Diabetic cardiomyopathy: a controversial entity: reply

We are most grateful to Dr Karamitsos et al. for showing such an avid interest in our paper.1 Upon its submission, we were acutely aware that we might well shake things up, as prior to confronting the actual study results we also used to support the notion of diabetic cardiomyopathy (DC). By way of addressing some of Dr Karamitsos’s queries,2 let me point out that our results were clearly owed to rather stringent inclusion criteria; a prerequisite condition for diagnosing/ruling out DC. All patients with microalbuminuria (with both normal and abnormal renal function) were excluded from the study due to arterial hypertension (AH), for fear of causing an undue bias.

Neither the diabetics nor the controls were at the time on any medication affecting the serum level of NT-proBNP and diastolic function. Finding patients with long-term diabetes without concomitant medications proved rather challenging and so an adequately sized population took 3 years to assemble. Presently, most of them remain on ACE-inhibitors or ARAs, with a view to retarding microalbuminuria.

A vast majority of echocardiographic parameters for the estimation of diastolic function (apart from those used specifically for diagnosing the restriction) is of little specificity and of rather dubious value in terms of adequately reflecting the left ventricular end-diastolic pressure. In our view, the best marker is actually the E/E’ ratio correlating with the left ventricle end-diastolic pressure. Importantly, according to the recently published ESC consensus document,3 ventriculography is not recommended at all, as a diagnostic tool for diastolic dysfunction.

In assessing our study population, we used diverse echocardiographic techniques, as well as the serum level of NT-proBNP (biochemical marker), in line with applicable guidelines. Furthermore, not only were the structural changes observed by ourselves in the histological samples found non-compliant with the criteria for specific cardiomyopathy recognition, but they also clearly proved heart non-specific, being routinely encountered in other organs in diabetics. It might well be, their incidence alone does not seem to be of sufficient haemodynamic significance to promote diastolic dysfunction (unless AH or coronary heart disease should also enter into the equation).

In our study (despite long-term diabetes, frequent retinopathy, and cardiac autonomic neuropathy), we did not observe any differences in echocardiographic parameters between diabetics and the controls. On the other hand, we tentatively hypothesized that the results of other studies conducted on much smaller populations may actually have been impacted by the influence of exogenous insulin (in different dosages) on vascular resistance; the speculative character of this hypothesis notwithstanding.

It should nevertheless be noted at this juncture that even if echocardiographic parameters in a particular population (i.e. diabetics here) should remain well within normal values, while differing slightly from another population (i.e. the actual basis for diagnosing DC in the reports to date), this gives no grounds whatsoever for diagnosing diastolic dysfunction, let alone contravening applicable guidelines.

We might then have to resign ourselves with Dr Karamitsos to accepting, even if reluctantly so, there is in fact no mystery about DC.

References

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Randomized, double-blind, placebo-controlled study to evaluate the effect of two dosing regimens of darbepoetin alfa in patients with heart failure and anaemia

We read with great interest the article by van Veldhuisen et al.1 who presented the results of randomized, double-blind, placebo-controlled study in anaemic patients with heart failure (HF), in whom anaemia was corrected with subcutaneous darbepoetin alfa and oral iron administration. Although several relatively small studies have shown that anaemia correction might be beneficial in HF patients, that large scale, multicentre trial revealed a much less favourable outcome.

Yet, although the authors made every effort to select the study population accurately and achieved great precision assessing anaemia aetiology and iron homeostasis, there are still several issues to be discussed. The high coefficient of variability (117%) of the basal ferritin level, a traditionally preferred clinical marker for body iron stores, as well as other markers of iron metabolism, suggests a significant diversification within the study group with regard to iron homeostasis.
Keeping in mind the complexity of aetiology of anaemia in HF patients, it is not clear whether authors fully differentiate between true iron deficiency, and anaemia of chronic disease. Although both types are characterized by decreased erythropoiesis, they vary in iron availability, this fact seems important, as the oral iron supplementation was guided by ferritin level in that study. As darbepoetin alfa supplementation enhances iron utilization for haeme synthesis, patients receiving darbepoetin alfa probably got more iron than placebo treated group. Indeed, a slight, but insignificant increase in ferritin, plasma iron, and TSAT in comparison to baseline was reported in body-weighted dose group of patients. Of note is the fact that five out of the total of six deaths occurred in the latter group.

Moreover, plasma contains also non-transferrin bound iron (NTBI)—not assessed in the present paper—which might contain a potentially toxic form of iron that could exert a harmful effect related to the increase of toxic cellular labile iron pool (LIP). The oxidative stress associated with inflammatory conditions frequently observed in HF accompanied by increase in NTBI may lead to an increase in the LIP (via both transferrin dependent and independent pathways) and formation of highly reactive oxygen species, causing an increased myocyte loss, alteration of myocyte function by affecting several excitation–contraction coupling proteins, and also interstitial fibrosis. Although the authors claimed six death incidents unrelated to the treatment regimen, they failed to demonstrate the cause of the fatal outcome. This vagueness might be at least partially cleared out if we could see an additional analysis which would incorporate an adjustment of factors involved in iron homeostasis, which might possibly account for the potential causes of the fatal outcome. It would also be welcome if the authors might provide the absolute amount of iron received by the patients studied to eliminate the association of deaths with the putative iron toxicity.

References

Randomized, double-blind, placebo-controlled study to evaluate the effect of two dosing regimens of darbepoetin alfa in patients with heart failure and anaemia: reply

We appreciate the comments by Drs Leszek and Kruszweski. It is clear that they recognize that the aetiology of anaemia in heart failure is complex and that the non-invasive assessment of body iron stores is challenging. Non-invasive determination of iron status typically includes ferritin and TSAT. Ferritin is an acute-phase reactant. Its level can change in complex and that the non-invasive assessment of iron status typically includes ferritin and TSAT. Ferritin is an acute-phase reactant. Its level can change independently of iron status, which limits its use as a marker for body iron stores. As Leszek and Kruszweski noted, the coefficient of variation for basal ferritin in the placebo and darbepoetin alfa groups is 112 and 117%, respectively. This is in contrast to the coefficient of variation for basal TSAT in the placebo and darbepoetin alfa groups of 32 and 35%, respectively. Thus, in our study, subjects with HB concentration between 9.0 and 12.5 g/dL and a TSAT ≥ 15% were randomized to receive placebo or darbepoetin alfa. All subjects received 200 mg/day of oral elemental iron unless ferritin was > 800 μg/L. During the study, the majority of subjects in each treatment group (> 76%) received oral iron. Iron utilization in the three treatment groups was similar. There were no dose adjustments of iron and no use of intravenous iron.

Significant efforts were undertaken to identify the causes of the six deaths. The lack of relation between death and the treatment regimens was determined by the individual investigators at the subjects’ sites; the authors reported the investigators’ findings. Demographics, co-morbidities, concomitant medications, and laboratory parameters, including HB and iron parameters, were closely scrutinized. Although iron toxicity is an interesting hypothesis, only three of the six subjects who died received oral iron for the duration of treatment (120–155 days). Two subjects who died in the weight-based dosing group did not receive oral iron. Additionally, the weight-based dosing subject who died 7 days after the first administration of darbepoetin alfa received iron for only 1 week. The aetiologies of death are most consistent with the natural history of heart failure. Patients with heart failure are ill and observational data suggest that the presence of anaemia in subjects with heart failure increases the risk of mortality and morbidity. The questions raised by Drs Leszek and Kruszewski highlight how important trials to identify new treatments for heart failure are. The currently enrolling RED-HF Trial will determine the impact of treatment of anaemia with darbepoetin alfa on morbidity and mortality in subjects with heart failure and will provide additional insights into the interplay of HB, iron, and clinical outcomes in heart failure.

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