

Figure S1. Flowchart for the literature search and selection.

Figure S2. Forest plot showing the comparison of allele C vs. allele T for all studies. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.

Study	Exposed group Events Total		group Total	Odds ratio	OR	95%-CI Weight
All CVE Gruchala 2003 Rubattu 2004 Zhang 2006 Lynch 2008 Barbato 2012 Francia 2013 Ziaee 2014 Siebert 2017 Pastori 2021 Random effects mode Heterogeneity: $I^2 = 100\%$		671 289 381 212 799	1013 731 459 58894 2334 575 1065 265 968 66304	*	2.09 0.97 0.81 0.13 7.44 1.05 4.05 0.06 0.04 0.64	[1.71; 2.54] 11.1% [0.68; 1.38] 11.1% [0.58; 1.14] 11.1% [0.12; 0.13] 11.2% [5.91; 9.35] 11.1% [0.68; 1.62] 11.1% [3.29; 4.98] 11.1% [0.04; 0.10] 11.0% [0.03; 0.07] 11.1% [0.19; 2.11] 100.0%
Atrial fibrillation Francia 2013 Siebert 2017 Random effects mode Heterogeneity: <i>I</i> ² = 99%,		289 212	575 265 840		1.05 0.06 0.25	[0.68; 1.62] 50.1% [0.04; 0.10] 49.9% [0.01; 4.21] 100.0%
Cerebrovascular even Rubattu 2004 Lynch 2008 Random effects mode Heterogeneity: $I^2 = 100\%$	83 153 867 17962 el 18115		731 58894 59625		0.97 0.00 0.05	[0.68; 1.38] 49.9% [0.00; 0.00] 50.1% [0.00; 17.67] 100.0%
Coronary heart disea Zhang 2006 Lynch 2008 Barbato 2012 Ziaee 2014 Random effects mode Heterogeneity: $I^2 = 100\%$	82 187 1475 17962 345 460 462 667 19276	671 381	459 58894 2334 1065 62752		0.81 0.01 7.44 4.05 0.67	[0.58; 1.14] 24.9% [0.01; 0.01] 25.1% [5.91; 9.35] 25.0% [3.29; 4.98] 25.0% [0.03; 13.63] 100.0%
Death Lynch 2008 Barbato 2012 Random effects mode Heterogeneity: <i>1</i> ² = 99%,		3	58894 747 59641	-		[0.02; 0.03] 51.7% [8.69; 110.61] 48.3% [0.00; 909.79] 100.0%
Myocardial infarction Gruchala 2003 Barbato 2012 Random effects mode Heterogeneity: $I^2 = 63\%$, Heterogeneity: $I^2 = 100\%$ Test for subgroup differe	376 675 14 117 $\tau^2 = 0.1094, p = 0.109$		1013 747 1760 4)	0.001 0.1 1 10 1000	2.09 3.77 2.55	[1.71; 2.54] 50.5% [1.91; 7.45] 49.5% [1.47; 4.43] 100.0%

Figure S3. Forest plot showing the comparison of CC vs. TT for all studies. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.

l Study	Exposed Events		Control Events		Odds ratio	OR	95%-Cl Weight
All CVE							
Gruchala 2003	35	63	163	232		0.53	[0.30; 0.94] 16.5%
Rubattu 2004	18	23	141	312			[1.58; 12.05] 9.5%
Zhang 2006	0	0	76	136			0.0%
Lynch 2008	701	2711	6127	23177	+	0.97	[0.89; 1.06] 24.6%
Barbato 2012	24	30	683	967		1.66	[0.67; 4.11] 10.9%
Francia 2013	3	5	121	244		1.52	[0.25; 9.29] 4.1%
Ziaee 2014	133	180	244	379		1.57	[1.06; 2.32] 20.1%
Siebert 2017	2	10	15	72		0.95	[0.18; 4.95] 4.7%
Pastori 2021	6	18	78	429		2.25	[0.82; 6.18] 9.6%
Random effects model		3040		25948		1.34	[0.84; 2.14] 100.0%
Heterogeneity: $I^2 = 68\%$, τ	² = 0.2639	9, p < 0.	01				
Atrial fibrillation							
Francia 2013	3	5	121	244		1.52	[0.25; 9.29] 46.3%
Siebert 2017	2	10	15	72			[0.18; 4.95] 53.7%
Random effects model		15		316		1.18	[0.35; 3.99] 100.0%
Heterogeneity: $I^2 = 0\%$, τ^2	r = 0, p = 0	.70					
Cerebrovascular event							
Rubattu 2004	18	23	141	312			[1.58; 12.05] 28.6%
Lynch 2008	147		984	23177	-		[1.08; 1.55] 71.4%
Random effects model		2734		23489		2.14	[0.66; 6.91] 100.0%
Heterogeneity: $I^2 = 81\%$, τ	= 0.6020	0, p = 0.	.02				
Coronary heart diseas							
Zhang 2006	0	0	76	136			0.0%
Lynch 2008	199	2711		23177			[0.73; 0.98] 43.7%
Barbato 2012	24	30	683	967			[0.67; 4.11] 19.8%
Ziaee 2014	133	180	244	379			[1.06; 2.32] 36.5%
Random effects model		2921		24659		1.19	[0.74; 1.94] 100.0%
Heterogeneity: $I^2 = 80\%$, τ	= 0.1273	3, p < 0.	.01				
Death							
Lynch 2008	404	2711	3010	23177	+	1.17	[1.05; 1.31] 100.0%
Myocardial infarction	. –	• -			_		
Gruchala 2003	35	63	163	232		0.53	[0.30; 0.94] 100.0%
Heterogeneity: $I^2 = 73\%$, τ	f = 0.1658	3, <i>p</i> < 0.	.01				
Test for subgroup difference	ces: $\chi_5^2 = 8$	8.73, df =	= 5 (p = 0	.12)	0.1 0.5 1 2 10		

Figure S4. Forest plot showing the comparison of CT vs. TT for all studies. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.

	Exposed gro	oup	Control	group				
Study	Events T				Odds ratio	OR	95%-CI	Weight
All CVE					1			
Gruchala 2003	306	549	163	232		0.53	[0.38; 0.74]	12.7%
Rubattu 2004		107	141	312		0.95	[0.61; 1.48]	9.6%
Zhang 2006	82	187	76	136		0.62	[0.40; 0.96]	9.5%
Lynch 2008	3291 12	540	6127	23177	+	0.99	[0.94; 1.04]	20.7%
Barbato 2012	297	400	683	967		1.20	[0.92; 1.56]	14.8%
Francia 2013	44	87	121	244		1.04	[0.64; 1.70]	8.5%
Ziaee 2014	196	307	244	379		0.98	[0.71; 1.34]	13.1%
Siebert 2017	23	121	15	72		0.89	[0.43; 1.85]	5.0%
Pastori 2021	13	110	78	429		0.60	[0.32; 1.13]	6.2%
Random effects mode	el 14	408		25948	\diamond	0.86	[0.71; 1.05]	100.0%
Heterogeneity: $I^2 = 64\%$,	$\tau^2 = 0.0529, p$	< 0.(01					
Atrial fibrillation								
Francia 2013	44	87	121	244		1.04	[0.64; 1.70]	63.2%
Siebert 2017		121	15	72		0.89	[0.43; 1.85]	36.8%
Random effects mode		208		316		0.99	[0.66; 1.49]	100.0%
Heterogeneity: $I^2 = 0\%$, τ	$z^2 = 0, p = 0.73$							
Cerebrovascular ever							FO 04 4 401	<u> </u>
Rubattu 2004		107	141	312		0.95	[0.61; 1.48]	32.8%
Lynch 2008	573 12		984	23177		1.08	[0.97; 1.20]	67.2%
Random effects mode		647		23489		1.07	[0.97; 1.19]	100.0%
Heterogeneity: $I^2 = 0\%$, τ	$z^2 = 0, p = 0.58$							
Coronary heart disea								
Zhang 2006		187	76	136		0.62	[0.40; 0.96]	16.5%
Lynch 2008	1077 12			23177	+	1.00	[0.93; 1.08]	35.1%
Barbato 2012		400	683	967		1.20	[0.92; 1.56]	25.6%
Ziaee 2014		307	244	379		0.98	[0.71; 1.34]	22.8%
Random effects mode		434		24659	\$	1.00	[0.93; 1.08]	100.0%
Heterogeneity: $I^2 = 53\%$,	$\tau^2 = 0, p = 0.0$	9						
Death								
Lynch 2008	1768 12	540	3010	23177		1.10	[1.03; 1.17]	100.0%
Myocardial infarction								
Gruchala 2003		549	163	232		0.53	[0.38; 0.74]	100.0%
Heterogeneity: $I^2 = 67\%$,								
Test for subgroup different	nces: $\chi_5^2 = 23.7$	5, df	= 5 (p <	0.01)	0.5 1 2			

Figure S5. Forest plot showing the comparison of (CC + CT) vs. TT for all studies. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.

E Study	xposed Events		Contro	l group Total	Odds ratio	OR	95%-CI	Weight
-	Lvents	TOLAT	Lvents	TOLAT		UK	90 /0-CI	weight
All CVE	0.44	040	400	000	_	0.50	10.00. 0.741	0.5%
Gruchala 2003	341	612	163	232		0.53	[0.39; 0.74]	8.5%
Rubattu 2004	65	130	141	312		1.21	[0.81; 1.83]	8.4%
Zhang 2006	82	187	76	136		0.62	[0.40; 0.96]	8.3%
Lynch 2008		15251	6127	23177		0.99	[0.94; 1.03]	8.8%
Larifla 2012	48	114	19	104		3.25	[1.75; 6.05]	7.9%
Barbato 2012	321	430	683	967		1.22	[0.95; 1.58]	8.6%
Cannone 2013	149	404	55	1219	-#-	12.37	[8.82; 17.33]	8.5%
Francia 2013	47	92	121	244	- <u>*</u> -	1.06	[0.66; 1.72]	8.2%
Ziaee 2014	329	487	244	379		1.15	[0.87; 1.53]	8.6%
Rubattu 2016	65	103	193	276		0.74	[0.46; 1.18]	8.3%
Siebert 2017	25	131	15	72		0.90	[0.44; 1.83]	7.7%
Pastori 2021	19	128	78	429		0.78	[0.45; 1.35]	8.1%
Random effects model	2	18069		27547	\diamond	1.23	[0.75; 2.02]	100.0%
Heterogeneity: $I^2 = 96\%$, τ^2	2 = 0.7035	5, p < 0.	01					
Atrial fibrillation	EF	404	05	1010	_	7 50	[4 62: 42 26]	24 40/
Cannone 2013	55	404	25	1219	L	7.53	[4.62; 12.26]	34.1%
Francia 2013	47	92	121	244		1.06	[0.66; 1.72]	34.2%
Siebert 2017	25	131	15	72		0.90	[0.44; 1.83]	31.7%
Random effects model Heterogeneity: $I^2 = 95\%$, τ^2	² = 1.3313	627 B, p < 0.	01	1535		1.95	[0.51; 7.50]	100.0%
Cerebrovascular event								
Rubattu 2004	65	130	141	312		1.21	[0.81; 1.83]	32.6%
Lynch 2008	720	15251	984	23177	-	1.12	[1.01; 1.23]	34.1%
Cannone 2013	78	404	188	1219		1.31	[0.98; 1.76]	33.3%
Random effects model		15785		24708	\$	1.14	[1.04; 1.25]	100.0%
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, p = 0	.57						
Coronary heart disease								
Zhang 2006	82	187	76	136		0.62	[0.40; 0.96]	16.4%
Lynch 2008		15251	1986	23177	9	0.97	[0.91; 1.05]	17.3%
Larifla 2012	48	114	19	104		3.25	[1.75; 6.05]	15.6%
Barbato 2012	321	430	683	967	-	1.22	[0.95; 1.58]	17.0%
Cannone 2013	149	404	55	1219		12.37	[8.82; 17.33]	16.8%
Ziaee 2014	329	487	244	379	<u> </u>	1.15	[0.87; 1.53]	16.9%
Random effects model	2	16873		25982		1.79	[0.75; 4.28]	100.0%
Heterogeneity: $I^2 = 98\%$, τ^2	- = 1.1530), p < 0.	01					
Death Lynch 2008	2172	15251	3010	23177		1.11	[1.05; 1.18]	50.9%
Cannone 2013		404	50				[1.05; 1.16]	50.9% 49.1%
Random effects model		404	50	24396			[0.35; 37.32]	49.1%
Heterogeneity: $I^2 = 99\%$, τ^2			01	24330		5.05	[0.55, 57.52]	100.070
Myocardial infarction								
Gruchala 2003	341	612	163	232		0.53	[0.39; 0.74]	34.1%
Cannone 2013	55	404	29	1219		6.47	[4.06; 10.30]	33.0%
Rubattu 2016	65	103	193	276		0.74	[0.46; 1.18]	32.9%
Random effects model	-	1119		1727		1.36	[0.29; 6.30]	100.0%
Heterogeneity: $I^2 = 97\%$, τ^2	$^{2} = 1.7920$), p < 0.	01				_	
Heterogeneity: $I^2 = 97\%$, τ^2	$^{2} = 0.8865$	5, <i>p</i> < 0.	01					
Test for subgroup difference	es: χ ₅ ² = 2	2.67, df =	= 5 (p = 0.	75)	0.1 0.5 1 2 10			

Figure S6. Forest plot showing the comparison of CC vs. (CT + TT) for all studies. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.

	xposed Events	• •	Contro Events	l group Total	Odds ratio	OR	95%-CI	Weight
All CVE					I			
Gruchala 2003	35	63	469	781		0.83	[0.50; 1.39]	17.0%
Rubattu 2004	18	23	188	419		4.42	[1.61; 12.14]	7.2%
Zhang 2006	0	0	158	323			[]	0.0%
Lynch 2008	701	2711	9418	35717	4	0.97	[0.89; 1.06]	31.6%
Barbato 2012	24	30	980	1367		1.58	[0.64; 3.89]	8.6%
Francia 2013	3	5	165	331		1.51	[0.25; 9.15]	2.7%
Ziaee 2014	133	180	440	686		1.58	[1.10; 2.28]	22.2%
Siebert 2017	2	10	38	193	_	1.02	[0.21; 5.00]	3.4%
Pastori 2021	6	18	91	539		2.46	[0.90; 6.73]	7.3%
Random effects model		3040		40356	\diamond	1.40	[0.96; 2.04]	100.0%
Heterogeneity: $I^2 = 64\%$, τ^2	= 0.1453	8, p < 0.0	01					
Atrial fibrillation								
Francia 2013	3	5	165	331		1.51	[0.25; 9.15]	44.3%
Siebert 2017	2	10	38	193		1.02	[0.21; 5.00]	55.7%
Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	- 0 0	15		524		1.21	[0.37; 3.99]	100.0%
Heterogeneity: $I^{-} = 0\%$, $\tau^{-} =$	= 0, p = 0	.75						
Cerebrovascular event								
Rubattu 2004	18	23	188	419		4.42		19.8%
Lynch 2008	147	2711	1557	35717		1.26	[1.06; 1.50]	80.2%
Random effects model		2734		36136		2.13	[0.63; 7.18]	100.0%
Heterogeneity: $I^2 = 83\%$, τ^2	= 0.6541	, p = 0.0	02					
Coronary heart disease								
Zhang 2006	0	0	158	323				0.0%
Lynch 2008	199	2711	3063	35717		0.84	[0.73; 0.98]	49.5%
Barbato 2012	24	30	980	1367		1.58	[0.64; 3.89]	14.1%
Ziaee 2014	133	180	440	686		1.58	[1.10; 2.28]	36.4%
Random effects model		2921		38093		1.19	[0.74; 1.93]	100.0%
Heterogeneity: $I^2 = 82\%$, τ^2	= 0.1273	8, <i>p</i> < 0.0	01					
Death					L			
Lynch 2008	404	2711	4778	35717		1.13	[1.02; 1.27]	100.0%
Myocardial infarction								
Gruchala 2003	35	63	469	781		0.83	[0.50; 1.39]	100.0%
Heterogeneity: $I^2 = 67\%$, τ^2	= 0.0762	2, p < 0.0	01	• • •				
Test for subgroup difference	es: χ ₅ = 3	.62, df =	= 5 (p = 0.	61)	0.1 0.5 1 2 10			

Figure S7. Forest plot showing the comparison of CT vs. (TT + CC) for all studies. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.

Study	Exposed g Events			l group Total	Odds ratio	OR	95%-CI	Weight
All CVE					1			
Gruchala 2003	306	549	469	781	- _	0.84	[0.67; 1.04]	7588.3%
Rubattu 2004	47	107	188	419		0.96	[0.63; 1.48]	2081.2%
Zhang 2006	82	187	158	323	+	0.82	[0.57; 1.17]	2893.0%
Lynch 2008	3291 1	2540	9418	35717	+	0.99	[0.95; 1.04]	98639.5%
Barbato 2012	297	400	980	1367		1.14	[0.88; 1.47]	5835.1%
Francia 2013	44	87	165	331		1.03	[0.64; 1.65]	1708.7%
Ziaee 2014	196	307	440	686		0.99	[0.75; 1.31]	4783.2%
Siebert 2017	23	121	38	193		0.96	[0.54; 1.70]	1150.7%
Pastori 2021	13	110	91	539		0.66	[0.35; 1.23]	991.0%
Common effect mode		4408		40356	\$	0.99	[0.94; 1.03]	
Heterogeneity: $I^2 = 0\%$, τ	$p^2 = 0, p = 0.0$	63						
Atrial fibrillation								
Francia 2013	44	87	165	331		1.03	[0.64; 1.65]	1708.7%
Siebert 2017	23	121	38	193		0.96	[0.54; 1.70]	1150.7%
Common effect mode		208		524		1.00	[0.69; 1.44]	
Heterogeneity: $I^2 = 0\%$, τ	$z^2 = 0, p = 0.8$	85						
Cerebrovascular ever	nt							
Rubattu 2004	47	107	188	419		0.96	[0.63; 1.48]	2081.2%
Lynch 2008	573 1		1557	35717		1.05	[0.95; 1.16]	33807.7%
Common effect mode		2647		36136	\diamond	1.05	[0.95; 1.15]	
Heterogeneity: $I^2 = 0\%$, τ	$p^2 = 0, p = 0.7$	70						
Coronary heart disea	se							
Zhang 2006	82	187	158	323	+	0.82	[0.57; 1.17]	2893.0%
Lynch 2008	1077 1	2540	3063	35717	÷	1.00	[0.93; 1.08]	54631.3%
Barbato 2012	297	400	980	1367		1.14	[0.88; 1.47]	5835.1%
Ziaee 2014	196	307	440	686		0.99	[0.75; 1.31]	4783.2%
Common effect mode		3434		38093	\$	1.00	[0.94; 1.07]	
Heterogeneity: $I^2 = 0\%$, τ	$z^2 = < 0.0001$, p = 0).53					
Death	4700 4	~ - · ~						
Lynch 2008	1768 1	2540	4778	35717		1.06	[1.00; 1.13]	73655.7%
Myocardial infarction								
Gruchala 2003	306	549	469	781		0.84	[0.67; 1.04]	7588.3%
Heterogeneity: I ² = 0%, τ	$r^2 = 0.0005, \mu$	p = 0.5	59		1 1 1			
Test for subgroup differen	nces: $\chi_5^2 = 7.4$	41, df :	= 5 (p = 0.	.19)	0.5 1 2			

Figure S8. Forest plot showing the comparison of C vs. T for studies with Hardy-Weinberg equilibrium. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.

E Study	xposed g Events	•	Control o Events	• •	Odds ratio	OR	95%-CI	Weight
All CVE								
Rubattu 2004	83	153	402	731	+	0.97	[0.68; 1.38]	25.0%
Barbato 2012	345	460	671	2334		7.44	[5.91; 9.35]	25.2%
Francia 2013	50	97	289	575	+	1.05	[0.68; 1.62]	24.9%
Pastori 2021	25	146	799	968		0.04	[0.03; 0.07]	24.9%
Random effects mode		856		4608		0.76	[0.10; 6.11]	100.0%
Heterogeneity: $I^2 = 99\%$, a	$c^2 = 4.4669$, p < 0	.01					
Atrial fibrillation								
Francia 2013	50	97	289	575	+	1.05	[0.68; 1.62]	100.0%
Cerebrovascular even	t							
Rubattu 2004	83	153	402	731	÷	0.97	[0.68; 1.38]	100.0%
Coronary heart diseas	e							
Barbato 2012	345	460	671	2334		7.44	[5.91; 9.35]	100.0%
Death								
Barbato 2012	13	117	3	747		31.00	[8.69; 110.61]	100.0%
Myocardial infarction								
Barbato 2012	2 14		26	747		3.77	[1.91; 7.45]	100.0%
Heterogeneity: $I^2 = 99\%$,								
Test for subgroup differen	ces: $\chi_5^- = 1$	36.22,	at = 5 (p <	< 0.01)	0.01 0.1 1 10 100			

Figure S9. Forest plot showing the comparison of CC vs. TT for studies with Hardy-Weinberg equilibrium. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.

E	xposed gr	oup	Control	group				
Study	Events T	otal	Events	Total	Odds ratio	OR	95%-CI	Weight
All CVE					1			
Rubattu 2004	18	23	141	312		4.37	[1.58; 12.05]	372.4%
Barbato 2012	24	30	683	967		1.66	[0.67; 4.11]	468.8%
Francia 2013	3	5	121	244		1.52	[0.25; 9.29]	117.7%
Pastori 2021	6	18	78	429		2.25	[0.82; 6.18]	376.4%
Common effect model		76		1952		2.39	[1.40; 4.10]	
Heterogeneity: $I^2 = 0\%$, τ	$p^2 = 0, p = 0.$	53						
Atrial fibrillation								
Francia 2013	3	5	121	244		1.52	[0.25; 9.29]	117.7%
Cerebrovascular even	t							
Rubattu 2004	18	23	141	312		4.37	[1.58; 12.05]	372.4%
Coronary heart diseas	e							
Barbato 2012	24	30	683	967		1.66	[0.67; 4.11]	468.8%
Heterogeneity: $I^2 = 0\%$, τ	$p^{2} = 0, p = 0.$	62						
Test for subgroup differen	ices: $\chi_3^2 = 2.2$	21, df	= 3 (p =)	0.53) (0.1 0.5 1 2 10			

Figure S10. Forest plot showing the comparison of CT vs. TT for studies with Hardy-Weinberg equilibrium. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.

E	Exposed gr	oup	Control	group				
Study	Events T	otal	Events	Total	Odds ratio	OR	95%-CI	Weight
All CVE Rubattu 2004 Barbato 2012 Francia 2013 Pastori 2021 Common effect mode Heterogeneity: / ² = 28%,	-	107 400 87 110 704 <i>p</i> = 0	141 683 121 78	312 967 244 429 - 1952		0.95 1.20 1.04 0.60 1.04	[0.61; 1.48] [0.92; 1.56] [0.64; 1.70] [0.32; 1.13] [0.86; 1.26]	1965.2% 5536.4% 1603.1% 971.8%
Atrial fibrillation Francia 2013	44	87	121	244		1.04	[0.64; 1.70]	1603.1%
Cerebrovascular ever Rubattu 2004	nt 47	107	141	312		0.95	[0.61; 1.48]	1965.2%
Coronary heart diseas Barbato 2012 Heterogeneity: $I^2 = 0\%$, τ Test for subgroup differen	297 ² < 0.0001,			967 0.78)	0.5 1 2	1.20	[0.92; 1.56]	5536.4%

Figure S11. Forest plot showing the comparison of (CC + CT) vs. TT for studies with Hardy-Weinberg equilibrium. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom; CVE, cardiocerebrovascular events.

E Study	xposed g Events		Control Events	• •	Odds ratio	OR	95%-CI	Weight
All CVE Rubattu 2004 Barbato 2012 Francia 2013 Rubattu 2016 Pastori 2021 Common effect model Heterogeneity: $l^2 = 21\%$,		130 430 92 103 128 883 1, p = 0	141 683 121 193 78	312 967 244 276 429 2228		.21 .22 .06).74).78 .07	[0.81; 1.83] [0.95; 1.58] [0.66; 1.72] [0.46; 1.18] [0.45; 1.35] [0.90; 1.27]	2214.6% 5342.0% 1630.3% 1656.3% 1267.1%
Atrial fibrillation Francia 2013	47	92	121	244	1	.06	[0.66; 1.72]	1630.3%
Cerebrovascular even Rubattu 2004	t 65	130	141	312	1	.21	[0.81; 1.83]	2214.6%
Coronary heart diseas Barbato 2012	e 321	430	683	967	1	.22	[0.95; 1.58]	5342.0%
Myocardial infarction Rubattu 2016 Heterogeneity: $I^2 = 9\%$, τ^2 Test for subgroup differen				276 0.45)	0.5 1 2).74	[0.46; 1.18]	1656.3%

Figure S12. Forest plot showing the comparison of CC vs. (CT + TT) for studies with Hardy-Weinberg equilibrium. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom; CVE, cardiocerebrovascular events.

E	xposed g	roup	Control	group				
Study	Events	Total	Events	Total	Odds ratio	OR	95%-CI	Weight
All CVE								
Rubattu 2004	18	23	188	419		4.42	[1.61; 12.14]	377.1%
Barbato 2012	24	30	980	1367		1.58	[0.64; 3.89]	471.8%
Francia 2013	3	5	165	331		1.51	[0.25; 9.15]	118.3%
Pastori 2021	6	18	91	539		2.46	[0.90; 6.73]	379.9%
Common effect model		76		2656		2.41	[1.41; 4.13]	
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, p = 0).48						
Atrial fibrillation								
Francia 2013	3	5	165	331		1.51	[0.25; 9.15]	118.3%
Cerebrovascular event	t							
Rubattu 2004	18	23	188	419		4.42	[1.61; 12.14]	377.1%
Caranam, haart diasaa	-							
Coronary heart diseas Barbato 2012	e 24	30	980	1367		1.58	[0.64; 3.89]	471.8%
Heterogeneity: $I^2 = 0\%$, τ^2			300	1007		1.50	[0.04, 0.09]	11.070
Test for subgroup different			= 3 (p =	0 48)	0.1 0.5 1 2 10			
. correct casgroup anorona	2000. _A 3 2	, ui	5 (p	00)				

Figure S13. Forest plot showing the comparison of CT vs. (CT + TT) for studies with Hardy-Weinberg equilibrium. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom; CVE, cardiocerebrovascular events.

	posed grou Events Tota		• •	Odds ratio		95%-CI	Weight.
Study	Events Tota	u Events	s iotai	Odds ratio	OR	95%-CI	Weight
All CVE Rubattu 2004 Barbato 2012 Francia 2013 Pastori 2021 Common effect model Heterogeneity: $l^2 = 0\%$, τ^2	47 10 297 40 44 8 13 11 70 = < 0.0001, p	0 980 7 165 0 91 4	419 1367 331 539 2656		0.96 1.14 1.03 0.66 1.03	[0.63; 1.48] [0.88; 1.47] [0.64; 1.65] [0.35; 1.23] [0.85; 1.24]	2101.2% 5995.2% 1722.1% 995.5%
Atrial fibrillation Francia 2013	44 8	7 165	331	_	1.03	[0.64; 1.65]	1722.1%
Cerebrovascular event Rubattu 2004	47 10	7 188	419		0.96	[0.63; 1.48]	2101.2%
Coronary heart disease Barbato 2012 Heterogeneity: $I^2 = 0\%$, τ^2 Test for subgroup difference	297 40 = 0, p = 0.77		1367 0.89)	0.5 1	1.14 2	[0.88; 1.47]	5995.2%

Figure S14. Egger's publication bias plot and P-value for the comparison of (CC + CT) vs. TT. Each data-point represents a separate study for the indicated association.

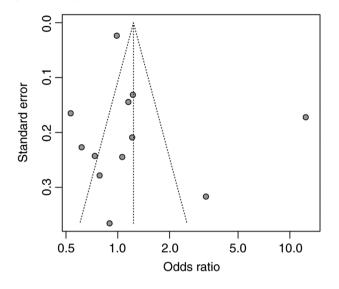


Figure S15. Sensitivity analysis for testing the stability of the overall estimate in the recessive model for studies. OR, odds ratio.

Study	Odds ratio	OR	95%-CI	P-value	Tau2	Tau	12
Omitting Gruchala 2003		1.56	[1.03; 2.38]	0.04	0.1498	0.3871	68%
Omitting Rubattu 2004		1.20	[0.89; 1.62]	0.23	0.0619	0.2488	46%
Omitting Zhang 2006		1.40	[0.96; 2.04]	0.08	0.1453	0.3812	64%
Omitting Lynch 2008		- 1.58	[1.02; 2.46]	0.04	0.1500	0.3873	44%
Omitting Barbato 2012		1.40	[0.91; 2.16]	0.12	0.1834	0.4283	67%
Omitting Francia 2013		1.41	[0.94; 2.09]	0.09	0.1595	0.3993	69%
Omitting Ziaee 2014		1.40	[0.87; 2.26]	0.16	0.2099	0.4582	55%
Omitting Siebert 2017		1.44	[0.96; 2.16]	0.08	0.1675	0.4093	69%
Omitting Pastori 2021		1.32	[0.90; 1.93]	0.16	0.1338	0.3657	63%
Random effects model		1.40	[0.96; 2.04]	0.08	0.1453	0.3812	64%

Figure S16. Sensitivity analysis for testing the stability of the overall estimate in the homozygote model for studies with Hardy-Weinberg equilibrium. OR, odds ratio.

Study		Od	lds ra	tio		OR	95%-CI	P-value	Tau2	Tau I2
Omitting Rubattu 2004			+	• • •	-	1.82	[0.95; 3.46]	0.07	0	0 0%
Omitting Barbato 2012					<u> </u>	2.97	[1.55; 5.72]	< 0.01	0	0 0%
Omitting Francia 2013						2.50	[1.42; 4.39]	< 0.01	0	0 0%
Omitting Pastori 2021			-			2.44	[1.30; 4.58]	< 0.01	0.0969	0.3114 9%
Common effect mode	I				>	2.39	[1.40; 4.10]	< 0.01	0	0 0%
	0.2	0.5	1	2	5					

Figure S17. Sensitivity analysis for testing the stability of the overall estimate in the recessive model for studies with Hardy-Weinberg equilibrium. OR, odds ratio.

Study	Odds ratio	OR	95%-CI	P-value	Tau2	Tau	12
Omitting Rubattu 2004	+ 	1.81	[0.95; 3.46]	0.07	0	0	0%
Omitting Barbato 2012	— <u></u>	3.10	[1.61; 5.96]	< 0.01	0	0	0%
Omitting Francia 2013		2.52	[1.43; 4.43]	< 0.01	0.0329	0.1815	10%
Omitting Pastori 2021		2.40	[1.28; 4.49]	< 0.01	0.1393	0.3732	20%
Common effect model		2.41	[1.41; 4.13]	< 0.01	0	0	0%
	0.2 0.5 1 2 5						

Figure S18. Forest plot for the subgroup analysis for NOS score in the recessive model regarding composite cardio-cerebrovascular event outcome. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom; NOS, Newcastle-Ottawa scale.

E: Study	•		Control Events	• •	Odds ratio	OR	95%-CI	Weight
NOS score = 8								
Gruchala 2003	35	63	469	781		0.83	[0.50; 1.39]	17.3%
Barbato 2012	24	30	980	1367		1.58	[0.64; 3.89]	10.4%
Random effects model		93		2148		1.03	[0.57; 1.85]	27.7%
Heterogeneity: $I^2 = 32\%$, τ	² = 0.065 ²	1, p = ().23					
NOS_score = 7								
Rubattu 2004	18	23	188	419		4.42	[1.61; 12.14]	9.0%
Lynch 2008	701	2711	9418	35717		0.97	[0.89; 1.06]	25.2%
Ziaee 2014	133	180	440	686		1.58	[1.10; 2.28]	20.6%
Pastori 2021	6	18	91	539		2.46	[0.90; 6.73]	9.1%
Random effects model		2932		37361		1.74	[0.94; 3.21]	63.9%
Heterogeneity: I^2 = 83%, τ	² = 0.2846	6, p < 0).01					
NOS_score = 6								
Zhang 2006	0	0	158	323				0.0%
Francia 2013	3	5	165	331		1.51	[0.25; 9.15]	3.7%
Siebert 2017	2	10	38	193	+	1.02	[0.21; 5.00]	4.6%
Random effects model		15		847		1.21	[0.37; 3.99]	8.4%
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, p = 0	.75						
Random effects model	0	3040		40356		1.40	[0.96; 2.04]	100.0%
Heterogeneity: $I^2 = 64\%$, τ								
Test for subgroup difference	es: χ ₂ ² = 1	.51, df	= 2 (p = 0	0.47)	0.1 0.5 1 2 10			

Figure S19. Forest plot for the subgroup analysis for year of publication in the recessive model regarding composite cardio-cerebrovascular event outcome. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom.

E	xposed g	group	Control	group				
Study	Events	Total	Events	Total	Odds ratio	OR	95%-CI	Weight
~2012								
Gruchala 2003	35	63	469	781		0.83	[0.50; 1.39]	17.3%
Rubattu 2004	18	23	188	419		4.42	[1.61; 12.14]	9.0%
Zhang 2006	0	0	158	323				0.0%
Lynch 2008	701	2711	9418	35717		0.97	[0.89; 1.06]	25.2%
Barbato 2012	24	30	980	1367		1.58	[0.64; 3.89]	10.4%
Random effects model		2827		38607		1.36	[0.71; 2.59]	61.9%
Heterogeneity: <i>I</i> ² = 70%, τ 2013~	2 = 0.3198	8, p = ().02					
Francia 2013	3	5	165	331		1.51	[0.25; 9.15]	3.7%
Ziaee 2014	133	180	440	686		1.58	[1.10; 2.28]	20.6%
Siebert 2017	2	10	38	193		1.02	[0.21; 5.00]	4.6%
Pastori 2021	6	18	91	539		2.46	[0.90; 6.73]	9.1%
Random effects model		213		1749		1.63	[1.17; 2.26]	38.1%
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, <i>p</i> = 0	0.80					-	
Random effects model		3040		40356		1.40	[0.96; 2.04]	100.0%
Heterogeneity: I^2 = 64%, τ								
Test for subgroup difference	ces: $\chi_1^2 = 0$).23, df	= 1 (p =	0.63)	0.1 0.5 1 2 10			

Figure S20. Forest plot for the subgroup analysis for year in the recessive model regarding study region. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom.

E	xposed (group	Control	group				
Study	Events	Total	Events	Total	Odds ratio	OR	95%-CI	Weight
Europe								
Gruchala 2003	35	63	469	781		0.83	[0.50; 1.39]	17.3%
Rubattu 2004	18	23	188	419		4.42	[1.61; 12.14]	9.0%
Barbato 2012	24	30	980	1367		1.58	[0.64; 3.89]	10.4%
Francia 2013	3	5	165	331	<u>*</u>	1.51	[0.25; 9.15]	3.7%
Siebert 2017	2	10	38	193		1.02	[0.21; 5.00]	4.6%
Pastori 2021	6	18	91	539	+	2.46	[0.90; 6.73]	9.1%
Random effects model		149		3630		1.63	[0.90; 2.93]	54.2%
Heterogeneity: $I^2 = 51\%$, τ	$r^2 = 0.2523$	2, p = 0	0.07					
Asia								
Zhang 2006	0	0	158	323				0.0%
Ziaee 2014	133	180	440	686		1.58	[1.10; 2.28]	20.6%
America								
Lynch 2008	701	2711	9418	35717		0.97	[0.89; 1.06]	25.2%
Random effects model Heterogeneity: $I^2 = 64\%$, τ	$^{2} = 0.145$			40356		1.40	[0.96; 2.04]	100.0%
Test for subgroup difference	$\cos (\chi_2^- = 8)$	s.91, df	= 2 (p = 0)	J.U1)	0.1 0.5 1 2 10			

Figure S21. Forest plot for the subgroup analysis for sample size in the recessive model regarding composite cardio-cerebrovascular event outcome. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom.

E	xposed g	group	Control	group				
Study	Events	Total	Events	Total	Odds ratio	OR	95%-CI	Weight
>500								
Gruchala 2003	35	63	469	781		0.83	[0.50; 1.39]	17.3%
Lynch 2008	701	2711	9418	35717	+	0.97	[0.89; 1.06]	25.2%
Barbato 2012	24	30	980	1367		1.58	[0.64; 3.89]	10.4%
Ziaee 2014	133	180	440	686	- <u></u> -	1.58	[1.10; 2.28]	20.6%
Pastori 2021	6	18	91	539	+	2.46	[0.90; 6.73]	9.1%
Random effects model		3002		39090		1.21	[0.87; 1.68]	82.6%
Heterogeneity: $I^2 = 63\%$, τ	$e^2 = 0.0728$	B, p = 0	0.03					
<500	10	00	400	440	_	4 40	[4 64, 40 44]	0.00/
Rubattu 2004	18	23 0		419		4.42	[1.61; 12.14]	9.0% 0.0%
Zhang 2006 Francia 2013	0 3	5	165	323 331		1.51	[0.25; 9.15]	3.7%
Siebert 2017	2	10	38	193		1.02	[0.23, 9.13]	4.6%
Random effects model	_	38	00	1266		2.28	[0.84; 6.20]	17.4%
Heterogeneity: $I^2 = 27\%$, τ).25	1200		2120	[0:04, 0:20]	111-170
Random effects model	-	3040		40356		1.40	[0.96; 2.04]	100.0%
Heterogeneity: $I^2 = 64\%$, τ								
Test for subgroup difference	ces: $\chi_1^2 = 1$.40, df	= 1 (p =	0.24)	0.1 0.5 1 2 10			

Figure S22. Forest plot for the subgroup analysis for underlying disease in the recessive model regarding composite cardio-cerebrovascular event outcome. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; df, degrees of freedom.

Ex	kposed g Events		Control Events	• •	Odds ratio	OR	95%-CI	Weight
Coronary heart disease	•							
Gruchala 2003	35	63	469	781		0.83	[0.50; 1.39]	17.3%
Zhang 2006	0	0	158	323			. , ,	0.0%
Barbato 2012	24	30	980	1367		1.58	[0.64; 3.89]	10.4%
Ziaee 2014	133	180	440	686	- <u>-</u> -	1.58	[1.10; 2.28]	20.6%
Siebert 2017	2	10	38	193		1.02	[0.21; 5.00]	4.6%
Random effects model		283		3350		1.24	[0.82; 1.89]	52.9%
Heterogeneity: $I^2 = 29\%$, τ	² = 0.0699	9, p = 0).24					
Ischemic stroke								
Rubattu 2004	18	23	188	419		4.42	[1.61; 12.14]	9.0%
Hypertension								
Lynch 2008	701	2711	9418	35717	E I	0.97	[0.89; 1.06]	25.2%
Atrial fibrillation								
Francia 2013	3	5	165	331		1.51	[0.25; 9.15]	3.7%
Pastori 2021	6	18	91	539		2.46	[0.90; 6.73]	9.1%
Random effects model		23		870		2.19	[0.91; 5.27]	12.8%
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, <i>p</i> = 0	.64						
Random effects model		3040		40356		1.40	[0.96; 2.04]	100.0%
Heterogeneity: $I^2 = 64\%$, τ^2	² = 0.1453	3, p < 0	0.01					
Test for subgroup difference				0.01)	0.1 0.5 1 2 10			
	-							