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# Atypical Antipsychotics and the Risk of Sudden Cardiac Death

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# Sudden Cardiac Death

- *“The unexpected natural death from a cardiac cause heralded by abrupt loss of consciousness within a short time period, generally less than 1 hour from the onset of symptoms.”*
- Majority cardiovascular deaths; >400,000 sudden cardiac deaths annually
- 85%-90% ventricular tachyarrhythmias
- Medications may contribute to risk

# Typical Antipsychotics and Sudden Cardiac Death

- Long suspected causing sudden cardiac death (2 reports 1963 sudden arrhythmic deaths)
- Many known to inhibit potassium channels and prolong QT
- Numerous case reports of torsade de pointes and sudden cardiac death
- Four epidemiologic studies show increased risk

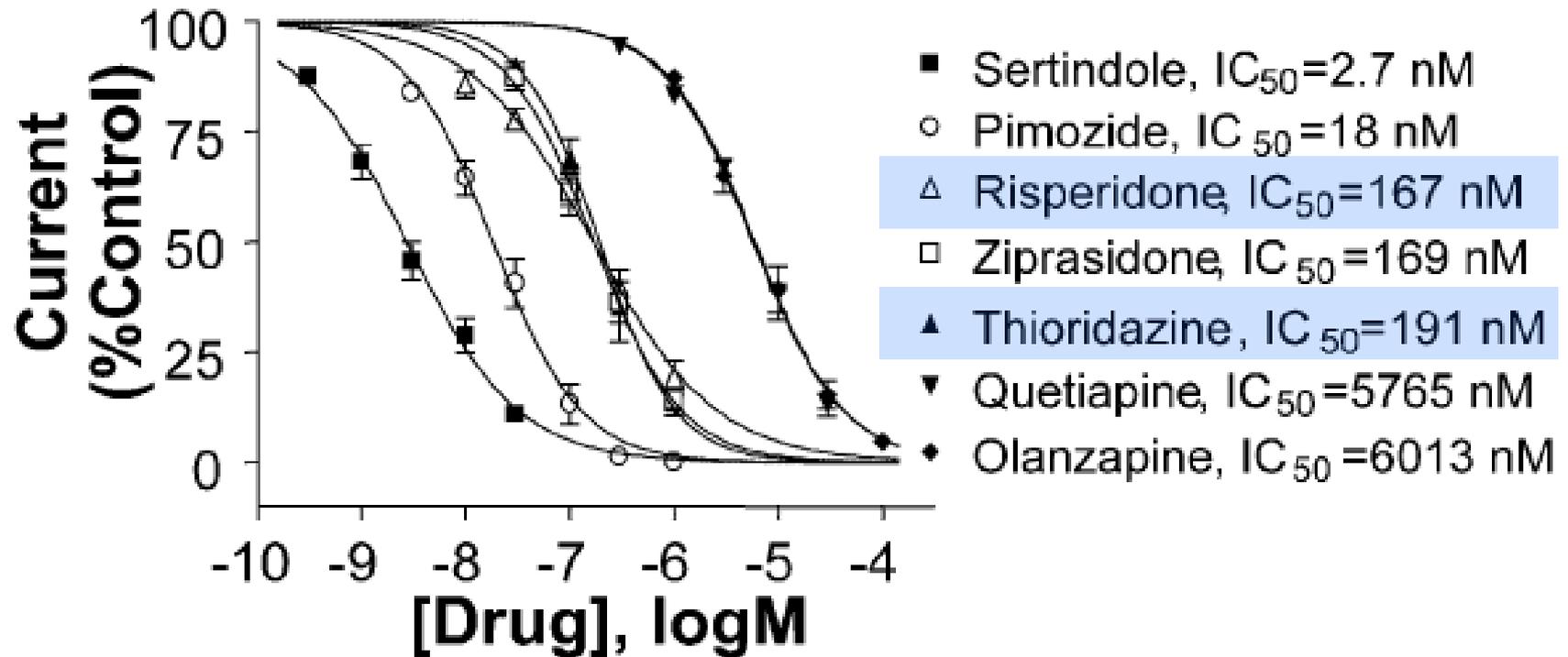
# Atypicals and Sudden Cardiac Death

- Hope that risk lower than that for typical antipsychotics
- Inhibit potassium channels
- Prolong QT
- Case reports of torsade de pointes

# Antipsychotic Effects on $I_{Kr}$

Chinese hamster ovary cell model

C



# Effects on QT<sub>c</sub>

**Table III.** Mean change in QTc and heart rate from baseline to steady state. Results of Pfizer Study 054<sup>[8]</sup>

Drug	QTc (Bazett) [msec]	QTc (Fridericia) [msec]	Heart rate (beats per min)
Thioridazine	+35.8	+29.6	+5.7
Ziprasidone	+20.6	+15.6	+4.6
Quetiapine	+14.5	+4.8	+11.2
Risperidone	+10.0	+3.0	+6.4
Olanzapine	+6.4	+1.1	+6.5
Haloperidol	+4.7	+7.3	-2.9

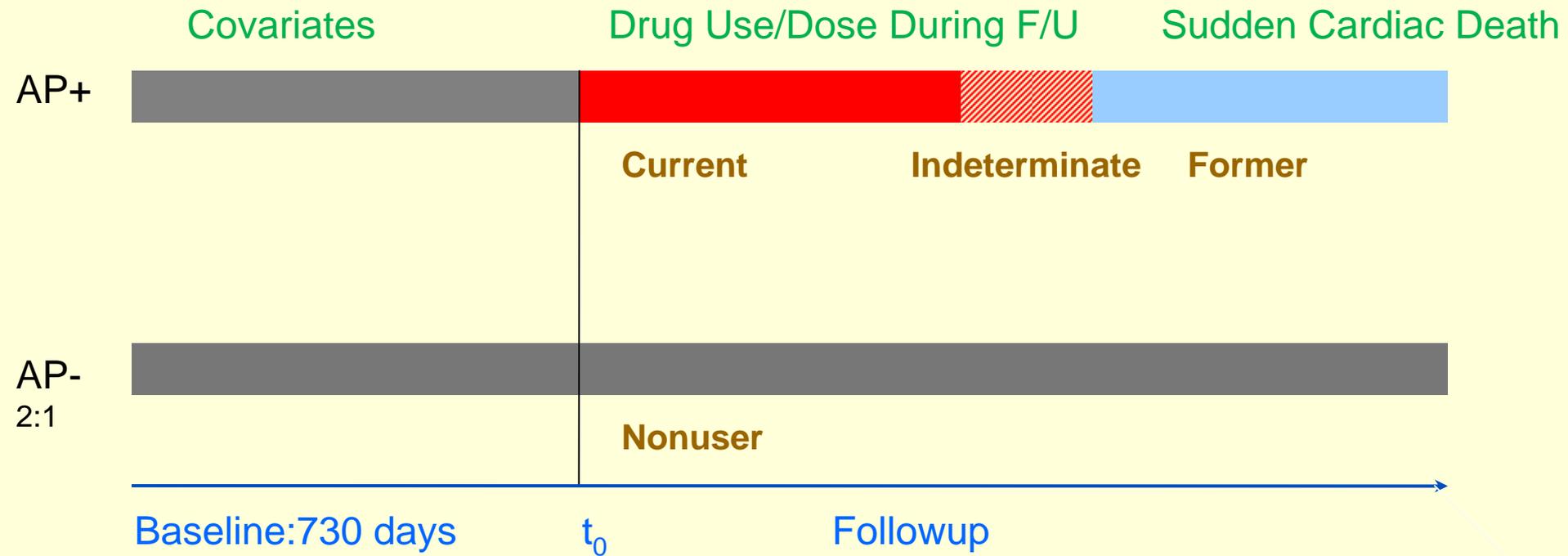
# Study Question

Do typical and atypical antipsychotics differ with regard to risk of sudden cardiac death?

# Cohort: Design and Data Sources

- Retrospective cohort, 1990-2005
- Tennessee Medicaid (TennCare) data
  - enrollment
  - pharmacy
  - hospital
  - outpatient
- Linked with death certificates and all-payers hospital discharge data

# Study Overview



# Cohort: Eligibility and Followup

- Inclusion/exclusion criteria
  - Age 30-74
  - 2 years enrollment
  - Not nursing home
  - Rx, visit each past 2 yrs
  - No serious illness
  - No recreational drugs
- Followup terminates
  - End of study
  - No longer qualifies
  - Excludes hospital stay+30d
  - Enrollment loss
  - Death

# Sudden Cardiac Death: Definition

- *Sudden fatal pulseless condition in community consistent with ventricular tachyarrhythmia occurring in the absence of a known noncardiac condition as the proximate cause of the death.*
- **Excludes:**
  - Deaths in hospital
  - Not sudden
  - Noncardiac
  - Different cardiac etiology

# Computer Case Definition

- Qualifying deaths:
  - Not hospital
  - Cause compatible with sudden cardiac death
  - no ED care day of death inconsistent with sudden cardiac death
- Validation by medical record review
  - 1990-1993, prior study (n=616), PPV = 86%
  - 1994-2005, sample (n=174), PPV = 87%
    - AP user, PPV = 86.4%
    - AP nonuser, PPV = 87.4%

# Confounders (Poisson Regression)

1. Demographic factors
2. Baseline cardiovascular/somatic risk score
  - a. >60 variables: drugs, diagnoses, care utilization
  - b. Estimates (Poisson regression) endpoint probability in nonusers antipsychotics
  - c. Like propensity scores, facilitates parsimonious models
3. Baseline psychiatric/neurologic comorbidity
4. Hospital admission, ED visit during followup
5. Other drugs during followup possibly  $\uparrow$  risk sudden death (e.g, amitriptyline)

# Study cohort at baseline

- 93,300 antipsychotic users
  - 44,218 single typical
  - 46,089 single atypical
- 186,600 nonuser controls

# Baseline Demographics

Characteristic	Primary Cohort	
	Nonuser (N= 186,600)	Current User (N= 93,300)
Mean year of cohort entry	1998	1998
Study follow-up (yr)		
Median	2.2	2.9
Interquartile range	0.9–4.8	1.2–6.1
Age (yr)	45.7±11.8	45.7±11.8
Male sex (%)	34.8	34.8
Nonwhite race (%)‡	30.0	28.5
Urban residence (%)	56.6	57.5
Medicaid enrollment due to disability (%)	37.4	62.9
Cardiovascular risk score§	9.6±5.8	9.2±5.8

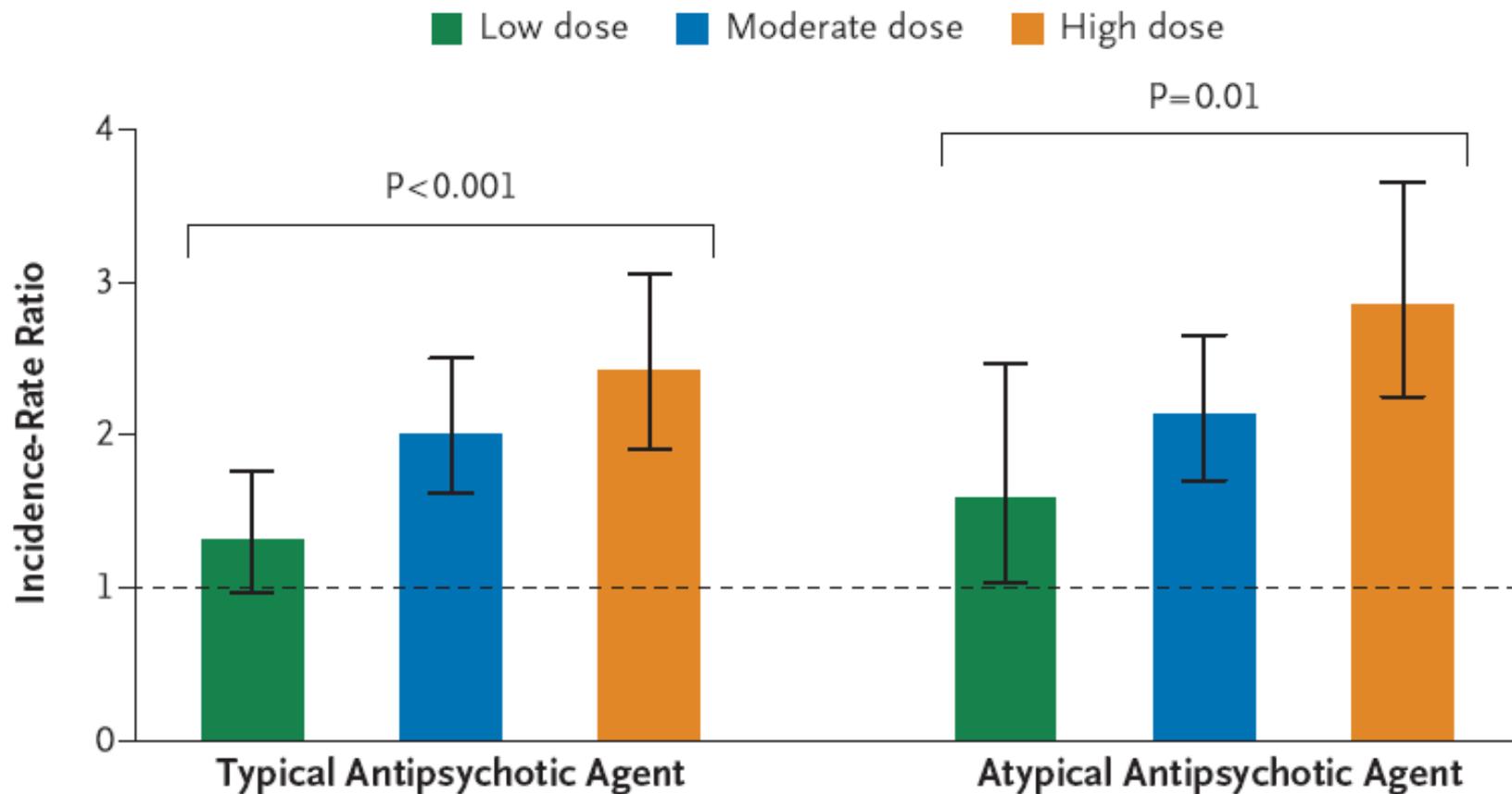
# Baseline Psychiatric

Characteristic	Primary Cohort	
	Nonuser (N = 186,600)	Current User (N = 93,300)
Psychiatric characteristics (%)		
Use of moderate or high dose of antipsychotic drug**	NA	69.0
Schizophrenia	1.4	21.3
Other psychosis	1.0	9.7
Bipolar disorder	2.6	18.2
Major depression or other mood disorder	17.2	48.4
Dementia	0.6	3.1
Alcohol or prescription-drug dependency	4.9	8.3
History of suicide attempt	1.2	3.5
Previous stay in psychiatric hospital	3.8	21.7
Use of lithium	1.2	9.3
Use of mood stabilizer	8.3	24.0
Use of antidepressant	41.5	73.0
Use of benzodiazepine	34.1	56.0

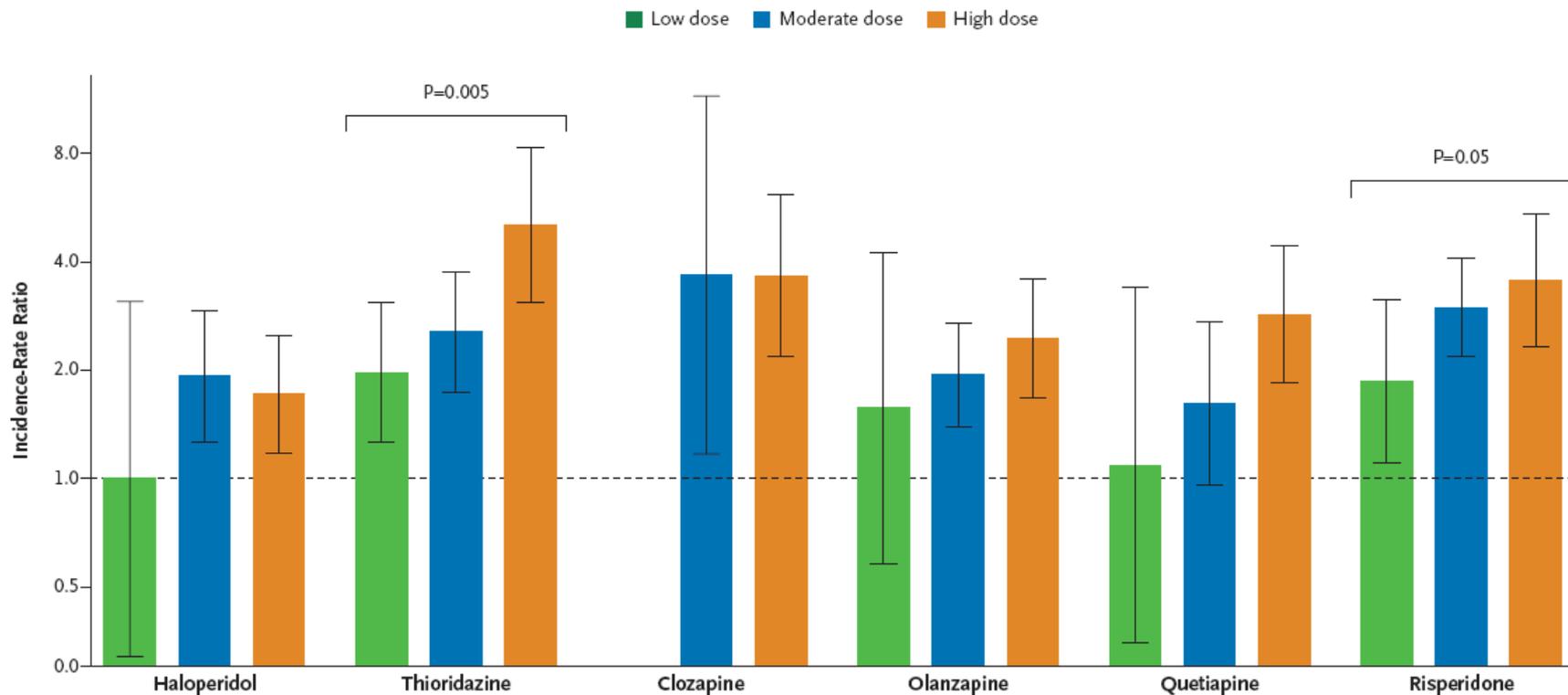
**Table 2.** Adjusted Incidence-Rate Ratios for Sudden Cardiac Death, According to Use or Nonuse of Antipsychotic Drugs.\*

User Status	No. of Person-Years	No. of Sudden Deaths	Incidence-Rate Ratio (95% CI)	P Value
Nonuser	624,591	895	Reference group	
Former user	189,981	311	1.13 (0.98–1.30)	0.08
Current user†				
Typical agent				
Any	86,735	255	1.99 (1.68–2.34)	<0.001
Haloperidol	21,728	58	1.61 (1.16–2.24)	0.005
Thioridazine	15,715	65	3.19 (2.41–4.21)	<0.001
Atypical agent				
Any	79,589	223	2.26 (1.88–2.72)	<0.001
Clozapine	4,654	19	3.67 (1.94–6.94)	<0.001
Olanzapine	27,257	75	2.04 (1.52–2.74)	<0.001
Quetiapine	17,355	40	1.88 (1.30–2.71)	<0.001
Risperidone	24,589	85	2.91 (2.26–3.76)	<0.001

# Sudden Cardiac Death IRRs: Antipsychotic Type and Dose



<b>No. of Deaths</b>	46	104	105	22	108	93
<b>No. of Person-Years</b>	21,438	33,671	31,626	10,435	41,513	27,641
<b>Incidence-Rate Ratio</b>	1.31	2.01	2.42	1.59	2.13	2.86
<b>95% CI</b>	0.97–1.77	1.62–2.50	1.91–3.06	1.03–2.46	1.70–2.65	2.25–3.65



No. of Deaths	3	23	32	20	28	17	0	3	16	4	40	31	3	15	22	15	46	24
No. of Person-Years	1342	7014	13,372	6238	7254	2223	63	593	3999	1640	15,395	10,222	2433	7983	6939	5894	12,950	5745
Incidence-Rate Ratio	1.00	1.92	1.72	1.97	2.55	5.05	—	3.67	3.66	1.57	1.94	2.45	1.09	1.62	2.85	1.86	2.98	3.56
95% CI	0.3–3.1	1.3–2.9	1.2–2.5	1.3–3.1	1.7–3.8	3.1–8.3	—	1.2–11.5	2.2–6.1	0.6–4.2	1.4–2.7	1.7–3.6	0.3–3.4	1.0–2.7	1.8–4.4	1.1–3.1	2.2–4.1	2.3–5.4

**Figure 2.** Adjusted Incidence-Rate Ratios for Sudden Cardiac Death among Current Users of Six Frequently Prescribed Antipsychotic Drugs, According to Dose.

# Propensity Score Analysis

- Propensity Scores
  - Facilitates matching by many variables
  - Score:  $p[\text{AP+}/\text{covariates}]$
- Cohort
  - No baseline diagnosis indicating schizophrenia or related psychosis
  - Propensity-score-matched (adaptive)

# PS Matched Cohorts

Characteristic	Cohort Matched for Propensity Score†	
	Nonuser (N= 116,069)	Current User (N= 67,824)
Psychiatric characteristics (%)		
Use of moderate or high dose of antipsychotic drug**	NA	62.0
Schizophrenia	0	0
Other psychosis	0	0
Bipolar disorder	14.2	17.1
Major depression or other mood disorder	51.3	52.6
Dementia	2.9	2.9
Alcohol or prescription-drug dependency	9.6	7.9
History of suicide attempt	3.5	3.5
Previous stay in psychiatric hospital	15.0	14.7
Use of lithium	6.1	7.6
Use of mood stabilizer	22.2	24.4
Use of antidepressant	76.3	79.4
Use of benzodiazepine	58.8	61.6

**Table 3.** Adjusted Incidence-Rate Ratios for Sudden Cardiac Death in the Cohort Matched for Propensity Score, According to Use or Nonuse of Antipsychotic Drugs and According to Dose.\*

Variable	No. of Person-Years	No. of Sudden Deaths	Incidence-Rate Ratio (95% CI)	P Value
Nonuser	390,072	705	Reference group	
Former user	159,415	243	0.93 (0.80–1.08)	0.30
Dose‡				
Typical agent				
Low	16,293	36	1.13 (0.81–1.59)	0.47
Moderate	18,203	55	1.59 (1.20–2.11)	0.001
High	7,735	34	2.70 (1.90–3.84)	<0.001
Atypical agent				
Low	8,237	18	1.52 (0.94–2.44)	0.08
Moderate	25,694	58	1.68 (1.28–2.22)	<0.001
High	11,921	40	2.69 (1.93–3.73)	<0.001

# Alternative Analyses

<b>Analysis</b>	<b>Typical</b>	<b>Atypical</b>
	IRR (95% CI)	
New users	1.74 (1.14-2.67)	1.86 (1.35-2.57)
<365 days use	1.73 (1.09-2.72)	1.87 (1.29-2.73)
1998-2005	1.78 (1.35-2.35)	2.03 (1.65-2.50)

# Study Limitations

- Case-Definition
- Confounding
- Generalizability

# Study Limitations: Confounding

- Cardiovascular disease
  - Extensive set medications, diagnoses considered
  - Cohort required to have regular medical encounters
- Smoking
  - Much of effect mediated by cardiovascular disease
  - Sensitivity analysis
  - Propensity-score-matched cohort findings
- Poor self care
  - Cohort required to have regular medical encounters
  - Lack increased risk former users, dose-response
  - Propensity-score-matched cohort findings
- Psychiatric illness *per se*
  - Propensity-score-matched cohort findings

# Conclusions

- Atypical antipsychotic users had a dose-related increased risk for sudden cardiac death
- Magnitude increased risk not different from that for typical antipsychotics
- Several lines of evidence indicate the increased risk is due to the drugs *per se*