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Wink K

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Inconsistency in trials on mortality and morbidity in patients with pharmacologic antihypertensive treatment

K.Wink

In the "classical" randomized controlled hypertension intervention trials there are inconsistent results in terms of the reduction of mortality and morbidity with pharmacological treatment.

Reasons for these inconsistencies can be found in an insufficient sample size, high rates of dropouts and dropins, compliance and insufficient blood pressure control and power of the studies. Secular trends seem to confirm the underestimation of the therapeutic effect on mortality and morbidity.

Further results of ongoing and beginning studies are necessary to clarify which is the best drug, dose and targed blood pressure to reduce mortality and morbidity with pharmacologic treatment of hypertension. *J Clin Basic Cardiology 1999; 2: 123–5.*

Nearly all patients with uncomplicated hypertension have no complaints and if there are symptoms there is no significant difference to normotensives [1]. However, persons with elevated blood pressure values have a cardiovascular risk [2, 3]. Therefore, in generally there is no symptomatic but a prognostic indication, to treat high blood pressure, first by life style modification and then by pharmacological treatment.

The pharmacological treatment is based on the assumption that lowering blood pressure values by drugs is a surrogate endpoint for mortality and morbidity. This hypothesis can only be tested by randomized controlled studies.

Randomized controlled studies

17 hypertension intervention studies were carried out, 10 with placebo controls [4–14], 3 with untreated controls [15–17] and 4 studies [18–21] in which antihypertensive drugs were compared.

Placebo controlled studies

From 1967 to 1997 the Veterans Administration Cooperative Studies on Antihypertensive Agents (VA), the U.S. Public Health Service Hospitals Cooperative Study (US Public Health), the Australian Therapeutic Trial in Mild Hypertension (Australian), the European Working Party On High Blood Pressure in The Elderly Trial (EWPHE), the Medical Research Council trial of treatment in older adults (MRC), the Systolic Hypertension in the Elderly Program (SHEP), the Swedish Trial in Old Patients with Hypertension (STOP), the Shanghai Trial of Nifedipine in the Elderly (STONE) and the Systolic Hypertension in Europe (Syst-Eur) Study were achieved. These studies were carried out with different numbers of patients, drugs and durations (two to seven years).

The results of these trials were inconsistent in terms of reduction in mortality and morbidity with pharmacological treatment in comparison with placebo.

Studies with untreated controls

The Primary Prevention Trial in Gothenburg (Gothenburg-study), the Treatment of Mild Hypertension in Oslo (Oslo-study) and a randomized trial of treatment of hypertension in elderly patients in primary care (Coope et al. [16]) with different antihypertensive drugs over 4.3 to 5 years also showed no consistent influence on mortality and morbidity in the group of the drug treatment compared with the untreated group.

Studies with comparison of antihypertensive drugs

In the International Prospective Primary Prevention-Study in Hypertension (IPPPSH-study), Heart Attack Primary Prevention in Hypertension Trial (HAPPHY-study), the Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY-study) and Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS), there was no clear superiority of one to another antihypertensive drug in terms of reduction of mortality and morbidity.

Studies with significant endpoints

A significant reduction of total mortality by pharmacological treatment was shown by the STOP-, MRC- (only borderline significance) and MAPHY-study.

A significant reduction of cardiovascular mortality was reached in the Australian and EWPHE-study and a borderline significance in the STOP-study.

A significant reduction of cardiovascular morbidity could be seen in several studies (VA I, VA II, EWPHE, STOP, SHEP, STONE, Gothenburg and with borderline significance Australian, Oslo, Coope et al., MIDAS).

The combined endpoint of cardiovascular mortality and morbidity was significantly reduced in the SHEP- and Syst-Eur- and with borderline significance in the MRC-study.

Analysis of the studies

Total mortality, cardiovascular mortality and cardiovascular morbidity were inconsistently influenced in the studies. The reasons for these inconsistencies can be found in sample size estimation, inclusion and exclusion criteria, dropouts and dropins, drugs (classes and doses), compliance of the patients, blood pressure lowering effect and power of the studies.

Sample size

To prove a significant and clinically relevant reduction of an endpoint, a sample size estimation is necessary. The sample size depends besides the α- and β-error with eg, 5 % respectively 20 % from the number of endpoints and the clinically relevant reduction of the endpoint.

If eg, there is only a 1 % incidence of endpoints a greater sample size is necessary to show an eg, 40 % reduction than if the incidence of endpoints is eg, 10 %.

In patients with uncomplicated hypertension there is only a low incidence of mortality and morbidity endpoints with a range between 1 and 10 %. To prove a clinically relevant decrease of an endpoint, over 16000 respectively 4000 patients are necessary.

Correspondence to: Prof. Dr. med. K. Wink, Victor-Kretz-Str. 11, D-77723 Gengenbach, Germany

In most studies the sample size is not large enough to prove a clinically relevant decrease in total mortality, cardiovascular mortality and cardiovascular morbidity. The sample size was only sufficient to test clinically relevant decrease of cardiovascular mortality in the MRC-study and for cardiovascular events in the SHEP- and Syst-Eur-Study.

In-/exclusion criteria
There was a great difference of initial blood pressure to include patients, eg, diastolic blood pressure 105–120 mmHg in the STOP-study and < 90 mmHg in the SHEP-study with patients with isolated systolic hypertension.

In the most studies, patients with target organ damage were excluded. Therefore, most patients were at a low risk for cardiovascular events.

Dropouts and Dropins
It is unavoidable that in studies going over years, patients will drop out. No patients were lost to follow-up in the STOP- and MIDAS-study, but 25 % for morbidity endpoints in the MRC-study.

Many dropouts of patients weaken the results of a study. For medical and ethical reasons patients allocated to the placebo group becoming worse must change to the group of active treatment.

The rate of dropins ranged from 10 % (Australian-study) to 53 % (MRC-study).

Dropins lower the cardiovascular risk in the placebo-group and raise it in the group of active treatment.

Drugs
In the studies published from 1967 to 1996 mainly beta-blockers and diuretics were used. Only in "newer" studies from 1996 to now were calcium channel blockers, ACE-inhibitors and angiotensin II receptor antagonists used. In the thiazide group of diuretics the dosis has changed from 100 mg/day in 1967 to 12.5–50 mg/day in 1997. Results can be dependent on the classes and doses of drugs.

Significantly decreased endpoints were reached in studies where beta-blockers and diuretics were used, for all endpoints (total mortality, cardiovascular mortality, cardiovascular morbidity).

In studies where calcium-channel blockers and ACE-inhibitors were used, only cardiovascular morbidity and the combined endpoint of cardiovascular mortality and morbidity were positively influenced.

Compliance of the patients
The compliance for drugs in hypertensive patients will be about 50 %. It depends on the duration of the therapy, the adverse events and outcome. The higher the compliance, the better the blood pressure control and probably the outcome.

Bloodpressure lowering effect
The optimal blood pressure should be < 120/80 mmHg. These values were never reached in studies where patients with elevated systolic and diastolic blood pressure were included. But also blood pressures of 130/85 mmHg, perhaps without cardiovascular risk, were on average reached only in a few studies (eg, Oslo-study).

Better blood pressure control can influence mortality and morbidity. In the cited studies there seemed to be no correlation between the blood pressure lowering and the impact on outcome. In the Glasgow-study [22], a retrospective trial, the mortality was lower if lower blood pressure levels were achieved. In the Dalby-study [23], the treated hypertensive patients had higher blood pressure values and incidences of cerebrovascular and coronary diseases after three years than normotensives. In the VHAS-study [24], there were with equal decreases of blood pressure, the same total mortality, cardiovascular mortality and morbidity in the verapamil and chlorthalidon group after a two year treatment.

In the ABCD-study [25] with patients with hypertension and diabetes, the incidence of fatal or non fatal myocardial infarction was significantly higher in the group with calcium channel blocker (nisoldipine) than in the ACE-inhibitor-group (enalapril). The decrease of blood pressure seemed to be comparable after 5 years of treatment.

Also in the FACET-Study [26], the incidence of cardiovascular events (secondary endpoints) was significantly higher in the calcium channel blocker-group (amlodipine) than in the ACE-inhibitor-group (fosinopril) with significantly greater reduction in systolic pressure in patients treated with amlodipine than in those treated with fosinopril and the same reduction in diastolic blood pressure in both treatment groups after 3.5 years.

In the GLANT-study [27], the incidence of cerebro- and cardiovascular events was not significantly higher in the group of calcium antagonists compared with the group of delapril, although the blood pressure lowering was significantly greater with calcium channel blockers than with the ACE-inhibitor.

In the BBB-study [28], the incidence of strokes and myocardial infarction was not different in spite of one group which being treated intensively (diastolic blood pressure ≤ 80 mmHg) and the other group remained with unchanged blood pressure (diastolic blood pressure 90–100 mmHg).

Just now, it is not sure which blood pressure lowering will be best for a positive influence on mortality and morbidity and which is the best drug. The issue of the best blood pressure lowering value is addressed in the HOT-study [29] with three target diastolic pressure groups of ≤ 90, ≤ 85 and ≤ 80 mmHg. The drugs used in this trial were felodipine, a calcium channel blocker, then ACE-inhibitors or beta-blockers, and then diuretics. In this study there was no correlation between the grade of blood pressure lowering and the incidence of mortality and morbidity end points [30].

Power of the studies
The power, ie, the real probability of existing differences or true positive results, should be > 80 % by convention.

This value is reached only in a few studies (eg, SHEP for cardiovascular morbidity). Therefore most of the cited studies are underpowered.

Impact of reasons of inconsistencies on mortality and morbidity

The insufficient number of patients included in the studies lead to more frequent negative results. If there was a higher sample size there could be more positive results. Therefore, it can not be excluded that the therapeutic effect of pharmacological treatment in terms of mortality and morbidity is underestimated.

From the in-/exclusion criteria patients with high risk are mostly excluded. In patients with higher risk and more endpoints it is easier to show a therapeutic effect. Therefore, the in-/exclusion criteria produce the assumption that therapeutic effect is underestimated.

Dropouts weaken the results and dropins lower the risk of the placebo and raise the risk of the group of active treatment. The difference of the risk between the two treatment groups becomes smaller and the therapeutic effect is underestimated.

During the last 30 years of research work in terms of an impact of pharmacological treatment on mortality and morbidity the classes and the doses (eg, thiazide) have changed. Therefore, it is not excluded that in former studies the therapeutic effect would be underestimated.

The compliance in hypertensive patients is low. The low compliance of drugs yields not only to lower rate of adverse drugs reactions, but also to underestimation of the efficacy.

In the most studies, there is not sufficient blood pressure control. Although the optimal blood pressure decrease is not known, there is the suspicion that the insufficient blood pressure lowering underestimates the possible effect of drugs to reduce mortality and morbidity.

Most of the studies are underpowered. With a higher power, more positive results can be expected. Therefore, underpowering means an underestimation of the therapeutic effect.

Taking together the reasons for inconsistencies of the results of these "classical" hypertension intervention trials, they all give evidence for an underestimation of the reduction of mortality and morbidity with pharmacological treatment.

This seemed to be confirmed by the Framingham Heart Study [31]. There was a secular trend to lower total and cardiovascular mortality in the cohort of 1960 and 1970 followed up for 10 to 20 years in the treated group compared with the group without treatment for hypertension.

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