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Guideline-Directed Medical Therapy in the First Fortnight: Rapid Sequencing Against Traditional Titration in Heart Failure

Ronan Fitzgibbon-Hayes[1*], Katharina Obermoser[2], Luka Benčina-Zorc[3]

[1]*Department of Heart Failure Services, Nore Valley Institute of Cardiology, Carlow, Ireland*
[2]*Department of Pharmacy, Traun Heart Centre, Linz, Austria*
[3]*Department of Heart Failure Nursing, Sava Heart Centre, Ljubljana, Slovenia*

*Correspondence to: Ronan Fitzgibbon-Hayes, Department of Heart Failure Services, Nore Valley Institute of Cardiology, Carlow, Ireland
E-mail: r.fitzgibbonhayes@nvic.ie

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Abstract

Four drug classes -- an ARNI/ACEI/ARB, a beta-blocker, a mineralocorticoid receptor antagonist, and an SGLT2 inhibitor -- each reduce death and hospitalization in heart failure with reduced ejection fraction, yet real-world patients rarely receive all four at meaningful doses within any useful timeframe. The STRONG-HF trial randomized 1,078 patients after acute heart failure hospitalization to a high-intensity strategy reaching 100% of recommended doses by two weeks post-discharge, or to usual care; the composite of heart-failure readmission or death by 180 days occurred in 15.3% versus 23.3% (RR 0.66, 95% CI 0.50-0.86). PIONEER-HF and EMPULSE separately showed that starting an ARNI or an SGLT2 inhibitor in hospital, rather than waiting for outpatient stability, is feasible and effective on their own pillar-specific endpoints. None of this comes free: 58% of STRONG-HF's high-intensity patients had at least one safety indicator -- hyperkalemia in 28%, hypotension in 9.4%, severe renal dysfunction in 5.2% -- and a dedicated safety analysis found these indicators did not, on their own, predict a worse outcome. Set against this is a stark real-world comparison: a 2026 Veterans Health Administration registry of 52,850 newly diagnosed patients found only 21.2% ever reached quadruple therapy, at a median of 197 days when they did. This review sets rapid in-hospital sequencing against traditional outpatient titration on the evidence actually published, including the monitoring burden and adherence realities that complicate any simple recommendation to move faster.

Keywords: *Guideline-directed medical therapy; Heart failure with reduced ejection fraction; Drug titration; Patient compliance; Hyperkalemia*

Introduction

Four drug classes now carry a class I guideline recommendation in heart failure with reduced ejection fraction: an angiotensin receptor-neprilysin inhibitor (or, failing that, an ACE inhibitor or ARB), a beta-blocker, a mineralocorticoid receptor antagonist (MRA), and a sodium-glucose cotransporter-2 (SGLT2) inhibitor. For most of the past two decades, guidance assumed these drugs would be introduced one at a time in an outpatient clinic, each up-titrated over weeks to months before the next was started. That sequential model is now being challenged directly, both by trials that start several pillars together in hospital and by a growing literature documenting how badly the traditional model performs once patients leave the trial setting.

This review sets the evidence for rapid, in-hospital sequencing of guideline-directed medical therapy (GDMT) against the traditional outpatient titration model it is meant to replace, and asks what a cardiologist, pharmacist, or heart-failure nurse should actually take from that comparison -- including the safety monitoring burden that a faster strategy

demands.

The clinical logic for speed is straightforward: hospitalization for heart failure is itself a high-risk period, readmission rates in the following months are steep, and every week a patient spends without a pillar of GDMT is a week of unmitigated risk. The traditional counter-argument is equally straightforward: starting four new drug classes at once multiplies the chance of hypotension, hyperkalemia, and acute kidney injury, and a hospitalized patient's physiology is already unstable. Both arguments have been tested, not just asserted, and this review examines what that testing actually showed. The choice has been framed explicitly in the literature as one between simultaneous initiation of all four pillars at once and a rapid but staged sequence completed within days rather than months -- 'optimizing therapy with the need for speed' [5].

Material and Methods

This is a narrative review drawing on the STRONG-HF randomized trial and its dedicated safety-indicator analysis, the PIONEER-HF and EMPULSE randomized trials of single-pillar in-hospital initiation, the CHAMP-HF outpatient registry, a 2026 Veterans Health Administration registry analysis of time to quadruple therapy, and a professional-society editorial and news report on real-world implementation barriers, identified through the sources cited above and citation tracking between them, without a pre-registered protocol or systematic search string. All percentages, ratios, hazard ratios, and confidence intervals reported here are taken directly from the cited sources; none has been invented, estimated, or extrapolated.

Results

STRONG-HF: rapid multi-pillar up-titration reduces readmission and death

STRONG-HF randomized 1,078 patients hospitalized for acute heart failure to a high-intensity care strategy -- reaching 100% of recommended GDMT doses by two weeks after discharge, with frequent safety-monitoring visits -- or to usual care [1]. The primary composite of heart-failure readmission or death from any cause by 180 days occurred in 15.3% of the high-intensity group versus 23.3% of usual care (RR 0.66, 95% CI 0.50-0.86) [1]. Figure 1 sets this result out directly. HF readmission alone was similarly reduced, 9.5% versus 17.1% (RR 0.56, 95% CI 0.38-0.81) [1]. Figure 2 contrasts this trial's two-week dosing timeline against the far longer clock that traditional sequential titration runs on in real-world practice [1,7]. By 90 days, target dosing was already common with high-intensity care and rare with usual care: 55% versus 2% for RAS blockers, 49% versus 4% for beta-blockers, and 84% versus 46% for MRAs [1]. Figure 3 sets these three drug classes out together.

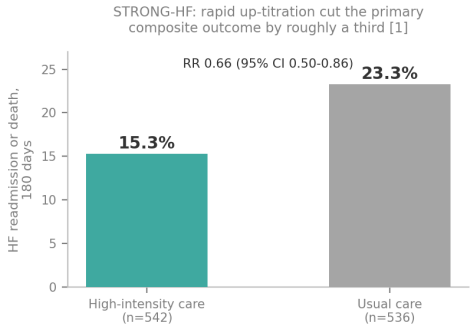

Figure 1: Primary composite outcome (HF readmission or death, 180 days), high-intensity versus usual care, STRONG-HF trial [1].

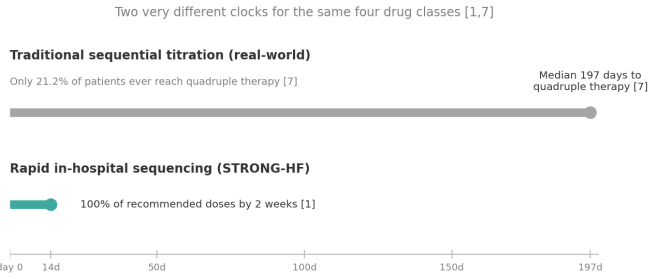

Figure 2: Traditional real-world time to quadruple therapy versus the STRONG-HF high-intensity dosing timeline [1,7].

STRONG-HF's high-intensity protocol compresses into two weeks what the traditional model spreads across months: an early post-discharge review, a target-dose ceiling reached by day 14, and a structured safety check at 90 days confirming the doses had held across all three drug classes shown in Figure 3, with no single pillar left behind while the others advanced [1].

That last point is itself informative: the benefit of the high-intensity strategy did not depend on any one pillar

reaching target dose disproportionately faster than the others, which argues against the idea that a single drug class is doing most of the work while the rest are along for the ride.

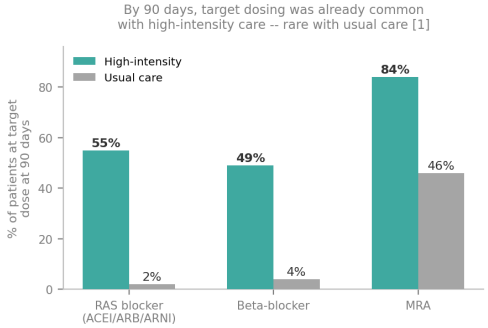

Figure 3: Percentage of patients at target dose at 90 days by drug class, high-intensity versus usual care, STRONG-HF trial [1].

Single-pillar in-hospital initiation: PIONEER-HF and EMPULSE

Two further randomized trials tested whether a single pillar, rather than all four, could be started safely in hospital rather than deferred to outpatient stability. PIONEER-HF randomized 881 patients with acute decompensated heart failure to in-hospital initiation of sacubitril-valsartan or enalapril; NT-proBNP fell substantially more with sacubitril-valsartan, a ratio of change of 0.71 (95% CI 0.63-0.81) over weeks 4-8, and HF rehospitalization was lower, 8.0% versus 13.8% (HR 0.56, 95% CI 0.37-0.84) [3]. EMPULSE randomized 530 patients with acute heart failure to in-hospital initiation of empagliflozin or placebo, and found a clinical-benefit win ratio of 1.36 (95% CI 1.09-1.68, P=0.0054), with clinical benefit in 53.9% versus 39.7% of patients [4]. Figure 4 places these pillar-specific results alongside STRONG-HF's own ratios on a single forest-plot-style summary; every effect estimate from a rapid or in-hospital strategy landed below 1.0 in its own pivotal trial [1,3].

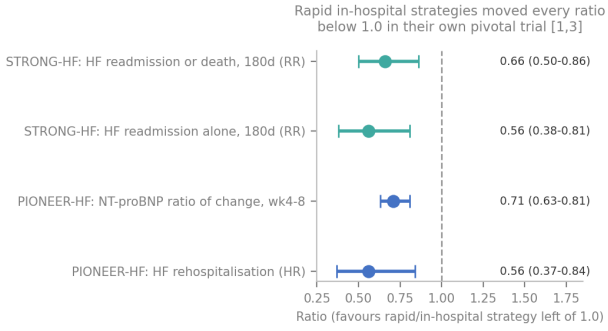

Figure 4: Effect estimates favoring rapid or in-hospital initiation across STRONG-HF and PIONEER-HF, each on its own reported metric [1,3].

PIONEER-HF and EMPULSE share a design feature worth making explicit: both tested a single pillar started in hospital against an active or placebo comparator that patients would otherwise have received anyway, rather than testing whether starting that pillar changes the safety of the other three started alongside it. STRONG-HF is the only trial reviewed here that actually tested multi-pillar up-titration as a single strategy, which is why its own safety analysis, examined next, carries more weight for the multi-pillar question this review is actually asking [1-4].

The honest complication: safety signals are common, not rare

None of this speed comes free. A dedicated STRONG-HF safety analysis found that 58% of high-intensity patients had at least one safety indicator during follow-up visits: hyperkalemia in 28%, hypotension (systolic blood pressure below 95 mmHg) in 9.4%, severe renal dysfunction (eGFR below 30) in 5.2%, and bradycardia (heart rate below 55 bpm) in 8.5% [2]. Figure 5 sets these four indicators out together. Reassuringly, having a safety indicator was not itself associated with a worse primary outcome (event rate 15% with a safety indicator versus 14.2% without, P=0.54) [2] -- but that reassurance depends entirely on the indicator being caught, which requires the frequent monitoring visits the high-intensity protocol built in and that routine outpatient care typically does not. PIONEER-HF's own safety comparison was reassuring in a different way: worsening renal function (13.6% vs 14.7%), hyperkalemia (11.6% vs 9.3%), and symptomatic hypotension (15.0% vs 12.7%) did not differ significantly between sacubitril-valsartan and enalapril [3], suggesting the ARNI itself is not the source of added risk when started in hospital.

Rapid up-titration surfaces safety signals
frequently -- STRONG-HF, high-intensity arm [2]

Safety indicator (high-intensity arm)	Prevalence
Hyperkalemia	28%
Hypotension (SBP <95 mmHg)	9.4%
Severe renal dysfunction (eGFR <30)	5.2%
Bradycardia (HR <55 bpm)	8.5%
Any one of the above	58%

Figure 5: Prevalence of individual safety indicators in the STRONG-HF high-intensity arm [2].

The four indicators in Figure 5 are not an arbitrary checklist: they track directly onto the physiology each pillar is expected to disturb. Renin-angiotensin-system blockade and MRA use both raise serum potassium and can reduce eGFR; every one of the four pillars can lower systolic blood pressure; and a beta-blocker started alongside the others is the most plausible driver of bradycardia. A rapid strategy is, by construction, one that stresses renal function, potassium homeostasis, and blood pressure at the same time rather than one drug class at a time, which is exactly why STRONG-HF built structured monitoring visits into its high-intensity protocol rather than leaving safety review to routine outpatient scheduling [1,2].

It is also worth restating what the STRONG-HF safety analysis did and did not test: it described how often each indicator arose and whether having one predicted the 180-day

primary outcome, not whether responding to an indicator by pausing or reducing a dose changed that patient's subsequent trajectory. The trial's message for practice is therefore narrower than 'these signals are safe to ignore' -- it is closer to 'these signals were caught early enough, and acted on, that they did not translate into worse outcomes in this specific, closely monitored cohort' [1,2].

The real-world comparator: traditional titration measured in months, not weeks

The case for speed is strongest once traditional titration's real-world pace is measured directly rather than assumed. The CHAMP-HF outpatient registry found that only 18% of ACE inhibitor/ARB users, 14% of ARNI users, and 28% of beta-blocker users were at target dose, and that just 1% of eligible patients were simultaneously at target dose for all three of ACEI/ARB/ARNI, beta-blocker, and MRA [6]. A 2026 Veterans Health Administration registry of 52,850 patients with newly diagnosed HFrEF extended this picture with a specific timeline: only 11,217 (21.2%) ever reached quadruple therapy over a median 2.9-year follow-up, and among those who did, the median time to reach it was 197 days (interquartile range 49-528 days) [7]. Figure 6 plots this real-world timeline against STRONG-HF's own two-week benchmark. Table 1 summarizes the design and result of the three anchor randomized trials reviewed above, and Table 2 sets the registry-measured real-world attainment figures out together.

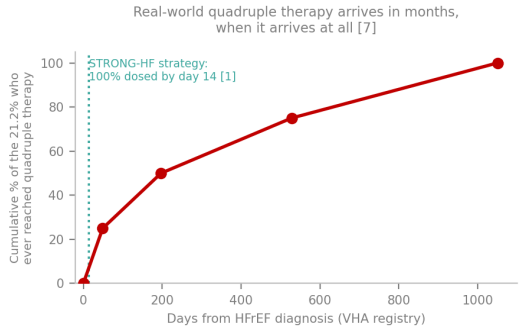

Figure 6: Real-world cumulative time to quadruple guideline-directed medical therapy, plotted from the reported interquartile range, against the STRONG-HF high-intensity timeline [1,7].

Trial	N	Setting/intervention	Primary result
STRONG-HF [1]	1,078	Multi-pillar up-titration by 2 weeks post-discharge	RR 0.66 (0.50-0.86) for readmission/death
PIONEER-HF [3]	881	In-hospital ARNI vs enalapril	NT-proBNP ratio 0.71 (0.63-0.81)
EMPULSE [4]	530	In-hospital SGLT2i vs placebo	Win ratio 1.36 (1.09-1.68)

Table 1: Design, setting, and primary-outcome result of the three anchor randomized trials of rapid or in-hospital GDMT initiation reviewed here [1,3,4].

Discussion

Taken together, the randomized evidence favors moving faster: whether all four pillars are sequenced together in the two weeks after an acute heart-failure hospitalization, or a single pillar is simply started in hospital rather than deferred, the trials reviewed here consistently moved their primary effect estimate in the direction of benefit. The real-world registries reviewed alongside them make the opposite case just as clearly: traditional sequential titration, as it is actually practiced rather than as guidelines describe it, delivers quadruple therapy to a minority of patients, over a timeline measured in months rather than weeks, with target dosing for even a single drug class remaining the exception rather than the rule.

The safety data complicate any reading of this as a simple 'faster is better' conclusion. A safety indicator arose in well over half of STRONG-HF's high-intensity patients, and while these indicators did not themselves predict a worse outcome, that finding depended on a monitoring infrastructure -- frequent structured follow-up visits with laboratory and clinical review -- that most health systems do not currently provide outside a trial. Rapid sequencing without that monitoring capacity is not the strategy STRONG-HF actually tested, and generalizing its result to a setting without comparable follow-up is an extrapolation the trial itself cannot support.

Real-world adherence and prescribing inertia are not simply a matter of clinical caution, either: commentary accompanying this literature has pointed to cost, prior-authorization burden, and clinician hesitancy as distinct barriers to rapid initiation outside the controlled conditions of a trial, alongside a genuine and so far untested question of whether starting four new drug classes simultaneously in an outpatient setting, without hospital-level monitoring, carries the same safety profile documented here [8]. No randomized trial has yet compared truly simultaneous four-drug initiation against a rapid but staged sequence, a gap the literature reviewed here does not close.

Access barriers reported alongside this literature are concrete rather than attitudinal: annual out-of-pocket costs for an SGLT2 inhibitor have been reported in the range of $1,000 to $1,600, ARNI therapy carries a comparable burden, and prior-authorization paperwork for sacubitril-valsartan alone has been reported to consume the equivalent of half a day per week of heart-failure nursing time at one center -- a burden the older, generic pillars do not carry [8]. Physician hesitancy compounds this: one commentator surveyed in this literature estimated that roughly one-third of heart-failure specialists still prefer a slower, sequential approach even when a faster one is feasible [8]. None of these barriers are addressed by the trial evidence itself, which was gathered under conditions -- research-nurse support, protocolized visits, no

prior-authorization delay -- that a typical outpatient clinic does not replicate.

Study limitations

This is a narrative review, not a systematic review with a pre-registered protocol, and its reference list mixes full peer-reviewed trial publications with a registry analysis and a news report whose original commentary could not be independently re-verified word for word (reference 8). STRONG-HF, PIONEER-HF, and EMPULSE each tested a different combination of pillars and settings, so their effect estimates in Figure 4 are not directly comparable to one another and are presented on each trial's own metric rather than pooled. The CHAMP-HF and Veterans Health Administration registries are observational and cannot establish that faster titration alone, rather than the closer follow-up that typically accompanies it, drives better real-world outcomes. Finally, no trial identified here tested truly simultaneous initiation of all four pillars on day one against a rapid but staged two-week sequence, so this review cannot say which of those two rapid strategies is preferable, only that both outperform traditional outpatient pacing as it is actually practiced.

Conclusion

Rapid sequencing of guideline-directed medical therapy, whether as STRONG-HF's structured two-week multi-pillar strategy or as single-pillar in-hospital initiation in PIONEER-HF and EMPULSE, reduced heart-failure readmission and improved pillar-specific outcomes relative to waiting for outpatient stability. That benefit was accompanied by a real and frequent burden of safety indicators -- hyperkalemia, hypotension, and renal dysfunction chief among them -- that were managed successfully only within a monitoring structure most routine practice does not yet replicate. Traditional sequential titration, meanwhile, continues to under-deliver in the real world by a wide margin, reaching a minority of eligible patients over a timeline of months. The honest clinical conclusion is not that speed is free of risk, but that the risk of speed, properly monitored, appears smaller than the risk of the slow, poorly-monitored default that traditional titration has become in practice.

Registry	Metric	Result
CHAMP-HF [6]	ACEI/ARB users at target dose	18%
CHAMP-HF [6]	ARNI users at target dose	14%
CHAMP-HF [6]	Beta-blocker users at target dose	28%
CHAMP-HF [6]	Eligible patients at target dose, all 3 classes simultaneously	1%
VHA registry [7]	Newly diagnosed patients ever reaching quadruple therapy	21.2%
VHA registry [7]	Median time to quadruple therapy, when reached	197 days

Table 2: Real-world guideline-directed medical therapy attainment in two independent registries, against which the rapid in-hospital strategies of Table 1 should be judged [6,7].

Set against Table 1's randomized results, Table 2's registry figures are the clearest single argument in this literature for moving faster: a strategy that reaches target dosing for most patients within 90 days, as STRONG-HF's high-intensity arm did, is being compared against a real-world default that reaches quadruple therapy in only around one in five patients, over a median timeline more than ten times as long as the two weeks STRONG-HF's protocol allowed [1,7]. Whichever safety burden rapid sequencing carries, it is a burden measured in a trial with structured monitoring -- not a burden invisible to the traditional default, which simply fails to reach most patients at all.

A separate cohort analysis of 33,036 patients newly diagnosed with HFrEF puts a number on what moving faster could plausibly achieve: 82% of the cohort was eligible for all four drug classes at diagnosis, yet only 15.3% of eligible patients were actually prescribed quadruple therapy and 41.5% were prescribed triple therapy over 2021-2023 [9]. Modeling rapid in-hospital initiation of all four pillars against the dual therapy (ACE inhibitor/ARB plus beta-blocker) that eligible patients more commonly receive in practice projected a 10.4% absolute reduction in 12-month mortality, a number needed to treat of 10; against no GDMT at all, the projected absolute reduction was 24.8%, a number needed to treat of 4 [9]. Those projections are modeled rather than observed, and they share the same limitation as the registry comparisons above -- they cannot by themselves separate the effect of the drugs from the effect of the closer follow-up that rapid initiation tends to travel with -- but they make concrete what the gap between eligibility and real-world prescribing in Table 2 is actually likely to cost.

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