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Persistence of Mortality Reduction After the End of Randomized Therapy in Clinical Trials of Blood Pressure–Lowering Medications

William J. Kostis, Lutgarde Thijs, Tom Richart, John B. Kostis, Jan A. Staessen

Abstract—Long-term follow-up of clinical trials of blood pressure–lowering medications has suggested a continuation of event reduction after study completion. We evaluated the persistence of mortality benefit of these agents after the end of clinical trials, when all of the patients were advised to take the same open-label therapy. We performed a meta-analysis of randomized clinical trials using blood pressure–lowering medications, used in patients with hypertension, myocardial infarction, or left ventricular systolic dysfunction, (n=18; 132 854 patients; 11 988 deaths) when a second report describing results after the end of the trial was available. During the randomized (first) phase, 80% (interquartile range: 75% to 83%) of the patients randomized to receive active therapy actually received it compared with 16% (interquartile range: 7% to 22%) of those randomized to control. In this phase, mortality was lower in the intervention group (odds ratio: 0.84 [95% CI: 0.79 to 0.90]; $P<0.0001$). Mortality was also lower during the open-label follow-up (second) phase (odds ratio: 0.85 [95% CI: 0.79 to 0.91]; $P<0.0001$), when all of the patients were advised to take the same therapy, and rates of receiving active therapy were similar in the 2 groups (59% [interquartile range: 46% to 77%], among those originally randomized to active, and 43% [interquartile range: 20% to 68%], in the control). Several sensitivity analyses indicated stability of the effects. In studies of antihypertensive medications, a decrease in overall mortality persists after the end of trial phase, when most patients in both the intervention and control groups receive active therapy. These analyses imply that earlier intervention would result in better clinical outcomes. **(*Hypertension*. 2010; 56:1060-1068.) • Online Data Supplement**

Key Words: ACEIs ■ blood pressure–lowering medications ■ β-blockers ■ diuretics ■ clinical trials ■ mortality ■ legacy effect

Clinical trials of blood pressure–lowering medications, usually lasting ≤5 years, and meta-analyses of such studies showed lower mortality among patients randomized to active therapy.[1–5] Investigators of some of the clinical trials have published findings of a persistent benefit of these medications after the end of the trials when all of the participants were advised to take active therapy. A legacy effect has been described in diabetes mellitus when persistent microvascular and macrovascular benefits were maintained or realized years after the end of an intensive glucose control randomized study.[6] To address the question of whether blood pressure–lowering medications confer a similar legacy effect, we performed a meta-analysis of randomized, controlled trials of these drugs. Studies where these medications were used for the treatment of hypertension, acute myocardial infarction (AMI), or systolic left ventricular dysfunction/heart failure (HF-LVD) are included in the analysis. The purpose of this article is to present a quantitative overview of the persistence of the effect on all-cause mortality after discontinuation of randomized therapy and to relate this effect to the actual percentages of patients in the intervention and control groups who received active therapy during the randomized and open-label follow-up phases of each study.

Methods

Data Sources and Searches

A systematic literature search of randomized clinical trials of the effect of blood pressure–lowering medications was performed up to June 2010 using Medline, Embase, the Cochrane Library, and clinicaltrials.gov according to the QUOROM statement.[7]

Study Selection

We identified 3428 titles with open-label follow-up after the end of randomized trials, using a search strategy as described in Figure 1 and online supplementary Table S1 (please see http://hyper.ahajournals.org). One additional study pair was obtained from the published abstract of an oral presentation.[8,9] Trials were eligible for inclusion

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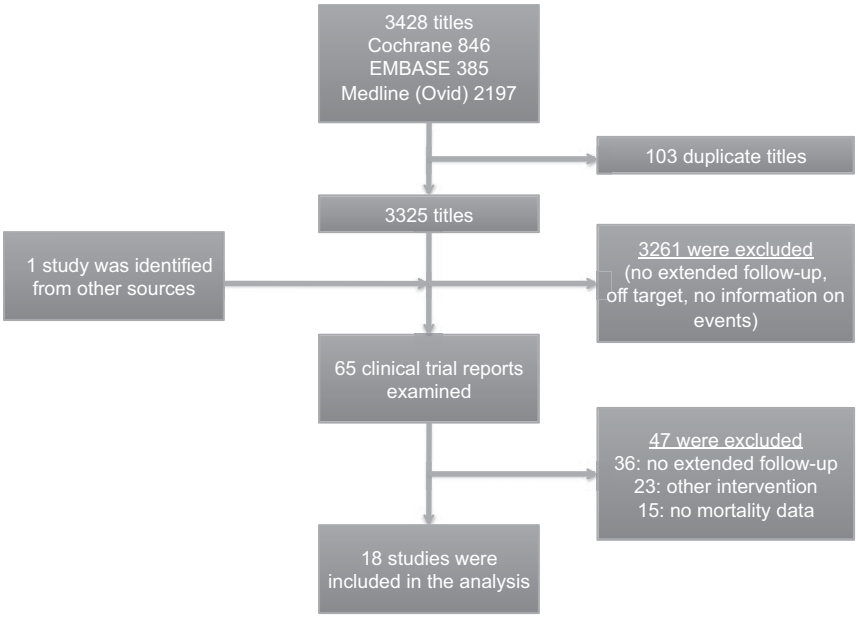


Figure 1. Search strategy.

if they were randomized; if they pertained to blood pressure–lowering medications; if all-cause mortality data were published or presented for both the randomized and open-label follow-up periods before June 30, 2009; and if the number of deaths in any of the 4 analysis cells (randomized active, randomized control, open-label active, or open label control) was >5. A total of 65 potentially appropriate studies were identified and reviewed, but only 18 study pairs fulfilled the inclusion criteria (Tables 1 and 2).[8–40] Enrollment criteria for the clinical trials included in the analysis were hypertension, HF-LVD, and AMI.

Table 1. Study Indications and Medications

Study	Indication	Medication Class	Intervention	Control
AIRE	HF-LVD	ACEI	Ramipril	Placebo
ANBP2	HTN	ACEI	Enalapril	HCTZ
CCS-1	AMI	ACEI	Captopril	Placebo
CONSENSUS	HF-LVD	ACEI	Enalapril	Placebo
FAMIS	AMI	ACEI	Fosinopril	Placebo
GISSI-3	AMI	ACEI	Lisinopril	Placebo
Goteborg	AMI	β-blocker	Metoprolol	Placebo
HDFP	HTN	Diuretic	Chlorthalidone, reserpine	Referred
ISIS-4	AMI	ACEI	Captopril	Placebo
MRFIT	HTN	Diuretic	Chlorthalidone, HCTZ	Placebo
SHEP	HTN	Diuretic	Chlorthalidone, atenolol	Placebo
SMILE	AMI	ACE inhibitor	Zofenopril	Placebo
SOLVD-P	HF-LVD	ACEI	Enalapril	Placebo
SOLVD-T	HF-LVD	ACEI	Enalapril	Placebo
SYST-EUR	HTN	Diuretic	Nitrendipine, enalapril	Placebo
Timolol	AMI	β-blocker	Timolol	Placebo
TRACE	HF-LVD	ACEI	Trandolapril	Placebo
UKPDS-BP	HTN	β-blocker	Atenolol, captopril	Less tight

AIRE indicates Acute Infarction Ramipril Efficacy; ANBP2, Australian National Blood Pressure 2; SHEP, Systolic Hypertension in the Elderly Program; P, prevention arm; T, treatment arm; SYST-EUR, Systolic Hypertension in Europe; TRACE, Trandolapril Cardiac Evaluation; BP, blood pressure; HCTZ, hydrochlorothiazide.

Data Extraction and Quality Assessment

Data on the type of intervention, medications used in the active intervention group, type of control, inclusion criteria, average follow-up, and the total number of patients and total number of deaths separately for the first phase and for the second phase were

Table 2. Study Demographics and Inclusion Criteria

Study	Mean Age, y	Men, %	Inclusion Criteria	References
AIRE	65	74	AMI and evidence of HF	37, 38
ANBP2	72	49	SBP >160 mm Hg	8, 9
CCS-1	64	75	Suspected AMI	35,36
CONSENSUS	70	70	Severe (NYHA class IV) HF	14, 15
FAMIS	60	87	AMI with thrombolysis	34
GISSI-3		88	AMI	28, 29
Goteborg	76	76	AMI	32, 33
HDFP	51	54	DBP >90 mm Hg	10, 11
ISIS-4	66	74	Suspected AMI	39, 40
MRFIT	46	100	Men aged 35 to 57 y at risk for CHD	12, 13
SHEP	72	43	SBP 160 to 219 mm Hg; DBP <90 mm Hg	22, 23
SMILE	64	73	Anterior AMI	16
SOLVD-P	59	89	EF ≤0.3 without HF	18, 19
SOLVD-T	61	81	Chronic HF and EF ≤0.35	17
SYST-EUR	70	67	SBP 160 to 219 mm Hg; DBP <95 mm Hg	24, 25
Timolol	61	79	AMI	30, 31
TRACE	67	72	AMI with EF <0.35	20, 21
UKPDS-BP	56	56	T2DM and SBP ≥160 mm Hg and/or DBP ≥90 mm Hg	26, 27

SBP indicates systolic blood pressure; T2DM, type 2 diabetes mellitus; DBP, diastolic blood pressure; HF, heart failure; NYHA, New York Heart Association; EF, ejection fraction; CHD, coronary heart disease; AIRE, Acute Infarction Ramipril Efficacy; ANBP2, Australian National Blood Pressure 2; SHEP, Systolic Hypertension in the Elderly Program; P, prevention arm; T, treatment arm; SYST-EUR, Systolic Hypertension in Europe; TRACE, Trandolapril Cardiac Evaluation; BP, blood pressure.

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Table 3. Duration of Follow-Up and Active Medication Use in First Phase

Study	First Phase Follow-Up, mo	First Phase % on Active	
		Active Group	Control Group
AIRE	15.0		
ANBP2	49.0		
CCS-1	1.0	92	5
CONSENSUS	6.0	83	1
FAMIS	3.0	80	16
GISSI-3	6.0	82	13
Goteborg	3.0	81	19
HDFP	60.0		
ISIS-4	1.0	83	13
MRFIT	83.0	74	52
SHEP	54.0		
SMILE	1.5	75	5
SOLVD-P	37.4	76	15
SOLVD-T	41.4	84	20
SYST-EUR	24.0		
Timolol	17.0	71	23
TRACE	37.0		
UKPDS-BP	101.0	77	80

AIRE indicates Acute Infarction Ramipril Efficacy; ANBP2, Australian National Blood Pressure 2; SHEP, Systolic Hypertension in the Elderly Program; P, prevention arm; T, treatment arm; SYST-EUR, Systolic Hypertension in Europe; TRACE, Trandolapril Cardiac Evaluation; BP, blood pressure.

Table 4. Duration of Follow-Up and Active Medication Use in Second Phase

Study	Second Phase Follow-Up, mo	Second Phase % on Active	
		Active Group	Control Group
AIRE	44.0		
ANBP2	71.0		
CCS-1	22.0	44	43
CONSENSUS	24.0	78	52
FAMIS	21.0	61	19
GISSI-3	20.0	34	17
Goteborg	21.0	56	54
HDFP	40.0		
ISIS-4	23.0	16	20
MRFIT	46.0	57	43
SHEP	118.0		
SMILE	10.5	75	26
SOLVD-P	23.0	85	87
SOLVD-T	19.0	85	87
SYST-EUR	48.0		
Timolol	44.0	53	22
TRACE	24.0		
UKPDS-BP	120.0	75	73

AIRE indicates Acute Infarction Ramipril Efficacy; ANBP2, Australian National Blood Pressure 2; SHEP, Systolic Hypertension in the Elderly Program; P, prevention arm; T, treatment arm; SYST-EUR, Systolic Hypertension in Europe; TRACE, Trandolapril Cardiac Evaluation; BP, blood pressure.

retrieved. For the Cooperative North Scandinavian Enalapril Survival (CONSENSUS) Study, where 2 reports of open-label follow-up at 2 different time intervals were available,[15,41] the first one[15] was used in the analysis, because the majority of patients were dead at the 10-year follow-up.[41] Aspects of trial design, including randomization, allocation concealment, comparison of baseline characteristics, defined eligibility criteria, placebo or other control, blinding (patients, investigators, or assessment of vital status), percentage lost to follow-up, intention-to-treat analysis, the presence of >5 deaths in all of the analysis cells, and the Jadad score are presented in the Table S2.[42] The number of patients and the number of deaths in the randomized (active and placebo) groups were tabulated separately for the first phase and the second phase. The percentages of patients who received active therapy among those randomized to active therapy and separately among those randomized to control were also tabulated for both phases of each study. Different methods of follow-up and ascertaining use of active medication were used by the investigators of the studies included in the analysis. In the majority (Chinese Cardiac Study [CCS-1],[36] CONSENSUS,[15] Fosinopril in Acute Myocardial Infarction Study [FAMIS],[34] Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico [GISSI-3],[29] Goteborg,[33] International Study of Infarct Survival-4 (ISIS-4),[40] Survival of Myocardial Infarction Long-Term Evaluation [SMILE],[16] and United Kingdom Prospective Diabetes Study Group [UKPDS][27]), most patients were seen in the clinical trial office. The remaining patients were contacted through mailed questionnaires, as were all of the participants in the Timolol Trial.[31] Death registries were used to ascertain vital status in the Multiple Risk Factor Intervention Trial [MRFIT],[13] Studies of Left Ventricular Dysfunction [SOLVD]-Prevention Arm,[19] and SOLVD-Treatment Arm.[17] At the end of the first phase of the studies, patients were instructed to receive active therapy, with the exception of FAMIS, GISSI-3, and SMILE, where angiotensin-converting enzyme inhibitors (ACEIs) were prescribed as needed clinically. There is variability across studies in the methodology used to ascertain use of active therapy in the intervention and control groups. In some trials, patient interviews and pill counts were used (eg, SOLVD, Hypertension Detection and Follow-up Program [HDFP], CONSENSUS, and Timolol). However, there is marked variability of the time after randomization when medication use was reported. Also, the specific criteria (eg, percentage of pills taken) varied in these studies. In other trials (eg, CCS-1, SMILE, and UKPDS-Blood Pressure), only the percentages of patients receiving active medication, without further clarification, are presented. Exact methods of measuring adherence are not described in the articles for the second phases of the trials.

Data Synthesis and Analysis

All-cause mortality in the active intervention and the control groups for the first phase and for the second phase were calculated. Statistical analyses were performed using JMP 7.0 (SAS Institute) and Comprehensive Meta-Analysis 2.2[43] (Biostat). Odds ratios and 95% CIs were calculated for all-cause mortality using the intention-to-treat approach. Weighted pooled treatment effects were calculated for the first phase and for the second phase. These analyses were done overall and separately for each study phase, for each type of intervention (eg, ACEI), and for each type of indication (eg, hypertension) using random-effects models. Heterogeneity of the effects was evaluated by the use of the I^2 and Q statistics.[44] Analysis of the percentage of patients who received active therapy was done in 12 study pairs with information on these variables for both phases of each study pair.[12–19,26–36,39,40] Sensitivity analysis was performed by analyzing only studies with data on the percentage of patients who received active therapy, by excluding the smallest 3 studies,[14,15,35,36,39,40] by excluding the 3 studies with low percentage of follow-up in the second phase,[36,38,40] and by performing the analysis 18 times, removing 1 study at a time. Publication bias was examined by constructing funnel plots,[43] by Duval and Tweedie's Trim and Fill,[44] and the fail-safe N models of Rosenthal[45] and Orwin.[46]

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Table 5. Percentage of Participants in the Second Phase

	Percentage in Second Phase			
Study	Active	Control	Overall	References
AIRE	36	39	37	37, 38
ANBP2	100	100	100	8, 9
CCS-1	55	54	55	35, 36
CONSENSUS	100	100	100	14, 15
FAMIS	100	100	100	34
GISSI-3	100	100	100	28, 29
Goteborg	100	100	100	32, 33
HDFP	100	100	100	10, 11
ISIS-4	1	1	1	39, 40
MRFIT	100	100	100	12, 13
SHEP	100	100	100	22, 23
SMILE	100	100	100	16
SOLVD-P	100	100	100	18, 19
SOLVD-T	100	100	100	17
SYST-EUR	81	79	80	24, 25
Timolol	85	84	84	30, 31
TRACE	100	100	100	20, 21
UKPDS-BP	95	95	95	26, 27

AIRE indicates Acute Infarction Ramipril Efficacy; ANBP2, Australian National Blood Pressure 2; SHEP, Systolic Hypertension in the Elderly Program; P, prevention arm; T, treatment arm; SYST-EUR, Systolic Hypertension in Europe; TRACE, Trandolapril Cardiac Evaluation; BP, blood pressure.

Table 6. No. of Patients, No. of Deaths, and Death Rate in the First Phase

	First Phase Active			First Phase Control		
Study	N	Dead, n	Death Rate, %	N	Dead, n	Death Rate, %
AIRE	1014	170	17	992	222	22
ANBP2	3044	195	6	3039	210	7
CCS-1	6814	617	9	6820	654	10
CONSENSUS	127	50	39	126	68	54
FAMIS	131	11	8	134	7	5
GISSI-3	4827	312	6	4828	341	7
Goteborg	698	40	6	697	62	9
HDFP	5458	340	6	5455	421	8
ISIS-4	29 028	2088	7	29 022	2231	8
MRFIT	4019	175	4	3993	171	4
SHEP	2363	212	9	2369	241	10
SMILE	772	50	6	784	65	8
SOLVD-P	2111	313	15	2117	334	16
SOLVD-T	1285	452	35	1284	510	40
SYST-EUR	2398	138	6	2297	148	6
Timolol	945	98	10	939	152	16
TRACE	876	304	35	873	369	42
UKPDS-BP	758	134	18	390	83	21

AIRE indicates Acute Infarction Ramipril Efficacy; ANBP2, Australian National Blood Pressure 2; SHEP, Systolic Hypertension in the Elderly Program; P, prevention arm; T, treatment arm; SYST-EUR, Systolic Hypertension in Europe; TRACE, Trandolapril Cardiac Evaluation; BP, blood pressure.

Results

Description of Trials

The 18 trials included in the analysis are described in Tables 1 and 2. Eleven of the 18 trials pertain to the use of ACEI, 4 to diuretics, and 3 to β-blockers. Seven trials pertained to AMI, 6 to hypertension, and 5 to HF-LVD.

In 132 854 patients, 11 988 deaths occurred during the first phase (average follow-up: 30 months). In 60 558 patients enrolled in the second phase (average follow-up: 41 months), 7249 deaths occurred (Tables 3 through 8). One-hundred percent of the patients who were alive at the end of the first phase were followed in the second phase in 12 of the 18 trials. In 3 instances (ISIS-4, Acute Infarction Ramipril Efficacy, and CCS-1),[36,38,40] investigators reported only on a subset of the patients. We performed sensitivity analysis excluding these 3 studies. In the remaining studies, the percentage of patients followed in the second phase was 81%, 85%, and 95% (Tables 3 through 8).

Use of Active Therapy

During the first phase, 80% (interquartile range: 75% to 83%) of the patients randomized to active therapy actually received it, compared with 16% (interquartile range: 7% to 22%) of those randomized to the control. Thus, as expected, patients randomized to active therapy were ≈5 times as likely to receive it than those randomized to control. After the end of the randomized phase, both groups received active therapy in similar proportions (43% [interquartile range: 20% to 68%] among patients initially randomized to control and 59% [interquartile range: 46% to 77%] among those initially randomized to active therapy; Tables 3 through 8).

All-Cause Mortality

Overall, all-cause mortality was lower in the active intervention groups for the first phase and for the second phase when all of the patients were advised to take active therapy (Figure 2). During the first phase of the trials, there was a statistically significant decrease in all-cause mortality with an odds ratio of 0.84 (95% CI: 0.79 to 0.90; $P<0.0001$). Odds ratio for mortality was <1 in all of the studies except FAMIS and MRFIT. The decrease in mortality was significant for the different indications (OR for the hypertension trials: 0.91 [95% CI: 0.85 to 0.98], $P=0.0108$; for HF-LVD: 0.78 [95% CI: 0.67 to 0.89], $P=0.0002$; for AMI: 0.85 [95% CI: 0.76 to 0.96], $P=0.0083$) and the different classes of medications used (for ACEI: 0.86 [95% CI: 0.80 to 0.93], $P=0.0001$; for β-blockers: 0.67 [95% CI: 0.56 to 0.80], $P<0.0000$; for diuretics: 0.87 [95% CI: 0.78 to 0.97], $P=0.0102$; Figure 3). There was no statistically significant heterogeneity among the groups.

During the second phase, a decrease in overall mortality, similar in magnitude to that seen in the first phase, was observed (OR: 0.85 [95% CI: 0.79 to 0.91]; $P<0.0001$). Odds ratio for mortality was <1 in all of the studies except GISSI-3. The decrease in mortality remained significant

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Table 7. No. of Patients, No. of Deaths, and Death Rate in the Second Phase

	Second Phase Active			Second Phase Control		
Study	N	Dead, n	Death Rate, %	N	Dead, n	Death Rate, %
AIRE	302	83	27	301	117	39
ANBP2	2849	467	16	2829	480	17
CCS-1	3391	404	12	3358	463	14
CONSENSUS	77	39	51	58	32	55
FAMIS	120	8	7	127	12	9
GISSI-3	4515	115	3	4480	107	2
Goteborg	658	92	14	635	120	19
HDFP	5145	334	6	5034	364	7
ISIS-4	334	50	15	362	78	22
MRFIT	3844	142	4	3822	182	5
SHEP	2151	757	35	2128	777	37
SMILE	722	27	4	719	46	6
SOLVD-P	1798	173	10	1783	238	13
SOLVD-T	833	152	18	774	145	19
SYST-EUR	1826	157	9	1691	153	9
Timolol	718	129	18	659	128	19
TRACE	572	88	15	504	83	16
UKPDS-BP	592	239	40	292	128	44

AIRE indicates Acute Infarction Ramipril Efficacy; ANBP2, Australian National Blood Pressure 2; SHEP, Systolic Hypertension in the Elderly Program; P, prevention arm; T, treatment arm; SYST-EUR, Systolic Hypertension in Europe; TRACE, Trandolapril Cardiac Evaluation; BP, blood pressure.

Table 8. No. of Patients, No. of Deaths, and Death Rate in Both Phases Together

	Both Phases Together					
	Active			Control		
Study	N	Dead, n	Dead Rate, %	N	Dead, n	Dead Rate, %
AIRE	1014	253	25	992	339	34
ANBP2	3044	662	22	3039	690	23
CCS-1	6814	1021	15	6820	1117	16
CONSENSUS	127	89	70	126	100	79
FAMIS	131	19	15	134	19	14
GISSI-3	4827	427	9	4828	448	9
Goteborg	698	132	19	697	182	26
HDFP	5485	674	12	5455	785	14
ISIS-4	29 028	2138	7	29 022	2309	8
MRFIT	4019	317	8	3993	353	9
SHEP	2363	969	41	2369	1018	43
SMILE	772	77	10	784	111	14
SOLVD-P	2111	486	23	2117	572	27
SOLVD-T	1285	604	47	1284	655	51
SYST-EUR	2398	295	12	2297	301	13
Timolol	945	227	24	939	280	30
TRACE	876	392	45	873	452	52
UKPDS-BP	758	373	49	390	211	54

AIRE indicates Acute Infarction Ramipril Efficacy; ANBP2, Australian National Blood Pressure 2; SHEP, Systolic Hypertension in the Elderly Program; P, prevention arm; T, treatment arm; SYST-EUR, Systolic Hypertension in Europe; TRACE, Trandolapril Cardiac Evaluation; BP, blood pressure.

during the second phase for all 3 of the indications (OR for hypertension: 0.90 [95% CI: 0.84 to 0.97], $P=0.0037$; for HF-LVD: 0.79 [95% CI: 0.65 to 0.95, $P=0.0140$; for AMI: 0.81 [95% CI: 0.70 to 0.94], $P=0.0051$) and all 3 of the medication classes (OR for ACEI: 0.82 [95% CI: 0.73 to 0.93], $P=0.0014$; for β-blockers: 0.83 [95% CI: 0.70 to 0.97], $P=0.0217$; for diuretics, 0.89 [95% CI: 0.82 to 0.96], $P=0.0045$). Significant heterogeneity among the groups was not observed. A significant decrease in all-cause mortality in the active treatment group was observed when both phases were considered together (OR: 0.85 [95% CI: 0.81 to 0.89]; $P<0.0001$). The OR for mortality was <1 in all of the studies except FAMIS. Results were robust in a series of sensitivity analyses described in the online Data Supplement.

Discussion

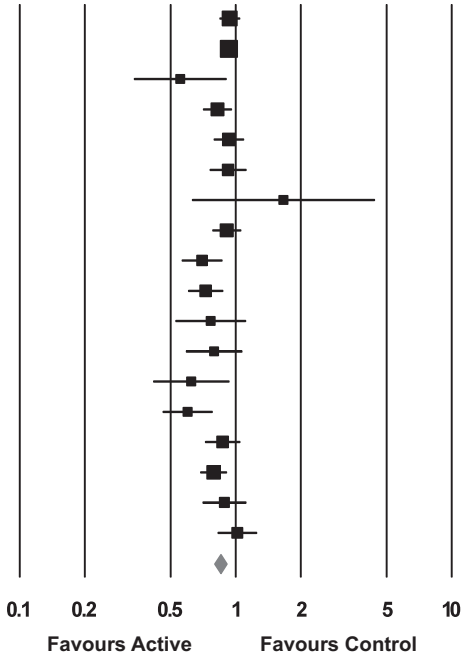
This analysis shows that the benefit of blood pressure–lowering medications persisted after discontinuation of blinded therapy when all of the study patients were advised to take the same therapy. This was not because of differences in the rates of receiving active therapy, because these rates were similar in the randomized groups during open-label follow-up. A substantial carryover effect of interventions has been observed in individual follow-up studies, with the actuarial curves continuing to diverge after discontinuation of blinded therapy (eg, HDFP and MRFIT).[10–13] Although the reasons for the persistent benefit are not well understood, they may be related to several factors. The prevention of nonfatal events, such as stroke or AMI, or decrease of infarction size and attenuation of left ventricular remodeling (eg, with ACEI) during the first phase may result in lower mortality during the longer follow-up. The benefit may be related to earlier time of initiation of active therapy and to prevention or regression of pathological and functional changes caused by hypertension (eg, atherosclerosis, left ventricular hypertrophy, carotid intima-media thickening, and stabilization of coronary plaques).

This analysis has important limitations. The second phases of the studies were not designed prospectively, and 3 follow-up studies report on subsets of patients rather than the entire cohort of patients who were alive at the end of the first phase. However, analysis excluding these trials yields similar odds ratios as when all of the studies were analyzed. Information on the use of active therapy is available for two thirds of the trials. Analyzing only the 12 trials with data on active medication use shows mortality effects of similar magnitude and statistical significance to those obtained when all 18 of the studies were analyzed. In addition, information on background drug therapy and on revascularization that may have affected all-cause mortality is unavailable for the majority of studies. However, it is unlikely that these background interventions would be unevenly distributed in the 2 randomized groups of the studies or more pronounced during the second phase.

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First Phase

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	p-Value
CCS-1	ACE-I	0.94	0.84	1.05	0.2831
ISIS-4	ACE-I	0.93	0.87	0.99	0.0233
CONSENSUS	ACE-I	0.55	0.34	0.91	0.0204
SOLVD-T	ACE-I	0.82	0.70	0.97	0.0174
SOLVD-P	ACE-I	0.93	0.79	1.10	0.3910
ANPP2	ACE-I	0.92	0.75	1.13	0.4304
FAMIS	ACE-I	1.66	0.62	4.43	0.3090
GISSI-3	ACE-I	0.91	0.78	1.07	0.2411
AIRE	ACE-I	0.70	0.56	0.87	0.0016
TRACE	ACE-I	0.73	0.60	0.88	0.0012
SMILE	ACE-I	0.77	0.52	1.12	0.1724
UKPDS-BP	B-BLOCKER	0.79	0.58	1.08	0.1401
GOTEBORG	B-BLOCKER	0.62	0.41	0.94	0.0242
TIMOLOL	B-BLOCKER	0.60	0.46	0.79	0.0002
SHEP	DIURETIC	0.87	0.72	1.06	0.1604
HDFP	DIURETIC	0.79	0.68	0.92	0.0018
SYST-EUR	DIURETIC	0.89	0.70	1.13	0.3245
MRFIT	DIURETIC	1.02	0.82	1.26	0.8744
		0.84	0.79	0.90	0.0000



Second Phase

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	p-Value
CCC-1	AMI	0.85	0.73	0.98	0.0215
ISIS-4	AMI	0.64	0.43	0.95	0.0259
CONSENSUS1	HF-LVD	0.83	0.42	1.65	0.6025
SOLVD-T	HF-LVD	0.97	0.75	1.25	0.8018
SOLVD-P	HF-LVD	0.69	0.56	0.85	0.0005
ANBP2	HTN	0.96	0.83	1.10	0.5609
FAMIS	AMI	0.68	0.27	1.74	0.4252
GISSI-3	AMI	1.07	0.82	1.39	0.6278
AIRE	HF-LVD	0.60	0.42	0.84	0.0031
TRACE	HF-LVD	0.92	0.66	1.28	0.6276
SMILE	AMI	0.57	0.35	0.92	0.0229
UKPDS-BP	HTN	0.87	0.65	1.15	0.3257
GOTEBORG	AMI	0.70	0.52	0.94	0.0173
TIMOLOL	AMI	0.91	0.69	1.19	0.4883
SHEP	HTN	0.94	0.83	1.07	0.3679
HDFP	HTN	0.89	0.76	1.04	0.1403
SYST-EUR	HTN	0.95	0.75	1.19	0.6383
MRFIT	HTN	0.77	0.61	0.96	0.0205
		0.85	0.80	0.91	0.0000

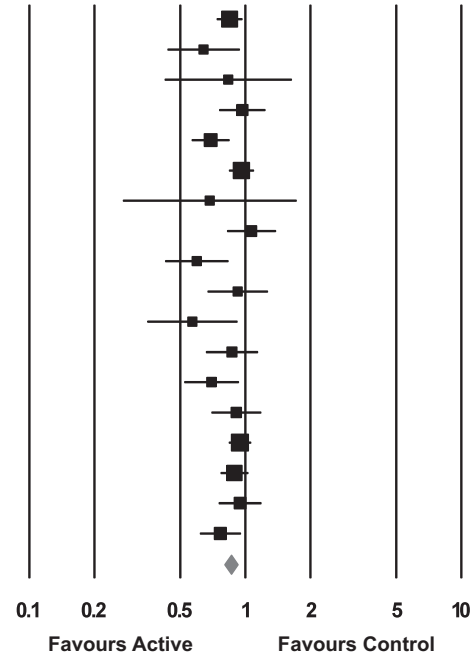


Figure 2. Forest plot for all-cause mortality for the randomized (first) phase (top) and the open-label (second) phase (bottom) of the reviewed studies. Solid squares represent the odds ratios in individual trials and have a size proportional to the inverse of the variance. Horizontal lines, diamonds, and square denote the 95% CIs for individual trials and summary statistics. Pooled estimates were computed from random-effect models. The *P* value for interaction is 0.31 for the first phase and 0.40 for the second phase.

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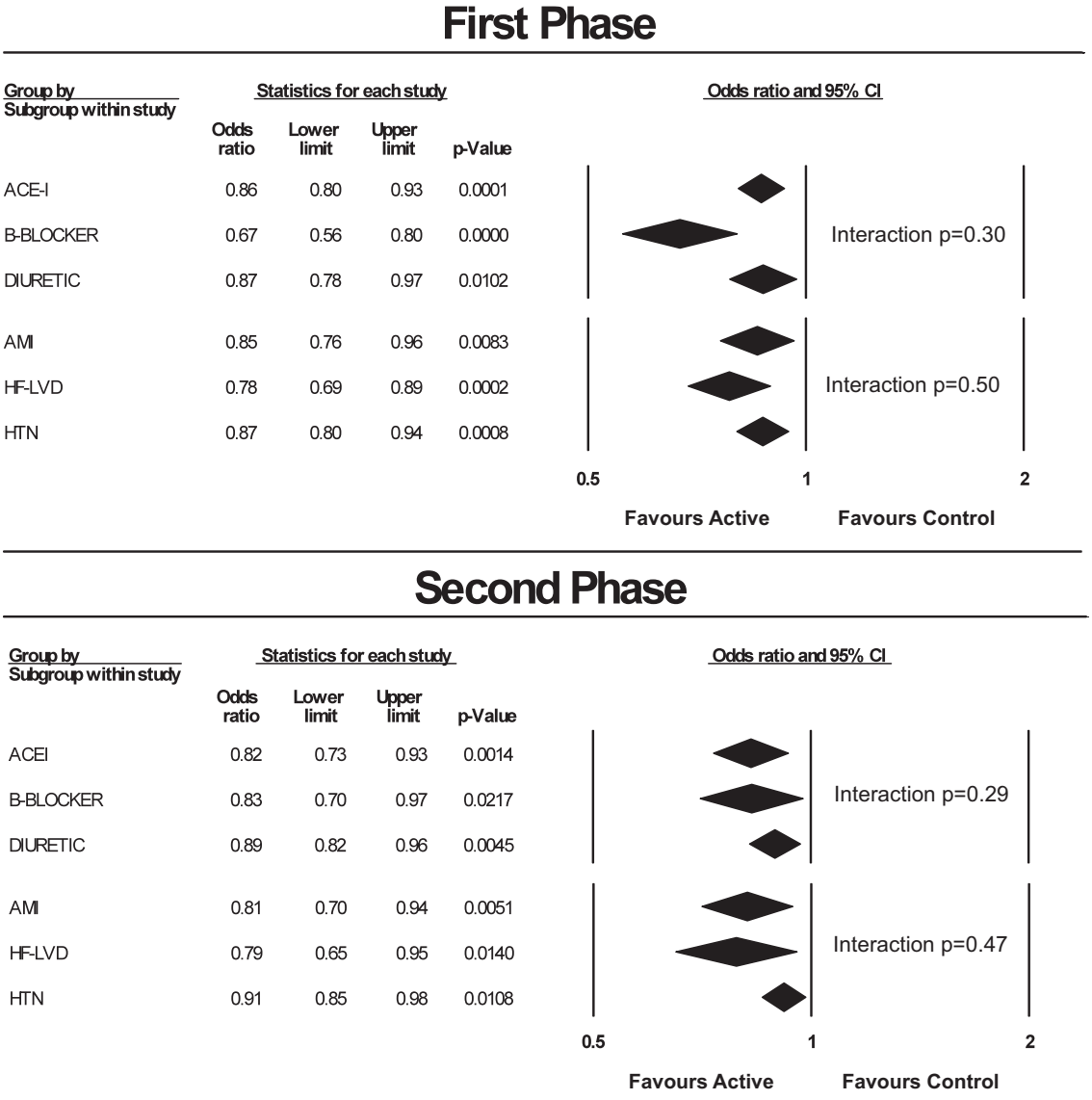


Figure 3. Forest plot for all-cause mortality for the randomized (first) phase (top) and the open-label (second) phase (bottom) by drug class and by indication. HTN indicates hypertension therapy. For further explanation, see Figure 2.

The analysis also has significant strengths. It is unlikely that the findings can be explained by chance because of the magnitude and consistency of the effects across studies, indications, and medication class. Numerous sensitivity analyses indicate the stability of the effects. The high quality of the studies included in the analysis, our efforts to diminish publication bias by extensive searches and personal communication, and the selection of all-cause mortality as the end point lend validity to the results of the meta-analysis.

The findings of this study have important implications. Earlier treatment of hypertension, left ventricular dysfunction, and coronary heart disease may improve clinical outcomes by preventing or retarding atherosclerosis; subclinical changes, such as left ventricular hypertrophy; and clinical events, such as AMIs. Also, the widespread use of blood pressure–lowering medications, as well as statins, has probably changed the epidemiology of hypertension and cardiac disease. These data indicate that long-term follow-up should be included in the design of clinical trials. Information from such trials will elucidate the effects of medications used for the treatment of cardiovascular disease and the outcome of treated patients in the long term. In addition, these studies will help healthcare workers and guideline writers decide on the advisability of early initiation of specific therapies.

The analyses reported here indicate a persistent benefit of blood pressure–lowering medications on mortality after the end of clinical trials and imply that earlier intervention would result in better clinical outcomes.[25,47]

Perspectives

This study highlights the continuing benefit of blood pressure–lowering medications after discontinuation of the randomized phase of clinical trials when patients in both the active intervention and control groups receive active therapy. The findings were consistent across indications for which the medications were given and across medication class (ACEI,

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β-blockers, and diuretics) and remained robust in several sensitivity analyses. The mechanisms underlying the persistent benefit may be related to prevention of nonfatal events, for example, myocardial infarction, or to prevention or regression of atherosclerosis and subclinical pathological or physiological cardiovascular abnormalities resulting in lower mortality at a later time. The data imply that earlier initiation of therapy will result in significant clinical benefits.

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Disclosures

None.

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PERSISTENCE OF MORTALITY REDUCTION AFTER THE END OF RANDOMIZED THERAPY IN CLINICAL TRIALS OF BLOOD PRESSURE LOWERING MEDICATIONS

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Table S1. Search Strategy
database: ovid medline(r) <1950 to june week 3 2010>
search strategy:

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7 indapamide.tw. (856)
8 minoxidil.tw. (1260)
9 exp angiotensin converting enzyme inhibitors/ (36044)
10 captopril.tw. (9980)
11 enalapril.tw. (5146)
12 cilazapril.tw. (527)
13 enalaprilat.tw. (923)
14 fosinopril.tw. (399)
15 lisinopril.tw. (1779)
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35 nicardipine.tw. (3132)
36 nifedipine.tw. (16731)
37 nimodipine.tw. (3001)
38 nisoldipine.tw. (945)
39 nitrendipine.tw. (2586)
40 verapamil.tw. (18785)
41 exp adrenergic beta-antagonists/ (71535)
42 alprenolol.tw. (912)

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45 bisoprolol.tw. (779)
46 metoprolol.tw. (4984)
47 nadolol.tw. (955)
48 oxprenolol.tw. (952)
49 pindolol.tw. (2544)
50 propranolol.tw. (27872)
51 exp adrenergic alpha-antagonists/ (43493)
52 labetalol.tw. (1626)
53 prazosin.tw. (9476)
54 beta block$.tw. (24316)
55 exp diuretics/ (62857)
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57 triamterene.tw. (825)
58 bumetanide.tw. (2493)
59 furosemide.tw. (9138)
60 or/1-59 (379482)
61 exp renal dialysis/ (79489)
62 exp kidney failure, chronic/ (66768)
63 61 or 62 (114139)
64 exp clinical trial/ (614940)
65 exp random allocation/ (68835)
66 exp single blind method/ (14102)
67 exp double blind method/ (107130)
68 (random$ adj5 trial$).tw. (130634)
69 (random$ adj5 allocation$).tw. (1606)
70 (blind$ adj5 method$).tw. (10462)
71 or/64-70 (727942)
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78 stroke.tw. (98509)
79 heart failure.tw. (77109)
80 cerebrovascular.tw. (29390)
81 or/72-80 (1985555)
82 60 and 63 and 71 and 81 (469)
83 (60 and 71 and 81) not 63 (26195)
84 limit 83 to randomized controlled trial (13719)
85 limit 84 to humans (13651)
86 limit 85 to "all adult (19 plus years)" (12237)
87 drug therapy.mp. or drug therapy/ (168408)

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88	86 and 87 (2197)		
89	from 88 keep 1-2197		
cochrane database			
#1	mesh descriptor antihypertensive agents explode all trees	20259	
#2	(antihypertensive* next (agent* or drug))	7237	
#3	chlorothiazide		133
#4	chlorthalidone		509
#5	hydralazine		493
#6	hydrochlorothiazide	2426	
#7	indapamide		329
#8	minoxidil		183
#9	mesh descriptor angiotensin-converting enzyme inhibitors explode all trees		5215
#10	captopril		2140
#11	enalapril		2296
#12	cilazapril		257
#13	enalaprilat		155
#14	fosinopril		223
#15	lisinopril		820
#16	perindopril		557
#17	ramipril		680
#18	saralasin		23
#19	teprotide		5
#20	mesh descriptor losartan explode all trees		743
#21	losartan		1110
#22	imidazole		231
#23	irbesartan		354
#24	candesartan		520
#25	eprosartan		109
#26	valsartan		504
#27	olmesartan		92
#28	telmisartan		281
#29	(ace near/2 inhibitor*)		2537
#30	(angiotensin near/2 receptor antagonist*)		1064
#31	mesh descriptor calcium channel blockers explode all trees	6835	
#32	amlodipine		1250
#33	diltiazem		1426
#34	felodipine		615
#35	nicardipine		601
#36	nifedipine		3196
#37	nimodipine		575
#38	nisoldipine		275
#39	nitrendipine		557
#40	verapamil		1777
#41	mesh descriptor adrenergic beta-antagonists explode all trees		8902
#42	alprenolol		163

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#43	atenolol		2666
#44	carvedilol		612
#45	bisoprolol		460
#46	metoprolol		2241
#47	nadolol		341
#48	oxprenolol		394
#49	pindolol		848
#50	propranolol		4139
#51	mesh descriptor adrenergic alpha-antagonists explode all trees	2651	
#52	labetalol		555
#53	prazosin		772
#54	beta block		3094
#55	mesh descriptor diuretics explode all trees		4857
#56	spironolactone		746
#57	triamterene		252
#58	bumetanide		160
#59	furosemide		1515
#60	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59)		39107
#61	mesh descriptor renal dialysis, this term only	2989	
#62	mesh descriptor kidney failure, chronic, this term only	2851	
#63	(#61 or #62)		4428
#64	mesh descriptor cardiovascular diseases, this term only		3231
#65	mesh descriptor mortality, this term only	349	
#66	mesh descriptor myocardial infarction, this term only	7182	
#67	mesh descriptor stroke, this term only	2884	
#68	mesh descriptor heart failure, this term only	4335	
#69	mesh descriptor cerebrovascular disorders, this term only	1399	
#70	(#64 or #65 or #66 or #67 or #68 or #69)	18020	
#71	((#60 and #70) and not #63)		3918
#72	randomized		365521
#73	(#71 and #72)		3345
#74	adults		264869
#75	(#73 and #74)		946

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embase

s1	33318	antihypertensive agent
s2	2578	chlorothiazide
s3	862	chlorthalidone
s4	14440	hydralazine
s5	17523	hydrochlorothiazide
s6	2893	indapamide
s7	4528	minoxidil
s8	12403	losartan
s9	22670	imidazole
s10	3522	irbesartan
s11	4915	candesartan
s12	991	eprosartan
s13	4553	valsartan
s14	935	olmesartan
s15	2051	telmisartan
s16	57585	dipeptidyl carboxypeptidase inhibitor
s17	26587	captopril
s18	17990	enalapril
s19	2126	fosinopril
s20	8548	lisinopril
s21	4526	perindopril
s22	7351	ramipril
s23	2933	saralasin
s24	857	teprotide
s25	4857	angiotensin 2 receptor antagonist
s26	11769	angiotensin receptor antagonist
s27	1282	angiotensin ii antagonist
s28	31029	calcium channel blocking agent
s29	10230	amlodipine
s30	21166	diltiazem
s31	4174	felodipine
s32	7192	nicardipine
s33	37270	nifedipine
s34	6685	nimodipine
s35	2562	nisoldipine
s36	5671	nitrendipine
s37	41044	verapamil
s38	67068	beta adrenergic receptor blocking agent
s39	4323	alprenolol
s40	21039	atenolol
s41	6141	carvedilol

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s42 4051 bisoprolol
s43 20851 metoprolol
s44 4062 nadolol
s45 4915 oxprenolol
s46 9249 pindolol
s47 73903 propranolol
s48 9621 alpha adrenergic receptor blocking agent
s49 6784 labetalol
s50 20191 prazosin
s51 12761 diuretics
s52 16130 spironolactone
s53 4633 triamterene
s54 4568 bumetanide
s55 36405 furosemide
s56 3178 hypocholesterolemic agent
s57 1468 fibrates
s58 2080 niacin
s59 10179 nicotinic acid
s60 2741 lovastatin
s61 10974 pravastatin
s62 15561 simvastatin
s63 1213 fluvastatin
s64 12182 atorvastatin
s65 2807 rosuvastatin
s66 2448 ezetimibe
s67 2008 cholestyramine
s68 2338 colestipol
s69 357 colesevelam
s70 7618 clofibrate
s71 5727 gemfibrozil
s72 4655 fenofibrate
s73 10696 antidiabetic agent
s74 4959 sulfonylurea derivative
s75 2054 thiazolidinediones
s76 273299 insulin
s77 15056 metformin
s78 4339 chlorpropamide
s79 3103 glipizide
s80 1133 glyburide
s81 2142 glimepiride
s82 1645 repaglinide
s83 1339 nateglinide
s84 7561 rosiglitazone
s85 4729 troglitazone
s86 758 sitagliptin
s87 3628 acarbose

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6893014 clinical
669488 trial
s88 641058 clinical and trial
265690 randomized
3075060 controlled
669488 trial
s89 198780 randomized and controlled and trial
95161 random
18034 allocation
s90 1131 random and allocation
s91 8165 single blind procedure
s92 74910 double blind procedure
s93 76665 cardiovascular disease
s94 366363 mortality
s95 99602 heart infarction
s96 114658 stroke
s97 66191 ischemic heart disease
s98 63997 heart failure
s99 292765 s1:s45
s100 477314 s46:s87
292765 s99
477314 s100
s101 683841 s99 or s100
s102 652086 s88:s92
s103 668754 s93:s98
683841 s101
652086 s102
668754 s103
s104 30974 s101 and s102 and s103
s105 1823270 drug therapy
30974 s104
1823270 s105
s106 28725 s104 and s105
s107 285110 follow up
s108 105500 extended
285110 s107
105500 s108
s109 3594 s107 and s108
s110 649505 long
s111 502691 term
649505 s110
502691 s111
s112 364983 s110 and s111
364983 s112
285110 s107
s113 47864 s112 and s107

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3594 s109
47864 s113
s114 50596 s109 or s113
28725 s106
50596 s114
s115 586 s106 and s114
586 s115
366363 s94
s116 385 s115 and s94

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Table S2. Evaluation of the Quality of the Reports Included in the Meta-analysis

	Randomized (First) Phase				
Study	Randomization	Allocation concealment	Similarity of baseline characteristics	Defined eligibility	Placebo
AIRE	Yes	Yes	Yes	Yes	Yes
ANPP2	Yes	No	Yes	Yes	No
CCC-1	Yes	Yes	Yes	Yes	Yes
CONSENSUS	Yes	Yes	Yes	Yes	Yes
FAMIS	Yes	Yes	Yes	Yes	Yes
GISSI-3	Yes	No	Yes	Yes	Yes
GOTEBORG	Yes	No	Yes	Yes	Yes
HDFP	Yes	No	Yes	Yes	Yes
ISIS-4	Yes	No	Yes	Yes	Yes
MRFIT	Yes	No	Yes	Yes	No
SHEP	Yes	Yes	Yes	Yes	Yes
SMILE	Yes	Yes	Yes	Yes	Yes
SOLVD-P	Yes	Yes	Yes	Yes	Yes
SOLVD-T	Yes	Yes	Yes	Yes	Yes
SYST-EUR	Yes	Yes	Yes	Yes	Yes
TIMOLOL	Yes	Yes	Yes	Yes	Yes
TRACE	Yes	Yes	Yes	Yes	Yes
UKPDS-BP	Yes	No	Yes	Yes	No

Table S2. continued

	Randomized (First) Phase					
Study	Blind patients	Blind Investigators	Blind vital status	% lost to follow-up	ITT assessment	Jadad score
AIRE	Yes	Yes	Yes	0.05	Yes	5
ANPP2	No	No	Yes	2.71	Yes	4
CCC-1	Yes	Yes	Yes		Yes	4
CONSENSUS	Yes	Yes	Yes	0	Yes	5
FAMIS	Yes	Yes	Yes	0	Yes	4
GISSI-3	No	No	Yes	2.6	Yes	4
GOTEBORG	Yes	Yes	Yes	0	Yes	5

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HDFP	Yes	Yes	Yes	0.5	Yes	5
ISIS-4	Yes	Yes	Yes	3.0	Yes	4
MRFIT	No	No	Yes	0.23	Yes	4
SHEP	Yes	Yes	Yes	0.13	Yes	5
SMILE	Yes	Yes	Yes	0.1	Yes	5
SOLVD-P	Yes	Yes	Yes	0.11	Yes	5
SOLVD-T	Yes	Yes	Yes	0.08	Yes	5
SYST-EUR	Yes	Yes	Yes	5.05	Yes	5
TIMOLOL	Yes	Yes	Yes	0	Yes	5
TRACE	Yes	Yes	Yes	0	Yes	5
UKPDS-BP	No	No	Yes	1.22	Yes	3

Table S2. continued

	Open (Second) Phase		
Study	% lost to follow-up	Adherence data	References
AIRE	0	No	37, 38
ANPP2	0	No	8, 9
CCC-1	15.64	Yes	35, 36
CONSENSUS	0	Yes	14, 15
FAMIS	2.81	Yes	34
GISSI-3	3.67	Yes	28, 29
GOTEBORG	0	Yes	32, 33
HDFP	0.95	No	10, 11
ISIS-4	15.12	Yes	39, 40
MRFIT	0	Yes	12, 13
SHEP	0	No	22, 23
SMILE	0	Yes	16
SOLVD-P	0	Yes	18, 19
SOLVD-T	0	Yes	17
SYST-EUR	2.13	No	24, 25
TIMOLOL	0	Yes	30, 31
TRACE	0	No	20, 21
UKPDS-BP	1.02	Yes	26, 27

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Sensitivity Analysis and Estimation of Publication Bias

The overall conclusions of the paper and the ORs for mortality were not different when only studies with data on the percentage of patients who received active therapy were included, when the three studies with low percentage of follow up in the second phase[1-3] were excluded, as well as when the analysis included only the 15 larger studies. The ORs for mortality during the first phase were 0.86 (95% CI 0.80–0.94; p=0.0005) for the 12 studies with data on the percentage of patients who received active therapy and 0.83 (95% CI 0.77–0.89, p<0.0001) for the 15 larger studies. During the second phase the ORs were 0.81 (95% CI 0.74–0.89, p<0.0001) for the studies with data on the percentage of patients who received active therapy and 0.85, 95% CI 0.79–0.93, p<0.0001 for the 15 larger studies. When the three studies with low percentage of follow up in the second phase[1-3] were excluded the OR was 0.83, 95% CI 0.77–0.90, p<0.0001 for the first phase and 0.87, 95% CI 0.81-0.93 for the second phase. Also, similar odds ratios were observed when the analysis was repeated 18 times by removing one study at a time with ORs ranging from 0.83 (95% CI 0.78–0.89, p<0.0001) to 0.86 (95% CI 0.81–0.91; p<0.0001) for the first phase and from 0.84 (95% CI 0.78–0.90, p<0.0001) to 0.86 (95% CI 0.81–0.93; p<0.0001) for the second phase. Consistent trends by the age of participants were not observed. For studies with average age below 60, the OR was 0.87, 95% CI 0.80-0.96; for those in the 60-64 age group 0.86, 95% CI 0.79-0.94; for those between 65 and 69 0.62, 95% CI 0.41-0.94; and for those 70 or above 0.87, 95% CI 0.77-0.98. Also, meta-regression of log OR for mortality versus age did not reveal a significant trend (p=0.6460).

Publication bias was assessed by funnel plots and the Duval and Tweedie Trim and Fill method. The effects of medications in lowering mortality remained significant, OR 0.85, 95% CI 0.79–0.91, (including one imputed trial) for the first phase and for the second phase 0.87 (95% CI 0.81–0.94) with four imputed studies.[4] For the first phase Rosenthal's fail-safe N indicates that 223 missing studies would be needed to bring the p-value of the effect to greater than 0.05 for the first phase and 140 for the second phase.[5] Orwin's fail-safe N needed to bring the odds ratio to 0.95 is 28 for the first phase and 32 for the second phase.[6]

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