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Reply: Potential risk associated with direct modulation of the gut flora in patients with heart failure

We thank Chun Liang and colleagues for their comments on the design of the GutHeart trial[1,2], but disagree with their assertations regarding the potential risk associated with direct modulation of the gut flora. The authors refer to a recent study in which 28 patients with brain fogginess were compared with eight patients without brain fogginess.[3] The results of this study suggest that discontinuation of probiotics improves the symptoms of brain fogginess and reduces the incidence of small intestinal bacterial overgrowth and D-lactic acidosis. However, the probiotics taken by the patients with brain fogginess belonged to the bacterial kingdom.

Bacteria belonging to the *Lactobacillus* genus and some from the *Bifidobacterium* genus are important lactic acid producers, unlike the yeast *Saccharomyces boulardii*. In order to increase their lactic acid production, these yeasts need to be genetically modified,[4–6] which is not the case of *Saccharomyces boulardii CNCM I-745* used in the GutHeart trial. The deleterious effects of the bacterial probiotics described by Rao *et al*. therefore cannot be extended to the strain of *Saccharomyces boulardii* used in the GutHeart trial.

There is no evidence to suggest that small bowel bacterial overgrowth is induced by *Saccharomyces boulardii*. Conversely, two clinical studies[7,8] performed in paediatric patients with short bowel syndrome showed that *Saccharomyces boulardii* improved clinical symptoms and reduced bacterial overgrowth.[9] To reduce the risk of dysbiosis further, disorders of the bowel, such as short bowel syndrome, are an exclusion criterion in the GutHeart trial.

Liang *et al*. question the use of *Saccharomyces boulardii* in patients with gastrointestinal dysmotility, such as the one seen in patients with heart failure. Indeed, *Saccharomyces boulardii* is prescribed for treating and preventing diarrhoea, which is associated with increased bowel motility.[10] However, this probiotic was also shown to improve motility reductions induced by stress[11] and HSV-1 infection.[12]

Liang and colleagues are concerned that *Saccharomyces boulardii* might colonize the small bowel. However, the probiotic drug used in the GutHeart trial does not permanently colonize the gastrointestinal tract, and it is rapidly eliminated from the gut after the last intake.[13–16]

Finally, we fully agree that patient safety is critical in a proof-of-concept study, and all patients included in the GutHeart trial are closely monitored. Detailed safety data are registered and successively analysed. We will publish safety data. We biobank serum, plasma, and faecal samples for subsequent analysis of markers of dysbiosis and disease severity, as well as metabolic aspects of gut microbial functions. With subject enrolment almost complete, we still have not observed signs or symptoms of dysbiosis, lactacidosis, or cerebral dysfunction.

Liang and colleagues question the use of echocardiography for measuring the primary endpoint. Current guidelines recommend implanting intracardiac defibrillators in patients with heart failure and a left ventricular ejection fraction $<$35%. In contemporary cohorts of optimally treated patients with heart failure and reduced ejection fraction, MRI therefore cannot be used for accurate determination of left ventricular volumes and ejection fraction. Power calculations for the GutHeart trial were based on standard deviations from repeated echocardiograms performed at Oslo University Hospital.

We hope this letter meets the major concerns raised about the potential risks of direct modulation of the gut flora in patients with heart failure. We appreciate the interest Liang and colleagues have shown towards our study and the opportunity to discuss their concerns.

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References

1. He Z, Wang J, Chen Y, Cong X, Li N, Ding R, Hultgårdh-Nilsson A, Liang C. Potential risk associated with direct modulation of the gut flora in patients with heart failure. *ESC Heart Failure* 2019; **6**: 555–556.
2. Mayerhofer CCK, Awoyemi AO, Moscavitch SD, Lappegard KT, Hov JR, Aukrust P, Hovland A, Lorenzo A, Halvorsen S, Seljeflot I, Gullestad L, Trøseid M, Broch K. Design of the GutHeart-targeting gut microbiota to treat heart failure-trial: a Phase II, randomized clinical trial. *ESC Heart Failure* 2018; **5**: 977–984.
3. Rao SSC, Rehman A, Yu S, Andino NM. Brain fogginess, gas and bloating: a link between SIBO, probiotics and metabolic acidosis. *Clin Transl Gastroenterol* 2018; **9**: 162.
4. Pacheco A, Talaia G, Sa-Pessoa J, Bessa D, Goncalves MJ, Moreira R, Paiva S, Casal M, Queirós O. Lactic acid production in *Saccharomyces cerevisiae* is modulated by expression of the monocarboxylate transporters Jen1 and Ady2. *FEMS Yeast Res* 2012; **12**: 375–381.
5. Sauer M, Porro D, Mattanovich D, Branduardi P. 16 years research on lactic acid production with yeast—ready for the market? *Biotechnol Genet Eng Rev* 2010; **27**: 229–256.
6. Ookubo A, Hirasawa T, Yoshikawa K, Nagahisa K, Furusawa C, Shimizu H. Improvement of L-lactate production by CYB2 gene disruption in a recombinant *Saccharomyces cerevisiae* strain under low pH condition. *Biosci Biotechnol Biochem* 2008; **72**: 3063–3066.
7. Sadoun-Journo E, Gaillard J, Blehaut H, Goulet O, Bernasconi P, Ricour C. Grêle court dysfonctionnel compliqué de pullulation bactérienne chez l'enfant: effet de *Saccharomyces boulardii*. *Gastroenterol Clin Biol* 1994; **18**: A101.
8. Lyszkowska M, Popinska K, Idzik M, Ksiazyk P. eds. Probiotics in children with gut failure. *J Pediatr Gastroenterol Nutr* 2007; **44**: 126–126.
9. Goulet O, Joly F. Intestinal microbiota in short bowel syndrome. *Gastroenterol Clin Biol* 2010; **34**: S37–S43.
10. Camilleri M, Sellin JH, Barrett KE. Pathophysiology, evaluation, and management of chronic watery diarrhea. *Gastroenterology* 2017; **152**: 515–532.e2.
11. West C, Stanisz AM, Wong A, Kunze WA. Effects of *Saccharomyces cerevisiae* or *boulardii* yeasts on acute stress induced intestinal dysmotility. *World J Gastroenterol* 2016; **22**: 10532–10544.
12. Brun P, Scarpa M, Marchiori C, Sarasin G, Caputi V, Porzionato A, Giron MC, Palù G, Castagliuolo I. *Saccharomyces boulardii* CNCM I-745 supplementation reduces gastrointestinal dysfunction in an animal model of IBS. *PLoS One* 2017; **12**: e0181863.
13. Sovran B, Planchais J, Jegou S, Straube M, Lamas B, Natividad JM, Agus A, Dupraz L, Glodt J, da Costa G, Michel ML, Langella P, Richard ML, Sokol H. Enterobacteriaceae are essential for the modulation of colitis severity by fungi. *Microbiome* 2018; **6**: 152.
14. Samonis G, Falagas ME, Lionakis S, Ntaoukakis M, Kofteridis DP, Ntalas I, Maraki S. *Saccharomyces boulardii* and *Candida albicans* experimental colonization of the murine gut. *Med Mycol* 2011; **49**: 395–399.
15. McFarland LV. Systematic review and meta-analysis of *Saccharomyces boulardii* in adult patients. *World J Gastroenterol* 2010; **16**: 2202–2222.
16. Klein SM, Elmer GW, McFarland LV, Surawicz CM, Levy RH. Recovery and elimination of the biotherapeutic agent, *Saccharomyces boulardii*, in healthy human volunteers. *Pharm Res* 1993; **10**: 1615–1619.