

Embracing secondary mitral regurgitation with Carillon: past, present, and future

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Mitral regurgitation (MR) is a highly prevalent valvular heart disease.¹ Several national and international reports have identified MR as a frequent clinical condition in patients with heart failure (HF).^{2–4} In many cases, MR is moderate to severe and associated with high mortality and frequent hospitalizations.^{4–6} For optimal patient management, it is essential to distinguish between primary and secondary MR, as patient management and interventions differ significantly.¹

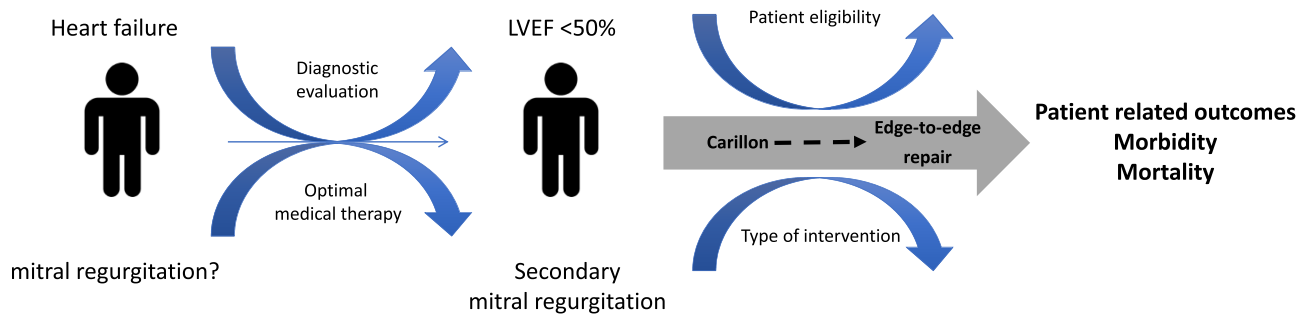
Secondary MR is a disease of the left heart. Left ventricular disease can be due to ischaemic or non-ischaemic remodeling, whilst atrial disease involving left atrial (LA) enlargement is most often due to elevation of filling pressure leading to atrial fibrillation further promoting LA dilatation.^{1,7} Surgical interventions were developed first to correct secondary MR, but recently, less invasive percutaneous interventions are primarily used.⁸ These include MitraClip, Carillon, Cardioband, PASCAL, Mitralign, and transcatheter mitral valve replacement, with best information available for MitraClip^{9–13} as the most used technique in clinical practice.^{14,15} The findings from clinical trials guiding clinical practice remain inconclusive. Management of secondary MR is a moving target, with both diagnostic and therapeutic challenges. Patients follow a disease trajectory, and it is important when the MR assessment is performed. Next to longitudinal component of worsening of LA and ventricular function, the patient volume status is important, as we generally overestimate MR grade in the congested patient.^{1,11,16,17} Therefore, HF therapies, particularly those that reduce left ventricular end-diastolic volume or cause reverse remodelling, need to be optimized prior to diagnostic work-up.^{1,18,19} The crucial role of medical therapy for patient selection and potential effects on trial results was evident in landmark MitraClip trials^{9,10} and should therefore be pursued throughout patient journey. Once patients are considered eligible for mitral valve intervention, the intervention type needs to be selected. Herein, several factors are important including patient, operator, and centre characteristics. Considering the MR prevalence and need for the intervention

beyond optimal medical therapy, it is evident that centres will have to perform larger numbers of interventions. In this context, less invasive procedures are needed in day clinic that would be attractive for all partners, including the health care system-related costs. From the latter perspective, repeated hospitalizations during patient journey are the main driver of financial burden; thus, an early inte

vention if proven to significantly reduce hospital admissions might be a preferable option (*Figure 1*).

In this issue of the journal, Giallauria and colleagues conducted an individual patient data meta-analysis of the Carillon mitral contour system.²⁰ The device was introduced into clinical practice more than a decade ago, and authors have included 209 patients from three clinical trials^{21–23} that compared the Carillon with control. Majority of participants were symptomatic men with left ventricular ejection fraction < 50% and mostly with secondary MR grade 2+ or worse. Analysis focused on echocardiographic parameters to assess severity of MR (mitral regurgitant volume and mitral regurgitant grade) and left ventricular remodelling (left ventricular end-diastolic and end-systolic volume). Functional capacity was evaluated with New York Heart Association class. Pooled analysis demonstrated the significant effect of Carillon on all parameters ($P < 0.005$ for all) except on left ventricular end-systolic volume, for which there was a trend towards reduction ($P = 0.09$). Analysis also included patient outcomes: HF-related hospitalizations were less common in Carillon group (45% vs. 64%, $P = 0.04$), whereas there was no effect on mortality. Importantly, a sensitivity analysis in MR grade 3+/4+ was performed; it confirmed the observations in the pooled group, with more pronounced reduction in HF-related hospitalizations (44% vs. 83%, $P = 0.04$).

The Carillon Mitral contour system procedure is relatively quick (usually up to 2 h), safe, and less invasive than other mitral valve procedures.²⁴ The device is inserted via the jugular vein into coronary sinus and can be performed by many HF physicians, as most of them have experience with

Figure 1 Patient journey of secondary mitral regurgitation in heart failure.

either pacemaker or interventional cardiology procedures. Operator independency is generally reached after three procedures. Some complications were reported, and these include those shared with other interventions (contrast-induced nephropathy, bleeding, and device dislodgment/fracture). Owing to anatomical relation of coronary sinus with left circumflex artery, extrinsic compression is possible. Coronary sinus venogram and coronary angiogram therefore need to be performed simultaneously at the start of the procedure and prior device release to assess interference with left circumflex artery.

The findings presented by Giallauria and colleagues are, along with original reports,^{25,26} important contribution to the literature and may already be relevant for clinical decisions in HF patients with secondary MR. Owing to less

invasive approaches, favourable effects on left ventricular volumes, and possibility of step-wise upgrade with other interventions, Carillon could be considered early in the patient trajectory for a timely and effective management (Figure 1). Ongoing trials (CARILLON, NCT NCT03142152; AFIRE NCT04529928) are expected to close some of the existing gaps and expand the patient population potentially eligible for secondary MR treatment with Carillon.

Conflict of interest

M. L. and M. B. received personal fees from Cardiac Dimensions.

References

1. El Sabbagh A, Reddy YNV, Nishimura RA. Mitral valve regurgitation in the contemporary era: insight into diagnosis, management, and future directions. *JACC Cardiovasc Imaging* 2018; **11**: 628–643.
2. Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozd J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavaliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L, Heart Failure Association of the ESC. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2013; **15**: 1173–1184.
3. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017; **19**: 1574–1585.
4. Cork DP, McCullough PA, Mehta HS, Barker CM, Gunnarsson C, Ryan MP, Baker ER, Van Houten J, Mollenkopf S, Verta P. Impact of mitral regurgitation on cardiovascular hospitalization and death in newly diagnosed heart failure patients. *ESC Heart Fail* 2020; **7**: 1502–1509.
5. Bursi F, Barbieri A, Grigioni F, Reggiani L, Zanasi V, Leuzzi C, Ricci C, Piovaccari G, Branzi A, Modena MG. Prognostic implications of functional mitral regurgitation according to the severity of the underlying chronic heart failure: a long-term outcome study. *Eur J Heart Fail* 2010; **12**: 382–388.
6. Kreuzer MM, Geis NA, Berlin N, Greiner S, Pleger ST, Bekeredjian R, Katus HA, Raake PW. Invasive hemodynamics and cardiac biomarkers to predict outcomes after percutaneous edge-to-edge mitral valve repair in patients with severe heart failure. *Clin Res Cardiol* 2019; **108**: 375–387.
7. Deferm S, Bertrand PB, Verbrugge FH, Verhaert D, Rega F, Thomas JD, Vandervoort PM. Atrial functional mitral regurgitation: JACC Review Topic of the Week. *J Am Coll Cardiol* 2019; **73**: 2465–2476.
8. Lavall D, Hagendorff A, Schirmer SH, Böhm M, Borger MA, Laufs U. Mitral valve interventions in heart failure. *ESC Heart Fail* 2018; **5**: 552–561.
9. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefèvre T, Piot C, Rouleau F, Carrié D, Nejari M, Ohlmann P, Leclercq F, Saint Etienne C, Teiger E, Leroux L, Karam N, Michel N, Gilard M, Donal E, Trochu JN, Cormier B, Armoiry X, Boutitie F, Maucort-Boulch D, Barnel C, Samson G, Guerin P, Vahanian A, Mewton N, MITRA-FR Investigators. Percutaneous

- repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018; **379**: 2297–2306.
10. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Marx SO, Cohen DJ, Weissman NJ, Mack MJ, Investigators COAPT. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018; **379**: 2307–2318.
 11. Ruschitzka F, Anker SD, Baumbach A, Abraham WT, Alfieri O, von Bardeleben RS, Bauersachs J, Bax JJ, De Bonis M, Boveda S, Celutkiene J, Cleland JG, Coats AJ, Dagres N, Deneke T, Falk V, Farmakis D, Filippatos G, Hausleiter J, Hindricks G, Jankowska EA, Lainscak M, Leclercq C, Lund LH, McDonagh T, Mehra MR, Metra M, Newton N, Müller C, Mullens W, Obaida JF, Ponikowski P, Praz F, Rudolph V, Vahanian A, Windecker S, Zamorano JL, Edvardsen T, Heidebuchel H, Seferovic PM, Prendergast B. Management of patients with heart failure and secondary mitral regurgitation: a joint position statement from the Heart Failure Association (HFA), European Association of Cardiovascular Imaging (EACVI), European Heart Rhythm Association (EHRA) and European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the European Society of Cardiology. *Eur Heart J* 2020 in press.
 12. Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, de Boer RA, Drexel H, Ben Gal T, Hill L, Jaarsma T, Jankowska EA, Anker MS, Lainscak M, Lewis BS, McDonagh T, Metra M, Milicic D, Mullens W, Piepoli MF, Rosano G, Ruschitzka F, Volterrani M, Voors AA, Filippatos G, Coats AJS. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019; **21**: 1169–1186.
 13. Kriebbaum SD, Boeder NF, Gaede L, Arnold M, Vigelius-Rauch U, Roth P, Sander M, Böning A, Bayer M, Elsässer A, Möllmann H, Hamm CW, Nef HM. Mitral valve leaflet repair with the new PASCAL system: early real-world data from a German multicentre experience. *Clin Res Cardiol* 2020; **109**: 549–559.
 14. Puls M, Lubos E, Boekstegers P, von Bardeleben RS, Ouarrak T, Butter C, Zuern CS, Bekeredjian R, Sievert H, Nickenig G, Eggebrecht H, Senges J, Schillinger W. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry. *Eur Heart J* 2016; **37**: 703–712.
 15. Pfister R, Baldus S. Atrioventricular valve disease: challenges and achievements in percutaneous treatment. *Clin Res Cardiol* 2018; **107**: 88–93.
 16. Straw S, Schlosshan D, Witte KK. Secondary mitral regurgitation: reducing the leak, expanding the science. *ESC Heart Fail* 2020.
 17. Hagendorff A, Doenst T, Falk V. Echocardiographic assessment of functional mitral regurgitation: opening Pandora's box? *ESC Heart Fail* 2019; **6**: 678–685.
 18. de Groot-de Laat LE, Huizer J, Lenzen M, Spitzer E, Ren B, Geleijnse ML, Caliskan K. Evolution of mitral regurgitation in patients with heart failure referred to a tertiary heart failure clinic. *ESC Heart Fail* 2019; **6**: 936–943.
 19. Kang DH, Park SJ, Shin SH, Hong GR, Lee S, Kim MS, Yun SC, Song JM, Park SW, Kim JJ. Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation. *Circulation* 2019; **139**: 1354–1365.
 20. Giallauria F, Di Lorenzo A, Parlato A, Testa C, Bobbio E, Vigorito C, Coats AJS. Individual patient data meta-analysis of the effects of the CARILLON® mitral contour system. *ESC Heart Fail* 2020 in press.
 21. Siminiak T, Wu JC, Haude M, Hoppe UC, Sadowski J, Lipiecki J, Fajadet J, Shah AM, Feldman T, Kaye DM, Goldberg SL, Levy WC, Solomon SD, Reuter DG. Treatment of functional mitral regurgitation by percutaneous annuloplasty: results of the TITAN Trial. *Eur J Heart Fail* 2012; **14**: 931–938.
 22. Lipiecki J, Siminiak T, Sievert H, Müller-Ehmsen J, Degen H, Wu JC, Schandrin C, Kalmucki P, Hofmann I, Reuter D, Goldberg SL, Haude M. Coronary sinus-based percutaneous annuloplasty as treatment for functional mitral regurgitation: the TITAN II trial. *Open Heart* 2016; **3**: e000411.
 23. Witte KK, Lipiecki J, Siminiak T, Meredith IT, Malkin CJ, Goldberg SL, Stark MA, von Bardeleben RS, Cremer PC, Jaber WA, Celemajer DS, Kaye DM, Sievert H. The REDUCE FMR trial: a randomized sham-controlled study of percutaneous mitral annuloplasty in functional mitral regurgitation. *JACC Heart Fail* 2019; **7**: 945–955.
 24. Gheorghe L, Ielasi A, Rensing BJWM, Eefting FD, Timmers L, Latib A, Swaans MJ. Complications following percutaneous mitral valve repair. *Front Cardiovasc Med* 2019; **6**: 146.
 25. Ruf TF, Kreidel F, Tamm AR, Geyer M, Hahad O, Zirbs JC, Schwidtal BL, Beiras-Fernandez A, Witte KK, Münzel T, von Bardeleben RS. Transcatheter indirect mitral annuloplasty induces annular and left atrial remodelling in secondary mitral regurgitation. *ESC Heart Fail* 2020; **7**: 1400–1408.
 26. Lipiecki J, Fahrat H, Monzy S, Caillot N, Siminiak T, Johnson T, Vogt S, Stark MA, Goldberg SL. Long-term prognosis of patients treated by coronary sinus-based percutaneous annuloplasty: single centre experience. *ESC Heart Fail* 2020. <https://doi.org/10.1002/ehf2.12955>