Table S1: Main characteristics of the studies Included in the meta-analysis

Study	Participants	Macrolide users(No)/control (No)	Age (mean)	Study type	Outcomes	Baseline disease	Macrolide type	Dosage regimen	Duration of follow up	Control
Berg 2005(1)	Outpatient clinic from Amiphia hospital - Amsterdam Netherland 1999-2001	208/216	64	RCT	Death, unstable angina, non-fatal MI, revascularization, stroke	documented coronary artery disease	clarithromycin	500mg/day (mean duration 15.7 days.	2 years	placebo
Berni 2017 (2)	UK Clinical Practice Research Database (CPRD) 1998-2012	165,267/ 865,294	56	cohort	First ever cardiovascular event (non-fatal MI, stroke, angina, transient ischemic attack), all-cause mortality and first ever arrhythmia	Lower and upper respiratory tract infection	Clarithromycin, erythromycin	NA	14, 37 days	Amoxicillin, Co-amoxiclav, penicillin V, cefalexin
Cercek 2003(3)	Seven centers in Europe, Israel and USA	716/723	65	RCT	Death, non-fatal MI, CABG/PTCA	unstable angina, or MI	Azithromycin	500mg for the first day followed by 250mg/day for 4 days	6 months	placebo
Chou 2015(4)	Taiwan national health insurance system;	459,988/ 1,102,358	45	cohort	Arrhythmia, cardiac mortality	NA	Azithromycin Clarithromycin	NA	Current use	Amoxicillin - clavulanate

Study	Participants	Macrolide users(No)/control (No)	Age (mean)	Study type	Outcomes	Baseline disease	Macrolide type	Dosage regimen	Duration of follow up	Control
Goldstein 2015(5)	Medical wards in Israeli hospital;	90/32	70	cohort	Legthening of QTc	CAP	Azithromycin	NA	Current use	Ampicillin-clavulanate, chloramphenicol, doxycycline, ceftriaxone
Grayston 2005(6)	28 centers in the USA 1999-2000	2004/2008	65	RCT	Cardiovascular mortality, MI, unstable angina, stroke	Documented stable coronary heart disease	Azithromycin	One year course of weekly 600mg azithromycin	3.9 years	placebo
Gurfinkel 1999 (7)	Patients with unstable angina	102/100	61	RCT	Severe recurrent ischemia, MI and death	unstable angina	Roxithromycin	150mg twice daily for 30 days	30 days, 90 days, 6 months	placebo
Gupta 1997 (8)	Outpatient clinic at George's hospital between February and September 1995	40/40	60	RCT	Cardiovascular events defined as non-fatal MI, unstable angina, coronary angioplasty, coronary artery bypass surgery and cardiovascular death	Males, Post MI	Azithromycin	500mg/day for 3 days or for 6 days	18 months	placebo

Study	Participants	Macrolide users(No)/control (No)	Age (mean)	Study type	Outcomes	Baseline disease	Macrolide type	Dosage regimen	Duration of follow up	Control
Jespersen 2009 (9)	Copenhagen, Denmark 1993–1999 (Jespersen et al., 2006))	2172/2200	65	RCT	All-cause mortality , MI, unstable angina Atrial fibrillation, Cardiovascular mortality, stroke, atrial fibrillation, peripheral vascular disease	History of MI, angina pectoris, percutaneous angioplasty or coronary bypass surgery.	Clarithromycin	500mg/day for 14 days	30days	placebo
Leowattana 2001 (10)	Thailand 1998-2000	43/41	61	RCT	Cardiovascular mortality , MI, unstable angina and coronary revascularization	acute coronary syndrome patients	Roxithromycin	30 days treatment with roxithromycin 150mg twice daily	90 days	placebo
Luchsinger 2002 (11)	Healthcare claims database (Virginia) 1991-1997	70,801/ 152,475	NS	cohort	MI	NA	Not specified	NA	NS	Non users of macrolides, quinolones, tetracycline, penicillin, cephalosporin, trimethoprim-sulfamethoxazole,

Study	Participants	Macrolide users(No)/control (No)	Age (mean)	Study type	Outcomes	Baseline disease	Macrolide type	Dosage regimen	Duration of follow up	Control
Meier 1999 (12)	General practices in UK 1992-1997	428/ 16,026	60-69 (median)	Nested case control	MI	NA	Not specified (erythromycin, clarithromycin, azithromycin)	NA	3 years preceding the index date	No antibiotics use
Mortensen 2014 (13)	Veteran administration health care system 2001-2012	31,863/ 31,863	77	cohort	Any cardiac event, arrhythmia, heart failure, MI	pneumonia	azithromycin	NA	90 days	Antibiotic therapy concordant with the 2007 IDSA/ATS guidelines for community acquired pneumonia
Mosholder 2017(14)	UK clinical practice research datalink (CPRD) 2001-2013	730747/267729	NA	cohort	MI, stroke, death	Various indications (mainly respiratory indications)	Clarithromycin Erythromycin	NA	2.4-3.9 years	Doxycyline
Muhlestein 2000 (15)	Utah, USA	150/152	63.5	RCT	Cardiovascular mortality, resuscitated cardiac arrest, MI, stroke, unstable angina and coronary revascularization	Coronary artery disease patients seropositive to C pneumoniae	Azithromycin	500mg/day for 3 days and then 500mg/week for 3 months	2 years	placebo
Neumann 2002 (16)	Germany	506/504	64	RCT	Restenosis	Post successful coronary stenting	Roxithromycin	300mg/day for 28 days	1 year	placebo

Study	Participants	Macrolide users(No)/control (No)	Age (mean)	Study type	Outcomes	Baseline disease	Macrolide type	Dosage regimen	Duration of follow up	Control
O'Connor 2003 (17)	1 clinical practices in North America, Europe, Argentina and India from 1997-2001	3866/3856	62	RCT	Death, MI, revascularization, angina	previous MI and chlamydia pneumoniae titer of 1 :16 or more	Azithromycin	600mg/day for 3 days during week 1, then 600mg/week during week2-12	14 months	placebo
Quinn 2017(18)	Ontario residents prescribed digoxin 1994-2012	2007/6013	86.5	Population-based nested case control	Sudden death	Digoxin users	Erythromycin, clarithromycin, azithromycin	NA	14 days	cefuroxime
Rao 2014(19)	US veterans	594,792/979,380	57	cohort	Serious cardiac arrhythmias, all cause death	NA	Azithromycin	5 days	10 days	amoxicillin
Ray 2004 (20)	Tennessee Medicaid, 1988-1993	5305/ 1,126,013 (person years)	43	cohort	Cardiac mortality	NA	Erythromycin	NA	Current use	Amoxicillin
Ray 2012 (21)	Tennessee Medicaid, 1992-2006	347,795/ 1,348,672	48	cohort	Cardiac mortality, all-cause mortality	NS	Azithromycin	5 days regimen	Current use	Amoxicillin

Study	Participants	Macrolide users(No)/control (No)	Age (mean)	Study type	Outcomes	Baseline disease	Macrolide type	Dosage regimen	Duration of follow up	Control
Root 2016 (22)	Clinical Practice Research Datalink, a UK primary care database	26,029/ 2523	53	cohort	Arrhythmia, cardiac mortality, MI	Helicobacter pylori	Clarithromycin (as a combination as part of Helicobacter pylori treatment)	1-2 weeks treatment duration	90 days	Helicobacter pylori treatment
Schembri 2013 (23)	EXODUS dataset (UK) 2009-2011; and Edinburgh pneumonia cohort (UK) 2005-2009;	281/1062 (COPD) 980/651 (CAP)	COPD cohort 72; CAP cohort 66 (median)	Cohort (2 cohorts)	Arrhythmia, cardiac mortality, cardiac arrest, MI, at least 1 CV event	COPD CAP	Clarithromycin	NA	1 year	NS
Sinisalo 2002 (24)	9 hospitals in different parts of Finland 1998-2000	74/74	63.5	RCT	MI, unstable angina, death, stroke	Unstable angina or non Q wave myocardial infarction.	Clarithromycin	500mg/day for 85 days	During treatment period, and average follow up of 555 days.	placebo

Study	Participants	Macrolide users(No)/control (No)	Age (mean)	Study type	Outcomes	Baseline disease	Macrolide type	Dosage regimen	Duration of follow up	Control
Stone 2002(25)	Coronary care units of 4 hospitals in London	111/214	66	RCT	Cardiovascular mortality, Readmission with MI or angina	Acute coronary syndrome	Azithromycin	500mg/day for one week in combination with metronidazole and omeprazole	1 year	Amoxicillin in combination with metronidazole and omeprazole or placebo
Straus 2005 (26)	150 general practitioners in the Netherlands 1995-2003	81/6197	70	case control	Sudden cardiac death	NA	Erythromycin, Clatithromycin	NA		Non use
Svanstrom 2013 (27)	Danish civil registration system 1997-2010	1,102,050/ 7,364,292	40	cohort	Cardiovascular mortality	NA	Azithromycin	NA	10,35 days	Penicillin V
Svanstrom 2014 (28)	Danish civil registration system 1997-2010	749,285/ 4,355,309	56	cohort	Cardiovascular mortality	NA	Clarithromycin Roxithromycin	Seven day treatment	7, 37 days	Penicillin V
Trac 2016(29)	The Ontario Health Insurance plan 2002-2013	503,612/ 503,612	74	cohort	Arrhythmias, all-cause mortality	NA	NS (Azithromycin, clarithromycin, erythromycin)	NA	30days	Non-macrolide (amoxicillin, cefuroxime, levofloxacin)

Study	Participants	Macrolide users(No)/control (No)	Age (mean)	Study type	Outcomes	Baseline disease	Macrolide type	Dosage regimen	Duration of follow up	Control
Trifiro 2017 (30)	A network of 7 population based health care databases in 5 European countries 1997-2010)	118/535	63.5	A nested case control	Ventricular arrhythmia	NA	Azithromycin	NA	Current exposure 7 days past exposure 7-89 days	Amoxicillin
Vainas 2005 (31)	Surgical clinics of a university hospital and two affiliated teaching hospitals, Netherlands	257/252	65	RCT	All-cause mortality , cerebral and coronary events	Patients with symptomatic peripheral arterial disease	Azithromycin	500mg/day for 3 days	2 years	placebo
Wong 2016 (32)	Hong Kong population based, 2005-2009	109,988/ 217,793	60	cohort	Arrhythmia, cardiac mortality, MI, other CV events	NA	Clarithromycin	NA	14 days	Amoxicillin
Zambon 2009 (33)	All residents of Italian province 1998-2003	NA/NA	70	case control	Arrhythmia/cardiac arrest	NA	Not specified	NA	Recent/ Immediately prior to the date of the event	Non users

NA ,not applicable; RCT, randomized controlled trial; MI, myocardial infarction; UK, United kingdom; USA, United States; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; COPD, chronic obstructive pulmonary disease; CAP, community-acquired pneumonia

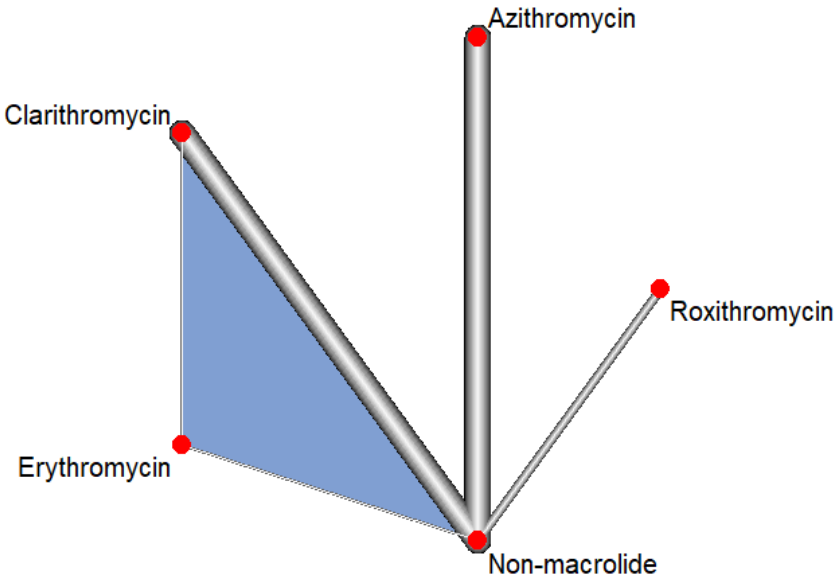

Figure S1: Network plot. **The nodes in the graph correspond to the treatments, and the edges (lines) display the direct comparisons between the different treatments reported in the studies. The thickness of each edge represents the number of studies directly comparing the two treatments.**

Table S2: The quality of observational Studies based on NOS, New Castle Scoring System (range 1-9 stars).

Study	Study type	NOS
Berni 2017	Retrospective cohort	4+2+3=9
Chou 2015	cohort	4+2+3=9
Goldstein 2015	cohort	4+0+3=7
Luchsinger 2002 (only OR)	cohort	4+1+3=8
Meier 1999	case control	4+1+2=7
Mortensen 2014	retrospective cohort	3+2+3=8
Mosholder 2017	retrospective cohort	4+2+3=9
Quinn 2017	nested case control	4+1+3=8
Ray 2004	cohort	4+2+3=9
Ray 2012	cohort	4+2+2=8
Root 2016	cohort	4+2+3=9
Schembri 2013	Cohort (2 cohorts)	4+2+3=9
Straus 2005	case control	4+1+3=8
Svanstrom 2013	cohort	4+2+3=9
Svanstrom 2014	cohort	4+1+3=8
Trac 2016	cohort	3+1+3=7
Trifiro 2017	nested case control	3+1+2=6
Wong 2016	cohort	4+2+3=9
Zambon 2009	case control	4+2+3=7

Table S3: Risk of bias for randomized control trials based on Cochrane tool for assessing risk of bias.

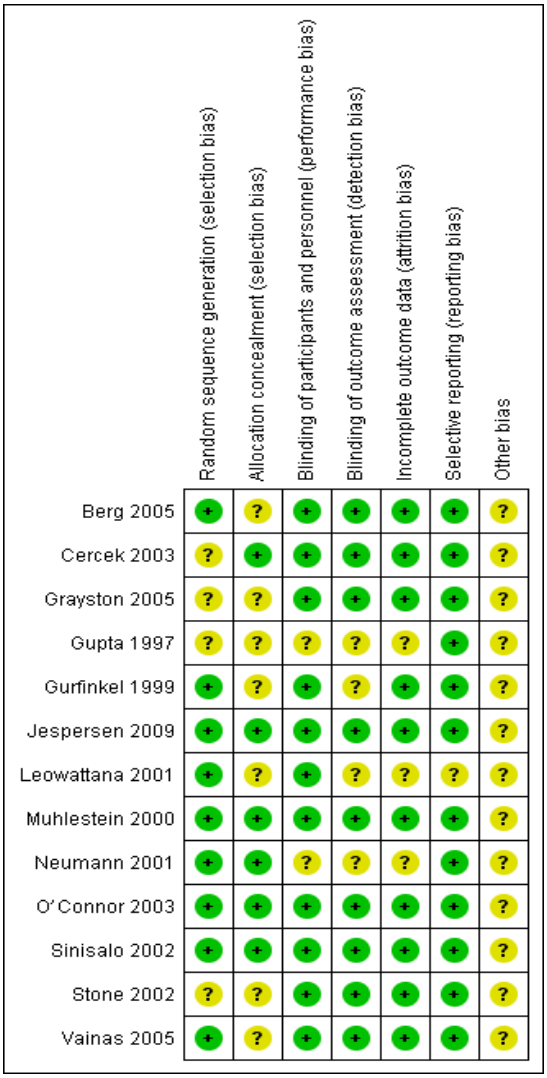

Table S4: Main characteristics of the studies Included in the arrhythmia analysis

First author	year	Study type	Macrolide users(No)/control (No)	Macrolide type	Control
Berni(2)	2017	cohort	165,267/ 865,294	Clarithromycin , Erythromycin	Amoxicillin, Co-amoxiclav, penicillin V, cefalexin
Chou(4)	2015	cohort	459,988/ 1,102,358	Azithromycin Clarithromycin	Amoxicillin - clavulanate
Goldstein(5)	2015	cohort	90/32	Azithromycin	Ampicillin-clavulanate, chloramphenicol , doxycycline, ceftriaxone
Jespersen(9)	2009	RCT	2172/2200	Clarithromycin	placebo
Rao(19)	2014	cohort	594,792/ 979,380	Azithromycin	amoxicillin
Trac(34)	2016	cohort	503,612/ 503,612	Not specified (Azithromycin, clarithromycin, erythromycin)	Non-macrolide (amoxicillin, cefuroxime, levofloxacin)
Trifiro(30)	2017	A nested case control	118/535	Azithromycin	amoxicillin
Wong(32)	2016	cohort	109,988/ 217,793	Clarithromycin	amoxicillin
Zambon(33)	2009	case control	NA/NA	Not specified	Non users

RCT, randomized controlled trial, NA, not applicable

Table S5: Main characteristics of the studies Included in the short-term cardiovascular mortality analysis

First author	year	Study type	Macrolide users(No)/control (No)	Macrolide type	Control
Chou(21)	2015	cohort	459,988/ 1,102,358	Azithromycin Clarithromycin	Amoxicillin - clavulanate
Jespersen(6)	2009	RCT	2172/2200	Clarithromycin	placebo
Quinn(27)	2017	Population-based nested case control	2007/6013	Erythromycin, Clarithromycin Azithromycin	Cefuroxime
Ray(28)	2004	cohort	5305/ 1,126,013 (person years)	Erythromycin	Amoxicillin
Ray(29)	2012	cohort	347,795/ 1,348,672	Azithromycin	Amoxicillin
Straus(30)	2005	case control	81/6197	Erythromycin, Clarithromycin	Non users
Svanstrom(31)	2013	cohort	1,102,050/ 7,364,292	Azithromycin	Penicillin V
Svanstrom(32)	2014	cohort	749,285/ 4,355,309	Clarithromycin, Roxithromycin	Penicillin V
Wong(15)	2016	cohort	109,988/ 217,793	Clarithromycin	Amoxicillin

RCT, randomized controlled trial

Table S6: Main characteristics of the studies Included in the myocardial infarction analysis

First author	year	Study type	Macrolide users(No)/control (No)	Macrolide type	Control
Berg(1)	2005	RCT	208/216	Clarithromycin	Placebo
Cercek (2)	2003	RCT	716/723	Azithromycin	Placebo
Grayston(3)	2005	RCT	2004/2008	Azithromycin	Placebo
Gurfinkel(4)	1999	RCT	102/100	Roxithromycin	Placebo
Gupta(5)	1997	RCT	40/40	Azithromycin	Placebo
Jespersen(6)	2009	RCT	2172/2200	Clarithromycin	Placebo
Leowattana(7)	2001	RCT	43/41	Roxithromycin	Placebo
Luchsinger(8)	2002	cohort	70,801/ 152,475	Not specified	Non users of macrolides, quinolones, tetracycline, penicillin, cephalosporin, trimethoprim-sulfamethoxazole
Meier(9)	1999	Case control	428/ 16,026	Not specified	No antibiotics use
Mortensen(10)	2014	cohort	31,863/ 31,863	Azithromycin	Antibiotic therapy concordant with the 2007 IDSA/ATS guidelines for community acquired pneumonia
Mosholder(11)	2017	cohort	730,747/267,729	Clarithromycin Erythromycin	doxycyline
Muhlestein(12)	2000	RCT	150/152	Azithromycin	Placebo
Neumann(13)	2002	RCT	506/504	Roxithromycin	Placebo
O'Connor(14)	2003	RCT	3866/3856	Azithromycin	Placebo
Root(15)	2016	cohort	26,029/ 2523	Clarithromycin (as a combination as part of Helicobacter pylori treatment)	Helicobacter pylori treatment

Schembri(16)	2013	cohort	281/1062 (COPD) 980/651 (CAP)	Clarithromycin	Not specified
Sinisalo(17)	2002	RCT	74/74	Clarithromycin	Placebo
Stone(18)	2002	RCT	111/214	Azithromycin	Amoxicillin in combination with metronidazole and omeprazole or placebo
Vainas(19)	2005	RCT	257/252	Azithromycin	Placebo
Wong(15)	2016	cohort	109,988/ 217,793	Clarithromycin	Amoxicillin

RCT, randomized controlled trial

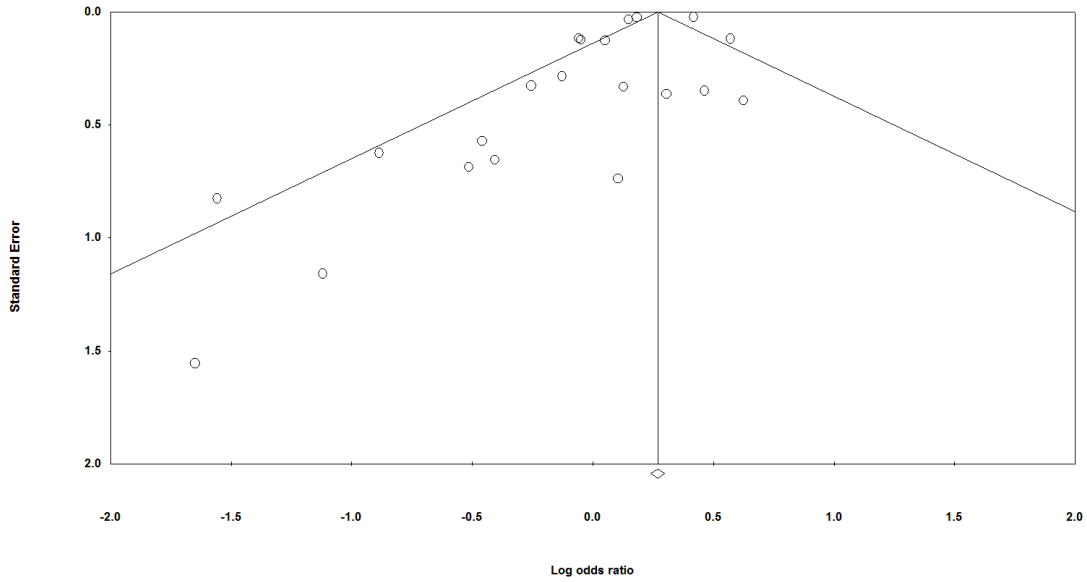

Figure S2: publication bias Funnel plot for MI analysis. **Plot depicts the distribution of the reported log odds ratio in each study in relation to each study's size (as manifest by its standard error), centered around the estimated pooled effect. Visual inspection of this plot suggests asymmetric reporting of smaller studies, as smaller studies were more likely to report benefit, or no risk, with macrolides. However, Egger's regression test did not reach significance (p=0.06).**

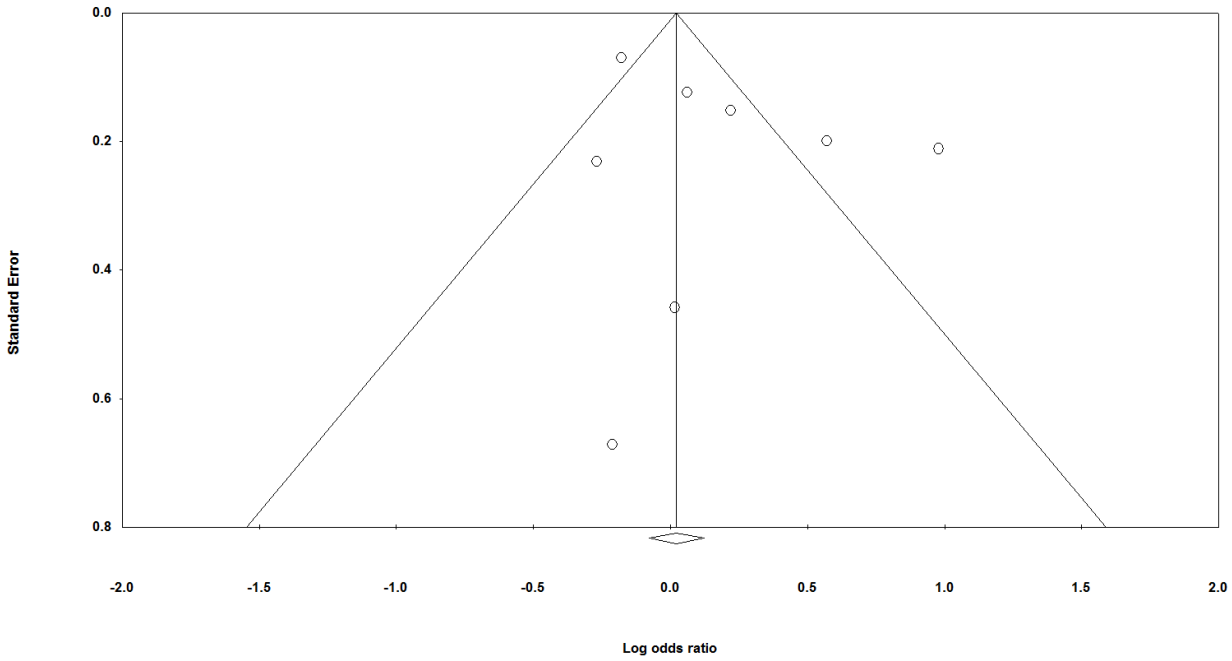

Figure S3: publication bias Funnel plot for arrhythmia analysis. **Plot depicts the distribution of the reported log odds ratio in each study in relation to each study's size (as manifest by its standard error), centered around the estimated pooled effect. Visual inspection of this plot and Egger's regression test did not indicate evidence of publication bias (p=0.25).**

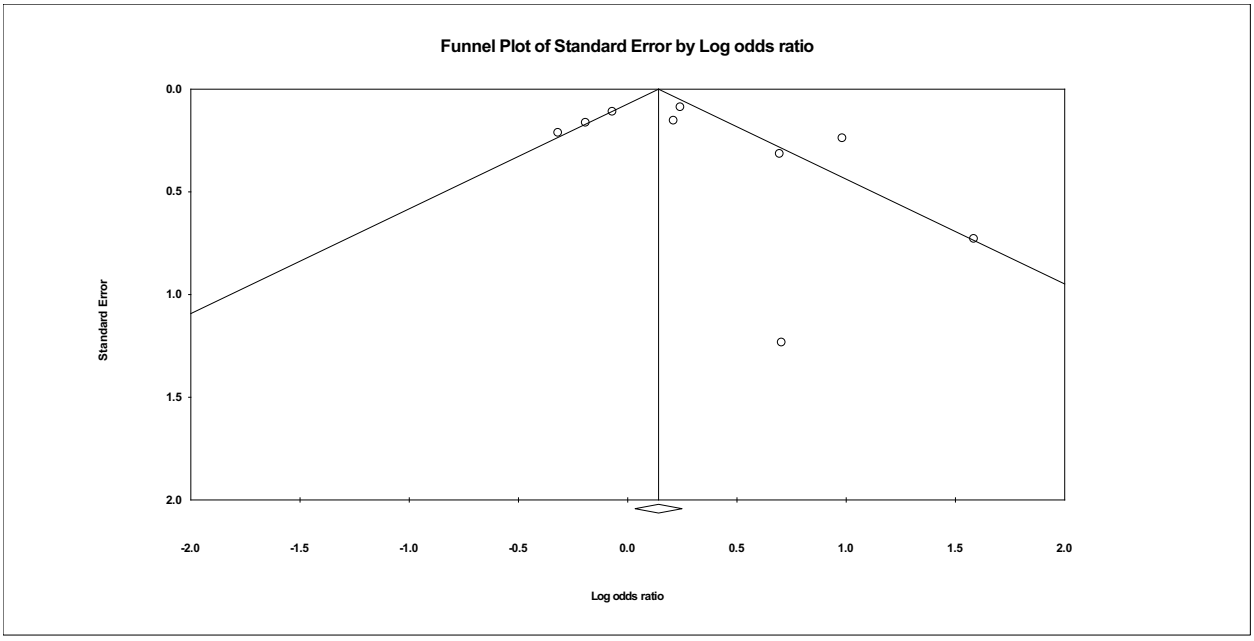

Figure S4: publication bias Funnel plot for cardiovascular mortality analysis. **Plot depicts the distribution of the reported log odds ratio in each study in relation to each study's size (as manifest by its standard error), centered around the estimated pooled effect. Visual inspection of this plot and Egger's regression test did not indicate evidence of publication bias (p=0.33)**.

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