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Endpoints for tricuspid regurgitation trans-catheter therapy trials☆

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ABSTRACT

Tricuspid regurgitation (TR), particularly functional or secondary TR, is increasingly recognized in clinical practice and when at least moderate in severity is associated with significant increase in mortality. In recent years multiple new trans-catheter devices have been developed to treat tricuspid regurgitation and are now undergoing clinical trial evaluations. The choice of appropriate endpoints in TR trials is particularly challenging as the disease is complex, often co-exists with left heart disease and pulmonary hypertension, and has not been extensively studied. Endpoints utilized in left heart disease trials have been applied with success to TR trials, and innovative trial designs will allow the initiation of pivotal randomized trials. Ultimately the development of TR specific endpoints may provide for more specific and robust assessment of these novel therapies.

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Introduction

Tricuspid regurgitation (TR) is a prevalent valve disorder of both primary (degenerative) and secondary (functional) etiologies, with the latter comprising the vast majority of cases.[1] There are multiple possible "etiologies" of functional TR including significant left heart valve disease, primary right ventricular (RV) disease, pulmonary hypertension (PH), atrial fibrillation (AFib) or heart failure (HF) either with reduced or preserved ejection fraction.[2–4] Data from the Framingham Heart Study suggest the overall prevalence of TR with at least mild severity is 14.8% in males and 18.4% in females.[5] The predictors of TR were age (OR 1.5/9.9 years; 95% CI 1.3 to 1.7), body mass index (OR 0.7/4.3 kg/m^2; 95% CI 0.6 to 0.8), and female gender (OR 1.2; 95% CI 1.0 to 1.6). By the 8th decade of life, 5.6% of females and 1.5% of males had TR of at least moderate severity. These findings have been confirmed in other population studies.[6] Some studies suggest over 1.6 million patients in the United States (US) may currently be suffering from this disease.[7]

Contemporary natural history and outcomes studies have shown an increased mortality associated with greater severity of TR.[4,8–11] The findings from these studies are consistent: 1) there is an independent relationship of TR to mortality (multivariable analysis) and 2) there is increasing mortality with increasing grades of TR severity. TR thus represents an important unmet treatment need given its prevalence, adverse prognosis, and symptom burden associated with progressive right HF.[12] Current guidelines recommend concomitant tricuspid valve (TV) intervention for severe primary or secondary TR at the time of

Abbreviations and acronyms: 6MWD, 6-minute walk distance; AFib, atrial fibrillation; CE, Conformité Européenne; CVD, cardiovascular disease; FDA, US Food and Drug Administration; HF, heart failure; MDR, Medical Device Regulation; PH, pulmonary hypertension; QoL, quality of life; RV, right ventricular; TR, tricuspid regurgitation; TV, tricuspid valve; US, United States.

☆ Statement of conflict of interest: see page 481.

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left heart sugery.[1] TR however is a progressive disease[13,14] and in patients who develop severe TR late after left heart valve surgery, reoperative mortality may be as high as 35%.[2,15–18] Recent retrospective studies suggest the in-hospital mortality associated with isolated TV surgery is ~9%[19,20] resulting in a growing interest in the transcatheter solutions for TR[21,22] and a need for standardized clinical trial pathways and endpoint definitions to evaluate outcomes in patients with TR.

TR however presents an unusual disease since it has been, until now, underappreciated and understudied. Our incomplete understanding of the complexity of TV disease and the role of the RV and the pulmonary vasculature, also affected by left heart disease, hampers the identification of specific TR morphologies and appropriate patient populations who may benefit from these therapies.[23] As our understanding of the pathophysiology and natural history of TR grows, transcatheter devices will evolve, appropriate treatment populations will be better defined, and clinical trial design with associated endpoints will necessarily change.

The path to device approval

Historically clinical trial designs have differed for European and US regulatory bodies. In Europe, Conformité Européenne (CE) mark process has until now required demonstration that the device is safe and performs both functionally and technically as the manufacturer intends through randomized trials or well performed registries with efficacy and long-term outcomes investigated after CE mark approval. Upcoming changes under the new Medical Device Regulation (MDR) are expected, however, to significantly increase approval requirements in Europe.[24]

For Food and Drug Administration (FDA) regulatory purposes, non-randomized early feasibility studies test safety and technical feasibility and generate preliminary efficacy data. PMA (Pre-Market Approval) has traditionally required randomized trials with “hard” clinical endpoints such as mortality (total or cardiovascular disease [CVD]) and HF hospitalizations. Recently the FDA has issued guidelines for a “breakthrough device” designation.[25] Under the Breakthrough Device Program innovative (“breakthrough”) devices, which treat life threatening or irreversibly debilitating disease may be approved based on surrogate endpoints, followed by post-marketing studies with longer term clinical endpoints.

Clinical endpoints

Natural history studies suggest the 1-year mortality for severe TR may be as high as ~20–30%.[4,8–11] Mortality is therefore a key endpoint in any TR therapy trial. As patients may die of cardio-renal as well as liver complications, total mortality as opposed to CVD mortality should be assessed.

Hospitalizations for HF (typically fluid overload) are an important endpoint. Diuretics, the mainstay of therapy for symptomatic TR,[1] may be administered in the emergency department, clinic, or even home setting. Intensification of diuretic therapy (oral or intravenous), could be used to define a HF hospitalization ‘equivalent event’. Data from the large PARADIGM trial has demonstrated that these hospitalization equivalent events have similar prognostic implications.[26]

Functional endpoints such as six- minute walk distance (6MWD) have frequently been used in HF,[27] pulmonary hypertension[28,29] and transcatheter device trials[30,31] and have been shown to correlate with hard outcomes thus is an accepted endpoint by regulatory agencies.[32] The limitations of 6MWD include the effect of comorbidities such as orthopedic issues and limited reproducibility and training effect. These limitations are reflected in the wide standard deviations in 6MWD data.

Quality of life (QoL) as assessed by HF specific questionnaires can also be incorporated. Both the Minnesota Living with HF and the Kansas City Heart Failure Questionnaire were originally developed for left HF, but appear to be useful for right HF as well, with improvement demonstrated in early feasibility studies of TR therapies.[33] The SF-12 or SF-36 scales, Rose dyspnea scale, and the EuroQol may also be used to capture more non-specific aspects of QoL.[34–38]

Supportive secondary endpoints could include echocardiographic findings such as reduction in TR and improvement in right heart volumes and function, as well as increase in cardiac output. Secondary clinical endpoints may include improvements in renal or hepatic function and decreases in edema measures. A reduction in diuretic requirement may also be an appropriate secondary endpoint as is a reduction in brain natriuretic peptides.

Safety assessments should include both short- and long-term procedural and device-related complications, and a primary safety endpoint (separate from the primary effectiveness endpoint) should be prespecified. The duration of follow-up must be sufficient to ensure durability of treatment effect relevant to the population and device being studied.

Except in the case of device vs. device trials, safety will typically need to be assessed with a performance goal, as the safety endpoints (such as hemorrhagic or vascular complications) will occur only in the device arm. Safety, however, should be interpreted in the context of efficacy, as a higher tolerance of complications may be acceptable if the efficacy signal is strong. Alternatively, a holistic measure, such as all-cause hospitalization may be utilized to compare the overall safety of the two arms, device and control. If a device is both efficacious and relatively safe, it should reduce overall hospitalizations compared to a control, which is typically medical therapy.

The reasonable choice of a comparator therapy in randomized trials for new TR devices will likely be medical therapy since the only Class I indication for surgery in secondary TR is at the time of left heart valve surgery. Indeed, given the high in-hospital mortality associated with isolated TR surgery of nearly 9%,[19,20] it may not be reasonable to randomize patients to open surgical intervention. Another possibility is to choose a control therapy characterized as best current clinical practice – either medical therapy or surgery – at the discretion of the Heart Team.

Composite endpoints and novel trial designs

Time to heart failure hospitalization and time to death may be combined into a composite endpoint, but it may be advantageous to incorporate both hard endpoints, functional and quality of life endpoints into a single composite endpoint. Moreover, as HF hospitalizations recur, including the number of heart failure hospitalizations over a 1 or 2 year time frame is also informative. One way to combine various disparate endpoints which are not equivalent in their severity and are also not assessed on the same scale is to use a hierarchal composite endpoint. One such methodology which is particularly applicable here is the Finkelstein-Schoenfeld[39] and its accompanying Win Ratio[40] methodology. In this approach death is typically assessed first, followed by HF hospitalization, followed by QoL and/or functional status, such as 6MWD. In the Finkelstein-Schoenfeld approach patient pairs are created by matching each patient in the treatment group with each patient in the control group. A win is declared if an endpoint is met, with assessment done in a hierarchal manner, such that a mortality event supersedes other events. If in the pair of patients being compared both are alive then the number of heart failure hospitalizations is compared, followed if a tie occurs (no hospitalizations or equal number of hospitalizations) by a comparison of QoL or functional status. Such methodology allows appropriate hierarchical treatment of endpoints and improves statistical power for a given sample size.

TR specific endpoints

Many of the endpoints, both hard clinical and surrogate endpoints have in essence been “borrowed” from HF trials and device trials aimed primarily at the left side of the heart. While undoubtedly also

applicable to some extent on the right side of the heart in general and for TR in particular, there are aspects of TR which are unique. Examples include symptoms of hepatic congestion, ascites, abdominal fullness, decreased appetite, nausea, and edema. It may be advantageous to develop and validate TR specific endpoints and instruments. These may include objective measurements such as inferior vena cava size as well as specific QoL instruments which assess the impact of TR related symptoms. Liver stiffness as a marker of liver congestion and systemic volume status, has recently been associated with worse outcomes in patients with HF, and may be particularly applicable to TR trials.[41]

Future directions and conclusions

TR has emerged as an important disease and innovation in device development is advancing at a rapid pace, particularly with transcatheter and/or minimally invasive approaches. Mimicking prior surgical approaches, trans-catheter annuloplasty, valve repair, and valve replacement are now in early-feasibility trials or are already embarking on pivotal trial pathways. The advent of the Breakthrough Devices Program will hopefully allow for innovation in trial design and the use of surrogate endpoints such as highlighted above for initial approval with a limited label for indicated clinical use. Post-approval studies would then be necessary for label extension and long-term approval and reimbursement. Trial design and endpoint determinations will require continuous updating as more data becomes available.

Statement of conflict of interest

Dr. Hahn reports speaker fees from Boston Scientific Corporation, Baylis Medical, Edwards Lifescience and Medtronic; consulting for Abbott Structural, Edwards Lifesciences, Gore&Associates, Medtronic, Navigate, and Philips Healthcare; non-financial support from 3mensio; Equity with Navigate; and is the Chief Scientific Officer for the Echocardiography Core Laboratory at the Cardiovascular Research Foundation for multiple industry-sponsored trials, for which she receives no direct industry compensation.

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