Win ratio analysis of the LANDMARK trial

Title	Win ratio analysis of the LANDMARK trial
Author(s)	Tobe, Akihiro;van Royen, Niels;Amat-Santos, Ignacio J.;Hudec, Martin;Bunc, Matjaz;Ijsselmuiden, Alexander;Pomar, Jose Luis;Rosseel, Liesbeth;Gamal, Amr;Iqbal, Javaid;Soo, Alan;McInerney, Angela;Garg, Scot;Chandra, Udita;Thakkar, Ashokkumar;Soliman, Osama;Onuma, Yoshinobu;Baumbach, Andreas;Serruys, Patrick W.
Publication Date	2025-05-23
Publisher	Elsevier
Repository DOI	https://doi.org/10.1016/j.ahj.2025.04.024

Win ratio analysis of the LANDMARK trial

Akihiro Tobe [1], Niels van Royen [2], Ignacio J. Amat-Santos [3,4], Martin Hudec [5], Matjaz Bunc [6], Alexander Ijsselmuiden [7,8,9], Jose Luis Pomar [10], Liesbeth Rosseel [11], Amr Gamal [12,13,14], Javaid Iqbal [15], Alan Soo [16], Angela McInerney [17], Scot Garg [18,19], Udita Chandra [20], Ashokkumar Thakkar [20], Osama Soliman [1], Yoshinobu Onuma [1], Andreas Baumbach [21,22], and Patrick W. Serruys [1]

Abstract The LANDMARK trial reported the non-inferiority of the Myval transcatheter heart valve (THV) series compared with the contemporary standard THV series (Sapien and Evolut) for a 30-day composite endpoint in patients with severe aortic stenosis. This exploratory study compared the performance of the Myval THV series with the contemporary THV series using the win ratio analysis. (Am Heart J 2025;289:1–5.)

BACKGROUND

The Myval series (Meril Life Sciences Pvt. Ltd., India) is a novel balloon-expandable transcatheter heart valve (THV). The recently published LANDMARK trial demonstrated its non-inferiority compared to the contemporary Sapien (Edwards Lifesciences, Irvine, CA, USA) and Evolut (Medtronic, Minneapolis, MN, USA) THV series in patients with severe symptomatic native aortic stenosis (AS), with respect to a primary composite endpoint consisting of seven events at 30 days.[1] These seven events differ greatly in clinical severity. Not only using the traditional method, where the occurrence of any single component event is counted as the primary endpoint, but also an analysis that takes clinical event severity into account is crucial. In this exploratory sub-analysis, we compared the performance of the Myval series with the contemporary THV series using the win ratio analysis to explore the individual hierarchized endpoints of the primary composite endpoint.

METHODS

Study population

The LANDMARK trial is a multi-center, randomized, open-label, non-inferiority trial conducted in 16 countries, which compares the safety and effectiveness between the Myval THV series and the contemporary THV series (Sapien and Evolut) in accordance with the third Valve Academic Research Consortium (VARC-3) recommendations.[2] The trial details are available elsewhere.[1,3,4] In brief, patients with severe symptomatic native AS were enrolled according to the European Society of Cardiology/European Association of Cardiothoracic Surgeons recommendations. The primary endpoint was a composite of seven events: all-cause death, all stroke, bleeding (VARC-3 type 3 or 4), acute kidney injury (AKI) stage 2-4, major vascular complication, moderate or severe prosthetic valve regurgitation (PVR), and conduction system disturbances resulting in a permanent pacemaker implantation (PPI) at 30 days in the intention-to-treat population (Supplementary Table 1). Between Jan 2021 and Dec 2023, 768 patients were randomized 1:1 to the Myval (n=384) or the contemporary (n=384) group. Echocardiograms, multi-slice computed tomography, and electrocardiograms were analyzed by independent core laboratories. The outcomes were adjudicated by a clinical event committee according to VARC-3. The 30-day clinical endpoint was assessed in 381 patients in each group. The primary composite endpoint occurred in 24.7% (94/381) of the Myval group and 27.0% (103/381) of the contemporary THV group, (a risk difference -2.3%; one-sided upper 95% confidence interval (CI) 3.8%; P for non-inferiority<0.0001) meeting the pre-

From the [1]Department of Cardiology, School of Medicine, University of Galway, Galway, Ireland, [2]Department of Cardiology, Radboud University Hospital, Nijmegen, Netherlands, [3]CIVERCV, Centro de Investigación Biomédica en red - Enfermedades Cardiovasculares, Spain, [4]Department of Cardiology, University Clinical Hospital of Valladolid, Valladolid, Spain, [5]Department of Acute Cardiology, Middle-Slovak Institute of Cardiovascular Diseases, Banska Bystrica, Slovakia, [6]Department of Cardiology, University Medical Centre Ljubljana, Ljubljana, Slovenia, [7]Department of Cardiology, Amphia Hospital, Breda, Netherlands, [8]Department of Interventional Cardiology, Maastricht University Medical Center, Maastricht, Netherlands, [9]Zuyderland Hospital, Limburg, Netherlands, [10]The Cardiovascular Institute Hospital Clinic & University of Barcelona, Barcelona, Spain, [11]Department of Cardiology, Algemeen stedelijk ziekenhuis Aalst, Aalst, Belgium, [12]Blackpool Victoria Hospital, Blackpool, United Kingdom, [13]School of Medicine, University of Liverpool, Liverpool, United Kingdom, [14]School of Medicine, Zagazig University, Egypt, [15]South Yorkshire Cardiothoracic Centre, Northern General Hospital, Sheffield, United Kingdom, [16]Department of Cardiothoracic Surgery, Galway University Hospital, Galway, Ireland, [17]Cardiology Department, Galway University Hospital, Galway, Ireland, [18]Department of Cardiology, Royal Blackburn Hospital, Blackburn, UK, [19]School of Medicine and Dentistry, University of Central Lancashire, Preston, UK, [20]Department of Clinical Research and Medical Writing, Meril Life Sciences Pvt. Ltd., Vapi, India, [21]Centre for Cardiovascular Medicine and Devices, William Harvey Research Institute, Queen Mary University of London and Barts Heart Centre, London, United Kingdom, [22]Cleveland Clinic London, London, United Kingdom

Trial registration number: NCT04275726 and EudraCT 2020-000137-40

Submitted November 6, 2024; accepted April 18, 2025

Corresponding author: Patrick W Serruys (Chairperson of LANDMARK trial), Department of Cardiology, School of Medicine, University of Galway, Galway, Ireland.

E-mail address: patrick.w.j.c.serruys@gmail.com.

0002-8703

https://doi.org/10.1016/j.ahj.2025.04.024

specified criteria for non-inferiority of the Myval group compared with the contemporary group. There were no significant differences in the occurrences of individual components of the primary composite endpoint.[1]

Win ratio method

Details of the win ratio analysis are provided elsewhere.[5-7] In brief, a win ratio analysis summarizes hierarchical pairwise comparisons of patients in terms of individual components of the composite endpoint, ranked according to their clinical relevance and gravity. In this post-hoc exploratory sub-analysis, the primary composite endpoint of the main trial at 30 days was assessed using the win ratio in the intention-to-treat population. The method to determine the ranking of the seven components is described below. The time to event was considered in this sub-analysis. There were no repeated same type of events within 30 days, therefore, only the first event in each level was used for the analysis.

Ranking of the events

To perform the win ratio analysis, it is essential to determine the ranking order and gravity of the individual components of the primary composite endpoint. A consensus regarding the rankings of the seven events was achieved using the Delphi method, which is a structured communication method to reach a consensus among experts in the field.[8] Ten cardiologists (eight interventional cardiologists and two cardiothoracic surgeons), consisting of five clinical event committee members (JLP, LR, AG, JI and AS) and the top five recruiters to the trial (NVR, IJAS, MH, MB and AI), were selected as the members of the Delphi. AT served as the facilitator. Three rounds of survey were anticipated and a consensus was considered to have been reached if the rankings matched in more than 70% of the respondents. Details of the Delphi method are provided in Supplementary Table 2.

Statistical analysis

The sample size of the LANDMARK trial was calculated to show non-inferiority of the Myval THV series compared to the contemporary THV series in terms of the primary composite endpoint, and was not designed for this post-hoc win-ratio sub-analysis.[3] The win ratio analysis was conducted with the same population as the primary endpoint analysis of the main trial, in accordance with the intention-to-treat principle, using $381 \times 381 = 145,161$ unmatched patient pairs. Win ratio was presented with 95% CI using BeBu and Lachin method.[9] Win difference (%wins - %losses) and win odds ([% wins + ½ ties] ÷ [% losses + ½ ties]) were calculated as well. All statistical tests were conducted at 5% level of significance. Two sensitivity analyses with different ranking orders were performed. Statistical analyses including the win ratio analysis were performed using R (version 4.3.2) with WinRatio package.

RESULTS

The surveys using the Delphi method began before the presentation of the primary analysis and were completed after it, running from 12 April 2024 to 28 May 2024. Three rounds of survey were conducted, and the final ranking order of gravity was: all-cause mortality, all stroke, bleeding (VARC-3 type 3 and 4), major vascular complication, moderate or severe PVR, AKI stage 2-4, and new PPI. The details and process of the survey are described in Supplementary Tables 3-5.

The result of win ratio analysis is shown in Figure 1. Five events (all-cause death, all stroke, major vascular complication, moderate or severe PVR, and new PPI) numerically favored the Myval THV series, and two events (bleeding and AKI) numerically favored the contemporary THV series. In total, there were 34,290 wins in Myval THV series and 30,636 wins in the contemporary THV series. Despite the numerically higher number of wins in the Myval THV series, the win ratio was not statistically significant (Win ratio: 34290/30636=1.12; 95% CI 0.84 to 1.48; p=0.43. Win difference: 2.52%. Win odds: 1.05). The results of the sensitivity analyses were presented in the Supplementary Figures 1 and 2.

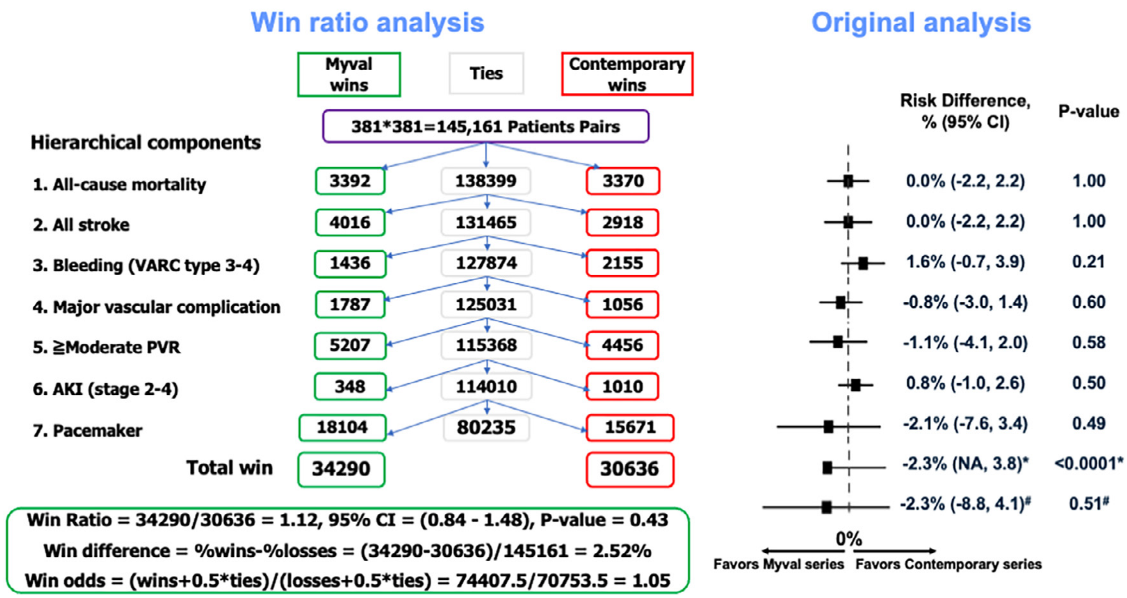
DISCUSSION

This post-hoc exploratory sub-analysis of the LANDMARK trial reported the statistically non-significant win ratio between the Myval THV series and the contemporary THV series, which did not contradict the primary analysis for non-inferiority of the primary composite endpoint.

Composite endpoints are used in clinical trials to enable powered studies using achievable sample sizes that can be recruited in a timely fashion and within realistic budgets. One of their shortcomings, however, is that they treat all events equally, irrespective of severity. The win ratio was developed to address this issue,[5] and has been used effectively in previous clinical trials.[10,11]

To perform the win ratio analysis, it is essential to make a ranking order of the components of the composite endpoint, which then needs to be accepted by a broad consensus. To achieve this, we surveyed ten cardiologists using the Delphi method and the rankings we obtained seemed reasonable. From a physician's perspective there was no disagreement that death was the most severe event, followed by stroke, which if disabling, would significantly impair a patient's quality of life. Hierarchical ranking between VARC type 3 or 4 bleeding and major vascular complications was more complex and somewhat controversial, as their definitions have some overlap and both can potentially lead directly to death. Moderate or severe PVR significantly impacts on prognosis but is often treatable (e.g. closure device for paravalvular leak and valve in valve for transvalvular leak).[12] AKI is also associated with mortality, but it often results from

Figure 1. Win ratio analysis (left) and Forest plot of the primary composite endpoint and its components from the original analysis (right). The 95% CI and P value are two-sided. *The one-sided 95% CI and P value for non-inferiority of the composite endpoint. # The two-sided 95% CI and P value for superiority of the composite endpoint. AKI=acute kidney injury, PVR=prosthetic valve regurgitation, VARC=Valve Academic Research Consortium



other more severe complications, can improve by itself and can be treated if necessary by renal replacement therapy.[13] The Delphi group consider PPI as the least severe event due to conflicting data regarding whether it increases or reduces the risk of mortality.[14]

The total number of wins numerically favored the Myval THV series, but the win ratio was not statistically significant, which is consistent with the original analysis of the primary composite endpoint (Myval 24.7% vs contemporary group 27.0%, $P_{non\text{-}inferiority}$ <0.0001, $P_{superiority}$ 0.51, Figure 1).[1] When we look into individual events, the respective occurrence rates of all-cause death and stroke at 30 days were the same in both two groups (all-cause death: 9/381 [2.4%], all stroke: 12/381 [3.1%] in both groups), however, in the win ratio analysis, the numbers of wins for all-cause death (3,392 vs 3,370) and all stroke (4,016 vs 2,918) were higher in the Myval group. One of the reasons of this difference between the occurrence rate and the number of wins is that time to event was considered in this win ratio analysis. For other events, the results between occurrence rates and win ratios were consistent.

There were 80,235 ties, accounting for 55% of the total patient pairs. The win ratio analysis provides the most precise estimate of the overall effect when ties are minimal or absent; however, a large proportion of ties can lead to an overestimation of the treatment effect in win ratio calculation.[15,16] To gain further insight, we calculated the win difference and win odds. While the win ratio is a measure of relative effect, the win difference represents the absolute effect. Additionally, the win odds account for the number of ties. The win difference was 2.52%, indicating a small absolute effect difference between the two groups. The win odds was 1.05, which is smaller than the win ratio of 1.12 and closer to 1. These results suggest that the treatment effect difference between the two groups is small.

There are several limitations of this post-hoc exploratory sub-analysis. First, since the win ratio measures the probability of winning, the statistical analysis may have a challenge to be applied in the context of non-inferiority study. Although the win ratio approach can be adapted to non-inferiority test, there is no established method to define non-inferiority margin and samples size. Second, each event, except all-cause death and new PPI, included a broad spectrum of severity; for example, all stroke included both disabling and non-disabling strokes. If the definitions of these events had been more specific, the ranking would have resulted in different outcomes. Third, the surveys to establish the ranking of events were completed after the primary analysis of the LANDMARK trial, which might have influenced the ranking process and potentially introduced hindsight bias, although the ranking was based on clinical experiences of ten physicians involved in this survey.[17] Fourth, to establish a ranking which was broadly accepted, we asked ten cardiologists using the Delphi method, however, the rankings may have been different if the survey had included different experts and/or a greater number. Nevertheless, the rankings obtained were reasonable. Fifth, the follow-up duration of 30 days was relatively short, and the win ratio provides relatively small incremental value to address repeated events.

CONCLUSIONS

The win ratio analysis of the primary composite endpoint of the LANDMARK trial numerically favored the Myval THV series compared with the contemporary THV series but was not statistically significant. These results corroborate the original analysis of the primary composite endpoint reporting the non-inferiority of the Myval THV series compared to the contemporary THV series.

Patient consent statement

Written informed consent was obtained from all the study participants before sharing the screening documents to check their eligibility for the trial.

Declaration of competing interest

Niels van Royen reports research grants from Abbot, Philips, Medtronic and Biotronik. Niels van Royen reports speaker fees from RainMed, Microport, Bayer and Abbot. Ignacio J Amat-Santos reports consulting fees from Medtronic, Abbott, Boston Scientific, Meril Life Sciences and Products & Features. Matjaz Bunc reports lecture fees from Meril Life Sciences, Edwards Lifesciences and Medtronic. Matjaz Bunc is a president of the working group for interventional cardiology, cardiology society of Slovenia. Alexander Ijsselmuiden reports institutional fees from Medtronic and Abbott, and consulting fees from Meril Life Sciences, Cardiawave, Angiocare, Abbott, Philips, Svelte and Pulsecath. Angela McInerney reports a consulting fee from Medtronic, and payment or honoraria for lectures from Medtronic, Abbot Vascular, Shockwave medical and Boston Scientific. Scot Garg reports consulting fees from Biosensors. Udita Chandra and Ashokkumar Thakkar are employees of Meril Life Sciences. Osama Soliman reports an institutional research grant from Meril Life Sciences. Andreas Baumbach reports consulting fees from Faraday Pharma, PiCardia and Meril Life Sciences. Andreas Baumbach is a member of data safety monitoring board of PiCardia. Patrick W Serruys reports consultancy fees from SMT, Novartis, Meril Life Sciences, Xeltis, and Philips. All other authors declare no competing interests.

CRediT authorship contribution statement

Akihiro Tobe: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Niels van Royen:** Writing – review & editing, Investigation. **Ignacio J. Amat-Santos:** Writing – review & editing, Investigation. **Martin Hudec:** Writing – review & editing, Investigation. **Matjaz Bunc:** Writing – review & editing, Investigation. **Alexander Ijsselmuiden:** Writing – review & editing, Investigation. **Jose Luis Pomar:** Writing – review & editing, Investigation. **Liesbeth Rosseel:** Writing – review & editing, Investigation. **Amr Gamal:** Writing – review & editing, Investigation. **Javaid Iqbal:** Writing – review & editing, Investigation. **Alan Soo:** Writing – review & editing, Investigation. **Angela McInerney:** Writing – review & editing. **Scot Garg:** Writing – review & editing. **Udita Chandra:** Resources, Formal analysis, Data curation. **Ashokkumar Thakkar:** Resources, Formal analysis, Data curation. **Osama Soliman:** Writing – review & editing, Formal analysis. **Yoshinobu Onuma:** Writing – review & editing, Methodology, Conceptualization. **Andreas Baumbach:** Writing – review & editing. **Patrick W. Serruys:** Writing – review & editing, Project administration, Methodology, Conceptualization.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author after the final long-term follow-up is published.

Funding

LANDMARK trial is funded by Meril Life Sciences.

Ethics approval statement

The study was conducted in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use standards for clinical research.

Declaration of generative AI in scientific writing

We declare that no artificial intelligence (AI) tools were used in the drafting or writing of this manuscript.

Acknowledgement

We sincerely appreciate the efforts of all LANDMARK investigators and site staff for their contribution to the trial.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2025.04.024.

References

1. Baumbach A, van Royen N, Amat-Santos IJ, Hudec M, Bunc M, Ijsselmuiden A, et al. LANDMARK comparison of early outcomes of newer-generation Myval transcatheter heart valve series with contemporary valves (Sapien and Evolut) in real-world individuals with severe symptomatic native aortic stenosis: a randomised non-inferiority trial. Lancet 2024.
2. Varc-3 Writing C, Genereux P, Piazza N, Alu MC, Nazif T, Hahn RT, et al. Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical research. Eur Heart J 2021;42(19):1825–57.
3. Kawashima H, Soliman O, Wang R, Ono M, Hara H, Gao C, et al. Rationale and design of a randomized clinical trial comparing safety and efficacy of myval transcatheter heart valve versus contemporary transcatheter heart valves in patients with severe symptomatic aortic valve stenosis: the LANDMARK trial. Am Heart J 2021;232:23–38.
4. Tobe A, Onuma Y, Soliman O, Baumbach A, Serruys PW. LANDMARK trial: update in study protocol. Am Heart J 2024;270:162–3.
5. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J 2012;33(2):176–82.
6. Redfors B, Gregson J, Crowley A, McAndrew T, Ben-Yehuda O, Stone GW, et al. The win ratio approach for composite endpoints: practical guidance based on previous experience. Eur Heart J 2020;41(46):4391–9.
7. Hara H, van Klaveren D, Kogame N, Chichareon P, Modolo R, Tomaniak M, et al. Statistical methods for composite endpoints. EuroIntervention 2021;16(18):e1484–95.
8. Khodyakov D, Grant Sean, Kroger Jack, Bauman Melissa. RAND Methodological Guidance for Conducting and Critically Appraising Delphi Panels. Santa Monica, CA: RAND Corporation; 2023.
9. Bebu I, Lachin JM. Large sample inference for a win ratio analysis of a composite outcome based on prioritized components. Biostatistics 2016;17(1):178–87.
10. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 2019;380(18):1695–705.
11. Tavares CAM, Azevedo LCP, Rea-Neto A, Campos NS, Amendola CP, Kozesinski-Nakatani AC, et al. Dapagliflozin for critically ill patients with acute organ dysfunction: the DEFENDER randomized clinical trial. JAMA 2024.
12. Sato H, Sorajja P. Paravalvular regurgitation: an overview of indications for closure and management strategies. Curr Cardiol Rep 2022;24(5):577–86.
13. Liao YB, Deng XX, Meng Y, Zhao ZG, Xiong TY, Meng XJ, et al. Predictors and outcome of acute kidney injury after transcatheter aortic valve implantation: a systematic review and meta-analysis. EuroIntervention 2017;12(17):2067–74.
14. Szotek M, Druzbicki L, Sabatowski K, Amoroso GR, De Schouwer K, Matusik PT. Transcatheter aortic valve implantation and cardiac conduction abnormalities: prevalence, risk factors and management. J Clin Med 2023;12(18).
15. Ajufo E, Nayak A, Mehra MR. Fallacies of using the win ratio in cardiovascular trials: challenges and solutions. JACC Basic Transl Sci 2023;8(6):720–7.
16. Pocock SJ, Gregson J, Collier TJ, Ferreira JP, Stone GW. The win ratio in cardiology trials: lessons learnt, new developments, and wise future use. Eur Heart J 2024;45(44):4684–99.
17. Butler J, Stockbridge N, Packer M. Win ratio: A seductive but potentially misleading method for evaluating evidence from clinical trials. Circulation 2024;149(20):1546–8.