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► **To cite this version:**

Nicolas Girerd. Is the correction of micronutrient deficiencies the next step in heart failure management?. Journal of Internal Medicine, 2022, pp.1-3. 10.1111/joim.13455 . hal-03564834

HAL Id: hal-03564834

<https://hal.univ-lorraine.fr/hal-03564834>

Submitted on 10 Feb 2022

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Is the correction of micronutrient deficiencies the next step in heart failure management?

Nutrition is one of the cornerstones of preventive cardiovascular medicine. However, aside from low cholesterol and low-salt regimens, physicians usually do not encourage specific diets in patients with cardiovascular disease. Nutrition supplementation is also very rarely prescribed, with the exception of omega-3 supplements, which have failed to obtain high-grade recommendation in the absence of strong evidence of their benefit.

In this context, the review published in this month's issue of the *Journal of Internal Medicine* by Bomer et al. [1] from the heart failure (HF) group at Groningen University will probably take most of us off guard. In this brilliant comprehensive review, the authors show convincing evidence building the case for micronutrients being an important component in HF. A detailed evaluation of current evidence regarding coenzyme Q10, zinc, copper, selenium, and iron is provided. Briefly, deciphering all available evidence published in the past decades, the authors show that metabolic perturbations have been repeatedly linked to poor cardiac performance possibly due to progressive cardiac energy deprivation arising from these perturbations. Micronutrients are key to the efficient use of macronutrients to produce ATP. These micronutrient deficits, present in up to 50% of patients, might actually promote the concept of "an engine out of fuel" in HF because of such deficits [1].

Among these five micronutrients (coenzyme Q10, zinc, copper, selenium, and iron), only iron is part of the routine daily practice of an HF physician. Indeed, in the 2021 ESC guidelines on HF [2], it is recommended that all patients with HF be periodically screened for iron deficiency (class I) and that intravenous (IV) iron supplementation should be considered in symptomatic HF patients recently hospitalized for HF with left ventricular ejection fraction (LVEF) <50% and iron deficiency (ferritin <100 ng/ml or serum ferritin 100–299 ng/ml with transferrin saturation [TSAT] <20%) to reduce the risk of HF hospitalization (class IIa) [2]. Apart from this specific iron recommendation, the Euro-

pean guidelines do not recommend other nutrient supplementation. In contrast with European guidelines, the Heart Failure Society of America (HFSA) specifically covered this nutritional aspect in a dedicated consensus on "Nutrition, Obesity, and Cachexia in Patients with Heart Failure" [3]. Yet, this American consensus does not further recommend supplementation, and moreover specifically mentions that "Other than in patients who are deficient in iron or other specific micronutrients, there is no clear role for routine micronutrient supplementation as a component of HF management" [3].

Why do the HF guidelines not formally recommend micronutrient supplementation (except for IV iron)?

The answer is actually fairly simple: the lack of trial evidence. As rightfully pointed out by the review of Bomer et al., there is no large trial evidence addressing a benefit of micronutrient supplementation aside from IV iron supplementation. There are no current trial data specifically dedicated to selenium and zinc in HF. For copper, the ongoing TRACER-HF trial (NCT0387518) is aimed at determining whether various dosages of PO INL1 (a copper-binding agent) decrease natriuretic peptides in ambulatory patients with HF and reduced ejection fraction. However, this phase 2 dose ranging trial is, at best, a preliminary step toward a practice-changing phase III trial.

For coenzyme Q10, the Q-SYMBIO trial provided interesting evidence in 420 patients with HF (mean LVEF 31%) randomized to coenzyme Q10 100 mg three times daily or placebo [4]. The trial showed that the primary long-term endpoint (composite major adverse cardiovascular events) was reached by 15% of the patients in the CoQ10 group versus 26% in the placebo group (hazard ratio: 0.50; 0.32–0.80; $p = 0.003$) [4]. It may appear surprising that such a positive trial performed in 400+ patients did not gain more traction. However, the statistical testing strategy, which considered multiple primary endpoints without an alpha spending function, and the fact that this moderately sized trial

lasted for almost a decade, may have hampered its ability to have an impact on the HF community. Such difficulties in trial interpretation and reasonable cautionary notes have previously been editorialized by Ezekowitz [5].

Lastly, one trial should be emphasized given its very practical approach based on multimicronutrient supplementation. In a placebo-controlled trial published in 2005, a group at UK's University of Hull led by John Cleland (also a coauthor of the review editorialized herein) reported the effect of long-term micronutrient supplementation in the form of capsules containing a combination of high-dose micronutrients (including zinc, copper, selenium, and coenzyme Q10 along with other micronutrients) in 30 patients with HF (mean LVEF 35%) [6]. In this trial, LV end-diastolic volumes decreased by 12% and LVEF increased by 5% over a 9-month period in the high-dose micronutrient group whereas these parameters remained stable in the placebo group [6].

Taken together, while these data unquestionably raise our interest regarding micronutrient effects in HF, they unfortunately cannot reach the level of evidence needed to modify routine clinical practice (and thus achieve the HF guidelines short-list).

How to ascertain whether micronutrient supplementation should be used in HF?

The answer most likely lies in a large, well-conducted trial. But what would be the ideal design of such a trial? First, the intervention: it is highly probable that the one-pill, multimicronutrient approach as outlined by Cleland's group is the key to success, covering "all" important micronutrients, as it maximizes the number of pathophysiological targets while improving patient adherence (who are already taking a number of pills for HF) and maintaining a reasonable cost. Ideally, this intervention should be placebo controlled to maximize the level of evidence. Second, the outcome is likely to be the typical standard in HF trials aimed at changing practices, that is, a combination of mortality and worsening HF (either hospitalized or treated in an ambulatory setting). If cost is an issue (a near certainty in the absence of a pharmaceutical sponsor), newer, more efficient approaches such as the win ratio [7] could be considered, enabling consideration of both hard endpoints (mortality and hospitalization) and patient-reported outcomes (e.g., quality of life).

Barriers to overcome in order to assess the effect of micronutrient supplementation in HF

Notwithstanding the latter, while the above solution appears fairly simple/conventional, the most stringent question here, as is the case for all trials, is funding. Even if the intervention appears seemingly straightforward, trials are a costly tool, and in the absence of sponsors, such large trials are very difficult to undertake. The very nature of micronutrients is also an issue in current Western health-care systems as they do not fall in the "medication" category but rather in the "food supplement" category. This can represent a sizeable barrier for any reimbursement scheme both in the USA and Europe. In addition, no patent can be issued on micronutrients, which further deters the industry to fund such a trial. Of note, the ongoing TRACER-HF trial is in fact testing a copper-binding agent (that can be patented) and not actual copper.

In the absence of industry financial support, only academic trials can provide solutions. This is obviously an arduous path. Yet, in another cardiovascular field, a trial from the George Institute for Global Health (the China Salt Substitute and Stroke Study—SSaSS trial) has recently proved that such a path is not completely unattainable [8]. In this large ($N = 20,995$) open-label, cluster-randomized trial conducted in individuals from 600 villages in rural China with a history of stroke or who were 60 years of age or older and had high blood pressure, the use of a potassium-based salt substitute (in lieu of salt) reduced the rates of stroke, major cardiovascular events, and death from any cause (rate ratio, 0.86; 0.77–0.96; $p = 0.006$) [8]. It took both the strength of the George Institute for Global Health, a worldwide recognized institution in public health, and the clinical research potential of China to achieve this impressive public health trial focusing on a dietary intervention. This example nonetheless shows that public institutions can sometimes overcome the barriers related to the absence of industry funding to evaluate non-medication-centered interventions. Obviously, micronutrient supplementation is more expensive than salt substitutes, and the inclusion of an HF population is indubitably more complex than a populational intervention; on the other hand, the event rate in HF is 5–10 times higher than in populational settings (15%–30% a year in HF vs. approximately 3% a year in the SSaSS trial), which, from a methodological standpoint, significantly decreases the

sample size of a potential trial while improving its feasibility.

All things considered, an array of evidence, brilliantly reviewed by Bomer et al. [1], indicates that micronutrient supplementation could represent an effective treatment in HF, since the failing myocardium may be “an engine out of fuel” due to a micronutrient deficit. The next logical step, given this convincing supporting evidence, is to undertake large (likely publicly funded) trials that ascertain whether a clinical benefit is obtained when using multimicronutrient supplementation. Let us hope that we can collectively find an answer to the challenge of funding such large trials for unpatentable interventions in rather specific populations, such as patients with HF, in a world where simple solutions are oddly difficult to implement.

Conflict of interest

Nicolas Girerd is supported by the French National Research Agency Fighting Heart Failure (ANR-15-RHU-0004), by the French PIA project Lorraine Université d'Excellence GEENAGE (ANR-15-IDEX-04-LUE) programs, and the Contrat de Plan Etat Région Lorraine and FEDER IT2MP. The author reports honoraria from AstraZeneca, Bayer, Boehringer, Lilly, Novartis, and Vifor Pharma.

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