Appendix 1: Supplementary tables [posted as supplied by author]

Table A: Description of studies

Study	Design	Sample size	Digoxin n	Control n	Follow-up duration (years)
Moss 1981[39]	Prospective cohort study of patients with acute MI at a single US CCU	972 who survived index hospitalisation	189	783	2.0
Ryan 1983[52]	Retrospective cohort study of patients with CAD (Coronary Artery Surgery Study registry)	14547 with CAD (≥70% narrowing defined by angiography)	2600	11947	4.5
Madsen 1984[40]	Prospective cohort study of patients with acute MI at 4 centres in US	1300 who survived index hospitalisation	464	836	0.9
Bigger 1985[41]	Prospective cohort study of patients with acute MI at a single US centre	504 who survived index hospitalisation	275	229	1.9
Byington 1985[60]	Post hoc analysis of acute MI patients randomised to beta-blocker versus placebo (BHAT trial)	1921 in placebo group, from a population of 3837	250	1671	2.1
Muller 1986[61]	Post hoc analysis of acute MI patients randomised to propranolol versus placebo (MILIS trial)	903 who survived index hospitalisation from a population of 985	281	622	2.1
Moss 1987[42]	Prospective cohort study of patients with acute MI at 9 US centres	867 patients who survived index hospitalisation	268	599	2.6
Xamoterol Study Group, 1988[68]	Randomised controlled trial comparing digoxin, xamoterol and placebo in HF (NYHA II-III)	142 with HF in digoxin and placebo groups from a population of 433	70	72	0.25
Captopril-Dig Group 1988[30]	Randomised controlled trial comparing digoxin, captopril and placebo in HF with reduced LVEF	196 with LVEF<40% in digoxin and placebo groups from a population of 300	96	100	0.5
DiBianco 1989[31]	Randomised controlled trial comparing digoxin, milrinone and placebo in HF (NYHA II-IV)	111 with HF in digoxin and placebo groups from a population of 230	62	49	0.25
Blackwood 1990[69]	Randomised controlled trial comparing digoxin, xamoterol and placebo in HF (NYHA II-III)	61 with HF in digoxin and placebo groups from a population of 123	31	30	0.25
Molstad 1991[43]	Prospective cohort study of patients with acute MI at a single Norwegian hospital	620 who survived index hospitalisation in sinus rhythm	159	461	2.0
Van Veldhuisen 1993[70]	Randomised controlled trial comparing digoxin, ibopamine and placebo in HF (NYHA II-III)	108 with HF in digoxin and placebo groups from a population of 161	55	53	0.5
Kober 1994[44]	Prospective cohort study of patients with acute MI admitted to a single centre in Denmark	584 who survived index hospitalisation	172	412	6.2

Study	Design	Sample size	Digoxin n	Control n	Follow-up duration (years)
Leor 1995[62]	Post hoc analysis of acute MI patients randomised to nifedipine versus placebo (SPRINT trial)	1731 who survived index hospitalisation	175	1556	1.0
Banerjee 1996[51]	Retrospective case control study of patients with acute HF admissions at a UK CCU	36 with acute HF secondary to IHD in sinus rhythm	18	18	8.2
DIG Trial 1997[9]	Randomised controlled trial comparing digoxin versus placebo in HF with reduced EF	6800 with LVEF ≤45% in sinus rhythm	3397	3403	3.1
Casiglia 1998[45]	Post hoc analysis of elderly patients free from HF and in sinus rhythm (CASTEL study)	1977 ≥ 65 years from a population of 2254	447	1530	12
Lindsay 1999[53]	Retrospective cohort study of HF patients in multiple UK centres (UK Heart study)	484 with HF, NYHA 1-3, in sinus rhythm	90	394	2.8
Reicher-Reiss 1999[63]	Post hoc analysis of prior MI patients randomised to bezafibrate versus placebo (BIP trial)	8173 with prior MI screened for the BIP study from a population of 14655	451	7722	3
Eichhorn 2000[54]	Post hoc analysis of 5 randomised controlled trials of carvedilol versus placebo in HF patients	606 with HF not taking carvedilol from a population of 1509	423	183	0.8
*Rathore 2003[10]	Post hoc analysis of the DIG trial stratified by SDC	3397 on digoxin: 572 SDC 0.5-0.8ng/mL, 322 0.9-1.1ng/mL, 277 >1.2ng/ml	3397	3403	3.1
Ghali 2004[64]	Post hoc analysis of HF patients randomised to metoprolol versus placebo (MERIT-HF)	2000 with LVEF ≤40% not taking metoprolol from a population of 3991	1282	718	1.8
*Domanski 2005[29]	Pooled analysis of HF patients randomised to enalapril versus placebo (SOLVD trials)	6,797 with LVEF ≤35%	2244	4553	3.5
*Adams 2005[104]	Post hoc analysis of the DIG trial stratified by SDC and gender	5209 with LVEF ≤45% in sinus rhythm survived 28 days and SDC determined	1578	3366	3.1
*Ahmed 2006[105]	Post hoc analysis of the DIG trial stratified by SDC and gender	1366 females in DIG trial with SDC determined	411	955	3.4
*Ahmed 2006[106]	Post hoc analysis of the DIG trial stratified by SDC	5548 in DIG trial with SDC at 1 month	1687	3861	3.3
Ahmed 2006[67]	Randomised controlled trial comparing digoxin versus placebo in HF with preserved EF	988 with LVEF >45% in sinus rhythm	492	496	3.1
*Ahmed 2007[107]	Post hoc analysis of the DIG trial stratified by SDC and age	5548 in DIG trial alive at 1 month with SDC determined	1687	3861	3.2
Hallberg 2007[46]	Prospective cohort study of patients admitted to CCU with AF and/or HF in RIKS-HIA registry	60 764 with AF and/or CHF from a population of 141,868	16426	44338	1.0

Study	Design	Sample size	Digoxin n	Control n	Follow-up duration (years)
*Ahmed 2008[108]	Post hoc analysis of the DIG trial stratified by low SDC, propensity score-matched analysis	982 with SDC 0.5-0.9ng/mL in DIG trial matched to placebo	982	982	3.5
Dhaliwal 2008[47]	Prospective cohort study of HF patients with reduced EF in a single US centre	347 with LVEF ≤45%	155	192	0.8
Gjesdal 2008[65]	Post hoc analysis of AF patients randomised to ximelagatran versus warfarin (SPORTIF trial)	7329 with AF	3911	3418	2.4
*Meyer 2008[109]	Reanalysis of DIG trial investigating composite outcome of HF mortality and HF hospitalisation	6800 with LVEF ≤45% in sinus rhythm	3397	3403	3.1
Fauchier 2009[55]	Retrospective cohort study of concomitant AF and HF patients in a single French centre	402 with AF + HF not on beta-blockers from a population of 1269	402	418	2.41
Gergiopoulou 2009[25]	Retrospective cohort study of HF patients undergoing cardiac transplant evaluation	455 with LVEF ≤30% and NYHA 2-4	227	228	1.4
Butler 2010[66]	Post hoc analysis of HF patients randomised to valsartan versus placebo (Val-HeFT trial)	5010 with symptomatic HF	3374	1636	3.1
Chan 2010[6]	Retrospective cohort study of ESRD patients on haemodialysis at multiple centre throughout the US	120,864 on haemodialysis	4549	116315	4.0
Friberg 2010[56]	Retrospective cohort study of AF patients at 2 Swedish centres (SCAF study)	2824 with AF	802	2022	4.6
Andrey 2011[48]	Prospective cohort study of HF patients at a single Spanish centre	4467 with new-onset HF	1428	3018	3.8
Flory 2012[26]	Retrospective Cohort of HF patients in a large UK primary care registry (THIN database)	57,229 with HF on ≥ 2 HF medications from a database of 5,000,000 individuals	20295	36934	n/s
*Freeman 2013[27]	Prospective cohort study of systolic HF patients with no prior digoxin use in North California, USA	2,891 with systolic HF	529	2362	2.5
Gheorghiade 2013[21]	Post hoc analysis of AF patients randomised to rate versus rhythm-control (AFFIRM trial)	2706 with AF paired digoxin with control from a population of 4060	1377	1329	3.4
Garcia-Rubira 2014[57]	Retrospective cohort study of ACS patients from multiple Spanish centres (ARIAM registry)	20,331 with ACS	244	20087	3.0
Whitbeck 2013[20]	Post hoc analysis of AF patients randomised to rate versus rhythm-control (AFFIRM trial)	4058 with AF	2153	1905	3.5

Study	Design	Sample size	Digoxin n	Control n	Follow-up duration (years)
*Jorge 2013[28]	Prospective cohort study of ICU admissions with decompensated HF (NYHA 3-4)	268 with decompensated HF (179 in sinus rhythm, 89 in AF)	n/s	n/s	3.3
Ahmed 2014[49]	Prospective cohort study of HF patients from multiple centres in Alabama, US.	1842 with HF and survived index hospitalisation from a population of 8555.	921	921	1.0
Flahavan 2014[58]	Retrospective cohort study of prostate cancer patients in an Irish cancer registry	5732 with prostate cancer	5341	391	4.3
Rodriguez-Manero 2014[50]	Prospective cohort study of AF patients enrolled in AFBAR trial in Spain	535 with AF not on beta blocker from a population of 777	212	323	2.9
Turakhia 2014[7]	Retrospective cohort study of AF patients from a US veterans register (TREAT AF study)	122,465 with non-valvular AF	28679	93787	5.0
Chao 2014[59]	Retrospective cohort study of AF patients in a Taiwanese health insurance register	4781 with AF with no anti-thrombotic therapy	829	3952	4.4
Shah 2014[8]	Retrospective cohort study of AF patients >65years in a Canadian population ±HF	100,599 with AF	23200	77399	4.0

* Study not included in meta-analysis. AF, atrial fibrillation; AFBAR, Atrial Fibrillation BARrbanza area; AFFIRM, AF Follow-Up Investigation of Rhythm Management; BHAT, Beta-Blocker Heart Attack Trial; BIP, Bezafibrate Infarction Prevention; CAD, coronary artery disease; CASTEL, Cardiovascular Study in the Elderly; CCU, Coronary Care Unit; DIG, Digitalis Investigation Group; ESRD, end stage renal disease; HF, heart failure; ICU, intensive care unit; IHD, ischaemic heart disease; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Chronic Heart Failure; MI, myocardial infarction; MILIS, Multicentre Investigation of Limitation of Infarct Size; NYHA, New York Heart Association functional class; RIKS-HIA, Registry of Information and Knowledge about Swedish Heart Intensive care Admissions; SCAF, Stockholm Cohort study of AF; SDC, serum digoxin concentration; SOLVD, Studies of Left Ventricular Dysfunction; SPORTIF, Stroke Prevention using an Oral Thrombin Inhibitor in AF III and V; SPRINT, Secondary Prevention Reinfarction Israeli Nifedipine Trial; Val-HeFT, Valsartan Heart Failure Trial; THIN, UK based The Health Information Network; TREAT-AF, The Retrospective Evaluation and Assessment of Therapies in AF.

Table B: Detailed characteristics of studies

Study	Age, years	Male %	Heart Failure %	AF %	Diabetes %	Prior MI %	Hypertension %	Anti-arrhythmics %	ACEi/ARB %	Beta-blocker %	Diuretic %
Moss 1981[39]	D 56 C 53	D 82 C 82	D 73 C 40	n/s	n/s	D 16 C 35	D 29 C 31	D 34 C 18	n/s	D 6 C 14	D 42 C 14
Ryan 1983[52]	n/s	n/s	D 36 C 4	n/s	n/s	D 80 C 56	n/s	n/s	n/s	n/s	D 60 C 17
Madsen 1984[40]	D 66 C 59	D 71 C 77	D 25 C 3	D 25 C 6	D 17 C 12	n/s	D 41 C 34	n/s	n/s	n/s	D 47 C 13
Bigger 1985[41]	n/s	D 77 C 77	D 47 C 10	D 18 C 3	D 27 C 14	D 31 C 17	D 51 C 47	D 18 D 7	n/s	D 6 C 16	D 41 C 12
Byington 1985[60]	D 59 C 55	D 84 C 85.2	D 60 C 13	n/s	D 13 C 11	D 24 C 13	n/s	n/s	n/s	0	D 46 C 14
Muller 1986[61]	D 60 C 55	n/s	D 20 C 2	n/s	D 22 C 15	D 31 C 12	n/s	D 11 C 2	n/s	D 22 C14	D 31 C 23
Moss 1987[42]	n/s	D 75 C 79	D 30 C 15	D 16 C 4	D 25 C 13	D 36 C 18	D 50 C 40	D 35 C 15	n/s	D 22 C 37	D 47 C 14
Xamoterol Study Group, 1988[68]	D 62 C 62	D 38 C 43	D 100 C 100	D 2 C 2	n/s	n/s	n/s	D 0 C 0	D 1 C 2	D 0 C 0	D 21 C 26
Captopril-Dig Group 1988[30]	D 58 C 57	D 88 C 78	D 100 C 100	0	n/s	n/s	n/s	n/s	0	n/s	n/s
DiBianco 1989[31]	D 60 C 60	D 77 C 74	D 100 C 100	n/s	n/s	D 50 C 51	n/s	D 32 C 26	n/s	n/s	n/s
Blackwood 1990[69]	60†	50†	D 100 C 100	n/s	n/s	n/s	n/s	D 0 C 0	n/s	n/s	D 56 C 56
Molstad 1991[43]	D 74 C 66	D 58.9 C 71.3	n/s	D 17 C 4	D 31 C 9	n/s	n/s	n/s	n/s	D 21 C 29	D 47 C 10
Van Veldhuisen 1993[70]	D 61 C 61	D 89 C 83	D 100 C 100	D 0 C 0	n/s	n/s	n/s	D 11 C 15	n/s	n/s	D 25 C 27
Kober 1994[44]	D 66 C 59	D 69 C 75	D 84 C 14	D 28 C 10	D 13 C 7	n/s	n/s	n/s	n/s	D 3 C 5	D 88 C 26

Study	Age, years	Male %	Heart Failure %	AF %	Diabetes %	Prior MI %	Hypertension %	Anti-arrhythmics %	ACEi/ARB %	Beta-blocker %	Diuretic %
Leor 1995[62]	D 60 C 57	D 74 C 75	D 40 C 11	D 32 C 6	D 26 C 19	D 23 C 16	D 40 C 43	D 36 C 28	n/s	D 12 C 20	D 76 C 20
Banerjee 1996[51]	D 63 C 63	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
DIG Trial 1997[9]	D 63 C 64	D 77.8 C 77.5	D 100 C 100	D 0 C 0	D 28 C 29	D 65 C 65	D 45 C 46	n/s	D 94.1 C 94.8	n/s	D 81 C 82
Casiglia 1998[45]	D 75 C 73	D 66 C 61	0	0	D 11 C 6	D 4 C 2	n/s	n/s	n/s	n/s	n/s
Lindsay 1999[53]	62[†]	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
Reicher-Reiss 1999[63]	D 62 C 60	D 82 C 82	n/s	n/s	D 32 C 22	D 100 C 100	D 31 C 32	D 18 C 6	D 42 C 11	D 7 C 34	D 69 C 15
Eichhorn 2000[54]	D 59 C 64	D 77 C 79	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
[*]Rathore 2003[10]	D 63 C 64	D 77.8 C 77.5	D 100 C 100	D 0 C 0	D 28 C 29	D 65 C 65	D 45 C 46	n/s	D 94.1 C 94.8	n/s	D 81 C 82
Ghali 2004[64]	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
[*]Domanski 2005[29]	n/s	n/s	D 100 C 100	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
[*]Adams 2005[104]	D 63 C 64	D 77.8 C 77.5	D 100 C 100	D 0 C 0	D 28 C 29	D 65 C 65	D 45 C 46	n/s	D 94.1 C 94.8	n/s	D 81 C 82
[*]Ahmed 2006[105]	D 65 C 65	D 0 C 0	D 100 C 100	D 0 C 0	D 33 C 35	D 51 C 50	D 57 C 56	n/s	D 94 C 93	n/s	D 86 C 84
[*]Ahmed 2006[106]	D 64 C 64	D 77 C 75	D 100 C 100	D 0 C 0	D 29 C 29	D 64 C 63	D46 C47	n/s	D 94 C 94	n/s	D 78 C 78
Ahmed 2006[67]	D 67 C 67	59[†]	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s	n/s
[*]Ahmed 2007[107]	D 63 C 64	D 77.8 C 77.5	D 100 C 100	D 0 C 0	D 28 C 29	D 65 C 65	D 45 C 46	n/s	D 94.1 C 94.8	n/s	D 81 C 82
Hallberg 2007[46]	D 77 C 75	D 55 C 59	D 49 C 34	n/s	D 28 C 23	D43 C 40	D 38 C 39	n/s	D 57 C 51	D 59 C 71	D 81 C 63

Study	Age, years	Male %	Heart Failure %	AF %	Diabetes %	Prior MI %	Hypertension %	Anti-arrhythmics %	ACEi/ARB %	Beta-blocker %	Diuretic %
*Ahmed 2008[108]	D 63 C 63	D 78 C 80	D 100 C 100	D 0 C 0	D 27 C 25	D 64 C 63	D 44 C 44	n/s	D 95 C 95	n/s	D 73 C 72
Dhaliwal 2008[47]	D 69 C 68	D 99 C 100	n/s	D 34 C 22	D 42 C 52	n/s	D 71 C 86	n/s	D 84 C 77	D 57 C 68	D 96 C 90
Gjesdal 2008[65]	D 71 C 71	D 67 C 72	n/s	D 100 C 100	D 26 C20	n/s	n/s	n/s	n/s	n/s	n/s
*Meyer 2008[109]	D 63 C 64	D 77.8 C 77.5	D 100 C 100	D 0 C 0	D 28 C 29	D 65 C 65	D 45 C 46	n/s	n/s	n/s	D 81 C 82
Fauchier 2009[55]	D 76 C 75	D 56 C 62	n/s	D 59 C 39	D 16 C 17	D 8 C 11	D 38 C 46	D 35 C 48	D 80 C 65	n/s	D 73 C 57
Gergiopoulou 2009[25]	D 501 C 54	D 67 C 71	n/s	D40 C31	n/s	n/s	n/s	n/s	D 73 C 70	D 90 C 93	n/s
Butler 2010[66]	D 62 C 63	D 74 C 66	D 100 C 100	D 18 C 5	D 29 C 19	n/s	D 7 C 6	n/s	D 94 C 91	D 32 C 41	D 90 C 76
Chan 2010[6]	D 69. C 63	D 60 C 54	n/s	n/s	D 70 C 63	n/s	n/s	n/s	D 45 C 41	D 60 C 51	n/s
Friberg 2010[56]	D 78 C 73	D 46 C 58	D 64 C 37	D 68 C 32	D 22 C 16	D 22 C 18	D 46 C 49	n/s	D 40 C 32	D 52 C 50	n/s
Andrey 2011[48]	D 71 C 70	D 47 C 48	n/s	D 60 C 28	D 37 C 32	D 30 C 33	D 47 C 45	n/s	D 79 C 78	D 43 C 37	D 89 C 77
Flory 2012[26]	n/s	D 47 C 48	n/s	D 41 C 9	D 14 C 17	D 17 C 21	D 43 C 47	n/s	D 31 C 32	D 19 C 24	D 59 C 55
*Freeman 2013[27]	D 68 C 70	D 67 C 67	D 100 C 100	D 40 C 19	D 30 C 34	D 8 C 15	D 60 C 67	D 3 C 5	D 37 C 47	D 40 C 51	D 30 C36
Garcia-Rubira 2014[57]	D 73 C 64	D 60 C 75	D 28 C 3	D 80 C 9	D 51 C 32	D 23 C 15	D 77 C 52	n/s	n/s	n/s	n/s
Gheorghiade 2013[21]	D 70 C 70	D 59 C 63	D 31 C 12	D 100 C 100	D 22 C 18	D 17 C 15	D 70 C 74	n/s	D 44 C 33	D 34 C 44	D 49 C 35
Whitbeck 2013[20]	n/s	60	n/s	D 100 C 100	n/s	D 18 C 16	D 69 C 73	n/s	67	58	n/s
*Jorge AF subgroup, 2013[28]	D 62 C 64	D 70 C 96	D100 C100	D 100 C 100	D 36 C 26	n/s	n/s	n/s	D 79 C 65	D 59 C 52	n/s

Study	Age, years	Male %	Heart Failure %	AF %	Diabetes %	Prior MI %	Hypertension %	Anti-arrhythmics %	ACEi/ARB %	Beta-blocker %	Diuretic %
*Jorge SR subgroup, 2013[28]	D 55 C 55	D 77 C 63	D100 C100	D 0 C 0	D 29 C 36	n/s	n/s	n/s	D 82 C 79.	D 84 C 81	n/s
Ahmed 2014[49]	D 76 C 75	D 45 C 40	n/s	D 39 C 16	D 36 C 45	D 24 C 22	D 69 C 72	D 13 C 12	36	D 31 C 31	D 86 C 77
Flahavan 2014[58]	D 78 C 73	D 100 C 100	n/s	n/s	n/s	n/s	n/s	n/s	D 71 C 53	D 25 C 22	n/s
Rodriguez-Manero 2014[50]	D 77 C 77	D 46 C 59	D 20 C 6	n/s	D 29 C 21	n/s	D 78 C 76	n/s	n/s	n/s	n/s
Turakhia 2014[7]	D 72 C 72	D 99 C 98	D 21 C 14	100	D 28 C 29	D 5 C 4	D 56 C 66	D 10 C 9	n/s	D 64 C 57	D 58 C 43
Chao 2014[59]	D 71 C 66	D 52 C 55	D 24 C 8	n/s	D 34 C 30	n/s	D 72 C 65	n/s	D 60 C 51	D 18 C 15	n/s
Shah AF+HF subgroup 2014[8]	D80 C80	D 47 C 50	D 100 C100	D 100 C 100	D 30 C 33	D 23 C 29	D 55 C 67	n/s	D 53 C 43	D 48 C 53	D 88 C 77
Shah AF subgroup 2014[8]	D 79 C 79	D 43 C 49	D 0 C 0	D 100 C 100	D 23 C22	D 10 C 13	C 55 C 63	n/s	D 31 C 27	D 40 C 44	D 51 C 38

* Studies not included in meta-analysis. †Digoxin and control groups combined. D, digoxin cohort; C, control cohort; SD, standard deviation; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; n/s, not specified; AF, atrial fibrillation; MI, myocardial infarction.

Table C: Risk of Bias Assessment (Observational Studies)

Study	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome	Incomplete outcome data	Selective reporting
Ahmed 2014[49]	High	Low	Low	Low	Unclear	Unclear
Andrey 2011[48]	Low	Low	Low	High	Unclear	Low
Banerjee 1996[51]	High	High	Unclear	Unclear	Low	Unclear
Bigger 1985[41]	Unclear	Unclear	Unclear	Unclear	Unclear	High
Butler 2010[66]	Low	Unclear	Low	Low	Low	Low
Byington 1985[60]	Unclear	Unclear	Low	Low	Unclear	Unclear
Casiglia 1998[45]	High	Unclear	Unclear	High	Unclear	Unclear
Chan 2010[6]	Unclear	High	Unclear	Unclear	Unclear	Unclear
Chao 2014[59]	Unclear	High	Low	Unclear	Unclear	Unclear
Dhaliwal 2008[47]	High	High	High	Unclear	Unclear	Unclear
Eichhorn 2000[54]	Low	Unclear	Unclear	Low	Unclear	Low
Fauchier 2009[55]	High	High	Unclear	High	High	Unclear
Flahavan 2014[58]	Low	High	Unclear	Unclear	Unclear	Unclear
Flory 2012[26]	Low	Low	Low	Low	Unclear	Low
Freeman 2013[27]	Unclear	Low	Unclear	Unclear	Unclear	Unclear
Friberg 2010[56]	Low	Low	Low	Low	Low	Low
Garcia-Rubira 2014[57]	Unclear	Low	Unclear	Unclear	Unclear	Low
Gergiopoulou 2009[25]	Low	Low	Low	Unclear	Low	Unclear
Ghali 2004[64]	Unclear	High	Low	Unclear	Low	Low
Gheorghiade 2013[21]	Unclear	Low	Low	Low	Unclear	Low

Study	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome	Incomplete outcome data	Selective reporting
Gjesdal 2008[65]	Unclear	High	Low	Unclear	Low	Unclear
Hallberg 2007[46]	High	High	Unclear	Low	Low	Unclear
Jorge 2013[28]	High	High	Unclear	High	Unclear	Low
Kober 1994[44]	High	High	Low	Low	Low	Unclear
Leor 1995[62]	Unclear	High	Unclear	High	Unclear	High
Lindsay 1999[53]	Unclear	High	Unclear	Unclear	Unclear	High
Madsen 1984[40]	Unclear	Unclear	Low	Unclear	High	Unclear
Molstad 1991[43]	Low	High	Unclear	Unclear	Unclear	Low
Moss 1987[42]	High	High	Unclear	Unclear	Unclear	High
Moss 1981[39]	High	High	Unclear	Unclear	Unclear	Unclear
Muller 1986[61]	Low	High	Unclear	Unclear	Unclear	Unclear
Reicher-Reiss 1999[63]	Unclear	High	Unclear	Unclear	Unclear	High
Rodriguez-Manero 2014[50]	Low	Unclear	Low	Unclear	Low	Unclear
Ryan 1983[52]	High	High	Unclear	Unclear	Unclear	Unclear
Shah 2014[8]	Unclear	Low	Unclear	Unclear	Unclear	Low
Turakhia 2014[7]	High	Unclear	Low	Unclear	Unclear	Low
Whitbeck 2013[20]	Unclear	Low	Low	Low	Unclear	Low

Risk of bias reported for each domain using the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS).

Table D: Risk of Bias Assessment (Randomised Studies)

Study	Sequence Generation	Allocation Concealment	Blinding of Personnel	Blinding of outcome	Incomplete outcome data	Selective reporting	Other threats to validity
Ahmed 2006[67]	Low	Low	Low	Low	Low	Low	Unclear
Blackwood 1990[69]	Unclear	Unclear	Low	Low	Low	Unclear	Unclear
Captopril-Dig Group 1988[30]	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear
DiBianco 1989[31]	Low	Low	Low	Low	Low	Low	Unclear
DIG Trial 1997[9]	Low	Low	Low	Low	Low	Low	Low
Meyer 2008[109]	Low	Low	Low	Low	Low	Low	Low
Van Veldhuisen 1993[70]	Unclear	Low	Low	Low	Low	Unclear	Unclear
Xamoterol Study Group 1988[68]	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear

Risk of bias of randomised studies performed using the Cochrane Tool for Randomised Controlled Trials.

Table E: Adjustment variables for all-cause mortality

Study	Variables adjusted in multivariate analysis
Bigger 1985[41]	Age, antiplatelet use, baseline beta-blocker use, cardiothoracic ratio, complexity of ventricular arrhythmia, complicated MI, diabetes diastolic BP, diuretic use, elevated LDH, employment status at the time of MI, haematocrit, HF, prior MI, smoking, ST segment depression.
Moss 1987[42]	Age >60, BUN >35, diabetes leg oedema, LVEF, NYHA class 3-4, rales>bibasilar, VED frequency code, repetitive VED.
Molstad 1991[43]	AF, age, baseline beta-blocker, calcium antagonist, diabetes, diuretic, ECG anterior wall infarction, ECG inferior wall infarction, ECG reciprocal changes, ECG uncertain location, gender, nitrate and potassium replacement potassium sparing diuretic, prior MI, serum creatinine, serum potassium, smoking.
Kober 1994[44]	AF or atrial flutter, age, calcium antagonist use, clinical HF, diabetes, digoxin, furosemide use, gender, LVEF, ventricular fibrillation.
Leor 1995[62]	Acute anterior MI, age, prior MI, prior stroke, serum LDH greater than four times the upper normal values, sinus tachycardia, ventricular tachycardia on Holter monitoring.
Lindsay 1999[53]	Age, anti-arrhythmic therapy, cardiothoracic ratio, diuretic dose, LVESD, NYHA class, presence of non-sustained ventricular tachycardia, serum sodium, standard deviation of the normal to normal 24-h RR interval.
Reicher-Reiss 1999[63]	Age, angina pectoris, antiarrhythmic use, aspirin, baseline beta-blocker use, calcium antagonist use, diabetes, hypertension, nitrate use, NYHA class, sex, smoking.
Dhaliwal 2008[47]	AF, age, angiotensin converting enzyme inhibitor use, angiotensin receptor blocker use, baseline beta-blocker use, LVEF, hospitalizations, NYHA class, presence of chronic renal insufficiency, prior HF.
Gjesdal 2008[65]	Age, baseline aspirin use, baseline beta-blocker use, BMI, CAD, diabetes, diastolic BP, gender, hypertension, left ventricle dysfunction, race, prior systemic embolic event, prior stroke or transient ischaemic attack, smoking status, study treatment (ximelagatran or warfarin), systolic BP, weight, years since first AF diagnosis.
Fauchier 2009[55]	ACE/ARB use, AF, age, alcohol abuse, antiplatelet use, baseline anticoagulation use, CAD, class III antiarrhythmic agent use, COPD, diabetes mellitus, diuretic use, gender, HF, hypertension, LVEF, pacemaker or implantable defibrillator, peripheral arterial disease, prior CABG, prior MI, prior PCI, prior stroke, renal insufficiency, thyroid disease, valvular disease, valve surgery.
Butler 2010[66]	ACE inhibitor, AF, age, aldosterone, amiodarone, aspirin, beta-blocker, BMI, diabetes, diuretic, GFR, haemoglobin, hypertension, log B-type natriuretic peptide, log C-reactive protein, log norepinephrine, log plasma renin activity, LV dimensions in diastole/body surface area, LVEF, jugular venous distension, NYHA class, oedema, paroxysmal nocturnal dyspnoea, pulse, race, sex, serum potassium, serum sodium, statin, systolic BP, third heart sound, uric acid, valsartan vs placebo treatment.

Study	Variables adjusted in multivariate analysis
Friberg 2010[56]	ACE inhibitor or ARB use, AF, age, alcohol or drug abuse, amiodarone, ASA score, beta-blocker use, cancer, cerebral haemorrhage, class 1 antiarrhythmic use, chronic pulmonary disease, date of last discharge from hospital, diabetes, hypertension, CHADS score, days at hospital in prior 3 years, HF, ischemic stroke or transient ischemic attack, left atrial diameter, LVEF, male, pacemaker, peripheral arterial disease, prior MI, years since first AF diagnosis, renal failure, sotalol, statin use, thyroid disease, treated only as an outpatient valve defect, valve surgery, warfarin contraindication, warfarin use.
Andrey 2011[48]	ACE inhibitor/ARB, aldosterone antagonise, amiodarone, anaemia, anticoagulant, beta-blocker, calcium antagonist, chronic liver disease, chronic renal failure, dementia, diuretic, EPO, gender, haemoglobin, hyperthyroidism, hypothyroidism, nitrate serum sodium <135, statin, systemic malignancy.
Flory 2012[26]	AF, anticoagulant use, aspirin use, age, COPD, diabetes HF, hypertension, potassium-sparing diuretic use, prior MI, prior stroke, sex, statin use.
Garcia-Rubira 2014[57]	AF, age, COPD, diabetes, familiar history, HF, hypertension, prior MI, renal disease, sex, smoke, ST elevation MI peripheral vascular disease, prior stroke.
Chao 2014[59]	ACE inhibitor/ARB, asthma, beta-blocker, calcium channel blocker, CHA_2DS_2-VASc score, COPD.
Flahavan 2014[58]	Age, aspirin use, beta-blocker use, benign prostatic hypertrophy medical treatment and treatment received in year after diagnosis (surgery, radiation, androgen deprivation therapy, comorbidity score, diabetes, NSAID use, smoking status, statin use, tumour stage, tumour grade, warfarin use, year of incidence.
Rodriguez-Manero 2014[50]	Age, antiarrhythmic use, baseline beta-blocker use, BMI, calcium channel blocker use, diabetes, dyslipidemia, HF, hypertension, ischemic heart disease, LVEF, prior stroke, smoking status, renal insufficiency.
Turakhia 2014[7]	Age, antiarrhythmic use, cardiovascular medication use, $CHADS_2$ score, Charlson comorbidity score, diabetes, GFR, HF, hypertension, prior stroke, race, sex.
Shah 2014[8]	ACE inhibitor, ARB, AF type (primary vs secondary diagnosis), age, amiodarone, aspirin, baseline beta-blocker use, bleeding history, clopidogrel, co-morbidities 2 years before and at AF admission (cancer, coronary artery disease, chronic kidney disease, COPD, diabetes, hypertension, hypothyroidism, liver disease, MI, valvular heart disease), diltiazem, diuretic, gender, NSAID, prior stroke or transient ischemic attack, sotalol, statin, verapamil, warfarin.

ACE, angiotensin converting enzyme, AF, atrial fibrillation; ARB, angiotensin receptor blocker; ASA, American society of anesthesiologists; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CAD, coronary artery disease; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; EPO, erythropoietin; GFR, glomerular filtration rate; HF, heart failure; LDH, lactic dehydrogenase; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic dimension, MI, myocardial infarction; NYHA, New York Heart Association; VED, ventricular ectopic depolarisations.

Table F: Studies published after meta-analysis completed

Study	Design	Sample size	Mortality results	Comments
Allen 2014[93]	Prospective observational cohort study using the ORBIT-AF registry	10,130 patients with AF (2,373 on digoxin)	No association of baseline digoxin use with mortality (adjusted HR with HF 0.98, 95% CI 0.81-1.19; without HF 1.12 (95% CI 0.87-1.43)	Abstract only
Hohnloser 2014[94]	Post-hoc analysis of PALLAS trial stratified by digoxin use	1,617 patients with permanent AF (526 on digoxin) in the placebo arm	No association of baseline digoxin use with mortality (unadjusted RR 0.62, 95% 0.17-2.25)	Digoxin group had more advanced HF and diuretic use; excludes dronedarone patients
Mulder 2014[95]	Post-hoc analysis of RACE II trial stratified by the use of digoxin after the dose-adjustment phase	608 patients with permanent AF (284 on digoxin)	Mortality significantly lower in digoxin patients compared to the no-digoxin group (HR 0.41, 95% CI 0.19-0.89)	No difference in primary composite endpoint
Gamst 2014[110]	Prospective observational cohort study of North Denmark	88,315 patients hospitalised with pneumonia (6,929 on digoxin)	Digoxin associated with increased mortality in AF cohort (adjusted HR 1.15, 95% CI 1.08-1.23) and non-AF cohort (adjusted HR 1.21, 95% CI 1.15-1.27)	No data on baseline characteristics between digoxin and control groups
Freeman 2015[96]	Retrospective cohort study (ATRIA-CVRN) of incident AF with no prior HF	14,787 propensity matched patients with AF (4231 on digoxin)	Digoxin associated with increased mortality (adjusted HR 1.71, 95% CI 1.52-1.93)	Significant residual differences in characteristics after propensity matching
Okin 2015[97]	Post hoc analysis of LIFE trial stratified by digoxin use	937 hypertensive patients with left ventricular hypertrophy in AF (372 on digoxin)	No association of in-treatment digoxin use with mortality (adjusted HR 1.04, 95% CI 0.73-1.48)	Includes propensity score adjustment for digoxin use
Pastori 2015[98]	Prospective single-centre observational cohort study of anticoagulated AF patients	815 patients with AF (171 on digoxin)	Digoxin associated with increased mortality (adjusted HR 2.22, 95% CI 1.42-3.48)	Digoxin group were older, with much higher rates of HF and permanent AF
Washam 2015[99]	Post-hoc analysis of ROCKET AF trial stratified by digoxin use	14,171 anticoagulated AF patients (5239 on digoxin)	Digoxin associated with increased mortality (adjusted HR 1.17, 95% CI 1.04-1.32)	Digoxin group had significantly more HF, diabetes and persistent AF

AF, atrial fibrillation; ATRIA-CVRN, Anticoagulation and Risk Factors in Atrial Fibrillation-Cardiovascular Research Network; CI, confidence interval; HF, heart failure; HR, hazard ratio; LIFE, Losartan Intervention For Endpoint Reduction in Hypertension study; ORBIT-AF, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; PALLAS, Permanent Atrial Fibrillation Outcome Study using Dronedarone on Top of Standard Therapy; RACE II, Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II study; ROCKET AF, Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Stroke and Embolism Trial in Atrial Fibrillation; RR, risk ratio.