Treatment of arterial hypertension in the very elderly: a meta-analysis of clinical trials

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Abstract

The benefits of lowering blood pressure are obvious for the population up to the age of 65 years, but whether and, if so, which treatment is beneficial in the very elderly population remains still a matter of debate. We conducted a meta-analysis of randomised controlled clinical trials with duration of at least 12 months and the analysis of cardiovascular endpoints in participants aged 75 years and over.

MEDLINE, CENTRAL (Cochrane Central Register of Controlled Trials) and the WHO-ISH Collaboration register were searched until October 20, 2009. Further, references from reviews, trials and previously published meta-analyses were analysed. A total of 10 studies were included providing morbidity and mortality data with a total of 8667 participants in the meta-analysis, with separate analyses for studies on isolated systolic hypertension. There were 148 non-fatal strokes and 287 cardiovascular morbidity and mortality events among treated patients, compared with 176 non-fatal strokes (p = 0.02) and 366 cardiovascular morbidity and mortality events (p = 0.0001) among control patients. Rates of heart failure were significantly reduced (64 vs. 121 events; p = 0.00001), total mortality remained unchanged (odds ratio 0.97). Further, 9 studies with 6933 participants were included in the systematic review of blood pressure reduction trials. The average blood pressure achieved at the end of the studies was 164/83 mmHg in the placebo group and 150/83 mmHg in the treatment group. At the beginning of the study blood pressure was 170.6/88.6 mmHg in the placebo group and 175.4/94.6 mmHg in the treatment group. Changes were only significant for systolic blood pressure in the treatment group (p = 0.0008).

Treating healthy subjects aged 75 years and older with moderate to severe hypertension reduces non-fatal strokes, cardiovascular morbidity and mortality and the incidence of heart failure but does not change total mortality.

Key words

- Antihypertensive treatment
- Clinical endpoints
- Elderly
- Hypertension

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1. Introduction

Why this meta-analysis?

Elevated blood pressure is a frequent diagnosis in the elderly and – owing to debilitating complications such as stroke or heart attack – a leading public health issue worldwide. The population of 65 years and older has the highest prevalence of hypertension and the lowest control rates [1]. According to the WHO/ISH classification hypertension is defined as diastolic blood pressure > 90 mmHg or systolic blood pressure > 140 mmHg. Repeated standardized readings should be taken after 5 min in the sitting position under practice conditions. Under these conditions, hypertension occurs in 70% of the elderly in Europe and in 60%–70% of elderly Americans [2].

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Beneficial clinical effects of treatment of arterial hypertension have been shown in a multitude of clinical studies for middle-aged patients and in those over 60 years of age. However, whether treatment is still beneficial in patients over 80 years remains a matter of debate. Many patients of this age group remain untreated, have inadequately controlled hypertension or are treated with inappropriate drugs [3]. In Germany, for the age group of the >75 year old men and women a prevalence of arterial hypertension of about 80% could be observed; of those, only 80% were diagnosed, and only 20% treated to target [4]. Despite evidence for positive treatment effects, there are concerns about an increased risk for events in patients with low blood pressure and several trials have been published describing this relationship as J-shaped. Especially in the vulnerable elderly this uncertainty is leading to reluctance in the use of antihypertensive agents [5]. The importance of answering these questions is rising with the fact that the octogenarians are the most rapidly growing segment of our population [6].

Until 1999, data on the protective effects of different antihypertensive drugs in hypertension in the very elderly have been limited to a subgroup analysis of trials originally designed for the age group of 60 years and older [7]. Since then, few clinical trials have been conducted to shed light on this important question, and therefore a new comprehensive literature search seemed to be necessary.

This is not a unique attempt as other meta-analyses on the same subject exist, for example [7–12], and recently a similar analysis by Bejan-Angoulvat et al. [13]. Musini et al. collected results of clinical trials in people 60 years and older and also conducted a subanalysis for the age group 80 years and older [14]. We extended the inclusion criteria to the age of 75 years and also accepted non placebo-controlled trials. These extensions of inclusion criteria were done in the light of the preponderance of one recent trial, the HYVET-trial [15] to cope with its obvious overruling in the meta-analysis by Musini et al. [14].

The recent analysis by Bejan-Angoulvat et al. [13] did not include the JATOS trial [16]. With this minor difference in mind, it still seems necessary to independently demonstrate congruent results on this important matter.

2. Methods

The conduct and the presentation of this meta-analysis are in accordance with the PRISMA statement [17].

2.1 Search strategy

The search included the electronic databases of MEDLINE and CENTRAL (Cochrane Central Register of Controlled Trials) until October 20, 2009 (no initiation limits) and, in addition, the WHO-ISH Collaboration register (August 1997). The trials registers “clinicaltrial.gov” and “controlled-trials.com” have been searched. The internet has been searched using “scholar.google.de”. The search strategy for screening the MEDLINE database was:


The search strategy for searching the other databases was:

“Hypertension” and “Blood pressure” and “Therapy” and “Elderly”.

This search led to 1092 hits. Both, title and abstract text of each record have been evaluated. In addition to the studies used in the subgroup meta-analysis of Guexflier et al. [7], three clinical studies (i.e., the HYVET trial, HYVET-Pilot trial and JATOS trial [15, 18, 16]) met the inclusion criteria (see below) for the actual meta-analysis on clinical endpoints. The search strategy for searching the CENTRAL database was:

“Hypertension” and “Blood pressure” and “Therapy” and “Elderly”.

This search led to 697 hits. Out of these, 26 trials have not been found in the MEDLINE-search, but did not report relevant clinical endpoints. Four of these trials are included in the analysis of blood pressure lowering effects.

2.2 Selection criteria

Randomised controlled trials on clinical endpoints of at least one year duration in hypertensive patients aged 75 years or older comparing antihypertensive drug therapy with placebo or no special treatment and assessing cardiovascular morbidity and mortality outcomes were included. All trials fulfilling the inclusion criteria were imported into an electronic bibliography as full text and arranged under predetermined conditions. Randomised controlled trials of at least six weeks duration in hypertensive patients aged 75 years or older comparing antihypertensive drug therapy with placebo or active treatment, assessing efficacy (blood pressure reduction) and tolerability were used in the analysis on blood pressure lowering effects.

2.2.1 Types of participants

Men and women of at least 75 years with arterial systo-diaistic or isolated systolic hypertension were included. Hypertension had to be defined as systolic blood pressure of at least 140 mmHg and/or diastolic blood pressure of at least 90 mmHg.

2.2.2 Types of interventions


2.2.3 Data collection and analysis

Outcomes assessed were total mortality, total cardiovascular morbidity and mortality, cardiovascular mortality, fatal and non-fatal strokes, coronary heart disease morbidity and mortality, coronary heart disease mortality, and heart failure.

Measures assessed for blood reduction trials were means and standard deviations of decrease in systolic and diastolic blood pressure comparing to placebo or no therapy, and assessing the reported adverse events. Unfortunately, data on renal failure were inconsistent in these studies, and were, thus, not ana-
lysed. No global quality scoring schemes for the assessment of the clinical trial conduct was used; however, important individual parameters of methodological quality have been assessed in detail. These included randomisation, allocation concealment, methods of blinding, percent of lost to follow-up. Each document was checked separately by a single person for the parameters mentioned above.

2.3 Statistics
Analyses of outcomes were based on intention-to-treat results. The RevMan (Review Manager) software was used (RevMan Version 5.0 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008), for statistics the SAS software Version 9.2 of the SAS System for Windows Copyright 2009, SAS Institute Inc. (USA).

Efficacy of each study was described by risk ratios and confidence intervals. Heterogeneity was tested by the I2 Test. Pooled risk differences obtained from a fixed-effects model were converted to numbers needed to treat using NNT = 1/risk difference. We calculated control rates, i.e. the number of events in the control group, to estimate the aggregate population risk for patients included in the individual trials. As not all trials contained all variables analysed, numbers of trials included in the analyses for the various parameters may differ as indicated in the legends. Means and standard deviations of blood pressure reduction of each included study were calculated and compared in a regression analysis.

3. Results
Ten studies on endpoints with a total of 8667 participants were included. Out of these trials, a total of seven have been included in the subgroup meta-analysis utilizing the INDNA database [7]. The HYVET trial and the HYVET-pilot trial were published in 2008 and 2003, respectively, the JATOS trial in 2008 [15, 18, 16]. The SHEP trial, the STOP trial and the SYST-EUR trial have been published after 1990, the remaining four studies before 1990.

Six of these studies were placebo-controlled, two studies observation controlled [18, 19], one study controlled by free therapy [20]; one study compared strict therapy versus mild therapy [16]. Three trials were especially designed for participants with isolated systolic hypertension [9, 21, 22]. 60% were female. The prevalence of smokers ranged from 4–11%, of stroke from 3–10%, of myocardial infarction from 3–10% and of diabetes mellitus from 7–24%. The age distribution ranged from 75–102 years with a median of 83 years. Most of the participants were recruited from industrialised countries. All except the CASTEL trial were multicenter studies.

Data of non-fatal outcomes from the EWPHE trial have not been included in our analyses, since these data are subject to a censoring bias [23]. Less than 10% of patients were lost to follow-up in all trials. There are six studies mentioning the method of blinding, eight studies describing the method of randomisation and four studies describing the method of allocation concealment. In more than 70% of trials, a thiazide-like diuretic was first line treatment in the observation group. All trials used a stepped care approach to reach a treatment effect. In SHEP pilot, SHEP, EWPHE and HYVET, treatment was started only on thiazide diuretics, in STOP and CASTEL it was started on either thiazide diuretic or β-blocker [15, 20–24].

Coope and Warrander used β-blockers, only, and in SYST-EUR calcium channel blockers plus ACE-inhibitors were applied [9, 19]. In HYVET pilot one treatment arm was started on a diuretic and another treatment arm on an ACE-inhibitor. The third trial arm aimed for observations without specific therapy [18]. In our meta-analysis we combined the two treatment arms with active therapy and compared them against the observation therapy arm. Second and third line drugs included diuretics, β-blockers, ACE-inhibitors, calcium channel blockers and centrally acting antiadrenergic agents. The results of the meta-analysis are compiled in Table 1.

The relative risk for non-fatal stroke was reduced to 0.78 (Fig. 1). Omitting the JATOS study, this effect becomes even more pronounced (0.68). Heterogeneity was 44% for this endpoint. For stroke mortality a trend

### Table 1: Active therapy vs. Control

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Active Therapy</th>
<th>Control</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coope and Warrander 1986</td>
<td>0</td>
<td>3</td>
<td>0.7%</td>
<td>1986</td>
</tr>
<tr>
<td>SHEP pilot</td>
<td>3</td>
<td>70</td>
<td>0.21 [0.05, 0.88]</td>
<td>1989</td>
</tr>
<tr>
<td>SHEP 1991</td>
<td>21</td>
<td>331</td>
<td>0.23 [0.32, 0.88]</td>
<td>1991</td>
</tr>
<tr>
<td>STOP 1991</td>
<td>10</td>
<td>122</td>
<td>1.10 [0.47, 2.83]</td>
<td>1991</td>
</tr>
<tr>
<td>SYST-EUR 1991</td>
<td>17</td>
<td>231</td>
<td>0.77 [0.42, 1.43]</td>
<td>1991</td>
</tr>
<tr>
<td>CASTEL 1994</td>
<td>6</td>
<td>47</td>
<td>0.91 [0.33, 2.52]</td>
<td>1994</td>
</tr>
<tr>
<td>JATOS 2008</td>
<td>35</td>
<td>935</td>
<td>1.52 [0.91, 2.55]</td>
<td>2008</td>
</tr>
<tr>
<td>HYVET pilot 2008</td>
<td>35</td>
<td>935</td>
<td>0.36 [0.11, 1.11]</td>
<td>2008</td>
</tr>
<tr>
<td>HYVET 2008</td>
<td>51</td>
<td>1932</td>
<td>0.73 [0.51, 1.04]</td>
<td>2008</td>
</tr>
</tbody>
</table>

Total (95% CI): 4520 (3963, 100.0%) 0.70 [0.63, 0.77]

| Test for overall effect: Z = 2.26 (P = 0.02) |

Fig. 1: Non-fatal stroke as outcome in 9 studies on antihypertensive treatment in patients aged 75 and above. M-H = Mantel-Haenszel-test, CI = confidence interval.
towards treatment causing a risk reduction of 0.83 was noted. Relative risk reduction for heart failure was 0.49 (Fig. 2). Heterogeneity was 33% in the I2 Test. For morbidity and mortality by cardiovascular disease, relative risk reduction was 0.75. In the three ISH trials risk reduction was less pronounced with a risk reduction of 0.77. For morbidity and mortality by coronary heart disease relative risk was 0.73. Stroke mortality was insignificantly changed to 0.83. Mortality of coronary heart disease showed a risk reduction of 0.79; however, there were only two studies aiming at this outcome. Mortality of cardiovascular conditions showed a discrete risk reduction of 0.94. For total mortality, the risk was at 0.97 (Fig 3) with a tendency to an increased treatment effect in the non-ISH studies (0.93). Without the HYVET-trial, a risk of 1.11 was measured. Total mortality remained unchanged (0.97).

Table 1: Endpoint effects in the meta-analysis of 10 trials on antihypertensive treatment in patients aged 75 and above.

<table>
<thead>
<tr>
<th></th>
<th>Stroke, non-fatal</th>
<th>Stroke, fatal</th>
<th>Congestive heart failure</th>
<th>Morbidity and mortality coronary heart disease</th>
<th>Mortality coronary heart disease</th>
<th>Morbidity and mortality cardiovascular disease</th>
<th>Mortality cardiovascular disease</th>
<th>Total mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined outcome RR with 95% CI</td>
<td>0.78 [0.63, 0.97]</td>
<td>0.83 [0.61, 1.13]</td>
<td>0.49 [0.37, 0.67]</td>
<td>0.73 [0.55, 0.96]</td>
<td>0.79 [0.58, 1.06]</td>
<td>0.75 [0.65, 0.86]</td>
<td>0.94 [0.81, 1.10]</td>
<td>0.97 [0.87, 1.08]</td>
</tr>
<tr>
<td>RRR</td>
<td>26%</td>
<td>22%</td>
<td>49.30%</td>
<td>40%</td>
<td>17%</td>
<td>21%</td>
<td>12%</td>
<td>11.30%</td>
</tr>
<tr>
<td>ARR</td>
<td>1.17%</td>
<td>0.56%</td>
<td>2.20%</td>
<td>2%</td>
<td>0.50%</td>
<td>2.40%</td>
<td>1%</td>
<td>1.73%</td>
</tr>
<tr>
<td>NNT</td>
<td>85</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>44%</td>
<td>7%</td>
<td>33%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-ISH-studies RR with 95% CI</td>
<td>0.89 [0.69, 1.15]</td>
<td>0.81 [0.58, 1.14]</td>
<td>0.47 [0.31, 0.69]</td>
<td>0.66 [0.45, 0.94]</td>
<td>0.72 [0.49, 1.05]</td>
<td>0.74 [0.62, 0.88]</td>
<td>0.93 [0.78, 1.11]</td>
<td>0.93 [0.82, 1.06]</td>
</tr>
<tr>
<td>RRR</td>
<td>23%</td>
<td>23%</td>
<td>1.90%</td>
<td>56.00%</td>
<td>26%</td>
<td>26%</td>
<td>16%</td>
<td>2.40%</td>
</tr>
<tr>
<td>ARR</td>
<td>0.80%</td>
<td>0.60%</td>
<td>54%</td>
<td>3%</td>
<td>0.60%</td>
<td>2.80%</td>
<td>1.50%</td>
<td>16.70%</td>
</tr>
<tr>
<td>NNT</td>
<td>53</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>0%</td>
<td>36%</td>
<td>36%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>59%</td>
</tr>
<tr>
<td>ISH-studies RR with 95% CI</td>
<td>0.59 [0.40, 0.86]</td>
<td>0.92 [0.43, 1.97]</td>
<td>0.53 [0.34, 0.84]</td>
<td>0.86 [0.56, 1.32]</td>
<td>0.92 [0.56, 1.52]</td>
<td>0.77 [0.60, 0.99]</td>
<td>0.98 [0.69, 1.38]</td>
<td>1.10 [0.88, 1.38]</td>
</tr>
<tr>
<td>RRR</td>
<td>42%</td>
<td>14%</td>
<td>46%</td>
<td>1.10%</td>
<td>8%</td>
<td>16%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>ARR</td>
<td>4.70%</td>
<td>3%</td>
<td>4%</td>
<td>16%</td>
<td>0.40%</td>
<td>4%</td>
<td>0.30%</td>
<td></td>
</tr>
<tr>
<td>NNT</td>
<td>21</td>
<td>25%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>24%</td>
<td>0%</td>
<td>52%</td>
<td>0%</td>
<td>34%</td>
<td>0%</td>
<td>0%</td>
<td>23%</td>
</tr>
<tr>
<td>blinded studies RR with 95% CI</td>
<td>0.69 [0.54, 0.88]</td>
<td>0.85 [0.60, 1.21]</td>
<td>0.47 [0.34, 0.65]</td>
<td>0.76 [0.57, 1.1]</td>
<td>0.84 [0.62, 1.15]</td>
<td>0.73 [0.62, 0.85]</td>
<td>0.93 [0.78, 1.12]</td>
<td>0.96 [0.85, 1.08]</td>
</tr>
<tr>
<td>RRR</td>
<td>29.30%</td>
<td>18.50%</td>
<td>50.80%</td>
<td>18%</td>
<td>22%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARR</td>
<td>1.50%</td>
<td>4.50%</td>
<td>2.10%</td>
<td>0.11%</td>
<td>1.30%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNT</td>
<td>66</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>17%</td>
<td>22%</td>
<td>40%</td>
<td>0%</td>
<td>32%</td>
<td>73%</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>Non-blinded studies RR with 95% CI</td>
<td>1.11 [0.74, 1.68]</td>
<td>0.76 [0.40, 1.43]</td>
<td>0.68 [0.33, 1.43]</td>
<td>0.43 [0.14, 1.26]</td>
<td>0.24 [0.05, 1.04]</td>
<td>0.89 [0.64, 1.23]</td>
<td>0.98 [0.71, 1.36]</td>
<td>1.07 [0.84, 1.36]</td>
</tr>
<tr>
<td>RRR</td>
<td>37%</td>
<td>9%</td>
<td>13%</td>
<td>21%</td>
<td>8%</td>
<td>0.90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARR</td>
<td>1.20%</td>
<td>0.20%</td>
<td>3%</td>
<td>3%</td>
<td>1.20%</td>
<td>6.30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNT</td>
<td>33%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>48%</td>
<td>19%</td>
<td>33%</td>
<td>0%</td>
<td>0%</td>
<td>34%</td>
<td>60%</td>
<td></td>
</tr>
</tbody>
</table>

RRR = relative risk reduction, RR = relative risk, ARR = absolute risk reduction, NNT = number needed to treat, ISH = isolated systolic hypertension, CI = confidence interval.
Nine trials on blood pressure lowering efficacy and tolerability profile of at least six weeks duration were found in addition to the HYVET and HYVET pilot trial; the efficacy of blood pressure reduction was analysed in 11 trials. The blood pressure characteristics of the other eight trials’ evaluation endpoints included in this review were not available. We included 6933 participants in total, 4974 participants in the treatment group and 1959 participants in the control group, respectively. The median duration of follow-up is 60 weeks, ranging from 6–208 weeks.

In the placebo group systolic blood pressure was 170.6 mmHg and diastolic blood pressure 88.6 mmHg at the study begin. These figures were 164.6 mmHg and 83.6 mmHg at study end.

In the active treatment group systolic blood pressure changed from 175.4 to 150 mmHg, diastolic blood pressure from 94.6 to 83 mmHg. Only the active therapy group showed a statistically significant effect on the systolic blood pressure compared with placebo (p = 0.0008). Regression analysis demonstrated that the treatment effect for systolic blood pressure was significantly more pronounced in the trials conducted after the year 2000 (p = 0.0015). Compared to placebo, every single drug class had a statistically significant effect on the reduction of systolic blood pressure with P-values between 0.0016–0.0042. Furthermore, active therapy showed a significant effect on diastolic blood pressure values compared to placebo (p = 0.043). The effect of β-blockers compared with placebo on the diastolic blood pressure in the present analysis is not significantly different (p = 0.7349). All other drug classes show significant effects compared with placebo (p = 0.034–0.01). Because of the small numbers of trial participants receiving specific drug classes the comparison of results obtained with particular drug classes was not feasible.

4. Discussion
Outcomes are clearly improved by antihypertensive treatment; this applies to disabling and restricting conditions like stroke, heart attack and heart failure. The reduction in fatal and nonfatal stroke found here is consistent with the results in the analysis conducted by Gueyffier et al. [7] and Bejan-Angoulvat et al. [13]. These results are also similar but slightly smaller in size than in the age group of the 60–70 year old participants, as described by Mulsow et al. [25]. However, a consider-
able heterogeneity for nonfatal stroke should be taken into account (\(p < 0.07\)).

The absent impact of treatment on death from any cause is in line with results from ref. [46]. This lack of effect is remarkable, as a reduction of major cardiovascular endpoints part of which may be lethal should be reflected by lower global mortality as well. Rates of death by stroke range as high as 50% in the age group in literature [26]. This absence of effect on overall mortality may reflect the fact that the studies are underpowered regarding this rarer event; on the other hand, there is still concern of causing harm to the very elderly. Increased mortality of any cause and of death from stroke by antihypertensive treatment as results of J-curve type effects have pointed to negative outcomes in over-treated individuals [5]. Death from any cause was significantly reduced only in the HYVET study and death caused by stroke only in two other studies (SHEP and SHEP pilot). Removing the HYVET trial, the risk of death is not significantly affected by active treatment. As this trial accounts for 54% of the weight in this meta-analysis, it is worth to discuss whether this trial should be given a priority in the evaluation of this parameter, and would be sufficient to substantiate even the mortality effect. Also, a considerable heterogeneity (\(p < 0.06\)) exists for this parameter. The fact that not only placebo-controlled trials but also open and active control trials were included, certainly contributed to this heterogeneity.

As the results of the HYVET trial suggest, prescription of newer drugs to elderly and very elderly patients might lead to a larger risk reduction. Increased intensity of antihypertensive therapy and blood pressure lowering between the groups could be a further explanation for the larger risk reduction. The meta-analysis by Bejan-Angoulvat et al. [13] was performed including the subgroup analysis from Gueyffier and the HYVET trial with total mortality as the main outcome. The authors suggest a possible correlation between total mortality and the intensity of antihypertensive treatment and the related reduction of systolic blood pressure. The treatment effect on stroke outcome is the only significantly changed endpoint which is most pronounced in patients with isolated systolic hypertension in our analysis. As shown in several studies, isolated systolic hypertension is known to be a predominant risk indicator for stroke [9, 21]; the results here promote isolated systolic hypertension into the status of a risk factor as its treatment is positively correlated with stroke risk reduction.

Risk reduction for heart failure of 0.49 (95% 0.37 – 0.67) was the largest treatment effect observed here. The general prevalence is about 2–3%, and rises in the age group 70–80 years to 10–20% [27]. Antihypertensive treatment in the very elderly thus seems to be more effective to prevent heart failure than stroke – a finding which has not yet been appreciated elsewhere.

The combined risk for morbidity and mortality from cardiovascular conditions is also significantly reduced by antihypertensive treatment. Even when removing the HYVET trial, a statistically significant risk reduction is observed. This result is in line with the Cochrane Collaboration reviews by Musini et al. and Mulrow et al. [14, 25] but not reported in [13]. As in most clinical trials, the patients included in the studies in this meta-analysis appeared to be healthier than those in the global population, as the overall rates of stroke, heart attack, the prevalence of diabetes, smoking and need for nursing care at baseline were low compared to other studies [3, 28].

It is still controversial how far blood pressure should be lowered in the elderly. Most commonly, 140 mmHg systolic blood pressure is set as the goal, e.g. in the guidelines of the ESH/ESC [29]. Based on the large HYVET study a systolic value of 150 mmHg seems to be both practical and safe to guarantee a positive benefit-risk ratio. The authors of the JATOS and CASE-J trials conducted post-hoc analyses assessing the optimal blood pressure. In the very elderly, it could be noticed that event rates rose with the reduction of systolic blood pressure lower than 140 mmHg. Taking the results from HYVET and the post-hoc analysis from JATOS and CASE-J together, the preferred treatment target would be a value between 140–150 mmHg systolic, with more evidence available for 150 than for 140 mmHg. It is obvious that treatment goals have to be individualized, and additional conditions (e.g. diastolic blood pressure which should not be lowered below 60 mmHg, or excessive blood pressure decreases upon postural changes) should be considered. In our search we found only two trials directly comparing strict versus mild treatment [16, 28]. Both trials were conducted in Japan. In the JATOS trial, mild treatment led to mean blood pressure values of 145.6/78.1 mmHg and strict treatment to values of 135.9/74.8 mmHg. In the strict treatment group the incidences of the primary endpoint were significantly lower. In the CASE-J trial cardiovascular risk was not different for systolic blood pressures from 140 – 149 mmHg compared with that for systolic blood pressures lower than 130 mmHg.

In this context, the differential therapy by different agent groups remains largely unclear. For elderly patients (aged 65 and above), renin-angiotensin system (RAS) blockers and long acting calcium antagonists seem preferable to other drug classes such as betablockers (higher incidence of diabetes mellitus, inferior endpoint results in LIFE [30]) or thiazide-type diuretics (potentially life-threatening electrolyte disorders, low compliance, superiority of the combination of ACE-inhibitor/calcium antagonist over ACE-inhibitor/thiazide-type diuretic in the ACCOMPLISH trial, [31]) as recommended e.g. in the ESC/ESH guideline [29]. The current meta-analysis did not allow for comparisons between different drug classes regarding their endpoint efficacy. In terms of drug class differentiation, we conducted a regression analysis that revealed that studies conducted after the year 2000 reached a more pro-
ounced decrease of systolic blood pressure. This is in line with the assumption that newer agents (RAS blockers and calcium antagonists as opposed to diuretics and betablockers) may be more effective than older ones. These results show that antihypertensive therapy significantly reduces cerebrovascular and cardiovascular morbidity in patients older than 75 years in good general condition and with mild to moderate systolic and systo-diastolic hypertension. The mortalities of coronary heart disease and cardiovascular events and the total mortality are not significantly reduced.

Renal failure was not consistently reported or even considered as exclusion criteria (HYVET) in the studies; to analyse renal function separately would be desirable as hypertension is a strong risk factor for renal failure.

Despite the additional inclusion of the JATOS trial, this meta-analysis largely confirms the recent findings by Bejan-Angoulvat et al. [13] but adds more detailed information on secondary endpoints. The optimal treatment size is not yet clear and should be carefully considered in future trials and clinical practice. Taking this together, the data describe an important example for the so-called compression of morbidity, a concept based on the desirable improvement of quality of life even in end-of-life situations in which extension of longevity cannot be provided.

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Conflicts of Interest

Petra Schall has nothing to declare. Martin Wehling was employed by AstraZeneca R&D, Mölnadal, as director of discovery medicine (= translational medicine) from 2004–2006, while on sabbatical leave from his professorship at the University of Heidelberg. After return to this position in January 2007, he received lecturing and consulting fees from Sanofi-Aventis, Novartis, Takeda, Roche, Pfizer, Bristol-Myers Squibb, Daiichi-Sankyo, Lilly and Novo-Nordisk.

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