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BRIEF REPORT

AI-Guided GDMT Optimization After HFrEF Hospitalization

The ASSIST-HF SIRIO Randomized Pilot Trial

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Heart failure (HF) remains a leading cause of morbidity, mortality, and health care use worldwide.[1,2] Patients discharged with newly diagnosed heart failure with reduced ejection fraction (HFrEF) are at particularly high risk of early rehospitalization and death, despite the availability of potent guideline-directed medical therapy (GDMT).[3] Rapid initiation and up-titration of the 4 foundational drug classes can markedly improve outcomes, but in routine practice implementation is often slow and incomplete because intensive follow-up and specialist time are difficult to scale.[4,5]

What is the clinical question being addressed?
Assessment of feasibility, acceptability, and safety of using a generative AI–powered virtual assistant to optimize GDMT in HFrEF patients.

What is the main finding?
An AI-powered virtual assistant is acceptable to patients and can safely and effectively guide HFrEF treatment.

Concurrently, advances in artificial intelligence (AI) and large language models (LLMs) have created the possibility of AI-enabled, guideline-anchored optimization of pharmacologic treatment, which could extend specialist expertise, while allowing human oversight.[6-9] We aimed to assess the feasibility of integrating an AI virtual assistant (VA), administered by nonmedical staff, into the outpatient management of patients with HFrEF, to safely optimize GDMT while meeting patient satisfaction.

METHODS

We performed a single-center, prospective, open-label, randomized pilot trial (NCT06400927) in 60 adults with newly diagnosed HFrEF and New York Heart Association (NYHA) functional class II-IV symptoms. Patients were randomized at hospital discharge 1:1 to VA-guided care delivered fortnightly by nonmedical/non-nursing staff (VA arm) or to usual care delivered by doctors or HF nurses (standard of care [SOC] arm), over 12-weeks (**Figure 1**).

A HFrEF-specific VA, SIRIO-HF, was built on a LLM, with retrieval-augmented generation and

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expert prompt engineering, explicitly grounded in contemporary HF guidelines.[6,7] Using carefully designed prompts, the VA delivers dynamically tailored, personalized, and guideline-concordant GDMT recommendations.

In the SOC arm, GDMT optimization was achieved through conventional clinic visits with physicians or HF nurses. In the VA arm, patients had fortnightly remote or face-to-face visits with a nonmedical administrator, who conducted scripted interviews, recording symptoms, vital signs, weight, and key laboratory values (including N-terminal pro-B-type natriuretic peptide [NT-proBNP], renal function, and electrolytes) and entered these into the VA via a secure interface. The VA generated real-time personalized treatment recommendations, covering GDMT titration, diuretic adjustment, and safety monitoring. A remote cardiologist, acting as human-in-the-loop to ensure safety, reviewed the recommendation and approved, modified, or rejected it before communicating this to the patient and issuing prescription(s).

Primary endpoints included feasibility, acceptability, and GDMT optimization with the use of the VA compared with SOC. Secondary endpoints included NYHA functional class, NT-proBNP, HF-related rehospitalization, quality of life (QoL), and VA-clinician agreement. Given the small sample size and pilot design, analyses of clinical outcomes were considered exploratory.

The study (NCT06400927) was approved by the United Kingdom Health Research Authority (Reference 24/WA/0086) and the local Research and Development Board and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. A comprehensive description of the trial design, workflow architecture, VA specifications, and statistical analysis plan is provided in the *JACC: Advances* Methods Companion published concurrently.[11]

RESULTS

FEASIBILITY AND ACCEPTABILITY. Of 75 screened patients, 66 were eligible and 60 were randomized (30 per arm), with 98% of eligible patients consenting to participate and only 1 dropout (in the SOC arm). Baseline characteristics were well-balanced between the study arms.

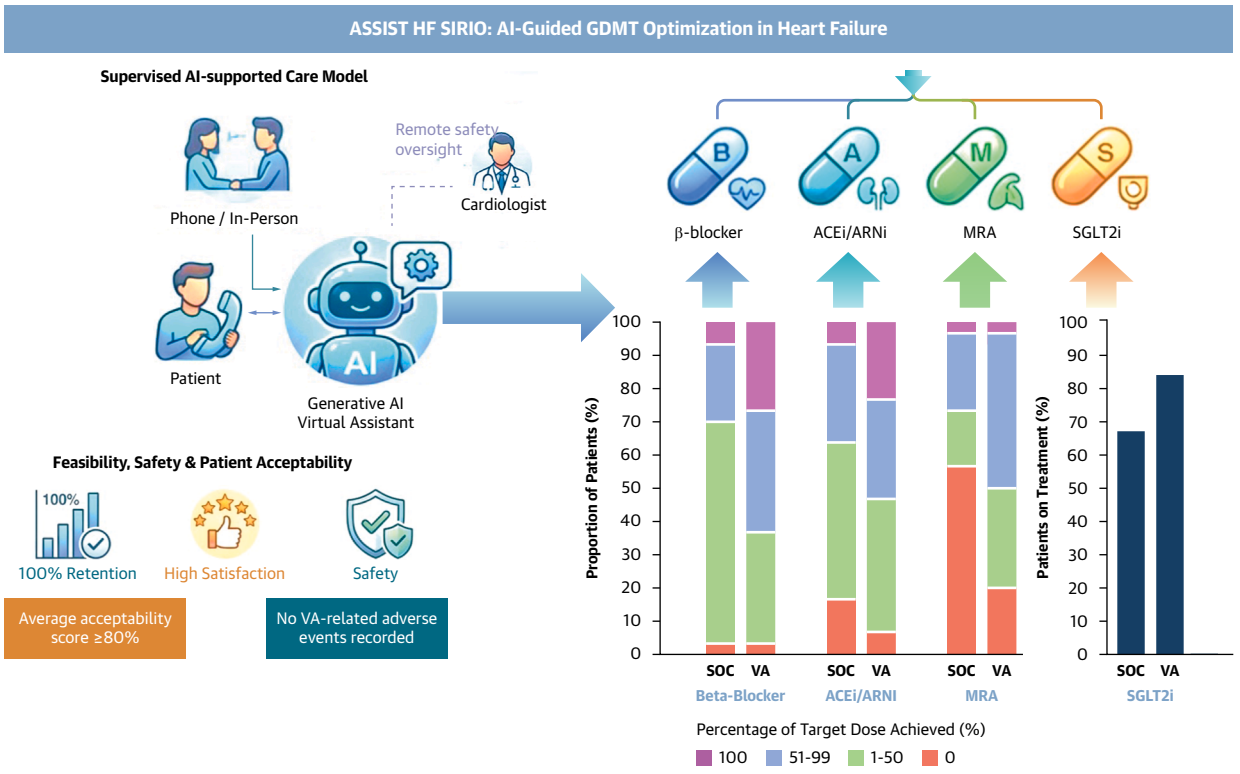
At 12 weeks, patient-reported acceptability, appropriateness, and feasibility scores for VA-guided care were high (90%, 92%, and 88%, respectively), with 87% of patients scoring >80% on the combined acceptability measure.

GDMT OPTIMIZATION. By 12 weeks (**Figure 1**), VA-guided care resulted in markedly higher GDMT optimization across all medication classes, with maximally tolerated doses of GDMT achieved more often in the VA arm than in the SOC arm (β-blockers 100% vs 52%; angiotensin receptor/neprilysin inhibitor [ARNI] 100% vs 37%; angiotensin-converting enzyme inhibitor [ACEi]/angiotensin II receptor blocker [ARB] 100% vs 35%; mineralocorticoid receptor antagonist [MRAs] 96% vs 20%; sodium-glucose cotransporter 2 inhibitors 96% vs 20%; $P < 0.001$ for each class). Dose distributions for ACEi/ARB/ARNI, β-blockers, and MRAs shifted toward higher doses, with a greater proportion of VA-arm patients reaching at least one-half the guideline-recommended dose (maximal or half-to-less-than-full maximal dose) compared with SOC: 50% vs 37% for ACEi/ARB/ARNI; 60% vs 30% for β-blockers; and 50% vs 26% for MRAs. At the end of the first visit (2 weeks), 83.3% of VA-arm patients were already on 3 to 4 GDMT classes vs 20% in the SOC arm. Median NT-proBNP decreased from 2,588 pg/mL (IQR: 1,484-3,771 pg/mL) at baseline to 388 pg/mL (151-890 pg/mL) at 12 weeks in the VA arm, compared with a reduction from 3,571 pg/mL (1,542-6,180 pg/mL) to 1,756 pg/mL (242-3,652 pg/mL) in the SOC arm, with lower NT-proBNP at follow-up in VA-treated patients. Among those with initial NYHA functional class III-IV symptoms, by 12 weeks, more patients in the VA than in the SOC arm had improved to NYHA functional class I (46.2% vs 14.3%). HF-related rehospitalizations occurred in 0 of 30 patients in the VA group vs 4 of 30 (13%) in the SOC group over 12 weeks, with higher QoL scores in the VA than in the SOC group (25.3 vs 19.6 points).

SAFETY AND AGREEMENT. Cardiologist-VA agreement on GDMT optimization was 100% in the early phase of the trial and 93.4% at the end of treatment. Disagreements were few and mainly reflected perceived "overcaution" in VA recommendation, such as extreme caution in the presence of borderline potassium values. There were fewer major cardiovascular events in the VA than the SOC arm (2 vs 6). Event numbers were small, and these comparisons are descriptive and exploratory. No adverse events were judged to be related to VA use.

INTERPRETATION. For the first time, we show that frequent VA-guided medication management, administered by nonmedical staff, in high-risk cardiovascular patients, is feasible, acceptable to patients, and achieves more rapid and comprehensive GDMT optimization at 12 weeks compared with usual care. Additional clinical benefits included greater

FIGURE 1 **Generative AI-Supported, Nonphysician-Delivered Model for GDMT Optimization in HFrEF: The ASSIST-HF SIRIO Trial**



The trial evaluated an AI-enabled workflow with a VA embedded in a supervised structure with nonmedical personnel and cardiologist oversight. Dosage of GDMT (dosage against maximal possible dose) in both study arms at EOT by medication class (ACEi, ARB, ARNI, BB, MRA). ACEi = angiotensin-converting enzyme inhibitor; AI = artificial intelligence; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; BB = beta-blocker; EOT = end-of-trial; GDMT = guideline-directed medical therapy; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; SOC = standard of care; VA = virtual assistant.

improvement in symptoms and QoL, fewer HF hospitalizations, and greater reduction in NT-proBNP. More than 80% of patients in the VA group were on 3 to 4 GDMT classes within the initial weeks, compared with only 20% with SOC.

The VA platform was not a simple algorithm- or score-based engine, as in previous navigator-led programs, but a generative AI agent built on a LLM, refined through advanced prompt engineering and retrieval-augmented generation, and explicitly anchored to contemporary HF guidelines.[10] The VA provided real-time personalized treatment recommendations based on information submitted by nonmedical staff in response to scripted questions, while a remote cardiologist acting as human-in-the-loop reviewed all treatment plans and retained full decision authority.

Conceptually, this architecture decouples contact intensity from specialist time; structured data collection and guideline application are delegated to nonmedical staff and the VA, while cardiologists focus on safety oversight. In this early-phase pilot, such a workflow proved to be operationally feasible and highly acceptable to patients, and it demonstrated favorable signals for GDMT optimization, NT-proBNP reduction, and HF rehospitalizations, without evidence of VA-related harm. ASSIST-HF SIRIO is, however, a small single-center pilot with 12-week follow-up, and all effect estimates are exploratory and hypothesis-generating.

To our knowledge, this is the first randomized pharmacologic management trial in medicine in which active treatment recommendations were generated by an advanced generative AI assistant within a human-supervised safety framework. This hybrid strategy may represent an effective, patient-centered approach to enhance out-patient HFrEF management and optimize health care resources.

Larger, multicenter trials are now required to confirm clinical efficacy and define how generative AI assistants can be safely integrated into diverse health systems.

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