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Preemptive Versus Urgent Heart Failure Hospitalization as a Surrogate for Mortality Risk in Heart Failure

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In heart failure (HF), the event that is most strongly reduced by guideline-directed medical therapy is acute HF leading to HF hospitalization (HFH). Acute HF or worsening HF (WHF) may also lead to urgent intravenous therapy in the outpatient or emergency department setting: a HF event (HFE). HFEs remain a key component of the composite primary end point in randomized controlled trials (RCTs). New drugs and interventions are granted regulatory approval, recommended in practice guidelines, and reimbursed by payers on the basis of reducing HFEs, even if there is no demonstrated effect on mortality rate.

WHAT DOES AN HFE REPRESENT?

A long-standing perception is that HFEs are markers of HF progression and a surrogate for mortality risk. WHF is accompanied by an early and likely sustained increased risk of rehospitalization and death, even after extensive adjustment for confounding factors. In RCTs, interventions that reduce HFEs also generally reduce mortality risk, although to a lesser magnitude or with lesser statistical certainty. This reinforces the dogma of downward shift of the trajectory of the patient with HF after each decompensation, originally depicted by Gheorghiade et al[1] (Figure, scenario 1).

Are there patients for whom an HFE is not associated with higher risk of death? Are there interventions that reduce mortality risk but not HFEs (apart from the obvious example of implantable cardioverter defibrillators)? Numerous observational studies suggest a counterintuitive discordance between HFEs and mortality risk.

STUDIES WITH HFE AND DEATH DISCORDANCE

Preemptive HFH in Mild Clinical Decompensation Leading to Slower Progression

This is illustrated as scenario 2 in the Figure. Analyses from SwedeHF (the Swedish Heart Failure Registry) suggest that interventions such as outpatient referral to HF nurses and follow-up with specialty versus primary care were associated with lower all-cause mortality rate but no difference in HFH. Management of patients with HF with reduced ejection fraction in the cardiology versus noncardiology setting was independently associated with lower risk of all-cause death, but higher risk of HFH.[2] Management by and follow-up with HF nurses, HF specialists, and HF multidisciplinary teams entails closer follow-up and a higher level of care, which may reduce mortality risk, but may also identify clinical decompensation at earlier, more benign and reversible stages. In this scenario, preemptive hospitalization of patients with mild clinical decompensation may lead to optimized care and ultimately reduce the risk of death. This is supported by recent data that have demonstrated that HFHs are followed by more frequent initiation and increases in dose

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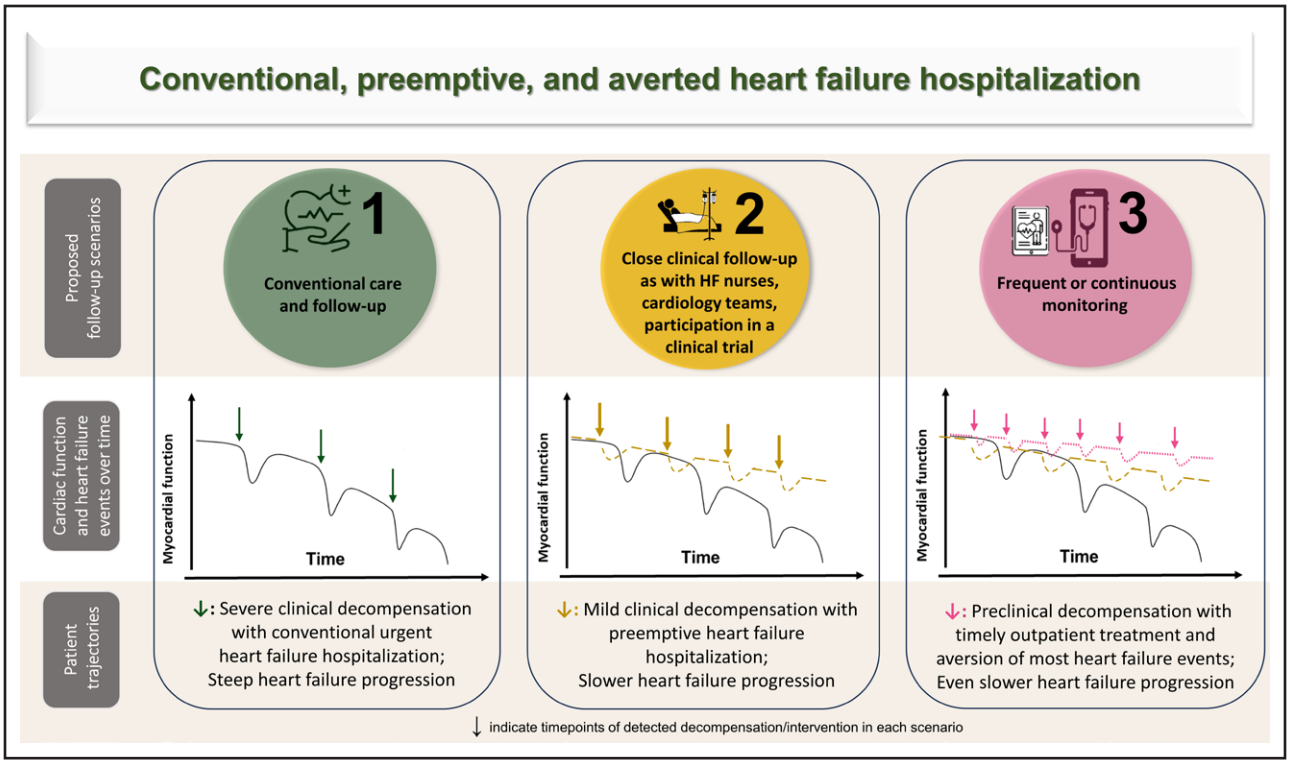

Figure. Possible differences in heart failure trajectory depending on level of vigilance and frequency of follow-up.
In scenario 1, representing usual real-world standard of care, patients experience urgent heart failure (HF) events because of severe clinical decompensation, each one of which has a subsequent effect on their myocardial function and prognosis. In scenario 2, which represents a setting of closer clinical follow-up (eg, follow-up with HF nurses, with specialists, during a HF randomized controlled trial), patients can experience urgent HF events (not depicted on the orange curve), but can also be admitted to the hospital preemptively for treatment of mild decompensation, which is detected in earlier stages. In this scenario, HF events are numerically greater, but less severe, and survival is improved. In scenario 3, which represents a setting of even closer follow-up, even when this is not face-to-face (eg, use of mobile-based telemonitoring services, presence of CardioMEMS), patients can experience urgent or preemptive HF events (not depicted on the pink curve), but many of these are prevented, as decompensation is recognized in its earliest stages and treated promptly with intensification of medical therapy in the outpatient setting. In this scenario, HF events are the least, and survival is even better. Adapted from Gheorghiade et al.[1] Used with permission from Elsevier.

of guideline-directed medical therapy among patients with HF.[3]

In the European Society of Cardiology Heart Failure Long-Term Registry, participation in an RCT was associated with lower 1-year mortality risk compared with nonparticipation, but not lower risk of HFH.[4] Again, closer and more specialized follow-up might have led to preemptive HFH. A similar, discordant association was evident between socioeconomic risk factors (ie, lower education, lower income, living alone) and higher mortality risk, but not greater risk of HFH, in SwedeHF. Patients with higher socioeconomic status might have had better access to care and HFH, in part in the preemptive setting, and thus lower risk of death.

Data from SwedeHF demonstrated that the use of an angiotensin receptor/neprilysin inhibitor was associated with 23% lower risk of mortality but no difference in cardiovascular or all-cause hospitalization compared with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. A similar study from the United States showed that use of an angiotensin receptor/neprilysin inhibitor was associated with a 20% lower risk of mortality and 14% lower risk of all-cause hospitalizations compared with use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. However, the risk of HFH did not differ significantly between the 2 treatment arms. In RCTs, angiotensin receptor/neprilysin inhibitors reduced both HFH and death, so this discordance may again indicate that early-adopter real-world use of angiotensin receptor/neprilysin inhibitors may have entailed increased monitoring and vigilance, resulting in detection of mild clinical decompensation and preemptive HFHs.

Detection of Preclinical Decompensation Leading to Averted HFEs and Even Slower Progression

This is illustrated as scenario 3 in the Figure. The STRONG-HF trial (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) demonstrated a 34% decrease in the risk of the composite of death or HFH at 180 days among patients randomized to high-intensity versus usual care,[5] suggesting that opportunities for preemptive

HFHs did not actually lead to (preemptive) HFHs. However, the frequency of follow-up visits was not a result of increased vigilance, but protocol-prescribed in the active arm. Biomarkers were used to guide treatment at every study visit, which may have facilitated detection of preclinical decompensation, averting both urgent and preemptive HFHs.[5] On the contrary, in other RCTs, the follow-up visits are prescribed by protocol, but the same numerically in both the intervention and the control arms. Thus, opportunities to detect preclinical or mild decompensation do not differ between the 2 groups, resulting in concordance between HFEs and death.

In the HERMeS trial (Heart Failure Events Reduction With Remote Monitoring and eHealth Support), structured telemonitoring combined with videoconferencing plus face-to-face visits versus face-to-face visits alone resulted in a 65% lower risk of cardiovascular death or WHF. The follow-up visits were again at fixed time points and numerically the same in both arms, but the intervention arm also had telemonitoring. In this case, telemonitoring may have detected preclinical decompensation and averted both preemptive and urgent HFEs. Studies with the CardioMEMS HF system are consistent with this notion of detection of preclinical decompensation leading to reductions in HFH.

A NEW TYPE OF HFE: PREEMPTIVE HFE

We propose that these observations taken together suggest the existence of the following 3 settings of WHF: conventional care and paradigm, in which patients experience urgent clinical signs and symptoms of WHF, seek emergency care, and are hospitalized, which correlates with steep progression of chronic HF and subsequent death (Figure, scenario 1); preemptive HFE, in which patients who have access to HF nurse clinics, HF teams, and vigilant cardiologists are hospitalized with mild clinical signs and symptoms, which may not be a risk marker but may lead instead to optimized care and likely to improved survival (Figure, scenario 2); and averted HFE, in which invasive hemodynamic monitoring, telemonitoring, or regular biomarker assessments detect preclinical decompensation and avert both urgent and preemptive HFH (Figure, scenario 3). If preemptive HFH is indeed a real entity, it may not be a marker of risk and subsequent death.

The examples cited are merely examples, and may not be representative of all settings and health care systems. The HFHs cited were not elective (such as for implantation of an implantable cardioverter defibrillator or cardiac resynchronization therapy), but we cannot rule out that some hospitalizations may have been milder than a conventional acute HF event. Clinical presentations of patients with acute HF vary considerably across HF registries and RCTs, demonstrating that HF decompensation covers a wide spectrum. Trials generally use adjudication, where preemptive hospitalization may not count, and an HFE instead represents distinct deterioration and is concordant with subsequent death. This further supports the data suggesting that preemptive hospitalizations occur earlier in the WHF process and can thus positively affect long-term outcomes.

ARTICLE INFORMATION

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