Prevalence of moderate-to-severe TR suitable for percutaneous intervention in TTE patients

Z H Teoh, J Roy, J Reiken, M Papitsas, J Byrne and M J Monaghan
Department of Cardiology, King’s College Hospital, London, UK
Correspondence should be addressed to Z H Teoh: zhi.teoh@nhs.net

Abstract
Moderate-to-severe tricuspid regurgitation is associated with higher mortality and morbidity yet remains significantly undertreated. The reasons for this are complex but include a higher operative mortality for patients undergoing isolated tricuspid valve surgery. This study sought to determine the prevalence of patients with moderate-to-severe tricuspid regurgitation and identify those who could be potentially suitable for percutaneous tricuspid valve intervention by screening patients referred for transthoracic echocardiography (ECHO) at a tertiary center. Our results showed that the prevalence of moderate-to-severe tricuspid regurgitation in our total ECHO patient population was 2.8%. Of these, approximately one in eight patients with moderate-to-severe tricuspid regurgitation would be potentially suitable for percutaneous intervention and suggests a large, unmet clinical need in this population.

Introduction
It is estimated that tricuspid regurgitation occurs in 8–35% of patients (1) with several studies demonstrating that severe tricuspid regurgitation is associated with higher morbidity and mortality, independent of age or biventricular systolic function (2, 3).

Despite this, current American Heart Association (AHA) and American College of Cardiology (ACC) guideline recommendations give a class I indication for tricuspid valve (TV) repair only for patients undergoing concomitant left-sided valve surgery (4). The 2017 European Society of Cardiology (ESC) and European Association for Cardio-thoracic Surgery (EACTS) guidelines mirror this recommendation, but also support surgery in symptomatic patients with severe isolated primary tricuspid regurgitation without right ventricular dysfunction (5). One of the major reasons for the limited recommendation is the elevated surgical mortality rate associated with isolated TV surgery, which may be as high as 9.8% (6, 7).

However, percutaneous interventions targeting tricuspid regurgitation have recently begun to emerge. These can broadly be categorized into several categories, namely edge-to-edge coaptation devices, annuloplasty devices, space occupying devices and caval valve implantation devices (8, 9). These have been shown to be safe, to reduce tricuspid regurgitation (TR) and to improve quality of life outcomes. Nonetheless, these have been limited to trials involving a relatively small number of patients (10, 11). Larger scale trials are expected to follow this.

Our team therefore sought to determine the prevalence of patients with moderate-to-severe TR and identify those who could be potentially suitable for percutaneous TV intervention.
Methods

Retrospective cross-sectional study of all patients at King’s College Hospital, London referred for TTE between January 1, 2016, and December 31, 2016. Clinical information about the severity of TR was obtained retrospectively from formalized transthoracic ECHO reports of patients. Other ECHO parameters assessed included left ventricular ejection fraction (LVEF), right ventricular systolic pressure (RVSP), presence of aortic valve stenosis or regurgitation, presence of mitral valve stenosis or regurgitation, presence of previous aortic or mitral valve interventions and previous TV replacement or repair.

All ECHO assessments and reports were done independently by British Society of Echocardiography–accredited echocardiographers who were not aware of the study at the time and were performed as part of a routine clinical service. The severity of TR was graded using standard quantitative criteria as specified by European Association of Cardiovascular Imaging (EACVI) and American Society of Echocardiography (ASE) guidelines (12, 13).

A two-step screening process was adopted for this study, based on the ECHO inclusion criteria for percutaneous TV annuloplasty (Trialign) from the SCOUT trial as published by Hahn et al. (10). First, patients were screened based on their ECHO report for eligibility for percutaneous TV annuloplasty. This was defined using all of the following criteria: LVEF >35%, RVSPs ≤60 mmHg and the absence of significant aortic or mitral valve regurgitation or stenosis. Significant valve pathology was defined as the presence of ≥moderate valvular regurgitation or stenosis based on EACVI/ASE guidelines.

As tricuspid annular plane systolic excursion (TAPSE) was not specifically reported in a significant number of the ECHO reports, ECHO images for patients who fulfilled all the above criteria were re-assessed retrospectively by an experienced echocardiographer who was blinded to the age, gender and TR severity with the ECHO images fully anonymized for patient identifiable data. ECHO parameters re-assessed included TAPSE, presence of pacemaker leads, etiology of TR, vena contracta, tricuspid annulus dimensions, right ventricular dimensions, distance of TV annulus plane to right ventricular apex and right ventricular fractional area change (RVFAC). It was not possible to re-assess the effective regurgitant orifice area (EROA) in a significant number of patients due to insufficient image quality. As per the SCOUT trial ECHO exclusion criteria, the study excluded patients with previous tricuspid replacement or repair, pacemaker leads or primary TR. Only patients over the age of 18 years were included in the study.

The initial retrospective analysis and screening for patients with moderate-to-severe TR was registered and approved by the King’s College Hospital quality improvement and audit committee. Subsequently, analysis and reassessment of the ECHO images were performed with the data fully anonymized and therefore did not require further ethical committee approval and was discussed with the audit.

Results

Overall, 12 000 patients were referred for Transthoracic Echo between January 1, 2016, and December 31, 2016, at King’s College Hospital, London. Three hundred thirty-eight patients were reported as having at least moderate TR.

Their baseline demographics are shown in Table 1. The mean age was 74±14.4 years and 60.4% were women. Thirty-two (9.5%) patients had previous mitral valve intervention, 33 (9.8%) had previous aortic valve intervention and 6 (1.8%) had both previous aortic and mitral valve intervention.

Therefore, the prevalence of moderate-to-severe TR within the Echo referral patient population at King’s College Hospital, London was 2.8%.

As illustrated in Fig. 1, based on their ECHO report, 126 (37.3%) patients with moderate-to-severe TR had

<table>
<thead>
<tr>
<th>Baseline demographics of the 338 patients with moderate-to-severe tricuspid regurgitation.</th>
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<tr>
<td><strong>Age (years)</strong></td>
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<td><strong>Female (%)</strong></td>
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<tr>
<td><strong>Prior myocardial infarction (%)</strong></td>
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<td><strong>Prior PCI (%)</strong></td>
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<td><strong>Hypertension (%)</strong></td>
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<td><strong>Hyperlipidemia (%)</strong></td>
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<td><strong>History of pulmonary hypertension (%)</strong></td>
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<td><strong>Diabetes (%)</strong></td>
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<td><em><em>Chronic renal disease</em> (%)</em>*</td>
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<td><strong>Peripheral vascular disease (%)</strong></td>
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<td><strong>Cerebrovascular disease (%)</strong></td>
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<td><strong>Atrial fibrillation (%)</strong></td>
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Values are mean±s.d.

*Renal Function n/a for 19 patients.

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.
LVEF >35%, absence of previous significant mitral or aortic valve pathology and RVSP ≤ 60 mmHg.

Subsequent further reassessment of their ECHO images revealed that 44/338 (13%) or approximately one in eight patients would be potentially eligible for percutaneous TV intervention based on their ECHO parameters. Other ECHO parameters are presented in Table 2.

**Discussion**

Severe TR is independently associated with worsening morbidity and mortality outcomes (2, 3). Despite this, the indications for isolated TV surgery are limited to those patients undergoing concomitant left-sided valve surgery or those with isolated TR with right ventricular...
dysfunction. With these conservative guidelines, only a proportion of this subgroup of patients will undergo TV surgery, principally because of the increased mortality rates in this cohort. As a result, TR remains significantly undertreated; estimated to be <0.5% of patient population in the United States (14).

The advent of less-invasive percutaneous interventions targeting the TV could potentially address this – a large, currently unmet clinical need. Many of these techniques are based upon proven surgical techniques, but to date have only been studied in small feasibility trials (9, 10, 11, 15, 16, 17, 18).

The number of patients who would be potentially eligible or benefit from these percutaneous interventions is still unknown. Based upon the ECHO eligibility criteria for percutaneous TV annuloplasty, as described by Hahn et al. (10), this study aimed to quantify the prevalence of this particular group within our TTE referral patient population; recognizing that this will underestimate the prevalence of this pathology in the general population.

Approximately one in eight patients with moderate-to-severe TR would potentially be eligible for percutaneous TV annuloplasty based on their echocardiographic parameters.

### Study limitations

However, there remain certain limitations to this retrospective study. The echocardiographers were not aware that patients were being screened for potential percutaneous intervention and did not perform tricuspid-specific ECHO views. Therefore, in a few cases, certain ECHO parameters crucial for determining eligibility were missing from their reports.

More importantly, the reports did not differentiate between primary or secondary TR. Currently, percutaneous tricuspid intervention is only available to patients with secondary TR.

In order to mitigate against this, a two-step analysis process was designed for this study. In the first step, patients were identified based on ECHO parameters (LVEF, mitral/aortic pathology and RVSP) already reported on their ECHO. In the second step, patients still deemed eligible had their ECHO images re-analyzed for further ECHO parameters including etiology of TR, TAPSE and so on as outlined in the ‘Methods’ section.

However, the lack of dedicated tricuspid-specific ECHO views meant that certain ECHO criteria still could not be measured due to image quality. This included tricuspid EROA, which would require 3D ECHO for precise analysis.

Furthermore, RVSP was assessed by measuring the TR jet maximum velocity and right atrial pressure via the collapsibility index. In patients with severe TR, this could theoretically underestimate the RVSP. However, the use of more accurate measurement techniques, for example right heart catheterization to screen patients would not be possible, be it for practical or ethical reasons in this cohort; neither was it utilized in the initial percutaneous TV annuloplasty feasibility study as described by Hahn et al. (10), which this study was based upon.

### Conclusion

In summary, moderate-to-severe TR is associated with significant poor outcomes, but remains undertreated for complex reasons, including concerns around increased operative risk. Percutaneous interventions which target the TV have the potential to address this large, unmet clinical need. Our study demonstrates that approximately one in eight patients with moderate-to-severe TR would potentially be eligible for percutaneous intervention.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

### Table 2

| Tricuspid annular plane systolic excursion (TAPSE) (cm) | 1.88 ± 0.47 |
| TR vena contracta (cm) | 0.69 ± 0.17 |
| TV annular diameter (cm) | 3.87 ± 0.71 |
| RV diameter (cm) | 3.33 ± 0.63 |
| Distance from TV annulus plan to RV apex (cm) | 7.03 ± 0.94 |
| RVFAC (%) | 37.05 ± 10.95 |

Values are mean ± S.D.

LVEF, left ventricular ejection fraction; RV, right ventricle; RVFAC, right ventricular fractional area change; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation; TV, tricuspid valve.
References


