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Persisting Symptomatic Severe Secondary Mitral Regurgitation in Heart Failure Patients

P. Wheen[1,2,3], D. O'Callaghan[2], P. Murray[3], C. Minelli[4], L. Byrne[5], R. Armstrong[2], V. Maher[3], P. Shiels[4], S. Fleming[5], C. Daly[2]

1. *School of Medicine, Trinity College, Dublin, Ireland.*
2. *St. James Hospital, James Street, Dublin 8, Ireland.*
3. *Tallaght University Hospital, Dublin 24, Ireland.*
4. *Midlands Regional Hospital, Tullamore, Co. Offaly, Ireland.*
5. *Midlands Regional Hospital, Portlaoise, Co. Laois, Ireland.*

Abstract

Aims

We aimed to assess the rate of persisting severe symptomatic secondary mitral regurgitation (MR) in a newly diagnosed heart failure (HF) population following optimisation of guideline directed medical therapy (GDMT), cardiac resynchronisation therapy (CRT) and revascularisation.

Methods

We assessed all new patients referred to our hospital group's HF clinics. We retrospectively reviewed these patients at HF clinic enrolment, HF programme completion, as well as most recent follow up.

Results

Of the 242 new patients referred to our HF clinics, there were 10 patients (4.1%) who had either persisting symptomatic severe secondary MR at HF programme completion, or had undergone mitral valve surgery. There were no percutaneous mitral valve repairs at the time of these patients' referrals. The rates of ACE/ARB/ARNI, BB and MRA use were 87.8%, 94.1%, and 49.8% in those with mid ranged, or reduced ejection fraction. The rates of ICD and CRT therapy were 15.1% and 4.4% at follow up. Patients with severe MR had higher time adjusted rates of death or hospitalization for heart failure.

Conclusion

In a well-treated newly diagnosed HF population, repeat assessment at HF programme completion suggests 4.1% of patients have a persisting indication for percutaneous mitral valve repair based on persisting severe symptomatic secondary MR.

Introduction

Secondary, or functional, mitral regurgitation (MR) is associated with cardiomyopathy and heart failure (HF). Various pathophysiological processes which do not predominantly affect the mitral valve leaflets themselves lead to failure of coaptation, and subsequent secondary MR[1]. HF with severe secondary MR is associated with adverse outcomes relative to HF without severe secondary MR, with an annualised mortality of between 22.4% and 23.2%,[2, 3], and up to 45% at 4 years on optimal medical therapy.[4]

The severity of secondary MR is improved by treatment of the underlying cardiomyopathy with angiotensin converting enzyme inhibitors (ACE-I)[5], beta blockers[6] and, more recently, with sacubitril/valsartan[7]. Cardiac Resynchronisation Therapy (CRT) is also associated with a significant reduction in secondary MR in selected patients with left bundle branch block[8]. In addition to treatment with optimal medical therapy (OMT), MR severity is also dependent upon volume status. Until 2018, there had been no studies that showed that specifically addressing the mitral regurgitation, rather than the underlying cardiomyopathy, improves mortality. Previous trials of surgical repair of secondary MR (outside of concomitant CABG surgery) have shown some symptom improvement without survival benefit.[9]

More recently, percutaneous mitral valve repair became an option for symptomatic severe secondary mitral regurgitation refractory to medical therapy, most commonly with a MitraClip system (Abbott). Evidence of a mortality benefit was shown in the COAPT trial[3], but not in the Mitra-FR trial[2]. Analysis of the differences between these trials suggest that the benefit of MitraClip remains with patients who have severe secondary MR, disproportionate to the underlying cardiomyopathy, who have been fully uptitrated on medical therapy.[10]

The most appropriate time to assess suitability for percutaneous mitral valve intervention in secondary MR is on completion of a HF programme, when maximally uptitrated on OMT and euvolaemic.[11] There have been no studies assessing an annualised referred population upon completion of their HF programme, and assessing the residual incidence of severe secondary MR.

Our hospital group (Dublin Midlands Hospital Group) serves a population of approximately 820,000 people[12], and consists of 7 public hospitals, 2 of which are specialist maternity and paediatric hospitals. There are 4 heart failure clinics run across the remaining 5 hospital sites. We aimed to assess the point prevalence of moderate to severe, and severe MR ("significant MR") among newly diagnosed HF patients who were referred to our hospital group's HF programmes across our hospital group, following GDMT optimisation, and appropriate device therapy.

Methods

All new patients who were referred to one of our 4 heart failure programmes were retrospectively reviewed. Re-referrals and inappropriate referrals were excluded. Patients were only included if they attended at least one HF outpatient clinic. We assessed a 12 month period (January to December 2017) of referrals in the 2 larger hospitals (>50 new referrals annually), and a 24 month period of referrals (July 2016 - June 2018) in each of the smaller hospitals (<50 new referrals annually), and provided adjustments for an annual rate.

All patients undergo standardised assessments on enrolment to our HF programmes, in electronic format in two centres, or paper format in the other two centres. We retrospectively reviewed these patients' baseline characteristics at the date of first visit to the HF clinic. We reviewed symptoms, medications, weight and laboratory results when they were assessed to be euvolaemic and also on maximally tolerated GDMT. The date of maximally tolerated GDMT was taken as the first date after which no further GDMT dose increases were made, and they were assessed as euvolaemic - "medically optimised". We reviewed their first repeat echocardiogram after this medically optimised date and recorded the left ventricular ejection fraction (LVEF), severity of mitral regurgitation (MR), left atrial (LA) diameter, left ventricular internal dimension in diameter (LVIDd), tricuspid regurgitation (TR) severity and right ventricular systolic pressure (RVSP). We recorded the severity of MR from both the referral and follow up echocardiograms.

Estimated glomerular filtration rate was calculated using the Cockroft-Gault equation. In 2017, three of the four centres were measuring NT pro BNP, and one centre was measuring BNP.

We reviewed these patients most recent follow up, recording NYHA, medication use, mortality, and the number of hospitalisations for heart failure. We recorded new ICD implantation, new CRT implantation, and any mitral valve intervention. Mortality follow up was available on 95.0% of patients, with a full clinical follow up available in 92.6%, and full echocardiographic follow up in 76.8%.

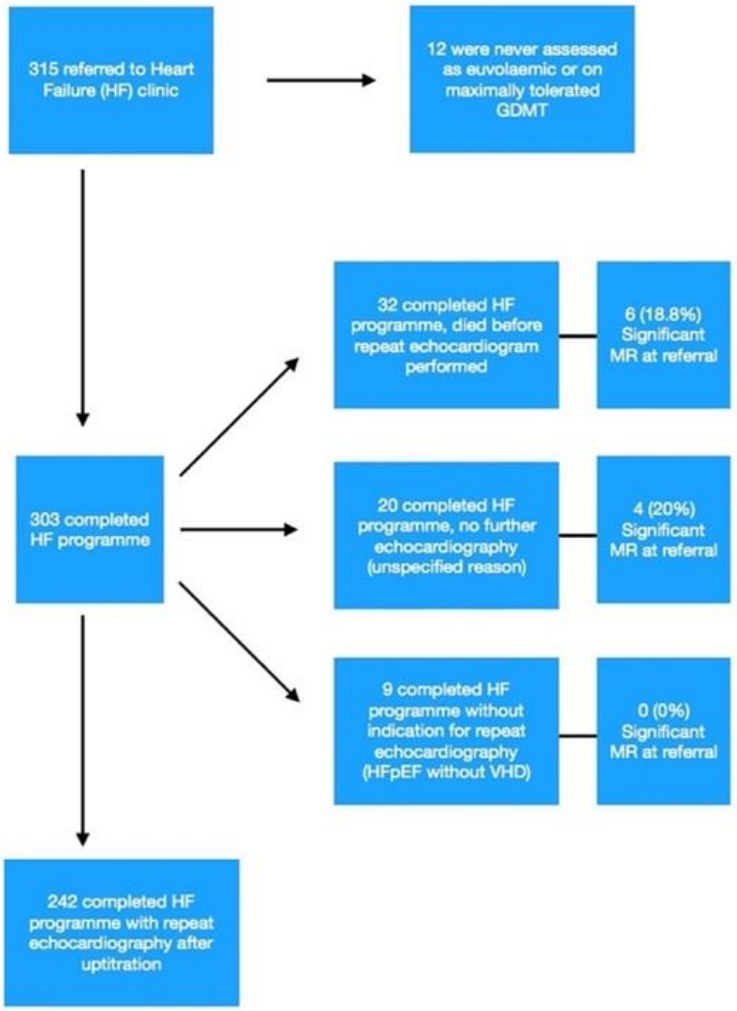
Full ethics approval was given by the Research Ethics Committees at each participating center: SJH/TUH REC, reference REC: 2019-11 List 43 (4), Midlands Research Ethics Committee; reference 040919PW.

Results

HF referrals

There were 315 new attenders to HF clinics in 2017 across our hospital group. 289 patients attended a HF clinic where they were deemed euvolaemic and on maximally tolerated GDMT, at a mean of 4.7 months (+/- 4.4) following enrolment. 242 had repeat echocardiography following this date. The details of the 73 patients who didn't undergo repeat echocardiography are summarized in Figure 1. 3 patients (1.2%) underwent surgical mitral valve repair following enrolment.

Figure 1: *Patient Flow Diagram.*



Rate of Severe MR

Of the 242 patients with full echocardiographic follow up, the rate of significant MR at HF programme completion (n=12), or surgical mitral valve repair (n=3), was 6.2%, reduced from 8.3% at HF programme enrolment. No patient underwent a percutaneous mitral valve repair. Of the 12 patients who had persistent significant MR at completion, 8 were still symptomatic, and 1 had improvement of MR following CRT insertion which was performed after HF programme completion, leading to 4.1% of patients referred to our heart failure services as potentially suitable for percutaneous mitral valve repair (Table 2), including those referred for mitral valve surgery. The rate of severe symptomatic MR (or mitral valve surgery) per HF clinic was not significantly different among the hospitals (p=0.369). The annualised number of newly referred patients suitable for mitral valve repair for secondary mitral regurgitation in our hospital group serving a general population (child and adult) of 820,000 was 9.5 patients per year (1.16 patients per 100,000).

Table 1: *Results.*

Table 1: Results	Hospital 1	Hospital 2&5	Hospital 3	Hospital 4	Total
Number of HF patients with complete follow up	107	68	42	25	242
Severe (symptomatic) MR after HF programme	9 (6)	2 (0)	1 (1)	0	12 (7)
Underwent MVR	1	2	0	0	3
MVR or persisting severe MR	10	4	1	0	15
MVR or persisting symptomatic severe MR (%)	7 (6.5%)	2 (2.9%)	1 (2.4%)	0 (0%)	10 (4.1%)

Patient Baseline Characteristics

Baseline characteristics are shown in Table 2. There are few significant differences between the two groups, partly due to the small numbers of patients (12) with significant MR at HF programme completion. There was no significant difference in NT-proBNP levels between the two groups at referral, however by the time of HF programme completion, there was a significantly higher level of NT-proBNP in patients with significant MR. Similarly, there was no significant difference in LVEF at time of referral to HF clinic, however there was a significant difference between the groups at the time of HF programme completion. LVEF improved in the group without significant MR ($p<0.0001$), but failed to improve in those patients with significant MR ($p=0.847$).

Table 2: *Baseline Characteristics.*

Table 2: Baseline Characteristics	Completion (%)	Completed HF programme (n=242)	Significant MR at completion (n=12)	Non significant MR at completion (n=230)	p value
Age, mean (SD)	100	68.7 (13.7)	72.3 (12.3)	68.5 (13.7)	0.36
Male Sex, n (%)	100	154 (63.6)	5 (41.6)	149 (64.8)	0.10
Ischaemic Aetiology of HF, n (%)	100	108 (44.6)	4 (33.3)	104 (45.2)	0.42
Hypertension, n (%)	100	128 (52.9)	7 (58.3)	121 (52.6)	0.70
Diabetes, n (%)	100	57 (23.6)	5 (41.6)	52 (22.6)	0.13
Dyslipidaemia, n (%)	100	86 (35.5)	6 (50)	80 (34.8)	0.28
LBBB, n (%)	100	56 (23.1)	2 (16.7)	54 (23.5)	0.59
Atrial fibrillation, n (%)	100	119 (49.2)	4 (33.3)	115 (50)	0.26

Table 2: Baseline Characteristics	Completion (%)	Completed HF programme (n=242)	Significant MR at completion (n=12)	Non significant MR at completion (n=230)	p value
MI, n (%)	100	95 (39.3)	4 (33.3)	91 (39.6)	0.67
CABG, n (%)	100	36 (14.9)	3 (25)	33 (14.3)	0.31
PCI, n (%)	100	78 (32.2)	2 (16.7)	76 (33.0)	0.24
Stroke/TIA, n (%)	100	24 (9.9)	2 (16.7)	22 (9.6)	0.42
NYHA 1, n (%)	100	98 (40.5)	4 (33)	94 (40.9)	
NYHA 2, n (%)	100	129 (53.3)	7 (58.3)	122 (53.0)	
NYHA 3, n (%)	100	13 (5.4)	1 (8.3)	12 (5.2)	
NYHA 4, n (%)	100	1 (0.4)	0 (0)	1 (0.4)	
Creatinine, mean (SD)	97.9	117.8 (52.0)	125.1 (56.5)	117.4 (51.9)	0.64
eGFR, mean (SD)	97.9	59.0 (23.7)	46.4 (24.2)	59.6 (23.0)	0.07
NT-pro BNP, median (IQR) at referral*	79.3*	1926 (794-4119.5)	6853 (3705-10880)	2000 (794-4119.5)	0.263
NT-pro BNP, median (IQR) at HF completion*	70.2*	780 (258-1710.5)	3454 (1563-6271)	739 (252-1568)	**<0.0001**
Potassium, mean (SD)	97.1	4.60 (0.50)	4.69 (0.72)	4.60 (0.49)	0.58
Left Ventricular Ejection Fraction (LVEF), mean (SD) at referral	97.9	33.8 (12.4)	30.1 (11.6)	34.0 (12.4)	0.396
Left Ventricular Ejection Fraction (LVEF), mean (SD) at completion	98.5	39.8 (11.9)	29.5 (13.8)	40.2 (11.6)	**0.027**
LVIDd (mm), mean (SD)**	100	49 (10)	45 (8)	49 (10)	0.27
LA diameter (mm), mean (SD)	96.7	49 (9.7)	53.3 (14.3)	49.0 (9.4)	0.21
At least moderately severe Tricuspid Regurgitation, n (%)	96.7	30 (12.3)	3 (25)	27 (11.7)	0.17

* One HF clinic reported BNP levels (as opposed to NT pro-BNP), so these values were not used for comparison. Euvolaemic NT-pro BNP levels were available in 92.2 % of HF patients in the remaining centres.
** We also reviewed indexed LVIDd, and there was no significant difference between the groups, however indexing for BSA was only available in 49% of patients.

Heart Failure Subtypes

Of the 315 patients referred, 200 patients had HFrEF, 51 patients had HFmrEF and 64 patients had HFpEF. The HF subtype was taken from the lowest recorded LVEF on any echocardiogram.

HF treatment

In those who had HFrEF/HFmrEF, the rate of HF medication use was high at HF programme completion (at a mean of 3.8 months after referral), and at longer follow up (at a mean of 16.4 months after referral). Rates of medication and device use at HF programme completion (and at follow up) were: ACE/ARB 81.0% (70.4%), ARNI 6.8% (15.1%), BB 94.1% (92.5%), MRA 49.8% (48.2%), ICD 8.3% (15.1%) and CRT 2.3% (4.4%). More sacubitril/valsartan, and less ACE-I or ARB was used at follow up. Rates of device therapy were significantly higher at long term follow up due to waiting lists for device implantations exceeding the mean duration of HF enrolment in our hospital group.

Survival from Hospitalisation or Death

There was significantly lower time-adjusted survival (freedom from death, or hospitalisation for ADHF) in patients with significant MR, as compared to those patients without significant MR (Log Rank, p=0.004) (Figure 2). Overall mortality at 1 year was 9.2%.

Figure 2: *Survival from death or hospitalisation for heart failure.*

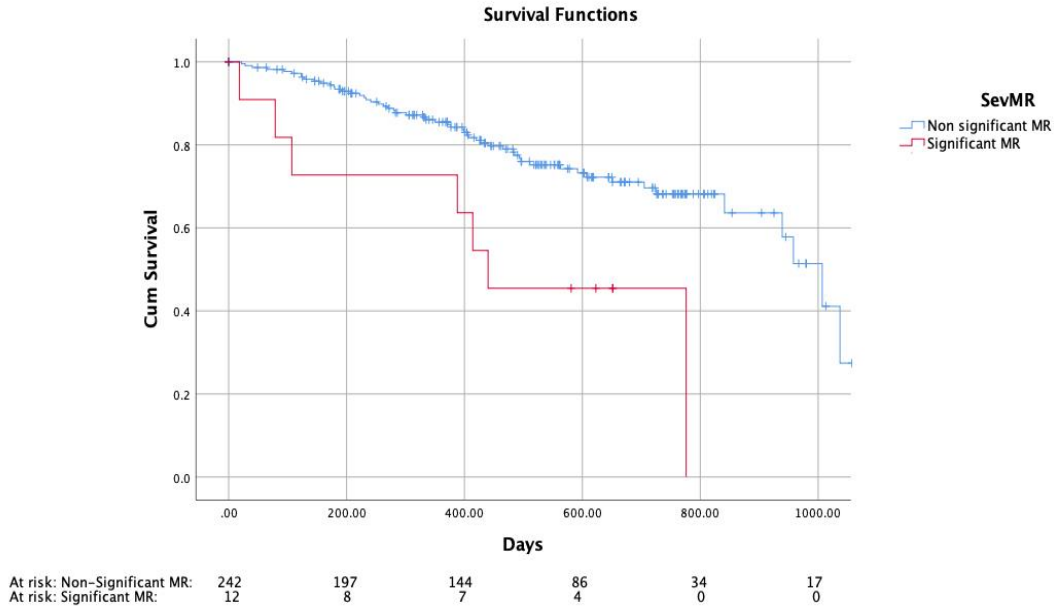


Figure 2: Kaplan Meier Survival curves (Survival from Death or hospitalisation from Heart Failure). This shows a significantly increased time-adjusted hazard of survival from death or hospitalisation for decompensated HF in HF patients with persisting significant secondary MR, in comparison to HF patients without persisting significant secondary MR (Log Rank, p=0.004). Heart Failure admissions and deaths were included from the date of HF optimisation.

Factors associated with Significant MR and Death or Hospitalisation for Heart Failure

Using Cox Univariate analysis, significant factors associated with hospitalisation or death included; Age, Ischaemic aetiology of HF, Diabetes, eGFR and NT pro-BNP.

Discussion

The main purpose of our paper is to predict the expected need for the percutaneous mitral valve repair programme in Ireland. Our data suggests that 4.1% of patients referred to a HF programme will have persistent symptomatic severe secondary MR by HF programme completion. There was a trend of increased rates of severe MR in the larger HF clinics, likely representing referral bias of sicker patients to larger academic teaching hospitals.

The general population served by these HF clinics is 820,000 people. We estimate an annual rate of 1.16 persons per 100,000 general population developing a potential indication for percutaneous mitral valve repair. There are some limitations to estimating population rates from this study - Ireland does not have a single tier healthcare system, and so inclusion of only the public hospital system may underestimate prevalence in the general population. There are however no private HF clinics within the network, and we would see both private and public patients in all our HF clinics. In addition, only those patients who were seen at a HF clinic would contribute to this estimate – our study inclusion method will miss patients hospitalized with HF and severe secondary MR who do not follow up with the HF clinic, or who die before their first HF clinic appointment, or any community and outpatient diagnoses of severe symptomatic HF with severe secondary MR without referral to the HF clinic, although we expect the majority of such patients to be ineligible for mitral valve intervention. Due to analysis of an entire hospital group, we would expect very few referrals lost to outside our network. This strengthens the methodology of inclusion of smaller HF clinics to approximate closer true population incidence.

This rate of 4.1% of persistent symptomatic secondary MR following completion is significantly lower than might be inferred from analysis of MR rates in other studies. The EuMiClip registry suggested significant MR was present in 1.6% of all patients referred for echocardiography, for any indication, across 19 centers, and another study reported 0.75% of all patients who had had an echocardiogram. However, an analysis of mitral interventions in the USA reported implantation numbers per 100,000 persons in a general adult population over the years 2013-2016 for any indication were 0.2, 0.6, 1.1, and 1.7 respectively[13], mirroring our population estimate.

In this real world study, GDMT medication use was high. The overall rate of ACE/ARB/ARNI was 87.8%, and BB was 94.1% at programme completion. At baseline in COAPT, they reported rates of 67.1 and 90% respectively; and in MitraFR they reported rates of 83.9% and 89.5%. Although we primarily looked at patients once they had reached euvolaemia and maximally tolerated uptitration, there may be patients who undergo percutaneous mitral valve repair who are unable to undergo any medication uptitration.

We propose this high use of GDMT to be a significant reason for the lower than expected rate of severe secondary MR in our HF population. Although this may also represent less severe HF in our population, our reported baseline characteristics suggest a significant burden of HF in our population (mean LVEF 33.8%, and mean HF completion NT-proBNP of 780). This is supported by the reducing burden of severe symptomatic secondary MR from HF programme enrolment (8.3%) to HF programme completion (4.1%), reinforcing the significant role that medical therapy has in reducing severity secondary MR.

Our outcome data also reinforces the increased hazard of death or hospitalization for HF in patients with significant secondary MR, in comparison with all new HF diagnoses (Figure 2). This difference is notable in that we present outcome data with newly diagnosed HF patients, after the point at which they have completed medical optimization and reached euvolaemia. A significantly increased risk of death or hospitalization for heart failure was still present in those patients who had persisting significant secondary MR.

We have included the patients who underwent mitral valve surgery in our overall rate, as the new ACC guidelines suggest MDT consideration of percutaneous mitral valve repair, ahead of consideration for mitral valve surgery.[11] We also excluded patients who reported NYHA 1 dyspnoea from our final results - despite evidence that physicians frequently underreport physical limitations[14], and that these patients may still be suitable for intervention on mortality and morbidity grounds, we are limited by our retrospective approach, and so have excluded these patients from our final results.

A significant limitation to our paper is the lack of reported individual echocardiographic data, such as effective orifice areas (EROs), or regurgitant volumes (RVs), and our reliance on the overall impression of mitral regurgitation severity. However, our similar rates across the hospital group suggest consistency. We also reassessed prospectively a select number of patients (n=16) who had had at least moderate MR on their HF programme completion echocardiogram as a small validation sample. Using detailed prospective transthoracic echocardiography, we found no patient whose severity would be increased with a more comprehensive assessment.

Our study proposes a rate of the expected need for percutaneous mitral valve repair for a new HF population after medical optimisation, as well as an estimate of the expected need of percutaneous mitral valve repairs for secondary MR in the general population. It also highlights the significant role that GDMT and resynchronization have in reducing the amount of severe symptomatic secondary MR through the HF programme.

Declaration Conflicts of Interest:
None of the authors report any conflicts of interest.

Corresponding Author:
Dr Peter Wheen,
Department of Cardiology,
St. James Hospital,
James Street,
Dublin 8,
Republic of Ireland.
E-Mail: peter.wheen@gmail.com

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