RESEARCH LETTER

doi:10.1002/ejhf.3575
Online publish-ahead-of-print 21 January 2025

The DIGIT-HF trial: Key amendments of study design

DIGIT-HF is a multicentre, randomized, double-blind, placebo-controlled trial designed to investigate the effect of digitoxin versus placebo on the composite primary endpoint of time to all-cause death and hospital admission for worsening heart failure (HFH) (whichever occurs first) in patients with heart failure (HF) and reduced ejection fraction (HFrEF).[1] The DIGIT-HF trial is conducted in compliance with the German Drug Law (AMG), the German Good Clinical Practice (GCP) ordinance, ICH GCP guidelines, and other applicable ethical and regulatory requirements. The DIGIT-HF trial is registered at EudraCT (2013-005326-38).

Since recruitment of the first patient in May 2015, seven key protocol amendments have been implemented to specify and clarify its content, particularly to improve the recruitment to reach the required number of primary endpoint events (*Figure 1*; for details see online supplementary *Table S1*). Due to the lower than expected recruitment rate, a blinded sample size/trial duration re-estimation was conducted 40 months after beginning of recruitment. It was estimated that the study duration needed to be extended to observe the required number of 734 primary endpoint events. Consequently, the required number of patients was reduced from 2190 to 1653. Following successful application for continued funding, the trial conduct was extended until the end of 2024 with an increased number of recruitment sites.

The main challenge of the trial was the lower than expected recruitment, which was probably due to the initial overestimation of the number of patients to be recruited per trial site, although the observed pooled event rate for the primary endpoint was similar as assumed in the sample size calculation. Therefore, the number of trial sites was increased from initially 40 to finally 65. This included extension of the trial to motivated investigators in Austria and Serbia.[2] In addition, several competing clinical trials recruiting HFrEF populations funded by pharmaceutical companies (e.g. DAPA-HF, EMPEROR-Reduced)[3,4] started during the DIGIT-HF trial period, which probably impaired recruitment into DIGIT-HF as well.

The COVID-19 pandemic also affected recruitment because screening/baseline visits intended to be performed in presence could not be scheduled. Furthermore, trial extension to Serbia was strongly delayed by COVID-19 pandemic just after solving all regulatory issues (e.g. digitoxin is not available and approved in Serbia) mandatory for starting the trial at 10 study sites in Serbia, which significantly affected final recruitment numbers. Overall, the COVID-19 pandemic did affect the study conduct by for example, changing the in-person visits to telephone visits, which may have significantly impaired collection of events, in particular HFH events. To explore potential impact of COVID-19 on the study results, COVID-related data (e.g. respiratory infections, vaccinations) have been collected and will be analysed. Further COVID-related supplementary analyses may be conducted, for example, separately analysing the pre-COVID-19 data.

A second blind review of trial data in December 2022 revealed that the required number of 367 primary endpoint events for the pre-planned interim analysis had not been achieved. Because the probability for early trial termination due to overwhelming efficacy was very low, the initially planned interim analysis was not performed. Consequently, the full alpha of 0.05 can be used for the final analysis and 716 primary endpoint events need to be observed to demonstrate the expected hazard ratio of 0.811 with a power of 80%.

The most recent protocol amendment (Version 8.0, date 20 July 2023, in online supplementary material) re-defined the key secondary endpoints of all-cause death, HFH and (recurrent) HFH. Analysis of time to first HFH alone is not of high clinical relevance as it ignores the fatal worsening event death, which constitutes about 30% of the primary endpoint events in the current trial (based on a blind review). Furthermore, censoring patients who had not experienced HFH before death is statistically inappropriate, as this leads to informative censoring. Therefore, including death as a fatal worsening event is more meaningful from both clinical and statistical aspects. As this coincides with the primary endpoint, time to first HFH was removed from the list of key secondary endpoints. The absolute and relative frequency of the first HFH as a component of the primary endpoint will be presented. Analysis of recurrent HFH would have similar problems if death is ignored. Furthermore, including death as an additional event may better prevent a potential type I error inflation associated with the analysis of recurrent HFH alone.[5] Therefore, the composite of recurrent HFH and all-cause death instead of recurrent HFH was defined as a new key secondary endpoint.

To control the overall type I error, a hierarchical testing procedure for the primary and key secondary endpoints was pre-specified with the following testing order: (1) superiority of digitoxin versus placebo in the primary endpoint, (2) non-inferiority of digitoxin versus placebo regarding time to all-cause death, (3) superiority of digitoxin versus placebo regarding the composite of recurrent HFH and all-cause death. The testing order reflects the relative clinical relevance/importance of the endpoints and implies the clinical decision-making process. For example, all-cause mortality is the first key secondary endpoint after the primary endpoint, since the most important component of the composite endpoint should not be negatively impacted by the experimental treatment. Composite recurrent HFH endpoint is the second key secondary endpoint after all-cause mortality. As indicated in the European Medicines Agency chronic HF guideline,[6] the main challenge in the analysis and interpretation of recurrent event endpoints is the presence of terminal events (e.g. death), which limit the number of events per subject. In consequence, a lower number of events in one as compared to the other treatment group may simply be the result of an increased mortality in the former treatment group. Thus, excluding a detrimental effect on all-cause mortality in the first step is a pre-requisite for concluding a positive effect on the composite recurrent HFH endpoint. If all confirmatory null hypotheses of the main study can successfully be rejected, substudies will be assessed confirmatory in the pre-defined order.

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DIGIT-HF: summary of key protocol changes

	Initial Protocol (2014)	Final Protocol (2023)
Trial duration	Trial/funding period: 2014-2019 Recruitment: 36 months First-patient-in: 05/2015	Recruitment lower than expected Trial extension/funding until 2025 Last-patient-in: 30.09.2023 Last-patient-out: 30.09.2024
Trial sites	40 (Germany)	65 (Germany, Austria, Serbia)
Number of patients	2190	1653 (due to extension of trial duration)
Number of primary endpoint events	734	716 (due to no interim-analysis, two-sided α = 0.05 for the final analysis)
Key secondary endpoints	- All-cause mortality - Hospital admission for WHF - Recurrent hospital admission for WHF	1. All-cause mortality 2. Recurrent hospital admission for WHF and terminal event of all-cause mortality
Standard of care	BB, ACEi/AT1-RB, MRA if indicated: ivabradine, CRT, ICD	BB, ACEi/AT1-RB, MRA, ARNI, SGLT2i if indicated: ivabradine, CRT, ICD

Figure 1 Summary of key protocol changes during the DIGIT-HF trial. ACEi, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor–neprilysin inhibitor; AT_1-RB, angiotensin 1 receptor blocker; BB, beta-blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor; WHF, worsening heart failure.

Otherwise, substudies will be evaluated descriptively with a two-sided alpha of 5%.

The primary analysis will be conducted on the intention-to-treat (ITT) population including all randomized patients who took at least one dose of the study drug. Patients will be analysed as randomized regardless of their actual treatment (digitoxin or placebo). Initially, the per-protocol population was specified to all patients who achieved the target serum concentration of digitoxin (preferably 8–18 ng/ml [10.5–23.6 nmol/L]), complied with the study protocol until the end of the observational period, and remained in the treatment arm to which they were allocated by randomization. This was further refined to all patients of the ITT population that had attended visit 3 (12 months $\pm$7 days), achieved digitoxin serum concentrations of <2.5 nmol/L (if randomized to placebo) or had a digitoxin serum concentration of 5–30 nmol/L (if randomized to digitoxin), and experienced no active decision against the randomized therapy.

As various win ratio analyses have been performed in recent HF trials, we further pre-specified secondary analyses of (1) hierarchical composite of all-cause death, number of HFH, and time to first HFH, and (2) hierarchical composite of all-cause death, number of HFH, time to first HFH, change from baseline in New York Heart Association class and change from baseline in quality of life, both assessed using a win ratio method, to provide additional insights into the understanding of the treatment effect (statistical analysis plan, sections S2.4 and S10 in online supplementary material).

During the recruitment phase of DIGIT-HF, recommendations of the European Society of Cardiology for pharmacological treatment of HFrEF were extended to also include angiotensin receptor–neprilysin inhibitors and sodium–glucose cotransporter 2 inhibitors.[7,8] Because the aim of the trial was to investigate a potential benefit of digitoxin in HFrEF patients on top of standard of care based on guideline recommendations, standard of care for study participants in the trial protocol was extended by these substance classes.

The principal findings of the DIGIT-HF trial are anticipated to be made available in 2025, potentially offering important new insights into the efficacy and safety of cardiac glycosides, specifically digitoxin, in the treatment of advanced HFrEF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

Open Access funding enabled and organized by Projekt DEAL.

Funding

The DIGIT-HF study is funded by the Federal Ministry of Education and Research, Germany (BMBF: 01KG1303 and 01KG1907) the Braukmann-Wittenberg-Herzstiftung, and the German Heart Foundation.

Conflict of interest: U.B. and J.B. represent the study heads of the DIGIT-HF-study and applied for funding of DIGIT-HF described above. U.B., J.B., A.K., H.v.d.L., C.V., S.S., and M.B. are members of the DIGIT-HF trial steering committee. U.B. received travel support and honoraria for lectures/consulting from Alnylam Pharmaceutical, Amgen, AstraZeneca, Bayer Vital, Novartis, and Pfizer and institutional research support from Alnylam Pharmaceuticals, all not related to the current manuscript. D.B. was competitively selected for 'CORE100Pilot', which is an advanced clinician-scientist programme co-funded by the Else Kröner Fresenius Foundation and the Ministry for Science and Culture of the State of Lower Saxony. D.B. received honoraria for lectures/consulting from Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Edwards Lifesciences, Pfizer, all not related to the current manuscript. P.M.B reports personal fees from AstraZeneca, Ingelheim Boehringer and the German Research Foundation, all not related to the current manuscript. C.V. reports honorary for lectures or consulting from Abbott, Medtronic, BMS and Zoll. M.B. is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation; TTR 219, project number 322900939) and reports personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Edwards, Medtronic, Novartis, ReCor, Servier and Vifor during the conduct of the study. J.B. received honoraria for lectures/consulting from Novartis, Vifor, Bayer, Pfizer, Boehringer Ingelheim, AstraZeneca, Cardior, CVRx, BMS, Amgen, Corvia, Norgine, Edwards, Roche not related to this article; and research support for the department from Zoll, CVRx, Abiomed, Norgine, Roche, all not related to the current manuscript. All other authors have nothing to disclose.

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References

1. Bavendiek U, Berliner D, Davila LA, Schwab J, Maier L, Philipp SA, *et al.* Rationale and design of the DIGIT-HF trial (DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure): A randomized, double-blind, placebo-controlled study. *Eur J Heart Fail* 2019;**21**:676–684. https://doi.org/10.1002/ejhf.1452
2. van Veldhuisen DJ, Bauersachs J. Digitalis in heart failure: Declining use and ongoing outcome trials. *Eur Heart J* 2023;**44**:1976–1978. https://doi.org/10.1093/eurheartj/ehad185
3. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, *et al.*; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008. https://doi.org/10.1056/NEJMoa1911303
4. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, *et al.*; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**:1413–1424. https://doi.org/10.1056/NEJMoa2022190
5. Fritsch A, Schlömer P, Mendolia F, Mütze T, Jahn-Eimermacher A. Efficiency comparison of analysis methods for recurrent event and time-to-first event endpoints in the presence of terminal events – application to clinical trials in chronic heart failure. *Stat Biopharm Res* 2021;**15**:268–279. https://doi.org/10.1080/19466315.2021.1945488
6. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure. 20 July 2017. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-chronic-heart-failure-revision-2_en.pdf. Accessed 5 August 2024.
7. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
8. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2024;**26**:5–17. https://doi.org/10.1002/ejhf.3024

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