Clinical Outcomes after Transcatheter Aortic Valve Replacement (TAVR) Using Valve Academic Research Consortium (VARC) Definitions: A Weighted Meta-Analysis of 3,519 Patients from 16 Studies

Philippe Généreux, MD

Director Angiographic Core Laboratory,

Columbia University Medical Center and the Cardiovascular Research Foundation, New York, NY

Director, TAVI program, Hôpital du Sacré-Coeur de Montréal, Montréal, Canada

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COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

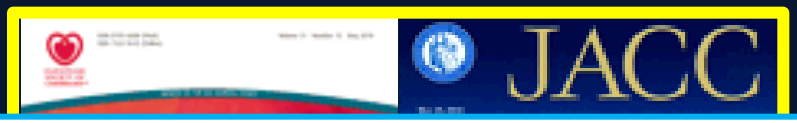
Disclosure Statement of Financial Interest

Philippe Généreux, MD

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• None	

January 2011 VARC MANUSCRIPT



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CLINICAL RESEARCH
Valvular medicine

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CLINICAL RESEARCH **Valvular Medicine**

Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation Clinical Trials

A Consensus Report From the Valve Academic Research Consortium

Martin B. Leon, Nicolo Piazza, Eugenia Nikolsky, Eugene H. Blackstone, Donald E. Cutlip, Arie Pieter Kappetein, Mitchell W. Krucoff, Michael Mack, Roxana Mehran, Craig Miller, Marie-angéle Morel, John Petersen, Jeffrey J. Popma, Johanna J. M. Takkenberg, Alec Vahanian, Gerrit-Anne van Es, Pascal Vranckx, John G. Webb, Stephan Windecker, Patrick W. Serruys

New York, New York

Background

- Recently, the published Valve Academic Research Consortium (VARC) definitions have helped to add uniformity for reporting outcomes after Transcatheter Aortic Valve Replacement (TAVR).
- We sought to perform a weighted meta-analysis to determine rates of major outcomes after TAVR using VARC definitions and to evaluate their current use in the literature.

EXPEDITED PUBLICATION

Clinical Outcomes After Transcatheter Aortic Valve Replacement Using Valve Academic Research Consortium Definitions

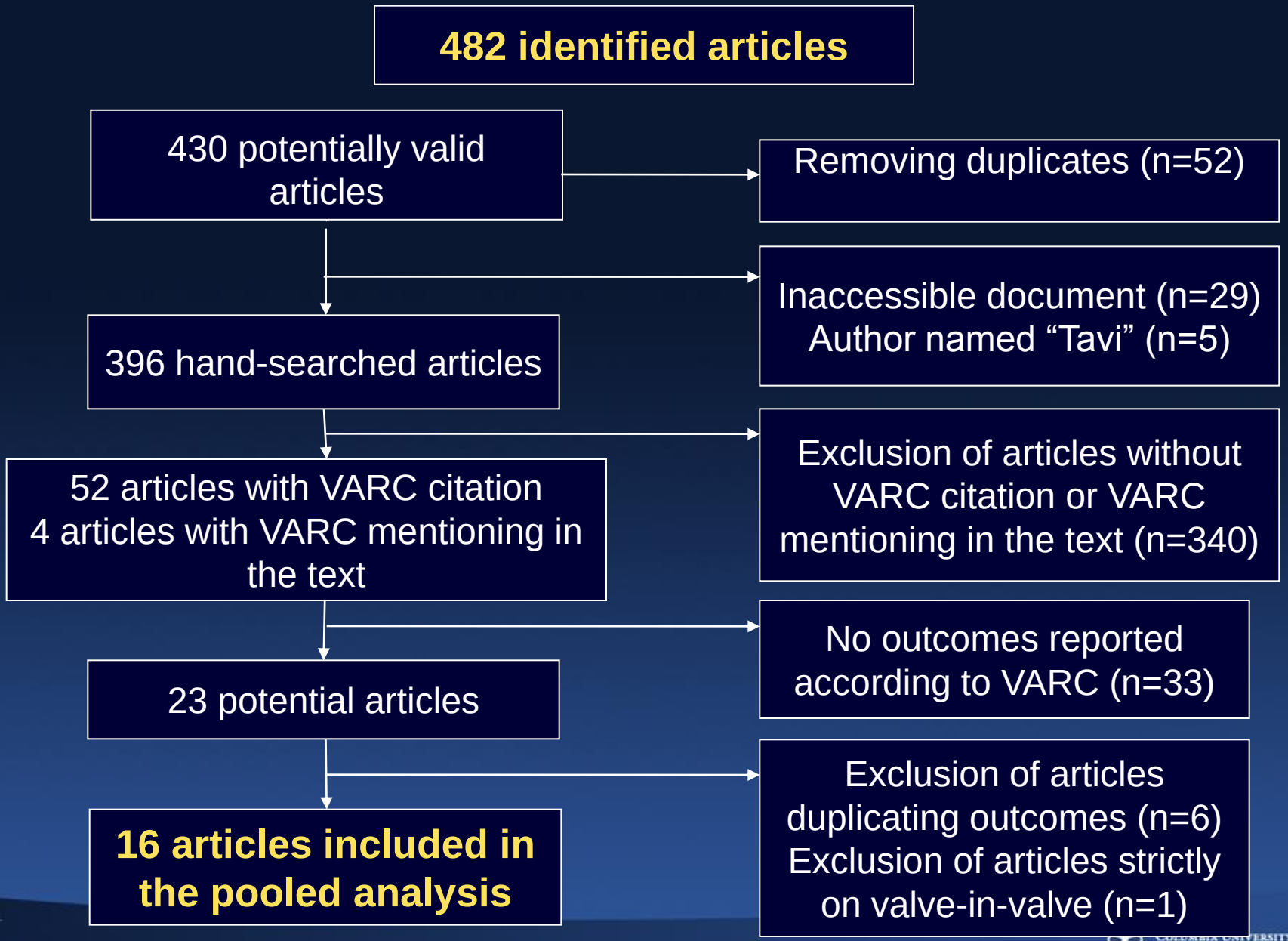
A Weighted Meta-Analysis of 3,519 Patients From 16 Studies

Philippe Généreux, MD,*† Stuart J. Head, MSc,‡ Nicolas M. Van Mieghem, MD,§
Susheel Kodali, MD,* Ajay J. Kirtane, MD, SM,* Ke Xu, PhD,* Craig Smith, MD,*
Patrick W. Serruys, MD, PhD,§ A. Pieter Kappetein, MD, PhD,‡ Martin B. Leon, MD*

New York, New York; Montréal, Québec, Canada; and Rotterdam, the Netherlands

Methods

- A comprehensive search of multiple electronic databases *from January 1st 2011 through October 12th 2011* was conducted using predefined criteria.
- We included studies reporting at least one outcome using VARC definitions.



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Results

- A total of *16 studies including 3,519 patients* met inclusion criteria and were included in the analysis.
- Outcome rates were first presented as *the minimum and maximum rates reported* among selected articles.
- *Cumulative rates* for each VARC outcome were then obtained from a pooled analysis
- *Summary rate estimates* and 95% confidence intervals (CIs) were obtained using a *random effects model*
- To assess *heterogeneity* across trials, we used the *Cochrane Q statistic* consistency among studies

Results

- 14 registries or retrospective analysis
- 2 RCT
- ***1,903 Edwards Lifesciences prosthesis (54.1%)*** and ***1,186 Medtronic CoreValve prosthesis (33.7%)*** implantations were identified.
- The type of implanted device was not clearly reported by authors in 430 patients (12.2%).
- TF (≈2/3),TA (≈1/3), SC and TAo

TAVR Outcomes - VARC Meta-Analysis (16 studies; 3,519 patients)

Endpoint	*Pooled Estimate (%)*	*[95% CI]*
STS score	8.7	[7.0, 10.3]
Log Euroscore	22.8	[20.3, 25.3]
Age (years)	81.5	[80.8, 82.2]
Female	52.0	[46.3, 57.6]
NYHA 3 or 4	82.0	[77.5, 86.5]
AVA (cm^2)	0.61	[0.53, 0.68]
Mean gradient (mmHg)	47.6	[45.7, 49.5]

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VARC outcomes after TAVR

Outcomes	Reported Rate min,max (%)	Cumulative rate	I^2 (%)	Rate Estimated (%)	[95% CI]
Device Success	80.0-100.0	1748/1899	93.2	92.1	[88.7,95.5]
Mo					.1]
CV					.3]
Mo					6.9]
CV					9.5]
MI ≤ 72h	0.0-5.6	34/3018	88.9	1.1	[0.2,2.0]

Most frequent modes of failure to device success:

1)Moderate to severe aortic regurgitation (7.4%; 95% CI: 4.6% to 10.2%)

2)Aortic valve area (AVA) ≤1.2 cm2 (4.8%; 95% CI: 3.0% to 6.6%)

3) Failure of delivery or implantation of the valve in the correct position (3.5%; 95% CI: 2.2% to 5.6%)

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Neurological complications after TAVR

Outcomes	Reported Rate min,max (%)	Cumulative rate	I^2 (%)	Rate Estimated (%)	[95% CI]
Major	0.8-9.0	84/2730	70.7	3.2	[2.1,4.8]
Minor	0.0-1.7	12/1450	54.6	1.0	[0.5,1.9]
TIA	0.0-12.0	18/1826	83.4	1.2	[0.0,2.3]
Major +Minor	1.0-6.8	68/1706	67.4	4.0	[2.4,6.3]
All	1.3-21.0	103/1892	72.8	5.7	[3.7,8.9]

Minor—Modified Rankin score <2 at 30 and 90 days
Major—Modified Rankin score ≥2 at 30 and 90 days

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Vascular complications after TAVR

Outcomes	Reported Rate min,max (%)	Cumulative rate	I^2 (%)	Rate Estimated (%)	[95% CI]
Major	5.0-23.3	282/2417	81.3	11.9	[8.6,16.4]
Minor	5.6-28.3	203/2142	88.8	9.7	[6.7,14.0]
All	9.5-51.6	511/2740	92.6	18.8	[14.5,24.3]

Bleeding after TAVR

Outcomes	Reported Rate min,max (%)	Cumulative rate	I^2 (%)	Rate Estimated (%)	[95% CI]
Life Threatening	7.0-25.9	207/1350	86.1	15.6	[11.7,20.7]
Major	2.9-47.0	298/1363	96.6	22.3	[17.8,28.3]
Minor	3.0-16.0	95/987	81.9	9.9	[6.9,14.3]
All	26.8-77.0	408/987	98.4	41.4	[35.5,47.6]
Transfusion ≥1 unit	6.3-80.0	386/906	85.3	42.6	[19.8,62.4]

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Acute Kidney Injury
Modified RIFFLE criteria

Change in serum creatinine *(up to 72 h)* compared with baseline

Stage 1. **Increase in serum creatinine to 150% to 200% (*1.5 to 2.0 x increase* compared with baseline) or increase of >0.3 mg/dl (>26.4 mmol/l)**

Stage 2. **Increase in serum creatinine to 200% to 300% (*2.0 to 3.0 x increase* compared with baseline) or increase between >0.3 mg/dl (>26.4 mmol/l) and <4.0 mg/dl (<354 mmol/l)**

Stage 3*. **Increase in serum creatinine to ≥300% (*>3 x increase* compared with baseline) or serum creatinine of ≥4.0 mg/dl (≥354 mmol/l) with an acute increase of at least 0.5 mg/dl (44 mmol/l)**

**Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.*

AKI after TAVR

Outcomes	Reported Rate min,max (%)	Cumulative rate	I^2 (%)	Rate Estimated (%)	[95% CI]
AKI I	3.2-24.6	149/1150	91.1	13.3	[9.8,18.0]
AKI II	0.8-5.3	29/1150	64.9	2.7	[1.5,5.3]
AKI III	1.0-10.2	98/1929	73.0	5.3	[3.5,8.2]
AKI II-III	3.0-15.0	93/1275	80.9	7.5	[5.1,11.4]
AKI I-II-III	6.5-34.1	232/1150	94.8	20.4	[16.2,25.8]

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Composite Endpoint

- *Combined safety endpoint (at 30 days)*
- All-cause mortality
- Major stroke
- Life-threatening bleeding
- Acute kidney injury—Stage 3
- Peri-procedural MI
- Major vascular complication
- Repeat procedure for valve-related dysfunction (surgical or interventional therapy)

Combined efficacy endpoint (at 1 yr or longer)

- All-cause mortality (after 30 days)
- Failure of current therapy for AS, requiring hospitalization for symptoms of valve-related or cardiac decompensation
- Prosthetic heart valve dysfunction (aortic valve area <1.2 cm2 and mean aortic valve gradient ≥20 mm Hg or peak velocity ≥3 m/s, OR moderate or severe prosthetic valve AR)

PPM and Composite end-points after TAVR

Outcomes	Reported Rate min,max (%)	Cumulative rate	I^2 (%)	Rate Estimated (%)	[95% CI]
PPM	3.4-50.0	396/2914	95.9	13.9	[10.6,18.9]
Composite endpoint Safety 30-day	17.0-61.8	420/1286	96.6	32.7	[27.5,38.8]
Composite endpoint efficacy 1-year	70.2-72.2	209/294	0.0	71.1	[65.6,76.0]

Permanent Pace-maker

- ***Medtronic Corevalve™*** **prosthesis use was associated with a significant higher rate of PPM implantation compared to the *Edwards's* prosthesis *(28.9%, 95% CI [23.0,36.0] vs. 4.9%, 95% CI [3.9,6.2]*, p value < 0.0001).**

Other TAVR related complications

Outcomes	Reported Rate min,max (%)	Cumulative rate	I^2 (%)	Rate Estimated (%)	[95% CI]
Multiple valve implanted	0.6-4.1	38/2208	62.1	1.8	[1.1,3.1]
Mean Gradient $\geq$ 20 mmhg	0.0-2.9	11//1064	85.2	1.0	[0.0,2.1]
Valve embolization	0.0-5.6	45/2329	85.9	1.7	[0.2,3.3]
Valve in valve	0.0-9.0	43/2014	80.9	2.3	[1.3,4.5]
Conversion to open surgery	0.0-5.6	23/2189	84.1	1.3	[0.0,2.6]
Repeat procedure for valve dysfunction	0.0-4.1	31/1920	51.7	1.8	[1.0,3.7]
Unplanned CPB use	0.0-1.9	15/1081	78.0	1.3	[0.3,2.2]

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Other TAVR related complications

Outcomes	Reported Rate min,max (%)	Cumulative rate	I^2 (%)	Rate Estimated (%)	[95% CI]
Coronary obstruction	0.0-3.0	13/1984	54.1	0.7	[0.4,1.1]
Left Ventricle perforation	0.2-0.8	3/702	0.0	0.4	[0.1,1.5]
Tamponade	0.6-4.6	29/1097	74.4	2.7	[1.7,4.2]
Annulus rupture	0.3-0.8	3/560	0.0	0.5	[0.2,1.7]
Aortic rupture	0.8-1.0	5/539	0.0	0.9	[0.4,2.2]
Aortic dissection	0.9-1.7	5/468	0.0	1.1	[0.4,2.5]
Endocarditis	0.3-1.1	5/832	0.0	0.6	[0.2,1.4]
Valve thrombosis	0.0-2.7	2/380	93.5	1.2	[0.3,2.2]
LVOT rupture	0.6	1/165	-	0.6	[0.1,4.3]
VSD	0.6	1/165	-	0.6	[0.1,4.3]

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Limitations

- First generation devices in early TAVR experience
- Study-level pooled analysis
- Reported outcomes from 14 out of 16 studies were mainly self- or site reported.
- High heterogeneity
- No systematic comparison of the devices or approaches has been attempted

Conclusion

- VARC definitions *have already been used* successfully in the literature and are being rapidly adopted by the TAVR community.
- Although VARC definitions have brought uniformity and standardization reporting outcomes after TAVR, *appropriate recognition and ascertaining, reporting and adjudication of outcomes should be reinforced* and will ensure that TAVR study results are a valid reflection of "real-world" clinical events.

Conclusion

- **However, slight *modifications are needed* and may improve their application in the future.**

VARC - 2

- VARC was designed as a dynamic process with appropriate updates and revisions.
- The VARC 2: a second manuscript has been published.

EXPEDITED REVIEW Heart Valve Disease

Updated Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation

The Valve Academic Research Consortium-2 Consensus Document†

A. Pieter Kappetein,* Stuart J. Head, Philippe Généreux, Nicolo Piazza, Nicolas M. van Mieghem, Eugene H. Blackstone, Thomas G. Brott, David J. Cohen, Donald E. Cutlip, Gerrit-Anne van Es, Rebecca T. Hahn, Ajay J. Kirtane, Mitchell W. Krucoff, Susheel Kodali, Michael J. Mack, Roxana Mehran, Josep Rodés-Cabau, Pascal Vranckx, John G. Webb, Stephan Windecker, Patrick W. Serruys, Martin B. Leon

Rotterdam, the Netherlands

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