Risk of Major Cardiovascular and Cerebrovascular Events in Users of Lisdexamfetamine and Other Medications for Attention-Deficit/Hyperactivity Disorder in Denmark and Sweden: A Population-Based Cohort Study

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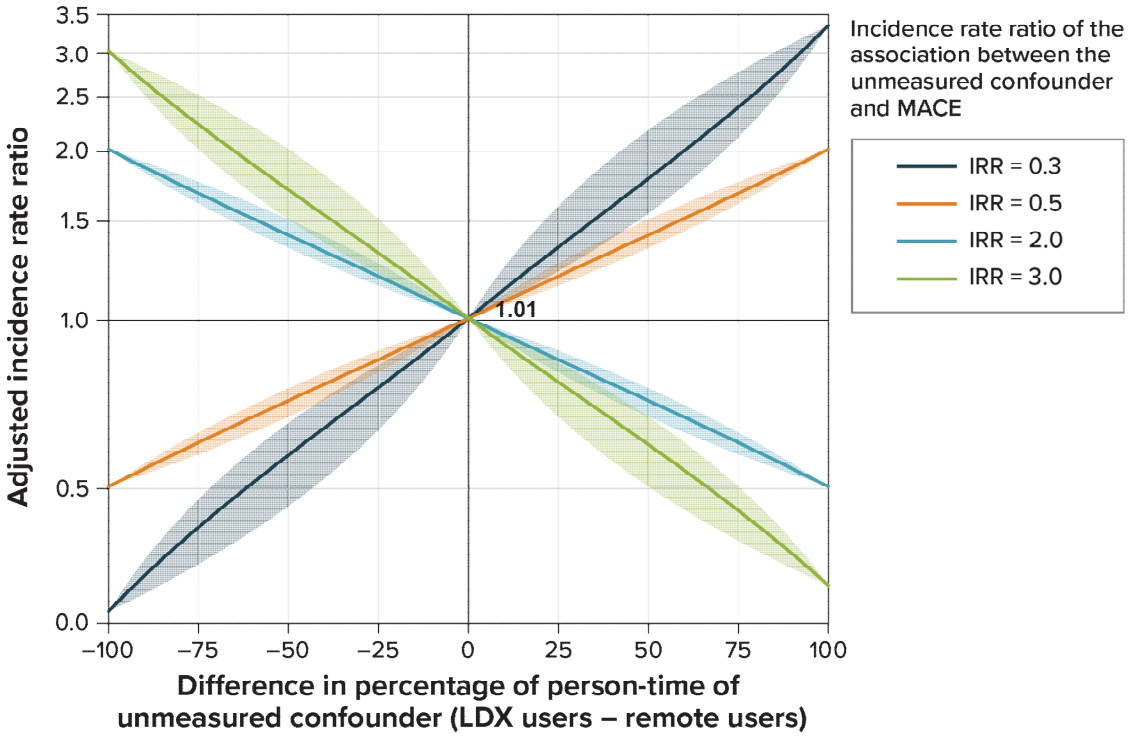
Bias Analysis of Unmeasured Confounding

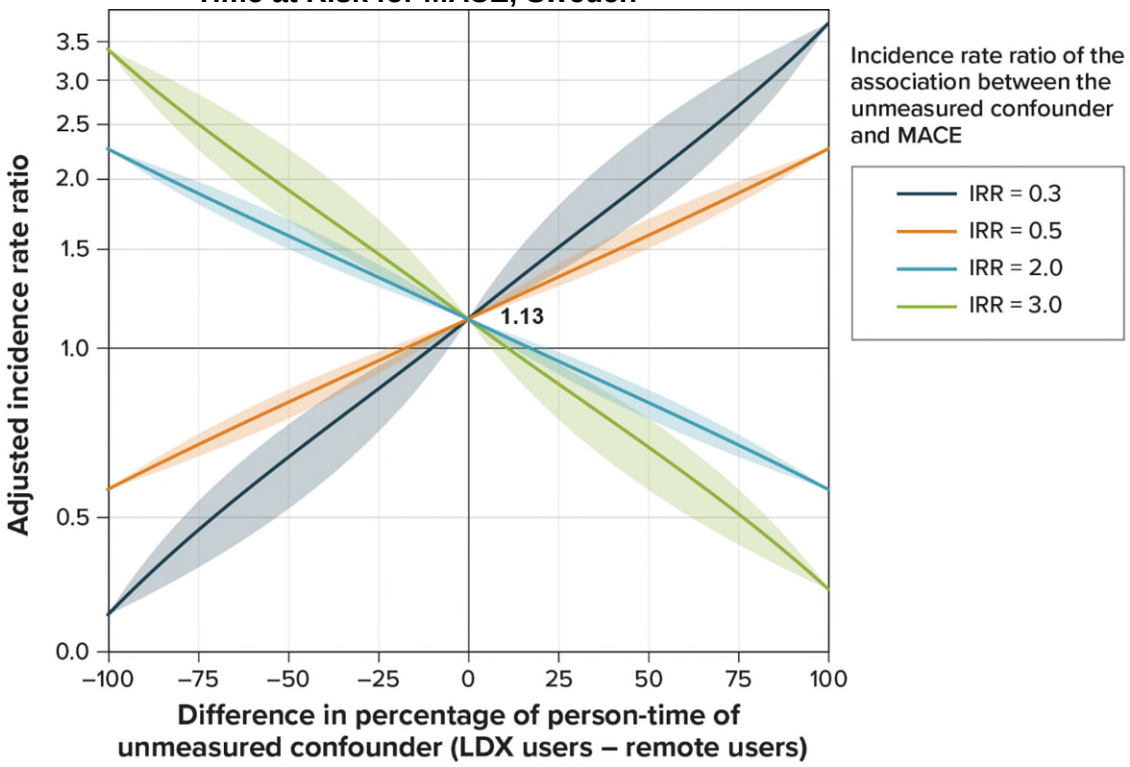
A bias analysis was conducted to assess the potential impact on the results of residual confounding due to unmeasured variables or poorly measured variables, such as those for which proxies were used. The incidence rate ratio (IRR) adjusted for different hypothetical scenarios of unmeasured confounding was calculated (Figure S1 and S2). In these figures, different IRRs of the association between an unmeasured confounder and major adverse cardiovascular and cerebrovascular events (MACE) (0.3, 0.5, 2.0, and 3.0) and a range of differences in percentage (from −100% to +100%) of person-time of an unmeasured confounder between the two cohorts (LDX users – Previous users) were used to derive the IRR adjusted for the potential unmeasured confounder. For example, in Denmark, in an extreme scenario (IRR, 0.3 for the unmeasured confounder and MACE and 100% difference of person-time between lisdexamfetamine dimesylate [LDX] users and previous users), the adjusted IRR for MACE would be approximately 3.5. In a scenario with an IRR between an unmeasured confounder and MACE of 2 and a 25% difference of person-time between LDX users and previous users, the adjusted IRR for MACE would be 1.30 (the adjusted IRR observed in the main analysis was 1.01). In Sweden, bias analysis for an unmeasured confounder showed similar results. In both countries, only in extreme scenarios of an unmeasured confounder strongly associated with MACE and much more prevalent in LDX users than in previous users would the adjusted IRR for MACE be higher than 3.

Figure S1. Sensitivity Analysis: Bias Analysis, Incidence Rate Ratio After Adjusting for an Unmeasured Confounder, by Confounder Prevalence During Current Time at Risk for MACE, Denmark



IRR: incidence rate ratio; LDX: lisdexamfetamine dimesylate; MACE: major adverse cardiovascular and cerebrovascular events.

Figure S2. Sensitivity Analysis: Bias Analysis, Incidence Rate Ratio After Adjusting for an Unmeasured Confounder, by Confounder Prevalence During Current Time at Risk for MACE, Sweden



IRR: incidence rate ratio; LDX: lisdexamfetamine dimesylate; MACE: major adverse cardiovascular and cerebrovascular events.

Exploratory and Sensitivity Analyses

Table S1. Exploratory Analysis: Adjusted Incidence Rates and Incidence Rate Ratios for MACE for LDX Patients and Previous Users, Trimmed Population for Denmark, Sweden, and Pooled

	LDX Users				Remote Users				
Endpoint	Number of Patients	Number With Outcome[a]	PY[b]	IR per 1,000 PY (95% CI)[c]	Number of Patients[d]	Number With Outcome[a]	PY[b]	IR per 1,000 PY (95% CI)[c]	IRR[c,e] (95% CI)
Denmark									
Sex									
Male	2,887	<5		1.39 (0.52-3.72)	14,390	48	24,724.0	1.77 (1.28-2.44)	0.79 (0.28-2.25)
Female	2,629	N.R.		1.68 (0.69-4.10)	13,104	28	22,550.8	1.27 (0.87-1.85)	1.33 (0.44-4.03)
Age (years)									
18-29	2,706	<5		N.E.	13,768	<5		N.E	4.24 (0.75-23.88)
30-39	1,406	<5		N.E.	6,967	N.R.		N.E	2.62 (0.55-12.55)
40-49	1,027	<5		1.66 (0.41-6.67)	4,970	33	8,833.5	3.56 (2.48-5.12)	0.47 (0.10-2.10)
> 50	377	<5		7.76 (2.50-24.14)	1,789	31	3,285.7	9.39 (6.57-13.44)	0.83 (0.25-2.76)
Impact of long-term exposure[f]									
Long-term LDX users vs. long-term previous users	1,939	N.R.		2.41 (1.08-5.38)	17,060	53	25,547.4	2.01 (1.50-2.70)	1.20 (0.49-2.92)
Daily dose at index date									
20 mg	856	<5		2.39 (0.33-17.49)					1.54 (0.19-12.52)
30 mg	3,694	N.R.		N.E.					1* (Ref.)
40 mg	61	0	35.9	N.E.					N.E.
50 mg	476	0	518.0	N.E.					N.E.

Endpoint	LDX Users				Remote Users				
	Number of Patients	Number With Outcome[a]	PY[b]	IR per 1,000 PY (95% CI)[c]	Number of Patients[d]	Number With Outcome[a]	PY[b]	IR per 1,000 PY (95% CI)[c]	IRR[c,e] (95% CI)
60 mg	53	0	41.9	N.E.					N.E.
70 mg	297	<5		N.E.					1.61 (0.20-13.06)
Other	79	0	98.1	N.E.					N.E.
Impact of other ADHD treatments									
Current single LDX users vs. previous users	4,437	N.R.		1.76 (0.84-3.69)	27,494	76	47,274.7	1.61 (1.27-2.03)	1.10 (0.48-2.49)
Current LDX users with other ADHD medications[g] vs. previous use	4,051	<5		1.26 (0.31-5.04)	27,494	76	47,274.7	1.60 (1.27-2.03)	0.78 (0.18-3.33)
Previous history of cardiovascular disease									
Yes	464	0	478.3	N.E.	2,271	35	3,954.2	8.66 (6.09-12.30)	N.E.
No	5,052	9	5,029.6	1.77 (0.92-3.41)	25,223	41	43,320.6	0.95 (0.69-1.30)	1.87 (0.86-4.06)
Diagnosis of ADHD									
Yes	2,351	N.R.		2.23 (0.92-5.39)	11,926	22	19,153.9	1.16 (0.75-1.80)	1.92 (0.59-6.20)
No	3,165	<5		1.19 (0.45-3.18)	15,568	54	28,120.8	1.88 (1.42-2.49)	0.64 (0.22-1.83)
Previous history of psychiatric disease									
Yes	2,588	N.R.		2.39 (1.07-5.34)	13,204	44	22,326.7	1.90 (1.38-2.61)	1.26 (0.50-3.16)
No	2,928	<5		0.94 (0.30-2.94)	14,290	32	24,948.1	1.30 (0.90-1.86)	0.73 (0.20-2.61)
Sweden									
Sex									

	LDX Users				Remote Users				
Endpoint	**Number of Patients**	**Number With Outcome[a]**	**PY[b]**	**IR per 1,000 PY (95% CI)[c]**	**Number of Patients[d]**	**Number With Outcome[a]**	**PY[b]**	**IR per 1,000 PY (95% CI)[c]**	**IRR[c,e] (95% CI)**
Male	20,234	43	23,108.9	6.31 (4.68-8.51)	100,763	87	62,753.4	4.72 (3.83-5.83)	1.34 (0.80-2.22)
Female	19,929	20	21,915.8	4.63 (2.99-7.18)	99,626	57	59,987.1	5.58 (4.30-7.23)	0.83 (0.41-1.67)
Age (years)									
18-29	18,285	2	18,878.5	0.42 (0.10-1.67)	93,893	13	57,558.0	0.77 (0.45-1.33)	0.54 (0.12-2.45)
30-39	11,041	8	13,066.8	1.22 (0.61-2.44)	54,184	27	32,966.8	1.38 (0.95-2.01)	0.88 (0.28-2.81)
40-49	6,988	25	8,501.0	12.64 (8.54-18.71)	34,332	38	21,207.6	8.56 (6.23-11.76)	1.48 (0.68-3.20)
> 50	3,849	28	4,578.4	25.18 (17.38-36.47)	17,980	66	11,008.1	26.15 (20.55-33.29)	0.96 (0.54-1.71)
Impact of long-term exposure[f]									
Long-term LDX users vs. long-term previous users	16,416	31	19,334.2	5.22 (3.67-7.42)	43,861	8	10,408.5	2.52 (1.26-5.04)	2.07 (0.87-4.90)
Daily Dose at index date									
20 mg	5,918	4	3,905.8	4.28 (1.61-11.40)					0.96 (0.34-2.72)
30 mg	28,062	41	33,631.0	4.47 (3.29-6.07)					1* (Ref.)
40 mg	393	0	316.3	N.E.					N.E.
50 mg	3,044	9	3,746.2	8.89 (4.62-17.08)					1.99 (0.97-4.10)
60 mg	164	0	114.4	N.E.					N.E.
70 mg	1,605	4	1,981.4	7.49 (2.81-19.95)					1.68 (0.60-4.69)
Other	894	5	1,227.1	14.78 (6.15-35.51)					3.31 (1.31-8.38)
Impact of other ADHD treatments									

Endpoint	LDX Users				Remote Users				
	Number of Patients	Number With Outcome[a]	PY[b]	IR per 1,000 PY (95% CI)[c]	Number of Patients[d]	Number With Outcome[a]	PY[b]	IR per 1,000 PY (95% CI)[c]	IRR[c,e] (95% CI)
Current single LDX users vs. previous users	35,592	41	34,167.2	4.55 (3.35-6.18)	200,389	144	122,740.5	5.06 (4.30-5.95)	0.90 (0.50-1.61)
Current LDX users with other ADHD medications[g] vs. previous users	26,027	22	10,857.4	6.81 (4.48-10.34)	200,389	144	122,740.5	5.15 (4.38-6.07)	1.32 (0.85-2.06)
Previous history of cardiovascular disease									
Yes	4,390	23	5,054.8	13.88 (9.22-20.89)	21,496	73	13,065.3	16.86 (13.40-21.20)	0.82 (0.44-1.55)
No	35,773	40	39,969.8	4.79 (3.52-6.54)	178,893	71	109,675.2	3.49 (2.77-4.41)	1.37 (0.79-2.39)
Diagnosis of ADHD									
Yes	33,239	49	37,271.7	4.66 (3.52-6.16)	171,112	113	103,924.7	3.92 (3.26-4.71)	1.19 (0.74-1.90)
No	6,924	14	7,753.0	8.54 (5.06-14.42)	29,277	31	18,815.8	8.33 (5.86-11.84)	1.03 (0.54-1.93)
Previous history of psychiatric disease									
Yes	29,879	53	33,671.0	5.02 (3.83-6.57)	146,942	123	89,552.0	4.32 (3.62-5.15)	1.16 (0.75-1.80)
No	10,284	10	11,353.6	7.86 (4.23-14.61)	53,447	21	33,188.6	8.56 (5.58-13.13)	0.92 (0.29-2.86)

	LDX Users				Remote Users				
Endpoint	**Number of Patients**	**Number With Outcome[a]**	**PY[b]**	**IR per 1,000 PY (95% CI)[c]**	**Number of Patients[d]**	**Number With Outcome[a]**	**PY[b]**	**IR per 1,000 PY (95% CI)[c]**	**IRR[c,e] (95% CI)**
Pooled									
Sex									
Male	23,121	44-47		N.E.	115,153	135	87,477.4	1.62 (1.16-2.25)	1.21 (0.77-1.91)
Female	22,558	25-29		N.E.	112,730	85	82,537.9	1.05 (0.81-1.35)	0.95 (0.53-1.71)
Age (years)									
18-29	20,991	3-6		N.E.	107,661	14-17		N.E.	1.45 (0.19-10.91)
30-39	12,447	9-12		N.E.	61,151	32-36		N.E.	1.33 (0.47-3.73)
40-49	8,015	26-29		N.E.	39,302	71	30,041.1	2.58 (1.26-5.30)	1.00 (0.34-2.92)
> 50	4,226	29-32		N.E.	19,769	97	14,293.8	7.38 (4.74-11.49)	0.94 (0.56-1.57)
Impact of long-term exposure									
Long-term LDX users vs long-term previous users	18,355	36-40		N.E.	60,921	61	35,955.9	1.33 (0.51-3.50)	1.59 (0.86-2.95)
Daily dose at index date									
20 mg	6,774	5-8		N.E.					1.05 (0.41-2.68)
30 mg	31,756	46-50		N.E.					1* (Ref.)
40 mg	454	0	352.2	4.70 (0.56-39.66)					N.E.
50 mg	3,520	9	4,264.2	2.29 (1.21-4.32)					N.E.
60 mg	217	0	156.3	7.22 (1.02-51.24)					N.E.
70 mg	1,902	5-8		N.E.					1.66 (0.66-4.18)
Other	973	5	1,325.2	4.16 (1.80-9.59)					N.E.

Endpoint	LDX Users				Remote Users				
	Number of Patients	Number With Outcome[a]	PY[b]	IR per 1,000 PY (95% CI)[c]	Number of Patients[d]	Number With Outcome[a]	PY[b]	IR per 1,000 PY (95% CI)[c]	IRR[c,e] (95% CI)
Impact of other ADHD treatments									
Current single LDX users vs previous users	40,029	46-50		N.E.	227,883	220	170,015.2	1.36 (1.00-1.85)	0.96 (0.60-1.54)
Current LDX users with other ADHD vs previous users	30,078	23-26		N.E.	227,883	220	170,015.2	1.36 (1.00-1.85)	1.26 (0.83-1.93)
Previous history of cardiovascular disease									
Yes	4,854	23	5,533.1	4.24 (2.29-7.85)	23,767	108	17,019.5	6.92 (4.41-10.85)	N.E.
No	40,825	49	44,999.4	1.24 (0.72-2.16)	204,116	112	152,995.8	0.77 (0.53-1.12)	1.53 (0.97-2.40)
Diagnosis of ADHD									
Yes	35,590	54-58		N.E.	183,038	135	123,078.6	1.10 (0.93-1.30)	1.27 (0.82-1.96)
No	10,089	15-18		N.E.	44,845	85	46,936.6	1.82 (1.47-2.25)	0.90 (0.53-1.56)
Previous history of psychiatric disease									
Yes	32,467	58-62		N.E.	160,146	167	111,878.7	1.61 (1.13-2.29)	1.18 (0.79-1.75)
No	13,212	11-14		N.E.	67,737	53	58,136.7	0.91 (0.46-1.82)	0.83 (0.35-1.94)

ADHD = attention-deficit/hyperactivity disorder; ATC = Anatomical Therapeutic Chemical Classification System; CI = confidence interval; LDX = lisdexamfetamine dimesylate; MACE = major cardiovascular endpoint; PY = person-years.

[a] Patients with MACE during current use.

[b] Patient-years accumulated over current/remote use, as defined for primary analysis, in patients at risk for MACE.

[c] Using random-effects meta-analysis for the pooled population.

[d] Total remote users represents total patient/index dates after matching and trimming.

[e] Using Poisson regression model adjusting for quintiles of the propensity score for the Danish and Swedish populations.

[f] Current LDX users with ≥12 months of cumulative exposure to LDX, i.e., those with ≥12 months duration of current LDX use.

[g] Other ADHD medications include amphetamine, dexamphetamine, methylphenidate, and atomoxetine. In addition, dexmethylphenidate (ATC code: N06BA11) users, if any, will be treated as users of methylphenidate.
* This is a trend-dose analysis among only LDX users.

Table S2. Sensitivity Analysis: Incidence Rates and Incidence Rate Ratios for MACE for LDX Patients and Remote Users, Trimmed Population in Denmark, Sweden, and Pooled

	LDX Users				Remote Users				
Endpoint	**Number of Patients**	**Number With Outcome[a]**	**PY[b]**	**IR per 1,000 PY (95% CI)[c]**	**Number of Patients[d]**	**Number With Outcome[a]**	**PY[b]**	**IR per 1,000 PY (95% CI)[c]**	**IRR[c,e] (95% CI)**
Denmark									
Impact of definition of exposure time									
Extending current use to 1* duration of prior dispensing	5,516	9	5,858.3	1.52 (0.79-2.93)	27,494	76	47,274.7	1.60 (1.27-2.03)	0.95 (0.45-2.00)
Post-LDX users[f]									
Post-LDX users vs previous users	4,250	13	5,557.9	2.27 (1.32-3.93)	27,494	76	47,274.7	1.61 (1.27-2.03)	1.42 (0.75-2.67)
Post-LDX users with no other ADHD treatment vs. previous users	3,536	7	3,554.5	1.94 (0.93-4.08)	27,494	76	47,274.7	1.60 (1.26-2.02)	1.22 (0.54-2.74)
Post-LDX users with use of other ADHD treatment vs. previous users	2,234	6	2,003.3	2.89 (1.29-6.45)	27,494	76	47,274.7	1.61 (1.28-2.04)	1.79 (0.76-4.22)
Intention to treat analysis	5,516	22	11,065.8	1.94 (1.27-2.96)	27,494	76	47,274.7	1.60 (1.27-2.03)	1.21 (0.71-2.07)
Impact of inclusion criteria									
Using same inclusion criteria in both study cohorts, current LDX vs previous use	564	0	515.1	N.E.	2,792	7	5,456.0	1.29 (0.59-2.82)	N.E.

	LDX Users				Remote Users				
Endpoint	**Number of Patients**	**Number With Outcome[a]**	**PY[b]**	**IR per 1,000 PY (95% CI)[c]**	**Number of Patients[d]**	**Number With Outcome[a]**	**PY[b]**	**IR per 1,000 PY (95% CI)[c]**	**IRR[c,e] (95% CI)**
Impact of previous exposure									
Current LDX users with no use of ADHD medication within the last 180 days vs previous users	4,369	N.R.		1.53 (0.73-3.22)	27,494	76	47,274.7	1.60 (1.26-2.02)	0.96 (0.42-2.19)
Current LDX users with previous use of ADHD medication within the last 180 days vs previous users	1,147	<5		1.97 (0.49-7.87)	27,494	76	47,274.7	1.61 (1.27-2.03)	1.22 (0.29-5.10)
Sweden									
Impact of definition of exposure time									
Extending current use to 1*duration of prior dispensing	40,194	66	48,043.5	1.99 (1.56-2.54)	200,339	144	122,738.0	1.78 (1.51-2.09)	1.12 (0.74-1.69)
Post-LDX users[f]									
Post-LDX users vs. previous users	32,327	59	42,266.5	1.76 (1.36-2.27)	200,389	144	122,808.9	1.52 (1.30-1.80)	1.16 (0.75-1.77)
Post-LDX users with no other ADHD treatment vs. previous users	24,122	32	28,401.8	1.42 (1.00-2.01)	200,389	144	122,808.9	1.51 (1.28-1.78)	0.94 (0.58-1.52)
Post-LDX users with use of other ADHD treatment vs. previous users	8,205	27	13,864.7	2.42 (1.66-3.52)	200,389	144	122,808.9	1.51 (1.28-1.78)	1.60 (0.95-2.69)
Intention to treat analysis	40,163	122	88,365.4	1.77 (1.48-2.12)	200,389	144	122,740.5	1.56 (1.33-1.84)	1.13 (0.78-1.66)

Endpoint	LDX Users				Remote Users				
	Number of Patients	Number With Outcome[a]	PY[b]	IR per 1,000 PY (95% CI)[c]	Number of Patients[d]	Number With Outcome[a]	PY[b]	IR per 1,000 PY (95% CI)[c]	IRR[c,e] (95% CI)
Impact of inclusion criteria									
Using same inclusion criteria in both study cohorts, current LDX users vs. previous users	5,206	7	5,163.7	2.24 (1.07-4.70)	25,310	17	15,727.4	1.72 (1.07-2.76)	1.30 (0.53-3.19)
Impact of previous exposure									
Current LDX users with no use of ADHD medication within the last 180 days vs previous users	13,892	16	12,970.3	1.89 (1.16-3.09)	200,389	144	122,740.5	1.83 (1.56-2.16)	1.03 (0.57-1.86)
Current LDX users with previous use of ADHD medication within the last 180 days vs previous users	26,271	47	32,054.3	2.14 (1.61-2.85)	200,389	144	122,740.5	1.83 (1.56-2.16)	1.17 (0.75-1.81)
Pooled									
Impact of definition of exposure time									
Extending current use carry over to 1*duration of prior dispensing	45,710	75	53,901.8	1.39 (1.11-1.75)	227,833	220	170,012.8	1.36 (1.00-1.85)	1.08 (0.75-1.55)
Post-LDX users[f]									
Post-LDX users vs. previous users	36,577	72	47,824.3	1.70 (1.04-2.79)	227,883	220	170,083.6	1.36 (1.00-1.85)	1.23 (0.86-1.76)
Post-LDX users with no other ADHD treatment vs. previous users	27,658	39	31,956.4	1.35 (0.81-2.25)	227,883	220	170,083.6	1.36 (1.00-1.85)	1.00 (0.66-1.52)

Endpoint	LDX Users				Remote Users				
	Number of Patients	Number With Outcome[a]	PY[b]	IR per 1,000 PY (95% CI)[c]	Number of Patients[d]	Number With Outcome[a]	PY[b]	IR per 1,000 PY (95% CI)[c]	IRR[c,e] (95% CI)
Post-LDX users with use of other ADHD treatment vs. previous users	10,439	33	15,868.0	2.11 (1.50-2.96)	227,883	220	170,083.6	1.36 (1.00-1.85)	1.65 (1.06-2.57)
Intention-to-treat analysis		144		1.57 (1.12-2.22)		220		1.36 (1.00-1.85)	1.16 (0.85-1.58)
Impact of inclusion criteria									
Using same inclusion criteria in both study cohorts, current LDX users vs. previous users	5,770	7	5,678.7	1.33 (0.65-2.71)		24		1.14 (0.76-1.70)	N.E.
Impact of previous exposure									
Current LDX users with no use of ADHD medication within the last 180 days vs previous users	18,261	21-25		N.E.	227,883	220	170,015.3	1.36 (1.00-1.85)	1.01 (0.62-1.63)
Current LDX users with previous use of ADHD medication within the last 180 days vs previous users	27,418	48-51		N.E.	227,883	220	170,015.3	1.36 (1.00-1.85)	1.17 (0.77-1.78)

ADHD = attention-deficit/hyperactivity disorder; CI = confidence interval; IR = incidence rate; IRR = incidence rate ratio; LDX = lisdexamfetamine dimesylate; MACE = major cardiovascular endpoint; PY = person-years.

[a] Patients with MACE during use as described for each sensitivity analysis.

[b] Patient-years accumulated over use, as defined for each sensitivity analysis, in patients at risk for MACE.

[c] Using random-effects meta-analysis for the pooled population.

[d] Total remote users represents total patient/index dates after matching and trimming.

[e] Using Poisson regression model adjusting for quintiles of the propensity score for the Danish and Swedish populations.

[f] Post-LDX is the sum of all periods of time between episodes of LDX use or time after the last episode of current LDX use and the end of follow-up.