s47F

From: s47F
Sent: Monday, 20 February 2023 8:01 AM
To: PL Reviews
Subject: RE: Proposed scope: PLAC Meeting #34 –15 December 2022 - TAVI review [SEC=OFFICIAL:Sensitive]

Thanks for progressing this s47F
I have written to s47F seeking additional background in terms of CAG minutes and details of previous applications. I'll chase this up.
I wonder whether we should also include the application that was considered at the Dec PLAC.
I can speak to s47E re utilisation data if you like – I agree this would be useful.
I can raise at Leaders meeting today – s47C.
Best Regards
s47F

From: s47E(d)
Sent: Friday, 17 February 2023 10:42 AM
To: s47F
Cc: s47F
Subject: Proposed scope: PLAC Meeting #34 –15 December 2022 - TAVI review [SEC=OFFICIAL:Sensitive]

Hi s47F

Thanks for forwarding me through the minutes from PLAC.

Based on the PLAC recommendation, I propose this review be focused HTA – comparative clinical effectiveness and cost effectiveness of TAVIs currently listed on the PL.
Prior to undertaking the assessment/review, I believe utilisation data analysis should also be considered as this will give us some insights on usage and any trends (from my research I note that patient population and risk category are critical factors for TAVI surgery) to inform HTA.

Once we agree on the approach I will start drafting the scope, identify stakeholders and prepare for comms to go out.
There are 5 devices (with benefit of $22,932) on the Nov 22 PL s47C, s47G

s47C, s47G

Let me know of your views. I'm happy to have a chat with the s47C to find out more.

Thanks
s47F

From: s47F @Health.gov.au>
Sent: Tuesday, 14 February 2023 11:38 AM
To: s47E(d) @Health.gov.au>
Subject: FW: PLAC Meeting #34 –15 December 2022 - TAVI review [SEC=OFFICIAL:Sensitive]

FYI – please use this to scope proposed PL review.

Cheers

s47F
, Prostheses List Reform Taskforce

Technology Assessment & Access Division | Health Resourcing Group
Australian Government Department of Health
T: 02 6289 s47F | E: s47F @health.gov.au
M: s47F
Location: Sirius Building s47F
GPO Box 9848, Canberra ACT 2601, Australia

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders past and present.

From: s47F
Sent: Thursday, 9 February 2023 11:44 AM
To: s47F @health.gov.au>
Subject: RE: PLAC Meeting #34 –15 December 2022 - TAVI review [SEC=OFFICIAL:Sensitive]

Thank you s47F – this is very helpful.

Cheers

s47F
, Prostheses List Reform Taskforce

Technology Assessment & Access Division | Health Resourcing Group
Australian Government Department of Health
T: 02 6289 s47F | E: s47F @health.gov.au
M: s47F
Location: Sirius Building s47F
GPO Box 9848, Canberra ACT 2601, Australia

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders past and present.

Building a stronger, healthier country
Yesterday today and tomorrow

From: s47F [redacted]@health.gov.au>
Sent: Wednesday, 8 February 2023 11:28 AM
To: s47F [redacted]@Health.gov.au>
Subject: PLAC Meeting #34 –15 December 2022 - TAVI review [SEC=OFFICIAL:Sensitive]
Importance: High

s47F [redacted]

As discussed, see extract from the Minutes below.
Thanks

s38, s47C, s47E, s47G [redacted]

s47C [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

thanks

Any spelling mistakes are credit to the Dragon voice recognition program

s47F [redacted]
[redacted], Prostheses List Administration

Prostheses List Reform Taskforce | Technology Assessment and Access Division | Health Resourcing Group
Australian Government Department of Health and Aged Care
T: 02 6289 s47F | E: s47F @health.gov.au
Location Sirius Building, s47F

The Department of Health acknowledges the Traditional Custodians of Australia and their continued connection to land, sea and community. We pay our respects to all elders, past and present.

s47F [redacted]

From: s47F [redacted]
Sent: Tuesday, 7 March 2023 4:34 PM
To: s47F [redacted]; s47F [redacted]
Subject: Re: FOR REVIEW: Review Scope - Transcatheter Aortic Valve Implantation (TAVI) review [SEC=OFFICIAL]

Thank you s47F [redacted] - we have some more information from s47F [redacted] and s47F [redacted] that is important to bring into our planning but this is good to help us finalise.

s47F [redacted]

Sent from Workspace ONE Boxer

On 7 March 2023 at 16:00:18 AEDT, s47F [redacted]@health.gov.au> wrote:

Hi s47F [redacted] & s47F [redacted]

Please find here the link for the review scope D23-745216 for the TAVI review.
While I was researching on MSAC assessment for TAVI, I found out this factsheet on TAVI D17-2600584 that you might find useful.

Appreciate your comments/feedback on the scope.

Thanks
s47F [redacted]

[SEC=OFFICIAL]

s47F

From: s47F
Sent: Wednesday, 8 March 2023 12:02 PM
To: s47F
Cc: s47F
Subject: RE: PLAC minutes [SEC=OFFICIAL]

Hi s47F below is the TRIM link for the PLAC minutes.

D22-3759780

Cheers
s47F

From: s47F @health.gov.au>
Sent: Wednesday, 8 March 2023 11:44 AM
To: s47F @health.gov.au>
Cc: s47F @Health.gov.au>
Subject: PLAC minutes [SEC=OFFICIAL]

Hi s47F
I understand you have a copy of the PLAC minutes where the TAVI post listing review was recommended.
Can you please forward me a copy?
Thanks
s47F

s47F [redacted]

From: s47F [redacted]
Sent: Monday, 20 February 2023 4:10 PM
To: s47F [redacted]
Cc: s47F [redacted]; s47F [redacted]; s47F [redacted]; s47F [redacted]
Subject: RE: Tasks for PL AGILE Taskboard [SEC=OFFICIAL]

Hi s47F [redacted]

Thanks for the reminder.

s47C [redacted]

Any questions, please let me know.

Thanks & regards
s47F [redacted]

From: s47F [redacted] @Health.gov.au>
Sent: Monday, 20 February 2023 10:55 AM
To: s47F [redacted] @health.gov.au>; s47F [redacted] @health.gov.au>; s47F [redacted] @health.gov.au>; s47F [redacted] @health.gov.au>; s47F [redacted] @health.gov.au>
Cc: s47F [redacted] @Health.gov.au>; s47F [redacted] @Health.gov.au>; s47F [redacted] @Health.gov.au>
Subject: Tasks for PL AGILE Taskboard [SEC=OFFICIAL]

Hi all,

Just a friendly reminder to have a think of the individual tasks required in completing each milestone in the Project, for the next 4 weeks. If you already know of these tasks, please send them through to me and I can start to populate the Taskboard prior to our planning meeting this afternoon.

We will use the meeting this afternoon to populate the taskboard with each task.

Kind Regards,

s47F [redacted]

s47F [redacted] **to** s47F [redacted]

Prostheses List Reform Taskforce

Technology Assessment and Access Division
Australian Government Department of Health and Aged Care
T: 02 6289 s47F [redacted]
E: s47F [redacted] @health.gov.au
Location: Sirius Building s47F [redacted]
PO Box 9848, Canberra ACT 2601, Australia

The Department of Health and Aged Care acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present.

s47F

From: s47F
Sent: Thursday, 23 February 2023 3:33 PM
To: s47E(d)
Subject: RE: For Review - PLRT DWU 27 Feb -03 March 2023 [SEC=OFFICIAL]

Hi s47F

That's great! Thanks for being proactive.
I won't generally write any specific dates unless we have it agreed/confirmed/published, but rather I would include months.
Also please update the dates for reviews, as we just discussed now.

Thanks
s47F

From: s47E(d) @Health.gov.au>
Sent: Wednesday, 22 February 2023 3:13 PM
To: s47F @health.gov.au>
Cc: s47E(d) @Health.gov.au>
Subject: For Review - PLRT DWU 27 Feb -03 March 2023 [SEC=OFFICIAL]

Hi s47F

My updates in red below for your review please:

s47C

Kind Regards,

s47F

s47F **to** s47F

Prostheses List Reform Taskforce

Technology Assessment and Access Division
Australian Government Department of Health and Aged Care
T: 02 6289 s47F
E: s47F @health.gov.au
Location: Sirius Building s47F
PO Box 9848, Canberra ACT 2601, Australia

The Department of Health and Aged Care acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present.

From: s47E(d) @Health.gov.au>
Sent: Wednesday, 22 February 2023 12:06 PM
To: s47F @health.gov.au>; s47F @Health.gov.au>; s47F @health.gov.au>; s47F @health.gov.au>; s47F @health.gov.au>; s47F @health.gov.au>; s47F @Health.gov.au>; s47F @health.gov.au>; s47F @health.gov.au>; s47F @health.gov.au>; s47F @Health.gov.au>
Cc: s47E(d) @Health.gov.au>
Subject: Due COB Thur 23 Feb - PLRT DWU 27 Feb -03 March 2023 [SEC=OFFICIAL]

Hi all,

s47C

Kind Regards,

s47F

s47F **to** s47F

Prostheses List Reform Taskforce

Technology Assessment and Access Division
Australian Government Department of Health and Aged Care
T: 02 6289 s47F
E: s47F @health.gov.au
Location: Sirius Building s47F

PO Box 9848, Canberra ACT 2601, Australia

The Department of Health and Aged Care acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present.

s47F

From: s47F
Sent: Friday, 24 February 2023 12:36 PM
To: s47F ; s47F
Cc: s47F ; s47F ; s47F
Subject: RE: Proposed scope: PLAC Meeting #34 –15 December 2022 - TAVI review [SEC=OFFICIAL:Sensitive]

Hi s47F
Thank you for providing this table so promptly.
As discussed, the main extra information we need is prioduct level data (ie data by billing ocde) going back to 2017-18, when these devices first appeared on PL.
I'll await your discussions re s47F re this.
Please contact me if I can assist further.
Best regards
s47F

From: s47F @Health.gov.au>
Sent: Friday, 24 February 2023 12:25 PM
To: s47F @health.gov.au>; s47F @health.gov.au>
Cc: s47F @health.gov.au>; s47F @health.gov.au>; s47F @health.gov.au>
Subject: RE: Proposed scope: PLAC Meeting #34 –15 December 2022 - TAVI review [SEC=OFFICIAL:Sensitive]

Good Afternoon s47F

Please find attached the file containing completed data request cleared by our EL1.
Please note Transcatheter Aortic Valve Implants are predominantly used once per separation. Table and chart not provided due to suppression rules.

Let me know if you have any questions.

Kind Regards,
s47F

P.S. At this stage I have not been able to provide data at Billing code level and instead provided aggregate figures for Transcatheter Aortic Valve Implants (TAVI) in the base table
as I will need further consultation from s47F once he comes back next week.

s47F
Data Analyst – Geospatial and Hospital Analytics Section
Data & Analytics

Health Economics & Research Division | Strategy, Evidence and Research Group
Australian Government Department of Health and Aged Care
E: s47F @health.gov.au

From: s47F @health.gov.au>
Sent: Monday, 20 February 2023 10:23 AM
To: s47F @Health.gov.au>; s47F @health.gov.au>
Cc: s47F @health.gov.au>; s47F @health.gov.au>
Subject: RE: Proposed scope: PLAC Meeting #34 –15 December 2022 - TAVI review [SEC=OFFICIAL:Sensitive]

Thanks for our discussion just now [redacted]
As discussed, just an overview of total numbers and benefit amounts by product, with totals, for the preceding 10 FYs to give us an idea of trend for this device type.
Then when you're able, a more granular look at the most recent completed FY under the range of available categories (ie PMBS, ICD code etc).
Please let me know if you require any further assistance.
Best Regards
[redacted]

From: [redacted]@Health.gov.au>
Sent: Monday, 20 February 2023 9:52 AM
To: [redacted]@health.gov.au>; [redacted]@health.gov.au>
Cc: [redacted]@health.gov.au>; [redacted]@health.gov.au>
Subject: RE: Proposed scope: PLAC Meeting #34 –15 December 2022 - TAVI review [SEC=OFFICIAL:Sensitive]

Too easy [redacted] I was trying to confirm the level of detail you wanted . It seems I sent the follow up mail at the same time I received the response from you.

From: [redacted]@health.gov.au>
Sent: Monday, 20 February 2023 9:49 AM
To: [redacted]@Health.gov.au>; [redacted]@health.gov.au>
Cc: [redacted]@health.gov.au>; [redacted]@health.gov.au>
Subject: RE: Proposed scope: PLAC Meeting #34 –15 December 2022 - TAVI review [SEC=OFFICIAL:Sensitive]

Thanks [redacted]
If its not too much trouble, could you do 10 years data? My understanding is that there are only 5 items on the list.
Cheers
[redacted]

From: [redacted]@Health.gov.au>
Sent: Monday, 20 February 2023 9:29 AM
To: [redacted]@health.gov.au>; [redacted]@health.gov.au>
Cc: [redacted]@health.gov.au>; [redacted]@health.gov.au>
Subject: RE: Proposed scope: PLAC Meeting #34 –15 December 2022 - TAVI review [SEC=OFFICIAL:Sensitive]

Good Morning [redacted]

Yes, I can progress this data for you. Are there any time constraints that I should be working on as I aim to send it to you before the end of this week. Also how many years' worth of data would you need?

Looking forward for your response.

Kind Regards,
[redacted]

From: [redacted]@health.gov.au>
Sent: Monday, 20 February 2023 8:06 AM
To: [redacted]@health.gov.au>; [redacted]@Health.gov.au>
Cc: [redacted]@health.gov.au>
Subject: FW: Proposed scope: PLAC Meeting #34 –15 December 2022 - TAVI review [SEC=OFFICIAL:Sensitive]

Hi [redacted] and [redacted]
We need some PL utilisation data around Transcatheter Aortic Valve Implants (TAVIs) for a review (see below).
[redacted] is this something you can progress or is it best to wait until [redacted] gets back?

Best Regards
s47F

s47F

Medical Adviser

Technology Assessment and Access Division
Health Resourcing Group
Australian Government Department of Health
T: 03 9665 s47F | E: s47F @health.gov.au
Location: s47F
GPO Box 9848 MDP 122, Melbourne VIC 3001, Australia

The Department of Health acknowledges the Traditional Custodians of Australia and their continued connection to land, sea and community. We pay our respects to all Elders past and present.

From: s47E(d) @Health.gov.au>
Sent: Friday, 17 February 2023 10:42 AM
To: s47F @Health.gov.au>
Cc: s47F @health.gov.au>
Subject: Proposed scope: PLAC Meeting #34 –15 December 2022 - TAVI review [SEC=OFFICIAL:Sensitive]

Hi s47F

Thanks for forwarding me through the minutes from PLAC.

Based on the PLAC recommendation, I propose this review be focused HTA – comparative clinical effectiveness and cost effectiveness of TAVIs currently listed on the PL.
Prior to undertaking the assessment/review, I believe utilisation data analysis should also be considered as this will give us some insights on usage and any trends (from my research I note that patient population and risk category are critical factors for TAVI surgery) to inform HTA.

Once we agree on the approach I will start drafting the scope, identify stakeholders and prepare for comms to go out.
There are 5 devices (with benefit of $22,932) on the Nov 22 PL s47C, s47G

Let me know of your views. s47C

Thanks

s47F

From: s47F @Health.gov.au>
Sent: Tuesday, 14 February 2023 11:38 AM
To: s47E(d) @Health.gov.au>
Subject: FW: PLAC Meeting #34 –15 December 2022 - TAVI review [SEC=OFFICIAL:Sensitive]

FYI – please use this to scope proposed PL review.

Cheers

s47F
, Prostheses List Reform Taskforce

Technology Assessment & Access Division | Health Resourcing Group
Australian Government Department of Health
T: 02 6289 s47F | E: s47F @health.gov.au
M: s47F
Location: Sirius Building s47F
GPO Box 9848, Canberra ACT 2601, Australia

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders past and present.

From: s47F
Sent: Thursday, 9 February 2023 11:44 AM
To: s47F @health.gov.au>
Subject: RE: PLAC Meeting #34 –15 December 2022 - TAVI review [SEC=OFFICIAL:Sensitive]

Thank you s47F – this is very helpful.

Cheers

s47F
, Prostheses List Reform Taskforce

Technology Assessment & Access Division | Health Resourcing Group
Australian Government Department of Health
T: 02 6289 s47F | E: s47F @health.gov.au
M: s47F
Location: Sirius Building s47F
GPO Box 9848, Canberra ACT 2601, Australia

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders past and present.

Building a stronger, healthier country
Yesterday today and tomorrow

From: s47F [redacted]@health.gov.au>
Sent: Wednesday, 8 February 2023 11:28 AM
To: s47F [redacted]@Health.gov.au>
Subject: PLAC Meeting #34 –15 December 2022 - TAVI review [SEC=OFFICIAL:Sensitive]
Importance: High

s47F [redacted]

As discussed, see extract from the Minutes below.
Thanks

s47C [redacted]

s47C

thanks

Any spelling mistakes are credit to the Dragon voice recognition program

s47F

, Prostheses List Administration

Prostheses List Reform Taskforce | Technology Assessment and Access Division | Health Resourcing Group
Australian Government Department of Health and Aged Care
T: 02 6289 s47F | E: s47F @health.gov.au
Location Sirius Building, s47F

The Department of Health acknowledges the Traditional Custodians of Australia and their continued connection to land, sea and community. We pay our respects to all elders, past and present.

s47F

From: s47F
Sent: Monday, 27 February 2023 12:28 PM
To: s47F
Subject: RE: FOR REVIEW: TAVI review - Initial letter to sponsors | Commencement of a review [SEC=OFFICIAL]

No worries s47F – thanks for letting me know.
Let me know if you would prefer to schedule a meeting to go through planning for this review so that we can discuss together? I 'd be able to answer your questions.

Kind regards
s47F

From: s47F @Health.gov.au>
Sent: Monday, 27 February 2023 12:24 PM
To: s47F @health.gov.au>
Subject: RE: FOR REVIEW: TAVI review - Initial letter to sponsors | Commencement of a review [SEC=OFFICIAL]

s47F – I will have a look, but I am not sure we have done all the planning we need in order to actually know what we are doing and why?

I may just need a little time to get up to speed – I haven't even read the PLAC Paper on this one yet.

Cheers

s47F
, Prostheses List Reform Taskforce

Technology Assessment & Access Division | Health Resourcing Group
Australian Government Department of Health
T: 02 6289 s47F | E: s47F @health.gov.au
M: s47F
Location: Sirius Building s47F
GPO Box 9848, Canberra ACT 2601, Australia

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders past and present.

From: s47F @health.gov.au>
Sent: Monday, 27 February 2023 12:13 PM
To: s47F @Health.gov.au>
Subject: FOR REVIEW: TAVI review - Initial letter to sponsors | Commencement of a review [SEC=OFFICIAL]

Hi s47F

Please find here the link for the initial email draft D23-638811 for TAVI review sponsors advising them of the commencement of the review and how they can participate in the review, etc.

Let me know of your thoughts.

We can send this out ASAP/by this week – *we will also need to update our webpage ASAP to reflect the current status of the reviews*.

Thanks
s47F

s47F [redacted]

From: s47F [redacted]
Sent: Wednesday, 1 March 2023 9:23 AM
To: s47F [redacted]; s47F [redacted]; s47F [redacted]
Cc: s47F [redacted]
Subject: RE: TAVI information [SEC=OFFICIAL]

Thanks for the reminder.
Sounds like Thursday is best.

From: s47F [redacted] @health.gov.au>
Sent: Wednesday, 1 March 2023 9:21 AM
To: s47F [redacted] @health.gov.au>; s47F [redacted] @Health.gov.au>; s47F [redacted] @health.gov.au>
Cc: s47F [redacted] @health.gov.au>
Subject: RE: TAVI information [SEC=OFFICIAL]

Hi s47F [redacted]

A majority of the reform team will be at Mental Health First Aid training today 9.30-3

From: s47F [redacted] @health.gov.au>
Sent: Wednesday, 1 March 2023 8:52 AM
To: s47F [redacted] @Health.gov.au>; s47F [redacted] @health.gov.au>
Cc: s47F [redacted] @health.gov.au>; s47F [redacted] @health.gov.au>
Subject: RE: TAVI information [SEC=OFFICIAL]

Thanks s47F [redacted]
Later today or tomorrow suits me, though please not after 4 today, I'm coaching the kids cricket.
Cheers
s47F [redacted]

From: s47F [redacted] @Health.gov.au>
Sent: Tuesday, 28 February 2023 5:15 PM
To: s47F [redacted] @health.gov.au>; s47F [redacted] @health.gov.au>
Cc: s47F [redacted] @health.gov.au>; s47F [redacted] @health.gov.au>
Subject: RE: TAVI information [SEC=OFFICIAL]

s47F [redacted] and s47F [redacted]

s47F [redacted] and I are pulling together our plan to conduct the Post Listing Review about TAVI's following advice from PLAC.

We want to make sure we develop our approach to this review with the 'outcome' in mind i.e. what information does the review need to provide to enable us to resolve the outstanding s47G [redacted].

s47F [redacted] is looking to book a quick ½ hour meeting with yourselves this week or if not possible, next week.

This will help us determine the type of review and the scope, before we notify sponsors and commence work with the reviewer.

Appreciate your availability.

Cheers

[redacted], Prostheses List Reform Taskforce

Technology Assessment & Access Division | Health Resourcing Group
Australian Government Department of Health
T: 02 6289[redacted] | E: [redacted]@health.gov.au
M: [redacted]
Location: Sirius Building [redacted]
GPO Box 9848, Canberra ACT 2601, Australia

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders past and present.

From: [redacted]@health.gov.au>
Sent: Tuesday, 20 December 2022 4:18 PM
To: [redacted]@health.gov.au>
Cc: [redacted]@health.gov.au>; [redacted]@Health.gov.au>
Subject: TAVI information [SEC=OFFICIAL]

Hi [redacted]
The post listing review team began discussing the TAVI review yesterday.
This seems to be focused mainly on the appropriateness of the listing of the [redacted] device, though will likely require consideration of the evidence for all listed devices and may have some broader policy implications for the device type.
Would it be possible to have copies of the relevant sections of minutes recording CAG discussion, and the PLAC recommendation to conduct a review. This will help us frame the TAVI review.
Will it be possible to look at the evidence provided for the initial PL applications for each of the TAVIs?
Best Regards
[redacted]

[redacted]

Medical Adviser

Technology Assessment and Access Division

Health Resourcing Group
Australian Government Department of Health
T: 03 9665[redacted] | E: [redacted]@health.gov.au
Location: [redacted]
GPO Box 9848 MDP 122, Melbourne VIC 3001, Australia

The Department of Health acknowledges the Traditional Custodians of Australia and their continued connection to land, sea and community. We pay our respects to all Elders past and present.

Agenda Paper

Prostheses List Reform Project Board

Meeting number: 9

Date of Meeting: 15 March 2023

Agenda Item No: 9

Led by: s47F [redacted], Prostheses List Reform Taskforce

Prostheses List Post-listing Reviews and Post-listing Review Framework

Recommendation

That Board members:

- **Note** the progress on Prostheses List (PL) Post-listing Reviews
- **Note** the update on the post-listing review framework and the review system

Purpose

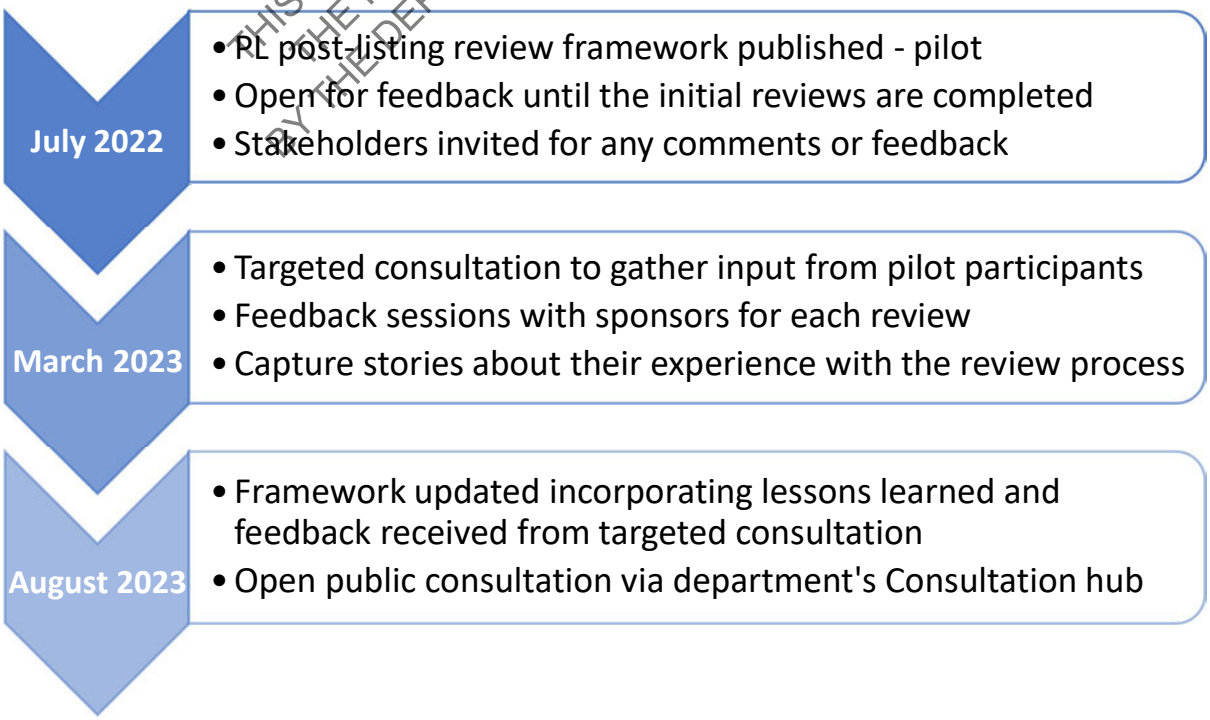
To provide members with an update on the Post-listing reviews, the Review framework and the Review system.

Background

Since the last update provided to the Project Board on 1 February 2023 (Meeting 8), there has been gradual progress on each of the post-listing reviews and the pilot of the framework that will continue to inform the future activities of establishing the review program.

Post-listing review framework

Planning has commenced to undertake the formal consultation on the post-listing review framework. The chart below depicts the activities for a staggered approach to this consultation:



Consultation on the review framework - timelines

Post-listing review system

Objective: To improve post-listing scrutiny to safeguard the PL and maintaining the integrity of the PL program.

As part of the PL Reforms, the Department is developing and implementing a post-listing review system to provide a more systematic approach. This system is being developed consistent with the capabilities of the Pharmaceutical Benefits Scheme (i.e. Post Market Reviews) and the Drug Utilisation Sub-Committee (DUSC). These existing frameworks are well regarded and considered effective. Adding the PL program to these capabilities will ensure there is a consistent approach across all HTA based programs.

The post-listing reviews are essential for the Department to monitor and assess that PL requirements are being complied with by industry participants that sponsor the devices listed on the PL and that the settings continue to be effective in meeting the policy outcomes.

Several guidance documents are being developed as part of establishing the system:

- Post-listing review – Allocation of tasks
- Post-listing reviews - Guidance for stakeholders
- Guidelines - Developing a Terms of Reference for a Review
- Prostheses List Post-listing Review Process Checklist

Post-listing reviews

On 12 May 2022, the Prostheses List Advisory Committee (PLAC) supported post-listing reviews for the following device types:

- Surgical guides and biomodels
- Metal-backed patella
- Spinal cord stimulators
- Urogynaecological mesh devices (mid-urethral slings).

The post-listing review of metal-backed patella has been completed. Key review findings and recommendations were considered by the PLAC with the delegate deciding to reduce the benefits of these devices to be consistent with all-polythene patella. The outcome was included in the March 2023 PL update.

Progress on each of the post-listing reviews:

	Surgical guides and biomodels	Spinal cord stimulators	Urogynaecological mesh (mid-urethral slings)	Transcatheter aortic valve implantation (TAVI)
Trigger	Concerns that these devices have been experiencing increased utilisation in a broader range of episodes of care than anticipated and whether or not they meet the current eligibility criteria for listing on the PL.	Concerns raised about the long-term safety and effectiveness of these devices	Concerns due to uncertainties about comparative clinical effectiveness and cost effectiveness of the existing PL benefit for these devices.	Concerns due to uncertainties about comparative clinical effectiveness and cost effectiveness of the existing PL benefit for these devices.
Reviewer	s47G [redacted]			**TBA**
Scope	Full post-listing review (including health technology assessment (HTA)) – to determine if these devices meet the eligibility criteria for listing on the PL – review of current utilisation, evidence base for the comparative clinical effectiveness and their role in clinical practice.	Focussed HTA considering the comparative clinical effectiveness and cost effectiveness	Focussed HTA considering the comparative clinical effectiveness and cost effectiveness (cost-minimisation analysis)	**TBA**
Progress to date	s47G [redacted] provided the final report on 3 March 2023. Currently reviewing the report to determine policy position based on the review findings and recommendations. Sponsors will be notified of the implementation of the findings.	Submissions to provide input to the review, closed on 10 March 2023. A draft report from s47G [redacted] is due in late March 2023.	Submissions to provide input to the review, closed on 28 February 2023. A draft report from s47G [redacted] is due in mid-April 2023.	**TBA**

s47C, s47F, s47G

s47C, s47F, s47G

s47C, s47F, s47G

s47C

Australian Government
Department of Health and Aged Care

Prostheses List Advisory Committee

Meeting #34

Thursday 15 December 2022

Videoconference

Attendees

Chair

Emeritus Professor Terry Campbell AM

Expert members

Professor Allan Glanville, Thoracic Medicine

Professor Bill Heddle, Cardiology

Associate Professor David Morgan OAM, Orthopaedic Surgery

Dr Orso Osti, Spinal Surgery

Professor Anne Simmons, Biomechanical Engineering

Associate Professor Rosemary Korda, Epidemiology

Dr Henry Ko, Health Consumer

Invited Attendees

s47F [redacted]

Department of Health

s47F [redacted]

Apologies

s47F [redacted]

s47F [redacted]

Departmental support

s47E(d) [redacted]

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s38, s47C, s47E, s47G

s47C, s47F, s47G

s47C, s47F, s47G

s47C, s47F, s47G

s47C, s47F, s47G

s38

s38

s38

s38

s38

s38

s38, s47G

s38

s38

s38, s47G

s47F [redacted]

From: s47F [redacted]
Sent: Wednesday, 22 March 2023 1:58 PM
To: s47F [redacted]
Subject: FW: Discussion re TAVIs [SEC=OFFICIAL]

From: s47F [redacted]
Sent: Wednesday, 1 March 2023 1:40 PM
To: s47F [redacted]
Subject: RE: Discussion re TAVIs [SEC=OFFICIAL]

Thanks s47F [redacted] I'll read with interest. Can this be a key document for the Post Listing Review or do we need to await publication?
Thanks for today's discussion. One more question: just wanting to check we have covered all the peak clinical groups for us to contact? I'm thinking s47G [redacted] more broadly. Any comments/suggestions? I usually make contact with the peak clinical groups and provide context re the review around the same time they receive their correspondence from the department.
Regards
s47F [redacted]

From: s47F [redacted]
Sent: Wednesday, 1 March 2023 1:28 PM
To: s47F [redacted]
Subject: RE: Discussion re TAVIs [SEC=OFFICIAL]

Hi s47F [redacted]
This is the paper I mentioned when we spoke

Regards
s47F [redacted]

From: s47F [redacted]@health.gov.au>
Sent: Wednesday, March 1, 2023 10:59 AM
To: s47F [redacted]
Subject: RE: Discussion re TAVIs [SEC=OFFICIAL]

Thanks s47F [redacted] I'll call shortly.

From: s47F [redacted]
Sent: Wednesday, 1 March 2023 10:47 AM
To: s47F [redacted]@health.gov.au>
Subject: RE: Discussion re TAVIs [SEC=OFFICIAL]

REMINDER: Think before you click! This email originated from outside our organisation. Only click links or open attachments if you recognise the sender and know the content is safe.

Sure s47F [redacted] I could talk now if you'd like (free till 12), or I have some times Thurs/Fri. What suits?

Regards
s47F

From: s47F @health.gov.au>
Sent: Wednesday, March 1, 2023 10:43 AM
To: s47F
Subject: Discussion re TAVIs [SEC=OFFICIAL]

Hi s47F
Hope you're well.
We're planning the post listing review of TAVIs.
Do you have time for a quick discussion re this?
s47F

s47F

Medical Adviser

Technology Assessment and Access Division
Health Resourcing Group
Australian Government Department of Health
T: 03 9665 s47F | E: s47F @health.gov.au
Location: s47F
GPO Box 9848 MDP 122, Melbourne VIC 3001, Australia

The Department of Health acknowledges the Traditional Custodians of Australia and their continued connection to land, sea and community. We pay our respects to all Elders past and present.

s47C

s47C

s47C

s47F

From: s47F
Sent: Monday, 6 March 2023 9:58 AM
To: s47F
Subject: RE: Focused HTAs [SEC=OFFICIAL:Sensitive]

Indeed – we are scoping out the TAVI PL Review so we were pretty sure it would suit a focussed HTA.

I will reach out to s47F to give her a scope of work.

Cheers

s47F
, Prostheses List Reform Taskforce

Technology Assessment & Access Division | Health Resourcing Group
Australian Government Department of Health
T: 02 6289 s47F | E: s47F @health.gov.au
M: s47F
Location: Sirius Building s47F
GPO Box 9848, Canberra ACT 2601, Australia

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders past and present.

From: s47F @health.gov.au>
Sent: Monday, 6 March 2023 9:49 AM
To: s47F @Health.gov.au>
Subject: FW: Focused HTAs [SEC=OFFICIAL:Sensitive]

s47F
Do you have some review for s47G to do?

thanks
Any spelling mistakes are credit to the Dragon voice recognition program

s47F
, Prostheses List Administration
Prostheses List Reform Taskforce
Location Sirius Building, s47F

From: s47F
Sent: Monday, 6 March 2023 8:33 AM

To: s47F [redacted] @health.gov.au>
Subject: Focused HTAs

REMINDER: Think before you click! This email originated from outside our organisation. Only click links or open attachments if you recognise the sender and know the content is safe.

Hi s47F [redacted]

Just to let you know, we have capacity at the moment for additional focused HTAs or other HTA work.

Kind regards,
s47F [redacted]

s47F [redacted]
M: s47F [redacted]
E: s47F [redacted]

s47F [redacted]

s47G [redacted]

Work Plan – Post-listing Reviews

The purpose of this work plan is to provide administration support to the PL Reform Taskforce (PLRT) and Office of Health Technology Assessment & Policy Branch (OHTAP) by ensuring the tasks for a Review are completed in a timely manner. This work sheet will also serve as for tracking and reporting purposes.

Roles and responsibilities:

· Medical officer (MO): Drafts discussion paper for review topic/s and provides input on technical aspects

· Drug utilisation section (DUS): Preliminary / Utilisation review with the assistance of Data analyst

· Post-market review section (PMR): Comprehensive and detailed review engaging a research consultant and/or HTA

· Taskforce: Oversight of the progress of tasks/activities, responsible for producing timely deliverables and also providing Admin support, making & implementing policy decisions

The tasks and activities will align to the Project plan (D21-5860639).

Post-listing reviews:

1. Surgical guides and biomodels
2. Spinal cord stimulators
3. Metal backed patellae - Completed in February 2023
4. Urogynaecological (mid-urethral slings) meshes
5. Transcatheter Aortic Valve Implantation (TAVI)

Review process : Post-listing reviews will be guided by the Post-listing Review Framework (D22-1164408).

Post-listing Reviews - High Level Tracking

Post-Listing Review	Type	Undertaken by	Status	Scope	Start Date	Comments	Completion Date	TRIM Ref
Surgical guides and biomodels	A full Post-market review incl. HTA	s47E(d), s47G [redacted]	In progress	Eligibility assessment, Evidence/literature review incl. clinical effectiveness	01-Jun-22	Final report received on 6/03, currently developing dept.'s response based on s47G findings to determine policy actions		E22-232217
Spinal cord stimulators	Focused HTA		In progress	Comparative clinical and cost effectiveness	01-Sep-22	Stakeholder submissions received on 10/03, s47G will provide a draft report on 14/04		E22-232214
Urogynaecological (mid-urethral slings) meshes	Focused HTA		In progress	Comparative clinical evidence and an economic analysis	01-Oct-22	Stakeholder submissions received on 28/02, s47G will provide a draft report on 14/04		E22-232220
Metal backed patella	Internal review		Completed	Comparative clinical effectiveness and cost effectiveness	01-Aug-22	Outcome: Benefits reduced & implemented in the March 2023 PL Update	01-Mar-23	E22-231865
Surgical guides and biomodels	Utilisation review		Completed	Utilisation data analysis	01-Mar-22	Completed	01-May-22	D22-1742616
Spinal cord stimulators	Utilisation review		Completed	Utilisation data analysis		Completed	01-May-22	D22-1742627

Journal Pre-proof

Three-Year Outcomes after Transcatheter or Surgical Aortic Valve Replacement in Low-Risk Patients with Aortic Stenosis

John K. Forrest, MD, G. Michael Deeb, MD, Steven J. Yakubov, MD, Hemal Gada, MD, Mubashir A. Mumtaz, MD, Basel Ramlawi, MD, Tanvir Bajwa, MD, Paul S. Teirstein, MD, Michael DeFrain, MD, Murali Muppala, MD, Bruce J. Rutkin, MD, Atul Chawla, MD, Bart Jenson, MD, Stanley J. Chetcuti, MD, Robert C. Stoler, MD, Marie-France Poulin, MD, Kamal Khabbaz, MD, Melissa Levack, MD, Kashish Goel, MD, Didier Tchétché, MD, Ka Yan Lam, MD, Pim A.L. Tonino, MD, Saki Ito, MD, Jae K. Oh, MD, Jian Huang, MD, MSc, Jeffrey J. Popma, MD, Neal Kleiman, MD, Michael J. Reardon, MD, for the Low Risk Trial Investigators

PII: S0735-1097(23)00411-4

DOI: https://doi.org/10.1016/j.jacc.2023.02.017

Reference: JAC 30025

To appear in: *Journal of the American College of Cardiology*

Received Date: 20 January 2023

Revised Date: 14 February 2023

Accepted Date: 15 February 2023

Please cite this article as: Forrest JK, Deeb GM, Yakubov SJ, Gada H, Mumtaz MA, Ramlawi B, Bajwa T, Teirstein PS, DeFrain M, Muppala M, Rutkin BJ, Chawla A, Jenson B, Chetcuti SJ, Stoler RC, Poulin M-F, Khabbaz K, Levack M, Goel K, Tchétché D, Lam KY, Tonino PAL, Ito S, Oh JK, Huang J, Popma JJ, Kleiman N, Reardon MJ, for the Low Risk Trial Investigators, Three-Year Outcomes after Transcatheter or Surgical Aortic Valve Replacement in Low-Risk Patients with Aortic Stenosis, *Journal of the American College of Cardiology* (2023), doi: https://doi.org/10.1016/j.jacc.2023.02.017.

Three-Year Outcomes after Transcatheter or Surgical Aortic Valve Replacement in Low-Risk Patients with Aortic Stenosis

Running title: Low-Risk TAVR vs Surgery at 3 Years

John K. Forrest MD[a], G. Michael Deeb MD[b], Steven J. Yakubov MD[c], Hemal Gada MD[d], Mubashir A. Mumtaz MD[d], Basel Ramlawi MD[e], Tanvir Bajwa MD[f], Paul S. Teirstein MD[g], Michael DeFrain MD[h], Murali Muppala MD[h], Bruce J. Rutkin MD[i], Atul Chawla MD[j], Bart Jenson MD[j], Stanley J. Chetcuti MD[b], Robert C. Stoler MD[k], Marie-France Poulin MD[l], Kamal Khabbaz MD[l], Melissa Levack MD[m], Kashish Goel MD[m], Didier Tchétché MD[n], Ka Yan Lam MD[o], Pim A. L. Tonino MD[o], Saki Ito MD[p], Jae K. Oh MD[p], Jian Huang MD, MSc[q], Jeffrey J. Popma MD[q], Neal Kleiman MD[r], Michael J. Reardon MD[r], for the Low Risk Trial Investigators*

*A complete list of Low Risk Trial Investigators are listed in the Supplementary Appendix.

[a]Yale University School of Medicine, New Haven, CT; [b]University of Michigan Health Systems Ok – University Hospital, Ann Arbor, MI; [c]OhioHealth Riverside Methodist Hospital, Columbus, OH; [d]University of Pittsburgh Medical Center, Harrisburg, PA; [e]Lankenau Heart Institute, Philadelphia, PA; [f]Aurora St Luke's Medical Center, Milwaukee, WI; [g]Scripps Clinic, La Jolla, CA; [h]HealthPark Medical Center, Fort Myers, FL; [i]North Shore University Hospital, Manhasset, NY; [j]Mercy Medical Center, Iowa Heart, Des Moines, IA; [k]Baylor Heart and Vascular Hospital, Dallas, TX; [l]Beth Israel Deaconess Medical Center, Boston, MA; [m]Vanderbilt University Medical Center, Nashville, TN; [n]Clinique Pasteur, Toulouse, France; [o]Catharina

Ziekenhuis, Eindhoven, Netherlands; [p]Echocardiography Core Laboratory, Mayo Clinic, Rochester, MN; [q]Medtronic, Mounds View, MN; [r]Methodist DeBakey Heart and Vascular Center, Houston, TX

Funding: Medtronic (Minneapolis, MN)

Disclosures: Dr Forrest has received grant support/research contracts and consultant fees/honoria/speakers bureau fees from Edwards Lifesciences and Medtronic. Dr Deeb serves on an advisory board for Medtronic and has received institutional grant support from Boston Scientific, Edwards LifeSciences, and Medtronic and has received fees as a proctor for Medtronic-sponsored SMART Trial. Dr Yakubov receives grants and personal fees from Medtronic and Boston Scientific. Dr Gada has received personal fees from Medtronic, Abbott Vascular, Becton Dickenson, and Boston Scientific. Dr Mumtaz serves as a consultant to and receives honoraria and research grants from Edwards Lifesciences, the Japanese Organization for Medical Device Development, Medtronic, and Z-Medical. Dr Ramlawi reports grants, personal fees and nonfinancial support from Medtronic, Liva Nova, and AtriCure. Dr Bajwa reports fees for consulting and proctoring from Medtronic. Dr Teirstein receives research grant and honoraria from Abbott, Boston Scientific, Cordis, and Medtronic; and serves on an advisory board for Boston Scientific and Medtronic. Dr DeFrain has nothing to disclose. Dr Muppala has nothing to disclose. Dr Rutkin serves as a consultant to and receives speaking honoraria from Edwards Lifescience and Medtronic. Dr Chawla serves as a proctor for Medtronic. Dr Jenson has nothing to disclose. Dr Chetcuti has received grants from Edwards Lifesciences, WL Gore Medical, Medtronic, and Boston Scientific as well as personal fees from Medtronic, Boston Scientific, and Jena. Dr Stoler serves as a consultant and to and receives honoraria from Biotronik Inc, Boston

Scientific Corporation, Edwards Lifesciences and Medtronic. Dr Poulin has nothing to disclose. Dr Khabbaz has nothing to disclose. Dr Levack reports personal fees from Medtronic. Dr Goel reports personal fees from Edwards Lifesciences and Abbott, and is consultant for Medtronic. Dr Tchétché receives honoraria or consultation fees from Abbott, Boston Scientific, Edwards Lifesciences, and Medtronic. Dr Lam has nothing to disclose. Dr Tonino has nothing to disclose. Dr Ito has nothing to disclose. Dr Oh receives grants from Medtronic Echo Core and personal fees from Medtronic Consulting. Dr Huang is a full-time employee and shareholder for Medtronic. Dr Popma is a full-time employee and shareholder for Medtronic. Dr Kleiman has received research grants from Medtronic, Abbott, Edwards Lifesciences, and Boston Scientific. Dr Reardon has received research grants from Abbott, Boston Scientific,WL Gore Medical, and Medtronic.

Correspondence: John K. Forrest MD, Yale University School of Medicine, 789 Howard Avenue, Dana 3-Cardiology Section, New Haven, Connecticut 06519, USA. Email: john.k.forrest@yale.edu.

Acknowledgment: Susan Chow, PhD, CMPP, an employee of Medtronic, drafted the Methods and created figures and tables for the preparation of this manuscript under the direction of the lead author.

ABSTRACT

Background: Randomized data comparing outcomes of transcatheter aortic valve replacement (TAVR) to surgery in low surgical risk patients at time points beyond 2 years is limited. This presents an unknown for physicians striving to educate patients as part of a shared decision-making process.

Objective: We evaluated 3-year clinical and echocardiographic outcomes from the Evolut Low Risk trial.

Methods: Low-risk patients were randomized to TAVR with a self-expanding, supra-annular valve or surgery. The primary endpoint of all-cause mortality or disabling stroke and several secondary endpoints were assessed at 3 years.

Results: There were 1414 attempted implants (730 TAVR; 684 surgery). Patients had a mean age of 74 years and 35% were women. At 3 years, the primary endpoint occurred in 7.4% of TAVR patients and 10.4% of surgery patients (HR, 0.70; 95% CI, 0.49–1.00; p=0.051). The difference between treatment arms for all-cause mortality or disabling stroke remained broadly consistent over time: -1.8% at year 1; -2.0% at year 2; -2.9% at year 3. The incidence of mild paravalvular regurgitation (20.3% TAVR vs. 2.5% surgery) and pacemaker placement (23.2% TAVR vs. 9.1% surgery; p<0.001) were lower in the surgery group. Rates of moderate or greater paravalvular regurgitation for both groups were <1% and not significantly different. Patients who underwent TAVR had significantly improved valve hemodynamics (mean gradient 9.1mmHg TAVR vs. 12.1mmHg surgery; p<0.001) at 3 years.

Conclusions: Within the Evolut Low Risk study, TAVR at 3 years showed durable benefits compared to surgery with respect to all-cause mortality or disabling stroke.

CONDENSED ABSTRACT: Three-year outcomes were assessed following TAVR with a self-expanding valve or surgery in patients from the Evolut Low Risk trial. There were 1414 attempted implants (730 TAVR; 684 surgery). At 3 years, the primary endpoint of all-cause mortality or disabling stroke was 7.4% with TAVR and 10.4% with surgery (HR, 0.70; 95% CI, 0.49–1.00; p=0.051); the difference between treatment arms remained broadly consistent over time: -1.8% year 1; -2.0% year 2; -2.9% year 3. Within the Evolut Low Risk study, TAVR at 3 years showed durable benefits compared to surgery with respect to all-cause mortality or disabling stroke.

KEY WORDS: TAVR, SAVR, aortic stenosis, low risk, self-expanding

ABBREVIATIONS

CEC = Clinical Events Committee

KCCQ = Kansas City Cardiomyopathy Questionnaire

TAVR = transcatheter aortic valve replacement

VARC-3 = Valve Academic Research Consortium 3

CLINICAL TRIAL: (ClinicalTrials.gov number, NCT02701283).

INTRODUCTION

For patients with severe symptomatic aortic stenosis undergoing valve replacement, transcatheter aortic valve replacement (TAVR) has become the dominant therapy, surpassing surgical aortic valve replacement in procedural volume across the US.[1] Much of the data supporting TAVR comes from patients at increased risk for surgery,[2-7] and while recent data in low-risk patient populations has shown promising short-term (£2 year) outcomes,[8-11] there is a lack of intermediate and longer-term data for low-risk patients. Clear differences between TAVR and surgery have been demonstrated including recovery time,[4,9,10] paravalvular regurgitation,[2,4,5,7] hemodynamics,[10,12,13] ease of coronary access,[14] structural valve deterioration,[15] and need for new pacemaker.[10,12,13] The impact that these differences have on clinical outcomes for low-surgical risk individuals has not been evaluated beyond 2 years. This lack of data presents an unknown for physicians striving to fully educate patients as part of a shared decision-making process.[16,17]

The Evolut Low Risk trial randomized patients with severe aortic stenosis who had an indication for aortic valve replacement and were low risk for surgery to either TAVR or surgery. All patients in the Evolut Low Risk trial have now completed 3-year follow-up, and we herein provide an analysis of 3-year clinical outcomes.

METHODS

Study Design

The Evolut Low Risk trial (NCT02701283) is a multinational, prospective, randomized study comparing the safety and effectiveness of TAVR with a self-expanding and supra-annular bioprosthesis to surgery in patients with severe aortic valve stenosis. The study is being conducted at 86 sites in Australia, Canada, France, Japan, Netherlands, New Zealand, and the

United States. Full details of the study design, trial oversight, and randomization procedure have been described previously.[8] The study protocol was approved by the Institutional Review Board at each site. The study was conducted in accordance with Good Clinical Practice principles and the Declaration of Helsinki.

Patients

Complete inclusion and exclusion criteria have been reported previously.[8] In brief, eligible patients had severe aortic valve stenosis with trileaflet aortic valve morphology and a low predicted risk of death (< 3%) from surgery as assessed by local multidisciplinary heart team. An independent Screening Committee confirmed patient eligibility and anatomic suitability for both TAVR and SAVR. All patients provided informed, written consent. Enrolled patients were randomized 1:1 to undergo TAVR with a self-expanding, supra-annular valve (CoreValve, Evolut R, or Evolut PRO; Medtronic) or surgery between March 2016 and May 2019. Surgical valve type was at the investigator discretion but mechanical valves were not permitted. Patients are being followed for 10 years.

Study Endpoints

The primary study endpoint of the Evolut Low Risk trial was a nonhierarchical composite of all-cause mortality or disabling stroke at 2 years in the intention-to-treat population using Bayesian adaptive statistic methods.[8] The prespecified endpoints reported in this analysis include 3-year incidences of all-cause mortality and disabling stroke as well as valve performance as determined by Doppler echocardiographic assessment, quality of life as assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ), New York Heart Association (NYHA) functional class, and 3-year safety events including new permanent pacemaker implantation, prosthetic valve endocarditis, prosthetic valve thrombosis, and aortic valve rehospitalization. Post hoc analyses at

3 years included the composite of all-cause mortality, disabling stroke, and aortic valve hospitalization; the severity of prosthesis-patient mismatch, using Valve Academic Research Consortium 3 (VARC-3) criteria;[18] and the impact of paravalvular regurgitation or permanent pacemaker implantation at 30 days on mid-term clinical outcomes. Stroke was defined and adjudicated as described previously.[8]

A Clinical Events Committee (CEC) adjudicated all endpoints. An Echocardiography Core Laboratory (Mayo Clinic, Rochester, MN) evaluated all echocardiograms, and core laboratory assessments were used for echocardiographic trial endpoints.

Statistical analysis

Safety events and quality of life outcomes were assessed in patients who underwent an attempted implant ("as-treated" cohort). Annual echocardiographic measurements were assessed in the implanted cohort. Continuous variables were reported as mean ± SD or median (Q1, Q3), and categorical variables were reported as frequencies and percentages. Adverse events were reported as Kaplan Meier estimates and compared between treatment arms by log-rank test and using hazard ratios and 95% confidence intervals (CIs). For the primary endpoint, the difference in Kaplan Meier rates between TAVR and surgery groups were reported at yearly intervals. For the primary endpoint and components, the proportional hazards assumption was checked using the Grambsch-Therneau test and all $p>0.05$ supporting this assumption was not violated. Rates of moderate or greater paravalvular regurgitation and moderate or greater prosthesis-patient mismatch are reported with risk difference (TAVR-surgery) and 95% CIs. The impact of permanent pacemaker implantation and paravalvular regurgitation on 3-year clinical outcomes were landmarked at 30 days post-procedure. A post-hoc subgroup analysis was performed using Cox proportional hazards regression models. No statistical technique was used to impute missing

data. No adjustments were made for multiplicity. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients

An aortic valve replacement was attempted in 1414 patients, of whom 730 underwent TAVR and 684 underwent surgery **(Supplemental Figure 1**). Between years one and three, 20 patients in the TAVR group exited the study (18 withdrew and 2 were lost to follow-up) and 28 patients in the surgery group exited the study (21 withdrew and 7 were lost to follow-up). As a result, at 3 years data were available for 704 patients (96.4%) in the TAVR group and 624 patients (91.2%) in the surgery group.

Baseline characteristics were broadly similar between treatment groups (**Table 1)**. At the time of treatment, mean age for all patients was 74 years, 35.3% were women, and the mean Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score was 2.0% in the TAVR group and 1.9% in the surgery group. The median (Q1, Q3) duration of follow-up is 48.4 (38.9, 52.3) months in the TAVR group and 48.1 (36.8, 50.6) months in the surgery group.

Clinical Outcomes

The primary endpoint of all-cause mortality or disabling stroke at 3 years was 7.4% in the TAVR group and 10.4% in the surgery group (hazard ratio, 0.70; 95% CI, 0.49 to 1.00; log-rank p=0.051) **(Table 2**). The difference in Kaplan Meier (KM) rates for the primary endpoint of all-cause mortality or disabling stroke for TAVR and surgery remained broadly consistent over time: -1.8% at year 1; -2.0% at year 2; -2.9% at year 3 **(Central Illustration**). At 3 years, all-cause mortality was 6.3% in the TAVR group and 8.3% in the surgery group (hazard ratio, 0.75; 95% CI, 0.51 to 1.17; p=0.16), and disabling stroke was 2.3% in the TAVR group and 3.4% in

the surgery group (hazard ratio, 0.65; 95% CI, 0.34 to 1.24; p=0.19; **Table 2 and Figure 1**). The composite endpoint of all-cause mortality, disabling stroke, or aortic valve rehospitalization was 13.2% in the TAVR group and 16.8% the surgery group (hazard ratio, 0.76; 95% CI, 0.58 to 1.00; p=0.050; **Figure 2**). No significant interactions in the treatment effect were observed for all-cause mortality or disabling stroke among various demographic groups **(Figure 3)**.

Rates of myocardial infarction at 3 years were low (3.4% TAVR vs 2.3% surgery, hazard ratio, 1.46; 95% CI, 0.76 to 2.78; p=0.25) **(Table 2**). Patients who underwent TAVR had a lower incidence of atrial fibrillation (13.1% vs. 40.0%, hazard ratio, 0.27; 95% CI, 0.22 to 0.35; p<0.001), while new permanent pacemaker implantation was higher in the TAVR group (23.2% vs 9.1%, hazard ratio, 2.81; 95% CI, 2.08 to 3.79; p<0.001). In an analysis of all-cause mortality landmarked at 30 days, 3-year data demonstrated that patients who had prior pacemaker had the highest mortality (17.5%), followed by patients who received a new pacemaker within 30 days of TAVR (9.8%), followed by patients without a new pacemaker at 30 days (4.6%). **(Supplemental Results and Supplemental Table 2**).

Rates of aortic valve reintervention were similar between the two groups (1.0% TAVR vs. 0.9% surgery, hazard ratio, 1.06; 95% CI, 0.36 to 3.15; p=0.92) **(Table 2).** Clinical (0.3% TAVR vs. 0.2% surgery; p=0.61) and subclinical (0.4% TAVR vs. 0.5% surgery; p=0.91) valve thrombosis rates were very low in both groups **(Table 2).** Between 30 days and 3 years, a total of 9 patients had a CEC-adjudicated repeat aortic valve replacement (4 in patients who received a TAVR index procedure and 5 in surgical patients). Among the TAVR patients, all 4 reinterventions consisted of surgical aortic valve replacement – 3 due to leaflet tears in patients who had a 34mm Evolut R valve and 1 due to endocarditis. Among the 5 surgical patients, 4 underwent redo surgical aortic valve replacement (3 due to endocarditis and 1 due to valve

thrombosis), and 1 patient underwent valve-in-valve TAVR (TAV-in-SAV) due to stenosis of the surgical valve (**Supplemental Table S3).**

Echocardiographic Findings

At 3 years, patients in the TAVR group had consistently significantly lower aortic valve mean gradients (9.1mmHg TAVR vs. 12.1mmHg surgery; difference, -3.0; 95% CI, -3.6 to -2.4; p<0.001) and larger effective orifice areas (2.2 cm^2 TAVR vs. 2.0 cm^2 surgery; difference, 0.2; 95% CI, 0.2 to 0.3; p<0.001) (**Figure 4A**). Moderate or greater prosthesis-patient mismatch was 10.6% in TAVR patients and 25.1% in surgery patients (difference, -14.%; 95% CI, -19.6% to -9.4%) **(Table 2**). Mild paravalvular regurgitation was more frequent in the TAVR group (20.3% vs. 2.5%) **(Table 2)**. At 3 years, there was no significant difference in the presence of moderate or greater paravalvular regurgitation (0.9% TAVR vs. 0.2% surgery; difference, 0.7%; 95% CI, -0.2% to 1.6%) **(Table 2)**. Between years 1 and 3, there was no increase in paravalvular regurgitation observed for either TAVR or surgical groups (**Figure 4B).** The degree of paravalvular regurgitation on 30-day echocardiography was not associated with the rate of all-cause mortality or disabling stroke at 3 years in a landmarked analysis **(Supplemental Figure 2**).

Quality of Life

Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score demonstrated that patients who underwent TAVR had a more rapid improvement in quality of life (at 30 days) and that both groups had maintained improvements between years 1 and 3. At 3 years there was an approximately 20-point increase from baseline KCCQ for both groups consistent with a very large improvement in quality of life.[18,19] (**Figure 5**). Improvement in New York Heart Association score by at least 1 functional class from baseline to 3 years occurred in 72.7% of TAVR and 68.1% of surgery patients.

DISCUSSION

The major finding from this study of low-risk patients undergoing aortic valve replacement is that at three years, patients who received TAVR with a self-expanding, supra-annular valve had a lower rate of death or disabling stroke compared to patients undergoing surgery (7.4% vs 10.4%, hazard ratio, 0.70; 95% CI, 0.49 to 1.00; p=0.051). Furthermore, during the first three years after aortic valve replacement, the absolute difference in the primary outcome of death or disabling stroke between patients who underwent TAVR compared with surgery remained broadly consistent: year 1 delta -1.8%, year 2 delta -2.0%, and year 3 delta -2.9%.

Since the first randomized studies comparing TAVR to surgery were conducted in high-risk patients,[2,3] there has been a steady expansion of populations for whom a transcatheter approach is a viable and potentially advantageous alternative to surgery.[4,5,8,9] As TAVR has moved into younger populations, the importance of understanding intermediate and long-term data has become paramount. Unfortunately, such data are limited due in part to the fact that while all commercial TAVR procedures in the US are tracked through a national registry (STS/American College of Cardiology Transcatheter Valve Therapy [STS/ACC TVT] Registry), patients within this database are followed for only 1 year.[1] For low-risk patients in whom short-term benefits must be balanced with long-term durability, this lack of intermediate and longer-term data is particularly important. Given many variables that go into choosing a therapy for low-risk patients, the current ACC/AHA guidelines recommend that for patients between the age of 65-80 years, a shared decision-making process should be utilized by heart teams when discussing options for aortic valve with replacement.[17] These 3-year results demonstrating sustained valve performance and a low rate of mortality or disabling stroke with TAVR provide

patients and their physicians significant information that will further guide this shared decision-making process.

All patients within this study underwent TAVR with a self-expanding, supra-annular valve (CoreValve/Evolut platform) with tall commissures designed to optimize hemodynamics and decrease bioprosthetic leaflet stress.[6] There is evidence that this design results in improved hemodynamics when compared to valves that function at the annular level.[2,8,20] In our analysis at 3 years, there was a significant difference in moderate or greater prosthesis-patient mismatch (10.6% TAVR vs. 25.1% surgery). Prosthesis-patient mismatch after surgical aortic valve replacement has been associated with the development of structural valve deterioration in multiple studies,[21-23] and recent data from O'Hair and colleagues using pooled data from the CoreValve US High Risk and SURTAVI clinical trials demonstrated that at 5-years there was a two-fold increase in structural valve deterioration for patients who had surgery compared with TAVR, and that this was associated with increased mortality.[15] Longer-term follow-up within our study will help to further our understandings of the impact that hemodynamics have on both surgical and transcatheter valve durability.

One of the early challenges of TAVR was the significant amount of moderate or severe paravalvular regurgitation seen with first generation transcatheter valves[12,24] and associated with an increased risk of mortality at 5 years.[25] Within this study, the majority of patients underwent TAVR with the Evolut R platform, which unlike the first generation CoreValve can be repositioned to achieve a desired implant depth prior to final release. At 3 years there was no difference in moderate or greater paravalvular regurgitation for patients who had TAVR compared with surgery (0.9% vs. 0.2%), and while differences in mild paravalvular regurgitation remained significant (20.1% vs. 2.4%), this finding at 30 days was not associated with an

increased incidence of mortality or disabling stroke at 3 years. In addition, since this study was completed, the Evolut R valve has been replaced with the Evolut PRO and PRO+ valves which have an external pericardial wrap on the lower valve frame that has been shown to further reduce paravalvular regurgitation.[26] The incidence of new pacemakers has long been an Achilles heel of TAVR with self-expanding supra-annular valves, and in this study the rate remained significantly higher for TAVR than surgery at 3 years (23.2% vs. 9.1%). While recent procedural adaptations, including the use of the "cusp-overlap" implant technique, have been shown to decrease need for permanent pacemaker placement after TAVR,[27] the increased rate of pacemakers in this study stands in contrast to balloon-expandable transcatheter valves where the rate of new pacemakers in low-risk patients after TAVR was comparable to surgery.[11]

This study has several important limitations. First, while these three-year data are reassuring, longer term data for low-risk patients are needed and patients enrolled in this study will be followed for 10 years. This is particularly true for valve reintervention rates, which are too low at 3 years to allow for appropriate statistical analysis. Second, this study did not evaluate the ability to engage the coronary arteries after TAVR and recent studies have suggested that the supra-annular nature of the Evolut valve may make coronary reaccess more difficult.[28] While some of these challenges may be mitigated by proper commissural alignment,[29] a recent analysis by Faroux and colleages demonstrated that STEMI after TAVR is associated with increased mortality, longer door-to-balloon times, and higher percutaneous coronary intervention failure rates.[30] In addition, a subset of low-risk patients may outlive the durability of their bioprosthetic valve, and although transcatheter valve in valve (TAV-in-TAV) may be feasible in selected patients,[31] for those in whom TAV-in-TAV is not possible, surgical explant of a transcatheter valve may have increased risks.[32] Given these limitations, while these data demonstrate that low-

risk patients with severe aortic stenosis who undergo TAVR with a self-expanding supra-annular bioprosthesis have consistent outcomes compared to surgery with respect to all-cause mortality or disabling stroke at three years, further follow-up is needed due to the infrequent number of primary outcome events, and as such providers and patients should continue to engage in a shared decision-making process when faced with decisions regarding aortic valve replacement.

CONCLUSIONS

At three years, low surgical risk patients who underwent TAVR with a self-expanding supra-annular bioprosthesis had durable benefits with regards to all-cause mortality and disabling stroke compared to surgical aortic valve replacement.

CLINICAL PERSPECTIVES

Competency in Patient Care and Procedural Skills: Compared to patients undergoing surgical aortic valve replacement at 3 years, those at low surgical risk who undergo TAVR have favorable outcomes in terms of avoidance of all-cause mortality and disabling stroke.

Translational Outlook: Longer term studies involving low-risk patients are in progress to assess prosthetic valve durability after TAVR.

REFERENCES

1. Carroll JD, Mack MJ, Vemulapalli S et al. STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement. Ann Thorac Surg 2021;111:701-722.
2. Adams DH, Popma JJ, Reardon MJ et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790-8.
3. Leon MB, Smith CR, Mack M et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-607.
4. Reardon MJ, Van Mieghem NM, Popma JJ et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med 2017;376:1321-1331.
5. Leon MB, Smith CR, Mack MJ et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med 2016;374:1609-20.
6. Popma JJ, Adams DH, Reardon MJ et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol 2014;63:1972-81.
7. Smith CR, Leon MB, Mack MJ et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187-98.
8. Popma JJ, Deeb GM, Yakubov SJ et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med 2019;380:1706-1715.
9. Mack MJ, Leon MB, Thourani VH et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med 2019;380:1695-1705.
10. Forrest JK, Deeb GM, Yakubov SJ et al. 2-Year Outcomes After Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients. J Am Coll Cardiol 2022;79:882-896.

11. Leon MB, Mack MJ, Hahn RT et al. Outcomes 2 Years After Transcatheter Aortic Valve Replacement in Patients at Low Surgical Risk. J Am Coll Cardiol 2021;77:1149-1161.

12. Gleason TG, Reardon MJ, Popma JJ et al. 5-Year Outcomes of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement in High-Risk Patients. J Am Coll Cardiol 2018;72:2687-2696.

13. Van Mieghem NM, Deeb GM, Søndergaard L et al. Self-expanding Transcatheter vs Surgical Aortic Valve Replacement in Intermediate-Risk Patients: 5-Year Outcomes of the SURTAVI Randomized Clinical Trial. JAMA Cardiol 2022;7:1000-1008.

14. Rogers T, Greenspun BC, Weissman G et al. Feasibility of Coronary Access and Aortic Valve Reintervention in Low-Risk TAVR Patients. JACC: Cardiovascular Interventions 2020;13:726-735.

15. O'Hair D, Yakubov SJ, Grubb KJ et al. Structural Valve Deterioration After Self-Expanding Transcatheter or Surgical Aortic Valve Implantation in Patients at Intermediate or High Risk. JAMA Cardiol 2022.

16. Coylewright M, Forrest JK, McCabe JM, Nazif TM. TAVR in Low-Risk Patients: FDA Approval, the New NCD, and Shared Decision-Making. J Am Coll Cardiol 2020;75:1208-1211.

17. Otto CM, Nishimura RA, Bonow RO et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2021;77:e25-e197.

18. Généreux P, Piazza N, Alu MC et al. Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. J Am Coll Cardiol 2021;77:2717-2746.

19. Spertus JA, Jones PG, Sandhu AT, Arnold SV. Interpreting the Kansas City Cardiomyopathy Questionnaire in Clinical Trials and Clinical Care: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;76:2379-2390.

20. Hahn RT, Leipsic J, Douglas PS et al. Comprehensive Echocardiographic Assessment of Normal Transcatheter Valve Function. JACC Cardiovasc Imaging 2019;12:25-34.

21. Flameng W, Herregods MC, Vercalsteren M, Herijgers P, Bogaerts K, Meuris B. Prosthesis-patient mismatch predicts structural valve degeneration in bioprosthetic heart valves. Circulation 2010;121:2123-9.

22. Flameng W, Rega F, Vercalsteren M, Herijgers P, Meuris B. Antimineralization treatment and patient-prosthesis mismatch are major determinants of the onset and incidence of structural valve degeneration in bioprosthetic heart valves. J Thorac Cardiovasc Surg 2014;147:1219-24.

23. Johnston DR, Soltesz EG, Vakil N et al. Long-term durability of bioprosthetic aortic valves: implications from 12,569 implants. Ann Thorac Surg 2015;99:1239-47.

24. Mack MJ, Leon MB, Smith CR et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2477-84.

25. Makkar RR, Thourani VH, Mack MJ et al. Five-Year Outcomes of Transcatheter or Surgical Aortic-Valve Replacement. N Engl J Med 2020;382:799-809.

26. Forrest JK, Mangi AA, Popma JJ et al. Early Outcomes With the Evolut PRO Repositionable Self-Expanding Transcatheter Aortic Valve With Pericardial Wrap. JACC Cardiovasc Interv 2018;11:160-168.

27. Ben-Shoshan J, Alosaimi H, Lauzier PT et al. Double S-Curve Versus Cusp-Overlap Technique: Defining the Optimal Fluoroscopic Projection for TAVR With a Self-Expanding Device. JACC Cardiovasc Interv 2021;14:185-194.

28. Barbanti M, Costa G, Picci A et al. Coronary Cannulation After Transcatheter Aortic Valve Replacement: The RE-ACCESS Study. JACC Cardiovasc Interv 2020;13:2542-2555.

29. Tarantini G, Nai Fovino L, Scotti A et al. Coronary Access After Transcatheter Aortic Valve Replacement With Commissural Alignment: The ALIGN-ACCESS Study. Circ Cardiovasc Interv 2022;15:e011045.

30. Faroux L, Lhermusier T, Vincent F et al. ST-Segment Elevation Myocardial Infarction Following Transcatheter Aortic Valve Replacement. J Am Coll Cardiol 2021;77:2187-2199.

31. Landes U, Richter I, Danenberg H et al. Outcomes of Redo Transcatheter Aortic Valve Replacement According to the Initial and Subsequent Valve Type. JACC Cardiovasc Interv 2022;15:1543-1554.

32. Bapat VN, Zaid S, Fukuhara S et al. Surgical Explantation After TAVR Failure: Mid-Term Outcomes From the EXPLANT-TAVR International Registry. JACC Cardiovasc Interv 2021;14:1978-1991.

FIGURE LEGENDS

Figure 1. Time-to-Event All-Cause Mortality and Disabling Stroke. Kaplan-Meier estimates and log-rank p values for the primary endpoint components of all-cause mortality (A) and disabling stroke (B). TAVR = transcatheter aortic valve replacement

Figure 2. Time-to-Event All Cause Mortality, Disabling Stroke, or Aortic Valve Hospitalization. Kaplan-Meier estimates and log-rank p values are shown for the composite endpoint of all-cause mortality, disabling stroke, or aortic valve hospitalization through 3 years. Patients in the TAVR group had lower rates of the composite endpoint at 3 years. AV = aortic valve; HR = hazard ratio; TAVR = transcatheter aortic valve replacement

Figure 3. Three-Year Death or Disabling Stroke by Baseline Demographics. A consistency of treatment effect was observed across eight demographic subgroups. Black squares indicate the hazard ratio for TAVR vs surgery, and horizontal lines indicate the 95% confidence intervals. No adjustment was made for multiplicity. COPD = chronic obstructive pulmonary disease; KCCQ = Kansas City Cardiomyopathy Questionnaire; KM = Kaplan Meier; STS = Society of Thoracic Surgeons**.** P values are based on the Cox proportional hazards model. CI = confidence interval; HR = hazard ratio

Figure 4. Hemodynamic Valve Performance. Aortic valve mean gradient and effective orifice area and parvalvular regurgitation through 3 years for the TAVR and surgery groups as reported by the echocardiography core laboratory. Panel A. Patients in the TAVR group had significantly lower mean gradient ($p<0.001$) and significantly larger effective orifice area ($p<0.001$) at all follow-up timepoints. Mean (SD) values are reported for each timepoint. Panel B. Between years 1 and 3, there was no increase in paravalvular regurgitation observed for either TAVR or surgical

groups. EOA = effective orifice area; MG = mean gradient; TAVR = transcatheter aortic valve replacement

Figure 5. Kansas City Cardiomyopathy Questionnaire. Mean KCCQ overall summary scores by study visit are shown in the graph. Mean ± SD change in KCCQ score from baseline and difference with 95% confidence intervals for each time point are shown in the table. KCCQ = Kansas City Cardiomyopathy Questionnaire; surgery = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement

Central Illustration. Three-year outcomes from the Evolut Low Risk Trial. Patients in the Evolut Low Risk trial were randomized to TAVR with a self-expanding, supra-annular valve or surgery and followed for 3 years. Kaplan Meier time-to-event curves for the primary endpoint of all-cause mortality or disabling stroke were compared in the TAVR and surgery groups at Years 1, 2, and 3 of the study. HR = hazard ratio; KM = Kaplan Meier; TAVR = transcatheter aortic valve replacement

Table 1. Baseline Patient Characteristics

Characteristic	TAVR (N = 730)	Surgery (N = 684)
Age, yr	74.1 ± 5.8	73.7 ± 5.9
Body surface area, m^2	2.0 ± 0.2	2.0 ± 0.2
Female sex	266 (36.4)	233 (34.1)
STS-PROM score, %	2.0 ± 0.7	1.9 ± 0.7
NYHA functional class		
I	76 (10.4)	63 (9.2)
II	472 (64.7)	428 (62.6)
III	181 (24.8)	190 (27.8)
IV	1 (0.1)	3 (0.4)
Diabetes	229 (31.4)	210 (30.7)
Hypertension	618/729 (84.8)	564/683 (82.6)
Chronic lung disease, COPD	106/700 (15.1)	118/655 (18.0)
Peripheral arterial disease	54/723 (7.5)	56/683 (8.2)
Cerebrovascular disease	74 (10.1)	82 (12.0)
Previous coronary artery bypass graft	18 (2.5)	14 (2.0)
Previous valve	0 (0.0)	0 (0.0)
Previous percutaneous coronary intervention	103 (14.1)	88 (12.9)
Previous myocardial infarction	49 (6.7)	33 (4.8)
Atrial fibrillation/atrial flutter	112/727 (15.4)	98/682 (14.4)
Pre-existing permanent pacemaker or defibrillator	24 (3.3)	26/683 (3.8)
SYNTAX Score I	1.9 ± 3.7	2.1 ± 3.9
Left ventricular ejection fraction, %	61.7 ± 7.9	61.9 ± 7.7

Data are presented as n (%) or mean ± standard deviation. There were no significant differences (P<0.05) in baseline characteristics between study groups. COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; TAVR = transcatheter aortic valve replacement

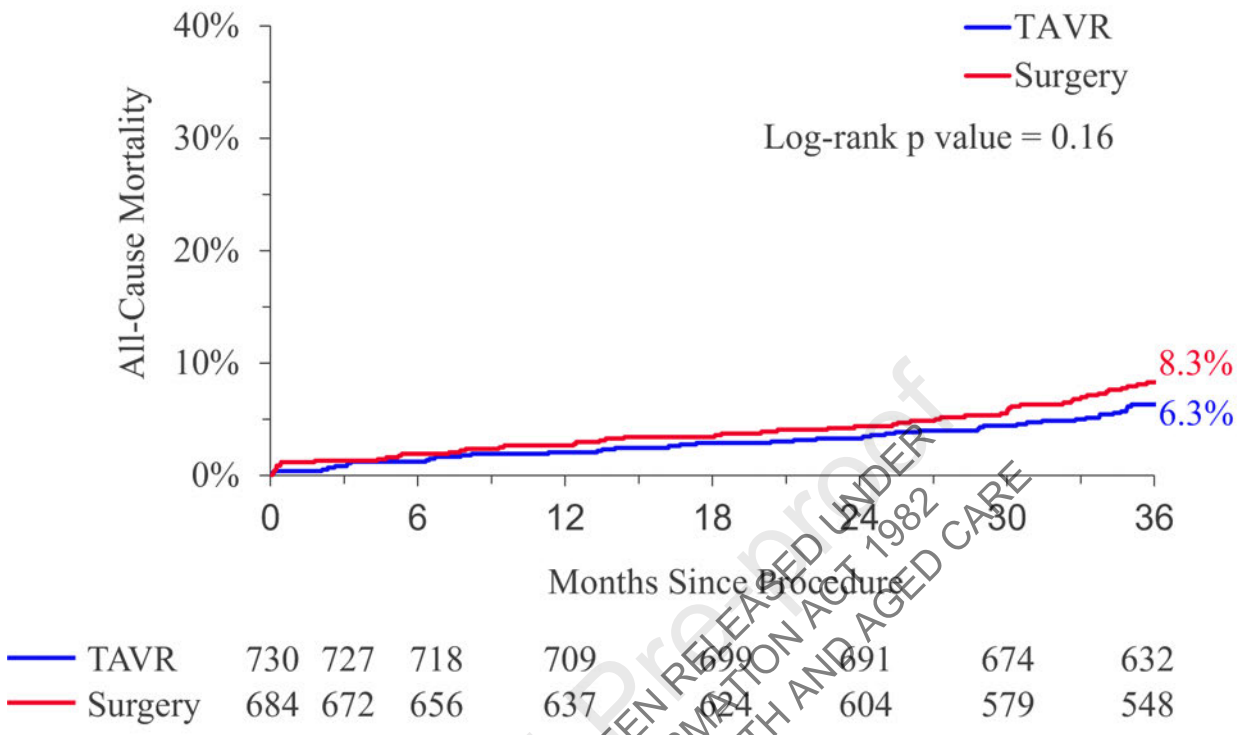
Table 2. Three Year Clinical Outcomes and Valve Performance

Outcome	TAVR	Surgery	Hazard Ratio or Risk Difference[a] (95% CI)	P Value[b]
Clinical Outcomes				
All-cause mortality or disabling stroke	53 (7.4)	67 (10.4)	0.70 (0.49, 1.00)	0.051
All-cause mortality	45 (6.3)	53 (8.3)	0.75 (0.51, 1.12)	0.16
Cardiovascular death	29 (4.1)	36 (5.6)	0.72 (0.44, 1.17)	0.18
All stroke	53 (7.4)	43 (6.6)	1.13 (0.76, 1.69)	0.55
Disabling stroke	16 (2.3)	22 (3.4)	0.65 (0.34, 1.24)	0.19
Aortic valve hospitalization[c]	52 (7.4)	59 (9.2)	0.78 (0.54, 1.14)	0.20
All-cause mortality, disabling stroke, or aortic valve hospitalization	95 (13.2)	110 (16.8)	0.76 (0.58, 1.00)	0.050
Major vascular complication	30 (4.1)	25 (3.7)	1.12 (0.66, 1.90)	0.67
Myocardial infarction	24 (3.4)	15 (2.3)	1.46 (0.76, 2.78)	0.25
Permanent pacemaker implant[d]	162 (23.2)	58 (9.1)	2.81 (2.08, 3.79)	<0.001
Atrial fibrillation*	94 (13.1)	271 (40.0)	0.27 (0.22, 0.35)	<0.001
Valve endocarditis	5 (0.7)	8 (1.3)	0.56 (0.18, 1.70)	0.30
Valve Performance				
Reintervention	7 (1.0)	6 (0.9)	1.06 (0.36, 3.15)	0.92
Paravalvular regurgitation[e]				<0.001
None/trace	426 (78.7)	435 (97.3)	-	
Mild	110 (20.3)	11 (2.5)	-	
Moderate	4 (0.7)	1 (0.2)	-	
Severe	1 (0.2)	0 (0)	-	
≥ Mild	115/541 (21.3)	12/447 (2.7)	18.6% (14.8, 22.3)	<0.001
≥ Moderate	5/541 (0.9)	1/447 (0.2)	0.7% (-0.2, 1.6)	0.16
Prosthesis-patient mismatch[e]				<0.001
None	437/489 (89.4)	295/394 (74.9)		
Moderate	45/489 (9.2)	80/394 (20.3)	-	
Severe	7/489 (1.4)	19/394 (4.8)	-	
≥ Moderate	52/489 (10.6)	99/394 (25.1)	-14.5% (-19.6, -9.4)	
Valve thrombosis				
Clinical[f]	2 (0.3)	1 (0.2)	1.84 (0.17, 20.25)	0.61
Subclinical[g]	3 (0.4)	3 (0.5)	0.91 (0.18, 4.50)	0.91

[a]Clinical outcomes are presented as n (Kaplan-Meier estimate %) with hazard ratio (95% CI); paravalvular regurgitation (PVR) and prosthesis-patient mismatch (PPM) are presented as n/N (%) with risk difference (95% CI). [b]P values were based on the chi-square test for PVR and PPM; p values for all other clinical outcomes were based on the log-rank test. [c]Not adjudicated by the Clinical Events Committee (CEC). [d]Patients with pacemaker or implantable cardioverter defibrillator at baseline are not included. Not adjudicated by the CEC. [e]PVR and PPM through 3 years was reported by the echocardiography core laboratory. PPM was defined per Valve

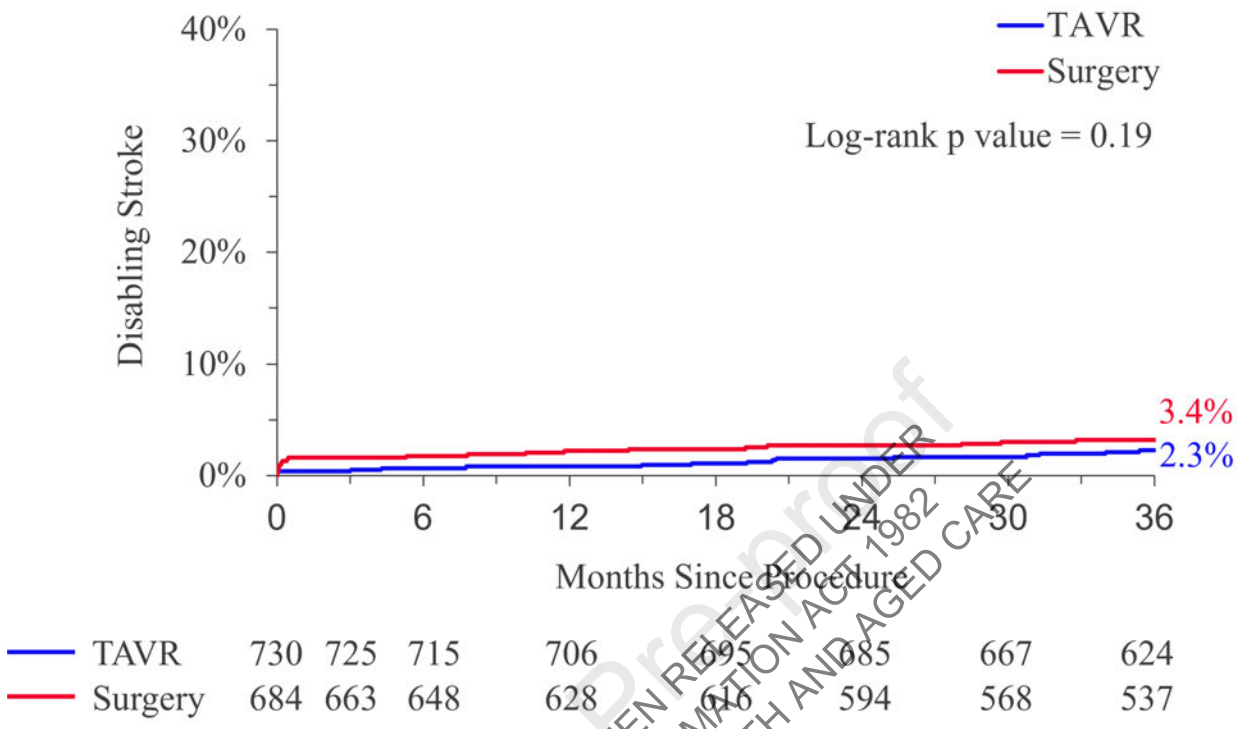
Academic Research Consortium 3 (VARC-3) criteria. [f]Clinical valve thrombosis rates were CEC adjudicated and defined as any thrombus not caused by infection attached to or near the trial valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment and is associated with any of the following clinical sequelae: any ischemic stroke, any peripheral embolic event, ST segment elevation or non-ST elevation myocardial infarction, or hemodynamic impairment associated with a worsening heart failure. [g]Subclinical valve thromboses were defined as those without evident clinical sequelae causing a hemodynamic impediment meeting the following criteria: increase in aortic regurgitation resulting in moderate or severe, a post-discharge mean gradient of ≥ 20 mmHg that increased by > 50%, or a decrease in the Doppler Velocity Index (DVI) by > 50%. CI = confidence intervals; TAVR = transcatheter aortic valve replacement

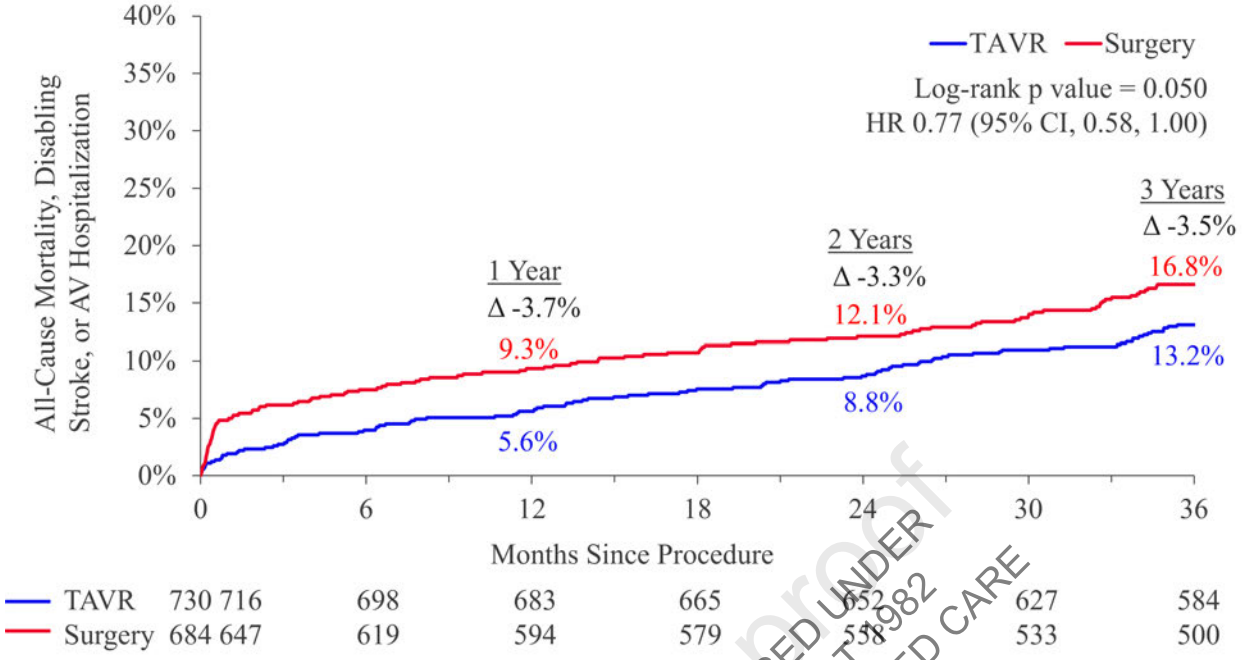
A.



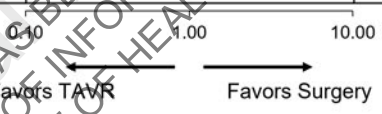
TAVR	730	727	718	709	699	691	674	632
Surgery	684	672	656	637	624	604	579	548

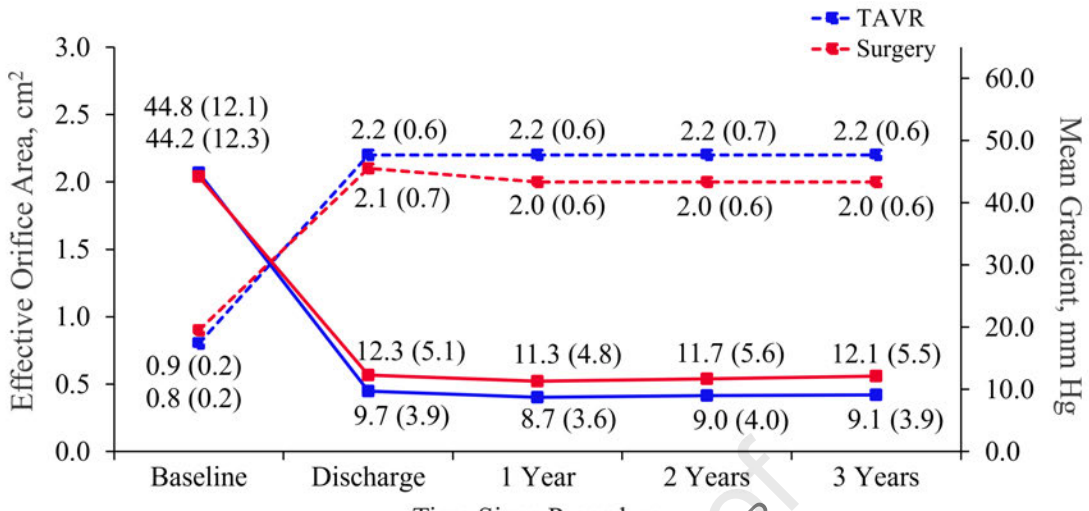
B.



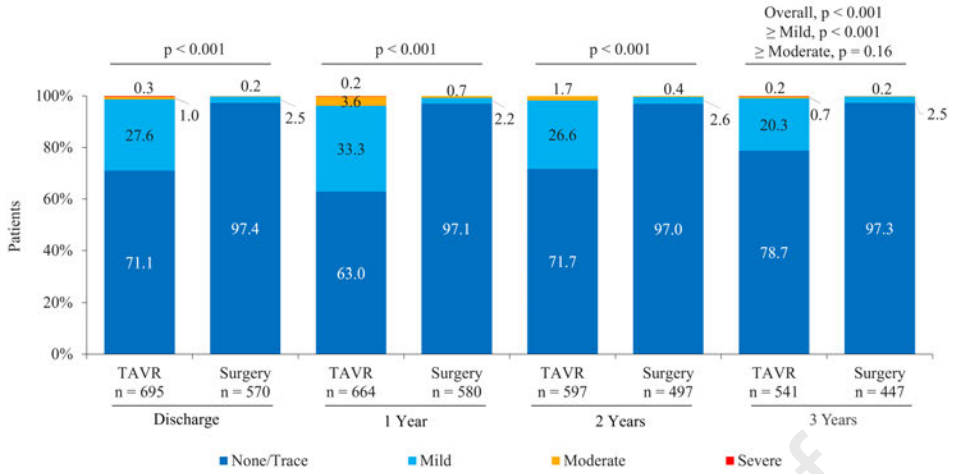


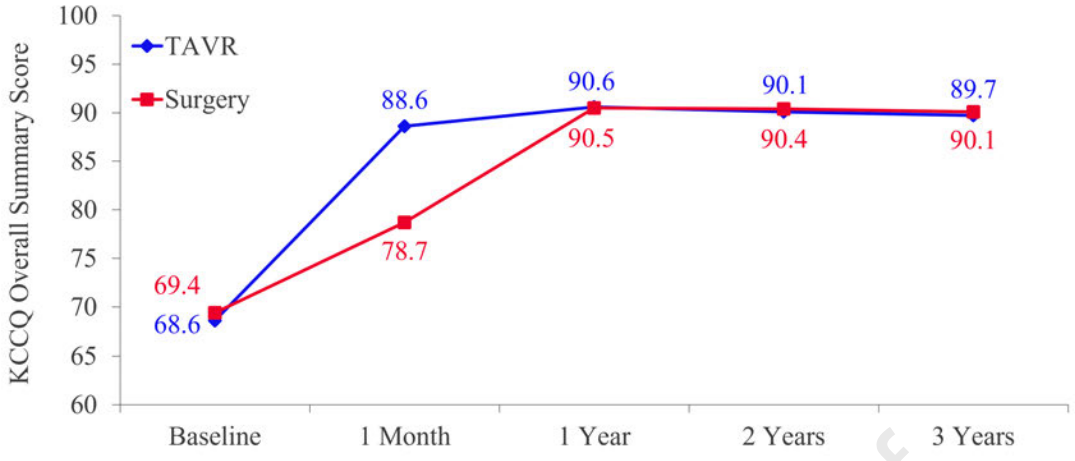
Variable	TAVR n/N (KM rate at 3 years)	Surgery n/N (KM rate at 3 years)	HR (95% CI)	P value for Interaction
Age, years				0.9462
< 75	20/352 (5.7)	27/351 (8.0)	0.71 (0.40-1.26)	
≥ 75	33/378 (9.1)	40/333 (13.0)	0.68 (0.43-1.07)	
Sex				0.4090
Male	35/464 (7.8)	50/451 (11.7)	0.64 (0.41-0.98)	
Female	18/266 (6.8)	17/233 (7.8)	0.89 (0.46-1.73)	
Body mass index, kg/m^2				0.7084
≤ 30	24/369 (6.6)	33/351 (9.9)	0.65 (0.39-1.10)	
> 30	29/361 (8.2)	34/333 (10.8)	0.75 (0.45-1.23)	
STS Score, %				0.5503
< 2	23/404 (5.8)	33/384 (9.0)	0.62 (0.37-1.06)	
≥ 2	30/326 (9.4)	34/300 (12.0)	0.77 (0.47-1.26)	
New York Heart Association				0.7127
I/II	36/548 (6.7)	45/491 (9.7)	0.78 (0.41-1.47)	
III/IV	17/182 (9.7)	22/193 (11.9)	0.77 (0.47-1.26)	
Baseline KCCQ				0.4271
≤ 72	29/367 (8.1)	41/342 (12.7)	0.62 (0.38-0.99)	
> 72	23/360 (6.5)	25/338 (7.8)	0.83 (0.47-1.45)	
COPD				0.6262
No	45/594 (7.8)	55/537 (10.9)	0.89 (0.35-2.25)	
Yes	8/106 (7.6)	10/118 (8.8)	0.83 (0.47-1.45)	
Baseline atrial fibrillation				0.4493
No	38/615 (6.3)	53/584 (9.6)	0.89 (0.42-1.89)	
Yes	14/112 (13.0)	13/98 (14.4)	0.83 (0.47-1.45)	





No. of patients					
TAVR EOA	637	576	565	535	493
Surgery EOA	596	406	525	434	396
TAVR MG	717	703	662	607	547
Surgery MG	679	632	597	514	456





Change from Baseline				
TAVR	20.0 ± 21.1	21.6 ± 20.6	20.9 ± 20.8	20.1 ± 20.6
Surgery	9.2 ± 22.3	20.7 ± 20.3	20.0 ± 20.0	19.3 ± 21.1
Difference (95% CI)	10.7 (8.4, 13.0)	0.9 (-1.3, 3.1)	0.9 (-1.4, 3.2)	0.8 (-1.7, 3.2)

SUPPLEMENTAL APPENDIX

Three-Year Outcomes After Transcatheter or Surgical Aortic Valve Replacement in Low-Risk Patients with Aortic Stenosis

John K. Forrest MD, G. Michael Deeb MD, Steven J. Yakubov MD, Hemal Gada MD, Mubashir A. Mumtaz MD, Basel Ramlawi MD, Tanvir Bajwa MD, Paul S. Teirstein MD, Michael DeFrain MD, Murali Muppala MD, Bruce J. Rutkin MD, Atul Chawla MD, Bart Jenson MD, Stanley J. Chetcuti MD, Robert C. Stoler MD, Marie-France Poulin MD, Kamal Khabbaz MD, Melissa Levack MD, Kashish Goel MD, Didier Tchétché MD, Ka Yan Lam MD, Pim A. L. Tonino MD, Saki Ito MD, Jae K. Oh MD, Jian Huang MD, MSc, Jeffrey J. Popma MD, Neal Kleiman MD, Michael J. Reardon MD, for the Low Risk Trial Investigators

Table of Contents

Contents

SUPPLEMENTAL TABLE 1. STUDY SITES AND PRINCIPAL INVESTIGATORS

Abbott Northwestern Hospital – Minneapolis Heart Institute Minneapolis, Minnesota	Principal investigator: Paul Sorajja
Abrazo Arizona Heart Hospital Phoenix, Arizona	Principal investigators: Timothy Byrne, Merick Kirshner
Aurora/St Luke's Hospital Milwaukee, Wisconsin	Principal investigators: Tanvir Bajwa, John Crouch
Baylor Saint Luke's Medical Center Houston, Texas	Principal investigators: Joseph Coselli, Guilherme Silva
Baylor Jack and Jane Hamilton Heart and Vascular Hospital Dallas, Texas	Principal investigators: Robert Hebeler, Robert Stoler
Baystate Medical Center Springfield, Massachusetts	Principal investigators: Ashequl Islam, Anthony Rousou
Beth Israel Deaconess Medical Center Boston, Massachusetts	Principal investigators: Marie-France Poulin, Kamal Khabbaz
Bon Secours Heart & Vascular Institute Richmond, Virginia	Principal investigators: Mark Bladergroen
Cardiovascular Institute of the South / Terrebonne General Medical Center Houma, Louisiana	Principal investigators: Peter Fail, Donald Netherland
Catharina Hospital Eindhoven Eindhoven, The Netherlands	Principal investigators: Ka Yan Lam, W.A.L. Tonino

Centre Hospitalier Régional Universitaire (CHRU) de Lille Lille, France	Principal investigators: Arnaud Sudre
Clinique Pasteur Toulouse Toulouse, France	Principal investigators: Pierre Berthoumieu, Didier Tchétché
Delray Medical Center Delray Beach, Florida	Principal investigators: Houman Khalili
Duke University Medical Raleigh, North Carolina	Principal investigators: G. Chad Hughes, J Kevin Harrison
El Camino Hospital Mountain View, California	Principal investigators: Ajanta De, Pei Tsau
Erasmus Medical Center Rotterdam Rotterdam, The Netherlands	Principal investigators: Nicolas M. van Mieghem
Fiona Stanley Hospital Murdoch, Western Australia	Principal investigators: Robert Larbalestier, Gerald Yong
Geisinger Medical Center Danville, Pennsylvania	Principal investigators: Shikhar Agarwal, William Martin
Good Samaritan Hospital Cincinnati, Ohio	Principal investigators: Steven Park
Houston Methodist DeBakey Heart & Vascular Center Houston, Texas	Principal investigators: Neal Kleiman, Michael Reardon

Institut Universitaire de Cardiologie et de Pneumologie de Québec Québec, Canada	Principal investigators: Siamak Mohammadi, Josep Rodes-Cabau
Integris Baptist Medical Center Oklahoma City, Oklahoma	Principal investigators: Jeffrey Sparling, C. Craig Elkins
Jewish Hospital Louisville, Kentucky	Principal investigators: Brian Ganzel
Keck Hospital of University of Southern California USC Los Angeles, California	Principal investigators: Ray V. Matthews, Vaughn A. Starnes
Kokura Memorial Hospital Fukuoka, Japan	Principal investigators: Kenji Ando
L'Hôpital Privé Jacques Cartier Massy Massy, France	Principal investigators: Bernard Chevalier, Arnaud Farge
Lee Memorial Health System Fort Myers, Florida	Principal investigators: Michael DeFrain, Murali Muppala
Lehigh Valley Hospital Cedar Crest Allentown, Pennsylvania	Principal investigators: William Combs
London Health Sciences Centre London, Ontario, Canada	Principal investigators: Rodrigo Bagur, Michael Chu
Los Robles Hospital & Medical Center Thousand Oaks, California	Principal investigators: Gregory Fontana, Visha Dev
Loyola University Medical Center Maywood, Illinois	Principal investigators: Ferdinand Leya, J. Michael Tuchek

Massachusetts General Hospital Boston, Massachusetts	Principal investigators: Ignacio Inglessis, Arminder Jassar
McGill University Health Centre Montreal, Québec, Canada	Principal investigators: Nicolo Piazza, Kevin Lacappelle
Medical University of South Carolina Charleston, South Carolina	Principal investigators: Daniel Steinberg, Marc Katz
MedStar Union Memorial Hospital Baltimore, Maryland	Principal investigators: John Wang
Mercy General Hospital Rancho Cordova, California	Principal investigators: Joseph Kozina, Frank Slachman
Mercy Hospital Springfield Springfield, Missouri	Principal investigators: Robert Merritt
Mercy Medical Center – Iowa Heart Des Moines, Iowa	Principal investigators: Atul Chawla, Bart Jensen
Methodist Hospital San Antonio, Texas	Principal investigators: Jorge Alvarez
Monash Health MonashHeart Melbourne, Victoria, Australia	Principal investigators: Robert Gooley, Julian Smith
Montreal Heart Institute Montréal, Québec, Canada	Principal investigators: Reda Ibrahim, Raymond Cartier
Morton Plant Hospital Clearwater, Florida	Principal investigators: Joshua Rovin

National Cerebral and Cardiovascular Center Osaka, Japan	Principal investigators: Tomoyuki Fujita
North Shore University Hospital Manhasset, New York	Principal investigators: Bruce Rutkin
OhioHealth Riverside Methodist Hospital Columbus, Ohio	Principal investigator: Steven Yakubov
Oregon Health and Science Univ Portland, Oregon	Principal investigators: Howard Song, Firas Zahr
Osaka University Hospital Osaka, Japan	Principal investigators: Shigeru Miyagawa
Piedmont Heart Institute Atlanta, Georgia	Principal investigators: Vivek Rajagopal, James Kauten
University of Pittsburgh Medical Center Pinnacle Harrisburg Campus Harrisburg, Pennsylvania	Principal investigators: Hemal Gada, Mubashir Mumtaz
Royal North Shore Hospital St. Leonards, Australia	Principal investigators: Ravinay Bhindi, Peter Brady
Saint John Hospital and Medical Center Detroit, Michigan	Principal investigators: Sanjay Batra, Thomas Davis
Saint Joseph's Hospital Health Center Liverpool, New York	Principal investigators: Ayman Iskander
Saint Vincent Heart Center of Indiana Indianapolis, Indiana	Principal investigators: David Heimansohn, James Hermiller

Sakakibara Heart Institute Tokyo, Japan	Principal investigators: Itaru Takamisawa
Sanford Medical Center Fargo Fargo, North Dakota	Principal investigators: Thomas Haldis
Sapporo Higashi Tokushukai Hospital Sapporo, Japan	Principal investigators: Seiji Yamazaki
Scripps Memorial Hospital La Jolla La Jolla, California	Principal investigators: Paul Teirstein
Sendai Kousei Hospital Sendai, Japan	Principal investigators: Norio Tada
Shonan Kamakura General Hospital Kamakura, Japan	Principal investigators: Shigeru Saito
Spectrum Health Hospitals Grand Rapids, Michigan	Principal investigators: William Merhi, Stephane Leung
St Vincent's Hospital, Sydney Sydney, Australia	Principal investigators: David Muller
St. Antonius Hospital Nieuwegein Nieuwegein, The Netherlands	Principal investigator: Robin Heijmen
St. Francis Hospital Roslyn, New York	Principal investigators: George Petrossian, Newell Robinson
Strong Memorial Hospital Rochester, New York	Principal investigators: Peter Knight, Frederick Ling

Sunnybrook Health Sciences Centre Toronto, Canada	Principal investigators: Sam Radhakrishnan, Stephen Fremes
Swedish Medical Center Cherry Hill Seattle, Washington	Principal investigators: Eric Lehr, Sameer Gafoor
Tallahassee Research Institute Tallahassee, Florida	Principal investigators: Thomas Noel
The Alfred Hospital Melbourne, Australia	Principal investigators: Antony Walton
The Johns Hopkins Hospital Baltimore, Maryland	Principal investigator: Jon Resar
The Mount Sinai Medical Center New York, New York	Principal investigators: David Adams, Samin Sharma
The Ohio State University Wexner Medical Center Columbus, Ohio	Principal investigators: Scott Lilly
The University of Kansas Hospital Kansas City, Kansas	Principal investigators: Peter Tadros, George Zorn
The University of Vermont Medical Center Burlington, Vermont	Principal investigators: Harold Dauerman, Frank Ittleman
Toronto General Hospital Toronto, Canada	Principal investigators: Erik Horlick, Chris Feindel
University Hospital Salt Lake City, Utah	Principal investigators: Frederick Welt, Vikas Sharma

University Hospitals Cleveland Medical Center (Case Medical Center) Cleveland, Ohio	Principal investigator: Alan Markowitz
University of Colorado Hospital Aurora, Colorado	Principal investigators: John Carroll, David Fullerton
University of Maryland Medical Center Baltimore, Maryland	Principal investigators: Bartley Griffith, Anuj Gupta
University of Miami Hospital Miami, Florida	Principal investigators: Eduardo de Marchena, Tomas Salerno
University of Michigan Health System Ann Arbor, Michigan	Principal investigators: Stanley Chetcuti, G. Michael Deeb
University of Pittsburgh Medical Center Pittsburgh, Pennsylvania	Principal investigators: Ibrahim Sultan
Vanderbilt University Medical Center Nashville, Tennessee	Principal investigators: Kashish Goel
Waikato Hospital Hamilton, New Zealand	Principal investigators: Sanjeevan Pasupati
Wake Forest Baptist Medical Center Winston-Salem, North Carolina	Principal investigators: Neal Kon, David Zhao
Winchester Medical Center Winchester, Virginia	Principal investigator: Basel Ramlawi
Yale New Haven New Haven, Connecticut	Principal investigators: John Forrest

RESULTS

Impact of 30-day permanent pacemaker implantation at 30 days on mid-term clinical outcomes. Patients in the TAVR group were stratified by the need for permanent pacemaker implantation (PPI) (baseline PPI vs new PPI within 30 days of the implant procedure vs no PPI within 30 days of the implant procedure) and followed through 3 years to assess impact on all-cause mortality. The analysis of clinical outcomes was landmarked at 30 days post-procedure. Baseline characteristics of the three groups are shown in **Supplemental Table 2.** The number of patients available for evaluation at 30 days was 24 in the baseline PPI group, 124 in the new PPI within 30 days group, and 576 in the no PPI within 30 days group; the number of patients at risk at 3 years was 18, 102, and 509, respectively. TAVR patients who entered the study with a permanent pacemaker had higher rates of all-cause mortality at 3 years than patients who received a new permanent pacemaker within 30 days of implant or those without a permanent pacemaker within 30 days (17.5% vs 9.8% vs 4.6%, respectively).

TABLES

Supplemental Table 2. Baseline Characteristics in TAVR Patients by Permanent Pacemaker Implantation[a]

Characteristics	Baseline PPI (N=24)	New PPI within 30 days (N=124)	No PPI within 30 days (N=576)
Age, yrs	74.3 ± 6.3	74.7 ± 5.3	74.0 ± 5.9
Body surface area, m^2	2.1 ± 0.2	2.0 ± 0.2	2.0 ± 0.2
Female sex	7 (29.2)	40 (32.3)	217 (37.7)
STS score, %	2.2 ± 0.8	1.9 ± 0.6	1.9 ± 0.7
NYHA functional class			
I	1 (4.2)	18 (14.5)	57 (9.9)
II	13 (54.2)	72 (58.1)	381 (66.1)
III	10 (41.7)	34 (27.4)	137 (23.8)
IV	0 (0.0)	0 (0.0)	1 (0.2)
Diabetes	5 (20.8)	40 (32.3)	181 (31.4)
Hypertension	20 (83.3)	106 (85.5)	486/575 (84.5)
COPD	5 (20.8)	16/119 (13.4)	84/551 (15.2)
Peripheral arterial disease	2 (8.3)	6/122 (4.9)	46/571 (8.1)
Cerebrovascular disease	3 (12.5)	12 (9.7)	59 (10.2)
Previous coronary artery bypass graft	2 (8.3)	4 (3.2)	12 (2.1)
Previous valve	0 (0.0)	0 (0.0)	0 (0.0)
Previous PCI	4 (16.7)	12 (9.7)	84 (14.6)
Previous myocardial infarction	3 (12.5)	6 (4.8)	38 (6.6)
Atrial fibrillation/atrial flutter	13 (54.2)	16 (12.9)	84/573 (14.7)
SYNTAX score I	2.3 ± 4.4	2.5 ± 4.5	1.8 ± 3.5
Left ventricular ejection fraction, %	59.2 ± 9.1	62.3 ± 6.3	61.7 ± 8.1

Data are presented as n (%) or mean ± SD. [a]Patients who exited or died at ≤30 days were excluded. COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PPI = permanent pacemaker implantation; SYNTAX = SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery coronary scoring system

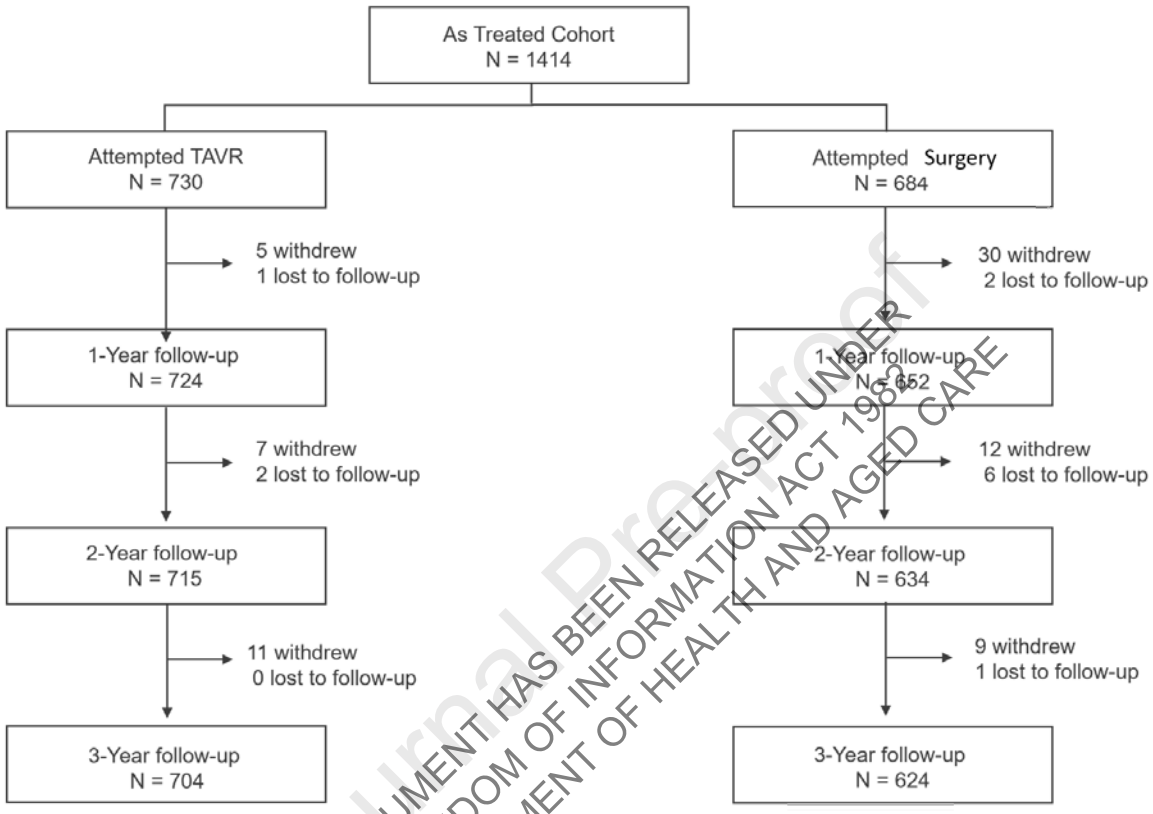
Supplemental Table 3. Reintervention Between 30 Days and 3 Years

Days	Assignment	Valve Type	Etiology	Event
91	TAVR	34 mm Evolut R	Leaflet tear and aortic insufficiency	Surgical aortic valve replacement
173	Surgery	29 mm Trifecta	Endocarditis	Surgical aortic valve replacement
241	Surgery	23 mm Perimount	Thrombosis	Surgical aortic valve replacement
386	TAVR	34 mm Evolut R	Leaflet tear and aortic insufficiency	Surgical aortic valve replacement
437	Surgery	25 mm Trifecta	Endocarditis	Surgical aortic valve replacement
556	TAVR	34 mm Evolut R	Endocarditis	Surgical aortic valve replacement
644	Surgery	25 mm Trifecta	Endocarditis	Surgical aortic valve replacement
735	TAVR	34 mm Evolut R	Leaflet tear and aortic insufficiency	Surgical aortic valve replacement
751	Surgery	27 mm Mosaic	Stenosis	Transcatheter aortic valve replacement

TAVR = transcatheter aortic valve replacement

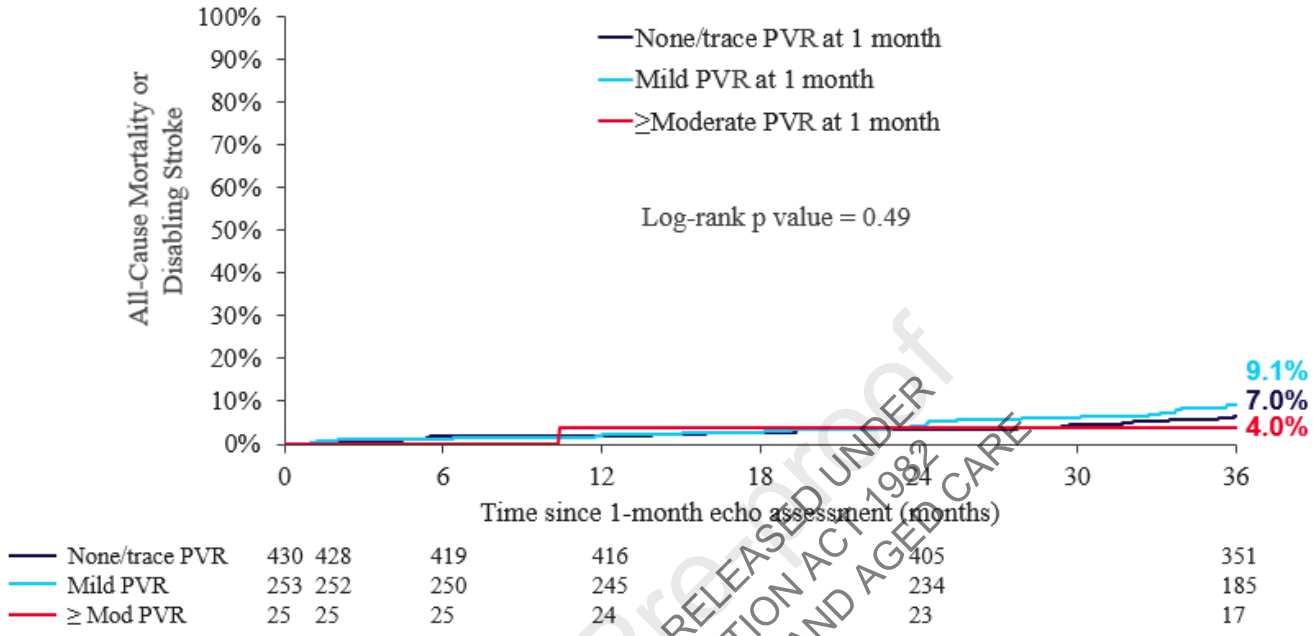
FIGURES

Supplemental Figure 1: Patient Flow Through 3 Years



Supplemental Figure 1: At 3 years, data were available for 704 patients (96.4%) in the TAVR group and 624 patients (91.2%) in the surgery group. Patients who died were counted as known status for each time point. TAVR = transcatheter aortic valve replacement.

Supplemental Figure 2: Landmark Analysis: Impact of Paravalvular Regurgitation on Three Year Mortality or Disabling Stroke



Supplemental Figure 2. Impact of paravalvular regurgitation at the 1-month echocardiogram on midterm clinical outcomes. Patients in the TAVR group were stratified by none/trace PVL vs mild PVL vs ≥ moderate PVL at the 1-month echocardiography assessment and then followed through 3 years to assess impact on all-cause mortality or disabling stroke. The analysis was landmarked at the 1-month echocardiography date. Clinical outcomes are presented as Kaplan Meier estimates. Paravalvular regurgitation was based on echocardiography core laboratory assessment. PVR = paravalvular regurgitation

ESC European Society of Cardiology

European Heart Journal (2023) **44**, 836–852
https://doi.org/10.1093/eurheartj/ehac642

Document 20
META-ANALYSIS
Valvular heart disease

Transcatheter versus surgical aortic valve replacement in lower-risk and higher-risk patients: a meta-analysis of randomized trials

Yousif Ahmad [1]*, James P. Howard [2], Ahran D. Arnold [2], Mahesh V. Madhavan[3,4], Christopher M. Cook[5], Maria Alu [4], Michael J. Mack[6], Michael J. Reardon [7], Vinod H. Thourani[8], Samir Kapadia [9], Hans Gustav Hørsted Thyregod [10], Lars Sondergaard[10], Troels Højsgaard Jørgensen[10], William D. Toff [11], Nicolas M. Van Mieghem [12], Raj R. Makkar[13], John K. Forrest[1], and Martin B. Leon[3,4]

[1]Yale School of Medicine, Yale University, 135 College Street, Suite 101, New Haven, CT 06510, USA; [2]National Heart and Lung Institute, Imperial College London, Du Cane Road, London W120HS, UK; [3]Division of Cardiology, Department of Medicine, Columbia University Medical Center/New York-Presbyterian Hospital, W. 168th St. New York, NY 10032, USA; [4]Clinical Trials Center, The Cardiovascular Research Foundation, 1700 Broadway, New York, NY 10019, USA; [5]Essex Cardiothoracic Center, Nether Mayne, Basildon SS16 5NL, UK; [6]Department of Cardiovascular Disease, Baylor Scott and White Health, 4700 Alliance Blvd, Plano, TX 75093, USA; [7]Houston Methodist DeBakey Heart & Vascular Center, 6565 Fannin St Suite 1901, Houston, TX 77030, USA; [8]Department of Cardiovascular Surgery, Marcus Valve Center, Piedmont Heart and Vascular Institute, 95 Collier Rd NW Suite 5015, Atlanta, GA 30309, USA; [9]Cleveland Clinic, 9500 Euclid Ave. Cleveland, OH 44195, USA; [10]The Heart Centre, Rigshospitalet, Copenhagen University Hospital, Section 2151, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark; [11]Department of Cardiovascular Sciences, University of Leicester and NIHR Leicester Biomedical Research Centre, Glenfield Hospital, University Rd, Leicester LE1 7RH, UK; [12]Department of Interventional Cardiology, Thoraxcenter, Erasmus University Medical Center, Dr. Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands; and [13]Cedars-Sinai Medical Center, Smidt Heart Institute, S San Vicente Blvd, Los Angeles, CA 90048, USA

Received 3 May 2022; revised 9 October 2022; accepted 26 October 2022; online publish-ahead-of-print 20 January 2023

See the editorial comment for this article 'Transcatheter aortic valve implantation: a blueprint for evidence-based evaluation of technological innovation', by T. Pilgrim *et al.*, https://doi.org/10.1093/eurheartj/ehac635.

Abstract

Aims Additional randomized clinical trial (RCT) data comparing transcatheter aortic valve implantation (TAVI) with surgical aortic valve replacement (SAVR) is available, including longer term follow-up. A meta-analysis comparing TAVI to SAVR was performed. A pragmatic risk classification was applied, partitioning lower-risk and higher-risk patients.

Methods and results The main endpoints were death, strokes, and the composite of death or disabling stroke, occurring at 1 year (early) or after 1 year (later). A random-effects meta-analysis was performed. Eight RCTs with 8698 patients were included. In lower-risk patients, at 1 year, the risk of death was lower after TAVI compared with SAVR [relative risk (RR) 0.67; 95% confidence interval (CI) 0.47 to 0.96, $P = 0.031$], as was death or disabling stroke (RR 0.68; 95% CI 0.50 to 0.92, $P = 0.014$). There were no differences in strokes. After 1 year, in lower-risk patients, there were no significant differences in all main outcomes. In higher-risk patients, there were no significant differences in main outcomes. New-onset atrial fibrillation, major bleeding, and acute kidney injury occurred less after TAVI; new pacemakers, vascular complications, and paravalvular leak occurred more after TAVI.

Conclusion In lower-risk patients, there was an early mortality reduction with TAVI, but no differences after later follow-up. There was also an early reduction in the composite of death or disabling stroke, with no difference at later follow-up. There were no significant differences for higher-risk patients. Informed therapy decisions may be more dependent on the temporality of events or secondary endpoints than the long-term occurrence of main clinical outcomes.

* Corresponding author. Tel: +1 203 737 2142, Fax: +1 203 737 7457, Emails: yousif.ahmad@yale.edu; dryousifahmad@gmail.com

Structured Graphical Abstract

Key Question

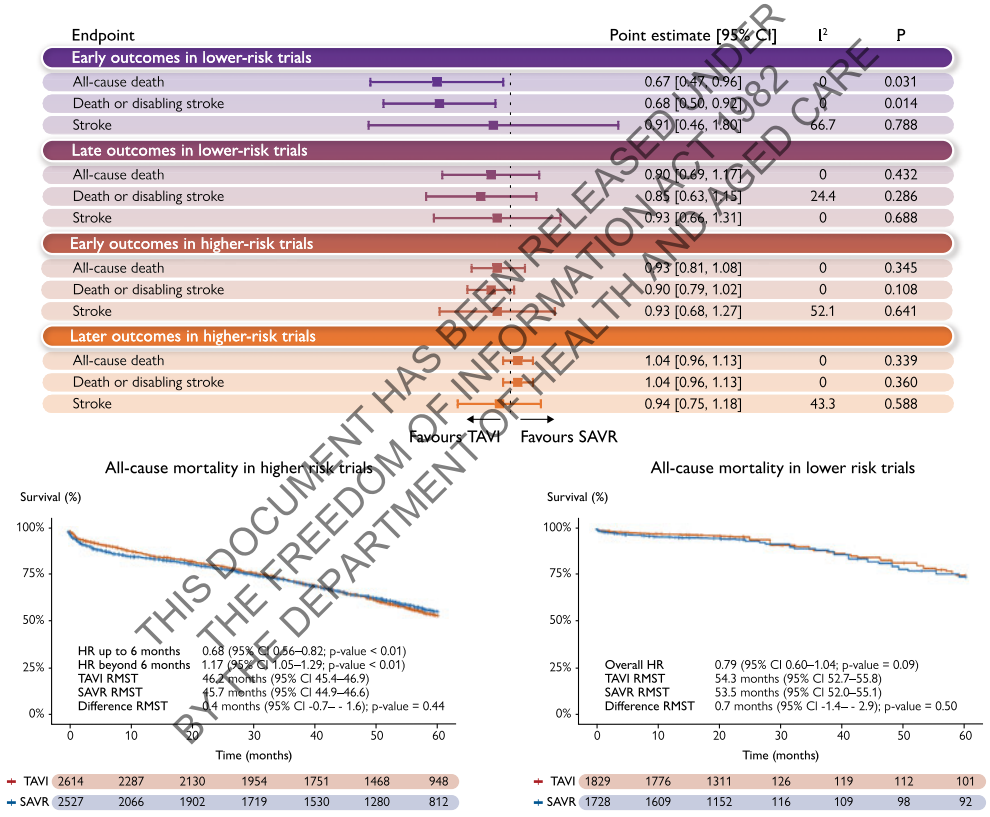
What are the clinical outcomes for patients with symptomatic severe aortic stenosis treated with either transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR) in randomized controlled trials (RCTs)? RCTs were pragmatically classified as lower or higher risk trials.

Key Finding

In lower risk trials, there was an early reduction in all-cause mortality and death or disabling stroke with TAVI. After 1-year, outcomes were similar with TAVI and SAVR. In higher risk trials, there was no difference in main outcomes. Certain secondary endpoints consistently favoured TAVI or SAVR.

Take Home Message

Early outcomes favour TAVI over SAVR in lower risk patients, but there are no longer-term differences. In higher risk trials, main outcomes are also similar. Informed therapy decisions may be more dependent on temporality of events or secondary endpoints than long-term main outcomes.



Summary of clinical outcomes following TAVI and SAVR, categorized into earlier and later events, and lower- and higher-risk trials.

Keywords Aortic stenosis • Transcatheter aortic valve replacement • Surgical aortic valve replacement • Meta-analysis

Introduction

Transcatheter aortic valve implantation (TAVI) has emerged as a safe and effective therapy for patients with severe aortic stenosis. TAVI was initially established in patients at prohibitive or extreme surgical risk,[1] and thereafter has been evaluated in randomized clinical trials (RCTs) against surgical aortic valve replacement (SAVR) for patients at high,[2,3] intermediate[4,5] and low[6,7] surgical risk. Clinical guidelines recommend an integrative approach to therapeutic decision-making incorporating clinical, anatomical, and procedural factors. Among the clinical factors, European guidelines recommend TAVI for patients aged 75 years or older, irrespective of surgical risk, and as the preferred or alternative therapy to SAVR for aortic stenosis patients at high or intermediate surgical risk. US guidelines also focus on age and life

expectancy to guide therapeutic decisions, with a recommendation for TAVI in preference to SAVR for patients aged 80 and older, and as an equal alternative to SAVR for patients aged 65 and older.[8,9]

The emphasis has recently shifted to lower-risk patients, with multiple randomized trials demonstrating surprisingly favorable early outcomes after TAVI compared with SAVR.[6,7] Since event rates are reduced in these trials, they will be relatively underpowered for clinically important but low-frequency events such as mortality. The application of meta-analysis methodology may therefore be useful to help clarify optimal therapy choices. Moreover, new clinical trial data comparing TAVI with SAVR has recently become available, including longer term follow-up of five trials[10–14] and one new lower-risk trial.[15] We therefore sought to perform an updated systematic review and meta-analysis comparing TAVI vs. SAVR for severe aortic stenosis, using a simple and pragmatic classification of surgical risk (higher and lower risk) and timing of events (early and later).

Methods

The present analysis was reported in accordance with published preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidance[16] and was prospectively registered at the International prospective register of systematic reviews (PROSPERO) international prospective register of systematic reviews (CRD42020175286). Ethical approval was not required for this study-level meta-analysis.

Search strategy

We performed a systematic search of the MEDLINE, Cochrane Central Register of Controlled Trials, and Embase databases from December 2000 to April 2022 for all trials comparing TAVI and SAVR for severe aortic stenosis. Our search strings included ('severe aortic stenosis' or 'severe symptomatic aortic stenosis') , ('TAVI' or 'transcatheter aortic valve replacement') and ('SAVR' or 'aortic valve replacement'). We hand-searched the bibliographies of selected studies and meta-analyses to identify further eligible studies. Abstracts were reviewed for suitability and articles were accordingly retrieved. Conference abstracts from the American Heart Association, the American College of Cardiology, the European Society of Cardiology, Transcatheter Therapeutics (TCT), Transcatheter Valve Therapies , and EuroPCR were also searched for eligible studies. Two independent authors performed the search and literature screening (YA and ADA), with disputes resolved by consensus.

Inclusion criteria

Only RCTs were eligible. Trials were eligible if they reported clinical outcome data following randomization to TAVI or SAVR. Observational studies were not eligible. At least 1 year of follow-up was required.

Endpoints

The main outcomes were all-cause mortality, all strokes, and the composite of death or disabling stroke, as reported in each trial. Secondary endpoints included cardiac (or cardiovascular) death, disabling stroke, myocardial infarction, new permanent pacemaker implantation, aortic valve reintervention, major bleeding, major vascular complications, paravalvular leak (at least mild and at least moderate considered separately), new-onset atrial fibrillation, re-hospitalization, and acute kidney injury. Each trial's definition of each adverse event was used. Principal investigators of each trial were contacted to provide additional data when relevant if not reported in the index publications. The UK TAVI trial reported aortic regurgitation rather than paravalvular leak specifically, but these data were used for the endpoints related to the paravalvular leak.

Data extraction and analysis

Two authors (YA and ADA) independently abstracted the data from included trials, verified by a third author (JH). Included studies were assessed using the Cochrane Risk of Bias 2.0 tool.[17,18] Tests for publication bias would only be performed in the event of 10 or more trials being included for analysis.[19]

Outcomes were analysed on an intention-to-treat basis wherever available. Although the Evolut low-risk[7] trial publication initially used Bayesian methodology to project 2-year results, the full 2-year results for Evolut low-risk were recently published,[11] and the principal investigators and sponsors also provided additional 2-year results, which had not previously been reported, which were used for this analysis. The SURTAVI[5] trial used similar methodology, but a subsequent publication[20] utilized the complete 2-year follow-up data. The 5-year results of SURTAVI were recently presented at TCT 2021,[14] and the principal investigators and sponsors also provided additional 5-year results, which had not been previously reported. These 5-year results of SURTAVI have recently been published.[14] The NOTION trial 8-year follow-up data[12] was utilized in this analysis, using the intention-to-treat population, and once again, the principal investigators provided additional data for this analysis, which has not previously been reported.

We used survival analyses using hazard ratios (HRs) to assess the entire follow-up duration of each trial, which is the most appropriate methodology for time-to-event data and also takes into account variable follow-up duration. We extracted the hazard ratios with their associated 95% confidence intervals (CI) and *P*- values. If HRs were not reported for a trial in the index publications, the principal investigators and sponsors were contacted to provide this data. The HRs and 95% CI at the latest follow-up available were utilized for all trials. A random-effects meta-analysis was performed of the natural logarithm of the HRs and their associated standard errors using the restricted maximum likelihood (REML) estimator. The standard error was calculated by dividing the difference between the natural logarithms of the upper and lower 95% CI by 2 × the appropriate normal score (1.96). Where the lower 95% CI approached zero, the standard error was calculated using only the difference between the natural logarithm of the upper 95% CI and the natural logarithm of the point estimate. We also separately examined early effects by extracting event counts at 1 year, which we present as relative risks (RRs). Outcomes were classified as early if they occurred at 1 year. If trials reported outcomes beyond 1 year, they were eligible to be included in our analyses of later outcomes. This was performed by assessing HRs and 95% CI for the entire follow-up duration of each trial, to account for variable follow-up duration.

In order to assess the entire follow-up duration of each trial (including those with only 1-year follow-up available), we also performed a reconstructed individual patient data analysis based on digitizing survival curves from Kaplan–Meier plots, combined with the total number of patients in each arm, the total number of events in each arm, and the number of patients at risk at various time intervals. These analyses were performed for all the main outcomes of all-cause mortality, death or disabling stroke, and stroke (if Kaplan–Meier plots were only available for the outcome of 'disabling stroke' then this was used). Principal investigators and sponsors of trials were contacted to contribute additional Kaplan–Meier plots if they were not available in published manuscripts or conference abstracts. The digitization and extraction of the individual patient data were performed using the Shiny application.[21] Kaplan–Meier analyses and Cox proportional hazard models were fitted using the extracted individual patient data using the 'survival' package for R; pooled Kaplan–Meier plots were generated using the 'survminer' package to visually present the data. To calculate a HR from the synthetic individual patient data, we used a Cox frailty model. Heterogeneity across trials was assessed for each endpoint by testing for an interaction between the trial and the randomized treatment effect; the inclusion of a γ frailty term was used to account for heterogeneity between trials, with trials modelled as a random effect using random intercepts. The significance of the variance parameter was assessed with the likelihood ratio test.

The trial arm (TAVI or SAVR) was modelled as a fixed effect. This was performed using the 'coxph' function from the 'survival' package within R.

The proportional hazards assumption was tested for each of the endpoints by use of Schoenfeld residuals and visual inspection of the Schoenfeld residuals and Kaplan–Meier plots. Formal testing was performed using the 'cox.zph' function from the 'survival' package in R. If the proportional hazards assumption was violated, models that allowed for time-varying HRs were used. For these models, we identified a single cutoff and calculated HRs before and after this cutoff. The cutoff was identified by visual inspection of the Schoenfeld residuals and Kaplan–Meier plots, and the proportional hazards assumption was tested within the timepoints identified by this cutoff to ensure they were not violated. In instances where the proportional hazards assumption was violated, we also performed sensitivity analyses with a proportional odds model fitted with a frailty term for study-level heterogeneity (modelled as a random intercept) using the 'logitSurv' function from the 'mets' package in R. These analyses are reported as odds ratios (OR), with 95% CI and *P*-values.

Finally, to assess total lifetime lost, we calculated the restricted mean survival time (RMST) for each major endpoint and compared the difference between the groups.

Sensitivity analyses were performed excluding each trial in turn for the primary outcome of all-cause mortality, and further sensitivity analyses were performed excluding transapical cases. Finally, we performed sensitivity analyses using the HKSJ random-effects model for all our main analyses.[22] We used the I^2 statistic to assess heterogeneity.[23] Low heterogeneity was defined as 0%–25%, moderate heterogeneity was defined as 25%–50% and significant heterogeneity was defined as >50%.

Trials were classified into two groups on the basis of surgical risk: a higher-risk group and a lower-risk group. The higher-risk group included trials of extreme, high, and intermediate/high-risk; the lower-risk group included trials of low and low/intermediate-risk. This classification was made by the authors on the basis of a review of the included trials. For purposes of illustration, the lower risk trials were PARTNER 3 (mean age ~73 years, mean STS PROM ~1.9%), Evolut Low-Risk (mean age ~74 years, mean STS PROM ~1.9%), NOTION (mean age ~79 years, mean STS PROM ~3.0%) and UK TAVI (median age ~81 years and median STS PROM ~2.6%). In comparison, the higher risk trials were PARTNER 1A (mean age ~84 years, mean STS PROM ~11.7%), CoreValve High-Risk (mean age ~83 years, men STS PROM ~7.4%), PARTNER 2 (mean age ~81.6 years, mean STS PROM ~5.8%) and SURTAVI (mean age ~79.8 years, mean STS PROM ~4.5%). Sensitivity analyses were performed for the main outcomes, including all trials irrespective of risk classification.

Subgroup analyses were performed for these risk groups to look for evidence of a treatment interaction, as well as for access route (transfemoral vs. non-transfemoral). Interactions between clinical outcomes and surgical risk and access site were assessed using a multivariate meta-analysis model with the variable in question as a moderator.

Mean values are expressed as mean ± SD unless otherwise stated. Significance testing was performed at the two-tailed 5% significance level. The statistical programming environment R[24] with the metafor package[25] was used for all statistical analyses.

Results

Eight trials were eligible for this meta-analysis.[5,7,10,13,15,26–28] When considering multiple publications from different time points for individual trials, 12 additional publications or abstracts were also included.[2–4,6,11,12,14,20,29–32] The search strategy and results are shown in Supplementary material online, *Figure S1* of the supplementary appendix. A total of 8698 patients were included, with 4443 randomized to TAVI and 4255 randomized to SAVR, 3557 lower-risk patients and 5141 higher-risk patients. The maximum available follow-up duration for this analysis was 1 year in one trial,[15] 2 years in two trials,[10,11] 5 years in four trials[13,14,27,28] and 8 years in one trial.[12] The weighted mean follow-up duration across all trials was 46.5 months.

The characteristics of the included trials are summarized in *Table 1*. The risk of bias of each trial is shown in the Supplementary material online, *Table S1* of the supplementary appendix. Definitions of outcomes used in each included trial are reported in the Supplementary material online, *Table S2* of the supplementary appendix. The estimates of the frailty parameters for heterogeneity in the reconstructed individual patient data analyses are shown in Supplementary material online, *Table S8*, with most analyses showing significant study-level heterogeneity. Schoenfeld residual plots to assess proportional hazards are shown in Supplementary material online, *Figures S17–S30*.

All-cause mortality

A summary of outcomes for all-cause mortality is shown in *Figure 1*. Across the four lower-risk trials, the point estimate for early events with TAVI compared with SAVR was RR 0.67 (95% CI 0.47–0.96, $P = 0.03$). There was no important statistical heterogeneity ($I^2 = 0.0\%$). At longer term follow-up, the point estimate for all-cause mortality with TAVI compared with SAVR was HR 0.90 (95% CI 0.69–1.17, $P = 0.43$). There was no important statistical heterogeneity ($I^2 = 0.0\%$). The UK TAVI trial has only reported 1-year outcomes to date and so was not included in the longer term follow-up analysis.

Across the four higher-risk trials, the point estimate for early events with TAVI compared with SAVR was RR 0.93 (95% CI 0.81–1.08, $P = 0.35$). There was no important statistical heterogeneity ($I^2 = 0.0\%$). At longer term follow-up, the point estimate for all-cause mortality with TAVI compared with SAVR was HR 1.04 (95% CI 0.96–1.13, $P = 0.34$). There was no important statistical heterogeneity ($I^2 = 0.0\%$).

When assessing the entire follow-up duration of each trial together using a reconstructed individual patient data meta-analysis, the proportional hazards assumption was not violated for the lower-risk trials (Schoenfeld residual *P*- value = 0.25). There was no significant difference in all-cause mortality between TAVI and SAVR in the lower risk trials (overall HR 0.79, 95% CI 0.60–1.04, $P = 0.09$). There was significant heterogeneity ($P < 0.001$). The RMST was overall 0.7 months greater with TAVI than with SAVR, but this difference was not statistically significant (54.3 months vs. 53.5 months, $P = 0.50$). The pooled Kaplan–Meier plot for death in lower-risk trials is shown in *Figure 2A*.

For the higher risk trials, the proportional hazards changed over time (Schoenfeld residual *P*-value < 0.001). Time-varying analyses using a 6-month cutoff retained the proportional hazards assumption (Schoenfeld residual *P*-value for first time-period = 0.28; Schoenfeld residual *P*-value for second time-period = 0.97). There was a lower risk of death with TAVI up to 6 months (HR up to 6 months 0.68, 95% CI 0.56–0.82, $P < 0.01$), with a greater risk of death with TAVI beyond 6 months (HR beyond 6 months 1.17, 95% CI 1.05–1.29, $P < 0.01$). When assessing the entire duration of follow-up using the proportional odds model, there was no difference between the two groups (OR 1.07, 95% CI 0.95–1.20, $P = 0.27$). The RMST was overall 0.4 months greater with TAVI than SAVR, but this difference was not statistically significant (46.2 months vs. 45.7 months, $P = 0.44$). The pooled Kaplan–Meier plot for death is shown in *Figure 2B*.

Stroke

A summary of outcomes for stroke is shown in *Figure 3*. Across the four lower-risk trials, the point estimate for early events with TAVI compared to SAVR was RR 0.91 (95% CI 0.46–1.80, $P = 0.79$). There was significant statistical heterogeneity ($I^2 = 66.7\%$). At longer term follow-up, the point estimate for stroke with TAVI compared to SAVR was HR 0.93 (95% CI 0.66–1.31, $P = 0.69$). There was no important statistical heterogeneity

Table 1 Characteristics of included studies

Author	Study acronym	Year	Region	*n*	Mean Age[a]	Follow-up[b]	Entry criteria	TAVI Type	Primary outcome[c]	Secondary outcomes[c]
Smith *et al.*[2]	PARTNER 1A	2011	Germany, North America	699	84.1 (± 6.6)	5	Severe, symptomatic AS AVA ≤0.8 cm^2 (index 0.5 cm^2/m^2) or peak velocity ≥4 m/s or mean PG ≥40 mmHg high-risk for SAVR (surgeon and cardiologist agreed 30d mortality ≥15% and/or STS score ≥10).	Edwards Sapien Balloon expandable, bovine pericardium	All-cause mortality at 1y	All-cause mortality at longer follow-up durations. CV mortality, Stroke/TIA, MI, vascular complications, bleeding, endocarditis, renal failure, new pacemaker.
Adams *et al.*[3]	CoreValve high-risk	2014	USA	797	83.2	5	Severe, symptomatic AS AVA ≤0.8 cm^2 (index 0.5 cm^2/m^2) or peak velocity >4 m/s or mean PG >40 mmHg high-risk for SAVR (surgeon and cardiologist agreed 30d mortality ≥15% and 30d mortality/irreversible complications <50%. STS PROM score considered).	Medtronic CoreValve Self-expanding, porcine pericardium	All-cause mortality at 1y	MACE (death from any cause, MI, any stroke and reintervention) and its components. NYHA, KCCQ and SF-12 improvement. Change in AV gradient and AVA (core lab).
Thyregod *et al.*[29]	NOTION	2015	Denmark, Sweden	280	79.1 (± 4.8)	8	Severe, symptomatic AS AVA ≤1 cm^2 (index 0.6 cm^2/m^2) and either peak velocity >4 m/s or mean PG >40 mmHg. Asymptomatic if LV posterior wall thickness ≥17 mm. All risk statuses.	Medtronic CoreValve Self-expanding, porcine pericardium	Composite of all-cause mortality, stroke and MI, at 1y	Primary outcome components, CV death, prosthesis reintervention, cardiogenic shock, endocarditis, pacemaker, atrial fibrillation/flutter, vascular, renal, bleeding complications, AVA, AV gradient, AR.
Leon *et al.*[4]	PARTNER 2A	2016	North America	2032	81.6	5	Severe, symptomatic AS AVA ≤0.8 cm^2 (index 0.5 cm^2/m^2) or peak velocity >4 m/s or mean PG >40 mmHg Intermediate-risk for SAVR (Heart Team including surgeon agreed STS PROM 30d mortality 4–8%.	Edwards Sapien XT Balloon expandable, bovine pericardium	Composite of all-cause mortality or disabling stroke at 2y	All-cause mortality, disabling stroke hospitalization, reintervention, NYHA, KCCQ, EuroQOL, SF-36, AVA, AV gradients, AR.
Reardon *et al.*[5]	SURTAVI	2017	Europe, North America	1746	79.8 (±6.2)	5	Severe, symptomatic AS AVA ≤1.0 cm^2 (index 0.6 cm^2/m^2) with peak velocity >4 m/s or mean PG >40 mmHg or Doppler velocity index <0.25 Intermediate-risk for SAVR (heart team agreed STS PROM 30d mortality 3–15%.	Medtronic CoreValve Evolut R Self-expanding, porcine pericardium	Composite of all-cause mortality or disabling stroke at 2y	MACCE: all-cause mortality, MI, any stroke, any reintervention. AV gradient, AVA, NYHA, KCCQ.

Continued

Table 1 *Continued*

Author	Study acronym	Year	Region	*n*	Mean Age[a]	Follow-up[b]	Entry criteria	TAVI Type	Primary outcome[c]	Secondary outcomes[c]
Mack *et al.*[6]	PARTNER 3	2019	US, Australia, New Zealand, Japan	1000	73.3 (±5.8)	2	Severe, symptomatic AS AVA ≤1.0 cm^2 (index 0.6 cm^2/m^2) with peak velocity ≥4 m/s or mean PG ≥40 mmHg. Asymptomatic if LVEF <50% or abnormal exercise test. Low-risk for SAVR (heart team agreed STS PROM 30d mortality <4%.	Edwards Sapien 3 Balloon expandable, bovine pericardium	Composite of all-cause mortality, stroke or re-hospitalization at 1y	Stroke, composite of death or stroke, new-onset AF at 30d, hospitalization duration, composite of death or low KCCQ at 30 d. NYHA, KCCQ, 6MWT.
Popma *et al.*[7]	Evolut low-risk	2019	North America, Australia, Europe, Japan	1468	74	2	Severe, symptomatic AS AVA ≤1.0 cm^2 (index 0.6 cm^2/m^2) with peak velocity ≥4 m/s or mean PG ≥40 mmHg. Asymptomatic if LVEF <50%. Asymptomatic: peak velocity ≥5 m/s or mean PG ≥60 mmHg or LVEF <50% or abnormal exercise test. Low-risk for SAVR (Heart Team agreed STS PROM 30d mortality ≤3%.	Medtronic CoreValve Evolut R Evolut PRO Self-expanding, porcine pericardium	Composite of all-cause mortality or disabling stroke at 2y	All-cause mortality, disabling stroke, lifethreatening bleed, major vascular complications, stage II or III acute kidney injury (composite), new PPM at 30d. Endocarditis, thrombosis, all stroke, life threatening bleeding, reintervention at 1 yr. Mean gradient, AVA, NYHA, KCCQ at 1y.
Toff *et al.*[15]	UK TAVI	2022	UK	913	81.0 (±4.4)	1	Severe, symptomatic AS Age ≥80 or ≥70 with intermediate or high-risk as determined by multidisciplinary team	Any CE marked valve	All-cause mortality at 1y	All-cause mortality at 2,3,4,5y. Stroke, composite of all-cause mortality or stroke, composite of all-cause mortality or disabling stroke, conduction disturbance requiring permanent pacemaker, endocarditis, reintervention, vascular complications, major bleeding, renal replacement therapy, MLWHF, EQ-5D-5L, NYHA, 6MWT, TTE measures.

[a]Mean age in years (+/- SD); value for TAVI group provided where values differ between TAVI and SAVR groups and overall value not reported.
[b]Follow-up in years (longest follow-up provided if multiple analyses).
[c]Further details of definitions are provided in Table 3 in the supplementary material.
AS, aortic stenosis; STS PROM, Society of Thoracic Surgeons Predicted Risk Of Mortality; AV, aortic valve; AVA, aortic valve area; MI, myocardial infarction; NYHA, New York Hospital Association functional class; KCCQ, Kansas City Cardiomyopathy Questionnaire; SF-12, medical outcomes study 12-item short form general health survey; LV, left ventricle; LVEF, left ventricular ejection fraction; AR, aortic regurgitation; CV, cardiovascular; 6MWT, 6 m walk test; MLWHF, Minnesota Living With Heart Failure Questionnaire; PPM, permanent pacemaker; MACE, major adverse cardiac event; PG, pressure gradient.

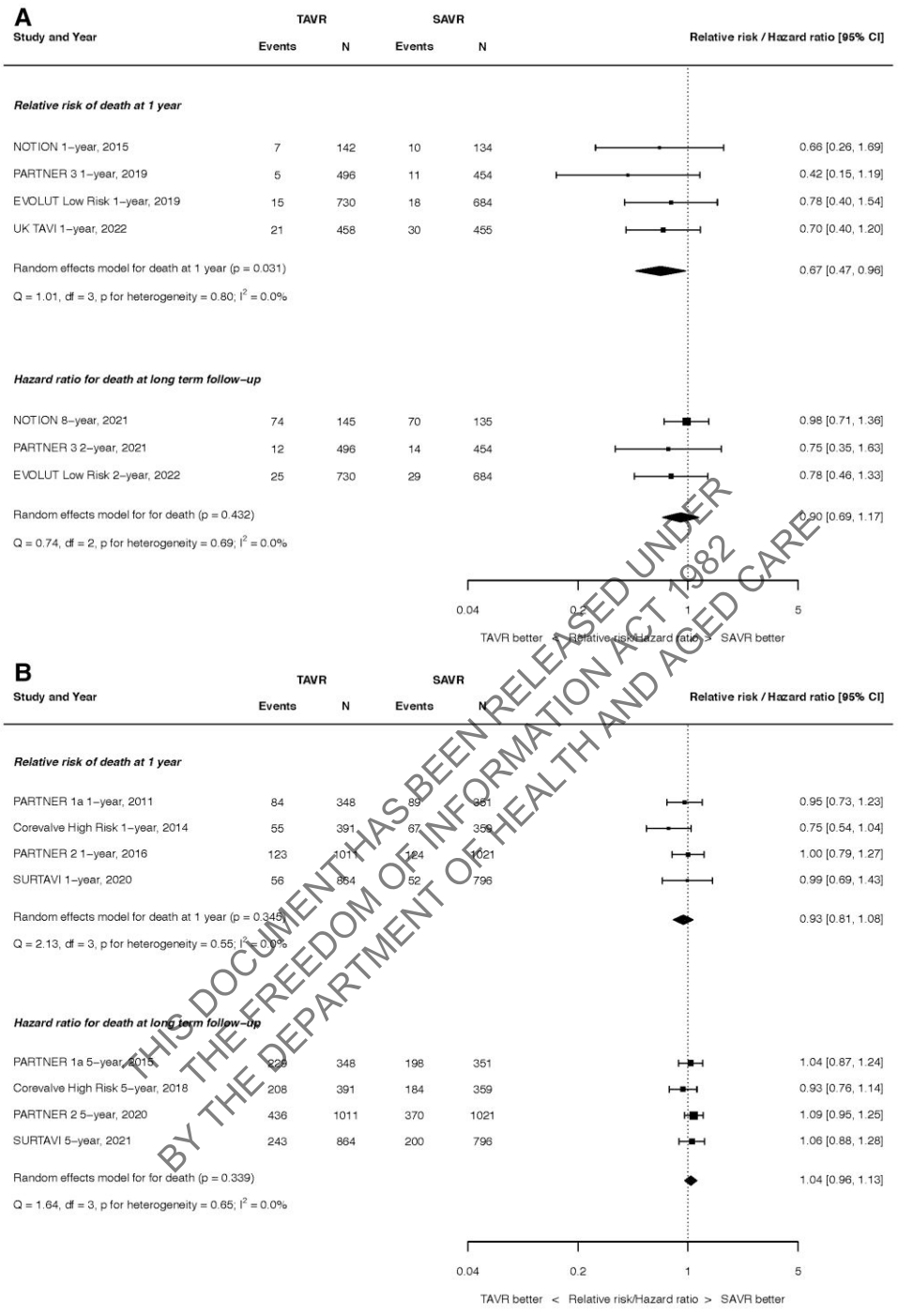


Figure 1 Outcomes for all-cause mortality following transcatheter aortic valve implantation and surgical aortic valve replacement in (*A*) lower-risk trials and (*B*) higher-risk trials. The top panels show early events (assessed at 1-year) and the bottom panels show late events (assessed beyond 1-year).

($I^2 = 0.0\%$). The UK TAVI trial has only reported 1-year outcomes to date and so was not included in the longer term follow-up analysis.

Across the four higher-risk trials, the point estimate for early events with TAVI compared to SAVR was RR 0.93 (95% CI 0.68–1.27, $P = 0.64$). There was significant statistical heterogeneity ($I^2 = 52.1\%$). At longer term follow-up, the point estimate for stroke with TAVI compared to SAVR was HR 0.94 (95% CI 0.75–1.18, $P = 0.59$). There was moderate statistical heterogeneity ($I^2 = 43.3\%$).

When assessing the entire follow-up duration of each trial together using a reconstructed individual patient data meta-analysis, proportional hazards changed over time in the lower risk trials (Schoenfeld residual P-value = 0.006). Time-varying analyses using a 3-month cutoff retained the proportional hazards assumption (Schoenfeld residual P-value for the first time period = 0.38; Schoenfeld residual P-value for second time period = 0.66). There was a lower risk of stroke with TAVI up to 3 months (HR up to 3 months 0.52, 95% CI 0.30–0.88, $P = 0.01$),

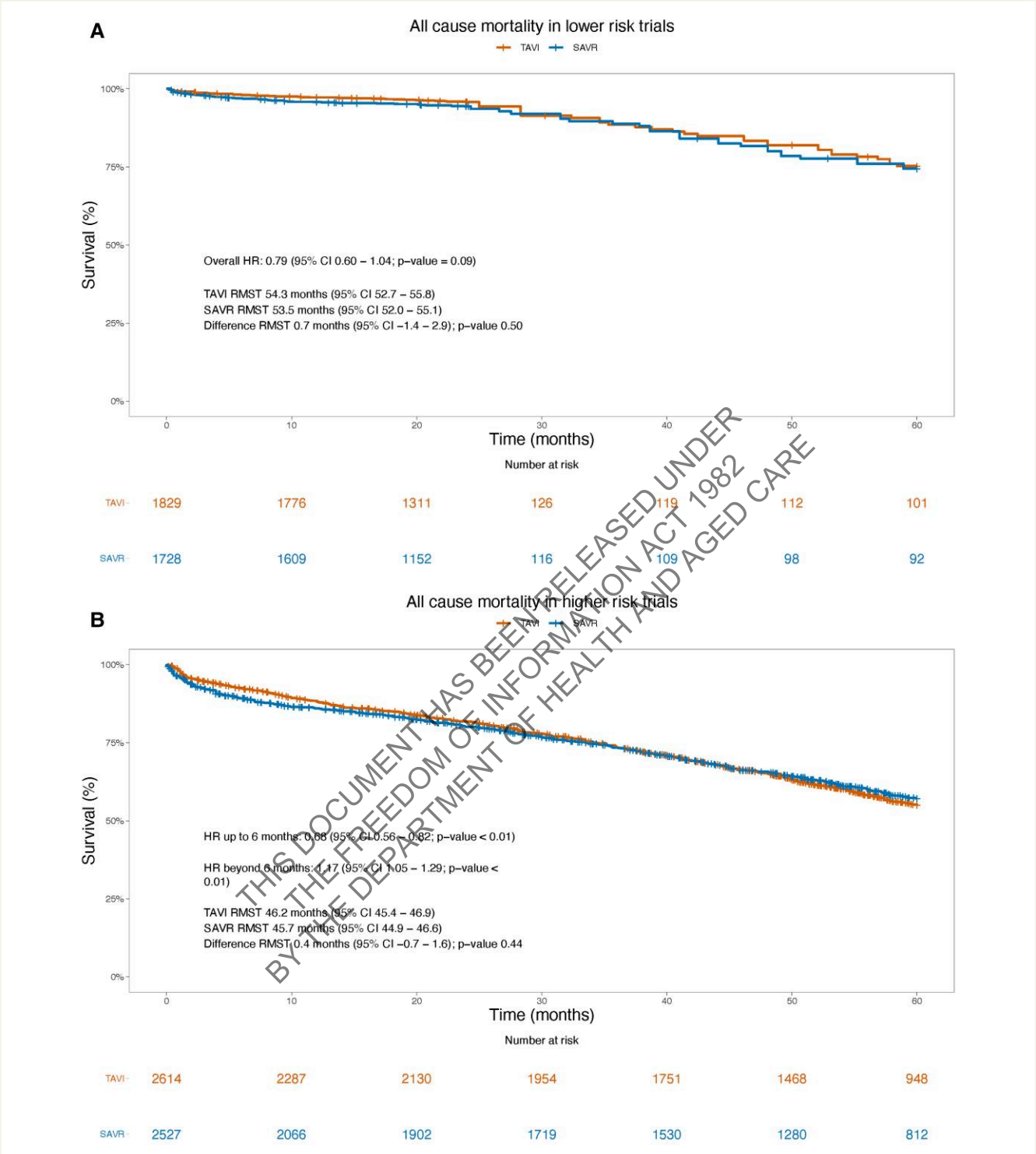


Figure 2 Pooled Kaplan–Meier plot of reconstructed individual patient data analysis for all-cause mortality following transcatheter aortic valve implantation and surgical aortic valve replacement in (*A*) lower-risk trials and (*B*) higher-risk trials.

with a greater risk beyond 3 months (HR 2.14, 95% 1.22–3.78, $P < 0.01$). When assessing the entire duration of follow-up using the proportional odds model, there was no significant difference between the two groups (OR 1.03, 95% CI 0.71–1.49, $P = 0.87$). RMST was overall 0.4 months greater with SAVR than with TAVI but this difference was not statistically significant (57.3 months vs. 57.8 months, $P = 0.47$). The pooled Kaplan–Meier plot for stroke in lower risk trials is shown in *Figure 4A*.

When assessing the entire follow-up duration of each trial together using a reconstructed individual patient data meta-analysis, proportional hazards changed over time in the higher-risk trials (Schoenfeld residual *P*-value = 0.045). Time-varying analyses using a 3-month cutoff retained

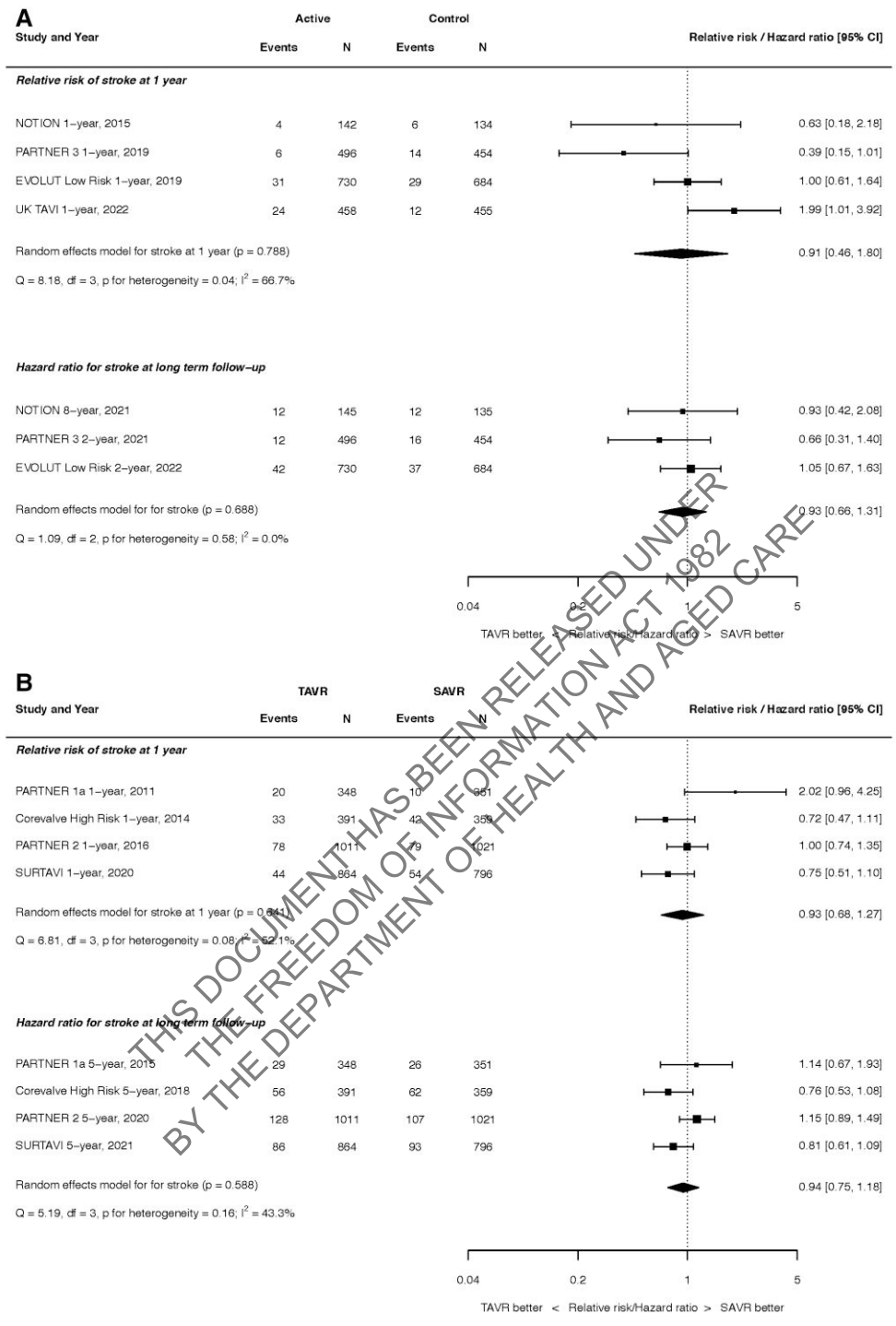


Figure 3 Outcomes for stroke following transcatheter aortic valve implantation and surgical aortic valve replacement in (*A*) lower-risk trials and (*B*) higher-risk trials. The top panels show early events (assessed at 1-year) and the bottom panels show late events (assessed beyond 1-year).

the proportional hazards assumption (Schoenfeld residual *P*- value for first time-period = 0.052; Schoenfeld residual *P*-value for the second time-period = 0.35). The effect size up to 3 months was HR 0.87 (95% CI 0.68–1.12, *P* = 0.28), and the effect size beyond 3 months was HR 1.06 (95% CI 0.82–1.37, *P* = 0.65). When assessing the entire duration of follow-up using the proportional odds model, there was no significant difference between the two groups (OR 0.96, 95% CI 0.79–1.15, *P* = 0.63). RMST was overall 0.4 months greater with TAVI than with SAVR but this difference was not statistically significant (55.3 months vs. 54.9 months, *P* = 0.40). The pooled Kaplan–Meier plot for stroke in higher risk trials is shown in *Figure 4B*.

For these analyses, the outcome of a disabling stroke was used for SURTAVI and Evolut low-risk, while for all other trials, all strokes were used.

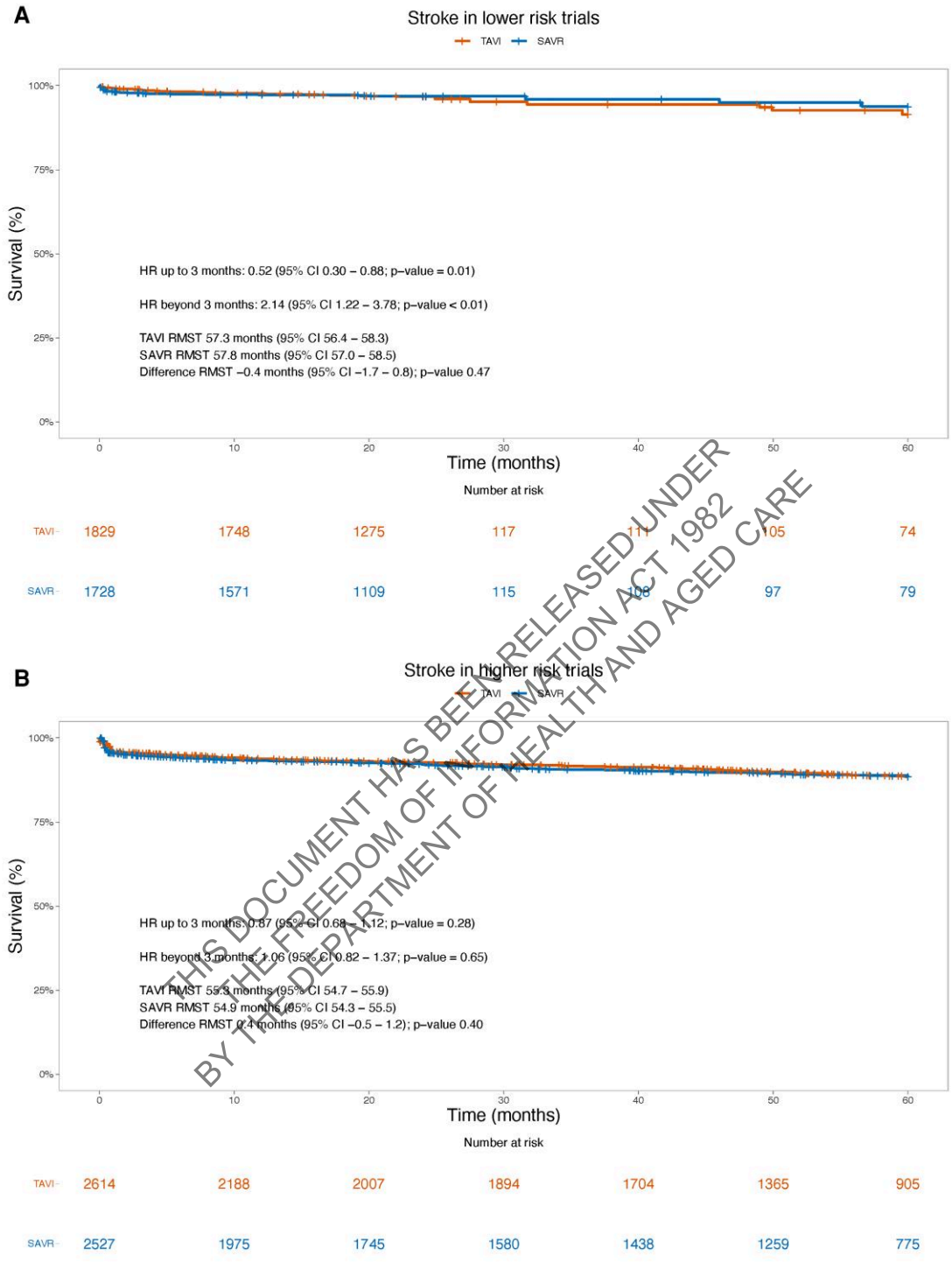


Figure 4 Pooled Kaplan–Meier plot of reconstructed individual patient data analysis for stroke following transcatheter aortic valve implantation and surgical aortic valve replacement in (*A*) lower-risk trials and (*B*) higher-risk trials.

Death or disabling stroke

A summary of outcomes for the composite endpoint of all-cause mortality or disabling stroke is shown in *Figure 5*. Across the four lower-risk studies, the point estimate for early events with TAVI compared to SAVR was RR 0.68 (95% CI 0.50–0.92, $P = 0.01$). There was no important statistical heterogeneity ($I^2 = 0.0\%$). At longer term follow-up, the point estimate for death or disabling stroke with TAVI compared to SAVR was HR 0.85 (95% CI 0.63–1.15, $P = 0.29$). There was mild

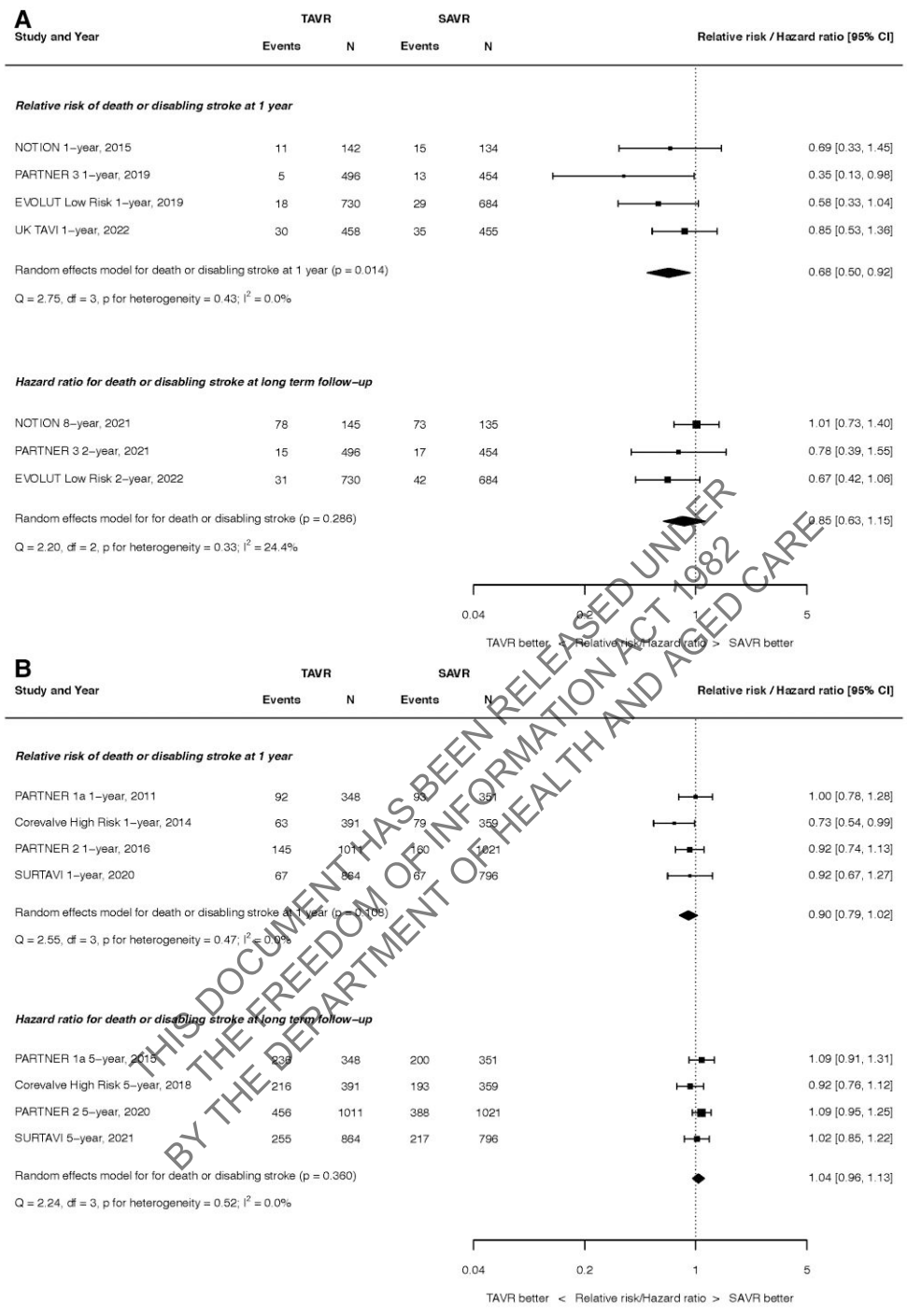


Figure 5 Outcomes for death or disabling stroke following transcatheter aortic valve implantation and surgical aortic valve replacement in (*A*) lower-risk trials and (*B*) higher-risk trials. The top panels show early events (assessed at 1 year) and bottom panels show late events (assessed beyond 1 year).

statistical heterogeneity ($I^2 = 24.4\%$). The UK TAVI trial has only reported 1-year outcomes to date and so was not included in the longer term follow-up analysis. Of note, unlike the other trials, the NOTION trial and the UK TAVI trial utilized a composite of death or stroke, rather than death or disabling stroke, but both were included in this meta-analysis.

Across the four higher-risk trials, the point estimate for early events with TAVI compared to SAVR was RR 0.90 (95% CI 0.79–1.02, $P = 0.11$). There was no important statistical heterogeneity ($I^2 = 0.0\%$). At longer term follow-up, the point estimate for death or disabling stroke with TAVI compared to SAVR was HR 1.04 (95% CI 0.96–1.13, $P = 0.36$). There was no heterogeneity ($I^2 = 0.0\%$).

When assessing the entire follow-up duration of each trial together using a reconstructed individual patient data meta-analysis of the lower-risk trials, the proportional hazards assumption was not violated (Schoenfeld residual *P*-value = 0.06). There was no significant difference

between the two groups (HR 0.85, 95% 0.67–1.08, $P = 0.18$). RMST was overall 0.3 months greater with TAVI, but this difference was not statistically significant (52.6 months vs. 52.3 months, $P = 0.78$). The pooled Kaplan–Meier for death or disabling stroke in the lower risk trials is shown in *Figure 6A*.

Across the higher-risk trials, proportional hazards changed over time (Schoenfeld residual *P*-value <0.01). Time-varying analyses using a 6-month cutoff retained the proportional hazards assumption (Schoenfeld residual *P*-value for first time-period = 0.65; Schoenfeld residual *P*- value for second time-period = 0.75). There was a reduced risk of death or disabling stroke with TAVI up to 6 months (HR 0.73, 95% CI 0.62–0.85, $P < 0.01$), with an increased risk beyond 6 months (HR 1.20, 95% CI 1.09–1.33, $P < 0.01$). When assessing the entire follow-up duration using the proportional odds model, there was no significant difference between the two groups (OR 1.09, 95% CI 0.97–1.23, $P = 0.12$). RMST was overall 0.4 months greater with TAVI, but this difference was not statistically significant (44.8 months vs. 44.4 months, $P = 0.48$). The pooled Kaplan–Meier plots for death or disabling stroke in the higher risk trials are shown in *Figure 6B*.

Again, the NOTION trial and the UK TAVI trial utilized a composite of death or stroke, rather than death or disabling stroke, but both were included in this analysis.

Other clinical outcomes

A summary of other clinical outcomes is presented in *Figure 7*, Supplementary material online, *Tables S3 and S4* of the supplementary appendix. These secondary clinical outcomes were assessed at the 1-year timepoint.

In the lower-risk group, there was no significant difference between TAVI and SAVR for myocardial infarction and aortic valve reintervention at 1 year. TAVI was associated with an increased risk of new permanent pacemaker insertion, > mild and > moderate paravalvular leak and major vascular complications. TAVI was associated with a decreased risk of disabling stroke, cardiac death (although not statistically significant, $P = 0.05$), re-hospitalization, acute kidney injury, disabling stroke, new-onset atrial fibrillation, and major bleeding.

In the higher-risk group, there was no significant difference between TAVI and SAVR for cardiac death, myocardial infarction, or disabling stroke at 1 year. TAVI was associated with an increased risk of new permanent pacemaker insertion, aortic valve reintervention, > mild and > moderate paravalvular leak, and major vascular complications. TAVI was associated with a decreased risk of new-onset atrial fibrillation, acute kidney injury, and major bleeding.

Subgroup analyses

There was no evidence of a significant interaction between surgical risk and all-cause mortality (*P* for interaction = 0.28). There was evidence of a significant interaction between the use of transfemoral access and all-cause mortality, with a benefit with transfemoral access vs. non-transfemoral (*P* for interaction = 0.0004).

Sensitivity analyses

Jackknife analysis excluding each trial in turn for all-cause mortality also showed broadly consistent results (see Supplementary material online, *Tables S5 and S6*). Additional exploratory sensitivity analyses were performed with all trials combined irrespective of risk classification and are shown in Supplementary material online, *Figures S2–S4*. Sensitivity analyses excluding transapical cases are shown in Supplementary material online, *Figures S5–S7*. All of our main meta-analyses were also performed using the HKSJ model, with the results shown in the Supplementary material online, *Figures S8–S13*. Finally, pooled Kaplan–Meier plots of reconstructed individual patient data analyses are shown for all trials combined irrespective of risk classification in Supplementary material online, *Figures S14–S16*.

Discussion

This study represents the most up-to-date systematic review and meta-analysis of randomized trials comparing TAVI to SAVR for the treatment of severe aortic stenosis, incorporating all newly available randomized data. This includes 2-year follow-up from PARTNER 3, 5-year follow-up from PARTNER 2A, the 1-year results of the UK TAVI trial, complete 2-year follow-up results from Evolut Low-Risk, 5-year follow-up from SURTAVI, and 8-year follow-up from NOTION. Some of these data have not previously been reported, and the majority have not been previously synthesized with appropriate meta-analytic methodology. We pragmatically categorized trials into higher-risk and lower-risk groups, and clinical events as occuring early (occurring up to 1 year) or later (occurring after 1 year). This provides a practical framework for discussing the relative outcomes of TAVI and SAVR in different clinical settings with patients and caregivers.

The main findings are summarized in the *Structured Graphical Abstract*. Across lower-risk trials, the early risk of death after TAVI was lower than SAVR (RR 0.67) and reached statistical significance ($P = 0.031$) with no heterogeneity ($I^2 = 0.0\%$). The early risk of the composite of death or disabling stroke was also significantly reduced with TAVI (RR 0.68, $P = 0.014$). The other main outcome of stroke showed no early differences between TAVI and SAVR therapies (RR 0.91, $P = 0.788$). The UK TAVI trial has only reported 1 year outcomes to date and so was not included in the longer term analyses for lower-risk trials. Across the other three lower-risk trials, no significant difference was seen after TAVI or SAVR for any of these main outcomes. The overall RMST was 0.7 months greater with TAVI, but this difference did not reach statistical significance. The longer term follow-up planned for these lower-risk trials (up to 10 years) will help to inform whether equivalence of these main outcomes is sustained.

Across higher-risk trials, during the first year of follow-up, the risk of death, stroke, and the composite of death or disabling stroke was not significantly different between TAVI and SAVR. Similarly, with longer term follow-up, the risk of death, stroke and the composite of death or disabling stroke was not significantly different between TAVI and SAVR. However, when time-varying analyses of the higher risk trials were performed using reconstructed individual patient data, TAVI was associated with a lower risk of death up to 1 year, but a higher-risk of death beyond 1 year with no significant difference overall. The RMST was overall 0.4 months greater with TAVI, but this difference was not statistically significant.

We also demonstrate a consistent pattern of other clinical outcomes in both higher and lower-risk patients: new-onset atrial fibrillation, major bleeding, and acute kidney injury occurred less frequently after TAVI, whereas new pacemaker insertion, vascular complications, and paravalvular leak all occurred more commonly after TAVI.

Our study differs from previous meta-analyses[33–35] in several ways. First, it includes all newly available clinical trial data, with the longest recorded follow-up and some previously unreported data. Second, we have partitioned events as 'early' and 'later' to provide a pragmatic framework for clinicians to discuss the available trial data with their patients. Third, we did not analyse all of the trials of TAVI vs. SAVR together, from the initial foundational trials in high-risk patients to the more

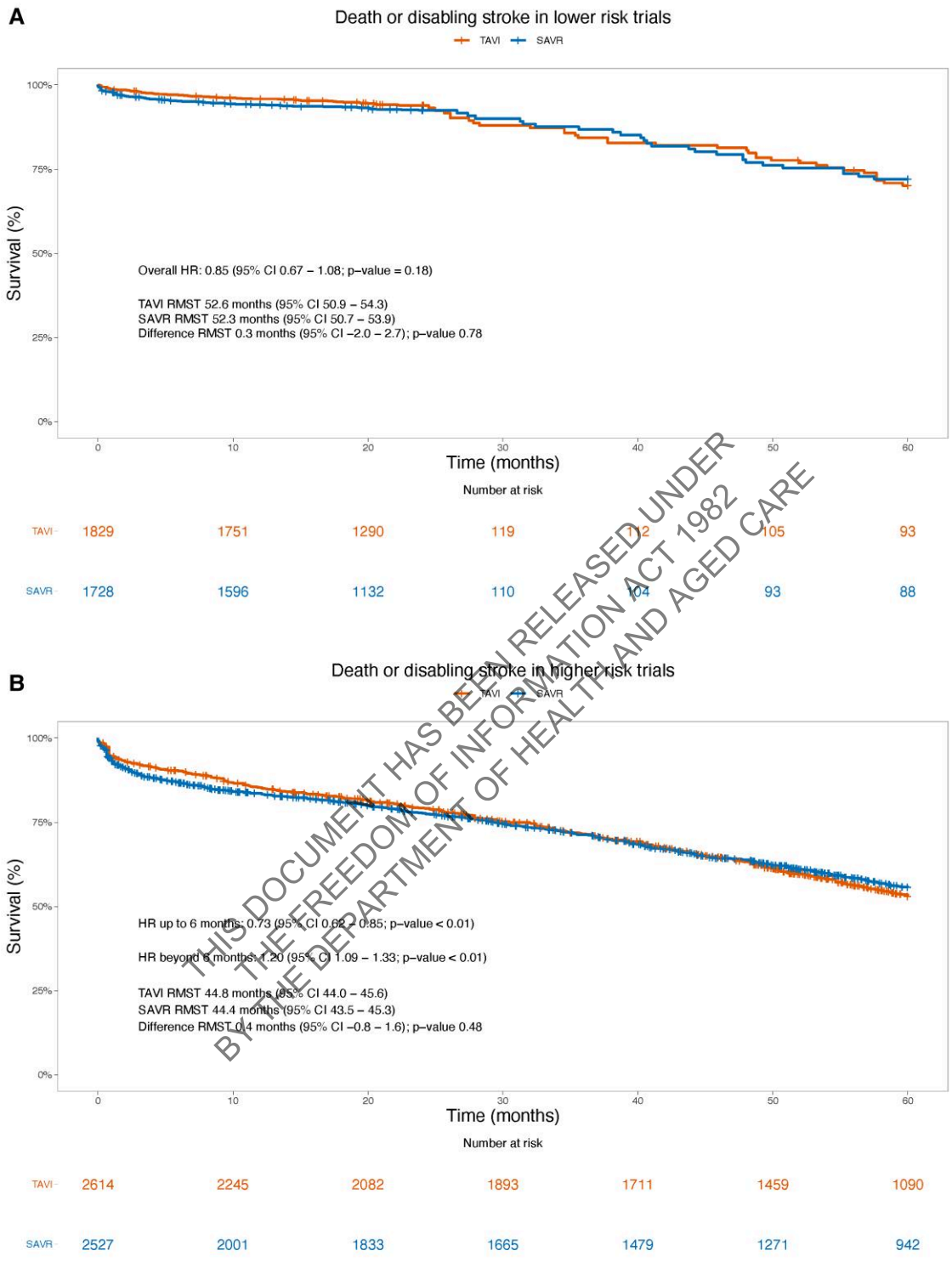


Figure 6 Pooled Kaplan–Meier plot of reconstructed individual patient data analysis for death or disabling stroke following transcatheter aortic valve implantation and surgical aortic valve replacement in (*A*) lower-risk trials and (*B*) higher-risk trials.

contemporary low-risk trials. We instead used a pragmatic classification of 'higher' and 'lower' risk trials, which avoided grouping together trials with inherently different patient populations, varying generation TAVI technologies, and evolving procedural methods. For the longer term follow-up analyses, we used HRs, which took account of the variable follow-up duration between trials and enabled us to include the entire follow-up duration of each trial. Finally, we performed reconstructed individual patient data meta-analyses by digitizing published Kaplan–Meier curves

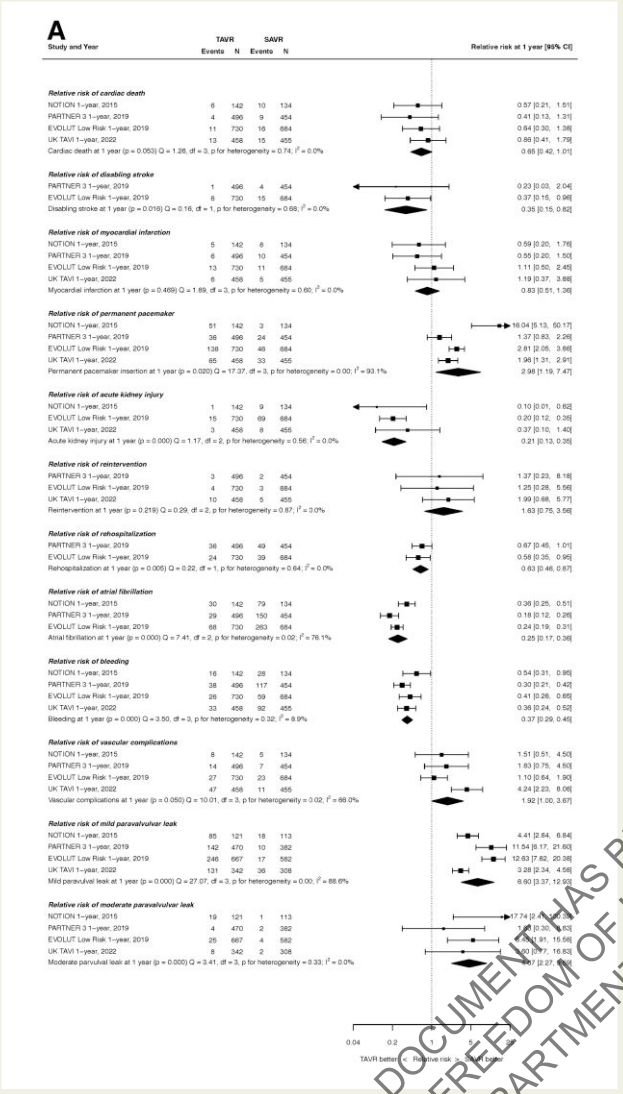


Figure 7 Outcomes for other secondary clinical endpoints following transcatheter aortic valve implantation and surgical aortic valve replacement in (*A*) lower-risk trials and (*B*) higher-risk trials. All endpoints are relative risks at 1 year.

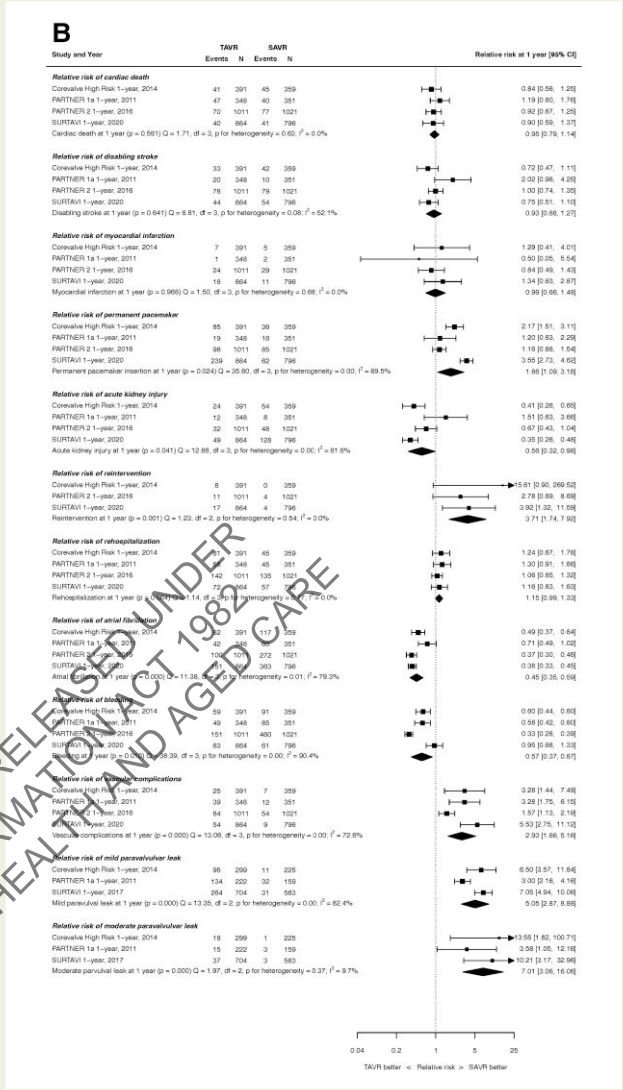


Figure 7 Continued

to generate pooled Kaplan–Meier plots and performed time-varying analyses in cases where the proportional hazards assumption was violated. This allowed us to assess the entire follow-up duration of each trial, calculating the overall RMST for each group. The pooled Kaplan–Meier plots are used to visually present the findings of the reconstructed individual patient data analyses, but were not used for formal statistical analyses comparing outcomes between the two groups.

As TAVI has moved into the realm of lower-risk patients, so the rate of events observed in clinical trials has diminished. For example, 1-year mortality rates were 24.2% in the TAVI group and 26.8% in the SAVR group in the high-risk PARTNER 1A trial in 2011; in the intermediate-risk PARTNER 2 trial in 2012, these dropped to 12.3% after TAVI and 12.9% after SAVR; and finally, in the low-risk PARTNER 3 trial in 2019, the 1-year mortality rates were 1.0% after TAVI and 2.5% after SAVR. A similar pattern is seen in the RCTs of the self-expanding platforms. In CoreValve high-risk, the 1-year mortality rate was 14.2% in the TAVI group and 19.1% in the SAVR group; in the intermediate-risk SURTAVI trial, the rates were 6.7% with TAVI and 6.8% with SAVR; and in the Evolut low-risk trial, the 1-year mortality was 0.8% with TAVI and 2.2% with SAVR. Meta-analysis is particularly useful in pooling results across trials with low event rates, which individually may have limited power to assess the treatment effect of a new therapy. The present analysis helps to incorporate and synthesize the totality of the trial data, including the longest follow-up available.

Our analysis has some important clinical implications. As mentioned, there appear to be clear patterns in terms of secondary clinical outcomes, some of which occur more frequently after TAVI and others more frequently after surgery and are broadly consistent in both the higher and lower risk categories. In the lower-risk trials, disabling stroke and rehospitalization occurred less frequently after TAVI; there was no significant difference for these outcomes in the higher-risk trials. In the higher-risk trials, aortic valve reintervention occurred more frequently following TAVI. The profile of events that occurred more frequently after TAVI tends to be outcomes that may assume greater relevance during long term follow-up (paravalvular leak, reintervention, and new pacemakers). Conversely, the events that occurred more frequently after SAVR tend to be outcomes that may be of greater short-term relevance (new-onset

atrial fibrillation, acute kidney injury, major bleeding). This may explain the early mortality benefit observed with TAVI in lower-risk patients, which was attenuated during later follow-up. Another possibility that could explain this phenomenon could be a depletion of higher-risk patients during the first year, leaving a different risk profile after 1 year in the SAVR group as compared to the TAVI group. Nevertheless, it is important to note that the overall survival was non-significantly greater with TAVI than with SAVR in both the higher and lower risk groups.

Similarly, some of the early adverse outcomes associated with surgery may contribute to an increased length of hospital and intensive care unit (ICU) stay with SAVR compared to TAVI. Any differences in the length of hospital stay and the length of ICU stay are particularly pertinent in the current coronavirus pandemic era, wherein limited resource availability (ICU space, ventilators, etc.) may have implications for the overall optimal delivery of care to patients.[36] The minimalist approach to TAVI, without the need for general anesthesia or ICU recovery, which has become the standard, drastically impacts resource consumption and patient perceptions, particularly during a respiratory pandemic.

Our analysis is not able to conclusively assess device durability. There have been concerns that transcatheter heart valves may not be as durable as surgical valves, and only long-term randomized data can answer that question. Surgical bioprosthetic valves are generally felt to have a 10-year longevity, but such estimates depend very much on the definitions used and the population and methodology of any particular study. Interestingly, the NOTION trial[12] found a lower risk of structural valve deterioration after TAVI as compared to surgery at 8-years (13.9 vs. 28.3%, $P = 0.0017$), although the risk of bioprosthetic valve failure was similar in the two arms (8.7 vs. 10.5%, $P = 0.61$). Although modestly sized, the NOTION trial provides the longest follow-up data available for the comparative durability of transcatheter and surgical bioprosthetic valves. These results are consistent with recently presented data of a pooled analysis from the CoreValve high-risk and SURTAVI randomized trials,[14,27] and the non-randomized CoreValve Extreme Risk Pivotal trial,[37] and CoreValve Continued Access Study.[38] This pooled analysis found that the 5-year rate of structural valve deterioration occurred significantly less frequently after TAVI with a self-expanding valve as compared to SAVR (2.57 vs. 4.38%, $P < 0.001$).[39]

We categorized trials into higher- and lower-risk groups, as an expression of the underlying baseline risk. Definitions of surgical risk have historically been predominantly based on the STS risk score, although it has been suggested this may represent an overestimate of surgical risk[40] and is not necessarily applicable to patients undergoing TAVI. Indeed, the UK TAVI trial uniquely eschewed risk scores as part of the eligibility criteria and adopted a clinical approach that was based solely on the heart team assessment and the age of the patient. Although the average age and STS scores of patients in UK TAVI were somewhat higher than in the other lower-risk trials, 30-day mortality was similar to that in the PARTNER-3 and Evolut low-risk trials, and TAVI was noninferior to SAVR with respect to all-cause mortality at 1 year. Our grouping of trials into two broad categories of risk attempted to avoid the potential pitfalls of comparing treatment effects across markedly different populations and allowed for advances in TAVI technology and procedural methods that have occurred over the past decade.

Limitations

(i) We could only report the available data and important data elements were not captured in all trials. (ii) There were differences in methodology and reporting across the trials, with variations in follow-up duration, entry criteria and primary endpoints, although heterogeneity was absent or low in the main meta-analyses. The definitions of clinical events and subgroups were also not uniform. These are problems common to all meta-analyses, and clinical trialists should consider standardizing definitions of events and subgroups across trials to better permit synthesis of analyses across trials. One of our key outcomes was all-cause mortality because it is not susceptible to differences between trials; this is reflected in the lack of heterogeneity for the results in both the lower and higher-risk groups for all-cause mortality ($I^2 = 0.0\%$). (iii) This was a study-level meta-analysis and therefore we could not perform detailed subgroup analyses. Our reconstructed individual patient data analyses were not a true IPD meta-analysis and were dependent on the quality of the figures and data points from the available Kaplan–Meier plots. There was significant study-level heterogeneity observed for the reconstructed individual patient data analyses. (iv) We included all trials comparing TAVI to SAVR. Since the inception of TAVI, there have been myriad advances in both technology and technique; therefore, our analysis may not accurately capture the clinical effect of contemporary TAVI in all risk categories. By considering higher and lower-risk trials separately, we hope to partially account for this limitation. (v) Longer term follow-up is currently lacking for many of the trials, with the longest follow-up duration being 5 years in higher-risk trials and there being little long-term follow-up in the lower-risk trials (aside from the 8-year follow-up of the modestly sized NOTION trial). Longer term data are required to explore whether equivalence in hard clinical outcomes such as death and stroke is sustained, and whether there are any differences in other important longer term outcomes, such as valve durability. (vi) A limitation of this analysis is the inability to compare different TAVI systems due to the complexity of generational iterations of TAVI devices. (vii) Finally, we only included randomized trials, which have the benefit of avoiding bias in the form of measured and unmeasured confounders but inherently randomize only the fraction of patients who meet the strict eligibility criteria. The results of our analysis may not apply to patients who were excluded from some or all of the trials, such as those with specific high-risk features or markers of complexity, such as bicuspid aortic valves, preexisting bioprosthetic or mechanical heart valves, or additional significant valvular lesions needing concomitant treatment.

Conclusions

In lower-risk patients, there was an early mortality reduction associated with TAVI, but no differences after later follow-up. There was also an early reduction in the composite of death or disabling stroke associated with TAVI, with no significant difference at later follow-up. There was no difference in the risk of stroke at earlier or later time points. In higher-risk patients, there were no differences between TAVI and SAVR for the occurrence of death, stroke, or the composite of death or disabling stroke at early and later time points. New-onset atrial fibrillation, bleeding, and acute kidney injury occur less frequently after TAVI, whereas new pacemaker insertion, vascular complications, and paravalvular leak occur more frequently after TAVI. The findings in this study emphasize the importance of secondary endpoints as well as the importance of temporality of events in informing therapy decisions for lower-risk patients. Longer-term follow-up will be needed to further clarify optimal therapy choices for these patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

We would like to acknowledge Colleen Gilbert from Medtronic, who assisted with contribution of additional data and Kaplan-Meier plots from the CoreValve Pivotal High Risk trial, the SURTAVI trial and the Evolut Low Risk trial, and Erin Rogers from Edwards who assisted in contribution of additional Kaplan-Meier plots from the PARTNER 2 trial.

Funding

J.P.H. is funded by the British Heart Foundation (FS/ICRF/22/26039).

Conflict of interest: A.D.A. reports honoraria and sponsorship from Medtronic and Bayer. M.M. was supported by a grant from the National Institutes of Health/National Heart, Lung, and Blood Institute to Columbia University Irving Medical Center (T32 HL007854). C.M.C. reports speaker fees from Philips Volcano. M.J.M. has served as a co-principal investigator for Edwards Lifesciences and Abbott; and as a study chair for Medtronic. M.J.R. served as national surgical PI on SURTAVI, Evolut Low-Risk, Reprise III, Acurate, Portico NG and Vantage and received research support from Medtronic, Boston Scientific, Abbott Medical, Gore. R.R.M. has received research grants from Edwards Lifesciences, Abbott, Medtronic, and Boston Scientific; has served as national Principal Investigator for Portico (Abbott) and Acurate (Boston Scientific) U.S. investigation device exemption trials; has received personal proctoring fees from Edwards Lifesciences; and has received travel support from Edwards Lifesciences, Abbott, and Boston Scientific. V.H.T. is an advisor or research support from Abbott Vascular, Cyrolife, Atricure, Edwards Lifesciences, Shockwave, and JenaValve; and has received consulting fees from Edwards Lifesciences, Boston Scientific, Abbott, Gore Vascular, and JenaValve. L.S. has received consultant fees and/or institutional research grants from Abbott, Boston Scientific, Edwards Lifesciences, Medtronic, Symetis, and SMT. N.V.M. has received institutional research grants from Abbott, ACIST Medical Systems, Boston Scientific, Biotronik, Medtronic, Edwards Lifesciences, Abiomed, Daiichi Sankyo, Pie Medical and PulseCath. J.K.F. is a consultant for Edwards Lifesciences and Medtronic and receives grant support from Edwards Lifesciences and Medtronic. M.B.L. has received research support to his institution from Edwards Lifesciences, Medtronic, Boston Scientific, and Abbott; has served on Advisory Boards for Medtronic, Boston Scientific, Gore, Meril Lifescience, and Abbott; and has served as the Co-Principal Investigator of the PARTNER 3 trial (Edwards Lifesciences, no direct compensation).

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author. The datasets were predominantly derived from sources in the public domain, from the trial journal publications and their supplementary appendices.

References

1. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, *et al.* Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;**363**:1597–1607. https://doi.org/10.1056/NEJMoa1008232
2. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, *et al.* Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;**364**:2187–2198. https://doi.org/10.1056/NEJMoa1103510
3. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, *et al.* Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;**370**:1790–1798. https://doi.org/10.1056/NEJMoa1400590
4. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, *et al.* Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;**374**:1609–1620. https://doi.org/10.1056/NEJMoa1514616
5. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, *et al.* Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2017;**376**:1321–1331. https://doi.org/10.1056/NEJMoa1700456
6. 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**:1695–1705. https://doi.org/10.1056/NEJMoa1814052
7. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, *et al.* Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019;**380**:1706–1715. https://doi.org/10.1056/NEJMoa1816885
8. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, *et al.* 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *Circulation* 2021;**143**:e72–227. https://doi.org/10.1161/CIR.0000000000000923
9. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, *et al.* 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2022;**43**:561–632. https://doi.org/10.1093/eurheartj/ehab395
10. Leon MB, Mack MJ, Hahn RT, Thourani VH, Makkar R, Kodali SK, *et al.* Outcomes 2 years after transcatheter aortic valve replacement in patients at low surgical risk. *J Am Coll Cardiol* 2021;**77**:1149–1161. https://doi.org/10.1016/j.jacc.2020.12.052
11. Forrest JK, Deeb GM, Yakubov SJ, Rovin JD, Mumtaz M, Gada H, *et al.* Two- year outcomes after transcatheter versus surgical aortic valve replacement in low-risk patients. *J Am Coll Cardiol* 2022;**79**:882–896. https://doi.org/10.1016/j.jacc.2021.11.062
12. Jørgensen TH, Thyregod HGH, Ihlemann N, Nissen H, Petursson P, Kjeldsen BJ, *et al.* Eight-year outcomes for patients with aortic valve stenosis at low surgical risk randomized to transcatheter vs. Surgical aortic valve replacement. *Eur Heart J* 2021;**42**:2912–2919. https://doi.org/10.1093/eurheartj/ehab375
13. Makkar RR, Thourani VH, Mack MJ, Kodali SK, Kapadia S, Webb JG, *et al.* Five-year outcomes of transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2020;**382**:799–809. https://doi.org/10.1056/NEJMoa1910555
14. Van Mieghem NM, Deeb GM, Søndergaard L, Grube E, Windecker S, Gada H, *et al.* Self-expanding transcatheter vs surgical aortic valve replacement in intermediate-risk patients: 5-year outcomes of the SURTAVI randomized clinical trial. *JAMA Cardiol* 2022;**7**:1000–1008. https://doi.org/10.1001/jamacardio.2022.2695
15. UK TAVI Trial Investigators, Toff WD, Hildick-Smith D, Kovac J, Mullen MJ, Wendler O, *et al.* Effect of transcatheter aortic valve implantation vs surgical aortic valve replacement on all-cause mortality in patients with aortic stenosis: a randomized clinical trial. *JAMA* 2022;**327**:1875–1887. https://doi.org/10.1001/jama.2022.5776
16. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**:264–269. https://doi.org/10.7326/0003-4819-151-4-200908180-00135
17. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al.* Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898. https://doi.org/10.1136/bmj.l4898
18. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al.* The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928. https://doi.org/10.1136/bmj.d5928
19. The Cochrane Collarobation. *Cochrane Handbook for Systematic Reviews of Interventions —10.4.3.1 Recommendations on testing for funnel plot asymmetry*: The Cochrane Collaboration, 2011.
20. Van Mieghem NM, Popma JJ, Deeb GM, Yakubov SJ, Serruys PW, Windecker S, *et al.* Complete 2-year results confirm Bayesian analysis of the SURTAVI trial. *JACC Cardiovasc Interv* 2020;**13**:323–331. https://doi.org/10.1016/j.jcin.2019.10.043
21. Liu N, Zhou Y, Lee JJ. IPDfromKM: reconstruct individual patient data from published kaplan-meier survival curves. *BMC Med Res Methodol* 2021;**21**:111. https://doi.org/10.1186/s12874-021-01308-8
22. Cornell JE, Mulrow CD, Localio R, Stack CB, Meibohm AR, Guallar E, *et al.* Random-effects meta-analysis of inconsistent effects: a time for change. *Ann Intern Med* 2014;**160**:267–270. https://doi.org/10.7326/M13-2886
23. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539–1558. https://doi.org/10.1002/sim.1186
24. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2016. Available from: https://www.R-project.org/.
25. Conducting Meta-Analyses in R with the metafor Package | Viechtbauer | Journal of Statistical Software. [cited 23 Oct 2017]; Available from: https://www.jstatsoft.org/article/view/v036i03.
26. Thyregod HGH, Ihlemann N, Jørgensen TH, Nissen H, Kjeldsen BJ, Petursson P, *et al.* Five-year clinical and echocardiographic outcomes from the NOTION randomized clinical trial in patients at lower surgical risk. *Circulation* 2019;**139**:2714–2723. https://doi.org/10.1161/CIRCULATIONAHA.118.036606
27. Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, *et al.* Five-year outcomes of self-expanding transcatheter versus surgical aortic valve replacement in high-risk patients. *J Am Coll Cardiol* 2018;**72**:2687–2696. https://doi.org/10.1016/j.jacc.2018.08.2146
28. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, *et al.* Five-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised

controlled trial. *Lancet* 2015;**385**:2477–2484. https://doi.org/10.1016/S0140-6736(15)60308-7
29. Thyregod HGH, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, *et al.* Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis. *J Am Coll Cardiol* 2015;**65**:2184–2194. https://doi.org/10.1016/j.jacc.2015.03.014
30. Søndergaard L, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, *et al.* Two-year outcomes in patients with severe aortic valve stenosis randomized to transcatheter versus surgical aortic valve replacement: the all-comers nordic aortic valve intervention randomized clinical trial. *Circ Cardiovasc Interv* 2016;**9**:e003665. https://doi.org/10.1161/CIRCINTERVENTIONS.115.003665
31. Reardon MJ, Adams DH, Kleiman NS, Yakubov SJ, Coselli JS, Deeb GM, *et al.* Two-year outcomes in patients undergoing surgical or self-expanding transcatheter aortic valve replacement. *J Am Coll Cardiol* 2015;**66**:113–121. https://doi.org/10.1016/j.jacc.2015.05.017
32. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, *et al.* Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012;**366**:1686–1695. https://doi.org/10.1056/NEJMoa1200384
33. Siontis GCM, Overtchouk P, Cahill TJ, Modine T, Prendergast B, Praz F, *et al.* Transcatheter aortic valve implantation vs. Surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. *Eur Heart J* 2019;**40**:3143–3153. https://doi.org/10.1093/eurheartj/ehz275
34. Siontis GCM, Praz F, Pilgrim T, Mavridis D, Verma S, Salanti G, *et al.* Transcatheter aortic valve implantation vs. Surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials. *Eur Heart J* 2016;**37**:3503–3512. https://doi.org/10.1093/eurheartj/ehw225
35. Thourani VH, Edelman JJ, Holmes SD, Nguyen TC, Carroll J, Mack MJ, *et al.* The international society for minimally invasive cardiothoracic surgery expert consensus statement on transcatheter and surgical aortic valve replacement in low- and intermediate-risk patients: a meta-analysis of randomized and propensity-matched studies. *Innovations (Phila)* 2021;**16**:3–16. https://doi.org/10.1177/1556984520978316
36. Chung CJ, Nazif TM, Wolbinski M, Hakemi E, Lebehn M, Brandwein R, *et al.* The restructuring of structural heart disease practice during the COVID-19 pandemic. *J Am Coll Cardiol* 2020;**75**:2974–2983. https://doi.org/10.1016/j.jacc.2020.04.009
37. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, *et al.* Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol* 2014;**63**:1972–1981. https://doi.org/10.1016/j.jacc.2014.02.556
38. Arnold SV, Afilalo J, Spertus JA, Tang Y, Baron SJ, Jones PG, *et al.* Prediction of poor outcome after transcatheter aortic valve replacement. *J Am Coll Cardiol* 2016;**68**:1868–1877. https://doi.org/10.1016/j.jacc.2016.07.762
39. Reardon MJ. Five-year incidence, outcomes, and predictors of structural valve deterioration of transcatheter and surgical aortic bioprostheses: insights from the CoreValve US Pivotal and SURTAVI trial. In Washington DC; 2022. https://www.crtonline.org/presentation-detail/5-year-incidence-outcomes-predictors-of-structural.
40. Martin GP, Sperrin M, Ludman PF, de Belder MA, Gale CP, Toff WD, *et al.* Inadequacy of existing clinical prediction models for predicting mortality after transcatheter aortic valve implantation. *Am Heart J* 2017;**184**:97–105. https://doi.org/10.1016/j.ahj.2016.10.020

Corrigendum

https://doi.org/10.1093/eurheartj/ehad023
Online publish-ahead-of-print 19 January 2023

Corrigendum to: The year in cardiovascular medicine 2022: the top 10 papers in dyslipidaemias

This is a corrigendum to: Lale Tokgozoglu, Carl Orringer, Alberico Catapano, The year in cardiovascular medicine 2022: the top 10 papers in dyslipidaemias, *European Heart Journal*, 2023, ehac750, https://doi.org/10.1093/eurheartj/ehac750

In the originally published version of this manuscript the affiliations for author Alberico Catapano were incorrect. Affiliation number 3 has been changed from 'Department of Pharmacological Sciences' to 'Department of Pharmacological and Biomolecular Sciences'. An additional affiliation 4 has also been added, 'IRCCS Multimedia, Milano, Italy.'

These errors have been corrected.

Journal Pre-proof

Thirty-Day Clinical Outcomes of a Self-Expanding Transcatheter Aortic Valve: The International PORTICO NG Study

Michael J. Reardon, MD, Bassem Chehab, MD, Dave Smith, MD, Antony S. Walton, MBBS, Stephen G. Worthley, MD, Ganesh Manoharan, MD, Ibrahim Sultan, MD, Gerald Yong, MD, Katherine Harrington, MD, Paul Mahoney, MD, Neal Kleiman, MD, Raj R. Makkar, MD, Gregory Fontana, MD, Augustin DeLago, MD, Ravi K. Ramana, DO, Nicholas Bates, PhD, Lars Sondergaard, MD

PII: S1936-8798(23)00460-0

DOI: https://doi.org/10.1016/j.jcin.2023.02.002

Reference: JCIN 6831

To appear in: *JACC: Cardiovascular Interventions*

Received Date: 22 January 2023

Revised Date: 6 February 2023

Accepted Date: 6 February 2023

Please cite this article as: Reardon MJ, Chehab B, Smith D, Walton AS, Worthley SG, Manoharan G, Sultan I, Yong G, Harrington K, Mahoney P, Kleiman N, Makkar RR, Fontana G, DeLago A, Ramana RK, Bates N, Sondergaard L, Thirty-Day Clinical Outcomes of a Self-Expanding Transcatheter Aortic Valve: The International PORTICO NG Study, *JACC: Cardiovascular Interventions* (2023), doi: https://doi.org/10.1016/j.jcin.2023.02.002.

Thirty-Day Clinical Outcomes of a Self-Expanding Transcatheter Aortic Valve: The International PORTICO NG Study

Michael J. Reardon[1], MD, Bassem Chehab[2], MD, Dave Smith[3], MD, Antony S. Walton[4,5], MBBS, Stephen G. Worthley[6], MD, Ganesh Manoharan[7], MD, Ibrahim Sultan[8], MD Gerald Yong[9], MD, Katherine Harrington[10], MD, Paul Mahoney[11], MD, Neal Kleiman[12], MD, Raj R. Makkar[13], MD, Gregory Fontana[14], MD, Augustin DeLago[15], MD, Ravi K. Ramana[16,17], DO, Nicholas Bates[18], PhD, Lars Sondergaard[19], MD

Affiliations:

[1] Department of Cardiovascular Surgery, Houston Methodist DeBakey Heart and Vascular Center, Houston, Texas, USA

[2] Department of Cardiology, Ascension Via Christi Hospital, University of Kansas, Wichita, Kansas, USA

[3] Morriston Hospital, Swansea Bay University Health Board, Swansea, UK

[4] Department of Interventional Cardiology, Alfred Hospital, Melbourne, Victoria, Australia

[5] Monash University, Melbourne, Victoria, Australia

[6] Department of Cardiology, Macquarie University Hospital, New South Wales, Australia

[7] Regional Cardiology Centre, Royal Victoria Hospital, Belfast, UK

[8] Division of Cardiac Surgery, Department of Cardiothoracic Surgery, Heart and Vascular Institute, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

[9] Department of Cardiology, Fiona Stanley Hospital, Murdoch, Western Australia, Australia

[10] Department of Cardiothoracic Surgery, The Heart Hospital Baylor Plano, Plano, Texas, USA

[11] Department of Cardiovascular Services, The Sentara Heart Center, Norfolk, Virginia, USA

[12] Department of Cardiology, Section of Interventional Cardiology, Houston DeBakey Heart and

Vascular Center, Houston, Texas, USA

[13] Cedars-Sinai Medical Center, Los Angeles, California, USA

[14] Cardiovascular Institute, Hospital Corporation of America, Los Robles Hospital and Medical Center, Thousand Oaks, CA, USA

[15] Division of Cardiology, Albany Medical Center, Albany, NY, USA

[16] Division of Cardiology, Advocate Christ Medical Center, Oak Lawn, Illinois, USA

[17] Heart Care Centers of Illinois, Palos Park, Illinois, USA

[18] Structural Heart Clinical Affairs, Abbott Medical, St. Paul, Minnesota, USA

[19] Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Running title: Navitor Valve Procedural and Short-Term Outcomes

Address for Correspondence:

Michael J. Reardon, MD

Department of Cardiovascular Surgery

Houston Methodist Hospital

6550 Fannin, Ste 1401

Houston, TX 77030

email: mreardon@houstonmethodist.org

Word count: ~3,145

Disclosures:

MJR reports consultant fees and/or institutional research grants from Abbott, Boston Scientific, Medtronic, and Gore Medical; BC reports speaker, consultancy and proctor fees for Abbott, Edwards Lifesciences, Medtronic and CSI

DS reports speaker and proctor fees for Abbott, Edwards Lifesciences and Biosensors

ASW is a proctor, on medical advisory boards, and receives grant support from Abbott, Medtronic, and Edwards Lifesciences

SGW has received speaker fees and proctorship from Abbott and HighLife Medical, as well as consultancy fees from Edwards Lifesciences

GM is a proctor for Abbott and Medtronic

IS is a consultant for Abbott, Artivion, Medtronic and Terumo Aortic

GY is a proctor for Abbott

KH reports consultancy for Abbott and Boston Scientific, speaker fees for Boston Scientific, Artivion, and Edwards Lifesciences, as well as proctor fees for Edwards Lifesciences

PM has received speaker fees, as well as a consultant and proctor for Abbott, Medtronic, Edwards Lifesciences and Boston Scientific

NK participate as an Investigator for Abbott, Boston Scientific and Edwards Lifesciences

RRM is a proctor for Edwards Lifescience, a consultant for Cordis and Medtronic, and has received research grants from Abbott, Edwards Lifesciences and Boston Scientific

GF is a consultant, proctor, and speaker for Abbott and Medtronic

AD received speaker fees and is a consultant for Edwards Lifesciences and Boston Scientific and a proctor for Abbott, Edwards Lifesciences and Boston Scientific

RKR is a consultant for Abbott, Medtronic, Boston Scientific, Edwards Lifesciences

NB is an employee of Abbott

LS has received consultant fees and/or institutional research grants from Abbott, Boston Scientific, Medtronic, and Sahajanand Medical Technologies.

ABSTRACT

Objectives: The purpose of the PORTICO NG Study is to evaluate the safety and effectiveness of the Navitor™ valve in patients with symptomatic, severe aortic stenosis (AS) who are at high or extreme surgical risk.

Background: The self-expanding, intra-annular Navitor™ valve includes an outer cuff to reduce paravalvular leak (PVL) and large stent cells for future coronary access.

Methods: PORTICO NG is a prospective, multicenter, global study with follow-up at 30 days, 1 year, and annually through 5 years. The primary endpoints are all-cause mortality and moderate or greater PVL at 30 days. Assessment of VARC-2 events and valve performance are assessed by an independent Clinical Events Committee and echocardiographic core laboratory.

Results: A total of 260 subjects were treated at 26 clinical sites across Europe, Australia, and the US between September 2019 and August 2022. Mean age was 83.4±5.4 years, 57.3% were female, and the average STS score was 3.9±2.1%. At 30 days, the rate of all-cause mortality is 1.9%, and no subjects have moderate or greater PVL. The rate of disabling stroke is 1.9%, life-threatening bleeding 3.8%, stage 3 acute kidney injury 0.8%, major vascular complications 4.2%, and new permanent pacemaker implantation 19.0%. Hemodynamic performance included a mean gradient of 7.4±3.5 mmHg and effective orifice area of 2.00±0.47 cm^2.

Conclusions: The Navitor™ valve is safe and effective for the treatment of subjects with severe AS who are at high or greater risk for surgery, supported by low rates of adverse events and PVL. ClinicalTrials.gov identifier: NCT04011722.

KEY WORDS; aortic stenosis, transcatheter aortic valve implantation, transcatheter aortic valve replacement, paravalvular leak, Navitor

CONDENSED ABSTRACT

The PORTICO NG Study evaluates the safety and effectiveness of the self-expanding, intra-annular Navitor™ valve with an active outer cuff in patients with symptomatic, severe aortic stenosis who are at high or extreme surgical risk. The primary endpoints are all-cause mortality and moderate or greater PVL at 30 days. The rate of all-cause mortality was 1.9%, and no subjects had moderate or greater PVL. Hemodynamic performance included a mean gradient of 7.4±3.5 mmHg and effective orifice area of 2.00±0.47 cm^2 at 30 days.

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

EOA = effective orifice area

NYHA = New York Heart Association

PPI = permanent pacemaker implantation

PVL= paravalvular leak

TAVR = Transcatheter aortic valve replacement

VARC = Valve Academic Research Consortium

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is the preferred treatment for patients with symptomatic, severe aortic stenosis (AS) who are at high or extreme surgical risk, based on short- and long-term data from several landmark trials (1-4). Current guidelines highlight age (i.e., patient life expectancy), surgical risk, anatomical features, valve durability and shared decision making with the patient's local Heart Team to determine the best therapy option (5,6).

Paravalvular leak (PVL) remains an important post-procedural complication that can have a negative impact on patient survival. Consequently, next-generation TAVR devices include design modifications to mitigate the risk of PVL (7-9). The Navitor™ valve (Abbott Structural Heart, Minneapolis, MN, USA) is the newest of these next-generation devices to obtain FDA approval.

The valve retains the large stent cells of its predecessor for future coronary access, while adding an outer fabric cuff, known as the NaviSeal™ cuff, to actively reduce the risk of PVL (**Central Illustration**). The valve, combined with the FlexNav™ delivery system (Abbott Structural Heart, Minneapolis, MN, USA), is known as the Navitor TAVR System and allows for valve recapture, repositioning, and redeployment. Here we report the 30-Day outcomes of all subjects enrolled in the PORTICO NG Study, which focused on safety and effectiveness of the Navitor TAVR System in patients with symptomatic, severe AS who are at high or extreme surgical risk.

METHODS

Study Design

The PORTICO NG Study (ClinicalTrials.gov: NCT04011722) is a prospective, multi-center, global study initiated to evaluate the safety and effectiveness of the Navitor transcatheter

aortic valve replacement (TAVR) System, which includes the use of the FlexNav delivery system for valve delivery. The design of the study and procedural aspects have been described in detail previously (Sondergaard et al. 2023 *In Press*).

Briefly, the study population included subjects with symptomatic, severe native AS that were deemed high or extreme risk for surgical aortic valve replacement according to the Society of Thoracic Surgeons Predicted Risk of Operative Mortality (STS-PROM) score or Heart Team consensus due to frailty or co-morbidities not captured by the STS-PROM score. Subjects were reviewed by an independent subject selection committee to confirm subjects' eligibility, valve size, and access route prior to implantation. Baseline CT were assessed by an independent core laboratory and utilized in the subject selection process. Key imaging exclusion criteria include bicuspid aortic valve or a non-calcified native aortic valve.

Subjects underwent TAVR via a transfemoral or alternative access route using the Navitor TAVR System. Valve sizes 23, 25, 27, and 29 mm were used in this study, covering an aortic annulus diameter between 19 and 27 mm based on pre-procedural multi-slice computed tomography (MSCT). Subjects with an aortic annulus diameter >27 mm were implanted with the 35 mm valve (i.e., Navitor Titan) and studied in a separate cohort not described in this report. The 23- and 25-mm valves can be implanted using the 14-Fr equivalent small delivery system in access vessels with a diameter ≥ 5.0 mm and the 27- and 29-mm valves can be implanted using the 15-Fr equivalent large delivery system in diameters ≥ 5.5 mm. Study assessments occurred at baseline, implant procedure, discharge and 30 days. Annual follow-up visits are scheduled through 5 years and are ongoing. This paper reports the primary and descriptive endpoints through 30 days for all subjects enrolled in the study.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the appropriate Institutional Review Board/Ethics Committee of each investigational site and by the applicable regulatory authorities. All patients provided informed consent prior to participation. This study is sponsored by Abbott.

Endpoints

The primary safety endpoint is all-cause mortality at 30 days and the primary effectiveness endpoint is moderate or greater PVL at 30 days. The secondary endpoint is a non-hierarchical composite of all-cause mortality, disabling stroke, life threatening bleeding, acute kidney injury (stage 3), or major vascular complications at 30 days. Additional outcomes at 30 days including permanent pacemaker implantation, valve hemodynamics by valve size, and subject functional status are also reported. An independent Clinical Events Committee (CEC) adjudicated events according to the Valve Academic Research Consortium 2 (VARC-2) definitions (10). An independent echocardiographic core laboratory (MedStar Health Research Institute, Washington, D.C., USA) assessed echocardiographic data.

Statistical Methods

Baseline characteristics, procedural outcomes and study endpoints were summarized using descriptive statistics. Paired t-test (echocardiographic data) and the Wilcoxon signed-rank test (NYHA class) were used to compare outcomes at 30 days relative to baseline and/or discharge in subjects with available data. Analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Subject Disposition

Between September 2019 and August 2022, 260 subjects underwent implantation with a Navitor valve. All subjects, with the exception of five subject deaths within 30 days, completed their 30-Day visit. Subject demographic and baseline data are summarized in **Table 1**. The mean age was 83.4±5.4 years, 57.3% of subjects were female, and 55.0% of subjects were in NYHA class III or IV. The mean STS-PROM score was 3.9±2.1%, subjects averaged 1.4 frailty factors, and 18.5% were considered extreme risk. Common comorbidities included coronary artery disease (59.6%), pre-existing cardiac arrhythmia (58.5%), diabetes (28.8%), kidney disease (24.2%), and lung disease (24.2%).

Procedural Characteristics

Procedural characteristics and outcomes are provided in **Table 2**. Conscious sedation was used in 31.9% of subjects and transfemoral access was used in most (99.6%) cases; one subject (0.4%) received the Navitor™ valve via subclavian access. The delivery system integrated sheath was used for valve deployment in most (89.2%) procedures; the implanting physician preferred an external introducer sheath in the remaining patients. Resheathing was performed in roughly half (46.9%) of cases. Pre-balloon valvuloplasty (recommended per IFU) was performed in 95.4% of procedures and post-balloon valvuloplasty in 28.1% of procedures. The 23mm valve was implanted in 5.4%, the 25mm in 25.4%, the 27mm in 39.6%, and the 29mm in 29.6% of the subjects. The mean implant depth was 4.2 mm, with the average depth on the non-coronary cusp of 3.7 mm.

Procedural success was 97.3%. Five subjects (1.9%) required a second Navitor valve due to an unfavorable valve position: valve migration during delivery system removal in two subjects, and initial supra-annular position in three subjects. Two subjects (0.8%) received a

vascular plug to mitigate PVL during the procedure; these events are further discussed below. Importantly, no conversions to SAVR or procedural mortality occurred.

30-Day Outcomes

The acute safety outcomes are presented in **Table 3**. The primary safety endpoint, all-cause mortality at 30 days, was 1.9%. Four deaths (1.5%) within 30 days were adjudicated as cardiovascular due to an unrecognized femoral artery dissection in one subject, an aortic dissection in one subject, a disabling stroke resulting in subsequent decline in health in one subject and multiple complications consisting of a disabling stroke, acute respiratory failure and renal failure in one subject. One death (0.4%) was due to pneumonia (COVID-19 negative) and adjudicated as non-cardiovascular.

The composite safety endpoint was 7.7%; ten subjects (3.8%) experienced life-threatening bleeding, five (1.9%) experienced a disabling stroke, two subjects (0.8%) experienced stage 3 acute kidney injury (both required dialysis), and eleven subjects (4.2%) experienced a major vascular complication (**Central Illustration**). Eight major vascular complications were access site related, with six occurring at the TAVR access site and two at a non-TAVR access site. The three non-access site major vascular complications were a left ventricle perforation in two subjects and an aortic dissection in one subject, which led to this subject's death one day post-TAVR. A new permanent pacemaker was implanted in 44 subjects, representing 16.9% of all subjects and 19.0% of pacemaker naïve subjects.

Hemodynamics

The mean transvalvular gradient was reduced from baseline, 41.4 ± 12.6 mmHg, to 7.4 ± 3.5 mmHg at 30 days and the EOA increased from baseline, 0.72 ± 0.18 cm^2, to 2.00 ± 0.47 cm^2 at 30 days (**Central Illustration**).

In addition, hemodynamics was assessed by individual valve size (**Figure 1**). Single-digit mean gradients were observed at 30 days across all valve sizes. Valve EOAs were larger at 30 days compared to baseline across all valve sizes, with EOA related to valve size (i.e., larger the valve, larger the EOA).

The primary effectiveness endpoint, moderate or greater paravalvular leak (PVL) at 30 days, was 0% (**Central Illustration**). Most subjects (79.8%) were assessed as having none or trace PVL at 30 days, while 20.2% of subjects had mild PVL, as determined by the echocardiographic core laboratory (**Figure 2**).

NYHA Functional Class

Most subjects (55.0%) were in NYHA class III/IV at baseline, and this percentage decreased to 3.6% at 30 days (**Figure 3**). The NYHA class improved in most subjects (86.5%), with 66.5% of subjects reported in NYHA class I at 30 days.

DISCUSSION

We report the acute clinical and echocardiographic outcomes of patients treated with the novel Navitor valve, an iterative self-expanding, intra-annular transcatheter valve design with an active outer cuff (i.e., NaviSeal cuff). The results from this study support the safety and effectiveness of the Navitor TAVR System in patients with symptomatic, severe AS.

Procedural vascular plugs

While most subjects (97.3%) completed their TAVR procedure successfully, seven subjects required an additional intervention; five subjects received a second Navitor valve and two subjects were implanted with a vascular plug to mitigate PVL. Treatment of PVL post-TAVR was left at the discretion of the implanter. For these two cases, moderate PVL was observed following very deep valve positions where the NaviSeal cuff was not fully engaged

with the annulus, and after post-dilatation did not improve PVL to a satisfactory level, the implanter chose to use a vascular plug to eliminate the PVL. Both subjects were discharged with ≤ trace PVL with mean gradients <10 mmHg. As the VARC-2 definition does not describe the use of vascular plugs, a conservative approach was used with classification of these subjects as procedural failures.

Hemodynamics

Prior studies evaluating the predicate Portico™ valve (Abbott Structural Heart, Minneapolis, MN, USA) have demonstrated consistent single-digit mean transvalvular gradients and large EOAs in both pre-market and real-world clinical evaluations at 30 days (11-14). The current study confirmed the low mean transvalvular gradient (7.4 ± 3.5 mmHg) and large EOA (2.00 ± 0.47 cm^2) associated with the use of the self-expanding Navitor valve with intra-annular leaflet position. Furthermore, analysis of individual valve sizes revealed favorable hemodynamics with no differences between small and large valves. The initial benefit observed with low transvalvular gradients has potential implications for long-term valve durability, such as structural valve deterioration and bioprosthetic valve failure. Further follow-up in the PORTICO NG Study is needed to validate valve durability.

The design of transcatheter heart valves may influence the hemodynamic performance. Thus, the cylindric inflow portion of the Navitor stent frame allows for better leaflet opening than the tapered inflow portion of the stent frame on the Evolut™ platform (Medtronic, Minneapolis, MN). The Sapien™ valve (Edwards Lifesciences, Irvine, CA) is design with tapered leaflets, which causes a degree of restriction on the hemodynamic performance.

Paravalvular Leak

The frequency of moderate or greater PVL has diminished over time in Abbott-sponsored studies, in large part due to design advances of both the Abbott TAVR valve and delivery system. In the PORTICO IDE Study, which utilized the Portico valve with the first-generation delivery system, the rate of moderate or greater PVL was 6.3% at 30 days (11). In the PORTICO I Study, which evaluated the Portico valve with the first-generation delivery system in a real-world setting, the rate of moderate or greater PVL trended downwards to 3.9% (12).

After the commercialization of the FlexNav delivery system, the Portico valve was studied in the Global FlexNav cohort where the rate of moderate or greater PVL was 2.8% at 30 days (13). Similar to the Global FlexNav cohort, the concurrently enrolled CONFIDENCE Registry evaluated outcomes of the Portico valve in two equally, but consecutively, enrolled cohorts; the first with the first-generation delivery system and the second with the FlexNav delivery system. The overall rate of moderate or greater PVL in the CONFIDENCE Registry was 2.1% at 30 days, with the first-generation delivery system cohort averaging 2.4% and the FlexNav delivery system cohort averaging 1.8% (14).

The addition of the NaviSeal cuff to mitigate PVL has been successful as we report 0% moderate or greater PVL with the Navitor™ valve at 30 days. This represents an improvement compared with its predecessor in similar high and extreme risk patient populations.

New Permanent Pacemaker Implantation

The rate of new permanent pacemaker implantation (19.0%) within 30 days in the PORTICO NG Study may be caused by several factors, including site experience with the predecessor Portico TAVI System, inclusion of patients with pre-existing conduction abnormalities, and procedural factors such as implant depth, manipulations (e.g., resheathing), and that cusp-overlap technique was not routinely used during the study period.

Study Limitations

In the PORTICO NG Study it was prespecified to utilize VARC-2 criteria, and with the recent update to VARC-3, endpoints may be less useful for comparison for future studies. The current report only includes Navitor valve sizes 23-29 mm, which encompasses aortic mean diameters between 19-27 mm and does not include an evaluation of this design iteration in larger annular sizes. The 35 mm valve (i.e., Navitor Titan) covers aortic mean diameter ranges between 27-30 mm and is studied separately in the PORTICO NG Study. Additionally, implant depth was assessed by the site using fluoroscopic images, which have limited accuracy.

CONCLUSIONS

This study demonstrated that the Navitor TAVR System is safe and effective for the treatment of symptomatic, severe AS in patients who are at high or greater surgical risk. While a vascular plug was used in two subjects to treat PVL during the index procedure, the addition of the NaviSeal cuff to enhance sealing effectively mitigated PVL as no subjects experienced moderate or greater PVL at 30 days.

ACKNOWLEDGEMENT

The authors would like to thank all the investigators and institutions participating in the PORTICO NG Study, Kai Koo, PhD and Feiyi Jia, PhD (Abbott) for their contributions to data analysis, and Jillian Kolles, MS (Abbott) for her assistance in manuscript preparation including the creation of tables and figures.

CLINICAL PERSPECTIVES

WHAT IS KNOWN?

TAVR is an effective alternative to surgery to treat patients with symptomatic, severe aortic stenosis who are at high or extreme surgical risk.

WHAT IS NEW?

The Navitor valve, with an intra-annular leaflet position, offers favorable clinical outcomes through 30 days. The Navitor valve with the active outer cuff demonstrates favorable hemodynamics in all valve sizes, including a reduction in PVL compared to its predicate device.

WHAT IS NEXT?

Refining the implant technique to lower the rate of new permanent pacemaker implantation is a crucial next step for self-expanding valves. Long-term follow-up of patients implanted with the Navitor valve is needed to assess valve durability.

REFERENCES

1. Leon MB, Smith CR, Mack M et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. The New England journal of medicine 2010;363:1597-607.
2. Popma JJ, Adams DH, Reardon MJ et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol 2014;63:1972-81.
3. Smith CR, Leon MB, Mack MJ et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. The New England journal of medicine 2011;364:2187-98.
4. Adams DH, Popma JJ, Reardon MJ et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. The New England journal of medicine 2014;370:1790-8.
5. Otto CM, Nishimura RA, Bonow RO et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;143:e72-e227.
6. Vahanian A, Beyersdorf F, Praz F et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2021.
7. Möllmann H, Holzhey DM, Hilker M et al. The ACURATE neo2 valve system for transcatheter aortic valve implantation: 30-day and 1-year outcomes. Clinical research in cardiology : official journal of the German Cardiac Society 2021;110:1912-1920.

8. Manoharan G, Grube E, Van Mieghem NM et al. Thirty-day clinical outcomes of the Evolut PRO self-expanding transcatheter aortic valve: the international FORWARD PRO study. EuroIntervention 2020;16:850-857.

9. Nazif TM, Cahill TJ, Daniels D et al. Real-World Experience With the SAPIEN 3 Ultra Transcatheter Heart Valve: A Propensity-Matched Analysis From the United States. Circulation Cardiovascular interventions 2021;14:e010543.

10. Kappetein AP, Head SJ, Généreux P et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. European heart journal 2012;33:2403-18.

11. Makkar RR, Cheng W, Waksman R et al. Self-expanding intra-annular versus commercially available transcatheter heart valves in high and extreme risk patients with severe aortic stenosis (PORTICO IDE): a randomised, controlled, non-inferiority trial. Lancet (London, England) 2020;396:669-683.

12. Sondergaard L, Rodes-Cabau J, Hans-Peter Linke A et al. Transcatheter Aortic Valve Replacement With a Repositionable Self-Expanding Prosthesis: The PORTICO-I Trial 1-Year Outcomes. J Am Coll Cardiol 2018;72:2859-2867.

13. Fontana GP, Bedogni F, Groh M et al. One-Year Results of the Portico Transcatheter Aortic Heart Valve Using the Next-Generation FlexNav Delivery System. Journal of the Society for Cardiovascular Angiography & Interventions 2022:100562.

14. Mollmann H, Linke A, Nombela-Franco L et al. Procedural Safety and Device Performance of the Portico™ Valve from Experienced TAVI Centers: 30-Day Outcomes in the Multicenter CONFIDENCE Registry. Journal of clinical medicine 2022;11.

FIGURE LEGENDS

Figure 1. Hemodynamics by Valve Size

Both small (23 and 25 mm) and large (27 and 29 mm) valves demonstrated hemodynamic improvement from baseline to 30 days, where single digit mean transvalvular gradients and large effective orifice areas were measured. Error bars represent ± one standard deviation. EOA, effective orifice area.

Figure 2. Degree of Paravalvular Leak Over Time

Following the TAVR procedure, most subjects (83.7%) were assessed by the core laboratory as having none or trace PVL at discharge. This trend was observed at 30 days where most subjects (79.8%) were assessed as having none or trace PVL. No subjects were graded as having moderate or greater PVL. Note: Data include two subjects where a vascular plug was implanted during the index procedure to reduce the degree of PVL; both subjects had PVL graded as trace by the core lab at 30 days.

Figure 3. NYHA Functional Classification Over Time

At 30 days, most subjects (96.4%) were in NYHA class I/II, compared to only 45.0% of subjects in NYHA class II at baseline. NYHA, New York Heart Association.

Central Illustration. Primary Outcomes with the Self-Expanding Transcatheter Heart Valve with Intra-annular Leaflet Position

The Navitor TAVR System is optimized to provide favorable clinical and echocardiographic outcomes. The Navitor valve demonstrates favorable hemodynamics, as evidenced by a low mean transvalvular gradient, a large effective orifice area, no moderate or greater paravalvular

leak, and low rates of acute safety events through 30 days. EOA, effective orifice area; PVL, paravalvular leak.

Table 1: Baseline Characteristics

Characteristic	N=260
Age, years	83.4 ± 5.4
Female	149 (57.3)
Risk and frailty assessments	
STS-PROM Score, %	3.9 ± 2.1
STS-PROM Score ≥ 7%	23 (8.8)
EuroSCORE II, %	3.4 ± 2.3
NYHA Class III or IV	143 (55.0)
Extreme risk	48 (18.5)
Total Frailty Score, mean	1.4 ± 0.8
Katz Index of Activities of Daily Living (≤ 4)	8 (3.1)
Grip Strength	200 (76.9)
15-foot walk test	144 (58.3)
Albumin (< 3.5 g/dl)	32 (12.3)
Medical history	
Balloon valvuloplasty	16 (6.2)
Cancer	78 (30.0)
Cardiac arrhythmia (any)	152 (58.5)
Atrial fibrillation	64 (24.6)
First degree AV block	29 (11.2)
Third degree AV block	2 (0.8)
Left anterior fascicular block	10 (3.8)
Left bundle branch block	19 (7.3)
Right bundle branch block	31 (11.9)
Cerebrovascular accident	14 (5.4)
Cerebrovascular disease	18 (6.9)
Chronic lung disease	63 (24.2)
Coronary artery bypass graft	32 (12.3)
Coronary artery disease	155 (59.6)
Diabetes	75 (28.8)
Hostile mediastinum/prohibitive chest deformity	4 (1.5)
Hypertension	224 (86.2)
Internal Mammary Artery	3 (1.2)
Kidney disease	63 (24.2)
Myocardial infarction	31 (11.9)
Non-ambulatory	11 (4.3)
PTCA with stent	65 (25.0)
PTCA without stent	20 (7.7)
Peripheral vascular disease	24 (9.2)
Pre-existing permanent pacemaker	28 (10.8)
Pulmonary hypertension	35 (13.5)
Subject taking anticoagulants	66 (25.4)

Transient ischemic attack	20 (7.7)
Any present or historical tobacco use	94 (36.2)
Echocardiographic parameters	
Effective orifice area, cm^2	0.7 ± 0.2
Mean aortic valve gradient, mmHg	46.2 ± 13.0
Ejection fraction, %	59.3 ± 9.4
Mitral regurgitation ≥ moderate, %	42 (16.2)

Values are mean ± SD or n (%) that reflect missing values. AV, Atrioventricular; PTCA, Percutaneous transluminal coronary angioplasty.

Table 2: Procedural Characteristics

Characteristic	N=260
Procedural success[1]	253 (97.3)
Procedural failure	7 (2.7)
Additional TAVR device in subject	5 (1.9)
Other[2]	2 (0.8)
Conscious sedation	83 (31.9)
Valve deployed with FlexNav DS Integrated Sheath	232 (89.2)
Implanted valve size	
23 mm	14 (5.4)
25 mm	66 (25.4)
27 mm	103 (39.6)
29 mm	77 (29.6)
Pre-balloon valvuloplasty	248 (95.4)
Post-balloon valvuloplasty	73 (28.1)
Access Site	
Transfemoral	259 (99.6)
Subclavian/axillary	1 (0.4)
Resheathing[3]	122 (46.9)
1 resheath	80 (30.8)
2 resheaths	27 (10.4)
>2 resheaths	15 (5.8)
Final Deployed Stent Depth, mm	4.2 ± 2.0
Deployed Stent Depth from NCC, mm	3.7 ± 2.2
Deployed Stent Depth from LCC, mm	4.7 ± 2.1
Subjects with final deployed stent depth within 3-5 mm	124 (47.7)
Total procedure time, min	69.5 ± 30.1
TAVR implantation time, min	10.6 ± 6.9
Total fluoroscopy time, min	19.9 ± 8.7
Total Contrast Volume, cc	122.0 ± 65.0
Length of hospital stay, median (Q1, Q3)	2.0 (1.0, 4.0)

Values are mean ± SD or n (%) that reflect missing values. TAVR, transcatheter aortic valve replacement; DS, delivery system; NCC, non-coronary cusp; LCC, left coronary cusp

[1] Procedural success is defined as absence of procedural mortality and correct positioning of a single prosthetic heart valve into the proper anatomical location.

[2] Two subjects received a vascular plug to mitigate PVL during the procedure.

[3] For the first valve implanted.

Table 3: Outcomes Through 30 Days

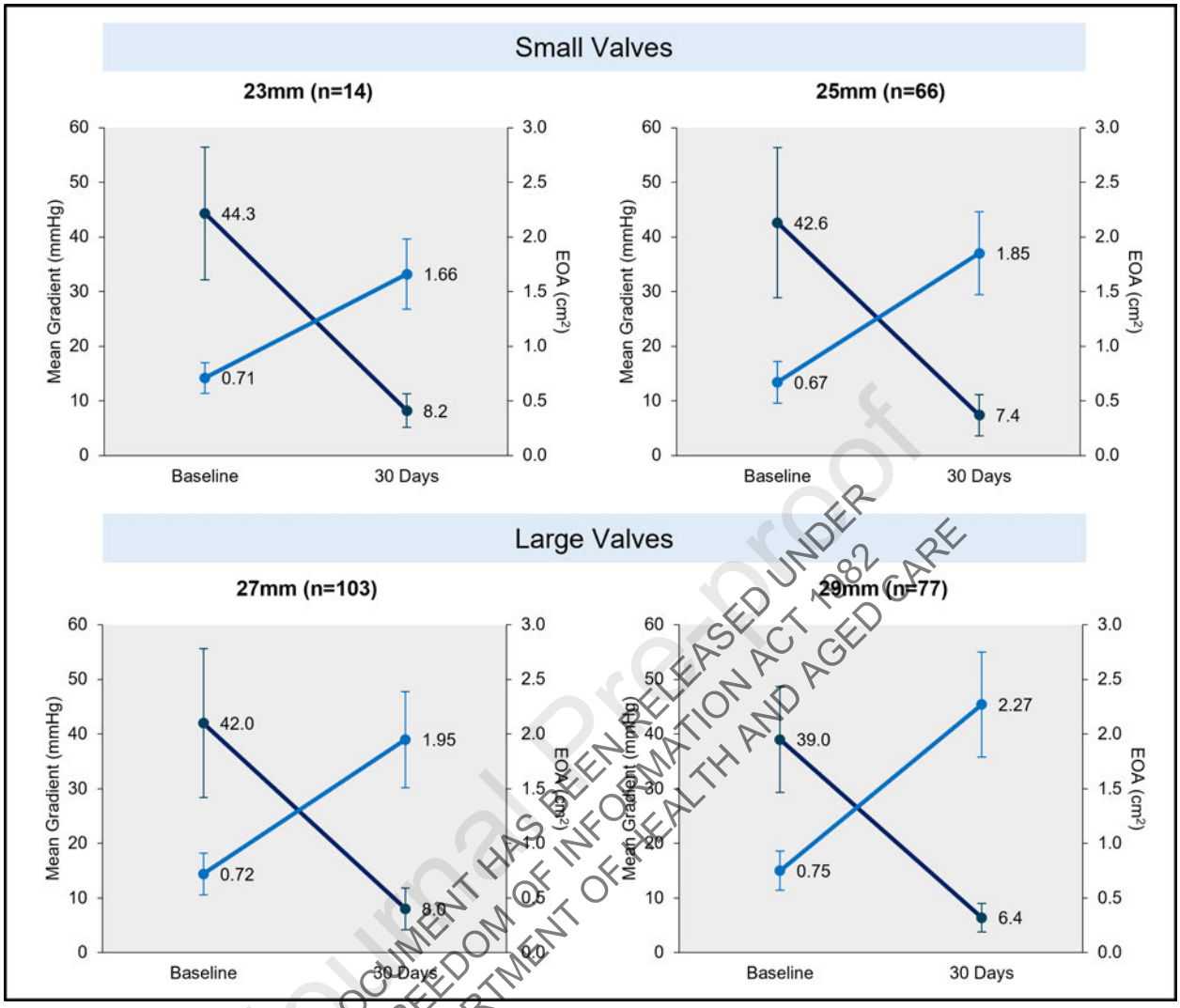
Outcome	(N=260)
Composite Safety Endpoint[1]	20 (7.7)
All-cause mortality	5 (1.9)
Cardiovascular mortality	4 (1.5)
Acute kidney injury	
Stage 2	3 (1.2)
Stage 3	2 (0.8)
Bleeding	
Life-threatening	10 (3.8)
Requiring transfusion	6 (2.3)
Major bleeding	12 (4.6)
Neurological events	
Disabling stroke	5 (1.9)
Non-disabling stroke	5 (1.9)
Transient Ischemic Attack (TIA)	2 (0.8)
Vascular complications	
Major vascular complication	11 (4.2)
Vascular access site	8 (3.1)
Non-access site	3 (1.2)
Minor vascular complication	16 (6.2)
Overall pacemaker implantation[2]	44 (16.9)
New pacemaker implantation (n=232)[3]	44 (19.0)

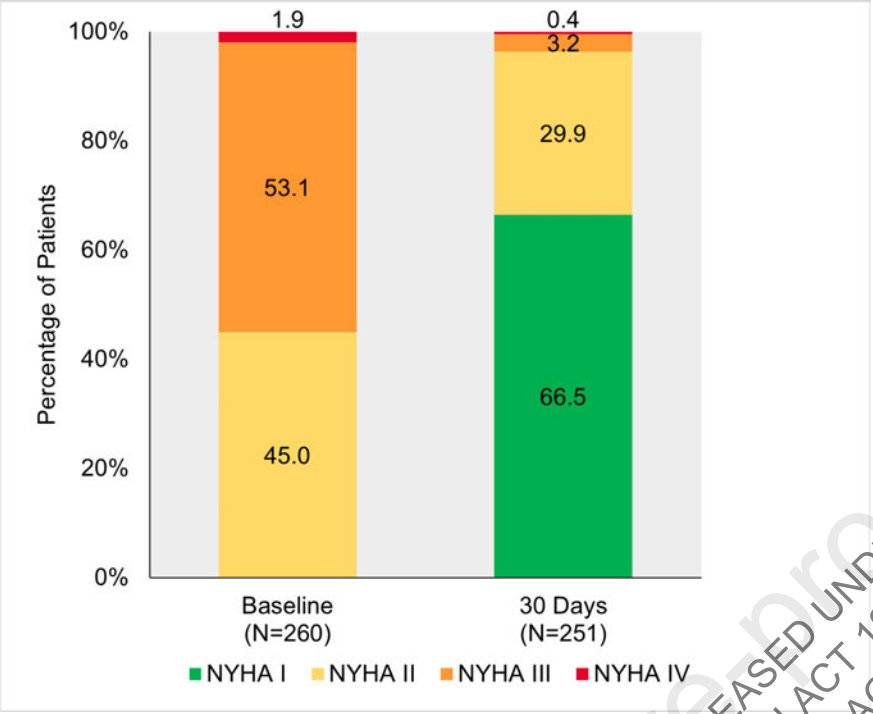
Data presented as n (%).

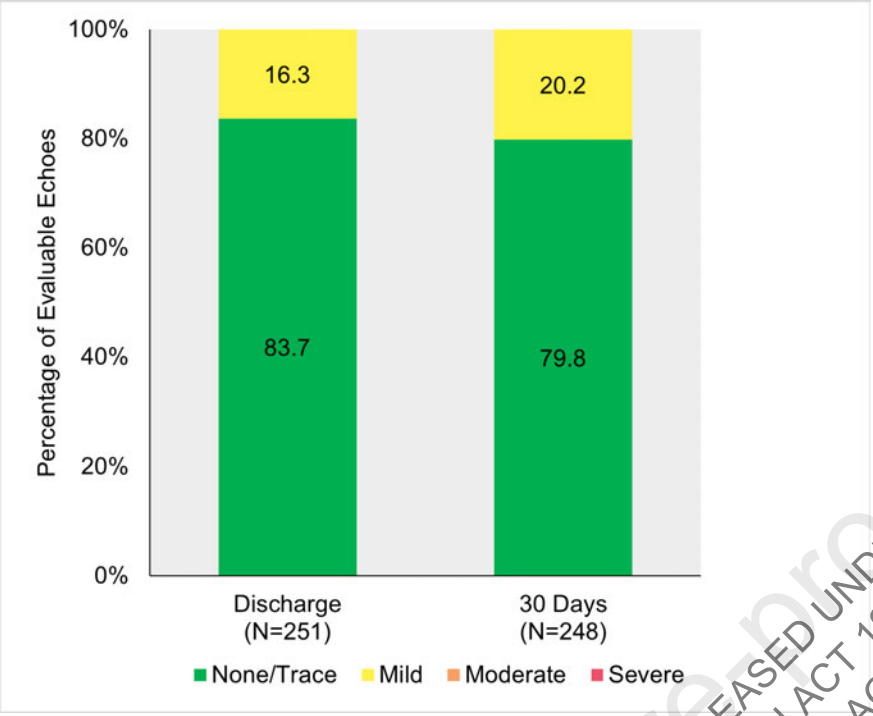
[1] The composite safety endpoint includes all-cause mortality, disabling stroke, life-threatening bleeding, stage 3 acute kidney injury, and major vascular complication.

[2] Including patients in whom pacemakers were implanted at baseline.

[3] Excluding patients with implanted pacemakers at baseline.







CENTRAL ILLUSTRATION: 30-Day Outcomes of the International PORTICO NG Study, N=260