

Web Table 1. Arrhythmic and Ischemic cardiovascular events in long term RCTs of Inhaled anticholinergics

Study	Treatment groups (Number of participants)	Arrhythmia	Angina	MI	Stroke	CV Death	Mortality	Comment
Ipratropium bromide								
Anthonisen et al 2002	Ipratropium (1961)	11	4	3 fatal 41 nonfatal	2 fatal 10 nonfatal	18	54	
	Placebo (1962)	3	2	2 fatal 29 nonfatal	1 fatal 8 nonfatal	7	44	
Tiotropium Handihaler								
Casaburi et al, 2002	Tiotropium (n=550)	NR	NR	3	4	6	7	
	Placebo (n=371)	NR	NR	1	1	1	7	
Wedzicha et al, 2008	Tiotropium (665)	NR	NR	Fatal: 4 Non-fatal:2	Fatal:2 Non-fatal:1 TIA:1	19 (2.8%)	38	In subjects with baseline CVD the (3%) deaths in SFC patients and tiotropium patients (8%). No more in each group reported clinically significant EKG abnormalities
	Salmeterol-fluticasone(658)	NR		Fatal: 2 Non-fatal:1	Non-fatal: 2 TIA:1	9 (1.3%)	21	
Powrie et al, 2007	Tiotropium (69)	NR	NR	Fatal: 1 Non-fatal:2	0	1	1	
	Placebo (73)	NR	NR	Fatal: 1	0	1	2	
Chan et al, 2007	Tiotropium (n=608)	NR	NR	1 % (n=6)	NR	NR	17	
	Placebo (n=350)	NR	NR	0.03% (n=1)	NR	NR	4	
Tonnel et al 2008	Tiotropium (n=266)	NR	NR	NR	1	1	3	
	Placebo (n=288)	NR	NR	NR	0	0	6	
Ambrosino et al 2008	Tiotropium (n=117)	NR	NR	NR	NR	NR	NR	
	Placebo (N=117)	NR	NR	NR	NR	NR	NR	
Niewoehner, 2005	Tiotropium (n=914)	Atrial fibrillation=2	NR	NR	NR	7	22	
	Placebo(n=915)	Atrial fibrillation=9	NR	NR	NR	7	19	
Brusasco, et al 2003	Tiotropium 18 mcg(n=402)	NR	NR	1(non-fatal)	1 (non-fatal)	0	1	
	Placebo(n=400)	NR	NR	3 (non-fatal)	2 (non-fatal)	2	5	
Dusser et al 2006	Tiotropium 18 mcg (n=500)	NR	NR	NR	NR	NR	NR	
	Placebo (510)	NR	NR	NR	NR	NR	NR	

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Tashkin et al 2008*	Tiotropium 18 mcg (2986)	Arrhythmia=7 Supraventricular Arrhythmia=1 Atrial fibrillation=69 Atrial tachycardia=2 SVT=8 Tachyarrhythmia=5	48	67	Composite Stroke=82 Ischemic stroke=8 TIA=27	24	381	
	Placebo (3006)	Arrhythmia=10 Supraventricular Arrhythmia=1 Atrial fibrillation=67 Atrial tachycardia=0 SVT=8 Tachyarrhythmia=2	31	85	Composite Stroke=80 Ischemic stroke=3 TIA=23	25	411	
Vogelmeier et al 2011* NCT00563381	Tiotropium 18 mcg (3707)	Arrhythmia=1 Supraventricular Arrhythmia=1 Atrial fibrillation=12 Atrial tachycardia=0 SVT=1 Tachyarrhythmia=1	Angina pectoris=9 Unstable angina=2 Acute coronary syndrome=2	Myocardial infarction 20 Acute MI 3 Myocardial Ischemia: 11	Ischemic stroke=3 TIA=3	8	66	
	Serevent (3669)	Arrhythmia=1 Supraventricular Arrhythmia=0 Atrial fibrillation=14 Atrial tachycardia=0 SVT=0 Tachyarrhythmia=0	Angina pectoris=5 Unstable angina=2 Acute coronary syndrome=2	Myocardial infarction= 13 Acute MI= 1 Myocardial Ischemia: 6	Ischemic stroke=2 TIA=2	6	73	
Worth et al 2011	Tiotropium 18 mcg (415)	17 (4.1)	7 (1.7)	NA	2	1	2(0.48)	RR of CCV AES compared to pla (1.02, 2.73)
	Placebo (1185)	26 (2.2)	6(0.5)	NA	7	5	7(0.59)	

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Tiotropium Respimat								
Bateman et al 2010 [Pooled two one-year trials]	Tiotropium 5 Respimat (670)	NA	0.4%	0.3%	NA	NA	16 (2.39)	NA
	Tiotropium 10 Respimat (667)	NA	1%	0.1%	NA	NA	18 (2.7)	NA
	Placebo (653)	NA	0.2%	0.9%	NA	NA	10(1.53)	NA
Bateman et al 2010* 205.372	Tiotropium 5 Respimat (n=1989)	Arrhythmia=2 Supraventricular Arrhythmia=NR Atrial fibrillation=3 Atrial tachycardia=0 SVT=1 Tachyarrhythmia=0	Angina 4 Angina unstable 1 ACS=3	MI 5 Acute MI 2 Myocardial Ischemia: 5	Ischemic stroke=2 TIA=NA	22	52	All arrhythmias showed towards n with tiotropium except endpoint of arrhythmias which include prefer LBBB, RBBB and Supraventricular systole. Trend towards increased angina and cardiac ischemic even excluding MI. Decreased risk for t serious ischemic outcome of MI
	Placebo (n=2002)	Arrhythmia=1 Supraventricular Arrhythmia=NR Atrial fibrillation=2 Atrial tachycardia=0 SVT=1 Tachyarrhythmia=0	Angina 3 Angina unstable= 5 ACS=2	MI 5 Acute MI 5 Myocardial Ischemia: 0	Ischemic stroke=1 TIA=NA	12	38	

NR= Not reported

*Additional Serious Adverse Events data for Angina, Arrhythmia, Myocardial Infarction, and Stroke were extracted

In POET and UPLIFT sudden death, unexplained death or death from unknown cause which have been classified as general disorders and not cardiac death

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