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## Journal Reviews

# Escalating diuretic strategy beats ultrafiltration in decompensated heart failure

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**Background:** Ultrafiltration is an alternative strategy to diuretic therapy for the treatment of patients with acute decompensated heart failure. Little is known about the efficacy and safety of ultrafiltration in patients with acute decompensated heart failure complicated by persistent congestion and worsened renal function.

**Methods:** We randomly assigned a total of 188 patients with acute decompensated heart failure, worsened renal function, and persistent congestion to a strategy of stepped pharmacologic therapy (94 patients) or ultrafiltration (94 patients). The primary endpoint was the bivariate change from baseline in the serum creatinine level and body weight, as assessed 96 h after random assignment. Patients were followed for 60 days.

**Results:** Ultrafiltration was inferior to pharmacologic therapy with respect to the bivariate end point of the change in the serum creatinine level and body weight 96 h after enrollment ( $p = 0.003$ ), owing primarily to an increase in the creatinine level in the ultrafiltration group. At 96 h, the mean change in the creatinine level was  $-0.04 \pm 0.53$  mg per deciliter ( $-3.5 \pm 46.9$   $\mu\text{mol}$  per liter) in the pharmacologic-therapy group, as compared with  $+0.23 \pm 0.70$  mg per deciliter ( $20.3 \pm 61.9$   $\mu\text{mol}$  per liter) in the ultrafiltration group ( $p = 0.003$ ). There was no significant difference in weight loss 96 h after enrollment between patients in the pharmacologic-therapy group and those in the ultrafiltration group (a loss of  $5.5 \pm 5.1$  kg [ $12.1 \pm 11.3$  lb] and  $5.7 \pm 3.9$  kg [ $12.6 \pm 8.5$  lb], respectively;  $p = 0.58$ ). A higher percentage of patients in the ultrafiltration group than in the pharmacologic-therapy group had a serious adverse event (72% vs. 57%,  $p = 0.03$ ).

**Conclusions:** In a randomized trial involving patients hospitalized for acute decompensated heart failure, worsened renal function, and persistent congestion, the use of a stepped pharmacologic-therapy algorithm was superior to a strategy

of ultrafiltration for the preservation of renal function at 96 h, with a similar amount of weight loss with the two approaches. Ultrafiltration was associated with a higher rate of adverse events.

## 1. Perspective

Improving the quality of life is an important goal in care of patients of advanced heart failure (HF) and is probably as important as achieving mortality benefits. Recently published CARRESS–HF<sup>1</sup> trial addressed one such strategy. In this study, ultrafiltration as an initial therapy was compared with I.V. diuretics to achieve decongestion in patients admitted with decompensated HF. Traditionally, escalating doses of diuretics have been used to achieve desired results. However, newer techniques like continuous veno-venous hemo-filtration have been considered as a better initial therapy for achieving best fluid volume status, hypothesizing that slow and controlled loss minimizes hemodynamic variations and neurohormonal activation. Earlier published UNLOAD<sup>2</sup> study in the same subset of patients showed that dialysis produced greater weight and fluid loss than diuretics and decreased 90-day resource utilization for HF. The CARRESS–HF study had a meticulously designed stepped up pharmacological care arm to tackle the criticism of underdosing of diuretics in the UNLOAD study.

The pharmacologic regimen consisted of bolus (half of his daily outpatient oral loop diuretic dose) and continuous I.V. infusion of loop diuretic with provisional addition of thiazide (metolazone). Assessment and escalation of diuretics was done every 2 days, with addition of inotropes or vasodilators depending on whether SBP was less or greater than 120 mm Hg, respectively.

The primary endpoint was net change in serum creatinine and weight at 96 h. Results showed that similar weight loss occurred in both groups (average about 5 kg) but statistically significant increase in creatinine in ultrafiltration group. There was no difference between the two groups in terms of death or hospitalization for heart failure, but increased serious adverse events in the ultrafiltration group (72% vs 57%), mainly due to renal failure, GI hemorrhage, and sepsis.

We believe that although, study is limited by non-blinded design which may have introduced bias and also does not provide a clear answer about safest and most effective rates of

fluid removal, it establishes the fact that optimal diuretic dosing as advocated by the authors, is still a better initial approach in diuretic responsive patients of decompensated heart failure with persistent fluid overload.

The result of this trial should not undermine the utility of ultrafiltration which still remains important treatment strategy for diuretic unresponsive patients, rather sub serve for conducting future studies with aim of finding adequate ultrafiltration rates that may produce better results.

## REFERENCES

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Vivek Y. Reddy, Shephal K. Doshi, Horst Sievert, Maurice Buchbinder, Petr Neuzil, Kenneth Huber, Jonathan L. Halperin, David Holmes, on behalf of the PROTECT AF Investigator, Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation 2.3-year follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection In Patients With Atrial Fibrillation) trial. *Circulation* 2013;127:720–729.

**Background:** The multicenter PROTECT AF study (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) was conducted to determine whether percutaneous left atrial appendage closure with a filter device (Watchman) was noninferior to warfarin for stroke prevention in atrial fibrillation.

**Methods and results:** Patients ( $n = 707$ ) with nonvalvular atrial fibrillation and at least 1 risk factor (age  $>75$  years, hypertension, heart failure, diabetes, or prior stroke/transient ischemic attack) were randomized to either the Watchman device ( $n = 463$ ) or continued warfarin ( $n = 244$ ) in a 2:1 ratio. After device implantation, warfarin was continued for  $\approx 45$  days, followed by clopidogrel for 4.5 months and lifelong aspirin. Study discontinuation rates were 15.3% (71/463) and 22.5% (55/244) for the Watchman and warfarin groups, respectively. The time in therapeutic range for the warfarin group was 66%. The composite primary efficacy endpoint included stroke, systemic embolism, and cardiovascular death, and the primary analysis was by intention to treat. After 1588

patient-years of follow-up (mean  $2.3 \pm 1.1$  years), the primary efficacy event rates were 3.0% and 4.3% (percent per 100 patient-years) in the Watchman and warfarin groups, respectively (relative risk, 0.71; 95% confidence interval, 0.44–1.30% per year), which met the criteria for noninferiority (probability of noninferiority  $>0.999$ ). There were more primary safety events in the Watchman group (5.5% per year; 95% confidence interval, 4.2%–7.1% per year) than in the control group (3.6% per year; 95% confidence interval, 2.2%–5.3% per year; relative risk, 1.53; 95% confidence interval, 0.95–2.70).

**Conclusions:** The “local” strategy of left atrial appendage closure is noninferior to “systemic” anticoagulation with warfarin. PROTECT AF has, for the first time, implicated the left atrial appendage in the pathogenesis of stroke in atrial fibrillation.

## 1. Perspective

Balancing the benefits incurred by preventing stroke and systemic embolism versus risks of major bleed has been the cornerstone of developing effective anticoagulation strategies in atrial fibrillation (AF). Recently approved oral anticoagulants when compared to warfarin showed reduction in incidence of stroke/embolism by 20–34%, ICH by 50–70%. However, rate of major bleed has remained same with Dabigatran and Rivaroxaban, and only Apixaban showing 30% reduction in such events.<sup>1</sup> The data from these trials highlight an important fact, that an anticoagulant will always predispose an individual to risk of bleeding and fatal hemorrhagic strokes no matter how good it is. The recently published 2.3-year follow-up of the PROTECT AF<sup>2</sup> trial which looked at the strategy of occluding the left atrial appendage (LAA), is very important as it marks the first attempt of devising ways of preventing thromboembolic events without subjecting individuals to excessive bleeding risk. In this unblinded, multicenter study, 707 patients of nonvalvular AF (CHADS2 score of  $\geq 1$ ) were randomized to either the Watchman device ( $n = 463$ ) or warfarin ( $n = 244$ ) in a 2:1 ratio. Patients in device arm received warfarin for minimum of 45 days (more as guided by TEE), dual antiplatelet for 4.5 months thereafter and followed by lifelong aspirin. Eighty seven percent of patients receiving the device were able to discontinue warfarin at day 45 with number increasing to 95% by year-end.

The efficacy as assessed by composite of any stroke, cardiovascular or unexplained death, or systemic embolism was similar in both groups (3%/year in the device vs. 4.3%/year in the controls) proving noninferiority.

Excessive bleeding and procedure related events occurred more frequently in the device (5.5%) than in the control arm (3.6%). While the incidence decreased over time in device group it accrued in controls (post-procedure: 2.5%/year versus 4.3%/year). Similarly, on long term follow-up lower rate of major bleeding in device group (RR 0.35) were observed. The results indicate that after successful deployment, the device proved to be superior to well controlled systemic anticoagulation.

We believe that one of the biggest limitations of this study is the relatively small number of patients enrolled as compared to other studies involving new oral anticoagulants. Drawing indirect conclusions seems inappropriate even