Streamlined **H**eart failure **O**ptimization p**R**otocol for patients with reduced left ventricular ejection fraction: Insights from the **SHORT** trial

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SUMMARY

- Clinical question: Does a streamlined protocol accelerate the initiation of guideline-directed medical therapy in ambulatory patients with heart failure and reduced left ventricular ejection fraction?
- Main finding: Streamlined prescribing halved clinic visits and shortened optimization from 112 to 29 days compared to conventional care.

MANUSCRIPT

In patients with heart failure and reduced left ventricular ejection fraction (HFrEF), early introduction of four guideline-directed medical therapies (GDMT) reduces morbidity and mortality[1, 2]. Conventional sequencing of GDMT takes months and delays optimization[3, 4]. STRONG-HF demonstrated that rapid initiation of GDMT during and after hospitalization improved outcomes; however, its relevance to initiating GDMT in stable outpatients with HFrEF remains unclear[5]. To address this uncertainty, we designed the efficacy of a **S**treamlined **H**F **O**ptimization p**R**otocol for patients with reduced left ventricular ejection fraction **T**rial (SHORT trial).

This investigator-initiated, prospective, parallel-group, open-label, randomized controlled trial recruited adults with HF and echocardiographic evidence of left ventricular ejection fraction (LVEF) of 40% or less. Patients required an N-terminal pro-B-type natriuretic peptide (NT-proBNP) of at least 600 pg/mL, or at least 400 pg/mL if hospitalized for HF within 12 months, or at least 900 pg/mL if they were in atrial fibrillation or flutter. Patients had to be naïve to or taking no more than 25% target doses of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), or beta-blockers before enrolment. Patients already established on angiotensin receptor-neprilysin inhibitors (ARNi), mineralocorticoid receptor antagonists (MRA), or sodium-glucose co-transporter 2 inhibitors (SGLT2i) were excluded. Full inclusion and exclusion criteria are described on clinicaltrials.gov (NCT05021419).

Potential trial subjects were mailed a patient information pack, then contacted by telephone and invited to a screening visit. Eligible patients who consented to participate were randomly assigned in parallel (1:1) to a streamlined or standard optimization strategy. Randomization was stratified by four physiological variables at screening, including age, sex, baseline systolic blood pressure, and estimated glomerular filtration rate.

In the standard arm, there was stepwise introduction of GDMT, beginning with ACEi/ARB and beta-blocker, followed by the addition of MRA, conversion to ARNi, and sequential introduction of SGLT2i. In the streamlined arm, ARNi, SGLT2i, and beta-blocker were introduced at the first visit, with MRA introduced at second visit. Titration of GDMT continued until each patient achieved target doses or further titration was limited by blood pressure, heart rate, renal function, or drug-related adverse effects, as per the European Society of Cardiology guidelines[6]. If necessary, participants were supplied with a blood pressure monitor and weighing scale for use during the trial.

The primary endpoint was time to GDMT optimization (reaching target doses or tolerability limits). Secondary endpoints included number of clinic visits to optimization, proportion of target doses achieved, NT-proBNP changes, Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, and a composite of cardiovascular death or worsening HF.

The study protocol was approved by the West Midlands-South Birmingham Research Ethics Committee, affiliated with the United Kingdom Health Research Authority (approval number 21/WM/0236). All analyses were conducted by intention-to-treat and performed using R, Version 4.4.2 (R Foundation for Statistical Computing). A P-value <0.05 was considered statistically significant.

Sixty-one patients were invited to enroll between July 2022 and December 2023. Of these, 60 patients consented to participate and were randomly assigned to the streamlined and standard optimization arms. One participant in the standard arm declined further medication optimization after 14 days, did not attend the final follow-up visit at six months, but permitted the analysis of data collected before withdrawal. There was no crossover of participants.

The characteristics of the patients enrolled at baseline were balanced between the treatment arms. The median age of the participants was 72.5 years (IQR, 44-81 years), and 30% were female. Median NT-proBNP was 2434 pg/mL (IQR, 780-5398 pg/mL), LVEF 32%

(IQR, 25-36%), and serum creatinine 92 umol/L (IQR, 59-125 umol/L).

Median time to optimization of GDMT was 29 days in the streamlined arm versus 112 days in the standard arm (Figure 1, P<0.001). Streamlined patients required a median of 5 (IQR, 4-6) appointments versus 10 (IQR, 8-11) for standard care (P<0.001). Both groups reached a median of 50% of target doses of ACEi/ARB/ARNI, beta-blockers, and MRA, and a median of 100% of target dose of SGLT2i. At six months, NT-proBNP was 508 pg/ml (IQR, 252-1741 pg/ml) in the standard group and 1020 pg/ml (IQR, 269-2048 pg/ml) in the streamlined group P=0.6). At six months, KCCQ was 70 (IQR, 51-86) in the standard group and 72 (IQR, 56-86) in the streamlined group (P>0.9). The composite endpoint (cardiovascular death or worsening HF) occurred exclusively in the standard group (5 cases) versus none in the streamlined group (P=0.0087). Adverse events were comparable. There were fewer HF-related hospitalizations in the streamlined arm. No increase in hypotension, renal dysfunction, or hyperkalemia was observed.

The SHORT trial demonstrates that a streamlined GDMT strategy in newly diagnosed ambulatory HFrEF patients accelerates optimization without increasing adverse events. Compared to standard care, a streamlined approach halved the time to optimization and reduced clinic visits. Patients randomized to streamlined optimization had a lower incidence of the composite endpoint of cardiovascular death or worsening HF compared to standard care. It may be hypothesized that streamlined optimization reduces the window of vulnerability for early decompensation[5, 7].

SHORT confirms and extends STRONG-HF's findings to ambulatory outpatients with HFrEF, suggesting that aggressive optimization of GDMT is feasible and associated with clinical benefit in the real world.

The limitations of our study include a small sample size, a single-center design, and the predominance of Caucasian patients. Our composite clinical endpoint should be interpreted

cautiously because of the low event rate. Further validation is required, particularly in sicker populations. Nonetheless, the pragmatic inclusion criteria and low attrition rate strengthen the generalizability of our findings.

A streamlined GDMT protocol safely accelerates optimization and reduces the risk of early clinical deterioration in ambulatory HFrEF patients. This approach warrants validation in larger, multi-center trials.

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FIGURE LEGEND

Figure 1: Time to GDMT optimization in the streamlined versus standard arms. The streamlined protocol achieved GDMT optimization in a median of 29 days, significantly faster than the standard arm (112 days). The figure shows median, interquartile range, and outliers.