Reply to: Reduced mortality due to phlebotomy in moderately iron-loaded HFE Haemochromatosis? The need for clinical trials.

Edouard Bardou-Jacquet, Fabrice Lainé, Yves Deugnier

cardiovascular standpoint, there is evidence that low hepcidin levels that are associated with *HFE* p.C282Y homozygosity, leads to low reticuloendothelial cell iron levels despite high total body iron and that this can lead to reduced levels of atherosclerosis (the so called "hemochromatosis paradox") [4].

2. As noted by the authors, those with SF between the ULN and 1000 μg/L had increased medical care compared to the average person and this may have resulted in other lifestyle changes that were beneficial. For example lifestyle changes in subjects with fatty liver disease such as diet and exercise, can improve liver function and morbidity. No information is given by the authors on body mass index and any changes in this following appropriate intervention.
3. Individuals with SF between ULN and 1000 μg/L are less prone to iron deficiency anemia and this may result in health benefit.

The only way to answer the question of the role of venesection therapy in *HFE* p.C282Y homozygotes with SF between ULN and 1000 μg/L is to do a randomized study with half the cohort having normalization of SF and the other half not being treated. Until such data are available, the question of benefit from treating *HFE* p.C282Y homozygotes with SF between ULN and 1000 μg/L remains, in our view, unproven.

Conflict of interest

The authors who have taken part in this letter to the editor declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Reply to: "Reduced mortality due to phlebotomy in moderately iron-loaded HFE Haemochromatosis? The need for clinical trials"

To the Editor:
Australian colleagues raise concerns about our study [1], and the accompanying editorial [2]. We showed that *HFE* C282Y homozygotes with initial serum ferritin (SF) between the upper limit of normal and 1000 μg/L had significantly lower overall mortality than that of the general French population. Delatycki *et al.* disagree with our conclusion that this could be due to early management of patients, and putatively to the maintenance of low body iron stores through iron removal.

With respect to their comments about methodological aspects, we would like to stress the following points:

- We were able to provide the amount of iron removed in 64% of our patients. This high proportion demonstrates the efficacy of our recommendations. However, we agree that, for a significant number of patients, we had no reliable information about long-term maintenance therapy. Therefore, we have been cautious when discussing the putative role of venesection therapy in lowering mortality rate.
- Since the early 1990s, we deliver written guidelines and a personal follow-up notebook to every C282Y homozygote. With time, our recommendations did not vary with respect to the indications and management of initial and maintenance of

venesection therapy [3]. They were taken back by the French Haute Autorité de Santé [4]. Then, all our patients received the same information about both initial and maintenance therapy for several decades.

- Delatycki *et al.* discuss about morbidity aspects. However we studied mortality and not morbidity. Fortunately a large proportion of patients with breast or colon cancer do not die from their malignancy. Thus it is not correct to compare mortality and morbidity data. This is likely also true for cardiovascular disease.

More importantly, iron stores in the body of patients who were not venesected because of normal SF at diagnosis were and remained higher than in those with moderately increased SF who were early enrolled in a phlebotomy program. Indeed, maintenance of SF below 50 μg/L results in lower than normal body iron stores. Therefore, assimilating two sub-groups that were absolutely not identical with respect to iron burden raises serious concerns.

For all these reasons we persist to hypothesize that the discrepancy in mortality data between patients with normal SF and those with moderately increased SF strongly supports a beneficial role of early management of hemochromatosis. However we agree that, as already stressed in our manuscript, we did not demonstrate that iron removal *per se* was responsible for decreasing mortality. Other factors must be discussed (lifestyle modifications, medical follow-up etc.). Nevertheless, the fact that patients had lower mortality when treated for mild hemochromatosis was well shown in this study, regardless of its precise cause.

Finally, in our view, a randomized study of venesection therapy in mild hemochromatosis is neither realistic nor ethical. Moreover, the AASLD guidelines endorsed by Powell *et al.* do not suggest to perform such a study and recommend that «... C282Y homozygotes who have an elevated ferritin (but <1000 μg/L) should proceed to phlebotomy ...» [5].

Conflict of interest

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References

[1] Bardou-Jacquet E, Morcet J, Manet G, Laine F, Perrin M, Jouanolle AM, et al. Decreased cardiovascular and extrahepatic cancer-related mortality in treated patients with mild HFE hemochromatosis. J Hepatol 2015;62:682–689.

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Preservation injury of the distal extrahepatic bile duct of donor livers is representative for injury of the intrahepatic bile ducts

To the Editor:

We recently published an article in the *Journal of Hepatology* describing the histology of biopsies taken from the distal end of the extrahepatic bile duct of donor livers at the time of transplantation [1]. This study demonstrated the presence of severe biliary injury, characterized by loss of the lining biliary epithelium, mural stroma necrosis, as well as injury of the peribiliary glands (PBG) and peribiliary vasculature. Injury of deep PBG and peribiliary vasculature was identified as significant predictors of later development of non-anastomotic biliary strictures (NAS) after transplantation [1]. Severe injury and loss of the lining biliary epithelium is almost universally found in over 90% of donor extrahepatic bile duct biopsies taken at the time of transplantation [2,3]. The observation that the degree of injury of PBG and vascular plexus correlates strongly with the development of NAS after transplantation suggests that insufficient regeneration of biliary epithelial lining after liver transplantation, due to destruction of the progenitor cell niche (i.e. the PBGs) and insufficient blood supply to bile ducts, is a critical component in the pathogenesis of NAS [1,4]. In our previous study, as well as two other studies on bile duct histology of donor livers, biopsies could only be obtained from the distal end of the donor extrahepatic bile duct [2,3]. It is, however, unknown whether the degree of injury at this level is representative for the degree of injury in the rest of the biliary tree, including intrahepatic bile ducts.

To investigate whether histological injury detected in biopsies taken from the distal end of a donor liver bile duct is