ONLINE FIRST

Scan for Author Video Interview

ADHD Medications and Risk of Serious Cardiovascular Events in Young and Middle-aged Adults

Laurel A. Habel, PhD
William O. Cooper, MD, MPH
Colin M. Sox, MD, MS
K. Arnold Chan, MD, ScD
Bruce H. Fireman, MA
Patrick G. Arbogast, PhD
T. Craig Cheetham, PharmD, MS
Virginia P. Quinn, PhD, MPH
Sascha Dublin, MD, PhD
Denise M. Boudreau, PhD, RPh
Susan E. Andrade, ScD
Pamala A. Pawloski, PharmD
Marsha A. Raebel, PharmD
David H. Smith, RPh, PhD
Ninah Achacoso, MS
Connie Uratsu, RN
Alan S. Go, MD
Steve Sidney, MD, MPH
Mai N. Nguyen-Huynh, MD, MAS
Wayne A. Ray, PhD
Joe V. Selby, MD, MPH

Context More than 1.5 million US adults use stimulants and other medications labeled for treatment of attention-deficit/hyperactivity disorder (ADHD). These agents can increase heart rate and blood pressure, raising concerns about their cardiovascular safety.

Objective To examine whether current use of medications prescribed primarily to treat ADHD is associated with increased risk of serious cardiovascular events in young and middle-aged adults.

Design, Setting, and Participants Retrospective, population-based cohort study using electronic health care records from 4 study sites (OptumInsight Epidemiology, Tennessee Medicaid, Kaiser Permanente California, and the HMO Research Network), starting in 1986 at 1 site and ending in 2005 at all sites, with additional covariate assessment using 2007 survey data. Participants were adults aged 25 through 64 years with dispensed prescriptions for methylphenidate, amphetamine, or atomoxetine at baseline. Each medication user (n=150 359) was matched to 2 nonusers on study site, birth year, sex, and calendar year (443 198 total users and nonusers).

Main Outcome Measures Serious cardiovascular events, including myocardial infarction (MI), sudden cardiac death (SCD), or stroke, with comparison between current or new users and remote users to account for potential healthy-user bias.

Results During 806 182 person-years of follow-up (median, 1.3 years per person), 1357 cases of MI, 296 cases of SCD, and 575 cases of stroke occurred. There were 107 322 person-years of current use (median, 0.33 years), with a crude incidence per 1000 person-years of 1.34 (95% CI, 1.14-1.57) for MI, 0.30 (95% CI, 0.20-0.42) for SCD, and 0.56 (95% CI, 0.43-0.72) for stroke. The multivariable-adjusted rate ratio (RR) of serious cardiovascular events for current use vs nonuse of ADHD medications was 0.83 (95% CI, 0.72-0.96). Among new users of ADHD medications, the adjusted RR was 0.77 (95% CI, 0.63-0.94). The adjusted RR for current use vs remote use was 1.03 (95% CI, 0.86-1.24); for new use vs remote use, the adjusted RR was 1.02 (95% CI, 0.82-1.28); the upper limit of 1.28 corresponds to an additional 0.19 events per 1000 person-years at ages 25-44 years and 0.77 events per 1000 person-years at ages 45-64 years.

Conclusions Among young and middle-aged adults, current or new use of ADHD medications, compared with nonuse or remote use, was not associated with an increased risk of serious cardiovascular events. Apparent protective associations likely represent healthy-user bias.

JAMA. 2011;306(24):2673-2683
Published online December 12, 2011. doi:10.1001/jama.2011.1830 www.jama.com

Between 2001 and 2010, use of medications labeled for treatment of attention-deficit/hyperactivity disorder (ADHD) increased even more rapidly in adults than in children.[1] According to a 2006 US Food and Drug Administration (FDA) advisory committee briefing on the safety of ADHD medications, more than 1.5 million US adults were taking stimulants in 2005, and adults received approximately 32% of all issued prescriptions.[2] The increase in

For editorial comment see p 2723.

Author Video Interview available at www.jama.com.

Author Affiliations: Division of Research, Kaiser Permanente Northern California, Oakland (Drs Habel, Go, Sidney, Nguyen-Huynh, and Selby, Mr Fireman, and Mss Achacoso and Uratsu); Department of Pediatrics (Dr Cooper), Division of Pharmacoepidemiology, Department of Preventive Medicine (Drs Cooper and Ray), and Department of Biostatistics (Dr Arbogast), Vanderbilt University, Nashville, Tennessee; Harvard Pilgrim Health Care Institute, Department of Population Medicine, Harvard Medical School, Boston, Massachusetts, and Department of Pediatrics, Boston University School of Medicine, Boston (Dr Sox); OptumInsight Epidemiology, Waltham, Massachusetts (Dr Chan); Pharmacy Analytical Service, Kaiser Permanente Southern California, Downy (Dr Cheetham); Research and Evaluation Department, Kaiser Permanente Southern California, Pasadena (Drs Cheetham and Quinn); Group Health Research Institute, Seattle, Washington (Drs Dublin and Boudreau); Departments of Epidemiology (Dr Dublin) and Pharmacy (Dr Boudreau), University of Washington, Seattle; Meyers Primary Care Institute, Worcester, Massachusetts (Dr Andrade); HealthPartners Research Foundation, Bloomington, Minnesota (Dr Pawloski); Institute for Health Research, Kaiser Permanente Colorado, and School of Pharmacy, University of Colorado at Denver (Dr Raebel); Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon (Dr Smith); and Departments of Epidemiology, Biostatistics and Medicine, University of California, San Francisco (Dr Sidney).
Corresponding Author: Laurel A. Habel, PhD, Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Fifth Floor, Oakland, CA 94612 (laurel.habel@kp.org).

©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/13/2015

ADHD diagnoses is likely the primary cause of increased prescribing,[3,4] although stimulants also are approved for treatment of narcolepsy[5] and may be used off-label to treat obesity[6] and fatigue related to depression,[7] stroke,[8] or traumatic brain injury.[9] Adults with ADHD are commonly treated with the stimulant classes methylphenidate and amphetamine and increasingly with a nonstimulant agent, atomoxetine.

Placebo-controlled studies in children and adults indicate that stimulants and atomoxetine elevate systolic blood pressure levels by approximately 2 to 5 mm Hg and diastolic blood pressure levels by 1 to 3 mm Hg and also lead to increases in heart rate.[10,11] Although these effects would be expected to slightly increase risk for myocardial infarction (MI), sudden cardiac death (SCD), and stroke,[12] clinical trials have not been large enough to assess risk of these events.

In a summary from the FDA Adverse Event Reporting System, cardiac arrest, MI, and sudden unexplained death were among the top 50 adverse events reported after use of amphetamines and methylphenidate.[2] Although 1 study among children suggested markedly elevated risks of SCD,[13] cardiovascular safety data from pharmacoepidemiologic studies are limited and inconsistent,[13-16] especially among adults.[17,18]

The aim of this study was to examine whether current use of medications used primarily to treat ADHD is associated with increased risk of MI, SCD, or stroke in adults aged 25 through 64 years. Study drugs included all agents with a labeled indication for treatment of ADHD in either children or adults as of December 31, 2005.

METHODS

The study was conducted in parallel with a study of ADHD drug use and serious cardiovascular events in youths aged 2 through 24 years.[19]

Data Sites

Study sites included Vanderbilt University (Tennessee State Medicaid data), Kaiser Permanente (KP) California (northern and southern KP regions), Optum Insight Epidemiology (data from a large health insurance plan), and the HMO Research Network (Harvard Pilgrim Health Care; Fallon Community Health Plan; Group Health Cooperative of Puget Sound; HealthPartners; KP Georgia; KP Northwest; and KP Colorado). The selected sites provide geographic and sociodemographic diversity and have similar computerized data structures.

The start date for the availability of computerized data differed across study sites, ranging from 1986 to 2002. Follow-up concluded at the end of 2005 so that mortality searches could be conducted using complete state death records and the National Death Index. The study was approved by the institutional review boards of each participating institution and by the FDA Research in Human Subjects Committee. The requirement for participant informed consent was waived.

Study Participants

Eligible individuals were aged 25 through 64 years with at least 12 months of continuous health plan coverage and pharmacy benefits before cohort entry (time zero). Individuals were excluded if they had 1 or more of the following diagnoses (based on *International Classification of Diseases, Ninth Revision* [*ICD-9*] or *International Classification of Diseases, Tenth Revision* [*ICD-10*] codes) within 365 days before cohort entry: sickle cell disease, cancer (other than nonmelanoma skin cancer), human immunodeficiency virus infection, organ transplant, liver failure/hepatic coma, end-stage renal disease, respiratory failure, or congestive heart failure. When these diagnoses occurred after cohort entry, follow-up time was censored.

At each contributing site, we assembled the eligible members and periods when all eligibility criteria were met. For each exposed period (ie, at least 1 ADHD prescription), starting with the earliest, we randomly selected 2 unexposed periods from all members with no ADHD medication use at cohort entry and the same sex and birth year.

Study Medications and Exposure Categories

Medication use was based on prescription fills from electronic pharmacy records. ADHD medications included stimulant-class medications (methylphenidate, amphetamines, pemoline) and atomoxetine, a selective norepinephrine reuptake inhibitor. Amphetamines included dextroamphetamines and amphetamine salts. Although infrequently used and not structurally similar to the other stimulants, pemoline was included because of its labeled indication for ADHD. Each person-day of follow-up was classified into mutually exclusive exposure categories according to ADHD drug use, based on prescription dispensing dates and days supply.

Current use was defined as the period between prescription start date and end of days supply (including up to a 7-day carryover from previous prescriptions). *Indeterminate use* was the first 89 days after end of current use. *Former use* began at 90 days after end of current use and ended at 364 days after last current use. Greater than 364 days since end of last days supply was considered *remote use*. *Nonuse* referred to person-days with no current use and no past use (back to 365 days before cohort entry). Past users and nonusers could become current users during follow-up; when this occurred, their person-time was classified as described above. Less than 1% of nonusers became users after baseline. Current use was further categorized based on specific medications (amphetamines, methylphenidate, atomoxetine, multiple ADHD drugs, or pemoline) and on prespecified duration categories (1-30 days, 31-90 days, 91-182 days, 183-365 days, ≥366 days).

We consider current use the most etiologically relevant exposure. Risk during current use was compared with risk during nonuse. In addition, to account for potential selection bias or unmeasured confounding that could arise from users being more or less healthy than nonusers, we restricted some analyses to ever users of ADHD medications. These analyses compared rates during periods of current use with rates during periods 365 days or more after

 ©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/13/2015

use ended (ie, remote use). These analyses are less influenced by potential confounders that are unmeasured and stable over time, but analyses assume no medication effects that remain after discontinuation.

Study End Points

Potential end points were identified from claims and vital records (diagnoses and *ICD* codes provided in eTable 1, available at http://www.jama.com). For members with death not identified from these sources and whose health plan enrollment ended prior to end of study period, we performed National Death Index searches.

Medical records, including hospitalizations, reports from emergency medical services, autopsies, and death certificates, were requested for all potential SCDs (n=411) and strokes (n=980) and for a random 31% sample of potential MIs (n=433) for assessment by trained adjudicators (primary care physicians for MI and SCD, neurologists for stroke).

Of the 371 MI cases with sufficient records available, 353 (95%) were confirmed by adjudication. *Myocardial infarction* was defined as an acute event involving hospitalization with characteristic changes in cardiac enzyme levels and either symptoms or characteristic electrocardiographic changes.[20,21] *Sudden cardiac death* was defined as witnessed sudden death in a community setting, preceded by typical symptoms of cardiac ischemia. Deaths were excluded when documentation suggested a noncardiac cause (eg, motor vehicle crash) or if clinically severe heart disease was present and sudden cardiac death was not unexpected (eg, end-stage congestive heart failure). *Stroke* was defined as an acute neurologic deficit of sudden onset that persisted more than 24 hours, corresponded to a vascular territory, and was not explained by other causes such as trauma, infection, vasculitis, extracranial hemorrhage leading to hypotension, or profound hypotension from another cause. Strokes that occurred during a hospitalization were excluded.

All MIs, other than those determined by adjudication to be noncases (n=18), were included in analyses. For potential SCD cases without available or adequate hospital or autopsy records (n=203), we used an *ICD-9/ICD-10* code–based definition with a previously reported positive predictive value of 86%.[22] SCD cases based on the code-based definition (n=157), as well as those confirmed by clinical adjudication (n=139), were included in primary analyses. For potential strokes with insufficient hospital or autopsy records for clinical adjudication (n=179) or for which records were unavailable (n=69), we used a code-based definition to identify probable strokes. Probable strokes had *ICD-9/ICD-10* codes with a positive predictive value of 80% or greater, based on those strokes for which records were available. Strokes confirmed by adjudication (n=451) and those with insufficient records meeting the diagnostic code–based definition (n=124) were included as events in primary analyses (eTable 2A and B). In secondary analyses, we included all electronically identified SCDs or strokes except those confirmed as nonevents by adjudication.

Confounders

To control for potential differences in cardiovascular disease (CVD) risk between exposed and unexposed individuals, we constructed a summary cardiovascular risk score (CRS).[23,24] The CRS was based on inpatient and outpatient diagnoses (from claims or encounter databases) and pharmacy records and included CVD and medications, mental health conditions (excluding ADHD) and use of psychotropic medications, other health conditions (eg, diabetes mellitus, obesity, smoking-related) and medications, and health care utilization (TABLE 1 and eTable 3).

For each end point (MI, SCD, stroke, or any serious cardiovascular event), a separate score was created from a Poisson regression model among all patients, adjusted for ADHD medications and matching variables (age, sex, data site, calendar year at cohort entry). The score was the linear predictor from the coefficients of the resulting regression model, excluding the coefficients for ADHD medications and the matching variables.

In primary analyses, several CRS variables not thought to be on the causal pathway between medication use and our outcomes were treated as time varying (eTable 3). In secondary analyses, all CRS variables were based on diagnoses or medication use in the 365 days prior to cohort entry and fixed at baseline. For the new-user analyses, we used the CRS for comparisons of current vs remote use and constructed a propensity score[25] for current vs nonuse of ADHD medications at cohort entry, using variables included in the CRS.

Unmeasured Confounders

To examine the possible extent and direction of unmeasured confounding by risk factors for CVD on which information was not or was inconsistently available in the electronic health care records, we conducted sensitivity analyses using information on potential confounders from 2 sources. Race/ethnicity, smoking, obesity, history of CVD, and drug abuse were obtained from the adjudicated records of MI, SCD, and stroke cases. In addition, race/ethnicity, income, education, smoking, obesity, and family history of CVD were available for approximately 200 000 KP Northern California members aged 25 through 64 years who completed a mailed survey for a different study in 2007 (eMethods). Electronic pharmacy records for ADHD medications were obtained for survey participants.

We used multivariable logistic regression to examine the association between potential confounders (from either survey or chart reviews) and use of ADHD medications. For variables associated with use of ADHD medications, we assessed the extent of their potential confounding effect on rate ratios (RRs) for MI, SCD, or stroke associated with ADHD medications, using external adjustment methods.[26-28] This approach assumed that associations in our study population were similar to those

©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/13/2015

Table 1. Selected Characteristics of Study Cohort at Baseline[a]

Characteristic	Current Use	Nonuse
No. of unique individuals	150 359	292 839
No. of membership periods[b]	152 852	293 749
Year of cohort entry, median	2003	2003
Person-years during follow-up[c]	107 322	533 540
Demographic and Clinical		
Demographics		
Age, median (IQR), y	42 (34-49)	42 (34-49)
Male sex	70 245 (46.0)	135 002 (46.0)
Medicaid enrollment	14 786 (9.7)	29 171 (9.9)
ADHD medication		
Amphetamines	57 824 (37.8)	
Methylphenidate	70 923 (46.4)	
Atomoxetine	19 283 (12.6)	
Pemoline	3973 (2.6)	
Multiple	849 (0.6)	
Cardiovascular disease within past year[d]		
Acute MI	340 (0.2)	689 (0.2)
Ischemia	3998 (2.6)	6857 (2.3)
Coronary revascularization	253 (0.2)	643 (0.2)
Congestive heart failure	1112 (0.7)	1759 (0.6)
Arrhythmia	3560 (2.3)	5076 (1.7)
Stroke/transient ischemic attack	1826 (1.2)	2075 (0.7)
Congenital heart disorder	331 (0.2)	556 (0.2)
Coronary artery anomaly	66 (0.0)	89 (0.0)
Peripheral vascular disease	1225 (0.8)	1651 (0.6)
Hypertension	22 562 (14.8)	39 011 (13.3)
Hyperlipidemia[e]	28 613 (18.7)	42 601 (14.5)
Mental health claims within past year		
ADHD	46 356 (30.3)	455 (0.2)
Major depression	61 417 (40.2)	23 296 (7.9)
Bipolar disorder	11 196 (7.3)	2682 (0.9)
Anxiety	30 472 (19.9)	15 670 (5.3)
Psychotic disorders	2494 (1.6)	1833 (0.6)
Other selected medical conditions within past year		
Diabetes[e]	8972 (5.9)	15 862 (5.4)
Obesity	9119 (6.0)	11 439 (3.9)
Smoking	11 579 (7.6)	14 717 (5.0)
Alcohol/substance abuse	7965 (5.2)	4514 (1.5)
Suicide attempt	795 (0.5)	410 (0.1)
Injury	30 655 (20.1)	37 559 (12.8)
Seizure	3062 (2.0)	2854 (1.0)
Asthma	11 627 (7.6)	12 432 (4.2)
Use of cardiovascular drug within past year[d]		
Loop diuretic	4328 (2.8)	4932 (1.7)
Digoxin	587 (0.4)	1130 (0.4)
Nitrates	1941 (1.3)	3298 (1.1)
Anticoagulant	1768 (1.2)	2421 (0.8)
Platelet inhibitor	996 (0.7)	1675 (0.6)
Antiarrhythmic agents	556 (0.4)	631 (0.2)
ACE inhibitor	10 719 (7.0)	19 796 (6.7)
Angiotensin receptor blocker	3652 (2.4)	5988 (2.0)
β-Blocker	12 431 (8.1)	19 091 (6.5)
Calcium-channel blocker	7028 (4.6)	12 233 (4.2)
Thiazide diuretic	12 471 (8.2)	20 008 (6.8)
Other antihypertensive	1668 (1.1)	2192 (0.7)

(continued)

in our external samples and did not address joint confounding by several unmeasured covariates.

Statistical Analysis

Follow-up began at cohort entry and ended at 1 of the 4 end points (MI, SCD, stroke, or any of these serious cardiovascular events), death, end of insurance coverage or pharmacy benefit, day before 65th birthday, or end of study period (December 2005), whichever came first. Poisson regression was used to estimate the association of ADHD medication use with risk of serious cardiovascular events, while adjusting for potentially confounding variables. Covariates in the full model included study site, age (5-year dummy categories), sex, calendar year (1986-1992, 1993-1999, 2000-2001, 2002-2003, 2004-2005), and CRS (specified as decile dummies). Matching variables (site, age, sex, calendar year at cohort entry) were included in the full model because, although matching ensured balance with respect to these variables at baseline, it did not ensure balance during follow-up.

To minimize biases related to underascertainment of events occurring early in therapy,[29] we also conducted analyses restricted to new users of ADHD medications (no use in the year prior to baseline). In these analyses, risk during periods of current use was compared with risk during periods remote from last use. Current use among new users also was compared with nonuse (in their matches).

To examine whether associations could be influenced by prior disease conditions, we conducted subgroup analyses. In one analysis, users were restricted to those with a prior diagnosis of ADHD and compared with matched nonusers. Additional subgroups were based on prior CVD, prior non-ADHD psychiatric diagnoses or medication use, age (25-44 vs 45-64 years) during follow-up, and data site.

When examining rates of any serious cardiovascular event in the full cohort, we had 80% power to detect RRs of 1.23 for current use vs nonuse and 1.30 for current use vs remote use. In

 ©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/13/2015

new-user analyses, the least detectable RRs were 1.31 for current use vs nonuse and 1.38 for current vs remote use.

All analyses were performed using SAS version 9.1. For all RR estimates, 95% confidence limits were reported.

RESULTS

The study included a total of 443 198 adults, of whom 150 359 were users of ADHD medications at baseline. Methylphenidate accounted for 45% of current use; amphetamine, for 44%; atomoxetine, for 8%; and pemoline, for 3%.

Characteristics of Study Population

Baseline characteristics of users and nonusers are reported in Table 1; characteristics of person-time by medication use are reported in eTable 3. Cardiovascular diseases were generally uncommon and similar or modestly more prevalent in users than nonusers. As expected, ADHD was substantially more common among current users than nonusers. This also was true for other psychiatric conditions. The prevalences of cardiovascular risk factors were modestly higher during periods of remote use than during periods of current use or nonuse.

Number of Events and RRs in the Full Cohort

During 806 182 person-years of follow-up (median, 1.3 [interquartile range, 0.6-2.6] years per person), 1357 cases of MI, 296 cases of SCD, and 575 cases of stroke occurred. There were 107 322 person-years of current use (median, 0.33 [range, 0.0-13.5] years per user), with a crude incidence per 1000 person-years of 1.34 (95% CI, 1.14-1.57) for MI, 0.30 (95% CI, 0.20-0.42) for SCD, and 0.56 (95% CI, 0.43-0.72) for stroke.

In analysis adjusted for matching variables only, the RR of MI, SCD, or stroke for current vs nonuse of ADHD medications was 0.97 (95% CI, 0.84-1.12). After also adjusting for the CRS, the RR was modestly lower (0.83 [95% CI, 0.72-0.96]). Results were similar for specific medications and across end points (FIGURE 1 and eTable 4). Rate ratios also were similar for ischemic or hemorrhagic stroke (eTable 5A and B). Findings for SCD and stroke changed only minimally when all electronically identified cases were included except those adjudicated as noncases (eTable 6A and B). Overall results were essentially unchanged when all variables in the CRS were fixed at baseline (eTable 7).

Table 1. Selected Characteristics of Study Cohort at Baseline[a] (continued)

Characteristic	Current Use	Nonuse
Demographic and Clinical (cont.)		
Use of psychotropic medications within past year		
Antipsychotic, any	14 618 (9.6)	5371 (1.8)
Tricyclic antidepressant	14 224 (9.3)	9907 (3.4)
Antidepressants, other or SSRI/SNRI	81 639 (53.4)	36 962 (12.6)
Benzodiazepines	43 695 (28.6)	25 956 (8.8)
Lithium	4177 (2.7)	1002 (0.3)
Modafinil	4732 (3.1)	383 (0.1)
Insomnia medications	15 270 (10.0)	6732 (2.3)
Thioridazine	307 (0.2)	181 (0.1)
Mood stabilizers, without seizure	22 426 (14.7)	8631 (2.9)
Clonidine/guanfacine, without hypertension	2000 (1.3)	659 (0.2)
Use of other selected medications within past year		
β-Agonist	18 971 (12.4)	20 835 (7.1)
Epinephrine	1342 (0.9)	1274 (0.4)
Asthma medications, other	39 645 (25.9)	45 102 (15.4)
Seizure medications, any	24 139 (15.8)	10 397 (3.5)
Theophylline compounds (asthma medication)	960 (0.6)	1200 (0.4)
COX-2 inhibitors	10 666 (7.0)	10 838 (3.7)
Other drugs to improve blood flow	216 (0.1)	250 (0.1)
Clonidine	2602 (1.7)	1787 (0.6)
Phosphodiesterase type 5 inhibitors	5183 (3.4)	4504 (1.5)
Triptans	7164 (4.7)	5298 (1.8)
Oral contraceptives	18 379 (12.0)	28 590 (9.7)
Hormones, menopausal	18 026 (11.8)	23 388 (8.0)
Health Care Utilization Within Past Year		
Cardiovascular visits		
Emergency, ≥1	5728 (3.7)	7697 (2.6)
Inpatient, ≥1	6022 (3.9)	7130 (2.4)
Physician, 1-4	43 474 (28.4)	65 256 (22.2)
Physician, ≥5	13 242 (8.7)	17 713 (6.0)
Psychiatric visits[f]		
Emergency, ≥1	4417 (2.9)	2897 (1.0)
Inpatient, ≥1	7761 (5.1)	3827 (1.3)
Physician, 1-4	43 538 (28.5)	26 703 (9.1)
Physician, ≥5	40 176 (26.3)	11 048 (3.8)
Other visits		
Emergency, ≥1	7885 (5.2)	9594 (3.3)
Inpatient, ≥1	5812 (3.8)	5595 (1.9)
Physician, ≥1	55 386 (36.2)	69 134 (23.5)
No. of different medications[g]		
1	24 309 (15.9)	61 193 (20.8)
≥2	108 955 (71.3)	116 680 (39.7)

Abbreviations: ACE, angiotensin-converting enzyme; ADHD, attention-deficit/hyperactivity disorder; COX-2, cyclooxygenase 2; IQR, interquartile range; MI, myocardial infarction; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Data are presented as No. (%) unless otherwise indicated.

[b] All variables in table included in cardiovascular risk score, except demographics and ADHD. Percentages are based on membership periods. There were 299 indeterminate and former users at baseline.

[c] Follow-up time based on combined end point (MI, sudden cardiac death, or stroke).

[d] Variables used to define history of cardiovascular disease for subgroup analyses in Figure 2.

[e] Including medications.

[f] Excluding ADHD visits.

[g] Excluding ADHD medications.

©2011 American Medical Association. All rights reserved.

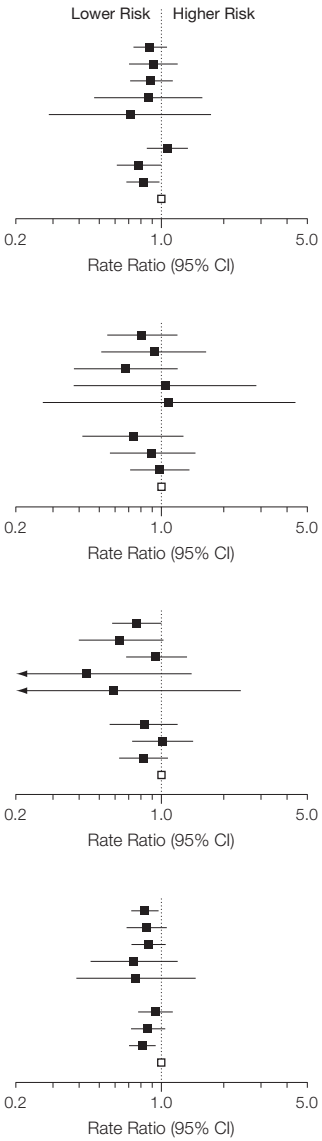
Downloaded From: http://jama.jamanetwork.com/ on 10/13/2015

Analyses Restricted to Users of ADHD Medications (Remote Use Comparison)

Among ever users of ADHD medications, the adjusted RR of serious cardiovascular events was nearly the same during periods of current use as during follow-up periods more than 1 year after use ended (RR, 1.03 [95% CI, 0.86-1.24]) (TABLE 2). This 1.24 estimated upper bound for the RR would correspond to an absolute risk difference of 0.17 serious cardiovascular events per 1000 person-years in adults aged 25 through 44 years (ages at which the absolute risk was only 0.87 per 1000 person-years) and of 0.68 serious cardiovascular events per 1000 person-years in adults aged 45 through 64 years (ages at which the absolute risk during current use was 3.5 per 1000 person-years).

Figure 1. Adjusted Rate Ratios for Serious Cardiovascular Events Associated With Use vs Nonuse of ADHD Medications

Outcome and ADHD Medication Use	Person-Years	No. of Events	Rate Ratio (95% CI)
MI			
Current use	113 324.2	152	0.88 (0.74-1.05)
Amphetamines	49 080.1	59	0.92 (0.70-1.19)
Methylphenidate	51 232.8	77	0.89 (0.71-1.13)
Atomoxetine	8424.8	11	0.87 (0.48-1.57)
Pemoline	3047.3	5	0.71 (0.29-1.71)
Multiple	1539.1	0	NA
Indeterminate use	53 896.7	86	1.07 (0.85-1.33)
Former use	47 858.5	65	0.78 (0.61-1.00)
Remote use	69 792.9	147	0.82 (0.68-0.97)
Nonuse	559 743.1	907	1 [Reference]
SCD			
Current use	107 525.0	32	0.80 (0.55-1.18)
Amphetamines	46 910.0	13	0.93 (0.52-1.63)
Methylphenidate	47 887.1	13	0.67 (0.38-1.18)
Atomoxetine	8257.6	4	1.04 (0.38-2.82)
Pemoline	2995.7	2	1.08 (0.27-4.37)
Multiple	1474.5	0	NA
Indeterminate use	51 814.0	14	0.73 (0.42-1.26)
Former use	46 263.5	20	0.90 (0.57-1.44)
Remote use	68 102.6	50	0.98 (0.71-1.35)
Nonuse	535 515.5	180	1 [Reference]
Stroke			
Current use	111 935.5	63	0.76 (0.58-1.00)
Amphetamines	48 672.9	19	0.63 (0.40-1.01)
Methylphenidate	50 332.3	39	0.94 (0.68-1.32)
Atomoxetine	8371.1	3	0.44 (0.14-1.38)
Pemoline	3030.1	2	0.59 (0.15-2.39)
Multiple	1529.2	0	NA
Indeterminate use	53 327.8	31	0.83 (0.57-1.19)
Former use	47 333.0	39	1.01 (0.73-1.41)
Remote use	69 202.3	67	0.82 (0.63-1.07)
Nonuse	553 458.5	375	1 [Reference]
MI, SCD, or stroke			
Current use	107 322.4	234	0.83 (0.72-0.96)
Amphetamines	46 826.5	88	0.85 (0.68-1.05)
Methylphenidate	47 792.3	120	0.87 (0.72-1.04)
Atomoxetine	8248.2	17	0.74 (0.46-1.19)
Pemoline	2985.2	9	0.75 (0.39-1.45)
Multiple	1470.1	0	NA
Indeterminate use	51 709.6	125	0.94 (0.78-1.13)
Former use	46 120.8	121	0.86 (0.72-1.04)
Remote use	67 489.0	243	0.81 (0.70-0.93)
Nonuse	533 540.4	1391	1 [Reference]



Rate ratios are adjusted for site, age, sex, calendar year, and cardiovascular risk score (some variables within score are time varying). ADHD indicates attention-deficit/hyperactivity disorder; MI, myocardial infarction; NA, not applicable; SCD, sudden cardiac death.

New-User Analyses

In the new-user cohort, baseline characteristics of new users of ADHD medication were generally similar to characteristics of all ADHD medication users (eTable 8). Cardiovascular diseases were similar or slightly more prevalent in new users than nonusers. ADHD and other psychiatric conditions were substantially more common in new users than in nonusers. In the new-user analyses, RRs for current vs remote use were close to 1.0 for MI, stroke, and the combined end point (TABLE 3). Although not statistically significant, RRs for methylphenidate were 1.26 (95% CI, 0.88-1.80) for MI, 1.44 (95% CI, 0.90-2.30) for stroke, and 1.20 (95% CI, 0.91-1.59) for the combined end point—somewhat higher than the RRs for the other drugs.

For the combined end point, there was no pattern of increasing risk with increasing duration of current use or for any window of time. For current use (all durations combined) vs remote use, the RR for the combined end point was 1.02. The upper bound of the CI was 1.28; this would amount to an additional 0.19 events per 1000 person-years at ages 25 through 44 years and an additional 0.77 events per 1000 person-years at ages 45 through 64 years.

Subgroup Analyses

Rate ratios were similar in all subgroup analyses (FIGURE 2 and eTable 9). Although we did observe differences in event rates, cohort characteristics, and RRs by data site, RRs for current use were not statistically significantly elevated at any site (eTables 10, 11, and 12).

Sensitivity Analyses—Unmeasured Confounding

Information from review of medical records of MI, SCD, and stroke cases and the external survey population suggested that several factors (obesity, smoking, family history of CVD) were not or were only very weakly associated with use of ADHD medications and there-

©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/13/2015

fore were unlikely to be important confounders. However, in these data, users of ADHD medications more often had some college education compared with nonusers (17% vs 10%, adjusting for age). In addition, 5% of the stimulant users were black or Hispanic vs 12% of the nonusers. If similar patterns for race/ethnicity and education were also present in our full study cohort, and if each of these characteristics independently multiplied the risk of serious cardiovascular events by 2.4, then these 2 unmeasured factors would yield a healthy-user bias substantial enough to account for an apparent RR of 0.83 (as in our comparison of current use vs nonuse), given a true RR of 1.0.

COMMENT

In our population-based cohort of more than 440 000 young and middle-aged adults, including more than 150 000 users of ADHD medications identified through filled prescriptions, we found no evidence of an increased risk of MI, SCD, or stroke associated with current use compared with nonuse or re-

Table 2. Adjusted Rate Ratios for Serious Cardiovascular Events Associated With Periods of Current Use of Attention-Deficit/Hyperactivity Disorder Medications vs Periods Remote From Last Use

Medication Status	Person-Years	No. of Events	Rate/1000 Person-Years	RR (95% CI) Unadjusted	Adjusted Matching-Variables[a]	Adjusted[b]
MI						
Current use	113 324.2	152	1.34	0.64 (0.51-0.80)	0.98 (0.78-1.23)	1.08 (0.86-1.36)
Amphetamines	49 080.1	59	1.20	0.57 (0.42-0.77)	0.99 (0.73-1.34)	1.12 (0.83-1.52)
Methylphenidate	51 232.8	77	1.50	0.71 (0.54-0.94)	1.00 (0.76-1.32)	1.10 (0.83-1.45)
Atomoxetine	8424.8	11	1.31	0.62 (0.34-1.14)	0.99 (0.54-1.84)	1.06 (0.57-1.96)
Pemoline	3047.3	5	1.64	0.78 (0.32-1.90)	0.87 (0.36-2.13)	0.87 (0.36-2.12)
Multiple	1539.1	0	0.00	NA	NA	NA
Indeterminate use	53 896.7	86	1.60	0.76 (0.58-0.99)	1.19 (0.91-1.56)	1.31 (1.00-1.71)
Former use	47 858.5	65	1.36	0.64 (0.48-0.86)	0.92 (0.68-1.23)	0.96 (0.71-1.28)
Remote use	69 792.9	147	2.11	1 [Reference]	1 [Reference]	1 [Reference]
SCD[c]						
Current use	107 525.0	32	0.30	0.41 (0.26-0.63)	0.79 (0.50-1.24)	0.82 (0.52-1.29)
Amphetamines	46 910.0	13	0.28	0.38 (0.21-0.69)	0.85 (0.46-1.58)	0.94 (0.51-1.76)
Methylphenidate	47 887.1	13	0.27	0.37 (0.20-0.68)	0.66 (0.36-1.23)	0.68 (0.37-1.27)
Atomoxetine	8257.6	4	0.48	0.66 (0.24-1.83)	1.14 (0.41-3.18)	1.06 (0.38-2.95)
Pemoline	2995.7	2	0.67	0.91 (0.22-3.74)	1.11 (0.27-4.59)	1.10 (0.27-4.56)
Multiple	1474.5	0	0.00	NA	NA	NA
Indeterminate use	51 814.0	14	0.27	0.37 (0.20-0.67)	0.70 (0.39-1.28)	0.74 (0.41-1.35)
Former use	46 263.5	20	0.43	0.59 (0.35-0.99)	0.94 (0.56-1.58)	0.92 (0.55-1.55)
Remote use	68 102.6	50	0.73	1 [Reference]	1 [Reference]	1 [Reference]
Stroke[d]						
Current use	111 935.5	63	0.56	0.58 (0.41-0.82)	0.90 (0.63-1.28)	0.93 (0.65-1.31)
Amphetamines	48 672.9	19	0.39	0.40 (0.24-0.67)	0.70 (0.42-1.18)	0.77 (0.46-1.29)
Methylphenidate	50 332.3	39	0.77	0.80 (0.54-1.19)	1.15 (0.77-1.72)	1.15 (0.77-1.72)
Atomoxetine	8371.1	3	0.36	0.37 (0.12-1.18)	0.55 (0.17-1.75)	0.54 (0.17-1.71)
Pemoline	3030.1	2	0.66	0.68 (0.17-2.78)	0.74 (0.18-3.04)	0.72 (0.18-2.96)
Multiple	1529.2	0	0.00	NA	NA	NA
Indeterminate use	53 327.8	31	0.58	0.60 (0.39-0.92)	0.96 (0.63-1.48)	1.01 (0.65-1.54)
Former use	47 333.0	39	0.82	0.85 (0.57-1.26)	1.24 (0.85-1.85)	1.23 (0.83-1.83)
Remote use	69 202.3	67	0.97	1 [Reference]	1 [Reference]	1 [Reference]
MI, SCD, or stroke[c,d]						
Current use	107 322.4	234	2.18	0.61 (0.51-0.72)	0.96 (0.80-1.15)	1.03 (0.86-1.24)
Amphetamines	46 826.5	88	1.88	0.52 (0.41-0.67)	0.93 (0.73-1.19)	1.05 (0.82-1.34)
Methylphenidate	47 792.3	120	2.51	0.70 (0.56-0.87)	1.01 (0.81-1.26)	1.07 (0.86-1.34)
Atomoxetine	8248.2	17	2.06	0.57 (0.35-0.94)	0.90 (0.55-1.48)	0.92 (0.56-1.50)
Pemoline	2985.2	9	3.01	0.84 (0.43-1.63)	0.95 (0.49-1.85)	0.93 (0.48-1.82)
Multiple	1470.1	0	0.00	NA	NA	NA
Indeterminate use	51 709.6	125	2.42	0.67 (0.54-0.83)	1.09 (0.88-1.35)	1.17 (0.94-1.45)
Former use	46 120.8	121	2.62	0.73 (0.59-0.91)	1.06 (0.85-1.32)	1.07 (0.86-1.33)
Remote use	67 489.0	243	3.60	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviations: MI, myocardial infarction; NA, not applicable; RR, rate ratio; SCD, sudden cardiac death.
[a] Adjusted for site, age, sex, and calendar year (ie, matching variables).
[b] Adjusted for site, age, sex, calendar year, and cardiovascular risk score (some variables within score are time varying).
[c] Analyses excluded the 3 Health Maintenance Organization Research Network (HMORN) sites (Fallon Community, Kaiser Permanente [KP] Georgia, KP Northwest) that did not provide data on SCD end points.
[d] Analyses excluded the 2 HMORN sites (Fallon Community, KP Georgia) that did not provide data on stroke end points.

©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/13/2015

mote use of ADHD medications. We also found little support for an increased risk with any specific medication or with longer duration of current use. Results were similar when users were restricted to new users. Rate ratios did not appear to be influenced by prior CVD or by prior non-ADHD psychiatric conditions. They also were similar across age groups. As expected, event rates were substantially higher in the Medicaid population; however, the RR for current use was similar to that in other sites.

Our study has several limitations. Use of ADHD medications was based on electronic pharmacy records of filled prescriptions. Filled prescriptions may

Table 3. Adjusted Rate Ratios for Serious Cardiovascular Events Associated With Periods of New Use of Attention-Deficit/Hyperactivity Disorder Medications vs Periods Remote From Last Use

Medication Status	Person-Years	No. of Events	Rate/1000 Person-Years	RR (95% CI) Unadjusted	Adjusted Matching-Variables[a]	Adjusted[b]
MI						
Current use	55 533.9	77	1.39	0.67 (0.50-0.89)	1.04 (0.77-1.39)	1.08 (0.81-1.45)
Amphetamines	23 265.6	24	1.03	0.50 (0.32-0.77)	0.86 (0.55-1.34)	0.94 (0.60-1.46)
Methylphenidate	23 930.8	42	1.76	0.84 (0.59-1.20)	1.23 (0.86-1.75)	1.26 (0.88-1.80)
Atomoxetine	6475.3	9	1.39	0.67 (0.34-1.31)	1.06 (0.54-2.10)	1.06 (0.54-2.10)
Pemoline	1114.4	2	1.79	0.86 (0.21-3.49)	0.76 (0.19-3.07)	0.75 (0.18-3.03)
Multiple	747.7	0	0.00	NA	NA	NA
Duration, d[c]						
1-30	7526.3	11	1.46	0.70 (0.38-1.30)	1.26 (0.68-2.33)	1.31 (0.70-2.43)
31-90	9656.8	11	1.14	0.55 (0.29-1.01)	1.01 (0.54-1.88)	1.06 (0.57-1.96)
91-182	9556.3	8	0.84	0.40 (0.20-1.47)	0.71 (0.35-1.47)	0.75 (0.36-1.53)
183-365	11 221.9	16	1.43	0.68 (0.41-1.15)	1.13 (0.67-1.92)	1.19 (0.70-2.01)
≥366	16 425.2	29	1.77	0.85 (0.56-1.27)	1.09 (0.72-1.64)	1.15 (0.76-1.73)
Indeterminate use	31 090.0	52	1.67	0.80 (0.58-1.11)	1.27 (0.92-1.77)	1.32 (0.95-1.84)
Former use	35 087.7	55	1.57	0.75 (0.55-1.04)	1.08 (0.78-1.49)	1.08 (0.78-1.49)
Remote use	55 194.2	115	2.08	1 [Reference]	1 [Reference]	1 [Reference]
SCD[d]						
Current use	52 203.2	15	0.29	0.34 (0.19-0.62)	0.61 (0.34-1.09)	0.62 (0.34-1.11)
Amphetamines	22 002.7	3	0.14	0.16 (0.05-0.53)	0.34 (0.11-1.10)	0.38 (0.12-1.22)
Methylphenidate	22 056.6	8	0.36	0.43 (0.20-0.92)	0.70 (0.33-1.50)	0.69 (0.32-1.46)
Atomoxetine	6348.4	3	0.47	0.57 (0.18-1.82)	0.95 (0.29-3.09)	0.90 (0.28-2.91)
Pemoline	1091.6	1	0.92	1.10 (0.15-7.96)	0.90 (0.12-6.63)	0.93 (0.13-6.77)
Multiple	703.9	0	0.00	NA	NA	NA
Duration, d[c]						
1-30	7217.4	2	0.28	0.33 (0.08-1.37)	0.67 (0.16-2.79)	0.68 (0.16-2.81)
31-90	9195.9	2	0.22	0.26 (0.06-1.07)	0.56 (0.13-2.30)	0.56 (0.14-2.33)
91-182	9026.0	4	0.44	0.53 (0.19-2.30)	1.09 (0.39-3.04)	1.11 (0.40-3.10)
183-365	10 511.3	1	0.10	0.11 (0.02-0.83)	0.22 (0.03-1.59)	0.22 (0.03-1.62)
≥366	15 129.8	5	0.33	0.40 (0.16-1.00)	0.57 (0.22-1.43)	0.57 (0.22-1.43)
Indeterminate use	29 752.7	13	0.44	0.52 (0.28-0.97)	0.94 (0.50-1.75)	0.96 (0.52-1.79)
Former use	33 877.6	16	0.47	0.57 (0.32-1.00)	0.89 (0.50-1.57)	0.88 (0.50-1.56)
Remote use	53 926.6	45	0.83	1 [Reference]	1 [Reference]	1 [Reference]
Stroke[e]						
Current use	54 569.3	41	0.75	0.73 (0.49-1.10)	1.10 (0.73-1.65)	1.09 (0.72-1.64)
Amphetamines	22 965.2	10	0.44	0.43 (0.22-0.83)	0.72 (0.37-1.41)	0.77 (0.39-1.53)
Methylphenidate	23 335.7	26	1.11	1.09 (0.68-1.73)	1.53 (0.96-2.45)	1.44 (0.90-2.30)
Atomoxetine	6429.4	3	0.47	0.46 (0.14-1.46)	0.66 (0.20-2.11)	0.64 (0.20-2.04)
Pemoline	1099.7	2	1.82	1.78 (0.43-7.28)	1.48 (0.36-6.08)	1.39 (0.34-5.72)
Multiple	739.3	0	0.00	NA	NA	NA
Duration, d[c]						
1-30	7421.0	4	0.54	0.53 (0.19-6.08)	0.93 (0.34-2.57)	0.92 (0.33-2.53)
31-90	9511.8	6	0.63	0.62 (0.27-1.43)	1.10 (0.47-2.57)	1.08 (0.46-2.51)
91-182	9398.0	9	0.96	0.94 (0.46-1.89)	1.59 (0.78-3.23)	1.55 (0.76-3.14)
183-365	11 018.6	4	0.36	0.35 (0.13-0.98)	0.56 (0.20-1.55)	0.55 (0.20-1.53)
≥366	16 087.6	16	0.99	0.97 (0.56-1.69)	1.19 (0.68-2.09)	1.21 (0.69-2.11)
Indeterminate use	30 657.1	20	0.65	0.64 (0.38-1.06)	1.00 (0.60-1.66)	1.0 (0.60-1.67)
Former use	34 644.6	26	0.75	0.73 (0.46-1.17)	1.05 (0.66-1.68)	1.04 (0.65-1.65)
Remote use	54 702.5	56	1.02	1 [Reference]	1 [Reference]	1 [Reference]

(continued)

 ©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/13/2015

Table 3. Adjusted Rate Ratios for Serious Cardiovascular Events Associated With Periods of New Use of Attention-Deficit/Hyperactivity Disorder Medications vs Periods Remote From Last Use (continued)

Medication Status	Person-Years	No. of Events	Rate/1000 Person-Years	RR (95% CI) Unadjusted	Adjusted Matching-Variables[a]	Adjusted[b]
MI, SCD, or stroke[d,e]						
Current use	52 094.6	125	2.40	0.65 (0.52-0.81)	1.00 (0.80-1.26)	1.02 (0.82-1.28)
Amphetamines	21 955.8	37	1.69	0.46 (0.32-0.65)	0.80 (0.56-1.13)	0.87 (0.61-1.23)
Methylphenidate	22 008.8	69	3.14	0.85 (0.65-1.12)	1.22 (0.92-1.60)	1.20 (0.91-1.59)
Atomoxetine	6340.4	14	2.21	0.60 (0.35-1.03)	0.93 (0.54-1.60)	0.91 (0.53-1.56)
Pemoline	1088.1	5	4.60	1.25 (0.51-3.03)	1.07 (0.44-2.61)	1.02 (0.42-2.49)
Multiple	701.4	0	0.00	NA	NA	NA
Duration, d[c]						
1-30	7215.7	16	2.22	0.60 (0.36-1.00)	1.08 (0.65-1.80)	1.10 (0.66-1.83)
31-90	9191.7	19	2.07	0.56 (0.35-0.90)	1.04 (0.65-1.66)	1.05 (0.66-1.69)
91-182	9018.3	18	2.00	0.54 (0.33-0.88)	0.96 (0.59-1.55)	0.97 (0.60-1.57)
183-365	10 494.1	20	1.91	0.52 (0.33-0.82)	0.85 (0.53-1.34)	0.86 (0.54-1.37)
≥366	15 055.5	47	3.12	0.85 (0.62-1.16)	1.06 (0.77-1.46)	1.10 (0.80-1.51)
Indeterminate use	29 694.2	82	2.76	0.75 (0.58-0.97)	1.19 (0.92-1.55)	1.22 (0.94-1.58)
Former use	33 774.3	97	2.87	0.78 (0.61-0.99)	1.13 (0.88-1.44)	1.11 (0.87-1.41)
Remote use	53 450.1	197	3.69	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviations: MI, myocardial infarction; NA, not applicable; RR, rate ratio; SCD, sudden cardiac death.
[a] Adjusted for site, age, sex, and calendar year (ie, matching variables).
[b] Adjusted for site, age, sex, calendar year, and cardiovascular risk score (some variables within score are time varying).
[c] Duration does not include pemoline use (pemoline only and pemoline with other attention-deficit/hyperactivity disorder medications).
[d] Analyses excluded the 3 Health Maintenance Organization Research Network (HMORN) sites (Fallon Community, Kaiser Permanente [KP] Georgia, KP Northwest) that did not provide data on SCD end points.
[e] Analyses excluded the 2 HMORN sites (Fallon Community, KP Georgia) that did not provide data on stroke end points.

not represent medications actually consumed, and days supply may not represent actual periods of use. Nonetheless, electronic pharmacy databases have been found to be excellent sources of information on drug use.[30] We did not obtain dose data and therefore could not examine if risk varied by this factor. Although we used a strict definition of current use, minimizing misclassification of this exposure, we had limited ability to assess medication adherence using standard definitions. Despite its large size, the study had only moderate power for several comparisons, including current vs remote use in the new-user analyses and in comparisons for individual drugs. The study did not include adults 65 years and older; therefore, results cannot be generalized to this age group.

We reviewed medical records and death certificates to confirm SCD and stroke diagnoses. However, records were unavailable for some of our electronically identified cases. We used an *ICD-9/ICD-10* code–based definition for these cases, and misclassification of some cases may have occurred. If nondifferential with respect to ADHD medication use, this misclassification would bias RRs toward the null.

The accuracy of ADHD diagnoses in adults from claims and encounter databases is limited. However, previous studies have validated *ICD 9/ICD-10* code–based definitions of many important covariates, including diabetes, congestive heart failure, peripheral vascular disease, and hypertension, reporting positive predictive values exceeding 90% for each condition.[31-33] Although we adjusted for numerous established and potential cardiovascular risk factors, there were some factors, primarily psychiatric conditions and medications, for which the prevalence was substantial in users of ADHD medications but rare in nonusers. Thus, we had limited ability to adjust for these variables. Important residual confounding by psychiatric conditions and medications seems unlikely, because most are not established risk factors for CVD, they were not or were only modestly related to risk in our cohort, and results were similar when we restricted analyses to participants with or to those without these psychiatric conditions or medication use.

There appears to be a modest amount of healthy-user bias influencing our RR comparisons of current use vs nonuse. Results are less prone to this bias when analyses are restricted to ever users of ADHD medications, and we compared periods of current use with follow-up periods remote from use. In these comparisons, the RR for serious cardiovascular events was 1.03 in the full cohort and 1.02 in new users, indicating that the incidence of these events while currently receiving ADHD medications is similar to the incidence during periods while not receiving these medications. In sensitivity analyses, we saw evidence for 2 potential sources of a modest amount of healthy-user bias: a higher percentage of users were white and college educated.

Clinical trials have provided limited information on the cardiovascular safety of ADHD medications, primarily because these trials have been too small to evaluate serious events such as MI, SCD, or stroke.[34,35] Postmarketing surveillance data from the Adverse Event Reporting System[2] and from the National Electronic Injury Surveillance System[36] have suggested a potential elevation in

©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/13/2015

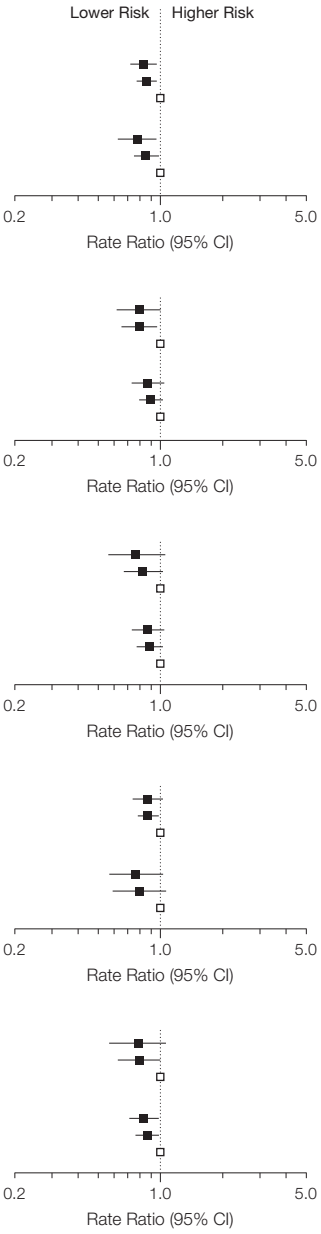
risk of serious cardiovascular events. However, with these surveillance systems, which capture only a small percentage of adverse events, false signals may occur if clinicians suspect, and are thus more likely to report, adverse events for a particular drug.

The findings of the current study were similar to those of our parallel study in youths aged 2 through 24 years, in which we found no evidence of increased risk for serious cardiovascular events in current users of ADHD medications compared with nonusers.[19] To our knowledge, only 2 pharmacoepidemiologic studies of ADHD medications and CVD in adults have reported results.[17,18] These studies, which were substantially smaller than ours, used electronic pharmacy records and medical encounter data, with similarly limited information on some potentially important risk factors. In one study, users of ADHD medications had a more than 3-fold higher rate of transient ischemic attacks but a 30% lower rate of cerebrovascular accidents, although the latter was not statistically significant.[17] In contrast, no increase in SCDs among children, adolescents, or young adults was observed in a second cohort study conducted in the General Practice Research Database.[18]

In conclusion, in this cohort of young and middle-aged adults, current or new use of ADHD medications identified from filled prescriptions, compared with nonuse or remote use, was not associated with an increased risk of serious cardiovascular events. A modestly elevated risk cannot be ruled out, given limited power and a lack of complete information on some potentially important risk factors and other factors related to use of these medications.

Figure 2. Subgroup Analyses for Combined End Point (Myocardial Infarction, Sudden Cardiac Death, or Stroke), Use vs Nonuse of ADHD Medications

Subgroup and ADHD Medication Use	Person-Years	No. of Events	Rate Ratio (95% CI)
Cohort			
Full			
Current use	107 322.4	234	0.83 (0.72-0.95)
Past use	165 319.4	489	0.85 (0.77-0.95)
Nonuse	533 540.4	1391	1 [Reference]
New-user			
Current use	52 094.6	125	0.77 (0.63-0.94)
Past use	116 918.7	376	0.85 (0.75-0.98)
Nonuse	317 514.4	957	1 [Reference]
History of CVD			
No			
Current use	70 748.1	79	0.79 (0.62-1.00)
Past use	106 497.1	148	0.79 (0.65-0.95)
Nonuse	391 881.9	562	1 [Reference]
Yes			
Current use	36 574.2	155	0.87 (0.73-1.03)
Past use	58 822.3	341	0.89 (0.79-1.01)
Nonuse	141 658.5	829	1 [Reference]
Non-ADHD psychiatric conditions			
No			
Current use	28 355.6	43	0.76 (0.56-1.04)
Past use	49 324.2	103	0.82 (0.67-1.01)
Nonuse	407 981.5	884	1 [Reference]
Yes			
Current use	78 966.8	191	0.87 (0.73-1.03)
Past use	115 995.3	386	0.88 (0.77-1.01)
Nonuse	125 558.9	507	1 [Reference]
ADHD diagnosis			
No			
Current use	69 757.4	177	0.86 (0.74-1.01)
Past use	131 054.7	434	0.87 (0.78-0.97)
Nonuse	385 962.7	1113	1 [Reference]
Yes			
Current use	37 564.9	57	0.76 (0.57-1.01)
Past use	34 264.7	55	0.79 (0.59-1.05)
Nonuse	152 357.3	283	1 [Reference]
Age, y			
25-44			
Current use	54 106.9	47	0.78 (0.57-1.06)
Past use	85 786.7	102	0.79 (0.63-1.00)
Nonuse	271 667.1	250	1 [Reference]
45-64			
Current use	53 215.5	187	0.83 (0.71-0.97)
Past use	79 532.7	387	0.86 (0.76-0.97)
Nonuse	261 873.3	1141	1 [Reference]



Rate ratios are adjusted for site, age, sex, calendar year, and cardiovascular risk score (some variables within score are time varying), except for new users (adjusted for propensity score). ADHD indicates attention-deficit/hyperactivity disorder; CVD, cardiovascular disease.

Published Online: December 12, 2011. doi:10.1001/jama.2011.1830

Author Contributions: Dr Habel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Habel, Cooper, Sox, Chan, Fireman, Cheetham, Ray, Selby.
Acquisition of data: Habel, Cooper, Sox, Chan, Cheetham, Quinn, Dublin, Boudreau, Andrade, Pawloski, Raebel, Smith, Uratsu, Selby.
Analysis and interpretation of data: Habel, Cooper, Sox, Chan, Fireman, Arbogast, Cheetham, Quinn, Achacoso, Uratsu, Go, Sidney, Nguyen-Huynh, Ray, Selby.
Drafting of the manuscript: Habel.
Critical revision of the manuscript for important intellectual content: Cooper, Sox, Chan, Fireman, Arbogast, Cheetham, Quinn, Dublin, Boudreau, Andrade, Pawloski, Raebel, Smith, Achacoso, Uratsu, Go, Sidney, Nguyen-Huynh, Ray, Selby.
Statistical analysis: Cooper, Fireman, Arbogast, Achacoso, Uratsu.
Obtained funding: Habel, Cooper, Chan, Quinn, Selby.
Administrative, technical, or material support: Chan, Quinn, Andrade, Achacoso, Uratsu, Selby.
Study supervision: Habel, Cooper, Sox, Chan, Quinn, Andrade, Smith.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Habel reported receiving grants from Merck for a study of herpes zos-

 ©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/13/2015

ter in patients with cancer, from Takeda for a study of pioglitazone and cancer, and from sanofi-aventis for a study of insulin and cancer. Dr Chan reported receiving support for travel to meetings for the purpose of the study or other purposes from the US Food and Drug Administration (FDA) and that he is a part-time employee of OptumInsight, a for-profit company that receives funding from medical product manufacturers to provide consultation and conduct research on medical products; because OptumInsight is a part of UnitedHealthGroup, Dr Chan has received UnitedHealthGroup stock options. Dr Dublin reported receiving a Merck/American Geriatrics Society New Investigator Award (honorarium paid directly to Dr Dublin) for unrelated work. Dr Andrade reported that the Meyers Primary Care Institute has received funding from GlaxoSmithKline and Novartis Pharmaceuticals, manufacturers of medications used to treat ADHD. Dr Smith reported that the Center for Health Research received funding from Abbott Laboratories to conduct a natural history study of patients with chronic kidney disease and from GlaxoSmithKline to study the burden of diabetes. Dr Sidney reported receiving grants or grants pending from the National Heart, Lung, and Blood Institute, the National Institute of Neurological Disorders and Stroke, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Thrasher Research Fund. Dr Nguyen-Huynh reported receiving grants or grants pending from the American Heart Association. No other authors reported disclosures.

Funding/Support: This project was funded in part under contract numbers HHSA290-2005-0042 (Vanderbilt) and HHSA290-2005-0033 (Harvard Pilgrim Health Care Institute) from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services, as part of the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) program. The project was also funded by the FDA under contracts 223-2005-10012 (Kaiser Permanente Northern California), 223-2005-10100C (Vanderbilt), 223-2005-20006C (Ingenix), and 223-2005-10012C (Harvard Pilgrim Health Care Institute). The project was also funded by the National Institute on Aging under contract K23AG028954 (Group Health Research Institute).

Role of the Sponsors: Individuals from the AHRQ and FDA were on the study Steering Committee and provided input into the study design and conduct of the study and interpretation of the data. The AHRQ and FDA had no role in the preparation, review, or approval of the manuscript.

Disclaimer: The authors of this article are responsible for its content. Statements in the article should not be construed as endorsement by the AHRQ or the US Department of Health and Human Services.

Online-Only Material: The eMethods, eTables 1-12, and the Author Video Interview are available at http://www.jama.com.

Additional Contributions: We acknowledge and thank the following individuals for their contributions to this project: Andrew Mosholder, MD (FDA), member of Scientific Steering Committee; James Daugherty, MS, and Judith Dudley, BS (Vanderbilt University School of Medicine), programming; Chantal Avila, MA (Kaiser Permanente Southern California), project management; Yan Luo, PhD, and Wansu Chen, MS (Kaiser Permanente Southern California), programming; Mary Kershner, BSN (Kaiser Permanente Colorado), chart reviews and abstraction; April Duddy, MS (Harvard Pilgrim Health Care Institute), project management; Luana Acton, BS, Julie Munneke, BA, and Heidi Krause, BA (Kaiser Permanente Northern California), project management; and Jean Lee, BA, and Monica Highbaugh, AA (Kaiser Permanente Northern California), medical record retrieval and abstraction. All individuals acknowledged were compensated for their time.

REFERENCES

1. New Report: America's State of Mind. Medco Web site. http://medco.mediaroom.com/. 2011. Accessed November 16, 2011.

2. Food and Drug Administration. Drug Safety and Risk Management Advisory Committee meeting. http://www.fda.gov/ohrms/dockets/ac/cder06.html#DrugSafetyRiskMgmt. Food and Drug Administration Web site. February 9-10, 2006. Accessed November 21, 2011.

3. Montejano L, Sasané R, Hodgkins P, Russo L, Huse D. Adult ADHD: prevalence of diagnosis in a US population with employer health insurance. *Curr Med Res Opin*. 2011;27(suppl 2):5-11.

4. Wilens TE, Morrison NR, Prince J. An update on the pharmacotherapy of attention-deficit/hyperactivity disorder in adults. *Expert Rev Neurother*. 2011;11(10):1443-1465.

5. Challman TD, Lipsky JJ. Methylphenidate: its pharmacology and uses. *Mayo Clin Proc*. 2000;75(7):711-721.

6. Leddy JJ, Epstein LH, Jaroni JL, et al. Influence of methylphenidate on eating in obese men. *Obes Res*. 2004;12(2):224-232.

7. Frierson RL, Wey JJ, Tabler JB. Psychostimulants for depression in the medically ill. *Am Fam Physician*. 1991;43(1):163-170.

8. Tharwani HM, Yerramsetty P, Mannelli P, Patkar A, Masand P. Recent advances in poststroke depression. *Curr Psychiatry Rep*. 2007;9(3):225-231.

9. Warden DL, Gordon B, McAllister TW, et al; Neurobehavioral Guidelines Working Group. Guidelines for the pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury. *J Neurotrauma*. 2006;23(10):1468-1501.

10. Hammerness PG, Surman CB, Chilton A. Adult attention-deficit/hyperactivity disorder treatment and cardiovascular implications. *Curr Psychiatry Rep*. 2011;13(5):357-363.

11. Stiefel G, Besag FM. Cardiovascular effects of methylphenidate, amphetamines and atomoxetine in the treatment of attention-deficit hyperactivity disorder. *Drug Saf*. 2010;33(10):821-842.

12. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360(9349):1903-1913.

13. Gould MS, Walsh BT, Munfakh JL, et al. Sudden death and use of stimulant medications in youths. *Am J Psychiatry*. 2009;166(9):992-1001.

14. Winterstein AG, Gerhard T, Shuster J, Johnson M, Zito JM, Saidi A. Cardiac safety of central nervous system stimulants in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics*. 2007;120(6):e1494-e1501.

15. Schelleman H, Bilker WB, Strom BL, et al. Cardiovascular events and death in children exposed and unexposed to ADHD agents. *Pediatrics*. 2011;127(6):1102-1110.

16. Winterstein AG, Gerhard T, Shuster J, Saidi A. Cardiac safety of methylphenidate versus amphetamine salts in the treatment of ADHD. *Pediatrics*. 2009;124(1):e75-e80.

17. Holick CN, Turnbull BR, Jones ME, Chaudhry S, Bangs ME, Seeger JD. Atomoxetine and cerebrovascular outcomes in adults. *J Clin Psychopharmacol*. 2009;29(5):453-460.

18. McCarthy S, Cranswick N, Potts L, Taylor E, Wong IC. Mortality associated with attention-deficit hyperactivity disorder (ADHD) drug treatment: a retrospective cohort study of children, adolescents and young adults using the general practice research database. *Drug Saf*. 2009;32(11):1089-1096.

19. Cooper WO, Habel LA, Sox CM, et al. ADHD drugs and serious cardiovascular events in children and young adults. *N Engl J Med*. 2011;365(20):1896-1904.

20. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol*. 2000;36(3):959-969.

21. Meier MA, Al-Badr WH, Cooper JV, et al. The new definition of myocardial infarction: diagnostic and prognostic implications in patients with acute coronary syndromes. *Arch Intern Med*. 2002;162(14):1585-1589.

22. Chung CP, Murray KT, Stein CM, Hall K, Ray WA. A computer case definition for sudden cardiac death. *Pharmacoepidemiol Drug Saf*. 2010;19(6):563-572.

23. Miettinen OS. Stratification by a multivariate confounder score. *Am J Epidemiol*. 1976;104(6):609-620.

24. Arbogast PG, Ray WA. Use of disease risk scores in pharmacoepidemiologic studies. *Stat Methods Med Res*. 2009;18(1):67-80.

25. Glynn RJ, Schneeweiss S, Stürmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol*. 2006;98(3):253-259.

26. Suissa S, Edwardes MD. Adjusted odds ratios for case-control studies with missing confounder data in controls. *Epidemiology*. 1997;8(3):275-280.

27. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf*. 2006;15(5):291-303.

28. Schneeweiss S, Glynn RJ, Tsai EH, Avorn J, Solomon DH. Adjusting for unmeasured confounders in pharmacoepidemiologic claims data using external information: the example of COX2 inhibitors and myocardial infarction. *Epidemiology*. 2005;16(1):17-24.

29. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol*. 2003;158(9):915-920.

30. West SL, Strom BL, Polle C. Validity of pharmacoepidemiologic drug and diagnosis data. In: Strom BL, ed. *Pharmacoepidemiology*. Philadelphia, PA: John Wiley & Sons Ltd; 2005:709-765.

31. de Burgos-Lunar C, Salinero-Fort MA, Cárdenas-Valladolid J, et al. Validation of diabetes mellitus and hypertension diagnosis in computerized medical records in primary health care. *BMC Med Res Methodol*. 2011;11:146.

32. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of *ICD-10* diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011;11:83.

33. Grijalva CG, Chung CP, Stein CM, et al. Computerized definitions showed high positive predictive values for identifying hospitalizations for congestive heart failure and selected infections in Medicaid enrollees with rheumatoid arthritis. *Pharmacoepidemiol Drug Saf*. 2008;17(9):890-895.

34. Adler LA, Zimmerman B, Starr HL, et al. Efficacy and safety of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, double-blind, parallel group, dose-escalation study. *J Clin Psychopharmacol*. 2009;29(3):239-247.

35. Peterson K, McDonagh MS, Fu R. Comparative benefits and harms of competing medications for adults with attention-deficit hyperactivity disorder: a systematic review and indirect comparison meta-analysis. *Psychopharmacology (Berl)*. 2008;197(1):1-11.

36. Cohen AL, Jhung MA, Budnitz DS. Stimulant medications and attention deficit-hyperactivity disorder. *N Engl J Med*. 2006;354(21):2294-2295.

©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/13/2015