all cause mortality.
1. Univariate Cox proportional hazards model. Exposure was modeled using low-risk medications as the reference group
2. Multivariate Cox proportional hazards model including main exposure and propensity score as regression splines. Exposure was modeled using low-risk medications as the reference group

Supplementary eTable 7. Sensitivity analysis excluding patients under combination therapy

Main exposure	Crude HR (95% CI)[1]	Adjusted HR (95% CI)[2]		
		Overall	< 2 years from baseline	< 5 years from baseline
High risk of metabolic side effect antipsychotics	2.79 (1.67 - 4.67)	2.61 (1.44 - 4.71)	2.48 (0.79 - 7.79)	2.03 (1.07 - 3.87)
Intermediate risk of metabolic side effect antipsychotics	3.18 (1.91 - 5.31)	2.59 (1.43 - 4.69)	2.07 (0.71 - 6.07)	1.89 (1.02 - 3.51)

Abbreviations: HR: Hazard ratio, 95% CI: 95% confidence interval.
Primary composite outcome: myocardial infarction, stroke, peripheral artery disease, acute coronary syndrome or new revascularization procedure.
1. Univariate cox proportional hazards model. Exposure was modeled using low-risk medications as the reference group
2. Inverse probability weighting of a marginal structural cox model. Exposure was modeled using low-risk medications as the reference group

Supplementary eTable 8. Hazards ratio of major cardiovascular events during follow up for high and low risk antipsychotic medication

Main exposure	Crude HR (95% CI)[1]	Adjusted HR (95% CI)[2]		
		Overall	< 2 years from baseline	< 5 years from baseline
High risk of metabolic side effect antipsychotics	1.61 (1.20 - 2.15)	1.57 (1.17 - 2.12)	1.85 (1.05 - 3.27)	1.61 (1.14 - 2.27)

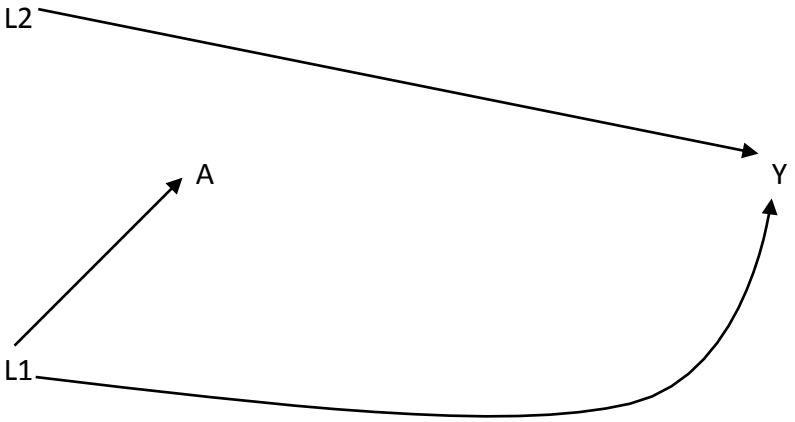
Abbreviations: HR: Hazard ratio, 95% CI: 95% confidence interval.
Primary composite outcome: myocardial infarction, stroke, peripheral artery disease, acute coronary syndrome or new revascularization procedure.
1. Univariate Cox proportional hazards model. Exposure modeled using low-risk group as baseline category
2. Inverse probability weighting of a marginal structural cox proportional model. Exposure modeled using low-risk group as baseline category

Supplementary eTable9. Hazards ratio of major cardiovascular events during follow up for high, intermediate and low risk antipsychotic medication including antipsychotic dose as a covariate.

Main exposure	Crude HR (95% CI)[1]	Adjusted HR (95% CI)[2]		
		Overall	< 2 years from baseline	< 5 years from baseline
High risk of metabolic side effect antipsychotics	3.05 (1.84 - 5.06)	2.67 (1.49 - 4.79)	2.50 (0.82 - 7.64)	2.12 (1.13 - 3.98)
Intermediate risk of metabolic side effect antipsychotics	3.15 (1.89 - 5.24)	2.57 (1.43 - 4.65)	2.11 (0.72 - 6.23)	1.91 (1.03 - 3.54)

Abbreviations: HR: Hazard ratio, 95% CI: 95% confidence interval.
Primary composite outcome: myocardial infarction, stroke, peripheral artery disease, acute coronary syndrome or new revascularization procedure.
1. Univariate Cox proportional hazards model. Exposure was modeled using low-risk medications as the reference group.
2. Inverse probability weighting of a marginal structural cox proportional model. Exposure was modeled using low-risk medications as the reference group.

Supplementary eFigure 1. Acyclic graph under the null (potential confounders included in propensity score calculation)



The figure represents the structural relationship of measured covariates in the setting of the present study. A represents the main exposure and Y the primary outcome. L1 and L2 are vectors of measured covariates. The relationships depicted are under the null since no a-priori relationship between A and Y is present.

Reference:

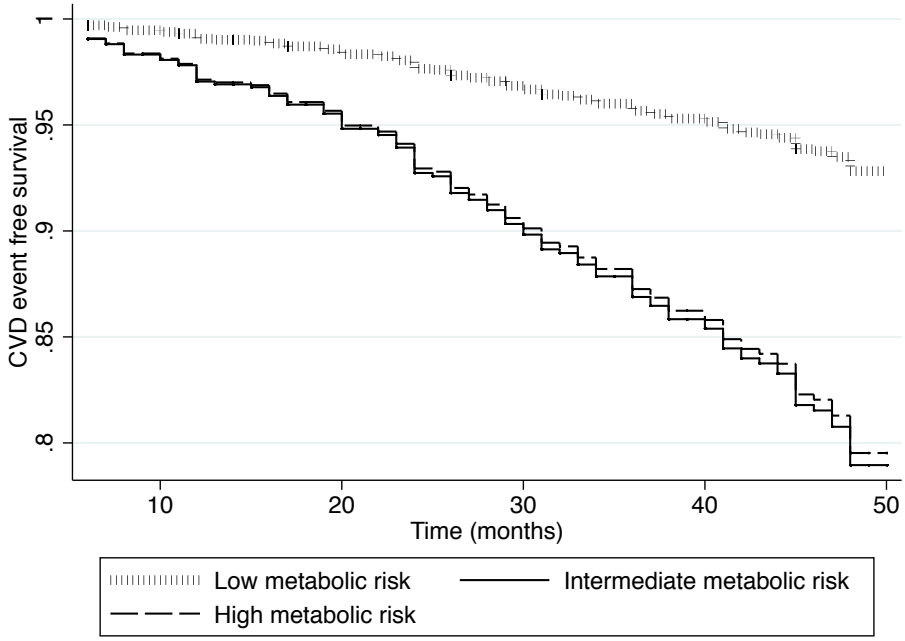
A: Antipsychotic treatment

Y: Major cardiovascular events

L1: age, nursing home, chronic heart failure, previous myocardial infarction, gender, baseline diabetes, previous stroke, previous arrhythmia, dementia, renal failure, statin use, cholinesterase inhibitors, treatment with antidepressants

L2: chronic obstructive pulmonary disease, smoking status, systolic blood pressure, aspirin/clopidogrel, steroids.

Supplementary eFigure 2. Estimated proportion of patients free of major cardiovascular events under either high, intermediate or low metabolic risk exposures[1].



Abbreviations: CVD: cardiovascular disease

Major cardiovascular events: composite of myocardial infarction, stroke, peripheral arterial disease or new revascularization procedure.

1. Multivariate proportional hazards model including propensity score as regression splines.

Supplementary eFigure 3. Estimated cumulative survival for high- and low-risk medication groups.