U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL SAFETY REVIEW AND EVALUATION

OBSERVATIONAL STUDIES

NDA/Serial Number:	N/A-Drug Class Review-Link TSI#114: SAFETY-000114 Attention Deficit Hyperactivity Disorder Drugs Safety Issue: cardiovascular disorders in young and middle-aged adults
Drug Name:	Multiple treatments for attention deficit hyperactivity disorder (ADHD)
Applicant:	N/A
Document Review	ADHD Medications and Risk of Serious Coronary Heart Disease in Young and Middle-Aged Adults (April 29, 2011)
	ADHD Medications and Risk of Stroke in Young and Middle-Aged Adults (July 22, 2011)
Date(s):	November 15, 2011
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Keywords:

Observational study, propensity scores, confounder risk score, prevalent-user bias, ADHD medications, sudden cardiac death, stroke, myocardial infarction

Table of Contents

List of Tables

List of Figures

1 Executive Summary

Concerns have been raised that the medication used to manage attention deficit hyperactivity disorder (ADHD) is potentially associated with an increase in cardiovascular adverse events. To investigate the possible association, the Food and Drug Administration (FDA) and the Agency for Healthcare Research and Quality (AHRQ) co-funded separate studies in children and adults, which relied on data from computerized health records across multiple healthcare sites. This statistical review focuses solely on findings from the adult ADHD study. Cardiovascular endpoints investigated in the adult study were acute myocardial infarction (AMI), stroke and sudden cardiac death (SCD). Results from the adult study were submitted to FDA in two separate study reports. One study report presented results for the AMI and SCD endpoints, and the composite AMI or SCD endpoint (defined hereafter as AMI/SCD) endpoint; the other study report presented results for the stroke endpoint and composite AMI, SCD or stroke endpoint (defined hereafter as AMI/SCD/stroke).

The adult study used a retrospective cohort design to compare risk in adult subjects of age 25 to 64 who received an ADHD medication (current users and non-current users) to those who did not (non-users).

For the AMI endpoint 11 healthcare sites provided 844,615 patient-years of follow-up from 443,198 unique subjects. Analyses for the other endpoints were based on data from fewer sites with less overall follow-up.

The unadjusted event rates for current users, per 1,000 patient-years, were 1.34, 0.30, and 0.56 for AMI, SCD and stroke, respectively, and 1.62 and 2.18 for the composite endpoints AMI/SCD and AMI/SCD/stroke, respectively. The unadjusted event rates for non-users, per 1,000 patient-years, were 1.62, 0.34, and 0.68 for AMI, SCD and stroke, respectively, and 1.95 and 2.61 for the composite endpoints AMI/SCD and AMI/SCD/stroke, respectively.

The propensity score adjusted risks estimates were lower but not statistically significantly different for current users (incident and prevalent users) compared to non-users for AMI (RR=0.83; 95% CI = 0.69, 1.00), SCD (RR=0.83; 95% CI = 0.55, 1.25) and stroke (RR=0.75; 95% CI=0.55, 1.00), and statistically significantly lower for the composite endpoints AMI/SCD (RR=0.83; 95% CI = 0.69, 0.99) and AMI/SCD/stroke (RR=0.81; 95% CI=0.69, 0.94).

In the incident user analysis, which excluded prevalent ADHD users from the sample, the propensity score adjusted risks estimates were lower but not statistically significantly different for current users compared to non-users for AMI (RR=0.77; 95% CI = 0.59, 1.00), SCD (RR=0.62; 95% CI = 0.35, 1.10) and stroke (RR=0.89; 95% CI=0.61, 1.28), and statistically significantly lower for current users compared to non-users for AMI/SCD (RR= 0.74; 95% CI = 0.58, 0.94) and AMI/SCD/stroke (RR=0.77; 95% CI=0.63, 0.94).

Event rates and relative risks varied across healthcare sites. The only public healthcare site included in this study, Tennessee Medicaid, had event rates and comparative risks that differed from those derived from the private healthcare sites. Reasons for these patterns can not be determined from the data submitted. It is possible that the differences arose from underlying differences in data collection and quality as well as known and unknown health disparities between the Medicaid and non-Medicaid populations.

Beyond data quality limitations inherent in observational studies that use computerized healthcare records, the study design has the potential for generating biased results arising from the inclusion of ADHD medication users that received the medication prior to becoming cohort eligible (i.e., prevalent users). Specific biases prevalent users may introduce include an under ascertainment of events that occur early in therapy and the inability to control for disease risk factors that could be altered by the drug therapy (Ray, Am J of Epi, 2003; 159 (9)). The potential for prevalent user bias is notable since 51.0% of the person-time among current users was contributed by prevalent users. The incident user sensitivity analysis that compares incident users to non-users is considered the most credible analysis performed since it is not vulnerable to prevalent user bias.

The broad patient inclusion criteria, which did not require a diagnosis of ADHD, resulted in a non-user comparison group that may not yield clinically relevant comparisons as this group is characteristically different from the ADHD medication users. Differences in healthcare utilization between users and non-users may have also resulted in differential coding since it is more likely that a user was more recently (and perhaps more frequently) treated by a healthcare provider than a non-user. This difference can result in the non-users appearing ‘healthier’ at baseline than the user group due to a lack of reported medical conditions.

The final study reports lack sufficient details required to fully evaluate the study results and conclusions. These include, but are not limited to, a lack of statistical diagnostics necessary to assess measured baseline covariate balance and model fit, and an inadequate description of the study cohort.

In conclusion, findings across various analyses do not suggest an increase in cardiovascular and stroke risk associated with ADHD medication use compared to non-use. Study findings, however, should be interpreted within the confines of the study design limitations and the sub-optimal data-streams. Because of these concerns, the reviewer recommends against comparative or statistical assessments of cardiovascular and stroke risk associated with ADHD medication exposure using findings from this study. This recommendation extends to findings from the incident user analyses since the results could not be fully evaluated due to a lack of diagnostic information.

2 Introduction

2.1 Overview

Concerns have been raised that the medications used to treat attention deficit hyperactivity disorder (ADHD) may be associated with an increase in cardiovascular (CV) adverse events. In

2006, FDA and AHRQ co-sponsored a retrospective cohort study in children and a separate study in adults to investigate the possible association between exposure to ADHD medications and CV outcomes (specifically the occurrence of sudden cardiac death, acute myocardial infarction and stroke) using medical health records from multiple healthcare sites. Results from the adult study were presented to FDA in two study reports with results presented according to the study endpoint. The study report for the endpoints acute myocardial infarction (AMI) and sudden cardiac death (SCD) was submitted to FDA on April 29, 2011. The final report including the stroke endpoint was submitted to FDA on July 22, 2011. This review covers final results from both reports.

The Office of Surveillance and Epidemiology (OSE) submitted two statistical safety consult requests to the Division of Biometrics 7. The first, received March 4, 2009, asked for comments on the child study's finalized statistical analysis plan described in the study protocol (version 4.3, date: 10/31/2008; review completed June 12, 2009). The adult study analysis plan was similar to the child study and therefore was not separately reviewed. The second consult, received September 15, 2010, requested continued DB7 participation on the study team, and to provide comments and review the draft and final study reports.

This review is a complete and thorough statistical evaluation of the adult ADHD study reports. A separate review for the child study was completed and submitted to DARRTS on September 28, 2011 (addendum completed on November 3, 2011).

2.2 Data Sources

On April 29, 2011 the principal investigator for the adult ADHD study (Dr. Laurie Habel, Kaiser Permanente) submitted to FDA the AMI-SCD final study report entitled "ADHD Medications and Risk of Serious Coronary Heart Disease in Young and Middle-Aged Adults". On July 22, 2011 FDA received the adult stroke study report entitled "ADHD Medications and Risk of Stroke in Young and Middle-Aged Adults." This review additionally references the draft study report (AMI-SCD, date: 11/30/2010; stroke, date: 07/08/2011), study protocol (version 9.0, 9/18/2008) and information requested by FDA based on draft study reports.

Statistical Comment: Subject-level study data were not submitted to FDA; therefore, the study results could not be fully evaluated and replicated.

3 Statistical Evaluation

3.1 Data Analysis and Quality

Data were not submitted for review and therefore the quality of data can not be assessed.

3.2 Evaluation of Safety

3.2.1 Study Design

The study used a retrospective cohort design using computerized health record data from the following sites: Tennessee State Medicaid, Kaiser Permanente (KP) Northern California, KP Southern California, Ingenix i3 and the HMO Research Network (HMORN), which is comprised

of Harvard Pilgrim Health (Boston, MA), Fallon Community Health Plan (Worcester, MA), Group Health Cooperative of Puget Sound (Seattle, WA), HealthPartners (Minneapolis, MN), KP Georgia (Atlanta GA), KP Northwest (Portland, OR), and KP Colorado (Denver, CO). Overall, there were eleven sites used in this study. The follow-up interval differed by site based on the earliest availability computerized data, as shown in Table 1. Note: No attempt to standardize the study periods across sites (i.e. use only data from 2001-2005 for all sites) was made in the adjusted analyses.

Table 1. Study Period by Site

Site	Study Period
Tennessee Medicaid	1986-2005
KP California	
Northern Region	1998-2005
Southern Region	2001-2005
Ingenix i3	1998-2005
HMORN	1998-2005

† Source: Study protocol, Table 4

The cohort of eligible person-time was assembled from the enrollees of each health plan who were age 25 to 64 with at least 12 months of continuous health plan coverage and pharmacy benefits. Subjects were excluded if they had one of the following diagnoses 365 days prior to becoming cohort eligible: sickle cell disease, cancer diagnosis (other than non-melanoma skin cancer), HIV infection, organ transplant, liver failure or hepatic coma, end-stage renal disease, respiratory failure or severe congestive heart failure.

The study protocol specified the end of cohort eligibility as the earliest of the following dates: 1) the last day of the study December 31, 2005, 2) day prior to the 65th birthday, 3) the last day of membership of pharmacy benefits in a plan, 4) the day prior to development of an exclusion illness, 5) the day of death, or 6) the day of occurrence of a study endpoint. *Note that the AMI-SCD report did not specify the 4th point as a condition for ending cohort eligibility. The stroke report did not list reasons, including medical conditions, for ending cohort eligibility.*

The sample included all subjects with eligible patient-time of ADHD medication use. Follow-up for a subject began at their earliest cohort eligible day of ADHD medication use, defined as t_0 and referred to in this review as baseline. Subjects that received an ADHD medication prior to becoming cohort eligible were included in the sample and referred to as prevalent users. The formation of the cohort was done in chronological sequence starting at the earliest calendar day of cohort eligible ADHD medication use. Within site, a random sample of person-time from two subjects with no evidence of ADHD medication use on that date were matched at t_0 using age (year of birth) and gender. Subjects matched to an ADHD medication user were referred to as non-users. The pool of possible non-users included subjects who might eventually use an ADHD medication; this allowed a non-user to switch use status and become an ADHD medication user. In the event of a switch from non-use to use status, that subject was then matched to two subjects who had no evidence of ADHD medication use on the day of the switch.

The design permitted a subject that lost cohort eligibility (e.g., developed a serious illness) to contribute additional patient-time after regaining cohort eligibility. For an ADHD user that re-entered the cohort, he/she would be matched to two non-users at the day of cohort re-entry.

Reviewer's Comments: Two design choices that were made to maximize available exposed person-time were the inclusion of prevalent users and having varying site eligibility periods. This strategy, in the case of prevalent users, was done at the known expense of making the sample (thereby, comparisons) susceptible to bias. Because of this the protocol specified a sensitivity analysis limited to incident ADHD medication users. No sensitivity analysis was performed that standardized the eligibility periods across the healthcare sites (i.e., 2001-2005).

The biases associated with prevalent user designs are well described in the epidemiologic literature. In general, inclusion of prevalent users is not recommended as it can result in under ascertainment of the events that occur early in therapy prior to gaining cohort eligibility and the inability to control for disease risk factors that are altered by the drug therapy (R. Way, Am. J. Epidemiology 2003; 915-920). In this study, the potential for prevalent user bias is of concern since 51.0% of the patient-time contributed by current users was from prevalent users.

Because overall eligibility was not limited to subjects with medical diagnoses associated with receiving an ADHD medication (e.g., ADHD) the user and non-user populations were systematically different. These differences could confound the observed association of ADHD medication and the outcomes. The study report noted the difficulty of obtaining an appropriate population of medication users and stated in the study protocol (page 27) "the ideal comparison group would be patients with the same indications (ADHD, etc.) who were never exposed to psychostimulants. However, this group is likely to be quite small, particularly because recording the diagnosis of ADHD is likely to be more frequent when a drug is given".

There is a large possibility of differential health care utilization between users and non-users resulting in differential coding of patient characteristics. It is more likely that a user was more recently (and possibly more frequently) treated by a healthcare provider than a non-user. This can result in the non-users appearing 'healthier' at baseline than the user group due to a lack of reported medical conditions.

Exposure Status

Every person-day during the study observation period was classified according to probable use of an ADHD medication. Table 2 provides the definition of the four categories of ADHD use status per study report. *Note that the period descriptions for indeterminate and former users differ in the AMI-SCD study report compared to the study protocol (page 27) and stroke study report. Specifically, the study protocol and stroke report defined indeterminate use ending 89 days after last use while the AMI-SCD report specified indeterminate use ending 30 after last use.* Subjects that stopped using an ADHD medication were considered non-current users (i.e., indeterminate, former or remote users). For each ADHD drug prescription, the estimated days of use was derived from days supply added to the prescription fill date. Overlapping dates of use for the same or different ADHD medication allowed up to 7 days of cumulative stockpiling, under the assumption that the overlapping did not represent current use.

Table 2. Classification of ADHD use status

ADHD use status	Period Description
Study protocol and stroke study report	
Current use	Time between the prescription start date and the end of the days supply
Indeterminate use	Day after current use and lasting for ***89*** days
Former use	Between ***90*** and 365 days after last day of current use
Remote	366 days after last day of current use through the end of study follow-up
AMI-SCD study report	
Current use	Time between the prescription start date and the end of the days supply
Indeterminate use	Day after current use and lasting for ***30*** days
Former use	Between ***31*** and 365 days after last day of current use
Remote	366 days after last day of current use through the end of study follow-up

Study Endpoints

The study endpoints included: AMI requiring hospital admission, stroke and SCD. Composite endpoints of AMI or SCD (hereafter referred to as AMI/SCD), and AMI, SCD or stroke (hereafter referred to as AMI/SCD/stroke) were also evaluated. The composite endpoints of AMI or stroke and SCD or stroke were not investigated. The stroke study report presented results for all endpoints that included stroke (i.e., stroke and AMI/SCD/stroke); the AMI-SCD report presented results for AMI, SCD and AMI/SCD. A subject could experience more than one of the individual study endpoints. However, at most one event per subject was contributed to the composite endpoint.

Not all sites contributed to data for all endpoints, as shown in Table 3. While the objective of the study was not to compare risk across endpoints, lack of consistent data across sites prohibits any direct comparison of risk estimates across endpoints. All 11 sites contributed data for the AMI endpoint, while 3 HMORN sites (Fallon Community Health Plan, Kaiser Georgia and Kaiser Northwest) did not contribute data for the SCD endpoint, and two of these sites did not contribute to the stroke endpoint (Fallon Community Health Plan and Kaiser Georgia). A sensitivity analysis of the eight sites that provided data for all five endpoints was not performed.

Potential events were adjudicated by at least two adjudicators according to a predefined clinical definition. Case status for potential events with medical records that could not be adjudicated was determined by a computer case definition. The stroke endpoint was investigated according to overall, ischemic, hemorrhagic and all strokes excluding only those adjudicated as non-cases.

Table 3. Study sites contributing data for each study endpoint

Site	AMI	SCD	Stroke	AMI/SCD	AMI/SCD/Stroke
Tennessee Medicaid	Y	Y	Y	Y	Y
KP N. CA	Y	Y	Y	Y	Y
KP S. CA	Y	Y	Y	Y	Y
Ingenix i3	Y	Y	Y	Y	Y
Harvard Pilgrim	Y	Y	Y	Y	Y
Fallon Community	Y	-	-	-	-
Group Health	Y	Y	Y	Y	Y
HealthPartners	Y	Y	Y	Y	Y
KP Georgia	Y	-	-	-	-
KP Northwest	Y	-	Y	-	-
KP Colorado	Y	Y	Y	Y	Y

KP-Kaiser Permanente

Reviewer Comment: While there was no stated hypothesis, the primary study aim was to examine whether medications used primarily to treat ADHD are associated with an increased risk of serious coronary heart disease in adults 25-64 years of age.

3.2.2 Statistical Methodology

The adjusted incidence of the study endpoints were compared across levels of ADHD medication use status using Poisson regression. Three different confounder adjustment strategies were employed across the study endpoints, as shown in Table 4. Details of the different adjustment strategies are provided below. FDA requested that propensity score (PS) be used as an alternate approach to confounder risk scores (CRS) due to the method having been shown to have unfavorable statistical performance characteristics. The PS adjusted analysis is the statistical reviewer's preferred analytic strategy.

Table 4. Confounder adjustment strategy by endpoint

	Confounder Adjustment Strategy		
Endpoint	Covariate	CRS	PS
AMI	-	Y	Y
SCD	-	Y	Y
stroke	Y	Y	Y
AMI/SCD	-	Y	Y
AMI/SCD/stroke	Y	Y	Y

CRS-confounder risk score; PS-propensity score. Dash represents adjustment strategy not evaluated for the endpoint

Covariates that were included in all regression models, irrespective of adjustment strategy, were time-varying ADHD medication use status, site, age categories (25-30, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64), gender, and calendar year (1986-92, 1993-99, 2000-1, 2002-3, 2004-5). Non-users served as the primary reference group.

Covariate Adjusted

In addition to the covariates listed above, the covariate adjusted analysis included the number of different non-ADHD medication in the year prior to t_0 (0,1,2,3,4,5,6,7-8,9-10,11+) and dichotomous variables that were considered risk factors for stroke. Risk factors for stroke include the following covariates: AMI, anticoagulants, platelet inhibitors, hypertension, prior stroke/TIA, peripheral vascular disease, obesity, smoking, diabetes, hyperlipidemia, alcohol/substance abuse, triptan use, oral contraceptives and menopausal hormones. *Note: From the report it is unclear whether these dichotomous variables were treated as fixed at baseline or were time-varying.*

Several covariates (not including those that were considered risk factors for stroke) were considered for inclusion into the statistical model if, when included, it resulted in a change in the estimated rate ratio larger than 10% for ADHD medication. The only covariate that satisfied this criterion was *the number of different non-ADHD medication in the year prior to t_0.*

Confounder Risk Score

For each endpoint, separate CRS were estimated from a Poisson regression model that included as covariates the matching variables (i.e., site, age, gender), ADHD medication status (time-varying), claims or prescription in the 365 days preceding t_0 and time-varying covariates. The CRS model included over 100 covariates. Refer to the study reports for the variable listing (AMI-SCD, page 11). The CRS was defined as the predicted value from the Poisson model excluding the estimated coefficients for the matching covariates and ADHD medication status. The inclusion of time-varying covariates in the CRS model resulted in time-dependent CRS. The CRS was grouped into deciles and entered as a covariate in the Poisson regression model.

Reviewer Comment: CRS, for purposes of controlling for confounding in observational studies, has been criticized in the statistical literature. A concern is that the CRS adjusted standard errors may be downwardly biased which results in downwardly biased P-values and overly narrow confidence intervals (Rothmann et al. (2008), Modern Epidemiology 3rd ed., pg 446-7.). This issue occurs when there is strong correlation between measured covariates and exposure (Pike et al. (1979), Epidemiology and Community Health). In this study ADHD medication use (exposure) is highly correlated with psychiatric conditions and medications (covariates) that were included in the CRS model. It is important to note, however, that ADHD status was not included in the CRS model for this reason. Because of this the investigators performed a subgroup analysis restricted to subjects with a diagnosis or claim for ADHD in the 365 days prior to cohort entry.

Propensity Scores

PS was defined as the probability of current ADHD medication use compared to subjects that were not current users (i.e., non-users and noncurrent users) at baseline given the measured baseline covariates included in the PS model. PS were estimated using a logistic regression model that included all covariates that were used in the CRS model with the time-varying covariates fixed at baseline. The PS model was fit to all study subjects and was not site specific. A separate PS was estimated for the incident user cohort. The estimated PS was grouped into deciles and entered as a covariate in the Poisson regression model

The two adult study reports did not include PS diagnostics, which is considered an element of a solid PS analysis. From a July 19, 2011 communication it was noted that supplemental material submitted to FDA included material to assess covariate balance. However, the only supplemental material the statistical reviewer received was from 26 February 2011. The supplemental material included insufficient information to assess covariate balance. That submission included a histogram of PS distribution by user groups (see Figure 1) and parameter estimates for the PS model. In the July 19, 2011 communication it was also stated no diagnostic information for the incident user analysis was provided to FDA. Without the diagnostic information the merits of the PS analyses can not be assessed. It is inappropriate to presume that by adjusting for PS in the final model that the benefits of PS (e.g., controlling confounding) are automatically realized.

Reviewer Comments:
1) PS analyses of the overall cohort violated a PS assumption due to the inclusion of prevalent users. Specifically, the PS model that included data from prevalent users incorrectly adjusted for post-treatment initiation measurements. The potential consequences of this are a misclassification of subjects into PS deciles, and biased risk estimates resulting from controlling for variables that may fall along the causal pathway of the primary endpoint. This assumption can easily be addressed by restricting the sample to only incident or new users, which was done by the investigators in a sensitivity analysis. Note that the AMI-SCD report only presented PS adjusted results for the incident user analysis; PS results from the overall cohort, provided in investigators' supplemental material are presented in this review. The stroke study report included PS analyses for both the overall and incident user cohort.

2) In the overall and incident user analyses, the PS assumption that each subject must have a true non-zero probability (positivity assumption) of receiving an ADHD medication was possibly violated as a consequence of the broad inclusion criteria. The proportion of patients in the non-user comparison group with an ADHD diagnosis (a factor likely to predict receiving an ADHD medication) was only 0.2%. Since this proportion is extremely small, the reference group likely includes a large number of patients that would never have any chance of receiving an ADHD drug. Additional evidence that supports this concern is given by the mass of the PS distribution for non-users being near zero (Figure 1). This violation would be difficult to avoid in these available data given the study design, which did not restrict to subjects with a diagnosis of ADHD.

Sensitivity Analyses

There were two sensitivity analyses performed that modified study design parameters. The first was an incident user analysis that excluded prevalent users along with the non-users originally matched to the prevalent users. The second analysis considered only patients that received an ADHD medication (i.e., non-users were excluded from the sample) which had the former users serve as the reference group in the statistical analysis.

Other sensitivity analyses were conducted in different patient subgroups. Patient subgroups analyzed were defined by 1) prior history of cardiovascular disease (CVD), 2) non-ADHD psychiatric diagnosis or medications, 3) ADHD diagnosis, and 4) age 25-44, and 45-64. CVD was defined was according to the following diagnoses or medication use within the year prior to baseline: acute myocardial infarction, ischemia, coronary revascularization, CHF, arrhythmia,

stroke or TIA, congenital heart disorder, coronary artery anomaly, peripheral vascular disease, hyperlipidemia, hypertension, loop diuretic, digoxin, nitrates, anticoagulant, platelet inhibitor, anti-arrhythmic agents, ACE inhibitor, angiotensin receptor blocker, beta-blocker, calcium-channel blocker, thiazide diuretic, and other antihypertensive drugs.

Reviewer Comments: The credibility of the overall analysis and sensitivity analyses, except for the incident user analysis, is questionable since each analysis is vulnerable to prevalent user bias. The additional uncertainty (due to the wider confidence interval due to smaller sample size) and risk estimates derived from the incident user analysis is favored over potential bias in the overall. The increased precision from the overall analysis is not ideal as the narrower confidence interval will be centered on around a potentially biased risk estimate.

3.2.3 Results

Disposition and Follow-up

Across the different study endpoints the number of sites that contributed data varied. For AMI 11 sites provided 844,615 patient-years of follow-up from 443,198 unique subjects, of which 292,540 were classified as a non-user at baseline, 299 as non-current and 150,359 as current. For the stroke endpoint 9 sites contributed 835,257 patient-years of follow-up. The SCD endpoint had 8 sites contribute 809,221 patient-years of follow-up. The unique number of subjects that contributed data for the stroke and SCD endpoints were not reported in either study report.

Table 5 shows the number of subjects per site and user status at baseline. *Note, that site-specific counts are not based on unique subjects but the number of baseline records contributing to the PS analysis (unique subject counts by site were not provided by investigators).* The five largest sites (Ingenix i3, KP N CA, KP S CA, Tennessee, and Harvard Pilgrim) made up almost 90% of the sample.

Table 5. Number of subjects at baseline by site and ADHD medication use status

Site (# at baseline)*	Non-user n	Non-current n	Current N
Overall (N=443,198)	292,540	299	150,359
Tennessee Medicaid (N=43,371)	28,901	13	14,457
KP N CA (N=36,450)	24,289	11	12,150
KP S CA (N=19,947)	13,295	0	6,652
Ingenix i3 (N=266,787)	177,638	281	88,868
Harvard Pilgrim (N=29,566)	17,669	0	11,897
Fallon Community (N=2,698)	1,672	0	1,026
Group Health (N=14,986)	9,412	0	5,574
HealthPartners (N=12,707)	8,028	0	4,679
KP Georgia (N=2,284)	1,498	0	786
KP Northwest (N=10,730)	6,741	0	3,989
KP Colorado (N=7,380)	4,606	0	2,774

KP-Kaiser Permanente; Site-specific counts are not based on unique subjects; they are based on baseline records contributing to PS analysis.
* Site-specific counts from supplemental material dated 2/25/2011

There were 3,647 subjects that exited and re-entered the cohort; 1,148 and 2,409 of these subjects exited and re-entered as non-users and current users, respectively. Less than 1% of non-

users became current users (exact count not provided). The numbers of prevalent users overall, and by site, were not provided; however, prevalent users contributed 51.0% and 29.2% of the patient-years among currents users and non-current users, respectively.

Demographics

Table 6 shows current- and non-user cohort characteristics at baseline. For almost all measured characteristics the percentage of subjects in the current user group was larger than the percentage in the non-user group. This feature of the sample may be suggestive of 1) major differences between the two non-randomized groups possibly related to inclusion of subjects without a requirement of an ADHD diagnosis, and/or 2) the possible consequence of differential healthcare utilization across subjects and sites. Compared to non-users, current users were more likely to have a mental health claim for ADHD (30.3% v. 0.2%), major depression (40.2% v. 7.9%) anxiety (19.9% v. 5.3%), smoke (7.6% v. 5.0%) or have asthma (7.6% v. 4.2%). Current users versus non-users were more likely to have received an antipsychotic (9.6% v. 1.8%) or antidepressant (other or SSRI/SNRI, 53.4% v. 12.6%). The percentages of documented cardiovascular diseases or conditions in the year prior to cohort entry were similar between current- and non-users and small (< 3%) except for hypertension (13%) and hyperlipidemia (19%), which occurred more frequently but were similar between groups. The proportion of patients receiving more than one medication (other than an ADHD medication) was almost double in the current user group compared to the non-user group. This imbalance is likely associated with higher proportion of patients in the current use groups with medical conditions.

Reviewer Comment: Cohort characteristics have to be interpreted cautiously as they only reflect the sample that was included in the AMI analysis. It is not expected, however, that summaries for the other endpoints would have differed dramatically as the sites that did not contribute information were small in terms of patient-years of data contributed to the study.

Table 6. Cohort characteristics at baseline pooled across sites

Characteristic	Current Use* N= 152,852 n (%)		Non-use* N= 293,749 n (%)	
Median year of cohort entry	2003		2003	
Demographics				
Median age (years)	42		42	
Male gender	70245	(46.0)	135002	(46.0)
Medicaid enrollment	14786	(9.7)	29171	(9.9)
Cardiovascular disease within past year				
Acute MI	340	(0.2)	689	(0.2)
Ischemia	3998	(2.6)	6857	(2.3)
Coronary revascularization	253	(0.2)	643	(0.2)
CHF	1112	(0.7)	1759	(0.6)
Arrhythmia	3560	(2.3)	5076	(1.7)
Stroke/TIA	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	22562	(14.8)	39011	(13.3)
Hyperlipidemia**	28613	(18.7)	42601	(14.5)
Mental health claims within past year				
ADHD	46356	(30.3)	455	(0.2)
Major depression	61417	(40.2)	23296	(7.9)
Bipolar disorder	11196	(7.3)	2682	(0.9)
Anxiety	30472	(19.9)	15670	(5.3)
Psychotic disorders	2494	(1.6)	1833	(0.6)
Other selected medical conditions within past year				
Diabetes**	8972	(5.9)	15862	(5.4)
Obesity	9119	(6.0)	11439	(3.9)
Smoking	11579	(7.6)	14717	(5.0)
ETOH/substance abuse	7965	(5.2)	4514	(1.5)
Suicide attempt	795	(0.5)	410	(0.1)
Injury	30655	(20.1)	37559	(12.8)
Seizure	3062	(2.0)	2854	(1.0)
Asthma	11627	(7.6)	12432	(4.2)
Use of cardiovascular drug within past year				
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)
Anti-arrhythmic agents	556	(0.4)	631	(0.2)
ACE inhibitor	10719	(7.0)	19796	(6.7)
Angiotensin receptor blocker	3652	(2.4)	5988	(2.0)
Beta-blocker	12431	(8.1)	19091	(6.5)
Calcium-channel blocker	7028	(4.6)	12233	(4.2)
Thiazide diuretic	12471	(8.2)	20008	(6.8)
Other antihypertensive	1668	(1.1)	2192	(0.7)
Use of psychotropic medications within past year				
Antipsychotic, any	14618	(9.6)	5371	(1.8)
Tricyclic antidepressant	14224	(9.3)	9907	(3.4)
Antidepressants, other or SSRI/SNRI	81639	(53.4)	36962	(12.6)

Benzodiazepines	43695	(28.6)	25956	(8.8)
Lithium	4177	(2.7)	1002	(0.3)
Modafinil	4732	(3.1)	383	(0.1)
Insomnia meds	15270	(10.0)	6732	(2.3)
Thioridazine	307	(0.2)	181	(0.1)
Mood stabilizers, w/o seizure	22426	(14.7)	8631	(2.9)
Clonidine/guanfacine, w/o HT	2000	(1.3)	659	(0.2)
Use of other selected medications within past year				
Beta-agonist	18971	(12.4)	20835	(7.1)
Epinephrine	1342	(0.9)	1274	(0.4)
Asthma med, other	39645	(25.9)	45102	(15.4)
Seizure med, any	24139	(15.8)	10397	(3.5)
Theophylline compounds (asthma med)	960	(0.6)	1200	(0.4)
COX-2 inhibitors	10666	(7.0)	10838	(3.7)
Other drugs to improve blood flow	216	(0.1)	250	(0.1)
Clonidine	2602	(1.7)	1787	(0.6)
pde5 inhibitors	5183	(3.4)	4504	(1.5)
Triptans	7164	(4.7)	5298	(1.8)
Oral contraceptives	18379	(12.0)	28590	(9.7)
Hormones, menopausal or misc	18026	(11.8)	23388	(8.0)
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	43474	(28.4)	65256	(22.2)
Physician, 5+	13242	(8.7)	17713	(6.0)
***Psychiatric visits**[#]*				
Emergency, 1+	4417	(2.9)	2897	(1.0)
Inpatient, 1+	7761	(5.1)	3827	(1.3)
Physician, 1-4	43538	(28.5)	26703	(9.1)
Physician, 5+	40176	(26.3)	11048	(3.8)
Other visits				
Emergency, 1+	7885	(5.2)	9594	(3.3)
Inpatient, 1+	5812	(3.8)	5595	(1.9)
Physician, 1+	55386	(36.2)	69134	(23.5)
No. of different medications*				
1	24309	(15.9)	61193	(20.8)
2+	108955	(71.3)	116680	(39.7)

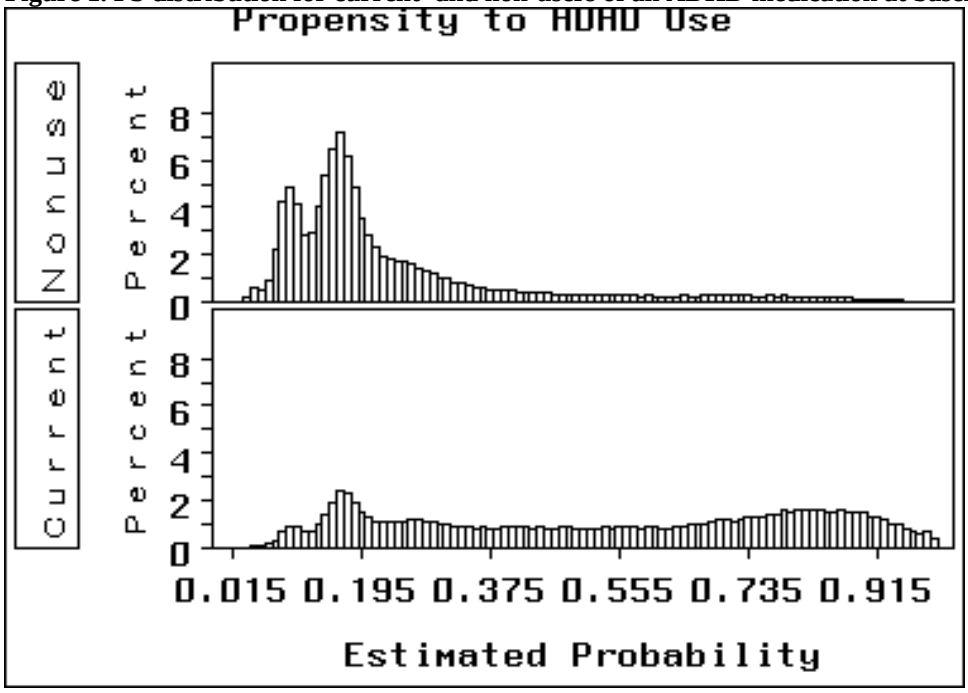
*Numbers are for membership periods at baseline or cohort entry (t0); actual counts of unique individuals are 150,359 for current users and 292,540 for non-users at baseline. Note, there were 299 indeterminate and former users at baseline (for a total of 150,658 users at baseline); ** Including medications; [#] Excluding ADHD visits; *** Excluding ADHD medications

Propensity Scores Analysis

No information was provided in the study reports or supplemental material to support a conclusion that PS were able to balance measured baseline covariates. Figure 1 shows the distribution of estimated PS values by user group at baseline in the overall sample that includes prevalent users. From this plot, one can only evaluate whether the PS distributions have a common support or overlap. It is not possible to infer from this plot whether the PS were able to balance baseline covariates, which is important given the potential for confounding. The PS distribution for non-users tended to be concentrated near zero, whereas the PS distribution for current users was uniform over the range of possible values (0, 1).

Reviewer Comment: The dissimilarity of PS distributions is evidence that the two user groups are different at baseline. The concentration of scores near zero in the non-user group further suggests that these subjects had little or no likelihood of receiving an ADHD medication. Again, this is likely due to the sample not being restricted to subjects with medical diagnoses associated with receiving an ADHD medication.

Figure 1. PS distribution for current- and non-users of an ADHD medication at baseline



Overall Results

Table 7 provides results from analyses of the study endpoints across the different confounder adjustment methods employed.

A total of 1357 AMI events were identified among 844,615 patient-years of observation. There were 907 events among non-users (1.62 events per 1,000 patient-years) and 152 events in current ADHD medication users (1.34 events per 1,000 patient years). The estimated PS adjusted rate ratio (RR) comparing current users to non-users was 0.83 with a 95% confidence interval (CI) that includes the null value one (95% CI=0.69, 1.00). The risk estimates comparing former and remote users to non-users were of a similar magnitude and variability as the comparison involving current users.

A total of 296 SCD events were identified among 809,221 patient-years of observation (0.4 events per 1,000 patient-years). *Recall three HMORN sites did not contribute information to the SCD endpoint; these sites also did not contribute to the two composite endpoints.* The PS adjusted RR comparing current-users to non-users was 0.83 with a 95% CI that included one (95% CI =0.55, 1.25). Comparisons of the other ADHD medication use status to non-use resulted in CI that included one.

A total of 575 strokes were identified among 835,258 patient-years of observation (0.69 events per 1,000 patient-years). *Note two HMORN sites did not contribute information to this endpoint.* The PS adjusted RR for current users compared to non-users was 0.75 with an upper CI limit just above one (95% CI = 0.55, 1.00). Comparisons of the other ADHD medication use status to non-use resulted in CI that included one.

For the composite AMI/SCD endpoint, 1582 events were identified among 807,044 patient-years (1.96 events per 1,000 patient-years). From the PS adjusted analysis the estimated RR comparing current users to non-users was 0.83 with a CI that excluded one (95% CI=0.69, 0.99).

For the AMI/SCD/stroke composite endpoint 2114 events were observed from 806,182 patient-years of follow-up (2.62 events per 1,000 patient-years). From the PS adjusted analysis current users had a statistically significant lower risk than non-users (RR=0.81, 95% CI=0.69, 0.94).

Reviewer Comment: The accuracy of these risks estimates and risk bounds is questionable given the multiple deficiencies in the study design and analysis issues.

Results suggest that ADHD medication exposure is not associated with an increase in CV risk. It is inappropriate, however, to conclude that, because the adjusted risk estimates for current users compared to non-users were below 1 (and in some instances have a 95% CI that excludes 1), that ADHD medication confers a protective effect for the respective study endpoints.

Despite the reviewer's preference for PS over CRS, the two confounder adjustment approaches yielded similar results.

Table 7. Overall CRS and PS adjusted results

Endpoint (patient years)	n (rate/1,000 py)	Covariate adjusted RR (95% CI)	CRS adjusted RR (95% CI)	PS adjusted RR (95% CI)
AMI				
Current (113,324)	152 (1.34)	-	0.88 (0.74, 1.05)	0.83 (0.69, 1.00)
Indeterminate (53,897)	86 (1.60)	-	1.07 (0.85, 1.33)	1.02 (0.81, 1.29)
Former (47,856)	65 (1.36)	-	0.78 (0.61, 1.00)	0.79 (0.61, 1.02)
Remote (69,793)	147 (2.11)	-	0.82 (0.68, 0.97)	0.87 (0.72, 1.05)
Nonuser (559,743)	907 (1.62)	-	reference	reference
SCD				
Current (107,525)	32 (0.30)	-	0.80 (0.55, 1.18)	0.83 (0.55, 1.25)
Indeterminate (51,814)	14 (0.27)	-	0.73 (0.42, 1.26)	0.76 (0.43, 1.34)
Former (46,264)	20 (0.43)	-	0.90 (0.57, 1.44)	1.02 (0.63, 1.65)
Remote (68,103)	50 (0.73)	-	0.98 (0.71, 1.35)	1.11 (0.79, 1.57)
Nonuser (535,516)	180 (0.34)	-	reference	reference
All Stroke				
Current (111,936)	63 (0.56)	0.77 (0.59, 1.02)	0.76 (0.58, 1.00)	0.75 (0.55, 1.00)
Indeterminate (53,328)	31 (0.58)	0.82 (0.57, 1.20)	0.83 (0.57, 1.19)	0.81 (0.55, 1.19)
Former (47,333)	39 (0.82)	0.99 (0.71, 1.40)	1.01 (0.73, 1.41)	1.05 (0.74, 1.41)
Remote (69,202)	67 (0.97)	0.76 (0.58, 1.00)	0.82 (0.63, 1.07)	0.88 (0.66, 1.17)
Nonuser (553,459)	375 (0.68)	reference	reference	reference
AMI/SCD				
Current (107,383)	174 (1.62)	-	0.87 (0.74, 1.02)	0.83 (0.69, 0.99)
Indeterminate (51,739)	97 (1.87)	-	1.02 (0.83, 1.26)	0.99 (0.79, 1.23)
Former (46,163)	84 (1.82)	-	0.83 (0.66, 1.03)	0.85 (0.68, 1.08)
Remote (67,689)	186 (2.75)	-	0.83 (0.71, 0.98)	0.90 (0.76, 1.06)
Nonuser (534,071)	1041 (1.95)	-	reference	reference
AMI/SCD/stroke				
Current (107,322)	234 (2.18)	0.80 (0.69, 0.92)	0.83 (0.72, 0.96)	0.81 (0.69, 0.94)
Indeterminate (51,710)	125 (2.42)	0.90 (0.75, 1.09)	0.94 (0.78, 1.13)	0.93 (0.77, 1.13)
Former (46,121)	121 (2.62)	0.83 (0.68, 1.00)	0.86 (0.72, 1.04)	0.91 (0.75, 1.10)
Remote (67,489)	243 (3.60)	0.76 (0.66, 0.87)	0.81 (0.70, 0.93)	0.88 (0.76, 1.01)
Nonuser (533,540)	1391 (2.61)	reference	reference	reference

py=patient years, nonusers as reference group. Confidence limits not adjusted for multiple comparisons. CRS=confounder risk score, PS=propensity score, composite endpoints represents the first occurrence of any event, dash used when no information on respective model were provided.

By Site Analyses

Table 8 provides event counts and patient-time by site for the SCD, AMI and stroke endpoints. The number of events and person-time was not provided for the composite endpoints. For each endpoint the unadjusted event rate in the single public site, Tennessee Medicaid, was notably larger than estimates from the other sites.

Table 8. Events and rates per 1000 patient-years by site and endpoint

	SCD		AMI		All Stroke	
Site	py	n (rate/1,000 py)	py	n (rate/1,000 py)	py	n (rate/1,000 py)
Ingenix/I3	390,657	86 (0.22)	390,090	451 (1.16)	390,462	168 (0.43)
KP N CA	99,011	23 (0.23)	98,722	161 (1.63)	98,921	71 (0.72)
KP S CA	34,335	18 (0.52)	34,277	40 (1.17)	34,316	29 (0.85)
TN Medicaid	123,028	150 (1.22)	122,205	446 (3.65)	122,570	210 (1.71)
Fallon Community	--	--	5,009	3 (0.60)	--	--
Group Health	42,813	5 (0.12)	42,676	68 (1.59)	42,770	23 (0.54)
Harvard Pilgrim	67,341	2 (0.03)	67,202	74 (1.10)	67,310	22 (0.33)
HealthPartners	32,162	8 (0.25)	32,058	52 (1.62)	32,126	25 (0.78)
KP CO	19,874	4 (0.20)	19,823	29 (1.46)	19,854	13 (0.65)
KP Mid-Atlantic	--	--	5,651	4 (0.71)	--	--
KP NW	--	--	26,902	29 (1.08)	26,928	14 (0.52)

py-patient-years; KP-Kaiser Permanente; Events and py for composite endpoints not provided; dash represents endpoint not measured at respective site

Table 9 shows CRS and covariate adjusted results (no PS adjusted results provided) for selected sites (Tennessee, i3, KP N. CA and KP S. CA) as presented in the study report. Sites with few events or those sites that did not collect data on all endpoints were omitted from the site-specific analyses. Risk estimates for the Tennessee site qualitatively differed from the other sites. In the Tennessee site, the estimated RR was 0.63 and 0.65 for the AMI and AMI/SCD endpoint, respectively, and both CIs excluded one. For the stroke endpoint, the estimated RR comparing current-users to non-users was near or below one for the non-Tennessee sites, and above one with a CI including one for the Tennessee site (RR=1.23, 95% CI=0.76, 2.00). Results for AMI/SCD/stroke composite endpoint were not provided in the final report.

Reviewer Comment: The heterogeneous event rate and risk in the public site may be due to systematic differences in data collection and quality as well as known and unknown health disparities in this patient population. These differences call into question the overall appropriateness of combining public and private healthcare site for this type of study. An analysis limited to the private sites was not performed.

Table 9. Site-specific analyses by event for selected sites

Endpoint	I3 RR (95% CI)	KP N. CA RR (95% CI)	KP S. CA RR (95% CI)	Tennessee RR (95% CI)
AMI‡				
Current	0.93 (0.71, 1.23)	0.85 (0.51, 1.40)	0.97 (0.42, 2.26)	0.63 (0.41, 0.97)
Indeterminate	0.89 (0.61, 1.29)	2.04 (1.18, 3.52)	1.32 (0.40, 4.37)	0.98 (0.63, 1.55)
Former	0.58 (0.36, 0.92)	0.85 (0.37, 1.94)	1.36 (0.41, 4.51)	1.08 (0.75, 1.56)
Remote	0.95 (0.69, 1.31)	1.46 (0.90, 2.37)	0.53 (0.07, 3.96)	0.69 (0.53, 0.90)
Nonuser	reference	reference	reference	reference
SCD‡				
Current	0.89 (0.49, 1.62)	1.51 (0.52, 4.44)	0.56 (0.15, 2.05)	0.62 (0.30, 1.29)
Indeterminate	0.62 (0.25, 1.56)	0.87 (0.11, 6.77)	0.56 (0.07, 4.42)	0.95 (0.44, 2.07)
Former	0.39 (0.12, 1.24)	2.26 (0.61, 8.30)	NE	0.93(0.48, 1.80)
Remote	0.97 (0.48, 1.99)	0.84 (0.18, 3.83)	1.78 (0.38, 8.40)	1.07 (0.72, 1.58)
Nonuser	reference	reference	reference	reference
All Stroke†				
Current	0.68 (0.41, 1.14)	0.53 (0.23, 1.23)	1.07 (0.39, 2.99)	1.23 (0.76, 2.00)
Indeterminate	0.87 (0.47, 1.59)	1.03 (0.39, 2.69)	1.04 (0.23, 4.81)	0.54 (0.22, 1.32)
Former	1.03 (0.57, 1.87)	1.03 (0.39, 2.72)	1.53 (0.41, 5.66)	0.96 (0.54, 1.72)
Remote	0.44 (0.21, 0.92)	0.59 (0.24, 1.46)	1.95 (0.52, 7.26)	0.88 (0.61, 1.26)
Nonuser	reference	reference	reference	reference
AMI/SCD‡				
Current	0.96 (0.74, 1.23)	0.93 (0.59, 1.47)	0.88 (0.44, 1.78)	0.65 (0.45, 0.95)
Indeterminate	0.88 (0.62, 1.24)	1.88 (1.11, 3.19)	1.09 (0.39, 3.06)	1.01 (0.68, 1.49)
Former	0.56 (0.36, 0.87)	1.06 (0.53, 2.09)	0.81 (0.25, 2.63)	1.08 (0.78, 1.49)
Remote	0.93 (0.69, 1.26)	1.28 (0.80, 2.05)	1.05 (0.32, 3.44)	0.77 (0.62, 0.96)
Nonuser	reference	reference	reference	reference

KP – Kaiser Permanente; NE – not estimated; † Covariate adjusted; ‡ CRS adjusted. Confidence limits not adjusted for multiple comparisons.

Incident User Sensitivity Analysis

Table 10**Error! Reference source not found.** displays event rates for both the incident user and the prevalent user samples. Among current users, the unadjusted event rates do not appear to differ across endpoints for incident and prevalent users. Among non-users, the unadjusted event rates were greater among non-users that were included in the incident user analysis than the non-users that were excluded from this analysis; these patients were excluded because they were matched to the prevalent users at baseline. This pattern suggests that prevalent users may have systematically differed from incident users with respect to matching variables related to the study endpoints (i.e., age). This finding can not be verified by the reviewer since the incident user descriptive statistics for the current- and non-users were not included in either study report.

Table 10. Unadjusted rates for the incident and prevalent user sample

Endpoint	Incident user sample n (rate/1,000 py)	Prevalent user sample n (rate/1,000 py)
Current user		
AMI	77 (1.39)	75 (1.30)
SCD	15 (0.29)	17 (0.31)
All Stroke	41 (0.75)	22 (0.38)
AMI/SCD	87 (1.67)	87 (1.57)
AMI/SCD/stroke	125 (2.40)	109 (1.97)
Non-user		
AMI	607 (1.82)	300 (1.33)
SCD	133 (0.42)	47 (0.22)
All Stroke	262 (0.80)	113 (0.50)
AMI/SCD	710 (2.23)	331 (1.53)
AMI/SCD/stroke	957 (3.01)	434 (2.01)

py=patient years

Table 11 shows results from the sensitivity analyses of the incident user cohort. *Non-users that were matched to the prevalent users at baseline were excluded from these analyses.* For the three non-composite endpoints, the estimated risk for current users was less than risk for non-users, with the CIs around the risk estimate all including one. For the composite endpoints (AMI/SCD and AMI/SCD/stroke) the estimated risk rate was statistically significantly lower among current users compared to non-users; this finding was consistent across the different adjustment methods. Comparative risks for current users compared to non-users from the overall and incident user analyses exhibited similar risk patterns. However, it is difficult to directly compare results given that the subjects in the reference group from the overall analysis that were excluded in the incident user cohort may differ in important ways related to the study outcomes. Furthermore, a judgment regarding the adequacy of the incident user analysis can not be made since diagnostic information needed to evaluate it was not provided for review.

Table 11. Incident User Analysis

Endpoint (patient years)	n (rate/1,000 py)	Covariate adjusted RR (95% CI)	CRS adjusted RR (95% CI)	PS adjusted RR (95% CI)
AMI				
Current (55,534)	77 (1.39)	-	0.80 (0.63, 1.02)	0.77 (0.59, 1.00)
Non-current (121,372)	222 (1.83)	-	0.80 (0.68, 0.93)	0.84 (0.71, 1.00)
Nonuser (333,498)	607 (1.82)	-	reference	reference
SCD				
Current (52,203)	15 (0.29)	-	0.63 (0.37, 1.08)	0.62 (0.35, 1.10)
Non-current (117,557)	74 (0.63)	-	0.99 (0.74, 1.32)	1.06 (0.76, 1.46)
Nonuser (318,821)	133 (0.42)	-	reference	reference
All Stroke				
Current	41 (0.75)	0.79 (0.56, 1.12)	0.87 (0.62, 1.21)	0.89 (0.61, 1.28)
Indeterminate	20 (0.65)	0.71 (0.45, 1.13)	0.80 (0.50, 1.26)	0.82 (0.51, 1.33)
Former	26 (0.75)	0.74 (0.49, 1.11)	0.83 (0.55, 1.24)	0.88 (0.57, 1.35)
Remote	56 (1.02)	0.72 (0.54, 0.98)	0.80 (0.59, 1.07)	0.86 (0.63, 1.18)
Nonuser	262 (0.80)	reference	reference	reference
AMI/SCD				
Current (52,129)	87 (1.67)	-	0.76 (0.61, 0.95)	0.74 (0.58, 0.94)
Non-current (117,125)	285 (2.43)	-	0.83 (0.73, 0.96)	0.87 (0.75, 1.02)
Nonuser (317,903)	710 (2.23)	-	reference	reference
AMI/SCD/stroke				
Current	125 (2.40)	0.68 (0.56, 0.82)	0.77 (0.63, 0.94)	0.77 (0.63, 0.94)
Indeterminate	82 (2.76)	0.80 (0.63, 1.01)	0.92 (0.74, 1.19)	0.94 (0.74, 1.19)
Former	97 (2.87)	0.74 (0.60, 0.91)	0.84 (0.72, 1.11)	0.89 (0.72, 1.11)
Remote	197 (3.69)	0.72 (0.61, 0.84)	0.76 (0.68, 0.95)	0.81 (0.68, 0.95)
Nonuser	957 (3.01)	reference	reference	reference

py=patient years, current user includes only new users and excludes prevalent users, nonuser reference group. Confidence limits not adjusted for multiple comparisons. Covariate adjusted analyses were not performed for all endpoints. Dash used to when results from respective model were not provided.

Other Sensitivity Analyses

Section 5.1 in the appendix displays results presented in the study report from sensitivity analyses performed across study endpoints. For all sensitivity analyses, the estimated RR comparing current users to non-users was below one with a CI including one. However, given the numerous limitations noted, the accuracy of these estimates is suspect.

Reviewer Comment: The apparent consistency of results across various sensitivity analyses and endpoints with the overall analyses should not be taken as evidence that the RR and 95% CI from the overall analyses are unbiased. Bias is likely still present due to study design issues that were discussed above.

4 Summary and Conclusions

4.1 Statistical Issues and Collective Evidence

Overall Findings

Across the different study endpoints the number of sites that contributed data varied. For the AMI endpoint, there were 11 sites that provided 844,615 patient-years of follow-up from 443,198 unique subjects, of which 292,540 were classified as a non-user at baseline, 299 as non-current and 150,359 as current. For the stroke endpoint, there were 9 sites that contributed 835,257 patient-years of follow-up. For the SCD endpoint, there were 8 sites that contributed 809,221 patient-years of follow-up.

The percentage of subjects in the current user group with prior medical conditions was larger than in the non-user group. Current users were more likely than non-users to have a mental health claim for ADHD (30.3% v. 0.2%), major depression (40.2% v. 7.9%), anxiety (19.9% v. 5.3%), smoke (7.6% v. 5.0%), have asthma (7.6% v. 4.2%), received an antipsychotic (9.6% v. 1.8%) or antidepressant (other or SSRI/SNRI, 53.4% v. 12.6%). Current users had greater healthcare utilization in the year prior to cohort entry, including cardiovascular visits, and were more likely to have used a medication (not including ADHD medications) when compared to non-users.

The unadjusted event rates for current ADHD users, per 1,000 patient-years, were 1.34, 0.30, and 0.56 for AMI, SCD and stroke, respectively; for the composite endpoints AMI/SCD and AMI/SCD/stroke the unadjusted event rates were 1.62 and 2.18, respectively. The unadjusted event rates for non-users, per 1,000 patient-years, was 1.62, 0.34, and 0.68 for AMI, SCD and stroke, respectively, and 1.95 and 2.61 for the composite endpoints AMI/SCD and AMI/SCD/stroke, respectively.

Overall, the PS adjusted risk estimates were lower but not statistically significantly different for current users compared to non-users for AMI (RR=0.83; 95% CI = 0.69, 1.00), SCD (RR=0.83; 95% CI = 0.55, 1.25) and stroke (RR=0.75; 95% CI=0.55, 1.00), and statistically significantly lower for the composite endpoints AMI/SCD (RR=0.83; 95% CI = 0.69, 0.99) and AMI/SCD/stroke (RR=0.81; 95% CI=0.69, 0.94).

In the incident user analysis, the PS adjusted risk estimates were statistically significantly lower for current users compared to non-users for AMI/SCD (RR= 0.74; 95% CI = 0.58, 0.94) and AMI/SCD/stroke (RR=0.77; 95% CI=0.63, 0.94); the estimated risk was lower but not statistically significantly different for AMI (RR=0.77; 95% CI = 0.59, 1.00), SCD (RR=0.62; 95% CI = 0.35, 1.10) and stroke (RR=0.89; 95% CI=0.61, 1.28). None of these comparisons were adjusted for multiple comparisons despite the need particularly when comparing individual events and the composite of events sequentially (e.g. AMI, AMI/SCD, AMI/SCD/stroke).

Event rates were heterogeneous across healthcare sites. The only public healthcare site included in this study, Tennessee Medicaid, had the largest event rate for the individual endpoints, and accounted for 446 of the 1357 AMIs, 150 of the 296 SCDs, and 210 of the 575 strokes.

Major Statistical Issues

The study results are vulnerable to systematic biases due to inclusion of prevalent users in the sample. The specific bias that prevalent users may introduce include under ascertainment of events that occur early in therapy and the inability to control for disease risk factors that could be altered by the drug therapy. The potential impact may be large since 51.0% of patient-time of current users came from prevalent users. The exact number of prevalent users, overall and by site, was not provided in the final report or supplemental material.

The broad patient inclusion criteria, which did not require a diagnosis of ADHD, resulted in a non-user comparison group that may not yield clinically relevant comparisons as this group is characteristically different from the ADHD medication users. Differences in health care utilization between users and non-users may have also resulted in differential coding since it is more likely that a user was more recently (and perhaps more frequently) treated by a health care provider than a non-user. This can result in the non-users appearing healthier than the user group due to a lack of reported medical conditions.

No diagnostic information was provided to demonstrate that propensity scores were able to balance measured baseline covariates. Without this information, the fit of the PS models can not be assessed, and the statistical properties afforded by the methodology can not be assumed. The disparate distribution of estimated propensity scores for non-users and current users at baseline supports the concern that the exposure groups are characteristically different with regard to baseline covariates.

Because of statistical performance concerns associated with the CRS methodology, including the potential for an inflated type-I error, the statistical reviewers prefers analyses that were PS adjusted. However, CRS and PS adjusted results did not substantively differ.

PS analyses performed on the full sample violated a major PS model assumption by adjusting for post-treatment measurements resulting from the inclusion of prevalent users. The potential consequences of this are a misclassification of subjects into PS deciles, and biased risk estimates resulting from controlling for variables that may fall along the causal pathway of the primary endpoint.

In both the overall and incident user analysis the PS positivity assumption that each subject must have a true non-zero probability of receiving an ADHD medication was possibly violated as a consequence of the broad inclusion criteria. Figure 1 illustrates this concern as the distribution of the estimated PS was near zero for the majority of non-users.

Event rates and comparative risk estimates in the single public healthcare site, Tennessee Medicaid, differed from the other sites. While this study was not designed to detect differences across sites, these differences give some concern of systematic differences between the Medicaid site and the non-Medicaid sites and the appropriateness of combining data across these sites.

The final study reports lacked adequate description of the study sample, including how many subjects were in each site, and details on the incident user sample (descriptive statistics, events

and patient-counts). Consequently, necessary evaluations of more appropriate analyses (i.e. incident-user versus non-user) were not performed adding to challenges in drawing conclusions from these data.

4.2 Conclusion and Recommendations

Concerns have been raised that the medication used to manage ADHD is possibly associated with an increase in CV adverse events. To investigate this possible association, FDA and AHRQ co-funded separate studies in adults and children investigating the endpoints of AMI, stroke and SCD using computerized health records across multiple healthcare sites. This review assessed the design and analysis of the ADHD study in young and middle-age adults using investigator supplied study reports and supplemental material including summary-level data. No subject-level data were provided for the review.

Across the various analyses, the findings do not suggest an increase in cardiovascular and stroke risk associated with ADHD medication use compared to non-use. These study findings, however, should be interpreted within the confines of the study design limitations and the sub-optimal data-streams. As a result, the reviewer recommends against comparative assessments of cardiovascular and stroke risk associated with ADHD medication exposure based on findings from this study. This recommendation extends to findings from the incident user analyses since the results could not be fully evaluated due to a lack of diagnostic information.

5 APPENDIX

5.1 Other sensitivity analyses results

Table 12. Rate ratios of AMI, overall and by subgroup

Cohort/ subgroup	Person-yrs	Number Events	Rate/1,000 person-yrs	IRR**	95% CI
Excluding pts with history of CVD					
Current	74944.5	57	0.76	0.87	0.65 – 1.15
Former*	110860.6	98	0.88	0.82	0.66 – 1.03
Nonuser	411874.8	374	0.91	1.00	reference
Including pts with history of CVD					
Current	38379.7	95	2.48	0.88	0.70 – 1.09
Former*	60687.4	200	3.30	0.89	0.76 – 1.05
Nonuser	147868.3	533	3.60	1.00	reference
Including pts with non-ADHD psychiatric diagnosis or medications					
Current	83597.7	116	1.39	0.85	0.68 - 1.05
Former*	120563.2	227	1.88	0.86	0.72 - 1.02
Nonuser	131529.1	318	2.42	1.00	reference
Excluding pts with non-ADHD psychiatric diagnosis or medications					
Current	29726.5	36	1.21	0.93	0.67 - 1.31
Former*	50984.8	71	1.39	0.85	0.67 - 1.09
Nonuser	428214.0	589	1.38	1.00	reference
Users restricted to those with ADHD					
Current	40340.4	44	1.09	0.85	0.62 – 1.15
Former*	36377.5	39	1.07	0.83	0.60 – 1.15
Nonuser	559743.1	907	1.62	1.00	reference
Users restricted to those with no ADHD					
Current	72983.7	108	1.48	0.88	0.72 – 1.08
Former*	135170.5	259	1.92	0.87	0.76 – 1.00
Nonuser	559743.1	907	1.62	1.00	reference
Users restricted to those with ADHD					
Current	40340.4	44	1.09	0.87	0.63 - 1.22
Former*	36377.5	39	1.07	0.87	0.62 - 1.23
Nonuser (matched to user)	163375.7	195	1.19	1.00	reference
Users restricted to those with no ADHD					
Current	72983.7	108	1.48	0.88	0.72 - 1.08
Former*	135170.5	259	1.92	0.86	0.75 - 1.00
Nonuser (matched to user)	401332.6	717	1.79	1.00	reference
Restricted to ages 25-44					
Current	56642.9	28	0.49	0.89	0.59 – 1.34
Former*	88442.5	64	0.72	0.92	0.68 – 1.24
Nonuser	282979.1	147	0.52	1.00	reference
Restricted to ages 45-64					
Current	56681.2	124	2.19	0.87	0.72 – 1.06
Former*	83105.5	234	2.82	0.85	0.73 – 0.98
Nonuser	276764.0	760	2.75	1.00	reference

Confidence limits not adjusted for multiple comparisons
* Includes indeterminate, former and remote users;
**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)

Table 13. Rate ratios of SCD, overall and by subgroup

Cohort/ subgroup	Person-yrs	Number Events	Rate/1,000 person-yrs	IRR**	95% CI
Excluding pts with history of CVD					
Current	70840.5	9	0.13	0.74	0.36 – 1.49
Former*	106783.9	22	0.21	0.80	0.49 – 1.31
Nonuser	392748.3	71	0.18	1.00	reference
Including pts with history of CVD					
Current	36684.5	23	0.63	0.87	0.55 – 1.38
Former*	59396.2	62	1.04	0.99	0.72 – 1.35
Nonuser	142767.2	109	0.76	1.00	reference
Including pts with non-ADHD psychiatric diagnosis or medications					
Current	79128.1	28	0.35	0.89	0.57 - 1.39
Former*	116646.1	70	0.60	0.96	0.69 - 1.33
Nonuser	126215.2	77	0.61	1.00	reference
Excluding pts with non-ADHD psychiatric diagnosis or medications					
Current	28396.9	4	0.14	0.64	0.24 - 1.76
Former*	49534.0	14	0.28	0.88	0.50 - 1.55
Nonuser	409300.3	103	0.25	1.00	reference
Users restricted to those with ADHD					
Current	37621.3	7	0.19	0.78	0.36 – 1.68
Former*	34354.8	6	0.17	0.68	0.30 – 1.54
Nonuser	535515.5	180	0.34	1.00	reference
Users restricted to those with no ADHD					
Current	69903.7	25	0.36	0.83	0.54 – 1.26
Former*	131825.3	78	0.59	0.93	0.71 – 1.23
Nonuser	535515.5	180	0.34	1.00	reference
Users restricted to those with ADHD					
Current	37621.3	7	0.19	0.78	0.34 - 1.80
Former*	34354.8	6	0.17	0.67	0.28 - 1.63
Nonuser (matched to user)	152760.2	30	0.20	1.00	reference
Users restricted to those with no ADHD					
Current	69903.7	25	0.36	0.83	0.54 - 1.28
Former*	131825.3	78	0.59	0.95	0.71 - 1.25
Nonuser (matched to user)	387546.8	150	0.39	1.00	reference
Restricted to ages 25-44					
Current	54141.3	9	0.17	0.78	0.37 – 1.65
Former*	85960.3	14	0.16	0.54	0.29 – 1.02
Nonuser	271947.4	39	0.14	1.00	reference
Restricted to ages 45-64					
Current	53383.7	23	0.43	0.79	0.50 – 1.23
Former*	80219.8	70	0.87	1.02	0.76 – 1.36
Nonuser	263568.1	141	0.53	1.00	reference

Confidence limits not adjusted for multiple comparisons
* Includes indeterminate, former and remote users
**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Table 14. Rates ratios of All Stroke overall and by subgroup

Cohort/ subgroup	Person-yrs	Number Events	Rate/1,000 person-yrs	RR**	95% CI
No history of CVD					
Current	73971.4	18	0.24	0.64	0.38 - 1.07
Former*	109565.1	36	0.33	0.75	0.51 - 1.12
Nonuser	407018.7	143	0.35	1.00	reference
History of CVD					
Current	37964.1	45	1.19	0.85	0.61 - 1.19
Former*	60298.1	101	1.68	0.89	0.70 - 1.13
Nonuser	146439.8	232	1.58	1.00	reference
History of non-ADHD psychiatric condition					
Current	82584.4	57	0.69	0.89	0.65 - 1.23
Former*	119457.2	115	0.96	0.93	0.73 - 1.20
Nonuser	130622.4	137	1.05	1.00	reference
No history of non-ADHD psychiatric condition					
Current	29351.0	6	0.20	0.44	0.19 - 0.99
Former*	50406.0	22	0.44	0.72	0.46 - 1.13
Nonuser	422836.1	238	0.56	1.00	reference
Users with ADHD					
Current	39770.6	10	0.25	0.45	0.24 - 0.85
Former*	35909.7	13	0.36	0.65	0.37 - 1.15
Nonuser	553458.5	375	0.68	1.00	reference
Users with no ADHD					
Current	72164.9	53	0.73	0.89	0.66 - 1.20
Former*	133953.5	124	0.93	0.86	0.69 - 1.07
Nonuser	553458.5	375	0.68	1.00	reference
Users with ADHD					
Current	39770.6	10	0.25	0.48	0.25 - 0.96
Former*	35909.7	13	0.36	0.68	0.37 - 1.26
Nonuser (matched to user)	161163.5	78	0.48	1.00	reference
Users with no ADHD					
Current	72164.9	53	0.73	0.89	0.65 - 1.21
Former*	133953.5	124	0.93	0.87	0.69 - 1.08
Nonuser (matched to user)	397220.2	298	0.75	1.00	reference
Ages 25-44					
Current	55964.8	12	0.21	0.74	0.39 - 1.42
Former*	87552.8	26	0.30	0.84	0.52 - 1.37
Nonuser	279646.7	66	0.24	1.00	reference
Ages 45-64					
Current	55970.7	51	0.91	0.77	0.57 - 1.05
Former*	82310.4	111	1.35	0.83	0.66 - 1.04
Nonuser	273811.8	309	1.13	1.00	reference

Confidence limits not adjusted for multiple comparisons
* Includes indeterminate, former and remote users
**Adjusted for site, age, sex, calendar year, and established stroke risk factors

Table 15. Rates ratios of AMI/SCD overall and by subgroup

Cohort/ subgroup	Person-yrs	Number Events	Rate/1,000 person-yrs	IRR**	95% CI
Excluding pts with history of CVD					
Current	70766.5	62	0.88	0.87	0.66 – 1.14
Former*	106563.6	115	1.08	0.82	0.67 – 1.01
Nonuser	392069.5	425	1.08	1.00	reference
Including pts with history of CVD					
Current	36616.7	112	3.06	0.87	0.71 – 1.07
Former*	59027.2	252	4.27	0.91	0.78 – 1.05
Nonuser	142001.1	616	4.34	1.00	reference
Including pts with non-ADHD psychiatric diagnosis or medications					
Current	79020.3	136	1.72	0.86	0.70 - 1.05
Former*	116231.9	284	2.44	0.87	0.75 - 1.02
Nonuser	125760.0	380	3.02	1.00	reference
Excluding pts with non-ADHD psychiatric diagnosis or medications					
Current	28363.0	38	1.34	0.90	0.65 - 1.25
Former*	49358.8	83	1.68	0.87	0.69 - 1.10
Nonuser	408310.5	661	1.62	1.00	reference
Users restricted to those with ADHD					
Current	37577.2	47	1.25	0.84	0.63 – 1.13
Former*	34282.5	42	1.23	0.80	0.59 – 1.09
Nonuser	534070.5	1041	1.95	1.00	reference
Users restricted to those with no ADHD					
Current	69806.0	127	1.82	0.88	0.73 – 1.06
Former*	131306.2	325	2.48	0.89	0.78 – 1.01
Nonuser	534070.5	1041	1.95	1.00	reference
Users restricted to those with ADHD					
Current	37577.2	47	1.25	0.85	0.62 - 1.17
Former*	34284.5	42	1.23	0.82	0.58 - 1.14
Nonuser (matched to user)	152442.2	213	1.40	1.00	reference
Users restricted to those with no ADHD					
Current	69806.0	127	1.82	0.88	0.73 - 1.06
Former*	131306.2	325	2.48	0.89	0.78 - 1.01
Nonuser (matched to user)	386414.1	832	2.15	1.00	reference
Restricted to ages 25-44					
Current	54122.0	35	0.65	0.85	0.59 -1.22
Former*	85833.7	77	0.90	0.83	0.63 – 1.08
Nonuser	271744.9	184	0.68	1.00	reference
Restricted to ages 45-64					
Current	53261.3	139	2.61	0.87	0.73 – 1.04
Former*	79757.0	290	3.64	0.88	0.77 – 1.01
Nonuser	262325.7	857	3.27	1.00	reference

Confidence limits not adjusted for multiple comparisons
* Includes indeterminate, former and remote users
**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

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