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SYSTEMATIC REVIEW AND META-ANALYSIS

Is Blood Pressure Lowering in the Very Elderly With Previous Stroke Associated With a Higher Risk of Adverse Events?

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BACKGROUND: We investigated whether blood pressure lowering for secondary prevention is associated with a reduction in recurrent stroke risk and/or a higher risk of adverse events in very elderly compared with younger trial participants.

METHODS AND RESULTS: This is a random effects meta-analysis of randomized controlled trials of blood pressure lowering for secondary stroke prevention to evaluate age-stratified (<80, ≥80 years) risk of adverse events. Ovid-MEDLINE was searched for trials between 1970 and 2020. Summary-level data were acquired including outcomes of stroke, cardiovascular events, mortality, and adverse events. Seven trials were included comprising 38 596 participants, of whom 2336 (6.1%) were aged ≥80 years. There was an overall reduction in stroke risk in the intervention group compared with controls (risk ratio [RR], 0.90 [95% CI, 0.80, 0.98], I^2=49%), and the magnitude of risk reduction did not differ by age subgroup (<80, ≥80 years). There was no increase in the risk of hypotensive symptoms in the intervention group for patients aged <80 years (RR, 1.19 [95% CI, 0.99], 1.44, I^2=0%), but there was an increased risk in those ≥80 years (RR, 2.17 [95% CI, 1.22], 3.86, I^2=0%). No increase was observed in the risk of falls, syncope, study withdrawal, or falls in either age subgroup.

CONCLUSIONS: Very elderly people in secondary prevention trials of blood pressure lowering have an increased risk of hypotensive symptoms, but with no statistical increase in the risk of falls, syncope, or mortality. However, evidence is lacking for frail elderly with multiple comorbidities who may be more vulnerable to adverse effects of blood pressure lowering.

Key Words: blood pressure ■ elderly ■ hypertension ■ secondary prevention ■ stroke

Hypertension is the most important modifiable risk factor for stroke, and its treatment is effective for stroke prevention.[1] Physicians are often reluctant to aggressively lower blood pressure (BP) in the elderly for fear of adverse effects such as falls and syncope.[2–4] This concern is also reflected in guidelines such as the 2017 American Heart Association guidelines, which recommend a cautious approach to BP control in frail very elderly adults.[5] The European Society of Hypertension and European Society of Cardiology 2018 guidelines recommend individualized targets for such people, based on the individual's functional status rather than age alone.[6] Similarly, the 2019 NICE (National Institute of Health and Care Excellence)

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CLINICAL PERSPECTIVE

What Is New?

- In this meta-analysis of trials, there was an increased risk of hypotensive symptoms in people aged ≥80 years receiving blood pressure lowering therapy for secondary stroke prevention.
- There was no observed increase in the risk of falls, syncope, or mortality, but methodological variation and sample sizes prevented definitive conclusions for these outcomes.

What Are the Clinical Implications?

- A modest degree of blood pressure lowering may not increase the risk of falls, syncope, or mortality in relatively robust elderly people.
- Evidence is still lacking for frail elderly who may be more vulnerable to adverse effects of blood pressure lowering.

guidelines recommend targeting BP <150/90 mm Hg in those age >80 years, and individualized decision making for those with frailty or multimorbidity.[7] Indeed, observational evidence has demonstrated that older people in general may be at higher risk of adverse outcomes related to BP lowering,[8–10] including falls[11] and mortality.[9] This may be because of age-related physiological changes such as arterial stiffening and reduced baroreceptor reflexes, which are not present in younger people.[12]

Elderly persons with previous stroke who are likely to have poor vascular health, additional comorbidities, or frailty,[13] might be particularly vulnerable to adverse effects from BP lowering. Recent results from SPRINT (Systolic Blood Pressure Intervention Trial) in primary prevention indicate that aggressive BP lowering may be safe in the elderly; however, those with previous stroke were excluded.[14] Some trials of secondary stroke prevention included subgroup analyses of efficacy and safety of BP lowering in older participants defined with a cutoff of 65 years, and hence their findings may not be generalizable to very elderly.[15,16] Furthermore, in other subgroup analyses, BP relevant adverse events such as falls were not measured.[14,17] In 1 trial, intensive BP lowering (target systolic BP <130 mm Hg compared with 130–149 mm Hg) was associated with a higher risk of unsteadiness on standing, but not with other adverse events.[16] Therefore, there is uncertainty regarding the safety and efficacy for BP reduction for secondary stroke prevention in the very elderly.

We aimed to conduct an aggregate data meta-analysis of randomized controlled trials to determine whether BP lowering for secondary stroke prevention in the very elderly (≥80 years) results in a lower stroke risk and/or a higher risk of adverse events than for those younger than 80 years. This age cutoff was chosen because the prevalence of frailty increases markedly after 80 years of age.[18] We hypothesized that, in those undergoing BP lowering for secondary stroke prevention, age (<80, ≥80 years) will modify the effect of BP lowering on the risk of further stroke and a range of adverse events relevant to BP reduction.

METHODS

Data supporting the findings of this study are available from the corresponding author upon reasonable request. This systematic review and meta-analysis of subgroups was planned and conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[19] and the recommendations of the Cochrane Collaboration.

Study Selection: Inclusion Criteria

Randomized controlled trials of BP lowering that enrolled people with prior cerebrovascular disease were eligible for inclusion. To be considered as trials of BP lowering, they had to examine an intervention that was one of: antihypertensive agent (single or multiple) compared with either placebo or an alternative regimen. For trials in which not all participants had pre-existing cerebrovascular disease, only the subgroup of patients with known cerebrovascular disease was included in the meta-analysis.

Exclusion Criteria

Studies were excluded if the achieved BP in the intervention group was not lower than in the control group or if they did not include participants ≥80 years.

Search Strategy

We developed a search strategy using MEDLINE (January 1970–September 2020). We utilized the following terms: (exp Stroke or stroke*.tw) AND (Blood pressure/ or exp Hypertension/ or (blood pressure or hypertension).tw) AND (exp aged/ or "aged, 80 and over"/ or elderly.tw), limited to randomized controlled trials as per the Cochrane Handbook.

Outcomes

The primary outcomes were the following: fatal and nonfatal stroke, hypotensive symptoms, falls, syncope, and serious adverse events. Secondary outcomes included the following: electrolyte abnormalities, acute kidney injury, study withdrawal, hospitalization for heart failure, fatal and nonfatal myocardial infarction, and all-cause death. The definitions of outcomes sometimes

differed between studies and these are listed in full in Table S1.

If the outcomes of interest were not reported in the published data, study investigators were contacted to provide summary data relevant to the aims. Three attempts were made to establish contact and obtain data, and those who confirmed availability of data were sent a standardized template to provide meta-data.

Statistical Analysis

Published and unpublished summary data provided by study authors were pooled and the findings of individual studies were integrated via meta-analysis, using the DerSimonian and Laird procedure. Random effects models were fit to allow for heterogeneity in underlying risk between trials. Meta-analyses were performed using Revman software (Version 5). Heterogeneity was further evaluated using the I^2 statistic. Pooled risk ratios were generated with 95% CIs and α=0.05 was used to define statistical significance. To assess risk of bias, participating study characteristics (including date conducted, sample size, mean follow-up duration, and primary outcome) were compared with nonparticipating studies. We also investigated risk of publication bias via a funnel plot. Risk of bias because of missing outcome data was assessed as low risk because in all cases, where outcomes were collected within a trial, data were provided for all randomized participants.

The second and third authors independently completed the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) template for each included trial.[20] Meta-regression was performed to explore the possibility that the extent of BP lowering within trials, as well as within age groups, was associated with the risk of stroke and/or relevant BP-related adverse effects. The results of these meta-regressions were used to guide analyses of interactions between age groups (<80, ≥80 years) and extent of BP lowering as required. Meta-regression was performed using the *metareg* procedure in Stata (version 16.0, StataCorp, College Station, TX). We performed a leave-one-out sensitivity analysis by repeating analysis for the stroke/nonfatal stroke outcome, each time leaving out 1 of the 4 largest included studies (for this outcome), to determine the extent to which results depend on the inclusion of these large studies.

RESULTS

The search yielded 3533 results, including 2914 nonduplicate citations to be screened using the inclusion and exclusion criteria. Of these, 2892 articles were excluded, leaving 22 articles for full text review from which 5 articles were subsequently excluded. Reasons for exclusion at this stage were if studies did not include participants >80 years or those with previous stroke. Of the 17 trial authors who were approached for data, 7 responded and were able to provide data. Of the 7 trials, 4 were conducted only in people with prior cerebrovascular disease: Dutch-TIA (Dutch Transient Ischaemic Attack trial),[21] PROGRESS (Perindopril Progress Against Recurrent Stroke trial),[22] PRoFESS (Prevention Regimen for Effectively avoiding Secondary Stroke trial),[23] and SPS3 (Secondary Prevention of Small Subcortical Strokes trial).[24] The remaining 3 trials did not exclusively comprise participants with known cerebrovascular disease but had subgroup data available for people with cerebrovascular disease: ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial),[25] TRANSCEND (Telmisartan Randomized Assessment Study of ACE Intolerant Subjects with Cardiovascular Disease trial),[26] and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial)[27] (Figure S1). Comparison between the participating trials and the trials for which we received no response (nonparticipating) are shown in Table.[17,28–36] Some of the trials had not collected data pertaining to all the outcomes of interest. Table S1 shows available data for the outcomes of interest, and outcomes not measured. The definition of the outcomes varied between trials; outcome definitions and trial characteristics can also be found in Table S1.

Our analysis using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) indicated that there was a low risk of bias across these trials. However, SPS3 was open-label because of the use of BP targets and was the only trial that was not double blinded.

Sample Characteristics

We received sample characteristic data in age subgroups (<80 years, ≥80 years) from all 7 trial investigators (Tables S2 and S3). Summary data were made available on a total of 38 596 participants, of whom 2336 were aged ≥80 years. The mean achieved BP difference between intervention and control groups across all trials was 5.6 mm Hg systolic and 2.8 mm Hg diastolic (BP data at the end of follow-up was not available for DUTCH-TIA). The extent of BP reduction across trials ranged from 2.4 to 12 mm Hg systolic and 0.8 to 5 mm Hg diastolic. The lowest degree of BP lowering was seen in ADVANCE (2.4 mm Hg systolic and 0.8 mm Hg diastolic at study follow-up) and the highest was in PROGRESS (9 mm Hg systolic and 4 mm Hg diastolic at study follow-up, Tables S4 and S5). The mean average duration of follow-up was 3.8 years (range, 2.5–4.7 years) across the trials. These data,

Table 1. Comparison of Participating and Nonparticipating Trials*

Trial	Year	Type of intervention	Sample size, No.	Mean follow-up, y	Primary outcome HR	Mean age, y (SD)	Female sex, %	Achieved reduction in SBP, mm Hg (SE)†
Participating trials								
Dutch-TIA[21]	1993	Atenolol/placebo	1473	2.6	1.00	64.2 (10.2)	35	NA
PROGRESS[22]	2001	Perindopril±indapamide / placebo	6105	3.9	0.73	64 (10)	30	9 (0.3)
ADVANCE[27‡]	2007	Perindopril+indapamide/placebo	11 140	4.3	0.91	66 (6)	43	5.6 (0.2)
TRANSCEND[26‡]	2008	Telmisartan/placebo	5926	4.7	0.92	67 (7.5)	39	4.0 (19.8)
PROFESS[23]	2008	Telmisartan/placebo	20 332	2.5	0.95	66.1 (8.6)	36	3.8 (0.1)
ONTARGET[25‡]	2008	Ramipril+telmisartan/ramipril/ telmisartan	25 620	4.7	0.99	66.4 (7.2)	27	2.4 (NA)
SPS3[24]	2013	SBP <130/SBP 130–149 mm Hg target	3020	3.7	0.81	63 (10.7)	37	11 (0.02)
Nonparticipating trials								
HSCS[28]	1974	Deserpine+methlyclothiazide/ placebo	452	3	ND	59 (NA)	40	NA
STOP-Hypertension[29‡]	1991	Atenolol+hydrochlorothiazide± amiloride±metoprolol±pindolol/ placebo	1627	2.1	0.60§	75.7 (3.7)	63	19.5
SHEP[30‡]	1991	Chlorthalidone±atenolol/placebo	4736	4.5	0.64	71.6 (6.7)	57	11.1
PATS[31]	1995	Indapamide/placebo	5665	2	0.78	60.1 (8.3)	28	6.8
TEST[32]	1995	Atenolol/placebo	720	N/A	0.79§	70.1 (8.6)	40	4
HOPE[33‡]	2002	Ramipril/placebo	9297	5	0.78§	66 (7)	27	3.1
SCOPE[34‡]	2003	Candesartan/placebo	4964	3.7	0.89§	76.4 (NA)	64	3.2
HYVET[17‡]	2008	Indapamide±perindopril/placebo	3845	1.8	0.70	83.6 (3.2)	60	15
JATOS[35‡]	2008	Efonidipine/control (open-label)	4418	2	1.00	73.6 (5.3)	61	9.3
VALISH[36‡]	2009	SBP <140/SBP 140–149 mm Hg target	3079	3.1	0.89	76.1	62	5.4

ADVANCE indicates Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial; Dutch-TIA, Dutch Transient Ischaemic Attack trial; HOPE, Heart Outcomes Prevention Evaluation; HR, hazard ratio; HSCS, Hypertension-Stroke Cooperative Study; HYVET, The Hypertension in the Very Elderly Trial; JATOS, The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; NA, not available; ND, no significant difference; ONTARGET, Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; PATS, Post-Stroke Antihypertensive Treatment Study; PROFESS, Prevention Regimen for Effectively avoiding Secondary Stroke trial; PROGRESS, Perindopril Progress Against Recurrent Stroke trial; SCOPE, The Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; SBP, systolic blood pressure; STOP, hypertension: Swedish Trial in Old Patients with Hypertension; TEST, Tenormin after Stroke and TIA; TRANSCEND, Telmisartan Randomized Assessment Study of ACE Intolerant Subjects with Cardiovascular Disease trial; and VALISH, The Valsartan in Elderly Isolated Systolic Hypertension Study.

*Nonparticipating trials comprise trials whose authors were contacted, but from whom we did not receive a response.

†Difference in SBP reduction-active vs control at last follow-up, SE given for included trials only.

‡Denotes trials that also included participants without known cerebrovascular disease.

§Relative risk.

in addition to hazard ratios for each study and the type of intervention, are shown in Table.

Fatal and Nonfatal Stroke

For the whole sample (including participants of all ages) there was a statistically significant risk reduction for fatal and nonfatal stroke in the intervention group compared with controls (risk ratio [RR], 0.90 [95% CI, 0.80, 0.98], I^2=49%). In the age-based subgroup analysis (Figure 1),[21] there was a statistically significant 11% risk reduction for stroke in the intervention group compared with controls among those aged <80 years (RR, 0.89 [95% CI, 0.80, 0.98], I^2=41%), and a 9% reduction for the intervention group among those aged ≥80 years, which did not reach statistical significance (RR, 0.91 [95% CI, 0.73, 1.14], I^2=0%).

Hypotensive Symptoms

For the whole sample, there was a 27% increased risk of hypotensive symptoms in the intervention group (RR, 1.27 [95% CI, 1.07, 1.52], I^2=0%). For the age-based subgroup analysis, there was no increase in this risk among those aged <80 years (RR, 1.19 [95% CI, 0.99, 1.44], I^2=0%), but a more than 2-fold increase in risk in the intervention group (RR, 2.17 [95% CI, 1.22, 3.86], I^2=0%) among those aged ≥80 years (Figure 2).

Falls, Serious Adverse Events, and Study Withdrawal

There was no increase in the risk of falls (RR, 0.93 [95% CI, 0.74, 1.16], I^2=16%) (Figure 3), serious adverse events (RR, 1.03 [95% CI, 0.96, 1.10], I^2=72%), or study withdrawal (RR, 1.03 [95% CI, 0.94, 1.13], I^2=75%), in the intervention group in the whole sample, with similar findings in both age subgroups.

Syncope

There was a 29% increased risk of syncope in the intervention group in the whole sample that was statistically significant (RR, 1.29 [95% CI, 1.02, 1.63], I^2=0%) (Figure 4). There was a 29% higher risk of syncope in those <80 years (RR, 1.29 [95% CI, 1.00, 1.65]), but no significant effect of the intervention in those ≥80 years (RR, 1.17 [95% CI, 0.49, 2.81]).

Electrolyte Abnormalities, Renal Impairment

There was a 78% increased risk of electrolyte abnormalities (RR, 1.78 [95% CI, 1.00, 3.17], I^2=0%) in the whole sample, but no difference in renal impairment (RR, 1.04 [95% CI, 0.72, 1.49], I^2=60%) in the intervention group compared with controls. However, only 2 trials provided data for these outcomes. No differences

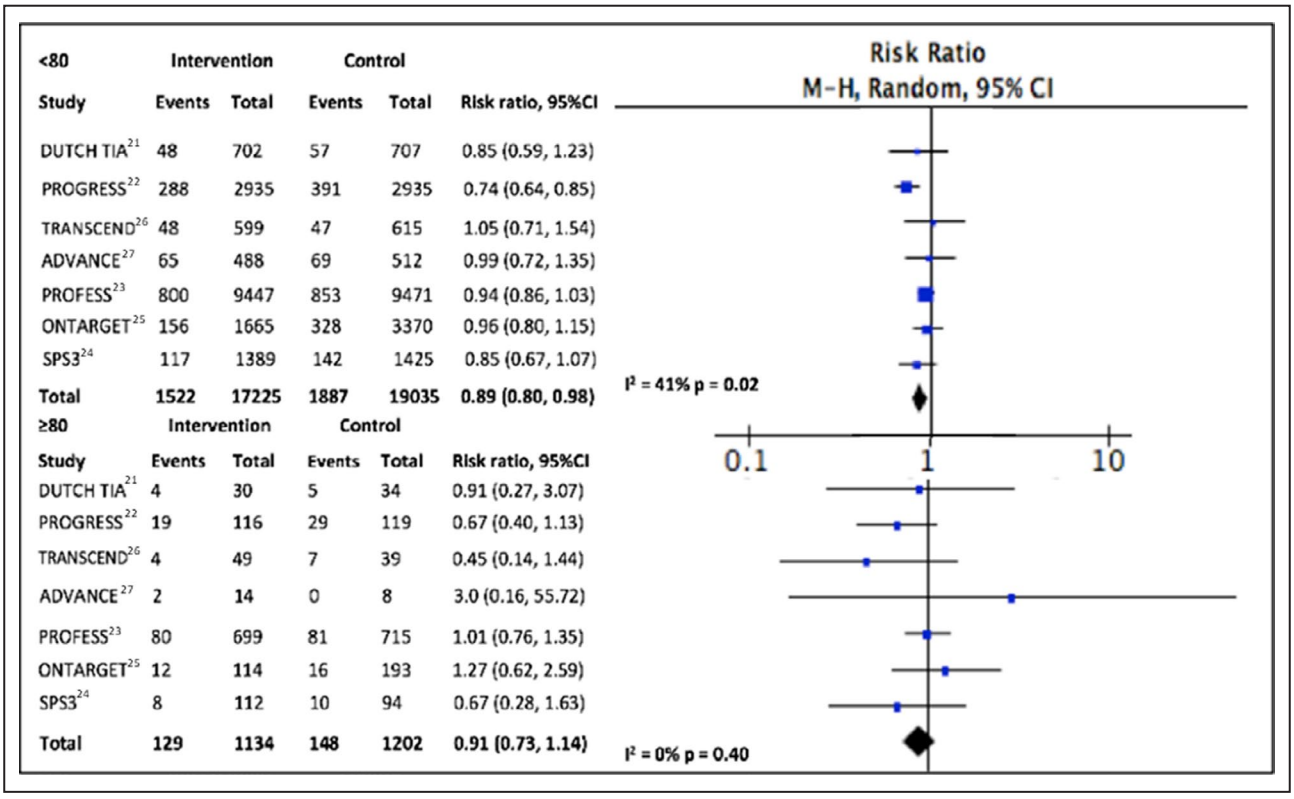

Figure 1. Comparison of intervention and control for stroke outcome in age subgroups.
M-H indicates Mantel-Haenszel.

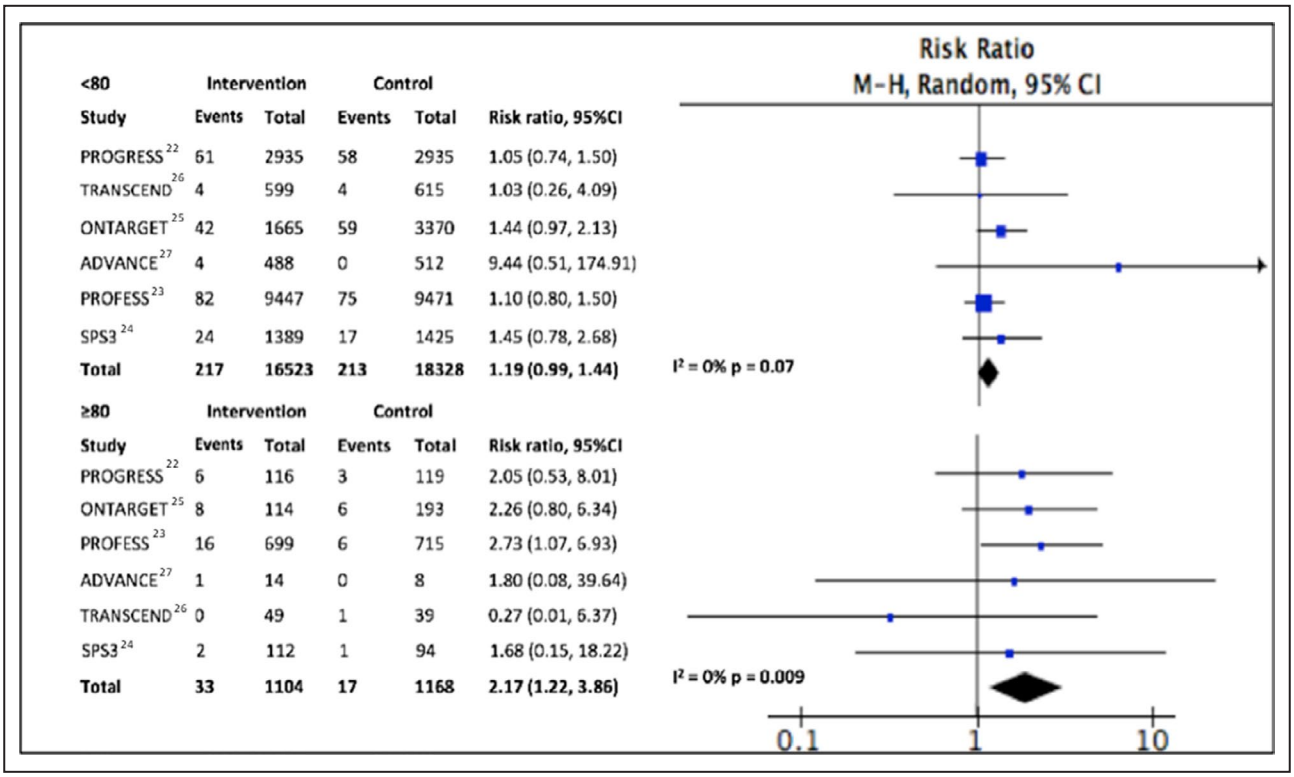

Figure 2. Comparison of intervention and control for hypotensive symptoms outcome in age subgroups.
M-H indicates Mantel-Haenszel.

were observed in the risk of these outcomes in either age subgroup.

All-Cause Death, Hospitalization for Heart Failure, Fatal and Nonfatal Myocardial Infarction

There was no increase in the risk of all-cause death (RR, 1.03 [95% CI, 0.96, 1.09], I^2=0%), hospitalization for heart failure (RR, 0.97 [95% CI, 0.85, 1.11], I^2=0%), or fatal and nonfatal myocardial infarction (RR, 0.93 [95% CI, 0.79, 1.10], I^2=43%) in the intervention group in the whole sample. No differences were observed between intervention and control groups in the age subgroups.

Outcomes

For the outcomes above for which forest plots are not included in this article, respective forest plots can be found in Figures S2 through S19. Funnel plot for assessing publication bias for the outcome of fatal and nonfatal stroke is additionally displayed in Figure 5.

Meta-Regression of Extent of BP Lowering, Age, and Relevant Outcomes

In analysis of study-level data reported for all ages, every mm Hg of BP lowering in a trial was associated with, on average, a statistically significant 4% reduction in the risk of fatal and nonfatal stroke in the intervention arm of that trial, compared with control (β=0.96 [95% CI, 0.94, 0.99]). This holds for the data reported for the younger subgroup (β=0.97 [95% CI, 0.93, 0.99]), but the estimated reduction for the older subgroup of ≈7% was not statistically significant (β=0.93 [95% CI, 0.84, 1.04]). Overall, at the study level, additional units of BP lowering were not associated with a statistically significant change in the risk of hypotensive symptoms (β=0.97 [95% CI, 0.91, 1.03]), and this result was consistent across younger (β=0.98 [95% CI, 0.91, 1.06]) and older subgroups (β=0.96 [95% CI, 0.78, 1.18]).

Compared with those aged ≥80 years, being aged <80 was not associated with a greater reduction in risk of fatal and nonfatal stroke (β=0.99 [95% CI, 0.7, 1.38]). Being aged <80 years was associated with, on average, a 47% reduction in risk (β=0.53 [95% CI, 0.26, 1.09]) of hypotensive symptoms. To better understand this finding, we evaluated the presence of an interaction between extent of BP lowering and age (<80 years compared with ≥80 years) for the outcome of hypotensive symptoms, but did not detect a statistically significant interaction (β for interaction, 1.02 [95% CI, 0.85, 1.23]).

Sensitivity Analysis

The sensitivity analysis for the stroke/nonfatal stroke outcome showed that omitting 1 of the 4 larger studies

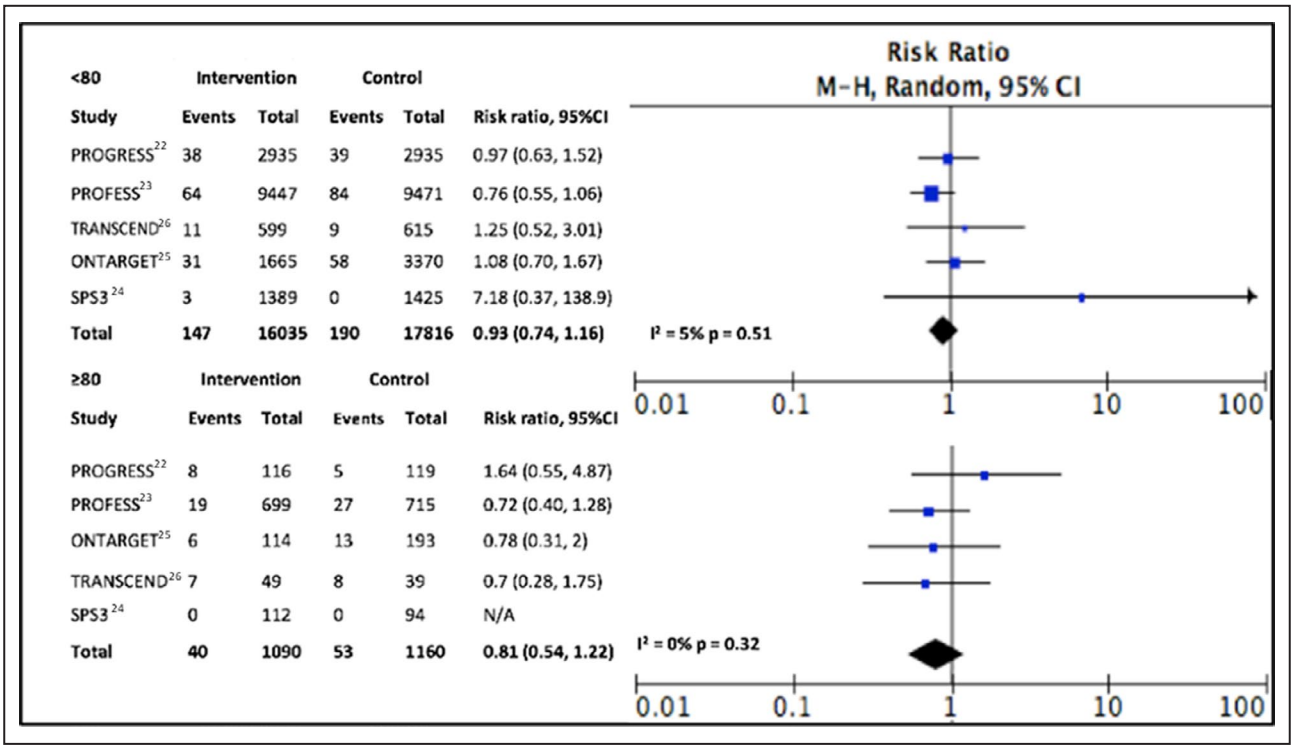

Figure 3. Comparison of intervention and control for falls outcome in age subgroups.
M-H indicates Mantel-Haenszel.

for this outcome (PROFESS, PROGRESS, ONTARGET, SPS3) resulted in RR estimates between 0.87 (95% CI, 0.76, 0.98) and 0.94 (95% CI, 0.88, 1.01) compared with 0.89 (95% CI, 0.80, 0.98) with all studies included (Figures S20 through S23).

DISCUSSION

In this aggregate data meta-analysis, we confirmed that BP reduction for secondary stroke prevention was associated with a reduction in stroke risk in people <80 years of age. In the very elderly (≥80 years), the magnitude of risk reduction was similar but did not reach statistical significance. Those ≥80 years also experienced greater risk of hypotensive symptoms but without demonstrable increase in risk of falls or syncope. Observed risk of other BP-related adverse outcomes was not increased in the whole sample, or in either age subgroup.

The relatively small magnitude of BP lowering (≈11%) across the included trials (mean systolic BP reduction in intervention compared with control group=5.6 mm Hg) may explain the magnitude of observed risk reduction in stroke. Notably, PROGRESS had the greatest degree of BP lowering across the trials and also had the greatest reduction in stroke risk, compared with others (PROFESS, ONTARGET) reporting only modest BP reduction. The recently published primary prevention SPRINT trial confirmed that the extent of BP lowering is important in stroke risk reduction,[14] a conclusion also supported by our meta-regression. However, it should be noted that the statistical importance of our meta-regression is limited given the small number of trials. There was also substantial heterogeneity (I^2=49%) in the whole group analysis for the stroke outcome, compared with other outcomes. This may be because of the heterogeneity in the extent of BP lowering between trials as described above. However, our results were robust to sensitivity analysis, indicating that a single trial did not overly influence point estimates.

In our study, hypotensive symptoms were increased 2-fold in the intervention arm in those aged ≥80 years. Although meta-regression did not suggest that age interacts with the extent of BP lowering to modify risk of hypotensive symptoms, this analysis was limited by the small number of included studies, and thus is not definitive. Moreover, we found no increased risk of study withdrawal or serious adverse events related to BP lowering in the older subgroup. In a subgroup analysis of the SPS3 study, there was a higher rate of unsteadiness when standing in the older subgroup (≥75 years) undergoing BP lowering, but the risk of other adverse events such as fall with injury and orthostatic syncope was not increased.[16] In the SPRINT trial, intensive BP lowering did not result in an increased rate of serious adverse events, injurious falls, or hypotension in

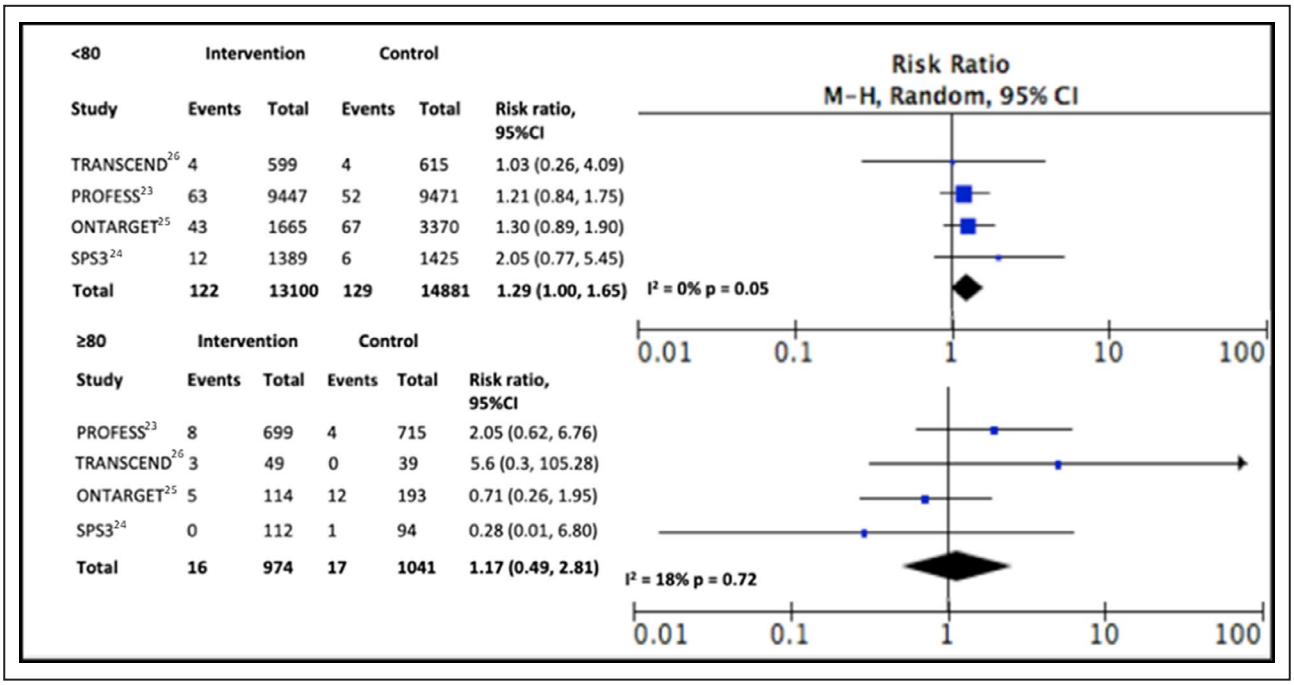

Figure 4. Comparison of intervention and control for syncope outcome in age subgroups.
M-H indicates Mantel-Haenszel.

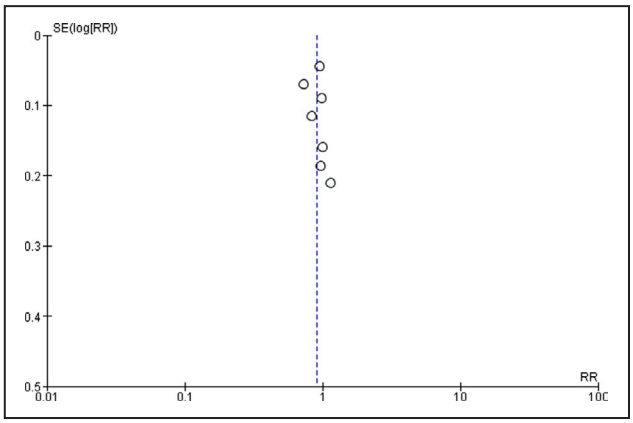

Figure 5. Funnel plot of comparison, fatal and nonfatal stroke.
RR indicates risk ratio.

people aged >75 years.[14,37] Although these results did not differ when adjusted for frailty scoring, the overall degree of frailty in this group was low,[38] raising questions regarding the generalizability of these results to very elderly people with previous stroke who may have greater degrees of frailty.

A previous meta-analysis of trials of BP lowering for primary prevention showed that while BP lowering was associated with a reduction in cardiovascular events (stroke, coronary heart disease, heart failure, and cardiovascular death), a greater degree of BP reduction was associated with greater odds of discontinuation.[39] The odds of discontinuation were greater when achieved systolic BP was <130 mm Hg.[39] The fact that the mean extent of BP reduction in our study was small may explain why we did not observe an elevated risk of withdrawal in the intervention group in our analysis.

Although these studies collectively provide some evidence to suggest that modest BP lowering in the very elderly with previous stroke may be safe, it must be noted that participants in these clinical trials were generally healthier and more able than frail older people with issues of chronic multimorbidity and polypharmacy who are more commonly encountered in clinical practice.[40] Furthermore, in our study, the number of falls and syncope were low in the elderly subgroup, likely because of the comparatively smaller size of this subgroup and limited power to examine these outcomes. Further randomized controlled trials that examine BP reduction in such frail older adults are required to resolve this uncertainty.

Strengths and Limitations

A strength of this study is that it comprises a pooled sample of very elderly participants with previous stroke from double-blind randomized controlled trials, with the advantage of minimizing confounding bias. However, there are some limitations. Firstly, as discussed, these studies were not designed to specifically investigate the effect of advanced age on the treatment effect or side effect profile of BP reduction for secondary stroke prevention. Secondly, the overall pooled sample in the very elderly subgroup was comparatively small, limiting

our ability to detect differences in the outcomes of interest. Additionally, the adverse events related to BP reduction such as syncope, hypotensive symptoms, falls, and electrolyte abnormalities were not necessarily strictly defined or consistent between trials, and many were defined by physician opinion, perhaps resulting in unmeasured bias because of variation in clinical practice. Furthermore, although achieved BP was lower in the active group compared with the control group in all trials, some trials were designed to examine effects of particular agents or combination of agents on cardiovascular risk, rather than examining the effects of BP lowering. Although the funnel plot of included trials was suggestive of low publication bias, only 7/17 (41%) of eligible trials could be included, and as such selection bias cannot be excluded. Included trials also differed from those not included in some ways such as mean age and extent of BP reduction. Such trials were typically older, with authors unable to be contacted (or, when contacted unable to retrieve data). Inclusion of these trials may have allowed us to form stronger conclusions.

Finally, we used a cutoff age of 80 years as a proxy for frailty and multimorbidity. However, there may be substantial differences in the degree of frailty between individuals of the same age. Although the studies in our meta-analysis collectively provide some evidence to suggest that modest BP lowering in the very elderly with previous stroke may be safe, it must be noted that participants in these trials, by virtue of exclusion criteria, would have been generally healthier and more able than frail older people with issues of chronic multimorbidity and polypharmacy.[31] Further randomized controlled trials that examine BP reduction in such frail older adults may be required to resolve this uncertainty.

CONCLUSIONS

In conclusion, very elderly people receiving BP lowering therapy in trials of secondary stroke prevention have an increased risk of hypotensive symptoms. There is insufficient power from this aggregate data meta-analysis to definitively conclude benefit in this elderly age group from BP lowering for secondary stroke prevention, or risk of major adverse events such as falls, syncope, or death. Evidence is lacking specifically for frail older people with multiple comorbidities that may render them more vulnerable to the effects of BP lowering.

APPENDIX

BP-VEPS (Blood Pressure in the Very Elderly with Previous Stroke) study investigators: Damien Tharmaratnam, Christopher C. Karayiannis, Taya A. Collyer, Hisatomi Arima, Leslie A. McClure, John Chalmers, Craig S. Anderson, Oscar R. Benavente, Carole L. White, Ale Algra, Chris Moran, Thanh G. Phan, Wei C. Wang, and Velandai Srikanth.

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ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S5
Figures S1–S23

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SUPPLEMENTAL MATERIAL

Table S1. Availability of Data and Definitions of Outcomes.

	Serious Adverse Events	Hypotensive Symptoms	Syncope	Falls	Electrolyte Abnormalities	Renal Impairment	Study Withdrawal	Fatal/Non-fatal Stroke	Heart failure	Fatal/Non-fatal MI
Dutch TIA	n/a	n/a	n/a	n/a	n/a	n/a	n/a	Fatal: Death from stroke. Non-fatal stroke: relevant clinical features + imaging changes +/- increase handicap of ≥1 grade on MRS	n/a	Fatal: Death + non-fatal definition; ≥2of: chest discomfort, cardiac enzyme levels more than twice the upper limit of normal, or the development of Q waves
PROGRESS	n/a	Dizziness or hypotension	n/a	No formal definition	Any abnormality of Sodium and/ or Potassium	New or worsening nephropathy	No formal definition	Fatal or disabling stroke	Hospitalization for heart failure	Non-fatal or fatal MI
ADVANCE	n/a	Dizziness or hypotension	n/a	n/a	n/a	New or worsening nephropathy	No formal definition	Non-fatal stroke	Hospitalization for heart failure	Non-fatal MI, death due to Coronary disease
PROFESS	Results in death, life threatening, persistent or significant disability, requires hospitalisation	No formal definition; similar to ONTARGET definition	No definition provided	No formal definition; dictionary definition suggested	n/a	n/a	n/a	Fatal or non-fatal stroke; ischemic or hemorrhagic or uncertain cause. Transient ischemic attack data collected separately	New or worsening heart failure	Fatal or non-fatal MI need supporting Electrocardiogram/ enzymes
ONTARGET	See PROFESS definition	Dizziness, exertional and postural dizziness, hypotension, orthostatic hypotension, presyncope	No predefined definition	No formal definition; dictionary definition suggested	n/a	n/a	n/a	Fatal or non-fatal stroke with supporting CT scan	Hospitalization for heart failure	Fatal or non-fatal MI, need supporting Electrocardiogram/ enzymes
TRANSCEND	See PROFESS definition	No formal definition; similar to ONTARGET definition	No definition provided	Dictionary definition suggested	n/a	n/a	n/a	Fatal or non-fatal stroke with supporting CT scan	Hospitalization for heart failure	Fatal or non-fatal MI; need supporting Electrocardiogram/ enzymes
SPS3	Includes: unsteadiness, blurred vision, dizziness, light-headedness, palpitations	Complication of hypotension requiring medical evaluation/ therapy. Also includes mental status changes	Only recorded events of orthostatic syncope	Fall with injury secondary to hypotension	Any abnormality in sodium, potassium or calcium, magnesium and phosphate	n/a	Unable to locate patient, patient withdrew, physician request for withdrawal	Fatal or non-fatal ischemic stroke or hemorrhage. Needs to be confirmed with CT or MRI Brain scan + examination	Heart failure as determined by SPS3 investigator	Fatal or non-fatal MI defined by standard criteria consisting of electrocardiogram and cardiac enzymes

n/a: not available, MI: myocardial infarction, TIA: transient ischaemic attack, ECG: electrocardiogram, CT: computed-tomography, MRI: magnetic resonance imaging, MRS: modified Rankin scale

Table S2. Sample Characteristics of Younger Subgroup (<80 years).

<80		Sample size (n)	Age (years) , mean (SD)	BMI (kg/m^2), mean (SD)	Waist Circumference (cm), mean (SD)	Modified Rankin Score, mean (SD)	Female sex, n (%)	Smoker, n (%)	Ex-smoker, n (%)	Heavy alcohol use, n (%)	Hypertension, n(%)	Diabetes, n(%)	Dyslipiaemia, n (%)	Coronary Artery Disease, n (%)	Aspirin, n(%)	Statin, n (%)	Clopidogrel, n (%)	Difference between baseline and achieved BP (SBP mmHg), SD	Difference between baseline and achieved BP (DBP mmHg), SD
Dutch TIA	Intervention	702	63.7 (9.7)	n/a	n/a	n/a	232 (33)	337 (48)	n/a	n/a	201 (28.6)	34 (4.8)	18 (2.6)	41 (5.8)	702 (100)	n/a	n/a	n/a	n/a
	Control	707	63.5 (9.6)	n/a	n/a	n/a	267 (37.8)	346 (48.9)	n/a	n/a	205 (29)	37 (5.2)	20 (2.8)	41 (5.8)	707 (100)	n/a	n/a	n/a	n/a
PROGRESS	Intervention	2935	63.1 (9)	25.6 (3.8)	n/a	n/a	876 (29.8)	603 (20.5)	1115 (38)	230 (7.8)	1449 (49.4)	384 (13.1)	n/a	201 (6.8)	1757 (59.9)	230 (7.8)	n/a	14.2 (20.1)	n/a
	Control	2935	63.2 (8.9)	25.8 (3.8)	n/a	n/a	874 (29.8)	610 (20.8)	1097 (37.4)	250 (8.5)	1501 (51.1)	358 (12.2)	n/a	201 (6.8)	1713 (58.4)	222 (7.6)	n/a	10.8 (27)	n/a
TRANSCEND	Intervention	599	66.8 (6.7)	27.7 (4.8)	93.4 (12.6)	n/a	277 (46.2)	57 (9.5)	219 (36.6)	10 (1.7)	505 (84.3)	169 (28.2)	n/a	228 (38.1)	397 (66.3)	227 (37.9)	39 (6.5)	6.4 (15.6)	4.7 (9.6)
	Control	615	66.6 (6.9)	27.7 (4.8)	94 (12.8)	n/a	284 (46.2)	58 (9.4)	210 (34.1)	10 (1.6)	518 (84.2)	184 (29.9)	n/a	240 (39)	416 (67.6)	229 (37.2)	48 (7.8)	3.1 (16.1)	6.8 (8.4)
ADVANCE	Intervention	488	65.9 (6.3)	27.6 (4.7)	97.1 (12.3)	n/a	203 (41.6)	40 (8.2)	126 (25.8)	14 (2.9)	390 (79.9)	488 (100)	157 (32.2)	56 (11.5)	294 (60.2)	117 (24)	n/a	9.7 (23.6)	n/a
	Control	512	65.6 (6.2)	27.3 (4.1)	96.2 (12.4)	n/a	194 (37.9)	69 (13.5)	128 (25)	16 (3.1)	425 (83)	512 (100)	160 (31.3)	64 (12.5)	325 (63.5)	123 (24)	n/a	3.7 (22.5)	n/a
PROFESS	Intervention	9447	64.9 (7.5)	26.9 (5)	n/a	1.7 (1.1)	3288 (34.8)	2107 (22.3)	3401 (36)	368 (3.9)	7029 (74.4)	2711 (28.7)	n/a	n/a	4705 (49.8)	4421 (46.8)	1436 (15.2)	8.5 (16.3)	4.5 (9.9)
	Control	9471	64.9 (7.5)	26.9 (5.1)	n/a	1.7 (1.2)	3334 (35.2)	2112 (22.3)	3381 (35.7)	417 (4.4)	7027 (74.2)	2747 (29)	n/a	n/a	4717 (49.8)	4556 (48.1)	1449 (18.1)	4.4 (15.9)	2.3 (9.7)
ONTARGET	Intervention	1665	66.7 (6.7)	27.7 (4.9)	94.4 (13.5)	n/a	523 (31.4)	216 (13)	758 (45.5)	53 (3.2)	1340 (80.5)	556 (33.4)	n/a	683 (41)	1121 (67.3)	786 (47.2)	195 (11.7)	8.4 (16.2)	5.9 (9.7)
	Control	3370	66.7 (6.5)	27.8 (4.9)	94.7 (13.4)	n/a	1092 (32.4)	458 (13.6)	1486 (44.1)	108 (3.2)	2709 (80.4)	1112 (33)	n/a	1321 (39.2)	2241 (66.5)	1614 (47.9)	394 (11.7)	6.8 (16)	4.9 (9.7)
SPS3	Intervention	1389	61.6 (9.4)	29.1 (6.1)	98.9 (13.7)	1.3 (0.84)	521 (37.5)	304 (21.9)	562 (40.5)	186 (13.4)	1036 (74.6)	521 (37.5)	685 (49.3)	136 (9.8)	781 (56.2)	959 (69)	215 (15.5)	15.8 (21.5)	8.6 (11.6)
	Control	1425	62.0 (9.7)	29.4 (7.6)	99.9 (13.8)	1.3 (0.8)	479 (33.6)	307 (21.5)	554 (38.9)	182 (12.8)	1063 (74.6)	536 (37.6)	695 (48.8)	166 (11.6)	808 (56.7)	983 (69)	28 (25)	5.8 (20.8)	4.1 (11.7)

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, cm: centimetres, n/a: not available, SD: Standard deviation

Table S3. Sample Characteristics of Older Subgroup (≥80 years).

≥ 80		Sample size (n)	Age (years) , mean (SD)	BMI (kg/m^2), mean (SD)	Waist Circumference (cm), mean (SD)	Modified Rankin Score, mean (SD)	Female sex, n (%)	Smoker, n (%)	Ex-smoker, n (%)	Heavy alcohol use, n (%)	Hypertension, n(%)	Diabetes, n(%)	Dyslipiaemia, n (%)	Coronary Artery Disease, n (%)	Aspirin, n(%)	Statin, n (%)	Clopidogrel, n (%)	Difference between baseline and achieved BP (SBP mmHg), SD	Difference between baseline and achieved BP (DBP mmHg), SD
Dutch TIA	Intervention	30	82.6 (2.2)	n/a	n/a	n/a	18 (60)	6 (20)	n/a	n/a	7 (23.3)	5 (16.7)	0 (0)	1 (3.3)	30 (100)	n/a	n/a	n/a	n/a
	Control	34	83.0 (2.7)	n/a	n/a	n/a	17 (50)	4 (11.8)	n/a	n/a	7 ((20.6)	3 (8.8)	0 (0)	1 (2.9)	34 (100)	n/a	n/a	n/a	n/a
PROGRESS	Intervention	116	82.7 (2.4)	24.9 (3.7)	n/a	n/a	47 (40.5)	3 (2.6)	51 (44)	7 (6)	61 (52.6)	9 (7.8)	n/a	14 (12.1)	86 (74.1)	3 (2.6)	n/a	10.8 (27)	n/a
	Control	119	82.3 (2.3)	24.3 (3.1)	n/a	n/a	55 (46.2)	4 (3.4)	46 (38.7)	12 (10.1)	53 (44.5)	10 (8.4)	n/a	10 (8.4)	76 (63.9)	7 (5.9)	n/a	16.1 (26.1)	n/a
TRANSCEND	Intervention	49	83.1 (3.2)	26.1 (4)	92 (13.2)	n/a	31 (63.3)	2 (4.1)	16 (32.7)	1 (2)	39 (79.6)	13 (26.5)	n/a	20 (40.8)	35 (71.4)	22 (44.9)	3 (6.1)	7.3 (14.7)	6.8 (8.4)
	Control	39	82.4 (2.7)	26.0 (4.4)	91.4 (12.1)	n/a	21 (53.8)	1 (2.6)	14 (35.9)	3 (7.7)	32 (82.1)	8 (20.5)	n/a	10 (25.6)	21 (53.8)	12 (30.8)	6 (15.4)	3.3 (13.5)	2.5 (9)
ADVANCE	Intervention	14	81.5 (1.6)	26.5 (2.5)	97.5 (9.4)	n/a	5 (35.7)	0 (0)	9 (64.3)	1 (7.1)	13 (92.9)	14 (100)	3 (21.4)	4 (28.6)	10 (71.4)	3 (21.4)	n/a	16.9 (25.9)	n/a
	Control	8	82.8 (2.1)	26.7 (1.8)	94.5 (6.2)	n/a	1 (12.5)	0 (0)	3 (37.5)	0 (0)	6 (75)	8 (100)	3 (37.5)	4 (50)	5 (62.5)	2 (25)	n/a	2.8 (17.7)	n/a
PROFESS	Intervention	699	82.6 (2.6)	25.7 (4.5)	n/a	1.9 (1.3)	327 (46.8)	45 (6.4)	306 (43.8)	17 (2.4)	484 (69.2)	128 (18.3)	n/a	n/a	364 (52.1)	323 (46.2)	131 (18.7)	9.8 (13.3)	4.7 (10.2)
	Control	715	82.9 (2.9)	25.4 (4.3)	n/a	1.8 (1.3)	354 (49.5)	45 (6.3)	269 (37.6)	16 (2.2)	510 (71.3)	153 (21.4)	n/a	n/a	382 (53.4)	321 (44.9)	129 (18)	5.2 (16.7)	2.5 (10.4)
ONTARGET	Intervention	114	82.2 (2.6)	25.7 (3.8)	93.0 (11.5)	n/a	44 (38.6)	6 (5.3)	50 (43.9)	1 (0.9)	95 (83.3)	32 (28.1)	n/a	47 (41.2)	73 (64)	53 (46.5)	10 (8.8)	7.9 (20.2)	4.6 (11.1)
	Control	193	82.6 (2.5)	26.2 (4)	92.3 (13.6)	n/a	80 (41.5)	7 (3.6)	96 (49.7)	3 (1.6)	155 (80.3)	41 (21.2)	n/a	78 (40.4)	111 (57.5)	75 (38.9)	33 (17.1)	8.6 (18)	5.9 (10.1)
SPS3	Intervention	112	83.5 (2.7)	27.0 (5.9)	93.7 (12.6)	1.3 (0.82)	44 (39.3)	5 (4.5)	47 (42)	10 (8.9)	91 (81.3)	32 (28.6)	51 (45.5)	8 (7.1)	56 (50)	79 (70.5)	28 (25)	20.2 (23.1)	9.2 (11.6)
	Control	94	83.9 (3.2)	26.1 (4.2)	92.5 (10.5)	1.6 (0.91)	50 (53.2)	1 (1.1)	44 (46.8)	8 (8.5)	74 (78.7)	17 (18.1)	40 (42.6)	7 (7.4)	54 (57.4)	60 (63.8)	14 (14.9)	7.5 (22.3)	5.2 (11.3)

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, cm: centimetres, n/a: not available, SD: standard deviation

Table S4. Study Characteristics.

	Intervention	Control	Extent of BP Lowering	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Secondary Outcomes	Mean Follow up (years)
Dutch TIA	Atenolol 50mg	Placebo	n/a	TIA or minor Stroke (MRS 3 or less) in last 3 months	Cerebral ischemia due to causes other than arterial thrombosis or embolism, including AF, cardiac valve disease, recent myocardial infarction and disorders of blood coagulation	Death from all vascular causes, nonfatal stroke or nonfatal myocardial infarction	All cause death, death from vascular causes +/- non fatal stroke	2.7
PROGRESS	Perindopril 4mg +/-Indapamide	Placebo	9.0/4.0mmHg	History of stroke (ischemic of hemorrhagic) or TIA in the last 5 years, no BP criteria; those with uncontrolled BP advised to get on non-ACEI prior, clinically stable for 2 weeks after most recent vascular event	Other indication for ACEI (eg: HF), CI to ACEI, Intolerance to ACEI during open label run-in phase	Recurrent Stroke rates	Fatal or disabling stroke with disability, major vascular events (stroke, MI, death due to any vascular cause), all cause mortality	3.9
ADVANCE	Perindopril/ indapamide	Placebo	2.4/0.8mmHg systolic	Age≥55, T2DM Diagnosed at age≥30, history of major macrovascular or microvascular disease or ≥1 other risk factor for vascular disease	Definite indication for, or CI to any of the study treatment, definite indication for long term insulin therapy at time of study entry	Combined macro/ micro-vascular events, Major macrovascular events (nonfatal MI, nonfatal stroke), major microvascular events, new or worsening nephropathy	Mortality, major coronary events, all coronary events, Non fatal stroke, fatal stroke, total cerebrovascular events, HF, peripheral vascular events, All cardiovascular events, neuropathy, hospitalization	5.0

n/a: not available, TIA: transient ischaemic attack, AF: atrial fibrillation, MI: myocardial infarction, ACEI: angiotensin-converting enzyme inhibitor, ICH: intracranial hemorrhage, BP: blood pressure, HTN: hypertension, HF: heart failure, CI: contraindication, T2DM: type 2 diabetes mellitus, rx: treatment, CV: cardiovascular

Table S5. Study Characteristics.

	Intervention	Control	Extent of BP Lowering	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Secondary Outcomes	Mean Follow up (years)
PROFESS	Telmisartan 80mg	Placebo	3.8mmHg systolic	Age≥50, Ischemic stroke in prior 90-120 days	Hemorrhagic stroke	First recurrence of stroke	Composite of stroke, MI or death from vascular causes, Myocardial infarction, cardiovascular mortality, All cause mortality, New or worsening heart failure, Premature discontinuation	2.5
ONTARGET	Telmisartan 80mg + ramipril 10mg	Telmisartan 80mg or ramipril 10mg	2.4/1.4mmHg	Age≥55 + any of: Coronary artery disease, PVD, Cerebrovascular disease or High risk diabetes mellitus	Intolerance to ACE inhibitors, heart failure, constrictive pericarditis, liver disease, uncontrolled hypertension on therapy of >160/100 mmHg Multiple – see study manuscript	Death from CV causes, MI, stroke, or hospitalization for HF	Stroke, MI, death from CV causes, death fro any cause, angina, TIA, left ventricular hypertrophy, microvascular DM complications, new cancers	4.7
TRANSCEND	Telmisartan 80mg	Placebo	2.4mmHg systolic	Hx of intolerance to ACEI, age≥55, CAD, PVD, cerebrovascular disease or DM with end organ damage	ACE inhibitor intolerance, symptomatic heart failure, uncontrolled HTN on treatment.. Multiple; see study manuscript	Composite of: CV death, MI, stroke or hospitalization for heart failure, discontinuation, hypotensive symptoms	New diagnosis heart failure, nephropathy, new diagnosis DM, atrial fibrillation	4.7
SPS3	<130mmHg target group. Antihypertensives; thiazides, ACEI/ ARB, CCB, beta blockers, Other	130-149mmHg group and <130mmHg group)	11.0mmHg systolic	≥30 years, normo- or hyper-tensive, stroke within 180 days	Disabling stroke (MRS 4 or higher), previous ICH from non-traumatic causes, cortical ischemic stroke	Stroke; all stroke (ischemic, hemorrhagic)	AMI, admission for a major vascular event, death	3.5

CI: contraindication, MI: myocardial infarction, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin-receptor blocker, PVD: peripheral vascular disease, CV: cardiovascular, HF: heart failure, TIA: transient ischaemic attack, DM: diabetes mellitus, CAD: coronary artery disease, HTN: hypertension, AMI: acute myocardial infarction

Figure S1. Search Results.

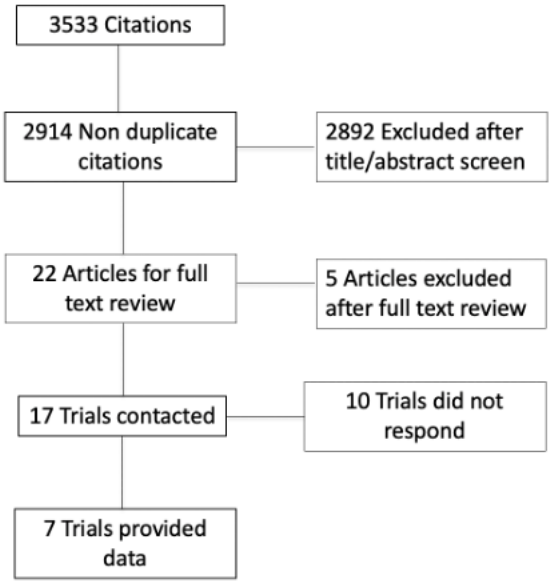
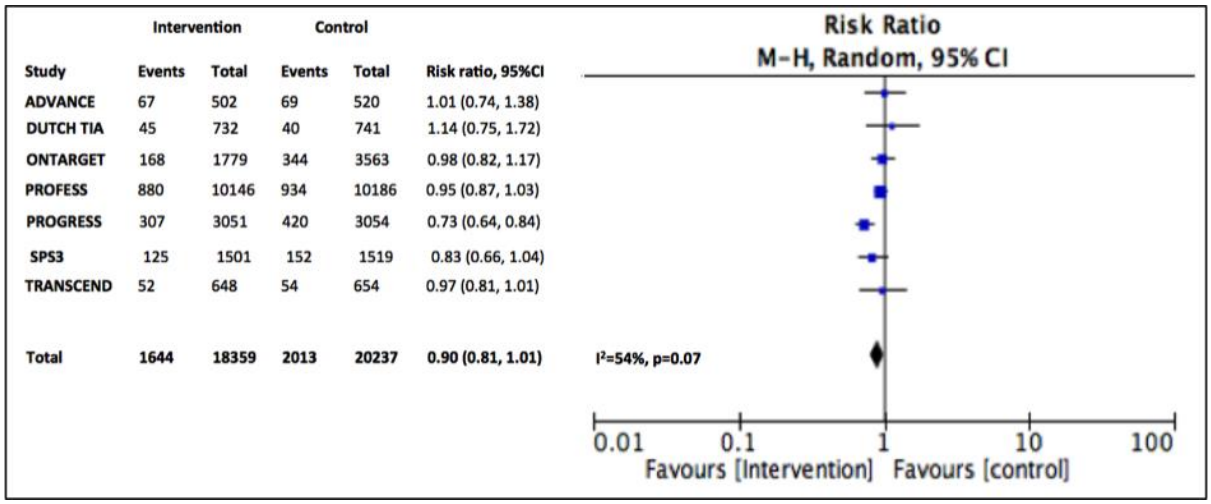
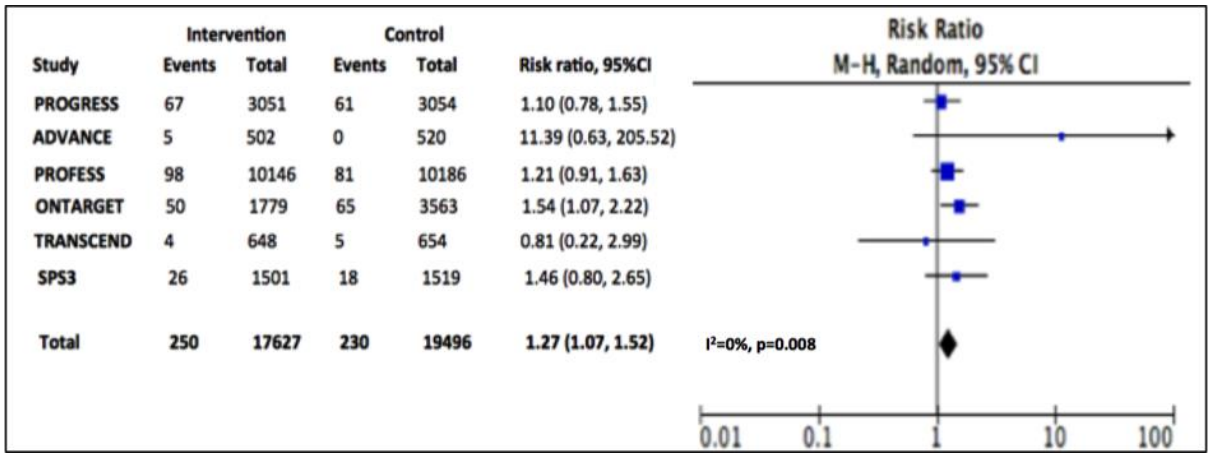


Figure S2. Stroke – Whole Sample Analysis.



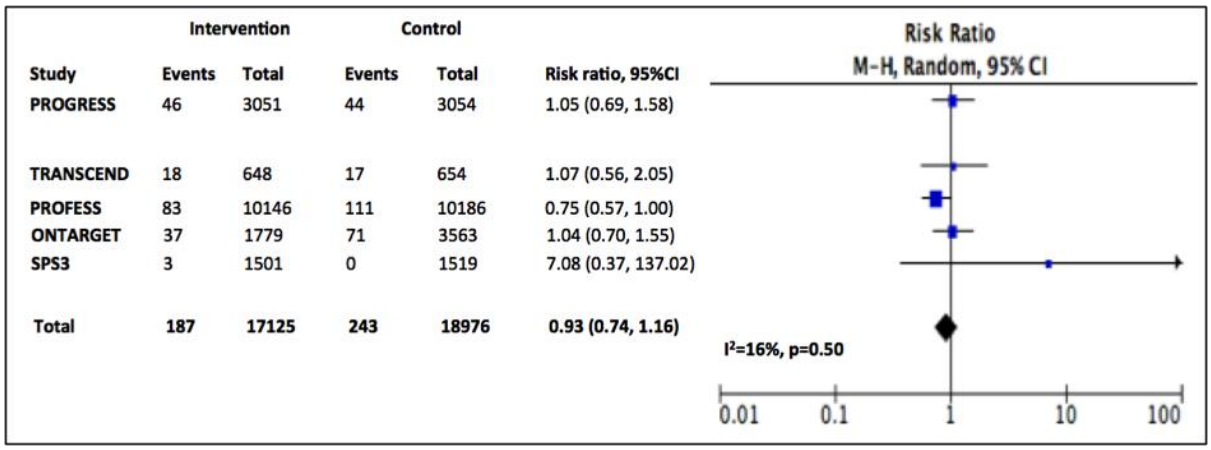
CI: confidence interval, M-H: Mantel-Haenszel

Figure S3. Hypotensive Symptoms - Whole Sample Analysis.



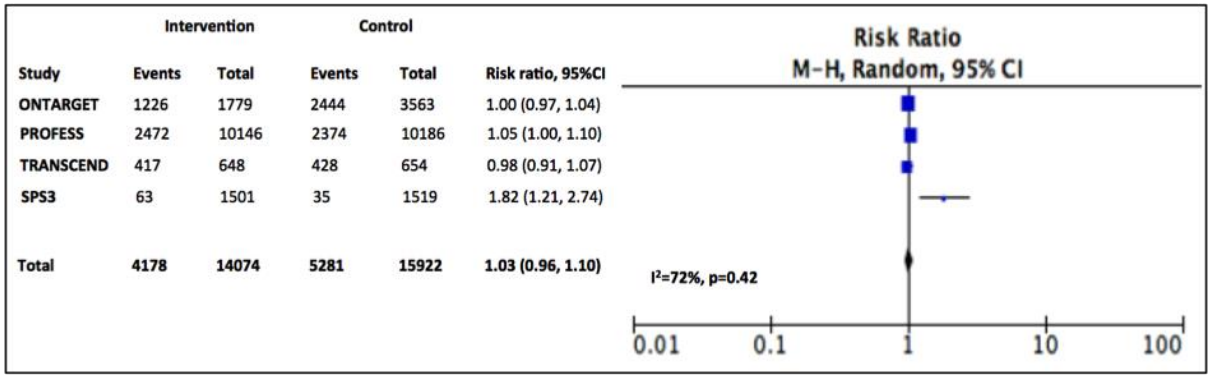
CI: confidence interval, M-H: Mantel-Haenszel

Figure S4. Falls – Whole Sample Analysis.



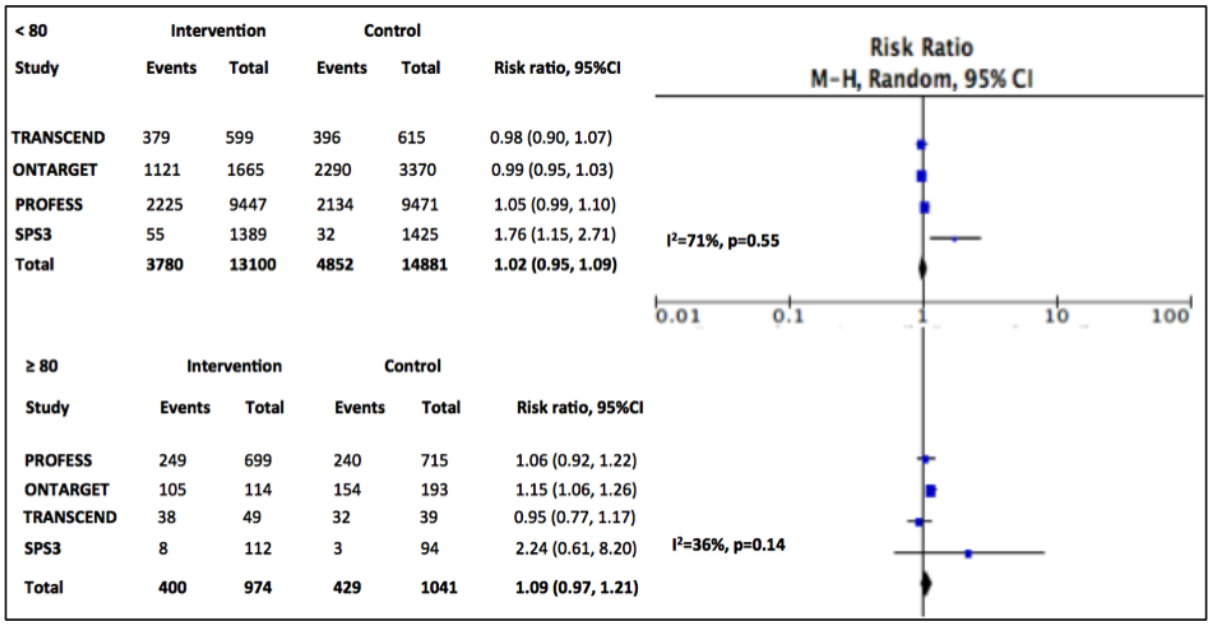
CI: confidence interval, M-H: Mantel-Haenszel

Figure S5: Serious Adverse Events – Whole Sample Analysis



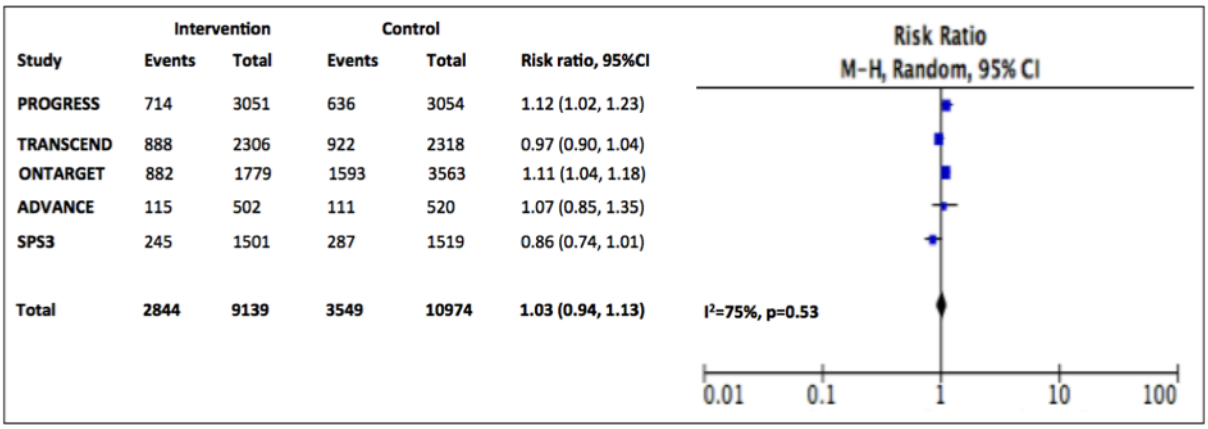
CI: confidence interval, M-H: Mantel-Haenszel

Figure S6: Serious Adverse Events In Age Subgroups



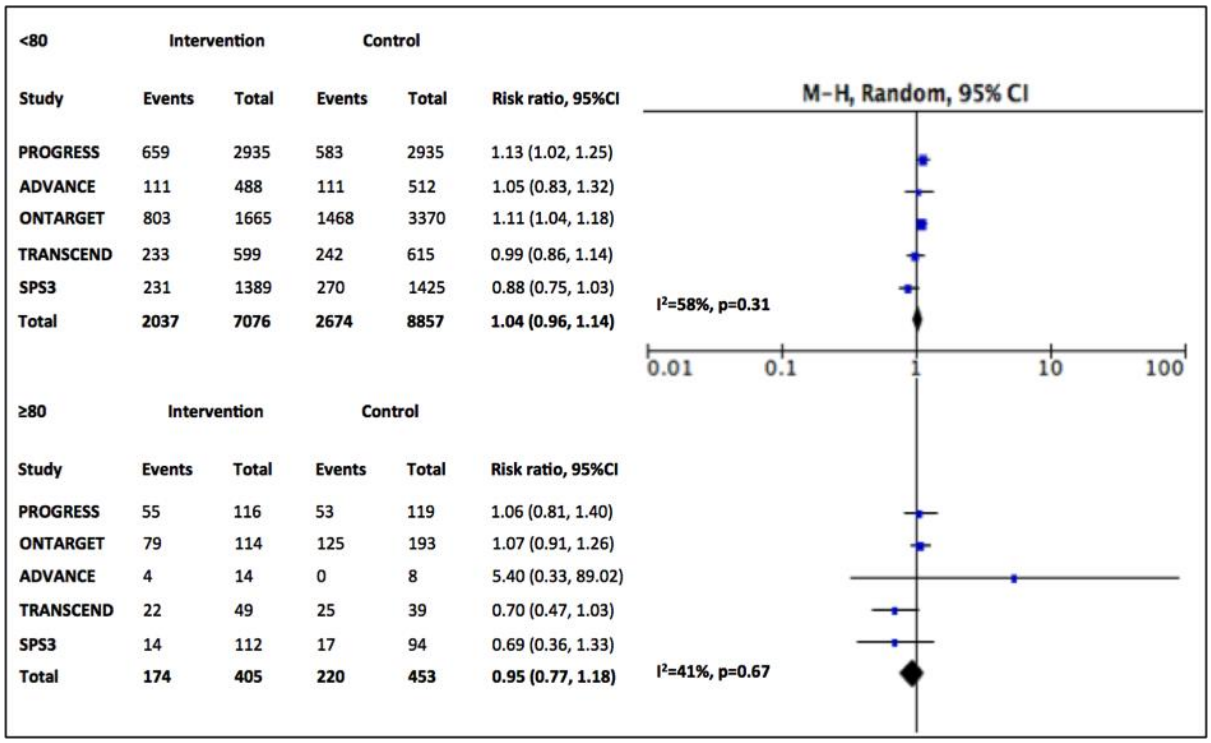
CI: confidence interval, M-H: Mantel-Haenszel

Figure S7: Study Withdrawal – Whole Sample Analysis



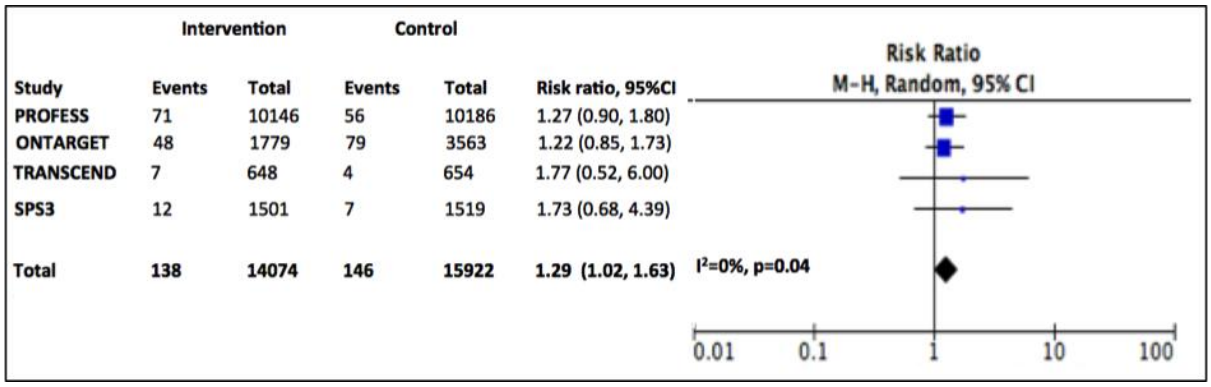
CI: confidence interval, M-H: Mantel-Haenszel

Figure S8: Study Withdrawal In Age Subgroups



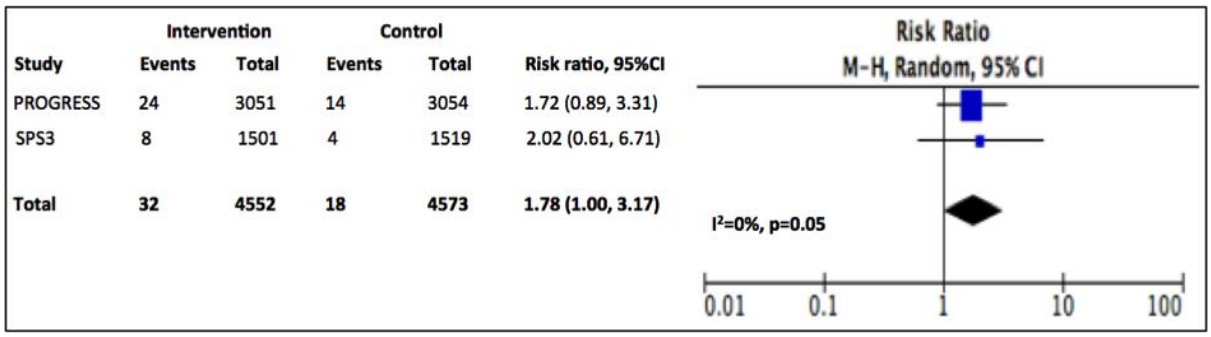
CI: confidence interval, M-H: Mantel-Haenszel

Figure S9: Syncope – Whole Sample Analysis



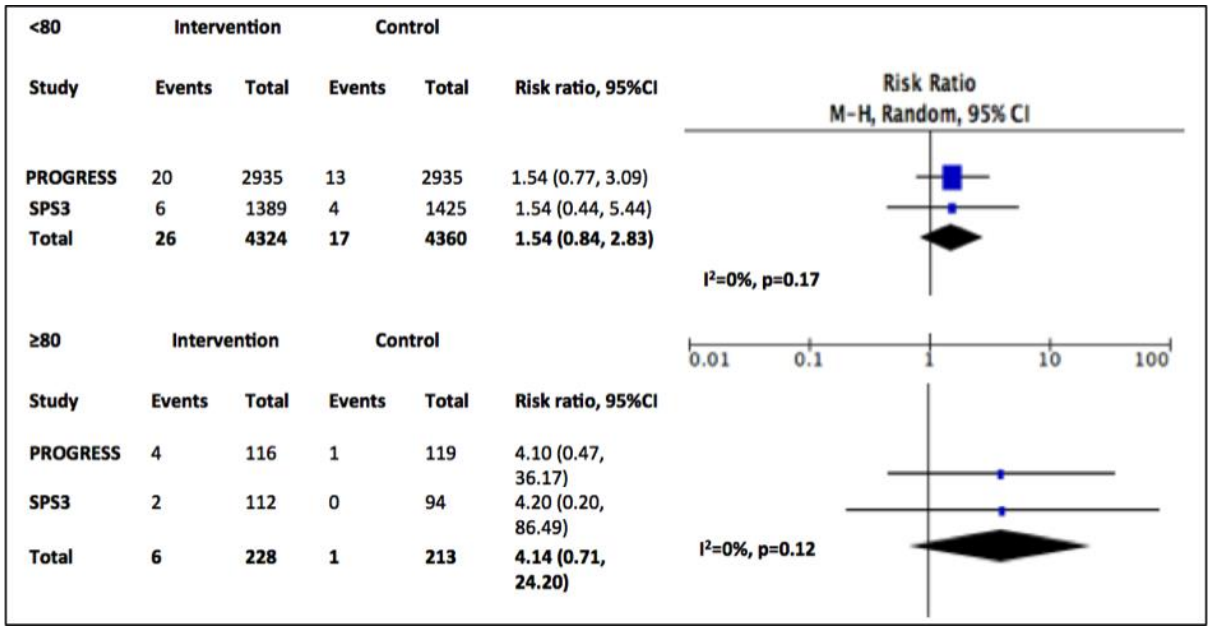
CI: confidence interval, M-H: Mantel-Haenszel

Figure S10: Electrolyte Abnormalities – Whole Sample Analysis



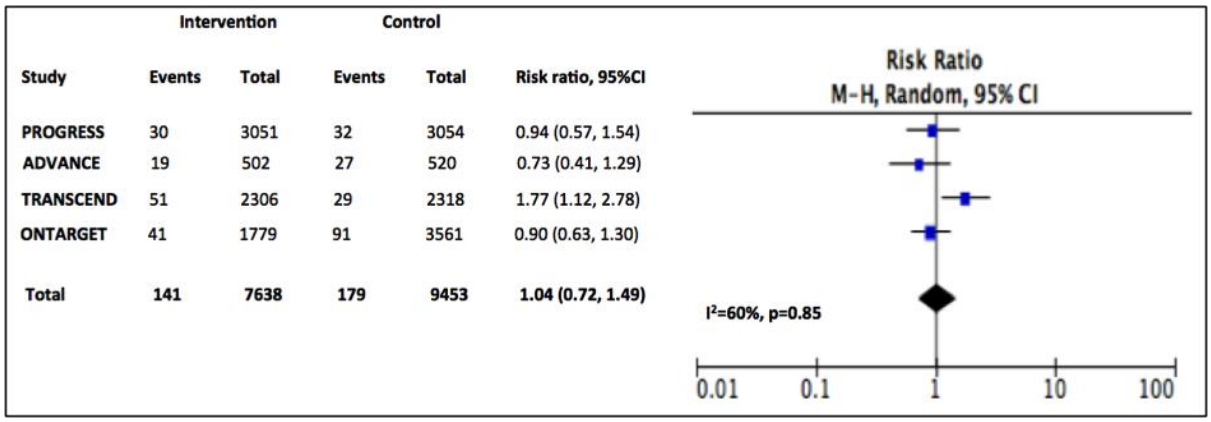
CI: confidence interval, M-H: Mantel-Haenszel

Figure S11: Electrolyte Abnormalities In Age Subgroups



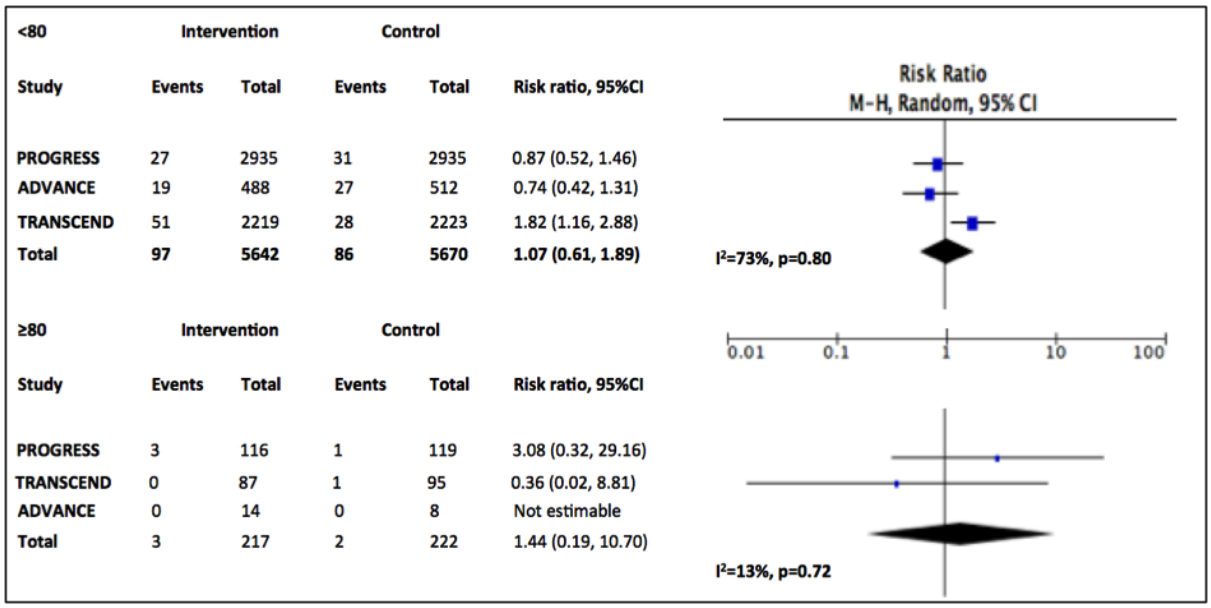
CI: confidence interval, M-H: Mantel-Haenszel

Figure S12: Renal Impairment – Whole Sample



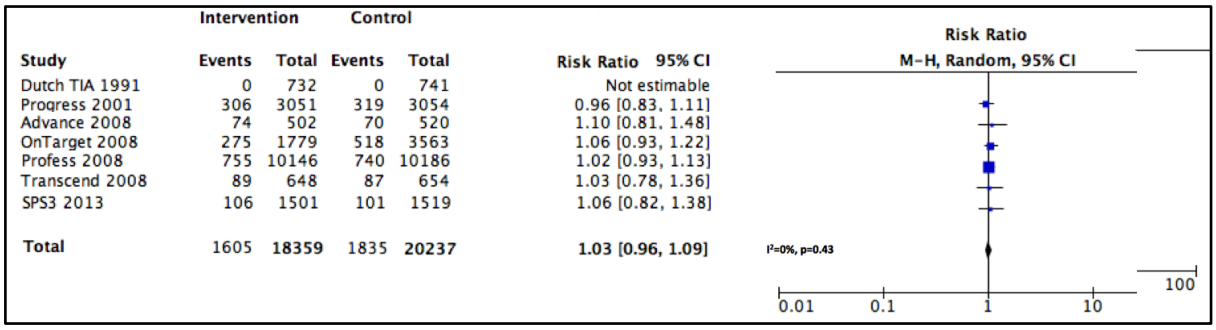
CI: confidence interval, M-H: Mantel-Haenszel

Figure S13: Renal Impairment In Age Subgroups



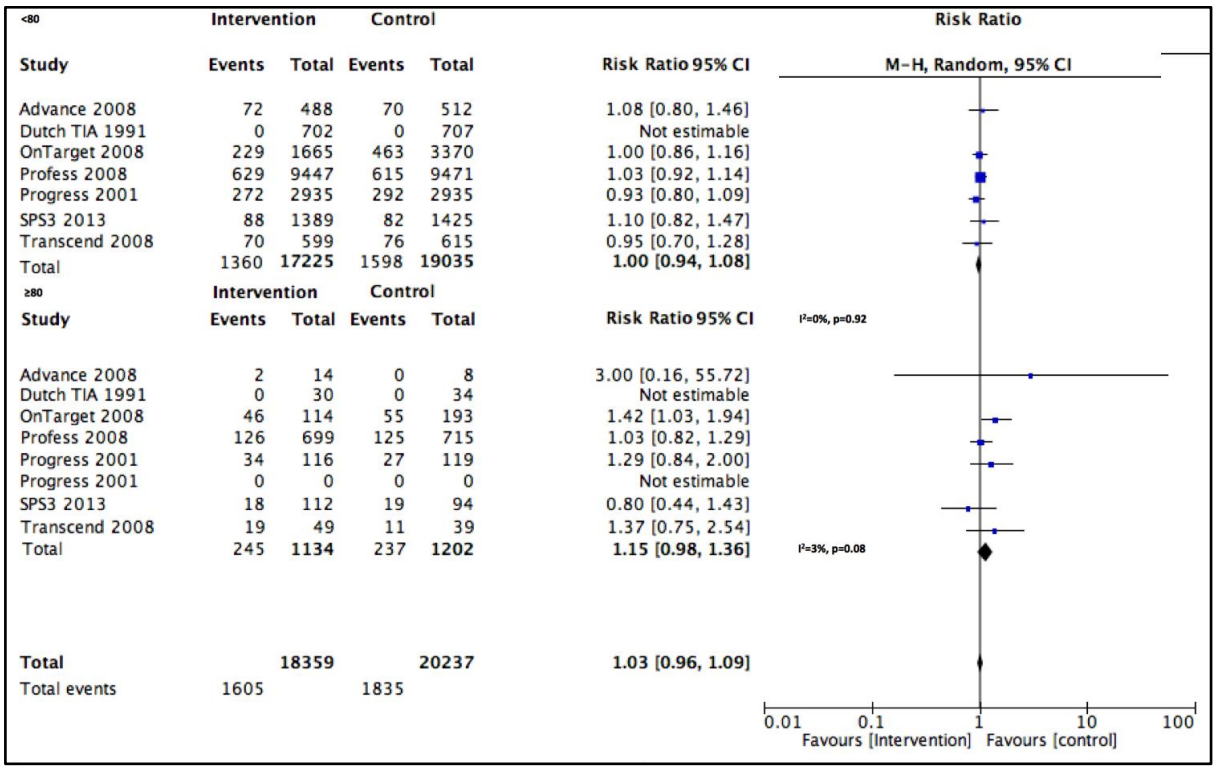
CI: confidence interval, M-H: Mantel-Haenszel

Figure S14: All Cause Death – Whole Sample



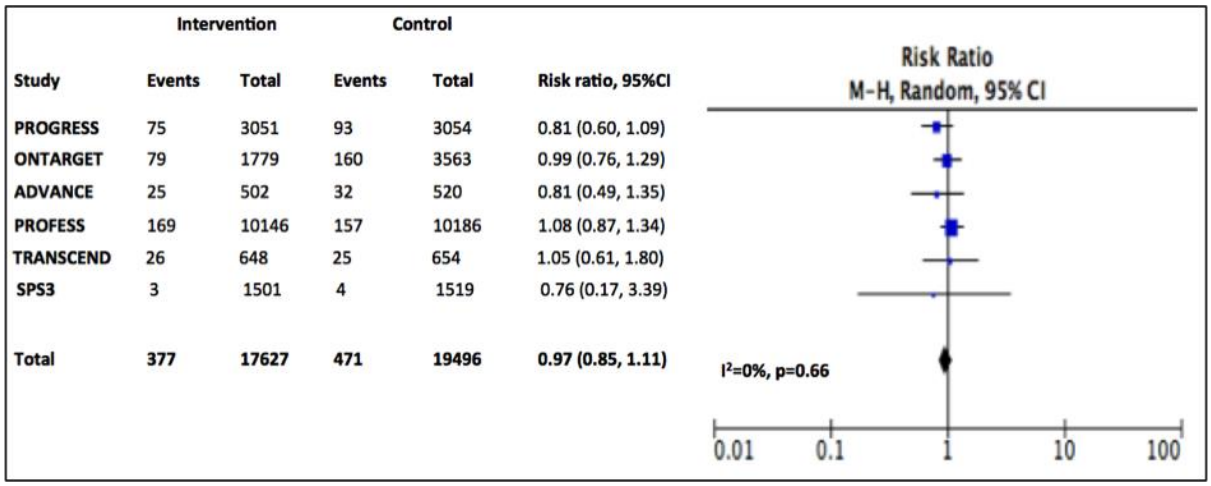
CI: confidence interval, M-H: Mantel-Haenszel

Figure S15: All Cause Death In Age Subgroups



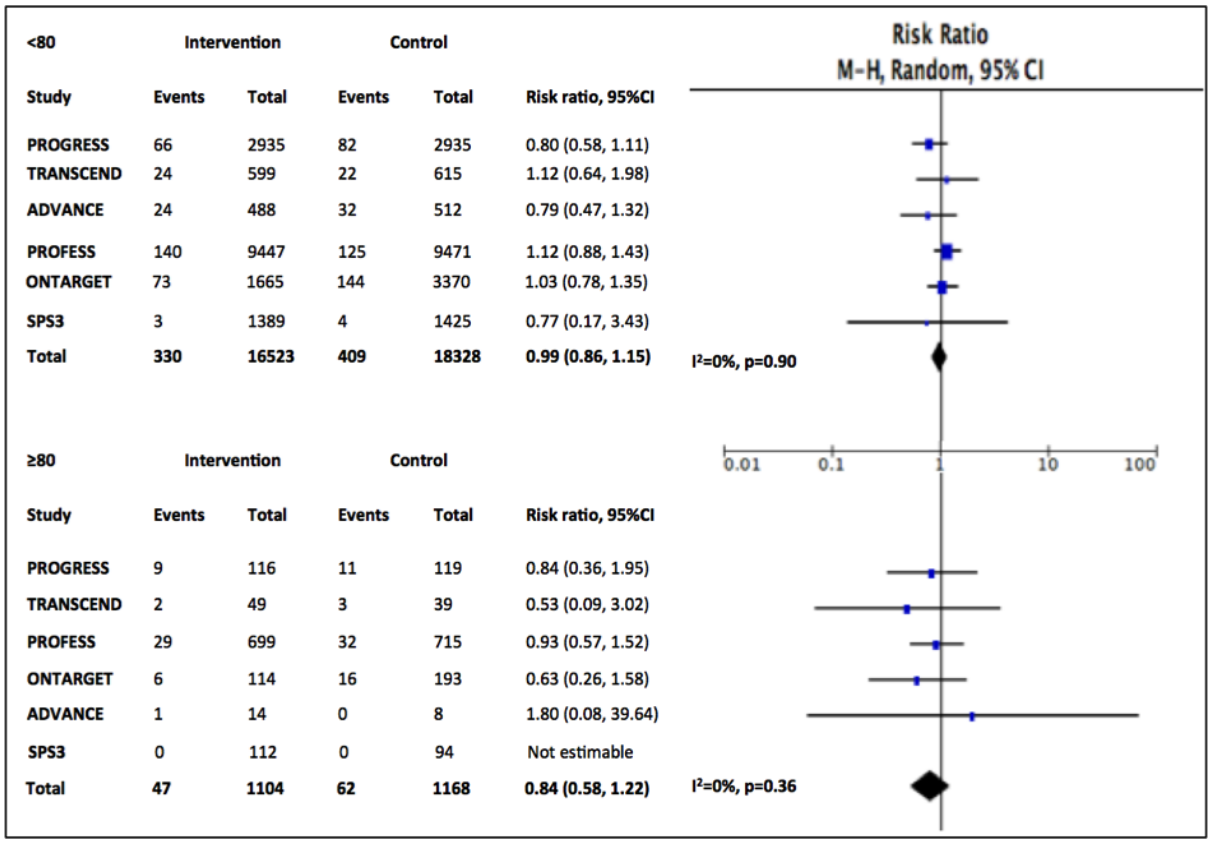
CI: confidence interval, M-H: Mantel-Haenszel

Figure S16: Hospitalisation For Heart Failure – Whole Sample Analysis



CI: confidence interval, M-H: Mantel-Haenszel

Figure S17: Hospitalisation For Heart Failure In Age Subgroups

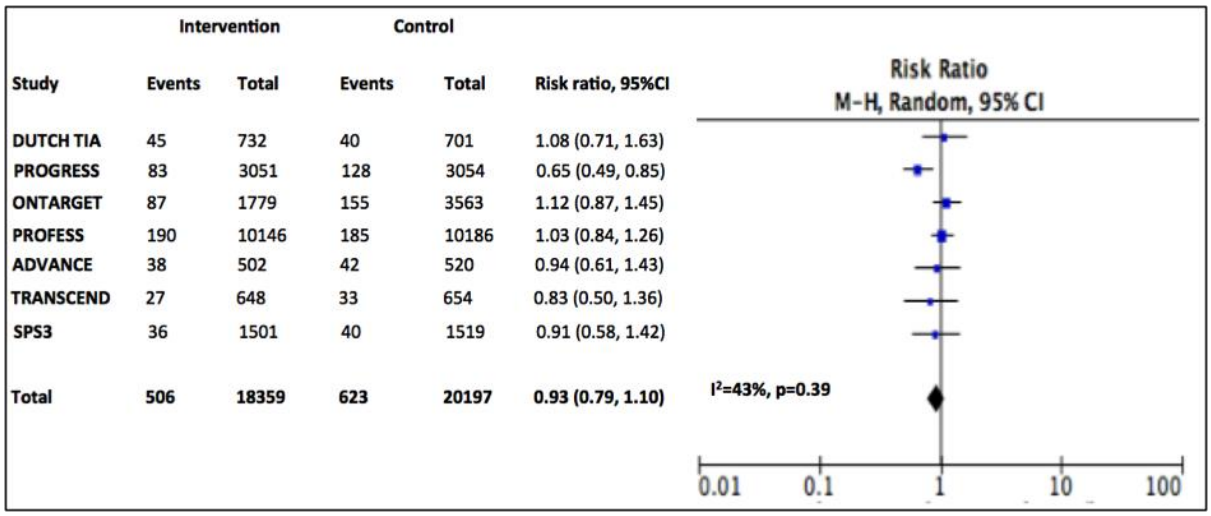


<80	Intervention		Control		
Study	Events	Total	Events	Total	Risk ratio, 95%CI
PROGRESS	66	2935	82	2935	0.80 (0.58, 1.11)
TRANSCEND	24	599	22	615	1.12 (0.64, 1.98)
ADVANCE	24	488	32	512	0.79 (0.47, 1.32)
PROFESS	140	9447	125	9471	1.12 (0.88, 1.43)
ONTARGET	73	1665	144	3370	1.03 (0.78, 1.35)
SPS3	3	1389	4	1425	0.77 (0.17, 3.43)
Total	**330**	**16523**	**409**	**18328**	**0.99 (0.86, 1.15)**
I^2=0%, p=0.90					

≥80	Intervention		Control		
Study	Events	Total	Events	Total	Risk ratio, 95%CI
PROGRESS	9	116	11	119	0.84 (0.36, 1.95)
TRANSCEND	2	49	3	39	0.53 (0.09, 3.02)
PROFESS	29	699	32	715	0.93 (0.57, 1.52)
ONTARGET	6	114	16	193	0.63 (0.26, 1.58)
ADVANCE	1	14	0	8	1.80 (0.08, 39.64)
SPS3	0	112	0	94	Not estimable
Total	**47**	**1104**	**62**	**1168**	**0.84 (0.58, 1.22)**
I^2=0%, p=0.36					

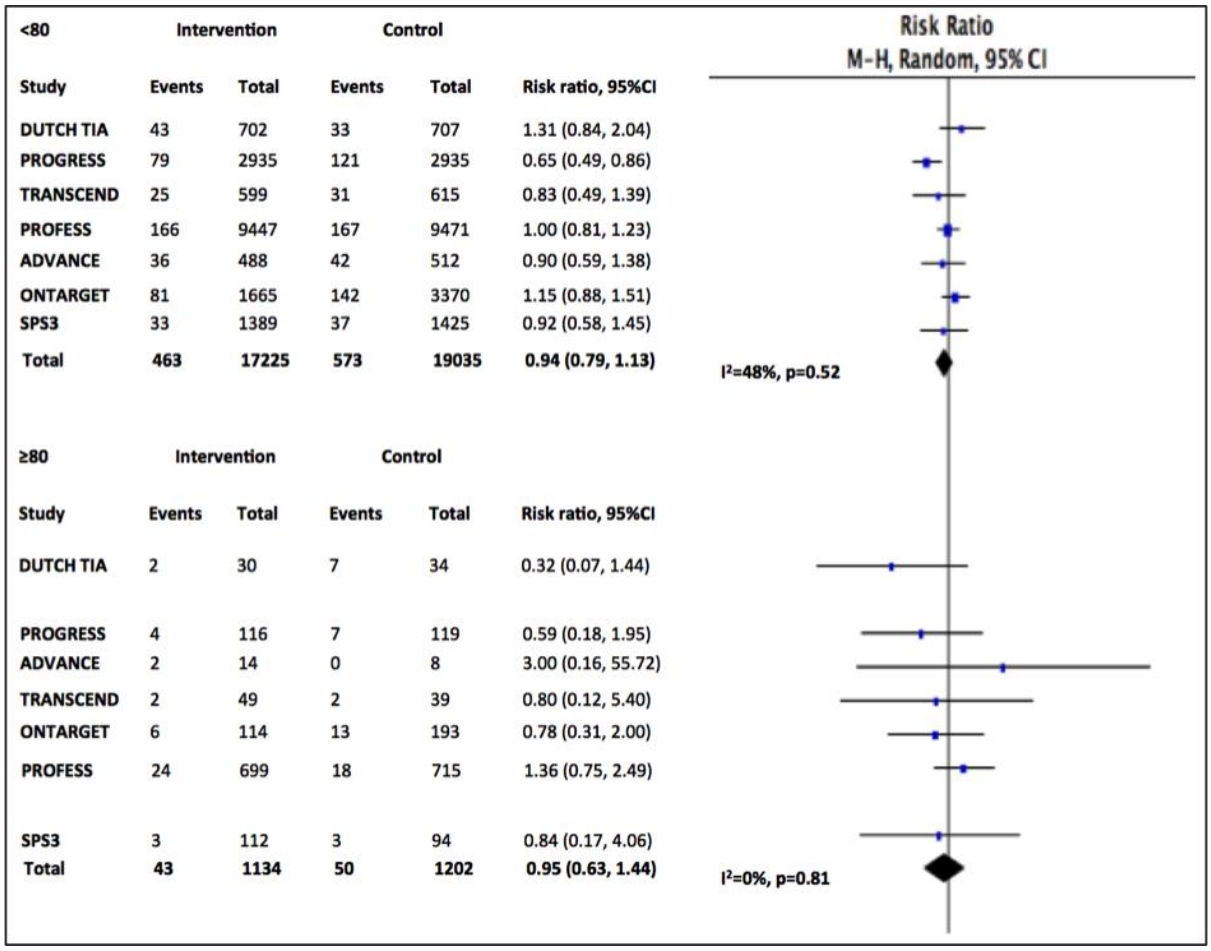
CI: confidence interval, M-H: Mantel-Haenszel

Figure S18: Fatal And Non-Fatal MI – Whole Sample Analysis



CI: confidence interval, M-H: Mantel-Haenszel

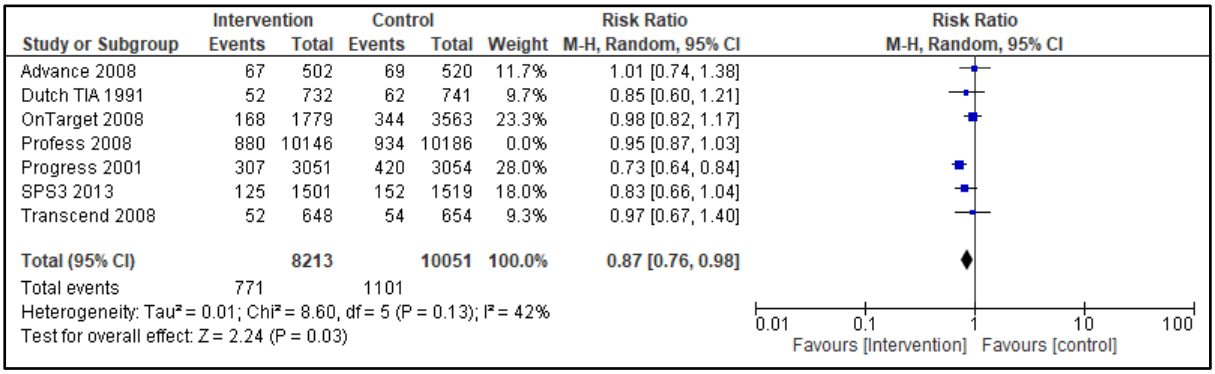
Figure S19: Fatal And Non-Fatal MI In Age Subgroups



CI: confidence interval, M-H: Mantel-Haenszel

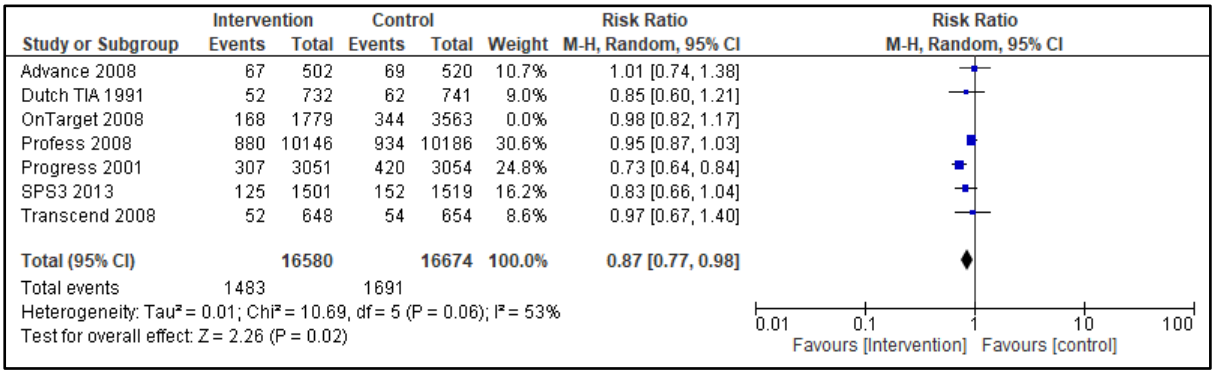
Leave one out analysis

Figure S20: Fatal and Non-Fatal Stroke Without PROFESS Study



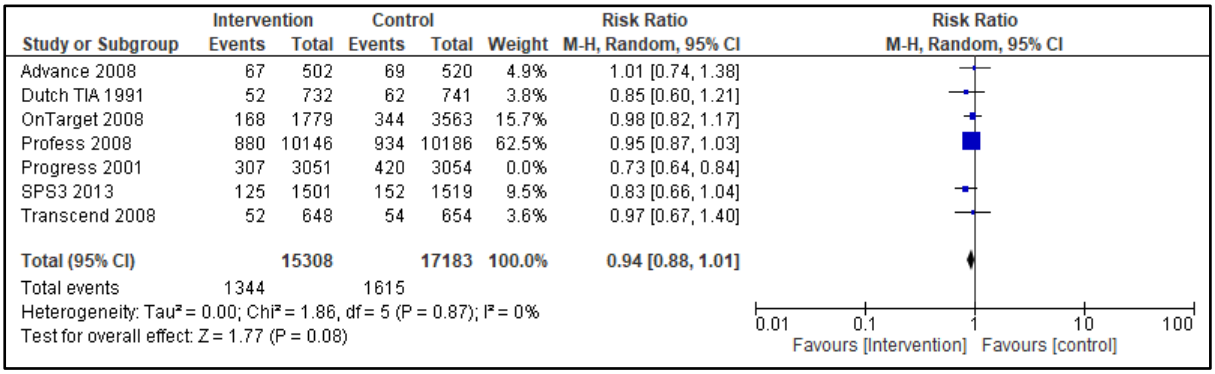
CI: confidence interval, M-H: Mantel-Haenszel

Figure S21: Fatal and Non-Fatal Stroke Without OnTARGET Study



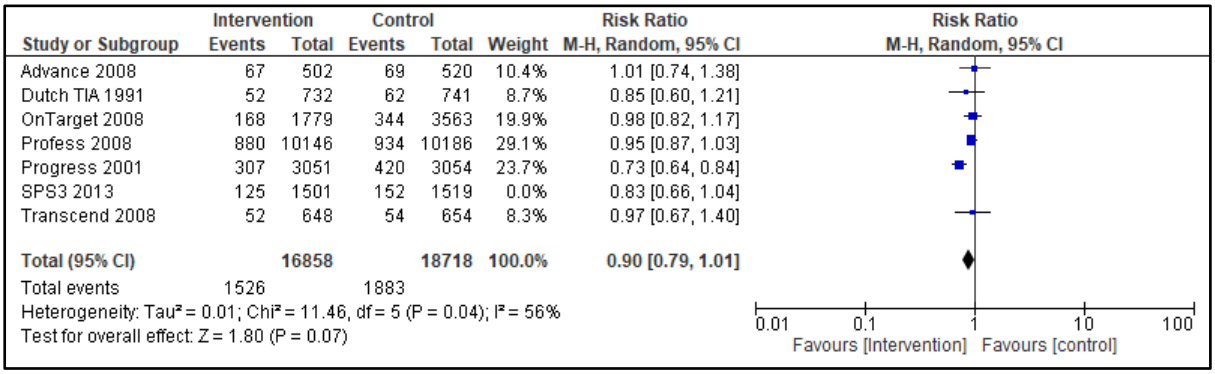
CI: confidence interval, M-H: Mantel-Haenszel

Figure S22: Fatal and Non-Fatal Stroke Without PROGRESS Study



CI: confidence interval, M-H: Mantel-Haenszel

Figure S23: Fatal and Non-Fatal Stroke Without SPS3 Study



CI: confidence interval, M-H: Mantel-Haenszel