

## Beta Blockers As First Drugs in HT Treatment An example of difficulties when making and interpreting meta-analyses.

Lars H. Lindholm

Editor, Hypertension News



Frans Messerli and co-workers were the first to challenge beta-blockers as acceptable first-line treatment for elderly hypertensives (1). They did so in 1998 in a meta-analysis that included only two (!) studies which reported events. A Swedish group followed in 2004-5 (2,3) with two more comprehensive meta-analyses. This gave rise to an intensive debate in the medical community as well as a "media storm", since treatment with a beta-blocker reduced the risk of stroke by only 19% in comparison with placebo or no treatment, about half of that expected from previous trials. Moreover, in comparison with other blood pressure lowering drugs, the risk of stroke was 16% higher (!) for beta-blockers.

In 2006, a Canadian group looking at a combination of cardiovascular events (death, stroke, and MI) found beta-blockers to be inferior to all other therapies for elderly (60+) hypertensives (4), similar to the Swedish finding for stroke (3). The Canadians, however, didn't find any difference in effect for younger (<60) patients. A contributing factor to this difference was that the Canadians included the results of the Captopril Prevention Project (CAPPP,) comprising 10,985 men and women aged 25-66 years from Sweden and Finland (mean follow-up 6.1 years), who were randomised to "conventional treatment" (a diuretic and/or a beta-blocker) or an ACE-inhibitor (5). Patients in CAPPP were younger (mean age 51.5 years) than those in previous large hypertension trials in Scandinavia. In the Canadian analysis of younger patients, CAPPP accounted for about half of the events (4). The CAPPP findings were excluded from the Swedish meta-analysis, since the percentage of patients who received a beta-blocker was unknown, as stated in the paper (3).

Randomisation in CAPPP had been made by sealed envelopes and there was unfortunately an imbalance at baseline, as low-risk patients were more likely to get "conventional treatment" than an ACE-inhibitor. Systolic blood pressure at baseline was 2-3 mm Hg higher in the ACE-inhibitor group and there were more patients with diabetes mellitus in that group (5). The relative risk of stroke in the ACE-inhibitor group was 25% higher in the patients treated with an ACE-inhibitor than in those receiving "conventional" treatment, RR 1,25 (95% CI 1,01-1,55). This is hardly surprising, if one considers the difference in systolic blood pressure at baseline and during the trial.

Needless to say, the findings of CAPPP were criticised and Sir Richard Peto, FRS, at Oxford wrote in The Lancet (6): "*differences between the two treatment groups in pre-randomisation height, weight, systolic, and diastolic blood pressure (with respective p-values of  $10^{-4}$   $10^{-3}$   $10^{-8}$   $10^{-18}$  respectively), show that the process of randomisation by sealed, numbered envelopes was frequently violated*". Also, "*the present report cannot be taken as coming from a properly randomised trial*".

So, **what** should one believe? Well, I leave that to the readers of Hypertension News to decide. Just remember that stroke is uncommon in younger patients (only 10,2% of all strokes in Sweden in 2005 and 2006 were in patients below 60), which makes comparisons difficult! Personally, I avoid using the findings of C(R)APPP!

In conclusion. First, when interpreting a meta-analysis, make sure that the trials included are the right ones! Second, if beta-blockers are less effective, have side-effects, and cost about the same as other blood pressure lowering drugs, why use them as first-line treatment of hypertension, unless there is a compelling indication?

### References:

1. Messerli FH, Grossman E, Goldbourt U. Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. JAMA 1998;279:1903-7 doi: 10.1001/jama.279.23.1903
2. Carlberg B, Samuelsson O, Lindholm LH. Atenolol in Hypertension: Is it a wise choice. Lancet 2004;364:1684-9 doi: 10.1016/S0140-6736(04)17355-8
3. Lindholm LH, Carlberg B, Samuelsson O. Should beta-blockers remain first choice in the treatment of primary

hypertension? A meta-analysis. Lancet 2005;366:1545-53 doi: 10.1016/S0140-6736(05)67573-3

4. Khan N, McAllister FA. Re-examining the efficacy of beta-blockers for the treatment of hypertension: a meta-analysis. CMAJ 2006;174:1737-42 doi.org/10.1503/cmaj.060110

5. Hansson L, Lindholm LH, Niskanen L et.al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: The Captopril Prevention Project (CAPPP) randomized trial. Lancet 1999;353:611-16 doi: 10.1016/S0140-6736(98)05012-0

6. Peto R. Failure of randomisation by "sealed" envelope. Lancet 1999;354:73 doi: 10.1016/S0140-6736(05)75340-X

Lars H Lindholm- lars.h.lindholm@umu.se

## NEWS, OLD NEWS, FAKE NEWS.

DOI: 10.30824/1903-10

***"I eat what I like and suffer thereafter"***

**Martin Luther (1483 – 1546)**

**Stephan Rössner, Professor Emeritus Apple Bay Obesity Research Centre, Bromma, Sweden**

Martin Luther's health has been discussed extensively by psychiatrist and clinicians over the years – he clearly had a complex psychiatric history of neuroticism and, most likely, a manic-depressive condition, while also suffering from a somatic condition.

Luther was born in 1483 in Eisleben in Germany and began his study in Erfurt in 1501. He admitted that he enjoyed the life of a student more than the studies themselves, engaging heavily in eating and drinking and even referred to the University as 'a pub and a brothel'(1) He woke everyday at 4 o'clock for a day filled with 'mechanical learning and tiring spiritual exercises'1. Here, academics taught Luther to be critical towards even the greatest philosophers and to test matters through his own experience. Luther resisted the concept that the Bible was the only tool for spiritual development and believed that common sense would not necessarily lead man to God.

In 1505 Luther was accepted into a monastery, however the early years were not easy as he was ostracized by his fellow monks who forced him to execute undesirable tasks as they despised the academic and learned young man. The University eventually reacted to this treatment of their scholar and had him admitted into proper ranks of the Order. Luther could now begin his career, where he eventually met his academic goals and became a Professor of Theology in 1512. Luther's critical approach to his work resulted in the famous '95 Theses' that he nailed on the church door of Wittenberg in 1517. This endeavor angered the Pope and caused Luther and his wife to live in constant fear of being imprisoned by the papal revenge system.

Despite this threat to his personal safety, Luther was also at risk due to his poor health throughout his life. At the age of only 20 years old, Luther developed a leg ulcer that never healed and it is believed he suffered from angina pectoris from 1527, however it is difficult now to evaluate the severity of his chest pains. Numerous paintings depict Luther becoming increasingly obese over time and it is likely that he suffered from high blood pressure, certainly experiencing continuous headaches and epilepsy or possibly Ménière's disease(1). In 1525 he had his first kidney stone, he suffered from continuous severe constipation, had bleeding haemorrhoids and suffered from insomnia. All of these medical problems began in the early 1520s, which he interpreted as provocations from Satan. Due to the early onset of his health problems, it is surprising that Luther managed to produce 124 publications, including a translation of the entire Bible from Hebrew into German and numerous religious publications.

In 1525, Luther married Katharina von Bora, who had been a nun. She had escaped from a cloister with eleven other nuns. Luther worked hard to find them work or a partner as their families did not want them back. With

