Reduction in Mitral Regurgitation During Therapy Guided by Measured Filling Pressures in the ESCAPE Trial

Maryse Palardy, MD; Lynne W. Stevenson, MD; Gudaye Tasissa, PhD; Michele A. Hamilton, MD; Robert C. Bourge, MD; Thomas G. DiSalvo, MD; Uri Elkayam, MD; James A. Hill, MD; Sharon C. Reimold, MD; for the ESCAPE Investigators

Background—Dynamic mitral regurgitation (MR) contributes to decompensation in chronic dilated heart failure. Reduction of MR was the primary physiological end point in the ESCAPE trial, which compared acute therapy guided by jugular venous pressure, edema, and weight (CLIN) with therapy guided additionally by pulmonary artery catheters (PAC) toward pulmonary wedge pressure ≤15 and right atrial pressure ≥8 mm Hg.

Methods and Results—Patients were randomized to PAC or CLIN during hospitalization with chronic heart failure and mean left ventricular ejection fraction ≤20%, and at least 1 symptom and 1 sign of congestion. MR and mitral flow patterns, measured blinded to therapy and timepoint, were available at baseline and discharge in 133 patients, and at 3 months in 104 patients. Changes in MR and related transmitral flow patterns were compared between PAC and CLIN patients. Jugular venous pressure, edema, and weights decreased similarly during therapy in the hospital for both groups. In PAC but not in CLIN patients, MR jet area, MR/left atrial area ratio, and E velocity were each significantly reduced and deceleration time increased by discharge. By 3 months, patients had clinical evidence of increased jugular venous pressure, edema, and weight since discharge, reaching significance in the PAC arm, and the change in MR was no longer different between the 2 groups, although the change in E velocity remained greater in PAC patients.

Conclusions—During hospitalization, therapy guided by PAC to reduce left-sided pressures improved MR and related filling patterns more than therapy guided clinically by evidence of systemic venous congestion. This early reduction did not translate into improved outcomes out of the hospital, where volume status reverted toward baseline. (Circ Heart Fail. 2009;2:181-188.)

Key Words: cardiomyopathy • mitral valve • regurgitation • heart failure • hemodynamics

Mitral regurgitation (MR) is a central feature of progression of dilated left ventricular failure, in which it plays a role as both cause and effect.1,2 From the spectrum of asymptomatic left ventricular dysfunction through evaluation for transplantation, the severity of MR carries strong prognostic weight.3–6

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Acute therapy tailored to reduce measured left-ventricular filling pressures in decompensated heart failure has been shown to cause marked reduction in MR.7 In the absence of inotropic therapy, the increase in forward stroke volume results primarily from redistribution of regurgitant volume.8,9 Echocardiographic measurements focusing precisely on the mechanics of MR in dilated heart failure have demonstrated that the major change during therapy with vasodilators and diuretics is attributable to reduction of effective regurgitant orifice area.9 This reduction in regurgitant orifice area is related in part to decrease in mitral annular distension with improved leaflet coaptation.9 Although therapy in these studies was targeted toward pulmonary capillary wedge (PCW) pressure ≤15 mm Hg, it was not known whether similar reduction of MR would result from therapy guided by clinical examination, which is dominated by evidence of right-sided pressures as approximated from jugular vein inspection.10

The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial was designed to compare the impact of therapy guided by clinical assessment of filling pressures with therapy guided additionally by pulmonary artery catheterization (PAC) for patients hospitalized with an exacerbation of...
advanced heart failure. The primary clinical outcome variable of days alive out of hospital during the 6 months was neutral. The primary physiological variable was prespecified to be MR, selected for its importance in prognosis, its sensitivity to filling pressures, and the ability to be measured blindly without potential influence from patient or physician knowledge of treatment arm. The hypothesis was that MR would be more effectively reduced when therapy to relieve congestion was guided by filling pressure goals of PCW pressure ≤15 and right atrial pressure (RAP) ≤8 mm Hg in addition to clinical assessment of volume status, which reflects predominantly right-sided filling pressures.

Methods

Trial Design
ESCAPE trial randomized 433 patients at 26 sites between January 18, 2000 and November 17, 2003. Inclusion criteria included hospitalization with chronic advanced heart failure despite recommended therapies. Patients were randomly assigned to therapy guided by PAC (PAC group) or by clinical assessment (CLIN group), as previously described.1 The goals in both groups were reduction of filling pressures, assessed by jugular venous pressure (JVP), edema, and symptoms in the CLIN group and additionally with goals of PCW pressure ≤15 and RAP ≤8 mm Hg in the PAC group. After discharge, the protocol specified that patients return for clinical assessment and adjustment of medications at 2 weeks, 1 month, 2 months, and 3 months after hospital discharge.

Clinical Data
Changes in weight, estimated JVP, and edema, as assessed on the 0 to 4 scale, were determined between baseline and discharge. In those patients randomized to PAC, differences between RAP and PCW pressure at the time of insertion and removal were also described.

Echocardiographic Examinations
All sites provided the echocardiographic core laboratory with a validation echocardiogram according to defined standardized views for 2-dimensional and Doppler measurements, as prespecified for review before initiation. The protocol specified that echocardiograms be obtained in patients at the time of randomization (baseline), hospital discharge (DC), and at 3 months. However, to maximize enrollment, it was emphasized that neither randomization nor discharge should be delayed due to difficulties in scheduling echocardiograms.

Echocardiograms were analyzed at the core laboratory at the University of Texas Southwestern in Dallas. All studies were analyzed blinded to randomization and study order. The studies were analyzed offline by a single sonographer using a calibrated ultrasound measuring system. A portion of the studies was remeasured to evaluate intraobserver variability. Two-dimensional and Doppler echocardiographic parameters were measured in accordance with American Society of Echocardiography criteria. Available measurements included mitral regurgitant color jet area from the apical 4 chamber view, left ventricular end-diastolic dimension, left ventricular ejection fraction using apical single plane disc method, left atrial area (LAA) measured from the apical 4 chamber view. The protocol included calculation of mitral regurgitant volume and effective regurgitant orifice from color proximal isovelocity surface area on the apical projection, but these measurements could not be included in the analysis because too few recorded tapes provided adequate data on the majority of patients. The mitral regurgitant color jet area was measured and the ratio of this area to LAA determined. These were considered to be adequate for measurement if the origin of the jet was seen at the level of the mitral valve and the borders of the jet were clearly delineated. The LAA was measured if the left atrial borders were clearly identified.

Statistics
Continuous variables were summarized by mean and standard deviation (SD) statistics. Paired t tests were used to assess significance of changes between baseline and discharge and baseline and 3 months. Standard t tests were used to compare changes in the PAC group with changes in the CLIN group. A P value <0.05 was statistically significant. The question of whether the 2 strategies led acutely to different reduction of MR was considered to be separate from the question of whether there were differences sustained at 3 months, for which the outpatient therapies and compliance would be important factors. Thus the strategies were compared separately at the 2 time points. No correction was made for multiple comparisons.

Results
Study Population
Both baseline and discharge echocardiograms were available for analysis in 198 patients (Figure 1). Measurements of MR were adequate for comparison between baseline and discharge for 133 patients, in whom demographics and hemodynamics confirmed severe heart failure with reduced ejection fraction (average 20%), low systolic blood pressure compared with most hospitalized heart failure populations (average 104 mm Hg), and markedly elevated JVPs (Table 1). Baseline profiles were not different between the 133 patients with paired MR measurements, the 106 patients who had an echocardiogram at baseline but not at discharge, and the 65 for whom both echocardiograms were obtained but change in MR could not be assessed from the views provided (Table 1). Estimated JVP elevation and edema were comparable in the 2 randomized groups CLIN and PAC, and the resting PCW
pressure was 25±9 mm Hg and RAP 13±9 mm Hg in the PAC group. Left ventricular (LV) dilation, left ventricular ejection fraction, MR, and flow patterns were comparable in the 2 groups at baseline (Table 2).

Changes From Baseline to Discharge

Patient weight decreased significantly in both groups during therapy in hospital, by 3.2±3.8 kg in the CLIN group and 4.1±5.7 kg in the PAC group, without significant difference between groups (P=0.24). Estimated JVP and edema decreased comparably in both groups (Figure 2). For the PAC group, measured PCW decreased by average 8±9 mm Hg and RAP by 5±12 mm Hg.

The MR color jet area decreased by 2 cm² in the PAC group (P<0.004), but did not change in the CLIN group but not in the CLIN group (between group difference for change P=0.02). There was a significant decrease in E wave velocity in the PAC group but not in the CLIN group (between group P=0.01). Decel time increased significantly only in PAC patients (P=0.05), without significant between-group difference. Changes in pulmonary vein inflow patterns could be measured at baseline and discharge in only 61 patients, but there was a trend for increasing systolic/diastolic ratio only in the PAC group (difference between PAC and CLIN P=0.14). Left ventricular dimensions and ejection fraction did not change significantly from randomization to the time of discharge.

Changes From Baseline to 3 Months

Increase in Evidence of Fluid Retention After Discharge

By 3 months after discharge, JVP and weights had increased back toward baseline in both groups, changes which were significant in the PAC group. Peripheral edema increased significantly in both groups (Figure 2).

| Table 1. Clinical Characteristics of Patients With and Without Echocardiograms and MR Measurements |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Baseline and Discharge MR Measurement (SD)       | Baseline and Discharge MR Measurement (SD)       | Baseline and Discharge MR Measurement (SD)       | Baseline and Discharge MR Measurement (SD)       |
| N                                               | 66                                              | 67                                              | 133                                             |
| Age                                             | 58 (15)                                         | 56 (13)                                         | 57 (14)                                         |
| Gender                                          | 74%                                             | 77%                                             | 76%                                             |
| Minority                                        | 27%                                             | 37%                                             | 32%                                             |
| CAD                                             | 44%                                             | 51%                                             | 48%                                             |
| Baseline LVEF                                   | 20 (6)                                          | 20 (5)                                          | 20 (7)                                          |
| SBP, mm Hg                                      | 104 (12)                                        | 104 (15)                                        | 104 (14)                                        |
| Est JVP, mm Hg                                  | 13 (4)                                          | 13 (4)                                          | 13 (4)                                          |
| Creatinine, mg dL                               | 1.5 (0.6)                                       | 1.6 (0.6)                                       | 1.5 (0.6)                                       |
| RAP,* mm Hg                                     | 14 (11)                                         | 14 (11)                                         | 12 (6)                                          |
| PCW,* mm Hg                                     | 25 (10)                                         | 25 (10)                                         | 24 (10)                                         |

LVEF indicates left ventricular ejection fraction; CAD, coronary artery disease; SBP, systolic blood pressure; Est JVP, clinician-estimated jugular venous pressure; RAP, right atrial pressure.

*Obtained only in patients randomized to PAC-guided therapy.

Table 2. Mitral Regurgitation and Flow Patterns: Baseline and Changes During Hospitalization

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|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| CLIN                                            | PAC-Guided Therapy                              | P Value* Within Group                            | P Value* Between Groups                           |
| MR area, cm² (n=133)                            | MR area, cm² (n=132)                             | MR area, cm² (n=134)                             | MR area, cm² (n=136)                             |
| Baseline                                        | Change                                          | Baseline                                        | Change                                          |
| 10.3±6.7                                        | 0.3±4.2                                         | 9.3±6.7                                        | −2.0±5.4                                        |
| 0.3±0.2                                         | 0.0±0.1                                         | 0.3±0.2                                        | −0.1±0.2                                        |
| 97±29                                           | 7±41                                            | 100±30                                         | −8±25                                           |
| 147±63                                          | 7±54                                            | 135±37                                         | 19±67                                           |
| 0.5±1.1                                         | −0.25±0.5                                       | 0.5±0.4                                         | 0.24±1.0                                        |
| 3.3±0.7                                         | 0.02±0.28                                       | 3.4±0.6                                        | −0.02±0.28                                      |
| 20±9                                            | −0.4±8.0                                        | 20±10                                          | −0.2±9.7                                        |

Decel indicates deceleration; LVEDD, left ventricular end-diastolic dimension; LVEDI, left ventricular end-diastolic dimension index; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; Sys/Dias, systole/diastole.

*P values listed if <0.20.
Of the 198 patients with echoes at baseline and discharge, 124 had echoes also at 3 months. An additional 43 patients had paired echoes at baseline and 3 months but not at discharge (Figure 1). After 3 months, there was no longer a difference seen between the PAC and CLIN groups for either MR area or MR/LAA area (Table 3). MR/LAA area was reduced compared with baseline in both groups, and MR area was reduced compared with baseline in the CLIN group. Mitral flow patterns continued to show trends for improved filling for patients after initial tailored therapy with PAC. The reduction in E velocity in PAC patients was less than at discharge, but remained significantly reduced compared with the CLIN patients at 3 months. At 3 months, Decel time remained longer than at baseline for PAC (P<0.02), but not for CLIN. LV end-diastolic dimensions remained unchanged for all groups. In the absence of detectable change in LV dimension, the 5 point increase in LV ejection fraction in the PAC group at 3 months compared with baseline (P<0.01) may be a chance finding and is of unclear clinical significance.

Discussion

The primary physiological end point of the ESCAPE trial was MR, which was more effectively reduced when therapy to relieve congestion was guided by pulmonary artery catheter goals than by clinical assessment alone during hospitalization. The reduction of MR was accompanied by parallel improvement seen in the inflow E velocity and in the Decel time, which both reflect left ventricular filling and may be surrogates for left ventricular filling pressures. The differences seen between the strategies at hospital discharge were largely lost after 3 months of outpatient management, during which therapy was guided in both groups only by clinical assessment, which revealed increased fluid retention after discharge.

Assessment of Filling Pressures

Serial assessment of filling pressures is a level I recommendation accompanying adjustment of diuretics to treat fluid retention in the outpatient setting. Inpatient hospitalization is associated with excess volume in 83% patients admitted in the ADHERE registry, and it is recommended that optimal volume status be restored before discharge, based on clinical assessment. The most helpful clinical sign used to detect
elevated left-sided filling pressures in chronic heart failure remains the elevated JVP, as confirmed recently by the analysis of physician estimates of hemodynamics for the ESCAPE trial.10 However, the JVP actually reflects right-sided filling pressures. For most patients with chronic heart failure, right and left-sided filling pressures track together,14 but it is not known whether the degree of elevation is sufficiently mirrored to optimize the left side consistently during serial assessment of the right side. Furthermore, clinical examination of jugular veins can be done well by experts, but is still less reliable than direct measurement.10,15 Reduction of JVP during therapy in the hospital was similar in both the CLIN and PAC arms, as was reduction of peripheral edema. The overall fluid loss, as estimated by acute change in weight, was similar in the 2 groups, although numerically greater in the PAC arm. Nonetheless, there was slightly but significantly less renal dysfunction in the PAC arm than the CLIN arm.16 It is plausible but cannot be proven from existing data that monitoring of the left-sided filling pressures guided adjustment of the “optimal” amount of diuresis and vasodilation for individual patients, achieving more normal left-sided filling pressures than when they were assessed indirectly from the JVPs and other clinical signs reflecting the right side of the heart.

Reduction of MR
MR is at least moderate in almost all patients at the time of hospital admission with decompensated heart failure and dilated left ventricular failure.17–19 Therapy tailored to reduce measured filling pressures to near-normal levels has been shown to decrease valvular regurgitation.17,20 This decrease in mitral regurgitant volume during unloading therapy was recognized initially with nitroprusside and has been shown to be the major component of increased stroke volume during vasodilator and diuretic therapy.8,17,21 This redistribution of flow can be attributed to reduction of effective regurgitant orifice area.9 Most of the studies quantitating reduction of MR were performed during monitoring with a pulmonary artery catheter to guide reduction of filling pressures, but lessons learned from these studies have been translated into therapy without invasive monitoring. Thus it was not known whether similar results could be achieved during contemporary therapy guided by refined clinical assessment alone. The clinical importance of MR, its relationship to elevated filling pressures, and the ability to isolate its measurement from knowledge of treatment strategy were key factors in the decision to define MR as the primary physiological variable in the ESCAPE trial, comparing an invasive hemodynamic strategy with clinical assessment.

The reduction of MR in the PAC arm between baseline and discharge seems to be a robust finding. The improvements between baseline and discharge for PAC patients, and the difference between CLIN and PAC strategies are evident whether analyzing the absolute changes in MR measurements, or the relative changes expressed as a percentage of baseline values (Table 2 and Figure 3). The clinical significance of this change in MR is emphasized by concordant improvements in other measurements. The E velocity declined only in the PAC arm, consistent with a meaningful decrease in left ventricular filling pressure, reflecting MR reduction.22,23 E velocity has been correlated with MR regurgitant fraction severity.22,23 Decel time, which increased significantly only in the PAC patients, has correlated inversely with PCW pressures.24 Left ventricular end-diastolic dimension is generally insensitive to acute changes, particularly without inotropic therapy, and did not change in this study. Pulmonary vein profiles could be measured at baseline and discharge in only 61 patients, with a trend toward improvement only in the PAC group.

Outcomes After Hospital Discharge
Although MR at the time of discharge was significantly reduced in the PAC arm compared with the CLIN arm at discharge, 6-month outcomes were no different between the groups.11 The failure of acute reduction of MR to improve outcomes in this trial could indicate that (1) MR is an epi-phenomenon that is not itself important to outcomes, (2) any benefit of reduced MR can be outweighed by deleterious effects of the therapies used, or (3) reduced MR is associated with improved outcomes only if it can be sustained after discharge.

The presence and severity of MR have consistently been associated with worse prognosis throughout the spectrum of heart failure, from asymptomatic patients early postinfarction through candidates for cardiac transplantation.3,4,6,25 Changes in prognostic factors do not necessarily translate into changes in prognosis, although the contribution of MR to elevate left-sided filling pressures and to reduce effective forward
stroke volume make it attractive as a therapeutic target. Surgery to repair MR in heart failure has not led to better outcomes,26 in part because MR often recurs or is replaced by mitral stenosis.27 For the related measurement of Decel time, better outcome has been associated with restrictive pattern reversibility and prolongation of the Decel time in patients during heart failure therapy,28–31 shown by Xie et al32 in 1994 and recently by Grayburn et al33 in the Beta-blocker Evaluation of Survival Trial.

With regard to the therapies used in hospital to decrease volume, the overall use of diuretics was similar in the 2 arms, with a trend toward slightly lower diuretic use at discharge in the PAC arm.16 Inotropic therapy was associated with a worse outcome in the ESCAPE trial, and there was slightly higher use of inotropic therapy in the PAC arm than the CLIN arm, but there was still no difference in outcomes when patients receiving inotropic therapy were excluded from analysis.11

With regard to maintenance of early improvement in MR, the changes observed in the hospital were less evident at 3 months in the PAC group, although improvements in the E velocity and Decel time that occurred in the PAC group were still significant at 3 months. Once ventricular remodeling is advanced, perhaps a large acute reduction in MR cannot easily be maintained. On the other hand, there was a significant decrease in MR after discharge in the CLIN group during heart failure management such that the CLIN and PAC groups converged by 3 months of outpatient heart failure management.

It is known from similar populations that most of the interventions during the 3 months after hospital discharge involve telephone-directed adjustments in diuretic regimens, most commonly based on changes in weight at home.34 Weight changes at home are less reliable than previously thought for changes in ventricular filling pressures.35 The ESCAPE protocol specified that patients return for clinical assessment and adjustment of medications at 2 weeks, 1 month, 2 months, and 3 months after hospital discharge. The physicians assessing fluid status during these visits were the same as those whose assessments correlated well with measured right-sided pressures at the time of randomization.10 Despite these frequent opportunities for adjustment of medications, this study reveals that JVPs and weights increased between discharge and 3 months, changes which were significant in the PAC patients. This may also relate to the decrement reported between 1 month and 3 months in the symptomatic improvement seen in the PAC patients (as reflected in Minnesota Living with Heart Failure scores).11 It is not clear whether these changes could have been prevented by even greater vigilance, or whether physiological factors in advanced heart failure limit prolonged maintenance of lower volume status achieved during hospitalization.

There was a late increase in left ventricular ejection fraction in both CLIN and PAC, with an improvement of 5 percentage points in the PAC arm that reached significance. Multiple mechanisms could be invoked to explain such an improvement, including lower wall stress and reduced myocardial oxygen demand, better coronary perfusion and coronary venous drainage. However, the absence of demonstrable changes in ventricular dimensions may render this more likely to be a chance finding.

**Limitations**

Multiple protocol issues complicate the interpretation of these results. The substantial amount of missing data confounds analysis, but comparison of groups with and without echoes and with and without measurable MR does not suggest any systematic bias of this missing data. The echoes that were obtained did not have consistently adequate views for measurement. Thus, the requirement that each site provide a validation echocardiographic tape with all of the key views did not ensure that subsequent tapes provided similar image quality.

At best, echocardiographic evaluation at multiple sites remains technically challenging in patients with low ejection fraction, and changes are affected by multiple factors as the pressure gradient between LV and left atria can vary widely, influenced by systemic blood pressure, contractile reserve and diastolic pressure, not solely on the size of the abnormal regurgitant orifice. The ability to index the color jet of MR to LAA does provide some improvement in correlation with angiographic evaluation of MR.36 The measurement of E velocity and Decel time provided more quantitative evaluation and clearly supported the significance of the changes observed in MR.

It is unfortunate that the data obtained did not allow more quantitative estimation in a larger number of patients. However, the data obtained are consistent with more rigorous prospective data that was obtained previously from several nonrandomized experiences in single center investigations, demonstrating significant reduction of MR for therapy guided by a strategy using invasive monitoring. For this larger study in 26 centers, the use of a core laboratory to perform all measurements blinded to therapy and timepoint increases the confidence in the results obtained.

With all the limitations, this is a unique dataset in which to assess the impact of current heart failure therapy guided with and without a PAC, as well as the limited influence of acute hemodynamic improvement on outcomes after hospital discharge.

**Conclusions**

This study of strategies for decompensated heart failure demonstrates that MR was more effectively reduced when measured right and left-sided filling pressures were used to guide therapy in hospital than when estimated JVP and edema were reduced to a similar level during clinical assessment alone. Current management of volume status after discharge may not be adequate to maintain improvements that can be achieved in hospital. The limitations of outpatient therapy may reflect disparity between visible right and occult left-sided filling pressure elevations, difficulty in assessing left-sided filling pressures, and more relaxed goals for volume status in patients who seem stable in the nonacute setting. It is not known whether other strategies would better sustain the acute reduction in MR or whether chronic reduction in MR would translate into improved clinical outcomes with advanced heart failure.
Disclosures
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References
CLINICAL PERSPECTIVE

Therapy during heart failure hospitalization focuses on relief of elevated filling pressures, which can currently be guided by clinical assessment with or without invasive monitoring. In the randomized ESCAPE study in decompensated chronic dilated heart failure, comparison of the clinical and invasive strategies showed that mitral regurgitation was effectively reduced in hospital only with the invasive strategy, targeting right atrial pressure ≤8 mm Hg and pulmonary capillary wedge pressure ≤15 mm Hg, not with the clinical assessment strategy, which targeted and achieved similar reduction of elevated jugular venous pressure, edema, and orthopnea. It has been shown earlier that renal function was also slightly better with the invasive strategy, as was symptomatic improvement in the first month after discharge. However, these differences between strategies were lost by 3 months, during which there was evidence of recurrent increases in filling pressures. As there was no difference in 6 month rehospitalization or survival between the clinical and invasive strategies, there is currently no rationale for routine use of invasive monitoring to adjust therapy or to reduce mitral regurgitation. The key components of outpatient therapy for advanced heart failure remain optimal tolerated doses of neurohormonal antagonists and diuretic therapy to maintain fluid balance. It is not clear whether future strategies to decrease recurrent heart failure events should select different targets during hospitalization, or develop better strategies to maintain acute reductions in filling pressures and mitral regurgitation during chronic heart failure management.
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