an impaired regulation of leptin[7]. The finding of elevated leptin levels in cardiac failure patients stage NYHA II or III is supported by Filipatos et al. and others[8]. From their data, however, it appears that leptin levels tend to decrease in cachectic patients with more advanced stages of the disease, which has only recently been confirmed by others[9]. This does not necessarily contradict our observations.

The patients reported in our study presented with normal or slightly elevated body mass index and did not reach the stage of cachexia (BMI ± SEM: 25.8 ± 1.17 kg.m⁻²). The leptin levels indicated leptin levels in less severely affected when comparing leptin levels. Elevated body mass index and did presented with normal or slightly observations. It does not necessarily contradict our observations.

A possible explanation for increased leptin levels in less severely affected patients and decreased levels in cachectic end stage heart failure patients may be the predominant decline of muscle mass in milder degrees of the disease, with subsequent reduction of the lean/fat ratio, which is supposed to be responsible for increased leptin production. The further loss of body weight in cachectic patients with advanced disease is due to an additional decline in adipose tissue mass and may thus be associated with a decrease in leptin levels, as has been recently suggested[9].

Whether leptin is implicated in the pathogenic process of the disease or more likely is affected as part of the several components deranged in the disorder of cardiac failure needs to be further clarified.

References


AT1-receptor blockers

I very much enjoyed the timely and comprehensive review of AT1-receptor blockers by R. Willenheimer et al. (Eur Heart J 1999; 20: 997–1008). The authors have provided a complete review of the clinical use of these agents in hypertension and heart failure. I share the authors’ excitement that their role in the management of cardiovascular disease will soon be further delineated, as several morbidity and mortality studies are completed over the next few years. There are two errors in the paper, however, that should be corrected.

First, the stated dose of losartan in ELITE II (50 mg twice daily) is incorrect. Patients in ELITE II were randomized to losartan 12.5 mg once daily or captopril 12.5 mg three times daily. These doses were then titrated to 50 mg once daily and 30 mg three times daily, respectively, as tolerated[10].

Second, the authors refer to a meta-analysis that was claimed to be performed by the U.S. Food and Drug Administration (FDA), showing no significant differences in antihypertensive efficacy among the AT1-receptor blockers. In fact, the FDA has never performed such an analysis. Rather, the reference should be to a currently unpublished meta-analysis that was sponsored by Merck & Company and presented in Merck-sponsored satellite symposia at both the International Symposium on Angiotensin II Antagonism (London) and the American Society of Hypertension (New York) meetings in 1999. This analysis was performed with data, obtained from the placebo-controlled trials that were registered with the FDA in support of losartan, valsartan, irbesartan, and candesartan. A second meta-analysis, based on published comparisons between the various AT1-receptor blockers and other classes of antihypertensive agents, was also presented. Both of these Merck-sponsored meta-analyses appeared to demonstrate a strong trend in favour of the antihypertensive efficacy of irbesartan and candesartan over that of losartan and valsartan. Moreover, in Table 7 of this paper, all of the studies listed showed comparability vs enalapril, but only irbesartan was comparable to the highest dose of enalapril (40 mg).

Meta-analyses must always be interpreted with caution since they pool data from diverse trials using different study designs and different patient populations. They are best used as hypothesis-generating exercises, to be followed by definitive, prospective, randomized trials. In fact, such blinded, randomized, head-to-head trials demonstrate superior antihypertensive efficacy of the newest AT1-receptor blockers (irbesartan[11] and candesartan[12]) compared to the maximum recommended once daily dose and the recommended starting dose of losartan, respectively. These clinical trial results should be considered with recently published studies demonstrating that irbesartan provides more complete and more sustained blockade of endogenous angiotensin II than losartan or valsartan in healthy subjects[13,14].

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References


A reply

We read with great interest the letter by William M. Petkun commenting upon our paper about AT1-receptor blockers, recently published in this journal[1]. We are pleased that Dr Petkun enjoyed the paper.

It is obviously correct that the target doses in ELITE were 50 mg once daily for losartan and 50 mg three times daily for captopril (this was correctly stated in the original manuscript but somehow altered in the printing process).

Regarding the meta-analysis that showed no significant differences between AT1-receptor blockers in terms of blood pressure lowering efficacy, indeed, the US Food and Drug Administration (FDA) approved product information for the different AT1-receptor blockers indicate comparable efficacy in terms of blood pressure reduction. A review of these data was presented by Professor B. Williams as an independent abstract at the Second International Symposium on Angiotensin II Antagonism in London earlier this year[2]. Professor Williams was an invited speaker at this meeting. The FDA regulatory review data show that the placebo-corrected reductions in trough diastolic blood pressure for AT1-receptor blocker monotherapy in 7339 patients receiving recommended therapeutic doses of AT1-receptor blockers were quite similar. The reductions were 4–8 mmHg for candesartan, 5–8 mmHg for irbesartan, 3.5–7.5 mmHg for losartan, and 3–5 mmHg for valsartan. Similar equivalence was found for systolic blood pressure reduction.

At this meeting Professor Williams also presented (in the same independent abstract) a meta-analysis of 43 published randomized and controlled trials including 11 281 patients, subsequently to be published in a peer-reviewed journal[3]. The meta-analysis shows that there are absolutely no clinically meaningful differences between losartan, valsartan, candesartan, and irbesartan in terms of blood pressure lowering efficacy. Comparisons were made for recommended starting doses of monotherapy, recommended titration doses of monotherapy, and for starting doses of combination therapy with 12.5 mg hydrochlorothiazide (due to an insufficient number of published trials it was not possible to perform a meta-analysis of the higher AT1-receptor blocker doses in combination with hydrochlorothiazide). The ranking of the four AT1-receptor blockers regarding systolic and diastolic blood pressure reduction, as well as responder rate, based on monotherapy starting doses, monotherapy titration doses, and combination therapy with hydrochlorothiazide, showed no trends in favour of any of the agents whatsoever. Each of the agents ranked best as well as worst in one or another of the nine comparisons.

We fully agree that meta-analyses have to be interpreted with caution for the reasons presented by Dr Petkun. However, individual, small studies should also be interpreted with caution. Dr Petkun claims that three studies (12–4) in Dr Petkun’s letter show superior antihypertensive efficacy of irbesartan and candesartan compared to losartan. All of these studies may be, and have been, criticised for flaws in the design and execution. For example, in the study by Oparil et al. (11) in Dr Petkun’s letter there was a 2.3 mmHg difference in trough seated diastolic blood pressure in favour of irbesartan. However, the study may be criticised because efficacy was evaluated by per-protocol analysis, and 27% of the randomized cohort was excluded from the efficacy analysis. The study by Andersson et al. (13) in Dr Petkun’s letter may be criticised because the only significant difference it showed was a difference in trough sitting diastolic blood pressure reduction when comparing the starting dose of losartan (50 mg x 1) with the maximum recommended dose of candesartan (16 mg). The maximum recommended losartan dose (100 mg x 1) was never compared with candesartan.

The three studies referred to by Dr Petkun (12–4) in Dr Petkun’s letter were all included in the meta-analysis by Conlin et al.[1]. It is obvious that the results of these three studies are not accordant with the general result based on all studies included in this meta-analysis. Therefore, it is evident to us that the meta-analysis clearly shows that incorrect conclusions can be drawn from individual studies, especially since the studies examining the blood pressure lowering efficacy of AT1-receptor blockers so far conducted have been quite small.

In this context it is also important to mention that one has to be aware of publication bias. We can only judge data presented to us.

Dr Petkun refers to two studies showing that irbesartan compared to losartan and valsartan in healthy subjects provides more complete and sustained blockade of exogenous angiotensin II. The clinical significance of such findings is unknown and we should obviously not make a decision of how to treat patients with hypertension based on such findings.

Dr Petkun seems to insinuate that a study or a meta-analysis sponsored by a drug company cannot be trusted. If this were so we would not be able to rely on any data from clinical trials on AT1-receptor blockers, since they have all been sponsored by drug companies. This is indeed a very important point. We have to be very critical and cautious about bias when we read any paper. This is particularly true and our own critical minds are the only available protection against bias.

The blood pressure lowering efficacy is of course important when choosing an agent for the treatment of hyper-