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Clinical Insights

A PUBLICATION DELIVERING CONCISE CLINICAL DATA

IMPACT OF RESIDUAL TR ON PROGNOSIS

SUMMARY

- *The safety of TTV repair is well documented,* ***but residual Tricuspid Regurgitation (TR) severity post procedure may potentially impact the prognosis.***
- *Recent publications on TR include one year outcomes from:*
  - *bRIGHT: first prospective, open label, multicenter, postmarket registry to evaluate TriClip™ Transcatheter Edge-to-Edge Repair System's safety and performance in a real world setting.*[1]
  - *TRIGISTRY: retrospective international multicenter registry across 10 countries and 33 centers, including 645 adult patients with severe isolated functional TR on a native valve who underwent medical management or surgical intervention or TTVI.*[2]
  - *EuroTR registry: real world registry including patients who underwent Tricuspid Transcatheter Edge-to-Edge Repair (T-TEER) for symptomatic TR from 2016 to 2022.*[3]
- *All three studies aim to evaluate the impact of residual TR on short or mid term mortality.*
- *bRIGHT and EuroTR use a 5 degrees TR severity grading approach, while TRIGISTRY uses a 3 degrees approach.*

BACKGROUND

Tricuspid regurgitation (TR) is a substantial health burden due to high rates of morbidity, mortality, and hospitalizations for heart failure that increase with the severity of the regurgitation (Fig. 1), as Benfari demonstrated analyzing more than 11.000 patients affected by HFrEF. The rapid evolvement of transcatheter tricuspid valve intervention (TTVI) enabled the treatment of TR even in patients with advanced or prohibitive surgical risk. The safety of TTV repair is well documented, but different degrees of severity of residual TR are observed in patients post procedure and may potentially impact the prognosis.

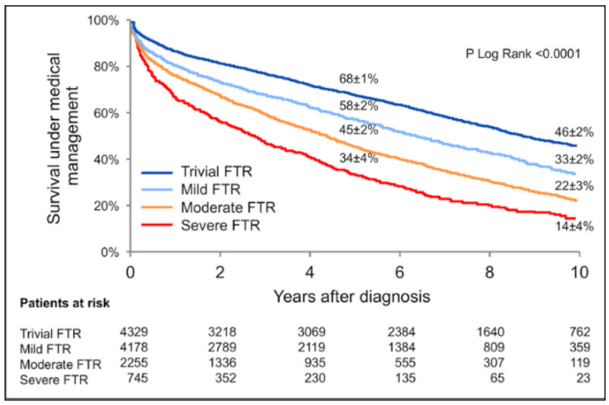


Fig. 1 Benfari et al. "Excess Mortality Associated with Functional Tricuspid Regurgitation Complicating Heart Failure With Reduced Ejection Fraction." Circulation 140, no. 3 (July 16, 2019): 196–206.

METHODS

bRIGHT is the first prospective, open label, multicenter, post market registry to evaluate the safety and performance of the TriClip TEER System in a contemporary, non selected real world cohort, using central assessment of events and echocardiographic characteristics, which enrolled 511 consecutive subjects at 26 sites in Europe from 26 August 2020 to 6 September 2022.[1]

TRIGISTRY is a retrospective international multicenter registry across 10 countries and 33 centers including adult patients with severe isolated functional TR on a native valve who were conservatively/medically managed, underwent an isolated TV surgery, or underwent TTVI. Clinical, laboratory, echocardiographic, and outcomes information were collected locally by each center. In TRIGISTRY, 645 adult patients underwent TTV repair (MitraClip™, TriClip™, PASCAL‡, CardioBand‡, Trialign‡, TriCinch‡) for severe isolated functional TR on a native TV; 509 patients (79%) were treated with T-TEER system, 125 patients (19%) with annuloplasty and 11 patients (1%) with other techniques.

The study population consisted of 613 patients after the exclusion of 16 patients (2.5%) who died after the intervention during the same hospitalization and 16 patients (2.5%) in whom TR residual severity was not documented at discharge.[2]

The **EuroTR** registry included patients who underwent T-TEER (MitraClip™/TriClip™ and PASCAL‡) for symptomatic TR from 2016 to 2022. The presented analysis includes 1286 patients, excluding those with concomitant Mitral TEER or missing information on pre or post procedural TR severity.[3]

These three registries collected different data at baseline and at follow up, but all of them have a common denominator: trying to evaluate the impact of residual TR (at discharge or at 30 days) on short (1 year) or mid term (2 years) mortality. Patients enrolled in the three studies might have different baseline characteristics and TR phenotypes, therefore they can't be compared. The baseline characteristics of the populations enrolled in the three studies are reported in table 1. The populations of the three studies are coming from a real world setting with very few exclusion criteria.

The **American Society of Echocardiography Guidelines**[4] **recommend** a multiparametric and hierarchical approach to TR assessment, which culminates in **a 3 class grading scheme** (mild [1+], moderate [2+], and severe [3+]) that continues to be used clinically. The increasing mortality risk associated with increasing TR severity supports an **extended grading scheme**, stratifying the "severe" grade of TR into severe (3+), massive (4+), and torrential (5+), as **recommended by the recent TVARC 2023.**[5]

bRIGHT and EuroTR use the 5 degrees scheme while TRIGISTRY uses a 3 degrees approach extended to 4, splitting the moderate (2+) into two additional categories mild to moderate and moderate to severe (as shown in Figure 2) – adopting the measurement from the mitral regurgitation evaluation recommendations.

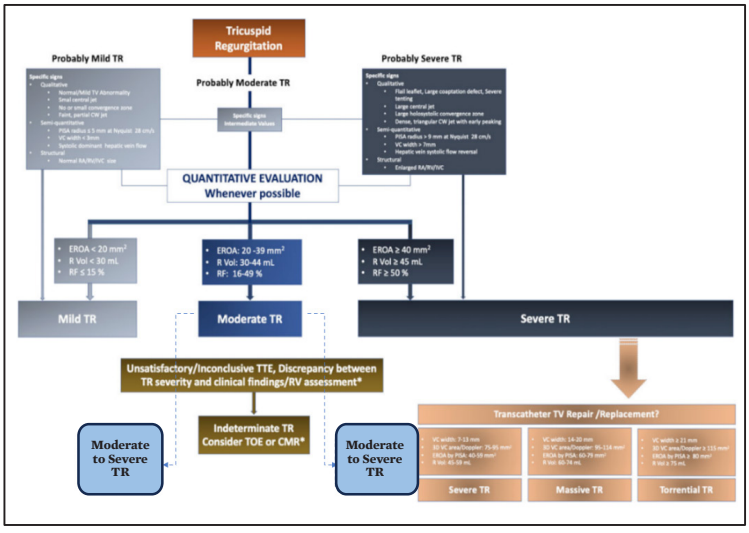


Fig. 2 Lancellotti, Patrizio, Pibarot P, et al. "Multi Modality Imaging Assessment of Native Valvular Regurgitation: An EACVI and ESC Council of Valvular Heart Disease Position Paper." European Heart Journal Cardiovascular Imaging, March 16, 2022, jeab253.

Table 1 [1,2,3]

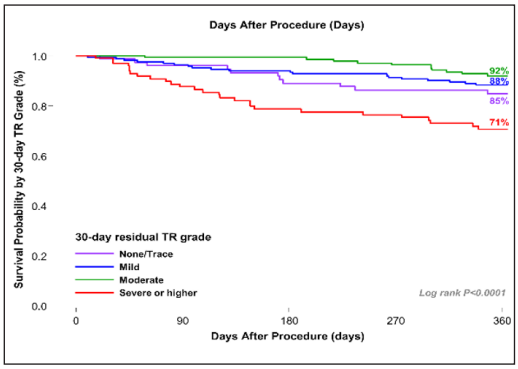
Variable	*bRIGHT*	*TRIGISTRY*	*EuroTR*
	N=511	N=613	N=1286
Age (years)	79 ± 7	78 ± 8	78.0 ± 8.9
Female sex	56%	60%	53.6%
NYHA Class III or IV	80%	86%	83.8%
Prior CRT/CRT-D/ICD/PM	23%	29%	28.2%
TR etiology			
Primary	0%	0%	7.6%
Secondary	90%	100%	84.1%
Mixed	10%	0%	8.3%
Baseline TR severity			
Severe	10%	na	47.0%
Massive	61%		33.4%
Torrential	27%		17.3%
EUROscore II (%)	7.6 ± 8.0	na	6.5 ± 5.8
Coaptation gap (mm)	6.49 ± 2.7	na	6.3 ± 3.1
LVEF (%)	56 ± 10	54 ± 11	53.5 ± 11.2
RV TAPSE (cm)	1.7 ± 0.4	na	1.71 ± 0.45
Moderate / Severe RV dysf.	na	23%	na
RVEDD (cm)	4.6 ± 0.9	na	4.89 ± 0.96
TV annulus diameter in AP4CH	na	44 ± 6	45.2 ± 8.4
sPAP (mmHg)	40 ± 12	45 ± 15	43.2 ± 14.6
Chronic renal disease	40%	na	na
GFR (mL/min)	na	53 ± 20	46.8 ± 24.1

bRIGHT enrolled 88% of patients with massive/torrential TR, EuroTR 50.7% while TRIGISTRY did not distinguish between severe, massive and torrential severity at baseline.

KEY RESULTS

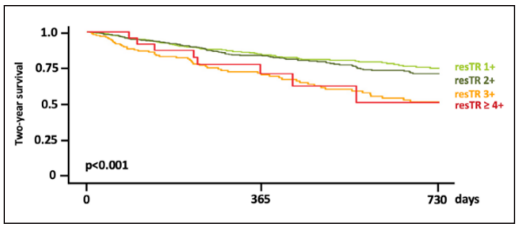
bRIGHT

In **bRIGHT,** paired analysis (n=317) showed that TR grade was moderate or less in 85% of subjects at 30 days and in 81% of subjects at 1 year. Separation by 30-day residual TR grade showed that survival was significantly lower at 1 year in subjects with TR severe or higher at 30 days (70.6%; P<0.0001 overall) compared with subjects with moderate (91.9%; P<0.0001), mild (88.2%, P=0.0003), or trace TR (84.8%, P=0.03). **Subjects with residual moderate, mild or trace TR did not have significantly different survival at 1 year (P=0.40).**



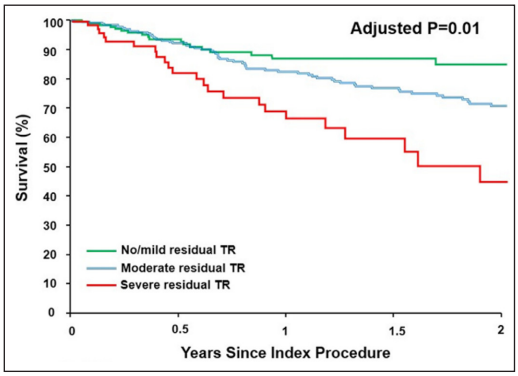
EUroTR

EuroTR presented similar outcomes to bRIGHT, extending the analysis up to two years. Residual TR ≥3+ (severe) after T-TEER was associated with reduced 2-year survival probability (54.2% vs. 74.4% in patients with residual TR ≤2+, p<0.001). Of note, **reducing TR severity to ≤1+ did not lead to significantly higher survival rates compared to residual TR 2+** (76.2% in patients with TR ≤1+ vs. 73.1% in patients with TR 2+, p=0.461).

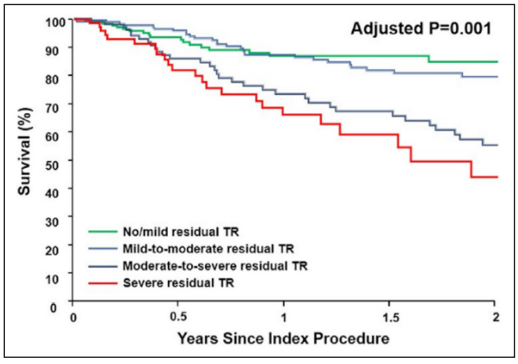


TRIGISTRY

TRIGISTRY data was analyzed in 2 ways, considering the residual TR at discharge: once **using a 3-degree grading scheme** and then using a 4-degree grading scheme. Survival was markedly different between patients with no/mild, moderate, and severe residual TR (85%, 70%, and 44%, respectively; P = 0.0001). The survival rates of patients with no/mild residual and moderate TR were both significantly better than the survival of patients with severe TR. Importantly, **the survival of patients with moderate residual TR was not significantly different than the survival of patients with no/mild residual TR.**



Adopting the 4-grade grading scheme, of the 319 patients with moderate TR at discharge, 201 had mild to moderate residual TR (33% of the overall study population), and 118 had moderate to severe residual TR (19%). The 2-year survival rate was markedly different between the 4 groups (85%, 80%, 55%, and 44% in patients with no/mild, mild to moderate, moderate to severe, and severe residual TR, respectively).



PERSPECTIVE

Even if TTVI is still in an early stage of development, therapies can be divided in two groups: repair (mainly through T-TEER) and replacement. Transcatheter replacement devices have been designed to eliminate TR, which is not always achieved with TEER. In regards to safety, the two therapies show two different safety profiles.

Based on the intent of the therapy, one should understand if TR elimination is providing a better prognosis for the patient. There is not yet a clear answer now, but the three studies presented here drive in a similar direction: there seems to be no statistically significant difference in 1 year and 2 year survival for patients with no/mild versus moderate residual TR at 30 days.

The charts here below represent the survival at 1 or 2 years for the three studies; on the left severe TR is shown for all the three studies; on the right the chart shows curves for trace, mild or moderate residual TR of all the three studies.

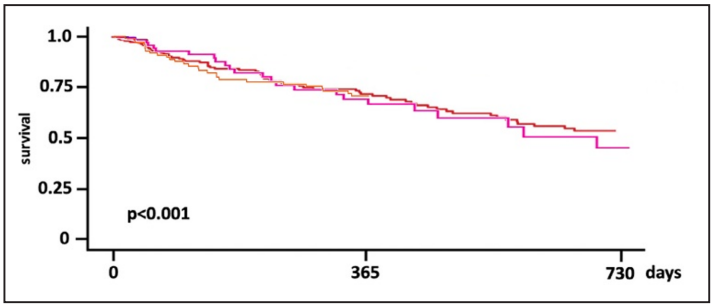


Fig. 3 KM Curves from TRIGISTRY, EuroTR, and bRIGHT showing 2-year survival of patients with residual severe TR.

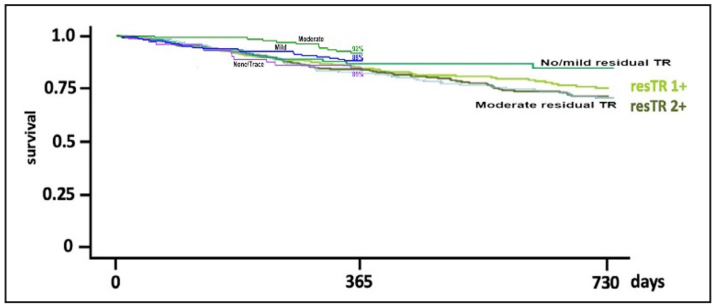


Fig. 4 KM Curves from TRIGISTRY, EuroTR, and bRIGHT showing 2-year survival of patients with residual TR moderate or less. The different curves represent the different residual TR grades.

The severe TR KM curves (left picture) are completely overlapping, demonstrating that population enrolled in different countries and centers, defined as real world or treated as clinical practice, are impacted the same way by a residual at least severe TR.

The no / mild / moderate KM curves (right picture) are also well aligned, showing similar trends in the survival probability and reinforcing again the similar outcome of moderate or less TR. This is clearly stated by Lurz and Stolz in bRIGHT and EuroTR; Dreyfus in TRIGISTRY comes to the same conclusion and tries to further analyze the data, proposing a more granular approach to evaluate patients with moderate TR.

The introduction of the 4 degrees in the lower spectrum of the TR could be allowing a more precise evaluation of the prognosis, as the extension in the higher range is permitting. TR in fact can assume any value in the range from none to torrential in a continuous way, but we should validate if this stratification is really needed, to better predict the impact on prognosis.
With all these considerations, at the moment there is no clear evidence if there is a sort of minimal threshold of residual TR (like moderate), below which the benefit is not getting better or if bringing down to none/mild residual TR allows for a long term better prognosis.

Based on the evidence of these three studies, achieving TR moderate or less seem to be sufficient to result in a mortality benefit. Longer follow-ups and additional studies in the future will provide better applicability of the therapies available for patients with tricuspid regurgitation.

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Important Safety Information

TRICLIP™ G4 SYSTEM

INDICATIONS

The TriClip™ G4 System is indicated for improving quality of life and functional status in patients with symptomatic severe tricuspid regurgitation despite optimal medical therapy, who are at intermediate or greater risk for surgery and in whom transcatheter edge to edge valve repair is clinically appropriate and is expected to reduce tricuspid regurgitation severity to moderate or less, as determined by a multidisciplinary heart team.

CONTRAINDICATIONS

The TriClip G4 System is contraindicated in patients with the following conditions: Intolerance, including allergy or untreatable hypersensitivity, to procedural anticoagulation; Untreatable hypersensitivity to Implant components (nickel titanium alloy, cobalt chromium alloy); Active endocarditis or other active infection of the tricuspid valve.

POTENTIAL ADVERSE EVENTS

The following events have been identified as possible complications of the TriClip G4 Procedure. Allergic reactions or hypersensitivity to latex, contrast agent, anaesthesia, device materials and drug reactions to anticoagulation, or antiplatelet drugs; Additional treatment/surgery from device related complications; Bleeding; Blood disorders (including coagulopathy, hemolysis, and heparin induced thrombocytopenia (HIT)); Cardiac arrhythmias (including conduction disorders, atrial arrhythmias, ventricular arrhythmias); Cardiac ischemic conditions (including myocardial infarction, myocardial ischemia, unstable angina, and stable angina); Cardiac perforation; Cardiac tamponade; Chest pain; Death; Dyspnea; Edema; Embolization (device or components of the device); Endocarditis; Fever or hyperthermia; Fluoroscopy and transesophageal echocardiogram (TEE) related complications: Skin injury or tissue changes due to exposure to ionizing radiation, Esophageal irritation, Esophageal perforation, Gastrointestinal bleeding; Hypotension/hypertension; Infection including: Septicemia; Nausea or vomiting; Pain; Pericardial effusion; Stroke/cerebrovascular accident (CVA) and transient ischemic attack (TIA); System organ failure: Cardio respiratory arrest, Worsening heart failure, Pulmonary congestion, Respiratory dysfunction or failure or atelectasis, Renal insufficiency or failure, Shock (including cardiogenic and anaphylactic); Thrombosis; Tricuspid valve complications, which may complicate or prevent later surgical repair, including: Chordal entanglement/rupture, Single leaflet device attachment (SLDA), Dislodgement of previously implanted devices, Tissue damage, Tricuspid valve stenosis, Worsening, persistent or residual regurgitation; Vascular access complications which may require additional intervention, including: Wound dehiscence, Bleeding of the access site, Arteriovenous fistula pseudoaneurysm, aneurysm, dissection, perforation (rupture), vascular occlusion, Embolism (air, thrombus), Peripheral nerve injury; Venous thrombosis (including deep vein thrombosis) and thromboembolism (including pulmonary embolism).

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3200 Lakeside Dr., Santa Clara, CA. 95054 USA

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