Comparison of Survival in Patients With Clinically Significant Tricuspid Regurgitation With and Without Heart Failure (From the Optum Integrated File)

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This study aimed to quantify survival rates for patients with tricuspid regurgitation (TR) using real-world data. Several clinical conditions are associated with TR, including heart failure (HF), other valve disease (OVD), right-sided heart disease (RSHD), and others that impact mortality. Optum data from January 1, 2007, through December 31, 2018 included patients age ≥18 years with TR and 12 months of continuous health plan enrollment before TR. Exclusion criteria were end-stage renal disease or known/primary organ pathology. Cohorts were created hierarchically: (1) TR with HF; (2) TR with OVD (no HF); (3) TR with RSHD only (no OVD or HF); (4) TR only. Survival was estimated using a Cox hazard model with an interaction term for TR severity and adjusted for patient demographics and Elixhauser co-morbidities. A total of 33,686 met study inclusion (1) TR with HF (26.6%); (2) TR with OVD (36.7%); (3) TR with RSHD only (17.1%); (4) TR only (19.6%). TR patients (regardless of severity) with HF, OVD or RSHD had an increased risk of mortality compared with patients with TR alone. TR severity was also significantly associated (hazard ratio = 1.33; p = 0.0002) with an increased risk of all-cause mortality. In conclusion, TR severity is significantly associated with an increased risk of all-cause mortality, independent of associated conditions including HF, OVD, or RSHD. In patients with severe TR, the mortality risk is most pronounced for patients who had RSHD without HF or OVD before their TR diagnosis. **(Am J Cardiol 2021;144:125−130)**

Tricuspid regurgitation (TR), the most common form of tricuspid valve (TV) disease, often occurs as a consequence of mal-coaptation of the TV leaflets. This results in retrograde blood flow to the right atrium and the subsequent loss of forward flow which commonly causes dyspnea, hepatic congestion, systemic venous congestion, ascites and edema.[1] Because patients with TR may remain asymptomatic and not demonstrate clinical sequelae until it progresses in severity, the true prevalence of TR is difficult to ascertain. Recent estimates have put age-and sex-adjusted prevalence of moderate or greater TR in the United States at 0.55%, which translates to about 1.8 million Americans.[2-4] Due to the narrow treatment avenues currently recommended for TR, and the fact that it is frequently overshadowed by its associated conditions until reaching an advanced stage, the effects and consequences of TR remain underrecognized, contributing to a lack of timely treatment despite its poor prognosis.[1−3, 5−9] This study aimed to quantify survival rates for patients with TR at varying levels of severity and with several associated conditions using real-world data from Optum's de-identified, all-payer, integrated database of United Healthcare claims and Humedica electronic health records.

Methods

This study used data from the Optum Integrated File, which contains data from both claims and EHRs for patients across the United States.[10] The combination of claims and

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Relevant industry relationships and financial interests are as follows: Colin M. Barker, David P. Cork, Peter A. McCullough, Hirsch S. Mehta, Michael Ryan, William Irish, and Candace Gunnarsson have consulting relationships with Edwards Lifesciences. Dr. Barker is an advisory board member for Medtronic and Boston Scientific. Dr. Cork has a consulting relationship with Abbott Laboratories and participates in a speaker's bureau for Boston Scientific. Dr. Mehta has a consulting relationship with Abbott Laboratories, Boston Scientific and participates in a speaker's bureau for Actelion Pharmaceuticals, Bayer Healthcare Pharmaceuticals and Bristol-Myers Squibb Company. Joanna Van Houten, Sarah Mollenkopf, and Patrick Verta are employees of Edwards Lifesciences, the study sponsor.

See page 129 for disclosure information.

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clinical data provide a comprehensive view of a patient's clinical interactions with the healthcare system. Optum data provide a continuum of treatment and cost, such as medications by therapeutic area, provider notes with treatment rationale, and cost by procedure and condition. All data used to perform this analysis were deidentified and accessed in compliance with the Health Insurance Portability and Accountability Act. As a retrospective analysis of a deidentified database, the research was exempt from IRB review under 45 CFR 46.101(b)(4).

Patients in the Optum Integrated File from January 1, 2007 through December 31, 2018 who were 18 years or older were included for analysis if they had a minimum of 1 diagnosis code for tricuspid insufficiency without a record of end-stage renal disease, tricuspid valve prolapse or primary organ disease. Patients were required to have 12 months of continuous health plan enrollment before first TR diagnosis and 1 month of continuous enrollment post-TR diagnosis. The 1-month post-TR diagnosis was used as a landmark period to capture TR severity. Patients were categorized as having severe TR disease if they had pulmonary hypertension coupled with 1 of the following conditions: Ascites, edema, or hepatic insufficiency, either before TR diagnosis or during the landmark period. Patients were also categorized as having severe TR if they had a record of TR surgery at the time of TR diagnosis, during the landmark period, or if severe TR was documented in the EMR physician notes in the Humedica database. Patients with functional TR are commonly coded with a diagnosis of tricuspid stenosis and/or rheumatic TR. Therefore, patients with both a code for non-rheumatic and rheumatic TR were included for analysis provided they only had a record of 1 rheumatic code, which was considered a coding error.

Patients were assigned cohorts based on the following hierarchy: first, any patient with a record of HF either before, on or 1 month following their TR diagnosis (landmark period) were assigned to the TR with HF cohort, regardless of any other diagnoses of interest (OVD or RSHD). Next, for those patients remaining, if they had a record of OVD (either mitral or aortic), before their TR diagnosis, at the time of their TR diagnosis, or 1 month following their TR diagnosis (landmark period) they were assigned to the cohort TR with OVD (no HF). Finally, for the TR patients remaining, if a record of 1 or more of the following conditions: right ventricular dysfunction (RVD), chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension (PAH), or atrial fibrillation (AF) were present either before, during or 1 month after their TR diagnosis, these patients were classified as having right sided heart disease (RSHD) and assigned to the cohort TR with RSHD only (no OVD or HF). All patients remaining were categorized as TR only (no HF, OVD or RSHD). Therefore for this analysis the final cohorts were as follows: (1) TR with HF; (2) TR with OVD (no HF); (3) TR with RSHD only (no OVD or HF); and (4) TR only (reference group).

Survival was estimated using a Cox hazard model with an interaction term for severe TR (defined as a claims record of ascites, edema, and hepatic insufficiency or a physician note of severe TR) and adjusted for patient demographics (age, sex, race, income, payor, and region) and Elixhauser co-morbidities. Hazard ratios (HR) and 95% confidence intervals (CI) were provided as measures of strength of association and precision, respectively.

Results

A total of 33,686 patients were distributed across the cohorts as follows: (1) TR with HF (8,952 [26.6%]); (2) TR with OVD but no HF (12,367 [36.7%]); (3) TR with RSHD only (no HF, no OVD) (5,749 [17.1%]); and (4) TR only (6,618 [19.6%]) (Figure 1). The TR with HF cohort had a higher average Elixhauser Co-morbidity Index score—with a mean standard deviation (SD) score of 11.5 (3.7) compared with the cohorts without HF with mean (SD) co-morbidity scores ranging from 5.7 (3.0) to 8.1 (3.3). See Table 1. Before multivariable modeling, time to death for each cohort at 2 years were as follows: TR with HF 17.6%; TR with OVD but no HF 4.7%; TR with RSHD only 7.0%; and (4) TR only 2.6%. See Kaplan Meier Curves Figure 2.

Patients diagnosed with TR (regardless of severity) and at least 1 additional clinical condition had a significantly increased risk of mortality compared with patients with TR alone (Table 2). TR severity was associated with a 33% (HR = 1.33; p = 0.0002) increased risk of all-cause mortality, independent of co-morbidities (HF, OVD, or RSHD). The effect of TR severity on mortality risk was most pronounced in patients without HF, with the highest risk in patients with RSHD only, followed by patients with TR and OVD (Figure 3). The effect of TR severity on 2-year mortality was similar for patients with TR alone and those with TR and HF.

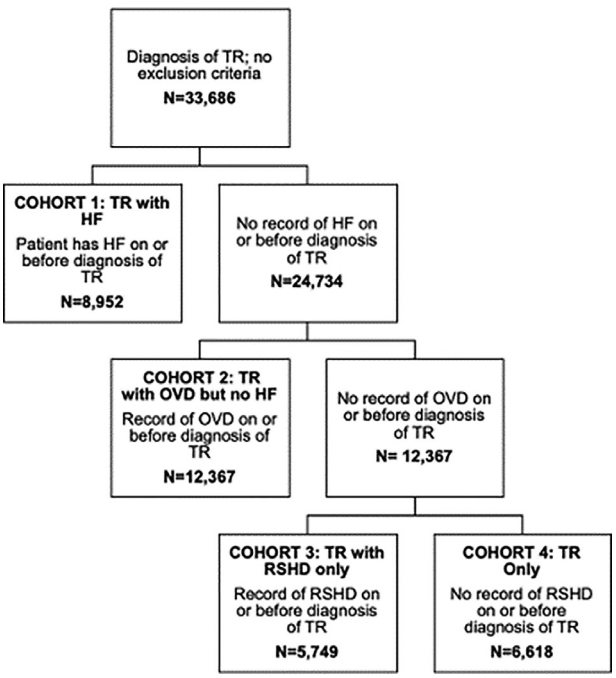

Figure 1. **Attrition diagram:** Patients were categorized in a hierarchical structure based on the presence first of HF, then OVD, followed by one or more of the following RSHDs: right ventricular dysfunction, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary arterial hypertension, or atrial fibrillation. HF = heart failure; OVD = other valve disease; RSHD = right-sided heart disease; TR = tricuspid regurgitation.

Table 1
Patient characteristics by cohort

Characteristics, No. (%)*	TR with HF (N = 8,952)	TR with OVD but No HF (N = 12,367)	TR with RSHD only (No HF, No OVD; N = 5,749)	TR only (No HF, No OVD, No RSHD; N = 6,618)
Age (years)				
Mean (SD)	73 (11.9%)	66 (15.9%)	71 (12.1%)	61 (17.1%)
Median (IQR)	76 (66-83%)	69 (56-78%)	73 (64-81%)	62 (49-74%)
Sex				
Male	4,451 (49.7%)	5,388 (43.6%)	2,634 (45.8%)	2,754 (41.6%)
Female	4,489 (50.1%)	6,972 (56.4%)	3,112 (54.1%)	3,860 (58.3%)
Unknown	12 (0.1%)	7 (0.1%)	3 (0.1%)	4 (0.1%)
Race				
White	7,130 (79.6%)	10,005 (80.9%)	4,861 (84.6%)	5,144 (77.7%)
Black	1,043 (11.7%)	1,053 (8.5%)	399 (6.9%)	654 (9.9%)
Asian	75 (0.8%)	281 (2.3%)	94 (1.6%)	187 (2.8%)
Other/Unknown	704 (7.9%)	1,028 (8.3%)	395 (6.9%)	633 (9.6%)
Region				
Northeast	846 (9.5%)	2,702 (21.8%)	858 (14.9%)	1,844 (27.9%)
Midwest	4,164 (46.5%)	5,003 (40.5%)	2,575 (44.8%)	2,428 (36.7%)
South	3,086 (34.5%)	3,859 (31.2%)	1,912 (33.3%)	1,947 (29.4%)
West	626 (7.0%)	531 (4.3%)	290 (5.0%)	241 (3.6%)
Unknown	230 (2.6%)	272 (2.2%)	114 (2.0%)	158 (2.4%)
Payor				
Commercial	3,829 (42.8%)	7,428 (60.1%)	2,839 (49.4%)	4,589 (69.3%)
Medicare	5,121 (57.2%)	4,936 (39.9%)	2,908 (50.6%)	2,028 (30.6%)
Unknown	2 (0.0%)	3 (0.0%)	2 (0.0%)	1 (0.0%)
Income†, $				
Mean (SD)	42,981 (10.6K)	44,468 (12.3K)	43,569 (11,2K)	45,255 (13.2K)
Median (IQR)	40,383 (36.3K-48.6K)	41,792 (36.3K-49.3K)	41,676 (36.3K-49.3K)	42,694 (36.3K-49.3K)
ECI Score				
Mean (SD)	11.5 (3.7)	6.8 (3.4)	8.1 (3.3)	5.7 (3.0)
Median (IQR)	11 (9-14)	6.(4.9)	8 (6-10)	5 (3-8)

ECI = Elixhauser Comorbidity Index; HF = heart failure; IQR = interquartile range; OVD = other valve disease; RSHD = right-sided heart disease; SD = standard deviation; TR = tricuspid regurgitation.

* All values reported as No, (%) unless otherwise specified.

† Sample sizes are reduced, as not everyone reported their income. Values for the 4 cohorts from left to right are 8,666; 11,995; 5,602; and 6,393.

Discussion

This retrospective analysis found that, regardless of severity, patients with TR and at least 1 additional condition of interest (HF, OVD, and RSHD) had a significantly increased risk of mortality compared with patients with TR alone. While mild TR is frequently observed in otherwise healthy, "disease-free" individuals, severe isolated TR is relatively rare.[4,11–13] The complex pathology of TR is such that it is usually found in conjunction with conditions like HF, OVD, or RSHD. Most studies evaluating independent effects of TR on mortality examine cohorts with at least 1 of the previously mentioned conditions.[2,14–17] In this analysis, we chose a control group of isolated, idiopathic TR (without significant co-morbidities) to better estimate the incremental burden of TR on mortality.

The 2-year all-cause mortality rates for patients with isolated, idiopathic TR (0.10 for severe TR and 0.07 for non-severe TR) was comparable to those reported by studies examining similar isolated TR populations. A study by Topilsky et al. showed that isolated TR independently predicted higher mortality compared with the general population with no identifiable heart disease (adjusted risk ratio: 1.68; 95% CI: 1.04 to 2.60; p = 0.03).[11]

Taking into account findings in this analysis as well as that of the Topilsky study[4] it is not surprising that a diagnosis of TR with added co-morbidities increases mortality. However, after taking TR severity into consideration, it is significantly associated with a 33% (HR: 1.33; p = 0.0002) increased risk of all-cause mortality, independent of any associated disease (HF, OVD, or RSHD). The finding by Nath et al. that TR severity was commonly associated with RV dilation and dysfunction and elevated right atrial pressure (the latter measured by inferior vena cava (IVC) dilation) may help support the concept that TR severity could be a more sensitive proxy for RVD compared with a visual analysis of RV systolic function.[16] This may help to explain our finding that TR severity had the most profound effect on mortality for patients with RSHD only.

Our analysis showed that 2-year mortality was significantly greater for patients with severe TR and HF compared with those with mild TR and HF. The same effect, with greater magnitude, was seen for patients with TR and RSHD or TR and OVD, without HF. The less-pronounced effect of TR severity on mortality for patients with HF is likely due to the complexity and poor outcomes associated with acute HF. This can be evidenced by the fact that the cohort of TR with HF only had the highest average

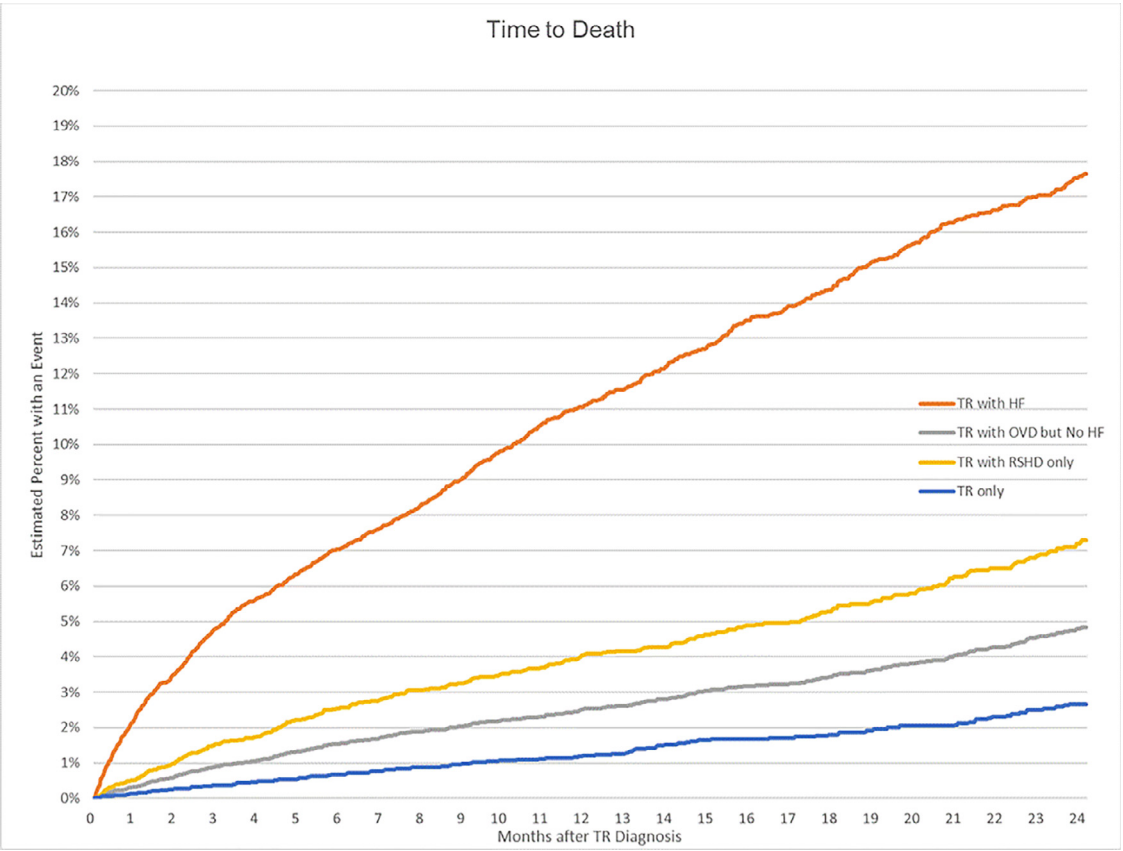

Figure 2. **Two-year Kaplan Meier curve − time to death:** Results of unadjusted 2-year time to death for each Cohort. HF = heart failure; OVD = other valve disease; RSHD = right-sided heart disease; TR = tricuspid regurgitation.

Table 2.
Multivariable regression results

Regression results (Reference group: TR only)	Hazard ratio	95% confidence interval	p Value
TR with HF	2.12	(1.76, 2.55)	<.0001
TR with OVD (no HF)	1.32	(1.09, 1.59)	0.0037
TR with RSHD only (no HF or OVD)	1.50	(1.24, 1.82)	<.0001

HF = heart failure; OVD = other valve disease; RSHD = right-sided heart disease; TR = tricuspid regurgitation.

Elixhauser co-morbidity index score compared with all other cohorts.

In light of previously published findings indicating the presence of TR as a major risk factor for patients with conditions such as HF, pulmonary hypertension, or OVD our results suggest that TR is not an innocent bystander when it comes to mortality.[8,14,16] Severe TR and pulmonary hypertension are often linked, and this was confirmed with the effect of TR severity on 2-year mortality for patients with TR and RSHD. Despite this proven association between TR severity and mortality, the indications for TV surgery are narrow. Current guidelines recommend that patients with severe functional TR should undergo TV repair or replacement (1) if they have a primary TR diagnosis (structural defect), (2) if they have progressive RV dysfunction, or (3) concomitantly with left-sided valve surgery. Despite this guideline recommendation, TV surgeries are relatively uncommon.[3,5–7,18] Newer, percutaneous approaches to treating TR are encouraging, as they provide minimally-invasive options for patients deemed too high-risk for surgical options.[2,19,20] Given that severe TR has been shown to have a significant, independent effect on mortality, further studies are needed to investigate the timing and efficacy of surgical and new transcatheter interventions for the treatment of TR.

This study has all the limitations of retrospective studies that rely on automated sources of data. We recognize that TR was ascertained through sources that are based on codes used for billing purposes. This could have been biased in terms of over- or undercoding. We could only control for known confounders—largely of generalized illness—and lacked the ability to control for unknown confounders, ideally by randomization, stratification, matching, and so on. Statistical modeling was used to control for the potential confounding effect of known variables with between-group differences. While statistical models controlled for several factors, models could not control for some variables that are not included in an administrative database, like

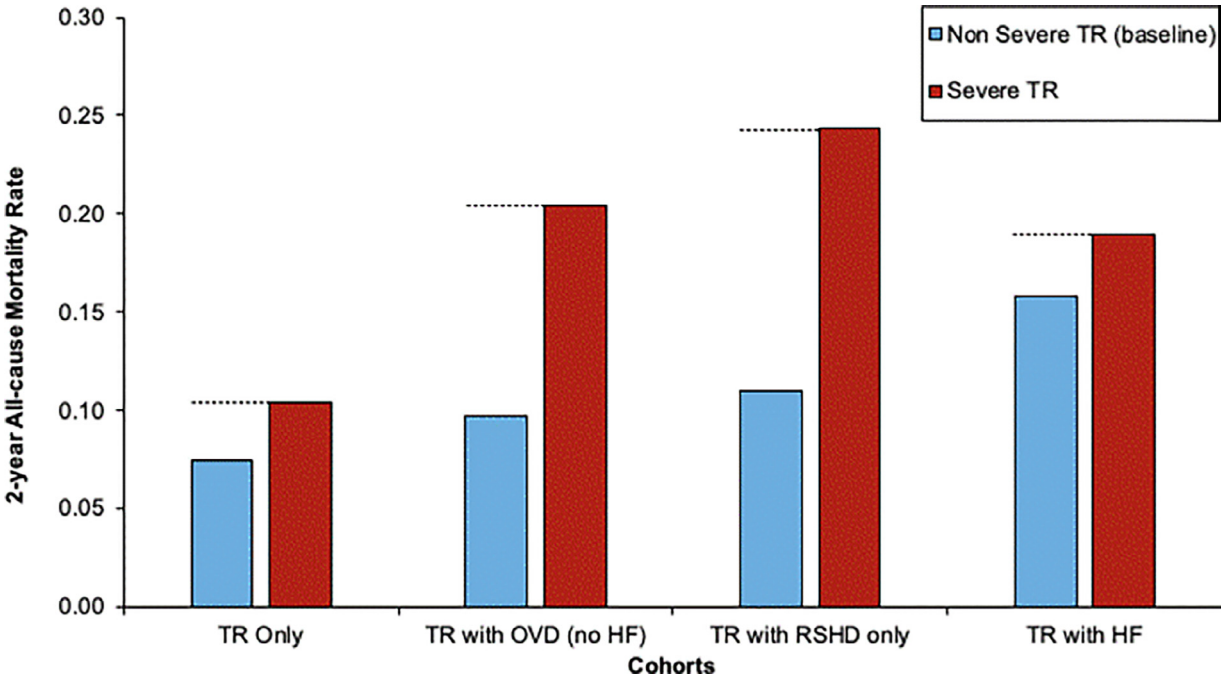

Figure 3. **Two-year all-cause mortality rate by cohort and severity**: Results of adjusted 2-year mortality for each cohort and TR severity. The effect of TR severity on mortality is more pronounced in patients without HF. HF = heart failure; OVD = other valve disease; RSHD = right-sided heart disease; TR = tricuspid regurgitation.

echocardiography results. We relied upon proxies in automated data that suggested clinically significant TR without having the quantitation of TR from imaging data. The use of proxies could have significantly reduced the proportion of patients with severe TR that would have been recognized by cardiac imaging. We did not grade the severity of TR with echocardiographic analysis. A strength of the present study, however, is that the large sample reflected real-world patient characteristics and outcomes across the country from different hospitals and physicians as compared with evidence from controlled clinical trials.

TR severity is significantly associated with an increased risk of all-cause mortality, independent of conditions including HF, OVD, or RSHD. In patients with severe TR, the mortality risk is most pronounced for patients who had RSHD without HF or OVD documented before the TR diagnosis.

Credit Statement

Colin M. Barker: Conceptualization, Writing – Original Draft, Writing – Review and Editing, Investigation, Methodology

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Peter A. McCullough: Conceptualization, Writing – Original Draft, Writing – Review and Editing, Investigation, Methodology

Hirsch S. Mehta: Conceptualization, Writing – Original Draft, Writing – Review and Editing, Investigation, Methodology

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Candace Gunnarsson: Conceptualization, Writing – Original Draft, Writing – Review and Editing, Investigation, Formal Analysis, Validation, Methodology

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William Irish: Conceptualization, Writing – Original Draft, Writing – Review and Editing, Investigation, Formal Analysis, Validation, Software, Methodology

Sarah Mollenkopf: Conceptualization, Writing – Original Draft, Writing – Review and Editing, Investigation, Supervision, Project Administration, Methodology

Patrick Verta: Conceptualization, Writing – Original Draft, Writing – Review and Editing, Investigation, Methodology

Disclosures

CMB, DPC, PAM, HSM, MR, WI, and CG have consulting relationships with Edwards Lifesciences. CMB is an advisory board member for Medtronic and Boston Scientific. DPC has a consulting relationship with Abbott Laboratories and participates in a speaker's bureau for Boston Scientific. HSM has a consulting relationship with Abbott Laboratories, Boston Scientific and participates in a speaker's bureau for Actelion Pharmaceuticals, Bayer Healthcare Pharmaceuticals and Bristol-Myers Squibb Company. JVH, SM, and PV are employees of Edwards Lifesciences, the study sponsor.

Data Sharing Statement

The data that support the findings of this study are available from Optum Integrated File, but restrictions apply to the availability of these data and were used under license for the current study; therefore, they are not publicly available.

Declaration of Competing Interest

This study was sponsored by Edwards Lifesciences. The external authors and study sponsors participated in the study design, data analysis, data interpretation, and development of the report, and gave approval to submit for publication.

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