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New Devices and Global Trends in Transcatheter Aortic Valve Implantation

Xavier Armario Bel

Universitat Autònoma de Barcelona

Doctoral Thesis

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Candidate

Xavier Armario Bel

Directors

Dabit Arzamendi Aizpurua

Darren Mylotte

Tutor

Dabit Arzamendi Aizpurua

Doctoral Programme in Medicine

Department of Medicine

Universitat Autònoma de Barcelona

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Abbreviations

AS = aortic valve stenosis.

CE = Conformité Européenne.

COVID-19 = coronavirus disease 2019.

EuroSCORE II = European System for Cardiac Operative Risk Evaluation II.

FDA = Food and Drug Administration.

LVOT = left ventricular outflow tract.

NYHA = New York Heart Association.

SARS-CoV-2 = acute respiratory syndrome coronavirus 2.

SAVR = surgical aortic valve replacement.

STS-PROM = Society of Thoracic Surgeons Predictor of Mortality.

TAVI = transcatheter aortic valve implantation.

THV = transcatheter heart valve.

Contents

Summary

Aortic valve stenosis (AS) is the most prevalent valvular heart disease in countries with higher development and economic status, and its prevalence is rapidly increasing as a consequence of the population ageing. Although surgical aortic valve replacement (SAVR) has been the standard treatment for patients with symptomatic severe AS, over the last two decades transcatheter aortic valve implantation (TAVI) has emerged as a safe and effective alternative to SAVR for the treatment of patients with symptomatic severe AS across all surgical risk categories.

Although TAVI devices have undergone significant iterations, the rates of residual paravalvular leak and permanent pacemaker implantation in patients undergoing TAVI remain high compared to those undergoing SAVR. The mechanically-expanding LOTUS aortic valve system (Boston Scientific) features the Adaptive Seal™ technology, designed to promote aortic annulus sealing and therefore minimise paravalvular leak, but this platform showed a high rate of permanent pacemaker implantation compared to other TAVI devices. To address this issue, the second-generation LOTUS Edge aortic valve system incorporates the Depth Guard™ technology, designed to minimise left ventricular outflow tract interaction and potentially reduce permanent pacemaker implantation. To date, no short-term safety and efficacy data of this device have been published.

On the other hand, while SAVR volume has remained stable, TAVI volume has increased dramatically over the last decade, especially in Europe and North America. It is well documented that the coronavirus disease 2019 (COVID-19) pandemic had a negative impact on patients with valvular heart disease, including patients with symptomatic severe AS. Nevertheless, although national and regional reports have suggested reduced TAVI procedural volume during the COVID-19 pandemic, there is no data detailing its impact on TAVI activity globally.

The aim of this doctoral thesis was to evaluate the short-term safety and efficacy of the novel LOTUS Edge aortic valve system and to assess the impact of the COVID-19 pandemic on global TAVI activity.

In the first study, the LOTUS Edge system showed satisfactory short-term safety and efficacy results among an all-comers patient population, including patients with complex anatomies (e.g., bicuspid aortic valve morphology). This device demonstrated favourable haemodynamic data and very low rate of clinically significant paravalvular leak at 30 days: none or trace paravalvular leak was reported in 84.4%, and moderate paravalvular leak occurred in 2.0%, with no cases of severe paravalvular leak. The need for new permanent pacemaker implantation, however, remained high: 25.9% among all patients and 30.8% among pacemaker-naive patients.

The second study demonstrated that the COVID-19 pandemic was associated with a considerable reduction in TAVI procedural volume worldwide. TAVI activity was considerably reduced during the first and second pandemic waves (monthly reduction of 15% and 7% in overall TAVI procedural volume, respectively, compared to the pre-pandemic period), but it gradually recovered and reached the pre-pandemic activity during the third pandemic wave. The impact of the COVID-19 pandemic on TAVI activity was more pronounced in Africa, Central-South America, and Asia, as well as in private hospitals, urban areas, low-volume centres, and in countries with lower development and economic statuses, higher COVID-19 incidence, and more stringent governmental public health responses.

Resum

L’estenosi valvular aòrtica (EA) és la valvulopatia més prevalent als països amb un desenvolupament i una economia més favorables, i la seva prevalença està augmentant ràpidament com a conseqüència de l’envelliment poblacional. Tot i que la substitució valvular aòrtica quirúrgica (SAVR) ha estat el tractament estàndard dels pacients amb EA greu simptomàtica, durant les últimes dues dècades la implantació valvular aòrtica transcatèter (TAVI) s’ha convertit en una alternativa segura i eficaç a la SAVR per al tractament dels pacients amb EA greu simptomàtica en totes les categories de risc quirúrgic.

Encara que els dispositius per a TAVI han experimentat millores significatives, les taxes de fuita paravalvular residual i d'implantació de marcapassos definitiu en pacients sotmesos a TAVI segueixen sent elevades en comparació amb aquells pacients que se sotmeten a SAVR. El dispositiu d’expansió mecànica LOTUS (Boston Scientific) inclou la tecnologia Adaptive Seal™, dissenyada per a promoure el segellat de l'anell aòrtic i, per tant, minimitzar la fuita paravalvular, però aquesta plataforma mostrà una taxa elevada d'implantació de marcapassos definitiu en comparació amb altres dispositius per a TAVI. Per a solucionar aquest problema, el dispositiu de segona generació LOTUS Edge incorpora la tecnologia Depth Guard™, dissenyada per a minimitzar la interacció amb el tracte de sortida del ventricle esquerre i, potencialment, reduir la necessitat de marcapassos definitiu. Fins ara, no s'han publicat dades de seguretat i eficàcia a curt termini d’aquest dispositiu.

D'altra banda, mentre que el volum de SAVR s'ha mantingut estable, el volum de TAVI ha augmentat espectacularment durant l'última dècada, especialment a Europa i Nord-Amèrica. Està ben documentat que la pandèmia de la COVID-19 tingué un impacte negatiu en pacients amb valvulopaties, inclosos pacients amb EA greu simptomàtica. No

obstant, encara que informes nacionals i regionals han suggerit una reducció del volum de procediments de TAVI durant la pandèmia de la COVID-19, no hi ha dades que detallin el seu impacte en l'activitat de TAVI a nivell mundial.

L'objectiu d'aquesta tesi doctoral era avaluar la seguretat i l'eficàcia a curt termini del nou dispositiu LOTUS Edge i avaluar l'impacte de la pandèmia de la COVID-19 en l'activitat global de TAVI.

En el primer estudi, el dispositiu LOTUS Edge mostrà resultats satisfactoris de seguretat i eficàcia a curt termini en la pràctica clínica habitual, inclosos pacients amb anatomies complexes (per exemple, vàlvula aòrtica bicúspide). Aquest dispositiu mostrà dades hemodinàmiques favorables i una taxa molt baixa de fuita paravalvular clínicament significativa als 30 dies: una fuita paravalvular nul·la o mínima s'informà en el 84,4%, i una fuita paravalvular moderada s'observà en el 2,0%, sense casos de fuita paravalvular greu. La necessitat de marcapassos definitiu, tanmateix, es mantingué alta: un 25,9% entre tots els pacients i un 30,8% en pacients sense marcapassos previ.

El segon estudi demostrà que la pandèmia de la COVID-19 s'associà a una reducció considerable del volum de procediments de TAVI a nivell mundial. L'activitat de TAVI es reduí considerablement durant la primera i segona onades pandèmiques (reducció mensual del 15% i 7% en el volum total de procediments de TAVI, respectivament, en comparació amb el període pre-pandèmia), però es recuperà gradualment i assolí l'activitat pre-pandèmica durant la tercera onada pandèmica. L'impacte de la pandèmia de la COVID-19 en l'activitat de TAVI fou més pronunciat a Àfrica, Centre- i Sud-Amèrica i Àsia, així com als hospitals privats, les zones urbanes, els centres de baix volum i als països amb un desenvolupament i una economia més desfavorables, una major incidència de la COVID-19 i unes respostes governamentals de salut pública més estrictes.

1. INTRODUCTION

1.1. Aortic valve stenosis

Aortic valve stenosis (AS) is the most prevalent valvular heart disease in countries with higher development and economic status,[1] and its prevalence is rapidly increasing as a consequence of the population ageing.[2] The degenerative aortic valve disease, characterised by thickening, fibrosis and calcification of the aortic valve leaflets, represents the most common cause of AS in those countries.[3] Known risk factors for degenerative aortic valve disease include advanced age, male sex, smoking, obesity, arterial hypertension, diabetes mellitus, and high plasma low-density lipoprotein cholesterol and lipoprotein(a) levels.[3] The presence of congenital aortic valve malformations, such as bicuspid aortic valves, has also shown to be a risk factor for degenerative aortic valve disease.[4]

AS is a progressive disease that can manifest with exertional dyspnoea, angina, syncope and, ultimately, heart failure.[5] After a long asymptomatic period, during which survival remains nearly normal, survival declines rapidly once symptoms develop.[5] The mean survival after the occurrence of angina, syncope, and heart failure is approximately 4, 2, and 1 years, respectively.[6]

Echocardiography is key to confirming the diagnosis and severity of AS.[7] Current recommendations for the echocardiographic assessment of patients with AS include the measurement of the mean transvalvular pressure gradient, peak transvalvular velocity, and valve area.[8] Severe AS is defined by a mean transvalvular pressure gradient ≥40 mmHg, peak transvalvular velocity ≥4.0 m/s, and valve area ≤1.0 cm^2 or ≤0.6 cm^2/m^2.[8]

Symptomatic severe AS is associated with a poor prognosis if left untreated.[1] To date, no medical therapy has been shown to modify the natural history of AS,[9] and aortic valve replacement, either surgical or transcatheter, is the only effective treatment for these patients.[7] Early intervention is strongly recommended in all patients with symptomatic

severe AS, except in those patients with important comorbidities in whom intervention is unlikely to improve quality of life, or those with concomitant conditions associated with a life expectancy <1 year.[7]

1.2. Surgical and transcatheter aortic valve replacement

Although surgical aortic valve replacement (SAVR) has been the standard treatment for patients with symptomatic severe AS, over the last two decades transcatheter aortic valve implantation (TAVI) has emerged as a safe and effective alternative to SAVR for the treatment of patients with symptomatic severe AS across all surgical risk categories.[10-16]

Surgical risk stratification to predict mortality after cardiac surgery is routinely performed in all patients with symptomatic severe AS who are being considered for aortic valve replacement. The most commonly used surgical risk scores are the Society of Thoracic Surgeons Predictor of Mortality (STS-PROM)[17,18] and the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II).[19] According to these surgical risk scores, patients are classified as high-risk (STS-PROM / EuroSCORE II >8%), intermediate-risk (STS-PROM / EuroSCORE II 4-8%), and low-risk (STS-PROM / EuroSCORE II <4%) for cardiac surgery.[7]

1.2.1. SAVR vs. TAVI: Scientific evidence

The first randomised clinical trial for TAVI was the PARTNER 1 trial (2010), in which high-risk patients with severe AS deemed unsuitable for cardiac surgery were randomised to TAVI vs. standard therapy, demonstrating for the first time the superiority of TAVI over standard therapy.[10] Subsequently, high-risk patients with severe AS considered suitable for cardiac surgery were randomised to TAVI vs. SAVR in the second part of the PARTNER 1 trial (2011) and the U.S. CoreValve trial (2014), both showing that TAVI was similar to SAVR in these patients.[11,12] A few years later, the PARTNER 2 trial (2016) and the SURTAVI trial (2017), which enrolled intermediate-risk patients with severe AS that were randomised to TAVI vs. SAVR, demonstrated that TAVI was

noninferior to SAVR for the combined endpoint of death from any cause or disabling stroke at 2 years.[13,14] Finally, low-risk patients with severe AS were studied in the PARTNER 3 trial (2019) and the Evolut Low Risk trial (2019), randomising them to TAVI vs. SAVR and demonstrating the noninferiority of TAVI over SAVR in this specific population.[15,16] However, all of these trials tested specific transcatheter heart valve (THV) devices in selected patient populations, limiting the applicability of the results to "real-world" clinical practice (**Table 1**).

The NOTION trial (2015) was the first study comparing TAVI vs. SAVR in an all-comers patient population.[20] Although this study included patients with severe AS regardless of their surgical risk category, the majority of them (81.8%) were considered low-risk patients. This study showed no significant differences for the composite endpoint of death from any cause, stroke, or myocardial infarction at 1 year between both groups. Recently, the DEDICATE trial (2024) compared the clinical outcomes of intermediate- and low-risk patients undergoing TAVI vs. SAVR in routine clinical practice, in which TAVI devices were selected according to operator discretion.[21] The study concluded that TAVI was noninferior to SAVR with respect to the primary endpoint of death from any cause or stroke at 1 year. Importantly, patients with adverse anatomical factors for either procedure, such as the presence of a bicuspid aortic valve morphology or complex coronary artery disease, were excluded from all the above-mentioned trials. Thus, the recently published NOTION-2 trial (2024) was the first randomised clinical trial comparing TAVI vs. SAVR including patients with bicuspid AS, who represented more than a quarter (27%) of the study sample.[22] Although the composite endpoint of death from any cause, stroke, or rehospitalisation at 1 year was similar between TAVI and SAVR among all patients and patients with tricuspid AS, the study showed a benefit of SAVR over TAVI among patients with bicuspid AS (**Table 2**).

Table 1. SAVR vs. TAVI: Randomised clinical trials in selected patient populations.

Trial	Year	Population	Sample	Groups	Design	Primary endpoint	Results and conclusions
PARTNER 1	2010	High-risk patients with severe AS unsuitable for cardiac surgery	358 patients	Balloon-expandable TAVI (n=179) vs. standard therapy (n=179)	Superiority	Death at 1 year	TAVI was superior to standard therapy (30.7% vs. 50.7%, respectively)
PARTNER 1	2011	High-risk patients with severe AS suitable for cardiac surgery	699 patients	Balloon-expandable TAVI (n=348) vs. SAVR (n=351)	Noninferiority	Death at 1 year	TAVI was noninferior to SAVR (24.2% vs. 26.8%, respectively)
U.S. CoreValve	2014	High-risk patients with severe AS suitable for cardiac surgery	747 patients	Self-expanding TAVI (n=390) vs. SAVR (n=357)	Noninferiority Superiority	Death at 1 year	TAVI was noninferior and superior to SAVR (14.2% vs. 19.1%, respectively)
PARTNER 2	2016	Intermediate-risk patients with severe AS	2,032 patients	Balloon-expandable TAVI (n=1,011) vs. SAVR (n=1,021)	Noninferiority	Death or disabling stroke at 2 years	TAVI was noninferior to SAVR (19.3% vs. 21.1%, respectively)
SURTAVI	2017	Intermediate-risk patients with severe AS	1,660 patients	Self-expanding TAVI (n=864) vs. SAVR (n=796)	Noninferiority	Death or disabling stroke at 2 years	TAVI was noninferior to SAVR (12.6% vs. 14.0%, respectively)
PARTNER 3	2019	Low-risk patients with severe AS	950 patients	Balloon-expandable TAVI (n=496) vs. SAVR (n=454)	Noninferiority Superiority	Death, stroke, or rehospitalisation at 1 year	TAVI was noninferior and superior to SAVR (15.1% vs. 8.5%, respectively)
Evolut Low Risk	2019	Low-risk patients with severe AS	1,403 patients	Self-expanding TAVI (n=725) vs. SAVR (n=678)	Noninferiority	Death or disabling stroke at 2 years	TAVI was noninferior to SAVR (5.3% vs. 6.7%, respectively)

AS = aortic valve stenosis; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation.

Table 2. SAVR vs. TAVI: Randomised clinical trials in all-comers patient populations.

Trial	Year	Population	Sample	Groups	Design	Primary endpoint	Results and conclusions
NOTION	2015	Patients with severe AS regardless of the surgical risk category	280 patients	Self-expanding TAVI (n=145) vs. SAVR (n=135)	Superiority	Death, stroke, or myocardial infarction at 1 year	TAVI was similar to SAVR (13.1% vs. 16.3%, respectively)
DEDICATE	2024	Intermediate- and low-risk patients with severe AS	1,414 patients	Any TAVI (n=701) vs. SAVR (n=713)	Noninferiority	Death or stroke at 1 year	TAVI was noninferior to SAVR (5.4% vs. 10.0%, respectively)
NOTION-2	2024	Low-risk patients with severe AS, including bicuspid AS	370 patients	Any TAVI (n=187) vs. SAVR (n=183)	Noninferiority	Death, stroke, or rehospitalisation at 1 year	TAVI was noninferior to SAVR (10.2% vs. 7.1%, respectively)

AS = aortic valve stenosis; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation.

1.2.2. SAVR vs. TAVI: Short-term data

The randomised clinical trials mentioned above compared the short-term clinical outcomes between TAVI and SAVR.[11-16,20-22] At 30 days, the rates of all-cause death, cardiovascular death, and all stroke were similar in both groups. Importantly, although the rate of disabling stroke was similar in high-risk and intermediate-risk patients undergoing SAVR or TAVI, in low-risk patients it was greater in those patients undergoing SAVR compared to those undergoing TAVI. The rates of acute kidney injury, major or disabling bleeding, and new-onset atrial fibrillation were shown to be higher in patients undergoing SAVR compared with those undergoing TAVI. On the other hand, the rates of residual paravalvular leak, major vascular complications, and permanent pacemaker implantation were greater in patients undergoing TAVI compared with those undergoing SAVR. No significant differences were observed in the rates of myocardial infarction, valve endocarditis, or valve thrombosis between SAVR and TAVI (**Table 3**).

Table 3. SAVR vs. TAVI: Short-term clinical outcomes.

Higher rates in SAVR	Similar rates	Higher rates in TAVI
	Death	
Acute kidney injury	Stroke*	Residual paravalvular leak
Major or disabling bleeding	Myocardial infarction	Major vascular complications
New-onset atrial fibrillation	Valve endocarditis	Permanent pacemaker imp.
	Valve thrombosis	

*The rate of disabling stroke in low-risk patients was greater in those patients undergoing SAVR compared to those undergoing TAVI.
SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation.

Haemodynamic data at 30 days was also compared between patients who had undergone TAVI vs. those who had undergone SAVR. Regardless of the surgical risk

category, lower mean transvalvular pressure gradient and larger effective valvular area at 30 days were consistently observed in those patients who had undergone TAVI.[11-16]

1.2.3. SAVR vs. TAVI: Long-term data

High- and intermediate-risk patients enrolled in the PARTNER 1 and PARTNER 2 trials, respectively, were followed-up for 5 years. At 5 years, the rate of death from any cause in high-risk patients was similar between TAVI and SAVR (67.8% vs. 62.4%, respectively), and there was no significant difference in the incidence of death from any cause or disabling stroke between TAVI and SAVR in intermediate-risk patients (47.9% vs. 43.4%, respectively).[23,24] On the other hand, 2-year results of low-risk patients included in the PARTNER 3 trial showed that the composite endpoint of death from any cause, stroke, or rehospitalisation was significantly lower in those patients who had undergone TAVI compared to those who had undergone SAVR (11.5% vs. 17.4%, respectively).[25] Nonetheless, the individual rates of death, stroke, and myocardial infarction were similar in both groups across all surgical risk categories.[23-25] Finally, patients enrolled in the NOTION trial were analysed at 2, 5, and 10 years, and no significant differences were observed for the composite endpoint of death from any cause, stroke, or myocardial infarction between TAVI and SAVR over this period of time.[26-28]

THVs durability has been a matter of concern, and this issue is particularly pertinent as TAVI indications expand towards younger, lower-risk patients. However, no long-term data have been available until the 10-year results of the NOTION trial were published in 2024.[28] In this study, bioprosthetic valve dysfunction was classified as structural valve deterioration, non-structural valve dysfunction, valve thrombosis, or valve endocarditis according to the Valve Academic Research Consortium 3 criteria.[29] This study showed that the rates of severe structural valve deterioration (10.0% vs. 1.5%,

respectively) and severe non-structural valve dysfunction (43.0% vs. 20.5%, respectively) were significantly higher in those patients who had undergone SAVR compared to those who had undergone TAVI. No significant differences were observed in the rates of valve endocarditis or valve thrombosis between SAVR and TAVI (**Table 4**).

Table 4. SAVR vs. TAVI: Long-term clinical outcomes.

Higher rates in SAVR	Similar rates	Higher rates in TAVI
New-onset atrial fibrillation Severe SVD Severe NSVD	Death Stroke Myocardial infarction Valve endocarditis Valve thrombosis	Residual paravalvular leak Permanent pacemaker imp.

NSVD = non-structural valve dysfunction; SAVR = surgical aortic valve replacement; SVD = structural valve deterioration; TAVI = transcatheter aortic valve implantation.

As observed in the short-term, haemodynamic data at medium- and long-term continued to be favourable in those patients who had undergone TAVI, who showed lower mean transvalvular pressure gradient and larger effective valvular area over time compared to those who had undergone SAVR.[11-16,20,26-28]

1.2.4. SAVR vs. TAVI: Guidelines recommendations

The choice between SAVR and TAVI should be based upon careful evaluation of clinical, anatomical, and procedural factors by the Heart Team, weighing the risks and benefits of each approach for an individual patient.[7] The Heart Team recommendation should be discussed with the patient and family to allow informed treatment choice.

The current European Society of Cardiology / European Association for Cardio-Thoracic Surgery guidelines for the management of valvular heart disease from 2021 recommends: SAVR in younger patients (<75 years) at low-risk for cardiac surgery (STS-

PROM / EuroSCORE II <4%) (class of recommendation I, level of evidence B); SAVR or TAVI in younger patients (<75 years) at intermediate-risk for cardiac surgery (STS-PROM / EuroSCORE II 4-8%) (class of recommendation I, level of evidence B); TAVI in younger patients (<75 years) at high-risk for cardiac surgery (STS-PROM / EuroSCORE II >8%) (class of recommendation I, level of evidence A); TAVI in older patients (≥75 years), regardless of the surgical risk (class of recommendation I, level of evidence A).[7] Importantly, in those patients with severe AS and concomitant cardiac conditions requiring intervention, such as complex coronary artery disease, significant aortic root or ascending aorta dilatation, and/or severe mitral or tricuspid valve disease, SAVR is recommended (class of recommendation I, level of evidence C) (**Table 5**).

Table 5. SAVR vs. TAVI: European guidelines recommendations from 2021.

Patients	Recommendation	COR	LOE
Younger patients (<75 years) at low-risk for cardiac surgery (STS-PROM / EuroSCORE II <4%)	SAVR	I	B
Younger patients (<75 years) at intermediate-risk for cardiac surgery (STS-PROM / EuroSCORE II 4-8%)	SAVR or TAVI	I	B
Younger patients (<75 years) at high-risk for cardiac surgery (STS-PROM / EuroSCORE II >8%)	TAVI	I	A
Older patients (≥75 years), regardless of the surgical risk	TAVI	I	A

Adapted and simplified from the European Society of Cardiology / European Association for Cardio-Thoracic Surgery guidelines for the management of valvular heart disease from 2021.[7]
COR = class of recommendation; EuroSCORE II = European System for Cardiac Operative Risk Evaluation II EuroSCORE II; LOE = level of evidence; SAVR = surgical aortic valve replacement; STS-PROM = Society of Thoracic Surgeons Predictor of Mortality; TAVI = transcatheter aortic valve implantation.

The last American College of Cardiology / American Heart Association guidelines for the management of patients with valvular heart disease from 2020 recommends: SAVR in younger patients (<65 years) at low- or intermediate-risk for cardiac surgery

(STS-PROM ≤8%) (class of recommendation I, level of evidence A); SAVR or TAVI in middle-aged patients (65-80 years) at low- or intermediate-risk for cardiac surgery (STS-PROM ≤8%) (class of recommendation I, level of evidence A); TAVI in older patients (>80 years) at low- or intermediate-risk for cardiac surgery (STS-PROM ≤8%) (class of recommendation I, level of evidence A); TAVI in patients at high-risk for cardiac surgery (STS-PROM >8%), regardless of the age (class of recommendation I, level of evidence A).[30] As in the European guidelines, the presence of concomitant cardiac conditions requiring intervention favours SAVR over TAVI (**Table 6**).

Table 6. SAVR vs. TAVI: American guidelines recommendations from 2020.

Patients	Recommendation	COR	LOE
Younger patients (<65 years) at low-risk or intermediate-risk for cardiac surgery (STS-PROM ≤8%)	SAVR	I	A
Middle-aged patients (65-80 years) at low-risk or intermediate-risk for cardiac surgery (STS-PROM ≤8%)	SAVR or TAVI	I	A
Older patients (>80 years) at low-risk or intermediate-risk for cardiac surgery (STS-PROM ≤8%)	TAVI	I	A
Patients at high-risk for cardiac surgery (STS-PROM >8%), regardless of the age	TAVI	I	A

Adapted and simplified from the American College of Cardiology / American Heart Association guidelines for the management of valvular heart disease from 2020.[30]
COR = class of recommendation; LOE = level of evidence; SAVR = surgical aortic valve replacement; STS-PROM = Society of Thoracic Surgeons Predictor of Mortality; TAVI = transcatheter aortic valve implantation.

1.3. Current devices for transcatheter aortic valve implantation

Since the first-in-human TAVI was performed by Alain Cribier in 2002, technical advances, device iterations, and increased operator experience have played an important role in improving clinical outcomes over the past two decades.[31,32]

According to the mechanism of valve expansion, TAVI devices can be classified into balloon-expandable and self-expanding THVs (**Figure 1**).[33] Current balloon-expandable THVs with Conformité Européenne (CE) mark in 2024 include SAPIEN 3 Ultra RESILIA (Edwards Lifesciences, Irvine, California) and Myval (Meril Life Sciences, Vapi, India). SAPIEN 3 Ultra RESILIA is the only balloon-expandable THV currently approved by the Food and Drug Administration (FDA). On the other hand, currently self-expanding THVs with CE mark in 2024 include Navitor (Abbott, Chicago, Illinois), Evolut FX (Medtronic, Minneapolis, Minnesota), ACURATE neo2 (Boston Scientific, Marlborough, Massachusetts), Trilogy (JenaValve Technology, Irvine, California), ALLEGRA (New Valve Technology, Muri, Switzerland), and Hydra (Vascular Innovations, Nonthaburi, Thailand). Navitor and Evolut FX represent the only self-expanding THVs currently approved by the FDA (**Table 7**).

Of note, although all of the devices mentioned above have been approved for the treatment of patients with aortic valve stenosis, only the Trilogy THV has received CE mark for the treatment of patients with aortic valve regurgitation.[34,35]

Figure 1. TAVI devices with CE mark and/or FDA approval in 2024.

CE = Conformité Européenne; FDA = Food and Drug Administration; TAVI = transcatheter aortic valve implantation; THV = transcatheter heart valve.

Table 7. TAVI devices with CE mark and/or FDA approval in 2024.

Manufacturer	Name	THV type	THV design	THV features	Frame material	Leaflets tissue	Skirt material	CE	FDA
Edwards Lifesciences	SAPIEN 3 Ultra RESILIA	Balloon-expandable	Intra-annular	Not repositionable Not retrievable	Cobalt-chromium alloy	Bovine pericardium	Polyethylene terephthalate	2024	2022
Meril Life Sciences	Myval	Balloon-expandable	Intra-annular	Not repositionable Retrievable	Cobalt-chromium-nickel alloy	Bovine pericardium	Polyethylene terephthalate	2019	No
Abbott	Navitor	Self-expanding	Intra-annular	Repositionable Retrievable	Nickel-titanium alloy (nitinol)	Bovine pericardium	NaviSeal™	2021	2023
Medtronic	Evolut FX	Self-expanding	Supra-annular	Repositionable Retrievable	Nickel-titanium alloy (nitinol)	Porcine pericardium	Porcine pericardium	2023	2021
Boston Scientific	ACURATE neo2	Self-expanding	Supra-annular	Not repositionable Not retrievable	Nickel-titanium alloy (nitinol)	Porcine pericardium	Porcine pericardium	2020	No
JenaValve Technology	Trilogy	Self-expanding	Supra-annular	Repositionable Not retrievable	Nickel-titanium alloy (nitinol)	Porcine pericardium	Porcine pericardium	2021	No
New Valve Technology	ALLEGRA	Self-expanding	Supra-annular	Repositionable Retrievable	Nickel-titanium alloy (nitinol)	Bovine pericardium	Bovine pericardium	2017	No
Vascular Innovations	Hydra	Self-expanding	Supra-annular	Repositionable Retrievable	Nickel-titanium alloy (nitinol)	Bovine pericardium	Bovine pericardium	2020	No

CE = Conformité Européenne; FDA = Food and Drug Administration; TAVI = transcatheter aortic valve implantation; THV = transcatheter heart valve.

1.3.1. Balloon-expandable vs. self-expanding THVs: Short-term data

To date, the two most used TAVI devices worldwide have been the different generations of the balloon-expandable THV from Edwards Lifesciences and the self-expanding THV from Medtronic.

The first-generation of these platforms were the balloon-expandable SAPIEN XT (Edwards Lifesciences) and the self-expanding CoreValve (Medtronic). The CHOICE randomised clinical trial (2014) was the first one to compare the short-term clinical outcomes between these two devices, showing that the balloon-expandable THV presented a higher rate of device success than the self-expanding THV (95.9% vs. 77.5%, respectively), mainly driven by the higher rate of moderate-severe paravalvular leak in the self-expanding group.[36] At 30 days, the incidence of death, stroke, myocardial infarction, bleeding, vascular complications, and acute kidney injury was similar between both groups. However, patients that received a self-expanding THV presented higher rates of moderate-severe paravalvular leak (18.3% vs. 4.1%) and permanent pacemaker implantation (37.6% vs. 17.3%). Of note, the rate of device success in patients with moderate-severe aortic valve calcification was significantly higher in the balloon-expandable group, while there were no significant differences in patients with moderate-severe left ventricular outflow tract (LVOT) calcification between the two groups.

The SOLVE-TAVI trial (2020) compared the short-term clinical outcomes of the second-generation balloon-expandable (SAPIEN 3, Edwards Lifesciences) and self-expanding (Evolut R, Medtronic) platforms.[37] In this study, the rates of device success were similar between the balloon-expandable (91.0%) and self-expanding (93.6%) systems, and the composite endpoint of death, stroke, moderate-severe paravalvular leak, and permanent pacemaker implantation at 30 days was equivalent between both groups. Nevertheless, the rates of moderate-severe paravalvular leak (3.4% vs. 1.5%) and

permanent pacemaker implantation (23.0% vs. 19.2%) were numerically higher in the self-expanding group.

More recently, the third-generation balloon-expandable (SAPIEN 3 Ultra, Edwards Lifesciences) and self-expanding (Evolut PRO/PRO+, Medtronic) systems were compared in the OPERA-TAVI registry (2022), which showed comparable rates of the primary efficacy outcome (85.9% vs. 87.4%, respectively).[38] However, balloon-expandable THV recipients presented a higher rate of the primary safety outcome (82.6% vs. 69.1%), which was driven by the higher rates of disabling stroke and permanent pacemaker implantation among self-expanding THV recipients. At 30 days, the incidence of death, non-disabling stroke, myocardial infarction, and moderate-severe paravalvular leak was similar between both groups, but the self-expanding group presented higher rates of disabling stroke (2.3% vs. 0.7%), mild paravalvular leak (39.4% vs. 20.3%) and permanent pacemaker implantation (17.9% vs. 10.1%). Importantly, the rate of the primary efficacy outcome between both groups was similar among a wide variety of complex anatomies, such as moderate-severe aortic valve calcification, moderate-severe LVOT calcification, bicuspid aortic valve morphology, and horizontal aorta. However, higher rates of the primary safety outcome in patients with moderate-severe aortic valve calcification were reported among balloon-expandable THV recipients.

To date, no study has compared the short-term clinical outcomes of the latest-iteration balloon-expandable (SAPIEN 3 Ultra RESILIA, Edwards Lifesciences) and self-expanding (Evolut FX, Medtronic) systems (**Table 8**).

Table 8. Balloon-expandable vs. self-expanding THVs: Short-term clinical outcomes.

Higher rates in BEV	Similar rates	Higher rates in SEV
None	Death Stroke* Myocardial infarction Bleeding Vascular complications Acute kidney injury	Residual paravalvular leak Permanent pacemaker imp.

*Higher rates of disabling stroke at 30 days were reported among SEV recipients compared to BEV patients using the third-generation platforms (Evolut PRO/PRO+ and SAPIEN 3 Ultra, respectively).[38]
BEV = balloon-expandable valve; SEV = self-expanding valve; THV = transcatheter heart valve.

The aforementioned studies as well as several observational registries compared short-term haemodynamic data of balloon-expandable vs. self-expanding THV systems. Regardless of the THV generation, lower mean transvalvular pressure gradient and larger effective valvular area at 30 days were consistently observed in the self-expanding group, which could be explained by their supra-annular design.[36-39] Moreover, the rate of patients with a mean transvalvular pressure gradient ≥20 mmHg at 30 days was higher among patients treated with a balloon-expandable platform.

1.3.2. Balloon-expandable vs. self-expanding THVs: Long-term data

5-year follow-up of patients enrolled in the CHOICE trial showed that there were no statistically significant differences between balloon-expandable and self-expanding THVs in the cumulative incidence of death from any cause, stroke, myocardial infarction, and repeat hospitalisation for heart failure.[40,41] Although the presence of moderate-severe paravalvular leak continued to be more frequent in the self-expanding group (12.1% vs. 1.1%) at 1 year, the rates of residual paravalvular leak were not significantly different between both groups at 5 years. As expected, the need for permanent pacemaker

implantation at 5 years remained higher in the self-expanding group (40.4% vs. 25.4%). Importantly, in the balloon-expandable group, the rate of moderate-severe structural valve deterioration was significantly higher (6.6% vs. 0.0%) and the cumulative incidence of clinical valve thrombosis was numerically higher (7.3% vs. 0.8%) at 5 years, with no significant differences in the rates of non-structural valve deterioration and valve endocarditis between the two platforms. These findings are in line with the 5-years follow-up of the UK TAVI registry, which also observed a significantly higher rate of severe structural valve deterioration among patients treated with the balloon-expandable platform (11.9% vs. 3.5%), driven by a substantial difference in patients treated with small THVs.[42]

Considering that the SOLVE-TAVI trial and the OPERA-TAVI registry were published in recent years, no long-term data are available to date on subsequent generations of balloon-expandable and self-expanding THVs (**Table 9**).

Table 9. Balloon-expandable vs. self-expanding THVs: Long-term clinical outcomes.

Higher rates in BEV	Similar rates	Higher rates in SEV
Severe SVD Clinical valve thrombosis	Death Stroke Myocardial infarction Residual paravalvular leak NSVD Valve endocarditis	Permanent pacemaker imp.

BEV = balloon-expandable valve; NSVD = non-structural valve deterioration; SEV = self-expanding valve; SVD = structural valve deterioration; THV = transcatheter heart valve.

As observed in the short-term, haemodynamic data at 5 years remained favourable in the self-expanding group, who showed lower mean transvalvular pressure gradient and larger effective valvular area compared to the balloon-expandable group. Although the

long-term clinical impact of these findings is still uncertain, it could have an impact on THV durability and might therefore be associated with worse clinical outcomes.[43] Long-term head-to-head comparisons between the current platforms are necessary to address this issue.

1.3.3. Mechanically-expanding THVs: The LOTUS aortic valve system

The LOTUS aortic valve system (Boston Scientific) is a mechanically-expanding THV with an intra-annular design. This system is composed of a nickel-titanium alloy (nitinol) frame with three bovine pericardium leaflets and features the Adaptive Seal™ technology at the lower half designed to promote aortic annulus sealing and therefore minimise paravalvular leak. It is a fully repositionable and retrievable system that allows complete deployment and functional assessment of the THV before final release.

After the first-in-human implantation of a LOTUS valve was performed in 2008, this device demonstrated its feasibility in the REPRISE I study and its safety and efficacy in the REPRISE II study.[44-46] Nonetheless, the modest sample size of these studies and their strict inclusion/exclusion criteria limited generalisability to a broader patient population. To address this issue, the RESPOND registry sought to evaluate the safety and efficacy of the LOTUS valve in a larger, all-comers patient population, including 1,014 patients with severe AS treated with this platform.[47] Device success, defined as successful vascular access, delivery, deployment, and system retrieval, was achieved in 98.1% of patients. At 30 days, the rates of all-cause death, all stroke, and disabling stroke were 2.2%, 3.0%, and 2.2%, respectively. Of note, the rates of residual paravalvular leak were low (92.0% none or trace, 7.7% mild, 0.3% moderate, and no cases of severe paravalvular leak) but the need for permanent pacemaker implantation was high (30.0% among all patients and 34.6% among pacemaker-naive patients). The device showed

favourable haemodynamic results with a mean transvalvular pressure gradient of 10.8±4.6 mmHg and an average effective valvular area of 1.8±0.4 cm^2 at discharge.

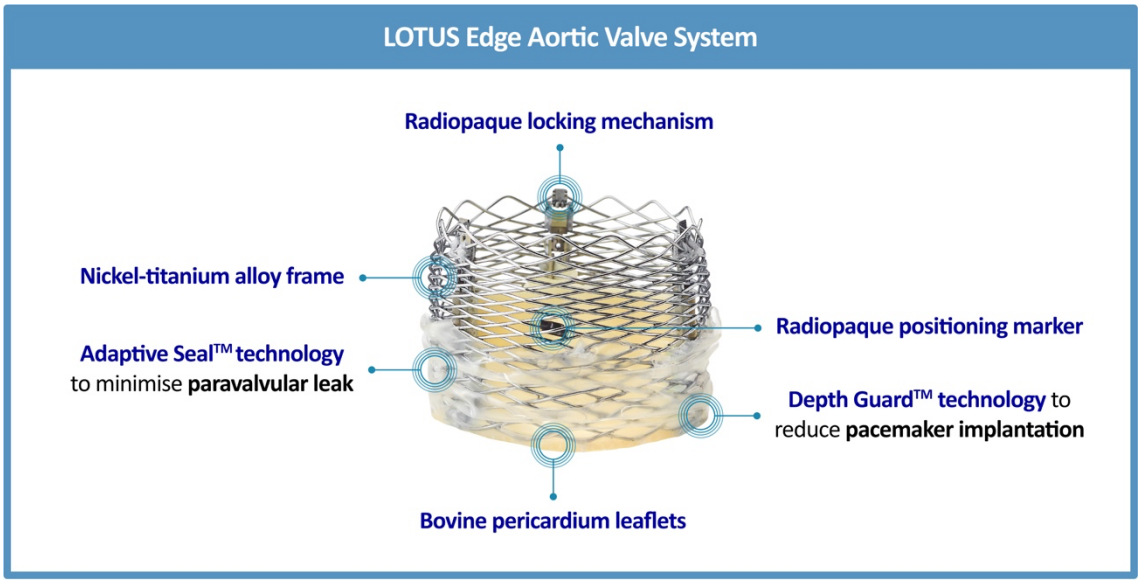
The mechanically-expanding LOTUS system was subsequently compared with the self-expanding CoreValve and Evolut R systems (Medtronic) in the REPRISE III randomised clinical trial.[48] The primary safety endpoint was the 30-day composite of all-cause mortality, all stroke, life-threatening or major bleeding, major vascular complications, and stage 2/3 acute kidney injury, while the primary effectiveness endpoint was the 1-year composite of all-cause mortality, disabling stroke, and moderate-severe paravalvular leak. The study demonstrated that the LOTUS system was non-inferior to the self-expanding platform for both the primary safety endpoint (20.3% vs. 17.2%, respectively) and the primary effectiveness endpoint (15.4% vs. 25.5%, respectively). Importantly, a lower incidence of moderate-severe paravalvular leak with the LOTUS system (0.9% vs. 6.8%) was offset by a higher rate of permanent pacemaker implantation with this platform (35.5% vs. 19.6%).

1.3.4. Mechanically-expanding THVs: The LOTUS Edge aortic valve system

The second-generation of this mechanically-expanding THV is the LOTUS Edge aortic valve system, which incorporates several design improvements on its predecessor, including increased flexibility of the delivery system catheter, enhanced visualisation of the locking mechanism, and the Depth Guard™ technology to minimise LVOT interaction and potentially reduce permanent pacemaker implantation (**Figure 2**). There are three THV sizes: 23 mm, 25 mm, and 27 mm, for native aortic annulus diameters of 20-23 mm, 23-25 mm, and 25-27 mm, respectively. This platform is delivered via an 18-F (for the 23 mm size) or 20-F (for the 25 mm and 27 mm sizes) introducer. The delivery

system requires a minimal femoral artery lumen diameter ≥6.0 mm (for the 23 mm size) or ≥6.5 mm (for the 25 mm and 27 mm sizes).

Figure 2. The LOTUS Edge aortic valve system.



The LOTUS Edge aortic valve system (Boston Scientific) is a mechanically-expanding THV with an intra-annular design. This fully repositionable and retrievable system allows complete deployment and functional assessment of the THV before final release. The Adaptive Seal™ technology promotes aortic annulus sealing and therefore minimise paravalvular leak, while the Depth Guard™ technology minimises LVOT interaction and potentially reduces permanent pacemaker implantation.
LVOT = left ventricular outflow tract; THV = transcatheter heart valve.

The LOTUS Edge aortic valve system received CE mark in September 2016. However, Boston Scientific recalled all devices in October 2016 due to delivery system issues, and again in February 2017 because of locking mechanism issues. After these issues were addressed by the company, the device received FDA approval in April 2019 and was commercially relaunched at the same time. To date, no short-term safety and efficacy data have been published for the relaunched LOTUS Edge aortic valve system.

1.4. Global trends in transcatheter aortic valve implantation

AS represents the most common valvular heart disease requiring surgical or transcatheter valve intervention in Europe and North America.[49] Use of SAVR and TAVI as complementary treatment options has allowed a substantial increase in the overall number of patients with AS undergoing aortic valve replacement in the past decade. Considering that the prevalence of AS is increasing rapidly due to the population ageing, the need for aortic valve replacement is expected to grow significantly in the coming decades.

Over the last decade, while SAVR volume has remained stable, TAVI volume has increased dramatically.[50-57] This growth in TAVI activity could be explained by several factors: first, the continuous improvement of TAVI technique and devices, which has contributed to reducing the rates of mortality and complications related to this procedure;[50-57] second, the expansion of TAVI indications to lower-risk patients;[13-16] third, the expansion of TAVI utilisation towards off-label indications, such as bicuspid aortic valve stenosis, pure or predominant aortic valve regurgitation, and failed aortic biologic prosthesis;[58-60] fourth, most patients undergoing TAVI have a swift recovery with short hospital stay and rapid return to normal activities, reason why TAVI has found to be more cost-effective than SAVR.[61,62]

Despite all of these factors mentioned above, geographical and socioeconomic inequalities in access to and utilisation of TAVI worldwide have been reported, and the rapid expansion of TAVI into low-risk patients and off-label indications in Europe and North America contrast with the low penetration of TAVI in the rest of the world.[63]

1.4.1. TAVI activity: Trends in Europe

In Europe, TAVI received CE mark for patients with severe AS considered at extreme- or high-risk for SAVR by 2007, and it was subsequently approved for patients at intermediate- and low-risk for SAVR in 2016 and 2020, respectively.

Although there are no global data on TAVI activity across Europe, several national registries reported country-level trends in TAVI volume over time.[50-54] All of these registries consistently showed that the annual number of TAVI procedures increased every year over the past decade. Importantly, the average age of patients undergoing TAVI remained unchanged, while the surgical risk profile of these patients decreased over time.

Nevertheless, substantial disparities in the number of TAVI procedures performed per million inhabitants across European countries were reported, and significant correlations between TAVI use and gross national income per capita and national healthcare spending per capita were suggested.[64,65] To address the heterogeneity in the implementation of TAVI across European countries, the European Association of Percutaneous Cardiovascular Intervention launched the *Valve for Life* initiative, which aimed to promote the interventional management of valvular heart disease among participating countries according to the guidelines recommendations.[66]

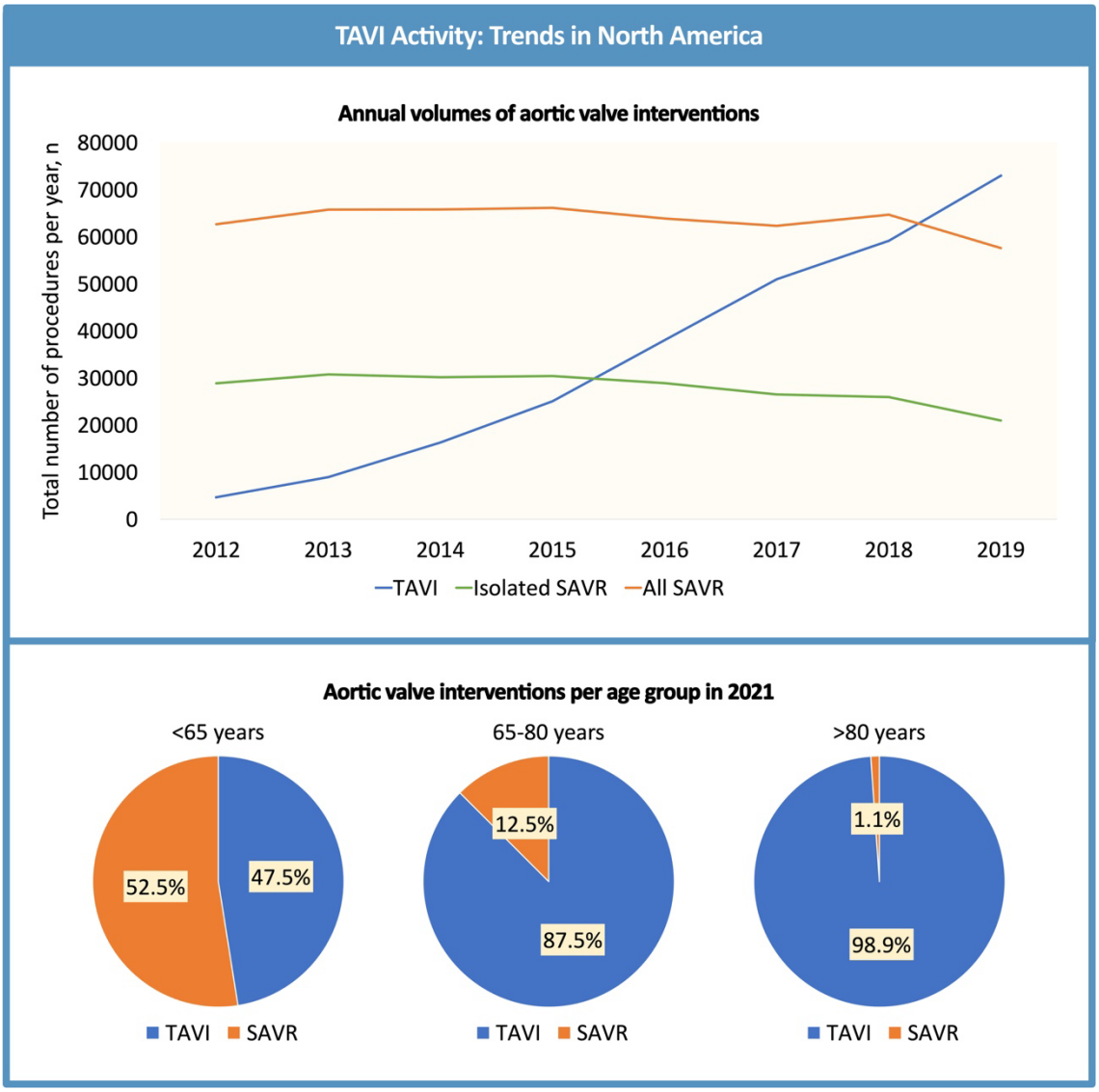
1.4.2. TAVI activity: Trends in North America

In the United States of America, TAVI approval by the FDA occurred in 2011 for patients with severe AS deemed at extreme-risk for SAVR. Subsequently, TAVI was approved for patients with severe AS at high-risk (2012), intermediate-risk (2016), and low-risk (2019) for SAVR.[55]

The Society of Thoracic Surgeons / American College of Cardiology registry, which collected data on 276,316 patients undergoing TAVI in the United States of America from 2011 to 2019, showed that the annual TAVI volume increased every year during the study period.[56] Of note, annual TAVI volume exceeded isolated SAVR volume in 2016, after TAVI was approved for intermediate-risk patients, and exceeded all forms of SAVR volume in 2019, coinciding with approval for low-risk patients. On the other hand, the annual SAVR volume remained stable until 2016 for isolated SAVR and 2019 for all forms of SAVR, when their volumes started to decline. Both the average age and surgical risk profile of patients undergoing TAVI decreased over the study period (**Figure 3**).

A recent registry on aortic valve interventions for isolated AS performed in the United States of America from 2015 to 2021 compared temporal trends according to the three age groups stated in the last American guidelines: <65 years (12.2%), 65-80 years (44.8%), and >80 years (43.0%).[57] Although this study observed a significant growth of TAVI volume in all age groups, it was especially dramatic among young patients (<65 years), in whom TAVI volume increased 2.7-fold during the study period. Thus, patients aged <65 years reached nearly equal volumes of TAVI (47.5%) and SAVR (52.5%) by 2021, while TAVI volumes clearly exceeded SAVR volumes in patients aged 65-80 years (87.5% vs. 12.5%, respectively) and >80 years (98.9% vs. 1.1%, respectively) by 2021 (**Figure 3**).

Figure 3. TAVI activity: Trends in North America.



Adapted from the Society of Thoracic Surgeons / American College of Cardiology Registry and the Vizient Clinical Data Base.[56,57]

SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation.

1.4.3. Impact of the COVID-19 pandemic on TAVI activity

The coronavirus disease 2019 (COVID-19) pandemic rapidly overwhelmed healthcare systems around the world. Healthcare resources were redirected to manage fallout from the emerging pandemic and established care pathways for many acute and chronic diseases were suspended. Public health messaging encouraged populations to

"stay at home" and travel restrictions were enforced to limit contagion. Such actions were associated with reduced hospitalisation for and increased mortality from cardiovascular diseases.[67,68] For example, hospital admission for acute coronary syndromes and activation of ST-segment elevation myocardial infarction pathways were reduced.[69,70]

The COVID-19 pandemic also had a negative impact on patients with valvular heart disease.[71-73] Patients with symptomatic severe AS necessitating SAVR or TAVI are especially vulnerable to treatment delays, and treatment deferral is associated with an increased risk of hospitalisation and death.[71-73] It is therefore concerning that national and regional reports have suggested reduced TAVI procedural volume during the COVID-19 pandemic.[74,75] For example, the UK TAVI registry, which included 15,142 TAVI cases performed in England between January 2017 and November 2020, showed that the monthly number of TAVI procedures was increasing before the COVID-19 pandemic, but it rapidly dropped following the outbreak of the COVID-19 pandemic, especially for elective cases.[74] A regional registry in Piedmont, Italy, compared the number of TAVI cases performed between March and April 2020 with the number of TAVI cases performed in the same period in 2019, showing a significant reduction (84.7%) in TAVI activity.[75] Nevertheless, there is no data detailing the impact of the COVID-19 pandemic on TAVI activity globally.

2. JUSTIFICATION

Over the past two decades, TAVI has emerged as a safe and effective alternative to SAVR for the treatment of patients with symptomatic severe AS across all surgical risk categories. Although TAVI devices have undergone significant iterations, with new generations of previous platforms and new devices arriving on the market, the rates of residual paravalvular leak and permanent pacemaker implantation in patients undergoing TAVI remain high compared to those undergoing SAVR, and both complications have been associated with increased mortality during follow-up. The mechanically-expanding LOTUS aortic valve system (Boston Scientific) features the Adaptive Seal™ technology, designed to promote aortic annulus sealing and therefore minimise paravalvular leak. This system showed good performance with low rates of residual paravalvular leak, but the need for permanent pacemaker implantation was high compared to other TAVI devices. To address this issue, the second-generation LOTUS Edge aortic valve system incorporates the Depth Guard™ technology, designed to minimise LVOT interaction and potentially reduce permanent pacemaker implantation. To date, no short-term safety and efficacy data have been published since the device was commercially launched in April 2019.

On the other hand, while SAVR volume has remained stable, TAVI volume has increased dramatically over the last decade, especially in Europe and North America. Indeed, several registries consistently showed that the annual number of TAVI procedures was increasing every year until the outbreak of the COVID-19 pandemic. It is well documented that the COVID-19 pandemic was associated with reduced hospitalisation for and increased mortality from cardiovascular diseases, and it also had a negative impact on patients with valvular heart disease, including patients with symptomatic severe AS. Nevertheless, although national and regional reports have suggested reduced TAVI procedural volume during the COVID-19 pandemic, there is no data detailing its impact

on TAVI activity globally. Moreover, the impact of the COVID-19 pandemic on a specific procedure such as TAVI is likely to have been heterogenous across diverse countries and healthcare systems and have been influenced by socioeconomic and other national factors, the incidence of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and the severity of governmental public health measures introduced in response to the pandemic.

3. HYPOTHESIS

The hypothesis of this doctoral thesis was that the LOTUS Edge aortic valve system shows satisfactory short-term safety and efficacy among an all-comers patient population, including patients with complex anatomies, while the COVID-19 pandemic considerably reduced TAVI procedural volume worldwide, especially during the first pandemic wave.

4. OBJECTIVES

The primary objective of this doctoral thesis was to evaluate the short-term safety and efficacy of the LOTUS Edge aortic valve system among an all-comers patient population, including patients with complex anatomies, and to assess the impact of the COVID-19 pandemic on global TAVI procedural volume, including different pandemic waves.

Secondary objectives included:

1) To study the haemodynamic performance and rates of residual paravalvular leak and permanent pacemaker implantation at 30 days among patients treated with the LOTUS Edge aortic valve system.
2) To study if the COVID-19 pandemic differentially impacted TAVI procedural volume according to geographic region, healthcare system, national socioeconomic status, COVID-19 incidence, and governmental public health responses.

5. COMPENDIUM OF PUBLICATIONS

5.1. TAVI with the LOTUS Edge system: Early European experience

Armario X, Rosseel L, Kharbanda R, Khogali S, Abdel-Wahab M, Van Mieghem NM, Tchétché D, Dumonteil N, De Backer O, Cotton J, McGrath B, Balakrishnan D, Ali N, Farhan S, Joseph J, Charbonnier G, Okuno T, McHugh F, Hildick-Smith D, Gilgen N, Hokken T, Spence MS, Frerker C, Angelillis M, Grygier M, Cockburn J, Bjursten H, Jeger RV, Teles R, Petronio AS, Pilgrim T, Sinning JM, Nickenig G, Søndergaard L, Blackman DJ, Mylotte D. Transcatheter Aortic Valve Replacement With the LOTUS Edge System: Early European Experience. *JACC Cardiovasc Interv* 2021;14(2):172-181. doi: 10.1016/j.jcin.2020.09.044. PMID: 33478633. Journal impact factor (2021): 11.075 (quartile 1, percentile 89.2).

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Transcatheter Aortic Valve Replacement With the LOTUS Edge System

Early European Experience

Xavier Armario, MD,[a] Liesbeth Rosseel, MD,[a] Rajesh Kharbanda, MD, PhD,[b] Saib Khogali, MD,[c] Mohamed Abdel-Wahab, MD,[d] Nicolas M. Van Mieghem, MD, PhD,[e] Didier Tchétché, MD,[f] Nicolas Dumonteil, MD,[f] Ole De Backer, MD, PhD,[g] James Cotton, MD,[c] Brian McGrath, MB BCh,[a] Deepu Balakrishnan, MD,[c] Noman Ali, MD, PhD,[h] Serdar Farhan, MD,[d] Jubin Joseph, MD, PhD,[b] Gaetan Charbonnier, MD,[f] Taishi Okuno, MD,[i] Fiachra McHugh, MD,[a] David Hildick-Smith, MD,[j] Nicole Gilgen, MD,[k] Thijmen Hokken, MD,[e] Mark S. Spence, MD,[l] Christian Frerker, MD,[m] Marco Angelillis, MD,[n] Marek Grygier, MD,[o] James Cockburn, MD,[j] Henrik Bjursten, MD,[p] Raban V. Jeger, MD,[k] Rui Teles, MD,[q,r] Anna S. Petronio, MD,[n] Thomas Pilgrim, MD,[i] Jan-Malte Sinning, MD,[s] Georg Nickenig, MD,[s] Lars Søndergaard, MD,[g] Daniel J. Blackman, MD,[h] Darren Mylotte, MB BCh, MD, PhD[a,t]

ABSTRACT

OBJECTIVES The aim of this study was to evaluate the short-term safety and efficacy of transcatheter aortic valve replacement (TAVR) with the LOTUS Edge system.

BACKGROUND The LOTUS Edge system was commercially re-released in April 2019. The authors report the first European experience with this device.

METHODS A multicenter, single-arm, retrospective registry was initiated to evaluate short-term clinical outcomes. Included cases are the first experience with this device and new implantation technique in Europe. Clinical, echocardiographic, and computed tomographic data were analyzed. Endpoints were defined according to Valve Academic Research Consortium-2 and were site reported.

RESULTS Between April and November 2019, 286 consecutive patients undergoing TAVR with the LOTUS Edge system at 18 European centers were included. The mean age and Society of Thoracic Surgeons score were 81.2 ± 6.9 years and 5.2 ± 5.4%, respectively. Nearly one-half of all patients (47.9%) were considered to have complex anatomy. Thirty-day major adverse events included death (2.4% [n = 7]) and stroke (3.5% [n = 10]). After TAVR, the mean aortic valve area was 1.9 ± 0.9 cm^2, and the mean transvalvular gradient was 11.9 ± 5.7 mm Hg. None or trace paravalvular leak (PVL) occurred in 84.4% and moderate PVL in 2.0%. There were no cases of severe PVL. New permanent pacemaker (PPM) implantation was required in 25.9% among all patients and 30.8% among PPM-naive patients.

CONCLUSIONS Early experience with the LOTUS Edge system demonstrated satisfactory short-term safety and efficacy, favorable hemodynamic data, and very low rates of PVL in an anatomically complex cohort. New PPM implantation remained high. Further study will evaluate if increasing operator experience with the device and new implantation technique can reduce the incidence of PPM implantation. (J Am Coll Cardiol Intv 2021;14:172–81)

From the [a]Department of Cardiology, Galway University Hospital, Galway, Ireland; [b]Department of Cardiology, John Radcliffe Hospital, Oxford, United Kingdom; [c]Heart and Lung Centre, New Cross Hospital, Wolverhampton, United Kingdom; [d]Department of Cardiology, Heart Center Leipzig, Leipzig, Germany; [e]Department of Interventional Cardiology, Erasmus University Medical Centre, Rotterdam, the Netherlands; [f]Department of Cardiology, Clinique Pasteur, Toulouse, France; [g]Department of Cardiology, Rigshospitalet University Hospital, Copenhagen, Denmark; [h]Department of Cardiology, Leeds Teaching Hospital, Leeds, United Kingdom; [i]Department of Cardiology, University of Bern, Bern, Switzerland; [j]Department of Cardiology, Royal Sussex County Hospital, Brighton, United Kingdom; [k]Department of Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland; [l]Department of Cardiology, Belfast City Hospital Trust, Belfast, United Kingdom; [m]Department of Cardiology, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany; [n]Cardiothoracic Department, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy; [o]1st Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland; [p]Department of Cardiothoracic Surgery, Skåne University Hospital, Lund, Sweden; [q]Department of Interventional Cardiology, UNICARV, Hospital de Santa Cruz, CHLO, Carnaxide, Portugal; [r]NOVA Medical School, Lisbon, Portugal; [s]Department of Cardiology, University Hospital Bonn, Bonn, Germany; and the [t]National University of Ireland Galway, Galway, Ireland.

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Transcatheter aortic valve replacement (TAVR) is a safe and effective alternative to surgical aortic valve replacement for the treatment of patients with symptomatic severe aortic valve stenosis across all surgical risk categories (1–7). The LOTUS aortic valve system (Boston Scientific, Marlborough, Massachusetts) is a mechanically expanding transcatheter heart valve (THV) with an intra-annular design and an adaptive seal to reduce the incidence of paravalvular leak (PVL). In the REPRISE III (Safety and Efficacy Study of Lotus Valve for Transcatheter Aortic Valve Replacement) trial, the LOTUS system was noninferior to the self-expanding CoreValve system (Medtronic, Minneapolis, Minnesota) for the coprimary safety and effectiveness composite endpoints (8). In this study, a lower incidence of PVL with the LOTUS system was offset by a higher rate of new permanent pacemaker (PPM) implantation. The LOTUS Edge system incorporated several iterative design improvements on its predecessor, including the Depth Guard technology to reduce the rate of new PPM implantation (**Central Illustration**). In 2017, the occurrence of important safety events mandated the commercial withdrawal of the LOTUS Edge device. In April 2019, the LOTUS Edge system received European Medicines Agency approval to recommence commercial implantation.

In this study, we present early short-term safety and efficacy results among an all-comers patient population treated with the re-released LOTUS Edge system in Europe.

SEE PAGE 182

METHODS

STUDY DESIGN. This was an investigator-initiated, multicenter, single-arm, retrospective registry of consecutive patients who underwent TAVR with the LOTUS Edge aortic valve system across 18 European centers during the first 8 months after commercial release in April 2019. Clinical, echocardiographic, multislice computed tomographic (MSCT), procedural, and clinical outcome data were retrospectively collected using an electronic case report form. Participation in the registry was voluntary, but enrolling centers were mandated to include all patients treated with the LOTUS Edge system. Patient selection for TAVR was performed per standard practice at each center. All data were site reported and collected into an anonymized patient-level database. The study was approved by the local ethics committee at each participating site and was conducted in accordance with the Declaration of Helsinki.

DEVICE DESIGN. The LOTUS Edge aortic valve system is a bioprosthetic THV that includes a braided Nitinol frame with 3 bovine pericardial leaflets and a polymer adaptive seal. The system has an intra-annular design and is deployed via mechanical expansion. This repositionable and retrievable system allows complete deployment and functional assessment of the THV before final release. Novel features of this system include increased flexibility of the delivery catheter, enhanced visualization of the locking mechanism, and Depth Guard technology designed to reduce left ventricular outflow tract (LVOT) interaction and potentially reduce PPM implantation (**Central Illustration**). There are 3 valve sizes, 23, 25, and 27 mm, for native annular diameters of 20 to 23, 23 to 25, and 25 to 27 mm, respectively. The delivery system requires a minimal femoral artery diameter of 6.5 mm and is compatible with the large LOTUS introducer set. All operators were requested to follow a newly developed implantation technique whereby the expanding valve is maintained at a shallow depth (<8 mm below the annular plane) throughout deployment.

ENDPOINTS. The primary objective of this study was to investigate the 30-day safety and efficacy of this novel THV system. All individual and composite endpoints were defined according to the Valve Academic Research Consortium-2 criteria (9). 30-day all-cause mortality was further divided into cardiovascular and noncardiovascular death, and stroke was adjudicated as disabling or nondisabling, according to the Valve Academic Research Consortium-2 definitions. Surgical risk stratification was calculated using the Society of Thoracic Surgeons Predictor of Mortality (STS-PROM) score version 2.9 (10,11). We defined complex anatomy as the presence of 1 of

ABBREVIATIONS AND ACRONYMS

AVA = aortic valve area
AVB = atrioventricular block
LBBB = left bundle branch block
LVOT = left ventricular outflow tract
MG = mean transvalvular pressure gradient
MSCT = multislice computed tomographic
PPM = permanent pacemaker
PVL = paravalvular leak
RBBB = right bundle branch block
STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality
TAVR = transcatheter aortic valve replacement
THV = transcatheter heart valve

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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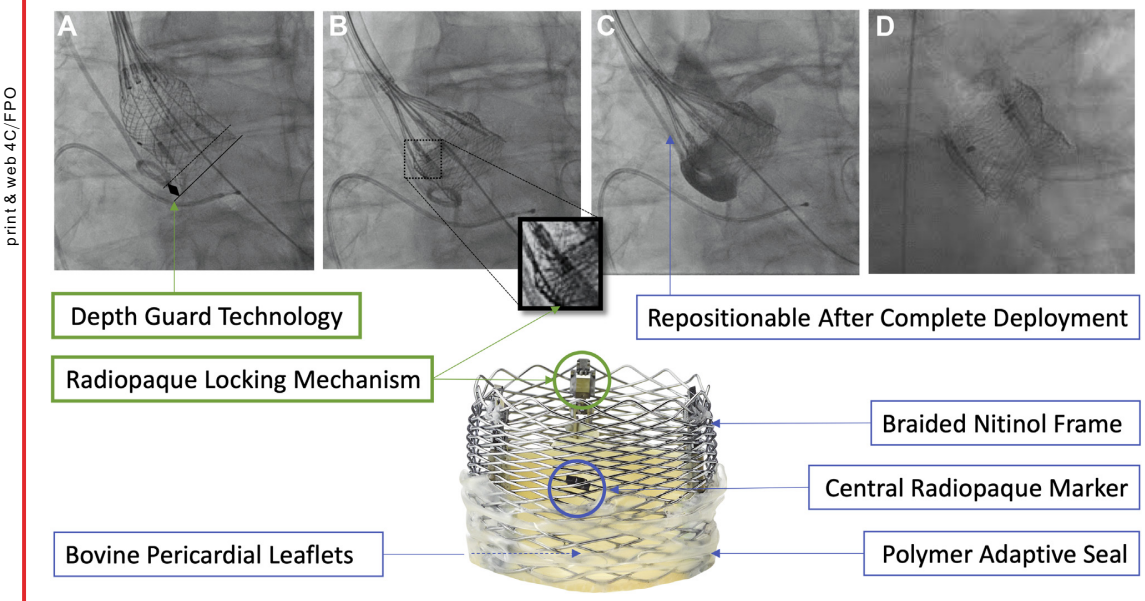
CENTRAL ILLUSTRATION **The LOTUS Edge Aortic Valve System**



Armario, X. et al. J Am Coll Cardiol Intv. 2021;14(2):172–81.

The LOTUS Edge system is an intra-annular and mechanically expanding transcatheter heart valve (THV) that consists of a braided Nitinol frame, 3 bovine pericardial leaflets, and a polymer adaptive seal with a central radiopaque marker. Novel features of this device are displayed in the **green boxes**. **(A)** Depth Guard technology reducing the interaction between the stent frame and the left ventricular outflow tract during deployment. **(B)** Radiopaque markers improving the visualization of the locking mechanism. **(C,D)** Complete deployment and functional assessment of the THV before final release.

the following conditions: severe aortic valve calcification, moderate to severe LVOT calcification, bicuspid aortic valve morphology, degenerated surgical biological prosthesis, or pure aortic valve regurgitation (Figure 1). These characteristics were site reported. Aortic valve and LVOT calcification were defined semiquantitatively as mild, moderate, or severe on the basis of MSCT imaging (12). Porcelain aorta was defined semiquantitatively on the basis of MSCT imaging. THV repositioning was defined as partial or complete recapture of the valve in the ascending aorta, while THV retrieval was defined as complete removal of the THV from the patient. Prosthesis-patient mismatch was classified as moderate (indexed aortic valve area [AVA] 0.65 to 0.85 cm^2/m^2) or severe (indexed AVA <0.65 cm^2/m^2). We reported the incidence of new PPM implantation as the rate of post-TAVR new PPM implantation in the whole patient population and among patients who were PPM naive. The decision for new PPM implantation was at the discretion of the participating center.

STATISTICAL ANALYSIS. Categorical variables are reported as frequencies and percentages. Continuous variables are presented as mean ± SD for normally distributed variables or as median and interquartile range for skewed variables. The chi-square test was performed to compare categorical variables. Student's *t*-test and the Mann-Whitney *U* test were used to compare normally distributed and skewed continuous variables, respectively. A univariate analysis for predictors of 30-day stroke was performed using all baseline characteristics and procedural factors considered potentially relevant in the development of this endpoint. Multivariate analysis was subsequently performed using variables with p values <0.20 in the univariate analysis. All statistical analysis was performed using SPSS Statistics version 25.0 (IBM, Armonk, New York).

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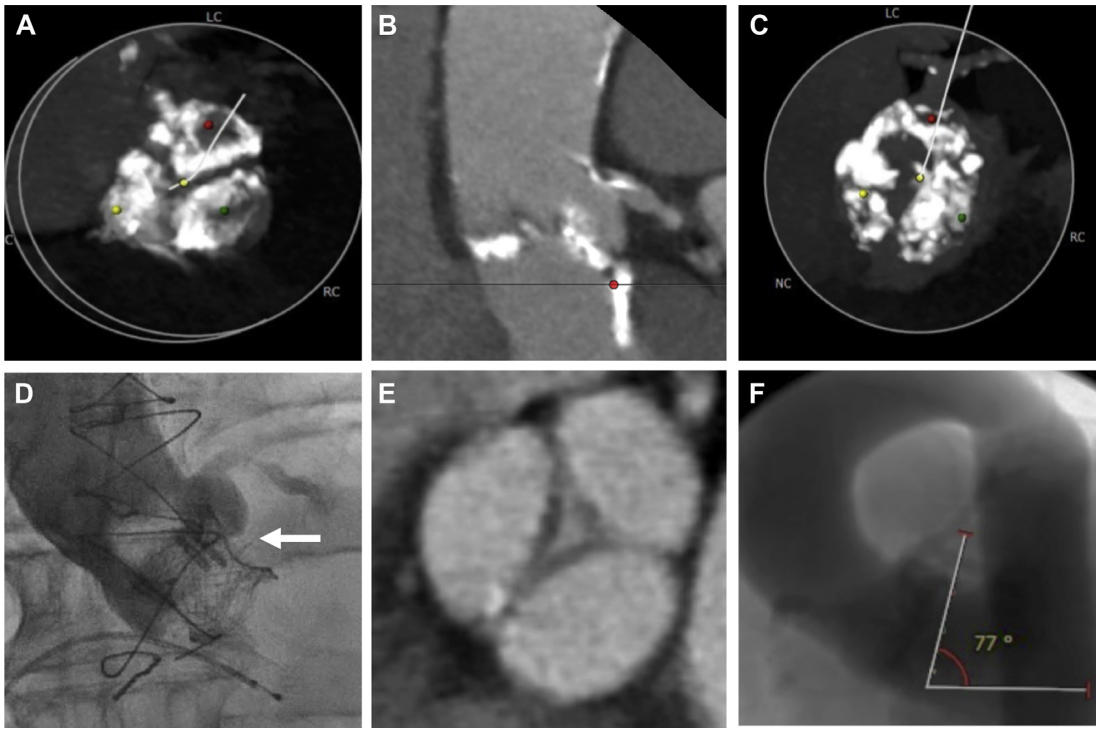
FIGURE 1 Complex Anatomies



Examples of complex anatomies treated with the LOTUS Edge system. **(A)** Severe aortic valve calcification. **(B)** Moderate to severe left ventricular outflow tract calcification. **(C)** Bicuspid aortic valve morphology. **(D)** Degenerated surgical biological prosthesis. **(E)** Pure aortic valve regurgitation. **(F)** Horizontal aorta.

RESULTS

BASELINE AND PROCEDURAL CHARACTERISTICS. Between April and November 2019, 286 consecutive patients treated with the LOTUS Edge system at 18 European centers were included. Baseline clinical characteristics are reported in Table 1. The mean age was 81.2 ± 6.9 years, 41.6% were women, and the mean STS-PROM score was 5.2 ± 5.4%. Almost three-quarters of patients (n = 207 [72.4%]) were in New York Heart Association functional class III or IV. At the time of the procedure, 46 patients (16.1%) had undergone prior PPM implantation, including 22 patients (7.7%) who had undergone elective pre-procedural PPM implantation because of underlying conduction abnormalities: 16 patients had right bundle branch block (RBBB) and 6 patients had left bundle branch block (LBBB) with or without first-degree atrioventricular block (AVB).

Baseline echocardiographic and MSCT data are outlined in Table 2. The average AVA and mean transvalvular pressure gradient (MG) were 0.7 ± 0.2 cm^2 and 45.9 ± 13.8 mm Hg, respectively. Moderate to severe aortic regurgitation was present in 11.5% (n = 33). Nearly one-half of all patients (47.9%) were considered to have complex anatomy: severe aortic valve calcification was reported in 37.5% (n = 99), moderate to severe LVOT calcification in 23.5% (n = 61), and bicuspid aortic valve in 9.9% (n = 28). Four patients were treated for degenerated surgical bioprosthesis (1.4%) and 3 patients for pure aortic valve regurgitation (1.1%). Patients in the complex anatomy group were younger (80.1 ± 7.2 years vs. 82.3 ± 6.3 years; p = 0.006), and had higher MG (48.5 ± 14.6 mm Hg vs. 43.4 ± 12.5 mm Hg; p = 0.002) and more frequent PPM implantation (21.2% vs. 11.4%; p = 0.03) at baseline.

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TABLE 1 Baseline Characteristics

	All Patients (N = 286)	Noncomplex Anatomy (n = 149)	Complex Anatomy (n = 137)	p Value
Age, yrs	81.2 ± 6.9	82.3 ± 6.3	80.1 ± 7.2	0.006
Female	119 (41.6)	65 (43.6)	54 (39.4)	0.47
STS-PROM score, %	5.2 ± 5.4	5.9 ± 6.5	4.4 ± 3.6	0.03
NYHA functional class III or IV	207 (72.4)	110 (73.8)	97 (70.8)	0.57
Body mass index, kg/m^2	27.6 ± 5.6	27.7 ± 6.1	27.6 ± 5.1	0.93
Diabetes mellitus	69 (24.1)	33 (22.1)	36 (26.3)	0.42
Atrial fibrillation	87 (30.4)	49 (32.9)	38 (27.7)	0.34
Permanent pacemaker	46 (16.1)	17 (11.4)	29 (21.2)	0.03
Prior myocardial infarction	34 (11.9)	20 (13.4)	14 (10.2)	0.40
Prior PCI	57 (19.9)	36 (24.2)	22 (16.1)	0.09
Prior CABG	32 (11.2)	18 (12.1)	14 (10.2)	0.62
Prior SAVR	4 (1.4)	0 (0.0)	4 (2.9)	0.04
Prior cerebrovascular accident	35 (12.2)	20 (13.4)	15 (10.9)	0.52
Peripheral vascular disease	64 (22.4)	38 (25.5)	26 (19.0)	0.19
Chronic lung disease	48 (16.8)	23 (15.9)	25 (18.5)	0.56
Glomerular filtration rate <30 ml/min	29 (10.1)	16 (11.1)	12 (9.0)	0.56

Values are mean ± SD or n (%). p values represent comparisons between noncomplex and complex anatomies.

CABG = coronary artery bypass grafting; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SAVR = surgical aortic valve replacement; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

TABLE 2 Baseline Imaging

	All Patients (N = 286)	Noncomplex Anatomy (n = 149)	Complex Anatomy (n = 137)	p Value
Echocardiography				
Left ventricular ejection fraction, %	53.5 ± 11.5	53.6 ± 10.4	53.3 ± 12.6	0.79
Aortic valve area, cm^2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.25
Mean transvalvular gradient, mm Hg	45.9 ± 13.8	43.4 ± 12.5	48.5 ± 14.6	0.002
Peak transvalvular gradient, mm Hg	77.0 ± 21.9	73.7 ± 20.3	80.7 ± 23.1	0.008
Moderate to severe aortic regurgitation	33 (11.5)	22 (14.8)	11 (8.0)	0.08
Computed tomography				
Aortic annulus				
Minimum diameter, mm	22.4 ± 3.2	22.1 ± 2.7	22.7 ± 3.7	0.18
Maximum diameter, mm	27.2 ± 2.7	27.2 ± 2.6	27.1 ± 2.8	0.83
Mean diameter, mm	24.6 ± 2.8	24.4 ± 2.0	24.9 ± 3.6	0.14
Perimeter, mm	72.5 ± 18.5	73.6 ± 16.2	71.5 ± 20.4	0.37
Area, mm^2	427.9 ± 166.2	436.9 ± 143.3	418.8 ± 186.5	0.39
Sinus of Valsalva				
Mean diameter, mm	32.1 ± 3.9	31.2 ± 4.0	33.0 ± 3.7	0.002
Sinotubular junction				
Minimum diameter, mm	28.7 ± 3.6	28.3 ± 3.7	29.1 ± 3.6	0.13
Coronary arteries				
Left coronary artery height, mm	14.4 ± 3.3	14.4 ± 3.3	14.4 ± 3.4	0.89
Right coronary artery height, mm	16.4 ± 3.4	16.5 ± 3.4	16.4 ± 3.4	0.80

Values are mean ± SD or n (%). p values represent comparisons between noncomplex and complex anatomies.

Procedures were predominantly performed under local anesthesia (n = 278 [97.2%]) via transfemoral access (n = 282 [98.6%]) (Table 3). During TAVR, aortic valve pre-dilatation was performed in 54.2% (n = 155) and post-dilatation in 2.1% (n = 6). Both pre- and post-dilatation were performed more frequently in the complex anatomy group (65.0% vs. 44.3% [p < 0.001] and 2.1% vs. 0.0% [p = 0.01], respectively). THV repositioning occurred in 40.9% of cases (n = 61) with noncomplex anatomy and 38.7% of cases (n = 53) with complex anatomy (p = 0.70). In 1 case, a 27-mm LOTUS Edge was retrieved because of failure to achieve an optimal position, and a 26-mm SAPIEN 3 (Edwards Lifesciences, Irvine, California) was successfully implanted.

PROCEDURAL AND CLINICAL OUTCOMES. In-hospital mortality occurred in four patients (1.4%): 1 left ventricular guidewire perforation with cardiac tamponade and conversion to open surgery (day 0), 1 presumed left ventricular guidewire perforation with cardiac tamponade (day 1), 1 cardiac arrest of uncertain origin (day 1), and 1 stroke (day 2) (Table 4). There were 9 strokes (3.1%), of which 3 (1.0%) were categorized as disabling. No cases of myocardial infarction or stage 2 or 3 acute kidney injury were observed. Life-threatening and major bleeding occurred in 0.7% (n = 2) and 3.1% (n = 9), respectively, while the rate of major vascular complications was 2.1% (n = 6). No cases of valve malpositioning were reported.

Thirty-day follow-up was available in 99.3% (n = 284). Between hospital discharge and 30 days, 3 further deaths occurred: 1 myocardial infarction (day 25), 1 acute cholecystitis with septic shock (day 22), and 1 multiorgan failure of uncertain etiology (day 12). The 30-day mortality rate was consequently 2.4% (n = 7); 2.1% (n = 6) were classified as cardiovascular deaths (Table 5). One additional nondisabling stroke occurred on day 29, yielding a 30-day stroke rate of 3.5% (n = 10); 1.0% (n = 3) were classified as disabling strokes. Logistic regression did not identify any independent predictor of 30-day stroke (Supplemental Table 1).

At 30 days, 12.0% of patients remained in New York Heart Association functional class III or IV (Figure 2). The mean AVA and MG were 1.9 ± 0.9 cm^2 and 11.9 ± 5.7 mm Hg, respectively (Figure 3). Twenty-two patients (8.9%) had MG ≥20 mm Hg. The rates of severe and moderate prosthesis-patient mismatch were 7.5% (n = 13) and 26.4% (n = 46), respectively. None or trace PVL was reported in 84.4% (n = 211), and moderate PVL occurred in 2.0% (n = 5), with no cases of severe PVL (Figure 3).

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The incidence of new PPM implantation was 25.9% among all patients and 30.8% among PPM-naive patients. The indications for new PPM implantation were as follows: 66.2% developed third-degree AVB, 9.5% had second-degree AVB, 17.6% had first-degree AVB with LBBB or RBBB, and 6.8% had isolated LBBB.

Post-procedural antithrombotic therapy was diverse: 24.4% were treated with single-antiplatelet therapy, 38.7% with dual antiplatelet therapy, and 36.9% with oral anticoagulant agents with or without antiplatelet agents. There were 3 cases of clinical valve thrombosis after TAVR, treated successfully with oral anticoagulation.

Procedural and clinical outcomes at 30 days dichotomized according to noncomplex or complex anatomy were similar, except for significantly lower rates of new PPM implantation (18.2% vs. 32.9%; p = 0.005) and moderate PVL (0.0% vs. 3.6%; p = 0.04) in the complex group.

Overall Valve Academic Research Consortium-2 device success was 89.5% (n = 256), early safety was 92.7% (n = 265), and clinical efficacy was 75.2% (n = 215) (Supplemental Table 2).

TABLE 3 Procedural Characteristics

	All Patients (N = 286)	Noncomplex Anatomy (n = 149)	Complex Anatomy (n = 137)	p value
Local anesthesia	278 (97.2)	144 (96.6)	134 (97.8)	0.55
Transfemoral access	282 (98.6)	147 (98.7)	135 (98.5)	0.93
Valve size				
23 mm	74 (25.9)	41 (27.5)	33 (24.1)	0.51
25 mm	105 (36.7)	60 (40.3)	45 (32.8)	0.19
27 mm	107 (37.4)	48 (32.2)	59 (43.1)	0.06
Pre-dilatation	155 (54.2)	66 (44.3)	89 (65.0)	<0.001
Post-dilatation	6 (2.1)	0 (0.0)	6 (2.1)	0.01
Repositioning	114 (39.9)	61 (40.9)	53 (38.7)	0.70
Fluoroscopy time, min	19.2 ± 8.2	18.8 ± 8.1	19.6 ± 8.3	0.48
Contrast volume, ml	121.6 ± 54.3	127.2 ± 56.5	115.0 ± 50.9	0.12

Values are n (%) or mean ± SD. p values represent comparisons between noncomplex and complex anatomies.

DISCUSSION

Herein we present the first European clinical experience with the LOTUS Edge system among an all-comers patient population. The salient features of this initial experience with this new technology and implantation technique are that the LOTUS Edge system is associated with satisfactory clinical outcomes and hemodynamic results and very low rates of clinically significant PVL in an anatomically complex patient cohort. The requirement for new PPM implantation, however, remains high.

In this study, the LOTUS Edge system showed similar clinical outcomes at 30 days compared with its predecessor, the LOTUS valve, in the RESPOND registry despite operators' having to relearn how to use the device after a 2-year hiatus on commercial implantation (13). The rates of 30-day mortality (2.4%) and stroke (3.5%) in the present study were similar to those reported in RESPOND (2.6% and 3.0%, respectively), albeit with a slightly higher mean STS-PROM score in RESPOND (6.0 ± 6.9%), which could be attributed to changes in the STS-PROM calculator over time. Other clinical outcomes, such as acute kidney injury, life-threatening bleeding, and major vascular complications, occurred infrequently, with incidences similar to prior contemporary TAVR studies (4–7). We did not observe any severe device-related safety events that mandated the withdrawal of the previous LOTUS Edge system in 2017.

The hemodynamic outcomes at 30 days (AVA 1.9 ± 0.9 cm^2, MG 11.9 ± 5.7 mm Hg) were nearly identical to those reported in RESPOND (AVA 1.8 ± 0.4 cm^2, MG

TABLE 4 Procedural Outcomes

	All Patients (N = 286)	Noncomplex Anatomy (n = 149)	Complex Anatomy (n = 137)	p Value
Mortality	4 (1.4)	3 (2.0)	1 (0.7)	0.36
Stroke	9 (3.1)	6 (4.0)	3 (2.2)	0.37
Nondisabling	6 (2.1)	4 (2.7)	2 (1.5)	0.47
Disabling	3 (1.0)	2 (1.3)	1 (0.7)	0.61
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	–
Acute kidney injury	8 (2.8)	2 (1.3)	6 (4.4)	0.12
Stage 1	8 (2.8)	2 (1.3)	6 (4.4)	0.12
Stage 2 or 3	0 (0.0)	0 (0.0)	0 (0.0)	–
Bleeding	27 (9.4)	16 (10.7)	11 (8.0)	0.43
Minor	16 (5.6)	10 (6.7)	7 (5.1)	0.57
Major	9 (3.1)	6 (4.0)	3 (2.2)	0.37
Disabling or life threatening	2 (0.7)	1 (0.7)	1 (0.7)	0.95
Vascular complications	22 (7.7)	16 (10.7)	6 (4.4)	0.04
Minor	16 (5.6)	11 (7.4)	5 (3.6)	0.17
Major	6 (2.1)	5 (3.4)	1 (0.7)	0.12
Valve malposition	0 (0.0)	0 (0.0)	0 (0.0)	–
Coronary obstruction	0 (0.0)	0 (0.0)	0 (0.0)	–
Annular rupture	0 (0.0)	0 (0.0)	0 (0.0)	–
Ventricular perforation	2 (0.7)	1 (0.7)	1 (0.7)	0.95
Cardiac tamponade	2 (0.7)	1 (0.7)	1 (0.7)	0.95
Surgical conversion	1 (0.3)	1 (0.7)	0 (0.0)	0.34
Hospitalization duration, days	5 (3–8)	5 (3–8)	5 (2–8)	0.49

Values are n (%) or median (interquartile range). p values represent comparisons between noncomplex and complex anatomies. All clinical outcomes are expressed according to the Valve Academic Research Consortium-2 definitions.

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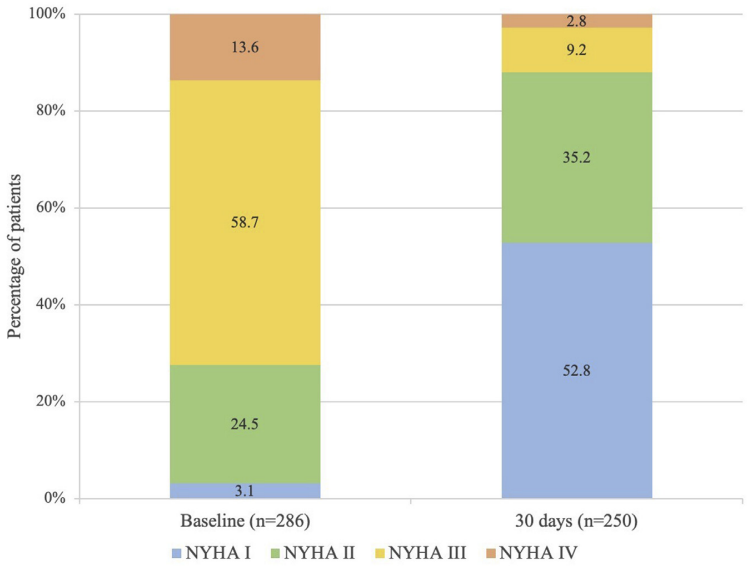
TABLE 5 Clinical Outcomes at 30 Days

	All Patients (N = 286)	Noncomplex Anatomy (n = 149)	Complex Anatomy (n = 137)	p Value
Mortality	7 (2.4)	3 (2.0)	4 (2.9)	0.62
Cardiovascular	6 (2.1)	3 (2.0)	3 (2.2)	0.92
Noncardiovascular	1 (0.3)	0 (0.0)	1 (0.7)	0.30
Stroke	10 (3.5)	6 (4.0)	4 (2.9)	0.61
Nondisabling	7 (2.4)	4 (2.7)	2 (1.5)	0.47
Disabling	3 (1.0)	2 (1.3)	2 (1.5)	0.93
Myocardial infarction	1 (0.3)	0 (0.0)	1 (0.7)	0.30
Clinical valve thrombosis	3 (1.0)	0 (0.0)	3 (2.2)	0.07
Valve endocarditis	0 (0.0)	0 (0.0)	0 (0.0)	–
Repeated procedure for valve-related dysfunction	0 (0.0)	0 (0.0)	0 (0.0)	–
New PPM implantation	74 (25.9)	49 (32.9)	25 (18.2)	0.005
Among PPM-naive patients	74 (30.8)	49 (37.1)	25 (23.1)	0.02
NYHA functional class III or IV (n = 250)	30 (12.0)	18 (13.4)	12 (10.3)	0.45
Aortic valve area, cm^2	1.9 ± 0.9	1.8 ± 0.5	2.0 ± 1.3	0.25
Mean transvalvular gradient, mm Hg	11.9 ± 5.7	11.4 ± 6.0	12.6 ± 5.3	0.11
Paravalvular leak (n = 250)				
None or trace	211 (84.4)	116 (84.7)	95 (84.1)	0.90
Mild	34 (13.6)	16 (11.7)	18 (15.9)	0.33
Moderate	5 (2.0)	5 (3.6)	0 (0.0)	0.04
Severe	0 (0.0)	0 (0.0)	0 (0.0)	–

Values are n (%) or mean ± SD. The p values represent comparisons between noncomplex and complex anatomies. All clinical outcomes are expressed according to the Valve Academic Research Consortium-2 definitions.

NYHA = New York Heart Association; PPM = permanent pacemaker.

FIGURE 2 Functional Class at Baseline and 30 Days



NYHA = New York Heart Association.

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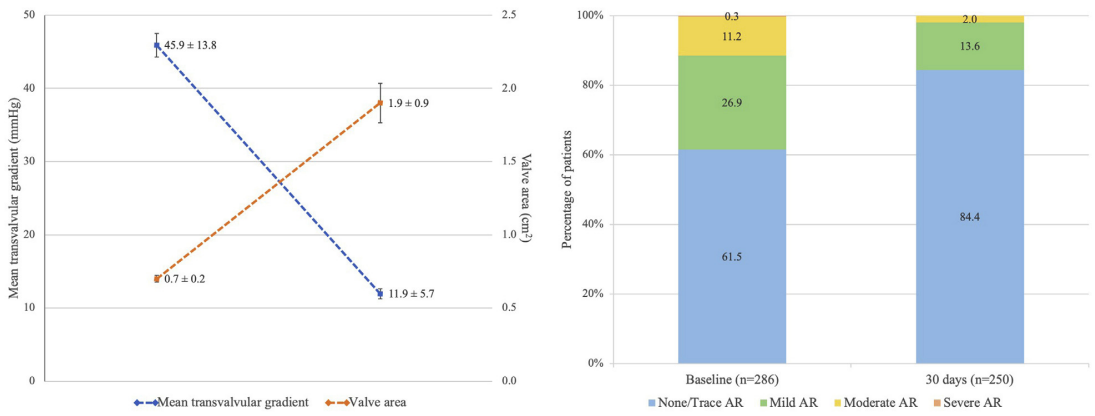
FIGURE 3 **Hemodynamic Data at Baseline and 30 Days**



Values are mean ± SD. **Error bars** represent 95% confidence interval. AR = aortic valve regurgitation.

10.8 ± 4.6 mm Hg), in the same range as those reported for the balloon-expandable SAPIEN 3 Ultra valve (AVA 1.6 ± 0.4 cm^2, MG 11.6 ± 4.3 mm Hg), but less favorable compared with the self-expanding Evolut PRO valve (AVA 2.0 ± 0.5 cm^2, MG 6.4 ± 2.1 mm Hg) (13–15). The role of post-dilatation of the LOTUS valve and the impact of residual transvalvular gradients on long-term durability warrants further study. In contrast, as increasing PVL has proved to be associated with increasing mortality (16–19), the very low rate of moderate to severe PVL in the present study (2.0%) is clearly reassuring. Indeed, surgery-like results are observed in this cohort, with 84.4% of patients experiencing none or trace PVL post-TAVR. These data represent the best-in-class PVL data for THVs, especially when considering the anatomic complexity of the patient population (20).

The incidence of new PPM implantation with the LOTUS Edge remains high compared with other commercially available THVs (14,15). At 30 days, 25.9% of all patients and 30.8% of PPM-naive patients required new PPMs. This rate is numerically lower than that reported with the LOTUS valve in the RESPOND registry (30.0% among all patients, 34.6% among PPM-naive patients) (13) and in the REPRISE III study (29.1% among all patients, 35.5% among PPM-naive patients) (8). The Depth Guard technology was introduced to reduce the rate of PPM implantation by minimizing interaction between the stent frame and the LVOT during deployment. The Depth Guard system allows the majority of late THV foreshortening to occur at the outflow rather than the inflow, where greater LVOT interaction can lead to conduction system injury. However, 2 important aspects should be considered when interpreting the incidence of new PPM implantation in our study. First, the present study represents the first LOTUS Edge cases performed at each center in nearly 2 years. Thus, operators had to refamiliarize themselves with the device and integrate a new and unproven deployment protocol. Increasing operator experience with the device and ongoing evolution of the implantation technique have the potential to reduce the incidence of new PPM implantation. Second, in this retrospective study, the decision for PPM implantation was at the discretion of the participating center. In one-quarter (24.4%) of cases, new PPMs were implanted for first-degree AVB with LBBB or RBBB or even for isolated LBBB. According to the current European Society of Cardiology guidelines, such conduction disturbances would represent nonapproved indications for PPM implantation (21). If we excluded those patients with nonapproved indications, the incidence of new PPM implantation would be 19.6% among all patients and 23.3% among PPM-naive patients.

Anecdotal evidence would suggest that the LOTUS system is preferentially used in Europe for the most complex anatomies, including bicuspid aortic valve morphology and severe aortic valve calcification. Indeed, nearly one-half (47.9%) of the cases included in our study met the definition for complex anatomy. The LOTUS system has several unique features that favor its use in complex anatomy: 1) the valve can be

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completely deployed and subsequently recaptured, repositioned, and finally retrieved if the result is suboptimal; 2) the leaflets are functional early during deployment, so hemodynamic embarrassment is rare; 3) the adaptive seal adjusts to the surrounding anatomy giving very low rates of PVL, even in the presence of severe aortic valve or LVOT calcification; and 4) the gradual expansion of the THV yields a low risk for annular rupture. In the present study, complex anatomy was not associated with higher rates of peri-procedural complications, stroke, new PPM implantation, significant PVL, or elevated transvalvular gradients compared with noncomplex anatomy. The absence of any cases of valve malpositioning, coronary obstruction, or annular rupture along with favorable hemodynamic status and very low rates of PVL support the contention that the LOTUS Edge system is an important alternative for complex situations. The trade-off for these advantages, however, may be a higher rate of new PPM implantation.

STUDY LIMITATIONS. The relatively small sample size of the study population and the retrospective design with only 30-day follow-up limit the development of firm conclusions. Nevertheless, these short-term data are the first reported since the LOTUS Edge system was withdrawn from the market in April 2017 and include important safety and efficacy information for the community. Site-reported endpoints and the absence of an echocardiographic and MSCT core laboratory also represent important limitations. The decision for PPM implantation was at the discretion of the participating center. Thus, the indications for PPM implantation differ among centers and can be influenced by both patient and operational factors. Operator inexperience with the device and implantation technique may have influenced the rate of some adverse events. The ongoing RESPOND EDGE study (NCT04009720) will provide additional information regarding patient outcomes with this THV system.

CONCLUSIONS

Early European experience with the LOTUS Edge aortic valve system demonstrated satisfactory short-term safety and efficacy, favorable hemodynamic data, and very low rates of clinically relevant PVL in an anatomically complex patient cohort. The requirement for new PPM implantation remained high. Further study will evaluate whether increasing operator experience with the device and the new implantation technique can reduce the incidence of new PPM implantation.

AUTHOR DISCLOSURES

Dr. Khogali is a proctor for Medtronic and Boston Scientific. Dr. Van Mieghem has received research grant support from Abbott Vascular, Boston Scientific, Edwards Lifesciences, Medtronic, PulseCath BV, and Daiichi-Sankyo; and is a consultant for Abbott Vascular, Boston Scientific, PulseCath BV, Medtronic, and Daiichi-Sankyo. Dr. Cotton is a proctor for Boston Scientific; and has received speaker fees from Abbott Vascular and Medtronic. Dr. Frerker has received lecture honoraria and travel support from Boston Scientific, Abbott Vascular, Edwards Lifesciences, and Medtronic. Dr. Grygier is a consultant and proctor for Boston Scientific and Medtronic; and has received consulting fees and institutional research grants from Abbott Vascular, Boston Scientific, and Medtronic. Dr. Bjursten is a consultant and proctor for Boston Scientific; and has received institutional research grants from Boston Scientific. Dr. Jeger has received speaker honoraria and research support from B. Braun; and has received speaker honoraria from Cardionovum. Dr. Teles has received consulting fees and institutional research grants from Medtronic, Boston Scientific, and Abbott Vascular. Dr. Petronio is a consultant for Medtronic, Boston Scientific, and Abbott Vascular. Dr. Pilgrim has received research grants to the institution from Boston Scientific, Biotronik, and Edwards Lifesciences; has received speaker fees from Boston Scientific and Biotronik; and is a consultant for HighLife SAS. Dr. Søndergaard has received consulting fees and institutional research grants from Abbott Vascular, Boston Scientific, Edwards Lifesciences, Medtronic, and Symetis. Dr. Mylotte is a consultant for Medtronic, Boston Scientific, and Microport. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Darren Mylotte, Department of Cardiology, Galway University Hospital, Newcastle Road, Galway H91 YR71, Ireland. E-mail: darren.mylotte@nuigalway.ie.

PERSPECTIVES

WHAT IS KNOWN? The LOTUS aortic valve system is a mechanically expanding THV for the treatment of symptomatic severe aortic valve stenosis. In 2017, the LOTUS Edge system was commercially withdrawn because of safety concerns.

WHAT IS NEW? In April 2019, the LOTUS Edge system was commercially relaunched. This study reports the first experience with this novel device in an all-comers population. These new data show satisfactory short-term safety and efficacy, with very low rates of clinically relevant PVL in an anatomically complex cohort. The requirement for new PPM implantation, however, remains high.

WHAT IS NEXT? Further study will evaluate whether the new implantation technique and an increasing operator experience can reduce the incidence of new PPM implantation.

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KEY WORDS aortic valve stenosis, transcatheter heart valve, transcatheter aortic valve replacement

APPENDIX For supplemental tables, please see the online version of this paper.

5.2. Impact of the COVID-19 pandemic on global TAVI activity: The COVID-TAVI study

Armario X, Carron J, Simpkin AJ, Elhadi M, Kennedy C, Abdel-Wahab M, Bleiziffer S, Lefèvre T, Wolf A, Pilgrim T, Villablanca PA, Blackman DJ, Van Mieghem NM, Hengstenberg C, Swaans MJ, Prendergast BD, Patterson T, Barbanti M, Webb JG, Behan M, Resar J, Chen M, Hildick-Smith D, Spence MS, Zweiker D, Bagur R, Teles R, Ribichini FL, Jagielak D, Park DW, Kornowski R, Wykrzykowska JJ, Bunc M, Estévez-Loureiro R, Poon K, Götberg M, Jeger RV, Ince H, Packer EJS, Angelillis M, Nombela-Franco L, Guo Y, Savontaus M, Al-Moghairi AM, Parasca CA, Kliger C, Roy D, Molnár L, Silva M, White J, Yamamoto M, Carrilho-Ferreira P, Toggweiler S, Voudris V, Ohno Y, Rodrigues I, Parma R, Ojeda S, Toutouzas K, Regueiro A, Grygier M, AlMerri K, Cruz-González I, Fridrich V, de la Torre Hernández JM, Noble S, Kala P, Asmarats L, Kurt IH, Bosmans J, Erglis M, Casserly I, Iskandarani D, Bhindi R, Kefer J, Yin WH, Rosseel L, Kim HS, O'Connor S, Hellig F, Sztejfman M, Mendiz O, Pineda AM, Seth A, Pllaha E, de Brito FS Jr, Bajoras V, Balghith MA, Lee M, Eid-Lidt G, Vandeloo B, Vaz VD, Alasnag M, Ussia GP, Tay E, Mayol J, Gunasekaran S, Sardella G, Buddhari W, Kao HL, Dager A, Tzikas A, Gudmundsdottir IJ, Edris A, Gutiérrez Jaikel LA, Arias EA, Al-Hijji M, Ertürk M, Conde-Vela C, Boljević D, Guadagnoli AF, Hermlin T, ElGuindy AM, de Oliveira Lima-Filho M, de Moura Santos L, Perez L, Maluenda G,Akyüz AR, Alhaddad IA, Amin H, So CY, Al Nooryani AA, Vaca C, Albistur J, Nguyen QN, Arzamendi D, Grube E, Modine T, Tchétché D, Hayashida K, Latib A, Makkar RR, Piazza N, Søndergaard L, McEvoy JW , Mylotte D. Impact of the COVID-19 Pandemic on Global TAVR Activity: The COVID-TAVI Study. *JACC Cardiovasc Interv* 2024;17(3):374-387. doi: 10.1016/j.jcin.2023.10.041. PMID: 38180419. Journal impact factor (2023): 11.7 (quartile 1, percentile 95.7).

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Impact of the COVID-19 Pandemic on Global TAVR Activity

The COVID-TAVI Study

Xavier Armario, MD,[a,b] Jennifer Carron, MB BCh,[a] Andrew J. Simpkin, PhD,[c] Mohamed Elhadi, MB BCh,[a] Ciara Kennedy, MB BCh,[a] Mohamed Abdel-Wahab, MD, PhD,[d] Sabine Bleiziffer, MD,[e] Thierry Lefèvre, MD,[f] Alexander Wolf, MD,[g] Thomas Pilgrim, MD,[h] Pedro A. Villablanca, MD,[i] Daniel J. Blackman, MD,[j] Nicolas M. Van Mieghem, MD, PhD,[k] Christian Hengstenberg, MD,[l] Martin J. Swaans, MD, PhD,[m] Bernard D. Prendergast, MD,[n] Tiffany Patterson, MD, PhD,[n] Marco Barbanti, MD,[o] John G. Webb, MD,[p] Miles Behan, MD,[q] Jon Resar, MD,[r] Mao Chen, MD, PhD,[s] David Hildick-Smith, MD,[t] Mark S. Spence, MB BCh, MD,[u] David Zweiker, MD,[v] Rodrigo Bagur, MD, PhD,[w] Rui Teles, MD,[x] Flavio L. Ribichini, MD,[y] Dariusz Jagielak, MD, PhD,[z] Duk-Woo Park, MD, PhD,[aa] Ran Kornowski, MD,[bb] Joanna J. Wykrzykowska, MD, PhD,[cc] Matjaz Bunc, MD, PhD,[dd] Rodrigo Estévez-Loureiro, MD, PhD,[ee] Karl Poon, MB BCh,[ff] Matthias Götberg, MD, PhD,[gg] Raban V. Jeger, MD,[hh] Hüseyin Ince, MD, PhD,[ii] Erik J.S. Packer, MD, PhD,[jj] Marco Angelillis, MD, PhD,[kk] Luis Nombela-Franco, MD, PhD,[ll] Yingqiang Guo, MD,[mm] Mikko Savontaus, MD,[nn] Abdulrahman M. Al-Moghairi, MD,[oo] Catalina Andreea Parasca, MD,[pp] Chad Kliger, MD,[qq] David Roy, MB BCh, MD,[rr] Levente Molnár, MD,[ss] Mariana Silva, MD,[tt] Jonathon White, MB BCh,[uu] Masanori Yamamoto, MD,[vv,ww,xx] Pedro Carrilho-Ferreira, MD,[yy] Stefan Toggweiler, MD,[zz] Vassileios Voudris, MD, PhD,[aaa] Yohei Ohno, MD, PhD,[bbb] Inês Rodrigues, MD,[ccc] Radosław Parma, MD, PhD,[ddd] Soledad Ojeda, MD, PhD,[eee] Kostas Toutouzas, MD,[fff] Ander Regueiro, MD, PhD,[ggg] Marek Grygier, MD, PhD,[hhh] Khaled AlMerri, MD,[iii] Ignacio Cruz-González, MD, PhD,[jjj] Viliam Fridrich, MD, PhD,[kkk] José M. de la Torre Hernández, MD, PhD,[lll] Stephane Noble, MD,[mmm] Petr Kala, MD, PhD,[nnn] Lluis Asmarats, MD, PhD,[ooo] Ibrahim Halil Kurt, MD,[ppp] Johan Bosmans, MD, PhD,[qqq] Martins Erglis, MD,[rrr] Ivan Casserly, MB BCh, MD,[sss,ttt] Dounia Iskandarani, MD,[uuu] Ravinay Bhindi, MB BCh, MD, PhD,[vvv] Joelle Kefer, MD,[www] Wei-Hsian Yin, MD, PhD,[xxx] Liesbeth Rosseel, MD,[yyy] Hyo-Soo Kim, MD, PhD,[zzz] Stephen O'Connor, MB BCh,[aaaa] Farrel Hellig, MB BCh,[bbbb] Matias Sztejfman, MD,[cccc] Oscar Mendiz, MD,[dddd] Andres M. Pineda, MD,[eeee] Ashok Seth, MD,[ffff] Elton Pllaha, MD,[gggg] Fabio S. de Brito, Jr, MD, PhD,[hhhh] Vilhelmas Bajoras, MD,[iiii] Mohammed A. Balghith, MD,[jjjj] Michael Lee, MD,[kkkk] Guering Eid-Lidt, MD,[llll] Bert Vandeloo, MD,[mmmm] Vinicius Daher Vaz, MD,[nnnn] Mirvat Alasnag, MD,[oooo] Gian Paolo Ussia, MD,[pppp] Edgar Tay, MD,[qqqq] Jorge Mayol, MD,[rrrr] Sengottuvelu Gunasekaran, MD,[ssss] Gennaro Sardella, MD,[tttt] Wacin Buddhari, MD,[uuuu] Hsien-Li Kao, MD,[vvvv] Antonio Dager, MD,[wwww] Apostolos Tzikas, MD, PhD,[xxxx] Ingibjörg J. Gudmundsdottir, MD,[yyyy] Ahmad Edris, MD,[zzzz] Luis Abel Gutiérrez Jaikel, MD,[aaaaa] Eduardo A. Arias, MD,[bbbbb] Mohammed Al-Hijji, MD,[ccccc] Mehmet Ertürk, MD,[ddddd] César Conde-Vela, MD,[eeeee] Darko Boljević, MD,[fffff] Adolfo Ferrero Guadagnoli, MD,[ggggg] Toomas Hermlin, MD, PhD,[hhhhh] Ahmed M. ElGuindy, MD,[iiiii] Moysés de Oliveira Lima-Filho, MD, PhD,[jjjjj] Luciano de Moura Santos, MD,[kkkkk] Luis Perez, MD,[lllll] Gabriel Maluenda, MD,[mmmmm,nnnnn] Ali Rıza Akyüz, MD,[ooooo] Imad A. Alhaddad, MD,[ppppp] Haitham Amin, MD,[qqqqq] Chak-Yu So, MD,[rrrrr] Arif A. Al Nooryani, MD,[sssss] Carlos Vaca, MD,[ttttt] Juan Albistur, MD,[uuuuu] Quang Ngoc Nguyen, MD, PhD,[vvvvv] Dabit Arzamendi, MD, PhD,[ooo] Eberhard Grube, MD,[wwwww] Thomas Modine, MD, PhD,[xxxxx] Didier Tchétché, MD,[yyyyy] Kentaro Hayashida, MD, PhD,[zzzzz] Azeem Latib, MD,[aaaaaa] Raj R. Makkar, MD,[bbbbbb] Nicolo Piazza, MD, PhD,[cccccc] Lars Søndergaard, MD,[dddddd] John William McEvoy, MB BCh, MHS, PhD,[a,eeeeee] Darren Mylotte, MB BCh, MD, PhD[a,eeeeee]

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ABSTRACT

BACKGROUND The COVID-19 pandemic adversely affected health care systems. Patients in need of transcatheter aortic valve replacement (TAVR) are especially susceptible to treatment delays.

OBJECTIVES This study sought to evaluate the impact of the COVID-19 pandemic on global TAVR activity.

METHODS This international registry reported monthly TAVR case volume in participating institutions prior to and during the COVID-19 pandemic (January 2018 to December 2021). Hospital-level information on public vs private, urban vs rural, and TAVR volume was collected, as was country-level information on socioeconomic status, COVID-19 incidence, and governmental public health responses.

RESULTS We included 130 centers from 61 countries, including 65,980 TAVR procedures. The first and second pandemic waves were associated with a significant reduction of 15% ($P < 0.001$) and 7% ($P < 0.001$) in monthly TAVR case volume, respectively, compared with the prepandemic period. The third pandemic wave was not associated with reduced TAVR activity. A greater reduction in TAVR activity was observed in Africa (−52%; $P = 0.001$), Central-South America (−33%; $P < 0.001$), and Asia (−29%; $P < 0.001$). Private hospitals ($P = 0.005$), urban areas ($P = 0.011$), low-volume centers ($P = 0.002$), countries with lower development ($P < 0.001$) and economic status ($P < 0.001$), higher COVID-19 incidence ($P < 0.001$), and more stringent public health restrictions ($P < 0.001$) experienced a greater reduction in TAVR activity.

CONCLUSIONS TAVR procedural volume declined substantially during the first and second waves of the COVID-19 pandemic, especially in Africa, Central-South America, and Asia. National socioeconomic status, COVID-19 incidence, and public health responses were associated with treatment delays. This information should inform public health policy in case of future global health crises. (J Am Coll Cardiol Intv 2024;17:374-387) © 2024 by the American College of Cardiology Foundation.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

GDP = gross domestic product

GNI = gross national income

HDI = Human Development Index

IRR = incidence rate ratio

SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

From the [a]Department of Cardiology, Galway University Hospital, Galway, Ireland; [b]Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain; [c]School of Mathematical and Statistical Sciences, University of Galway, Galway, Ireland; [d]Heart Center Leipzig, Leipzig, Germany; [e]Heart and Diabetes Center Northrhine-Westfalia, Clinic for Thoracic and Cardiovascular Surgery, Bad Oeynhausen, Germany; [f]Institut Cardiovasculaire Paris Sud, Massy, France; [g]Elisabeth-Krankenhaus Essen, Essen, Germany; [h]Bern University Hospital, Bern, Switzerland; [i]Henry Ford Hospital, Detroit, Michigan, USA; [j]Leeds General Infirmary, Leeds, United Kingdom; [k]Erasmus University Medical Center, Rotterdam, the Netherlands; [l]General Hospital of Vienna, Medical University, Vienna, Austria; [m]St. Antonius Hospital, Nieuwegein, Netherlands; [n]St Thomas' Hospital, London, United Kingdom; [o]Università degli Studi di Enna Kore, Enna, Italy; [p]St. Paul's Hospital, Vancouver, British Columbia, Canada; [q]Royal Infirmary of Edinburgh, Edinburgh, United Kingdom; [r]John Hopkins Hospital, Baltimore, Maryland, USA; [s]West China Hospital, Sichuan University, Chengdu, China; [t]Royal Sussex County Hospital, Brighton, United Kingdom; [u]Royal Victoria Hospital, Belfast, United Kingdom; [v]Medical University of Graz, Graz, Austria; [w]University Hospital, London Health Sciences Center, London, Ontario, Canada; [x]Hospital de Santa Cruz, CHLO, Nova Medical School, CEDOC, Lisbon, Portugal; [y]Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy; [z]Medical University of Gdansk, Gdansk, Poland; [aa]Asan Medical Center, Seoul, South Korea; [bb]Rabin Medical Center, Petah Tikva, Israel; [cc]University Medical Center Groningen, Groningen, the Netherlands; [dd]Ljubljana University Medical Center, Ljubljana, Slovenia; [ee]Hospital Universitario Álvaro Cunqueiro, Vigo, Spain; [ff]The Prince Charles Hospital, Brisbane, Australia; [gg]Clinical Sciences, Lund University, Skane University Hospital, Lund, Sweden; [hh]Basel University Hospital, Basel, Switzerland; [ii]University Medicine Rostock, Rostock, Germany; [jj]Haukeland University Hospital, Bergen, Norway; [kk]Azienda Ospedaliero Universitaria Pisana, Pisa, Italy; [ll]Hospital Clínico San Carlos, Madrid, Spain; [mm]West China Hospital, Sichuan University, Chengdu, China; [nn]Turku University Hospital, Turku, Finland; [oo]Prince Sultan Cardiac Center, Riyadh, Saudi Arabia; [pp]Emergency Institute for Cardiovascular Diseases, Bucharest, Romania; [qq]Lenox Hill/Northwell Health, New York, New York, USA; [rr]St. Vincent's Hospital, Sydney, Australia; [ss]Heart and Vascular Center, Semmelweis University, Budapest, Hungary; [tt]Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal; [uu]Auckland City Hospital, Auckland, New Zealand; [vv]Toyohashi Heart Center, Toyohashi, Japan; [ww]Nagoya Heart Center, Nagoya, Japan; [xx]Gifu Heart Center, Gifu, Japan; [yy]Hospital de Santa Maria, Lisboa, Portugal; [zz]Heart Center Lucerne, Lucerne, Switzerland; [aaa]Onassis Cardiac Surgery Center, Athens, Greece; [bbb]Tokai University School of Medicine, Isehara, Japan; [ccc]Hospital de Santa Marta, Lisboa, Portugal; [ddd]Medical University of Silesia, Katowice, Poland; [eee]Hospital Universitario Reina Sofía, Universidad de Córdoba,

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The COVID-19 pandemic rapidly overwhelmed health care systems around the world. Health care resources were redirected to manage fallout from the emerging pandemic and established care pathways for many acute and chronic diseases were suspended. Public health messaging encouraged populations to stay at home and travel restrictions were enforced to limit contagion. Such actions were associated with reduced hospitalization for and increased mortality from cardiovascular diseases.[1,2] For example, hospital admission for acute coronary syndromes (ACS) and activation of ST-segment elevation myocardial infarction pathways were reduced.[3,4]

The COVID-19 pandemic likely had a negative impact on patients with valvular heart disease as well.[5,6] Patients with symptomatic severe aortic valve stenosis necessitating surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR) are especially vulnerable to treatment delays, and treatment deferral is associated with an increased risk of hospitalization and death.[5,6] It is therefore concerning that single center and regional reports have suggested reduced TAVR procedural volume during the COVID-19 pandemic.[7,8] The impact of the COVID-19 pandemic on a specific procedure such as TAVR, however, is likely to have been heterogeneous across diverse countries and health care systems, and has been influenced by socioeconomic and other national factors, the incidence of severe acute respiratory syndrome coronavirus 2

Instituto Maimónides de Investigación Biomédica de Córdoba, Córdoba, Spain; [fff]Hippokration Hospital, Athens, Greece; [ggg]Hospital Clínic de Barcelona, Barcelona, Spain; [hhh]Poznan University School of Medical Sciences, Poznan, Poland; [iii]Chest Diseases Hospital, Kuwait City, Kuwait; [jjj]Hospital Universitario de Salamanca, Salamanca, Spain; [kkk]National Institute of Cardiovascular Diseases, Bratislava, Slovakia; [lll]Hospital Universitario Marqués de Valdecilla, Santander, Spain; [mmm]Geneva University Hospital, Geneva, Switzerland; [nnn]Centrum Kardiovaskulární a Transplantační Chirurgie, Brno, Czechia; [ooo]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [ppp]Adana City Training and Research Hospital, Adana, Turkey; [qqq]Antwerp University Hospital, Antwerp, Belgium; [rrr]Pauls Stradins University Hospital, Riga, Latvia; [sss]Mater Misericordiae University Hospital, Dublin, Ireland; [ttt]Mater Private Hospital, Dublin, Ireland; [uuu]American University of Beirut Medical Center, Beirut, Lebanon; [vvv]North Shore Private Hospital, Sydney, Australia; [www]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [xxx]Cheng Hsin General Hospital, Taipei, Taiwan; [yyy]Algemeen Stedelijk Ziekenhuis Aalst, Aalst, Belgium; [zzz]Seoul National University Hospital, Seoul, South Korea; [aaaa]St James's Hospital, Dublin, Ireland; [bbbb]Sunninghill Hospital, Johannesburg, South Africa; [cccc]Sanatorio Finochietto, Buenos Aires, Argentina; [dddd]Fundación Favaloro, Buenos Aires, Argentina; [eeee]University of Florida College of Medicine Jacksonville, Jacksonville, Florida, USA; [ffff]Fortis Escorts Heart Institute, New Delhi, India; [gggg]Mater Dei Hospital, Msida, Malta; [hhhh]Hospital Sirio Libanes, São Paulo, Brazil; [iiii]Division of Cardiology and Vascular Diseases, Vilnius University Hospital Santaros Clinics, Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [jjjj]King Abdulaziz Cardiac Center, Riyadh, Saudi Arabia; [kkkk]Queen Elizabeth Hospital, Hong Kong, Hong Kong; [llll]Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico; [mmmm]Department of Cardiology, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Belgium; [nnnn]Hospital do Coração Anis Rassi, Goiânia, Brazil; [oooo]King Fahd Armed Forces Hospital, Jeddah, Saudi Arabia; [pppp]Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy; [qqqq]National University Heart Center, Singapore, Singapore; [rrrr]Sanatorio Americano, Montevideo, Uruguay; [ssss]Apollo Hospitals, Chennai, India; [tttt]Policlinico Umberto I University, Rome, Italy; [uuuu]King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [vvvv]National Taiwan University Hospital, Taipei, Taiwan; [wwww]Angiografia de Occidente, Cali, Colombia; [xxxx]European Interbalkan Medical Center, Thessaloniki, Greece; [yyyy]University Hospital of Iceland, Faculty of Medicine, University of Iceland, Reykjavík, Iceland; [zzzz]Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates; [aaaaa]Hospital México, San José, Costa Rica; [bbbbb]Instituto Nacional de Cardiología, Mexico City, Mexico; [ccccc]Heart Hospital - Hamad Medical Corporation, Doha, Qatar; [ddddd]Istanbul Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, University of Health Science, Istanbul, Turkey; [eeeee]Instituto Nacional Cardiovascular, Lima, Peru; [fffff]Dedinje Cardiovascular Institute, Belgrade, Serbia; [ggggg]Instituto Nacional de Cirugía Cardíaca, Montevideo, Uruguay; [hhhhh]Tartu University Hospital, Tartu, Estonia; [iiiii]Aswan Heart Center, Aswan, Egypt; [jjjjj]Hospital das Clínicas de Ribeirão Preto, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, Brazil; [kkkkk]Santa Lúcia Hospital, Brasília, Brazil; [lllll]Hospital Clínico Regional Guillermo Grant Benavente, Concepción, Chile; [mmmmm]Hospital San Borja Arriaran, Santiago, Chile; [nnnnn]Clínica Alemana, Santiago, Chile; [ooooo]Ahi Evren Thoracic and Cardiovascular Surgery Training and Research Hospital, Health Sciences University, Trabzon, Turkey; [ppppp]Jordan Hospital, Amman, Jordan; [qqqqq]Mohammed Bin Khalifa Cardiac Center, Royal Medical Services, Awali, Bahrain; [rrrrr]Prince of Wales Hospital, Hong Kong, Hong Kong; [sssss]Al Qassimi Hospital, Sharjah, United Arab Emirates; [ttttt]Instituto de Cardiología Intervencionista Cardiovida SRL, Santa Cruz, Bolivia; [uuuuu]Hospital de Clínicas Dr Manuel Quintela, Montevideo, Uruguay; [vvvvv]Vietnam National Heart Institute, Hanoi, Vietnam; [wwwww]Heart Center Bonn, Bonn, Germany; [xxxxx]Center Hospitalier Universitaire, Bordeaux, France; [yyyyy]Clinique Pasteur, Toulouse, France; [zzzzz]Keio University School of Medicine, Tokyo, Japan; [aaaaaa]Montefiore Medical Center, Bronx, New York, USA; [bbbbbb]Cedars-Sinai Medical Center, Los Angeles, California, USA; [cccccc]McGill University Health Center, Montréal, Quebec, Canada; [dddddd]Rigshospitalet, Copenhagen, Denmark; and the [eeeeee]School of Medicine, University of Galway, Galway, Ireland.

George Dangas, MD, PhD, served as Guest Editor for this paper. Ole de Backer, MD, PhD, served as Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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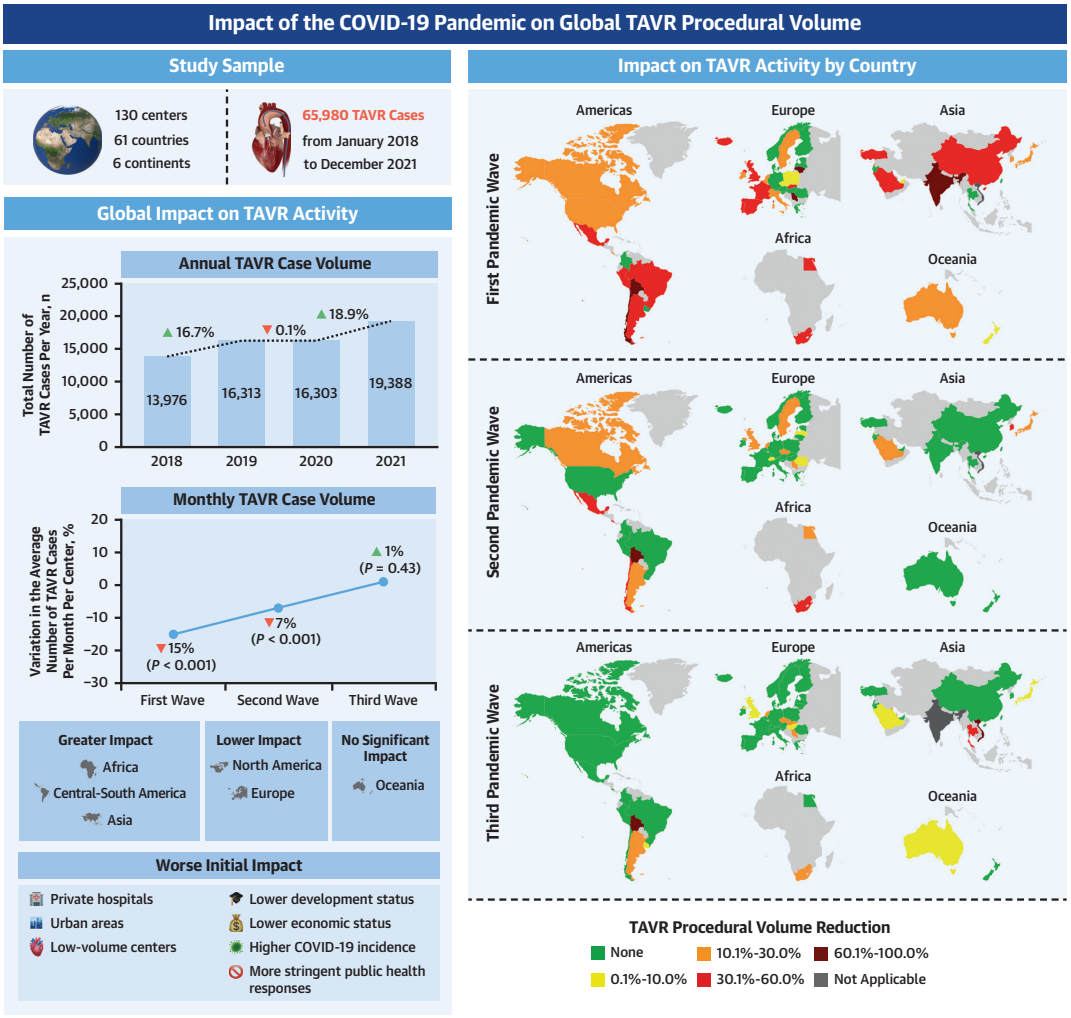
CENTRAL ILLUSTRATION **Global TAVR Activity Before and During the COVID-19 Pandemic**



Armario X, et al. J Am Coll Cardiol Intv. 2024;17(3):374-387.

The first and second pandemic waves were associated with a significant reduction of 15% ($P < 0.001$) and 7% ($P < 0.001$) in monthly transcatheter aortic valve replacement (TAVR) case volume, respectively, compared with the prepandemic period. The third pandemic wave was not associated with reduced TAVR activity. A greater reduction in TAVR activity was observed in Africa (−52%; $P = 0.001$), Central-South America (−33%; $P < 0.001$), and Asia (−29%; $P < 0.001$) compared with North America (−15%; $P < 0.001$) or Europe (−11%; $P < 0.001$). Private hospitals ($P = 0.005$), urban areas ($P = 0.011$), low-volume centers ($P = 0.002$), and countries with lower development ($P < 0.001$) and economic status ($P < 0.001$), higher COVID-19 incidence ($P < 0.001$), and more stringent public health restrictions ($P < 0.001$) experienced a greater reduction in TAVR activity.

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TABLE 1 Center Characteristics and TAVR Activity During the Period 2018-2021

	Europe (n = 66)	Asia (n = 32)	America		Oceania (n = 4)	Africa (n = 2)	Global (n = 130)
			Central-South (n = 18)	North (n = 8)			
Center characteristics							
Health care system							
Public	58 (87.9)	20 (62.5)	7 (38.9)	5 (62.5)	2 (50.0)	1 (50.0)	93 (71.5)
Private	6 (9.1)	11 (34.4)	10 (55.6)	3 (37.5)	1 (25.0)	1 (50.0)	32 (24.6)
Mixed	2 (3.0)	1 (3.1)	1 (5.6)	0 (0.0)	1 (25.0)	0 (0.0)	5 (3.8)
Demographic status							
Urban	52 (78.8)	29 (90.6)	17 (94.4)	6 (75.0)	3 (75.0)	1 (50.0)	108 (83.1)
Rural	14 (21.2)	3 (9.4)	1 (5.6)	2 (25.0)	1 (25.0)	1 (50.0)	22 (16.9)
TAVR volume							
Low	9 (13.6)	18 (56.3)	16 (88.9)	1 (12.5)	0 (0.0)	1 (50.0)	45 (34.6)
Intermediate	19 (28.8)	6 (18.8)	2 (11.1)	1 (12.5)	1 (25.0)	1 (50.0)	30 (23.1)
High	38 (57.6)	8 (25.0)	0 (0.0)	6 (75.0)	3 (75.0)	0 (0.0)	55 (42.3)
Development status							
HDI	0.912 ± 0.035	0.847 ± 0.087	0.801 ± 0.041	0.927 ± 0.002	0.941 ± 0.007	0.708 ± 0.001	0.879 ± 0.071
Economic status							
GDP per capita, $	49,363 ± 14,954	40,988 ± 24,030	19,718 ± 4,953	59,171 ± 8,175	50,200 ± 3,097	13,274 ± 1,435	43,307 ± 19,603
GNI per capita, $	47,991 ± 12,599	41,089 ± 23,341	18,979 ± 4,665	59,576 ± 9,031	48,675 ± 2,830	12,870 ± 1,499	42,490 ± 18,472
COVID-19 incidence[a]							
First wave	0.94 ± 0.85	1.39 ± 2.63	3.18 ± 2.43	1.89 ± 1.12	0.09 ± 0.09	0.75 ± 1.03	1.61 ± 2.05
Second wave	7.01 ± 5.96	2.25 ± 3.05	5.17 ± 2.53	6.95 ± 5.59	0.12 ± 0.11	1.59 ± 2.25	5.73 ± 5.52
Third wave	8.06 ± 7.08	3.74 ± 5.79	7.40 ± 6.27	7.40 ± 3.99	1.19 ± 0.87	1.94 ± 2.69	6.35 ± 6.67
COVID-19 stringency index							
First wave	36.0 ± 12.7	29.5 ± 18.1	40.0 ± 9.6	33.1 ± 2.6	31.2 ± 13.9	36.9 ± 12.0	35.1 ± 13.6
Second wave	24.6 ± 14.6	20.3 ± 16.8	29.6 ± 13.0	29.5 ± 8.5	26.8 ± 15.1	18.5 ± 9.2	24.9 ± 14.5
Third wave	26.8 ± 16.0	21.3 ± 13.9	21.8 ± 14.7	21.6 ± 8.9	34.1 ± 8.4	12.0 ± 9.8	24.3 ± 15.1
Annual TAVR procedural volume							
2018-2019							
TAVR cases in 2018	9,839	2,000	443	1,275	345	74	13,976
TAVR cases in 2019	11,670	2,154	479	1,431	499	80	16,313
Absolute variation	1,831	154	36	156	154	6	2,337
Relative variation, %	18.6	7.7	8.1	12.2	44.6	8.1	16.7
2019-2020							
TAVR cases in 2019	11,670	2,154	479	1,431	499	80	16,313
TAVR cases in 2020	11,919	2,065	386	1,331	555	47	16,303
Absolute variation	249	−89	−93	−100	56	−33	−10
Relative variation, %	2.1	−4.1	−19.4	−7.0	11.2	−41.3	−0.1
2020-2021							
TAVR cases in 2020	11,919	2,065	386	1,331	555	47	16,303
TAVR cases in 2021	13,596	2,990	570	1,605	548	79	19,388
Absolute variation	1,677	925	184	274	−7	32	3,085
Relative variation, %	14.1	44.8	47.7	20.6	−1.3	68.1	18.9

Values are n (%) or mean ± SD unless otherwise indicated. [a]COVID-19 incidence is reported as the monthly number of COVID-19 cases per thousand inhabitants.
GDP = gross domestic product; GNI = gross national income; HDI = Human Development Index; TAVR = transcatheter aortic valve replacement.

(SARS-CoV-2) infection, and the severity of governmental public health measures introduced in response to the pandemic.

Herein, we present the results of the COVID-TAVI (coronavirus disease - transcatheter aortic valve implantation) study detailing the impact of the COVID-19 pandemic on global TAVR activity, including a wide range of countries with distinct health care systems and demographic, development, and economic statuses.

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METHODS

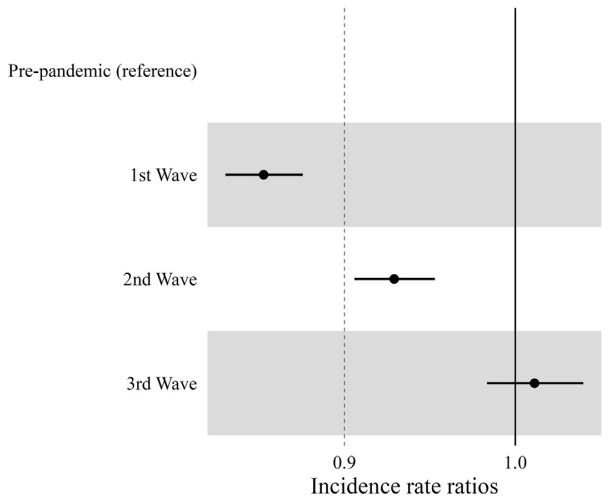
STUDY DESIGN. We undertook an investigator-initiated, multinational, retrospective study to create a registry on global TAVR activity before and during the COVID-19 pandemic. Individual TAVR centers were invited to voluntarily participate in the study. Centers were identified from a variety of sources: existing collaborative research projects, National Library of Medicine (PubMed) publications, international cardiovascular congresses, and national cardiovascular websites. We invited 292 centers, of which 162 (55.5%) responded and finally 130 (44.5%) submitted the required data.

We collected monthly TAVR case volume at each site prior to and during the COVID-19 pandemic (January 2018 to December 2021) using a dedicated report template. Regional and national demographic (population size and density), development (Human Development Index [HDI]) and economic data (gross domestic product [GDP] per capita and gross national income [GNI] per capita), COVID-19 incidence, and governmental public health responses to the pandemic were also recorded. The study was approved by the ethics committee at Galway University Hospital and was conducted in accordance with the Declaration of Helsinki.

ENDPOINTS AND DEFINITIONS. The objectives of this study were: 1) to assess the association of the COVID-19 pandemic with global TAVR procedural volume; 2) to study if the COVID-19 pandemic differentially impacted TAVR procedural volume according to geographic region, health care system, demographic, development, or economic status; and 3) to evaluate if the incidence of SARS-CoV-2 infection or the stringency of governmental public health measures impacted TAVR procedural volume.

The primary outcome of interest was the monthly variation in the average number of TAVR cases per center performed between January 2018 and December 2021. We defined the prepandemic period between January 2018 and the start of the COVID-19 pandemic. The pandemic period extended from the start of the pandemic until December 2021. We sought to assess the impact of sequential waves of the COVID-19 pandemic on TAVR volume during the study period, as differential responses to managing the effect of the pandemic on health care were evident globally.[9] Such responses could potentially mitigate, or exacerbate, the impact of a pandemic wave on TAVR volume. The start of the COVID-19 pandemic and the delineation of the pandemic waves were defined by country. Several definitions of COVID-19 pandemic wave exist but most have been focused on a specific country and do not readily apply to other jurisdictions.[10,11] In our study, a pandemic wave was arbitrarily defined as the time period between a significant (multiplication or division by at least 2) and sustained (duration of at least 1 month) increase and decrease in the weekly number of

FIGURE 1 COVID-19 Pandemic Waves



The coefficients of each COVID-19 pandemic wave term report the incidence rate ratio (IRR) of transcatheter aortic valve replacement (TAVR) procedures per month during each of the pandemic waves compared with prepandemic months. An IRR <1 suggests a reduction in the rate of TAVR compared with prepandemic months, while an IRR >1 suggests an increase in the rate of TAVR compared with prepandemic months.

TABLE 2 COVID-19 Pandemic Waves

	Variation in the Average Number of TAVR Cases per Month per Center		
	Rate (95% CI)	IRR (95% CI)	*P* Value
Prepandemic period	10.46 (8.19-12.72)	NA	NA
First wave	NA	0.85 (0.83-0.88)	<0.001
Second wave	NA	0.93 (0.91-0.95)	<0.001
Third wave	NA	1.01 (0.98-1.04)	0.43

IRR = incidence rate ratio; NA = not applicable; TAVR = transcatheter aortic valve replacement.

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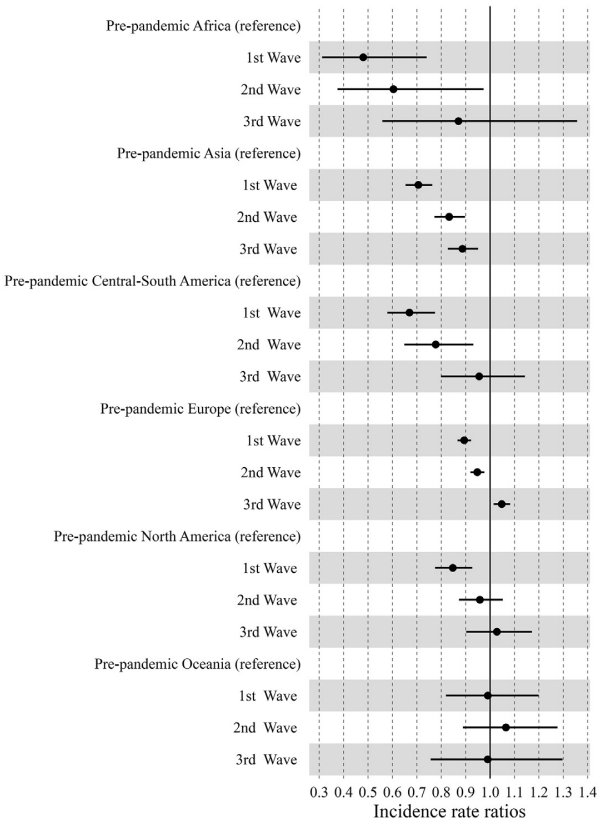
FIGURE 2 Geographic Region



The coefficients of each COVID-19 pandemic wave term report the IRR of TAVR procedures per month during each of the pandemic waves compared with prepandemic months. An IRR <1 suggests a reduction in the rate of TAVR compared with prepandemic months, while an IRR >1 suggests an increase in the rate of TAVR compared with prepandemic months. Abbreviations as in Figure 1.

COVID-19 cases per million people, regardless of the number of peaks within this time period (Supplemental Table 1).[12] The monthly variation in the average number of TAVR cases per center was analyzed during each pandemic wave and was compared with the prepandemic period.

Geographic regions included country and continent, each defined according to the United Nations Statistics Division based on the standard country or area codes for statistical use M49.[13] Participating centers self-reported their activity as public, private, or mixed. Centers were also classified as urban or rural according to the United Nations Statistical Commission criteria based on the population size and density.[14] Considering the self-reported total number of TAVR procedures performed in 2019, centers were classified as low-volume (<50 TAVRs/y), intermediate-volume (50-100 TAVRs/y), or high-volume (>100 TAVRs/y) centers.[15] The development status of countries was defined according to the United Nations Development Program criteria using the HDI,[16] and economic status was defined according to the World Bank criteria using the GDP per capita and GNI per capita, based on purchasing power parity.[17] All demographic, development, and economic data were collected from 2019, prior to the onset of the COVID-19 pandemic.

The COVID-19 incidence was reported as the monthly number of COVID-19 cases per 1,000 inhabitants from the Our World in Data project, a collaboration between the Oxford Martin Program on Global Development (University of Oxford, United Kingdom) and the Global Change Data Lab.[12] Governmental public health policies implemented by each country to mitigate the health and social impacts of the COVID-19 pandemic were defined according to the Oxford Coronavirus Government Response Tracker, which grades the severity of these measures using the COVID-19 stringency index.[18] This composite measure ranges from 0 (most lenient) to 100 (most strict) and is based on 9 response indicators, such as school/workplace closures and travel bans (Supplemental Table 2).

STATISTICAL ANALYSIS. To account for within-center and within-country clustering, we used a 3-level Poisson mixed model, with repeated measures of TAVR procedures treated as counts clustered within centers, which themselves are clustered within countries. A categorical variable that denoted the COVID-19 pandemic wave number was included, with prepandemic months set as the reference category, and pandemic waves 1, 2, and 3 allocated as defined previously. Because all countries were modelled together, it was not necessary for every country to experience 3 pandemic waves. The coefficients of each COVID-19 pandemic wave term report the incidence rate ratio (IRR) of TAVR procedures per month during each of the pandemic waves compared with prepandemic months. An IRR <1 suggests a reduction in the rate of TAVR compared with prepandemic months, while an IRR >1

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suggests an increase in the rate of TAVR compared with prepandemic months. We included random intercepts for centers within countries. Given the wide disparities between continents, we used mixed models for each continent separately, alongside the primary worldwide model, to investigate regional changes in TAVR activity during the COVID-19 pandemic. We then investigated the potential effect of country-level variables: health care system, demographic status, development status, economic status, COVID-19 incidence, and governmental public health responses. Because many of these variables were highly correlated, we used separate models for each variable individually alongside the time and pandemic wave variables. An interaction term between each country-level variable and pandemic wave was included to assess whether these variables were associated with a better or worse impact of COVID-19 on TAVR activity. The IRR for interaction terms is not for comparison with prepandemic months, but instead is for comparison with the reference category of the country-level factor (eg, private hospitals). Statistical significance was defined as a P value ≤0.05. All statistical analysis was performed using R, version 4.1 (R Foundation for Statistical Computing).

TABLE 3 Geographic Region

	Variation in the Average Number of TAVR Cases per Month per Center		
	Rate (95% CI)	IRR (95% CI)	P Value
Africa			
Prepandemic period	2.00 (0.04-3.96)	NA	NA
First wave	NA	0.48 (0.31-0.74)	0.001
Second wave	NA	0.60 (0.38-0.97)	0.038
Third wave	NA	0.87 (0.56-1.36)	0.54
America, Central-South			
Prepandemic period	1.22 (0.49-1.96)	NA	NA
First wave	NA	0.67 (0.58-0.77)	<0.001
Second wave	NA	0.78 (0.65-0.93)	0.006
Third wave	NA	0.96 (0.80-1.14)	0.62
America, North			
Prepandemic period	15.62 (9.19-22.06)	NA	NA
First wave	NA	0.85 (0.77-0.93)	<0.001
Second wave	NA	0.96 (0.87-1.05)	0.37
Third wave	NA	1.03 (0.90-1.17)	0.68
Asia			
Prepandemic period	5.48 (3.48-7.49)	NA	NA
First wave	NA	0.71 (0.65-0.76)	<0.001
Second wave	NA	0.83 (0.77-0.90)	<0.001
Third wave	NA	0.89 (0.83-0.95)	0.001
Europe			
Prepandemic period	15.17 (11.36-18.97)	NA	NA
First wave	NA	0.89 (0.87-0.92)	<0.001
Second wave	NA	0.95 (0.92-0.98)	<0.001
Third wave	NA	1.05 (1.01-1.08)	0.005
Oceania			
Prepandemic period	6.75 (3.23-10.27)	NA	NA
First wave	NA	0.99 (0.82-1.20)	0.92
Second wave	NA	1.07 (0.89-1.28)	0.50
Third wave	NA	0.99 (0.76-1.30)	0.94

Abbreviations as in Table 2.

RESULTS

We collected data from 130 TAVR centers in 61 countries across 6 continents, including 65,980 TAVR procedures during the study period (**Central Illustration**). Centers were European (n = 66 [50.8%]), Asian (n = 32 [24.6%]), Central-South American (n = 18 [13.8%]), North American (n = 8 [6.2%]), Oceanic (n = 4 [3.1%]), or African (n = 2 [1.5%]) (**Table 1**). Participating TAVR centers were primarily public (n = 93 [71.5%]) and urban (n = 108 [83.1%]), and were categorized as low volume (n = 45 [34.6%]), intermediate volume (n = 30 [23.1%]) and high volume (n = 55 [42.3%]), respectively.

In the year prior to the COVID-19 pandemic (2019 vs 2018), annual TAVR procedural volume increased among participating centers by 16.7% (2,337 procedures) (**Table 1**). In contrast, no growth in annual TAVR procedural volume was observed after the outbreak of the COVID-19 pandemic in 2020 compared with 2019 (decrease of 0.1%; 10 procedures). Annual TAVR procedural volume increased again by 18.9% (3,085 procedures) in 2021 compared with 2020 (Supplemental Table 3).

COVID-19 PANDEMIC WAVES. Within the study period, at least 3 distinct waves of COVID-19 pandemic could be identified in all countries, except in India, where only 2 waves were observed (Supplemental Table 1).

During the first and second pandemic waves, there was a significant reduction of 15% (IRR: 0.85; 95% CI: 0.83-0.88; $P < 0.001$) and 7% (IRR: 0.93; 95% CI: 0.91-0.95; $P < 0.001$) in overall monthly TAVR procedural volume, respectively, compared with the prepandemic period (**Figure 1**, **Table 2**, Supplemental Table 4). The third pandemic wave was not associated with a significant reduction in overall TAVR activity compared with the prepandemic period (IRR: 1.01; 95% CI: 0.98-1.04; $P = 0.43$).

GEOGRAPHIC REGION. During the first pandemic wave, a numerically greater reduction of TAVR activity was observed in Africa (−52%; IRR: 0.48; 95% CI: 0.31-0.74; $P = 0.001$), Central-South America (−33%; IRR: 0.67; 95% CI: 0.58-0.77; $P < 0.001$), and Asia (−29%; IRR: 0.71; 95% CI: 0.65-0.76; $P < 0.001$),

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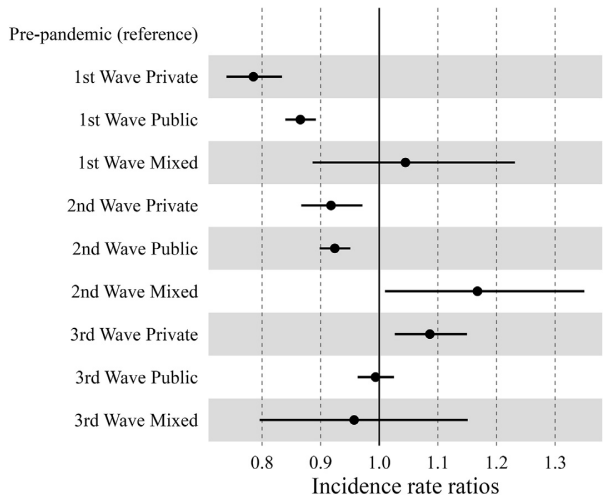
FIGURE 3 Health Care System



The coefficients of each COVID-19 pandemic wave term report the IRR of TAVR procedures per month during each of the pandemic waves compared with prepandemic months. An IRR <1 suggests a reduction in the rate of TAVR compared with prepandemic months, while an IRR >1 suggests an increase in the rate of TAVR compared with prepandemic months. Abbreviations as in Figure 1.

compared with North America (−15%; IRR: 0.85; 95% CI: 0.77-0.93; $P < 0.001$) or Europe (−11%; IRR: 0.89; 95% CI: 0.87-0.92; $P < 0.001$) (Figure 2) (Table 3). TAVR activity was unchanged during the first pandemic wave in Oceania (−1%; IRR: 0.99; 95% CI: 0.82-1.20; $P = 0.92$). A similar, yet lower magnitude, impact was observed during the second pandemic wave. The third pandemic wave was associated with a significant reduction of TAVR activity only in Asia (−11%; IRR: 0.89; 95% CI: 0.83-0.95; $P = 0.001$) and a significant increase in Europe (+5%; IRR: 1.05; 95% CI: 1.01-1.08; $P = 0.005$).

HEALTH CARE SYSTEM, DEMOGRAPHIC STATUS, AND TAVR VOLUME. During the first pandemic wave, private health centers experienced a greater reduction of TAVR activity compared with public centers ($P = 0.005$) (Figure 3, Table 4). Conversely, the third pandemic wave saw private centers experience a greater increase of TAVR activity than public centers ($P = 0.005$).

Urban centers experienced a greater reduction of TAVR activity compared with rural centers ($P = 0.011$) during the first pandemic wave (Figure 4). No significant variation in TAVR activity between urban and rural centers was observed in subsequent waves.

Low-volume centers experienced a greater reduction of TAVR activity compared with high-volume centers ($P = 0.002$) in the first pandemic wave (Figure 5). In contrast, low-volume centers experienced a greater increase of TAVR activity compared with high-volume centers ($P < 0.001$) during the third pandemic wave.

DEVELOPMENT AND ECONOMIC STATUSES. The impact of the COVID-19 pandemic on reducing TAVR activity was more substantial in countries with lower development and economics statuses (Table 5). Indeed, during the first pandemic wave, for every 1% increase of HDI, the reduction of TAVR procedural volume was attenuated by 2% (IRR: 1.02; 95% CI: 1.02-1.03; $P < 0.001$), and for every $10,000 increase of GDP per capita and GNI per capita, there was an attenuation of 5% (IRR: 1.05; 95% CI: 1.03-1.07; $P < 0.001$). These indices did not impact TAVR procedural volumes in subsequent pandemic waves.

COVID-19 INCIDENCE AND GOVERNMENTAL PUBLIC HEALTH RESPONSE. The impact of the COVID-19 pandemic on TAVR activity was greater in countries with higher COVID-19 incidence (Table 6). During the first pandemic wave, for every COVID-19 case per 1,000 inhabitants, the reduction in TAVR procedural volume was accentuated by 8% (IRR: 0.92; 95% CI: 0.90-0.94; $P < 0.001$). This association was not observed in subsequent pandemic waves.

Countries with more stringent governmental public health responses to the COVID-19 pandemic also had a greater impact on TAVR activity, and this association persisted throughout the 3 pandemic waves of the study period (Table 6). For every 10% of COVID-19 stringency index, the reduction in TAVR procedural volume was accentuated by 9% (IRR: 0.91; 95% CI: 0.89-0.92; $P < 0.001$), 4% (IRR: 0.96; 95% CI: 0.94-0.98; $P < 0.001$), and 2% (IRR: 0.98; 95% CI: 0.96-1.00; $P = 0.018$) during the first, second, and third pandemic waves, respectively.

DISCUSSION

We present an international registry of TAVR activity during the COVID-19 pandemic. The salient results are: 1) global TAVR activity was considerably reduced during the first pandemic wave, but it gradually recovered and reached the prepandemic activity

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during the third pandemic wave; 2) the impact of the COVID-19 pandemic on TAVR activity was more pronounced in Africa, Central-South America, and Asia than in North America or Europe, with no significant impact in Oceania; and 3) the impact of the COVID-19 pandemic on TAVR activity was initially more profound in private hospitals, urban areas, low-volume centers, and in countries with lower development and economic statuses, higher COVID-19 incidence, and more stringent governmental public health responses.

The initial reduction in TAVR activity in response to the COVID-19 pandemic can largely be explained by 3 related factors: 1) health care systems were initially overwhelmed with COVID-19 patients and hospital resources were focused on these cases; 2) patients were reluctant to attend health care centers due to fear of contagion; and 3) public health measures encouraged or enforced populations to stay at home.[7] The gradual recovery and ultimately return to prepandemic TAVR volume suggests that health care systems and patients adapted to the new reality in the era of the COVID-19 pandemic. The availability of personal protective equipment such as face masks reduced in-hospital transmission of SARS-CoV-2 and allowed some urgent care pathways to resume.[19] The development and rollout of vaccine programs against SARS-CoV-2,[20] the emergence of community immunity to SARS-CoV-2,[21] and the arrival of new variants of SARS-CoV-2[22] all contributed to the normalization of health care pathways and return to prepandemic TAVR volume during the third pandemic wave in our study. A similar pattern of initial reduction and subsequent normalization of case volume during the COVID-19 pandemic was reported in the setting of ACS.[9]

The magnitude of the reduction in TAVR volume during the first pandemic wave was modest overall, but it was much more profound in Africa, Central-South America, and Asia. These findings are in line with a lower impact on ST-segment elevation myocardial infarction activity reported across North America and Europe during the COVID-19 pandemic.[7] While several factors could influence this observation, many countries in these regions have both low development and economic statuses. Supporting this hypothesis, we observed a clear association between the TAVR volume reduction in the first pandemic wave and the national HDI and GDP/GNI per capita. The current study is not the first to document a significant disparity in cardiovascular care and variable penetrance of novel therapies, such as TAVR, according to the national socioeconomic status, regardless of the COVID-19 pandemic.[23-25] Considering that middle- and low-income countries represent the 80% of the worldwide population,[26] these findings are concerning.

Countries with higher COVID-19 incidence and more stringent public health responses showed a greater reduction in TAVR activity in the current study. Although a correlation between COVID-19 incidence and ACS admission rate has been suggested,[27] the role of lockdown policy stringency on

TABLE 4 Health Care System, Demographic Status, and TAVR Volume

	Variation in the Average Number of TAVR Cases per Month per Center		
	Rate (95% CI)	IRR (95% CI)	*P* Value
Health care system (public vs mixed vs private)			
Prepandemic period (private)	7.38 (3.09-11.66)	NA	NA
First wave			
Private (reference)	NA	0.79 (0.74-0.83)	<0.001
Public vs private	NA	1.10 (1.03-1.18)	0.005
Mixed vs private	NA	1.33 (1.12-1.59)	0.001
Second wave			
Private (reference)	NA	0.92 (0.87-0.97)	0.003
Public vs private	NA	1.01 (0.95-1.07)	0.83
Mixed vs private	NA	1.27 (1.09-1.49)	0.002
Third wave			
Private (reference)	NA	1.33 (1.12-1.59)	0.001
Public vs private	NA	0.91 (0.86-0.97)	0.005
Mixed vs private	NA	0.88 (0.73-1.07)	0.20
Demographic status (urban vs rural)			
Prepandemic period (rural)	9.73 (5.10-14.35)	NA	NA
First wave			
Rural (reference)	NA	0.92 (0.86-0.98)	0.014
Urban vs rural	NA	0.91 (0.85-0.98)	0.011
Second wave			
Rural (reference)	NA	0.97 (0.91-1.03)	0.31
Urban vs rural	NA	0.95 (0.89-1.02)	0.15
Third wave			
Rural (reference)	NA	1.07 (1.00-1.14)	0.05
Urban vs rural	NA	0.94 (0.87-1.01)	0.08
TAVR volume (low vs intermediate vs high)			
Prepandemic period (high)	19.73 (15.61-23.84)	NA	NA
First wave			
High (reference)	NA	0.88 (0.85-0.91)	<0.001
Intermediate vs high	NA	0.90 (0.83-0.97)	0.006
Low vs high	NA	0.86 (0.79-0.95)	0.002
Second wave			
High (reference)	NA	0.92 (0.90-0.95)	<0.001
Intermediate vs high	NA	1.01 (0.94-1.08)	0.83
Low vs high	NA	1.08 (0.99-1.18)	0.10
Third wave			
High (reference)	NA	0.86 (0.79-0.95)	0.002
Intermediate vs high	NA	0.99 (0.92-1.07)	0.81
Low vs high	NA	1.23 (1.13-1.34)	<0.001

Abbreviations as in Table 2.

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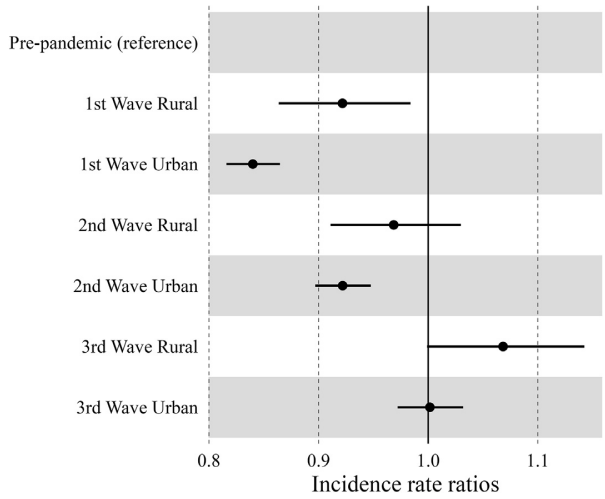
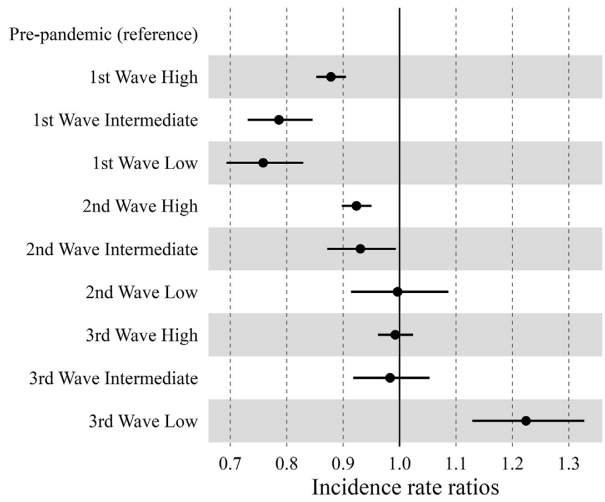
FIGURE 4 Demographic Status



The coefficients of each COVID-19 pandemic wave term report the IRR of TAVR procedures per month during each of the pandemic waves compared with prepandemic months. An IRR <1 suggests a reduction in the rate of TAVR compared with prepandemic months, while an IRR >1 suggests an increase in the rate of TAVR compared with prepandemic months. Abbreviations as in Figure 1.

FIGURE 5 TAVR Volume



The coefficients of each COVID-19 pandemic wave term report the IRR of TAVR procedures per month during each of the pandemic waves compared with prepandemic months. An IRR <1 suggests a reduction in the rate of TAVR compared with prepandemic months, while an IRR >1 suggests an increase in the rate of TAVR compared with prepandemic months. Abbreviations as in Figure 1.

cardiovascular care during the pandemic had not previously been established. While the application of containment measures, including school and workplace closures and restrictions on public gatherings, are known to reduce the transmission of the SARS-CoV-2 infection,[28,29] it is important to recognize the undesirable effects of these policies.

This information should inform World Health Organization and national public health policy in case of future global health crises. Established care pathways for high risk cardiovascular and other diseases should continue uninterrupted as reasonably achievable. Public health messaging should reinforce the importance of maintaining scheduled cardiovascular care, and health care systems should be assessed for and developed to become pandemic-resilient. Health care inequality continues to occur along socioeconomic, political, and ethnic lines, and appears to have been magnified during the COVID-19 pandemic. Addressing the social determinants of this inequity should be an important tenet of strategies to improve global health.

STUDY LIMITATIONS. Individual TAVR centers were invited to voluntarily participate in the study and may not be representative of TAVR centers globally. We were unable to identify TAVR centers in some countries, and national TAVR procedural volume during the COVID-19 pandemic is derived from a small sample size in several countries. While the results presented here for TAVR activity during the third pandemic wave may represent a return to normal prepandemic activities, they may also reflect the process of catching up on TAVR procedures that were cancelled or delayed earlier in the pandemic. For the purposes of clarity, we reported continent-level data, acknowledging that each continent includes a wide variety of different countries with heterogeneous socioeconomic data. Therefore, findings according to the geographic region should be interpreted with caution. Finally, it is important to acknowledge that factors independent from the COVID-19 pandemic could have impacted TAVR procedural volume.

CONCLUSIONS

The COVID-19 pandemic was associated with a considerable reduction in TAVR procedural volume worldwide. This impact was most acute during the first pandemic wave and waned as countries and health care systems adapted to the health crisis. The reduction in TAVR activity was more pronounced in Africa, Central-South America, and Asia, as well as in private hospitals, urban areas, low-volume centers,

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and countries with lower development and economic status, higher COVID-19 incidence, and more stringent governmental public health responses. This information should inform national public health policy in case of future global health crises.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Lefèvre has served as a proctor for Edwards Lifesciences; and received minor fees from Boston Scientific, Terumo, and Abbott. Dr Pilgrim has received research, travel, or educational grants to the institution without personal remuneration from Biotronik, Boston Scientific, Edwards Lifesciences, and ATSens; and speaker fees and consultancy fees to the institution from Biotronik, Boston Scientific, Edwards Lifesciences, Abbott, Medtronic, Biosensors, and Highlife. Dr Van Mieghem has received research grant support from Abbott Vascular, Boston Scientific, Edwards Lifesciences, Medtronic, Daiichi Sankyo, AstraZeneca, Teleflex; and advisory board fees from Abbott Vascular, Boston Scientific, Inari, JenaValve, Medtronic, Daiichi Sankyo, AstraZeneca, Siemens, Pie Medical, and Teleflex. Dr Swaans has served as a proctor/lecturer for Abbott Vascular, Boston Scientific, Bioventrix Inc, Cardiac Dimensions, Edwards Lifesciences, GE Healthcare, Medtronic, and Philips Healthcare. Dr Prendergast has received speaker/consultancy fees from Medtronic, MicroPort, Anteris, and Edwards Lifesciences. Dr Resar has received institutional research funding from Medtronic, Edwards Lifesciences, and Abbott; and served as a TAVR proctor for Medtronic. Dr Chen has served as a consultant for Venus MedTech. Dr Hildick-Smith has received research funds and speaker fees from Medtronic. Dr Spence has received TAVR proctoring and consultancy fees from Medtronic, Boston Scientific, and Edwards Lifesciences. Dr Bunc has served as a proctor for Abbott, Meril, Edwards Lifesciences, and Medtronic. Dr Molnár has served as a consultant for Medtronic and Abbott. Dr Toggweiler has served as a consultant and proctor for Medtronic, Boston Scientific, and Biosensors; has served as a proctor for Edwards Lifesciences and Abbott Vascular; has served as a consultant for Medira, Shockwave, Teleflex, atHeart Medical, Cardiac Dimensions, and Polares Medical; has received institutional research grants from Boston Scientific, Fumedica, and Novartis; has received speaker honoraria from Sanofi, AstraZeneca, ReCor Medical, and Daiichi Sankyo; and holds equity in Hi-D Imaging. Dr Ojeda has received consulting fees from Medtronic and Edwards Lifesciences; and speaker fees from Philips and Word Medica. Dr Toutouzas has served as a proctor for Medtronic, Abbott, Myval, and Boston Scientific. Dr AlMerri has served as a TAVR proctor for Medtronic. Dr Noble has served as a proctor for Medtronic; and received institutional grant support from Edwards Lifesciences, Boston Scientific, Abbott Vascular, and Medtronic. Dr Kala has served as a consultant for Boston Scientific; served on the Speakers Bureau for Edwards Lifesciences, Servier, and AstraZeneca; and received research support from Novartis. Dr Kurt has served as a TAVR proctor for Abbott. Dr Yin has served as a TAVR proctor for Medtronic, Edwards Lifesciences, and Abbott. Dr Sztejfman has served as a proctor for Boston Scientific, Edwards Lifesciences, Medtronic, Meril Life Sciences, and MicroPort. Dr Mendiz has served as a proctor for Medtronic, Boston Scientific, and Edwards Lifesciences. Dr Gunasekaran has received fees from Medtronic, Meril Life Sciences, Abbott, and Boston Scientific. Dr Kao has served as a proctor for Medtronic and Edwards Lifesciences. Dr Dager has served as a consultant for Medtronic. Dr Ferrero-Guadagnoli has served as a proctor for Boston Scientific, Edwards Lifesciences, and Medtronic. Dr Modine has served as a consultant for and received honorarium from Abbott, Medtronic, and Edwards Lifesciences. Dr Hayashida has served as a proctor for Edwards Lifesciences, Medtronic, and Abbott. Dr Makkar has received research grants from Abbott, Edwards Lifesciences, and Boston Scientific, and served as a consultant for Cordis and Medtronic. Dr Mylotte has received institutional grant funding from Boston Scientific and Medtronic; and personal fees from Boston Scientific, Medtronic, and MicroPort. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Darren Mylotte, Department of Cardiology, Galway University Hospital, Newcastle Road, Galway H91 YR71, Ireland. E-mail: darren.mylotte@universityofgalway.ie. @dmylotte.

TABLE 5 Development and Economic Statuses

	Variation in the Average Number of TAVR Cases per Month per Center		
	Rate (95% CI)	IRR (95% CI)	*P* Value
Development status (HDI)[a]			
Prepandemic period	10.46 (8.19-12.72)	NA	NA
First wave	NA	1.02 (1.02-1.03)	<0.001
Second wave	NA	1.00 (1.00-1.01)	0.13
Third wave	NA	1.00 (0.99-1.00)	0.56
Economic status (GDP per capita)[a]			
Prepandemic period	10.46 (8.19-12.72)	NA	NA
First wave	NA	1.05 (1.03-1.07)	<0.001
Second wave	NA	1.02 (1.00-1.04)	0.045
Third wave	NA	1.01 (0.99-1.03)	0.39
Economic status (GNI per capita)[a]			
Prepandemic period	10.46 (8.19-12.72)	NA	NA
First wave	NA	1.05 (1.03-1.07)	<0.001
Second wave	NA	1.01 (1.00-1.03)	0.11
Third wave	NA	1.00 (0.98-1.02)	0.86

[a]IRR for each 1% of HDI (development status) and each $10,000 of GDP/GNI per capita (economic status).
Abbreviations as in Tables 1 and 2.

TABLE 6 COVID-19 Incidence and Governmental Public Health Response

	Variation in the Average Number of TAVR Cases per Month per Center		
	Rate (95% CI)	IRR (95% CI)	*P* Value
COVID-19 incidence (monthly number of COVID-19 cases per thousand inhabitants)[a]			
Prepandemic period	10.46 (8.19-12.72)	NA	NA
First wave	NA	0.92 (0.90-0.94)	<0.001
Second wave	NA	1.00 (0.99-1.00)	0.38
Third wave	NA	1.00 (0.99-1.00)	0.49
Governmental public health response (COVID-19 stringency index)[a]			
Prepandemic period	10.46 (8.19-12.72)	NA	NA
First wave	NA	0.91 (0.89-0.92)	<0.001
Second wave	NA	0.96 (0.94-0.98)	<0.001
Third wave	NA	0.98 (0.96-1.00)	0.018

[a]IRR for each COVID-19 case per thousand inhabitants (COVID-19 incidence), and each 10% of COVID-19 stringency index (governmental public health response).
Abbreviations as in Tables 1 and 2.

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PERSPECTIVES

WHAT IS KNOWN? Patients with symptomatic severe aortic valve stenosis necessitating TAVR are especially vulnerable to treatment delays, and treatment deferral is associated with an increased risk of hospitalization and death. Single-center and regional reports have suggested reduced TAVR procedural volume during the COVID-19 pandemic. However, international reports on global TAVR activity are lacking.

WHAT IS NEW? This study reports the impact of the COVID-19 pandemic on global TAVR procedural volume, including centers across the globe. We report that the first and second waves of the COVID-19 pandemic were associated with a significant reduction in global TAVR activity, whereas the third wave did not. The impact of the COVID-19 pandemic on TAVR activity was heterogeneous across countries, and was influenced by socioeconomic and health care system factors, the magnitude of national COVID-19 incidence, and the severity of governmental public health measures introduced in response to the pandemic.

WHAT IS NEXT? The study results should inform World Health Organization and national public health policy in case of future global health crises. Public health messaging should reinforce the importance of maintaining scheduled cardiovascular care and health care systems should be assessed for and developed to become pandemic-resilient.

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KEY WORDS aortic valve stenosis, coronavirus disease 2019, transcatheter aortic valve replacement, valvular heart disease

APPENDIX For supplemental tables, please see the online version of this paper.

6. OVERALL SUMMARY OF THE RESULTS

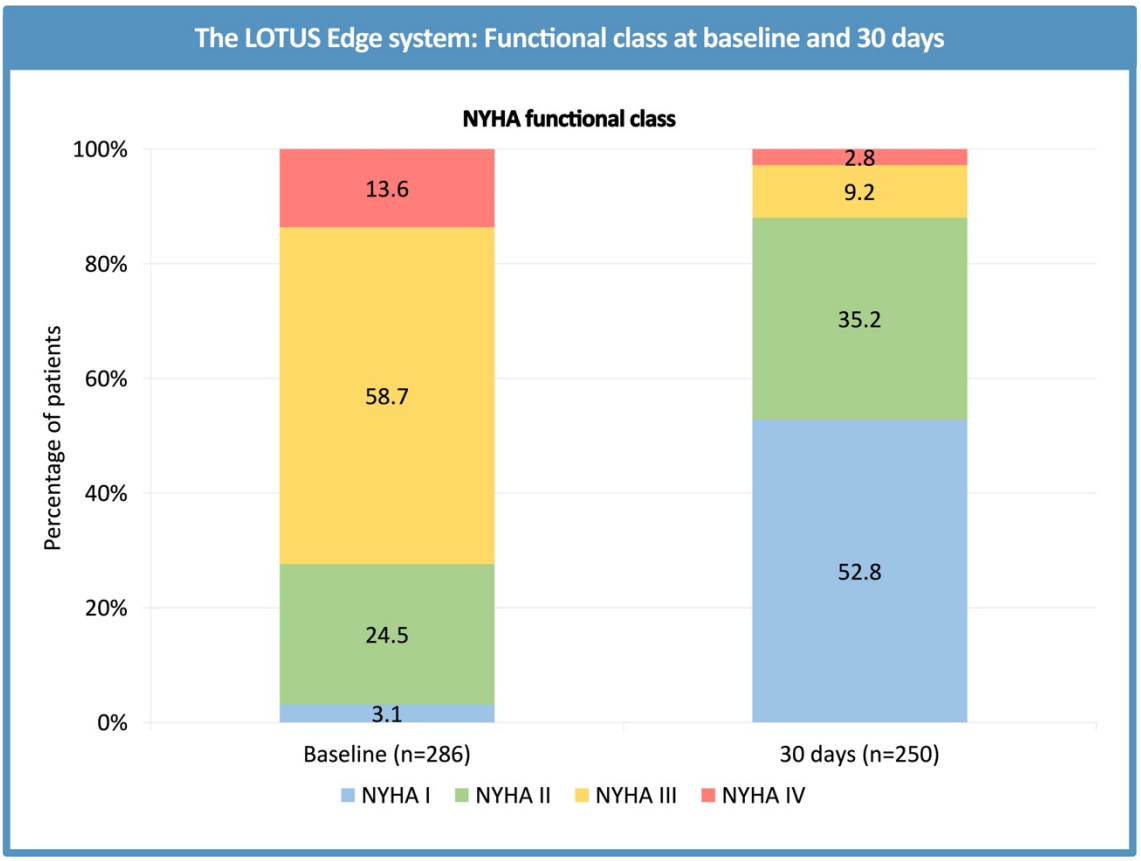
Between April and November 2019, 286 consecutive patients who underwent TAVI with the LOTUS Edge aortic valve system in 18 European centres were included in the first study. The mean age was 81.2 ± 6.9 years, 41.6% were female and the mean STS-PROM score was 5.2 ± 5.4%. Almost three-quarters of patients (72.4%) were in New York Heart Association (NYHA) functional class III or IV. The average valve area and mean transvalvular pressure gradient were 0.7 ± 0.2 cm^2 and 45.9 ± 13.8 mmHg, respectively. Moderate-severe aortic valve regurgitation was present in 11.5%. Nearly half of all patients (47.9%) were considered to have complex anatomy, including severe aortic valve calcification (37.5%), moderate-severe LVOT calcification (23.5%), bicuspid aortic valve morphology (9.9%), pure aortic valve regurgitation (1.1%), and failed aortic biologic prosthesis (1.4%).

The 30-day mortality rate was 2.4%; 2.1% were classified as cardiovascular death and 0.3% as non-cardiovascular death. The 30-day stroke rate was 3.5%; 1.0% were classified as disabling stroke and 2.4% as non-disabling stroke. Only 1 case (0.3%) of myocardial infarction was reported at 30 days. No cases of stage 2-3 acute kidney injury were observed. Life-threatening and major bleeding occurred in 0.7% and 3.1%, respectively, whilst the rate of major vascular complications was 2.1%. The incidence of permanent pacemaker implantation was 25.9% among all patients and 30.8% among pacemaker-naive patients. There were 3 cases (1.0%) of clinical valve thrombosis after TAVI treated successfully with oral anticoagulation, with no cases of valve endocarditis.

At 30 days, 12.0% of patients remained in NYHA functional class III or IV (**Figure 4**). The average valve area and mean transvalvular pressure gradient were 1.9 ± 0.9 cm^2 and 11.9 ± 5.7 mmHg, respectively. 8.9% of patients had a mean transvalvular pressure gradient ≥20 mmHg. The rates of severe (indexed valve area <0.65 cm^2/m^2) and moderate (indexed valve area 0.65-0.85 cm^2/m^2) prosthesis-patient mismatch were 7.5%

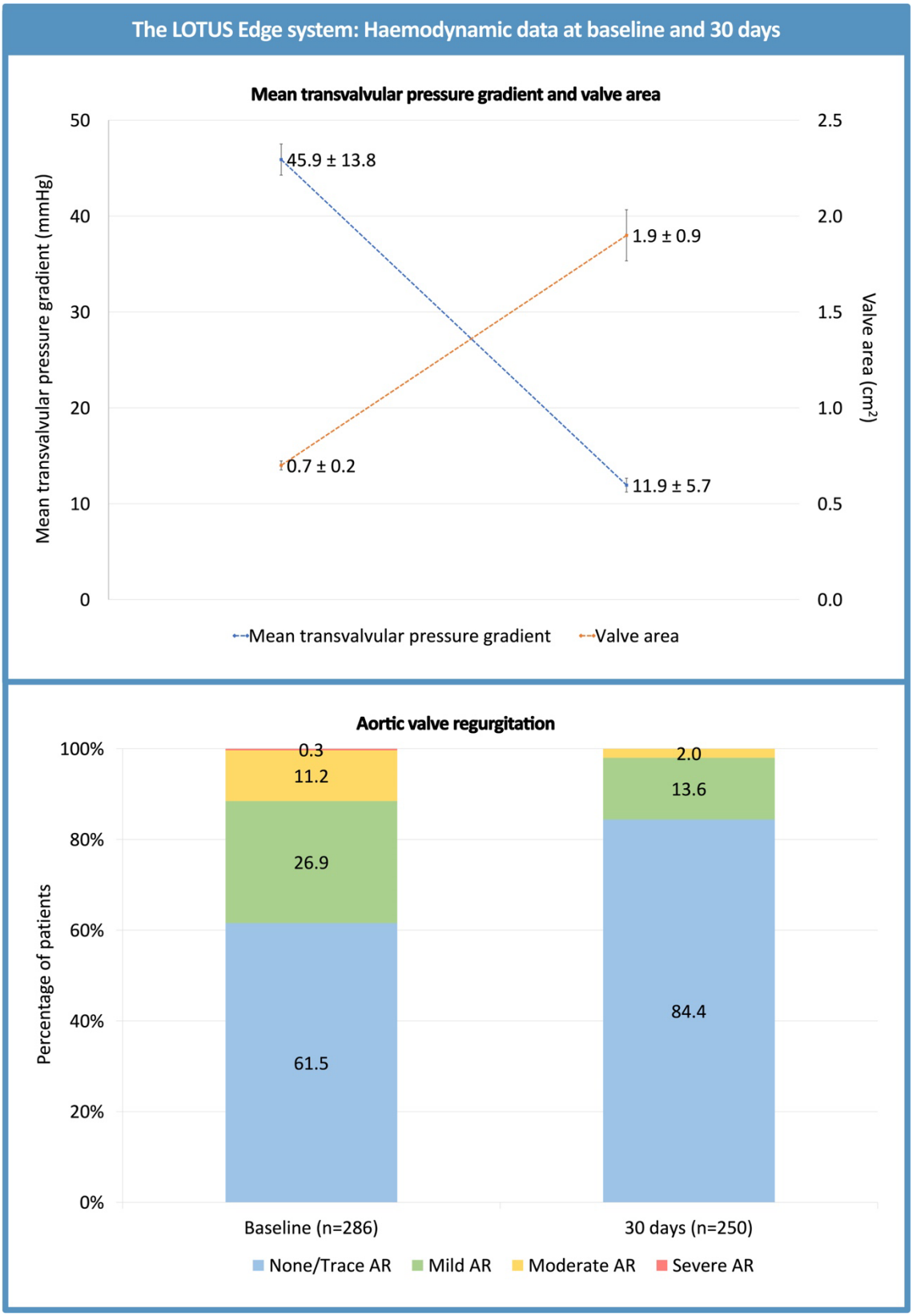
and 26.4%, respectively. None or trace paravalvular leak was reported in 84.4%, and moderate paravalvular leak occurred in 2.0%, with no cases of severe paravalvular leak (**Figure 5**).

Figure 4. The LOTUS Edge system: Functional class at baseline and 30 days.



NYHA = New York Heart Association.

Figure 5. The LOTUS Edge system: Haemodynamic data at baseline and 30 days.



Values are mean ± standard deviation. Error bars represent 95% confidence interval.

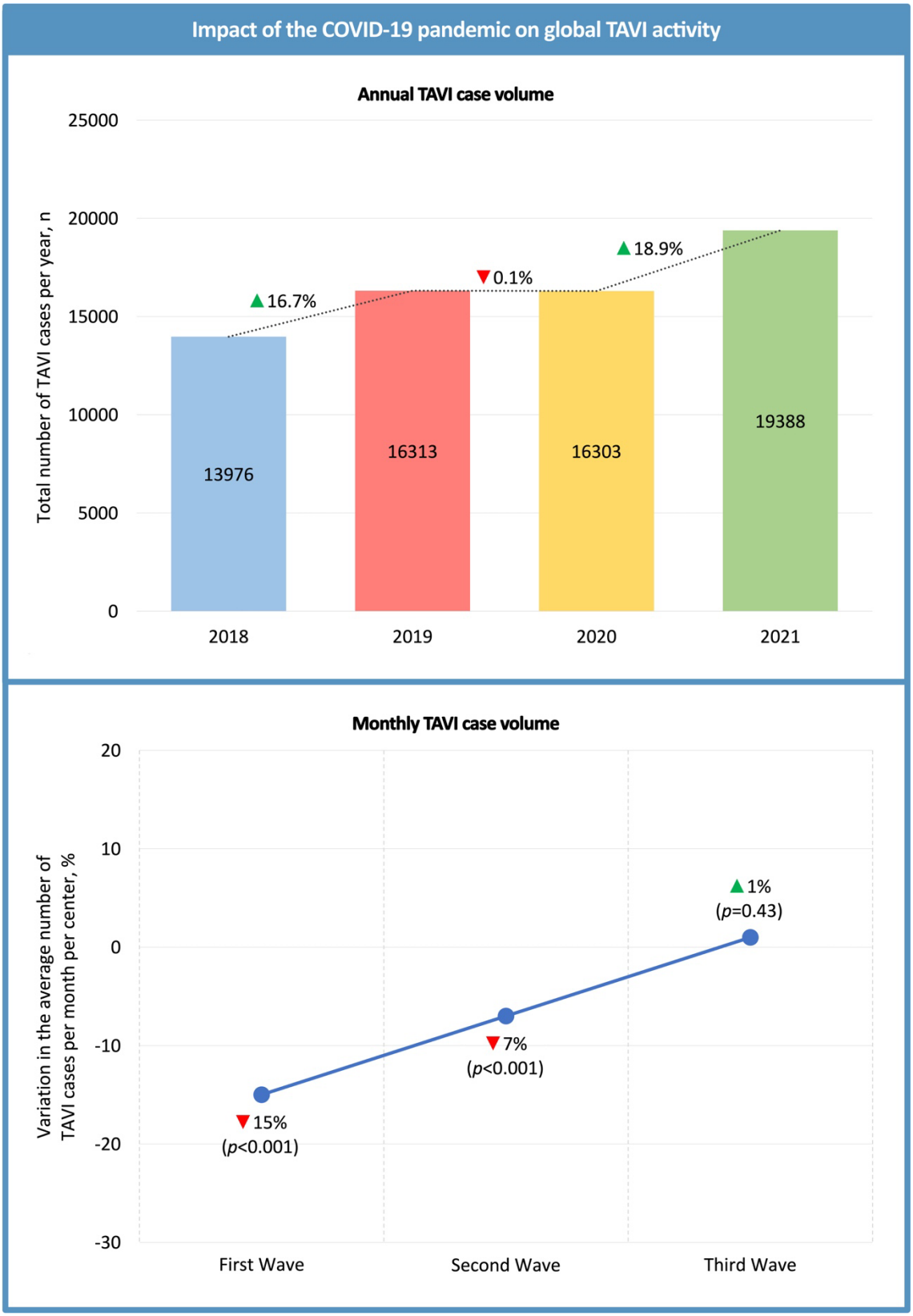
AR = aortic valve regurgitation.

The second study collected data from 130 centres in 61 countries across 6 continents, including 65,980 TAVI procedures during the study period (January 2018 to December 2021). Centres were European (50.8%), Asian (24.6%), Central-South American (13.8%), North American (6.2%), Oceanic (3.1%), or African (1.5%). Participating centres were primarily public (71.5%) and urban (83.1%), and were categorised as low- (34.6%), intermediate- (23.1%) and high-volume (42.3%).

In the year prior to the COVID-19 pandemic (2019 vs. 2018), annual TAVI procedural volume increased among participating centres by 16.7%. In contrast, no growth in annual TAVI procedural volume was observed after the outbreak of the COVID-19 pandemic in 2020 compared to 2019 (decrease of 0.1%). Annual TAVI procedural volume increased again by 18.9% in 2021 compared to 2020 (**Figure 6**).

Within the study period, at least three distinct waves of COVID-19 pandemic could be identified in all countries, except in India where only two waves were observed. During the first and second pandemic waves, there was a significant monthly reduction of 15% ($p<0.001$) and 7% ($p<0.001$) in overall TAVI procedural volume, respectively, compared to the pre-pandemic period. The third pandemic wave was not associated with a significant reduction in overall TAVI activity compared to the pre-pandemic period (**Figure 6**).

Figure 6. Impact of the COVID-19 pandemic on global TAVI activity.



COVID-19 = coronavirus disease 2019; TAVI = transcatheter aortic valve implantation.

During the first pandemic wave, a numerically greater reduction of TAVI activity was observed in Africa (-52%; p=0.001), Central-South America (-33%; p<0.001), and Asia (-29%; p<0.001), compared to North America (-15%; p<0.001) or Europe (-11%; p<0.001), while TAVI activity was unchanged in Oceania. Private hospitals (p=0.005), urban areas (p=0.011), and low-volume centres (p=0.002) experienced a greater reduction of TAVI activity in the first pandemic wave compared to public hospitals, rural areas, and high-volume centres, respectively. Countries with lower development (p<0.001) and lower economic (p<0.001) statuses showed a more substantial impact on TAVI activity in the early stages of the COVID-19 pandemic. Finally, the impact of the COVID-19 pandemic on TAVI activity was more pronounced in countries with higher COVID-19 incidence (p<0.001) and more stringent governmental public health responses to the pandemic (p<0.001).

7. OVERALL SUMMARY OF THE DISCUSSION

The first study presents the first European experience with the LOTUS Edge aortic valve system among an all-comers patient population. The salient features of the study are that the LOTUS Edge aortic valve system is associated with satisfactory short-term clinical outcomes, with favourable haemodynamic data and very low rate of clinically significant paravalvular leak at 30 days in an anatomically complex patient cohort. The requirement for new permanent pacemaker implantation, however, remains high.

In this study, the LOTUS Edge system showed similar clinical outcomes at 30 days when compared with its predecessor, the LOTUS system, in the RESPOND registry.[47] The rates of 30-day mortality (2.4%), stroke (3.5%), and myocardial infarction (0.3%) in the current study were similar to those reported in the RESPOND registry (2.2%, 3.0%, and 0.6%, respectively), albeit with slightly higher mean STS-PROM score in the RESPOND registry (6.0 ± 6.9%) compared to the current study (5.2 ± 5.4%), which could be attributed to changes in the STS-PROM calculator over time. Other clinical outcomes, such as acute kidney injury, major or life-threatening bleeding, and major vascular complications, occurred infrequently, similar to prior contemporary TAVI studies.[13-16] There were no reports of delivery system or locking mechanism issues which mandated the withdrawal of the LOTUS Edge system in 2016 and 2017.

The haemodynamic data at 30 days (effective valvular area of 1.9 ± 0.9 cm^2 and mean transvalvular pressure gradient of 11.9 ± 5.7 mmHg) were nearly identical to those reported in the RESPOND registry (1.8 ± 0.4 cm^2 and 10.8 ± 4.6 mmHg),[47] in the same range as those reported for the balloon-expandable SAPIEN 3 Ultra valve (1.6 ± 0.4 cm^2 and 11.6 ± 4.3 mmHg),[76] but less favourable as compared to the self-expanding Evolut PRO/PRO+ valve (2.0 ± 0.5 cm^2 and 6.4 ± 2.1 mmHg).[77] The impact of residual transvalvular pressure gradients on long-term THV durability warrants further study. On the other hand, as significant residual paravalvular leak has proven to be associated with

increasing mortality,[78-81] the very low rate of moderate to severe paravalvular leak in the current study (2.0%) is clearly reassuring. Indeed, surgery-like results were observed in this cohort with 84.4% of patients experiencing none or trace paravalvular leak at 30 days. These data represent the best-in-class paravalvular leak data for THVs, especially when considering the anatomical complexity of the patient population.[82]

The incidence of new permanent pacemaker implantation with the LOTUS Edge system remains high compared to other commercially available THVs.[76,77] At 30 days, 25.9% of all patients and 30.8% of pacemaker-naive patients required a new permanent pacemaker. This rate is numerically lower than that reported with the LOTUS system in the RESPOND registry (30.0% among all patients; 34.6% among pacemaker-naive patients)[47] and in the REPRISE III study (29.1% among all patients; 35.5% among pacemaker-naive patients).[48] The Depth Guard technology was introduced to potentially reduce the rate of permanent pacemaker implantation by minimising interaction between the stent frame and the LVOT during THV deployment. This technology allows the majority of THV foreshortening to occur at the outflow rather than the inflow, where greater LVOT interaction can lead to cardiac conduction system injury. However, two important aspects should be considered when interpreting the incidence of new permanent pacemaker implantation in the current study. First, this study represents the first cases performed with the LOTUS Edge system in each centre in nearly 2 years. Thus, operators had to refamiliarise themselves with the device and integrate a new and unproven deployment protocol. Increasing operator experience with the device and ongoing evolution of the implantation technique have the potential to reduce the incidence of new permanent pacemaker implantation. Second, in this retrospective study, the decision for permanent pacemaker implantation was at the discretion of the participating centre. In one quarter (24.4%) of cases, a new permanent pacemaker was implanted for first-degree

atrioventricular block with left or right bundle branch block, or even for isolated left bundle branch block. According to the current European Society of Cardiology guidelines, such conduction disturbances would represent non-approved indications for permanent pacemaker implantation.[83] If we excluded those patients with non-approved indication, the incidence of new permanent pacemaker implantation would be 19.6% among all patients and 23.3% among pacemaker-naive patients.

Anecdotal evidence would suggest that the LOTUS system is preferentially used in Europe for the most complex anatomies, including bicuspid aortic valve morphology, severe aortic valve calcification, and moderate-severe LVOT calcification. Indeed, nearly half (47.9%) of the cases included in the current study met the definition for complex anatomy. The LOTUS system has several unique features that favour its use in complex anatomy: (1) this THV can be completely deployed and functionally assessed before final release and can therefore be recaptured, repositioned, and finally retrieved if the result is suboptimal; (2) the leaflets are functional early during deployment so haemodynamic embarrassment is rare; (3) the frame expands gradually resulting in a low risk of aortic annulus rupture; (4) the Adaptive Seal technology adjusts to the surrounding anatomy which led to very low rate of residual paravalvular leak, even in the presence of significant aortic valve or LVOT calcification. In the current study, complex anatomy was not associated with higher rates of death, stroke, elevated transvalvular pressure gradients, significant paravalvular leak, or new permanent pacemaker implantation compared to non-complex anatomy. The absence of any cases of valve malpositioning, coronary artery obstruction, or aortic annulus rupture along with favourable haemodynamic results and very low rate of clinically significant paravalvular leak support the contention that the LOTUS Edge system is an important alternative for complex anatomies. The trade-off for

these advantages, however, may be a higher rate of new permanent pacemaker implantation.

The second study presents an international registry of TAVI activity during the COVID-19 pandemic. The salient features of this study are: (1) global TAVI activity was considerably reduced during the first pandemic wave, but it gradually recovered and reached the pre-pandemic activity during the third pandemic wave; (2) the impact of the COVID-19 pandemic on TAVI activity was more pronounced in Africa, Central-South America, and Asia than in North America or Europe, with no significant impact in Oceania; (3) the impact of the COVID-19 pandemic on TAVI activity was initially more profound in private hospitals, urban areas, low-volume centres, and in countries with lower development and economic statuses, higher COVID-19 incidence, and more stringent governmental public health responses.

The initial reduction in TAVI activity in response to the COVID-19 pandemic can largely be explained by three related factors: healthcare systems were initially overwhelmed with COVID-19 patients and hospital resources were focused on these cases; patients were reluctant to attend healthcare centres due to fear of contagion; and public health measures encouraged or enforced populations to stay at home.[73] The gradual recovery and ultimately return to pre-pandemic TAVI volume suggests that healthcare systems and patients adapted to the new reality of healthcare in the era of the COVID-19 pandemic. The availability of personal protective equipment such as face masks reduced in-hospital transmission of SARS-CoV-2 and allowed some urgent care pathways to resume.[84] As understanding of the pathophysiology and transmission of SARS-CoV-2 infection emerged, stringent public health restrictions were deescalated, pre-existing care for non-COVID-19 diseases was re-established and patients reengaged with healthcare providers.[85] Public campaigns, such as the *You can't pause a heart* and *We Care*,

reinforced the importance of seeking medical attention for cardiovascular disease.[86,87] The development and roll-out of vaccine programs against SARS-CoV-2,[88] the emergence of community immunity to SARS-CoV-2,[89] and the arrival of new variants of SARS-CoV-2,[90] all contributed to the normalisation of healthcare pathways and return to pre-pandemic TAVI volume during the third pandemic wave in the current study. A similar pattern of initial reduction and subsequent normalisation of case volume during the COVID-19 pandemic was reported in the setting of acute coronary syndromes.[91]

The magnitude of the reduction in TAVI volume during the first pandemic wave was modest overall, but it was much more profound in Africa, Central-South America, and Asia. These findings are in line with a lower impact on ST-segment elevation myocardial infarction activity reported across North America and Europe during the COVID-19 pandemic.[73] While several factors could influence this observation, many countries in these regions have both low development and economic statuses. Supporting this hypothesis, we observed a clear association between the TAVI volume reduction in the first pandemic wave and the national human development index, gross domestic product *per capita*, and gross national income *per capita*. It is manifest that high-income countries with more robust and resilient healthcare systems were able to adapt to the emerging pandemic and ultimately re-establish care pathways for non-COVID-19 diseases more rapidly than middle- and low-income countries with under-resourced and disjointed healthcare systems.[92] Moreover, the availability of key healthcare resources, including personal protective equipment, intensive care unit beds, and ultimately vaccines against SARS-CoV-2 infection was higher in wealthier countries.[92] The current study is not the first to document a significant disparity in cardiovascular care and variable penetrance of novel therapies, such as TAVI, according to the national socioeconomic status, regardless of the COVID-19 pandemic.[93-95] Considering that middle- and low-

income countries represent the 80% of the worldwide population, these findings are concerning.[96]

Countries with higher COVID-19 incidence and more stringent public health responses showed a greater reduction in TAVI activity in the current study. Although a correlation between COVID-19 incidence and acute coronary syndrome admission rate has been suggested,[97] the role of lockdown policy stringency on cardiovascular care during the pandemic had not previously been established. While the application of containment measures, including school and workplace closures and restrictions on public gatherings are known to reduce the transmission of the SARS-CoV-2 infection,[98,99] it is important to recognise the undesirable effects of these policies.

Collateral cardiovascular damage from missed diagnoses and delayed treatments occurred during the COVID-19 pandemic.[73] As untreated symptomatic severe AS has a poor prognosis, early intervention is strongly recommended, and a deferral in TAVI or SAVR during the COVID-19 pandemic might have led to an increase in mortality in those patients.[100] This information should inform World Health Organization and national public health policies in case of future global health crises. Established care pathways for high risk cardiovascular and other diseases should continue uninterrupted as reasonably achievable. Public health messaging should reinforce the importance of maintaining scheduled cardiovascular care and healthcare systems should be assessed for and developed to become pandemic-resilient. Health care inequality continues to occur along socioeconomic, political, and ethnic lines, and appear to have been magnified during the COVID-19 pandemic. Addressing the social determinants of this inequity should be an important tenet of strategies to improve global health.

8. CONCLUSIONS

The conclusions of this doctoral thesis are:

1) The LOTUS Edge aortic valve system presents satisfactory short-term safety and efficacy results among an all-comers patient population, including patients with complex anatomies.

2) The LOTUS Edge aortic valve system shows favourable haemodynamic data and very low rate of clinically significant paravalvular leak at 30 days. The requirement for new permanent pacemaker implantation, however, remains high.

3) The COVID-19 pandemic was associated with a considerable reduction in TAVI procedural volume worldwide. TAVI activity was considerably reduced during the first pandemic wave, but it gradually recovered and reached the pre-pandemic activity during the third pandemic wave.

4) The impact of the COVID-19 pandemic on TAVI activity was more pronounced in Africa, Central-South America, and Asia, as well as in private hospitals, urban areas, low-volume centres, and in countries with lower development and economic statuses, higher COVID-19 incidence, and more stringent governmental public health responses.

9. FUTURE LINES OF RESEARCH

Although the LOTUS Edge aortic valve system showed satisfactory short-term clinical outcomes in the current study, the requirement for new permanent pacemaker implantation remained high. Further studies will evaluate whether increasing operator experience with this novel device and the new implantation technique can reduce the incidence of new permanent pacemaker implantation. Long-term follow-up of those patients treated with the LOTUS Edge system will assess whether the favourable haemodynamic results and low rates of significant paravalvular leak observed at 30 days have an impact on THV durability. Finally, long-term head-to-head comparisons between the mechanically-expanding LOTUS Edge system and current balloon-expandable and self-expanding THVs in randomised controlled trials are warranted. Despite the promising results of the LOTUS Edge system, it should be noted that Boston Scientific announced a voluntary recall and product discontinuation in January 2021 due to complexities associated with the delivery system.

Over the last decade, global TAVI procedural volume has increased dramatically. Nevertheless, geographical and socioeconomic inequalities in access to and utilisation of TAVI worldwide have been reported and appear to have been magnified during the COVID-19 pandemic. Therefore, the information provided by the COVID-TAVI study should inform World Health Organization and national public health policies in the event of future global health crises. In this scenario, established care pathways for AS and other cardiovascular diseases should continue uninterrupted as reasonably achievable. Additionally, implementing short-stay protocols for TAVI may help mitigate the impact of such pandemics by reducing hospital resource utilisation while maintaining procedural volume.

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