






# Win ratio analysis for the 1-year composite endpoint: a substudy of the LANDMARK trial

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## Abstract

### Background

Conventional time-to-first event analyses for composite endpoints consider only the first event, whereas win ratio analyses account for event severity and recurrence.

### Methods

We performed a win ratio analysis of the 1-year composite endpoint in the LANDMARK trial, a multicentre, non-inferiority study that randomized patients with severe native aortic valve stenosis to receive either the Myval transcatheter heart valve (THV) series ( $n = 384$ ) or contemporary THVs ( $n = 384$ ), consisting of the Sapien and Evolut series ( $n = 192$  each). The 1-year composite endpoint included the following components, ranked in hierarchical order: all-cause death, disabling stroke, non-disabling stroke, and procedure- or valve-related hospitalization. For death and stroke events, wins or losses were determined according to the time-to-first-event principle. For procedure- or valve-related hospitalizations, the total number of events was compared. Win ratio analysis was also conducted for an extended composite endpoint that also included quality-of-life outcomes.

### Results

Among 147 456 ( $384 \times 384$ ) unmatched patient pairs, the win ratio for the primary composite endpoint was 1.02 (95% CI: 0.68–1.51;  $P = .94$ ), with 17 870 (12.1%) wins for the Myval group and 17 599 (11.9%) for the contemporary group. For the extended composite endpoint, the win ratio was 1.13 (95% CI: 0.82–1.55;  $P = .45$ ), with 27 007 (18.3%) wins for the Myval group and 23 920 (16.2%) for the contemporary group. Comparisons between the Myval and Sapien groups, and between the Myval and Evolut groups, were also not statistically significant.

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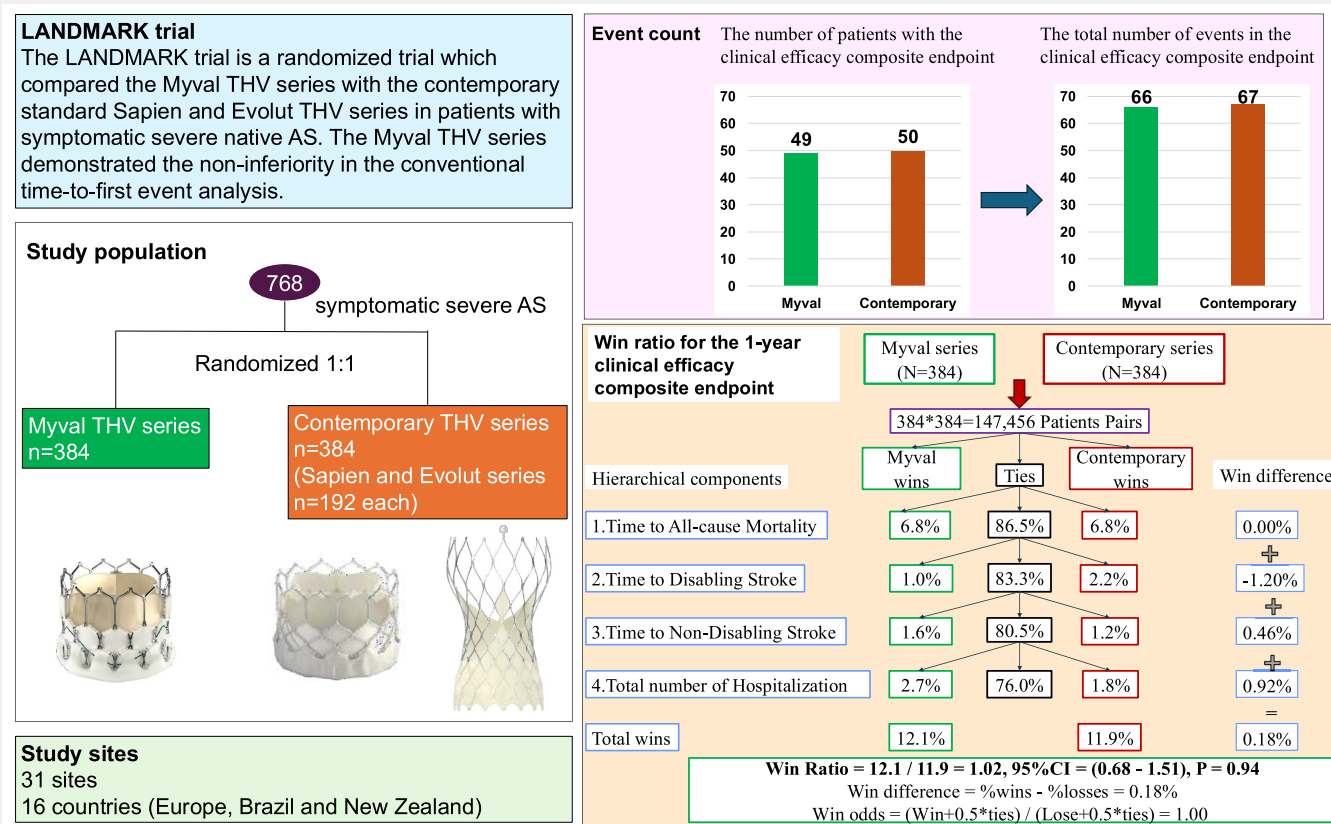
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## Conclusions

Win ratio analysis did not demonstrate a significant difference between Myval and contemporary THVs, consistent with the primary time-to-first event analysis of the LANDMARK trial.

## Graphical abstract



## Keywords

Transcatheter aortic valve implantation • LANDMARK trial • Win ratio • Myval • Sapien • Evolut

## Introduction

Transcatheter aortic valve implantation (TAVI) is a guideline-endorsed treatment option for patients with severe aortic stenosis.<sup>1–3</sup> Over the past decades, TAVI technology has advanced significantly, and several transcatheter heart valve (THV) systems have been developed and adopted in clinical practice.<sup>4</sup>

The Myval THV series is a novel balloon-expandable bioprosthesis that demonstrated comparable performance to the contemporary Sapien and Evolut THV series for the 1-year clinical efficacy composite endpoint in the LANDMARK trial.<sup>5</sup> The primary analysis used the conventional Kaplan–Meier method based on the time-to-first event principle. Although widely used in clinical research, this method has limitations: it considers only the first event among the components of the composite endpoint and does not account for event severity or recurrence. To address these limitations and gain a more comprehensive understanding of clinical outcomes in the LANDMARK trial, this study reassessed the 1-year clinical efficacy composite endpoint using a win ratio analysis.

## Methods

### Study design and participants

The LANDMARK trial (NCT04275726) was a prospective, open-label, multicentre, non-inferiority trial conducted at 31 sites across 16 countries (Germany, France, Sweden, the Netherlands, Italy, Spain, Portugal, Greece, Hungary, Poland, Slovakia, Slovenia, Croatia, Estonia, New Zealand, and Brazil). The study design was described previously.<sup>5–9</sup> Briefly, the LANDMARK trial evaluated the clinical and haemodynamic performance of the Myval balloon-expandable THV series compared with contemporary standard valves—the balloon-expandable Sapien and self-expanding Evolut series—in patients with symptomatic severe native aortic valve stenosis. Between 6 January 2021 and 5 December 2023, 768 patients were randomized in a 1:1 ratio to either the Myval THV series ( $n = 384$ ) or the contemporary THV series ( $n = 384$ ) arm. Randomization was performed based on the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score. The study demonstrated the non-inferiority of the Myval THV series compared with the contemporary THV series with respect to the 30-day early safety and effectiveness endpoint (a composite of all-cause mortality, all stroke, bleeding [type 3 and 4], major vascular complications, acute

**Table 1 First and total event counts**

	Myval THV series, N = 384	Contemporary THV series, N = 384	Sapien THV series, N = 192	Evolut THV series, N = 192
<b>First event count</b>				
All-cause mortality, <i>n</i> (KM%)	27 (7.2)	27 (7.1)	11 (5.8)	16 (8.4)
Fatal stroke, <i>n</i> (KM%)	5 (1.3)	2 (0.5)	0 (0)	2 (1.1)
Disabling stroke, <i>n</i> (KM%)	11 (3.0)	4 (1.1)	2 (1)	2 (1.1)
Non-disabling stroke, <i>n</i> (KM%)	5 (1.3)	7 (1.9)	5 (2.6)	2 (1.1)
Procedure- or valve-related hospitalization, <i>n</i> (KM%)	16 (4.3)	20 (5.4)	12 (6.4)	8 (4.4)
Composite endpoint, <i>n</i> (KM%)	49 (13.0)	50 (13.1)	25 (13.1)	25 (13.1)
QOL deterioration, <i>n</i> (%)	29/329 (8.8)	38/333 (11.4)	24 (14.1) ( <i>n</i> = 170)	14 (8.6) ( <i>n</i> = 163)
Extended composite endpoint, <i>n</i> (%)	75 (19.5)	87 (22.7)	48 (25.0)	39 (20.3)
<b>Total event count</b>				
All-cause mortality, <i>n</i>	27	27	11	16
Fatal stroke, <i>n</i>	5	2	0	2
Disabling stroke, <i>n</i>	11	4	2	2
Non-disabling stroke, <i>n</i>	5	7	5	2
Procedure- or valve-related hospitalization, <i>n</i>	18	27	18	9
Composite endpoint	66	67	36	31
QOL deterioration, <i>n</i>	29	38	24	14
Extended composite endpoint	95	105	60	45

KM, Kaplan–Meier; QOL, quality of life; THV, transcatheter heart valve.

kidney injury [stages 2–4], moderate or severe prosthetic valve regurgitation, and permanent pacemaker implantation) and the 1-year clinical efficacy composite endpoint (a composite of all-cause mortality, all stroke, and hospitalizations due to procedure- or valve-related causes).<sup>5,6</sup> Furthermore, the Myval series showed comparable outcomes when compared individually with the Sapien and Evolut series.<sup>5,10</sup> The trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Echocardiograms and electrocardiograms were analysed by two independent core labs (Echocardiogram: CORRIB core lab, Galway, Ireland. Electrocardiogram: CERC, Paris, France) using analysts blinded to the allocated treatment group. Endpoints were defined according to the Valve Academic Research Consortium-3 and adjudicated by a blinded, independent clinical events committee.<sup>11</sup>

## Statistical analysis

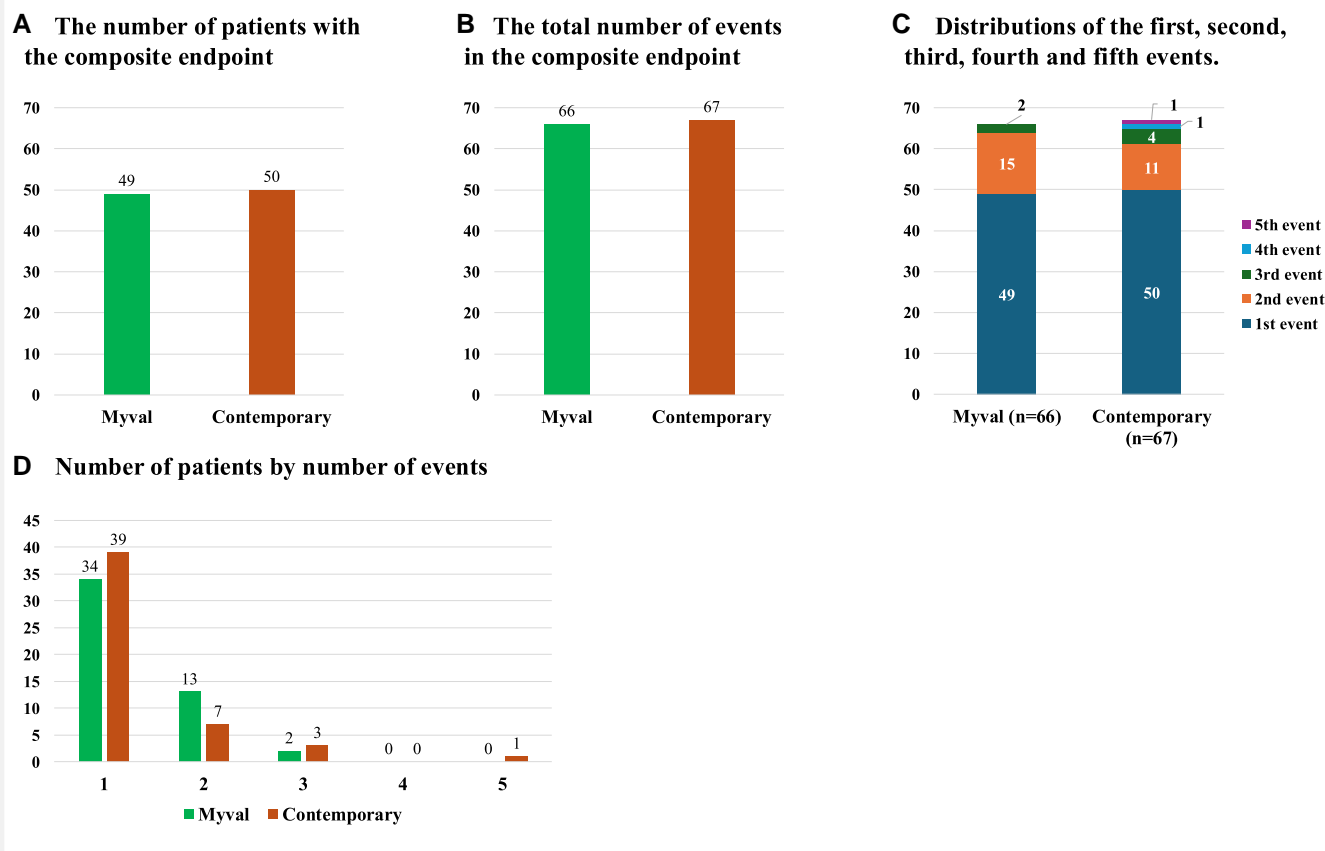
The win ratio analysis for the 1-year clinical efficacy composite endpoint was added in the statistical analysis plan of the LANDMARK trial, which was updated after publication of the 30-day primary outcome and before data lock and analysis of the 1-year outcome. In the present analysis, stroke was subdivided into disabling and non-disabling stroke. As a result, the primary composite endpoint included all-cause death, disabling stroke, non-disabling stroke, and procedure- or valve-related hospitalization. Event rates were assessed at day 365 from the index procedure. In total, 11 patients withdrew consent before 1 year. Events were counted up to the time of withdrawal. For all remaining patients, vital status at 1 year was available. For patients who died before the TAVI procedure, death was recorded as occurring on day 0. The conventional time-to-first-event curves, using the Kaplan–Meier method with hazard ratios (HRs) and log-rank *P*-values, have been previously published.<sup>5</sup> In the present study, outcomes were assessed using win ratio analysis<sup>12,13</sup> as described in detail

below. The analysis was performed using R version 4.3.3 by an independent statistician.

## Win ratio analysis

The win ratio analysis is a method for evaluating a composite endpoint which was proposed by Pocock *et al.* in 2012.<sup>13–15</sup> In brief, a win ratio analysis summarizes hierarchical pairwise comparisons of patients across the individual components of the composite endpoint, ranked by their clinical relevance and severity. An every patient-to-patient analysis is conducted for the highest-ranking event in the hierarchy, which is the most important/severe event. If a patient in group A has a better outcome compared with a patient in group B (e.g. a patient in group A does not have the event while a patient in group B has it), it is a win for group A. Conversely, if a patient in group B has a better outcome compared with a patient in group A, it is a win for group B. Otherwise, it is a tie. Next, in pairs tied at the highest-ranking event, win and tie outcomes for the second-ranking event are assessed. This process is repeated until the lowest-ranking event in the hierarchy. Win ratio is obtained by dividing the total number of wins in group A by that in group B.

We previously reported a *post hoc* win ratio analysis of the 30-day composite endpoint comprising seven events.<sup>16</sup> For the current study, the hierarchy of the four events comprising the 1-year composite endpoint was determined using the Delphi method before analysing 1-year outcomes but after the publication of the 30-day primary outcome. Ten physicians, who were either cardiologists or cardiac surgeons, including five members of the Clinical Event Committee (J.L.P., L.R., A.G., J.I., and A.S.) and the top five recruiters to the trial (N.V.R., I.J.A.-S., M.H., M.B., and A.I.) participated in the Delphi panel. The first author (A.T.) served as the facilitator. Each panel member was assigned 20 points and was asked to distribute these points among four events (all-cause mortality, disabling stroke, non-disabling



**Figure 1** Event counts and distribution of the composite endpoint. A, Number of patients with at least one composite endpoint event, which is identical to the number of patients with a composite endpoint event in a time-to-first event analysis. B, Total number of composite endpoint events, including recurrent events. C, Distributions of first, second, third, fourth, and fifth events. D, Distributions of the number of events per patient

stroke, and procedure- or valve-related hospitalization). The panel members were instructed to allocate the points from the perspective of a physician participating in a TAVI trial. A higher point indicated greater severity or importance of the event. Points had to be assigned as integers, and the total number of points had to be 20. The result is shown in [Supplementary Table S1](#). The obtained median points were 8.5 (first—third quartiles [Q1—Q3] 8–10), 7 (6.25–7), 2.5 (2–3) and 2 (1.25–2) for all-cause death, disabling stroke, non-disabling stroke, and procedure- or valve-related hospitalization, respectively.

Accordingly, the resulting severity ranking of the four events was as follows: all-cause mortality, disabling stroke, non-disabling stroke, and procedure- or valve-related hospitalization. For all-cause mortality, disabling stroke, and non-disabling stroke, wins or losses were assessed using the time-to-first-event principle: a patient with a later event was counted as the winner. For procedure- or valve-related hospitalizations, recurrent events were incorporated within the hierarchical win ratio framework by comparing the total number of hospitalizations between paired patients; the patient with fewer hospitalizations was considered the winner.

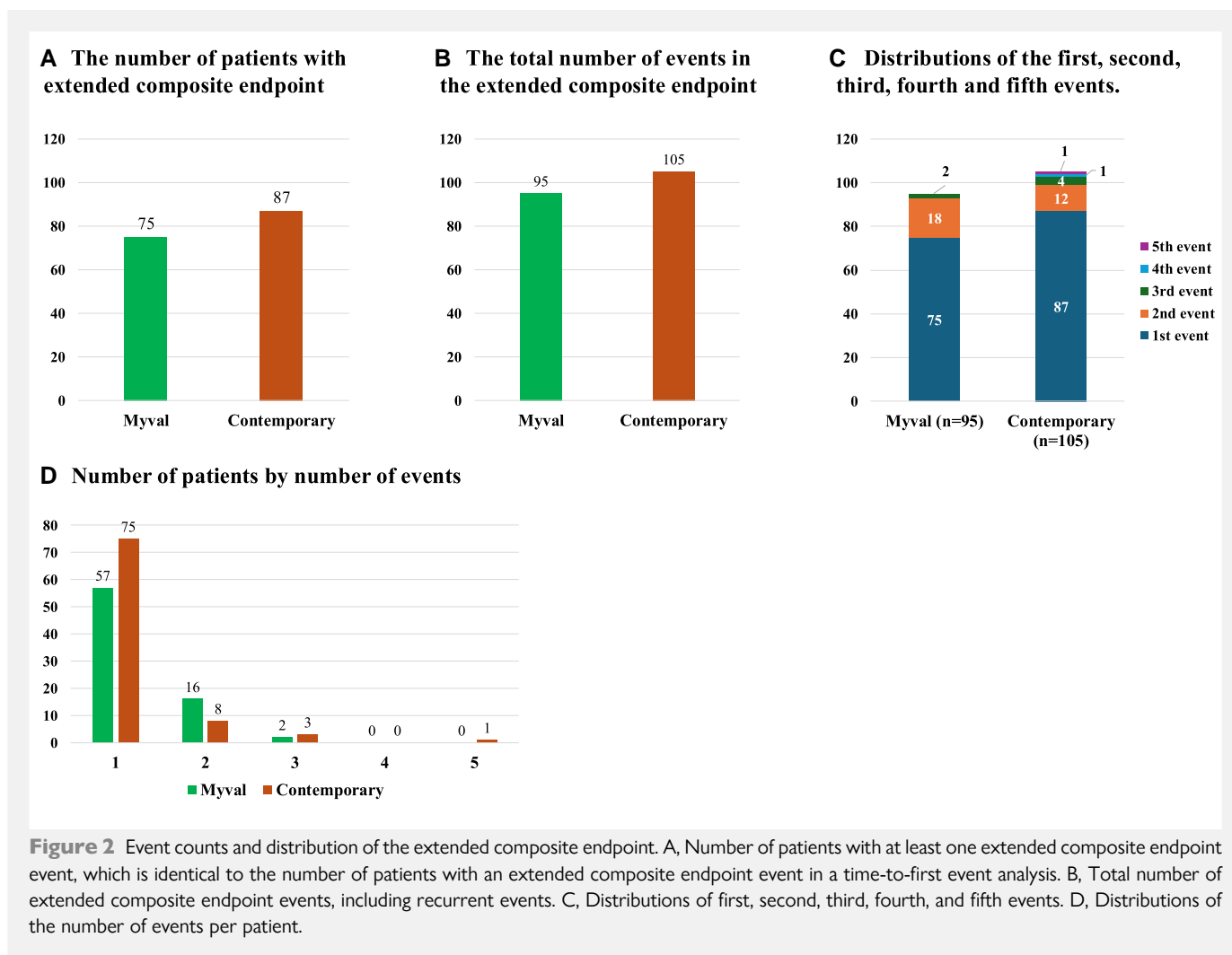
The extended composite endpoint included deterioration in quality of life (QOL), defined as a  $\geq 2.5$  point decrease from baseline to 1-year follow-up in both the physical and mental domains of the Short-Form 12 (SF-12).<sup>11</sup> Missing SF-12 data at 1 year ( $n = 65$ ) among patients who were alive and had not withdrawn consent were imputed using multiple imputation by the chained equation method.<sup>5</sup> The deterioration in QOL was ranked lowest among all components of the hierarchy. Win ratio analyses were performed using the R package WinRatio. The 95% confidence intervals (CIs) and *P*-values were calculated using the Bebu & Lachin method.<sup>17</sup> In addition to the win ratio, we reported the win difference and win odds. The win difference was defined as proportion of wins in the Myval group minus the proportion of wins in the control group. The win odds was calculated as

(win in the Myval group + 0.5\*ties)/(win in the control group + 0.5\*ties).<sup>14,18</sup>

## Results

Baseline patient and procedural characteristics have been previously published and were well-matched.<sup>5,6</sup> In short, the mean age was  $80.0 \pm 5.7$  years in the Myval group and  $80.4 \pm 5.4$  years in the contemporary group. Women comprised 50% ( $n = 193/384$ ) and 46% ( $n = 176/384$ ), respectively. The median STS-PROM score was 2.6% (Q1–Q3, 1.7–4.0%) in both groups. Prior myocardial infarction was present in 7% ( $n = 26$ ) and 6% ( $n = 23$ ), and prior stroke in 3% ( $n = 13$ ) and 2% ( $n = 8$ ), respectively. TAVI procedure was performed in 379 and 377 patients, respectively, and almost all patients (>99%) underwent transfemoral TAVI. Cerebral protection device was used in 13% ( $n = 48$ ) and 9% ( $n = 33$ ), respectively.

Using the conventional time-to-first-event approach, the number of patients with a composite endpoint event by day 365 was 49 in the Myval group and 50 in the contemporary group. In contrast, the total number of events was 66 and 67, respectively ([Table 1, Figure 1](#)). In the Myval group, the numbers of patients experiencing one, two, three, four, and five events were 34, 13, 2, 0, and 0, respectively, whereas in the contemporary group, the respective numbers were 39, 7, 3, 0, and 1. The 66 events in the Myval group comprised 27 deaths, 5 fatal strokes, 11 disabling strokes, 5 non-disabling strokes, and 18 procedure- or valve-related hospitalizations. The 67 events in the



**Figure 2** Event counts and distribution of the extended composite endpoint. A, Number of patients with at least one extended composite endpoint event, which is identical to the number of patients with an extended composite endpoint event in a time-to-first event analysis. B, Total number of extended composite endpoint events, including recurrent events. C, Distributions of first, second, third, fourth, and fifth events. D, Distributions of the number of events per patient.

contemporary group included 27 deaths, 2 fatal strokes, 4 disabling strokes, 7 non-disabling strokes, and 27 procedure- or valve-related hospitalizations (Table 1). No patient in either group experienced a recurrent stroke. There were two recurrent procedure- or valve-related hospitalizations in the Myval group and seven in the contemporary group.

The event counts and event distribution for the extended composite endpoint are shown in Table 1 and Figure 2. In the Myval group, the total number of events and the number of patients experiencing at least one component of the extended composite endpoint were 95 and 75, respectively. In the contemporary group, the corresponding figures were 105 and 87.

## Win ratio

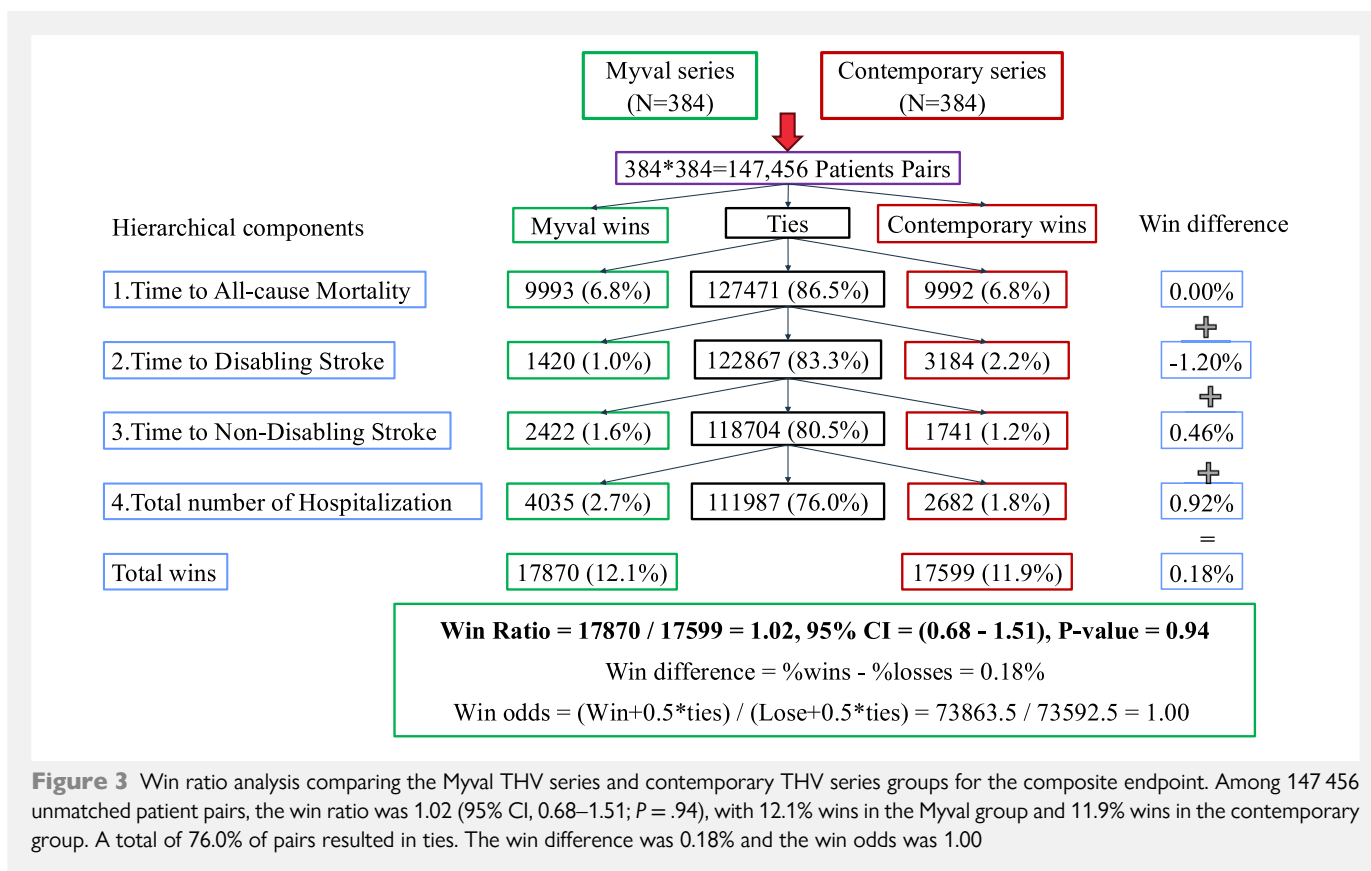
Win ratio analysis between the Myval and contemporary groups was performed on 147 456 (384 × 384) unmatched patient pairs. There was no significant difference in the primary composite endpoint with 17 870 (12.1%) wins for the Myval series and 17 599 (11.9%) for the contemporary series, resulting in a win ratio of 1.02 (95% CI: 0.68–1.51;  $P = .94$ , Figure 3). Mortality wins were balanced; the contemporary valves had numerically more wins for disabling stroke, whereas the Myval group had numerically more wins for non-disabling stroke and hospitalization. There were 111 987 (76.0%) pairs that ended in a tie. The win difference was 0.18%, and the win odds was 1.00.

Similarly, there was no significant difference in the extended composite endpoint, which included QOL, with 27 007 (18.3%) wins for the Myval series, and 23 920 (16.2%) wins for the contemporary series, yielding a win ratio of 1.13 (95% CI: 0.82–1.55;  $P = .45$ , Figure 4). The Myval group had numerically more wins for the QOL outcome; 96 529 (65.5%) pairs ended in a tie. The win difference was 2.09%, and the win odds was 1.04.

Win ratio analyses comparing the Myval and Sapien series, as well as the Myval and Evolut series, did not show any significant differences for the composite endpoint (Myval vs Sapien: win ratio = 0.99; 95% CI: 0.61–1.60;  $P = .98$ , Myval vs Evolut: win ratio = 1.04; 95% CI: 0.64–1.68;  $P = .88$ , Supplementary Figures S1 and S2) or for the extended composite endpoint (Myval vs Sapien: win ratio = 1.18; 95% CI: 0.82–1.71;  $P = .37$ , Myval vs Evolut: win ratio = 1.07; 95% CI: 0.72–1.60;  $P = .72$ , Supplementary Figures S3 and S4).

## Discussion

In summary, this *post hoc* analysis of the LANDMARK trial using win ratio analysis found no statistically significant difference in the composite or extended composite endpoint between the Myval and contemporary groups at 1 year. Similarly, no significant differences were observed between Myval and the Sapien or Evolut groups. These findings are consistent with the trial's primary results, which used the conventional time-to-first-event approach.<sup>5</sup>



**Figure 3** Win ratio analysis comparing the Myval THV series and contemporary THV series groups for the composite endpoint. Among 147 456 unmatched patient pairs, the win ratio was 1.02 (95% CI, 0.68–1.51;  $P = .94$ ), with 12.1% wins in the Myval group and 11.9% wins in the contemporary group. A total of 76.0% of pairs resulted in ties. The win difference was 0.18% and the win odds was 1.00

The time-to-first-event approach for composite endpoints is commonly used in clinical trials; however, its key limitation is that it ignores event severity and recurrence. In this method, a severe first event (e.g. death) in group A and a less severe first event (e.g. hospitalization) in group B contribute equally to the composite endpoint. Moreover, regardless of how many events a patient experiences (e.g. stroke followed by another stroke, or hospitalization followed by death), only the first event is ever counted. To address these limitations, various alternative statistical approaches for composite endpoints have been proposed, among which the win ratio is the most commonly used method. In the present study, the hierarchical ranking of events was determined using a Delphi method. Death and stroke were evaluated using the time-to-first-event principle, whereas procedure- or valve-related hospitalization was assessed by comparing the total number of events to account for recurrent hospitalizations. To date, several clinical trials have used win ratio to evaluate their primary composite endpoint.<sup>15,19,20</sup> For example, TAVR UNLOAD (the Transcatheter Aortic Valve Replacement to UNload the Left ventricle in patients with ADvanced heart failure trial) used the win ratio as the primary analytical method for their composite endpoint of all-cause mortality, disabling stroke, disease-related hospitalizations, and QOL outcomes.<sup>19</sup>

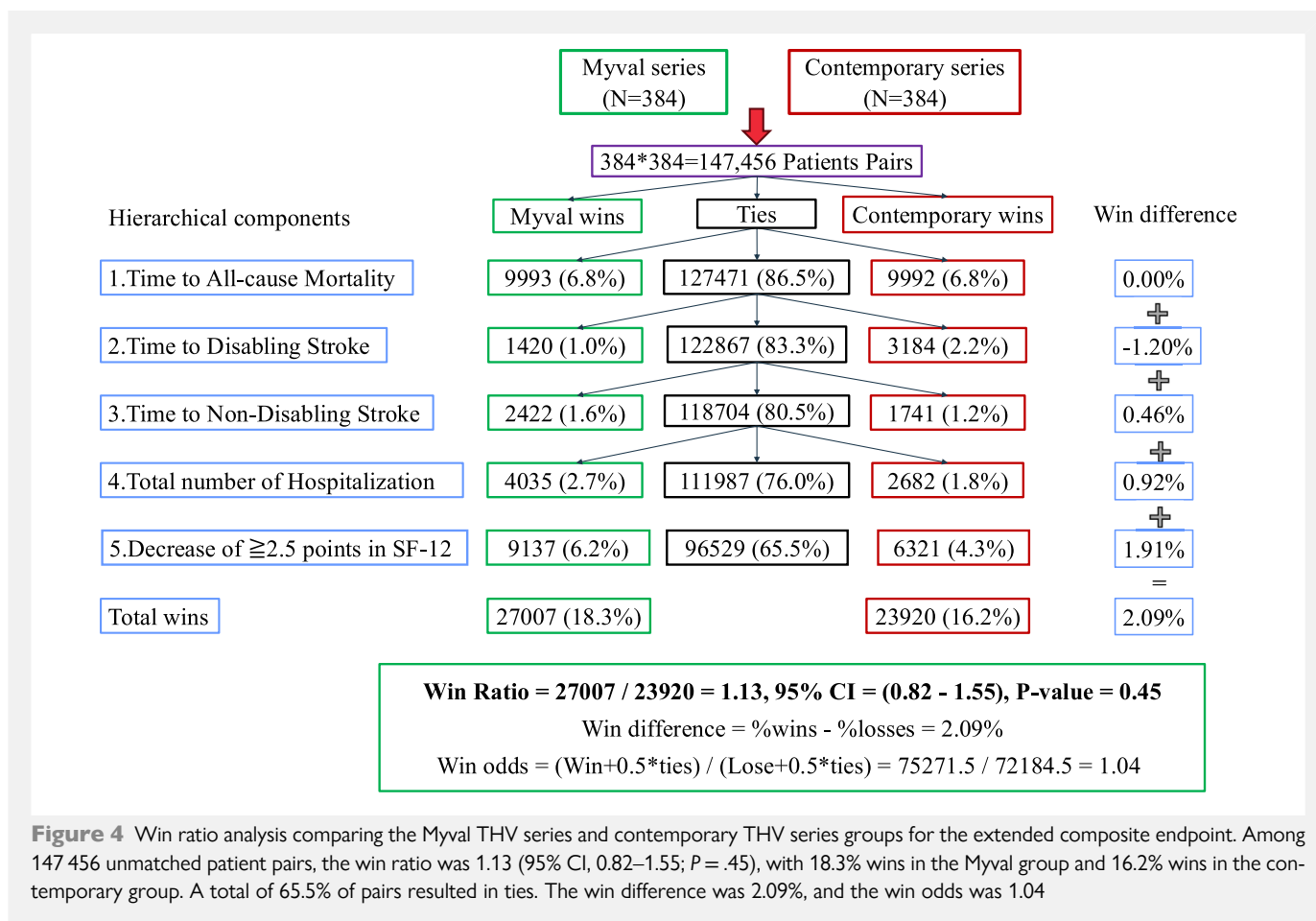
In the present study, the results of the win ratio analysis were consistent with the primary analysis using the time-to-first-event approach; however, discordant findings between these analytical methods have been previously described.<sup>21,22</sup> In the REC-CAGEFREE trial, there were no significant differences in the Kaplan–Meier estimates of net adverse clinical events (a composite of all-cause death, stroke, myocardial infarction, revascularization, and Bleeding Academic Research Consortium type 3 or 5 bleeding) with rates of 8.9% in the experimental arm and 8.6% in the control arm (risk difference: 0.36%, 95% CI: –1.75 to 2.47). In contrast, the win ratio analysis showed 14.4% wins

in the experimental arm and 10.1% wins in the control arm, yielding a statistically significant win ratio of 1.43 (95% CI: 1.12 to 1.83,  $P$ -value = .004).<sup>21</sup> This highlights the importance of assessing composite endpoints by considering event severity and recurrence.

In the current study, the majority of pairwise comparisons were tied (76.0% for the composite endpoint and 65.5% for the extended composite endpoint). Win ratio analyses provide the most precise estimate when ties are minimal; however, a high proportion can attenuate or inflate the estimated treatment effect.<sup>14,18</sup> A more comprehensive understanding of the analysis can be obtained by calculating the win difference and win odds. While the win ratio reflects a relative effect, the win difference represents the absolute difference, and the win odds incorporate the number of ties. The win difference between the Myval and contemporary groups was 0.18% for the composite endpoint and 2.09% for the extended composite endpoint, suggesting only a small absolute effect. The win odds were 1.00 and 1.04, respectively, which were smaller than the corresponding win ratios and closer to 1, suggesting that the difference in treatment effect between the two groups is small. Longer-term follow-up will capture a greater number of new and recurrent events, which may reduce the proportion of ties and provide a more informative assessment.

## Limitations

This study has several limitations. First, because the win ratio measures the probability of winning, its application in a non-inferiority trial remains challenging. Therefore, the present win ratio analysis should be considered exploratory and interpreted with caution and should not be viewed as evidence of confirmatory equivalence. Although a method for applying the win ratio to non-inferiority analysis has recently been proposed, this approach was not implemented in the present analysis.<sup>23</sup>



Second, the 1-year follow-up period may be insufficient to capture recurrent events or those related to THV durability. In the recently published 6–7-year follow-up data from the Evolut Low Risk trial, the TAVI arm showed a significantly higher rate of reintervention compared with surgical aortic valve replacement arm, highlighting the importance of long-term follow-up.<sup>24</sup> Because the LANDMARK trial plans to follow patients for up to 10 years, future analyses incorporating longer-term data will be important. Third, the event hierarchy was defined using a Delphi method involving 10 cardiologists or cardiac surgeons. Different results may be obtained with a different group of panel members. Moreover, event priorities from a patient perspective may not necessarily align with clinician-derived rankings.<sup>25,26</sup> Therefore, the generalizability of the assigned hierarchy should be interpreted with caution. Forth, the win ratio analysis was not prespecified in the original statistical analysis plan before the primary outcome analysis but was incorporated into an updated plan after publication of the 30-day primary outcome and prior data lock analysis of the 1-year outcome. Fifth, in the Myval group, the first generation Myval was used in 86%, whereas the next iteration, Myval Octacor, was used in only 8%. Therefore, the currently available newer iterations (e.g. Myval Octacor, OctaPro, and OctaPro+) may demonstrate different clinical performance.

## Conclusions

In the LANDMARK trial, the win ratio analysis did not show a significant difference in the composite endpoint at 1 year. These findings were consistent across all comparisons and aligned with the primary analysis using the conventional time-to-first-event approach.

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## Author contributions

Akihiro Tobe (Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing—original draft [lead]), Niels Van Royen (Investigation [equal], Writing—review & editing [supporting]), Ignacio J Amat-Santos (Investigation [equal], Writing—review & editing [supporting]), Martin Hudec (Investigation [equal], Writing—review & editing [supporting]), Matjaz Bunc (Investigation [equal], Writing—review & editing [supporting]), Alexander Ijsselmuiden (Investigation [equal], Writing—review & editing [supporting]), Jose Luis Pomar (Investigation [equal], Writing—review & editing [supporting]), Liesbeth Rosseel (Investigation [equal], Writing—review & editing [supporting]), Amr Gamal (Investigation [equal], Writing—review & editing [supporting]), Javid Iqbal (Investigation [equal], Writing—review & editing [supporting]), Alan Soo (Investigation [equal], Writing—review & editing [supporting]), Scot Garg (Writing—review & editing [lead]), Udita Chandra (Data curation, Resources [equal], Formal analysis [supporting]), Ashokkumar Thakkar (Data curation [lead], Formal analysis, Resources [equal]), Pieter C Smits (Formal analysis [equal], Writing—review & editing [supporting]), Marie-Claude Morice (Formal analysis [equal], Writing—review & editing [supporting]), Yoshinobu Onuma (Conceptualization, Methodology, Writing—review & editing [equal]), Andreas Baumbach (Writing—review & editing

