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A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

Optimal Blood Pressure Control using Fixed-dose Combination Antihypertensive Therapy: Insights from a COmparative Study of efficacy of Irbesartan/hydrochlorothiazide with valsartan/hydrochlorothiazide using home blood pressure Monitoring in the treAtment of mild to moderate hypertension (COSIMA)

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Hypertension remains an important public health problem despite the availability of a wide array of antihypertensive agents. Only a fraction of hypertensive individuals who receive treatment actually achieve normalization of their blood pressure (BP). Pharmacodynamic and pharmacokinetic differences between agents, even within the same class, can potentially lead to differences in efficacy. Historically, hypertension trials have focused on the comparison of individual agents. However, recent data from large clinical trials have demonstrated that many hypertensive patients require multiple agents in order to lower their BP to recommended levels. The COSIMA study was therefore designed to compare the efficacy of two fixed-dose, combination antihypertensive regimens in lowering BP as assessed by home BP monitoring (HBPM). In this issue of *Cardiology Scientific Update*, the preliminary results of COSIMA, as well as issues regarding the use of HBPM devices, are discussed.

Hypertension is a global medical and public health problem, affecting 26.4% of the worldwide adult population in 2000. It is projected to affect 29.2% of the population by 2025.[1] In spite of the availability of an ever-increasing number of antihypertensive agents, the control of high BP remains inadequate worldwide.[2-4] Therefore, finding the appropriate agents and regimens that would optimally lower BP is important to practicing physicians. Comparative studies have demonstrated that the pharmacodynamic and pharmacokinetic differences between pharmacologic agents, even within the same class, can translate into differences in BP-lowering efficacy.[5-8] These comparative hypertension trials to date have focused mainly on comparisons of single agents, or regimens that are based on single agents. However, data from large clinical trials have demonstrated that the majority of hypertensive patients require multiple antihypertensive agents to lower their BP to recommended target values.[5,6] Indeed, a recent meta-analysis of over 300 randomized placebo-controlled trials has demonstrated that combination low-dose drug treatment not only increases efficacy, but also reduces adverse effects.[9] First-line fixed-dose combination therapy is, therefore, a potentially attractive approach to optimally lower BP in hypertensive subjects. Until recently, there have been no studies that have compared the BP-lowering efficacy of different fixed-dose combination regimens.

The COSIMA trial

The COmparative Study of efficacy of Irbesartan/hydrochlorothiazide with valsartan/hydrochlorothiazide using home blood pressure Monitoring in the treAtment of mild to moderate hypertension (COSIMA) was designed to compare the fixed combinations, irbesartan 150 mg/hydrochlorothiazide (HCTZ) 12.5 mg and valsartan 80 mg/HCTZ 12.5 mg, over an 8-week, open-label, treatment period, in patients with persistent hypertension on HCTZ monotherapy.

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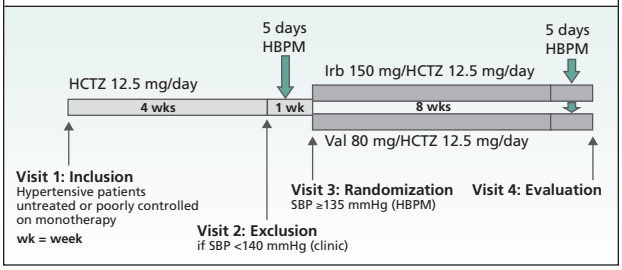
Figure 1: COSIMA study design and protocol



Study design

The study utilized a prospective, randomized, open-label, blinded endpoint (PROBE) design. Randomized patients used HBPM devices to provide BP data that was transferred automatically to the study centre for blinded analysis. Male or female patients who were ≥18 years and <80 years were eligible, with systolic BP (SBP) ≥160 mm Hg (untreated) or ≥140 mm Hg (on monotherapy). Exclusion criteria included secondary hypertension, type 1 or 2 diabetes, or a prescription for additional antihypertensive treatment. Patients were excluded after 4 weeks (visit 2) if SBP (obtained in the clinic) was <140 mm Hg. The exclusion criteria at 5 weeks (visit 3, at randomization) included noncompliance with the HBPM protocol and SBP (by HBPM) that was <135 mm Hg. At inclusion, the patients were started on a regimen of HCTZ 12.5 mg/day monotherapy for a duration of 5 weeks. After 4 weeks, patients with SBP (clinic) ≥140 mm Hg were given an HBPM device to carry out repeated measurements over 5 days. At the end of the monotherapy treatment period, patients with valid HBPM measurements and SBP ≥135 (by HBPM) were randomized to either valsartan/HCTZ or irbesartan/ HCTZ. Five days before the final visit (after 8 weeks of combination therapy), patients were again instructed to take home BP measurements over 5 days (Figure 1).

Blood pressure measurement

The study utilized the TensioDay® (TensioMed, Budapest, Hungary) HBPM device, an ambulatory BP monitor with wireless infra-red communication. Measurements were taken after 5 minutes of rest, with 3 measurements (at 1-minute intervals) in the morning before drug intake (6 am -10 am) and 3 measurements in the evening (6 pm - 11 pm). The data recorded by the HBPM device were then transferred to a central computer server via online data transfer each evening, between 23:00 and 06:00. Physicians were able to verify that the data had been sent and that the BP was within a controlled range. The central analysis of data was carried out completely blind to treatment. The first values of the first day for each period were not used. At least 12 measures for each patient were validated and had to be coherent.

Efficacy criteria and sample size calculation

The primary assessment criterion was the difference between the groups in the mean SBP change from baseline to the end of study (after 8 weeks of treatment). The secondary criteria included:

- change in mean SBP (HBPM) after 8 weeks of treatment
- change in mean SBP and diastolic blood pressure (DBP) at trough morning values (HBPM) after 8 weeks of treatment
- change in mean SBP and DBP trough (clinic measurement)
- percent of patients with BP normalized on HBPM after 8 weeks treatment
- percent of patients with BP normalized on clinic measurement after 8 weeks.

The trial assumed that 10% of the BP measurements using HBPM would be invalid. It was estimated that 400 patients were required to detect a difference in SBP of at least 3 mm Hg between the 2 groups, with a standard deviation of 10 mm Hg, using a two-tailed t test ($\alpha = 0.05$) with a power of 80%.

The study flow

A total of 800 patients were included in the initial phase of the study (HCTZ 12.5 mg/day monotherapy over 5 weeks). After 4 weeks, 120 patients were excluded because of normalization of BP (n=78), consent withdrawal (n=16), adverse events (n=16), or becoming ineligible (n=10), and 680 patients (with SBP ≥140 mmHg) were given an HBPM device with instructions to take BP measurements over 5 consecutive days. During the third visit, 216 patients were withdrawn from the study because BP normalized according to HBPM (n=188), invalid BP measurements (n =20), ineligibility (n=5), or adverse events (n=3). A total of 464 patients thus fulfilled the final selection criteria and were randomized; a total of 449 patients were included in the intention to treat (ITT) population. A small number of patients were withdrawn due to various administrative reasons, leaving 414 patients in the per protocol analysis (216 in the valsartan/HCTZ arm and 198 in the irbesartan/HCTZ arm).

Results

The preliminary results of the COSIMA trial were presented at the recent French Society of Arterial Hypertension Meeting in Paris, France. These results are not yet published and, therefore, may be subject to modification. The two randomized groups were well-matched: overall, 55% were male, the mean age was 60 years, and mean clinic BP 153/90 mm Hg, HBPM BP 149/89 mm Hg. Both treatments were effective in lowering BP. In the valsartan/HCTZ and the irbesartan/HCTZ group, there was a mean reduction in SBP/DBP of 10.6/7.4 mm Hg versus 13.4/7.4 mm Hg using HBPM, respectively. Clinic measurements showed slightly greater reductions in SBP, but similar reductions for DBP (Table 1). Mean BP reductions were greater in the irbesartan/HCTZ group than in the valsartan/HCTZ group by 2.8 mm Hg for SBP (HBPM) ($p = 0.0024$) and 2.2 mm Hg for DBP ($p = 0.0003$). The differences between the mean BPs for valsartan/ HCTZ and irbesartan/HCTZ were greater in the morning than in the evening (Table 2), suggesting a longer duration of action for the latter combination. More patients were normalized

Table 1: Changes in BP in the COSIMA study

	mmHg	Val/HCTZ N = 216	Irb/HCTZ N = 198	p-value Val/HCTZ vs Irb/HCTZ
HBPM* measurements	Change in SBP	-10.6	-13.4	-2.8 (p = 0.0024)
	Change in DBP	-7.4	-9.6	-2.2 (p = 0.0003)
Clinic† measurements	Change in SBP	-11.6	-14.8	-3.2 (p = 0.0047)
	Change in DBP	-6.8	-8.2	-1.4 (p = 0.0374)

*Mean values for HBPM
†Trough values for clinic
SBP = systolic blood pressure; DBP = diastolic blood pressure, Val = valsartan; Irb = irbesartan; HCTZ = hydrochlorothiazide

after 8 weeks treatment in the irbesartan/HCTZ group than in the valsartan/HCTZ group (Figure 2): 52.9% versus 33.3% ($p < 0.0001$).

The tolerability profile of the two treatments was comparable and the majority of adverse events were considered mild to moderate in intensity and unrelated to treatment. In total, 15.9% of patients in the valsartan/HCTZ group experienced at least one adverse event versus 18.0% of patients in the irbesartan/HCTZ (p = 0.44).

Comments

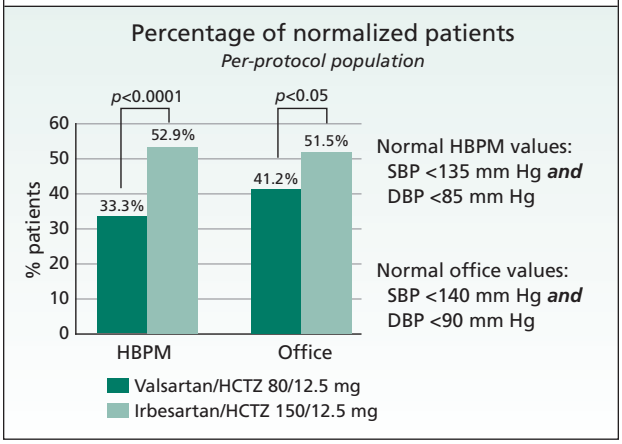
Until recently, comparative hypertension trials have focused mainly on comparisons of single agents or regimens that were based on single agents. However, few, if any of the major hypertension trials, have depended on a single drug. To achieve adequate BP control in the treatment groups, additional drugs have been used, making it difficult to determine whether the original drugs being tested, as opposed to the regimens built around them, were responsible for the clinical effects. Results of comparison trials of combination therapy are therefore relevant.

Table 2: Comparison of the differences in BP between morning and evening

	mmHg	Val/HCTZ N = 216	Irb/HCTZ N = 198	p-value Val/HCTZ vs Irb/HCTZ
Morning measurements	Change in SBP	-9.4	-12.7	-3.4 (p < 0.001)
	Change in DBP	-6.6	-8.9	-2.3 (p < 0.001)
Evening measurements	Change in SBP	-11.9	-14.3	-2.4 (p < 0.05)
	Change in DBP	-8.5	-10.5	-2.0 (p < 0.01)

SBP = systolic blood pressure; DBP = diastolic blood pressure, Val = valsartan; Irb = irbesartan; HCTZ = hydrochlorothiazide

Figure 2: Normalized blood pressure



Results of the COSIMA trial provide novel information on two aspects that are relevant to the management of patients with hypertension.

• The first aspect is that the COSIMA trial was the first to compare the BP-lowering efficacy of two fixed-dose combination anti-hypertensive regimens using a PROBE design in patients who were not controlled on diuretics. In a single agent comparison of two angiotensin-receptor blockers (ARBs),[8] irbesartan 150 mg produced greater reductions from baseline in SBP and DBP at trough and over 24 hours than valsartan 80 mg. This difference is presumably related to the different pharmacodynamic and pharmacokinetic properties of 2 agents from the same class. The current findings from the COSIMA study, therefore, suggest that differences in the BP-lowering potency of individual ARBs are maintained, even when a fixed dose of diuretic is added. At this point, it is unclear whether the difference in the BP-lowering effects of 2 fixed combination antihypertensive regimens translate into a difference in clinical outcomes. In this regard, the ongoing Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension (ACCOMPLISH) trial will be the first blinded and randomized study to prospectively compare the effects on the cardiovascular endpoints of 2 fixed-dose antihypertensive combinations.[10]

• A second novel aspect of the COSIMA trial is that it utilized a relatively new methodology of measuring BP – namely HBPM – to measure the BP response to therapy. These findings were then confirmed with more conventional office BP measurements. The methodology of ambulatory blood pressure monitoring (ABPM) and home BP monitoring have been supported by the latest European Society of Hypertension recommendations,[11] as well as the Seventh Report of the U.S. Joint National Committee (JNC 7) guidelines,[12] provided that there is sufficient scrutiny and that validated and certified devices are employed. The Canadian Hypertension Education Program also currently recommends the use of ABPM in accordance with specific guidelines for the diagnosis of hypertension, as well as the detection of

"white coat" effects in treated patients who do not reach target levels.[13,14] Besides identifying subjects that are "false-positive" for hypertension (ie, white-coat hypertensives), HBPM may also detect those that are "false-negative" for hypertension ("masked hypertensives"),[15-17] as well as patients who are resistant to therapy.

The prognostic value of HBPM has been examined in the Self-measurement of blood pressure at Home in the Elderly: Assessment and Follow-up (SHEAF) study.[15] In this study, office and home BP and cardiac risk factors were measured at baseline in a cohort of 4939 treated hypertensive patients who were recruited and followed up by their general practitioners without specific recommendations about their management. The cohort was then followed for a mean of 3.2 years. The thresholds defining uncontrolled hypertension were at least 140/90 mm Hg for office BP and 135/85 mm Hg for home BP. At the end of the follow-up, at least 1 cardiovascular event had occurred in 324 patients. For BP self-measurement at home, each 10-mm Hg increase in systolic BP increased the risk of a cardiovascular event by 17.2% (95% confidence interval [CI], 11.0%-23.8%).

Conversely, for the same increase in BP observed using office measurement, there was no significant increase in the risk of a cardiovascular event. In a multivariable model with patients having controlled hypertension (normal home and office BP) as the reference, the hazard ratio of cardiovascular events was 1.96 (95% CI, 1.27-3.02) in patients with uncontrolled hypertension (high BP with both measurement methods), 2.06 (95% CI, 1.22-3.47) in patients with normal office BP and elevated home BP, and 1.18 (95% CI, 0.67-2.10) in patients with elevated office BP and normal home BP. These findings, therefore, suggest that home BP measurement has a better prognostic accuracy than office BP measurement and add to the relevance of the findings of the COSIMA trial.

Summary

Results of the most recent clinical trials have reinforced the critical need for BP control to reduce cardiovascular risk.[18-20] Although the 2005 recommendations from the Canadian Hypertension Education Program (http://www.hypertension.ca/index2.html, (last accessed January 21, 2005) have not yet endorsed the use of combination therapy as initial therapy, given the emerging data, it is likely that clinicians will use combination therapy increasingly earlier in the treatment process in order to improve BP response and, hopefully, improve clinical outcomes.

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Dr. Moe discloses that he has previously participated in advisory meetings for Novartis and Sanofi-Synthelabo.

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