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Are Beta-Blockers Efficacious as First-Line Therapy for Hypertension in the Elderly?

K. Wink

To assess antihypertensive efficacy of beta-blockers and their effects on cardiovascular morbidity and mortality and all cause mortality in elderly patients with hypertension randomised placebo-controlled studies, trials with untreated controls and with comparison of antihypertensive drugs were selected from the literature, in which beta-blockers were used in hypertension of elderly patients. The relative risk reduction of primary endpoints, the significance and 95 % confidence interval were calculated.

There were six trials in which elderly patients were treated with beta-blockers for hypertension (three trials placebo-controlled, one study with untreated control, and two studies with comparison of antihypertensive drugs). There was no study with monotherapy of beta-blockers.

In combination with diuretics beta-blockers were superior to placebo and untreated controls in preventing cardiovascular events, especially strokes, but there was no superiority of beta-blockers to ACE-inhibitors and Ca-antagonists in preventing cardiovascular morbidity and mortality and total mortality in elderly patients with hypertension.

Beta-blockers are only in combination with diuretics efficacious in preventing cardiovascular morbidity and mortality in elderly patients with hypertension. *J Clin Basic Cardiol 2001; 4: 235–238.*

Key words: hypertension, beta-blockers, elderly, controlled studies

Beta-blockers are efficacious as first line therapy for hypertension in the prevention of cardiovascular morbidity and mortality and of all cause mortality. But is this valid also for elderly patients with hypertension?

To assess this question randomised placebo-controlled studies, trials with untreated controls and with comparison of antihypertensive drugs were selected from the literature, in which β-blockers were used in hypertension of elderly patients.

Methods

Studies including patients with hypertension ≥ 60 years old were evaluated. Each trial was scored for the number of patients included in the study, type of the study, in- and exclusion criteria, duration time of the trial, drugs and drug regimen, blood pressure lowering effects, sample size estimation, incidence of primary endpoints, the relative risk reduction, significance, power, and 95 % confidence interval.

Meta-analysis was not performed, because of the differences of study type, in- and exclusion criteria, drugs and drug regimen, drop-outs and drop-ins, and methods of analysis of the results in the studies.

Results

Six studies to evaluate efficacy in terms of outcome (morbidity and mortality) in elderly patients with hypertension are placed at our disposal (Tab. 1):

- the STOP-hypertension trial [1]
- the SHEP trial [2]
- the MRC trial of hypertension in older adults [3]
- the study of Coope and Warrender [4]
- the STOP-2 trial [5]
- the Nordic Diltiazem (NORDIL) study [6]

The STOP-Hypertension Trial [1]

This was a randomised, placebo-controlled, double blind multicenter study. 1627 patients 70 to 84 years old with hypertension (180–230 / ≥ 90 mmHg) or diastolic pressure above 105 mmHg irrespective of the systolic pressure without cardiovascular diseases within 12 months were treated over 25 months double blind with 50 mg atenolol, 25 mg hydrochlorothiazide + 2.5 mg amiloride, 100 mg metoprolol, or 5 mg pindolol once daily. If control of blood pressure was not achieved (> 160 and/or 95 mmHg after at least 2 months) the diuretic was added to any of the β-blockers or *vice versa*.

Blood pressure decreased in the active and placebo group over 4 years by 29/17 mmHg systolic respectively 2/7 mmHg diastolic.

It was assumed that 30 % of strokes and myocardial infarctions would be fatal and calculated that 6000 patients-years would be needed to show a significant reduction in primary endpoints with a statistical power of 90 % at the significance level of 0.05 by a two-tailed test.

In the intention-to-treat-analysis the relative risk of primary endpoints was significantly ($p < 0.01$) reduced by 38 % (incidences: 7.14 % / 11.53 % in the active respectively placebo group) with a power of about 85 %.

The SHEP Trial [2]

This was a randomised, placebo-controlled, double blind multicenter study. 4736 patients ≥ 60 up to ≥ 80 years old with isolated systolic hypertension (160–219 / < 90 mmHg) without history and/or signs of specified major cardiovascular diseases were treated over 4.5 years double blind with 12.5 mg/d chlorthalidone or placebo. If control of blood pressure was not achieved (< 160 mmHg systolic or a reduction of at least 20 mmHg) drug dosage was doubled or later 25 mg/d atenolol or 0.05 mg/d reserpine or double dose was added or substituted.

Blood pressure decreased in the active treatment and placebo group over 5 years by 26.5/15.0 mmHg systolic and 9.0/5.3 mmHg diastolic.

It was calculated that to detect a difference of at least 32 % in total stroke incidence, with 90 % power and a two-sided α of 0.05, a sample size of 4800 participants would be necessary.

In the intention-to-treat-analysis the risk of the primary endpoint was significantly ($p < 0.001$) reduced by 35 % (4.36 % / 6.71 % incidence in the active respectively placebo group) with a power of > 90 %.

The MRC Trial of Hypertension in Older Adults [3]

This was a randomised, placebo-controlled, single blind multicenter study. 4396 patients 65 to 74 years old with hypertension (160–209 / < 115 mmHg) without cardiovascular

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diseases within three months were treated over 5.8 years single blind with 2.5 or 5.0 mg amiloride and 25/50 mg hydrochlorothiazide respectively 50 mg atenolol daily compared with matching placebo. If control of blood pressure was not achieved (150 or 160 mmHg systolic after treatment of 6 months) the dosage was modified or the other drug was used.

Blood pressure decreased in the active treatment group about 15/7 mmHg and 10/5 mmHg systolic/diastolic in the placebo group.

It was estimated that the trial would require 5000 participants to provide a power of 90 % to detect a 30 % reduction in the rate of fatal and non-fatal strokes between the active and placebo group at a significance level of 2 %.

In the intention-to-treat-analysis the relative risk for the primary endpoint was reduced significantly ($p < 0.05$) by 24 % (incidences 4.63 % / 6.06 %) with a power of only 55 %. In the group getting only β-blockers the relative risk reduction was only 16 % (5.08 % / 6.06 %) and the difference was not significant.

Table 1. Studies with β-blockers in elderly patients with hypertension (abbreviations: m = male, f = female, ITT = intention-to-treat, aMI = acute myocardial infarction)

Study (year) (Number of patients, duration, age)	Study type	Drugs	Primary endpoint (placebo / verum)	Relative risk reduction	p-value	Power 95 % confidence interval
STOP (1991) (1627, 25 months, 70–84 years)	Randomised, placebo controlled	β-blockers + diuretics	All cardiovascular events: ITT: 11.53 % / 7.14 %	38 %	< 0.01	85 %
SHEP (1991) (4736, 4.5 years, ≥ 60 – ≥ 80 years)	Randomised, placebo controlled	Diuretics + β-blockers or reserpine	Fatal and non-fatal strokes: ITT: 6.71 % / 4.36 %	35 %	< 0.001	94 %
MRC (1992) (4396, 5.8 years, 64–74 years)	Randomised, placebo controlled	Diuretics or β-blockers + β-blockers or diuretics, Ca-antagonists	Fatal and non-fatal strokes: ITT: 6.06 % / 4.63 %	24 %	< 0.05	54 %
			Placebo / β-blockers: ITT: 6.06 % / 5.08 %	16 %	n.s.	19 %
Coope et al. (1986) (884, 4.4 years, 60–79 years)	Randomised, untreated controls (ITT-analysis)	Atenolol (70 %) bendrofluazide (60 %)	ITT: All strokes: 9.46 % / 5.49 %	42 %	n.s.	–
			Fatal strokes: 3.23 % / 0.95 %	71 %	< 0.05	30 %
			All coronary events: 8.17 % / 8.35 %	–2 %	n.s.	–
			Fatal cor. events: 6.24 % / 5.97 %	4 %	n.s.	–
			Non-fatal cor. events: 2.15 % / 2.39 %	–11 %	n.s.	–
			All strokes and coronary events: 17.63 % / 13.84 %	21 %	n.s.	–
STOP-2 (1999) (6614 m + f, 4.5 years, 70–84 years)	Comparison of antihypertensive drugs (ITT-analysis)	β-blockers + diuretics / ACE-inhibitors + Ca-antagonists	ITT: Cardiovascular mortality: 9.99 % / 9.95 %	–0.4 %	n.s.	–1.5 % / +1.6 %
			Fatal myocardial inf.: 2.50 % / 2.43 %	–3 %	n.s.	–0.7 % / +0.9 %
			Fatal strokes: 2.30 % / 2.18 %	6 %	n.s.	–0.6 % / +0.9 %
			Sudden deaths: 2.40 % / 2.52 %	5 %	n.s.	–0.9 % / +0.7 %
			All myocardial inf.: 6.96 % / 7.23 %	4 %	n.s.	–1.6 % / +1.0 %
			All strokes: 10.70 % / 9.59 %	–12 %	n.s.	–0.48 % / +2.6 %
			Total mortality: 16.67 % / 16.86 %	1 %	n.s.	–2.1 % / +1.7 %
NORDIL (2000) (10881 m + f, 4.5years, 50–74 years) (Δ20 % card.vasc. events, $2\alpha = 0.05$, $1\text{-}\beta = 0.80$)	Comparison of antihypertensive drugs (ITT-analysis)	Diltiazem / diuretics + β-blockers	Primary endpoints: 7.48 % / 7.34 %	–1.9 %	n.s.	–0.8 % / +1.1 %
			All strokes: 2.95 % / 3.6 %	–	p = 0.06	–1.3 % / ±0 %
			Fatal strokes: 0.4 % / 0.4 %	–14 %	n.s.	–0.2 % / +0.2 %
			All strokes plus TIA: 3.7 % / 4.3 %	–17 %	n.s.	–1.3 % / +0.1 %
			All myocardial inf.: 3.4 % / 2.9 %	–13 %	n.s.	–0.2 % / +1.2 %
			Fatal myocardial inf.: 0.52 % / 0.46 %	–14 %	n.s.	–0.2 % / +0.3 %
			Cardiovascular death: 2.4 % / 2.1 %	–14 %	n.s.	–0.3 % / +0.9 %
			Total mortality: 4.3 % / 4.2 %	–2.4 %	n.s.	–0.7 % / 0.9 %
			All cardiac events: 9.04 % / 8.6%	–5.1 %	n.s.	–0.6 % / +1.5 %

The Study of Coope and Warrender [4]
This was a randomised, non-blinded multicenter study with untreated controls. 884 patients 60 to 79 years old with hypertension (≥ 170 / ≥ 105 mmHg) mainly without cardiovascular diseases were treated for 4.4 years with atenolol or bendrofluazide and if blood pressure could not be controlled with α-methyldopa.

The blood pressure decreased compared to the untreated group about 18/11 mmHg systolic and diastolic.

It was estimated that there would be reduction of strokes and coronary events about 33 % (incidence 15 %, $\alpha = 0.05$, $1-\beta = 0.90$).

In the intention-to-treat-analysis a reduction of the risk of this primary endpoint was reached of about 21 %, the difference between the treatment groups was not significant. There was significant reduction only for the risk of fatal strokes, but with a power less than 80 %.

The STOP-2 Trial [5]
This was a randomised, non-blinded, multicenter study with comparison of antihypertensive drugs. In the trial 6614 patients 70 to 84 years old with hypertension (≥ 180 or ≥ 105 mmHg systolic or diastolic) were treated with β-blockers and diuretics or ACE-inhibitors and Ca-antagonists for 4.5 years.

Blood pressure decreased about 36/17 and 35/17.5 mmHg in the group with the old and new antihypertensive drugs.

It was assumed that a 25 % difference in cardiovascular mortality ($2\alpha = 0.05$, $1-\beta = 0.90$) between the treatment groups could be detected.

In the intention-to-treat-analysis there were no significant differences in the incidences of cardiovascular mortality and other outcome parameters. The 95 % confidence interval varied between –1.5 % and +1.6 % for cardiovascular mortality and between –2.1 % and +1.7 % for total mortality.

From the data it is not possible to see how many patients were treated with β-blockers and during the study there was a mixture of the different antihypertensive drugs. In the group of Ca-antagonists acute myocardial infarction and congestive heart failure was more often than in the group treated initially with ACE-inhibitors.

The Nordic Diltiazem (NORDIL) Study [6]
This was a randomised, non-blinded multicenter study with comparison of antihypertensive drugs. In the trial 10881 patients 50 to 74 years old with hypertension (≥ 100 mmHg diastolic) were treated with the Ca-antagonist diltiazem (180–360 mg/d) or diuretics, β-blockers or both for 2.5 years.

Blood pressure decreased about 20/19 and 23/19 mmHg with the diltiazem respectively diuretics/β-blocker-group.

It was assumed that a 20 % difference in the combined endpoint (fatal and non-fatal strokes, fatal and non-fatal myocardial infarction and other cardiovascular death) could be detected.

In the intention-to-treat analysis there were no significant differences in the incidences of the combined endpoints, fatal strokes, all strokes plus TIA, all myocardial infarction, cardiovascular death, total mortality, all cardiovascular events. However in all strokes the incidence of 2.95 % / 3.6 % nearly reached the level of significance with a 95 % confidence interval of –1,3 % / ±0 % in favour of diltiazem and in the patients with the incidences of the primary endpoints, all myocardial infarction, cardiovascular death, total mortality and all cardiovascular events were somewhat but not significantly lower in the diuretic/β-blocker-group, whereas the incidences of all strokes (plus TIA) were somewhat but not significantly lower in the diltiazem-group.

The 95 % confidence interval of the incidences of the primary endpoints varied from –0.8 %/± 1.1 %, that means they could be about 1 % worse or better in the two groups.

About 2/3 of the patients in the diuretic/β-blocker group were treated with β-blockers and about 13 % in the diltiazem group. Therefore superiority in the efficacy of diltiazem compared with diuretics and ß-blockers could not be shown, but there was no design for equivalence of both treatment groups.

Comment

The interpretation of results depends on the following criteria:
- Design
- Inclusion-/exclusion criteria
- Drugs
- Blood pressure lowering effect
- Outcome and power of the results

Design
The study design is essential to gain reliable results. The best design is the controlled study in a double blind and randomised manner to avoid bias.

The major purpose of control groups is to allow discrimination of the patient outcome caused by the test drug from outcomes caused by other factors, such as the natural progression of the disease.

The best way to control efficacy is the placebo concurrent control. Only by placebo control can actual treatment effects be identified and only placebo control can discern potential influences on the actual or apparent course of the disease. Also, the placebo concurrent control design allows blinding and randomization.

The principle difference between a placebo controlled study and a study with untreated controls is that subjects and investigators are not blind to treatment assignment.

In studies with comparison of antihypertensive drugs efficacy of the drug can be seen either by showing equivalence or by superiority of the test drug compared to the active control. The mentioned studies were designed to indicate superiority of beta-blocker over other antihypertensive drugs respectively of diltiazem to diuretics and beta-blockers. Bearing this in mind, raises the critical question of whether the trial was capable of distinguishing active from inactive treatments, eg if the control agent increases the incidence of endpoints and the test substance did not change the incidence the test medication can show an improvement of the outcome. If the endpoints improve, a comparison of the drugs is possible by calculation of the 95 % confidence intervals.

Inclusion-/Exclusion Criteria
In the SHEP trial [2] patients only with isolated systolic hypertension, in the other studies [1, 3–5] patients with systolic and diastolic hypertension and in the NORDIL study [6] patients with diastolic hypertension were included.

Patients with cardiovascular diseases, especially recently suffered myocardial infarction and stroke, were excluded.

Drugs
Beta-blockers were used in a different frequency in the various trials:
- In the STOP-trial [1] it can be assumed that about half of the patients were treated with β-blockers, but there was no separate analysis of the patients getting β-blockers.
- In the SHEP-study [2] the primary study medication was a diuretic and only if the blood pressure could not be controlled after doubling of the dose of diuretics, could β-blockers be added. It will be assumed that only one quarter of the patients were treated with β-blockers. A separate analysis of the patients with β-blockers was not performed.

- In the MRC-trial [3] it could be estimated that about half of the patients were treated with a β-blocker, there was a separate analysis of the efficacy of β-blockers on the outcome of patients with hypertension.
- In the study with untreated controls [4] β-blockers were used in 70 %.
- In the STOP-2-study [5] with comparison of antihypertensive drugs, about half of the patients were treated with β-blockers.
- In the NORDIL-study [6] about 2/3 of the patients in the diuretic/β-blocker-group were treated with β-blockers.

Blood pressure lowering effect

In all studies [1–3] there was a blood pressure lowering effect of the active treatment group compared to the placebo group, but the differences of blood pressure lowering varied from 5 to 27 mmHg systolic and 2 to 10 mmHg diastolic between the treatment groups.

The blood pressure decreased in the studies with untreated controls about 18/11 mmHg [4].

In the studies with active controls [5, 6], the blood pressure decreased about 36/17 and 35/17.5 mmHg respectively 20/19 and 23/19 mmHg in the two treatment groups.

Outcome

- In the STOP-study [1] the risk for the primary endpoint (all cardiovascular events) was significantly reduced by 38 % (intention-to-treat-analysis) with sufficient power (p > 80 %).
- In the SHEP-study [2], in patients with isolated systolic hypertension, the intention-to-treat-analysis showed a significant reduction of the risk for fatal and non-fatal strokes (primary endpoint) with sufficient power.
- In the MRC-study [3] there was a significant reduction of the risk of fatal and non-fatal strokes (intention-to-treat-analysis), but with a non-sufficient power (< 80 %). In the subgroup of patients treated with β-blockers there was no significant reduction of the risk of strokes.
- In the studies with untreated controls [4], in which 70 % of the patients were treated with β-blockers, there was a significant reduction of the risk of fatal strokes, but the power of the significant differences between the active and the untreated group showed no sufficient power (< 80 %).
- In the STOP-2 study [5] only the incidence of myocardial infarction, sudden death and total mortality was not significantly lesser in the group initially treated with β-blockers and diuretics. In the group initially treated with ACE-inhibitors or Ca-antagonists, myocardial infarction and congestive failure was more common in the group of Ca-antagonists, therefore positive differences between the two treatment groups in favour of old drugs are conditioned by the unfavourable results of the patients in the group of Ca-antagonists.
- In the NORDIL-study [6] there was only a non-significant trend for a lesser incidence of the combined endpoints, fatal and non-fatal myocardial infarction, cardiovascular death, total mortality and all cardiovascular events, but an almost significantly higher incidence of fatal and non-fatal strokes in the diuretic/β-blocker-group.

Conclusion

In all studies with elderly patients, hypertension was not treated with β-blockers alone and efficacy of outcome can only be judged for patients treated with β-blockers in combination with other antihypertensive drugs.

In the randomised placebo-controlled studies [1–3], β-blockers in combination with diuretics were superior in preventing cardiovascular events, especially fatal and non-fatal strokes in elderly patients with isolated systolic and systolic and diastolic hypertension.

Also, in the study [4] with untreated controls, fatal strokes were reduced by the β-blocker atenolol, but the power of the significant result was not sufficient (< 80 %).

The study [5], in which β-blockers and diuretics were compared with ACE-inhibitors and Ca-antagonists, and in the study [6], in which diuretics and β-blockers were compared with the Ca-antagonist diltiazem, there was no superiority of one treatment group.

β-blockers are only efficacious as first line therapy for hypertension in the elderly in combination with diuretics.

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