Digitalis in heart failure

Van Veldhuisen, Dirk J.; Bauersachs, Johann

Published in:
European Heart Journal

DOI:
10.1093/eurheartj/ehad185

Publication date:
2023

ESC European Society of Cardiology

European Heart Journal (2023) **44**, 1976–1978
https://doi.org/10.1093/eurheartj/ehad185

VIEWPOINT
Heart failure and cardiomyopathies

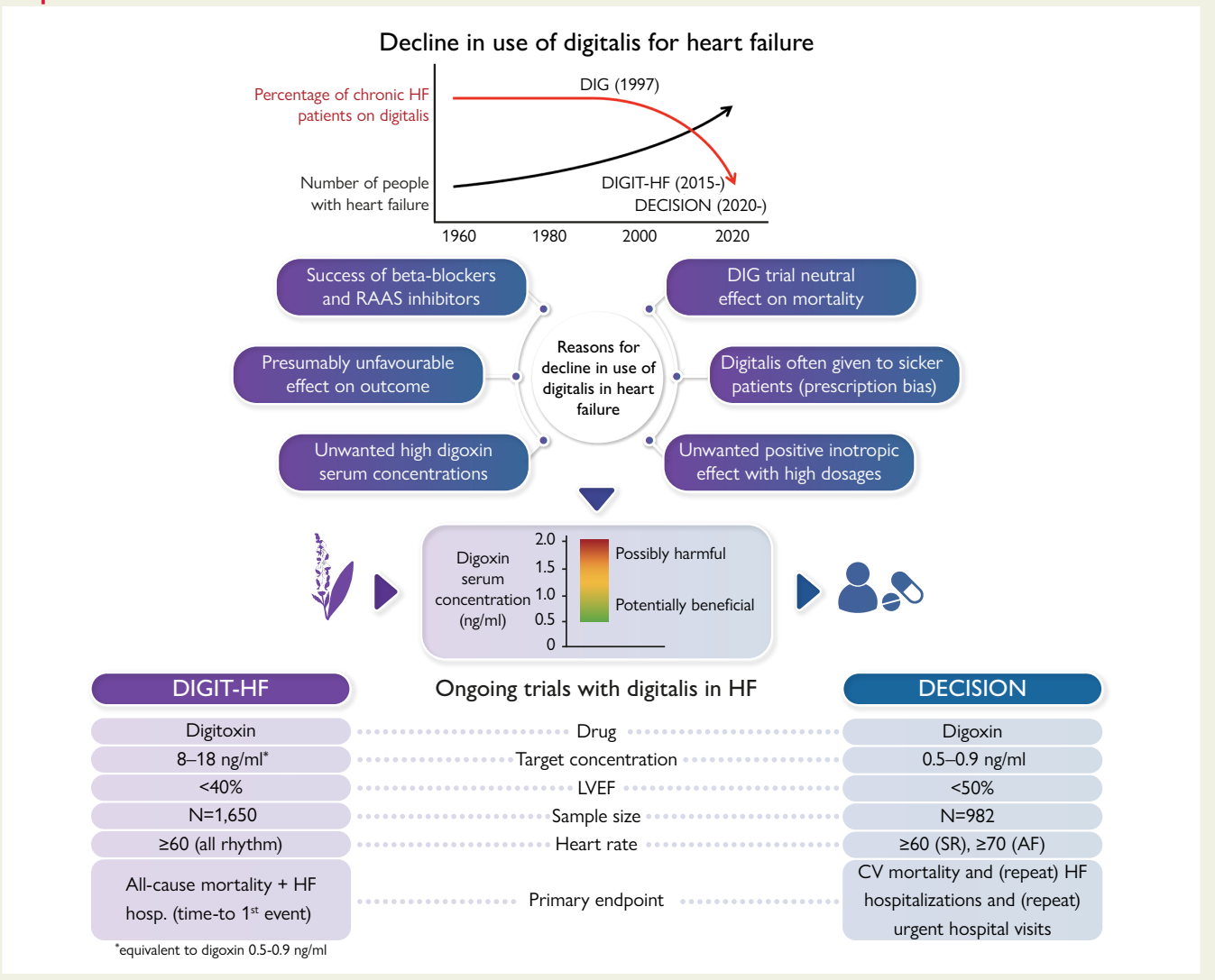
Digitalis in heart failure: declining use and ongoing outcome trials

Dirk J. van Veldhuisen [1]* and Johann Bauersachs [2]

[1]Department of Cardiology, University Medical Center Groningen, University of Groningen, PO Box 30.001, 9700RB Groningen, The Netherlands; and [2]Department of Cardiology and Angiology, Medical School Hannover, Hannover, Germany

Online publish-ahead-of-print 8 April 2023

Graphical Abstract



Reasons for the decline in use of digitalis in heart failure, importance of serum digoxin concentrations, and characteristics of two ongoing trials with digitalis in heart failure.

* Corresponding author. Tel: 31-50-3612355, Fax: 31-50-3614391, Email: d.j.van.veldhuisen@umcg.nl

Introduction

Digitalis glycosides (digoxin and digitoxin) are the oldest drugs in cardiovascular (CV) medicine and have generally been used in patients with heart failure (HF) and in those with atrial fibrillation (AF) or their combination.[1,2] Twenty-five years ago, digoxin was used by around two-thirds of patients with moderate to severe (systolic) HF, although there were large variations in its use in Europe, ranging from 85% in Germany to 40% in the United Kingdom.[3] Since then, however, the use of digoxin has markedly declined and in more recent HF trials, its use was reported to be <20%, or—most recently—not even mentioned anymore.

There are many reasons for this decline, some understandable and 'scientifically correct', but there are also many assumptions and myths which may be less rational, and may explain this decline. In the present viewpoint this will be discussed, and data will be provided of two currently ongoing prospective, placebo-controlled randomised clinical trials (RCTs) with digitalis[4,5] which will provide new contemporary data on the place of these drugs in HF.

Trials and guidelines

Only one large RCT trial has been published with digoxin in HF patients with sinus rhythm (SR) that examined outcome.[6] In this Digitalis Investigation Group (DIG) trial of 6800 patients, published in 1997, digoxin—when added to diuretics and ACE inhibitors—did not reduce all-cause mortality in mild to moderate HF, which was the primary endpoint of this trial.[6] Digoxin did, however, cause a 28% reduction of hospitalization for worsening HF ($P < 0.001$), one of the secondary endpoints. Interestingly, if the primary composite endpoint of CV death and HF hospitalization would have been used, now most commonly used in HF trials and accepted by the CV community, digoxin would have caused a statistically significant 15% reduction (hazard ratio 0.85; $P < 0.001$).[7]

Based on DIG,[6] the 2001 European Society of Cardiology (ESC) HF Guidelines recommended digoxin 'to improve the clinical status of patients with persisting HF symptoms … despite ACE inhibitor and diuretic treatment'.[8] From 2001 onwards, the place of digitalis glycosides has gradually declined and in the most recent 2021 ESC HF Guidelines, it reads that digoxin 'may be considered in patients with symptomatic HF (and SR) with reduced ejection fraction EF (HFrEF)' despite optimal medical treatment (recommendation level IIb-B).[9] In HF patients with AF, the effects of digoxin on outcome have never been investigated in a prospective, placebo-controlled RCT, although they were compared to those of bisoprolol on quality of life in a recent RCT.[10] This study, the RAte control Therapy Evaluation in permanent Atrial Fibrillation (RATE-AF) trial, included 160 patients of 60 years or older. Its primary endpoint was quality of life after 6 months, and there was no difference between groups, and reduction in heart rate was similar. However, at 12 months, many secondary endpoints were different and favoured low-dose digoxin (e.g. natriuretic peptides, symptoms, and adverse effects), and low-dose digoxin may therefore be considered as an alternative for beta-blockers in such patients.[10]

Interestingly, in the 2001 ESC HF Guidelines, cardiac glycosides were indicated for all HF patients,[8] but in 2021,[9] they received a class IIb recommendation for patients with sinus rhythm, because background medication at the time of DIG (only ACE inhibitors and diuretics) was considered limited in 2021. For HF patients with AF,[9] the recommendation was IIa, which was also due to the results of RATE-AF.[10]

Reasons for the declining role of digoxin in heart failure

In the past, digitalis was primarily seen as a (positive) inotropic drug, caused by inhibition of Na/K ATPase (or sodium pump). At that time positive inotropism was considered a favourable effect in HF because it was assumed to be needed to improve the pumping performance of the failing heart. In addition, digoxin had a negative chronotropic effect (on the atrio-ventricular node) which was also attractive in HF with AF. Because of these assumed favourable effects of positive inotropism, digoxin was often given in the maximally tolerated dose, and in 2001 it was written that the 'usual dose of oral digoxin is 0.25–0.375 mg daily'.[8] Later, however, it became clear from the DIG trial, but also from several other studies, that higher levels of digoxin (>1.2 ng/mL) were associated with an adverse outcome in HF, and that lower doses had a favourable effect.[11] Indeed, with lower doses, digoxin is a neurohormonal antagonist and improves plasma neurohormones, heart rate variability, and baroreceptor function (for review: see Van Veldhuisen et al.[12]). In the past 20–25 years, neurohormonal antagonists, such as beta-blockers and drugs that specifically block the renin-angiotensin system, were found to improve outcome.[9] All this evidence together made it increasingly clear that the place of positive inotropic drugs in HF would be small, if any.

In addition to the fact that in the past digoxin was primarily assumed to be a positive inotropic drug, which was increasingly unwanted in most patients with (mild to moderate, chronic) HF, several other factors played a role in its decline. Many post-hoc analyses suggested an unfavourable effect on outcome, but initially, most of these studies were not corrected for baseline differences, and digoxin was often given to the sickest patients, i.e. a 'prescription bias'[2] which was also shown in the DIG trial itself.[13] Later, several studies adjusted for baseline differences, but such studies cannot replace a well-designed RCT.[2] Further, digoxin is cheap, and was not promoted by the pharma industry after DIG (in contrast to other drugs). Lastly, beta-blockers were found to have benefits in HF in several outcome RCTs at the time,[9] and their results 'eclipsed' the findings of the DIG trial.[7]

Recent developments

In recent years, interest in digitalis has again increased, and it has been suggested that the CV community may have dismissed it too readily, and that its potential role should be reappraised. Also, because of its very low cost, digoxin is most probably cost-effective in HF. In addition, the recent RATE-AF study in patients with AF and symptoms of HF compared the effects of low-dose digoxin (mean 0.161 mg/day) vs. bisoprolol (mean dose 3.2 mg/day) with interesting findings, as discussed above.[10] Although these potential favourable effects should be considered exploratory, it is remarkable that there was no requirement for pacemaker therapy and no increases in pauses on low-dose digoxin, supporting the concept that low-dose digoxin may be (at least) as effective and possibly safer than higher doses.[14]

In addition to this RATE-AF study, there are currently two ongoing outcome RCTs in patients with HF, and both are using low-dose digitalis glycosides.[7,8] In addition, and in contrast to the DIG trial,[9] not only HF patients with sinus rhythm but also those in AF are investigated (see *Graphical Abstract*). The first is the DIGIT-HF trial (DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure) which is enrolling patients in Germany, Austria, and Serbia. In this study, the target serum concentration of digitoxin is 8–18 ng/mL, and in

humans, these concentrations are equivalent to digoxin concentrations of 0.5–0.9 ng/mL.[4] Digitoxin has similar pharmacodynamic effects as digoxin, but the pharmacokinetic profile is different, with a longer half-life.[4,15] Digitoxin is cleared by the liver when renal function decreases so it does not accumulate. In contrast to digoxin, there are no adequate powered RCTs with digitoxin in patients with HF. The second study is the DECISION trial (Digoxin Evaluation in Chronic heart failure: Investigational Study in Outpatients in the Netherlands) (ClinTrials.gov NCT03783429), and the target serum concentration of digoxin in that study is 0.5–0.9 ng/mL. This study is enrolling patients in the Netherlands only.[5] In DECISION, at least one-third of the total population will be women, since an earlier (post-hoc) substudy of DIG suggested an unfavourable effect on outcome in women.[16] Serum digoxin levels will be carefully monitored in the DECISION trial, and patients with severe renal dysfunction (glomerular filtration rate ≤ 30 mL/min/1.73 m^2) are excluded. Both trials will finish enrolment in 2023. Current enrolment in DIGIT-HF is >1150 patients (of planned 1650 after extension of follow-up and recalculation of sample size), and in DECISION is >750 patients (of planned 982). Results of both trials are expected in 2025. The two RCTs have some similarities, but also important differences in drugs used, study design, population, and inclusion criteria.

In conclusion, the use of digitalis glycosides for HF (and for AF) has markedly declined in the last 20–25 years, and reasons for this are discussed here. For a long time, no large trials were performed, but two current RCTs are examining outcome, and their results will define the future place of digitalis glycosides in the treatment of HF.

Data availability

No data were generated or analysed for this manuscript.

Conflict of interest

D.J.V.V. is the principal investigator of the DECISION trial, which is supported by the Netherlands Heart Foundation; there are no other conflicts of interest. J.B. is the study chair of the DIGIT-HF trial, which is supported by the Federal Ministry of Education and Research in Germany. J.B. received honoraria for lectures/consulting from Novartis, Vifor, Bayer, Pfizer, Boehringer Ingelheim, AstraZeneca, Cardior, CVRx, BMS, Amgen, Corvia, Norgine, and Roche not related to this article, and research support for the department from Zoll, CVRx, Abiomed, Norgine, and Roche, not related to this article.

References

1. Gheorghiade M, Van Veldhuisen DJ, Colucci WS. Contemporary use of digoxin in the management of cardiovascular disorders. *Circulation* 2006;**113**:2556–2564. https://doi.org/10.1161/CIRCULATIONAHA.105.560110
2. Bavendiek U, Davilla LA, Koch A, Bauersachs J. Assumption versus evidence: the case of digoxin in atrial fibrillation and heart failure. *Eur Heart J* 2017;**38**:2095–2099.
3. Van Veldhuisen DJ, Charlesworth A, Crijns HJGM, Lie KI, Hampton JR. Differences in drug treatment of chronic heart failure between European countries. *Eur Heart J* 1999;**20**:666–672. https://doi.org/10.1053/euhj.1998.1343
4. Bavendiek U, Berliner D, Aguirre Davila L, 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
5. Van der Meer P, Rienstra M, Van Veldhuisen DJ. A deleterious interaction between omecamtiv mecarbil and atrial fibrillation in patients with heart failure: an influence of digoxin? *Eur Heart J* 2022;**43**:2221–2223. https://doi.org/10.1093/eurheartj/ehac197
6. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;**336**:525–533. https://doi.org/10.1056/NEJM199702203360801
7. Castagno D, Petrie MC, Claggett B, McMurray J. Should we SHIFT our thinking about digoxin? Observations on ivabradine and heart rate reduction in heart failure. *Eur Heart J* 2012;**33**:1137–1141. https://doi.org/10.1093/eurheartj/ehs004
8. Remme WJ, Swedberg K. On behalf of the task force for the diagnosis and treatment of chronic heart failure, European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;**22**:1527–1560. https://doi.org/10.1053/euhj.2001.2783
9. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2121 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–3726. https://doi.org/10.1093/eurheartj/ehab368
10. Kotecha D, Bunting K, Gill SK, Mehta S, Stanbury M, Jones JC, *et al.* For the RATE-HF team. Effect of digoxin vs. bisoprolol for heart rate control in atrial fibrillation on patient-reported quality of life. The RATE-HF randomized clinical trial. *JAMA* 2020;**324**:2497–2508. https://doi.org/10.1001/jama.2020.23138
11. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcome in patients with heart failure. *JAMA* 2003;**289**:871–878. https://doi.org/10.1001/jama.289.7.871
12. Van Veldhuisen DJ, De Graeff PA, Remme WJ, Lie KI. Value of digoxin in heart failure and sinus rhythm: new features of an old drug? *J Am Coll Cardiol* 1996;**28**:813–819. https://doi.org/10.1016/S0735-1097(96)00247-1
13. Aguirre Davila L, Weber K, Bavendiek U, Bauersachs J, Wittes J, Yusuf S, *et al.* Digoxin-mortality: randomized vs. observational comparison in the DIG trial. *Eur Heart J* 2019;**40**:3336–3341. https://doi.org/10.1093/eurheartj/ehz395
14. Van Veldhuisen DJ. Low-dose digoxin in patients with heart failure: less toxic and at least as effective? *J Am Coll Cardiol* 2002;**39**:954–956. https://doi.org/10.1016/S0735-1097(02)01710-2
15. Bavendiek U, Bauersachs J. Digitalis glycosides. In: Seferović PM, Coats AJS, Filippatos G, Anker SD, Bauersachs J, Rosano G (eds.), *ESC Textbook on Heart Failure*. Oxford University Press, 2023.
16. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med* 2002;**347**:1403–1411. https://doi.org/10.1056/NEJMoa021266