# Why Majority of Heart Failure with Preserved Ejection Fraction Randomized Controlled Trials Fail?

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**Keywords:** Catheter ablation, atrial fibrillation, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, iron repletion, aldosterone antagonist

**Introduction:** Today, coronary failure with preserved ejection fraction (HFpEF) remains one among the toughest Gordian knots in cardiovascular medicine with no visible effective and acceptable therapies. due to the complexity, urgency, and gravity of the matter of HFpEF, this article has been divided into two parts – Part I deals with the outline of the matter , and partially II, the authors suggest innovative methodologies to affect the matter globally. Although we tested a size that integrates HFpEF, a less known complex syndrome due to maladaptive changes in the myocyte's structural , functional, and biochemical aspects. Inflammation appears to be the underlying string which weaves together nitrosative/ oxidative stress, endothelial dysfunction, downregulation of gas (NO) bioavailability/ NO-mediated signaling, impaired myocardial bioenergetics, disturbed calcium handling, and concentric hypertrophy. Most of the HF with reduced EF (HFrEF) randomized controlled trials (RCTs) are positive, while the bulk of HFpEF RCTs are either neutral, borderline, or negative resulting in an enormous vacuum within the therapeutic space of HFpEF. While few understand the statistical complexity of RCTs, many pretend to try to to so. Endeavor has been made within the present article to form the underlying concepts loud and lucid without going into statistical complexities. Attempts are being made to tackle this issue by adopting / experimenting with novel prototypes, enrichment tests, adaptive tests, paragliding studies, basket studies and machine-learning studies culminating in what could happen also be termed as "precision medicine, precision diagnosis, and precision therapy." we've compared two recent negative HFpEF RCT's (TOPCAT trial - Treatment of Preserved Cardiac Function coronary failure with an Aldosterone antagonist, INDIE trial — Inorganic nitrite delivery to improve HFpEF exercise potential with one successful HFrEF RCT (CASTLE AF trial — Catheter ablation vs traditional standard treatment) in Patients with Left Ventricular Dysfunction and Atrial Fibrillation), one negative HFrEF RCT (IRONOUT HF trial - Oral Iron Repletion Effects on Oxygen Uptake in Heart Failure), one positive HFmEF / HFpEF randomized, parallel-group, blinded, multicenter trial (REDUCE LAP-HF TRIAL Phase 2: A Study to guage the DC Devices, Inc. IASD™ System II to scale back Elevated Left Atrial Pressure in Patients with Heart Failure), one positive HFmEF / HFpEF non-randomized, multicenter, open label, single arm study (REDUCE LAP-HF TRIAL Phase 1: A Study to guage the DC Devices, Inc. IASD™ System II to scale back Elevated Left Atrial Pressure in Patients with Heart Failure) so as to know why majority of HFpEF Clinical Trials fail.

**Trial Summary:** Hypothesis: Catheter ablation is superior to medical therapy (rate or rhythm control) with reference to death or hospitalization for HF in HF with reduced ejection fraction (HFrEF) with fibrillation (AF).

**Background:** HFrEF is usually related to AF (vicious twins) as a comorbid condition. Such patients have increased risk of stroke, hospitalization for HF, and death. The 2002 AF Rhythm Management Follow-up Investigation (AFFIRM) trial was the primary and largest study (n = 4060) for matching rate-control and rhythm-control strategies for treating nonvalvular AF. AFFIRM has shown no survival advantage between rate-control and rhythm-control strategies in patients at high risk. Most of the HF with reduced EF (HFrEF) randomized controlled trials (RCTs) are positive, while the bulk of HFpEF RCTs are either neutral, borderline, or negative resulting in an enormous vacuum within the therapeutic space of HFpEF. While few understand the statistical complexity of RCTs, many pretend to try to to so. Endeavor has been made within the present article to form the underlying concepts loud and lucid without going into statistical complexities.

**Methods:** supported the above hypothesis, the 2018 Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and AF (CASTLE-AF) investigators randomized 363 patients to catheter ablation versus medical therapy and assessed for a primary outcome of death or hospitalization for HF. Inclusion criteria were Age ≥18 years, symptomatic paroxysmal or persistent AF, AF episodes had to be documented within the past 3 months before enrollment by electrocardiography, Holter, loop recorder, or implanted device, failure of antiarrhythmic therapy or patients unwillingness to require antiarrhythmic drugs, left ventricular dysfunction with left ventricular EF (LVEF) ≤35% (measured within last 6 weeks), ny Heart Association (NYHA) class II-IV and implanted defibrillator for primary or secondary prevention. Out of 363 patients, 179 patients underwent catheter ablation and 184 patients treated with medical therapy (rate or rhythm control) for AF also as guidelines-based therapy for HF. All the patients had NYHA Class II, III, or IV HF, an LVEF of 35% or less, and an implanted defibrillator. the first endpoint was a composite of death from any cause or hospitalization for worsening HF.

**Results:** The median follow-up was 37.8 months. within the ablation group, the first composite endpoint occurrence was significantly but within the medical therapy group. within the ablation group, fewer deaths were reported from any cause. there have been also less number of hospitalizations for worsening HF.

**Conclusion:** Compared to medical therapy, catheter ablation for AF in patients with HF was related to a significantly lower rate of primary composite endpoint occurrence of death from any cause or hospitalization for worsening HF [Table 1].

**Clinical Perspective:** CASTLE-AF provides data that prove that catheter ablation is related to improved rhythm control in patients with AF and symptomatic HFrEF. It also improves cardiovascular outcomes during this population, with lower rates of death and hospitalization for HF. The inclusion of a rate control arm in CASTLE-AF may be a critical initiative toward considering catheter ablation as a first-line treatment option for AF in patients with HFrEF. More good quality randomized controlled trials (RCTs) are needed before catheter ablation are often fully established as a first-line treatment option for AF with HFrEF.

| | Catheter ablation (n=179) | Medical therapy (rate or rhythm control) (n=184) |
|---|---|---|
| Death/hospitalization for HF | 51 (28.5) | 82 (44.6) |
| HR (95% CI); P; NNT | 0.62 (0.43-0.87); 0.007; 6 | |

Table 1: Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation trial primary outcome HF=Heart failure, HR=Hazard ratio, CI=Confidence interval, NNT=Number needed to treat.

Reference: Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018;378:417-27.

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