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Waiting Period Prior to ICD Implantation in Newly-Diagnosed HFrEF: A Window of Opportunity

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A critical "waiting period" of ~3 months is generally accepted in patients with newly-diagnosed heart failure with reduced ejection fraction (HFrEF) outside the context of an acute myocardial infarction prior to reassessing left ventricular (LV) ejection fraction and considering implantable cardioverter-defibrillator (ICD) therapy. This time window is offered to allow optimization of guideline-directed medical therapy (GMDT) to promote LV reverse remodeling, which if above a certain threshold, would render the need for an ICD unnecessary. Consideration for an ICD after this time-frame is endorsed by major professional groups,[1] serves as a key quality and performance measure, and is deemed "appropriate" by the Appropriate Use Criteria for ICD therapy.[2] This duration also guides reimbursement schema, e.g. the Centers for Medicare & Medicaid Services limit coverage for ICDs in non-ischemic dilated cardiomyopathy to after this 3-month waiting period.

Perhaps it is time to lengthen this time-frame prior to ICD decision-making in newly-diagnosed patients with HFrEF. In many cases, 3 months is not sufficient to truly optimize GDMT and allow adequate chance for LV recovery. Evolving risks of sudden cardiac death (SCD), recent expansion of the HF therapeutic armamentarium, and greater focus on shared decision-making, all support extension of this time window. We summarize these converging lines of evidence and critically appraise the merits of extending this traditional "waiting period." We contend that consideration for ICD implantation should only occur once GDMT has been achieved at target doses and may be deferred up to 1 year after diagnosis in

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appropriately-selected patients. As the Centers for Medicare & Medicaid Services plan to update the national coverage determination regarding ICD implantation over the next year, we believe this issue is timely and topical to address.

Landscape of Sudden Cardiac Death

Epidemiological studies[3] and clinical trials[4] over the last several decades have demonstrated that overall rates of SCD have declined, potentially reflecting greater uptake of GDMT, more complete coronary revascularization, and improved overall processes of care, including for comorbidities. After hospital discharge, patients face low-to-modest risks of SCD. Based on trials enrolling patients hospitalized for HFrEF with infrequent baseline utilization of ICDs (<15%), the estimated risks of SCD at 30 days is <1%, at 6 months is 2–4%, and at 1 year is 7% (Figure 1).[5,6]

This risk appears to accrue gradually and there does not appear to be a heightened period of SCD risk during the “vulnerable phase” after hospital discharge. This has been corroborated by data from over 30,000 patients enrolled in contemporary chronic HF trials.[4] Although the absolute risks of SCD increase with the duration of HF diagnosis, patients recently diagnosed with HF face low absolute rates of SCD.[4] “Real-world” experiences show that patients who receive wearable cardioverter-defibrillators experience rates of sustained ventricular tachyarrhythmias in 1% and 3% in non-ischemic and ischemic cardiomyopathies, respectively, at 3 months.[7]

Competing Risks of Death

The HF population in general is elderly with multi-morbidity burden. While SCD is an important consideration and is the most common mode of death in patients with chronic, stable HFrEF, progressive pump failure death and non-cardiovascular deaths predominate and account for twice the SCD event rate at each follow-up time-point after hospital discharge (Figure 1). This highlights the need for an individualized approach to determine the optimal timeline prior to ICD consideration based on age, functional status, hospitalization burden, and comorbidities.

Time to Optimize Guideline-Directed Medical Therapy

Neurohormonal modulation significantly reduces both HF-related death and SCD. There, however, remain many missed opportunities to modify the risk of SCD in patients with HFrEF. At the time of hospitalization for *de novo* HFrEF, prescription of GDMT is relatively low, even in clinical trial populations.[8] With progresses in GDMT, clinicians will require more time to optimize multi-drug regimens (Figure 2). The step-wise initiation of 3 or more agents safely with simultaneous ambulatory monitoring of laboratory parameters, hemodynamics, and symptoms, requires frequent medical contact. As suggested by recent guidelines,[9] most therapies require 1 to 3 dosing changes prior to achieving target doses, with titration intervals between 2 to 8 weeks. Even structured programs employing a nurse facilitator to guide aggressive titration to target doses of GDMT require ~6 months.[10] Merged data from the National Cardiovascular Data Registry (NCDR) ICD Registry and

Medicare administrative data show that only ~60% of patients filled any neurohormonal antagonist prescription prior to primary prevention ICD implant.[11] The variable interpretation of the timeline (as time from initial diagnosis of HFrEF or time on optimal GDMT) may contribute to this observed poor utilization of GDMT. There are dose-dependent effects of HF therapies on improvements in LV ejection fraction that may occur beyond the 3-month time window. Thus, taking time to achieve recommended doses is important and may take up to 1 year to not only optimize therapy, but to see the effect of optimal therapy after it has been achieved.

Reappraisal of Benefits with ICD Therapy

The recent DANISH (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality) trial in patients with non-ischemic cardiomyopathy and LV ejection fraction ≤35% reaffirm the uncertainty of ICD benefit in certain cohorts,[12] especially those with high uptake of GDMT or who face greater competing risks of mortality. Indeed, ICD therapy is of uncertain value in patients who experience recurrent hospitalizations or have severe comorbidities (class IIb, level of evidence B). Device implantation is met with procedural risks, costs, require routine follow-up, and may malfunction. As such, decisions to pursue ICD therapy should be well-informed, calculated, guided by individualized risk estimates of SCD vs. non-SCD death, and only occur after an adequate trial of GDMT.

A Path Forward

The course after HF diagnosis is riddled with hurdles and opportunities that may modify risks of SCD and non-SCD death (Figure 1). Advances in GDMT have introduced further uncertainty about the benefit of ICD implantation after initial HFrEF diagnosis. Few SCD events occur during the currently acceptable 3-month timeline and GDMT remains poorly optimized prior to many device implantations. In this context, a longer “waiting period” up to 1 year would facilitate several important goals:

- Initiation, up-titration, and optimization of multi-drug regimens, and assess their attendant effects on LV recovery
- Improve implementation and ensure adherence, especially in underrepresented or low-income populations
- Allow time for assessing and managing competing risks (HF-related death or other non-SCD modes of death) and comorbidities
- Permit greater opportunity for risk stratification for SCD including application of wearable cardioverter-defibrillators in select patients
- Provide sufficient time for patients to understand the HF syndrome, risks of SCD, and harms and benefits of ICD implantation

There will be a small, but significant, and accruing risk of SCD that will be incurred if the proposed extended timeline is routinely undertaken. Younger patients without significant comorbidities should continue to be evaluated for ICD therapy within the traditional

timeframe.[13] Precision medicine techniques (risk scores, deep phenotyping with biomarkers and imaging, etc.) may be used to identify other subgroups of patients who may benefit from shorter timelines to ICD consideration. The uncertain benefits of early ICD implantation in select patients reinforces the critical role of shared decision-making in guiding timing for individual patents. Cause-specific prognostic risk scores and better valuation of patients' goals and expectations are needed in clinical practice. Considering the modest early risks of SCD, high cost and other unintended consequences of ICD therapy, and the potential to obviate its need with GDMT, serious consideration should be afforded to extending the time period before proceeding with ICD implantation for primary prevention in appropriately-selected patients with newly-diagnosed HFrEF.

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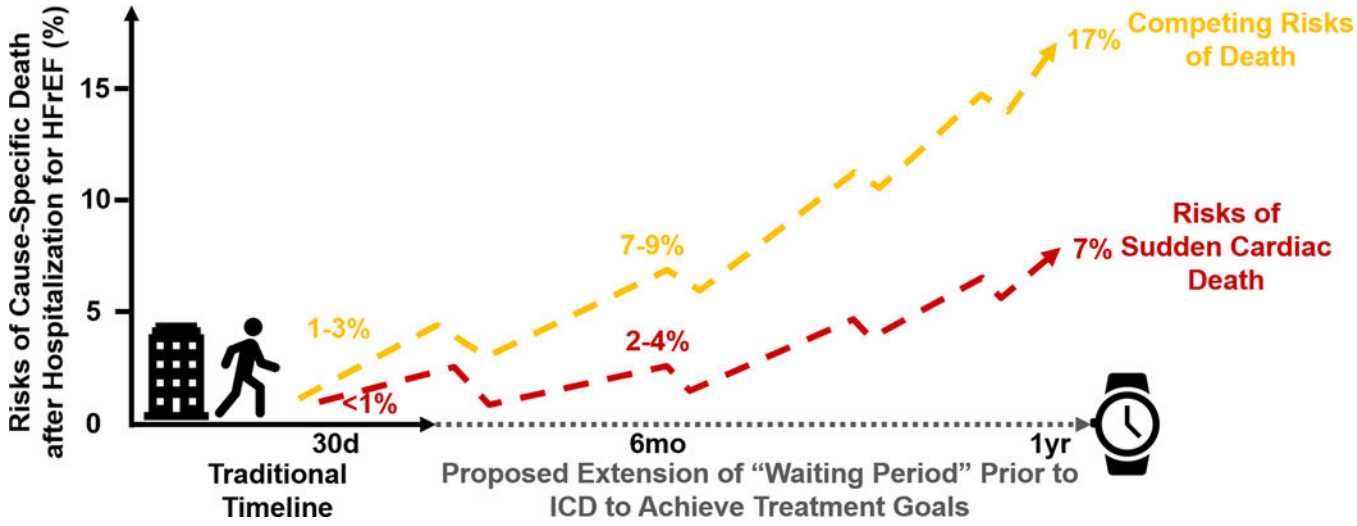

Figure 1. Risks of Sudden and Non-Sudden Death after Hospitalization for Heart Failure with Reduced Ejection Fraction

Cause-specific death risk estimates were derived from the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure), EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan),[5] and RELAX-AHF (Relaxin in Acute Heart Failure) trials.[6] Abbreviations: HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator.

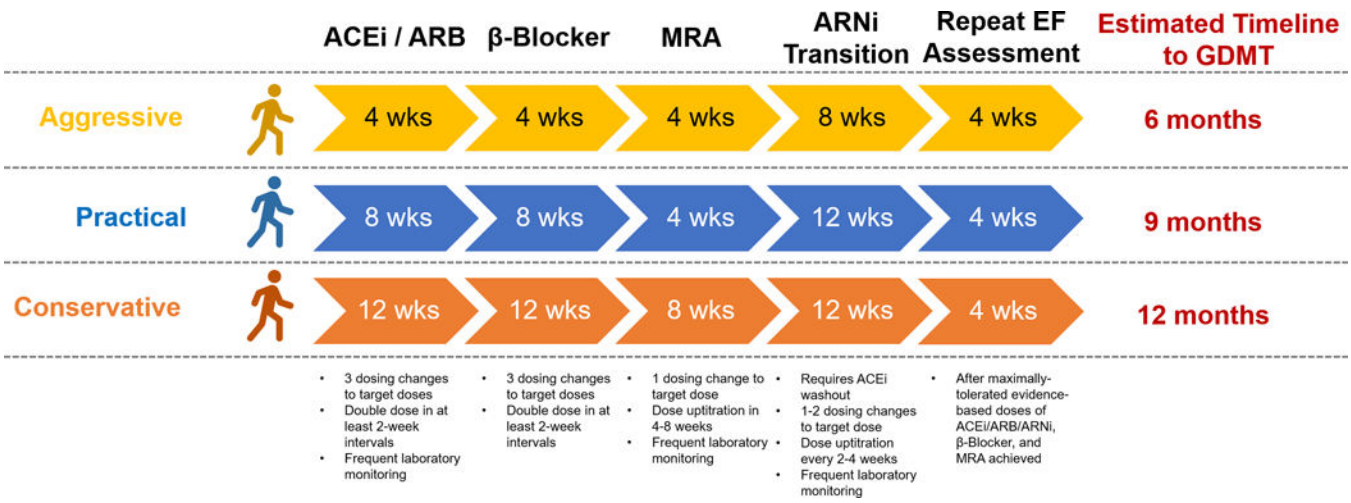

Figure 2. How Long Does It Take to Optimize Guideline-Directed Medical Therapy in Newly-Diagnosed Heart Failure with Reduced Ejection Fraction?

We have developed a theoretical timeline for the step-wise initiation and uptitration of 3–4 drugs in contemporary regimens for newly-diagnosed heart failure with reduced ejection fraction. Starting doses, target doses, titration schedule, and necessary laboratory monitoring were based on suggestions from the 2016 European Society of Cardiology Guidelines.[9] This generic timeline does not account for pre-existing therapies, specific order of initiation of therapies, or simultaneous drug uptitration. Abbreviations: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNi = angiotensin receptor neprilysin inhibitor; EF = ejection fraction; GDMT = guideline-directed medical therapy; MRA = mineralocorticoid receptor antagonist.