Win Ratio Analysis of 1-Year Outcomes in the LANDMARK Trial: Myval vs Contemporary THVs (Sapien or Evolut) in Patients with Symptomatic Severe Aortic Stenosis

Akihiro Tobe, MD

CORRIB Research Centre for Advanced Imaging and Core Laboratory, University of Galway, Galway, Ireland

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Disclosure of Relevant Financial Relationships

I, [Akihiro Tobe] DO NOT have any financial relationships to disclose.

Background

- *Myval* (Meril Life Sciences Pvt. Ltd., India) series is a novel balloon-expandable transcatheter heart valves (THV) system.
- The *LANDMARK Trial* is an RCT comparing the safety and effectiveness of the Myval THV series with the contemporary THV series (Sapien and Evolut) in patients with severe aortic stenosis.
- The Myval series demonstrated non-inferiority to the contemporary THVs for the 30-day primary composite endpoint.[1]
- One-year outcomes were comparable between the Myval and the contemporary THV series.[2]

1. Baumbach A. Lancet. 2024 Jun;403(10445):2695-2708. 2. Serruys PW et al. EuroPCR 2025

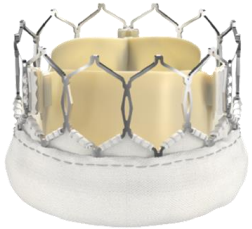
Purpose

- The primary analysis of the 1-year outcomes was performed using the conventional time-to-first event approach (Kaplan-Meier method).
- The purpose of this study is to apply a win ratio analysis to the 1-year composite endpoint, considering the event severity and recurrence.

Design of LANDMARK trial

Prospective, randomized, multicenter, open-label, non-inferiority trial

Patients with symptomatic severe native AS at 31 sites in Europe, Brazil and New Zealand



1:1 Randomization (N=768)

Myval THV Series (n=384)

Contemporary THV Series (Sapien:Evolut=1:1) (n=384)

30-day Primary Endpoint

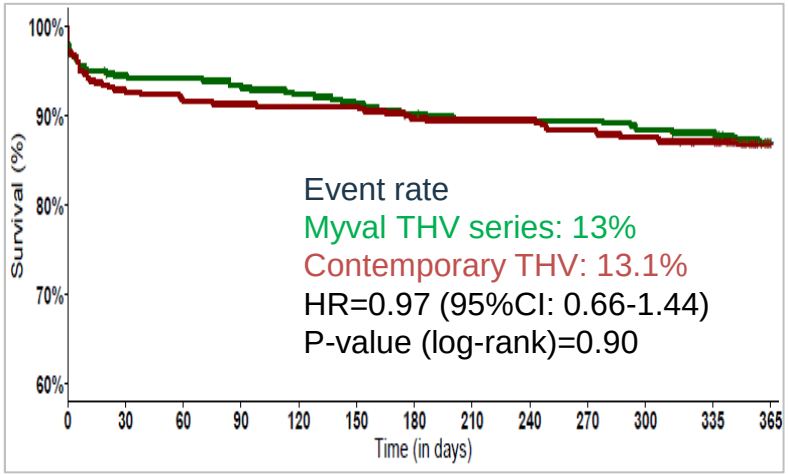
1-year Endpoint

Composite endpoint:
All-cause mortality, all stroke, or procedure/valve-related hospitalization

Extended composite endpoint:
All-cause mortality, all stroke, procedure/valve-related hospitalization, or QOL deterioration (≧2.5 points decrease of both physical and mental component of SF-12)

Primary result of 1-year outcomes

Composite endpoint:
All-cause death, all stroke, or procedure/valve-related hospitalization

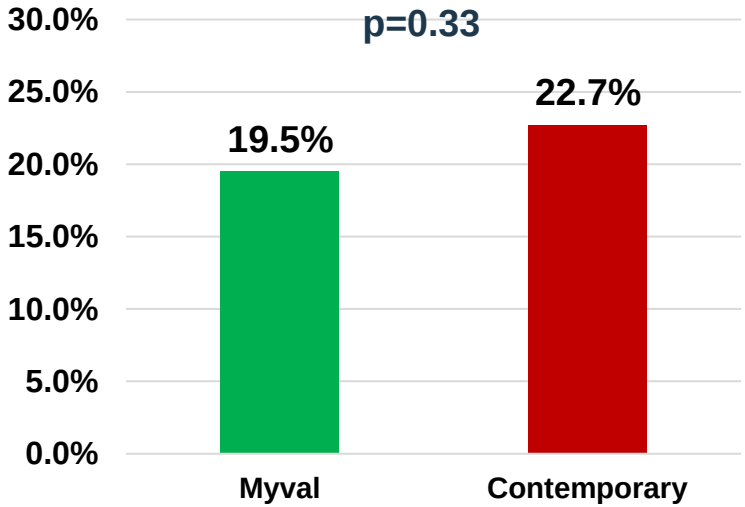


Events, n (%)	Myval THV Series (n= 384)	Contemporary THV series (n= 384)	P value
Composite endpoint, n (%)	49 (13.0)	50 (13.1)	1.00
All-cause mortality, n (%)	27 (7.2)	27 (7.1)	1.00
All stroke, n (%)	21 (5.7)	13 (3.4)	0.22
Fatal stroke, n (%)	5 (1.3)	2 (0.5)	0.45
Disabling Stroke*, n (%)	11 (3.0)	4 (1.1)	0.12
Non-disabling Stroke*, n (%)	5 (1.3)	7 (1.9)	0.77
Procedure/valve-related hospitalization, n (%)	16 (4.3)	20 (5.4)	0.61

**** Stroke with disability: modified Rankin Scale (mRS) of ≥2 at 90 days and increase of ≥1 from pre-stroke baseline. Stroke without disability: mRS of 0 or 1 at 90 days or no increase in mRS category from pre-stroke baseline.***

Primary result of 1-year outcomes

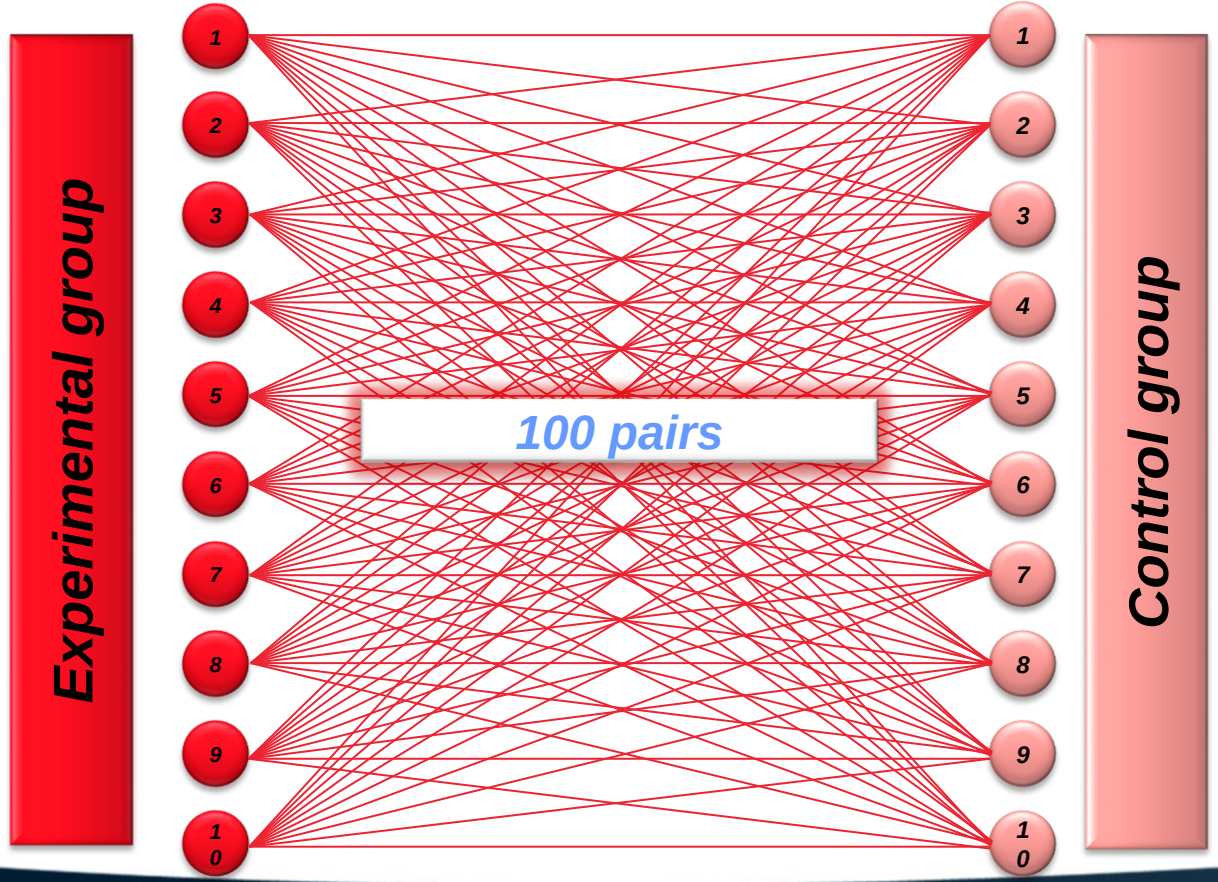
Extended composite endpoint:
All-cause death, all stroke, procedure/valve-related hospitalization, or QOL deterioration



Events, n (%)	Myval THV Series (n= 384)	Contemporary THV series (n= 384)	P value
Extended composite endpoint	75 (19.5)	87 (22.7)	0.33
All-cause mortality, n (%)	27 (7.2)	27 (7.1)	1.00
All stroke, n (%)	21 (5.7)	13 (3.4)	0.22
Fatal stroke, n (%)	5 (1.3)	2 (0.5)	0.45
Disabling Stroke, n (%)	11 (3.0)	4 (1.1)	0.12
Non-disabling Stroke, n (%)	5 (1.3)	7 (1.9)	0.77
Procedure or valve-related hospitalization, n (%)	16 (4.3)	20 (5.4)	0.61
QOL deterioration*	29 (8.8) (n=329)	38 (11.4) (n=333)	0.33

** Decrease of ≧2.5 points of both physical and mental domains of SF-12*

Methods: Win ratio

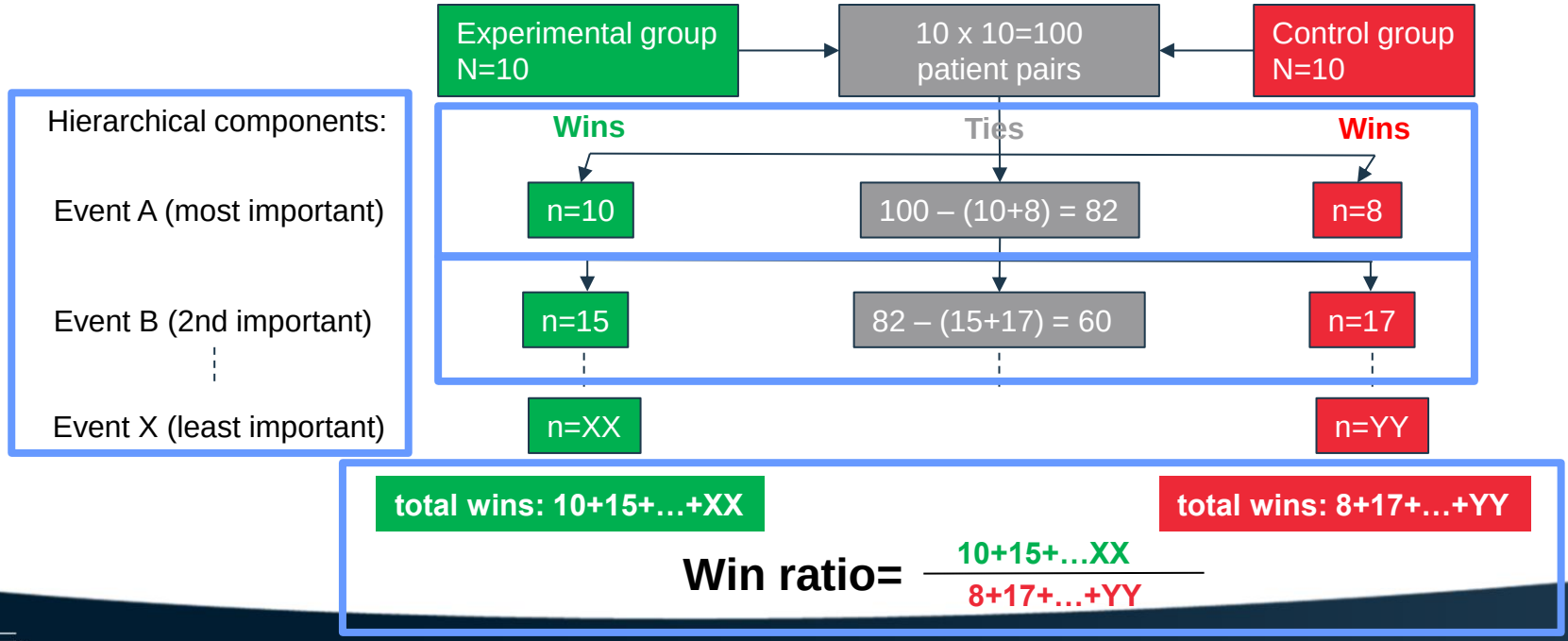


* Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. Stat Med. 1999 Jun 15;18(11):1341-54.

Methods: Win ratio

- The win ratio analysis take the event severity and recurrence into account.

Example



Methods: Win ratio

- Win ratio analysis was performed for the 1-year composite and extended composite endpoint.
- All stroke was divided into disabling and non-disabling stroke.
- The hierarchy of the events were determined by Delphi method consisting 10 cardiologists
- Death and stroke were analysed by time-to-first-event (later = winner), and hospitalization by the total number of events (fewer = winner).

composite endpoint

1. All-cause mortality
2. Disabling stroke
3. Non-disabling stroke

→ time-to-first event

4. Procedure/valve hospitalization → total number of events

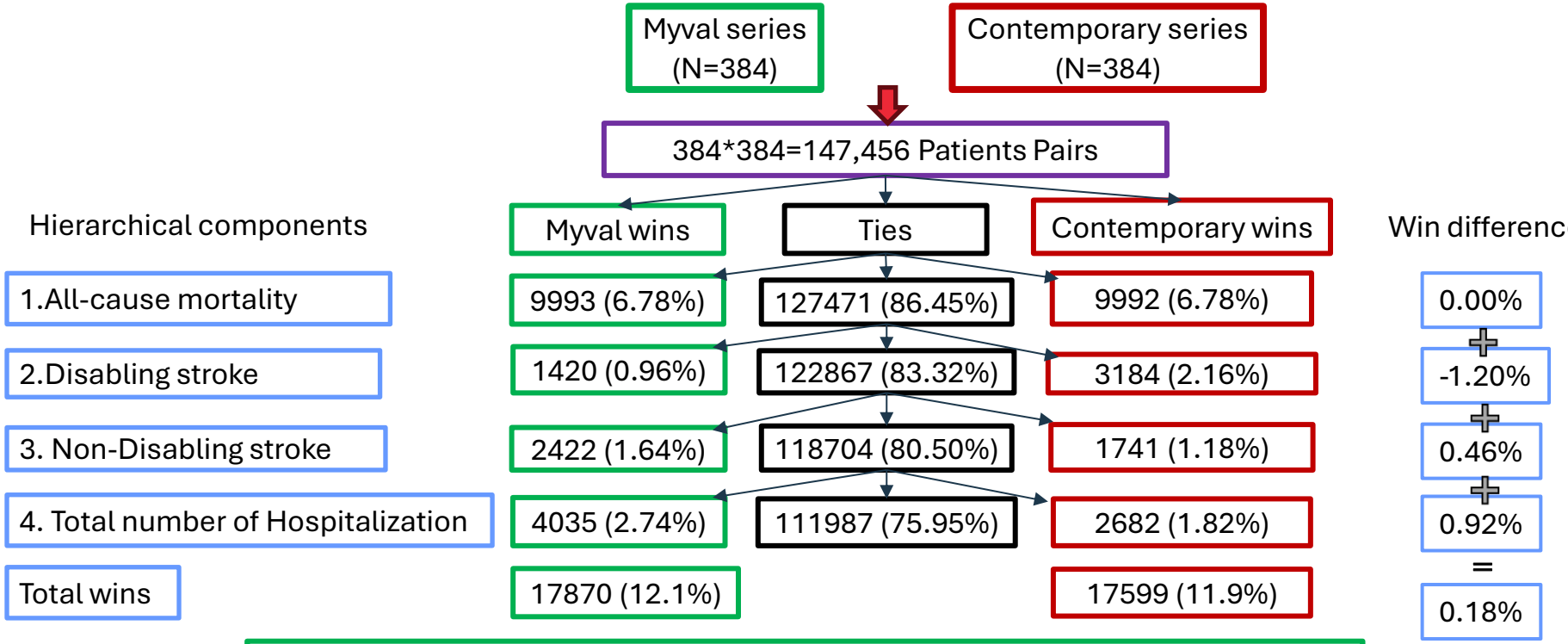
extended composite endpoint

1. All-cause mortality
2. Disabling stroke
3. Non-disabling stroke

→ time-to-first event

4. Procedure/valve hospitalization → total number of events
5. ≧2.5 points decrease in SF-12 → absence of presence

Results: composite endpoint

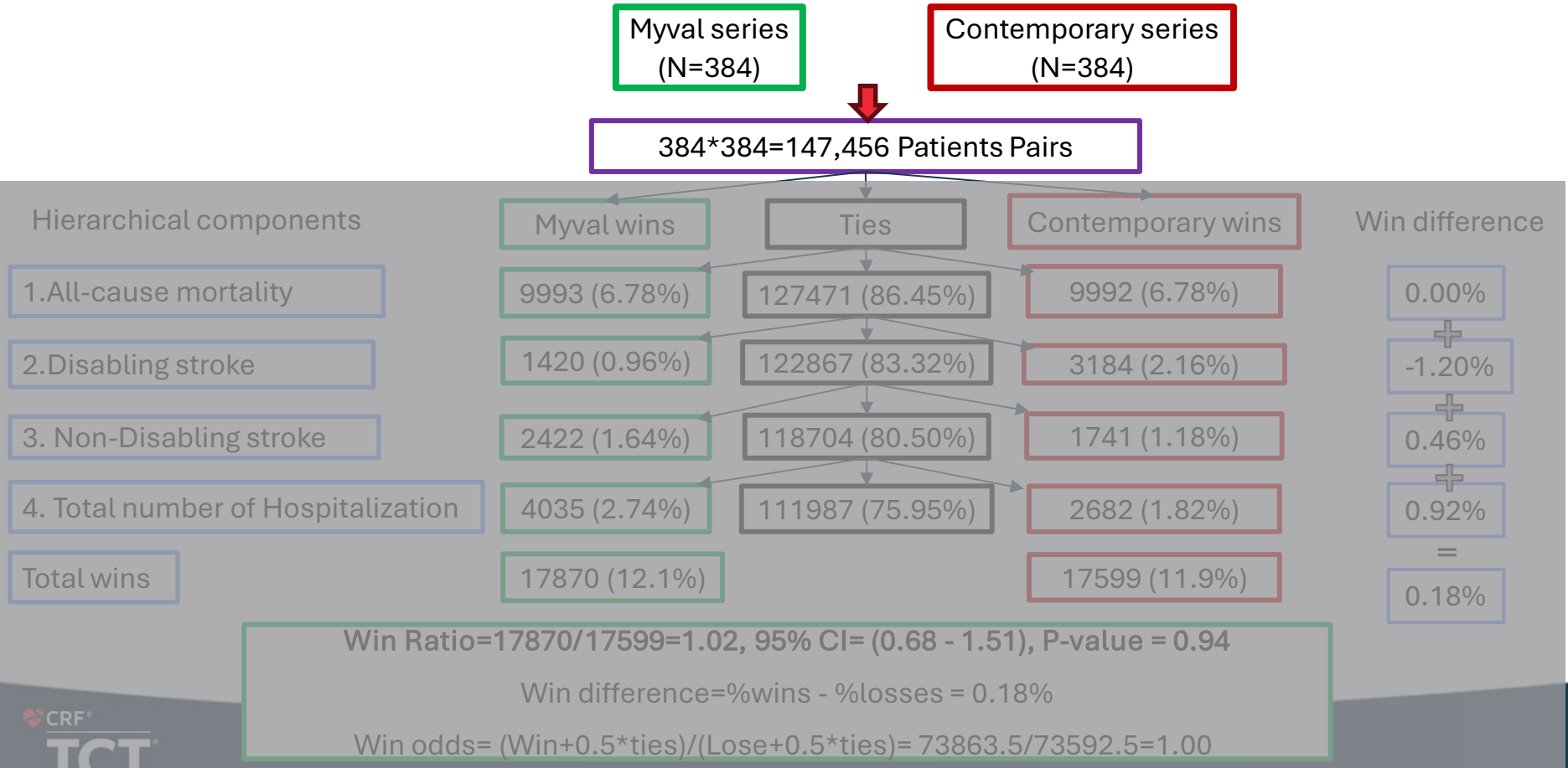


Win Ratio=17870/17599=1.02, 95% CI= (0.68 - 1.51), P-value = 0.94

Win difference=%wins - %losses = 0.18%

Win odds= (Win+0.5*ties)/(Lose+0.5*ties)= 73863.5/73592.5=1.00

Results: composite endpoint



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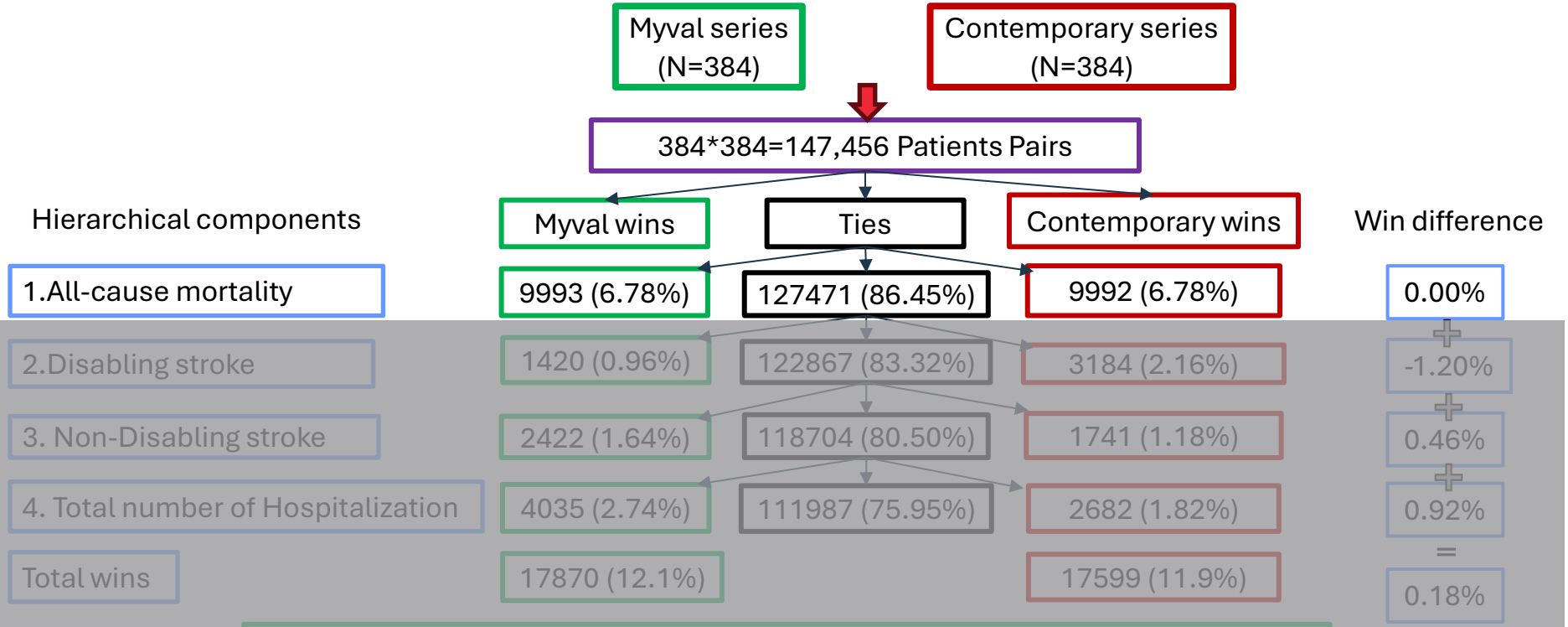

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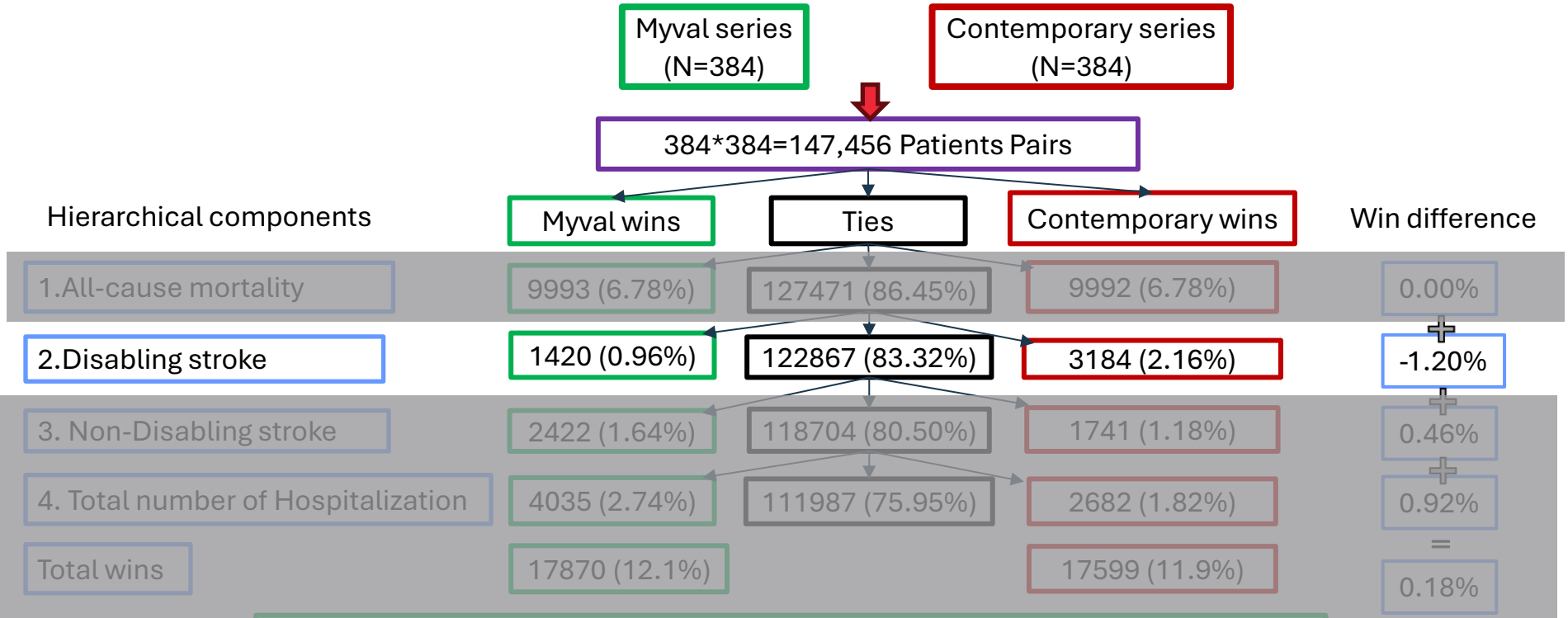

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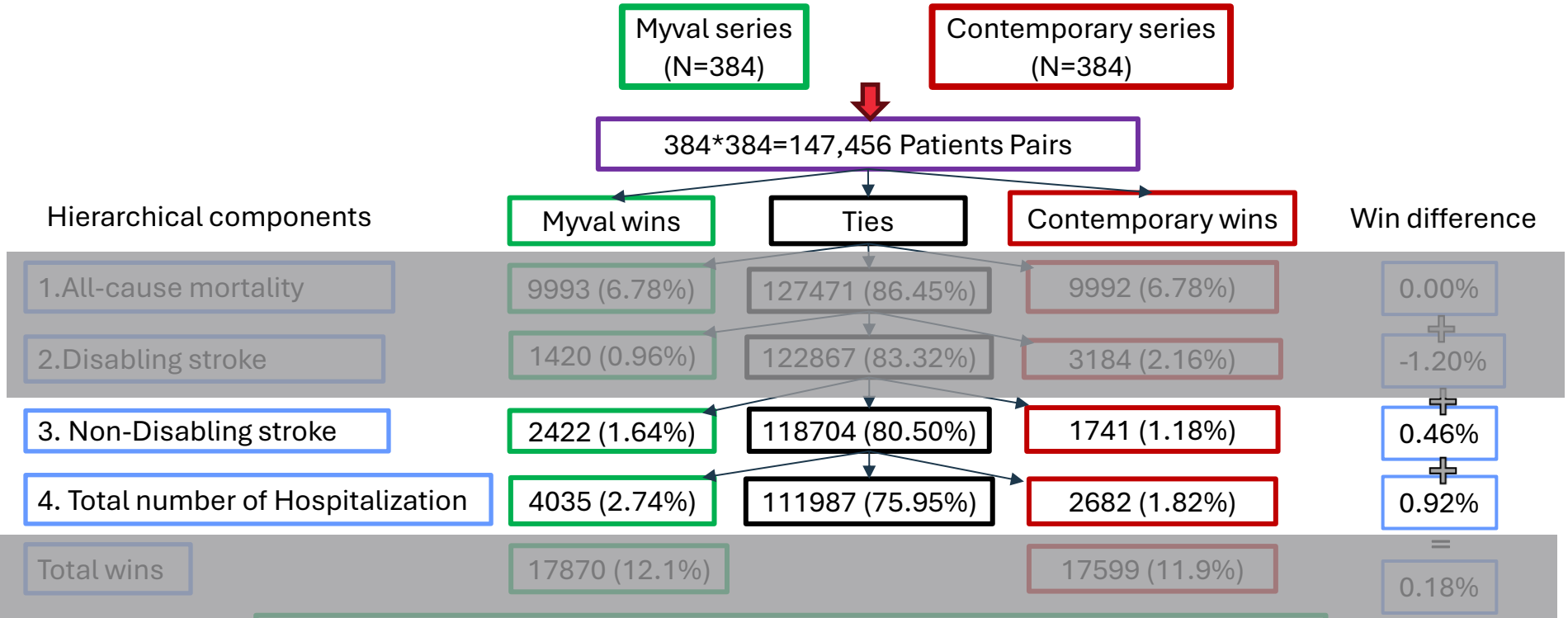

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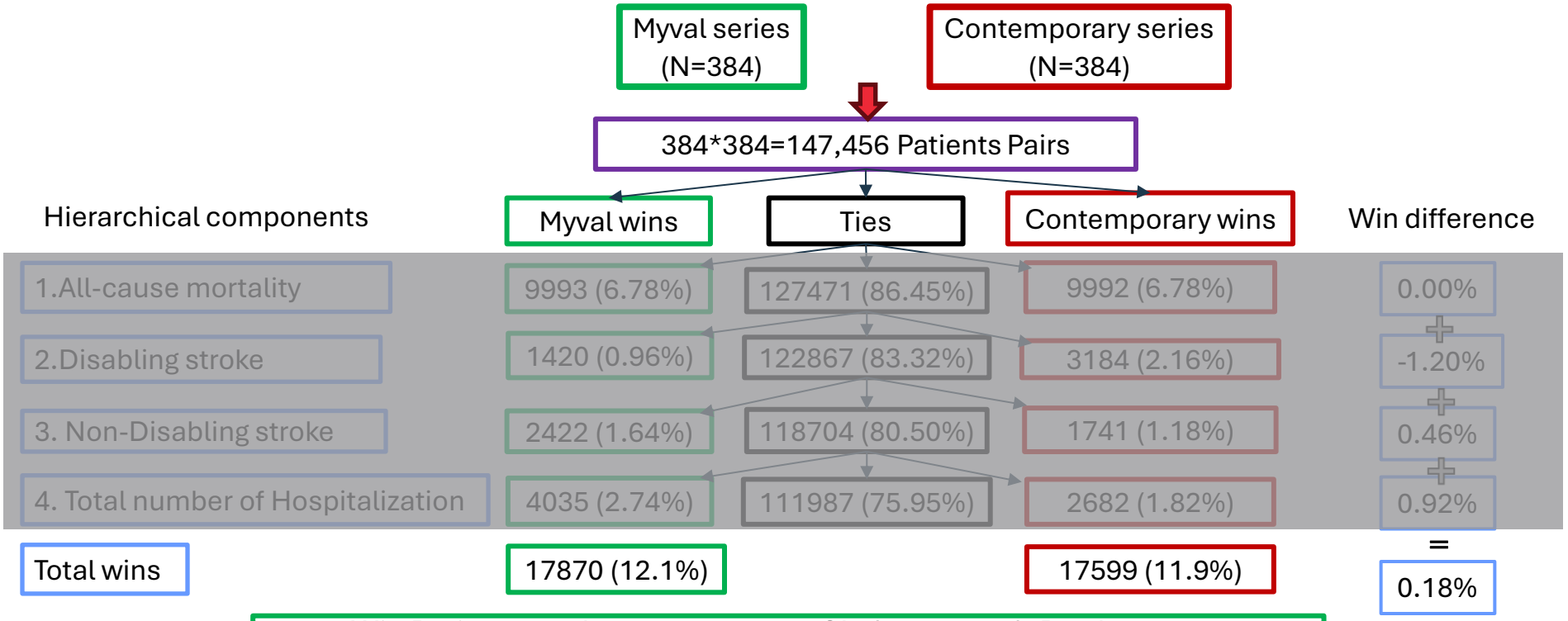
Results: composite endpoint



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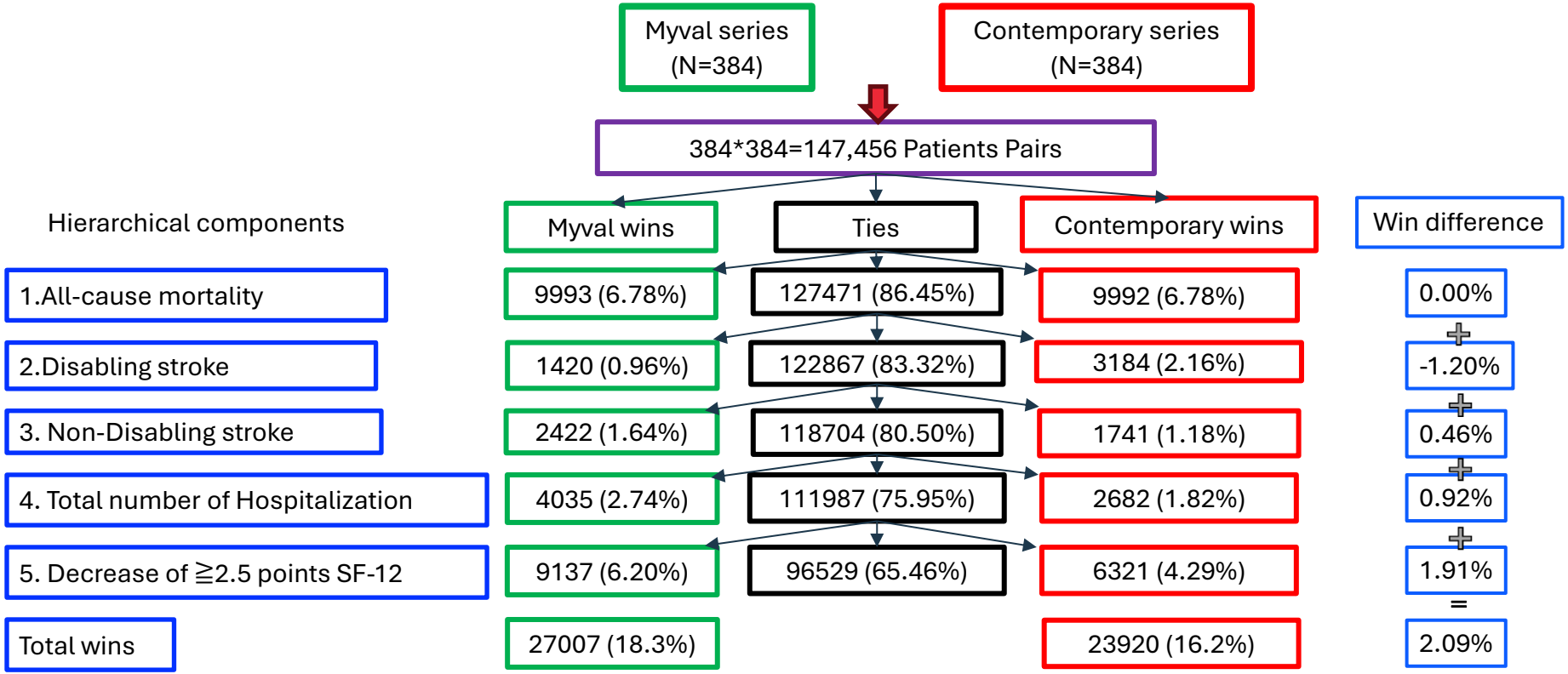
Results: extended composite endpoint

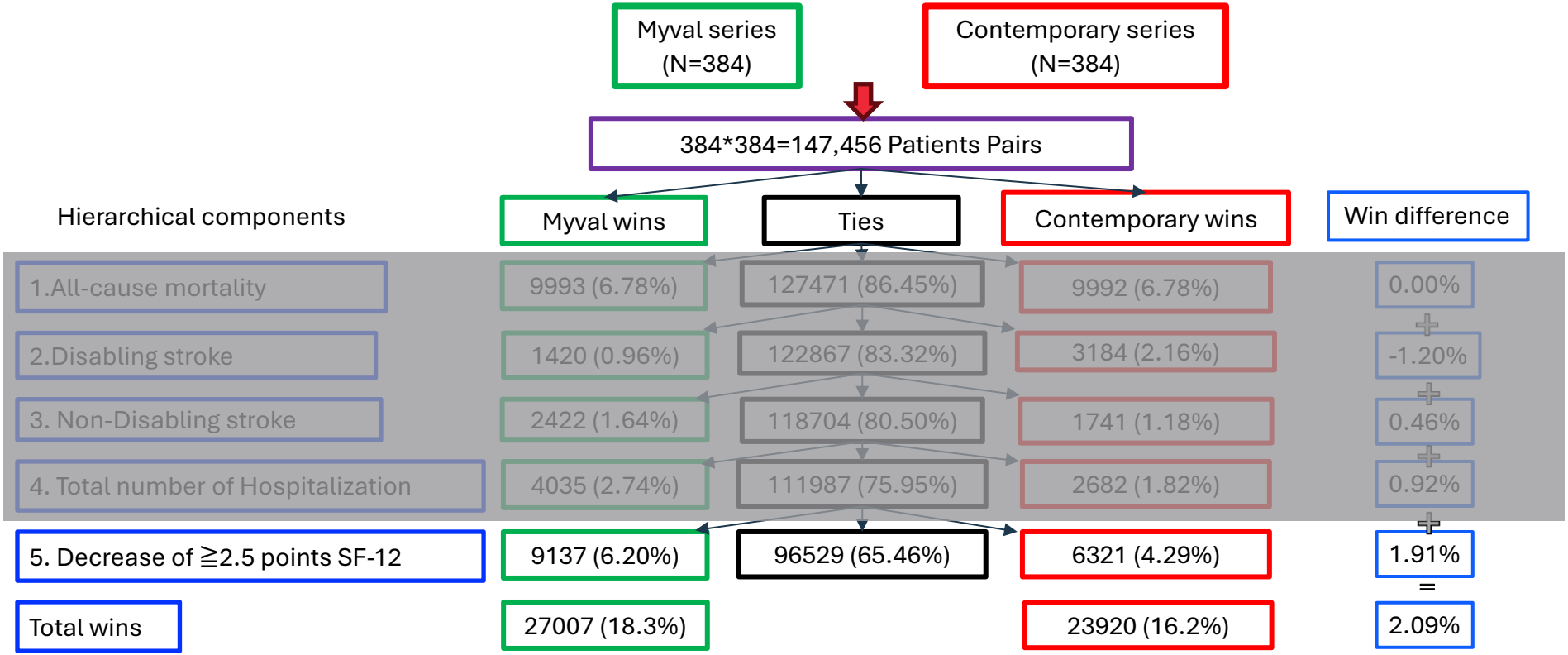


Win Ratio=27007/23920=1.13, 95% CI= (0.82 - 1.55), P-value = 0.45

Win difference=%wins - %losses = 2.09%

Win odds= (Win+0.5*ties)/(Lose+0.5*ties)= 75271.5/72184.5=1.04

Results: extended composite endpoint



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Win difference=%wins - %losses = 2.09%

Win odds= (Win+0.5*ties)/(Lose+0.5*ties)= 75271.5/72184.5=1.04

Discussion

- Composite endpoints are used in clinical trials and time-to-first event analysis is frequently used, however, one of their shortcomings is that they treat all events equally, irrespective of severity.
- The win ratio considers the severity and recurrence of the components of the composite endpoint.

Conclusion

- The win ratio between the Myval THV series and the contemporary THV series numerically favored Myval series but was not statistically significant, which did not contradict the primary analysis of the 1-year composite endpoint.