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PERSPECTIVE

A New Requirement for Publication: Access to Effective Drugs for Ethical Reasons, The Example of Heart Failure

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Abstract

The past decade has witnessed the publication of many trials in the field of heart failure, several of which have demonstrated that new drugs could potentially reduce major cardiac events and sometimes even decrease total mortality. Most medical practitioners have experimented with withdrawal of the drug under investigation, having no knowledge of what the patient had received, consistent with a blinded design. In some such cases, the patient's clinical status may be rapidly compromised after withdrawal, suggesting (i) that the patient had been receiving the active drug and (ii) that the drug under investigation might exert beneficial effects. The patients should receive early benefit from the drug, but they are left most often without this beneficial treatment not only until the trial results are complete but also until after the guidelines are updated and after the reimbursement (months to years after the results). Here, we propose that the study sponsor should plan from study conception that all participating patients (regardless of whether they are in the placebo or active drug group) will have access to the drug upon trial completion—once safety is verified and until the results are known. Nowadays, it is not conceivable to submit the results of a large trial for publication without approval from a suitable ethical committee. Similarly, the access to the effective drug should be considered as a requirement for clinical research, not only for ethics committee approval, and for the registration of the trial in an international database until publication.

Keywords Clinical research; Heart failure; Ethics

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The past decade has witnessed the publication of many trials in the field of heart failure (HF), several of which have demonstrated that new drugs could potentially reduce major cardiac events and sometimes even decrease total mortality. This has been the case for the PARADIGM trial, in which sacubitril–valsartan was compared with enalapril,[1] the DAPA-HF trial, in which dapagliflozin was tested as an add-on medication,[2] and similarly the EMPEROR-reduced trial with empaglifozin,[3] and finally VICTORIA[4] and more recently GALACTIC-HF, have provided interesting results. VICTORIA trial has provided evidence prompting interest in vericiguat. In the upcoming months, the results of other important trials are anticipated, particularly the GALACTIC trial with omecamtiv (DOI: 10.1056/NEJMoa2025797, not indexed in PubMed until now). All of these large trials are blinded and placebo controlled.

Medical practitioners who include patients in clinical trials have experimented with withdrawal of the drug under investigation, having no knowledge of what the patient had received, consistent with a blinded design. In some such cases, the patient's clinical status may be rapidly compromised after withdrawal, suggesting (i) that the patient had been receiving the active drug and (ii) that the drug under investigation might exert beneficial effects. However, it remains impossible to reach a firm conclusion prior to communication of the study results and the release of information regarding the drug received by the patients during the study (generally months after the results are available). Investigators typically request access to the study drug for their patients as soon as positive results are known. This is logical for many reasons. Notably, the patients have participated in a clinical trial, making a contribution to this research effort, and thus, for ethical

reasons, they should receive early benefit from the drug. Moreover, only scarce data are available regarding the impact of treatment withdrawal in this clinical setting. However, a small randomized study demonstrated that stopping drugs in patients who had recovered from dilated cardiomyopathy and HF could lead to quick post-withdrawal relapse.[5] This trial suggested that treatment should be continued indefinitely. Importantly, in the TRED study, all treatments were stopped in one arm, contrasting with the clinical research where only the drug under study is usually stopped, so that the patients remain under the full background therapy. In this context of clinical research, the treatment is stopped upon conclusion of the trial. When a process is developed to enable treatment access, it often begins several months later. Thus, patients are left without this beneficial treatment not only until the trial results are complete but also until after the guidelines are updated (often 1 or 2 years later) and after the reimbursement (months to years after the results).

At this point, we must distinguish two situations. When a drug that is already used for some indications is evaluated for other applications, the drug could be easily available (but not necessarily reimbursed in this new indication). For instance, in the COLCOT trial, colchicine was shown to reduce clinical events in patients admitted for acute coronary syndromes.[6] However, mortality was not significantly reduced (very few events). As the drug is already available and cheap, we cannot exclude that prescriptions may have been issued outside of the previously established indications. The relevant societies have not yet decided this drug's place in the guidelines. In this situation, it seems reasonable to wait for a formal decision, as the risk–benefit balance is not individually dramatically unbalanced (no demonstrated impact on mortality in contrast to well-established safety).

In contrast, in the context of trials with new drugs, protocols should be developed for provision of the drug as part of the initial study conception. Even if costly, such arrangements should be considered, including plans for the final cost of the drug when it is widely commercially available. Indeed, if such plans are not built into the study from the start, the drug may be not available at all until after completion of the process leading to the reimbursement, even in the event of a largely positive trial.

Taking together all of these considerations, we propose that the study sponsor should plan from study conception that all participating patients (regardless of whether they are in the placebo or active drug group) will have access to the drug upon trial completion—once safety is verified (which is often required during intermediate analyses from independent committees) and until the results are known. In the case of verified clinical benefits, and especially in cases with mortality reduction, the sponsor should have plans to provide the drug to participants at least until the reimbursement is obtained. In the event that reimbursement is not obtained (generally because the risk–benefit balance is not favourable or for medico-economic reasons advocated by the health authorities), the drug could be stopped under strict medical follow-up.

These propositions should raise some legal issues. Indeed, when a company provides a drug that is not approved by legislative authorities to some patients, there are regulations that this is not possible as all patients could claim the drugs. This could have huge legislative consequences. These points should be discussed by lawyers, and innovations should be proposed to address adequately these issues.

The topic discussed here with regard to HF should also be widely applicable in other medical settings. The proposed principles seem to be already been observed in some cases. However, we feel deeply that this practice should be the rule, not the exception. Nowadays, it is not conceivable to submit the results of a large trial for publication without approval from a suitable ethical committee. Similarly, the above-described principle—that is, access to the effective drug—should be considered as a requirement for clinical research and thereby a requirement for high-level publication of the results, for ethics committee approval, and for the registration of the trial in an international database.

References

1. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371**: 993–1004.
2. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; **381**: 1995–2008.
3. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-la Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; **383**: 1413–1424.
4. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CSP, Ponikowski P, Voors AA, Jia G, McNulty SE, Patel MJ, Roessig L, Koglin J, O'Connor CM. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2020; **382**: 1883–1893.
5. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, Jackson R, Rahneva T, Wage R, Smith G, Venneri L,

Tayal U, Auger D, Midwinter W, Whiffin N, Rajani R, Dungu JN, Pantazis A, Cook SA, Ware JS, Baksi AJ, Pennell DJ, Rosen SD, Cowie MR, Cleland JGF, Prasad SK. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet* 2019; **393**: 61–73.

6. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, López-Sendón J, Ostadal P, Koenig W, Angoulvant D, Grégoire JC, Lavoie MA, Dubé MP, Rhainds D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin MC, Roubille F. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019; **381**: 2497–2505.

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