Modern antihypertensive agents banned the life threatening complications of malignant hypertension. Nevertheless, chronic treatment of arterial hypertension is still costly, tedious, and at the population level rather unsuccessful. Even more worrisome is the fact that pharmacological blood pressure normalization in hypertensive patients fails short of neutralizing the cardiovascular risk to the level of normotensive individuals. Given these shortcomings, either permanent cure or long-term prevention of arterial hypertension is desperately awaited.

In this issue of Hypertension, Karin Skov and her coworkers present data from a well-conducted pharmacological study for the prevention of hypertension. The authors hypothesize that inhibition of the renin–angiotensin system in individuals with high familial risk may interfere with the self-accelerating process leading to the manifestation of hypertension. This study mimics the situation in young genetically hypertensive rats in which inhibitors of the system are known to delay the onset of the condition way beyond the active treatment period.

The present trial studied 110 normotensive young adults in whom both parents had essential hypertension. Double blind treatment with either candesartan or placebo was conducted for 1 year followed by 24 months of no treatment in both arms of the trial. The authors report that the primary outcome, ie, the mean 24-hour ambulatory blood pressure, was not different between the 2 groups in the follow-up period, ie, when no active treatment was given in either arm of the study. The authors conclude that temporary treatment of subjects with high familial risk does not delay the onset of hypertension beyond the active treatment period.

It is obvious from the authors’ conclusion that pharmacological prevention of hypertension is a dream that yet has to become true. The reasons for successful prevention of hypertension in susceptible rats but failure in humans at risk are uncertain but may include: (1) differences in genetics between rats (oligogenic) and humans (polygenic, complex); (2) differences in pathophysiology and/or early end organ damage; (3) treatment of different stages of the disease; (4) periods of treatment or follow-up that were too short.

However, why did inhibition of such a functionally active and potentially detrimental renin–angiotensin system fail to affect blood pressure during follow-up in the present study? Another simple explanation may be that blood pressure simply did not change at all in these young and healthy individuals. Indeed, on average ambulatory blood pressure measurements remained constant at normotensive blood pressure levels even in the placebo group (the difference between baseline and end of follow-up was ±1 mm Hg). Moreover, only 3 of 110 individuals in this trial developed arterial hypertension during this 3-year study. Thus, while careful blood pressure measurements as conducted in this trial permit documentation of even minor changes in blood pressure, this study was clearly underpowered or too short to test the effect of treatment on the incidence of arterial hypertension.

However, the work of Skov and coworkers also offers some hope. First, it is quite remarkable that active treatment with 16 mg of candesartan per day in normotensive individuals lowers systolic and diastolic office blood pressure by about 8 and 5 mm Hg, respectively. Likewise, mean ambulatory blood pressure was significantly lowered by about 4 mm Hg on average. This effect was accompanied by marked decreases in renal vascular resistance, filtration fraction, and left ventricular mass index. Thus, it can be concluded from the present as well as a similar study published recently that the renin–angiotensin system plays an enormous role in the regulation of blood pressure as well as the maintenance of renal hemodynamics and left ventricular geometry, even in healthy, normotensive subjects. Not only the extent of these effects is remarkable, but also the fact that active treatment with candesartan had placebo-like side effects in normotensive individuals who achieved relatively low blood pressure levels (about 112/66 mm Hg office blood pressure on average) by active treatment. These data in conjunction with the notion that an activated renin–angiotensin system is a primary source for target organ damage in patients with arterial hypertension should encourage further research on attempts to vaccinate against components of the renin–angiotensin system and thereby to neutralize the system long-term.

The finding that blood pressure remained normotensive throughout the follow-up period is in remarkable contrast with the TRial Of Prevention of HYpertension (TROPHY) study, the only other study on pharmacological prevention of hypertension. These investigators observed that candesartan treatment of prehypertensive individuals resulted in a slight but significant decrease of systolic blood pressure, even 2 years after active treatment (~2.0 mm Hg). Moreover, the TROPHY study suggested a marked reduction in new onset hypertension in persons receiving the angiotensin receptor blocker. Multiple differences between the 2 studies may explain the discrepancy. The TROPHY study was larger (772

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Universitätsklinikum Schleswig-Holstein, Campus Luebeck, Medizinische Klinik II, Luebeck, Germany.

Correspondence to Heribert Schunkert, Universitätsklinikum Schleswig-Holstein, Campus Luebeck, Medizinische Klinik II, Ratzeburger Allee 160, D-23538 Luebeck, Germany. E-mail heribert.schunkert@innere2.uni-luebeck.de


© 2007 American Heart Association, Inc.

Hypertension is available at http://www.hypertensionaha.org
DOI: 10.1161/HYPERTENSIONAHA.107.090910
Prehypertension

Prevention of hypertension

Non-pharmacological treatment

Prevention of events

Pharmacotherapy in patients with diabetes, chronic kidney disease or otherwise high CV risk

Intermittent pharmacological treatment?

Treatment strategies in prehypertension.

versus 110 individuals) and treated older patients (average age 48 versus 29 years) with higher average blood pressure (134/85 mm Hg versus 129/79 mm Hg). Moreover, active treatment was carried out for 2 rather than 1 year as in the present investigation. But are the findings of the TROPHY and the present study really that much different? The definition of hypertension in the TROPHY study has been questioned several times. Moreover, this study did not show any long-term effect on diastolic blood pressure. Thus, the main difference between the 2 studies lies in a 1- to 2-mm Hg difference in office systolic blood pressure two years after cessation of active treatment.

Given these somewhat disappointing data, one may ask what is the future role for preventive pharmacotherapy of individuals at risk for developing arterial hypertension? First, we need to define the rationale of such therapy (Figure).

One indication may be the reduction of cardiovascular risk. This is already elevated in individuals with diabetes mellitus and chronic kidney disease and blood pressure in the upper range what is now being defined as prehypertension. Here, it is important to understand that current guidelines already recommend medical therapy in such patients. Moreover, several trials in prehypertensive patients with vascular comorbidities suggest improved organ protection and even reduced mortality with treatment by antihypertensive agents.

Another benefit may be the prevention of manifest hypertension in young, low-risk individuals like those studied by Skov or the TROPHY investigators. Here, we are currently missing any clinically relevant long-term effects on blood pressure that might justify such treatment. For these remaining individuals at present time nonpharmacological treatment should be recommended. Unfortunately, the TROPHY study as well as the present work of Skov and her coworkers do not clearly define a patient group that may benefit from angiotensin receptor blockade for the prevention of subsequent manifestation of arterial hypertension.

Disclosures

H.S. has received lecture fees from MSD, Novartis, Sanofi-Aventis, Astra-Zeneca, and Pfizer and consulting fees from MSD/essex, Sanofi-Aventis, Novartis, and Astra-Zeneca.

References

A Dream Yet To Become True
Heribert Schunkert

Hypertension. 2007;50:39-40; originally published online May 7, 2007;
doi: 10.1161/HYPERTENSIONAHA.107.090910

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/50/1/39

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/