Review and Evaluation of Clinical Data:
Attention Deficit Hyperactivity Disorder (ADHD) Medications
in Children, Youth, Young and Middle aged Adults
and risk of Serious Cardiovascular Disease (CVD)

Submitted Materials:	Final Clinical Study Reports
Date of correspondence:	29 April 2011
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I. Executive Summary

In response to a 2006 Advisory Committee recommendation, a retrospective cohort study was conducted to examine the relationship between stimulant medication use and three endpoints: sudden cardiac death (SCD), myocardial infarction (MI) and stroke in adolescents aged 2-24 years of age using data from four large health plans to obtain data on stimulant medication dispensing and adjudication of the endpoints of interest. Two groups of patients were used for comparison of rates on the three endpoints: non-users vs. users (users further stratified by current, intermediate use (30-90 days post prescription), former users (90-364 days after last use) and remote user (>365 days). A propensity score analysis was used to calculate the hazard ratios for each of the groups.

Results from the youth study included data from 1.2 million patients aged 2-24 years of age comprising 2.58 million person years of follow-up and 373,667 person-years of current ADHD medication use (all stimulant medications, atomoxetine and pemoline). The adjusted rate ratio of serious cardiovascular disease (all three endpoints combined) in current users vs. nonusers was 0.67 (95% CI 0.28-1.64). Results from the secondary analysis that compared the adjusted rates of these endpoints using remote users as the reference group also showed no association.

In addition, the study team conducted additional studies to examine the risk of serious cardiovascular events (SCD, MI and stroke) in adults who take stimulant medications. Results from the adult studies included data from 152,852 current adult users of ADHD medications and 293,749 non-user adults comprising over 500,000 person-years follow-up for non-users and 100,000 person years of current-use exposure (all stimulant medications incl. atomoxetine and pemoline). The multiple variable adjusted rate ratio of combined SCD/AMI in current users vs. non-users was 0.87 (95% CI 0.74-1.02). For the adult stroke rate ratio, the multiple variable adjusted rate ratio of any stroke in current users vs. non-users was 0.77 (95% CI 0.59-1.02). A statistically significant decrease in SCD or MI rates in remote users (0.83 95% CI 0.71-0.98) when compared to non-users suggests that a "healthy user bias" may be present in patients assigned to current ADHD medication treatment vs. non-treatment.

Adult patients who took ADHD medications 0-30 days after the last day of current use had an adjusted rate of MI of 1.31 that almost reached statistical significance (95% CI 1.00-1.71) when compared to patients who took ADHD medications >1 year from last use. Further analysis showed that adult patients from the Tennessee Medicaid site who took ADHD medications 31-364 days after the last day of current use had a 1.57 times increase (95% CI 1.03-2.38) in

myocardial infarction rates when compared to adult patients who took ADHD medications >1 year from last use.

A trend was noted for a small (but not statistically significant) increased adjusted risk rate in SCD, MI and stroke in patients with former use of ADHD medications when compared to non-users in both the child-youth and adult studies. Of note, a site-by site analysis revealed that adults patients who took ADHD medications 0-30 days after last use at the Kaiser Permanente North site were 2.04 times more likely (95% CI 1.18-3.52) to have a myocardial infarction compared to non-users, with the combined endpoint of SCD/MI remaining statistically significant (1.88 95% CI 1.11-3.19) for this site.

A biologically plausible hypothesis that could potentially explain these findings could be an association of attenuated centrally-mediated sympathetic tone $\pm$ adrenergic receptor down-regulation with daily ADHD medication use, with consequently increased centrally-mediated sympathetic tone $\pm$ up-regulation of adrenergic receptors after discontinuation of daily stimulant use when compared to current users and non-users of stimulant medications. A recent study by Vitiello et al[1] which may provide some support for this hypothesis examined longitudinal blood pressure and heart rate changes in children who participated in the Multimodal Treatment of ADHD (MTA) study and demonstrated stimulant treatment had a persistent adrenergic effect on heart rates at years 3 to 8 that was significant with cumulative exposure regardless of current use.

It is this reviewer's recommendation that no labeling changes be taken at this point regarding an association between current ADHD medication use and cardiovascular risk. However, consideration should be given to addressing a possible association with increased rates of myocardial infarction within one (1) year following discontinuation of ADHD medication treatment in adult patients compared to non-users and/or current use- specifically the initial 30 days post treatment. This reviewer concurs with the recommendations made by OSE to examine the association between adult current use (and potentially post-treatment use) of ADHD medications and cardiovascular risks through a meta analysis of clinical trial data from adult ADHD medication trials.

II. Background

In 2006, the Agency conducted an Advisory Committee meeting to discuss a 2004 review of AERS post-marketing adverse events and an association between post-market use of mixed-amphetamine salts (ADDERALL) and methylphenidate with sudden cardiac death in 17 youths with evidence of cardiac abnormalities. A pharmacoepidemiological study to examine the association between stimulant use and sudden cardiac death in children was recommended by the Advisory Committee to further examine the issue.

In response to the recommendation, FDA staff and members of the child and adult youth study steering committee developed a consensus protocol and implemented a retrospective cohort

[1] Vitiello B, Elliott GR et al " Blood Pressure and Heart rate over 10 years in the Multimodal Treatment Study of Children with ADHD" *Am J Psychiatry* Sep 2011 in advance of printing. **doi: 10.1176/appi.ajp.2011.10111705**

study that used data from four large health plans (Tennessee Medicaid, Washington State Medicaid, Kaiser Permanente California (northern and Southern regions) and Ingenix i3 (primarily Northeast United States) to examine the relationship to stimulant medication use (+ atomoxetine) and sudden cardiac death (SCD), myocardial infarction (MI) and stroke. Members of the steering committee were as follows:

- William O. Cooper, MD, PhD.-Vanderbilt University (coordinating center)
- Laurel A. Habel, PhD.- Kaiser Permanente
- Colin Sox, MD, MS- HMO Research Network
- K. Arnold Chan, MD, ScD.-i3 Drug Safety
- Andrew D. Mosholder, MD, MPH- FDA
- Chunliu Zhan, MD, PhD- Agency for Healthcare Research and Quality (AHRQ)

A consensus protocol was developed with Agency input that was similar in design to the child study to investigate the association between adult SCD/MI and stroke with stimulant use, with Dr. Habel from Kaiser Permanente as the lead investigator. Due to FDA funding constraints at the time of development of the adult protocol, the steering committee decided to postpone further research into the stroke-portion of the adult studies until funds were obtained via a collaborative effort with the Agency for Healthcare Research and Quality (AHRQ). Since the stroke portion of the original SCD/MI and stroke protocol was separated from the original study design, the steering committee members elected to perform the adult stroke study as a separate study. Consequently the results from the adult studies were obtained via two separate reports based on data from identical patient populations.

This review will summarize the study and results from all three studies into two parts: the child-youth study SCD/MI and stroke study and the adult study with two separate result sections (one for SCD/MI results and one for stroke results).

III. Materials Used in Review

The primary sources of data used for this clinical review include the following:

- Attention Deficit Hyperactivity Disorder Medication and Risk of Serious Cardiovascular Disease in Children and Youth. Adverse Effects of Psychostimulant Medications Working Group (Final study report) - 29 April 2011 (revised tables 11 Aug 2011)
- ADHD Medications and Risk of Serious Coronary Heart Disease in Young and Middle-Aged Adults. Adverse Effects of Psychostimulant Medications Working Group (Final study report) - 29 April 2011.
- ADHD Medications and Risk of Stroke in Young and Middle-Aged Adults. Adverse Effects of Psychostimulant Medications Working Group - 22 Jul 2011

Additional review sources used in the review was the completed internal Agency review of the study results completed on 1 Sep 2011 by Andrew Mosholder, MD-medical officer, Office of Surveillance and Epidemiology.

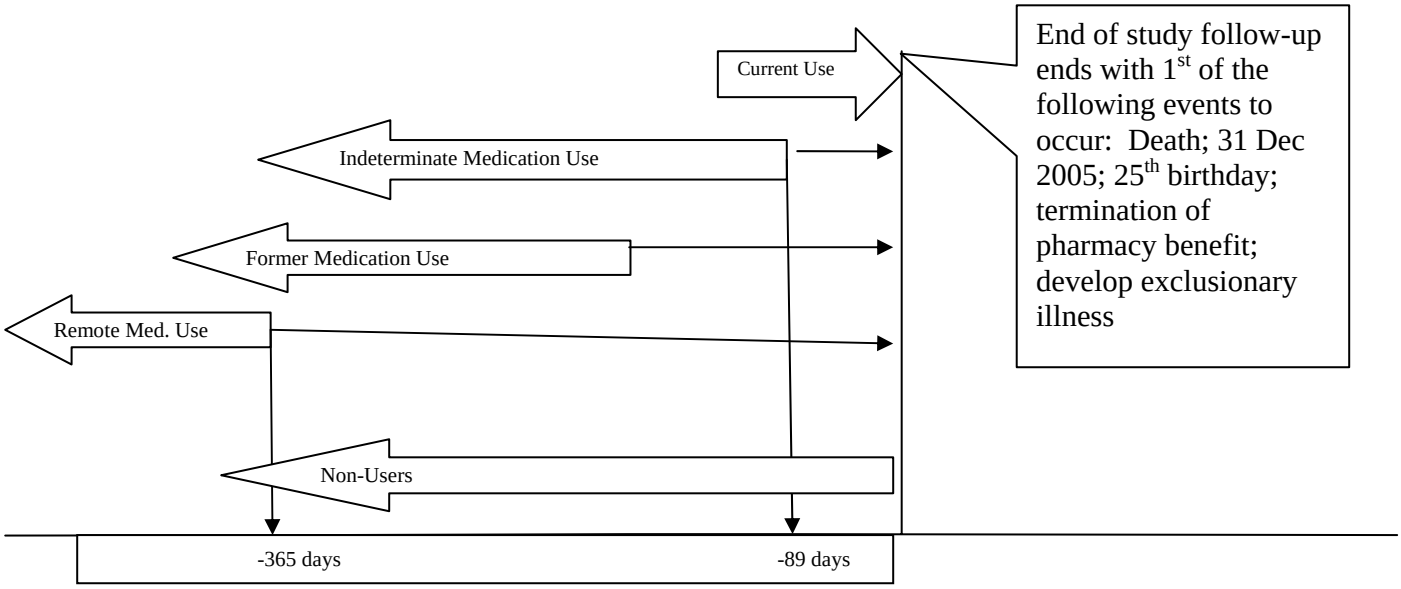
IV. Review of the Child-Youth Study Data

A. Study Design

The study design that was implemented for the youth study was a retrospective cohort study using data obtained from four large health plans (Tennessee State Medicaid, Washington State Medicaid, Kaiser Permanente California (north and south), and Ingenix i3 (primarily Northeast USA private fee-for service patients)) that was augmented with linkage to state death certificates for Tennessee, Washington State, Kaiser Permanente California or the National Death Index. ADHD medication use-data was obtained through use of automated pharmacy benefit claims (described below).

Hospital and Death data for person-eligible cohorts was obtained from each site based on the earliest availability of the site's computerized data (ranged from 1986 to 2000) and ended for all sites at the end of 2005 to allow for ascertainment of deaths. A National Death Index search of death certificates was also completed in order to capture those patients aged 18-24 who were no longer enrolled in one of the study health plans and who had died.

A visual diagram for a retrospective cohort design is presented below:



B. Cohorts

Entire study population cohort

For the youth study, a patient's health and pharmacy data records were eligible for inclusion into the entire study cohort if the patient met the following criteria:

1. Aged 2 to 24 years (WHO definition of youth)
2. Absence of serious illness
3. Data was available for the study

Patients were excluded if:

1. An eligible cohort member had an exclusionary illness (as per below) OR:
   - Sickle cell, Cystic Fibrosis, Cerebral Palsy, Cancer, HIV, Organ Transplant, Liver Failure, renal Dialysis (exception single inpatient episode), respiratory failure, other potentially lethal childhood diseases.
2. Had a hospital discharge in the preceding 365 days with a primary diagnosis of acute myocardial infarction or stroke

End of Cohort Eligibility

End of study follow-up (i.e. end of cohort eligibility) was defined as the earliest time when one of the five events occurred:

1. The last day of the study (2005)
2. When the patient reached the upper end of the study (age 24)
3. The last day of membership in a pharmacy benefit plan
4. The day prior to the development of an exclusion illness or
5. The day of death

It should be noted that patients often start and stop taking ADHD medications or enter/re-enter pharmacy benefit plan membership plans. Therefore, the study was designed to allow each youth to contribute more than one medication-use cohort-eligible period listed below for this study, as long as all of the criteria for study inclusion (listed above) were met.

- <u>Study Population Cohorts</u>

Medication-Use Cohorts

Medication use data for each person-time eligible cohort was obtained using automated pharmacy records which included the date a prescription was dispensed, drug name, dose, quantity and days supply. Data obtained for an ADHD medication user-cohort eligible was classified according to the probable use of ADHD medications as follows:

1. Current use cohort- a period of time when person-day follow-up occurred between the prescription start date and the end of the days supply
2. Indeterminate use cohort- a period of time when person-day follow-up from the last day of current use (end of the days supply) to 89 days after the last day of current use.
3. Former use cohort- a period of time when person-day follow-up occurred between 90 days after the end of current use and 364 days after end of current use
4. Remote use cohort- a period of time when person-day follow-up occurred 365 days or greater after the end of current use and lasted throughout the end of study follow-up.

Primary Analysis Comparison Cohort

In order to compare rates of sudden cardiac events in youths who were or had taken ADHD medications, the study employed the use of a non-user cohort to perform hypothesis testing. The non-user cohort was defined as:

- Random sample of person-time from two (2) entire-study cohort members with no evidence of ADHD medication use on a date that matched an ADHD medication cohort user based on calendar year of birth, age and gender.

Of note, Office of Surveillance and Epidemiology (OSE) steering committee representatives to the study were opposed to the primary comparison group being a non-user cohort as it was felt that the non-user cohort was inherently dissimilar to a user cohort and thus an inappropriate choice to use for hypothesis testing. Consequently OSE had raised objections to the full steering committee membership regarding the use of a non-user cohort as the control group in the primary analysis early in the planning stages of the study. Ultimately the steering committee members elected to keep the non-user cohort for the primary analysis based on a consensus vote, but agreed to conduct a secondary analysis using a user group that was chosen by the OSE steering committee members.

Secondary Analysis Comparison Cohort
A secondary analysis was conducted using remote users as the reference group at the request of OSE staff.

C. Study Medications

Pharmacy records were collected for the following medications in the entire study cohort to form the medication cohorts as previously defined:

- Amphetamine-related psychostimulants:
    - Methylphenidate
    - Dexmethylphenidate
    - dextroamphetamines and
    - amphetamine salts
- Pemoline
- Atomoxetine

D. Study Endpoints

The study endpoints were defined as follows:

- Sudden Cardiac Death (SCD) - sudden, pulse-less condition or collapse consistent with a ventricular tachyarrhythmia occurring in a community setting that was fatal or resuscitated (i.e. requiring CPR and defibrillation)
- Acute Myocardial Infarction (MI)- acute cardiac events meeting international diagnostic criteria for MI (combination of clinical symptoms, diagnostic cardiac enzyme elevation or ECG changes) that led to a cohort-member's hospitalization

- Stroke- acute neurological deficit of sudden onset that persisted more than 24 hours that was not explained by other causes, corresponding to a vascular area in the brain.

All endpoints were identified from computer data sources and confirmed via case adjudication with at least two cardiologist adjudicators from the lead site (Vanderbilt) for SCD and MI endpoints and at least two neurologist adjudicators from Vanderbilt for Stroke cases. All adjudicators were blinded to exposure status of all the cases adjudicated.

Approximately 21% of potential cases were adjudicated using a computer case definition as the medical records were unable to be adjudicated. Out of these cases, one additional SCD, one MI and 6 stroke cases were added to the analysis. The computer case definition was based on the positive predictive values of diagnosis codes leading to a potential case.

E. Analysis

The study compared the adjusted incidence of the SCD, MI and stroke endpoints between current users of ADHD medications and non users. The study calculated unadjusted rate differences for SCD, MI and stroke with 95% confidence intervals based on cohort assignment.

In order to estimate relative risk with corresponding hazard ratio, Cox regression analysis was employed for this study that included baseline and time-dependant variables.
For each member of the current and the two randomly selected patients for the non-user cohorts, baseline covariates which could reflect risk for cardiovascular disease and other co-morbid conditions (which included socioeconomic characteristics, medical care encounters suggesting psychiatric disorders, asthma and other resp. illnesses, seizures and other neurological disorders, unintentional injuries, cardiovascular diseases, and other diseases) were used to calculate a propensity score.

F. Results-Child/Youth Study

Demographics

A total of 1,200,436 children and youth were included in the study. Mean years of follow-up by site ranged from 1.5 to 3.9 years. Total person-year exposure by cohort group is presented below:

Table 1: Exposure by Cohort Group

Cohort by Use of ADHD medication	Person-Years Exposure
Current Users	373,667
Indeterminate Users (0-89 days post last use)	218,782
Former Users (90-364 days post last use)	388,693
Non-Users (Reference Group)	1,597,962

The results by site are shown below as taken from the final study report:

Table 2: Demographics by Site

Metric	Tennessee	Kaiser	Ingenix i3	Washington	Total

	Medicaid	Permanente California		State Medicaid	
Study Period	1986-2005	1999-2005	1998-2005	2000-2005	1986-2005
N in cohort	200,198	191,772	692,187	116,281	1,200,438
% Medicaid	100	4.4	0	100	27
Mean age (y)	8.7	11.1	12.0	10.0	11.1
Mean First day of Follow-up	1999.0	2002.1	2002.3	2002.2	2001.7
Mean Follow-up (Years)	3.9	2.6	1.5	2.1	2.1

For both non-user and current user cohorts, subjects were predominately male with nearly 60% of current users receiving a diagnosis of ADHD vs. 16% for non-users. Overall, the proportion of subjects in each cohort that had ever received any psychiatric care was nearly identical, with 55% of nonusers and 63% of current ADHD medication users receiving some psychiatric care. For this comparison, the study authors adjusted for baseline between users and non-user characteristics using the Brenner Method.

Table 3: Current-user Vs. Non-user Demographics

Metric	Non-user	Current-User
General Characteristics		
Mean Age (y)	11.4	11.1
Male %	70.7	71.1
Non-white, %	33.2	36.8
Reside in Metropolitan Area, %	76.7	77.1
Medical Co-morbidities (%)		
Asthma	26.7	22.1
Seizures	2.5	2.1
Life threatening Conditions	1.7	1.3
Obesity	1.3	1.2
Major Congenital Heart defect	0.9	0.8
Minor congenital heart defect	7.3	6.9
Diabetes (poor Control)	0.6 (0.2)	0.5 (0.2)
Psychiatric Conditions (%)		
ADHD diagnosis	15.8	57.4
Major Depression	11.8	10.4
Bipolar	1.9	2.1
Psychosis	0.6	0.5
Autism	1.3	1.4
Mental Retardation (Severe)	2.9 (0.0)	4.0 (0.0)

Prior Suicide Attempt	0.3	0.3
Psychotropic Medication Use (%)		
Antidepressants	17.2	15.0
Mood Stabilizers	4.0	4.2
Antipsychotics	4.4	5.2
Benzodiazepines	0.6	0.5
Use of Health Services (%)		
Psychiatric Hospitalization	2.2	1.9
Medical Hospitalization	4.6	4.1
Medical Emergency Department Visit	16.8	15.8
Any Psychiatric Care	55.0	63.1
Any Cardiovascular Care	6.7	6.0
Any Outpatient Visit	93.3	92.9
Any Prescription	37.0	31.7

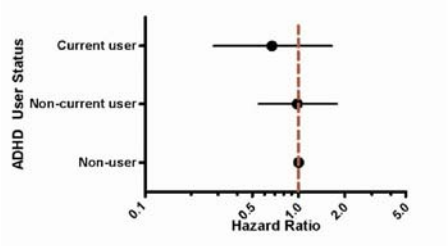
Primary Analysis (non-user as reference)
When comparing current users and non-current (composite of former and indeterminate users) to non-user cohorts, the rates of SCD, MI, Stroke as well as a composite of all endpoints (Endpoint of serious cardiovascular disease) were all less than rates seen in non-user cohorts as seen below.

Table 4: Occurrence of Individual Endpoints by current use of ADHD medications

ADHD Medication Use	**Person-Years**	**Events**	**Rate/100,000**	**Hazard Ratio***	**95% Confidence Interval**
Sudden Cardiac Death					
Non-User	1,597,962	17	1.1	1.00	Ref
Non-Current	607,475	13	2.1	1.52	0.65-3.57
Current User	373,667	3	0.8	0.88	0.23-3.34
Acute Myocardial Infarction					
Non-User	1,597,962	6	0.4	1.00	Ref
Non-Current	607,475	3	0.5	-	-
Current User	373,667	0	0		
Stroke					
Non-User	1,597,962	29	1.8	1.00	Ref
Non-Current	607,475	10	1.6	0.76	0.32-1.71
Current User	373,667	4	1.1	0.75	0.24-2.37
Serious Cardiovascular Disease					
Non-User	1,597,962	52	3.25	1.00	Ref
Non-Current	607,475	26	4.28	0.98	0.55-1.77
Current User	373,667	7	1.87	0.67	0.28-1.64
- Methylphendiate	192,257	4	2.08	0.61	0.19-1.93
- Amphetamine	137,448	1	0.73	-	-
- Atomoxetine	29,330	1	3.41	-	-
-Pemoline	14,632	1	6.83	-	-

*Cox Regression model incl. adjustments for site specific propensity score decile, site, medical conditions, psychiatric conditions, medical/psychiatric utilization variables, age, and calendar year.

Visual representation of the data was provided by the authors and is presented below:



When the analysis is restricted to new users of ADHD medication (i.e. only those patients who only had documented ADHD medication within the previous 365 days), current users again show event rates and hazard ratios less than rates observed with the reference group of non-users. However, non-current users (those patients in whom drug use was discontinued 0-365 days previous to the event) showed rates and hazard ratios which were numerically greater than non-users. This small increase in hazard ratios was not statistically significant. A similar pattern is seen when each endpoint is also examined.

Table 5: Occurrence of Serious Cardiovascular disease and each individual endpoint by ADHD medication use, restricted to new users of ADHD medication use

ADHD medication Use	**Person Years**	**Events**	**Rate/100,000**	**Hazard Ratio**	**95% Confidence Interval**
Composite Endpoint of Serious Cardiovascular Disease					
Non-User	1,597,962	52	3.3	1	Ref
Former/Indeterminate User	376,456	20	5.3	1.09	0.59-2.04
Current User	192,040	4	2.1	0.67	0.22-1.99
Sudden Cardiac Death					
Non-user	1,597,962	17	1.1	1.00	Ref
Non-Current User	376,456	8	2.1	1.14	0.42-3.11
Current User	192,040	2	1.0	0.75	0.18-3.22
Acute Myocardial Infarction					
Non-user	1,597,962	6	0.4	1.00	Ref
Non-Current User	376,456	3	0.8	-	-
Current User	192,040	0	0		
Stroke					
Non-user	1,597,962	29	1.8	1.00	Ref
Non-Current User	376,456	9	2.4	1.08	0.46-2.52
Current User	192,040	2	1.0	0.78	0.18-3.48

When the analysis was performed to examine the rate of serious cardiovascular events in recently exposed (i.e. current users and indeterminate users with use within the previous 89 days) and

former user (those with exposure 90-365 previous to event) to the reference group of non-users, rates and hazard ratios for recent users again are noted to be less compared to non-current users. However former users had numerically higher rates and hazard ratios than non-users though the results were NOT statistically significant.

Table 6: Occurrence of Serious Cardiovascular Disease by ADHD medication use, recent use

ADHD medication Use	Person Years	Events	Rate/100,000	Hazard Ratio	95% Confidence Interval
Composite Endpoint of Serious Cardiovascular Disease					
Non-User	1,597,962	52	3.3	1.00	REF
Former User	388,693	21	5.4	1.04	0.54-2.00
Recent User (current/indeterminate)	592,449	12	2.0	0.70	0.35-1.42

Finally, an analysis of the occurrence of serious cardiovascular disease by duration of ADHD medication use in current users demonstrated a small, numerically higher hazard ratio for less than 365 days worth of cumulative ADHD medication use when compared to non-users. However this result was NOT statistically significant.

Table 7: Occurrence of Serious Cardiovascular Disease by ADHD medication use, duration of use

ADHD medication Use	Person Years	Events	Rate/100,000	Hazard Ratio	95% Confidence Interval
Composite Endpoint of Serious Cardiovascular Disease					
Non-User	1,597,962	52	3.25	1.00	REF
Non-current use	607,475	26	4.28	0.98	0.54-1.76
Current user, < 1 year cumulative use	107,447	3	2.79	1.03	0.26-4.17
Current user, 1 year or greater cumulative use	266,220	4	1.50	0.53	0.19-1.54

Secondary Analysis

The results from the secondary analysis which compared the rates of either SCD, MI or stroke between current users of ADHD medication to former users (i.e. indeterminate and Remote users) using former users as a reference group mirrored that of the primary analysis, although the unadjusted rate/100,000 PY was highest in former users.

Table 8: Occurrence of serious cardiovascular disease by ADHD medication use (former use reference)

ADHD	Person	Events	Rate/100,000	Hazard	95%

medication Use*	Years		PY	Ratio**	Confidence Interval
Former Users	388,693	21	5.40	1.00	Ref
Non-User	1,597,962	52	3.25	0.91	0.54-1.56
Indeterminate User	218,782	5	2.29	0.73	0.27-1.95
Current User	373,667	7	1.87	0.61	0.24-1.55

*Former use began 90 days after current use ended and ended 364 days after current use ended. Indeterminate use included the period 89 days after last day of current use.
**Estimated with Cox Regression models (incl. site-specific propensity scores, site, medical conditions, psychiatric conditions, utilization variables, age, calendar year.

G. Summary

A recent case-control study by Gould et al[2] has suggested an association of increased rates of sudden cardiac death with ADHD medication use. Based on the results from this study, there appears to be no association of either sudden cardiac death, acute myocardial infarction, or stroke with current use of ADHD medication when compared to non-users or former users of ADHD medication. Statistical limitations present in this study have been noted by OSE statistical reviewers and have been made part of the final OSE statistical review (discussed in brief detail in **VI. Limitations** in this review).

A trend was noted for a small but statistically not significant increased adjusted risk rate in SCD, MI and Stroke in patients with former use of ADHD medications when compared to non-users in the primary analysis.

V. Review of the Adult SCD/MI and Stroke studies

A. Study Design

The study design for the adult SCD/MI and Stroke studies is similar to the youth study reviewed previously, with the exception of patients only aged 25-64 years of age were eligible for entry into a cohort.

The study excluded individuals if they had one or more of the following diagnoses during the 365 days prior to cohort entry: sickle cell disease, cancer (other than non-melanoma), HIV infection, organ transplant, liver failure or hepatic coma, end-stage renal disease, respiratory failure, or severe congestive heart failure. Of note, patients with severe congestive heart failure were not excluded from consideration for the SCD/MI endpoint if the condition occurred with the endpoint simultaneously (i.e. severe CHF occurred while in the cohort), since severe congestive heart failure may well be a consequence of the AMI endpoint or an acute condition leading to SCD.

[2] Gould MS et al " Sudden death and use of stimulant medications in youth". *Am J Psychiatry* 2009 Sep; 166(9):992-1001

As with the child studies, the study population for both the SCD/MI and stroke studies were comprised of members identified via medical and pharmacy records from the Tennessee Medicaid, Ingenix i3, Kaiser Permanente North California, Kaiser Permanente North California but also included data from seven members of the HMO Research Network [(HMORN)-Harvard Pilgrim Health care; Group Health Cooperative of Puget Sound; Health Partners; Kaiser Permanente Northwest; KP Mid-Atlantic; Fallon Community; and Kaiser Permanente Colorado]. Of note, Fallon Community, KPNW and KP mid-Atlantic did not contribute data to the SCD endpoint.

B. Study Endpoints

SCD/MI Study
The primary endpoint for the SCD/MI study were acute myocardial infarction requiring hospital admission and/or sudden cardiac death. Acute MI's were identified from hospital discharge diagnoses of ICD-9 code 410.X and by searching mortality files (via a National Death Index search or linkage with state mortality file for ICD-9 Codes of 410.X or ICD-10 codes 121.X or 122.x. Sudden cardiac death cases were identified primarily via death certificates obtained via a National Death Index search or linkage with state mortality files for all members not known to be alive on 31 Dec 2005. A secondary source for identifying potential cases of SCD/MI and stroke was hospital discharge data, incl. emergency room records.

For all potential cases, charts were requested or for cases identified via mortality records, copies of death certificates and autopsy records (if available) were obtained for adjudication by trained clinicians who were blinded to treatment status. For SCD cases without hospital or autopsy records, a computer-based case definition based on ICD-9 and 10 codes was developed and utilized. The computer-based case definition was previously developed and validated in a retrospective cohort study of SCD which had a positive predictive value of 86% in identifying SCD cases when compared to medical record reviews and clinical adjudication.

Stroke
For the stroke study, the primary endpoint was any stroke, defined as an acute neurological deficit of sudden onset that persisted more than 24 hrs, was vascular in nature, and not explained by any other cause. Strokes were identified primarily from hospital discharge diagnoses of stroke or ICD-9/10 codes that included subarachnoid, intracerebral, non-traumatic extradural, subdural or unspecified intracranial hemorrhage and occlusion of cerebral arteries. Strokes that occurred in hospital settings were excluded. The investigators also performed a separate analysis for ischemic and hemorrhagic strokes.

For all potential cases, charts were requested or for cases identified via mortality records, copies of death certificates and autopsy records (if available) were obtained for adjudication by a trained neurologist who was blinded to treatment status. For stroke cases without hospital or autopsy records, a computer-based case definition based on ICD-9 and 10 codes was developed and utilized.

Confounders

In order to control for potential differences in risk of coronary heart disease between cohort eligible's that were exposed to ADHD medications vs. unexposed, both the SCD/MI and stroke studies employed the use of a cardiovascular risk score (CRS) which included multiple variables based on cardiovascular diagnoses, claims or prescriptions that occurred within the 1 year period preceding cohort entry. The CRS score was set to time-varying for the primary analysis and were fixed at baseline for the secondary analysis in order to address concerns that some of the variables may be causally related between medication use and the endpoints of interest. In addition, the investigators also constructed propensity scores (as were used in the child study) for current vs. non-use at baseline using identical variables that were included in the CRS.

To address unmeasured confounders, the investigators used external adjustment methods based on information for race/ethnicity, smoking, obesity, history of cardiovascular disease and drug abuse in reviews of the medical records of stroke, SCD/MI cases and death certificates on all SCD cases and a sample of MI cases. Additionally, a 2006 survey of Kaiser Permanente members was used to obtain the same information for these members.

C. Cohorts Defined

The cohorts for the adult study were categorized and defined in similar fashion as with the child study for the adult stroke study.

However the definitions of indeterminate and former user categories in the adult SCD/MI study differs from the child study in that indeterminate use refers to the first 30 days (0-89 days in the child study) after the end of current use and former users defined as use between 31-364 days after current use (90-364 in the child study). The definitions of current, remote and non-users were identical for both the child and adult SCD/MI studies.

End of Cohort Eligibility

End of study follow-up (i.e. end of cohort eligibility) was defined as the earliest time when one of the four events occurred:

- The last day of the study (31 Dec 2005)
- When the patient reached the upper end of the study (age 65)
- The last day of membership in a pharmacy benefit plan
- The day of death, MI or Stroke event

As with the child study, cohort subjects were allowed to leave and re-enter the study should membership in the pharmacy and/or health plan be discontinued and later be re-enrolled. Out of the 443,198 total patients in the SCD/MI study, only 3,647 (0.8%) met this criteria, of which 1,148 of these subjects (31.5%) left and re-entered as non-users and 2,409 subjects (66.1%) left and re-entered as current users of ADHD medications.

D. Study Medications

Pharmacy records were collected for the following medications in the entire study cohort to form the medication cohorts as previously defined:

- Amphetamine-related psychostimulants
    - Methylphenidate
    - Dexmethylphenidate
    - dextroamphetamine and
    - amphetamine salts
- Pemoline
- Atomoxetine

E. Demographics-SCD, MI and Stroke studies

For both the SCD/MI study and the Stroke study, a total of 446,601 (current user 152,852; non-users 293,749) were included in the study at baseline. Mean years of follow-up by site ranged from 1.5 to 3.9 years. Total person-year exposure by cohort group during follow-up is presented below:

Table 9: Total Person-Years Exposure by Cohort

Cohort by Use of ADHD medication	Person-Years Exposure SCD and MI Study	Person-Years Exposure Stroke Study
Current Users	107,383	111,935
Indeterminate Users (0-30 days post last use)	51,739	53,327
Former Users (31-364 days post last use)	46,163	47,333
Remote (>365 days)	67,689	69,202
Non-Users (Reference Group)	534,070	553,458

For both non-user and current user cohorts, subjects were slightly more likely to be female (54%). As expected current users were more likely to have a mental health claim for a psychiatric disorder than non-users however only 30% of current users had an ADHD claim. The majority of mental health-care claims in current users was for major depression (40%), followed by ADHD, anxiety (20%), bipolar disorder (8%) and psychotic disorders (2%).

Current users were slightly more obese than non-users (6% vs. 3.9%) and more likely to have ETOH/Substance abuse, have an injury, seizure and asthma than non-users. Psychotropic medication use was consistently taken by greater proportions of current users than non-users, with antidepressants (53%), benzodiazepines (29%), mood stabilizers (15%) and insomnia medications (10%) receiving the greatest amount of use in current user population. Asthma medication, seizure medication and beta-agonist were used in greater proportion of current users and >12% of the group.

Table 10: Current and Non-user Demographics

Metric	Current N=152,852	Non-User N=293,749
General Characteristics		
Mean Age (y)	42	42
Male %	46	46

Medicaid enrollment	9.7%	9.7%
Cardiovascular Disease in past year		
Acute MI	0.2%	0.2%
Ischemia	2.6%	2.3%
CHF	0.7%	0.6%
Arrhythmia	2.3%	1.7%
Stroke/TIA	1.2%	0.7%
Hypertension	14.8%	13.3%
Hyperlipidemia (incl. those with medications)	18.7%	14.5%
Medical Co-morbidities		
Asthma	7.6%	4.2%
Seizures	2.0%	1.0%
ETOH/Substance abuse	5.2%	1.5%
Obesity	6.2%	3.9%
Suicide Attempt	0.5%	0.1%
Injury	20.1%	12.8%
Psychiatric Conditions		
ADHD diagnosis	30.3%	0.2%
Major Depression	40.2%	7.9%
Bipolar	7.3%	0.9%
Psychosis	1.6%	0.6%
Anxiety	19.9%	5.3%
Psychotropic Medication Use		
Antidepressants, non Tricyclic	53.4%	3.4%
Mood Stabilizers w/o seizure	14.7%	2.9%
Antipsychotics	9.6%	1.8%
Benzodiazepines	28.6%	8.8%
Tricyclic Antidepressant	9.3%	3.4%
Insomnia medications	10.0%	2.3%
Modafanil	3.1%	0.1%
Lithium	2.7%	0.3%
Clonidine/guanfacine	1.3%	0.2%
Cardiovascular Visits(%)		
Emergency 1+	3.7	2.6
Inpatient 1+	3.9	2.4
Physician 1-4	28.5	9.1
Physician 5+	8.7	6.0
Psychiatric Visits-excluding ADHD visits (%)		
Emergency 1+	2.9	1.0
Inpatient 1+	5.1	1.3
Physician 1-4	28.5	9.1
Physician 5+	26.3	3.8

Other visits (%)		
Emergency 1+	5.2	3.3
Inpatient 1+	3.8	1.9
Physician 1+	36.2	23.5
# of different medications-excluding ADHD medications (%)		
1	15.9	20.8
2+	71.3	39.7

F. Results- SCD and MI study

Primary Analysis

When comparing current users and non-current use cohorts (i.e. indeterminate, former and remote use) to non-user cohorts, the rates of SCD and MI as well as a composite of SCD and MI were all less than rates seen in non-user cohorts as seen below.

Table 11: Occurrence of Individual Endpoints by current use of ADHD medications

ADHD Medication Use	**Person-Years**	**Events (Rate/1,000 PY)**	**Unadjusted Rate Ratio (95%CI)**	**Adjusted Rate Ratio* (95% CI)**	**Adjusted Rate Ratio** (95%CI)**
Sudden Cardiac Death					
Nonuser	535,515	180 (0.34)	1.00	1.00	1.00
Current user	107,525	32 (0.30)	0.89 (0.61-1.29)	1.13 (0.77-1.64)	0.80 (0.55-1.18)
Indeterminate user	51,814	14 (0.27)	0.80 (0.47-1.38)	1.01 (0.58-1.74)	0.73 (0.42-1.26)
Former user	46,263	20 (0.43)	1.29 (0.81-2.04)	1.34 (0.84-2.13)	0.90 (0.57-1.44)
Remote user	68,102	20 (0.73)	2.18 (1.60-2.99)	1.43 (1.04-1.97)	0.98 (0.71-1.35)
ADHD medication users	273,705	116 (0.42)			
Acute Myocardial Infarction					
Nonuser	559,743	907 (1.62)	1.00	1.00	1.00
Current user	113,324	152 (1.34)	0.83 (0.70-0.98)	0.95 (0.80-1.12)	0.88 (0.74-1.05)
Indeterminate user	53,896	86 (1.60)	0.98 (0.79-1.23)	1.15 (0.92-1.44)	1.07 (0.85-1.33)

Former user	47,858	65 (1.36)	0.84 (0.65-1.08)	0.89 (0.69-1.14)	0.78 (0.61-1.00)
Remote user	69,792	147 (2.11)	1.30 (1.09-1.55)	0.97 (0.81-1.16)	0.82 (0.68-0.97)
ADHD medication users	284,872	450 (1.58)			
SCD or MI					
Nonuser	534,070	1041 (1.95)	1.00	1.00	1.00
Current user	107,383	174 (1.62)	0.83 (0.71-0.98)	0.97 (0.83-1.14)	0.87 (0.74-1.02)
Indeterminate user	51,739	97 (1.87)	0.96 (0.78-1.18)	1.15 (0.93-1.41)	1.02 (0.83-1.26)
Former user	46,163	84 (1.82)	0.93 (0.75-1.17)	0.99 (0.79-1.24)	0.83 (0.71-0.98)
Remote user	67,688	186 (2.75)	1.41 (1.21-1.65)	1.03 (0.88-1.20)	0.83 (0.71-0.98)
ADHD medication users	272974	541 (1.98)			

*Adjusted for site, age, calendar year
**Adjusted for site, age, calendar year, confounder risk score (CRS)

An analysis by ADHD medication showed a similar trend in fully adjusted rate ratios for both SCD (see Table 12) and AMI (Table 13) in that all ratios for stimulant-based medications were less than the rates seen in the reference group non-users. Rates for atomoxetine and pemoline were slightly greater than 1.00 for the SCD endpoint but were not significant.

Table 12: Occurrence of SCD by current use of specific ADHD medications

SCD By Specific ADHD medication					
Metric	**Person-Years**	**Events (Rate/1,000 PY)**	**Unadjusted Rate Ratio (95%CI)**	**Adjusted Rate Ratio* (95% CI)**	**Adjusted Rate Ratio** (95%CI)**
Current User	107,525	32 (0.30)	0.89 (0.61-1.29)	1.13 (0.77-1.64)	0.80 (0.55-1.18)
Amphetamines	46,910	13 (0.28)	0.82 (0.47-1.45)	1.22 (0.69-2.14)	0.93 (0.52-1.63)
Methylphenidate	47,887	13	0.81	0.95	0.67

		(0.27)	(0.46-1.42)	(0.54-1.68)	(0.38-1.18)
Atomoxetine	8257	4 (0.48)	1.44 (0.54-3.88)	1.63 (0.60-4.42)	1.04 (0.38-2.82)
Pemoline	2995	2 (0.67)	1.99 (0.49-8.00)	1.59 (0.39-6.44)	1.08 (0.27-4.37)
Nonuser	535,515	180 (0.34)	1.00	1.00	1.00

*Adjusted for site, age, calendar year
**Adjusted for site, age, calendar year, confounder risk score (CRS)

Table 13: Occurrence of AMI by current use of specific ADHD medications

AMI By Specific ADHD medication					
Metric	**Person-Years**	**Events (Rate/1,000 PY)**	**Unadjusted Rate Ratio (95%CI)**	**Adjusted Rate Ratio* (95% CI)**	**Adjusted Rate Ratio** (95%CI)**
Current User	113,324	152 (1.34)	0.83 (0.70-0.98)	0.95 (0.80-1.12)	0.88 (0.74-1.05)
Amphetamines	49,080	59 (1.20)	1.20 (0.74 (0.57-0.97)	0.95 (0.73-1.24)	0.92 (0.70-1.19)
Methylphenidate	51232	77 (1.50)	0.93 (0.74-1.17)	0.97 (0.77-1.23)	0.89 (0.71-1.13)
Atomoxetine	8424	11 (1.31)	0.81 (0.44-1.46)	0.96 (0.53-1.75)	0.87 (0.48-1.57)
Pemoline	3047	5 (1.64)	1.01 (0.42-2.44)	0.85 (0.35-2.04)	0.71 (0.29-1.71
Nonuser	559743	907 (1.62)	1.00	1.00	1.00

*Adjusted for site, age, calendar year
**Adjusted for site, age, calendar year, confounder risk score (CRS)

Finally, an analysis of the occurrence of SCD/AMI by duration of current ADHD medication use demonstrated a small, numerically higher fully adjusted hazard ratio for AMI in with 183-365 days worth of cumulative ADHD medication use when compared to non-users (Table 14) and for SCD with >366 days and 91-182 days worth of cumulative ADHD medication use (see Table 15). However this result was NOT statistically significant. When the analysis is restricted to ONLY new ADHD users, all fully adjusted hazard ratios are less than 1.00 (see Table 17).

Table 14. Rates of **acute myocardial infarction,** by use of ADHD medications

Medication status	**Person-yrs**	**Number Events**	**Rate/1,000 person-yrs**	**Unadjusted IRR**	**95% CI**	**Adjusted matching variables IRR***	**95% CI**	**Adjusted IRR****	**95% CI**
Duration of Current use [#]									
366+ days	52135.0	73	1.40	0.86	0.68 – 1.10	0.89	0.70 – 1.13	0.84	0.66 – 1.06
183-365 days	24237.3	38	1.57	0.97	0.70 – 1.34	1.24	0.90 – 1.72	1.17	0.85 – 1.62
91-182 days	14096.5	12	0.85	0.53	0.30 – 0.93	0.69	0.39 – 1.22	0.64	0.36 – 1.13
31-90 days	11704.9	12	1.03	0.63	0.36 – 1.12	0.83	0.47 – 1.47	0.77	0.44 – 1.37
1-30 days	8009.5	12	1.50	0.92	0.52 – 1.63	1.15	0.65 – 2.04	1.07	0.61 – 1.89
Nonuser	559743.1	907	1.62	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (ie, matching variables)
**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)
[#] Excludes current pemoline use.

Table 15. Rates of **sudden cardiac death,** by use of ADHD medications

Medication status	**Person-yrs**	**Number Events**	**Rate/1,000 person-yrs**	**Unadjusted IRR**	**95% CI**	**Adjusted matching variables IRR***	**95% CI**	**Adjusted IRR****	**95% CI**
Duration of Current use [#]									
366+ days	49222.4	19	0.39	1.15	0.72 – 1.84	1.40	0.87 – 2.25	1.03	0.64 – 1.66
183-365 days	23046.0	2	0.09	0.26	0.06 – 1.04	0.37	0.09 – 1.48	0.26	0.07 – 1.07
91-182 days	13371.1	5	0.37	1.11	0.46 – 2.71	1.53	0.63 – 3.74	1.05	0.43 – 2.57
31-90 days	11140.0	2	0.18	0.53	0.13 – 2.15	0.72	0.18 – 2.91	0.49	0.12 – 1.96
1-30 days	7660.5	2	0.26	0.78	0.19 – 3.13	0.96	0.24 – 3.87	0.63	0.16 – 2.56
Nonuser	535515.5	180	0.34	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (ie, matching variables)
**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)
[#] Excludes current pemoline use.
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Table 16. Rates of **acute myocardial infarction or sudden cardiac death,** by use of ADHD medications

Medication status	**Person-yrs**	**Number Events**	**Rate/1,000 person-yrs**	**Unadjusted IRR**	**95% CI**	**Adjusted matching variables IRR***	**95% CI**	**Adjusted IRR****	**95% CI**
Duration of Current use [#]									
366+ days	49112.8	88	1.79	0.92	0.74 – 1.14	0.98	0.79 – 1.22	0.89	0.71 – 1.10
183-365 days	23030.1	37	1.61	0.82	0.59 – 1.14	1.08	0.78 – 1.51	0.98	0.71 – 1.36
91-182 days	13364.9	15	1.12	0.58	0.35 – 0.96	0.76	0.46 – 1.27	0.68	0.41 – 1.13
31-90 days	11136.9	14	1.26	0.64	0.38 – 1.09	0.85	0.50 – 1.44	0.75	0.44 – 1.28
1-30 days	7659.5	13	1.70	0.87	0.50 – 1.50	1.09	0.63 – 1.88	0.95	0.55 – 1.64
Nonuser	534070.5	1041	1.95	1.00	reference	1.00	reference	1.00	reference

Table 17. Rates of **acute myocardial infarction or sudden cardiac death,** by use of ADHD medications (**NEW USERS ONLY)**

Medication status	**Person-yrs**	**Number Events**	**Rate/1,000 person-yrs**	**Unadjusted IRR**	**95% CI**	**Adjusted matching variables IRR***	**95% CI**	**Adjusted IRR****	**95% CI**
Duration of Current use [#]									
366+ days	15077.8	33	2.19	0.98	0.69 - 1.39	0.97	0.68 - 1.37	0.82	0.58 - 1.16
183-365 days	10500.2	16	1.52	0.68	0.42 - 1.12	0.89	0.54 - 1.46	0.75	0.45 - 1.23
91-182 days	9020.6	10	1.11	0.50	0.27 - 0.93	0.70	0.37 - 1.30	0.58	0.31 - 1.09
31-90 days	9193.0	13	1.41	0.63	0.37 - 1.10	0.92	0.53 - 1.60	0.78	0.45 - 1.34
1-30 days	7216.4	12	1.66	0.74	0.42 - 1.32	1.05	0.59 - 1.86	0.88	0.50 - 1.55
Nonuser	317903.0	710	2.23	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (ie, matching variables)

**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)

[#] Excludes current pemoline use.

This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Secondary Analysis

For the secondary analysis, the investigator's compared current, indeterminate and former use using remote users as the reference group. Current users of ADHD medications had a slightly elevated but not statistically significant increase in the fully adjusted rate ratio for MI (table 18). However indeterminate users had an even higher fully adjusted rate ratio of 1.31 that almost achieved significance (95% CI 1.00-1.71). Both the unadjusted and adjusted rate ratios for SCD were all less than 1.00 in the current, indeterminate and former users when compared to remote users (table 19).

Table 18. Rates of **acute myocardial infarction,** by use of ADHD medications

Medication status	**Person-yrs**	**Number Events**	**Rate/1,000 person-yrs**	**Unadjusted IRR**	**95% CI**	**Adjusted matching variables IRR***	**95% CI**	**Adjusted IRR****	**95% CI**
Current user	113324.2	152	1.34	0.64	0.51 – 0.80	0.98	0.78 – 1.23	1.08	0.86 - 1.36
Indeterminate user	53896.7	86	1.60	0.76	0.58 – 0.99	1.19	0.91 – 1.56	1.31	1.00 - 1.71
Former user	47858.5	65	1.36	0.64	0.48 – 0.86	0.92	0.68 – 1.23	0.96	0.71 - 1.28
Remote user	69792.9	147	2.11	1.00	reference	1.00	reference	1.00	reference

Table 19. Rates of **sudden cardiac death,** by use of ADHD medications

Medication status	**Person-yrs**	**Number Events**	**Rate/1,000 person-yrs**	**Unadjusted IRR**	**95% CI**	**Adjusted matching variables IRR***	**95% CI**	**Adjusted IRR****	**95% CI**
Current user	107525.0	32	0.30	0.41	0.26 – 0.63	0.79	0.50 – 1.24	0.82	0.52 – 1.29
Indeterminate user	51814.0	14	0.27	0.37	0.20 – 0.67	0.70	0.39 – 1.28	0.74	0.41 – 1.35
Former user	46263.5	20	0.43	0.59	0.35 – 0.99	0.94	0.56 – 1.58	0.92	0.55 – 1.55
Remote user	68102.6	50	0.73	1.00	reference	1.00	reference	1.00	reference

Table 19A. Rates of **acute myocardial infarction or sudden cardiac death,** by use of ADHD medications

Remote user	67688.6	186	2.75	1.00	reference	1.00	reference	1.00	reference
Medication status	**Person-yrs**	**Number Events**	**Rate/1,000 person-yrs**	**Unadjusted IRR**	**95% CI**	**Adjusted matching variables IRR***	**95% CI**	**Adjusted IRR****	**95% CI**
Current user	107383.3	174	1.62	0.59	0.48 – 0.73	0.95	0.77 – 1.17	1.04	0.85 - 1.29
Indeterminate user	51739.1	97	1.87	0.68	0.53 – 0.87	1.12	0.87 – 1.43	1.22	0.95 - 1.57
Former user	46163.0	84	1.82	0.66	0.51 – 0.86	0.96	0.74 – 1.25	0.99	0.76- 1.28

* Adjusted for site, age, sex, calendar year (ie, matching variables)
**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.

When the analysis was performed on the Tennessee Medicaid data, former use of ADHD medication was associated with a 1.57 times increase in MI rates when compared to remote use. This result was statistically significant (table 20).

Table 20. Rates of **acute myocardial infarction,** by use of ADHD medications– **Tennessee Medicaid only**

Medication status	**Person-yrs**	**Number Events**	**Rate/1,000 person-yrs**	**Unadjusted IRR**	**95% CI**	**Adjusted matching variables IRR****	**95% CI**	**Adjusted IRR****	**95% CI**
Current user	8831.8	22	2.49	0.73	0.45 - 1.18	0.81	0.50 - 1.31	0.91	0.56 - 1.48
Indeterminate user	5420.3	20	3.69	1.08	0.66 - 1.78	1.30	0.79 - 2.14	1.43	0.87 - 2.35
Former user	7540.1	32	4.24	1.25	0.82 - 1.89	1.50	0.99 - 2.29	1.57	1.03 - 2.38
Remote user	20557.5	70	3.41	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (ie, matching variables)
**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)

G. Results- Adult Stroke Study

Primary Analysis
When comparing current users and non-current use cohorts (i.e. indeterminate, former and remote use) to non-user cohorts, the fully adjusted rates of stroke were less than rates seen in non-user cohort (reference) as seen in table 21. Fully adjusted rates remained less than 1.00 even when restricted to new users of ADHD medications (table 22).

Table 21. Rates of **ALL stroke,** by use of ADHD medications (n=150,658 total users)

Medication status	**Person-yrs**	**Number Events**	**Rate/1,000 person-yrs**	**Unadjusted RR**	**95% CI**	**Adjusted matching variables RR***	**95% CI**	**Adjusted RR****	**95% CI**
ADHD medication users	281798.7	200	0.71						
Current user	111935.5	63	0.56	0.83	0.64 - 1.08	0.96	0.73 - 1.25	0.77	0.59 - 1.02
Indeterminate user	53327.8	31	0.58	0.86	0.59 - 1.24	1.02	0.71 - 1.48	0.82	0.57 - 1.20
Former user	47333.0	39	0.82	1.22	0.87 - 1.69	1.32	0.95 - 1.84	0.99	0.71 - 1.40
Remote user	69202.3	67	0.97	1.43	1.10 - 1.85	1.06	0.82 - 1.38	0.76	0.58 - 1.00
Nonuser	553458.5	375	0.68	1.00	reference	1.00	reference	1.00	reference

Table 22. Rates of **ALL stroke,** by use of ADHD medications **(NEW USERS only, n=96,502)**

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
ADHD medication users	174573.5	143	0.82						
Current user	54569.3	41	0.75	0.94	0.68 - 1.31	1.12	0.81 - 1.56	0.79	0.56 - 1.12
Indeterminate user	30657.1	20	0.65	0.82	0.52 - 1.29	1.02	0.64 - 1.60	0.71	0.45 - 1.13
Former user	34644.6	26	0.75	0.94	0.63 - 1.41	1.08	0.72 - 1.61	0.74	0.49 - 1.11
Remote user	54702.5	56	1.02	1.28	0.96 - 1.71	1.02	0.76 - 1.36	0.72	0.54 - 0.98
Nonuser	328754.2	262	0.80	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, and other variables in Table A-5 (some variables are time-varying)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

When the analysis was stratified by medication subtype, all rate ratios for current use of each medication that were adjusted for baseline cardiovascular disease or CV drugs use, numbers of medications, medical conditions that suggest cardiovascular risk (obesity, diabetes, TIA, smoking) and time varying medical conditions such as ETOH/substance abuse and time-varying medication use (triptans, oral contraceptives, hormone replacement therapy) were all less than the non-user cohort (see table 23). However, the unadjusted rate and adjusted rates of stroke (only adjusted for site, age, sex and calendar year) showed a sight, but not statistically significant increase for methylphenidate. This trend was also noted for new-users of ADHD medications, with only methylphenidate and pemoline noting a non-significant rate ratio >1.00 when fully adjusted (table 24).

Table 23. Rates of **ALL stroke,** by specific ADHD medication

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	111935.5	63	0.56	0.83	0.64 - 1.08	0.96	0.73 - 1.25	0.77	0.59 - 1.02
Amphetamines	48672.9	19	0.39	0.58	0.36 - 0.91	0.75	0.47 - 1.19	0.63	0.40 - 1.01
Methylphenidate	50332.3	39	0.77	1.14	0.82 - 1.59	1.23	0.88 - 1.71	0.96	0.69 - 1.35
Atomoxetine	8371.1	3	0.36	0.53	0.17 - 1.65	0.58	0.19 - 1.82	0.46	0.15 - 1.44
Pemoline	3030.1	2	0.66	0.97	0.24 - 3.91	0.79	0.20 - 3.16	0.59	0.15 - 2.38
Multiple	1529.2	0	0.00	--	--	--	--	--	--
Nonuser	553458.5	375	0.68	1.00	reference	1.00	reference	1.00	reference

Table 24. Rates of **ALL stroke,** by specific ADHD medication **(NEW USERS ONLY)**

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	54569.3	41	0.75	0.94	0.68 - 1.31	1.12	0.81 - 1.56	0.79	0.56 - 1.12
Amphetamines	22965.2	10	0.44	0.55	0.29 - 1.03	0.73	0.39 - 1.38	0.54	0.28 - 1.02
Methylphenidate	23335.7	26	1.11	1.40	0.93 - 2.09	1.56	1.04 - 2.34	1.04	0.69 - 1.58
Atomoxetine	6429.4	3	0.47	0.59	0.19 - 1.83	0.67	0.21 - 2.10	0.51	0.16 - 1.61
Pemoline	1099.7	2	1.82	2.28	0.57 - 9.17	1.51	0.37 - 6.09	1.07	0.27 - 4.35
Multiple	739.3	0	0.00	--	--	--	--	--	--
Nonuser	328754.2	262	0.80	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, and other variables in Table A-5 (some variables are time-varying)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Finally, an analysis of the occurrence of stroke by duration of current ADHD medication use demonstrated a small, numerically higher adjusted hazard ratio with 91-182 days worth of cumulative ADHD medication use when compared to non-users (table 25). Additionally, this trend was also seen when the analysis was restricted to new users of ADHD medications (table 26). However this result was NOT statistically significant.

Table 25. Rates of **ALL stroke,** by use of ADHD medications

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Duration of Current use [#]									
366+ days	51540.0	29	0.56	0.83	0.57 - 1.21	0.88	0.60 - 1.28	0.73	0.49 - 1.07
183-365 days	23938.3	9	0.38	0.55	0.29 - 1.07	0.72	0.37 - 1.39	0.58	0.30 - 1.13
91-182 days	13896.9	12	0.86	1.27	0.72 - 2.26	1.64	0.92 - 2.91	1.29	0.72 - 2.31
31-90 days	11539.6	7	0.61	0.90	0.42 - 1.89	1.16	0.55 - 2.45	0.92	0.43 - 1.95
1-30 days	7898.0	4	0.51	0.75	0.28 - 2.00	0.93	0.35 - 2.49	0.73	0.27 - 1.98
Nonuser	553458.5	375	0.68	1.00	reference	1.00	reference	1.00	reference

Table 26. Rates of **ALL stroke,** by use of ADHD medications (**NEW USERS ONLY)**

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Duration of Current use [#]									
366+ days	16087.6	16	0.99	1.25	0.75 - 2.07	1.22	0.73 - 2.02	0.89	0.53 - 1.49
183-365 days	11018.6	4	0.36	0.46	0.17 - 1.22	0.57	0.21 - 1.54	0.40	0.15 - 1.08
91-182 days	9398.0	9	0.96	1.20	0.62 - 2.34	1.62	0.83 - 3.16	1.11	0.57 - 2.18
31-90 days	9511.8	6	0.63	0.79	0.35 - 1.78	1.13	0.50 - 2.54	0.78	0.34 - 1.75
1-30 days	7421.0	4	0.54	0.68	0.25 - 1.82	0.95	0.35 - 2.56	0.66	0.24 - 1.78
Nonuser	328754.2	262	0.80	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, and other variables in Table A-5 (some variables are time-varying)
[#] Excludes current pemoline use.
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Secondary Analysis

As with the adult SCD/MI study, the investigator's compared current, indeterminate and former use using remote users as the reference group. Current users of ADHD medications had a slightly elevated but not statistically significant increase in the fully adjusted rate ratio. Former users had an even higher fully adjusted rate ratio (table 27).

When the analysis was stratified by medication type, the highest rates were seen in methylphenidate users, although the rate was not statistically significant (table 28).

Table 27. Rates of **ALL stroke,** by use of ADHD medications

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	111935.5	63	0.56	0.58	0.41 - 0.82	0.90	0.63 - 1.28	1.02	0.71 - 1.45
Indeterminate user	53327.8	31	0.58	0.60	0.39 - 0.92	0.96	0.63 - 1.48	1.08	0.70 - 1.67
Former user	47333.0	39	0.82	0.85	0.57 - 1.26	1.24	0.83 - 1.85	1.31	0.88 - 1.95
Remote user	69202.3	67	0.97	1.00	reference	1.00	reference	1.00	reference

Table 28. Rates of **ALL stroke,** by specific ADHD medication

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	111935.5	63	0.56	0.58	0.41 - 0.82	0.90	0.63 - 1.28	1.02	0.71 - 1.45
Amphetamines	48672.9	19	0.39	0.40	0.24 - 0.67	0.70	0.42 - 1.18	0.83	0.50 - 1.40
Methylphenidate	50332.3	39	0.77	0.80	0.54 - 1.19	1.15	0.77 - 1.72	1.27	0.85 - 1.90
Atomoxetine	8371.1	3	0.36	0.37	0.12 - 1.18	0.55	0.17 - 1.75	0.60	0.19 - 1.93
Pemoline	3030.1	2	0.66	0.68	0.17 - 2.78	0.74	0.18 - 3.04	0.78	0.19 - 3.19
Multiple	1529.2	0	0.00	--	--	--	--	--	--
Remote user	69202.3	67	0.97	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, and other variables in Table A-5 (some variables are time-varying)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

When the analysis was restricted to new-users only, current users had a slightly higher, but not statistically significant adjusted rate (see Table 29). Further stratification by medication type showed a similar trend with all medication users in that the highest rate of stroke in current, new users was with methylphenidate use (table 30). Although the result was not statistically significant, a higher rate was seen in methylphenidate new-users.

Table 29. Rates of **ALL stroke,** by use of ADHD medications **(NEW USERS ONLY)**

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	54569.3	41	0.75	0.73	0.49 - 1.10	1.10	0.73 - 1.65	1.09	0.73 - 1.65
Indeterminate user	30657.1	20	0.65	0.64	0.38 - 1.06	1.00	0.60 - 1.66	0.99	0.59 - 1.65
Former user	34644.6	26	0.75	0.73	0.46 - 1.17	1.05	0.66 - 1.68	1.02	0.64 - 1.63
Remote user	54702.5	56	1.02	1.00	reference	1.00	reference	1.00	reference

Table 30. Rates of **ALL stroke,** by specific ADHD medication **(NEW USERS ONLY)**

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	54569.3	41	0.75	0.73	0.49 - 1.10	1.10	0.73 - 1.65	1.09	0.73 - 1.65
Amphetamines	22965.2	10	0.44	0.43	0.22 - 0.83	0.72	0.37 - 1.41	0.74	0.38 - 1.47
Methylphenidate	23335.7	26	1.11	1.09	0.68 -	1.53	0.96 -	1.44	0.90 -

					1.73		2.45		2.31
Atomoxetine	6429.4	3	0.47	0.46	0.14 - 1.46	0.66	0.20 - 2.11	0.71	0.22 - 2.27
Pemoline	1099.7	2	1.82	1.78	0.43 - 7.28	1.48	0.36 - 6.08	1.48	0.36 - 6.11
Multiple	739.3	0	0.00	--	--	--	--	--	--
Remote user	54702.5	56	1.02	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, and other variables in Table A-5 (some variables are time-varying)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

G. Analysis by Site

Demographic analysis of the sites that comprised the patient data in the adult data set revealed that the Tennessee Medicaid population was a younger population that had higher rates of cardiovascular ischemia, arrhythmias, hypertension, and hyperlipidemia with a greater proportion of those patients with diabetes, smoking and substance abuse when compared to the other sites. The Tennessee Medicaid population also had the lowest proportion of ADHD claims (3.1%) but had the highest rates of depression claims amongst all sites.

The TN Medicaid population was more likely than other patient populations to have been prescribed an antipsychotic medication, mood stabilizer, SSRI or benzodiazepine medication over the past year and was more likely to have been prescribed beta-agonist, asthma medications, COX-2 inhibitors and seizure medications.

When compared to the other populations in the study, TN Medicaid patients were more likely to have been on $\geq$ 2 different non-ADHD medications within the past year. Also these patients were more likely to be seen an emergency room or had a inpatient admission for medical and psychiatric reasons within the past year, as well have visited a physician or psychiatric provider $\geq$5 times.

Looking at standard adjusted rates of MI/SCD and stroke per 1,000 person-years, the TN Medicaid population consistently had the highest rates of all the sites as seen below.

Table 31: Adjusted Rate Ratios of SCD/MI and Stroke by Site

Site	Person-Years	Number events	Rate/1,000 PY	RR*	95% CI
SCI/MI					
TN Medicaid	122,204	583	4.77	1.86	1.60-2.16
Kaiser North	98,720	181	1.83	1.10	0.92-1.32
Kaiser South	32,276	57	1.66	1.08	0.82-1.43
Group Health	42,676	71	1.66	1.03	0.80-1.32
Harvard	67,201	76	1.13	0.65	0.51-0.83
Health Partners	32,051	57	1.78	1.18	0.90-1.56
Kaiser CO	19,823	33	1.67	0.87	0.61-1.25
Ingenix/i3	390,090	524	1.34	1.00	Ref
Stroke					
TN Medicaid	122,570	210	1.71	1.76	1.39-2.23
Kaiser North	98,921	71	0.72	1.33	1.00-1.79
Kaiser South	34,316	29	0.85	1.45	0.97-2.17
Group Health	42,769	23	0.54	0.99	0.63-1.54

Harvard	67,310	22	0.33	0.63	0.40-0.99
Health Partners	32,126	25	0.78	1.63	1.07-2.49
Kaiser CO	19,853	13	0.65	1.10	0.62-1.96
Kaiser Northwest	26,928	14	0.52	0.88	0.51-1.52
Ingenix/i3	390,461	168	0.43	1.00	Ref

*adjusted for exposure, gender, age, year, site and cardiovascular risk score

An analysis of heterogeneity by site in the SCD/MI data set was performed using the non-user group as the reference group. Of significant note, adults who were indeterminate users of ADHD medications (i.e. 0-30 days after last current use) at the Kaiser Permanente North site were 2.04 times more likely (95% CI 1.18-3.52) to have a myocardial infarction compared to non-users (see Table 31a). The combined endpoint with SCD/MI (Table 31b) remained statistically significant (1.88 95% CI 1.11-3.19). On demographic analysis, KP north patients had the highest proportion of obesity amongst all of the clinical sites (table 32).

Table 31a. Rate ratios of **acute myocardial infarction** by site

		I3		**KPNC**		**KPSC**	**Tennessee Medicaid**	
Medication status	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
ADHD medication users								
Current user	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 user	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 user	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 user	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	1.00	reference	1.00	reference	1.00	reference	1.00	reference

Adjusted for age, sex, calendar year, CRS (some variables within score are time-varying)
Using the CRS created from the full cohort

Table 31b. Rate ratios of **acute myocardial infarction or sudden cardiac death** by site

		I3		**KPNC**		**KPSC**	**Tennessee Medicaid**	
Medication status	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
ADHD medication users								
Current user	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 user	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 user	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 user	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	1.00	reference	1.00	reference	1.00	reference	1.00	reference

Adjusted for age, sex, calendar year, CRS (some variables within score are time-varying)

Table 32. Characteristics of study cohort at baseline, **by site**

Characteristics	I3* N=266,787	KPNC* N=36,450	KPSC* N=19,947	HMORN* N=80,351	Tennessee Medicaid* N=43,371
Demographics					
Median age (years)	41	44	45	43	39
Male gender (%)	47.7%	46.3%	47.3%	46.2%	34.0%
Medicaid enrollment (%)	--	1.2%	0.9%	--	100.0%
Exposure					
Nonusers (N)	177,638	24,289	13,295	49,626	28,901
Current users (N)	88,868	12,150	6,652	30,725	14,470
New users (N)	52,665	7,899	4,350	18,001	13,956
Cardiovascular disease within past year					
Acute MI	0.2%	0.1%	0.2%	0.2%	0.5%
Ischemia	2.3%	1.1%	1.4%	1.7%	6.5%
Coronary revascularization	0.2%	0.1%	0.1%	0.1%	0.5%
CHF	0.4%	0.3%	0.4%	0.3%	3.1%
Arrhythmia	1.9%	0.6%	1.0%	1.7%	3.9%
Stroke/TIA	0.7%	0.3%	0.5%	0.6%	2.8%
Congenital heart disorder	0.2%	0.1%	0.1%	0.2%	0.4%
Coronary artery anomaly	0.0%	0.0%	0.0%	0.0%	0.1%
Peripheral vascular disease	0.5%	0.3%	0.3%	0.5%	2.0%
Hypertension	13.2%	10.0%	11.3%	10.8%	27.1%
Hyperlipidemia**	16.5%	9.4%	15.0%	13.9%	22.2%
Mental health claims within past year					
ADHD	9.6%	15.2%	14.9%	14.1%	3.1%
Major depression	15.9%	21.6%	20.2%	23.1%	27.4%
Bipolar disorder	2.2%	3.2%	3.0%	3.0%	8.9%
Anxiety	8.7%	11.0%	10.8%	11.1%	18.3%
Psychotic disorders	0.4%	0.8%	0.9%	0.6%	5.3%
Other selected medical conditions within past year					
Diabetes**	4.6%	5.2%	6.3%	4.6%	13.1%
Obesity	2.6%	17.6%	5.9%	4.3%	6.1%
Smoking	3.6%	10.9%	2.9%	6.9%	15.4%
ETOH/substance abuse	1.6%	4.5%	3.4%	2.7%	8.9%
Suicide attempt	0.2%	0.1%	0.2%	0.2%	1.2%
Injury	14.0%	15.0%	13.6%	14.9%	24.9%
Seizure	0.9%	0.6%	0.6%	0.9%	5.7%
Asthma	4.8%	5.9%	4.3%	5.4%	9.4%
Use of cardiovascular drug within past year					
Loop diuretic	1.4%	1.2%	1.3%	1.1%	9.1%
Digoxin	0.2%	0.3%	0.4%	0.3%	1.6%
Nitrates	0.7%	1.0%	1.1%	1.0%	4.7%
Anticoagulant	0.6%	0.6%	2.9%	0.8%	2.6%
Platelet inhibitor	0.5%	0.3%	0.4%	0.3%	2.2%
Anti-arrhythmic agents	0.1%	0.1%	0.2%	0.6%	0.5%
ACE inhibitor	5.9%	6.0%	8.0%	5.9%	14.3%
Angiotensin receptor blocker	2.5%	0.7%	1.1%	0.9%	4.0%
Beta- blocker	5.9%	7.5%	8.4%	7.3%	13.0%
Calcium-channel blocker	3.9%	3.0%	3.0%	3.0%	11.1%
Thiazide diuretic	7.0%	7.3%	8.5%	6.2%	10.6%
Other antihypertensive	0.7%	1.0%	1.5%	0.7%	1.9%
Use of psychotropic medications within past year					

Antipsychotic, any	2.6%	4.3%	4.5%	4.0%	17.0%
Tricyclic antidepressant	3.5%	6.0%	5.5%	5.9%	16.0%
Antidepressants, other or SSRI/SNRI	22.3%	28.2%	27.6%	31.8%	41.2%
Benzodiazepines	14.3%	12.9%	14.1%	14.1%	29.4%
Lithium	0.8%	1.4%	0.9%	1.2%	3.1%
Modafinil	1.1%	0.6%	1.6%	0.9%	1.8%
Insomnia meds	5.7%	1.7%	1.7%	2.5%	9.0%
Thioridazine	0.0%	0.1%	0.1%	0.1%	0.9%
Mood stabilizers, w/o seizure	5.6%	6.3%	5.7%	6.4%	17.4%
Clonidine/guanfacine, w/o HT	0.5%	0.4%	0.5%	0.6%	1.5%
Use of other selected medications within past year					
Beta-agonist	6.7%	11.0%	10.0%	9.5%	19.1%
Epinephrine	0.5%	0.4%	0.4%	0.8%	0.8%
Asthma med, other	18.3%	10.8%	11.8%	21.3%	29.2%
Seizure med, any	6.1%	6.7%	6.1%	6.8%	21.3%
Theophylline compounds	0.2%	0.3%	0.2%	0.3%	2.7%
COX-2 inhibitors	5.9%	0.8%	1.0%	1.2%	10.3%
Other drugs to improve blood flow	0.1%	0.1%	0.0%	0.1%	0.4%
Clonidine	0.6%	0.7%	0.9%	0.8%	3.7%
pde5 inhibitors	2.3%	3.0%	3.7%	1.9%	0.5%
Triptans	2.8%	2.5%	2.7%	2.4%	3.9%
Oral contraceptives	10.3%	9.8%	10.3%	11.7%	10.7%
Hormones, menopausal or misc	8.6%	10.4%	9.4%	9.6%	11.7%
Utilization within past year					
Cardiovascular visits					
Emergency, 1+	1.4%	2.3%	2.2%	3.2%	13.6%
Inpatient, 1+	2.0%	1.7%	3.1%	2.3%	11.1%
Physician, 1-4	25.2%	18.7%	19.4%	22.9%	29.0%
Physician, 5+	6.6%	2.1%	2.4%	4.9%	18.9%
Psychiatric visits#					
Emergency, 1+	0.6%	1.0%	0.9%	1.7%	9.0%
Inpatient, 1+	1.6%	1.7%	2.3%	2.0%	10.7%
Physician, 1-4	14.0%	18.2%	19.0%	17.3%	19.8%
Physician, 5+	9.4%	10.5%	8.8%	13.6%	22.5%
Other visits					
Emergency, 1+	2.0%	2.7%	2.8%	4.2%	16.9%
Inpatient, 1+	1.6%	1.9%	3.1%	1.9%	9.9%
Physician, 1+	25.9%	34.1%	22.9%	25.9%	40.9%
No. of different medications***					
1	19.9%	21.1%	20.7%	19.8%	10.8%
2+	47.8%	47.2%	47.9%	50.3%	72.0%

*Numbers are for membership periods at baseline or cohort entry (t_0).
** Including medications
# Excluding ADHD visits
*** Excluding ADHD medications
HMORN (HMO Research Network)-Group Health, Harvard Pilgrim, Healthpartners, KP Colorado, KP Northwest

H. Summary

Current use of ADHD medication was not associated with a significant increase in either SCD, MI or stroke rates when compared to non-users (primary analysis) or to remote users (secondary analysis). Previous ADHD medication use that occurred greater than 90 days after last day of use was associated with a significant decrease in adjusted rates of SCD and MI when compared

to non-users. It is likely that this decrease in risk may reflect a healthy user bias in current users vs. non-users which calls into question the choice of reference groups and the methods used to control confounding at baseline.

In contrast, previous ADHD medication use that occurred 0 to 89 days after last day of use was associated with slightly higher (but not statistically significant) increases in SCD/MI and strokes, with the exception of the Kaiser Permanente North site which had an adjusted MI rate 2.04 times greater than non-users (95% CI 1.18-3.52) and combined SCD/MI rate of 1.88 (95% CI 1.11-3.19). For the secondary analysis, previous ADHD medication use that occurred 0 to 89 days after last day of use was associated with an adjusted rate ratio for MI of 1.31 that almost achieved significance (95% CI 1.00-1.71) when compared to ADHD medication use that occurred >365 days after last use. When the analysis was restricted to the Tennessee Medicaid population, previous ADHD medication use that occurred 90-364 days after current use was associated with a 1.57 times increase (95% CI 1.03-2.38) in MI rates when compared to previous ADHD medication use that occurred >365 days after last day of use.

VI. Limitations

Three major concerns were noted during the development and analysis of the study designs that were raised by Agency staff to the steering committee members. Despite these noted limitations, the unadjusted rates of each endpoint appear to support the overall conclusions from the study that there does not appear to be an association between ADHD medication current use and SCD, MI or strokes in children, youths or adults.

A. Appropriateness of Non-users as Reference Group

In order to examine rates of each endpoint of interest, the choice of reference group is critical in order to reduce the effect of any unmeasured confounding which may account for differences in the rates seen in the two populations. The most logical reference group would be those patients with ADHD who have not been treated with any medication. However the likelihood that sufficient numbers of non-treated ADHD patients that could be identified from the population would be extremely small, FDA had recommended that former users of ADHD medications would be a more appropriate choice of reference group for both the child and adult studies since non-users are likely to be less similar to patients who use stimulants than those who previously used these medications. Despite FDA's recommendation of using former users as the reference group, the steering committee obtained consensus to use non-users as the reference group. However the steering committee also recommended that a secondary analysis would be performed using former users as a reference group.

Based on the primary analysis of the data in adults, former users of ADHD medications had statistically significantly reduced rates of SCD and MI's when compared to non-users when fully adjusted despite having the highest unadjusted rates of each endpoint for all the populations. One plausible explanation for these findings is that a "healthy user bias" may be contributing to the apparent cardio-protective effect seen with previous use of ADHD medications. In essence it could be possible that users of ADHD medications were likely healthier and more likely to have been prescribed or taking ADHD medications than non-users and thus were more likely to have

lower rates of SCD/MI or stroke before, during and after use of ADHD medications than non-users.

B. The Absence of an all-cause mortality Rate

For examination of a precisely defined mortality endpoint, it is important to calculate an all-cause mortality rate between comparison groups to examine if rates of death between populations are different and potentially associated to a difference in rates for the defined mortality endpoint. Although FDA staff had requested an all-cause mortality endpoint to be included in the analysis, this metric was not included in the final study report for either the youth or adult studies.

C. Use of Propensity Scores to adjust for Clinical Population confounding variables at baseline in the Child study and use of CRS in the adult study to adjust for confounding

In order to account for unmeasured confounding at baseline between user and non-user cohorts, the investigators calculated a site-specific propensity score to adjust for differences. Propensity scores calculate the probability at baseline that a particular individual is likely to use an ADHD medication. These scores are then converted into deciles and then included as a variable in the fully adjusted models. The use of propensity score adjustment can be considered valid if there is overlap between the propensity scores of the groups being compared.

Since the majority of non-user cohorts were not likely to have an ADHD diagnosis and thus have a low-propensity to use ADHD medications, there appeared to be little overlap between the user and non-user cohorts at each site when propensity scores were presented by decile for each site and aggregate. This raises concern that the use of propensity score adjustments at baseline may not have been employed properly in order to adjust for baseline differences in the two populations.

In addition, the cardiovascular risk score has not been widely accepted in the literature as propensity scores in order to adjust for confounding at baseline.

D. Use of Cox Proportional Hazards (child study) and Poisson Regression in the Adult studies

Both Cox proportional hazards and Poisson regression analysis assumes that the risk of the event of interest occurring is constant during the entire time period of measure. Although the risk of SCD may be constant while taking ADHD medications, the risk of MI and stroke are likely to be greater with constant use as these endpoints are causally related to long-term increases in blood pressure. Since stimulants are known to increase blood pressure, one can infer that the risk of MI and stroke are NOT constant with constant use.

VII. Conclusions and Recommendations

A. Youth Study

Based on the review from both the primary and secondary analysis, no association was seen between current ADHD medication use and sudden cardiac death, acute myocardial infarction or stroke rates in patients aged 2-24 years old.

Current labeling for stimulant products and atomoxetine contains a warning of an association between post-marketing reports of SCD and stimulant use with recommendations to obtain a focused clinical history and additional clinical work-up for patients with a family history of clinical history of cardiac abnormalities. In view of the results from this study and current labeling for stimulant and atomoxetine products, no regulatory action is indicated at this time with regards to stimulant use in children and adolescents and cardiovascular risk.

B. Adult Study

Based on the primary analysis of the adult study, there appears to be no association between SCD, MI or stroke in the adult population who currently receive ADHD medication. However site results from the primary analysis indicate a possible association between previous ADHD medication use (0-30 days after last use) and myocardial infarction in KP northern patients (RR 2.04 95% CI 1.18-3.52). The secondary analysis also suggests that a small increased risk of MI in Medicaid adults 31 days to 354 days after taking ADHD medication may be present when compared to adult users who last took ADHD medication > 1 year; a finding also seen in the entire population with a trend toward statistical significance.

A biologically plausible hypothesis that could potentially explain these findings could be an association of attenuated centrally-mediated sympathetic tone $\pm$ adrenergic receptor down-regulation with daily ADHD medication use, with consequently increased centrally-mediated sympathetic tone $\pm$ up-regulation of adrenergic receptors after discontinuation of daily stimulant use when compared to current users and non-users of stimulant medications. A recent study by Vitiello et al[3] which may provide some support for this hypothesis examined longitudinal blood pressure and heart rate changes in children who participated in the Multimodal Treatment of ADHD (MTA) study and demonstrated stimulant treatment had a persistent adrenergic effect on heart rates at years 3 to 8 that was significant with cumulative exposure regardless of current use.

Based on review of the primary analysis data and current medication labeling for stimulant products and atomoxetine, it is this reviewer's recommendation that no labeling changes be taken at this point. However, consideration should be given to addressing a possible association with increased sudden cardiovascular events post-therapy in adult patients administered stimulants. The potential for a withdrawal-emergent cardiovascular risk in adults with ADHD medication use was discussed with OSE reviewers who concluded that such a risk cannot be determined from claims-based data. In the opinion of the OSE staff, claims-based data cannot provide precise detail on patient compliance and thus accurate detail on when a patient discontinued the medication in the 0-30 day period after last days of prescription use.

[3] Vitiello B, Elliott GR et al " Blood Pressure and Heart rate over 10 years in the Multimodal Treatment Study of Children with ADHD" *Am J Psychiatry* Sep 2011 in advance of printing. **doi: 10.1176/appi.ajp.2011.10111705**

Ultimately this reviewer concurs with the recommendations made by OSE to examine the association between current use (and potentially post-treatment) of ADHD medications and cardiovascular risks through a meta analysis of adult clinical trial data. Such data would provide more precise and accurate information on compliance and use of medications in a placebo-controlled fashion which would permit a more precise analysis of cardiovascular risk and potentially a withdrawal-emergent cardiovascular risk with adult stimulant use.

APPENDIX

Table A-5. Rate ratios of **ALL stroke – standard adjustment**

Variable in model	Person-yrs	Number Events	Rate/1,000 person-yrs	RR*	95% CI
Exposure					
Medication utilization in 365 days prior to baseline**					
Amphetamines	48672.9	19	0.39	0.63	0.40-1.01
Methylphenidate	50332.3	39	0.77	0.96	0.69-1.35
Atomoxetine	8371.1	3	0.36	0.46	0.15-1.44
Pemoline	3030.1	2	0.66	0.59	0.15-2.38
Multiple	1539.3	0	0.00	0.00	
Indeterminate	53227.8	31	0.58	0.82	0.57-1.20
Former	47333.6	39	0.82	0.99	0.71-1.39
Remote	69202.3	67	0.97	0.76	0.58-1.00
Non-user	553458.5	375	0.68	1.00	reference
Demographics					
Gender					
Male	382804.1	274	0.72	1.30	1.08-1.56
Female	452452.1	301	0.67	1.00	reference
Age					
25-29	55385.3	3	0.05	0.05	0.01-0.15
30-34	97070.3	22	0.23	0.18	0.11-0.30
35-39	120673.6	37	0.22	0.17	0.11-0.27
40-44	150005.3	53	0.35	0.25	0.18-0.36
45-49	156251.2	93	0.59	0.39	0.29-0.53
50-54	129590.9	125	0.96	0.55	0.43-0.72
55-59	83875.8	129	1.54	0.72	0.56-0.92
60-64	42375.0	125	2.95	1.00	reference
Site					
KPNC	98921.4	71	0.72	1.33	1.00-1.79
KPSC	34316.0	29	0.85	1.45	0.97-2.17
Tennessee Medicaid	122570.1	210	1.71	1.76	1.39-2.23
HMORN					
Group Health	42769.7	23	0.54	0.99	0.68-1.54
Harvard Pilgrim	67310.0	22	0.33	0.63	0.40-0.99
HealthPartners	32126.2	25	0.78	1.63	1.07-2.49
KP Colorado	19853.5	13	0.65	1.10	0.62-1.96
KP Northwest	26928.4	14	0.52	0.88	0.51-1.52
Ingenix/I3	390461.8	168	0.43	1.00	reference
Year					
2004-2005	375280.3	242	0.64	1.46	0.53-3.97
2002-2003	237850.0	166	0.70	1.67	0.61-4.58
2000-2001	143704.8	81	0.56	1.41	0.51-3.89
1993-1999	73189.4	82	1.12	2.23	0.81-6.12
1986-1992	5232.7	4	0.76	1.00	reference
Cardiovascular disease in 365 days prior to baseline**					
Acute MI, primary	858.9	3	3.49	0.85	0.27-2.70
Acute MI, other	1047.8	6	5.73	1.58	0.70-3.60
Hypertension	109604.2	233	2.13	1.50	1.22-1.84
Use of cardiovascular drug in 365 days prior to baseline **					
Anticoagulant	7378.3	46	6.23	2.15	1.55-2.99
Platelet inhibitor	4186.9	31	7.40	1.32	0.88-1.97

Medication utilization in 365 days prior to baseline **					
No. of different medications***					
1	161573.7	59	0.37	1.08	0.77-1.51
2	118379.3	60	0.51	1.27	0.90-1.79
3	85939.2	51	0.59	1.23	0.86-1.78
4	61886.9	53	0.86	1.53	1.05-2.21
5	45182.9	46	1.02	1.52	1.03-2.25
6	32137.0	44	1.37	1.84	1.23-2.76
7-8	39336.1	82	2.08	2.21	1.53-3.18
9-10	19725.1	41	2.08	1.71	1.10-2.66
11+	18306.6	59	3.22	1.78	1.14-2.78
Medical conditions, ever/never[$]					
Obesity	82380.8	112	1.36	1.13	0.90-1.41
Smoking	105102.2	154	1.47	1.19	0.97-1.46
Diabetes[##]	69124.9	195	2.82	1.96	1.60-2.41
TIA, primary	2860.5	40	13.98	1.92	1.33-2.78
TIA, other	16577.4	126	7.60	3.45	2.69-4.44
Hyperlipidemia[##]	201392.8	289	1.44	0.96	0.78-1.17
Peripheral vascular disease	13801.6	57	4.13	1.11	0.82-1.51
Other selected medical conditions, time-varying[$$]					
ETOH/substance abuse, primary	3698.8	4	1.08	1.11	0.41-2.99
ETOH/substance abuse, other	19850.9	29	1.46	1.49	1.01-2.19
Use of other selected medications, time-varying[$$]					
Triptans	4705.5	5	1.06	1.67	0.69-4.06
Oral contraceptives	42449.6	27	0.64	1.58	1.06-2.36
Hormones, menopausal or misc	49331.7	63	1.28	1.04	0.78-1.39

*RRs adjusted for site, age, sex, calendar year, exposure, and each of the other variables in the table
**At baseline or cohort entry (t_0): if 'on' at baseline, remains on; if 'off' at baseline but goes 'on' during follow-up, stays off
*** Excluding ADHD medications
[$] Ever/never: once 'on' at baseline or during follow-up, remains on
[##] Including medications
[$$] Diagnosis: 'on' if any day in prior 365 is 'on', else 'off'; Meds: 'on' if has supply on the day, else 'off'
*RRs adjusted for all other variables in the table; All variables except the utilization variable, no. of different medications are must-haves. Only the utilization variable earned its way in using the 10% change in RR rule.

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/s/

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09/30/2011

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10/10/2011