Articles

Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial

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Summary

Background Despite treatment, there is often a higher incidence of cardiovascular complications in patients with hypertension than in normotensive individuals. Inadequate reduction of their blood pressure is a likely cause, but the optimum target blood pressure is not known. The impact of acetylsalicylic acid (aspirin) has never been investigated in patients with hypertension. We aimed to assess the optimum target diastolic blood pressure and the potential benefit of a low dose of acetylsalicylic acid in the treatment of hypertension.

Methods 18 790 patients, from 26 countries, aged 50–80 years (mean 61·5 years) with hypertension and diastolic blood pressure between 100 mm Hg and 115 mm Hg (mean 105 mm Hg) were randomly assigned a target diastolic blood pressure. 6264 patients were allocated to the target pressure ≤90 mm Hg, 6264 to ≤85 mm Hg, and 6262 to ≤80 mm Hg. Felodipine was given as baseline therapy with the addition of other agents, according to a five-step regimen. In addition, 9399 patients were randomly assigned 75 mg/day acetylsalicylic acid (Bamycor, Astra) and 9391 patients were assigned placebo.

Findings Diastolic blood pressure was reduced by 20·3 mm Hg, 22·3 mm Hg, and 24·3 mm Hg, in the ≤90 mm Hg, ≤85 mm Hg, and ≤80 mm Hg target groups, respectively. The lowest incidence of major cardiovascular events occurred at a mean achieved diastolic blood pressure of 82·6 mm Hg; the lowest risk of cardiovascular mortality occurred at 86·5 mm Hg. Further reduction below these blood pressures was safe. In patients with diabetes mellitus there was a 51% reduction in major cardiovascular events in target group ≤80 mm Hg compared with target group ≤90 mm Hg (p for trend=0·005). Acetylsalicylic acid reduced major cardiovascular events by 15% (p=0·03) and all myocardial infarction by 36% (p=0·002), with no effect on stroke. There were seven fatal bleeds in the acetylsalicylic acid group and eight in the placebo group, and 129 versus 70 non-fatal major bleeds in the two groups, respectively (p<0·001).

Interpretation Intensive lowering of blood pressure in patients with hypertension was associated with a low rate of cardiovascular events. The HOT Study shows the benefits of lowering the diastolic blood pressure down to 82·6 mm Hg. Acetylsalicylic acid significantly reduced major cardiovascular events with the greatest benefit seen in all myocardial infarction. There was no effect on the incidence of stroke or fatal bleeds, but non-fatal major bleeds were twice as common.

*Study organisation given at end of paper

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Introduction

The background and rationale of the Hypertension Optimal Treatment (HOT) Study have been presented previously in some detail.[1] In brief, it is well documented that treatment of hypertension reduces cardiovascular morbidity and mortality.[2,3] However, it is obvious that treated patients with hypertension remain at a greater risk of developing cardiovascular complications than matched normotensive individuals.[4,5] One possible explanation could be that the blood pressure of the patients with hypertension has not been lowered to strictly normotensive levels.[6] Indeed, epidemiological surveys in various parts of the world indicate that less than 30% of patients with hypertension have their blood pressure brought down below 140/90 mm Hg.[7,8] In addition, concerns have been expressed that too vigorous reduction in blood pressure may be associated with increased cardiovascular risk—the so-called J-curve concept.[9–12] The issue of how far blood pressure should be lowered to achieve the greatest benefit, in terms of reduced cardiovascular morbidity and mortality, has been a matter of scientific debate.[13] The real issue is not whether the relation between achieved blood pressure and cardiovascular events is J-shaped (it must be), but whether there are additional benefits, or risks, in lowering blood pressure of patients with hypertension to fully normotensive levels—ie, between 70 mm Hg and 85 mm Hg diastolic blood pressure—or whether there is little further benefit in lowering diastolic blood pressure much below 90 mm Hg.[14] This issue needed to be

addressed in a randomised and prospective trial and this was one of the reasons for doing the present study.

Another possible approach to improving treatment benefits in patients with hypertension is that of associating antihypertensive therapy with correction of other cardiovascular risk factors. Acetylsalicylic acid (aspirin) has been shown to reduce the incidence of stroke and myocardial infarction when given long term to healthy individuals or patients with previous cardiovascular events[15–17] but its effects in individuals without a history of cardiovascular disease have been less clear and more controversial.[18,19] However, no intervention studies with acetylsalicylic acid have been done in patients with hypertension, possibly because the use of acetylsalicylic acid has been associated with a small increase in the risk of cerebral haemorrhage; a risk that could be greater in hypertension.

The principal aims of this study were: to assess the association between major cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) and the target blood pressures ≤90 mm Hg, ≤85 mm Hg, and ≤80 mm Hg during antihypertensive treatment; to assess the association between major cardiovascular events and the diastolic blood pressure achieved during treatment; and to find out whether the addition of low doses of acetylsalicylic acid to antihypertensive treatment reduces the rate of major cardiovascular events.

Methods

Study population and organisation

The patient population in the HOT Study has been described previously.[20] In brief, 19 193 patients from 26 countries, aged 50–80 years (mean 61·5 years), with hypertension and a diastolic blood pressure between 100 mm Hg and 115 mm Hg (mean 105 mm Hg) were randomly assigned a target blood pressure and acetylsalicylic acid or placebo. Because of the suspicion of incorrect inclusion or data handling at one centre, 403 patients were excluded early in the trial. Patients were recruited from countries in Europe, North and South America, and Asia.[20] The average follow-up time was 3·8 years (range 3·3–4·9 years) and the total number of patient years was 71 051. The first patient was enrolled in October, 1992, randomisation ended in April, 1994, and the last day of follow-up was Aug 31, 1997.

Patients were randomly assigned to one of three diastolic blood pressure target groups: ≤90 mm Hg, ≤85 mm Hg, or ≤80 mm Hg with the Prospective, Randomised, Open with Blinded Endpoint evaluation (PROBE) design.[21] Patients were randomised in a double-blind way, to a low dose, 75 mg daily, of acetylsalicylic acid (Bamycor, Astra) or identical-looking placebo tablets. Patients were randomised on the basis of the following baseline
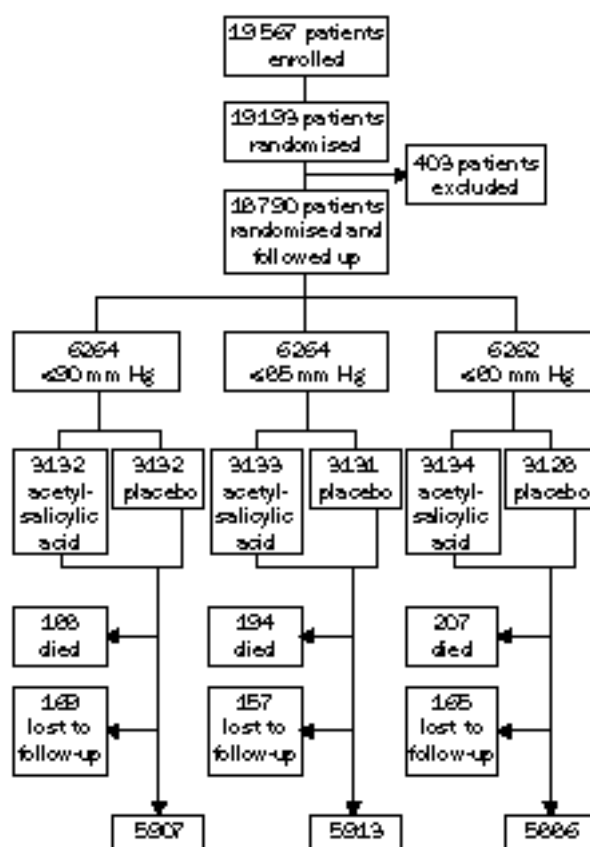

Figure 1: **Trial profile**

variables: age, sex, previous antihypertensive therapy, smoking, previous myocardial infarction, previous other coronary heart disease (CHD), previous stroke, and diabetes mellitus.[22] The randomisation was computer-generated based on communications by fax between investigators and the Study Coordinating Centre at Östra Hospital, Göteborg, Sweden. Patient characteristics by target group at randomisation are shown in table 1.

The HOT Study was approved by ethics committees in all participating countries and all patients gave their informed consent at the time of enrolment.

A total of 1904 investigators were involved in the study, mainly general practitioners and physicians at hospital outpatient clinics. The scientific aspects of the study were governed by the Executive and Steering Committees. An Independent Clinical Event Committee evaluated all events (masked). Throughout the study an Independent Safety Committee had full access to all events (open). In each country one or more monitors were in regular contact with the investigators to oversee the practical aspects of the study. An Independent Data Audit Committee visited randomly selected centres to audit the trial in accordance with the rules of the American Food and Drug Administration.

Treatment

Antihypertensive therapy, with the long-acting calcium antagonist felodipine at a dose of 5 mg once a day, was given to all patients. Additional therapy and dose increments in four further steps were prescribed to reach the randomised target blood pressure. Angiotensin converting enzyme (ACE) inhibitors or β-blockers were added at step two and dosage titrations were used at steps three (felodipine 10 mg once a day) or four (doubling the dose of either the ACE inhibitor or the β-blocker), with the possibility of adding a diuretic at step five.[1]

Blood pressures were measured with an oscillometric semi-automatic device (Visomat OZ, D2, International, Hestia, Germany). During the study the Visomat OZ, D2 apparatus was subjected to the tests of blood-pressure-measuring equipment

	Diastolic blood pressure target group		
	≤90 mm Hg (n=6264)	≤85 mm Hg (n=6264)	≤80 mm Hg (n=6262)
Age (years)	61·5 (7·5)	61·5 (7·5)	61·5 (7·5)
Body-mass index (kg/m²)	28·4 (4·7)	28·5 (4·7)	28·4 (4·6)
Diastolic blood pressure (mm Hg)	105 (3·4)	105 (3·4)	105 (3·4)
Systolic blood pressure (mm Hg)	170 (14·4)	170 (14·0)	170 (14·1)
Serum creatinine (μmol/L)	89 (26)	89 (23)	89 (23)
Serum cholesterol (mmol/L)	6·0 (1·1)	6·1 (1·1)	6·1 (1·2)
Men/women (%)	53/47	53/47	53/47
Previous treatment (%)	52·3	52·7	52·6
Smokers (%)	15·9	15·8	15·9
Previous MI (%)	1·6	1·5	1·5
Other previous CHD (%)	5·9	6·0	5·9
Previous stroke (%)	1·2	1·2	1·2
Diabetes mellitus (%)	8·0	8·0	8·0

Data are mean (SD) or % of group. MI=myocardial infarction; CHD=coronary heart disease.

Table 1: **Characteristics at randomisation**

	Diastolic blood pressure target group		
	≤90 mm Hg	≤85 mm Hg	≤80 mm Hg
Felodipine (%)	77	78	79
ACE inhibitors (%)	35	42	45
β-blockers (%)	25	28	32
Diuretics (%)	19	22	24

ACE=angiotensin converting enzyme.

Table 2: **Treatment at the end of the study**

proposed by the British Hypertension Society[23] and was found to meet those stringent criteria.[24]

Blood pressure was measured three times with the patient seated after they had had 5 min rest at each prerandomisation visit, at randomisation, 3 months, and 6 months after randomisation and thereafter twice a year; a final visit was made within 1 month of Aug 31, 1997.

Definition of events

Major cardiovascular events were defined as all (fatal and non-fatal) myocardial infarctions, all (fatal and non-fatal) strokes, and all other cardiovascular deaths. Silent myocardial infarctions were documented by taking an electrocardiogram (ECG) at randomisation and at the final visit.

A classification of all reported events was made by the Independent Clinical Event Committee based on all available information (hospital records, physician's records, death certificates, and necropsy reports). All events were classified without any knowledge of the actual medication or the treatment group to which the patients had been assigned. The approval rate of reported events by this committee was 76%.

If death occurred within 28 days of the onset of an event, that event was classified as fatal. If no obvious non-cardiovascular cause of death was identified, the death was subsequently classified as cardiovascular. For the diagnosis of non-fatal myocardial infarction at least two of the following criteria had to be fulfilled: central chest pain lasting for more than 15 min, transient elevation of enzymes indicating myocardial damage, or typical electrocardiographic changes. For the diagnosis of fatal myocardial infarction the above criteria were required or the diagnosis was to be stated in hospital records or described in the necropsy report.

A 12-lead resting ECG was recorded at randomisation and at the final visit. All ECGs were coded with the Minnesota code.[25] The baseline ECGs were coded for signs of myocardial infarction (codes 1:1 or 1:2) as well as for signs of ischaemia (codes 4:1-2 or 5:1-2). An ECG was recorded at randomisation in 96% of all patients. A final ECG was recorded in 89% of all patients. The final ECGs were coded only for myocardial infarction (codes 1:1 and 1:2). In total, 54 911 codings were made. The final ECGs were compared with the baseline ECGs by two independent technicians. If discrepancies arose, the ECG Committee members made the final classification. A finding of new Q or QS waves (codes 1:1 or 1:2), without clinical signs of myocardial infarction, was defined as a silent myocardial infarction.

Diagnosis of a non-fatal stroke required unequivocal signs or symptoms of remaining neurological deficit, with a sudden onset and a duration of more than 24 h. Diagnosis of a fatal stroke also required the criteria given above. Alternatively, the diagnosis could be given in the hospital records or described in the necropsy report.

Statistical methods

The power calculations were based on the STOP Hypertension study[26] in which the average cardiovascular risk increased, both below and above a diastolic blood pressure of 80 mm Hg, by 3% per mm Hg, with narrow confidence limits. On the basis of these calculations 40 000 patient years were expected to yield the necessary number of events.

In the analysis of trends and differences between target groups and the effects of acetylsalicylic acid compared with placebo, a Cox proportional-hazards model was used to calculate relative risks.

In the analysis of the different events in relation to achieved blood pressure (mean since entry) a Poisson model was used.[27] The

	Mean (SD) blood pressure by diastolic blood pressure target group		
	≤90 mm Hg	≤85 mm Hg	≤80 mm Hg
Systolic blood pressure (mm Hg)			
Baseline	169·8 (14·4)	169·5 (14·0)	169·7 (14·1)
Achieved*	143·7 (11·3)	141·4 (11·7)	139·7 (11·7)
Difference	26·2 (13·0)	28·0 (13·2)	29·9 (13·6)
Diastolic blood pressure (mm Hg)			
Baseline	105·4 (3·4)	105·4 (3·4)	105·4 (3·4)
Achieved*	85·2 (5·1)	83·2 (4·8)	81·1 (5·3)
Difference	20·3 (5·6)	22·3 (5·4)	24·3 (5·8)

*Mean of all blood pressures from 6 months of follow-up to end of study.

Table 3: **Blood pressure at baseline and achieved blood pressure in the study**

logarithm of the hazard rate was modelled as a continuous function of mean blood pressure by connected linear and quadratic pieces in specified intervals. Time dependent (updated) information was used for the covariates current age, time from entry, and blood pressure from every 6 months. Two-tailed tests were used.

Results

Study population

6264 patients were given the diastolic blood-pressure target of ≤90 mm Hg, 6264 a target of ≤85 mm Hg, and 6262 a target of ≤80 mm Hg (figure 1). In addition, 9399 patients were randomly assigned acetylsalicylic acid and 9391 patients were assigned placebo. A total of 491 (2·6%) patients were lost to follow-up. Most were lost early in the study—eg, 130 patients did not return for any of the follow-up visits. The loss in terms of patient years was 1269 (1·8%). The loss of patients in the three target groups was 169 from the ≤90 mm Hg target group, 157 from the ≤85 mm Hg target group, and 165 from the ≤80 mm Hg target group. 245 of those randomised to acetylsalicylic acid were lost and 246 were lost from the placebo group. The average age at randomisation of those lost was 61·3 years and was 61·5 years for those remaining in the study. Blood pressures of patients lost to follow-up and of patients remaining in the study were identical at randomisation. The age, sex distribution, previous morbidity, and previous antihypertensive treatment did not differ between those lost to follow-up and the remainder of the patients, who form the basis for this report.

Treatment

At the end of the study 78% of patients were still taking felodipine as baseline therapy, usually together with an ACE inhibitor (41%) or a β-blocker (28%; table 2). Side-
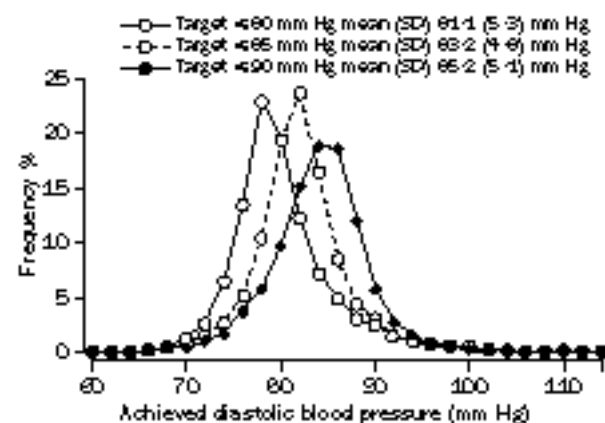

Figure 2: **Distribution of mean diastolic blood pressures from 6 months' follow-up to the end of the study**

Event	Number of events	Events/ 1000 patient-years	p for trend	Comparison	Relative risk (95% CI)
Major cardiovascular events					
≤90 mm Hg	232	9·9		90 vs 85	0·99 (0·83–1·19)
≤85 mm Hg	234	10·0		85 vs 80	1·08 (0·89–1·29)
≤80 mm Hg	217	9·3	0·50	90 vs 80	1·07 (0·89–1·28)
Major cardiovascular events, including silent myocardial infarction					
≤90 mm Hg	274	11·7		90 vs 85	0·99 (0·84–1·17)
≤85 mm Hg	276	11·8		85 vs 80	1·05 (0·88–1·24)
≤80 mm Hg	263	11·3	0·66	90 vs 80	1·04 (0·88–1·23)
All myocardial infarction					
≤90 mm Hg	84	3·6		90 vs 85	1·32 (0·95–1·82)
≤85 mm Hg	64	2·7		85 vs 80	1·05 (0·74–1·48)
≤80 mm Hg	61	2·6	0·05	90 vs 80	1·37 (0·99–1·91)
All myocardial infarction, including silent cases					
≤90 mm Hg	127	5·4		90 vs 85	1·19 (0·92–1·54)
≤85 mm Hg	107	4·6		85 vs 80	1·00 (0·76–1·30)
≤80 mm Hg	107	4·6	0·19	90 vs 80	1·19 (0·92–1·53)
All stroke					
≤90 mm Hg	94	4·0		90 vs 85	0·85 (0·64–1·11)
≤85 mm Hg	111	4·7		85 vs 80	1·24 (0·94–1·64)
≤80 mm Hg	89	3·8	0·74	90 vs 80	1·05 (0·79–1·41)
Cardiovascular mortality					
≤90 mm Hg	87	3·7		90 vs 85	0·97 (0·72–1·30)
≤85 mm Hg	90	3·8		85 vs 80	0·93 (0·70–1·24)
≤80 mm Hg	96	4·1	0·49	90 vs 80	0·90 (0·68–1·21)
Total mortality					
≤90 mm Hg	188	7·9		90 vs 85	0·97 (0·79–1·19)
≤85 mm Hg	194	8·2		85 vs 80	0·93 (0·77–1·14)
≤80 mm Hg	207	8·8	0·32	90 vs 80	0·91 (0·74–1·10)

Table 4: **Events in relation to target blood pressure groups (n=6264, 6264, and 6262 in the target groups ≤90 mm Hg, ≤85 mm Hg, and ≤80 mm Hg, respectively)**

effects caused by the study medication during the trial have been reported in detail.[28,29] In brief, the proportion of patients with reported side-effects decreased gradually throughout the trial, from 16·9% at 3 months to 2·2% at the final visit.

Blood pressure

Compared with blood pressure at the time of randomisation, average diastolic blood pressure was reduced by 20·3 mm Hg, 22·3 mm Hg, and 24·3 mm Hg and systolic blood pressure by 26·2 mm Hg, 28·0 mm Hg, and 29·9 mm Hg in the target groups ≤90 mm Hg, ≤85 mm Hg, and ≤80 mm Hg, respectively (table 3). In the three target groups, the diastolic blood pressure was reduced from a mean of 105 mm Hg to a mean of 85·2 mm Hg, 83·2 mm Hg, and 81·1 mm Hg, respectively. The distribution curves of diastolic blood pressure for the three target groups are shown in figure 2. A diastolic blood pressure greater than 90 mm Hg was found in 12% of the patients in the target group ≤90 mm Hg, 7% in the target group ≤85 mm Hg, and in 6% of the patients randomised to the target group ≤80 mm Hg. The proportion of patients reaching the randomised target blood pressure increased gradually up to the 36-month visit. There were no differences in achieved blood pressure between patients randomised to acetylsalicylic acid or placebo (142·0/83·2 mm Hg and 141·4/82·9 mm Hg, respectively).

Events in relation to target group

The results of this analysis are summarised in table 4. To make the results comparable with those of other intervention studies and since 14% of the ECGs could not be obtained, silent myocardial infarctions were analysed separately. Differences in event rates between the target

groups were rather small and only the trend for the rate of all myocardial infarction to be lower at a lower target blood pressure was of borderline significance (a 25% event reduction in the target group ≤85 mm Hg and a 28% reduction in the target group ≤80 mm Hg as compared with the target group ≤90 mm Hg).

In 1501 patients with diabetes mellitus at baseline (table 5), a decline in the rate of major cardiovascular events was seen in relation to the target group (p for trend=0·005). In the group randomised to ≤80 mm Hg the risk of major cardiovascular events was halved in comparison with that of the target group ≤90 mm Hg. This change was attenuated but remained significant when silent myocardial infarctions were included. The approximate halving of the risk was also observed for all myocardial infarction, although it was not significant. All stroke also showed a declining rate with lower target blood-pressure groups, with a risk reduction of about 30% in the ≤80 mm Hg target group *vs* ≤90 mm Hg target group. Cardiovascular mortality was also significantly lower in the ≤80 mm Hg target group than in each of the other target groups.

In 3080 patients with ischaemic heart disease (IHD) at baseline (defined as patients with previous myocardial infarction, other previous CHD, or the Minnesota codes 1:1-2, 4:1-2, or 5:1-2 in the baseline ECG) major cardiovascular events declined non-significantly in relation to target groups (77, 68, and 62, respectively, in the target groups ≤90 mm Hg, ≤85 mm Hg, and ≤80 mm Hg). All stroke showed a significant reduction (p for trend=0·046; 35, 30, and 20, respectively in the three target groups). There was a 43% reduction in ≤80 mm Hg target group compared with ≤90 mm Hg target group.

Event	Number of events	Events/ 1000 patient-years	p for trend	Comparison	Relative risk (95% CI)
Major cardiovascular events					
≤90 mm Hg	45	24·4		90 vs 85	1·32 (0·84–2·06)
≤85 mm Hg	34	18·6		85 vs 80	1·56 (0·91–2·67)
≤80 mm Hg	22	11·9	0·005	90 vs 80	2·06 (1·24–3·44)
Major cardiovascular events, including silent myocardial infarction					
≤90 mm Hg	48	26·2		90 vs 85	1·13 (0·75–1·71)
≤85 mm Hg	42	23·3		85 vs 80	1·42 (0·89–2·26)
≤80 mm Hg	30	16·4	0·045	90 vs 80	1·60 (1·02–2·53)
All myocardial infarction					
≤90 mm Hg	14	7·5		90 vs 85	1·75 (0·73–4·17)
≤85 mm Hg	8	4·3		85 vs 80	1·14 (0·41–3·15)
≤80 mm Hg	7	3·7	0·11	90 vs 80	2·01 (0·81–4·97)
All myocardial infarction, including silent cases					
≤90 mm Hg	18	9·7		90 vs 85	1·12 (0·57–2·19)
≤85 mm Hg	16	8·7		85 vs 80	1·07 (0·53–2·16)
≤80 mm Hg	15	8·1	0·61	90 vs 80	1·20 (0·60–2·38)
All stroke					
≤90 mm Hg	17	9·1		90 vs 85	1·30 (0·63–2·67)
≤85 mm Hg	13	7·0		85 vs 80	1·10 (0·50–2·40)
≤80 mm Hg	12	6·4	0·34	90 vs 80	1·43 (0·68–2·99)
Cardiovascular mortality					
≤90 mm Hg	21	11·1		90 vs 85	0·99 (0·54–1·82)
≤85 mm Hg	21	11·2		85 vs 80	3·0 (1·29–7·13)
≤80 mm Hg	7	3·7	0·016	90 vs 80	3·0 (1·28–7·08)
Total mortality					
≤90 mm Hg	30	15·9		90 vs 85	1·03 (0·62–1·71)
≤85 mm Hg	29	15·5		85 vs 80	1·72 (0·95–3·14)
≤80 mm Hg	17	9·0	0·068	90 vs 80	1·77 (0·98–3·21)

Table 5: **Events in patients with diabetes mellitus at baseline in relation to target blood pressure groups (n=501, 501, and 499 in the target groups ≤90 mm Hg, ≤85 mm Hg, and ≤80 mm Hg, respectively)**
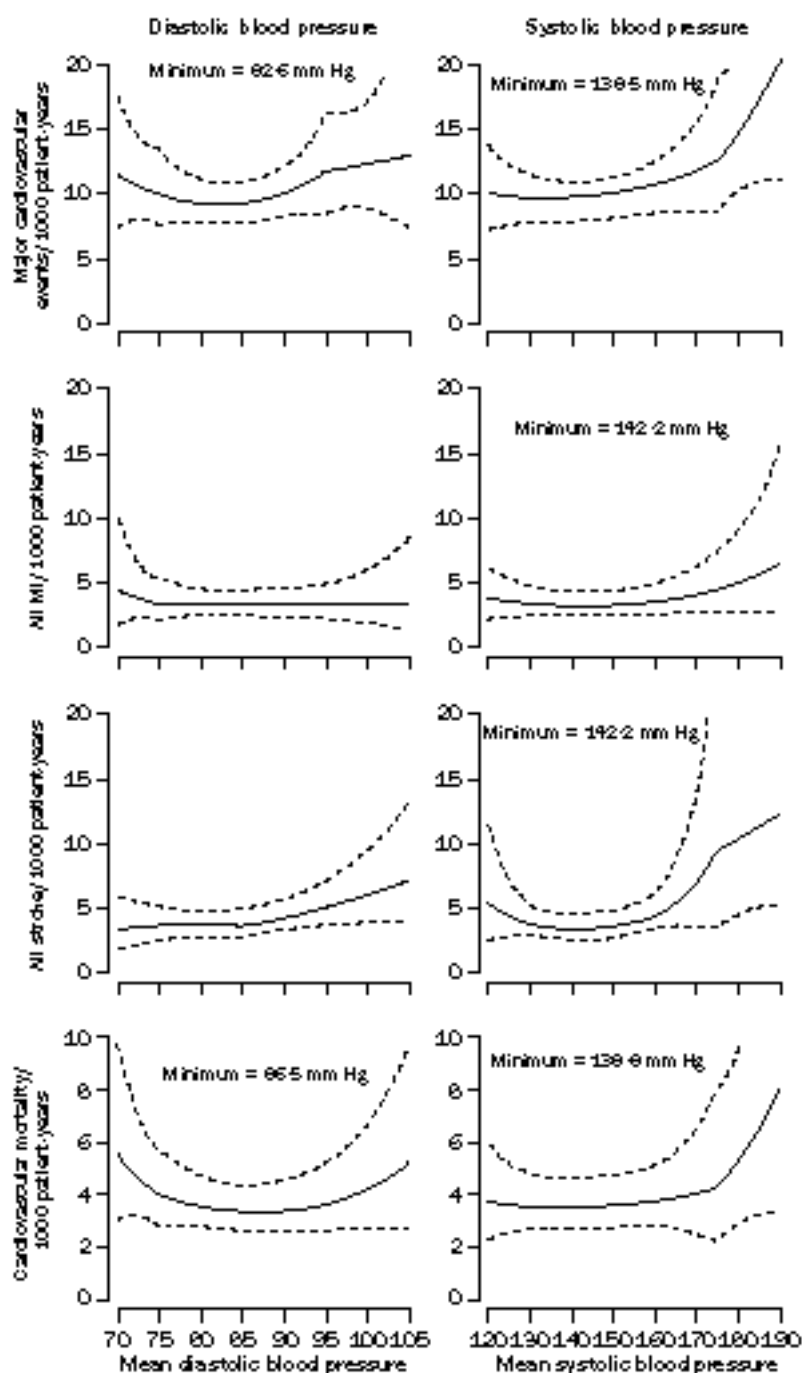
Figure 3: Estimated incidence (95% CI) of cardiovascular events in relation to achieved mean diastolic and systolic blood pressure
The blood pressure at the lowest point of the curve is indicated (minimum).

Events in relation to achieved blood pressure
Major cardiovascular events, all myocardial infarction, all stroke, and cardiovascular mortality in relation to the achieved diastolic and systolic blood pressure are shown in figure 3. The CIs are narrowest in the diastolic blood pressure range of 75–95 mm Hg and between 130 mm Hg and 170 mm Hg for systolic blood pressure, suggesting adequate precision of the estimated risk within these limits.

For major cardiovascular events the lowest point of risk was at a mean achieved diastolic blood pressure of 82·6 mm Hg and at a mean systolic blood pressure of 138·5 mm Hg.

For all myocardial infarction there was no definite minimum diastolic blood pressure, whereas the minimum

risk was reached at a systolic blood pressure of 142·2 mm Hg. For all stroke the lowest risk was below 80 mm Hg diastolic blood pressure and at 142·2 mm Hg for systolic blood pressure. The lowest risk of cardiovascular mortality was at 86·5 mm Hg and 138·8 mm Hg for diastolic and systolic blood pressure, respectively.

Effects of acetylsalicylic acid
The rates of various types of cardiovascular events in patients randomised to either acetylsalicylic acid or placebo is summarised in table 6.

Acetylsalicylic acid significantly (p=0·03) reduced major cardiovascular events by 15%. The benefit of acetylsalicylic acid was reduced to 9% when silent myocardial infarctions were included in the analysis. All myocardial infarction was 36% less frequent in the acetylsalicylic acid group, a significant difference (p=0·002). Inclusion of silent myocardial infarction reduced the benefit of acetylsalicylic acid to 15%. There was no difference in stroke incidence between patients randomised to acetylsalicylic acid or placebo. Cardiovascular mortality and total mortality were non-significantly lower by 5% (p=0·65) and 7% (p=0·36), respectively, in acetylsalicylic-acid treated patients compared with patients receiving placebo. The relative benefit of acetylsalicylic acid on major cardiovascular events and all myocardial infarction was about the same in the groups of patients with diabetes mellitus and IHD as in the whole HOT population.

In the context of the study comparing acetylsalicylic acid with its placebo, careful attention was paid to bleeding events (table 7). Fatal bleeds (including cerebral) were equally common in the two groups, but non-fatal major bleeds were significantly more frequent among patients receiving acetylsalicylic acid than in those receiving placebo (risk ratio 1·8, p<0·001); minor bleeds were also 1·8 times more frequent among patients who were on acetylsalicylic acid.

Discussion
Blood-pressure effects of treatment
An important finding is that substantial reductions in blood pressure can be achieved with a treatment regimen based on the long-acting calcium antagonist, felodipine. Even in patients who were receiving treatment before enrolment (52·6%) there was a striking further reduction in blood pressure with the treatment regimen used.[20] The overall reductions in diastolic and systolic blood pressures are striking—eg, in comparison with those reported in the meta-analysis by Collins and colleagues[2] (5–6 mm Hg reduction in diastolic blood pressure and 9–10 mm Hg in systolic blood pressure). However, the blood-pressure

Events	Number of events	Events/ 1000 patient-years	p	Relative risk (95% CI)
Major cardiovascular events				
Acetylsalicylic acid	315	8·9		
Placebo	368	10·5	0·03	0·85 (0·73–0·99)
Major cardiovascular events, including silent myocardial infarction				
Acetylsalicylic acid	388	11·1		
Placebo	425	12·2	0·17	0·91 (0·79–1·04)
All myocardial infarction				
Acetylsalicylic acid	82	2·3		
Placebo	127	3·6	0·002	0·64 (0·49–0·85)
All myocardial infarction, including silent cases				
Acetylsalicylic acid	157	4·4		
Placebo	184	5·2	0·13	0·85 (0·69–1·05)
All stroke				
Acetylsalicylic acid	146	4·1		
Placebo	148	4·2	0·88	0·98 (0·78–1·24)
Cardiovascular mortality				
Acetylsalicylic acid	133	3·7		
Placebo	140	3·9	0·65	0·95 (0·75–1·20)
Total mortality				
Acetylsalicylic acid	284	8·0		
Placebo	305	8·6	0·36	0·93 (0·79–1·09)

Table 6: **Events in relation to acetysalicylic acid (n=9399) or placebo (n=9391)**

	Acetylsalicylic acid (n=9399)	Placebo (n=9391)
Fatal bleeds		
Total	7	8
Gastrointestinal	5	3
Cerebral	2	3
Other	··	2
Non-fatal major bleeds		
Total	129	70
Gastrointestinal	72	34
Cerebral	12	12
Nasal	22	12
Other	23	12
Minor bleeds		
Total	156	87
Gastrointestinal	30	18
Nasal	66	24
Purpura	45	25
Other	15	20

Table 7: **Bleeding events reported in acetylsalicylic-acid treated and placebo-treated patients**

reduction observed in this study is not in relation to a placebo group but to baseline values, and we do not know how much the placebo effect would have subtracted from the blood-pressure reduction observed in the patients during active treatment.

The medication administered was well tolerated, the only reported adverse effects that exceeded 2% were dizziness, headache, leg oedema, flushing, and coughing, the latter three to a large extent attributable to the use of the calcium antagonist and ACE inhibitors. It is worth noting that a careful study of patient well-being showed an overall improvement as compared with baseline and that this improvement was better in the ≤80 mm Hg target group than in the other target groups. Well-being was also better the lower the achieved blood pressure and complaints of headache were fewer the lower the blood pressure.[30]

Effects of reduction of blood pressure on cardiovascular events

The small difference in the blood-pressure reduction in the three target groups made it difficult to recognise significant differences in event rates between the three groups, except for myocardial infarction. In patients with diabetes, the rates of major cardiovascular events and of cardiovascular deaths were lower the lower the target blood pressure. Furthermore, the number of events was lower than expected, despite a treatment follow-up period of 3·8 years (instead of the 2·5 years as initially planned). Moreover, 24% of all investigator-reported events were rejected by the Clinical Event Committee since they did not meet the classification criteria, leaving 724 validated cardiovascular events occurring in 683 patients, which substantially reduced the power of the study.

Further insight comes from the analysis of events in relation to achieved blood pressure, an analysis described in the study protocol. This analysis demonstrates the concept of the benefits induced by lowering blood pressure from the values prevailing at the time of randomisation into the normotensive range, down to and below the upper normal limit of 140/90 mm Hg. This analysis also gives

some indication of minimum blood pressures—ie, the values around which the maximum benefits of treatment can be expected, these being systolic values between 130 mm Hg and 140 mm Hg, and diastolic values between 80 mm Hg and 85 mm Hg.

In analysing event rates in relation to achieved blood pressure, a potential source of error is to involve future information. This has been avoided in our study by the method described. A time-dependent model—ie, a model updated in its covariates—was used. Since the model updated past mean of blood pressure, the time since randomisation, and the age every 6 months, no future information was used to analyse prospective event rate. Thus, only appropriate past information was used in estimation of curves and confidence bands. Nevertheless, the estimated curves must be interpreted with caution, especially at the lowest and highest levels of blood pressure. At the extreme ends of the curves, patients with high risks due to coexisting disorders, such as malignancies and alcohol abuse, may accumulate. This phenomenon may introduce bias in the conclusion on the optimum blood pressure during antihypertensive treatment.

Curves relating events to achieved blood pressure also give some indication of the number of events that could presumably be prevented in the study population by lowering blood pressure from the highest values present before randomisation, down to the minimum blood pressures. The major-cardiovascular-event curve suggests that from five to ten cardiovascular events can be prevented in every 1000 patients treated for 1 year. However, most of this benefit is achieved by lowering systolic blood pressure to about 140 mm Hg and diastolic blood pressure to about 90 mm Hg, and only a small further benefit is obtained by reducing blood pressure any further. This conclusion agrees with a previous post-hoc analysis of the Medical Research Council mild hypertension trial[31], which showed that the relation between on-treatment blood pressure and stroke flattens below systolic values of 135–140 mm Hg and diastolic values of 85–90 mm Hg, with no evidence of an increased incidence at lower values. Similar indications result from a post-hoc analysis of the IPPPSH Study.[32]

An additional lowering of blood pressure below minimum values does not produce a further reduction in events, but it is not harmful. There was no evidence of a J-shaped curve for the relation of major cardiovascular events, all myocardial infarction, all stroke, and

cardiovascular mortality with achieved blood pressures, at least in the ranges observed in our study (down to 70 mm Hg diastolic, and 120 mm Hg systolic). This was also true in the subgroup of more than 3000 patients with signs or history of ischaemic heart disease at randomisation.

We did find a slight, though non-significant, increase in cardiovascular deaths at the lowest level of blood pressure. As pointed out by Collins and Peto,[33] because of the relatively short duration of trials of antihypertensive therapy, analyses of mortality are potentially unreliable and "less informative than indirect assessment of that effect, based on analyses of the proportional effects of treatment on total stroke and on total coronary events". Also, the slight increase in cardiovascular mortality was not due to an increase in fatal myocardial infarctions or fatal strokes at the lowest achieved blood pressure.

There was also a small non-significant increase in total mortality with declining blood pressure, which was observed in the analysis of total mortality both in relation to target group and to achieved blood pressure. This increase was only partly accounted for by the increase in cardiovascular mortality. The small increment of total deaths in patients with the lowest blood pressures may be accounted for by the blood-pressure lowering of poor health rather than by treatment.

There was a very low event rate in this study, lower than expected when the sample size was calculated taking into account the event rates in actively treated patients in the trial meta-analysis by Collins and colleagues[2] as revised by Collins and Peto.[33] All deaths were 8·3 per 1000 patient years in our study compared with 12·3 in the Collins and Peto meta-analysis; cardiovascular mortality was 3·8 versus 6·5; all stroke 4·2 versus 4·4; and all myocardial infarction 3·0 versus 7·8, respectively. The event incidence was much lower in our study despite a higher mean age (61·5 years versus 56 years, respectively). Total mortality and cardiovascular mortality in the HOT population were lower than in the Renfrew-Paisley control population of similar age, a rate which was reported to be much lower than in the treated patients of the Glasgow Clinic.[5] It is therefore likely that the particularly low event rate in our study is due to the effective blood-pressure control—ie, only 8·5% of treated patients had diastolic blood pressures higher than 90 mm Hg. Alternatively, the particularly low rate of cardiovascular events may be attributed to the prevalence of modern antihypertensive agents in the treatment regimen (78% of patients receiving felodipine, 41% an ACE inhibitor, and 28% a β-blocker vs 22% receiving a diuretic).

Effects of association of acetylsalicylic acid with antihypertensive treatment

The effect of acetylsalicylic acid has not previously been assessed in a prospective randomised trial of patients with hypertension. Acetylsalicylic acid has, however, been extensively studied in secondary prevention of myocardial infarction or of ischaemic cerebrovascular disease. Meta-analyses of these studies[15] indicate that in these categories of patients, acetylsalicylic acid offers substantial protection against myocardial infarction, stroke, and cardiovascular death. Primary prevention of cardiovascular events by acetylsalicylic acid has been investigated in only two large studies,[18,19] with controversial effects, one trial reporting no effect on myocardial infarction or stroke,[18] the other a significant reduction in myocardial infarctions but a slightly increased risk of stroke among acetylsalicylic acid-

treated patients. Hypertension has often been considered a contraindication to acetylsalicylic acid because of the concern that possible benefits in the prevention of coronary events may be counterbalanced by an increased risk of cerebral bleeding.

The investigation of the effects of a small dose of acetylsalicylic acid versus placebo in treated patients with hypertension, as we did in this study, provides very clear evidence of a substantial beneficial action of acetylsalicylic acid on fatal and non-fatal acute myocardial infarctions, the incidence of which was reduced by as much as 36% (with the possibility of a benefit between 15 and 51%), and the prevention of 1·5 myocardial infarctions per 1000 patients treated for 1 year (and 2·5 myocardial infarctions per 1000 patient-years in patients with diabetes mellitus) in addition to the benefit achieved by antihypertensive therapy per se. The relative benefit of acetylsalicylic acid in patients with hypertension as far as myocardial infarction is concerned has been found similar to that observed in studies on patients with previous myocardial infarction or coronary disease.[17] This benefit was achieved without any additional risk of strokes, which occurred at the same rates in patients with hypertension receiving acetylsalicylic acid or placebo. Consequently, a significant benefit was also observed for major cardiovascular events, which were reduced by 15%. There was also a non-significant trend towards a lower cardiovascular mortality and total mortality in patients with hypertension receiving acetylsalicylic acid. Inclusion of silent myocardial infarction among events limited the benefits of acetylsalicylic acid, suggesting that silent myocardial infarctions may sometimes result as a less severe event, from the prevention of an acute myocardial infarction.

Although the number of fatal bleeds was similar in the acetylsalicylic acid and placebo groups, the overall rate of major and minor bleeds (mainly gastrointestinal and nasal) was about 1·8 times higher in the acetylsalicylic acid group. Excess bleeding was not higher in the patients in our study than reported with the same dose of acetylsalicylic acid in secondary prevention,[16] where the use of acetylsalicylic acid is now considered standard therapy. The advantages of using acetylsalicylic acid in hypertension have been shown in extremely well treated patients with hypertension, such as those in our study, and do not necessarily extend to less well treated patients with hypertension. Also acetylsalicylic acid has the same relative benefit in prevention of acute myocardial infarction as in patients with previous myocardial infarction. Because relative benefit is comparable in these two groups there is a lower absolute benefit of acetylsalicylic acid in well treated patients with hypertension because of their much lower risk of myocardial infarction.

Conclusion

The principal results of the HOT Study demonstrate the benefits of lowering blood pressure in patients with hypertension to 140 mm Hg systolic and 85 mm Hg diastolic, or lower. Efforts to lower blood pressure further, down to 120 mm Hg systolic and 70 mm Hg diastolic, appear to give little further benefit, but do not cause any significant additional risk. Active lowering of blood pressure was particularly beneficial in the subgroup of patients with diabetes mellitus. On the whole, the rate of cardiovascular events observed during treatment initiated with the calcium antagonist felodipine was much lower than that observed in previous prospective trials with

diuretic or β-blocker-initiated treatment, probably because of the pronounced lowering of blood pressure in this study.

Association of a small dose of acetylsalicylic acid with active antihypertensive treatment reduced the risk of acute myocardial infarction without exaggerating the risk of cerebral bleeding. Association of acetylsalicylic acid with antihypertensive therapy can therefore be recommended, provided that blood pressure is well controlled and the risk of gastrointestinal and nasal bleeding is carefully assessed.

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