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RESEARCH ARTICLE

Registries on transcatheter edge-to-edge repair in heart failure: Current evidence and future perspectives

Gianluigi Savarese[1]*†, Christian Basile[1,2†], Marianna Adamo[3], Stefan D. Anker[4], Antoni Bayes-Genis[5,6], Michael Böhm[7], Erwan Donal[8], Gerasimos S. Filippatos[9], Francesco Maisano[10], Piotr Ponikowski[11], Giuseppe M.C. Rosano[12], Ralph Stephan von Bardeleben[13], Marco Metra[3], and Javed Butler[14,15]

[1]Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden; [2]Department of Advanced Biomedical Sciences, University of Naples 'Federico II', Naples, Italy; [3]Cardiology, ASST Spedali Civili of Brescia, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; [4]Department of Cardiology and Berlin Institute of Health Center for Regenerative Therapies, German Center for Cardiovascular Research Partner Site Berlin, Charité Universitätsmedizin, Berlin, Germany; [5]Heart Institute, University Hospital Germans Trias i Pujol, CIBERCV, Badalona, Spain; [6]Department of Medicine, Universitat Autonoma de Barcelona, Barcelona, Spain; [7]Internal Medicine Clinic III, Cardiology, Angiology and Intensive Care Medicine, Saarland University, Homburg, Germany; [8]Université de Rennes, CHU Rennes, Inserm, LTSI-UMR, Rennes, France; [9]Department of Cardiology, Attikon University Hospital, National and Kapodistrian University of Athens, Athens, Greece; [10]Department of Cardiac Surgery, IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy; [11]Institute of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland; [12]Department of Medical Sciences, IRCCS San Raffaele Roma, Rome, Italy; [13]Department of Cardiology, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany; [14]Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA; and [15]Baylor Scott and White Research Institute, Dallas, TX, USA

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Aims Secondary mitral regurgitation (SMR) and tricuspid regurgitation (TR) are the most common valvular heart diseases in patients with heart failure (HF). Transcatheter edge-to-edge repair (TEER) devices designed for treating MR and TR have been successfully tested in randomized controlled trials, but methodological issues have often challenged their interpretation. This manuscript aimed to provide an overview of TEER registries on SMR and TR in HF, highlighting their key features, describing clinical characteristics and outcomes of patients receiving these devices, and exploring the available data limitations.

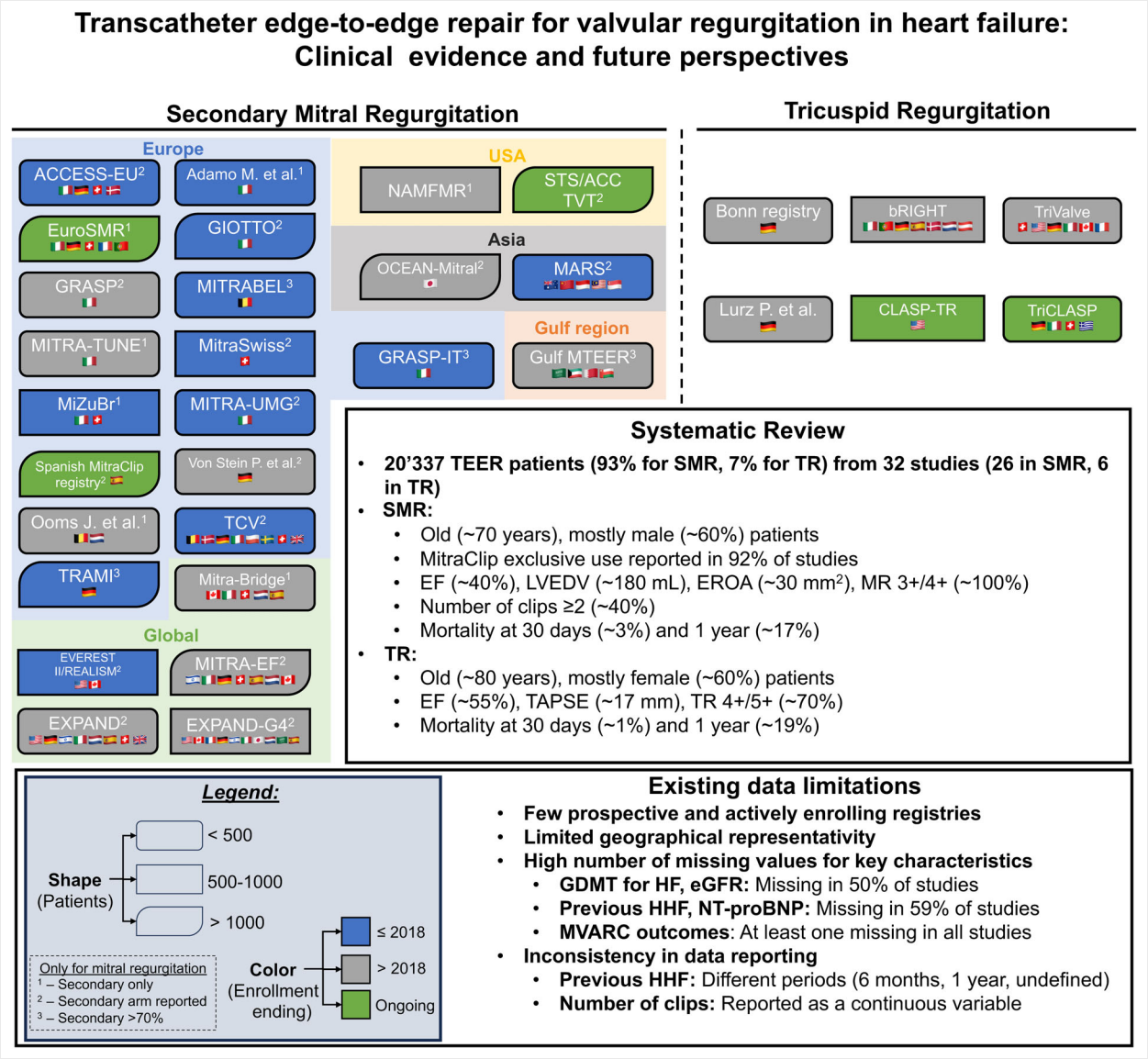
Methods and results PubMed, Web of Science, and EMBASE were searched for registries reporting on TEER in SMR or TR. Registries were excluded if single-centre and with <100 patients. Twenty-six registries (46% prospective, 12% ongoing), including a total cohort of 18 925 patients, were retrieved for TEER in SMR, and six registries (50% retrospective, 33% ongoing) reported on the use of TEER for TR in a total cohort of 1412 patients. Limited geographical representativity outside North America and Europe, high number of missing values, and inconsistency in data reporting were the main existing evidence limitations.

Conclusion Registries on TEER represent a key data source in a setting where it is difficult to conduct randomized controlled trials. However, limitations in design, patient characterization, and outcomes reporting restrain their use. A novel conceptual framework for future prospective TEER registries, as proposed in this document, might inform current practice, address relevant clinical questions and future trial design.

*Corresponding author. Department of Clinical Science and Education Karolinska Institutet, Stockholm South General Hospital, Sjukhusbacken 10, 118 83 Stockholm, Sweden. Tel: +46 725968340, Email: gianluigi.savarese@ki.se

†Contributed equally.

Graphical Abstract



Clinical evidence in transcatheter edge-to-edge valve repair. EF, ejection fraction; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; GDMT, guideline-directed medical therapy; HF, heart failure; HHF, hospitalization for heart failure; LVEDV, left ventricular end-diastolic volume; MR, mitral regurgitation; MVARC, Mitral Valve Academy Research Consortium; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SMR, secondary mitral regurgitation; TAPSE, tricuspid annular plane systolic excursion; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation.

Keywords Heart failure • Registries • Valvular heart disease • Mitral regurgitation • Tricuspid regurgitation • Transcatheter edge-to-edge repair

Introduction

Secondary mitral regurgitation (SMR) and tricuspid regurgitation (TR) are the most common valvular heart diseases in heart failure (HF),[1,2] and are related to left ventricular remodelling, papillary muscle displacement, and/or atrial dilatation by long-standing increased ventricular filling pressures and/or atrial fibrillation (AF).[3–5] Significant SMR and TR are associated with decreased

quality of life (QoL), increased risk of hospitalization for HF (HHF) and all-cause mortality.[6–11] Surgical therapies for SMR and TR remain controversial and challenging,[12–17] with medical therapy with diuretics mainly targeting symptom relief.

The MitraClip (Abbott, Santa Clara, CA, USA) and Pascal (Edwards Lifesciences, Irvine, CA, USA) systems are devices for transcatheter edge-to-edge repair (TEER) of mitral regurgitation (MR), while the TriClip system (Abbott, Santa Clara, CA, USA) is the only dedicated device for TR TEER.

Three randomized controlled trials (RCTs) on MitraClip in patients with HF and SMR showed the device's safety, which was also effective in the COAPT and RESHAPE-HF2 trials, while the MITRA-FR RCT was neutral.[18–20] The less severe MR and more severe ventricular remodelling, worst procedural results, along with the more lenient inclusion criteria and management of medical therapy in the MITRA-FR trial are likely to explain the different results.[21–23] The TRILUMINATE trial tested the TriClip system in patients with HF and severe symptomatic TR, showing the procedure's safety and a significant improvement in QoL but no effect on HHF or all-cause mortality.[24]

Observational data complement evidence from RCTs, which are challenged by difficulties in achieving a double-blind design or enrolling large and generalizable populations in the setting of TEER. Registries may contribute to disease characterization and provide key data on TEER responders' profiles, long-term effectiveness and safety, eligibility for treatments and their implementation in clinical practice.[25,26]

This systematic review aims to provide an overview of TEER registries on SMR and TR, highlighting their key features, clinical characteristics, and outcomes of enrolled patients, and to explore the limitations of the available data. We also propose a conceptual framework for the design and conduct of future prospective TEER registries to further improve the understanding of valve regurgitation and its treatment in patients with HF.

Methods

Registries reporting on TEER in MR or TR were searched on PubMed, Web of Science, and EMBASE from inception to 13 January 2024. Detailed eligibility criteria (online supplementary *Appendix S1*), the research strategy (online supplementary *Table S1*), the bias assessment (online supplementary *Table S2*), and the PRISMA flow diagram (online supplementary *Figure S1*) are reported in the online supplementary material.

Results

Secondary mitral regurgitation

Demographics, comorbidities, and clinical characteristics

Twenty-six registries (46% prospective, 12% ongoing), including a total cohort of 18 925 patients, were retrieved for TEER in SMR[27–61] (*Table 1*, *Figure 1*, *Graphical Abstract*, and online supplementary *Table S3*). Approximately 50% were conducted before the COAPT/MITRA-FR publication. Most registries were conducted in European countries (61%) and focused on the MitraClip device, with only one study and a minority of patients in the Gulf MTEER registry (2.9%) reporting on Pascal device utilization.[39,54] This is likely due to the different timing of CE mark approvals for the MitraClip (2008) and Pascal (2019) systems.

All studies reported data on age and sex, with 58% of registries reporting a mean/median age ≥73 years. Male patients represented ≥60% in 73% of the studies. The MITRA-TUNE registry enrolled the oldest population (median age 81 years) and the lowest proportion of males (39%),[44] likely due to the inclusion of only patients with atrial SMR, who are usually older, female, with AF and higher ejection fraction (EF).[62] In contrast, the MitraBridge registry enrolled the youngest population (median age 58 years), due to the inclusion of only heart transplant (HTx) candidates undergoing TEER.[27]

The prevalence of ischaemic MR ranged 28.1–82.2% and was reported in 50% of studies. A previous HHF was reported in 38% of studies, defined as occurring within 6 months in 22.3% of studies, 12 months in 44.4%, or left undefined in 33.3%; ∼50% of patients had an HHF within the previous 12 months. Despite being reported only in 50% of the studies, non-ischaemic MR and no HHF within 6 months before TEER were independent predictors of left ventricular reverse remodelling after MitraClip.[28]

The prevalence of comorbidities was reported in most studies: AF, type II diabetes mellitus (DM), and arterial hypertension (HT) in 96%, chronic obstructive pulmonary disease (COPD) in 81%, and chronic kidney disease (CKD) in 69%. When reported, ∼60% of patients had AF, ∼30% DM, ∼80% HT, ∼20% COPD, and ∼50% CKD. Coronary artery disease (CAD), prior stroke, and peripheral artery disease (PAD) were the least likely reported, that is, in 65%, 61%, and 42% of studies, respectively, and most of the reporting studies included ∼60% of patients with CAD, ∼10% with prior stroke, ∼17% with PAD. Despite being the least reported comorbidity, PAD was an independent predictor of mortality and HHF in both the GIOTTO and Spanish MitraClip registries.[37,49]

All studies reported New York Heart Association (NYHA) class, with 74.5–95% of patients in NYHA class III/IV. Fewer studies described body mass index (BMI) (58%), body surface area (BSA) (19%), heart rate (8%), systolic (8%) and diastolic (4%) blood pressure. The EuroSMR registry reported a U-shaped association in females and a linear correlation in males between BSA and 2-year all-cause mortality, suggesting a different prognostic role for TEER according to body type in males versus females.[33] Notably, no study reported these measurements at the follow-up after the procedure.

No dedicated post-operative risk score has been available for SMR TEER until recently,[63–66] so cardiac surgery scores were generally applied. Northern American registries used the Society of Thoracic Surgeons (STS) predicted risk of mortality score, whereas European registries considered the logistic EuroSCORE (older studies) or EuroSCORE II (more recent studies). Earlier studies showed higher mortality risk scores, as only patients who were symptomatic despite optimal medical therapy and at high surgical risk were referred for TEER before the updated 2020 American College of Cardiology/American Heart Association (ACC/AHA) and 2021 European Society of Cardiology/European Association

Table 1 Characteristics of transcatheter edge-to-edge repair registries on secondary mitral regurgitation

	ACCESS-EU[30,31]	Adamo et al.[28]	NAMFMR[32]	EuroSMR[33,56]	EVEREST II/ REALISM[34]	EXPAND[29]	EXPAND G4[35,36]	GIOTTO[37,57]	GRASP[38,58]	GRASP-IT[55]	Gulf MTEER[39]	MARS[40]	MITRABEL[41]	MITRA-EF[42]
Organization														
Region	Europe	Italy	USA	Europe	Global	Global	Global	Italy	Italy	Italy	Gulf region	Asia-Pacific	Belgium	Global
Design	P	R	R	R	P	P	P	P	R	R	R	R	P	R
N	393	184	525	1594	616	413	572	1153	399	304	176	88	41	1807
SMR (%)	100[b]	100[a]	100[a]	100[a]	100[b]	100[b]	100[b]	100[b]	100[b]	77.5[c]	77[c]	100[b]	98[c]	100[b]
Years of enrolment	2009–2011	2009–2016	2014–2020	2008–ongoing	2007–2013	2018–2019	2021–2022	2016–2020	2008–2019	2008–2013	2017–2019	2011–2014	2010–2013	2012–2022
Device	MitraClip	MitraClip	MitraClip	MitraClip	MitraClip	MitraClip	MitraClip	MitraClip	MitraClip	MitraClip	MitraClip (97.1%), Pascal (2.9%)	MitraClip	MitraClip	MitraClip
Demographics														
Age (years)	73 (8.9)	71 (9.8)	71 (13)	74 (10)	73.3 (10.5)	74.7 (10.1)	75.4 (9.3)	73 [68–80]	72.6 (8.9)	72 (10)	69.2 (10.6)	70.4 (10.1)	75 (9)	71.9 (8.8)
Male (%)	67.9	73.9	63	65.7	59.1	58.4	58.7	71	60	63.8	56.3	68.2	66	50.2
Comorbidities (%)														
AF	69.3	39.7	60	60	65	60.2	59.3	50	46	41.2	32.4	47.7	–	52
HT	76.2	61.9	84	75	88.6	84.1	80.2	73	79	67.5	81.8	62.5	–	71.6
DM	34.1	33.1	35	30	38.9	29.5	34.8	33	39	34.5	67.6	37.5	–	35.6
COPD	20.3	22.8	37	17	31.2	–	–	14.5	21.7	21.7	–	12.5	–	18.3
Clinical														
Post-operative risk score	24.8 (18.9)[d]	8.5 [5-15][e]	–	16.5 [9.5–27.8][d]	10.2 (6.9)[f]	9.8 (9.4)[e]	–	5.7 [3.3–9.3][e]	6.2 [3.6–10.8][e]	8 (7)[e]	4.3 (3.3)[f]	19 (14.4)[d]	22 (15)[d]	7.9 (3.8)[e]
NYHA class III–IV (%)	87.3	83.7	82	22[g]	80.5	83.1	75.5	83	86	17.1[g]	89.2	78.4	78	75.2
Echocardiography														
EF (%)	44.3[h]	32 (10)	32 (10)	35 (12)	43.2 (11.7)	39.4 (13.5)	39.1 (14.4)	32 [26–40]	32.9 (10.6)	37 (14)	37.9 (13.2)	36 (12)	32 (10)	32.8 (10.4)
MR 2+ (%)	2	0	4	3	19.8	–	32.6	1	0	0	1.1	0	0	5
MR 3+/4+ (%)	98.5	100	96	97	80.2	52.1	51.6	99	100	100	98.9	100	100	95
MR 4+ (%)	59	77.7	73	47	–	–	19	77	69	–	36.4	78.4	41	80
Procedural details (%)														
No. of clips ≥2	–	48.9	–	–	38	–	1.3 (0.6)[i]	1.7 (0.7)[i]	44.5	–	25.2	45	70.7	1.8 (0.7)[i]
Clinical outcome (%)														
Mortality	17.0[j]	19.6[k]	22[j]	29.6[k]	22.4[j]	17.7[j]	14.2[j]	18.6[j]	38[l]	42.4[k]	5.4[j]		27[j]	16.5[j]

	Mitra-SWISS[43,59]	MITRA-TUNE[44]	MITRA-UMG[45]	MiZuBr[46]	OCEAN-Mitral[47,60]	Ooms et al.[48]	Spanish MitraClip Registry[49,61]	STS/ACC TVT[50]	TCV[51,52]	TRAMI[53]	Von Stein et al.[54]	MitraBridge[27]
Organization												
Region	Switzerland	Italy	Italy	Europe	Japan	Europe	Spain	USA	Europe	Germany	Germany	Global
Design	P	R	R	R	P	R	P	P	P	M	R	P
N	560	87	109	565	1233	241	1089	5000	452	1064	141	119
SMR (%)	100[b]	100[a]	100[b]	100[a]	100[b]	100[a]	100[b]	100[b]	100[b]	71[c]	100[b]	100[a]
Years of enrolment	2011–2018	2009–2021	2012–2018	2008–2018	2018–2021	2011–2019	2012–ongoing	2019–ongoing	2011–2012	2010–2013	2019	2018–2021
Device	MitraClip	MitraClip	MitraClip	MitraClip	MitraClip	MitraClip	MitraClip	MitraClip	MitraClip	MitraClip	Pascal	MitraClip
Demographics												
Age (years)	76 [69–81]	81 [78–83]	74 (6)	71 (10)	78 [71–83]	72 [66–78]	75 [68–81]	73.1 (11.3)	72.8 (9.8)	75 [70–81]	73.8 (11.2)	58 [51–63]
Male (%)	63.6	39	70	78	60	70.5	69.6	57.6	68	61.8	66	76.5
Comorbidities (%)												
AF	56.5	100	47	47	66.2	54.4	62.5	61	27	41.4	71.6	35
HT	77.4	83	88	64	70.0	54.8	73.6	86.2	77.6	–	90.8	43
DM	25.7	22	39	28	32.2	27.8	30.7	35.6	33	30.5	29.1	27
COPD	14.4	21	25	22	9.3	16.6	23.5	–	20	19.2	21.3	8.5
Clinical												
Post-operative risk score	4.9 [2.8–9.5][e]	6 [3-10][e]	11.4 (11)[e]	10 [6-13][e]	9.1 [5.8–14.1][f]	2.7 [1.5–5.6][f]	7.4 [5.3–12.1][e]	–	21.9 (17.6)[d]	21.4 [12.4–35.4][d]	6.1 (5.1)[e]	3.5 [2.6–6.2][e]
NYHA class III–IV (%)	74.5	83	81	78	65.1	88.2	87.2	85.6	88	86.8	85.1	95

Table 1 (Continued)

	Mitra-SWISS[43,59]	MITRA-TUNE[44]	MITRA-UMG[45]	MiZuBr[46]	OCEAN-Mitral[47,60]	Ooms *et al.*[48]	Spanish MitraClip Registry[49,61]	STS/ACC TVT[50]	TCV[51,52]	TRAMI[53]	Von Stein *et al.*[54]	MitraBridge[27]
Echocardiography												
EF (%)	36 [28–50]	55 [50–60]	37 (8)	30 (10)	37 [29.8–49.6]	30 [25–35]	36 [30–52.5]	37 (14.7)	37 (13)	32.9[h]	41 (16)	26 [20–32]
MR 2+ (%)	0	0	0	0	11.6	0	0	5.3	1	–	0	0
MR 3+/4+ (%)	100	100	100	100	88.4	100	100	94.2	99	–	100	100
MR 4+ (%)	77.7	65.5	75	84	56.6	74.7	75	75.8	84.7	94.8	59.6	87.5
Procedural details (%)												
No. of clips ≥2	60.8	47	41	68	37	56	1 [1-2][i]	40.7	37	1.4 (0.6)[i]	26.2	66.5
Clinical outcome (%)												
Mortality	24.8[j]	40[k]	–	54[j]	10.9[j]	30.4[k]	9.8[j]	22.2[j]	15.0[j]	–	10.7[j]	11[l]

Only the characteristics reported in at least 75% of registries are shown. For a more detailed description of included registries see online supplementary *Table S3*. All data are mean (standard deviation) or median [interquartile range] unless otherwise specified. Data reported in blue are from a previous manuscript and not the most recent one.

AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EF, ejection fraction; HT, hypertension; M, mixed; MR, mitral regurgitation; NYHA, New York Heart Association; P, prospective; R, retrospective; SMR, secondary mitral regurgitation; STS, Society of Thoracic Surgeons.

[a]SMR only.

[b]SMR arm reported.

[c]SMR >70%.

[d]Logistic EuroSCORE.

[e]EuroSCORE II.

[f]STS predicted risk of mortality score.

[g]Only patients in NYHA class IV reported.

[h]% of patients with EF <30%.

[i]Number of clips implanted reported as a continuous variable.

[j]12 months.

[k]24 months.

[l]Median follow-up: MitraSwiss–13 months [6–35]; GRASP–2 years; MiZuBr–5 years; MitraBridge–532 days [188–986].

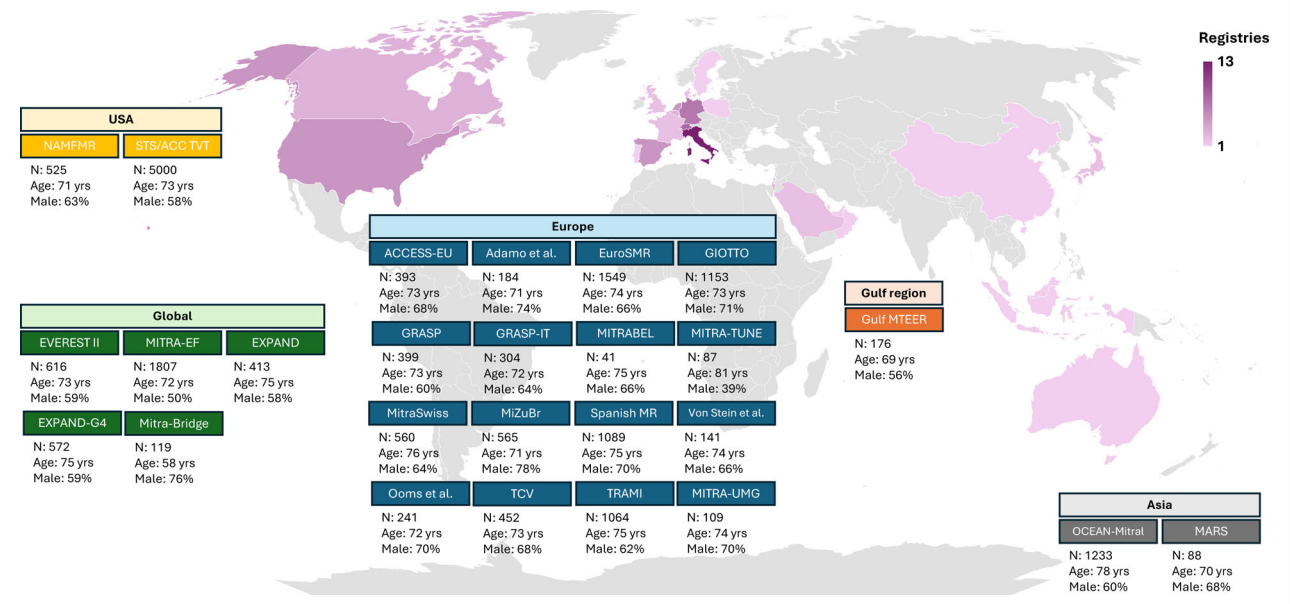


Figure 1 Geographical representation and main demographic characteristics of included registries on transcatheter edge-to-edge repair in secondary mitral regurgitation. Age value is mean/median as reported in the respective manuscript. N, number of patients; yrs, years.

for Cardio-Thoracic Surgery (ESC/EACTS) guidelines on valvular heart disease.[67,68]

Echocardiographic findings, laboratory data, and treatment

All studies reported MR severity. Moderate-to-severe (3+) or severe (4+) MR affected 80.2–100% of patients based on site reports, and 51–100% based on core echocardiographic laboratory measurements, with moderate (2+) MR present in 0–32.6%. The EVEREST II/REALISM, EXPAND, and EXPAND-G4 registries used a core echocardiographic laboratory,[29,34–36] with the latter two reporting significant differences between site-reported (100%) and core lab-reported (~50%) MR 3+/4+, while the EVEREST II/REALISM registry did not report site-assessed MR.

Ejection fraction was reported in all the studies, with a mean/median EF <50% except for the MITRA-TUNE study, which focused on atrial SMR.[62]

Data on other relevant echocardiographic parameters, for example, left ventricular end-diastolic volume (LVEDV), systolic pulmonary artery pressure (sPAP), and effective regurgitant orifice area (EROA), were reported in 69%, 65%, and 46% of studies, respectively. When reported, sPAP was always ≥39 mmHg, with 59% of studies reporting an sPAP ≥47 mmHg. This is relevant considering that sPAP is required for the evaluation of right ventricular–pulmonary arterial coupling, an independent predictor of all-cause mortality/HHF in the COAPT trial.[69] EROA, missing in ~50% of studies, is necessary to estimate SMR proportionality, crucial to characterize patients as COAPT-like or MITRA-FR-like.[21,22]

Laboratory measurements, for example, estimated glomerular filtration rate (eGFR), creatinine, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were reported in 46%, 35%, and 38% of studies, respectively. When reported, eGFR (<55 ml/min/1.73 m^2 in all reporting studies except for the MitraBridge registry) and/or creatinine (≥1.2 mg/dl in all reporting studies) highlighted a high risk for contrast-induced acute kidney injury.[70–72] Lower eGFR values or CKD independently predicted mortality in the GRASP and TCV registries, and mortality/HHF in the MiZuBr registry.[38,46,51,52]

Regarding HF therapies, renin–angiotensin system inhibitors (RASi)/angiotensin receptor–neprilysin inhibitor (ARNi) use was reported in 54% of the studies, beta-blockers in 50%, mineralocorticoid receptor antagonists (MRA) in 50%, and diuretics in 35%. Beta-blocker use was consistently high (72–91.4%), as was diuretic use (86.5–98.9%). RASi/ARNi (34–86.5%) and MRA (23.6–85.5%) use varied extensively. Device use was reported in 31% of studies for implantable cardioverter defibrillator (ICD), 46% for cardiac resynchronization therapy (CRT), and 19% for pacemaker.

Mitral Valve Academic Research Consortium outcomes and procedural results

The Mitral Valve Academic Research Consortium (MVARC) aimed to standardize clinical endpoints in MR TEER RCTs.[73,74] However, in the available registries MVARC definitions (online supplementary *Table S4*) were reported in only 37.5% of the studies, with every study missing at least one. MVARC technical success was high (95.3–99%).

Partial clip detachment and in-hospital mortality were reported in 42% and 46% of studies, respectively, with rates under 5%; the EXPAND-G4 registry, using the latest MitraClip G4 system, reported the lowest proportion of partial clip detachment (0.5%) and in-hospital mortality (0.5%).[35,36]

The number of clips used during the procedure was reported as either the percentage of procedures with at least two clips or as a continuous variable, and was reported in 81% of the studies. This inconsistency in reporting poses challenges when comparing different registries. The use of two or more clips, indicating a more complex procedure, was reported in 25.2–70.7% of cases, likely influenced by patient characteristics, centre experience, and device generation, with more recent studies (where latest generation devices were available) and those enrolling larger populations (and therefore likely involving more experienced centres) requiring less clips.

Post-discharge outcomes

Thirty-day mortality was reported in 54% of studies, showing a steady decline over time with MitraClip improvement: from 5.7% in the TRAMI registry (first-generation MitraClip),[53] to 3.3% in the STS/ACC TVT study (82% of third-generation MitraClip),[50] and 1.4% in the EXPAND G4 study (fourth-generation MitraClip).[35,36] Mortality beyond 30 days was described in 88% of studies and reported as 12-month mortality, 24-month mortality, or over the study median follow-up in 63.6%, 18.2%, and 18.2% of studies, respectively. Twelve-month mortality (~17%) and 24-month mortality (~30%) were comparable with the device arm of the COAPT trial (19.1% and 29.1%, respectively). HHF at 30 days was scarcely reported (15%), but more frequently reported beyond 30 days (69%); HHF risk ranged between 1.9% and 4.0% at 30 days and 11.7–38% at 12 months.

MR severity and NYHA class were reported in 31% and 38% of the studies at 30 days, and in 50% and 54% beyond 30 days, respectively. MR 3+/4+ and NYHA class III/IV decreased compared with the baseline evaluation both at 30 days (MR 3+/4+: 3–30%; NYHA class III/IV: 3.3–80%) and beyond 30 days (MR 3+/4+: 3–26.5%; NYHA class III/IV: 5–87.4%).

Only five studies (20.8%) reported measures of QoL: the STS/ACC TVT,[50] EXPAND,[29] and EXPAND-G4[35,36] registries applied the Kansas City Cardiomyopathy Questionnaire (KCCQ) scale, the ACCESS-EU registry used the Minnesota Living with Heart Failure Questionnaire scale,[30,31] and the EVEREST II/REALISM registry applied the Short Form 36 Health Survey Physical Component Summary scale.[34] All these studies reported an improvement in QoL following the procedure.

In the MitraBridge registry,[27] focused on HTx candidates, after a median follow-up of 532 days, 11.2% died, and 23.3% of patients had no longer indication for HTx because of significant clinical improvement (MR ≤2+ and NYHA class ≤III).

Mitral regurgitation proportionality and COAPT-like criteria

Given the conflicting evidence of the MITRA-FR and COAPT trials,[18,19] there is a significant need to better characterize patients who may benefit from TEER beyond symptom relief. The more severe MR and less severe ventricular remodelling, i.e., a disproportionately severe MR, in the COAPT trial were likely to explain the different results, as compared with the proportionately severe MR in the MITRA-FR trial.[21–23] This has led to the use of COAPT-like criteria for fostering the selection for TEER of patients similar to those enrolled in the COAPT trial and therefore more likely to benefit,[68] which consider the severity of MR (MR 3+/4+, NYHA class II–IV), absence of severe left ventricular impairment (EF ≥20%, left ventricular end-systolic diameter [LVESD] ≤70 mm), and absence of severe pulmonary hypertension (sPAP <70 mmHg). When reported in the included registries, mean/median EF ranged 26–43.2%, local-assessed MR severity was 3+/4+ in 80.2–100% of patients, mean/median LVESD ranged 33–61.5 mm, mean/median sPAP ranged 39–52 mmHg, and NYHA class was III–IV in 65.1–95% of patients, with therefore higher percentages of NYHA class II–IV. This highlights that patients enrolled in the reported registries were more likely COAPT-like than MITRA-FR-like.

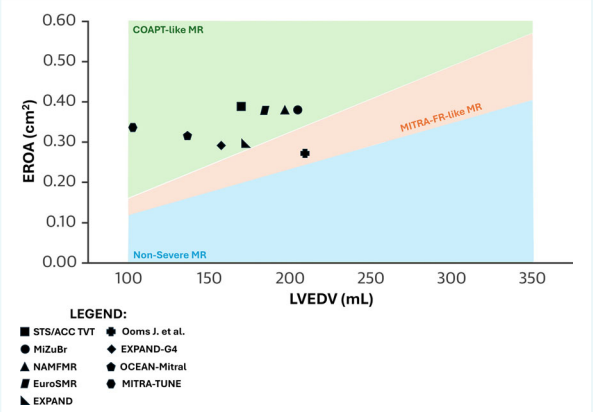


Figure 2 Proportionality/disproportionality of mitral regurgitation (MR) in registries reporting effective regurgitant orifice area (EROA) and left ventricular end-diastolic volume (LVEDV). Values are reported as mean/median in the overall population according to the respective manuscript.

This is further supported by the assessment of proportionality/disproportionality of SMR. This assessment, necessitating both LVEDV and EROA, was, however, only available for nine registries.[29,32,33,35,36,44,46–48,50,56,60] Among these, all registries reported a disproportionately severe SMR (COAPT-like MR), except for Ooms *et al.*,[48] reporting a proportionately severe SMR (MITRA-FR-like MR) (*Figure 2*).

Tricuspid regurgitation

Six registries (50% retrospective, 33% ongoing) reported on the use of TEER for TR in a total cohort of 1412 patients[75–80] (*Table 2*, online supplementary *Table S5*).

Demographics, comorbidities, and clinical characteristics

Earlier registries focused on using the MitraClip device in the tricuspid position, with enrolment starting in 2015/2016 for three registries[75,77,78,81] involving MitraClip, Pascal, and only later TriClip. The bRIGHT registry,[76] initiated in 2020, specifically included patients receiving TriClip. Ongoing registries, CLASP-TR and

Table 2 Characteristics of transcatheter edge-to-edge repair registries on tricuspid regurgitation

	Bonn registry[75]	bRIGHT[76]	TriValve[77]	Lurz et al.[78]	CLASP-TR[79]	TriCLASP[80]
Organization						
Region	Germany	Europe	Global	Europe	USA	Europe
Design	R	P	R	R	P	P
N	211	511	308	243	65	74
Years of enrolment	2015–2021	2020–2022	2015–2022	2016–2019	2019-Ongoing	2021-Ongoing
Device	TriClip (51.2%), PASCAL (25.1%) and MitraClip (23.7%) in tricuspid position	TriClip	MitraClip in tricuspid position	MitraClip in tricuspid position	PASCAL in tricuspid position	PASCAL in tricuspid position
Demographics						
Age (years)	78.3 (7.2)	78.9 (7.1)	76.4 (9.2)	77 (9)	77.4 (8.9)	80.3 (5.6)
Male (%)	45.5	44	44.2	50	44.6	41.9
BMI (kg/m^2)	26.1 (5.5)	–	26.1 (4.9)	27 (5)	–	–
Comorbidities and previous valve intervention (%)						
AF	92.4	86.3	61.8	88	89.2	95.9
HT	82.9	86.7	–	–	–	90.5
DM	24.2	22.3	27.7	–	15.4	29.7
CKD	–	39.5	–	21	43.1	55.4
COPD	18.5	13.1	23.1	24	16.9	–
Previous MV intervention	29.6	26.8	–	13	20.0	–
1-year prior HHF (%)	–	40.3	–	76	37.5	–
Clinical						
NYHA class III–IV (%)	86.3	80	91.1	92	70.8	77.0
EuroSCORE II	9.6 (6.7)	–	6.1 [3.7–10.4]	7.7 (7.0)	5.0 (4.7)	6.0 (5.0)
Echocardiography						
EF (%)	54.4 (10.3)	55.8 (10.6)	49.8 (13.9)	51 (14)	56.5 (7.1)	–
RVFAC (%)	43.2 (9.6)	39.4 (8.4)	–	–	36.9 (9.4)	–
TAPSE (mm)	17.9 (5.1)	17 (4.4)	16.7 (5.1)	17 (5)	14 (4)	18 (5)
TR severity massive/torrential (%)	54.5	88	50.2	95	71	15
TR severity torrential (%)	21.8	26.7	–	28	39	5
TR vena contracta, cm	–	0.85 (0.36)	0.99 (0.38)	1.00 (0.30)	1.4 (0.4)	–
TR EROA (cm^2)	–	0.80 (0.51)	0.64 (0.52)	0.57 (0.32)	0.7 (0.3)	0.4 (0.5)
Right ventricular end-diastolic diameter, cm	–	4.63 (0.92)	4.03 (1.27)	4.30 (0.80)	4.0 (0.9)	4.3 (6.4)
sPAP (mmHg)	36.8 (14.2)	–	41 (15.8)	49 (15)	–	43.8 (14.0)
Laboratory						
eGFR (ml/min/1.73 m^2)	50 (23.9)	–	47.1 (19.7)	48 (22)	53.8 (16.1)	–
NT-proBNP (pg/L)	4296 [3094–5498]	–	2760 [1502–5702]	3110 [1678–6276]	–	–
Treatments (%)						
ICD/CRT/pacemaker (%)	33.6	25.7	28.3	–	–	23.0
Procedural details						
Procedural time (min)	50.6 (25.8)	76 (39)	122.9 (52.1)	–	118.0 [77.0–205.0]	84.2 (48.5)
No. of clips	1.8 (0.8)	1.9 (0.7)	1.9 (0.9)	2 [2–2]	1 [1–2]	1.8 (0.6)
Hospital length (days)	–	–	4 [2–6]	–	2.6 (3.5)	5.1 (3.9)
In-hospital mortality	0	0.4	0	–	0	2.7
Outcomes at discharge						
TR severity massive/torrential (%)	2.4	10	3.3	–	–	1.9
Outcomes at 30 days						
Mortality (%)	–	1	3.3	–	3.1	2.9
NYHA class III–IV (%)	–	21	28	–	–	44.3
Outcomes at 12 months						
Mortality (%)	18.5	–	11	19[a]	10.8	–
HHF (%)	–	–	15.6	28[a]	18.5	–

Only the characteristics reported in at least 50% of registries are shown here. For a more detailed description of included registries see online supplementary *Table S5*. All data are mean (standard deviation) or median [interquartile range] unless otherwise specified.

AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; HHF, hospitalization for heart failure; HT, hypertension; ICD, implantable cardioverter defibrillator; MV, mitral valve; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; P, prospective; R, retrospective; RASi, renin–angiotensin system inhibitor; RVFAC, right ventricular fractional area change; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

[a]Median follow-up of 330 (interquartile range 175–402) days.

TriCLASP, focused on the Pascal device for TR started in 2019 and 2021, respectively.[79,80]

Despite these differences, patients' demographics and comorbidities were similar across registries. All registries reported on age and sex, with mean age ranging between 76.4 and 80.3 years, and male proportion between 41.9% and 50%. HHF in the year before the procedure was reported in 50% of registries, ranging between 37.5% and 76%. AF (prevalence 61.8–95.9%), was the only comorbidity reported in all registries, with DM (prevalence 15.4–29.7%) and COPD (prevalence 13.1–24%) being reported in 83% of registries, CKD (prevalence 21–55.4%) and previous mitral valve intervention (prevalence 13–29.6%) being reported in 67% of registries, HT (prevalence 82.9–90.5%) being reported in 50% of registries, and CAD (prevalence 29.9–55.5%), PAD (prevalence 11–17.1%) and prior stroke (prevalence 8–10.8%) being reported in 33% of registries. NYHA class III–IV was reported in all registries, ranging between 70.8% and 92%. No specific mortality prediction score for TEER in TR is available. The TRI-SCORE, used to predict in-hospital mortality after tricuspid valve surgery, was applied in 16% of the registries, and the EuroSCORE II in 83%.

Systolic/diastolic blood pressure, heart rate, and BSA were never reported. BMI was reported in 50% of registries (26.1–27 kg/m^2). In the Bonn registry, 1-year all-cause mortality was significantly higher in patients who were underweight or obese compared with normal-weight or overweight patients.[75]

Echocardiographic findings, laboratory data, and treatments use

All registries reported TR severity and tricuspid annular plane systolic excursion (TAPSE). A massive (4+) or torrential (5+) TR affected 15–88% of patients. The bRIGHT and TriCLASP registries used a core echocardiographic laboratory for TR grading, with the latter reporting a significant difference between site-assessed severe (3+) or greater TR (100%) versus core echo-assessed (82.8%). TAPSE ranged between 14 and 18 mm.

Tricuspid valve EROA (0.4–0.8 cm^2), left ventricular EF (49.8–56.5%), and right ventricular end-diastolic diameter (4.0–4.63 cm) were reported in 83% of the registries, and sPAP (36.8–49 mmHg) was reported in 67% of registries.

Regarding laboratory measurements, eGFR (47.1–53.8 ml/min/1.73 m^2) and NT-proBNP (2760–4296 pg/L) were reported in 67% and 50% of the registries, respectively.

The use of RASi/ARNi, beta-blocker, and MRA was reported in 33% of the registries, while diuretic use was reported only in 17%. Use of beta-blockers (86.3–94.8%), RASi/ARNi (70.2–99.1%), and diuretics (94.8%) was consistently high, while MRA use varied (44.1–90.5%). Device use (ICD/CRT/pacemaker) was described in 67% of the registries and ranged between 23% and 33.6%, with no registry reporting on devices' individual use.

Procedural results and post-discharge outcomes

Mean procedural time varied widely across registries (50.6–122.9 min), with the TriValve registry, exclusively reporting MR TEER device for TR, having the longest time. Procedural time was not linked with the number of clips implanted (1–2), TR severity at discharge (massive/torrential in 2.4–10% of patients), or in-hospital mortality (0–2.7%), which were consistent among registries. The bRIGHT registry reported the highest proportion of patients with massive/torrential TR at discharge (10%). However, when participating centres were stratified by number of performed procedures, the first quartile had the highest proportion of massive/torrential TR at 30 days (26%), highlighting the importance of centre's experience.

Mortality at 30 days (1–3.3%) and 1 year (10.8–19%), as well as HHF at 30 days (0–4.5%) and 1 year (15.6–28%), were consistent across the registries, though slightly higher when compared with the device arm of the TRILUMINATE trial (all-cause mortality: 8.8%; HHF: 14.9%).

Only the bRIGHT and triCLASP registries reported on QoL and used the KCCQ overall summary score collected at baseline (44.5–51.4 points) and at 30 days, showing a significant improvement of 13.4–19 points.

Discussion

Our systematic review highlights that available TEER registries still have room for improvement in enhancing geographic representation, patient enrolment, and the number and definition of reported variables and outcomes.

One major limitation of the registries conducted to date is the relative paucity of data collected outside North America and Western Europe, with only two registries including data from Asia and one from the Gulf region. Similar limitation affects RCTs in this setting, with COAPT enrolling patients only in the USA/Canada, RESHAPE-HF2 and MITRA-FR in Europe, and the TRILUMINATE trial in the USA and more limitedly in Canada/Europe. Additionally, many centres involved in data collection contributed to multiple registries, which might lead to the same populations being included across different registries.

Most concluded registries represented a snapshot/had limited enrolment time, which challenges the assessment of quality of care over time, particularly for TEER whose therapeutic success depends on operator's expertise. Therefore, prospective registries with continuous enrolment might better capture the evolving outcome following TEER, including longer-term effectiveness and safety.

There is also the need for a standardized approach to data collection. Some registries collected data retrospectively, which is likely to be linked with a reduced number of measured variables. The amount of missing data was high for all the evaluated variables (online supplementary *Tables S3* and *S5*). This led to inadequate control for confounding, mostly due to the inability of including not-collected variables in the models, being the most represented source of bias (online supplementary *Table S2*). Differences in the reporting and definitions of patients' characteristics, number of clips, post-operative risk scores, follow-up lengths, and QoL questionnaire challenge comparing findings obtained by different registries assessing the same procedure. Notably, it is impressive the frequent lack of variables related to the severity of HF, such as the proportion of patients with a previous HHF,

Table 3 Future registries on valvular transcatheter edge-to-edge repair in heart failure required and suggested feature set

Feature	M	S	Description
Demographics			
Sex at birth	X		
Date of birth	X		
Date of enrolment	X		
Patient's characteristics and comorbidities			
History of heart failure	X		Newly diagnosed, <6 months, ≥6 months
Last heart failure hospitalization	X		Never hospitalized, <6 months, 6–12 months, ≥12 months
Ischaemic mitral regurgitation aetiology	X		Yes, No
Tricuspid regurgitation aetiology	X		Functional, degenerative, mixed, device induced. Only if TEER for TR
History of coronary artery disease	X		Yes, No
Atrial fibrillation	X		Yes, No
Arterial hypertension	X		Yes, No
Diabetes mellitus	X		Yes, No
Chronic kidney disease	X		Yes, No
Chronic obstructive pulmonary disease	X		Yes, No
Peripheral artery disease	X		Yes, No
Prior stroke	X		Yes, No
Smoking status		X	Never, previous, active
Weight	X		kg
Height	X		cm
Systolic blood pressure	X		mmHg
Diastolic blood pressure	X		mmHg
Heart rate	X		bpm
NYHA class	X		I, II, III, IV
EuroSCORE II	X		
TRI-SCORE		X	Only If TEER for TR
KCCQ	X		Overall score
Echocardiography			
Left ventricular ejection fraction	X		%
Left ventricular end-diastolic diameter		X	mm
Interventricular septal end-diastolic diameter		X	mm
Posterior wall end-diastolic diameter		X	mm
Left ventricular end-diastolic volume	X		mL
Left atrial volume		X	mL
Diastolic dysfunction		X	Yes, No
Effective regurgitant orifice area – mitral valve	X		Only If TEER for SMR
Mitral regurgitation severity	X		Mild (1+), moderate (2+), Moderate-to-severe (3+), severe (4+)
Mitral valve gradient		X	mmHg
Tricuspid annular plane systolic excursion	X		mm
Tricuspid valve mean gradient		X	mmHg
Systolic pulmonary artery pressure	X		mmHg
Effective regurgitant orifice area – tricuspid valve	X		Only If TEER for TR
Tricuspid regurgitation severity	X		Only If TEER for TR. Mild (1+), moderate (2+), severe (3+), massive (4+), torrential (5+)
Right ventricular fractional area change		X	Only If TEER for TR
Laboratory examination			
Natriuretic peptides	X		NT-proBNP (preferred), BNP, ng/L
Creatinine	X		mg/dl
Potassium	X		mEq/L
Sodium		X	mEq/L

Table 3 (Continued)

Feature	M	S	Description
Haemoglobin	X		g/dl
Ferritin		X	μg/L
Transferrin saturation		X	%
Medical therapy and devices			
ACEi/ARB/ARNi	X		Yes, No. If Yes, report type and daily dose in mg. If No, report the cause of lack of prescription
Beta-blocker	X		Yes, No. If Yes, report type and daily dose in mg. If No, report the cause of lack of prescription
MRA	X		Yes, No. If Yes, report type and daily dose in mg. If No, report the cause of lack of prescription
SGLT2i	X		Yes, No. If Yes, report type and daily dose in mg. If No, report the cause of lack of prescription
Loop diuretic	X		Yes, No. If Yes, report type and daily dose in mg
Other diuretic		X	Yes, No. If Yes, report type and daily dose in mg
Digoxin	X		Yes, No. If Yes, report type and daily dose in mg
Nitrates	X		Yes, No. If Yes, report type and daily dose in mg
Oral anticoagulant	X		Yes, No. If Yes, report type and daily dose in mg
GLP-1 receptor agonist	X		Yes, No. If Yes, report type and daily dose in mg
Antiplatelet therapy	X		Yes, No. If Yes, report type and daily dose in mg
Statin		X	Yes, No. If Yes, report type and daily dose in mg
Ezetimibe		X	Yes, No. If Yes, report type and daily dose in mg
PCSK9i		X	Yes, No. If Yes, report type and daily dose in mg
Device	X		No, ICD, PMK, CRT-P, CRT-D
Procedural details			
Treated valve	X		Mitral valve, tricuspid valve
Device system used	X		MitraClip, Pascal, TriClip. Report generation/type of the device used
Procedural time		X	min
Fluoroscopy time		X	min
Number of clips	X		1, 2, 3, 4, ≥5
MVARC technical success	X		Only If TEER for SMR. Yes, No
Circulatory support		X	No, mechanical, inotropes, vasopressors. Multiple choices allowed
Partial clip detachment		X	Yes, No
Device embolization		X	Yes, No
Major bleeding (VARC-2 definition)	X		Yes, No
Stroke	X		Yes, No
Myocardial infarction	X		Yes, No
Acute kidney injury (VARC-2 definition)	X		Yes, No
Discharge			
In-hospital death	X		Yes, No
Mitral regurgitation severity	X		Only if TEER for SMR. As reported in the echocardiography section
Tricuspid regurgitation severity	X		Only if TEER for TR. As reported in the echocardiography section
NYHA class	X		I, II, III, IV
30-day follow-up			
Death	X		Yes, No
Hospitalization for heart failure	X		Yes, No
NYHA class	X		I, II, III, IV
Mitral regurgitation severity	X		Only if TEER for SMR. As reported in the echocardiography section
Tricuspid regurgitation severity	X		Only if TEER for TR. As reported in the echocardiography section
KCCQ	X		Overall score
MVARC device success	X		Only if TEER for SMR. Yes, No
MVARC procedural success	X		Only if TEER for SMR. Yes, No
ACEi/ARB/ARNi	X		Yes, No. If Yes, report type and daily dose in mg. If No, report the cause of lack of prescription

Table 3 (Continued)

Feature	M	S	Description
Beta-blocker	X		Yes, No. If Yes, report type and daily dose in mg. If No, report the cause of lack of prescription
MRA	X		Yes, No. If Yes, report type and daily dose in mg. If No, report the cause of lack of prescription
SGLT2i	X		Yes, No. If Yes, report type and daily dose in mg. If No, report the cause of lack of prescription
Loop diuretic	X		Yes, No. If Yes, report type and daily dose in mg
Digoxin	X		Yes, No. If Yes, report type and daily dose in mg
Nitrates	X		Yes, No. If Yes, report type and daily dose in mg
GLP-1 receptor agonist	X		Yes, No. If Yes, report type and daily dose in mg
1 year follow-up/yearly follow-up			
Death	X		Yes, No
Hospitalization for heart failure	X		Yes, No
NYHA class	X		I, II, III, IV
Mitral regurgitation severity	X		Only if TEER for SMR. As reported in the echocardiography section
Tricuspid regurgitation severity	X		Only if TEER for TR. As reported in the echocardiography section
KCCQ	X		Overall score
MVARC patient success	X		Only If TEER for SMR. Yes, No
ACEi/ARB/ARNi	X		Yes, No. If Yes, report type and daily dose in mg. If No, report the cause of lack of prescription
Beta-blocker	X		Yes, No. If Yes, report type and daily dose in mg. If No, report the cause of lack of prescription
MRA	X		Yes, No. If Yes, report type and daily dose in mg. If No, report the cause of lack of prescription
SGLT2i	X		Yes, No. If Yes, report type and daily dose in mg. If No, report the cause of lack of prescription
Loop diuretic	X		Yes, No. If Yes, report type and daily dose in mg
Digoxin	X		Yes, No. If Yes, report type and daily dose in mg
Nitrates	X		Yes, No. If Yes, report type and daily dose in mg
GLP-1 receptor agonist	X		Yes, No. If Yes, report type and daily dose in mg
Device implantation	X		No, ICD, PMK, CRT-P, CRT-D. If value other than No, report date of implantation

M are mandatory characteristics, S are suggested characteristics.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BNP, B-type natriuretic peptide; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; GLP-1, glucagon-like peptide-1; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; MRA, mineralocorticoid receptor antagonist; MVARC, Mitral Valve Academic Research Consortium; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; PMK, pacemaker; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation; VARC, Valve Academic Research Consortium.

or of echocardiographic or laboratory measurements related to cardiac function, as well as of simple clinical variables that have a major impact on prognosis and therapy implementation, such as heart rate, blood pressure, BMI, and kidney function. This is even more relevant when we consider that these variables, when reported, were associated with long-term mortality and/or HHF in the included registries.[28,38,46,49,51,52,55,58,61,75] Furthermore, post-procedural data reported in current registries are limited to major clinical outcomes, whereas it would be of major value to assess clinical variables associated with the implementation of guideline-directed medical therapy, a significant determinant of post-procedural outcomes.[82–85]

Given these limitations, in *Table 3* we propose a framework for future prospective TEER registries including 'mandatory' and 'suggested' sets of variables. A case report form based on these variables is also provided (online supplementary *Figure S2*). The reporting of key cardiovascular and non-cardiovascular comorbidities, together with demographics, should be mandatory given their prognostic role, and to foster the design of studies aiming to shape the profile of those patients more likely benefiting from TEER. Despite the recent derivation and validation of post-operative risk score for TEER, we recommend using the EuroSCORE II for ease of interpretability and the current better implementation in clinical practice. QoL should be reported at baseline, 30 days, and 1 year. KCCQ might be recommended, given its use in TEER RCTs. Among echocardiographic measurements, we suggest a set of critical parameters to characterize SMR or TR (EF, LVEDV, EROA, MR severity, TR severity, sPAP, TAPSE, left atrial volume indexed, right ventricular fractional area change). As clinical variables, the collection of weight, height, systolic and diastolic blood pressure, heart rate, and NYHA class should be mandatory. Regarding laboratory measurements, NT-proBNP, eGFR, creatinine, sodium, potassium, and haemoglobin are essential for prognostication and identifying potential reasons behind suboptimal guideline-directed medical therapy optimization; they should be collected at baseline, 30 days, and 1-year follow-up. Ongoing key HF and cardiovascular treatments and relative doses, including ICD/CRT/pacemaker, should be reported at baseline, 30 days, and 1-year follow-up. As procedural outcomes, we suggest reporting the number of clips used, MVARC technical success, major bleeding and acute kidney injury according to the VARC-2 definitions, peri-procedural stroke and myocardial infarction, length of hospital stay, and in-hospital mortality. As long-term outcomes, MVARC device, procedural, and patient success should be reported together with all-cause mortality and HHF at 30 days and 1 year. MR, TR, and NYHA class should be evaluated at baseline, discharge, 30 days, and 1 year. Variables considered at the 1-year evaluation may be collected yearly for future follow-up if feasible.

Conclusions

Registries on TEER represent a key data source in a setting where it is difficult to conduct RCTs. Limitations in design, geographic representation, patient characterization, and outcomes reporting restrain their current use. A more standardized approach to data collection, as proposed in this manuscript, might provide the next generation of TEER registries with more generalizable and better characterized prospectively enrolled populations, encourage pooling data from different registries, and ultimately address important clinical questions with more feasible and broader real-world studies.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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