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Cardiovascular Events in Elderly Patients with Isolated Systolic Hypertension. A Subgroup Analysis of Treatment Strategies in STOP-Hypertension-2

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Objective: To perform a subgroup analysis on those patients in STOP-Hypertension-2 who had isolated systolic hypertension. *Design and methods:* The STOP-Hypertension-2 study evaluated cardiovascular mortality and morbidity in elderly hypertensives comparing treatment with conventional drugs (diuretics, beta-blockers) with that of newer ones [angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists]. In all, 6614 elderly patients with hypertension (mean age 76.0 years, range 70–84 years at baseline) were included in STOP-Hypertension-2. In the present subgroup analysis of STOP-Hypertension-2, isolated systolic hypertension was defined as systolic blood pressure at least 160 mmHg and diastolic blood pressure below 95 mmHg, in accordance with the Syst-Eur and Syst-China study criteria. In total, 2280 patients in STOP-Hypertension-2 met these criteria. In the study, patients were randomized to one of three treatment groups: "conventional" antihypertensive therapy with beta-blockers or diuretics (atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, or fixed-ratio hydrochlorothiazide 25 mg plus amiloride 2.5 mg daily); ACE inhibitors (enalapril 10 mg or lisinopril 10 mg daily); or calcium antagonists (felodipine 2.5 mg or isradipine 2.5 mg daily). Analysis was by intention to treat. *Results:* The blood pressure lowering effect in patients with systolic hypertension was similar with all three therapeutic regimens: 35/13 mmHg in the conventional group ($n = 717$), 34/12 mmHg in the ACE inhibitor group ($n = 724$), and 35/13 mmHg in the calcium antagonist group ($n = 708$). Prevention of cardiovascular mortality, the primary endpoint of the study, did not differ between the three treatment groups. All stroke events, i.e. fatal and non-fatal stroke together, were significantly reduced by 25% in the newer-drugs group compared with the conventional group (95% CI 0.58–0.97; $p = 0.027$). This difference was attributable to reduction of non-fatal stroke while fatal stroke events did not differ between groups. New cases of atrial fibrillation were significantly increased by 43% (95% CI 1.02–1.99; $p = 0.037$) on "newer" drugs compared with "conventional" therapy, mainly attributable to the calcium antagonists. There were no significant differences between the three treatment groups with respect to the risks of myocardial infarction, sudden death or congestive heart failure. *Conclusions:* The analysis demonstrated that "newer" therapy (ACE inhibitors/calcium antagonists) was significantly better (25%) than "conventional" (diuretics/beta-blockers) in preventing all stroke in elderly patients with isolated systolic hypertension.
Key words: Hypertension, STOP-2, elderly, stroke, myocardial infarction.

INTRODUCTION

Systolic blood pressure (SBP) is a well-established and important predictor for cardiovascular disease and mortality [1]. In Western as well as Asian populations, SBP is positively and continuously related to the risk of stroke over a broad blood pressure (BP) range [1–3]. The Multiple Risk Factor Intervention Trial (MRFIT) [4] showed that the great majority of excess deaths occurred in those with a high-normal SBP or patients with Stage 1 hypertension, i.e. SBP in the range 130–159 mmHg. Data from insurance companies [5] as well as the Physicians' Health Study [6] further emphasize the importance of mild elevations of SBP for cardiovascular risk stratification. In addition, endpoint data from a variety of hypertension trials during the last decade show that cerebral stroke has become more frequent than myocardial infarction, not only in the elderly but also in middle-aged and younger hypertensives [7]. Thus, stroke prevention is likely to become a major focus in the management of

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Table I. *Baseline characteristics of patients with systolic hypertension in STOP-2*

	All patients in STOP-2 (n = 6614)	Patients with SH (n = 2280)	SH patients: conventional drugs group (n = 756)	SH patients: calcium antagonists group (n = 752)	SH patients: ACE inhibitors group (n = 772)
Demographic characteristics					
Age (years)	76.0	76.6	76.6	76.5	76.7
Males/females	33.2%/66.8%	25.1%/74.9%	21.8%/78.2%	26.6%/73.4%	26.8%/73.2%
Clinical characteristics					
Supine blood pressure (mmHg)	194/98	195/89	195/89	195/89	195/89
Standing blood pressure (mmHg)	187/101	189/94	190/94	189/94	188/93
Body-mass index (kg/m^2)	26.7	26.4	26.3	26.4	26.4
Serum cholesterol (mmol/l)	6.4	6.4	6.4	6.4	6.4
Serum triglycerides (mmol/l)	1.7	1.7	1.7	1.6	1.6
Blood glucose (mmol/l)	5.6	5.6	5.7	5.6	5.7
Smokers (%)	9.0	8.2	7.5	9.0	7.9
History					
Myocardial infarction	205 (3.1%)	80 (3.5%)	27 (3.6%)	34 (4.5%)	19 (2.5%)
Ischaemic heart disease	529 (8.0%)	215 (9.4%)	76 (10.1%)	66 (8.8%)	73 (9.5%)
Stroke	258 (3.9%)	94 (4.1%)	29 (3.8%)	34 (4.5%)	31 (4.0%)
Congestive heart failure	126 (1.9%)	41 (1.8%)	13 (1.7%)	13 (1.7%)	15 (1.9%)
Atrial fibrillation	311 (4.7%)	110 (4.8%)	34 (4.5%)	31 (4.1%)	45 (5.8%)
Other cardiovascular disease	337 (5.1%)	131 (5.7%)	43 (5.7%)	38 (5.1%)	50 (6.5%)
Diabetes mellitus	721 (10.9%)	299 (13.1%)	93 (12.3%)	98 (13.0%)	108 (14.0%)

SH, systolic hypertension.
Data for demographic and clinical characteristics are means unless marked otherwise.

hypertension, not only in Asian populations but also in the Western hemisphere.

In early outcome trials, evidence of benefits of blood pressure lowering treatment was mainly generated from trial data collected from randomized controlled trials based on diuretics and beta-blockers [8]. In later studies, strong evidence has been presented showing that also angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists reduce major cardiovascular events in hypertensive patients [8]. However, there is as yet weaker evidence of differences between treatment regimens based on different drug classes, e.g. the ACE inhibitors, calcium antagonists, beta-blockers and diuretics [8]. The focus of the Swedish Trial in Old Patients with Hypertension 2 (STOP-Hypertension-2 or, for short, STOP-2) study [9] was to compare cardiovascular mortality in elderly (70–84 years) hypertensive patients during treatment with "conventional" antihypertensive drugs (diuretics, beta-blockers) with that during treatment with "newer" drugs (ACE inhibitors or calcium antagonists). STOP-2 included patients with diastolic as well as isolated systolic hypertension. The "old" and "new" antihypertensive drug regimens were similar in prevention of cardiovascular mortality or major events [9].

The present paper reports a subgroup analysis in STOP-2 patients with isolated systolic hypertension in order to compare treatment regimens starting with "newer" therapies (ACE inhibitor or calcium antagonist) with "older" treatments (beta-blocker or diuretic).

PATIENTS AND METHODS

The patient population and the study design have been described previously [9]. In all, 6614 elderly patients with hypertension (mean age 76.0 years, range 70–84 years at baseline) from 312 health centres in Sweden were included in STOP-2. The mean follow-up time was 5.0 years and no patient was lost to follow-up. In the present subgroup analysis, we defined isolated systolic hypertension as SBP at least 160 mmHg with diastolic BP (DBP) below 95 mmHg, which is in agreement with some previously published trials [10–12]. There were 2280 patients in the STOP-2 cohort who met these criteria. Baseline characteristics of this subcohort are given in Tables I and II, including those from the total STOP-2 cohort for comparison. The STOP-2 patients with isolated systolic hypertension had a mean supine BP at entry of 195/89 mmHg, with only marginal differences between the randomized groups (Table I). Mean serum cholesterol was 6.5 mmol/l and blood glucose was 5.6 mmol/l. More than 20% of the patients had a history of cerebrocardiovascular disease at entry. Approximately 4% had a previous stroke and 13% were diabetic at entry into the study. There were no relevant differences in respect to the

Table II. *Proportion of patients in STOP-2 with systolic hypertension (n = 2280) and with Grade 1–3 systolic hypertension; isolated systolic hypertension 34.5%*

Grade of systolic hypertension	All STOP-2 ($n = 6614$)[a]	Systolic hypertension ($n = 2280$)
Grade 1 (140–159 mmHg)	1.3% ($n = 88$)	0.0% ($n = 0$)
Grade 2 (160–179 mmHg)	7.7% ($n = 512$)	0.6% ($n = 13$)
Grade 3 (≥180 mmHg)	90.8% ($n = 6003$)	99.4% ($n = 2267$)

[a]Eleven patients had systolic blood pressure below 140 mmHg.

history of cardiovascular disease between the different treatment groups in the STOP-2 systolic hypertension cohort.

Patients were randomized to one of three treatment groups: (i) conventional antihypertensive therapy (diuretics and/or beta-blockers, being either one of atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, or fixed-ratio hydrochlorothiazide 25 mg plus amiloride 2.5 mg daily); (ii) ACE inhibitors (enalapril 10 mg or lisinopril 10 mg daily); or (ii) calcium antagonists (felodipine 2.5 mg or isradipine 2.5 mg daily). If target BP (<160/95 mmHg) had not been reached at the 2-month visit or later, adjustments were made, initially with doubling the dose of the ACE inhibitors or the calcium antagonists given as the first step. If BP goals were not fulfilled, a beta-blocker could be added to the calcium antagonist and hydrochlorothiazide to the ACE inhibitor in those respective groups. In the conventional group, patients not reaching the target on beta-blockers or diuretics alone were given a combination of the two.

At the scheduled visits, BP was measured with a standard sphygmomanometer after a 5-min rest in the supine position. Outpatients were seen in the respective participating clinics twice yearly, except during the initial part of the study when dose titration and institution of combination treatment could necessitate more frequent visits. At each visit, BP and heart rate were measured. Adverse event recordings were also performed at these routine visits, and standard laboratory tests as well as resting ECGs were done once yearly. Assessment of prespecified endpoints was done by an independent endpoint committee [13]. The members of this committee were masked to the treatments and BP of the patients according to the PROBE technique [14]. All regional ethics committees in Sweden approved the study, and all patients gave their consent before entering the trial.

Statistical analysis

Analysis was by intention to treat. In every analysis, only the first occurrence of the specific study event was considered. Cox regression analysis used time since randomization as non-parametrically modelled time variable. The model adjusted for sex and age and for baseline status of diabetes and smoking. All calculations were performed using Stata software (version 5), and all statistical tests were two-sided.

RESULTS

At randomization, the STOP-2 patients with isolated systolic hypertension did not differ from the larger STOP-2 cohort in any major respect, apart from the DBP values, which were lower and within the normal range (Tables I and II).

The BP lowering effects were similar in the three randomized patient groups (Table III). The reduction in

Table III. *Effect of randomized treatments, conventional therapy, calcium antagonists and ACE inhibitors on blood pressure in patients with isolated systolic hypertension during the course of the STOP-2 trial*

Visit (month)	Total number	Conventional SBP/DBP, mmHg	(*n*)	CaA SBP/DBP, mmHg	(*n*)	ACE SBP/DBP, mmHg	(*n*)
Randomization	2280	194.4/88.2	756	194.2/88.6	752	194.2/88.1	772
1	2209	174.3/81.7	725	172.7/82.2	731	174.1/82.1	753
2	2212	169.6/80.2	725	171.2/81.9	738	172.0/82.1	749
6	2198	166.4/79.7	726	168.0/80.3	729	169.1/80.9	743
12	2167	167.2/80.2	715	167.8/80.4	716	169.1/81.1	736
24	2082	164.9/79.3	690	166.9/79.5	688	165.3/79.5	704
36	1975	164.3/78.9	654	164.8/78.1	648	164.9/78.3	673
48	1716	162.3/77.9	567	164.0/77.8	568	164.4/78.4	581
54	1443	160.0/76.5	485	160.5/75.7	469	160.8/76.3	489

SBP, systolic blood pressure; DBP, diastolic blood pressure; CaA, calcium antagonists; ACE, angiotensin-converting enzyme.

Table IV. *Frequency of events per 1000 patient years in patients with isolated systolic hypertension in STOP-2*

	Conventional drugs group	Calcium antagonists group	ACE inhibitors group
Cardiovascular mortality[a]	18.7	16.2	17.8
Fatal stroke	3.7	4.5	3.9
Fatal myocardial infarction	4.7	4.5	5.4
Sudden death	4.5	2.9	3.4
All fatal events	31.1	29.4	32.0
All myocardial infarction	15.4	17.6	16.1
All stroke	26.7	20.5	20.3
Nonfatal stroke	24.2	18.0	17.3
Diabetes mellitus	10.4	9.7	11.1
Transient ischaemic attack	2.7	2.1	3.7
Cardiovascular events	48.7	44.1	42.3
Atrial fibrillation	12.8	19.2	17.3
Congestive heart failure	17.0	20.6	16.6

[a]Primary endpoint.
ACE, angiotensin-converting enzyme.

supine BP in those surviving at least 24 months was, from baseline to the last visit: in the conventional group 34.7/12.7 mmHg ($n = 717$); in the ACE inhibitor group 34.2/12.0 mmHg ($n = 724$); and in the calcium antagonist group 34.9/13.5 mmHg ($n = 708$).

The three randomized treatment strategies conferred similar preventive effects in respect to cardiovascular mortality, the primary endpoint of the study (Table IV). Comparing the patient group randomized to treatment with "newer" drugs, i.e. ACE inhibitors or calcium antagonists ($n = 1524$), with that receiving "conventional" drugs, i.e. diuretics or beta-blockers ($n = 756$), there were no differences in the risk of having a primary endpoint, i.e. a fatal cardiovascular event (relative risk, RR, 0.89; 95% CI 0.66–1.19) (Table V). Moreover, there were no differences in terms of primary outcome when comparing calcium antagonists ($n = 752$) with conventional drugs (RR 0.85; 95% CI 0.60–1.20) or when comparing ACE inhibitors ($n = 772$) with conventional drugs (RR 0.93; 95% CI 0.67–1.29). Likewise, the incidence of the primary endpoint did not differ when comparing ACE inhibitors with calcium antagonists (RR 1.09; 95% CI 0.77–1.54) (Table V).

For all stroke events, i.e. fatal and non-fatal stroke together, there was a significant and 25% reduction in patients randomized to "newer" drugs compared with the conventionally treated group (RR 0.75; 95% CI 0.58–0.97; $p = 0.027$). While fatal strokes did not differ between any of the randomized treatment groups, there were significant reductions in non-fatal stokes (RR 0.71; 95% CI 0.54–0.94; $p = 0.015$) comparing "newer" vs "conventional" drugs, and (RR 0.70; 95% CI 0.50–0.96; $p = 0.029$) comparing ACE inhibitors and conventional therapies. A similar but non-significant reduction of non-fatal strokes was seen (RR 0.73; 95% CI 0.53–1.01; $p = 0.056$) comparing calcium antagonists with conventional therapy (Table V).

With respect to new cases of atrial fibrillation, there was an increased risk (RR 1.43; 95% CI 1.02–1.99; $p = 0.037$) in the patients randomized to "newer" drugs compared with those randomized to treatment with "conventional" drugs. Atrial fibrillation was particularly frequent (RR 1.53; 95% CI 1.05–2.21; $p = 0.026$) in patients on calcium antagonists compared with conventional drugs (Table V).

There were no significant differences between the three treatment groups with respect to the frequency of myocardial infarction, sudden death or congestive heart failure (Table V).

DISCUSSION

The present STOP-2 study in elderly patients with isolated systolic hypertension demonstrated that "newer" treatments such as calcium antagonists and ACE inhibitors provide more extensive stroke preventive effects than "conventional" treatment alternatives, i.e. beta-blockers and diuretics. Interestingly, the stroke reduction was present in spite of the higher frequencies of atrial fibrillation in the "newer" treatment group, indicating that the stroke preventive effects of the ACE inhibitors and the calcium antagonists are due to properties of these drug classes not yet fully recognized. The data from this subanalysis of STOP-2 are important since stroke is emerging as a major complication to especially systolic hypertension in the elderly [7] in the Western hemisphere. Since stroke incidence increases with advancing age, the elderly population will suffer the large majority of BP-related cerebrovascular disease [15–17]. The severity of the increase in SBP and DBP affects the

Table V. *Relative risk of cardiovascular mortality and morbidity in patients with systolic hypertension in STOP-2*

	New vs conventional			Calcium antagonists vs conventional			ACE inhibitors vs conventional			ACE inhibitors vs calcium antagonists		
	Haz. ratio	*p*-value	95%CI	Haz. ratio	*p*-value	95%CI	Haz. ratio	*p*-value	95%CI	Haz. ratio	*p*-value	95%CI
Cardiovascular mortality	0.89	0.42	0.66–1.19	0.85	0.35	0.60–1.20	0.93	0.66	0.67–1.29	1.09	0.63	0.77–1.54
Fatal stroke	1.11	0.74	0.59–2.09	1.20	0.62	0.59–2.44	1.04	0.92	0.50–2.16	0.83	0.60	0.41–1.66
Fatal myocardial infarction	0.99	0.99	0.57–1.75	0.91	0.77	0.47–1.76	1.08	0.80	0.58–2.04	1.20	0.58	0.63–2.27
Sudden death	0.69	0.23	0.37–1.28	0.65	0.27	0.30–1.39	0.72	0.37	0.35–1.48	1.14	0.74	0.51–2.55
All fatal events	0.97	0.81	0.78–1.21	0.94	0.62	0.72–1.21	1.01	0.91	0.79–1.31	1.08	0.54	0.84–1.40
All myocardial infarction	1.07	0.69	0.78–1.46	1.12	0.54	0.78–1.60	1.02	0.93	0.71–1.46	0.92	0.64	0.65–1.31
All stroke	**0.75**	**0.027**	**0.58–0.97**	0.76	0.071	0.56–1.02	0.74	0.054	0.55–1.01	0.98	0.91	0.71–1.35
Non-fatal stroke	**0.71**	**0.015**	**0.54–0.94**	0.73	0.056	0.53–1.01	**0.70**	**0.029**	**0.50–0.96**	0.96	0.80	0.68–1.35
Diabetes mellitus	0.97	0.89	0.64–1.47	0.90	0.68	0.55–1.47	1.05	0.85	0.65–1.67	1.15	0.56	0.71–1.86
Transient ischaemic attack	1.03	0.93	0.49–2.19	0.77	0.58	0.30–1.95	1.31	0.52	0.58–2.95	1.68	0.24	0.71–4.01
Cardiovascular events	0.86	0.12	0.72–1.04	0.88	0.27	0.71–1.10	0.84	0.12	0.68–1.05	0.95	0.68	0.76–1.19
Atrial fibrillation	**1.43**	**0.037**	**1.02–1.99**	**1.53**	**0.026**	**1.05–2.21**	1.36	0.11	0.93–1.98	0.89	0.50	0.63–1.25
Congestive heart failure	1.08	0.62	0.80–1.46	1.21	0.27	0.86–1.70	0.96	0.80	0.67–1.36	0.80	0.19	0.57–1.12

risk of both cerebral haemorrhage and cerebral infarction, but the influence on haemorrhage appears to be more pronounced than that on infarction [1, 15].

Several epidemiological studies and clinical trials have demonstrated that systolic hypertension is a particularly important risk factor for stroke and somewhat less so for coronary heart disease [1, 15]. In fact, large intervention trials, such as the MRFIT, have demonstrated that SBP is a stronger predictor for suffering a cardiovascular event than is DBP [4]. The reasons for this discrepancy regarding the cardiovascular risks related to diastolic and SBP elevations are not yet fully known. It has been hypothesized that while the diastolic form of hypertension is more dependent on increased peripheral resistance [1], the systolic form seems to be more related to a decreased compliance and an increased arterial stiffness [6, 18]. It is also generally accepted that systolic hypertension is more difficult to treat to normotensive levels compared with diastolic increases in BP [1, 18].

In a prospective overview of randomized intervention trials in hypertension, comparisons of a calcium antagonist-based therapy with placebo showed a 39% reduction of strokes [8]. There was a similar and 30% stroke reduction by an ACE inhibitor-based treatment compared with placebo [8]. In comparison with a conventional diuretic-based or beta-blocker-based therapy, the calcium antagonists provided a further significant 13% reduction of strokes, while the ACE inhibitor-based treatment had no further effect on strokes compared with the conventional antihypertensive therapy [8]. These data could suggest that calcium antagonists would offer a more extensive stroke protection than that of ACE inhibitors. However, comparative data on the prevention of stroke in patients on calcium antagonists and ACE inhibitors are yet available only for STOP-2, ABCD and ALLHAT [9 19, 20]. While there were no significant differences in stroke prevention between these regimens in the combined group of STOP-2 patients with diastolic as well as isolated systolic hypertension, the present subgroup analysis of STOP-2 patients with systolic hypertension demonstrated that newer therapy (calcium antagonists/ACE inhibitors) was significantly better (25%) compared with older treatments (diuretics/beta-blockers) in preventing all stroke. This result is also in line with the trials overview data from the Blood Pressure Lowering Treatment Trialists Collaboration meta-analysis assessing different treatment regimens [8].

When evaluating all stroke in STOP-2 in the patients with "newer" treatments (ACE inhibitors and calcium antagonists analysed jointly) compared with "conventional" treatments, there was a significant and 25% reduction in all strokes; this was fully attributable to a reduction in non-fatal strokes. There was, however, no such additional effect by the "newer" treatments on fatal

strokes or transient ischaemic attacks. Although the reductions in non-fatal strokes vs conventional diuretic and beta-blocker treatments were similar (27% vs 30%) in the patients randomized to calcium antagonists and ACE inhibitors, respectively, the stroke reduction was significant for ACE inhibitors only. The reason why the beneficial effect on stroke was limited to non-fatal and not fatal cases is not known. However, the fatal cases were relatively few which might lead to lack of statistical power. The additional stroke reduction in STOP-2 is of interest, as the results from the CAPPP study (21) indicated the possibility of an increased stroke rate with the ACE inhibitor captopril compared with the conventional diuretic or beta-blocker regimens. In CAPPP, this was assumed to be due to the slightly higher in-study BP levels seen in the ACE inhibitor arm compared with the conventional treatment arm in patients who were previously treated when they entered the study, as neither the BP difference nor the difference in stroke incidence was found in the substantial subcohort of patients who were previously untreated [21, 22]. Moreover, in the recent ANBP2 study [23], stroke reduction by the ACE inhibitor-based treatment was similar to that achieved by a diuretic-based treatment regimen. Thus, the current findings in the STOP-2 patients with systolic hypertension contrast to the findings in CAPPP and ANBP2 in that stroke reduction seemed to be more pronounced by an ACE inhibitor in elderly patients with isolated systolic hypertension. Taken together, it is therefore reasonable to believe that there is at least a comparable reduction of strokes in hypertensive patients starting on an ACE inhibitor compared with patients starting on a conventional diuretic or beta-blocker regimen.

Interestingly, in the STOP-2 patients with systolic hypertension, atrial fibrillation was increased in both of the newer-treatment groups, in particular in the patients randomized to the calcium antagonist treatment arm. Thus, the significant reduction in all strokes, in particular non-fatal strokes, in favour of the "newer" drugs therapy occurred in spite of the increased incidence of atrial fibrillation and risk of embolic episodes. Therefore the superior effect on stroke reduction by the "newer" treatments, also found for the calcium antagonist diltiazem in the NORDIL trial [24], seems to be related to some other inherent and not BP-related effect of the newer drugs, i.e. ACE inhibitors and calcium antagonists.

Thus, the present subanalysis on patients with isolated systolic hypertension in STOP-2, comparing BP lowering regimes based on different drug classes, provides some evidence that there may be potentially important differences between different pharmacological treatment strategies in their effects on cause specific outcomes. In particular, our present analysis in elderly patients with systolic hypertension adds support to the notion that an ACE inhibitor or a calcium antagonist-based treatment regimen will result in a further reduction in strokes compared with a treatment based on a diuretic or a beta-blocker.

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