ESC European Society of Cardiology

European Heart Journal (2019) **40**, 3605–3612
doi:10.1093/eurheartj/ehz554

FASTTRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

Short-term diuretic withdrawal in stable outpatients with mild heart failure and no fluid retention receiving optimal therapy: a double-blind, multicentre, randomized trial

Luis E. Rohde [1,2]*, Marciane M. Rover [3], Jose A. Figueiredo Neto[4], Luiz C. Danzmann[5,6], Eduardo G. Bertoldi [7], Marcus V. Simões[8], Odilson M. Silvestre [9], Antonio L. P. Ribeiro[10], Lidia Zytynski Moura[11], Luis Beck-da-Silva [1,2], Debora Prado [10], Roberto T. Sant'Anna[3], Leonardo H. Bridi[3], André Zimerman[1], Priscila Raupp da Rosa[6], and Andréia Biolo[1]

[1]Hospital de Clínicas de Porto Alegre and Faculdade de Medicina da Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos 2350, CEP 90035-903, Porto Alegre, RS, Brazil; [2]Hospital Moinhos de Vento, Rua Ramiro Barcelos 910, CEP 90035-004, Porto Alegre, RS, Brazil; [3]Instituto de Cardiologia, Fundação Universitária de Cardiologia, Porto Alegre, RS, Brazil; [4]Hospital Universitário da Universidade Federal do Maranhão, São Luis, MA, Brazil; [5]Hospital Universitário da Universidade Luterana do Brasil, Canoas, RS, Brazil; [6]Hospital São Lucas da Pontifícia Universidade Católica, Porto Alegre, RS, Brazil; [7]Hospital Escola da Universidade Federal de Pelotas, Pelotas, RS, Brazil; [8]Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Ribeirão Preto, SP, Brazil; [9]Universidade Federal do Acre, Rio Branco, AC, Brazil; [10]Hospital da Clinicas e Faculdade de Medicina da Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil; and [11]Hospital Universitário Cajuru da Pontifícia Universidade Católica, Curitiba, PR, Brazil;

Received 30 April 2019; revised 13 May 2019; editorial decision 15 July 2019; accepted 20 July 2019; online publish-ahead-of-print 19 August 2019

See page 3613 for the editorial comment on this article (doi: 10.1093/eurheartj/ehz679)

Aims Although loop diuretics are widely used to treat heart failure (HF), there is scarce contemporary data to guide diuretic adjustments in the outpatient setting.

Methods and results In a prospective, randomized and double-blind protocol, we tested the safety and tolerability of withdrawing low-dose furosemide in stable HF outpatients at 11 HF clinics in Brazil. The trial had two blindly adjudicated co-primary outcomes: (i) symptoms assessment quantified as the area under the curve (AUC) of a dyspnoea score on a visual-analogue scale evaluated at 4 time-points (baseline, Day 15, Day 45, and Day 90) and (ii) the proportion of patients maintained without diuretic reuse during follow-up. We enrolled 188 patients (25% females; 59 ± 13 years old; left ventricular ejection fraction = 32 ± 8%) that were randomized to furosemide withdrawal ($n = 95$) or maintenance ($n = 93$). For the first co-primary endpoint, no significant difference in patients' assessment of dyspnoea was observed in the comparison of furosemide withdrawal with continuous administration [median AUC 1875 (interquartile range, IQR 383–3360) and 1541 (IQR 474–3124), respectively; $P = 0.94$]. For the second co-primary endpoint, 70 patients (75.3%) in the withdrawal group and 77 patients (83.7%) in the maintenance group were free of furosemide reuse during follow-up (odds ratio for additional furosemide use with withdrawal 1.69, 95% confidence interval 0.82–3.49; $P = 0.16$). Heart failure-related events (hospitalizations, emergency room visits, and deaths) were infrequent and similar between groups ($P = 1.0$).

Conclusions Diuretic withdrawal did not result in neither increased self-perception of dyspnoea nor increased need of furosemide reuse. Diuretic discontinuation may deserve consideration in stable outpatients with no signs of fluid retention receiving optimal medical therapy.

* Corresponding author. Tel: + 55 51 33598342, Email: rohde.le@gmail.com

ClinicalTrials.gov Identifier NCT02689180.

Keywords Heart failure • Furosemide • Dyspnoea

Introduction

Drug therapy for heart failure (HF) has greatly improved in the last 4 decades and includes medications that potentially improve prognosis and drugs that predominantly relieve symptoms.[1] Although diuretics frequently play a central role in HF treatment, particularly in periods of clinical instability, their impact on HF-related morbidity and mortality is controversial. According to international registries,[2–4] most patients receive a loop diuretic during an episode of acute decompensation and the majority is discharged home taking a 'maintenance dose' of furosemide, the prototype of loop diuretics.

For most patients, diuretics lead to immediate and remarkable improvement of body congestion, but their net clinical effect on HF prognosis in the outpatient setting is uncertain. Observational studies suggest that use of high doses of diuretics might be related to unfavourable clinical consequences, with a dose dependent association with impaired survival.[5,6] However, few prospective studies were specifically designed to evaluate the clinical risks and benefits associated with chronic diuretic administration.[7,8] Current guidelines reinforce the lack of solid scientific evidence for its use, and the potential risks that might be involved.[1,9,10] In routine clinical practice, concerns about worsening of symptoms in HF patients limit furosemide withdrawing as an established recommendation.

Based on these uncertainties about diuretic use in chronic stable HF, the ReBIC-1 trial was designed to evaluate the safety and tolerability of withdrawing furosemide use in HF outpatients in a multicentre double-blind randomized clinical trial.

Methods

Trial design and enrolment criteria

ReBIC (*Rede Brasileira de Estudos em Insuficiência Cardíaca*) is a Brazilian research network created to develop clinical studies in HF and composed predominantly by tertiary care university hospitals. The ReBIC-1 trial is a randomized, double-blind, placebo-controlled trial that assessed the short-term safety and tolerability of discontinuation of furosemide in apparently euvolaemic (without evidence of clinical congestion) outpatients with chronic stable HF. The detailed protocol has been previously published.[11] In brief, ReBIC-1 enrolled HF outpatients with the following inclusion criteria: (i) age ≥ 18 years old; (ii) New York Heart Association (NYHA) functional Class I or II; (iii) left ventricular ejection fraction (LVEF) ≤ 45% assessed by transthoracic two-dimensional echocardiography performed within 12 months before the screening visit; (iv) no HF-related hospitalization or visit to the emergency room within 6 months before the screening visit; (v) treatment with a stable dose of furosemide (40 up to 80 mg/day) for at least 6 months before the screening visit; (vi) serum potassium < 5 mmol/L; and (vii) optimized HF treatment with an angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blockers (ARB) or angiotensin receptor neprilysin inhibitor, and beta-blockers, unless contraindicated or not tolerated. Patients with a clinical congestion score (CCS) > 5 points[12,13] were excluded. For other exclusion criteria, see Supplementary material online, *File (Protocol)*. The study was approved by the institutional review board at each site, and all patients provided written informed consent before enrolment and randomization. The study was registered at ClinicalTrials.gov (NCT02689180).

Funding and manuscript handling

ReBIC was sponsored by the Brazilian National Council for Scientific and Technological Development (CNPq, Brazil), a public governmental agency. Data management and analysis were performed at the network's coordinating centre at IATS (*Instituto de Avaliação de Tecnologias em Saúde*) and at *Hospital de Clínicas de Porto Alegre*. The authors are solely responsible for the design and conduct of this study, all study analyses, drafting and editing of the manuscript, and decision to submit the paper for publication.

Study logistics and randomization

Participants were randomly allocated in a 1:1 ratio to an intervention arm (withdrawal of furosemide) or a control arm (maintenance of furosemide at the same previous dosing). Randomization was stratified by centre and diuretic dose (40 mg/day and 80 mg/day) to allow balance between the two treatment arms. Randomization numbers were computer generated by the coordinator centre, independently for each centre and each furosemide dose in blocks of 6–8. After the initial assessment, eligibility confirmation and randomization, patients received two identical bottles of research pills at each visit: a bottle of morning pills to be ingested at 8:00 AM and a bottle of afternoon pills to be ingested at 2:00 PM.

During follow-up (90 days), researchers were oriented to maintain HF therapy unchanged, if possible. Up-titration of existing HF therapy was discouraged by the study protocol, considering that the follow-up period was relatively short. Both patients and researchers were blinded to group allocation.

Baseline and follow-up visits

Follow-up visits were at 15, 45, and 90 days after the randomization visit. At baseline and at the final visit all patients underwent (i) assessment of the CCS; (ii) routine laboratory evaluation; (iii) a standard 6-min walk test; (iv) self-assessment of dyspnoea using a visual analogue scale (VAS) method; and (v) measurement of NT-proBNP levels using total heparinized venous blood and a point-of-care equipment (*COBAS* h 232, measuring range 60–9000 pg/mL; F. Hoffmann-La Roche Ltd, Basel, Swiss).

Primary and secondary endpoints

The trial had two co-primary endpoints to evaluate the feasibility of furosemide withdrawal. First, dyspnoea was assessed using a VAS. Patients were asked to mark their level of dyspnoea on a horizontal line based on their sensation of shortness of breath during the last week. The VAS was scored from 0 to 100, and applied at baseline, Day 15, Day 45, and Day 90 after randomization. The VAS was independently and blindly re-

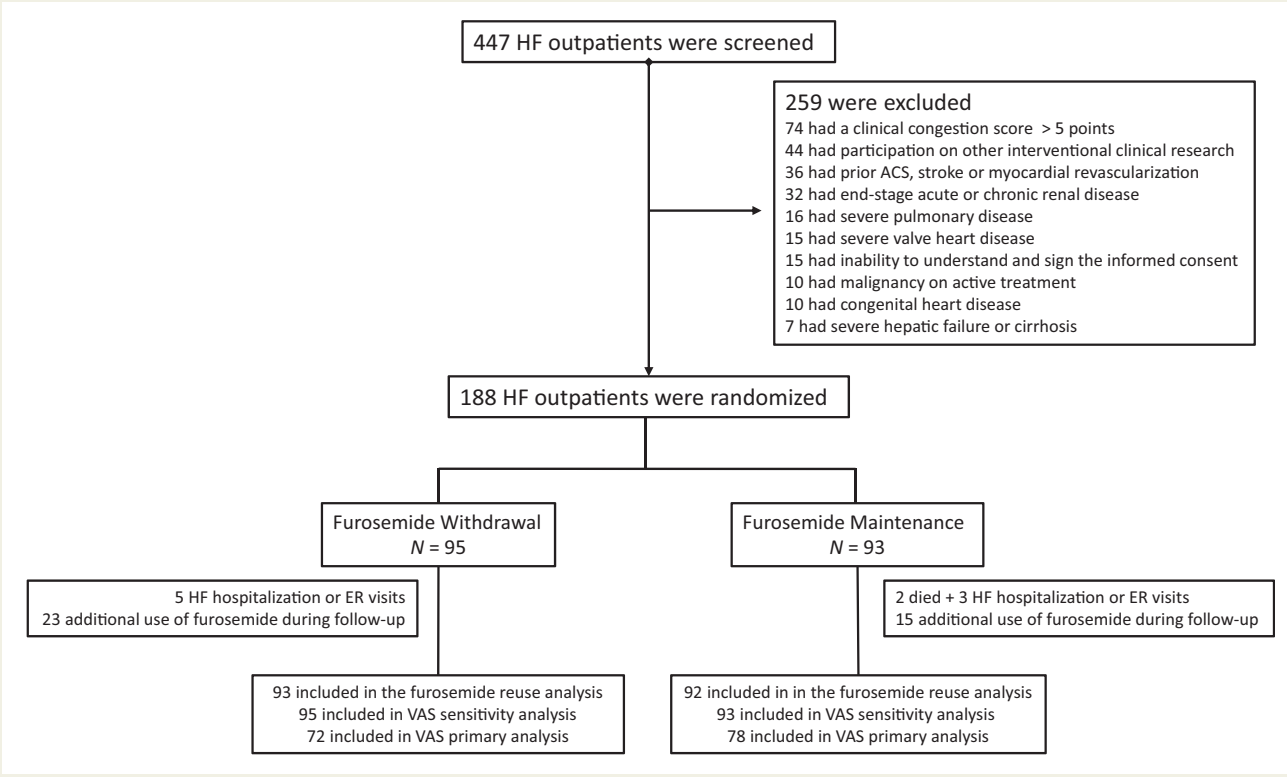


Figure 1 Consort diagram (screening, exclusions, randomization and analysis). ACS, acute coronary syndrome; ER, emergency room; HF, heart failure; VAS, visual-analogue scale.

assessed by the coordination centre for all enrolled patients. The area under the curve (AUC) of serial assessments of the dyspnoea VAS from baseline to the end of follow-up was the first co-primary efficacy endpoint.[14] The second co-primary endpoint was the proportion of patients maintained without loop diuretics during the follow-up period (90 days).

Criteria for initiation of loop diuretic during follow-up

Use of loop diuretics during study visits was decided by a physician blinded to group allocation, according to pre-defined clinical criteria. It was recommended the reuse of loop diuretics only if a patient has a clear clinical evidence of worsening of congestion (increases in the CCS > 5 points and increases in weight >2 kg along with new symptoms or increase in NYHA functional class). The endpoint adjudication committee was oriented to consider the temporary initiation of loop diuretic during follow-up as a primary event when (i) any temporary intravenous (IV) loop diuretic and (ii) any temporary oral (PO) loop diuretic greater than 4 days was used during the protocol. Unintended or accidental use of loop diuretic equal or less than 4 days was not considered an endpoint.

For the current analysis, we also evaluated the composite clinical endpoint of HR-related death, hospitalization, or emergency room visit during follow-up (secondary endpoint). Isolated variations in NT-proBNP levels were not used as an index of clinical congestion or to decide reuse of diuretics.

Statistical analysis and sample size

All analyses were performed according to the intention-to-treat principle. A *P*-value of less than 0.05 was considered statistically significant. Treatment groups were compared using a linear model for continuous variables, and by logistic regression for binary endpoints. Difference between the two treatment groups in the primary endpoint of patient-reported assessment of dyspnoea based on a VAS was assessed by the Wilcoxon rank sum test with continuity correction. Baseline NT-proBNP levels were dichotomized using the median values for subgroup analysis, as previously planned.[11] Heterogeneity was assessed using multiplicative interaction terms.

As previously reported by the DOSE trial,[14] we estimated the minimum clinically important change to be 600 points for the AUC of the dyspnoea VAS. The maximum possible score on the VAS AUC was 9000 points (100 points × 90 days). Initially, we used the same assumptions of the DOSE trial for the expected standard deviation in the dyspnoea VAS AUC (~1500 points). In addition, we performed a preliminary analysis of the first 20 randomized patients, to ensure that these pre-defined assumptions were not misleading.[11] Based on these findings, considering a difference of 600 units in the AUC, a statistical power of 80%, and 5% significance level, the required sample would be 110 in each group. Eventual missing data ($n = 6$) on the dyspnoea VAS (one out of four assessments) were interpolated using the mean of the available individual values to allow building of the curves. We also performed a sensitivity analysis of the dyspnoea VAS score ('worst-case scenario') imputing a score of 100 in the VAS for all patients with events or reuse of furosemide. For the co-primary endpoint (percentage of patients maintained without loop diuretics during the follow-up period) and based on previous studies on the use and withdrawal of HF drugs,[15,16] we estimated an absolute difference in additional furosemide use of 20% by the end of the protocol (25% in the withdrawal group ad 5% in the maintenance group). Based on these estimates, considering a statistical power of 80%, and 5%

Table 1 Clinical characteristics of the population

Clinical characteristics[a]	Furosemide withdrawal (*N* = 95)	Furosemide maintenance (*N* = 93)
Age (years)	60.8 (52.4–66.5)	61.1 (53.7–67.6)
Male sex, *n* (%)	70 (74)	70 (75)
NYHA Class I, *n* (%)	62 (65)	59 (63)
Cause of heart failure:		
Ischaemic heart disease, *n* (%)	34 (36)	29 (31)
Hypertensive heart disease, *n* (%)	18 (19)	20 (21)
Idiopathic cardiomyopathy, *n* (%)	28 (29)	22 (24)
Chagas disease, *n* (%)	2 (2)	4 (4)
History of atrial fibrillation, *n* (%)	15 (16)	9 (10)
Diabetes mellitus, *n* (%)	29 (30)	23 (25)
Clinical congestion score, points	2 (2–3)	2 (2–3)
Systolic blood pressure (mmHg)	120 (110–140)	120 (110–135)
Left ventricular ejection fraction, *n* (%)	32 (26–39.5)	32 (25–38)
Baseline therapy		
ACE inhibitor or ARB, *n* (%)	85 (89)	86 (92)
Beta-blocker, *n* (%)	95 (100)	93 (100)
Mineralocorticoid antagonist, *n* (%)	69 (73)	65 (70)
Thiazide diuretic, *n* (%)	7 (7)	6 (6)
ICD and/or CRT, *n* (%)	17 (18)	8 (9)
Creatinine (mg/dL)	1.1 (0.9–1.3)	1.1 (0.9–1.2)
Sodium (mg/dL)	140 (138–142)	140 (138–142)
Dyspnoea VAS score (mm)	20.5 (5–39)	20 (4.9–35)
NT-proBNP (pg/mL)	644 (287–1527)	696 (282–1776)
6-minutes' walk test (m)	378 (292–450)	384 (315–462)

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; NT-proBNP, N-terminal pro-brain natriuretic peptide; VAS, visual analogue scale.
[a]Continuous data are displayed as median (IQR). All *P*-values are greater than 0.05 for the comparisons of baseline characteristics across groups.

significance level, the required sample would be 59 in each group.[11] We achieved 82% and >100% of the planned sample size for the two co-primary endpoints, respectively. In September 2018, the coordinating committee decided to finalize the enrolment of patients, since inclusion rates in most centres decreased substantially overtime.

Results

Clinical characteristics of patient population

A total of 417 patients were screened and 188 patients were enrolled between October 2015 and August 2018 at 11 clinical sites in Brazil (*Figure 1*—Consort Diagram). Enrolment rates are described in the Supplementary material online, *Table S1* and *Figure S1*. The mean age of the patients was 59(±13) years; 25.5% were women, and 34% were black, and 65% were in NYHA functional Class I (*Table 1*).The predominant HF aetiologies were ischaemic heart disease and idiopathic cardiomyopathy, and the mean LVEF was 32(±8)%, ranging from 18% to 45%. Baseline drug therapy was stable and optimized: 100% of the studied patients were using a beta-blocker, 91% were using either an ACE inhibitor or an ARB, and 71.8% were using an aldosterone antagonist.

Primary outcomes

No significant difference between the two treatment groups was observed for the primary endpoint of patient-reported assessment of dyspnoea based on a VAS [median AUC 1875 (interquartile range, IQR 383–3360) in the withdrawal group and 1541 (IQR 474–3124) in the furosemide maintenance group; Wilcoxon rank sum test $P = 0.94$] (*Table 2* and *Figure 2*). Sensitivity analysis imputing a VAS score of 100 for missing values depicted similar results [median AUC 2258 (IQR 698–3975) in the withdrawal group and 2018 (IQR 570–3600) in the furosemide maintenance group; Wilcoxon rank sum test $P = 0.50$]. Supplementary material online, *Table S2* describes VAS analysis stratified by baseline NT-proBNP levels.

For the second co-primary endpoint, 70 patients (75.3%) in the withdrawal group and 77 patients (83.7%) in the maintenance group were free of furosemide reuse during follow-up. Withdrawing furosemide resulted in an odds ratio (OR) for additional furosemide use of 1.69; 95% confidence interval (CI) 0.82–3.49; $P = 0.16$. In subgroup analysis based on the median levels of baseline NT-proBNP (≤ or > 652 pg/mL), we also did not observe significant differences between groups (*P*-value for interaction = 0.53) (*Figure 3*). Regarding baseline dose of furosemide, only 34 (18% of the study sample) patients were using 80 mg/day. In subgroup analysis, we observed a trend to higher additional furosemide use with withdrawal only in patients using 80 mg/day (OR 4.73, 95% CI 0.82–27.1; $P = 0.07$); but not in patient using 40 mg/day (OR 1.25, 95% CI 0.55–2.85; $P = 0.59$; *P*-value for interaction = 0.17).

Secondary outcomes

Table 2 describes the secondary outcomes according to group allocation. Heart failure-related events (hospitalizations, emergency room visits, and deaths) were infrequent during follow-up and similar between patients that maintained or discontinued furosemide. Only two deaths (sudden cardiac deaths) were observed during the trial, both in the furosemide group. Median change in levels of NT-proBNP, creatinine and BUN, and changes in functional capacity assessed by the 6-minutes' walk test were not significantly different between groups and minor in magnitude. In addition, baseline and final NT-proBNP levels were significantly and similarly correlated in both groups (*Figure 4*). Supplementary material online, *Figures S2 and S3* depict individual values of NT-proBNP levels and weight at baseline and after 90 days of follow-up in both groups.

Adverse events

Adverse events were clinically minor in both groups, but numerically more frequent in the furosemide withdrawal group than in the furosemide maintenance group (45 vs. 37 events, respectively) (see Supplementary material online, *Table S3* for complete description of

Table 2 Primary and secondary outcomes

Endpoint	Furosemide withdrawal (*N* = 95)[a]	Furosemide maintenance (*N* = 93)[a]	Odds ratio (95% confidence interval)	*P*-value
Primary outcomes				
Additional use of furosemide, *n* (%)	23 (24.7)	15 (16.3)	1.69 (0.82 to 3.49)	0.16
AUC for VAS of dyspnoea	1875 (383–3360)	1541 (474–3124)	—	0.94
Secondary outcomes				
HF-related combined outcomes, *n* (%)	5 (5.4)	5 (5.4)	1.0 (0.30 to 3.3)	1.0
HF hospitalization/emergency room visit, *n* (%)	5 (5.4)	3 (3.2)	1.67 (0.41 to 6.8)	0.47
HF-related death, *n* (%)	0 (0)	2 (2)	—	—
Change in NT-proBNP at 90 days (pg/mL)	15 (-80 to 308)	42.5 (-177 to 210)	—	0.78
Change in 6-minutes' walk test at 90 days (m)	19.3 (-21.5 to 55.2)	4 (-28.7 to 56.8)	—	0.79
Change in weight at 90 days (kg)	0.4 (-1.2 to 2.0)	0.2 (-1.0 to 1.5)	—	0.96
Change in creatinine at 90 days (mg/dL)	-0.02 (-0.1 to 0.1)	0.03 (-0.1 to 0.1)	—	0.33
Change in BUN at 90 days (mg/dL)	-0.4 (-3.3 to 3.5)	-0.2 (-2.8 to 3.3)	—	0.52

AUC, area under the curve, HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; VAS, visual analogue scale.
[a]Continuous data are displayed as median (IQR). Two and one patient lost to follow-up for the assessment of clinical outcomes, respectively.

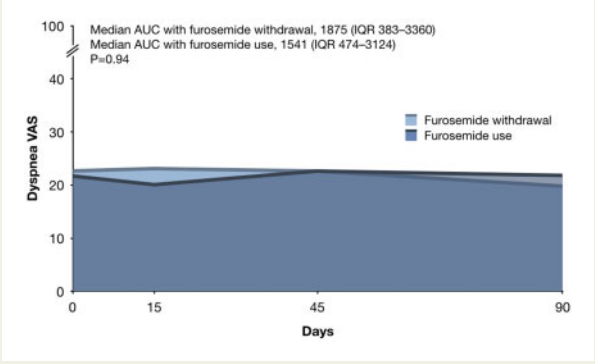


Figure 2 Patients' assessment of dyspnoea during the 90-days study period. Areas under the curves (AUC) of the median visual-analogue scale scores at each time point are shown for the group that withdrew furosemide as compared with the group that maintained furosemide use. IQR, interquartile range.

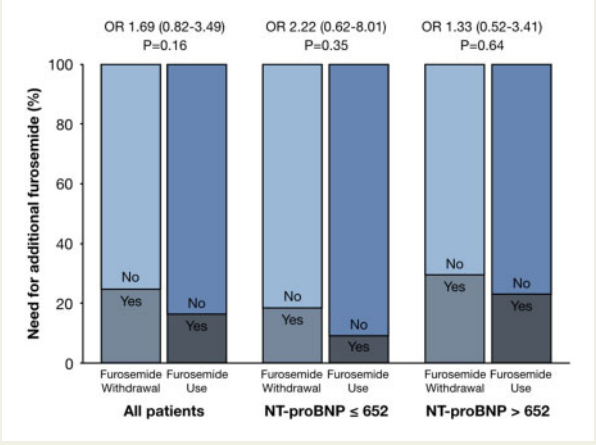


Figure 3 Proportion of patients free from (No) and in need of (Yes) additional furosemide use during the 90-days study period. 95% confidence intervals are described in parenthesis. NT-proBNP, N-terminal pro-brain natriuretic peptide levels and is expressed in pg/mL; OR, odds ratio for additional furosemide use in the withdrawal group.

adverse events). The most common reported complaints were dyspnoea/tiredness (10 vs. 6 events, respectively), and dizziness or symptoms related to hypotension (7 vs. 6 events, respectively), but these events were well balanced between groups. Facial and limb oedema were also reported by patients during the trial predominantly in those randomized to withdraw furosemide (7 vs. 0 events, respectively). Most of these patients [6 (86%)] had addition use of furosemide during the follow-up, but were self-limited and did not result in emergency room visits or hospital admissions. Interestingly, only two patients (1% of the study sample) spontaneously reported reduction in diuresis, both in the furosemide withdrawal group.

Discussion

The REBIC-1 trial evaluated whether diuretic withdrawal is a safe clinical strategy in stable outpatients with HF. Our main findings were that (i) the self-reported perception of dyspnoea was not changed in patients who stopped using furosemide and (ii) most study subjects tolerated diuretic withdrawal without the need of additional use of furosemide up to 90 days after randomization. Overall, both groups had an excellent short-term prognosis, with no clinically relevant increments in NT-proBNP levels and an event-free survival rate of HF-related hospitalizations or deaths close to 95%.

So far, data have been conflicting and methodologically flawed to support the clinical decision to maintain or withdraw furosemide in the outpatient setting. Several previous reports have suggested that chronic use of diuretics might be indeed deleterious, but they were intrinsically limited by the observational nature of most studies.

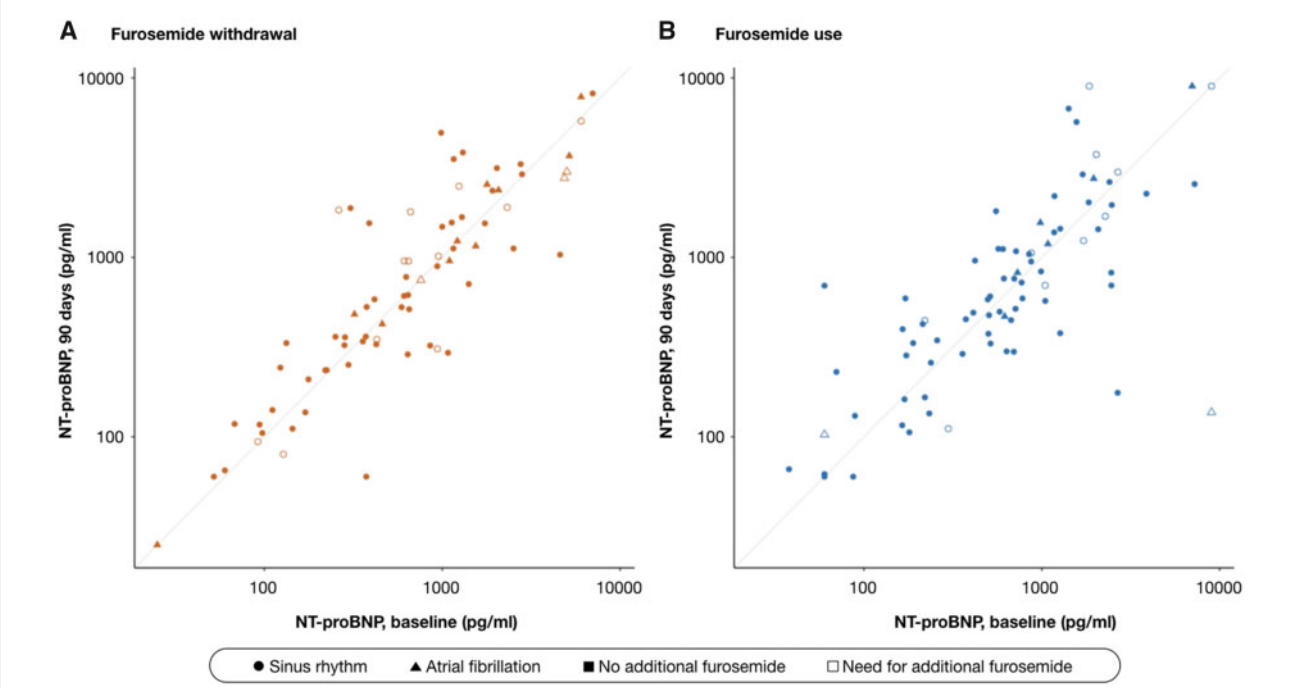
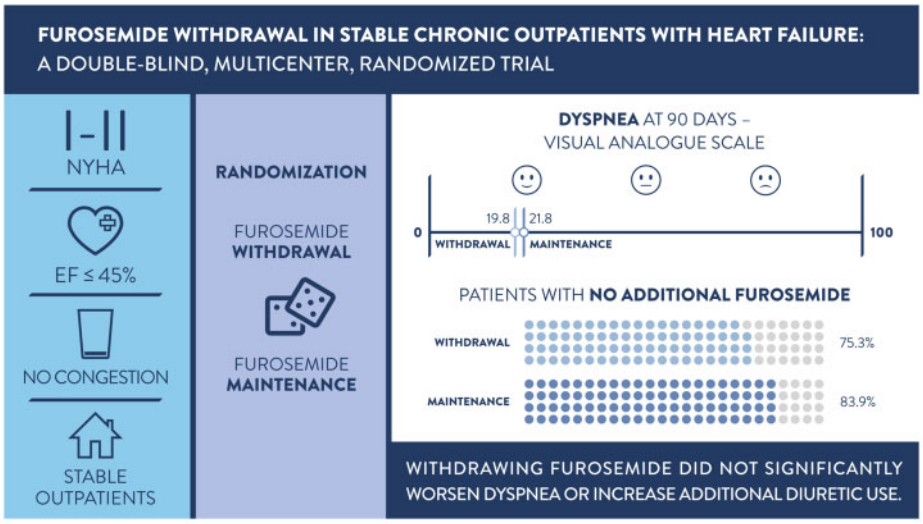


Figure 4 Correlation between baseline and final NT-proBNP levels. Furosemide withdrawal (*A*) or maintenance (*B*) had little impact on variation of NT-proBNP levels (Spearman's rank correlation coefficients = 0.86 and 0.75, respectively). NT-proBNP, N-terminal pro-brain natriuretic peptide levels and is expressed in pg/mL.

A sub-analysis of the SOLVD trial published in 2003 demonstrated an increase of 31% in the risk of HF hospitalization or death among patients taking non-potassium sparing diuretics compared with those not taking any diuretics.[17] A cohort study of advanced HF patients also detected a dose-dependent association between loop diuretic use and impaired survival. Patients in the highest quartile of diuretic dosing had a four-fold increase in the risk of dying, even after extensive covariate adjustment.[5] Recently, Pellicori *et al.*[18] also found a worse prognosis among patients receiving diuretics, but multivariate analysis identified that markers of congestion were independently associated with adverse outcomes, but not the use or dose of loop diuretics. Analysis reported from a specialized outpatient HF clinic suggest that higher doses of diuretics did not impair survival, but rather indicate greater severity of the patient's condition.[19]

Although loop diuretics are widely used to treat HF, it is surprising that few prospective studies have been designed to evaluate the impact of different strategies of diuretic adjustment in HF patients. The 'Diuretic Optimization Strategies Evaluation' trial[14] was pioneer in the scenario of acute decompensated HF, demonstrating no significant differences in patients' global assessment of symptoms or in deterioration of renal function irrespective of the mode of infusion or dose of administration of the diuretic therapy. Unfortunately, there is scarce contemporary data to guide diuretic adjustments in the outpatient setting.[7,8] In an uncontrolled study, McKie *et al.*[20] evaluated the effects of furosemide reduction in 32 patients with stable symptomatic HF, suggesting that it might be safe to reduce diuretics. Recently, 40 chronic HF patients using high dose loop diuretics were randomized to either continuation or reduction of furosemide doses. In this study, only one patient had to resume the dose of diuretics because of a marked increase in congestion-related symptoms.[16] Our study represents the first multicentre double-blind randomized initiative to assess different diuretic strategies in outpatient setting. Our findings indicate that furosemide withdrawal might be safe and well tolerated in a subgroup of relatively young and stable HF outpatients, with no clinically relevant impact on the self-perception of dyspnoea or in the rate of additional use of furosemide. Although our study was underpowered for comparisons between different doses of furosemide at baseline, subgroup analysis suggests caution in diuretic withdrawal in patients using 80 mg of furosemide daily.

International guidelines do not provide straightforward recommendations on how to deal with diuretics adjustments in stable HF outpatients. The 2013 ACCF/AHA Guideline for the Management of Heart Failure states that few patients with HF will be able to maintain target weight without the use of diuretics,[10] although the basis for such statement is unclear. Our results are in agreement and provide scientific evidence for the clinical recommendation that diuretics might be discontinued in selected asymptomatic euvolaemic or hypovolaemic patients, as suggested by the ESC guidelines.[9] Such strategy simplifies HF therapy and might reduce the inconvenient adverse effects of polypharmacy. Diuretic withdrawal might facilitate optimal use of life-saving therapies and may allow physicians to uptitrate the dose of inhibitors of the renin–angiotensin system, as both classes of drugs may be associated to azotaemia. One should be caution, however, in the perception that indiscriminately withdrawing HF medications is harmless. The recent results of the TRED-HF trial[21] suggest that the sequential withdrawal of loop diuretics, ACE/ARBs, beta-



Take home figure The ReBIC-1 trial. Outpatients with stable and mild heart failure symptoms, no or minimal clinical signs of congestion, and reduced left ventricular ejection fraction were randomized to continue or withdraw furosemide use in a double-blinded randomized protocol. Diuretic withdrawal did not change the self-perception of dyspnoea and was not associated with increased reuse of additional diuretics. EF: ejection fraction; NYHA: New York Heart Association functional class.

blockers, and mineralocorticoid receptor antagonists is associated with relapse in patients deemed to have recovered from dilated cardiomyopathy. Dovancescu *et al.*[22] also demonstrated that the omission of HF drugs for only 48 h led to a significant increase in NT-proBNP levels and reduction in transthoracic bio-impedance. These findings emphasize that even acute withdrawal of drugs may be harmful for stable HF outpatients. It is relevant to point out, however, that in this protocol all HF medications were omitted simultaneously, some patients might have been using high-dose diuretics, and the study design was not blinded.

Limitations of our study must be considered. Although our study design is double-blinded, we acknowledge that some patients might have realized that their medication has been discontinued. This does not seem to be a major concern, since the unintentional (patient driven) use of additional diuretics was similar between groups (data not shown) and the self-perception of diuresis reduction was reported by few patients. We also acknowledge that our study is underpowered to address the impact of discontinuation of furosemide in hard clinical outcomes, and there is uncertainty regarding the long-term effects of such strategy. Prospective larger studies are needed to conclusively address these issues. In addition, we recognize we were unable to achieve our pre-defined sample size for the AUC of the dyspnoea VAS, limiting the statistical confidence of our findings. As such, we cannot completely rule out a type II error. It is important to point out, however, that the mean difference in the AUC for the dyspnoea VAS score observed between groups in the ReBIC-1 trial was below the minimum clinically important change in the AUC that has been previously suggested.[14] The ReBIC-1 trial enrolled a relatively younger population of HF patients and our results might not apply to the very elderly. Finally, to avoid that one co-primary Endpoint may have confounded the other co-primary endpoint, we performed a sensitivity analysis in which patients that have restarted diuretics were assigned a VAS score of 100. Even using this 'worst-case scenario', there was not a substantial difference between groups.

Conclusion

The ReBIC-1 trial demonstrated that in outpatients with stable HF furosemide withdrawal did not change the self-perception of dyspnoea and was not associated with increased reuse of additional diuretics (*Take home figure*). Therefore, furosemide discontinuation might be a safe strategy that deserves consideration for selected a subgroup of HF patients in the outpatient setting, with cautious follow-up. These results apply only to relatively young patients with mild and stable symptoms, no or minimal clinical signs of congestion, a reduced LVEF, receiving optimal medical therapy.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

The ReBIC-1 investigators thanks the statistical assistance performed by Suzi Camey, PhD at *Grupo de Pesquisa e Pós-Graduação (GPPG) - Hospital de Clínicas de Porto Alegre*, and the careful review of the dataset performed by Eduardo Grespan, Medical Student (MS-III) and Pedro Engster, Medical Student (MS-IV).

Funding

Instituto de Avaliação em Tecnologia em Saúde (IATS) (in part); and National Council for Scientific and Technological Development (CNPq, Brazil) with grants for the establishment of the Brazilian Research Network In Heart Failure (# 467110/2014-0); CNPq (research fellowship 310679/

2016-8) and FAPEMIG (PPM-00428-17) to A.L.P.R. (in part); CNPq (research fellowship 30833/2017-1 to L.E.R.), in part.

Conflict of interest: Dr Rohde reports non-financial support from Instituto de Avaliação em Tecnologia em Saúde (IATS), grants from National Council for Scientific and Technological Development (CNPq, Brazil), during the conduct of the study; personal fees and other from Novartis, personal fees from Merck, outside the submitted work. Dr Rover reports personal fees from Novartis, outside the submitted work. Dr Figueiredo Neto reports grants and personal fees from Novartis, outside the submitted work. Dr Danzmann reports personal fees and other from Novartis, Servier, Astra Zeneca and Sanofi, outside the submitted work. Dr Bertoldi reports non-financial support from Instituto de Avaliação em Tecnologia em Saúde (IATS), grants from National Council for Scientific and Technological Development (CNPq, Brazil), during the conduct of the study. Dr Simões reports personal fees and other from Novartis, outside the submitted work. Dr Beck-da-Silva reports personal fees and other from Novartis, personal fees from Merck, outside the submitted work. Dr Sant'Anna reports personal fees from Medtronic, outside the submitted work. Dr Zimerman reports receiving a PhD scholarship by the Brazilian government. Dr Priscila reports non-financial support from Instituto de Avaliação em Tecnologia em Saúde (IATS) or National Council for Scientific and Technological Development (CNPq, Brazil), during the conduct of the study; personal fees and other from Novartis and Program to support the institutional development of the public health system (PROADI - SUS, Brazil) outside the submitted work. Dr Biolo reports grants from CNPQ - National Council for Scientific and Technological Development, during the conduct of the present study. Dr Silvestre, Dr Ribeiro, Dr Prado, Dr Zytynski Moura and Dr Bridi have nothing to disclose.

References

1. Comitê Coordenador da Diretriz de Insuficiência Cardíaca. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. *Arq Bras Cardiol* 2018;**111**:436–539.
2. Peacock WF, Costanzo MR, De Marco T, Lopatin M, Wynne J, Mills RM, Emerman CL; ADHERE Scientific Advisory Committee and Investigators. Impact of intravenous loop diuretics on outcomes of patients hospitalized with acute decompensated heart failure: insights from the ADHERE registry. *Cardiology* 2009;**113**:12–19.
3. Komajda M, Follath F, Swedberg K, Cleland J, Aguilar JC, Cohen SA, Dietz R, Gavazzi A, Van GW, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, Widimsky J, Freemantle N, Eastaugh J, Mason J. Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Euro Heart Failure Survey programme—a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. *Eur Heart J* 2003;**24**:464–474.
4. Albuquerque DC, Neto JD, Bacal F, Rohde LE, Bernardez-Pereira S, Berwanger O, Almeida DR; Investigators of the BREATHE Study. I Brazilian Registry of Heart Failure—clinical aspects, care quality and hospitalization outcomes. *Arq Bras Cardiol* 2015;**104**:433–442.
5. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. *Am J Cardiol* 2006;**97**:1759–1764.
6. Dini FL, Ghio S, Klersy C, Rossi A, Simioniuc A, Scelsi L, Genta FT, Cicoira M, Tavazzi L, Temporelli P. Effects on survival of loop diuretic dosing in ambulatory patients with chronic heart failure using a propensity score analysis. *Int J Clin Pract* 2013;**67**:656–664.
7. Cowley AJ, Stainer K, Wynne RD, Rowley JM, Hampton JR. Symptomatic assessment of patients with heart failure: double blind comparison of increasing doses of diuretics and captopril in moderate heart failure. *Lancet* 1986;**2**:770–772.
8. Richardson A, Bayliss J, Scriven AJ, Parameshwar J, Poole Wlison PA, Sutton GC. Double blind comparison of captopril alone against frusemide pus amiloride in mild heart failure. *Lancet* 1987;**2**:709–711.
9. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Associations (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.
10. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA Guideline for the Management of Heart Failure. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;**128**:e240–e327.
11. da Rosa PR, Rohde LE, Doebber M, Ribeiro ALP, Prado DP, Bertoldi EG, Figueiredo Neto JA, Kohler I, Beck-da-Silva L, Danzmann LC, Moura LZ, Rover M, Simões MV, Sant'Anna RT, Biolo A. Rational and design of a randomized, double-blind, multicenter trial to evaluate the safety and tolerability of furosemide withdrawal in stable chronic outpatients with heart failure: the ReBIC-1 trial. *Am Heart J* 2017;**194**:125–131.
12. Rohde LE, Beck-da-Silva L, Goldraich L, Grazziotin TC, Palombini DV, Polanczyk CA, Clausell N. Reliability and prognostic value of traditional signs and symptoms in outpatients with congestive heart failure. *Can J Cardiol* 2004;**20**:697–702.
13. Sauer J, Rabelo ER, Castro RA, Goldraich L, Rohde LE, Clausell N, Beck-da-Silva L. Nurses' performance in classifying heart failure patients based on physical exam: comparison with cardiologist's physical exam and levels of N-terminal pro-B-type natriuretic peptide. *J Clin Nurs* 2010;**19**:3381–3389.
14. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM; NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011;**364**:797–805.
15. Walma EP, Hoes AW, van Dooren C, Prins A, van der Does E. Withdrawal of long term diuretic medication in elderly patients: a double blind randomised trial. *BMJ* 1997;**315**:464–468.
16. Kapelios CJ, Kaldara E, Ntalianis A, Nana E, Pantsios C, Repasos E, Margari Z, Sousonis V, Malliaras K, Nanas JN. Lowering furosemide dose in stable chronic heart failure patients with reduced ejection fraction is not accompanied by decompensation: a randomized study. *Int J Cardiol* 2014; **177**:690–692.
17. Domanski M, Norman J, Pitt B, Haigney M, Hanlon S, Peyster E, Studies of Left Ventricular Dysfunction. Diuretic use, progressive heart failure, and death in patients in the Studies Of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol* 2003;**42**:705–708.
18. Pellicori P, Cleland JG, Zhang J, Kallvikbacka-Bennett A, Urbinati A, Shah P, Kazmi S, Clark AL. Cardiac dysfunction, congestion and loop diuretics: their relationship to prognosis in heart failure. *Cardiovasc Drugs Ther* 2016;**30**:599–609.
19. Laszczyńska O, Severo M, Friões F, Lourenço P, Silva S, Bettencourt P, Lunet N, Azevedo A. Prognostic effect of the dose of loop diuretic over 5 years in chronic heart failure. *J Card Fail* 2017;**23**:589–593.
20. Mckie PM, Schirger JA, Benike SL, Harstad LK, Chen HH. The effects of dose reduction of furosemide on glomerular filtration rate in stable systolic heart failure. *JACC Heart Fail* 2014;**2**:675–677.
21. 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.
22. Dovancescu S, Pellicori P, Mabote T, Torabi A, Clark AL, Cleland J. The effects of short-term omission of daily medication on the pathophysiology of heart failure. *Eur J Heart Fail* 2017;**19**:643–649.