<u>Use of Contrave®, naltrexone with bupropion, bupropion, or naltrexone and major adverse</u> cardiovascular events: a systematic literature review

Supplemental Material

Original Study Protocol

Search strategy:

The literature search strategy has been developed with the aim of identifying publications containing estimates of cardiovascular adverse events possibly associated with use of Contrave® (or Mysimba) or its components, naltrexone and bupropion. This search strategy is designed to capture available data on adverse events following use of Contrave® or its components.

Table 1.	Summary	of search	strategies	considered.

Search #	Search Terms	# Articles
1	(Contrave OR naltrexone OR bupropion OR Mysimba)	5271
2	(Contrave OR naltrexone OR bupropion OR Mysimba) AND (safety OR toxicity OR adverse OR cardiovascular OR heart OR cardiac OR myocardial OR coronary OR vascular OR atherosclerosis OR atherosclero* OR angina OR vasospasm OR stroke OR cerebrovascular OR cvd OR ischemic OR mace OR death OR mortality OR discontinu*)	2239
3	(Contrave OR naltrexone OR bupropion OR Mysimba) AND (safety OR toxicity OR adverse OR cardiovascular OR heart OR cardiac OR myocardial OR coronary OR vascular OR atherosclerosis OR atherosclero* OR angina OR vasospasm OR stroke OR cerebrovascular OR cvd OR ischemic OR mace OR death OR mortality OR discontinu*) NOT (opioid OR addict* OR overdose)	1054
4	(Contrave OR naltrexone OR bupropion OR Mysimba) AND (safety OR toxicity OR adverse OR cardiovascular OR heart OR cardiac OR myocardial OR coronary OR vascular OR atherosclerosis OR atherosclero* OR angina OR vasospasm OR stroke OR cerebrovascular OR cvd OR ischemic OR mace OR death OR mortality OR discontinu* OR blood pressure OR systolic OR diastolic OR ventric* OR stenosis OR aortic valve OR ECG or EKG or electrocardiogram OR *cardia OR "MI" OR palpitation OR fibrillation OR afib OR atrial flutter OR chest pain OR atria* OR pericarditis OR "CHF" OR "CAD")	2312
5	(Contrave OR naltrexone OR bupropion OR Mysimba) AND (safety OR toxicity OR adverse OR cardiovascular OR heart OR cardiac OR myocardial OR coronary OR vascular OR atherosclerosis OR atherosclero* OR angina OR vasospasm OR stroke OR cerebrovascular OR cvd OR ischemic OR mace OR death OR mortality OR discontinu* OR cardio* OR cardiac*)	2470
6	(Contrave OR naltrexone OR bupropion OR Mysimba) AND (safety OR toxicity OR adverse OR cardiovascular OR heart OR cardiac OR myocardial OR coronary OR vascular OR	2239

	atherosclerosis OR atherosclero* OR angina OR vasospasm OR stroke OR cerebrovascular OR cvd OR ischemic OR mace OR death OR mortality OR discontinu* OR myocarditis)	
7	(Contrave OR naltrexone OR bupropion OR Mysimba) AND (safety OR toxicity OR adverse OR cardiovascular OR heart OR cardiac OR myocardial OR coronary OR vascular OR atherosclerosis OR atherosclero* OR angina OR vasospasm OR stroke OR cerebrovascular OR cvd OR ischemic OR mace OR death OR mortality OR discontinu* OR blood pressure OR systolic OR diastolic OR ventric* OR stenosis OR aortic valve OR ECG or EKG or electrocardiogram OR *cardia OR "MI" OR palpitation OR fibrillation OR afib OR atrial flutter OR chest pain OR atria* OR pericarditis OR "CHE" OR "CAD" OR myocarditis)	2312
8	(Contrave OR naltrexone OR bupropion OR Mysimba) AND (safety OR toxicity OR adverse OR cardiovascular OR heart OR cardiac OR myocardial OR coronary OR vascular OR atherosclerosis OR atherosclero* OR angina OR vasospasm OR stroke OR cerebrovascular OR cvd OR ischemic OR mace OR death OR mortality OR discontinu* OR blood pressure OR systolic OR diastolic OR ventric* OR stenosis OR aortic valve OR ECG or EKG or electrocardiogram OR *cardia OR "MI" OR palpitation OR fibrillation OR afib OR atrial flutter OR chest pain OR atria* OR pericarditis OR "CHF" OR "CAD" OR myocarditis OR cardio* OR cardiac*)	2539

All articles are published from January 1, 2012 to September 30, 2021.

PubMed (MEDLINE®) will be searched for relevant publications, using search #8 (2539 articles).

Using the aforementioned search terms, a systematic literature review will be conducted. The review of the literature will occur in two phases:

• "Level 1": Using a literature search strategy, further described below, this review with identify articles that meet the criteria of interest. At this first-level review, the titles and abstracts retrieved through the literature search will be screened for potential relevance.

All articles will be screened in EndNote using the following exclusion criteria for Level 1:

- i. Animal studies (in vivo)
- ii. In vitro studies
- iii. Case reports/case series
- iv. Specific exposures other than bupropion and/or naltrexone
- v. Pharmacokinetics/pharmacogenetics
- vi. Policy, economics, health care access, clinical guidelines/recommendations
- vii. Reviews, editorials, commentaries without original data
- viii. Study protocols
- "Level 2": At this full-text review stage, additional exclusions may be made, as papers may actually not report findings of interest, or may have presented a second report of a single study that includes no additional information on cardiovascular events. Articles that fulfill inclusion criteria will be included in the data extraction process. To guide

inclusion and exclusion, the following PICOS (population, intervention, comparator, outcome, and study design) statement was developed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

- a. Level 2 Inclusion Criteria
 - i. Type of population: Human populations, not limited to the indicated population
 - ii. Type of intervention: Contrave, naltrexone, bupropion, Mysimba
 - iii. Type of comparator: placebo, or active comparator that is not Contrave, naltrexone, bupropion, or Mysimba
 - iv. Type of outcome: any clinically diagnosed cardiovascular endpoint, e.g. MACE, nonfatal myocardial infarction, nonfatal stroke, cardiovascular mortality, cerebrovascular disease, heart failure, atrial fibrillation, unstable angina, myocarditis, or hypertension
 - v. Type of studies: randomized control trials (RCTs), cohort and casecontrol studies, and other epidemiologic study designs (e.g. crosssectional)
 - vi. Publication date: on or after January 1, 2012
 - vii. Language: English
- b. Level 2 Exclusion Criteria
 - i. Intervention is not Contrave (or Mysimba), bupropion, or naltrexone
 - ii. Intervention is bupropion used in combination with other active ingredient (e.g. escitalopram)
 - iii. Intervention is naltrexone used in combination with other active ingredient (e.g. gabapentin)
 - iv. No comparator group for intervention drug
 - v. Outcome is laboratory value, symptom, or other endpoint other than a clinically diagnosed cardiovascular endpoint (e.g., electrocardiogram readings, cholesterol level, blood pressure)
 - vi. Type of publications: conference abstracts, case reports, non-peerreviewed data sources (i.e. grey literature)
 - vii. Non-human (animal) in vivo studies, in vitro studies
 - viii. No original data (e.g., reviews, editorials, commentaries, meta-analyses without previously unpublished data)

Articles that are included following Level 1 screening, and not freely available, will be ordered by Exponent to expedite the screening and abstraction process. Articles that are excluded during Level 1 screening will be classified in the EndNote library according to reasons for exclusion.

c. Data Extraction

Once Level 2 screening is complete, articles meeting inclusion criteria will be reviewed and summarized by data abstractors into data extraction table(s) that will include established data extraction fields, agreed upon in advance by study authors. All article extractions will be reviewed for accuracy and completeness by a second reviewer as a quality-control measure, and a third reviewer will be consulted, if necessary, to resolve any discrepancies.

Data abstraction fields

The following information was considered relevant a priori for extraction from each of the relevant studies: first author surname and/or source, year of publication, study design, calendar years of study, study country, total sample size, number of patients in safety analyses, underlying disease (indication), study inclusion criteria, study exclusion criteria, age range, distribution of patients by sex, baseline prevalence of conditions potentially relevant to the adverse events of interest (% diabetes, % smoking, BMI (mean), % overweight, % obese), experimental treatment type, experimental treatment dose, experimental treatment duration, comparator treatment type, comparator treatment dose, comparator treatment duration, adverse event classification system, duration of follow-up, cardiovascular adverse event type and definition, and, for each type of adverse event of interest, the number of reported events, adverse event measures and p-value/statistical significance of treatment vs comparator. These fields were entered into a spreadsheet for standardized data extraction. Any studies excluded from the literature review were noted separately along with the reason for exclusion.

For studies that reported "no adverse events," "no serious adverse events," or "no deaths," or where it could otherwise be clearly inferred that no cardiovascular adverse events occurred (or no serious cardiovascular events or no cardiovascular deaths occurred, respectively), minimal data abstraction was conducted to extract only the following information: first author surname and/or source, year of publication, number of patients in safety analyses, experimental treatment type, comparator treatment type, adverse event classification, duration of follow-up, cardiovascular adverse event type, and, for each type of adverse event of interest, the number of reported events, adverse event measures and p-value/statistical significance of treatment vs comparator.

Supplemental Tables

Please see accompanying excel spreadsheet, titled "Supplemental tables_manuscript", for supplemental tables 1-3.

Supplementa	I Table 1. Cor	trave® and naltrexe	one-bupropion	n studies report	ting on non-M	ACE c	ardiovas	cular adverse even	ts.		
Author	Year	Treatment	Study design	Study indication	Reported length of follow-up	No. Patie	onts	Outcome	Adverse event frequency, treatment group	Adverse event frequency, comparator group	Effect measure
					24 months					Naltrexone-bupropion + antidepressant:	
					or until natients					11/1150 (1.0%) Placebo + no antidepressant: 9/3317	Naltrexone-bupropion + antidepressant: Fisher's exact p = 0.01 (calculated)
					stopped					(0.3%)	Placebo + no antidepressant: Fisher's exact p = 0.82
					randomized treatment	8	1894	Angina unstable	Naltrexone-bupropion + no antidepressant: 10/3300 (0.3%)	Placebo + antidepressant: 4/1127 (0.4%)	(calculated) Placeho + antidepressant: Fisher's exact p = 0.76 (calculated)
					a countone		001	/ ingina anotabio	(0.076)	Naltrexone-bupropion + antidepressant:	
										4/206 (1.9%) Placebo + no antidepressant: 4/585	Naltrexone-bupropion + antidepressant: Fisher's exact p = 0.001 (calculated)
										(0.7%)	Placebo + no antidepressant: Fisher's exact p = 0.02
								Angina postoria	Neltrovene humanian + no entidenreceant: 0/900 (0.0%)	Placebo + antidepressant: 2/130 (1.5%)	(calculated) Pleashe + antidepresent: Eicher's event p = 0.02 (calculated)
								Angina pectona	Natice one-ouproport in antidepressant. 0/030 (0.0 %)	Naltrexone-bupropion + antidepressant:	
										2/206 (1.0%) Placebo + no antidepressant: 2/585	Naltrexone-bupropion + antidepressant: Fisher's exact p = 0.32 (calculated)
										(0.3%)	Placebo + no antidepressant: Fisher's exact p = 1.00
Molnture	2021	Contrave®	RCT	Weight loss	24 months	1	811		Nattravone hupropion + no antidepressant: 4/800 (0.4%)	Placebo + antidepressant: 0/130 (0.0%)	(calculated) Placebo + antidepreseant: Eicher's exact p = 1.00 (calculated)
montyro	2021	Contraveo		Troight 1000	Median 121	1		/ ingina anotabio	Naltrexone-bupropion:	Placebo:	HR (99.7% CI)
					weeks, interquartile			Hospitalization for	51/4,455 (1.1%) at end of study 47/4 455 (1.1%) at 50% interim	50/4,450 (1.1%) at end of study 43/4,450 (1.0%) at 50% interim	at end of study 1.01 (0.57-1.82) at 50% interim 1.09 (0.59-2.02)
Nissen	2016	Contrave®	RCT	Weight loss	range 114-	8	905	unstable angina	29/4,455 (0.7%) at 25% interim	23/4,450 (0.5%) at 25% interim	at 25% interim 1.26 (0.73-2.18)
									Naltrexone-bupropion + dipeptidyl peptidase 4 inhibitor:	Placebo + dipeptidyl peptidase 4 inhibitor: 1/317 (0.3%)	Placebo + dipeptidyl peptidase 4 inhibitor: Fisher's exact p = 0.38 (calculated)
				Type 2					Naltrexone-bupropion + glucagon-like peptide-1 receptor	Placebo + glucagon-like peptide-1	Placebo + glucagon-like peptide-1 receptor agonist: Fisher's
Wharton	2021	Contrave®	RCT	diabetes	52 weeks	1	317	Unstable angina	agonist: 8/339 (2.4%)	receptor agonist: 2/316 (0.6%)	exact p = 0.11 (calculated)
Halseth Hollander	2018 2013	Contrave® Contrave®	RCT RCT	Weight loss Weight loss	26 weeks 56 weeks	242 502		Hypertension Hypertension	Naltrexone-bupropion: 2/153 (1.3%) Contrave: 33/333 (9.9%)	Usual care: 0/89 (0%) Placebo: 7/169 (4.1%)	Fisher's exact p = 0.533 (calculated) Fisher's exact p = 0.02 (calculated)
								,,	1/109 (0.9%) naltrexone-bupropion stage 1	2/294 (0.7%) placebo stage 1	Placebo stage 1: Fisher's exact p = 1.00 (calculated)
		la is stable			40				0/114 /0%) nattrevone hunronion stage 2 re-randomized	0/111 (0%) placebo stage 2 re-	Placebo stage 2 re-randomized: Fisher's exact p = 1.00 (calculated)
		naltrexone + oral		Substance	12 weeks (6 weeks per				0/109 (0%) naltrexone-bupropion stage 2 not re-	0/69 (0%) placebo stage 2 not re-	Placebo stage 2 not re-randomized: Fisher's exact p = 1.00
Trivedi	2021	bupropion	RCT	use	stage)	4	403	Hypertension	randomized	randomized	(calculated)
									0/109 (0%) naitrexone-bupropion stage 1	0/294 (0%) placebo stage 1 0/111 (0%) placebo stage 2 re-	Placebo stage 1: Fisher's exact p = 1.00 (calculated) Placebo stage 2 re-randomized: Fisher's exact p = 1.00
		Injectable			12 weeks (6				0/114 (0%) naltrexone-bupropion stage 2 re-randomized	randomized	(calculated)
Trivodi	2021	naltrexone + oral	RCT	Substance	weeks per		402	Acute cardiac	1/109 (0.9%) naltrexone-bupropion stage 2 not re- randomized	0/69 (0%) placebo stage 2 not re- randomized	Placebo stage 2 not re-randomized: Fisher's exact p = 1.00 (calculated)
Triveu	2021	Dupropion	RGI	use	Stdge)		403	laiure	1/109 (0.9%) naltrexone-bupropion stage 1	2/294 (0.7%) placebo stage 1	Placebo stage 1: Fisher's exact p = 1.00 (calculated)
									1/114 (0.9%) naltrexone-bupropion stage 2 re-	0/111 (0%) placebo stage 2 re-	Placebo stage 2 re-randomized: Fisher's exact p = 1.00
		Injectable naltrexone + oral		Substance	12 weeks (6 weeks per				1/109 (0.9%) naltrexone-bupropion stage 2 not re-	0/69 (0%) placebo stage 2 not re-	(calculated) Placebo stage 2 not re-randomized: Fisher's exact p = 1.00
Trivedi	2021	bupropion	RCT	use	stage)		403	Cardiac disorders	randomized	randomized	(calculated)
										Naltrexone-bupropion + antidepressant: 3/206 (1 5%)	Naltrexone-bupropion + antidepressant: Fisher's exact p = 0.38 (calculated)
										Placebo + no antidepressant: 4/585	Placebo + no antidepressant: Fisher's exact p = 1.00
										(0.7%)	(calculated)
McIntyre	2021	Contrave®	RCT	Weight loss	104 weeks	8894		disease	Naltrexone-bupropion + no antidepressant: 6/890 (0.7%)	Placebo + antidepressant: 0/130 (0.0%)	Placebo + antidepressant: Fisher's exact p = 1.00 (calculated)
					Median 121				Naltrexone-bupropion:	Placebo:	HR (99.7% CI)
					weeks, interquartile				152/4,455 (3.4%) at end of study	170/4,450 (3.8%) at end of study	0.89 (0.64-1.23) at end of study
					range 114-			Coronary	132/4,455 (3.0%) at 50% interim	145/4,450 (3.3%) at 50% interim	0.91 (0.64-1.29) at 50% interim
Nissen	2016	Contrave®	RCI	vveight loss	128	8905		revascularization	0/109 (0%) naltrexone-bupropion stage 1	0/294 (0%) placebo stage 1	Placebo stage 1: Fisher's exact p = 1.00 (calculated)
									2/114 (1.8%) naltrexone-bupropion stage 2 re-	0/111 (0%) placebo stage 2 re-	Placebo stage 2 re-randomized: Fisher's exact p = 0.50
		Injectable naltrexone + oral		Substance	12 weeks (6 weeks per				randomized 0/109 (0%) naltrexone-bupropion stage 2 not re-	randomized 0/69 (0%) placebo stage 2 not re-	(calculated) Placebo stage 2 not re-randomized: Fisher's exact p = 1.00
Trivedi	2021	bupropion	RCT	use	stage)		403	Hematoma	randomized	randomized	(calculated)
		naltrexone + oral		Substance	12 weeks (6 weeks per			Hypertensive		1/403 (0.2%) after screening but prior to	
Trivedi	2021	bupropion	RCT	use	stage)		403	crisis	0/109 (0%) naltrexone-bupropion after randomization	randomization	Fisher's exact p = 1.00 (calculated)
									0/109 (0%) naitrexone-bupropion stage 1	1/294 (0.3%) placebo stage 1 0/111 (0%) placebo stage 2 re-	Placebo stage 1: Fisher's exact p = 1.00 (calculated) Placebo stage 2 re-randomized: Fisher's exact p = 1.00
									0/114 (0%) naltrexone-bupropion stage 2 re-randomized	randomized	(calculated)
								Othorstatic hypotension	0/109 (0%) naitrexone-bupropion stage 2 not re- randomized	0/69 (0%) placebo stage 2 not re- randomized	Placebo stage 2 not re-randomized: Fisher's exact p = 1.00 (calculated)
1				1	1	1			0/109 (0%) naltrexone-bupropion stage 1	0/294 (0%) placebo stage 1	Placebo stage 1: Fisher's exact p = 1.00 (calculated)
									1/114 (0.9%) naltrexone-bupropion stage 2 re-	0/111 (0%) placebo stage 2 re-	Placebo stage 2 re-randomized: Fisher's exact p = 1.00
		Injectable		Substance	12 weeks (6				randomized 0/109 (0%) naltrexone-bupropion stage 2 not re-	randomized 0/69 (0%) placebo stage 2 not re-	(calculated) Placebo stage 2 not re-randomized: Fisher's exact p = 1.00
Trivedi	2021	bupropion	RCT	use	stage)		403	Hypotension	randomized	randomized	(calculated)
Halseth	2018	Contrave®	RCT	Weight loss	26 weeks	242		Palpitations / tachycardia	Naltrexone-bupropion: 2/153 (1.3%)	Usual care: 0/89 (0%)	Fisher's exact p = 0.53 (calculated)
					Median 121	1					· ······
					weeкs, interquartile						
Niccon	2016	Contrava®	RCT	Weight loss	range 114-	2005		Balaitationa	Netrovene humenien: 10/4 4EE (0.4%)	Bloocho: 5/4 450 (0 1%)	Fisher's system = 0.007 (seleviteted)
14133611	2010	Comavee	Rot	weight loaa	120 WOOK3	0303		1 alpitations	0/109 (0%) naltrexone-bupropion stage 1	0/294 (0%) placebo stage 1	Placebo stage 1: Fisher's exact p = 1.00 (calculated)
										0/111 (0%) placebo stage 2 re-	Placebo stage 2 re-randomized: Fisher's exact p = 1.00
									1/109 (0.9%) naltrexone-bupropion stage 2 re-randomized	0/69 (0%) placebo stage 2 not re-	Placebo stage 2 not re-randomized: Fisher's exact p = 1.00
								Thrombophlebitis	randomized	randomized	(calculated)
1				1	1	1			0/109 (0%) naltrexone-bupropion stage 1	0/294 (0%) placebo stage 1	Placebo stage 1: Fisher's exact p = 1.00 (calculated)
1		Injectable		1	12 weeks /6	1			0/114 (0%) naltrexone-bupropion stage 2 re-randomized	1/111 (0.9%) placebo stage 2 re- randomized	Placebo stage 2 re-randomized: Fisher's exact p = 0.50 (calculated)
L.		naltrexone + oral	L	Substance	weeks per	1		Thrombophlebitis	0/109 (0%) naltrexone-bupropion stage 2 not re-	0/69 (0%) placebo stage 2 not re-	Placebo stage 2 not re-randomized: Fisher's exact p =
l'rivedi	2021	bupropion	RCT	use	stage)	\vdash	403	superficial	randomized 5/109 (4.6%) naltrexone-bubropion stage 1	5/294 (1.7%) placebo stage 1	Placebo stage 1: Fisher's exact p = 0.14 (calculated)
1				1	1	1			3/114 (2.6%) naltrexone-bupropion stage 2 re-	1/111 (0.9%) placebo stage 2 re-	Placebo stage 2 re-randomized: Fisher's exact p = 0.62
1		Injectable		Substance	12 weeks (6	1		1	randomized 2/109 (1.8%) naltrexone-bupropion stage 2 not re-	randomized 0/69 (0%) placebo stade 2 not re-	(calculated) Placebo stage 2 not re-randomized: Fisher's exact n = 0.52
Trivedi	2021	bupropion	RCT	USP	stage)	1	403	Vascular disorders	randomized	randomized	(calculated)

	DIE Z. DUDIOD	ion studies rep	orting on non-	WINNE UNIONASCI	ular adverse ev	ents.			
Author	Year	Study design	Study indication	Reported length of follow-up	No. Patients	Outcome	Adverse event frequency, treatment group	Adverse event frequency, comparator group	Effect measure
						Composite cardiovascular	1 743/131 562 (1 3%)	NRT : 1,237/32,237 (3.8%) Varenicline: 8 244/454 698 (1.8%)	Adjusted RR (95% Cl) = 0.75 (0.69-0.81) Adjusted RR (95% Cl) = 0.83 (0.78-0.87)
								NRT: 441/32,237 (1.4%), patient years: 5,835	
						Composite cardiovascular		Incidence rate per 1000 patient-years = 75.6	Adjusted HR (95% CI) = 0.66 (0.58-0.75)
				12 months, or patient therapy		events (time-to- event sensitivity	912/131,562 (0.7%), patient years 52,364	Varenicline: 2845/454,698 (0.6%) Incidence rate per 1000 patient-years =	
		Observation	Smoking	duration plus 30 days (time-to-		analyses) Composite	Incidence rate per 1000 patient-years = 17.4	29.8	Fisher's exact p = 0.007 (calculated)
Carney	2020	al cohort	cessation	event sensitivity)	618,497	cardiovascular Composite	1,534/121,416 (1.3%)	NRT: 715/26,004 (2.7%) NRT 1-year: 1,348/71,510 (1.9%)	Adjusted RR (95% CI) = 0.73 (0.67-0.81) Adjusted RR (95% CI) = 0.95 (0.77-1.17)
						cardiovascular events (1 year and	1-year: 96/5,838 (1.6%)	Varenicline 1-year: 595/39,094 (1.5%) NRT 6-mo: 802/71,510 (1.1%)	Fisher's exact p = 0.46 (calculated) Adjusted RR (95% Cl) = 1.02 (0.78-1.34)
					116,442	6 month follow-up) Composite	6-mo: 59/5,838 (1.0%)	Varenicline 6-mo: 331/39,094 (0.8%) NRT 1-year: 773/67,758 (1.1%)	Fisher's exact p = 0.23 (calculated) Adjusted RR (95% Cl) = 0.94 (0.72-1.22)
						cardiovascular events (patients	1-year: 63/5,578 (1.1%)	Varenicline 1-year: 404/37,585 (1.1%) NRT 6-mo; 439/67.758 (0.6%)	Fisher's exact p = 0.73 (calculated) Adjusted RR (95% CI) = 0.93 (0.65-1.34)
					110,921	with no history of Composite	6-mo: 33/5,578 (0.6%)	Varenicline 6-mo: 279/37,585 (0.7%)	Fisher's exact p = 0.24 (calculated)
						cardiovascular events (direct			
				Primary analysis 1 year, secondary		comparison between			
Carney	2021	Observation al cohort	Smoking cessation	analysis 6 months	44 932	bupropion and varenicline)	96/5 838 (1 6%)	Varenicline: 595/39 094 (1 5%)	Adjusted RR (95% CI) = 0.99 (0.79-1.23)
		Observation	Smoking			First degree composite (acute			
Graham	2014	al cohort	cessation	6 months	88,957	MI, stroke, death) Any major	61/14133 (0.4%)	Varenicline: 256/74824 (0.3%)	Adjusted HR (95% Cl) = 0.84 (0.58-1.23)
						cardiovascular event (anv of			
						acute coronary			
						ischaemic stroke,		Varaniclina: 57 events ner 8 268 nerson.	
				6 months		death) (Primary	60 events per 8,411 person-years, Incidence rate per	years, Incidence rate per 1,000 person-	HP (05% CI) = 1.04 (0.72.1.40)
				6 monuns		analyses)		Varenicline 6 weeks: 22 events per	HR(95% CI) = 1.04(0.72-1.49)
							6 weeks: 20 events per 2,039 person-years. Incidence rate per 1,000 years: 9.8	2,032 person-years. Incidence rate per 1,000 years: 10.8	HR (95% Cl) 6 weeks = 0.91 (0.50 - 1.67)
						Any major CV	12 weeks: 34 events per 4,022 person-years. Incidence	3,992 person-years. Incidence rate per	
				6 weeks, 12		acute coronary	rate per 1,000 years: 8.5	1,000 years: 8.0 Varenicline 12 months: 103 events per	HR (95% CI) 12 weeks = 1.05 (0.65 - 1.72)
				weeks, 12 months, 24		syndrome, ischaemic stroke,	12 months: 103 events per 15,905 person-years. Incidence rate per 1,000 years: 6.5	15,300 person-years. Incidence rate per 1,000 years: 6.7	HR (95% CI) 12 months = 0.96 (0.74 - 1.27)
		Observation	Smoking	months (secondary		or cardiovascular death) (secondary	24 months: 191 events per 27,948 person-years.	Varenicline 24 months: 193 events per 25,763 person-years. Incidence rate per	
Svanström	2012	al cohort	cessation	analyses)	35,852	analyses)	Incidence rate per 1,000 years: 6.8	1,000 years: 7.5	HR (95% Cl) 24 months = 0.91 (0.75 - 1.11)
						Angina/ischaemic			
						heart disease			
						angina/ischaemic			
						neart disease or admission for			
						neart disease or admission for coronary artery bypass grafting or			
		Observation	Smoking	6 months (primary		neart disease or admission for coronary artery bypass grafting or percutaneous coronary	Bupropion: 93 events per 8,386 person-years. Incidence	Varenicline: 82 events per 8,247 person- years. Incidence rate per 1,000 person-	HR (95% CI)
Svanström	2012	Observation al cohort	Smoking cessation	6 months (primary analyses) From first	35,852	neart disease or admission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1,000 person-years: 11.1	Varenicline: 82 events per 8,247 person- years. Incidence rate per 1,000 person- years: 9,9 Varenicline in tobacco users: 56/89,519	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI)
Svanström	2012	Observation al cohort	Smoking cessation	6 months (primary analyses) From first dispensing until occurrence of	35,852 202,897	neart disease or admission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1.000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%)	Varenicline: 82 events per 8,247 person- years: Incidence rate per 1,000 person- years: 9.9 Varenicline in tobacco users: 56/89,519 (0.06%) Varenicline products approved for	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI) Adjusted:0.98 (0.68-1.41)
Svanström	2012	Observation al cohort	Smoking cessation	6 months (primary analyses) From first dispensing until occurrence of outcome or end of first treatment	35,852 202,897 271,863	neart disease or admission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1.000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11.203 (0.05%)	Varenicline: 82 events per 8,247 person- years: Incidence rate per 1,000 person- years: 9.9 Varenicline in tobacco users: 56/89,519 (0.06%) Varenicline products approved for smoking cessation: 109/260,660 (0.04%)	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 1.02 (0.45-2.33)
Svanström	2012	Observation al cohort Observation al cohort	Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last	35,852 202,897 271,863 1,005,664	neart disease or admission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, infarction, intermediate coronary syndrome or	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1.000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452745,004 (0.06%)	Varenicline: 82 events per 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicline in tobacco users: 56/89,519 (0.06%) Varenicline products approved for smoking cessation: 109/260,660 (0.04%) All varenicline users: 109/260,660	HR (95% CJ) 1,12 (0.83 - 1.52) IRR (95% CJ) Adjusted: 0.98 (0.68-1.41) IRR (95% CJ) Adjusted: 1.02 (0.45-2.33) IRR (95% CJ) Adjusted: 0.66 (0.52-0.83)
Svanström Toh	2012	Observation al cohort Observation al cohort	Smoking cessation Smoking cessation Smoking	6 months (primary analyses) From first dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last	35,852 202,897 271,863 1,005,664	near disease or admission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial CV endpoints: acute myocardial intermediate coronary syndrome or hospitalization for congestive heart	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%)	Varenicline: 82 events per 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicline in tobacco users: 56/89,519 (0.06%) Varenicline products approved for smoking cessation: 109/260,660 (0.04%) All varenicline users: 109/260,660 (0.04%) Varenicline: 0/2016 (0.0%) NRT: 1/2022 (-0.1%)	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 1.02 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact p = 0.50 (calculated) NRT: Fisher's exact p = 1.00 (calculated)
Svanström Toh Benowitz	2012 2013 2018	Observation al cohort Observation al cohort RCT	Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7)	35,852 202,897 271,863 1,005,664 8058	near disease or admission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%)	Varenicline: 82 events per 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicline in tobacco users: 56/89,519 (0.06%) Varenicline products approved for smoking cessation: 109/260,660 (0.04%) All varenicline users: 109/260,660 (0.04%) Varenicline: 0/2016 (0.0%) NRT: 1/2022 (-0.1%) Placebo: 5/2014 (0.2%)	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 1.02 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact p = 0.02 (calculated) Placebo: Fisher's exact p = 0.02 (calculated) Placebo: Fisher's exact p = 0.02 (calculated) RR (95% CI)
Svanström Toh Benowitz	2012 2013 2018	Observation al cohort Observation al cohort RCT	Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7)	35,852 202,897 271,863 1.005,664 8058	near disease or admission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for hospitalization for hospitalization for heart failure (mirrary analysee)	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 589/131 562 (0.5%)	Varenicline: 82 events per 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicline in tobacco users: 56/89,519 (0.06%) Varenicline products approved for smoking cessation: 109/260,660 (0.04%) All varenicline users: 109/260,660 (0.04%) Varenicline: 0/2016 (0.0%) NRT: 1/2022 (-0.1%) Placebo: 5/2014 (0.2%) NRT: 47/32,237 (1.4%) Varenicline: 199/454 F84 (n.4%)	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 1.02 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact p = 0.05 (calculated) Placebo: Fisher's exact p = 0.02 (calculated) Placebo: Fisher's exact p = 0.02 (calculated) Placebo: Fisher's exact p = 0.02 (calculated) RR (95% CI) Adjusted: 0.84 (0.74-0.96) Fisher's exact p = 0.71 (calculater)
Svanström Toh Benowitz	2012 2013 2018	Observation al cohort Observation al cohort RCT	Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7)	35,852 202,897 271,863 1,005,664 8058	near disease or admission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure (primary analyses)	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 589/131,562 (0.5%)	Varenicline: 82 events per 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicline in tobacco users: 56/89,519 (0.06%) Varenicline products approved for smoking cessation: 109/260,660 (0.04%) All varenicline users: 109/260,660 (0.04%) Varenicline: 0/2016 (0.0%) NRT: 1/2022 (-0.1%) Placebox; 5/2014 (0.2%) NRT: 46/132,237 (1.5%), patient years: 5880 Incidence rate per 1000 natient.	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 1.02 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact p = 0.02 (calculated) Placebo: Fisher's exact p = 0.02 (calculated) Placebo: Fisher's exact p = 0.22 (calculated) RR (95% CI) Adjusted: 0.84 (0.74-0.96) Fisher's exact p = 0.71 (calculated) HR (95% CI)
Svanström Toh Benowitz	2012 2013 2018	Observation al cohort Observation al cohort RCT	Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7)	35,852 202,897 271,863 1,005,664 8058	near disease or admission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure heart failure (primary analyses)	Bupropion: 93 events per 8,388 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 588/131,562 (0.5%)	Vareniciline: 82 events per 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Vareniciline in tobacco users: 56/89,519 (0.06%) Vareniciline products approved for smoking cessation: 109/260,660 (0.04%) All vareniciline users: 109/260,660 (0.04%) Vareniciline: 0/2016 (0.0%) NRT: 1/2022 (-0.1%) Placebo: 5/2014 (0.2%) NRT: 46/132,237 (1.5%), patient years: 5.869, Incidence rate per 1000 patient- years: 25.2	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68 - 1.41) IRR (95% CI) Adjusted: 102 (0.45 - 2.33) IRR (95% CI) Adjusted: 0.66 (0.52 - 0.83) Varenicline: Fisher's exact p = 0.50 (calculated) Placebo: Fisher's exact p = 0.22 (calculated) Placebo: Fisher's exact p = 0.22 (calculated) RR (95% CI) Adjusted: 0.84 (0.74 - 0.96) Fisher's exact p = 0.71 (calculated) HR (95% CI) Adjusted: 0.77 (0.62 - 0.97)
Svanström Toh Benowitz	2012 2013 2018	Observation al cohort Observation al cohort RCT	Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7)	35,852 202,897 271,863 1,005,664 8058	near disease or admission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure heart failure (primary analyses)	Bupropion: 93 events per 8,388 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 588/131,562 (0.5%)	Vareniciline: 82 events per 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Vareniciline in tobacco users: 56/89,519 (0.06%) Vareniciline products approved for smoking cessation: 109/260,660 (0.04%) All vareniciline users: 109/260,660 (0.04%) Vareniciline: 0/2016 (0.0%) NRT: 1/2022 (-0.1%) Placebo: 5/2014 (0.2%) NRT: 46/32,237 (0.5%), patient years: 5.869, Incidence rate per 1000 patient- years: 25.2 Vareniciline: 570/454 688 (0.1%), natient	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68 - 1.41) IRR (95% CI) Adjusted: 1.02 (0.45 - 2.33) IRR (95% CI) Adjusted: 0.66 (0.52 - 0.83) Varenicline: Fisher's exact p = 0.50 (calculated) Placebo: Fisher's exact p = 0.22 (calculated) Placebo: Fisher's exact p = 0.22 (calculated) RR (95% CI) Adjusted: 0.84 (0.74 - 0.96) Fisher's exact p = 0.71 (calculated) HR (95% CI) Adjusted: 0.77 (0.62 - 0.97)
Svanström Toh Benowitz	2012 2013 2018	Observation al cohort Observation al cohort RCT	Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7) 12 months or Patient therapy duration phis 30	35,852 202.897 271,863 1.005,664 8058	neart failure (time- tailure (time- provember)).	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 588/131,562 (0.5%)	Vareniciine: 82 events per 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Vareniciine in tobacco users: 56/89,519 (0.06%) Vareniciine products approved for smoking cessation: 109/260,660 (0.04%) All vareniciine users: 109/260,660 (0.04%) MRT: 1/2022 (-0.1%) Placebo: 5/2014 (0.2%) NRT: 46/132,237 (1.4%) Vareniciine: 1994/54,698 (0.4%) NRT: 46/132,237 (0.5%), patient years: 5.869, Incidence rate per 1000 patient- years: 25.2 Vareniciine: 570/454,698 (0.1%), patient years: 25.84	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68 - 1.41) IRR (95% CI) Adjusted: 1.02 (0.45 - 2.33) IRR (95% CI) Adjusted: 0.66 (0.52 - 0.83) Varenicline: Fisher's exact p = 0.50 (calculated) Placebo: Fisher's exact p = 0.22 (calculated) Placebo: Fisher's exact p = 0.22 (calculated) RR (95% CI) Adjusted: 0.84 (0.74 - 0.96) Fisher's exact p = 0.71 (calculated) HR (95% CI) Adjusted: 0.77 (0.62 - 0.97)
Svanström Toh Benowitz Carney	2012 2013 2018 2020	Observation al cohort Observation al cohort RCT observational cohort	Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7) 12 months or Patient therapy duration plus 30 days	35,852 202.897 271.863 1.005.664 8058 618497	near disease or admission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure (primary analyses) heart failure (primary analyses)	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 588/131,562 (0.5%) Bupropion: 322/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1	Varenicilne: 82 events per 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicilne in tobacco users: 56/89,519 (0.06%) Varenicilne products approved for smoking cessation: 109/260,660 (0.04%) All varenicilne users: 109/260,660 (0.04%) MRT: 1/2022 (-0.1%) Placebo: 5/2014 (0.2%) NRT: 46/32,237 (1.4%) Varenicilne: 1994/54,698 (0.4%) NRT: 449/32,237 (0.5%), patient years: 5.869, Incidence rate per 1000 patient- years: 25.24	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68 - 1.41) IRR (95% CI) Adjusted: 1.02 (0.45 - 2.33) IRR (95% CI) Adjusted: 0.66 (0.52 - 0.83) Varenicline: Fisher's exact p = 0.02 (calculated) Placebo: Fisher's exact p = 0.02 (calculated) Placebo: Fisher's exact p = 0.22 (calculated) RR (95% CI) Adjusted: 0.84 (0.74 - 0.96) Fisher's exact p = 0.71 (calculated) HR (95% CI) Adjusted: 0.77 (0.62 - 0.97) NR
Svanström Toh Benowitz Carney	2012 2013 2018 2020 2020	Observation al cohort Observation al cohort RCT observational cohort	Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking	6 months (primary analyses) From first dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7) 12 months or Patient therapy duration plus 30 days	35,852 202,897 271,863 1.005,664 8058 618497	near disease or damission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure (primary analyses) heart failure (timery analyses) heart failure	Bupropion: 93 events per 8,388 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 588/131,562 (0.5%) Bupropion: 322/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1 Bupropion: 30/5 838 (0.5%)	Varenicilne: 82 events par 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicilne in tobacco users: 56/89,519 (0.06%) Varenicilne products approved for smoking cessation: 109/260,660 (0.04%) All varenicilne users: 109/260,660 (0.04%) MRT: 1/2022 (-0.1%) Placebc: 5/2014 (0.2%) NRT: 46/32,237 (1.5%), patient years: 5,869, Incidence rate per 1000 patient- years: 55.84, Incidence rate per 1000 patient-years: 5,9 NRT: 43/71,510 (0.6%) Xerenicilne: 17/80,P04 (0.4%)	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 1.02 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact p = 0.02 (calculated) Placebo: Fisher's exact p = 0.02 (calculated) Placebo: Fisher's exact p = 0.02 (calculated) RR (95% CI) Adjusted: 0.71 (calculated) HR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 1.13 (0.77-1.65) Eisher's exact p = 0.05 (calculated)
Svanström Toh Benowitz Carney Carney	2012 2013 2018 2020 2021	Observation al cohort Observation al cohort RCT observational cohort observational	Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7) 12 months or Patient therapy duration plus 30 days Primary analysis 1 year	35,852 202,897 271,863 1.005,664 8058 618497 116442	near disease or damission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure (primary analyses) heart failure (primary analyses) heart failure (primary analyses) heart failure (primary analyses)	Bupropion: 93 events per 8,388 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 588/131,562 (0.5%) Bupropion: 322/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1 Bupropion: 30/5,838 (0.5%) Bupropion: 1/2 / 20 / 20 / 20 / 20 / 20 / 20 / 20	Varenicilne: 82 events par 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicilne in tobacco users: 56/89,519 (0.06%) Varenicilne products approved for smoking cessation: 109/260,660 (0.04%) All varenicilne users: 109/260,660 (0.04%) Varenicilne: 0/2016 (0.0%) NRT: 4/022,2014 (0.2%) Placebo: 5/2014 (0.2%) NRT: 46/32,237 (1.5%), patient years: 5,869, Incidence rate per 1000 patient- years: 55,854, Incidence rate per 1000 patient- years: 59,854, Incidence rate per 1000 patient- years: 55,854 NRT: 4/37,7510 (0.6%) Yarenicilne: 17/39,094 (0.4%) Placebo comparator: 22,297	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 1.02 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact p = 0.02 (calculated) Placebo: Fisher's exact p = 0.02 (calculated) Placebo: Fisher's exact p = 0.22 (calculated) RR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 1.13 (0.77-1.65) Fisher's exact p = 0.06 (calculated)
Svanström Toh Benowitz Carney Kittle	2012 2013 2018 2020 2021 2021 2017	Observation al cohort Observation al cohort RCT observational cohort observational cohort	Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7) 12 months or Patient therapy duration plus 30 days Primary analysis 1 year	35,852 202,897 271,863 1.005,664 8058 618497 116442 7224	near disease or damission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure (primary analyses) heart failure (infartice) heart failure (primary analyses) heart failure pospitalization for congestive heart failure	Bupropion: 93 events per 8,388 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 589/131,562 (0.5%) Bupropion: 322/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1 Bupropion: 30/5,838 (0.5%) Bupropion: 1/4,297 (Proportion: 0.023%; 95% Cl, 0.001- 0.30%)	Varenicilne: 82 events par 8.247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicilne in tobacco users: 56/89,519 (0.06%) Varenicilne products approved for smoking cessation: 109/260,660 (0.04%) All varenicilne users: 109/260,660 (0.04%) MRT: 14/022 (-0.1%) Placebo: 5/2014 (0.2%) NRT: 46/32,237 (1.5%), patient years: 5,869, Incidence rate per 1000 patient- years: 55,854, Incidence rate per 1000 patient-years: 5,9 NRT: 43/371,510 (0.6%) Varenicilne: 17/38,054 (0.4%) Placebo comparator: 22,927 (Proportion, 0.068%; 95% Cl, 0.008- 0,247%)	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 1.02 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact p = 0.05 (calculated) Placebc. Fisher's exact p = 0.05 (calculated) Placebc. Fisher's exact p = 0.22 (calculated) RR (95% CI) Adjusted: 0.84 (0.74-0.96) Fisher's exact p = 0.71 (calculated) HR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 1.13 (0.77-1.65) Fisher's exact p = 0.05 (calculated) HR (95% CI) Adjusted: 1.13 (0.77-1.65) Fisher's exact p = 0.05 (calculated)
Svanström Toh Benowitz Carney Carney Kittle	2012 2013 2018 2020 2021 2021 2017	Observation al cohort Observation al cohort RCT observational cohort observational cohort	Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until occurrence of outcome or end of first treatment episode (7 daty after end of last 52 weeks (p. E7) 12 months or Patient therapy duration plus 30 days Primary analysis 1 year ≥ 6 weeks	35,852 202,897 271,863 1.005,664 8058 618497 116442 7224	near disease or damission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure (primary analyses) heart failure (primary analyses) heart failure pospitalization for congestive heart failure	Bupropion: 93 events per 8,388 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 589/131,562 (0.5%) Bupropion: 322/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1 Bupropion: 30/5,838 (0.5%) Bupropion: 1/4,297 (Proportion: 0.023%; 95% Cl, 0.001- 0.130%)	Varenicilne: 82 events par 8.247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicilne in tobacco users: 56/89,519 (0.06%) Varenicilne products approved for smoking cessation: 109/260,660 (0.04%) All varenicilne users: 109/260,660 (0.04%) Varenicilne: 0/2016 (0.0%) NRT: 4/022,2014 (0.2%) Placebo: 5/2014 (0.2%) NRT: 46/32,237 (1.5%), patient years: 5,869, Incidence rate per 1000 patient- years: 55,654, Incidence rate per 1000 patient- years: 55,654, Incidence rate per 1000 patient- years: 55,654, Incidence rate per 1000 patient-years: 5,9 NRT: 43/371,510 (0.6%) Varenicilne: 5/2044,698 (0.1%), patient Yeareiline: 5/26,454,698 (0.1%), patient Yeareiline: 5/26,454 (0.1%), patient Yeareiline: 5/26,454 (0.1%), pat	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 1.02 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact p = 0.05 (calculated) Placebc. Fisher's exact p = 0.02 (calculated) Placebc. Fisher's exact p = 0.22 (calculated) RR (95% CI) Adjusted: 0.74 (0.74-0.96) Fisher's exact p = 0.71 (calculated) HR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 1.13 (0.77-1.65) Fisher's exact p = 0.057 (calculated) HR (95% CI) Adjusted: 0.71 (0.33-1.51) Prometriku core matchedic 0.44 (0.44-4.41)
Svanström Toh Benowitz Carney Carney Kittle	2012 2013 2018 2020 2021 2017	Observation al cohort Observation al cohort RCT observational cohort RCT	Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7) 12 months or Patient therapy duration plus 30 days Primary analysis 1 year	35,852 202,897 271,863 1,005,664 8058 618497 116442 7224	near disease or damission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure pheart failure (primary analyses) heart failure bospitalization for congestive heart failure bospitalization for congestive heart failure	Bupropion: 93 events per 8,388 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11/203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 589/131,562 (0.5%) Bupropion: 322/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1 Bupropion: 30/5,838 (0.5%) Bupropion: 1/4,297 (Proportion: 0.023%; 95% Cl, 0.001- 0.130%)	Varenicilne: 82 events par 8.247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicilne in tobacco users: 56/89,519 (0.0%) Varenicilne products approved for smoking cessation: 109/260,660 (0.04%) All varenicilne users: 109/260,660 (0.04%) Varenicilne: 0/2016 (0.0%) NRT: 4/022 (-0.1%) Placebo: 5/2014 (0.2%) NRT: 4/32,237 (1.5%), patient years: 5,869, Incidence rate per 1000 patient- years: 55,854, Incidence rate per 1000 patient- years: 55,854, Incidence rate per 1000 patient- years: 55,854, Incidence rate per 1000 patient-years: 5,9 NRT: 43/71,510 (0.6%) Varenicilne: 157/345,698 (0.1%), patient years: 25,2 Varenicilne: 157/345,698 (0.1%), patient years: 25,2 NRT: 43/71,510 (0.6%) Varenicilne: 157/345,698 (0.1%), patient years: 25,2 NRT: 43/71,510 (0.6%) Varenicilne: 157/345,698 (0.1%), patient years: 25,2 NRT: 43/71,510 (0.6%) Varenicilne: 35/98,61,0.008- 0,247%) NRT: 302/106,759 (0.3%)	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 1.02 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact p = 0.050 (calculated) Placebo: Fisher's exact p = 0.022 (calculated) Placebo: Fisher's exact p = 0.22 (calculated) RR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 1.13 (0.77-1.65) Fisher's exact p = 0.05 (calculated) HR (95% CI) Adjusted: 1.13 (0.77-1.65) Fisher's exact p = 0.57 (calculated) HR (95% CI) Adjusted: 0.77 (0.33-1.51) Propensity score matched: 0.44 (0.14-1.44)
Svanström Toh Benowitz Carney Carney Kittle Kotz	2012 2013 2018 2020 2021 2021 2017 2015	Observation al cohort Observation al cohort RCT observational cohort RCT observational cohort	Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7) 52 weeks (p. E7) 12 months or Patient therapy duration plus 30 days Primary analysis 1 year 2 6 weeks 6 months	35,852 202.897 271.863 1.005.664 8058 618497 116442 7224 164766	neart disease or damission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure (primary analyses) heart failure (time- to-event sensitivity analyses) heart failure hospitalization for congestive heart failure hospitalization for congestive heart failure Heart failure	Bupropion: 93 events per 8,388 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2,006 (<0.1%) Bupropion: 588/131,562 (0.5%) Bupropion: 322/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1 Bupropion: 30/5,838 (0.5%) Bupropion: 1/4,297 (Proportion: 0.023%; 95% Cl, 0.001- 0.130%) Bupropion: 7/6,557 (0.1%)	Varenicilne: 82 events par 8.247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicilne in tobacco users: 56/89,519 (0.0%) Varenicilne products approved for smoking cessation: 109/260,660 (0.04%) All varenicilne users: 109/260,660 (0.04%) MRT: 401/22,2014 (0.2%) Placebo: 5/2014 (0.2%) NRT: 461/32,237 (1.5%), patient years: 5,869, Incidence rate per 1000 patient- years: 25.2 Varenicilne: 99/454,698 (0.1%), patient years: 55,854, Incidence rate per 1000 patient- years: 55,854, Incidence rate per 1000 patient- years: 59,854, Incidence rate per 1000 patient- years: 59,856, NRT: 302/106,759 (0.3%) Varenicline: 52/51,450 (0.1%)	HR (95% CI) 1.12 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 1.02 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact p = 0.05 (calculated) Placebc. Fisher's exact p = 0.022 (calculated) Placebc. Fisher's exact p = 0.022 (calculated) RR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.77 (0.63-0.97) Fisher's exact p = 0.057 (calculated) HR (95% CI) Adjusted: 0.71 (0.33-1.51) Propensity score matched: 0.44 (0.14-1.44) Fisher's exact p = 0.64 (calculated)
Svanström Toh Benowitz Carney Kittle Kotz	2012 2013 2018 2020 2021 2021 2017 2015	Observation al cohort Observation al cohort RCT observational cohort RCT observational cohort	Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7) 52 weeks (p. E7) 12 months or Patient therapy duration plus 30 days Primary analysis 1 year 2 6 weeks 6 months	35,852 202.897 271,863 1,005,664 8058 618497 116442 7224 164766	near disease or damission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure heart failure (primary analyses) heart failure hospitalization for congestive heart failure hospitalization for congestive heart failure heart failure heart failure hear	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 588/131,562 (0.5%) Bupropion: 322/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1 Bupropion: 30/5,838 (0.5%) Bupropion: 1/4,297 (Proportion: 0.023%; 95% Cl, 0.001- 0.130%) Bupropion: 7/6,557 (0.1%)	Varenicilne: 82 events par 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicilne in tobacco users: 56/89,519 (0.0%) Varenicilne products approved for smoking cessation: 109/260,660 (0.04%) All varenicilne users: 109/260,660 (0.04%) Placebo: 5/2014 (0.2%) Placebo: 5/2014 (0.2%) NRT: 4/3/22,237 (1.5%), patient years: 5,869, Incidence rate per 1000 patient- years: 25.2 Varenicilne: 99/454,698 (0.1%), patient years: 55,854, Incidence rate per 1000 patient- years: 55,854, Incidence rate per 1000 patient-years: 5,9 NRT: 302/106,759 (0.3%) Varenicilne: 52/51,450 (0.1%)	HR (95% CI) 112 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 102 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact p = 0.05 (calculated) Placebc. Fisher's exact p = 0.02 (calculated) Placebc. Fisher's exact p = 0.22 (calculated) RR (95% CI) Adjusted: 0.84 (0.74-0.96) Fisher's exact p = 0.02 (calculated) HR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.71 (0.33-1.51) Propensity scote matched: 0.44 (0.14-1.44) Fisher's exact p = 0.64 (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.89)
Svanström Toh Benowitz Carney Kittle Kotz	2012 2013 2018 2020 2021 2017 2015	Observation al cohort Observation al cohort RCT observational cohort RCT observational cohort	Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7) 12 months or Patient therapy duration plus 30 days Primary analysis 1 year 2 6 weeks 6 months	35,852 202.897 271.863 1.005,664 8058 618497 116442 7224 164766	near disease or damission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure (primary analyses) heart failure (imary analyses) heart failure hospitalization for congestive heart failure hospitalization for for hospitalization for for hospitalization for hospitalization for	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 588/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1 Bupropion: 30/5,838 (0.5%) Bupropion: 1/4,297 (Proportion: 0.023%; 95% Cl, 0.001- 0.130%) Bupropion: 7/6,557 (0.1%)	Varenicilne: 82 events par 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicilne in tobacco users: 56/89,519 (0.0%) Varenicilne products approved for smoking cessation: 109/260,660 (0.04%) All varenicilne users: 109/260,660 (0.04%) Placebcs 5/2014 (0.2%) Placebcs 5/2014 (0.2%) NRT: 4/32,237 (1.5%), patient years: 5,869, Incidence rate per 1000 patient- years: 25.2 Varenicilne: 99/454,698 (0.1%), patient years: 55.84, Incidence rate per 1000 patient- years: 59,854, Incidence rate per 1000 patient- years: 52,854, Incidence rate per 1000 patient- years: 59,854, Incidence rate per 1000 patient- years: 51,854, Incidence rate per 1000 patient- years: 52,854, Incidence rate per 1000 patient- years: 52,854, Incidence rate per 1000 patient- years: 51,854, Incidence rate per 1000 patient- years: 52,854, Incidence rate per 1000	HR (95% CI) 112 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 102 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact p = 0.05 (calculated) Placebo: Fisher's exact p = 0.02 (calculated) Placebo: Fisher's exact p = 0.22 (calculated) RR (95% CI) Adjusted: 0.71 (0.30-0.96) Fisher's exact p = 0.07 (calculated) HR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.71 (0.33-1.51) Propensity score matched: 0.44 (0.14-1.44) Fisher's exact p = 0.64 (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.89) Propensity score matched: 0.99 (0.06-15.89)
Svanström Toh Benowitz Carney Kittle Kotz Kotz	2012 2013 2018 2020 2021 2017 2015 2017 2017	Observation al cohort Observation al cohort RCT observational cohort RCT observational cohort observational cohort	Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7) 52 weeks (p. E7) 12 months or Patient therapy duration plus 30 days Primary analysis 1 year 2 6 weeks 6 months	35,852 202.897 271.863 1.005,664 8058 618497 116442 7224 164766 16679	neard tailures heard failure heart failure Heart failure Heart failure Heart failure	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 588/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1 Bupropion: 30/5,838 (0.5%) Bupropion: 1/4,297 (Proportion: 0.023%; 95% Cl, 0.001- 0.130%) Bupropion: 7/6,557 (0.1%)	Varenicilne: 82 events par 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicilne in tobacco users: 56/89,519 (0.0%) Varenicilne products approved for smoking cessation: 109/260,660 (0.04%) All varenicilne users: 109/260,660 (0.04%) Varenicilne: 0/2016 (0.0%) NRT: 46/32,237 (1.4%) Varenicilne: 1994/54,698 (0.4%) NRT: 440/32,237 (1.4%) Varenicilne: 1994/54,698 (0.4%) NRT: 440/32,237 (0.5%), patient years: 5,869, incidence rate per 1000 patient- years: 25.2 Varenicilne: 570/454,698 (0.1%), patient years: 55.84, Incidence rate per 1000 patient-years: 5,9 NRT: 302/106,759 (0.3%) Varenicilne: 52/51,450 (0.1%). NRT: 118/10,426 (1.1%) Varenicilne: 52/51,450 (0.5%)	HR (95% CI) 112 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 102 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact p = 0.050 (calculated) Placebo: Fisher's exact p = 0.22 (calculated) RR (95% CI) Adjusted: 0.44 (0.74-0.96) Fisher's exact p = 0.22 (calculated) HR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.71 (0.33-1.51) Propensity score matched: 0.44 (0.14-1.44) Fisher's exact p = 0.84 (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.89) Propensity score matched: 0.99 (0.06-15.89) Fisher's exact p = 1.00 (calculated)
Svanström Toh Benowitz Carney Kittle Kotz Kotz	2012 2013 2018 2020 2021 2017 2015 2017	Observation al cohort Observation al cohort RCT observational cohort RCT observational cohort observational cohort observational cohort	Smoking oessation Smoking oessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking	6 months (primary analyses) From first dispensing until dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7) 52 weeks (p. E7) 12 months or Patient therapy duration plus 30 days Primary analysis 1 year 2 6 weeks 6 months 6 months 6 months	35,852 202.897 271.863 1.005,664 8058 618497 116442 7224 164766 16679	neard taikease or damission for coronary artery bypass grafting bypass grafting oronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure (primary analyses) heart failure (time- to-event sensitivity analyses) heart failure hospitalization for congestive heart failure Heart failure Heart failure	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 588/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1 Bupropion: 30/5,838 (0.5%) Bupropion: 1/4,297 (Proportion: 0.023%; 95% Cl, 0.001- 0.130%) Bupropion: 7/6,557 (0.1%) Bupropion: 1/350 (0.3%) Bupropion: 16 events per 8,405 person-years. Incidence	Varenicilne: 82 events par 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicilne in tobacco users: 56/89,519 (0.0%) Varenicilne products approved for smoking cessation: 109/260,660 (0.04%) All varenicilne users: 109/260,660 (0.04%) Varenicilne: 0/2016 (0.0%) NRT: 4/02,237 (1.4%) Varenicilne: 1994/54,698 (0.4%) NRT: 4/02,237 (1.4%) Varenicilne: 1994/54,698 (0.4%) NRT: 4/02,237 (0.5%), patient years: 5,869, incidence rate per 1000 patient- years: 25.2 Varenicilne: 570/454,698 (0.1%), patient years: 55,854, Incidence rate per 1000 patient-years: 5,9 NRT: 302/106,759 (0.3%) Varenicilne: 52/51,450 (0.1%) NRT: 118/10,426 (1.1%) Varenicilne: 52/51,450 (0.1%) Varenicilne: 13/3,574 (0.5%) Varenicilne: 13/3,574 (0.5%) Varenicilne: 13/3,574 (0.0%)	HR (95% CI) 112 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 102 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact p = 0.05 (calculated) Placebo: Fisher's exact p = 0.22 (calculated) RR (95% CI) Adjusted: 0.84 (0.74-0.96) Fisher's exact p = 0.02 (calculated) HR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.71 (0.33-1.51) Propensity score matched: 0.44 (0.14-1.44) Fisher's exact p = 0.64 (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.89) Propensity score matched: 0.99 (0.06-15.89) Fisher's exact p = 1.00 (calculated) HR (95% CI)
Svanström Toh Benowitz Carney Carney Kittle Kotz Svanström	2012 2013 2018 2020 2021 2017 2015 2017 2017 2012	Observation al cohort Observation al cohort RCT observational cohort observational cohort observational cohort observational cohort	Smoking oessation Smoking oessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7) 52 weeks (p. E7) 53 weeks 54 weeks 54 weeks 55 weeks 56 months 56 months 56 months 56 months 56 months 57 months 57 months 57 months 57 months 57 months 57 months 58 months 58 months 58 months 58 months 58 months 58 months 57 months 58 months 58 months 57 months 57 months 58 mon	35,852 202.897 271.863 1.005,664 8058 618497 116442 7224 164766 16679 35852	neard tailure dairtission for coronary artery bypass graffus coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure (primary analyses) heart failure (primary analyses) heart failure hospitalization for congestive heart failure hospitalization for congestive heart failure Heart failure Heart failure	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 588/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1 Bupropion: 30/5,838 (0.5%) Bupropion: 1/4,297 (Proportion: 0.023%; 95% Cl, 0.001- 0.130%) Bupropion: 7/6,557 (0.1%) Bupropion: 1/350 (0.3%) Bupropion: 16 events per 8,405 person-years. Incidence rate per 1,000 person-years: 1.9	Varenicilne: 82 events par 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicilne in tobacco users: 56/89,519 (0.0%) Varenicilne products approved for smoking cessation: 109/260,660 (0.04%) All varenicilne: 0/2016 (0.0%) NRT: 1/2022 (-0.1%) Placebo: 5/2014 (0.2%) NRT: 46/32,237 (1.4%) Varenicilne: 1994/54,698 (0.4%) NRT: 440/32,237 (1.4%) Varenicilne: 1994/54,698 (0.4%) NRT: 440/32,237 (0.5%), patient years: 5,869, Incidence rate per 1000 patient- years: 25.2 Varenicilne: 570/454,698 (0.1%), patient years: 55.84, Incidence rate per 1000 patient-years: 5,9 NRT: 302/106,759 (0.3%) Placebo comparator: 22,927 (Proportion, 0.068%; 95% CI, 0.008- 0.247%) NRT: 302/106,759 (0.3%) Varenicilne: 52/51,450 (0.1%) NRT: 118/10,426 (1.1%) Varenicilne: 12016 (-0.5%) Varenicilne: 12016 (-0.1%)	HR (95% CI) 112 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 102 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicine: Fisher's exact p = 0.05 (calculated) Placebo: Fisher's exact p = 0.02 (calculated) Placebo: Fisher's exact p = 0.22 (calculated) RR (95% CI) Adjusted: 0.74 (0.74-0.96) Fisher's exact p = 0.02 (calculated) HR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.71 (0.33-1.51) Propensity scote matched: 0.44 (0.14-1.44) Fisher's exact p = 0.62 (calculated) HR (95% CI) Adjusted: 0.07 (0.03-1.51) Propensity scote matched: 0.99 (0.06-15.89) Propensity scote matched: 0.99 (0.06-15.89) Fisher's exact p = 0.62 (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.88) Propensity scote matched: 0.99 (0.06-15.89) Fisher's exact p = 0.62 (calculated) HR (95% CI) Adjusted: 0.40 (0.14-1.44) Fisher's exact p = 0.02 (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.88) Propensity scote matched: 0.99 (0.06-15.89) Fisher's exact p = 0.02 (calculated) HR (95% CI) Adjusted: 0.40 (0.14-1.44) Fisher's exact p = 0.02 (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.88) Propensity scote matched: 0.99 (0.06-15.89) Fisher's exact p = 0.02 (calculated) HR (95% CI) Adjusted: 0.40 (0.14-1.44) Fisher's exact p = 0.02 (calculated) HR (95% CI) Adjusted: 0.40 (0.14-1.44) Fisher's exact p = 0.02 (calculated) HR (95% CI) Adjusted: 0.40 (0.14-1.44) Fisher's exact p = 0.57 (calculated) HR (95% CI) Adjusted: 0.40 (0.14-1.44) Fisher's exact p = 0.57 (calculated) HR (95% CI) Adjusted: 0.40 (0.14-1.44) Fisher's exact p = 0.57 (calculated) HR (95% CI) Adjusted: 0.40 (0.14-1.44) Fisher's exact p = 0.57 (calculated) HR (95% CI) Adjusted: 0.40 (0.14-1.44) Fisher's exact p = 0.57 (calculated) HR (95% CI) Adjusted: 0.40 (0.14-1.44) Fisher's exact p = 0.57 (calculated) HR (95% CI) Adjusted: 0.40 (calculated) HR (95% CI) Adjusted: 0.45 (calculated) HR (95% CI) Adjusted: 0.45 (calculate
Svanström Toh Benowitz Carney Carney Köttle Kotz Svanström Benowitz	2012 2013 2018 2020 2021 2017 2015 2017 2017 2017 2018 	Observation al cohort Observational cohort observational cohort RCT observational cohort observational cohort observational cohort	Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7) 12 months or Patient therapy duration plus 30 days Primary analysis 1 year 2 6 weeks 6 months 6 months 6 months 5 months 5 months 5 months 5 months	35,852 202.897 271,863 1,005,664 8058 618497 116442 7224 164766 16679 35852 8058	neart disease or admission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure heart failure (primary analyses) heart failure hospitalization for congestive heart failure heart failure Heart failure Heart failure Heart failure Heart failure Heart failure hospitalization for constable angina.	Bupropion: 93 events per 8,388 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2006 (<0.1%) Bupropion: 588/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1 Bupropion: 30/5,838 (0.5%) Bupropion: 1/4,297 (Proportion: 0.023%; 95% Cl, 0.001- 0.130%) Bupropion: 7/6,557 (0.1%) Bupropion: 1/350 (0.3%) Bupropion: 1/6 events per 8,405 person-years. Incidence rate per 1,000 person-years: 1.9 Bupropion: 2/2006 (0.1%)	Varenicilne: 82 events par 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicilne in tobacco users: 56/89,519 (0.0%) Varenicilne products approved for smoking cessation: 109/260,660 (0.04%) All varenicilne users: 109/260,660 (0.04%) Placebo: 5/2014 (0.2%) NRT: 4/32,237 (1.5%) Placebo: 5/2014 (0.2%) NRT: 440/32,237 (1.5%) Varenicilne: 199/454,698 (0.4%) NRT: 440/32,237 (1.5%), patient years: 5,869, Incidence rate per 1000 patient- years: 25.2 Varenicilne: 570/454,698 (0.1%), patient years: 55,854, Incidence rate per 1000 patient-years: 5,9 NRT: 302/106,759 (0.3%) Placebo comparator: 22,927 (Proportion, 0.068%; 95% CI, 0.008- 0,247%) NRT: 118/10,426 (1.1%) Varenicline: 12016 (<0.1%) Varenicline: 12016 (<0.1%) Varenicline: 12016 (<0.1%) Varenicline: 12016 (<0.1%) NRT: 118/10,426 (1.1%)	HR (95% CI) 112 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 102 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact p = 0.05 (calculated) Placebo: Fisher's exact p = 0.02 (calculated) RR (95% CI) Adjusted: 0.44 (0.74-0.96) Fisher's exact p = 0.02 (calculated) HR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.77 (0.62-0.97) Fisher's exact p = 0.06 (calculated) HR (95% CI) Adjusted: 0.77 (0.33-151) Propensity score matched: 0.44 (0.14-1.44) Fisher's exact p = 0.64 (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.89) Propensity score matched: 0.99 (0.06-15.89) Fisher's exact p = 0.52 (calculated) HR (95% CI) Adjusted: 0.92 (0.05-2.56) Varenicline: Fisher's exact p = 0.52 (calculated) HR (95% CI) Adjusted: 0.45 (0.256) Zeronicline: Fisher's exact p = 0.52 (calculated) HR (95% CI) Adjusted: 0.40 (0.26-2.89) Propensity score matched: 0.99 (0.06-15.89) Fisher's exact p = 0.25 (calculated) HR (95% CI) Adjusted: 0.75 (0.256) Zeronicline: Fisher's exact p = 0.52 (calculated) HR (95% CI) Adjusted: 0.75 (0.256) Zeronicline: Fisher's exact p = 0.52 (calculated) HR (95% CI) Adjusted: 0.75 (0.256) Zeronicline: Fisher's exact p = 0.52 (calculated) HR (95% CI) Adjusted: 0.75 (0.256) Zeronicline: Fisher's exact p = 0.52 (calculated) HR (95% CI) Adjusted: 0.75 (0.256) Zeronicline: Fisher's exact p = 0.52 (calculated) HR (95% CI) Adjusted: 0.75 (0.256) Zeronicline: Fisher's exact p = 0.52 (calculated) HR (95% CI) Adjusted: 0.75 (Calculated) HR
Svanström Toh Benowitz Carney Carney Kittle Kotz Svanström Benowitz	2012 2013 2018 2020 2021 2017 2015 2017 2017 2017 2018	Observation al cohort Observational cohort observational cohort observational cohort observational cohort observational cohort observational cohort	Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7) 12 months or Patient therapy duration plus 30 days Primary analysis 1 year 2 6 weeks 6 months 6 months 6 months 6 months 5 2 weeks	35,852 202.897 271.863 1.005,664 8058 618497 116442 7224 164766 16679 35852 8058	neard tailusease or coronary artery bypass graffus bypass graffus coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure (primary analyses) heart failure (imary analyses) heart failure hospitalization for congestive heart failure heart failure hospitalization for congestive heart failure Heart failure Heart failure Heart failure hospitalization for constable angina angina (primary	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2,006 (<0.1%) Bupropion: 588/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1 Bupropion: 30/5,838 (0.5%) Bupropion: 1/4,297 (Proportion: 0.023%; 95% Cl, 0.001- 0.130%) Bupropion: 7/6,557 (0.1%) Bupropion: 1/350 (0.3%) Bupropion: 16 events per 8,405 person-years. Incidence rate per 1,000 person-years: 1.9 Bupropion: 2/2006 (0.1%)	Varenicilne: 82 events par 8,247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicilne in tobacco users: 56/89,519 (0.0%) Varenicilne products approved for smoking cessation: 109/260,660 (0.04%) All varenicilne users: 109/260,660 (0.04%) Placebo: 5/2014 (0.2%) NRT: 4/32,237 (1.5%) Placebo: 5/2014 (0.2%) NRT: 46/32,237 (1.5%) parenicilne: 1994/54,698 (0.4%) NRT: 440/32,237 (0.5%), patient years: 5,869, incidence rate per 1000 patient- years: 25.2 Varenicilne: 570/454,698 (0.1%), patient years: 55.854, Incidence rate per 1000 patient-years: 5,9 NRT: 302/106,759 (0.3%) Placebo comparator: 22,927 (Proportion, 0.068%; 95% CI, 0.008- 0.247%) NRT: 302/106,759 (0.3%) Varenicilne: 12016 (<0.1%) Varenicilne: 12016 (<0.1%) Varenicilne: 12016 (<0.1%) NRT: 118/10,426 (1.1%) Varenicilne: 12016 (<0.1%) NRT: 118/10,426 (1.1%) NRT: 118/10,426 (1.1%) NRT: 118/10,426 (1.1%) NRT: 118/10,426 (1.1%) NRT: 118/10,426 (1.1%) NRT: 118/10,420 (0.0%) NRT: 93/32,237 (0.3%)	HR (95% CI) HR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 1.02 (0.45-2.33) IRR (95% CI) Adjusted: 1.02 (0.45-2.33) Varenicline: Fisher's exact $p = 0.50$ (calculated) Placebo: Fisher's exact $p = 0.22$ (calculated) RR (95% CI) Adjusted: 0.04 (0.74-0.96) Fisher's exact $p = 0.02$ (calculated) HR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.71 (0.33-1.51) Propensity score matched: 0.44 (0.14-1.44) Fisher's exact $p = 0.04$ (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.89) Propensity score matched: 0.99 (0.06-15.89) Fisher's exact $p = 0.25$ (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.89) Propensity score matched: 0.99 (0.06-15.89) Fisher's exact $p = 0.25$ (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.89) Propensity score matched: 0.99 (0.06-15.89) Fisher's exact $p = 0.25$ (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.89) Propensity score matched: 0.99 (0.06-15.89) Fisher's exact $p = 0.25$ (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.89) Propensity score matched: 0.99 (0.06-15.89) Fisher's exact $p = 0.25$ (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.89) Propensity score matched: 0.99 (0.06-15.89) Fisher's exact $p = 0.25$ (calculated) HR (95% CI) Adjusted: 0.80 (0.59-1.07)
Svanström Toh Benowitz Carney Carney Köttle Kotz Svanström Benowitz	2012 2013 2018 2020 2021 2017 2015 2017 2015 2017 2012 2018	Observation al cohort Observational cohort observational cohort observational cohort observational cohort observational cohort observational cohort	Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7) 12 months or Patient therapy duration plus 30 days Primary analysis 1 year 2 6 weeks 6 months 6 months 6 months 5 2 weeks	35,852 202.897 271,863 1,005,664 8058 618497 116442 7224 164766 16679 35852 8058	near tisiseae or admission for coronary artery bypass grafting bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure heart failure (primary analyses) heart failure hospitalization for congestive heart failure heart failure Heart failure Heart failure Heart failure Heart failure hospitalization for constable angina angina (primary analyses)	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: <i>6</i> (11,203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2,006 (<0.1%) Bupropion: 588/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1 Bupropion: 30/5,838 (0.5%) Bupropion: 1/4,297 (Proportion: 0.023%; 95% Cl, 0.001- 0,130%) Bupropion: 7/6,557 (0.1%) Bupropion: 1/350 (0.3%) Bupropion: 16 events per 8,405 person-years. Incidence rate per 1,000 person-years: 1.9 Bupropion: 2/2006 (0.1%)	Varenicilne: 82 events par 8.247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicilne in tobacco users: 56/89,519 (0.0%) Varenicilne products approved for smoking cessation: 109/260,660 (0.04%) Varenicilne: 0/2016 (0.0%) NRT: 1/2022 (-0.1%) Placebo: 5/2014 (0.2%) NRT: 46/32,237 (1.4%) Varenicilne: 1994/54,698 (0.4%) NRT: 440/32,237 (1.5%), patient years: 5,869, Incidence rate per 1000 patient- years: 25,24 Varenicilne: 570/454,698 (0.1%), patient years: 55,854, Incidence rate per 1000 patient- years: 55,854, Incidence rate per 1000 patient- years: 55,854, Incidence rate per 1000 patient- years: 59,854, Incidence rate per 1000 patient- years: 59,854, Incidence rate per 1,000 patient- years: 1,510 (0.6%) Varenicilne: 17/29,094 (0.4%) Placebo comparator: 2/2,927 (Proportion, 0.068%; 95% CI, 0.008- 0,247%) NRT: 302/106,759 (0.3%) Varenicilne: 1/2016 (-0.1%) NRT: 118/10,426 (1.1%) Varenicilne: 1/2016 (-0.1%) NRT: 302/2022 (0.0%) NRT: 3032,237 (0.5%) Varenicilne: 1/2016 (-0.1%) NRT: 3032,237 (0.1%), patient years:	HR (95% CI) 112 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 102 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact p = 0.05 (calculated) Placebo: Fisher's exact p = 0.02 (calculated) RR (95% CI) Adjusted: 0.44 (0.74-0.96) Fisher's exact p = 0.71 (calculated) HR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.77 (0.62-0.97) HR (95% CI) Adjusted: 0.77 (0.62-0.97) HR (95% CI) Adjusted: 0.77 (0.62-0.97) HR (95% CI) Adjusted: 0.71 (0.33-151) Propensity score matched: 0.44 (0.14-1.44) Fisher's exact p = 0.62 (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.89) Propensity score matched: 0.99 (0.06-15.89) Fisher's exact p = 0.25 (calculated) HR (95% CI) Adjusted: 0.70 (23-0.59) Fisher's exact p = 0.52 (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.89) Propensity score matched: 0.99 (0.06-15.89) Fisher's exact p = 0.25 (calculated) HR (95% CI) Adjusted: 0.70 (23-2.56) Varenicline: Fisher's exact p = 0.52 (calculated) HR (95% CI) Adjusted: 0.80 (0.59-1.07) Fisher's exact p = 0.25 (calculated) HR (95% CI) Adjusted: 0.80 (0.59-1.07) Fisher's exact p = 0.25 (calculated) HR (95% CI) Adjusted: 0.80 (0.59-1.07) Fisher's exact p = 0.25 (calculated)
Svanström Toh Benowitz Carney Carney Köttle Kotz Svanström Benowitz	2012 2013 2018 2020 2021 2017 2015 2017 2015 2017 2018 2018	Observation al cohort Observational cohort RCT observational cohort RCT observational cohort observational cohort observational cohort observational cohort cohort observational cohort coho	Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation Smoking cessation	6 months (primary analyses) From first dispensing until dispensing until occurrence of outcome or end of first treatment episode (7 days after end of last 52 weeks (p. E7) 12 months or Patient therapy days Primary analysis 1 year 2 6 weeks 6 months 6 months 6 months 5 2 weeks	35,852 202.897 271,863 1,005,664 8058 618497 116442 7224 164766 16679 35852 8058	neart disease or admission for coronary artery bypass grafting or percutaneous coronary intervention] Composite of 3 CV endpoints: acute myocardial infarction, intermediate coronary syndrome or hospitalization for congestive heart failure heart failure (primary analyses) heart failure hospitalization for congestive heart failure heart failure Heart failure Heart failure Heart failure Heart failure Heart failure hospitalization for constable angina angina (primary analyses)	Bupropion: 93 events per 8,386 person-years. Incidence rate per 1,000 person-years: 11.1 Bupropion in tobacco users: 118/113,378 (0.09%) Bupropion products approved for smoking cessation: 6/11.203 (0.05%) All bupropion users: 452/745,004 (0.06%) Bupropion: 1/2,006 (<0.1%) Bupropion: 588/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.1 Bupropion: 30/5,838 (0.5%) Bupropion: 1/4,297 (Proportion: 0.023%; 95% Cl, 0.001- 0.130%) Bupropion: 7/6,557 (0.1%) Bupropion: 1/350 (0.3%) Bupropion: 16 events per 8,405 person-years. Incidence rate per 1,000 person-years: 1.9 Bupropion: 2/2006 (0.1%) Bupropion: 1/4/131,562 (0.1%)	Varenicline: 82 events par 8.247 person- years. Incidence rate per 1,000 person- years: 9.9 Varenicline in tobacco users: 56/89,519 (0.0%) Varenicline products approved for smoking cessation: 109/260,660 (0.04%) All varenicline users: 109/260,660 (0.04%) Placebic 5/2014 (0.2%) NRT: 4/32,237 (1.5%) Placebic 5/2014 (0.2%) NRT: 4/32,237 (1.5%), patient years: 5,869, Incidence rate per 1000 patient- years: 25,24 Varenicline: 99/454,698 (0.1%), patient years: 55,854, Incidence rate per 1000 patient- years: 1,510 (0.6%) Varenicline: 17/39,094 (0.4%) Placebo comparator: 2/2,927 (Proportion, 0.068%; 95% CI, 0.008- 0,247%) NRT: 302/106,759 (0.3%) Varenicline: 1/2016 (<0.1%) NRT: 118/10,426 (1.1%) Varenicline: 1/2016 (<0.1%) NRT: 3032,237 (0.5%) Varenicline: 1/2016 (<0.1%) NRT: 3032,237 (0.1%), patient years: 5,80, Incidence rate per 1,000 person- years: 1.6 Varenicline: 1/2016 (<0.1%) NRT: 3032,237 (0.3%) Varenicline: 1/2016 (<0.1%) NRT: 3032,237 (0.3%) Varenicline: 1/2016 (<0.1%) NRT: 3032,237 (0.3%) Varenicline: 5,804, Incidence rate per 1000 patient- years: 5,80, Incidence rate per 1000 patient-	HR (95% CI) 112 (0.83 - 1.52) IRR (95% CI) Adjusted: 0.98 (0.68-1.41) IRR (95% CI) Adjusted: 102 (0.45-2.33) IRR (95% CI) Adjusted: 0.66 (0.52-0.83) Varenicline: Fisher's exact $p = 0.50$ (calculated) Placebo: Fisher's exact $p = 0.22$ (calculated) RR (95% CI) Adjusted: 0.44 (0.74-0.96) Fisher's exact $p = 0.71$ (calculated) HR (95% CI) Adjusted: 0.77 (0.62-0.97) NR RR (95% CI) Adjusted: 0.77 (0.62-0.97) HR (95% CI) Adjusted: 0.77 (0.62-0.97) Fisher's exact $p = 0.57$ (calculated) HR (95% CI) Adjusted: 0.71 (0.33-151) Propensity score matched: 0.44 (0.14-1.44) Fisher's exact $p = 0.64$ (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.89) Propensity score matched: 0.99 (0.06-15.89) Fisher's exact $p = 0.25$ (calculated) HR (95% CI) Adjusted: 0.40 (0.06-2.89) Propensity score matched: 0.99 (0.06-15.89) Fisher's exact $p = 0.25$ (calculated) HR (95% CI) Adjusted: 0.80 (0.59-1.07) Fisher's exact $p = 0.25$ (calculated) HR (95% CI) Adjusted: 0.80 (0.59-1.07) Fisher's exact $p = 0.52$ (calculated) HR (95% CI) Adjusted: 0.80 (0.59-1.07) Fisher's exact $p = 0.52$ (calculated) HR (95% CI) Adjusted: 0.80 (0.59-1.07) Fisher's exact $p = 0.52$ (calculated) HR (95% CI) Adjusted: 0.70 (0.0001) (calculated) HR (95% CI) Adjusted: 0.72 (0.44-1.15)

1	1	Í			12 months, or		1		Varenicline: 304/454,698 (0.1%), patient	
			observational	Smoking	patient therapy duration plus 30		angina (time-to- event sensitivity	Bupropion: 77/131,562 (0.1%), patient years: 52,687,	years: 95,886, Incidence rate per 1000 patient-years:	
Carney	2020		cohort	cessation	days .	618497	analyses)	Incidence rate per 1000 patient-years: 1.5	3.2	Fisher's exact p = 0.33 (calculated)
_			observational	Smoking	Primary analysis				NRT: 146/71,510 (0.2%)	Adjusted: 0.96 (0.51-1.81)
Carney	2021		cohort	cessation	1 year	116442	angina	Bupropion: 11/5,838 (0.2%)	Varenicline: 77/39,094 (0.2%) Varenicline: 1/86 (1.2%), considered	Fisher's exact p = 1.00 (calculated)
				Smoking					"serious" Placebo: 13/106 (12.3%), one	Varenicline: Fisher's exact p = 0.22 (calculated)
Cinciripini	2013		RCT	cessation	6 months	294	Angina	Bupropion: 5/102 (4.9%)	considered "serious"	Placebo: Fisher's exact p = 0.08 (calculated)
				Smoking	veeks for primary					
Eisenberg	2013		RCT	cessation	analysis	392	unstable angina	Bupropion: 12/192 (6.3%)	Placebo: 11/200 (5.5%) Placebo comparator: 2/2,927	Fisher's exact p = 0.83 (calculated)
Kittle	2017		RCT	Smoking	> 6 weeks	7224	hospitalization for unstable angina	Bupropion vs. placebo: 2/4,297 (Proportion: 0.047%; 95%	(Proportion: 0.068%; 95% CI, 0.008- 0.247%)	Fisher's exact n = 1.00 (calculated)
ruuo	2011		nor	obodulon	= 0 110010		new-onset or	0,00000.0000	Varenicline: 3/2016 (0.1%)	Taner a exact p = 1.00 (calculated)
				Smoking			worsening peripheral		nicotine replacement therapy: 3/2022 (0.1%)	Varenicline: Fisher's exact p = 1.00 (calculated) NRT: Fisher's exact p = 1.00 (calculated)
Benowitz		2018	RCT	cessation	52 weeks	8058	vascular disease	Bupropion: 3/2006 (0.1%) (p. E7)	Placebo: 2/2014 (0.1%) (p. E7)	Placebo: Fisher's exact p = 0.69 (calculated)
							vascular disease		488/32,237 (1.5%)	Adjusted: 0.65 (0.57-0.74)
							(1 year fixed follow-	Bupropion: 592/131,562 (0.4%)	Varenicline: 3302/454,698 (0.7%) Nicotine replacement therapy :	Fisher's exact p < 0.00001 (calculated)
									185/32,237 (0.6%), patient years: 5,863, Incidence rate per 1000 patient-years:	HB (95% CI)
					10				31.6	Adjusted: 0.48 (0.39-0.60)
					Patient therapy		vascular disease	Bupropion: 306/131,562 (0.2%), patient years: 52,599,	patient years: 95,752,	
Carney		2020	Observation al cohort	Smoking cessation	duration plus 30 days	618497	(sensitivity analyses)	Incidence rate per 1000 patient-years: 5.8	Incidence rate per 1000 patient-years: 13.5	NR
			Observation	Smoking	Primary analysis		porinhoral		NPT: 202/71 510 (0.4%)	RR (95% CI)
Carney		2021	al cohort	cessation	1 year	116442	vascular disease	Bupropion: 28/5,838 (0.5%)	Varenicline: 179/39,094 (0.5%)	Fisher's exact p = 0.84 (calculated)
				Smoking			new diagnosis of peripheral			
Kittle		2017	RCT	cessation	≥ 6 weeks	7224	vascular disease	Bupropion: 0/4,297 (0%)	Placebo comparator: 0/2,927 (0%)	Fisher's exact p = 1.00 (calculated) HR (95% Cl)
									NPT: 430/106 750 /0 49/1	Adjusted: 0.83 (0.48-1.41)
									11111. 430/100,739 (U.4%)	Fropensity score matched: 1.62 (0.67-3.92)
Kotz		2015	Observation al cohort	Smoking cessation	6 months	164.766	peripheral vascular disease	Bupropion: 14/6,557 (0.2%)	Varenicline: 123/51,450 (0.2%)	Fisher's exact p = 0.79 (calculated)
										HR (95% CI)
			Observation	Smoking			Peripheral		NRT: 93/10,426 (0.9%)	Propensity score matched: 0.99 (0.06-15.80)
Kotz		2017	al cohort	cessation	6 months	16679	vascular disease	Bupropion: 1/350 (0.3%)	Varenicline: 17/3,574 (0.5%) Varenicline: 5/2016 (0.2%)	Fisher's exact p = 1.00 (calculated) Varenicline: Fisher's exact p = 0.45 (calculated)
Benowitz	2018		PCT	Smoking	52 weeks	8058	serious cardiac	Burronion: 2/2006 (0.1%)	NRT: 8/2022 (0.4%) Placebo: 3/2014 (0.1%)	NRT: Fisher's exact p = 0.11 (calculated)
Denowitz	2010			06338001	52 W66K3	0000	arriyunna	Bupropion: 2/2000 (0:178)	Placebo comparator: 2/2,927	Tracebo. Fisher's exact p = 1.00 (calculated)
Kittle	2017		RCT	Smoking cessation	≥ 6 weeks	7224	cardiac arrhythmias	Bupropion: 1/4,297 (Proportion: 0.023%; 95% Cl, 0.001- 0.130%)	(Proportion: 0.068%; 95% CI, 0.008- 0.247%)	Fisher's exact p = 0.57 (calculated)
										HR (95% CI) Adjusted: 0.66 (0.39-1.13)
	0045		observational	Smoking		101700		D	NRT: 563/106,759 (0.5%)	Propensity score matched: 0.43 (0.21-0.91)
KOIZ	2015		conort	cessation	6 months	164766	arrnytnmia	Bupropion: 14/6,557 (0.2%)	varenicline: 126/51,450 (0.2%)	NR HR (95% CI)
			observational	Smoking					NRT: 174/10 426 (1 7%)	Adjusted: 0.92 (0.34-2.50) Propensity score matched: 3 96 (0.44 - 35.41)
Kotz	2017		cohort	cessation	6 months	16679	Arrhythmia	Bupropion: 4/350 (1.1%)	Varenicline: 38/3,574 (1.1%)	Fisher's exact p = 0.79 (calculated)
							cardiac arrhythmia			
							(includes atrial and ventricular			
			observational	Smokina	6 months (primary		arrhythmias but not conduction	Bupropion: 32 events per 8.404 person-vears. Incidence	Varenicline: 20 events per 8,263 person- vears. Incidence rate per 1.000 person-	HR (95% CI)
Svanström	2012		cohort	cessation	analyses)	35852	block)	rate per 1,000 person-years: 3.8	years: 2.4	1.56 (0.90 - 2.78)
							Ischaemic Heart Disease (primary	Bupropion: 626/131,562 (0.5%)	NRT: 380/32,237 (1.2%)	RR (95% CI) Adjusted: 0.79 (0.69-0.91)
							analyses)		Varenicline: 3530/454,698 (0.8%) Nicotine replacement therapy :	Fisher's exact p < 0.00001 (calculated)
									129/32,237 (0.4%), patient years: 5,869,	
									22.0	Adjusted: 0.76 (0.60-0.96)
					12 months or patient therapy		Ischaemic Heart Disease (time-to-		Varenicline: 1143/454,698 (0.3%), patient years: 95,771,	
Carney	2020		Observation al cohort	Smoking cessation	duration plus 30 days	618 497	event sensitivity analyses)	Bupropion: 318/131,562 (0.2%), patient years: 52,597, Incidence rate per 1000 patient-years: 6.0	Incidence rate per 1000 patient-years: 11.9	Fisher's exact p = 0.55 (calculated)
			Observation	Con alvia a	Deimenne en ekenen		Ischaemic Heart	Durana 20/5 020 /0 50/)	Nicotine replacement therapy :	RR (95%CI)
Carney	2021		al cohort	cessation	1 year	116,442	analyses)	อสมาชุมเมน. อบาอ,อออ (0.อ76)	Varenicline: 159/39,094 (0.4%)	Fisher's exact p = 0.23 (calculated)
									Nicotine replacement therapy:	HR (95% GI): Adjusted: 0.67 (0.51-0.89)
Kotz	2015		Observation al cohort	Smoking	6 months	164 766	Ischaemic Heart Disease	Bupropion: 52/6,557 (0.8%)	2,148/106,759 (2.0%) Varenicline: 594/51 450 (1.2%)	Propensity score matched: 0.59 (0.37-0.93) Fisher's exact p = 0.007 (calculated)
							-		Nicotine replacement there:	HR (95% CI):
			Observation	Smoking			Ischaemic Heart		417/10,426 (4.0%)	Propensity score matched: 1.23 (0.49-3.12)
Kotz Cheon	2017 2017	_	al cohort RCT	cessation Psychiatric	6 months 6 weeks	16,679 103	Disease Tachycardia/Paloita	Bupropion: 11/350 (3.1%) Bupropion: 1/47 (2.1%)	vareniciine: 128/3,574 (3.6%) Aripiprazole: 0/56 (0.0%)	Fisher's exact p = 0.76 (calculated) Fisher's exact p = 0.46 (calculated)
				Smoking					Varenicline: 1/86 (1.2%)	Varenicline: Fisher's exact p = 0.38 (calculated)
Cinciripini	2013		RCT	cessation	6 months	294	Tachycardia/Palpita	Bupropion: 4/102 (3.9%)	Placebo: 3/106 (2.8%)	Placebo: Fisher's exact p = 0.72 (calculated)
Jatarinia	2012		Observation	Psychiatric	NR	40	Tachycardia/Palpita	Bupropion: 2/20 (10%)	Methylphenidate: 1/20 (5%)	Fisher's exact p = 1.00 (calculated)
Sheridan	2018	_	ai cohort	Psychiatric	NA 6 months	3749	Tachycardia/Palpita	виргоріоп: 1013/1433 (70.7%)	tricyciic antidepressant: 451/753 (59.9%) Varenicline: 39 events per 8,270 person-	Fisher's exact p < 0.00001 (calculated)
Svanström	2012		Observation al cohort	Smoking	(primary analyses)	35.852	Acute coronary syndrome	Bupropion: 33 events per 8,416 person-years. Incidence	years. Incidence rate per 1,000 person-	HR (95% CI) 0.83 (0.52-1.33)
ovalidation	2012			obodulon	dindiy000)	00,002		Tale per 1,000 percent years. 0.0	Jouro. 1.1	0.00 (0.02 1.00)
Maier	2020		RCT	Psychiatric	NR	108	Hospitalization for atrial fibrillation	Bupropion: 1/54 (1.9%)	Placebo: 0/54 (0.0%)	Fisher's exact p = 1.00 (calculated)
							peripheral arterial			
							disease [diagnosis			
							or periprieral arterial disease or			
			Observation	Smokina	6 months (primary		procedure to treat peripheral arterial	Bupropion: 71 events per 8,392 person-vears. Incidence	Varenicline: 78 events per 8,247 person- years. Incidence rate per 1.000 person-	HR (95% CI)
Svanström	2012		al cohort	cessation	analyses)	35,852	disease]	rate per 1,000 person-years: 8.5	years: 9.5	0.90 (0.65 - 1.23)
				Smoking			senous hypertensive			
Kittle	2017		RCT	cessation	≥ 6 weeks 6 months	7224	adverse event	Bupropion vs. placebo: 0/4,297 (0%)	Placebo comparator: 0/2,927 (0%) Varenicline: 11 events per 8,265 person-	NR
Svanström	2012		Observation al cohort	Smoking cessation	(primary analyses)	35 852	Transient ischaemic attack	Bupropion: 7 events per 8,409 person-years. Incidence rate per 1,000 person-years: 0.8	years. Incidence rate per 1,000 person- vears: 1.3	HR (95% CI) 0.63 (0.24 - 1.61)
							attent	,		

Supplement	upplemental Table 3. Naltrexone studies reporting on non-MACE cardiovascular adverse events.											
Author	Year	Study design	Study indication	Reported length of follow-up	No. Patients	Outcome	Adverse event frequency, treatment group	Adverse event frequency, comparator group	Effect measure			
Schmitz	2014	RCT	Substance use	12 weeks	81	Arrythmia	Naitrexone: 0/16 (0.0%)	Modafinii: 0/22 (0.0%) Levodopa/carbidopa: 1/25 (4.0%) Placebo: 0/18 (0.0%)	Modafinii: Fisher's exact p = 1.00 (calculated) Levodopa/carbidopa: Fisher's exact p = 1.00 (calculated) Placebo: Fisher's exact p = 1.00 (calculated)			
Lee	2016	RCT	Substance use	78 weeks	308	Death from cardiopulmonary arrest	Naltrexone: 0/153 (0.0%)	"Usual treatment": 1/155 (0.6%)	Fisher's exact p = 1.00 (calculated)			
Lee	2016	RCT	Substance use	78 weeks	308	DVT	Naltrexone: 0/153 (0.0%)	"Usual treatment": 1/155 (0.6%)	Fisher's exact p = 1.00 (calculated)			
Schmitz	2014	RCT	Substance use	12 weeks	81	DVT	Naltrexone: 0/16 (0.0%)	Modafinii: 0/22 (0.0%) Levodopa/carbidopa: 0/25 (0.0%) Placebo: 1/18 (5.6%)	(calculated) Levodopa/carbidopa: Fisher's exact p = 1.00 (calculated) Placebo: Fisher's exact p = 1.00 (calculated)			
							Oral naltrexone: 0/100 (0%)					
Krupitsky	2019	RCT	Substance use	48 weeks 78 weeks	200	Hypertension	Naltrexone implant: 8/100 (8.0%)	NA "Usual treatment": 1/155 (0.6%)	Fisher's exact p = 0.007 (calculated) Fisher's exact p = 1.00 (calculated)			
Spancar						ripperension	[Note: percentages are based on the total number of adverse events reported within the treatment group]	[Note: percentages are based on the total number of adverse events reported within the comparator group]				
"Opiate"	2018	RCT	Psychiatric	NR	37	Tachycardia/Palpitations	Naltrexone: 0/101 (0.0%)	Placebo: 5/76 (6.6%)	Fisher's exact p = 0.01 (calculated)			
Adhikari	2020	Other Observational	Substance use	12 weeks	78	Tachycardia/Palpitations	Naltrexone: 1/39 (2.5%)	Disulfiram: 5/39 (12.8%)	Fisher's exact p = 0.20 (calculated)			
Krupitsky	2019	RCT	Substance use	12-month open-label extension	114	Serious cardiomyopathy	Continued on nattrexone: 1/67 (1.5%) "judged as probably not related to" nattrexone extended-release	Switched from placebo to naltrexone: 0/47 (0%)	Fisher's exact p = 1.00 (calculated)			