Late-stage assessment guidance
GID-HTE10027 Transcatheter heart valves for transcatheter aortic valve implantation (TAVI) in people with aortic stenosis:
Addendum

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Contents

Abbreviations

Term	Definition
AKI	Acute Kidney Injury
AVA	Aortic Valve Area
BE	Balloon Expanding
CAD	Coronary artery disease
CVA	Cerebrovascular accident
CVT	Clinical valve thrombosis
ECG	Electrocardiogram
GFR	Glomerular Filtration Rate
HALT	Hypo attenuated leaflet thickening
iEOA	indexed effective orifice area
IQR	Interquartile Range
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
MDCT	Multi-detector CT
MDT	Multidisciplinary team
MI	Myocardial infarction
N/A	Not applicable
NR	Not reported
NYHA	New York Heart Association
PPI	Permanent pacemaker implantation;
PPMI	Permanent pacemaker implantation
PVL	Paravalvular leak
PVR	Paravalvular regurgitation
RCT	Randomised controlled trial
SE	Self-expanding
SLT	Subclinical leaflet thrombosis
STS	The Society of Thoracic Surgeons
SVD	Structural valve deterioration
TAPSE	Tricuspid annular plane systolic excursion
TAVI	Transcatheter aortic valve implantation
TAVR	Transcatheter aortic valve replacement
TEE	Transoesophageal echocardiogram
THV	Transcatheter Heart Valve

Term	Definition
TIA	Transient ischaemic attack
TTE	Transthoracic echocardiogram
VARC-2	Valve Academic Research Consortium-2
VARC-3	Valve Academic Research Consortium-3

1. Background

In response to comments received on the draft guidance, the aim of this supplementary report is to review and summarise 44 additional pieces of evidence. A total of 43 studies were identified by NICE: original Company Request for Information (N=11), stakeholder consultation responses (N=30) received *prior* to publication of draft guidance, see earlier EAG responses to consultation comments, and public consultation responses (N=2) received *after* publication of draft guidance. 1 additional reference (identified as a reference from 1 of the 43 studies identified by NICE) was also considered by the EAG.

2. Methods

The EAG reviewed full papers for the 44 identified studies and considered relevance to the Final Scope; categorising studies as not in scope, in scope but not key evidence and key evidence. For transparency, study characteristics were tabulated and EAG considerations of generalisability and limitations summarised. Where the EAG considered the study to be out of scope the reason(s) for exclusion were provided. Study results were only extracted for comparative studies comparing outcomes across different TAVI devices in line with the LSA objectives. Direction of results of key evidence were compared with those obtained from analysis of UK TAVI Registry data and evidence already considered within the original EAG report (where statistical comparisons were made to a reference device), to determine general trends.

3. Results

The EAG considered that of the additional 44 studies (Appendix 1), 22 were out of scope (see section 3.3), 20 were in scope but not considered key evidence (see section 3.2) and 2 were in scope and considered key evidence (see section 3.1), neither of which were reported to have received industry funding (Deharo et al. 2020; Thiele et al. 2020).

3.1 Key evidence

The study by Thiele et al. 2020 was an RCT of 2x2 factorial design. The first randomised comparison considered the use of general anaesthesia vs local anaesthesia with conscious sedation. The study's second randomised comparison compared self-expandable (Evolut R) vs balloon-expandable (Sapien 3) valves in 447 patients in Germany. The study was designed to have at least 80% power to detect equivalence in intention to treat analysis for the composite primary endpoint (all-cause mortality, stroke, moderate or severe paravalvular leak, permanent pacemaker) for both randomised comparisons at 30 days. The analyses assumed independence between the 2 randomised comparisons based on clinical plausibility and did not subsequently report any test for interactions between the randomised comparisons. The authors concluded equivalence for both randomised comparisons for the primary outcome. The only secondary endpoint that was not equivalent was permanent pacemaker implantation, compared at 30 days (19.2% for Sapien 3 compared with 23.0% for Evolut R, p=0.06 thus rejecting the equivalence hypothesis), suggesting a possible difference between valves for that outcome. However, the EAG note that the study was not powered to detect differences in individual components of the composite endpoint and no exploration of interactions between the randomised comparisons was reported.

The study by Deharo et al. 2020 was a retrospective cohort from a national hospitalisation database in France (including public and private hospital care) which compared Sapien 3 with Evolut R and reported analysis from a cohort of 10,549 propensity matched pairs (matching based on 38 variables) followed for a median of 232 days (0.6 years). Across all time points for matched pairs (n=10,549) Sapien 3 was associated with statistically lower pacemaker implantation at the time or after the procedure (RR: 0.72 (95%CI 0.69 to 0.76); p<0.0001), lower all-cause mortality at follow-up (OR: 0.88 (95%CI 0.82 to 0.95); p=0.005) and lower rehospitalisation at follow-up (OR: 0.84 (0.78 to 0.90); p<0.001). At 3 years follow-up (n=3,029) lower all-cause mortality was seen with Sapien 3 compared with Evolut R (RR: 0.63 (95%CI 0.52 to 0.78); p<0.0001). No statistically significant differences were observed between arms in all-cause stroke, and negative control outcomes (non-cardiovascular death, cancer, and urinary tract infection). The EAG note that this

analysis was based on routine administrative data, with relatively short term follow up, and lacked clinical detail (such as that obtained from the UK TAVI Registry) including mean aortic valve gradient, valve area, and paravalvular leak; however, the authors did conduct statistical analyses to control for as many confounders as possible using the dataset available to them.

The EAG considered the results of these 2 additional studies when compared with the key evidence and analysis of the UK TAVI Registry data described in the original EAG report, which reported on the TAVI devices listed in the Final Scope. The general trends were as follows:

- Mortality: A statistical difference in procedural mortality between 4 TAVI devices was reported in the retrospective cohort with propensity matching by Rudolph et al. 2024, Table 1. No evidence of a difference in in-hospital mortality was found between devices was observed by the multivariate analysis of the UK TAVI Registry. Equivalence in this outcome was also demonstrated in an RCT (Thiele et al. 2020) with 30 days follow-up. Differences in mortality were reported by 2 cohort studies which incorporated propensity matching (Deharo et al. 2020 up to 3 years; Costa et al. 2022 up to 1 year); both showing higher mortality in Evolut R compared with Sapien 3 valves. No statistical differences in mortality were observed from the EAG's multivariate analysis of UK TAVI Registry data linked to HES data (maximum follow up of 2.6 years).
- Stroke: Differences in in-hospital stroke were observed in multivariate analysis of the UK TAVI Registry data (higher for Evolut R, Evolut Pro+, Navitor and Sapien 3 when compared with Sapien 3 Ultra as the reference which was the most frequently used balloon-expanding valve within the dataset analysed), Table 2. No evidence of a difference in stroke outcomes post-discharge were observed across TAVI devices in multivariate analyses of the UK TAVI Registry (follow-up 2.6 years). There was also no evidence of a difference in stroke outcomes in the Registry data between self-expanding valves (either in-hospital or follow-up to 2.6 years) when compared with Evolut Pro+ (the most frequently used self-expanding valve within the dataset analysed). A total of 5 published studies also reported no difference in stroke outcomes

post-discharge; noting that the devices which were compared varied across studies. Only Costa et al. 2022 reported lower stroke at 1-year with Portico (predecessor to Navitor) when compared with Evolut R.

- Readmission for heart failure: Differences were reported by 2 cohort studies with propensity matching (Deharo et al. 2020 showed Evolut R had more readmissions for heart failure than Sapien 3; Costa et al. 2022 showed more rehospitalisations for heart failure for ACURATE neo compared with Evolut R, and more for ACURATE neo, Evolut Pro and Portico when compared with Sapien 3 and more for ACURATE neo and Portico when compared with Evolut R), Table 3, however the follow-up period was 12 months or shorter. Multivariate analysis of the UK TAVI Registry data did not find a difference in this outcome post-discharge between devices (follow-up to 2.6 years). An additional cohort study with propensity matching did not find evidence of a difference in this outcome at 1 year (Rudolph et al. 2024).
- Reintervention: No differences in reintervention were observed longitudinally in the multivariate analysis of the UK TAVI Registry data or 2 additional retrospective cohort studies which included propensity matching, Table 4.
- Paravalvular leak and aortic regurgitation: Differences in paravalvular leak or aortic regurgitation at discharge were found in the multivariate analysis of the UK TAVI Registry and 1 retrospective cohort with propensity matching (definition of outcome varied, devices compared varied), Table 5. The EAG note that no difference was observed in the moderate or severe prosthesis valve regurgitation at 30 days in the RCT which compared Sapien 3 and Evolut R. The EAG note that statistical differences were observed for this outcome between generations of devices by the same manufacturer: Nazif et al. 2021 and Abdelfattah et al. 2022 comparing Sapien 3 and Sapien 3 Ultra, Gozdek et al. 2023 and Forrest et al. 2020 comparing Evolut R and Evolut Pro. The EAG highlight that technology differences between Evolut Pro+ (generation listed in NICE Final Scope) and Evolut Pro (as reported in these studies) is limited to changes in the profile of the delivery system).
- Permanent pacemaker implantation: 4 studies (including 1 RCT and 2 cohorts with propensity matching, and the multivariate analysis of the UK TAVI Registry) all demonstrated lower pacemaker implantation rate with Sapien 3

and 3 Ultra when compared with Evolut R and Pro+ or Navitor at in-hospital, 30 day and 1 year timepoints, Table 6. Two studies (both cohort studies with propensity matching) also reported lower pacemaker with ACURATE neo at 1 year (Costa et al. 2022, Rudolph et al. 2024) when compared with Evolut R and Portico devices. However, the EAG note that from multivariate analysis of the UK TAVI Registry data, no difference in pacemaker implantation after discharge up to 31 months follow up was found between devices (see Table 24 in original EAG report). No difference was observed in pacemaker outcomes when considering only self-expanding valves from the UK TAVI Registry either (see Table 25 and 26 in the original EAG report).

Table 1: Summary of mortality outcomes from published studies and UK TAVI registry

[Note: grey cells indicate the reference valve used in statistical comparisons, green indicates statistically lower risk for the outcome compared with the reference, red indicates statistically higher risk; amber cells indicate that a reference valve was not used but a statistical difference between multiple valves was reported, **bold text** indicating results from the UK TAVI Registry; rows ordered by increasing duration of follow-up]

Study	Study design	Outcome	Timepoint	Myval Octacor	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Allegra	Evolut R	Evolut Pro+	Evolut FX	Hydra	Navitor	Trilogy
UK TAVI registry	**Retrospective cohort (multivariate analysis)**	**All-cause mortality**	**In-hospital**	**-**	**No statistical difference**	**Reference**	**No statistical difference**	**-**	**No statistical difference**	**No statistical difference**	**-**	**-**	**No statistical difference**	**-**
Merdler et al. 2023	Retrospective cohort	Mortality	In-hospital	-	-	-	-	-	-	Reference	No statistical difference	-	-	-
Rudolph et al. 2024	Retrospective cohort (with propensity matching)	All-cause mortality	Procedural	-	No reference; statistical difference between 4 valves reported	-	No reference; statistical difference between 4 valves reported **(ACURATE neo lowest)**	-	No reference; statistical difference between 4 valves	-	-	-	No reference; statistical difference between 4 valves **(Portico highest)**	-
Thiele et al. 2020	RCT (2x2 factorial design comparing anaesthesia and expansion type of device)	All-cause mortality	30 days	-	Reference	-	-	-	No statistical difference	-	-	-	-	-
Nazif et al. 2021	Retrospective cohort (with propensity matching)	All-cause mortality, cardiac death	30 days	-	Reference	No statistical difference	-	-	-	-	-	-	-	-
Gozdek et al. 2023	SR and MA (N=11 observational studies)	All-cause mortality	30 days	-	-	-	-	-	Reference	No statistical difference	-	-	-	-
Forrest et al. 2020	Retrospective cohort	All-cause mortality	30 days	-	-	-	-	-	Reference	No statistical difference (Pro)	-	-	-	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	All-cause mortality	1 year	-	Lower	-	Lower (ACURATE neo)	-	Reference	Lower (Pro)	-	-	No statistical difference (Portico)	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	All-cause mortality	1 year	-	Reference	-	No statistical difference (ACURATE neo)	-	Higher	No statistical difference (Pro)	-	-	Higher (Portico)	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	All-cause mortality	1 year	-	No statistical difference	-	Reference (ACURATE neo)	-	Higher	No statistical difference (Pro)	-	-	Higher (Portico)	-
Rudolph et al. 2024	Retrospective cohort (with propensity matching)	All-cause mortality	30 days and 1 year	-	No reference; no statistical difference	-	No reference; no statistical difference (ACURATE neo)	-	No reference; no statistical difference	-	-	-	No reference; no statistical difference (Portico)	-
UK TAVI registry	**Retrospective cohort (multivariate analysis)**	**All-cause mortality**	**Post-discharge up to 31 months**	**-**	**No statistical difference**	**Reference**	**No statistical difference**	**-**	**No statistical difference**	**No statistical difference**	**-**	**-**	**No statistical difference**	**-**
Deharo et al. 2020	Retrospective cohort (with propensity matching)	All-cause mortality	1 month and 1, 2, 3 years	-	Reference	-	-	-	Higher	-	-	-	-	-
Deharo et al. 2020	Retrospective cohort (with propensity matching)	Cardiovascular mortality	1 month and 1, 2, 3 years	-	Reference	-	-	-	Higher	-	-	-	-	-
Abdelfattah et al. 2022	Meta-analysis (N=7 observational studies)	All-cause mortality	NR	-	Reference	No statistical difference	-	-	-	-	-	-	-	-

Abbreviations: NR, not reported

Table 2: Summary of stroke outcomes from published studies and UK TAVI registry

[Note: grey cells indicate the reference valve used in statistical comparisons, green indicates statistically lower risk for the outcome compared with the reference, red indicates statistically higher risk; amber cells indicate that a reference valve was not used but a statistical difference between multiple valves was reported, **bold text** indicating results from the UK TAVI Registry; rows ordered by increasing duration of follow-up]

Study	Study design	Outcome	Timepoint	Myval Octacor	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Allegra	Evolut R	Evolut Pro+	Evolut FX	Hydra	Navitor	Trilogy
Rudolph et al. 2024	Retrospective cohort (with propensity matching)	Stroke	Procedural	-	No reference; no statistical difference	-	No reference; no statistical difference (ACURATE neo)	-	No reference; no statistical difference	-	-	-	No reference; no statistical difference (Portico)	-
UK TAVI registry	**Retrospective cohort (multivariable analysis)**	**Stroke**	**In-hospital**	**-**	**Higher**	**Reference**	**No statistical difference**	**-**	**Higher**	**Higher**	**-**	**-**	**Higher**	**-**
UK TAVI registry (subgroup analysis: self-expanding valves)	**Retrospective cohort (multivariable analysis)**	**Stroke**	**In-hospital**	**-**	**-**	**-**	**No statistical difference**	**-**	**No statistical difference**	**Reference**	**-**	**-**	**No statistical difference**	**-**
Thiele et al. 2020	RCT (2x2 factorial design comparing anaesthesia and expansion type of device)	Stroke	30 days	-	Reference	-	-	-	No statistical difference	-	-	-	-	-
Forrest et al. 2020	Retrospective cohort	Stroke	30 days	-	-	-	-	-	Reference	No statistical difference (Pro)	-	-	-	-
Nazif et al. 2021	Retrospective cohort (with propensity matching)	Stroke	Discharge and 30 days	-	Reference	No statistical difference	-	-	-	-	-	-	-	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	Stroke	1 year	-	No statistical difference	-	No statistical difference	-	Reference	No statistical difference (Pro)	-	-	Lower (Portico)	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	Stroke	1 year	-	Reference	-	No statistical difference	-	No statistical difference	No statistical difference (Pro)	-	-	No statistical difference	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	Stroke	1 year	-	No statistical difference	-	Reference	-	No statistical difference	No statistical difference (Pro)	-	-	No statistical difference	-
Rudolph et al. 2024	Retrospective cohort (with propensity matching)	Stroke	1 year	-	No reference; no statistical difference	-	No reference; no statistical difference (ACURATE neo)	-	No reference; no statistical difference	-	-	-	No reference; no statistical difference (Portico)	-
UK TAVI registry	**Retrospective cohort (multivariable analysis)**	**Stroke**	**Post-discharge up to 31 months follow-up**	**-**	**No statistical difference**	**Reference**	**No statistical difference**	**-**	**No statistical difference**	**No statistical difference**	**-**	**-**	**No statistical difference**	**-**
UK TAVI registry (subgroup analysis: self-expanding valves)	**Retrospective cohort (multivariable analysis)**	**Stroke**	**Post-discharge up to 31 months follow-up**	**-**	**-**	**-**	**No statistical difference**	**-**	**No statistical difference**	**Reference**	**-**	**-**	**No statistical difference**	**-**
Abdelfattah et al. 2022	Meta-analysis (N=7 observational studies)	Stroke	NR	-	Reference	No statistical difference	-	-	-	-	-	-	-	-

Abbreviations: NR, not reported

Table 3: Summary of readmission for heart failure outcomes from published studies and UK TAVI registry

[Note: grey cells indicate the reference valve used in statistical comparisons, green indicates statistically lower risk for the outcome compared with the reference, red indicates statistically higher risk; amber cells indicate that a reference valve was not used but a statistical difference between multiple valves was reported, **bold text** indicating results from the UK TAVI Registry; rows ordered by increasing duration of follow-up]

Study	Study design	Outcome	Timepoint	Myval Octacor	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Allegra	Evolut R	Evolut Pro+	Evolut FX	Hydra	Navitor	Trilogy
Forrest et al. 2020	Retrospective cohort	Valve related readmission	30 days	-	-	-	-	-	Reference	No statistical difference (Pro)	-	-	-	-
Deharo et al. 2020	Retrospective cohort (with propensity matching)	Rehospitalisation for heart failure	Median 0.6 years	-	Reference	-	-	-	Higher	-	-	-	-	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	Rehospitalisation for heart failure	1 year	-	No statistical difference	-	Higher (ACURATE neo)	-	Reference	No statistical difference (Pro)	-	-	Higher (Portico)	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	Rehospitalisation for heart failure	1 year	-	Reference	-	Higher (ACURATE neo)	-	No statistical difference	Higher (Pro)	-	-	Higher (Portico)	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	Rehospitalisation for heart failure	1 year	-	Lower	-	Reference (ACURATE neo)	-	Lower	No statistical difference (Pro)	-	-	No statistical difference	-
Rudolph et al. 2024	Retrospective cohort (with propensity matching)	Further hospitalisation, further hospitalisation due to complication related to the aortic valve intervention	1 year	-	No reference; no statistical difference	-	No reference; no statistical difference (ACURATE neo)	-	No reference; no statistical difference	-	-	-	No reference; no statistical difference (Portico)	-
UK TAVI registry	**Retrospective cohort (multivariable analysis)**	**Readmission for heart failure**	**Post-discharge up to 31 months follow-up**	**-**	**No statistical difference**	**Reference**	**No statistical difference**	**-**	**No statistical difference**	**No statistical difference**	**-**	**-**	**No statistical difference**	**-**
UK TAVI registry (subgroup analysis: self-expanding valves)	**Retrospective cohort (multivariable analysis)**	**Readmission for heart failure**	**Post-discharge up to 31 months follow-up**	**-**	**-**	**-**	**No statistical difference**	**-**	**No statistical difference**	**Reference**	**-**	**-**	**No statistical difference**	**-**

Table 4: Summary of reintervention outcomes from published studies and UK TAVI registry

[Note: grey cells indicate the reference valve used in statistical comparisons, green indicates statistically lower risk for the outcome compared with the reference, red indicates statistically higher risk; amber cells indicate that a reference valve was not used but a statistical difference between multiple valves was reported, **bold text** indicating results from the UK TAVI Registry; rows ordered by increasing duration of follow-up]

Study	Study design	Outcome	Timepoint	Myval Octacor	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Allegra	Evolut R	Evolut Pro+	Evolut FX	Hydra	Navitor	Trilogy
Nazif et al. 2021	Retrospective cohort (with propensity matching)	Aortic valve reintervention	Discharge and 30 days	-	Reference	No statistical difference	-	-	-	-	-	-	-	-
Rudolph et al. 2024	Retrospective cohort (with propensity matching)	Reintervention	1 year	-	No reference; no statistical difference	-	No reference; no statistical difference (ACURATE neo)	-	No reference; no statistical difference	-	-	-	No reference; no statistical difference (Portico)	-
UK TAVI registry	**Retrospective cohort (multivariable analysis)**	**Aortic reintervention (TAVI or SAVR)**	**Post-discharge up to 31 months follow-up**	**-**	**No statistical difference**	**Reference**	**No statistical difference**	**-**	**No statistical difference**	**No statistical difference**	**-**	**-**	**No statistical difference**	**-**

Table 5: Summary of paravalvular leak and aortic regurgitation outcomes from published studies and UK TAVI registry

[Note: grey cells indicate the reference valve used in statistical comparisons, green indicates statistically lower risk for the outcome compared with the reference, red indicates statistically higher risk; amber cells indicate that a reference valve was not used but a statistical difference between multiple valves was reported, **bold text** indicating results from the UK TAVI Registry; rows ordered by increasing duration of follow-up]

Study	Study design	Outcome	Timepoint	Myval Octacor	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Allegra	Evolut R	Evolut Pro+	Evolut FX	Hydra	Navitor	Trilogy
Rudolph et al. 2024	Retrospective cohort (with propensity matching)	PVL grade II or III	Discharge	-	No reference; statistical difference between 4 valves reported **(Sapien 3 lowest)**	-	No reference (ACURATE neo); statistical difference between 4 valves reported	-	No reference; statistical difference between 4 valves	-	-	-	No reference; statistical difference between 4 valves **(Portico highest)**	-
UK TAVI registry	**Retrospective cohort (multivariable analysis)**	**Aortic regurgitation**	**In-hospital**	**-**	**No statistical difference**	**Reference**	**Higher**	**-**	**Higher**	**Higher**	**-**	**-**	**Higher**	**-**
UK TAVI registry (subgroup analysis: self-expanding valves)	**Retrospective cohort (multivariable analysis)**	**Aortic regurgitation**	**In-hospital**	**-**	**-**	**-**	**No statistical difference**	**-**	**No statistical difference**	**Reference**	**-**	**-**	**No statistical difference**	**-**
Thiele et al. 2020	RCT (2x2 factorial design comparing anaesthesia and expansion type of device)	Moderate or severe prosthetic valve regurgitation	30 days	-	Reference	-	-	-	No statistical difference	-	-	-	-	-
Nazif et al. 2021	Retrospective cohort (with propensity matching)	Paravalvular regurgitation	Discharge and 30 days	-	Reference	Lower	-	-	-	-	-	-	-	-
Merdler et al. 2023	Retrospective cohort	Moderate or severe PVL	In-hospital and 30 days	-	-	-	-	-	-	Reference	No statistical difference	-	-	-
Abdelfattah et al. 2022	Meta-analysis (N=7 observational studies)	Moderate or severe PVL	NR	-	Reference	Lower	-	-	-	-	-	-	-	-
Gozdek et al. 2023	SR and MA (N=11 observational studies)	Moderate to severe PVL	NR	-	-	-	-	-	Reference	Lower (Evolut Pro)	-	-	-	-
Forrest et al. 2020	Retrospective cohort	Moderate to severe aortic regurgitation	NR	-	-	-	-	-	Reference	Lower (Evolut Pro)	-	-	-	-
Abdelfattah et al. 2022	Meta-analysis (N=7 observational studies)	Moderate or severe PVL	NR	-	Reference	Lower	-	-	-	-	-	-	-	-

Abbreviations: NR, not reported; PVL, paravalvular leak

Table 6: Summary of pacemaker implantation outcomes from published studies and UK TAVI registry

[Note: grey cells indicate the reference valve used in statistical comparisons, green indicates statistically lower risk for the outcome compared with the reference, red indicates statistically higher risk; amber cells indicate that a reference valve was not used but a statistical difference between multiple valves was reported, **bold text** indicating results from the UK TAVI Registry; rows ordered by increasing duration of follow-up]

Study	Study design	Outcome	Timepoint	Myval Octacor	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Allegra	Evolut R	Evolut Pro+	Evolut FX	Hydra	Navitor	Trilogy
UK TAVI registry	**Retrospective cohort (multivariable analysis)**	**PPI**	**In-hospital**	**-**	**No statistical difference**	**Reference**	**No statistical difference**	**-**	**Higher**	**Higher**	**-**	**-**	**Higher**	**-**
UK TAVI registry (subgroup analysis: self-expanding valves)	**Retrospective cohort (multivariable analysis)**	**PPI**	**In-hospital**	**-**	**-**	**-**	**No statistical difference**	**-**	**No statistical difference**	**Reference**	**-**	**-**	**No statistical difference**	**-**
Deharo et al. 2020	Retrospective cohort (with propensity matching)	PPI	At time or after procedure	-	Reference	-	-	-	Higher	-	-	-	-	-
Thiele et al. 2020	RCT	PPI	30 days	-	Reference	-	-	-	Higher	-	-	-	-	-
Nazif et al. 2021	Retrospective cohort (with propensity matching)	PPI	Discharge and 30 days	-	Reference	No statistical difference	-	-	-	-	-	-	-	-
Merdler et al. 2023	Retrospective cohort	PPI	Discharge and 30 days	-	-	-	-	-	-	Reference	No statistical difference	-	-	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	PPI	1 year	-	Reference	-	No statistical difference (ACURATE neo)	-	Higher	Higher (Pro)	-	-	Higher (Portico)	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	PPI	1 year	-	Lower	-	Lower (ACURATE neo)	-	Reference	No statistical difference (Pro)	-	-	No statistical difference (Portico)	-
Costa et al. 2022	Prospective cohort (with propensity score matching)	PPI	1 year	-	No statistical difference	-	Reference (ACURATE neo)	-	Higher	Higher (Pro)	-	-	Higher (Portico)	-
Rudolph et al. 2024	Retrospective cohort (with propensity matching)	New pacemaker or implantable cardiovertor defibrillators	1 year	-	No reference; statistical difference between 4 valves reported	-	No reference; statistical difference between 4 valves reported **(ACURATE neo lowest)**	-	No reference; statistical difference between 4 valves **(Evolut R joint highest: 21.6%)**	-	-	-	No reference; statistical difference between 4 valves **(Portico joint highest: 21.9%)**	-
UK TAVI registry	**Retrospective cohort (multivariable analysis)**	**PPI**	**Post-discharge up to 31 months follow-up**	**-**	**No statistical difference**	**Reference**	**No statistical difference**	**-**	**No statistical difference**	**No statistical difference**	**-**	**-**	**No statistical difference**	**-**
UK TAVI registry (subgroup analysis: self-expanding valves)	**Retrospective cohort (multivariable analysis)**	**PPI**	**Post-discharge up to 31 months follow-up**	**-**	**-**	**-**	**No statistical difference**	**-**	**No statistical difference**	**Reference**	**-**	**-**	**No statistical difference**	**-**
Abdelfattah et al. 2022	Meta-analysis (N=7 observational studies)	PPI	NR	-	Reference	No statistical difference	-	-	-	-	-	-	-	-
Gozdek et al. 2023	SR and MA (N=11 observational studies)	PPI	NR	-	-	-	-	-	Reference	No statistical difference	-	-	-	-

Abbreviations: MA, meta-anlaysis; NR, not reported. PPI, permanent pacemaker implantation; SR, systematic review

3.2 In-scope but not prioritised

Of the 20 studies considered relevant to the scope but not key evidence, the EAG identified the following limitations (note that multiple limitations may apply):

- 13 studies included older generation devices in the intervention arm or comparator arm or both (Costa et al. 2021; Durand et al. 2021; Gallo et al. 2021; Gozdek et al. 2020; Husser et al. 2019; Kalogeras et al. 2023; Lanz et al. 2019; Mauri et al. 2017; Okuno et al. 2023; Pellegrini et al. 2023; Senguttuvan et al. 2023; Tamburino et al. 2020; Van Belle et al. 2020). The EAG summarised published evidence in the original EAG report which demonstrated differences in outcomes between generations of TAVI devices by the same manufacturer, and therefore did not assume equivalence between generations of devices by the same manufacturer. The EAG also highlight that not all valve sizes are available for device generations by the same manufacturer (for example Sapien 3 is available in 29mm valve size, however the Sapien 3 Ultra is not currently available in the 29mm size). Therefore, the EAG would advise caution in interpreting studies reporting older generation valves as results may not be generalisable. Additional mixed effects modelling could be used to account for similarity (lower variance) between generations by the same manufacturer.
- 4 studies combined TAVI devices from different manufacturers in the comparator arm:
    - Non-inferiority RCT by Makkar et al. 2020a compared Portico (Abbott) with other commercially available devices (Edwards Lifescience: Sapien, Sapien XT, Sapien 3; Medtronic: CoreValve, Evolut R, Evolut R).
    - The systematic review and meta-analysis by Senguttuvan et al. 2023 combined results from 6 RCTs which compared balloon-expanding devices by Edwards Lifesciences (Sapien XT, Sapien 3) with self-expanding device CoreValve, Evolut, Evolut R (Medtronic), ACURATE neo (Boston Scientific), Portico (Abbott), all combined. This included 1 RCT (Thiele et al. 2020) which compared device generations listed in the Final Scope (Sapien 3 compared with Evolut R); which was considered separately by the EAG.

    - The network meta-analysis by D'Ascenzo et al. 2021 included 11 RCTs which compared balloon expanding (Sapien, Sapien XT, Sapien 3), self-expanding (CoreValve, Evolut R, Evolut Pro, ACURATE neo) and SAVR. This also included only 1 RCT which compared device generations listed in the Final Scope (Thiele et al. 2020); which was considered separately by the EAG.
    - The network meta-analysis by Ueyama et al. 2021 included 10 RCTs which compared balloon expanding (Sapien, Sapien XT, Sapien 3), self-expanding (CoreValve, Evolut R, Evolut Pro, ACURATE neo) and SAVR.
- 2 studies compared different generation devices from the same manufacturer against each other:
    - Prospective cohort by Tebar et al. 2024 compared ACURATE neo2 with ACURATE neo. Larger studies (for example Kim et al. 2022c, Scotti et al. 2022) and studies with matched baseline characteristics between arms (for example: Buono et al. 2022a) were already included in the original EAG report.
    - Retrospective cohort by Welle et al. 2021 compared Sapien 3 Ultra with Sapien 3. Larger studies (Abdelfattah et al. 2022; Russo et al. 2019 and studies with matched baseline characteristics between arms (for example Nazif et al. 2021; Cannata et al. 2023) were already included in the original EAG report.
- 1 study compared in-hospital outcomes between Myval (it is unclear if this included Myval Octacor which is the latest generation) with Sapien 3 and 3 Ultra (Ubben et al. 2024). However, the EAG had considered published comparative evidence with larger sample size (for example Santos-Martinez et al. 2022) and single arm studies with longer follow-up (for example Moscarella et al. 2024 which reported 2-year follow-up) in the original EAG report.
- 1 reported a meta-analysis of 6 observational studies (Li et al. 2020) comparing Sapien 3 (n=768) and Evolut R (n=896) but reported on procedural or 30-day outcomes only. The EAG note that larger sample sizes and longer

follow-up were included for these devices in the original EAG report (for example: Rudolph et al. 2024).

The EAG note that 4 studies were RCTs, all of which had a non-inferiority design, and were funded by industry (Pellegrini et al. 2023 was a subgroup analysis of Tamburino et al. 2020).

3.3 Not in scope (excluded)

The EAG considered that 22 studies were not in scope. A summary of reasons for exclusion included the following (note that multiple reasons for exclusion may apply):

- 9 studies did not compare outcomes by TAVI device:
    - Attinger-Toller et al. 2021 compared outcomes by age group,
    - Beyersdorf et al. 2021, Forrest et al. 2023 and Jorgensen et al. 2021 compared TAVI with SAVR,
    - Eckel et al. 2022 compared implantation performed in line with the official recommendation of the manufacturer (on-label sizing) or smaller annulus dimensions that were below the official recommendation (off-label sizing);
    - Guerreiro et al. 2020 compared transfemoral and non-transfemoral access routes;
    - Leone et al. 2023 compared outcomes between male and female patients;
    - Moscarella et al. 2023 compared outcomes of aortic valve-in-valve with mitral valve-in-valve;
    - Rheude et al. 2021 combined evidence from multiple TAVI devices to determine the prevalence of subclinical leaflet thrombosis and clinical valve thrombosis following TAVI,
    - Schofer et al. 2022 compared outcomes between different surgical risk categories;
- 2 studies did not explicitly report the TAVI device used (Schofer et al. 2022; Kornyeya et al. 2023 compared self and balloon-expanding devices but did not report which valves in balloon-expanding arm);

- 1 study reported replacement of the mitral valve not aortic valve (Blasco-Turrión et al. 2022);
- 1 study undertaken in a population out of scope (Sanchez-Luna et al. 2023 conducted exclusively in patients with aortic regurgitation).
- 1 was a non-systematic narrative review (Claessen et al. 2021);
- 9 studies were single arm and therefore could not determine incremental benefit of the TAVI device because of a lack of comparator arm (Cuevas et al. 2019; Jagielak et al. 2021; JenaValve Clinical Investigation Report, 2024; Kilic et al. 2024; Malhotra et al. 2024; Moscarella et al. 2023; Rück et al. 2024; Sanchez-Luna et al. 2023; Tarantini et al. 2021);
- 1 additional study was provided academic in confidence [redacted]

4. Conclusions

Following review of 44 studies not included in the original report by the EAG, the EAG consider that 2 additional studies are key evidence in addition to those previously described. The results from the 2 studies are similar to those already included by the EAG and they do not change the conclusion of the original EAG report.

Substantial evidence is available for some manufacturers, including longitudinal analysis and studies on older generations of the valves, which was acknowledged in the original EAG report. However, in the opinion of the EAG, this does not directly support the decision problem of the LSA in assessing the incremental benefit and cost variation of different TAVI devices. Results of the published key evidence were considered similar to the results of the UK TAVI Registry. Additional validation of the multivariate modelling conducted by the EAG (and summarised in the original EAG report) could use patient-level data from trials, in order to replicate RCT inclusion and exclusion criteria, and compared predicted outcomes against those observed in the trials at specified time points. However, this was considered by the EAG as not currently possible because of a lack of clinical information captured in the UK TAVI Registry (for example: STS score or EuroSCORE II to quantify surgical risk, jet velocity, aortic valve calcification, and the valves which could be suitable for

implantation in each patient are not currently recorded) and would need access to participant-level trial data to establish population characteristics.

Throughout the LSA process, the EAG has acknowledged the limitations associated with both the published literature and the UK TAVI Registry analysis. Because the patient-level data from the UK TAVI Registry can be adjusted to account for recorded confounders, the EAG considers that this data remains the most applicable and generalisable source of data to address the LSA decision problem. Further data collection (additional known confounders including documentation of valve choice) and follow-up would strengthen future analyses.

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Appendix: Summary of study characteristics (N=44)

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
1.	Attinger-Toller (JACC Cardiovasc Interv, 2021; 952-960) [SWISS TAVI Registry; NCT01368250] Switzerland (N=15)	Prospective cohort study from Swiss Registry (n=7,097) Follow-up: 1 year Funder: Study grant from the Swiss Heart Foundation and the Swiss Working Group of Interventional Cardiology and Acute Coronary Syndromes and is sponsored by research grants from Medtronic, Edwards Lifesciences, Boston Scientific, and Abbott. The study sponsors had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.	Between February 2011 and June 2018	*Inclusion:* Only patients treated with CE marked TAVI devices were considered. Device and access-site selection were at discretion of the TAVI operators, based on clinical and anatomical characteristics. *Exclusion:* NR	Total population (n=7,097) split and analysed by age Group (yrs) • <70 (n=324) • 70–79 (n=1,913) • 80–89 (n=4,353) • ≥90 (n=507) Valves used: CoreValve, Evolut R, Evolut Pro, Sapien/Sapien XT, Sapien 3, Lotus, Lotus Edge, ACURATE / ACURATE neo, Jenavalve, Portico, Direct Flow Medical, Allegra, Engager.	N/A	Not in scope: comparison of outcomes by age group not by valve used.
2.	Beyersdorf (Eur J Cardiothorac Surg, 2021; 1139-1146) Germany (N=92)	Prospective German Registry (n=18,010), including propensity matching based on all baseline characteristics, using nearest neighbour approach (n=3,460) Follow-up: 5 years Funder: Unrestricted grants from medical device companies (Edwards Lifesciences, Medtronic, Abbott, Boston Scientific), the German Center for Cardiovascular Research (DZHK), the German Heart Foundation, the German Ministry of Health and donations from Dr Rolf M. Schwiete Foundation. Funders had no role in the study design, in the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the article for publication.	Treated in 2011 or 2012 (month NR)	*Inclusion*: The criteria for TAVI implantation in 2011-2012 were based on the position statement of the German Society for Thoracic and Cardiovascular Surgery (DGTHG) and the German Society for Cardiology (DGK). *Exclusion*: first-line indications for TAVI (and who were not eligible for SAVR) such as frailty, re-do procedure, very high risk, prognosis-limiting secondary disease, porcelain aorta and incurable malignancy.	TAVI (n=8,942, including Sapien, Sapien XT, CoreValve, ACURATE TA, JenaValve, Other) compared with SAVR (n=9,068) Propensity score matched cohort included TAVI (n=1,820), SAVR (n=1,820)	N/A	Not in scope: No analysis comparing outcomes by device (main focus on TAVI versus SAVR). Named devices are older generations of those listed in Final Scope, but also includes miscellaneous other where the TAVI valve used was undefined. Comment by Carrel et al. 2020.
3.	Blasco-Turrión (J Clin Med, 2022; 5210) Setting NR (N=5)	Retrospective cohort, registry (n=11) Follow-up: 6 months Funder: Authors report no funding received.	Between 2019 and 2022 (month NR)	*Inclusion*: patients with mitral bioprosthesis degeneration. *Exclusion*: mitral valve-in-ring or valve-in-mitral annular calcification were not included in the registry.	Myval (n=11)	N/A	Not in scope – mitral valve being replaced (not aortic valve).
4.	Claessen (JAMA Cardiol, 2021; 102-112) Setting: NR	Narrative review (not systematic review) Funder: NR	N/A	N/A	Balloon-expandable valves: Sapien, Sapien XT, Sapien 3, Sapien 3 Ultra Self-expanding: CoreValve, CoreValve Evolut R, CoreValve Evolut Pro, CoreValve Evolut Pro+, ACURATE neo, ACURATE	N/A	Not in scope: Not systematic review, narrative review including devices not in scope.

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
					neo2, Portico, JenaValve, J-Valve Mechanically-expandable: LOTUS, LOTUS Edge, LOTUS Mantra		
5.	Costa (Cathet Cardio Intervent, 2021; 1167–1176) [OBSERVANT study] Italy (N=93)	Prospective cohort, registry (n=1,440) Clinical outcomes of 2 groups were compared after adjustment using inverse probability of treatment weighting (IPTW) and confirmed by sensitivity analysis with propensity score matching. Variables included in the propensity score were sex, age, body mass index, diabetes, coronary artery disease, severe renal impairment on dialysis, chronic obstructive pulmonary disease, severe frailty (Geriatric Status Scale 2 or 3), severe dyspnea (NYHA classification 3 or 4), pulmonary hypertension, left ventricle ejection fraction, EuroSCORE 2, active malignancy and critical status leading to emergent/urgent TAVI procedure. Follow-up: 5 years Funder: Supported by Italian Ministry of Health and Istituto Superiore di Sanità (Fasc. 1 M30) and partially by a grant from the Finalized Research Project	Between January 2010 and December 2012	*Inclusion*: Consecutive patients with severe aortic stenosis who underwent TAVI through a transfemoral approach *Exclusion*: NR	Medtronic CoreValve (n=830 in IPTW analysis, n=548 in propensity score matched analysis) Sapien (n=610 in IPTW analysis, n=548 in propensity score matched analysis)	*Primary endpoint* All-cause mortality at 5 years – IPTW adjustment: lower for Sapien 52.3%, compared to CoreValve 47.7% (p=0.04). *Secondary endpoints* Stroke, MI, vascular complications, AKI, in-hospital: No difference between arms. Mortality, in-hospital: Higher with CoreValve than Sapien, 4.3% compared with 2.3%, p=0.03. Permanent pacemaker implantation, in-hospital – IPTW adjustment: Higher with CoreValve than Sapien, 22.7% compared with 4.6%, p<0.01. Mean aortic gradient, mean (SD), before discharge – IPTW adjustment: Lower in CoreValve than Sapien, 9.1 (6.1) compared with 10.6 (5.3), p<0.01. Repeat hospitalizations for any cardiac cause, 5 years – IPTW adjustment: Higher for CoreValve 46.9% compared with Sapien 42.1%, p<0.01.	In scope but evidence not considered key evidence: Study reported older generations of valves not in scope, studies of in-scope valves were considered in the original EAG report (e.g. Costa et al. 2022, Rudolph et al. 2024).
6.	Cuevas (EuroIntervention, 2019; 71-73) Spain and Switzerland (N=5)	Prospective, single arm cohort (n=59) Follow-up: 30 days Funder: NR	Between April 2017 and January 2018	*Inclusion*: All patients deemed candidates for TAVI by the local Heart Team and treated with the Allegra valve. *Exclusion*: NR.	Allegra valve (n=59), no comparator	N/A	Not in scope: single-arm cohort making determination of incremental benefit difficult.
7.	D'Ascenzo (Int J Cardiol, 2021; 90-98) [PROSPERO ID CRD42020182407] Setting: NR	Systematic review and network meta-analysis (N=11 RCTs, n=9,752 patients) Follow-up: 2 years Funder: None	NR [Literature search between database inception to April 2020]	*Inclusion*: RCTs enrolling patients with symptomatic severe aortic stenosis and randomized to balloon-expanding TAVI, self-expanding TAVI or surgical aortic valve replacement. *Exclusion*: • enrolling less than 100 patients to avoid limited-sample bias • not published in English • observational, cross-sectional, or other non-RCT design • Boston Lotus valve due to different mechanism of implantation (mechanical expandable).	Balloon-expanding: Sapien, Sapien XT Sapien 3 Self-expanding: CoreValve, CoreValve Evolut R, CoreValve Evolut Pro, ACURATE neo Surgical aortic valve replacement (SAVR) was evaluated in 7 study arms with 4,006 patients, whereas ballon expanding TAVI and self-expanding TAVI respectively in 6 arms with 2,572 patients and 8 arms with 3,174 patients.	Mortality, 1 and 2 years: no statistical difference between balloon- and self-expanding TAVI devices. Stroke, 1 year: no statistical difference between balloon- and self-expanding TAVI devices. Aortic reintervention, 1 year: no statistical difference between balloon- and self-expanding TAVI devices. Pacemaker implantation, 30 days: Lower risk with balloon-expanding than self-expanding TAVI devices; OR 0.51 (95%CI 0.33 to 0.79). Paravalvular leak, 30 days: Lower risk with balloon-expanding than self-	In scope but evidence not considered key evidence: combines TAVI devices from multiple manufacturers together in self-expanding arm, and combines multiple generation devices together (not all in scope). Follow-up of 2 years restricted to mortality outcome only. Authors acknowledge that self-expanding devices are often used in patients with more challenging anatomies such as severe calcified aortic valves and complex arterial access through small ilio-femoral arteries. Trials included in this analysis had exclusion criteria based on valvular and ilio-femoral calcifications, therefore preventing comparison in these specific subsets.

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
						expanding TAVI devices; OR 0.31 (95%CI 0.17 to 0.55).	
8.	Deharo (Circulation, 2020; 260-268) France (N=1,546)	Longitudinal retrospective cohort study using national hospitalisation database (n=31,113) with propensity score matching on 38 variables, including baseline characteristics, year of implantation (Sapien 3 available before Evolut R) and hospital procedural volume for TAVI by quartile (n=20,918 after propensity matching). Follow-up: up to 3 years Funder: Authors reported no that no sources of funding were received.	Between 01 January 2014 and 31 Dec 2018 (Sapien 3 available since January 2014, Evolut R available since November 2015)	*Inclusion*: Adults with a single percutaneous procedure for aortic stenosis, treated with Sapien 3 or Evolut R. *Exclusion*: age <18 years, valve-in-valve TAVI procedure, and TAVI via non-percutaneous route.	Sapien 3 (n=10,459 after propensity matching) Evolut R (n=10,459 after propensity matching)	Combined endpoint (cardiovascular death, rehospitalisation for heart failure, all cause stroke) at 3 years: lower for Sapien 3, 53.4% (50.9 to 56.0), than for CoreValve, 58.0% (55.3 to 60.7), RR 0.60 for Sapien 3 vs CoreValve (95% CI 0.48 to 0.76); p<0.0001. All cause death at 3 years: lower for Sapien 3, 37.3% (34.8 to 40.0), than for CoreValve, 39.3% (36.5 to 42.1), RR 0.63 for Sapien 3 vs CoreValve (95% CI 0.52 to 0.78); p<0.0001. Cardiovascular death at 3 years: lower for Sapien 3, 15.4% (13.5 to 17.6), than for CoreValve, 17.5% (15.5 to 19.7), RR 0.80 for Sapien 3 vs CoreValve (95% CI 0.69 to 0.93); p=0.003. Rehospitalisation, up to 2 years: lower in Sapien 3 arm, RR 0.84 (95% CI 0.78 to 0.90); p<0.0001. Pacemaker implantation at time or after the procedure: lower in Sapien 3 than Evolut R arm, RR 0.72 (95% CI 0.69 to 0.76); p<0.0001.	Key evidence: devices in scope, difference in recruitment period between arms however year of implantation included in propensity matched analysis. The authors acknowledge that clinical variables (mean gradient, valve area, calcification, paravalvular leak) were not available in the national database and therefore could not be analysed. The authors also note that "*the CoreValve device has a smaller diameter introducer sheath, so may be used more frequently in patients with complex and small femoral access. We cannot exclude that some biases related to these anatomical considerations exist in our analysis.*"
9.	Durand (Clin Res Cardiol, 2021; 40-49) France (N=48)	Retrospective cohort study using FRANCE TAVI registry (n=5,857) Follow-up: in-hospital (only late discharge outcome compared between devices). Funder: Authors reported that device manufacturers partly funded the registry but had no role in data collection or analysis or in manuscript preparation.	Between 02 January 2013 and 31 December 2015	*Inclusion*: Consecutive patients having TAVI, using transfemoral approach, and discharged directly home. *Exclusion*: Patients who died during the index hospitalisation, transferred to another institution or rehabilitation centre, discharge destination unknown.	Sapien XT or Sapien 3 (n=4,044) CoreValve (n=1,813)	Multivariate analysis shows risk factor for late discharge (>6 days post op) greater in CoreValve group than in in Sapien XT / Sapien 3; HR 1.7 (95% CI 1.5 to 2.0); p<0.001.	In scope but evidence not considered key evidence: Includes older generation devices for both intervention and comparator arms; self-expanding valve group not differentiated for Sapien XT (out of scope) and Sapien 3 (in scope). CoreValve is an earlier generation of valves by Medtronic. EAG had included evidence related to devices in scope in original EAG report (for example: Rudolph et al. 2023). Study evaluates the influence of very early (within 3 days) and early (between 3 and 6 days), and late (>6 days) discharge on long-term outcomes. Valve type not separated for most outcomes.
10.	Eckel (J Clin Med 2022; 5313) [TAVI-SMALL registry] Germany (N=2)	Retrospective cohort analysis from registry (n=654) Follow-up: 30 days Funder: Authors reported no that no external funding were received.	Between June 2012 and December 2021	*Inclusion*: patients with severe native aortic stenosis who underwent transfemoral TAVI with ACURATE neo or ACURATE neo2. *Exclusion*: NR	ACURATE neo (n=464) or ACURATE neo2 (n=191); combined together.	N/A	Not in scope: comparison of the implant performed in line with the official recommendation of the manufacturer (on-label sizing) or below (off-label sizing); no comparison of devices.
11.	Forrest (J Am Coll Cardiol, 2023; 2163-2165) [Evolut Low risk trial; NCT02701283] Australia (N=5), Canada (N=6), France	RCT (n=1,414); reported in research letter. Follow-up: 4 years Funder: Medtronic	Between March 2016 and May 2019	*Inclusion*: aortic valve replacement in low surgical-risk patients with severe aortic stenosis. *Exclusion*: NR	CoreValve / Evolut R / Evolut Pro (n=730; all combined). SAVR (n=684)	N/A	Not in scope: TAVI vs SAVR comparison

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
	(N=3), Japan (N=8), the Netherlands (N=3), New Zealand (N=1), US (N=61)						
12.	Gallo (Circ Cardiovasc Interv, 2021; e010641) [HORSE registry] Canada (N=1), Denmark (N=1), Germany (N=3), Greece (N=1), Ireland (N=1), Italy (N=5), Spain (N=3), Switzerland (N=1)	Retrospective cohort, registry (n=3,862). Inverse probability-weighting (IPW) applied to adjust for baseline differences across 24 covariates considered (age, diabetes, BMI, hypertension, aortic regurgitation ≥ moderate, sex, NYHA III or IV functional class, aortic valve calcification ≥ moderate, left ventricle outflow tract calcification ≥ moderate, low gradient aortic stenosis, atrial fibrillation, COPD, peripheral artery disease, porcelain aorta, previous cardiac surgery, previous MI, previous percutaneous coronary interventions, previous pacemaker/defibrillators, previous stroke, ejection fraction, transcatheter prosthesis size, annulus perimeter size, STS score) Follow-up: procedural Funder: Authors report no funding received.	Between September 2014 and April 2020	*Inclusion*: consecutive patients who underwent transfemoral TAVI for severe aortic stenosis of native aortic valve with either Evolut R/Pro or ACURATE neo devices. *Exclusion*: Patients undergoing TAVI for pure aortic regurgitation, surgical prosthesis degeneration, or from non-transfemoral access. Patients undergoing Evolut R 34mm implantation were also excluded (no comparable vale size for ACURATE neo was available).	Evolut R or Evolut Pro (n=1,959) ACURATE neo (n=1,903)	*Non-horizontal aorta* • Device success, annulus rupture, valve embolization, need for second valve, emergency surgery, coronary obstruction, death, peri-procedural MI, stroke, all in-hospital: no difference between Evolut R/Pro and ACURATE neo devices after IPW adjustment. • Moderate or severe PVL, in-hospital: less likely with Evolut R/Pro than with ACURATE neo: IPW adjusted OR 0.25 (95% CI 0.11 to 0.55), p<0.001 • Permanent pacemaker, in-hospital: increased risk with Evolut R/Pro than ACURATE neo; 1.72 (1.29 to 2.30); p<0.001. • Major vascular complications, in-hospital: decreased risk associated with Evolut R/Pro than ACURATE neo, 0.51 (0.33 to 0.78), p=0.002. *Horizontal aorta*: • Device success, in-hospital: reduced with Evolut R/Pro than with ACURATE neo: OR 0.62 (0.46 to 0.83), p=0.002. • Mortality, procedural: increased risk with Evolut R/Pro than with ACURATE neo: OR 11.41 (1.47 to 88.55); p=0.020. • Permanent pacemaker, in-hospital: Increased risk with Evolut R/Pro compared with ACURATE neo: 2.83 (2.09 to 3.82); p<0.001. • Major vascular complications, in-hospital: decreased risk associated with Evolut R/Pro compared with ACURATE neo: 0.64 (0.42 to 0.98), p=0.0039. • Annulus rupture, valve embolization, need for second valve, emergency surgery, peri-procedural MI, stroke, moderate or sever PVL, in-hospital mortality, all in-hospital: no difference between Evolut R/Pro and ACURATE neo devices after IPW adjustment.	In scope but evidence not considered key evidence: main focus of study is aortic angulation and impact on procedural outcomes. EAG note that selection of device type and size was at the discretion of the attending physician at each centre. Older generation valve used in comparator arm (that is ACURATE neo instead of ACURATE neo2).
13.	Gozdek (J Clin Med, Feb 2020; 397) [**additional information gained from correction published in	Meta-analysis (N=6: including 1 RCT and 5 propensity score matched retrospective cohort studies) (n=2,818 patients).	Between 2012 and 2019, across N=6 studies.	*Inclusion*: • human study • study or study arms comparing directly strategy of transcatheter aortic valve	ACURATE neo (n=1,256) Sapien 3 (n=1,562)	Early safety (composite): no difference between groups. Device success: no difference between groups.	In scope but evidence not considered key evidence: Larger studies with MA comparing Sapien 3 with older generation ACURATE neo already included in the original EAG report (for

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
	Gozdek (J Clin Med, Mar 2020; 861) Setting: NR	Follow-up: ranged between 1 month to 12.7 months. Funder: Authors report funding acquisition not available.	[Literature search until October 2019]	replacement with ACURATE neo and Sapien 3 • RCT or propensity score matched observational study. *Exclusion*: • in-vitro study • single arm • adjustment not propensity score or methods not reported • outcomes of interest not reported • sub-studies or overlapping populations. [The EAG note that differing inclusion and exclusion criteria of 6 studies is reported in the Table A3 of the paper]		Major vascular complications, procedural: no difference between groups. AKI, procedural: no difference between groups. MI, periprocedural: no difference between groups. Stroke, timepoint NR: no difference between groups. Serious bleed, procedural: no difference between groups. **Permanent pacemaker implantation, timepoint NR: required less often after ACURATE neo 10.2% compared to SAPIEN 3 14.2% (RR: 0.72 (95%CI 0.58 to 0.89); p=0.002). **Mild PVL, timepoint NR: occurred less frequently in SAPIEN 3 recipients, 27.9% compared to ACURATE neo group, 45.0%; (RR 1.59 (1.39 to 1.83), p<0.00001). **Moderate to severe PVL, timepoint NR: uncommon in the entire series (2.3%); however, significant increase PVL risk with ACURATE neo (7.6%) compared to Sapien 3 (2.3%): (RR 3.06 (2.09 to 4.49); p<0.00001). All-cause mortality, 30 days: 61 (2.2%) patients died within the first 30 days, ACURATE neo (2.9%) and Sapien 3 (1.6%). ACURATE neo associated with 77% higher 30-day mortality risk (RR 1.77 (1.03 to 3.04); p=0.04).	example Yang et al. 2023; the EAG also note that all 6 studies included by Gozdek et al. 2020 were also included in the network meta-analysis by Yang et al. 2023).
14.	Guerreiro (Rev Port Cardiol, (Engl Ed) 2020; 705-717) [The Portuguese National Registry of Transcatheter Aortic Valve Implantation, RNCI-VaP)] Portugal (N=14; including public and private centres, voluntary data entry)	Prospective cohort (n=2,346) Follow-up: 30 day and 1 year Funder: Authors declare there is no specific funding for the registry which has been completely developed, maintained and sponsored by the Portuguese Association of Cardiovascular Intervention	Between January 2007 and December 2018	The decision regarding access route, prosthesis type and size were made according to each centre, taking into consideration the clinical and morphological assessment. *Inclusion*: symptomatic with severe aortic stenosis or prosthetic valve dysfunction for TAVI (discussed by heart team, procedures performed in hospital with on-site cardiac surgery), high risk for traditional SAVR or deemed inoperable. *Exclusion*: life expectancy with TAVI was ≤1 year, patient's quality of life was unlikely to improve with TAVI	Transfemoral access route (n=2,131) Non-transfemoral access route (n=214) The registry collects data on any type of commercial device. At the time of publication, 12 different valves and their iterations were included (CoreValve, Sapien, Portico, ACURATE neo, Lotus Edge, Direct Flow, Allegra, Engager). In analysed cohort: - CoreValve: 52% - Edwards valve: 30.9% - Other valve: 17.1% (assumed all self-expanding).	Study reported that valve type did not influence mortality; however no further detail reported.	Not in scope: focus on access route comparison (transfemoral compared with non-transfemoral); outcomes not differentiated by valve type. Voluntary registry, inclusion of results from private centres (proportion not reported), no audit process, also includes valves not in scope (for example Lotus, Direct Flow Medical); however proportions not reported.

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
15.	Husser (JACC Cardiovasc Interv, 2019; 1781-1793) [SELECT RBBB registry] Germany, Switzerland (N=7)	Retrospective cohort from registry (n=296) Included propensity matching (1:1 nearest neighbour) matched on sex, BMI, LVEF <35%, heart rate <60/min, aortic annular area, severe aortic cusps calcification covariates Follow-up: 30 days Funder: NR	Between January 2014 and July 2017	Consecutive patients undergoing TAVI using the ACURATE neo or the Sapien 3 for severe symptomatic aortic stenosis. *Inclusion*: pre-existent complete RBBB, no pacemaker at baseline. *Exclusion*: incomplete mult-islice CT data	ACURATE neo (n=98, and 65 after propensity matching) Sapien 3 (n=198, or 65 after propensity matching)	PPI at 30 days: lower rate with ACURATE neo compared to Sapien 3; OR of 0.37 (95% CI 0.17 to 0.78) in propensity matching (p=0.010), and OR: 0.37 (0.25 to 0.55) in IPTW analysis (p=<0.001). Device success, procedural-related death, annular rupture, cardiac tamponade, multiple valves, conversion to sternotomy, life-threatening bleeding, major vascular complications, stroke, AKI stage 2 or 3, MI, hospital stay, death, in-hospital: No statistical difference between arms. Mortality, 30 days: No statistical difference between arms.	In scope but evidence not considered key evidence: Larger studies with MA comparing Sapien 3 with older generation ACURATE neo already included in the original EAG report (for example Yang et al. 2023). Studies comparing newer generations (Sapien 3 Ultra and ACURATE neo2) previously considered in EAG report (for example Pellegrini et al. 2023).
16.	Jagielak (Cardiol J, 2021; 384-390) [NAUTILUS study] Brazil, Poland, Switzerland (N=8)	Prospective, single arm cohort (n=27) Follow-up: 30 days Funder: NR	NR	Consecutive patients with severe, symptomatic aortic stenosis at high surgical risk treated with Allegra. *Inclusion*: • age ≥75 years • symptomatic (New York Heart Association [NYHA] class II or greater), • severe degenerative native AS (mean transvalvular pressure gradient >40 mmHg and / /or aortic jet velocity >4.0 m/s and/or aortic valve area of <1.0 cm² [or aortic valve area index ≤0.6 cm2/m2]) • high risk for surgical aortic valve replacement with a logistic EuroSCORE ≥20% • documented agreement of the Heart Team that the patient is at high risk for surgery due to frailty and / or coexisting comorbidities. *Exclusion*: (among others in study protocol; no trial registration identified by the EAG) • unicuspid or bicuspid valve disease • non-calcified aortic valve disease • mixed valve disease with predominant aortic regurgitation greater than 3+ or with associated severe (greater than 3+) mitral regurgitation • aortic annulus size <19 mm or >29 mm • type of femoral access, or any other anatomical conditions that prevented safe placement of an 18 French introducer sheath and manipulation of the TAVI system (e.g. severe femoral-iliac obstructive calcification or tortuosity).	Allegra valve (n=27) using transfemoral approach (1 excluded as converted to balloon aortic valvuloplasty, 1 valve dislodged and converted to open heart surgery). No comparator.	N/A	Not in scope: single-arm cohort making determination of incremental benefit difficult. Study reported short-term follow-up; studies with larger sample size and with longer follow-up were considered in the original EAG report.
17.	JenaValve (Clinical Investigation Report, 2024) provided AiC [ALIGN-AS; NCT02732691] [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Not in scope: [redacted] The ALIGN-AS study was included in the original EAG report. Results from n=68 patients are available on the trial registration (NCT02732691); 30-day all-cause mortality 2.9%.

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
				[redacted]			
18.	Jørgensen (Eur Heart J, 2021; 2912-2919) [NOTION NCT01057173] Study protocol published in Thyregod (Trials, 2013; 11) Denmark (N=2), Sweden (N=1)	RCT (n=280) Follow-up: up to 8 years Funder: Authors declared funding by the Danish Heart Foundation and Medtronic	Between 2010 and 2013 (month NR)	*Inclusion*: • Patients aged ≥70 years • severe symptomatic degenerative aortic valve stenosis. • Asymptomatic patients could be included if they had left ventricular posterior wall thickness ≥17 mm, decreasing left ventricular ejection fraction, or new-onset AF. • Expected to survive for more than 1 year • Able to provide consent. *Exclusion:* • Isolated AV insufficiency • Other significant cardiac valve or septal diseases • Coronary artery comorbidity requiring revascularisation (PCI or CABG) • Intracardiac lesion (thrombus, tumour, vegetation) • Previous open cardiac surgery • Myocardial infarction or PCI within the last year • Stroke or transient ischemic attack within the last 30 days • Renal insufficiency requiring haemodialysis • Pulmonary insufficiency (FEV1 or diffusion capacity <40% of expected) • Active infectious disease requiring antibiotics • Emergency intervention (within 24 hours after the indication for intervention has been made) • Unstable pre-interventional condition requiring inotropic support or mechanical cardiac assistance • A known hypersensitivity or contraindication to nitinol, heparin, clopidogrel, acetyl salicylic acid, or contrast material • Currently participating in an investigational drug or another device study.	CoreValve (n=145) SAVR (n=135)	N/A	Not in scope: Comparison of TAVI vs SAVR; only 1 device used in TAVI arm, treated as single arms study. The authors acknowledge that the TAVI arm was restricted to use of CoreValve and that newer generations are available with sealing skirts, reduced profile of the delivery catheters, and positionability of the valve. The EAG note that 10-year results from NOTION was included in the original EAG report (Thyregod et al. 2024; including 145 patients treated with CoreValve.
19.	Kalogeras (J Am Heart Assoc, 2023; e028038) [Athens-London-Aortic-Stenosis, ATLAS registry] Greece, UK (N=2)	Retrospective cohort, registry (n=1,673) including propensity score matched analysis (n=278) based on age, mitral regurgitation, extensive calcification of the aorta, previous balloon aortic valvuloplasty, access site, with	Between August 2017 and February 2021	*Inclusion:* All patients with severe symptomatic aortic valve stenosis, final decision on appropriateness for TAVI, device selection and access route was determined by the Heart Team. Patients treated with Sapien 3 or Ultra valve ≤23mm or Evolut Pro/Pro+ ≤26mm were included in the “small cohort”.	Self-expanding (n=917): Evolut Pro, Pro+ and R (patients with large anatomies, annulus perimeter >81.7mm were treated with 34mm device only available for Evolut R during	Mortality: When adjusting for age, sex, baseline LV function, baseline degree of MR, epicardial coronary artery disease, extensive calcification of the aorta, no difference in mortality when comparing balloon-expandable with self-expanding, HR: 1.23 (95%CI	In scope but evidence not considered key evidence: Despite propensity score matching, differences in pre-operative heart rhythm were observed between matched groups.

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
		1:1 nearest neighbour matching with caliper of 0.1 Follow-up: median 15 months Funder: None			study period); n=139 after propensity matching Balloon-expanding (n=756): Sapien 3, Sapien 3 Ultra; n=139 after propensity matching	0.8 to 1.9); p=0.349. However, in propensity matched small cohort group higher survival in self-expanding group at 1 year (97% compared with 92.3%) and 3 years (91.8% compared with 78.7%), p=0.096. Peak aortic valve gradient, mmHg, at predischarge: In propensity matched 'small cohort' lower in self-expanding arm, 18 (8.3) compared with 25.2 (8.8); p<0.001. Mean aortic valve gradient, mmHg, at predischarge: In propensity matched 'small cohort' lower in self-expanding arm, 9.7 (4.6) compared with 13.5 (5.3); p<0.001. Residual moderate or severe paravalvular regurgitation, at discharge: In propensity matched 'small cohort' lower in self-expanding arm 4.4% compared with 2.2%; p<0.001. Valve malposition, bailout valve-in-valve, tamponade, conversion to full sternotomy, new pacemaker implantation, MI, bail out PCI, cerebrovascular accident, AKI (stage 3), life-threatening or major bleeding, major vascular complications, death, at discharge: No statistical difference in each complication between arms.	Authors acknowledge that the balloon-expanding valves were introduced later and therefore have shorter follow-up times.
20.	Kilic (Arch Med Sci, 2024; 410-419) Turkey, Italy, Greece (N=4)	Prospective cohort (n=207) Follow-up: 2 years Funder: NR	Between 2019 and -2021 (months not reported)	*Inclusion:* Consecutive patients presenting with degenerative severe aortic stenosis, treated with Myval, with 2 years follow-up. Patients were advised to undergo TAVI only if there were at high or intermediate risk for SAVR. *Exclusion:* NR	Myval	N/A	Not in scope: single-arm cohort making determination of incremental benefit difficult. Longitudinal follow-up at 2 years for Myval device was included in the original EAG report (for example: Moscarella et al. 2024).
21.	Kornyeva (Front Cardiovasc Med, 2023; 1175246) Germany (N=1)	Retrospective cohort, database (n=507), with propensity score matching (n=384). Authors report that since most variables where already balanced before matching, only the annulus perimeter, annulus area, and body surface area were entered into the logistic model to calculate the propensity score. Funder: NR	Between September 2014 and June 2020	*Inclusion:* Patients with small aortic annulus (CT-derived annular perimeter <72mm, or aortic annulus area <400mm2), who underwent TAVI with contemporary self-expanding or balloon-expanding valves identified by a database. *Exclusion:* Patients with a valve-in-valve procedures.	Self-expanding: Evolut R/Pro, Portico, ACURATE neo2, Balloon-expanding: NR	N/A	Not in scope: All self-expanding devices aggregated together, balloon-expanding valves not explicitly reported.
22.	Lanz (Lancet, 2019; 1619-1628) [SCOPE I trial: NCT03011346]	RCT, non-inferiority (n=739) Powered based on composite VARC-2 derived primary end point at 30 days (early safety and	Between 08 February 2018 and 02 February 2019	Patients aged 75 years or older with symptomatic, severe aortic stenosis who were deemed to be at increased surgical risk by the heart team constituted the target population and were screened for eligibility.	ACURATE neo (n=372) compared with Sapien 3 (n=367)	Primary endpoint at 30 days higher with ACURATE neo, 24% compared with 16%, p=0.42 non-inferiority. Secondary analysis of primary endpoint, p=0.0156.	In scope but evidence not considered key evidence: Includes comparison of device in scope with older generation device. Short-term outcomes.

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
	Germany, the Netherlands, Switzerland, UK (N=20 centres; including 1 from UK)	clinical efficacy: all-cause death, any stroke, life-threatening or disabling bleeding, major vascular complications, coronary artery obstruction requiring intervention, AKI stage 2 or higher, rehospitalisation for valve-related symptoms or congestive heart failure, valve-related dysfunction requiring repeat procedure, and valve-related dysfunction determined by echocardiography) predicted as 22% and assumed non-inferiority margin of 7.7%. Funder: Boston Scientific		*Inclusion:* • ≥75 years of age • Severe aortic stenosis was defined by an aortic valve area less than 1.0 cm2 or less than 0.6 cm2/m2 if indexed to body surface area. • Symptomatic (NYHA functional class>I, angina or syncope). • At increased risk for mortality if undergoing SAVR as determined by: - the heart team, or - an STS-PROM score >10%, or - a Logistics EuroSCORE>20%. • Heart team agrees on eligibility for participation. • Aortic annulus perimeter 66-85mm and area 338-573 mm2 based on multi-slice CT. • Minimum diameter of arterial aorto-iliac-femoral axis on 1 side ≥5.5mm. • Patient understand the purpose, potential risks and benefits of the trial, is able to provide written informed content [sic] and willing to participate in all parts of the follow-up. *Exclusion:* • Non-valvular, congenital or non-calcific acquired aortic stenosis, uni- or bicuspid aortic valve. • Anatomy not appropriate for transfemoral TAVR due to degree or eccentricity of calcification or tortuosity of aorto-iliac-femoral arteries. • Pre-existing prosthetic heart valve in aortic or mitral position. • Emergency procedures, cardiogenic shock (vasopressor dependence, mechanical hemodynamic support) or severely reduced left ventricular ejection fraction (<20%). • Concomitant planned procedure except for percutaneous coronary intervention. • Stroke or myocardial infarction (except type 2) in prior 30 days. • Planned non-cardiac surgery within 30 days after TAVR. • Severe coagulation conditions, inability to tolerate anticoagulation/antiplatelet therapy. • Evidence of intra-cardiac mass, thrombus or vegetation. • Active bacterial endocarditis or other active infection. • Hypertrophic cardiomyopathy with or without obstruction. • Contraindication to contrast media or allergy to nitinol. • Participation in another trial leading to deviations in the preparation and conduction of the intervention or the post-implantation management.		Implantation of multiple valves at time of procedure higher in ACURATE neo, 3% compared with 1%, p=0.0119. All-cause death at 30 days: no statistical difference between arms, 2% ACURATE neo compared with 1% Sapien 3; p=0.09. Stroke at 30 days: no statistical difference between arms, 2% in ACURATE neo and 3% with Sapien 3, p=0.33. AKI stage 2 or 3 at 30 days: higher in ACURATE neo arm, 3% compared with 1%, p=0.0340. Moderate or severe AR at 30 days: higher in ACURATE neo arm, 9.4% compared with 2.8%; p<0.0001.	Authors acknowledge that the trial was not powered for differences in individual clinical endpoints, secondary analysis did not account for multiple hypothesis testing, and results at risk of selection bias.
23.	Leone (Int J Cardiol, 2023; 16-23) [TAVI-SMALL 2 registry] International (N=16, high-volume centres)	Retrospective cohort, registry (n=1,378) Propensity score matching (including age, BMI, body surface area, hypertension, COPD, coronary artery disease, prior MI, peripheral vascular disease,	Between June 2011 and April 2020	*Inclusion:* Patients with severe native aortic valve stenosis and small artic annuli (annular area < 400mm2 and/or annular perimeter <72mm on CT) treated with transfemoral implantation of current-generation self-expanding (Evolut R, Evolut Pro, ACURATE neo, Portico) and balloon-expandable (Sapien 3). Local multidisciplinary heart teams	NR	N/A	Not in scope: all TAVI devices aggregated together, main analysis reports differences in outcomes between males and females; no analysis of results by TAVI device.

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		previous percutaneous transluminal angioplasty, prior CABG, previous pacemaker, or implantable cardiovertor-defibrillator, NYHA functional class III or IV, STS score, aortic annular perimeter). Funder: None		evaluated all patients and confirmed the indications for TAVI. *Exclusion:* valve-in-valve procedures, TAVI for pure aortic regurgitation, lack of pre-procedural CT.			
24.	Li (Ann Palliat Med, 2020; 700-708) Israel (N=2), Germany (N=2), Spain (N=1), US (N=1)	Meta-analysis (N=6 observational studies, n=1,664) Follow-up: 30 days Funder: Science and Technology Support Plan of Sichuan Province (2016FZ0078, 2018SZ0172); Science and Technology Innovative Research Groups Program of Sichuan Province (2017TD0004); "13th Five-Year" National key Research and Development Program of China (2016YFC1102204, 2017YFC1104204); 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University.	NR [Literature search between 2008 and 2018]	*Inclusion:* • Studies reporting outcomes of Sapien 3 versus Evolut R. • Randomized clinical trial, prospective or retrospective cohort observational studies. *Exclusion*: • Studies published in form of letter, review, editorial comment or a case report. • Un-extractable data for statistical analysis. • If duplicate data source occurred, 1 with the largest sample size was included to avoid duplicate publication.	Sapien 3 (n=768) vs Evolut R (n=896)	*Primary outcomes* • Procedural success: No statistical difference between arms, 94.1% in Sapien 3, 95.7% in Evolut R; OR 1.15 (95%CI 0.70 to 1.91) • 30-day all-cause mortality: No statistical difference between Sapien 3 and Evolut R; 1.6% and 2.1% respectively; OR 0.72 (0.33 to 1.57). *Secondary outcomes* • AKI post-procedure: Sapien 3 associated with higher risk, 4.1% vs. 2.0%; OR 2.34 (1.26 to 4.34) • Stroke at 30-days: No statistical difference between arms; 2.0% in both arms; OR 1.07 (0.51 to 2.25), • Bleeding (major and life-threating) post-procedure: No statistical difference between arms, 3.0% vs. 2.4%; OR 1.08 (0.56 to 2.08) • Major vascular complications, post-procedure: No statistical difference between arms, 4.3% vs. 3.4, OR 1.24 (0.71 to 2.17) • New permanent pacemaker implantation: Sapien 3 lower risk, 11.5% vs.17.0%; OR 0.69 (0.51 to 0.93). • Peak aortic valve gradient post-procedure: No statistical difference between groups [Standard Mean difference, SMD,1.14 (0.97 to 1.31). • Mean aortic valve gradient post-procedure: Sapien 3 higher mean aortic valve gradient [SMD: 1.24 (1.10 to1.39). • Mean LVEF post-procedure: higher in SAPIEN S3 group [SMD: 1.19 (1.04 to 1.33). • Moderate and severe PVL at 30 days: no statistical difference between valves, 1.6% vs.2.4%, OR 0.74 (0.25 to 2.15).	In scope but evidence not considered key evidence: Authors acknowledge that only 1 study reported long-term outcomes, that recapture and depth of implantation was not reported which may influenced results, that there was substantial heterogeneity between studies regarding pre-dilation and PVL. Publication bias was not assessed as there were less than ten studies included in the meta-analysis.
25.	Makkar (Lancet, 2020a; 669-683) [PORTICO IDE trial; NCT02000115] Australia and US (N=52)	RCT, non-inferiority (n=750) Powered based on 30.8% composite primary safety endpoint (all-cause death, disabling stroke, life threatening bleed requiring blood transfusion,	Between 30 May 2014 and 12 September 2014, and 21 August 2015 and 10 October 2017; paused for 11	Patients with symptomatic, severe aortic stenosis, considered high or extreme surgical risk by MDT. *Inclusion:* • IC1-Subjects must have co-morbidities such that the surgeon and cardiologist Co-Investigators concur that the predicted risk of operative mortality is ≥15% or a minimum STS	Portico (n=381) compared with any commercially available, FDA approved valve (Sapien, Sapien XT, Sapien 3, CoreValve, Evolut R, Evolut Pro) all combined (n=369)	Primary safety endpoint at 30 days was higher in Portico arm (13.8% compared with 9.6%, p=0.034 for non-inferiority, indicating non-inferiority criterion met in the intention to treat (ITT) population).	In scope but evidence not considered key evidence: Selection of the valve in the comparator arm was not randomly assigned but left to the discretion of the study site investigator. Comparator arm combination of valves from multiple manufacturers, therefore difficult to determine incremental benefit.

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		AKI requiring dialysis, major vascular complication at 30 days), and 25.0% composite primary efficacy endpoint (all-cause mortality or disabling stroke at 1 year), 80% power and 5% significance level to show non-inferiority. Funder: Abbott	months by funder.	score of 8%. A candidate who does not meet the STS score criteria of ≥ 8% can be included in the study if a peer review by at least 2 surgeons concludes and documents that the patient's predicted risk of operative mortality is ≥15%. The surgeon's assessment of operative comorbidities not captured by the STS score must be documented in the study case report form as well as in the patient medical record. • IC2-Subject is 21 years of age or older at the time of consent. • IC3-Subject has senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient >40 mmHg or jet velocity greater than 4.0 m/s or Doppler Velocity Index <0.25 and an initial aortic valve area (AVA) of ≤ 1.0 cm2 (indexed EOA ≤ 0.6 cm2/m2). (Qualifying AVA baseline measurement must be within 60 days prior to informed consent). • IC4-Subject has symptomatic aortic stenosis as demonstrated by NYHA Functional Classification of II, III, or IV. • IC5-The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site. • IC6-The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits. • IC7-Subject's aortic annulus is 19-27mm diameter as measured by CT conducted within 12 months prior to informed consent. Note: if CT is contraindicated and/or not possible to be obtained for certain subjects, a 3D echo and non-contrast CT of chest and abdomen/pelvis may be accepted if approved by the subject selection committee. *For a subject to be considered an Extreme Risk candidate they must meet IC2, 3, 4, 5, 6, 7 of the above criteria, and IC8.* • IC8-The subject, after formal consults by a cardiologist and 2 cardiovascular surgeons agree that medical factors preclude operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity should exceed 50%. The surgeons' consult notes shall specify the medical or anatomic factors leading to that conclusion and include a printout *Exclusion:* • EC1-Evidence of an acute myocardial infarction (defined as: ST Segment Elevation as evidenced on 12 Lead ECG) within 30 days prior to index procedure. • EC2-Aortic valve is a congenital unicuspid or congenital bicuspid valve,or is non-calcified as verified by echocardiography.		<u>Primary efficacy endpoint at 1 year</u> were similar between groups (14.8% Portico, compared with 13.4% in commercial valve group., p=0.0058 for non-inferiority indicating non-inferiority criterion met in the intention to treat (ITT) population). <u>Moderate/severe aortic regurgitation at 1 year</u> showed non-inferiority was not met (7.8% Portico compared with 1.5% commercially available valves, p=0.571). <u>Death at 2 years</u> in ITT population (22.3% Portico and 20.2% commercially available valves; p=0.40) was similar between groups. <u>Disabling stroke at 2 years</u> in ITT population (3.1% Portico compared with 5.0% commercial valves; p=0.23) was similar between groups.	Authors acknowledge that the valves used in the comparator arm had undergone multiple iterations since the initiation of the trial, which may have contributed to improved outcomes in comparator arm. The authors acknowledge that the comparator arm included both balloon-expandable, and supra-annular self-expandable valves combined which may have confounded results; the study was not powered for post-hoc analyses comparing individual valve types.

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				• EC3-Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation 3-4+). • EC4-Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to index procedure. • EC5-pre-existing prosthetic heart valve or other implant in any valve position, prosthetic ring, severe circumferential mitral annular calcification (MAC) which is continuous with calcium in the LVOT, severe (greater than 3+) mitral insufficiency, or severe mitral stenosis with pulmonary compromise. Subjects with pre-existing surgical bioprosthetic aortic heart valve should be considered for the Valve-in-Valve registry. • EC6-Blood dyscrasias as defined: leukopenia (WBC<3000 mm3), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count <50,000 cells/mm³). • EC7-History of bleeding diathesis or coagulopathy. • EC8-Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support. • EC9-Untreated clinically significant coronary artery disease requiring revascularization. • EC10-Hemodynamic instability requiring inotropic support or mechanical heart assistance. • EC11-Need for emergency surgery for any reason. • EC12-Hypertrophic cardiomyopathy with or without obstruction (HOCM). • EC13-Severe ventricular dysfunction with LVEF <20% as measured by resting echocardiogram. • EC14-Echocardiographic evidence of intracardiac mass, thrombus or vegetation. • EC15-Active peptic ulcer or upper GI bleeding within 3 months prior to index procedure. • EC16-A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media which cannot be adequately premedicated. • EC17-Recent (within 6 months prior to index procedure date) cerebrovascular accident (CVA) or a transient ischemic attack (TIA). • EC18-Renal insufficiency (creatinine > 3.0 mg/dL) and/or end stage renal disease requiring chronic dialysis. • EC19-Life expectancy <12 months from the time of informed consent due to non-cardiac comorbid conditions. • EC20-Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe			

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				"unfolding" and tortuosity of the thoracic aorta (applicable for transfemoral patients only). • EC21-Native aortic annulus size <19 mm or >27 mm per the baseline diagnostic imaging. • EC22-Aortic root angulation >70° (applicable for transfemoral patients only). • EC23-Currently participating in an investigational drug or device study. • EC24-Active bacterial endocarditis within 6 months prior to the index procedure. • EC25-Bulky calcified aortic valve leaflets in close proximity to coronary ostia. • EC26-Non-calcified aortic annulus • EC27-Iliofemoral vessel characteristics that would preclude safe placement of the introducer sheath such as severe obstructive calcification, or severe tortuosity (applicable for transfemoral patients only). Additional Exclusion Criteria (Transcatheter Access-Related) For selection of an appropriate alternative access delivery method, subjects were screened using the following access specific exclusion criteria: *Transaortic Subject Cohort Specific Exclusion Criteria* • EC1-Subject has pre-existing patent RIMA graft that would preclude access. • EC2-Subject has a hostile chest or other condition that complicates transaortic access. • EC3-Subject has a porcelain aorta, defined as an extensive circumferential calcification of the ascending aorta that would complicate TAo access. *Subclavian/Axillary Subject Cohort Specific Exclusion Criteria* • EC1-Subject's access vessel (subclavian/axillary) diameter will not allow for introduction of the applicable 18 Fr or 19 Fr delivery system. • EC2-Subject's subclavian/axillary arteries have severe calcification and/or tortuosity. • EC3-Subject's aortic root angulation is: Left Subclavian/Left Axillary: >70◦ Right Subclavian/Right Axillary: >30◦ • EC4-Subject has a history of patent LIMA/RIMA graft that would preclude access EC 5.			
26.	Malhotra (Heart Lung Circ, 2024; 324-331) Australia (N=1)	Single arm retrospective observational cohort study (n=60) Follow-up: 30 days Funder: No company funding	From 2021 until September 2022 (starting month not specified)	Consecutive patients treated with Navitor outside of a company-sponsored clinical trial. Specific inclusion and exclusion criteria not explicitly reported.	Navitor	*N/A*	Not in scope: single-arm cohort making determination of incremental benefit difficult. Study reported short-term follow-up; studies with larger sample size with longer follow-up were considered in the original EAG report. Furthermore, the cohort included 3 patients (5%) with bicuspid aortic valve disease, and in 21.67% patients the indication for TAVI was failed or degenerated SAVR, which may limit generalisability of results.

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
27.	Mauri (Circ Cardiovasc Interv, 2017; e005013) Germany (N=5)	Retrospective cohort with 1:1 propensity score matching (n=246, with 92 matched pairs) Propensity score was modelled with multivariate logistic regression model based on baseline characteristics: sex, age, left ventricular ejection fraction, annulus diameter, body surface area, and logistic EuroSCORE. A rigorous 1:1 nearest neighbour matching algorithm without replacement was used with a 0.2 caliper setting Funder: NR	Between February 2014 to August 2016	*Inclusion:* • Severe aortic stenosis (confirmed by echocardiography) • Small annular dimension (defined as an annulus area <400 mm2) • Transfemoral TAVR with either a Symetis ACURATE neo THV size small (Symetis SA, Ecublens, Switzerland) or an Edwards SAPIEN 3 THV size 23 mm (Edwards Lifesciences, Irvine, CA). • Eligibility for TAVI decided within local institutional heart team. *Exclusion:* NR	Self-expanding (ACURATE neo; older generation) vs balloon-expanding (Sapien 3)	• Death: No statistical difference between ACURATE neo and Sapien 3 arms at 30 days (p=1.00) and 1 year (p=0.23). • Stroke, procedural: No statistical difference between arms; p=1.00. • Vascular complications, procedural: No statistical difference between arms; p=0.152. • Bleeding, procedural: No statistical difference between arms, p=0.832. • PPI, procedural: No statistical difference between arms; p=0.678. • Paravalvular regurgitation: No statistical difference between arms at discharge (p=0.208) of 1 year (p=0.527). • Mean (SD) transvalvular gradients: statistically lower in ACURATE neo post-procedure, 9.3 (3.9) mmHg compared with 14.5 (5.5) mmHg in Sapien 3 group, p<0.001). Sustained at 1 year, 6.6 (2.7) in ACURATE neo and 17.5 (6.5) mmHg with Sapien 3; p=0.008. • Indexed effective orifice area, post-procedure: Statistically larger in ACURATE neo 0.96 (0.3) cm2/m2 compared with 0.80 (0.2) cm2/m2 with Sapien 3; p=0.003. Sustained at 1 year, 1.01 (0.3) cm2/m2 in ACURATE neo and 0.74 (0.2) cm2/m2 with Sapien 3; p=0.031. • Severe patient-prosthesis mismatch, 1 year: Lower rates with ACURATE neo, 3% compared with 22%, p=0.004.	In scope but evidence not considered key evidence: Includes older generation device for 1 manufacturer. Results restricted to patients with small annulus area. Authors acknowledge that propensity matching could not account for unknown or unmeasured confounders, centre effects were observed in 1 centre in Sapien 3 arm.
28.	Moscarella (Int J Cardiol, 2023; 35-45) International (N=17)	Prospective registry (n=97) Follow-up: 1 year Funder: NR	Between April 2019 to January 2022	*Inclusion:* Consecutive patients with severe symptomatic aortic bioprosthetic heart valve failure and mitral bioprosthetic heart valve or annuloplasty ring failure undergoing transcatheter aortic valve in valve and mitral valve in valve or valve-in-ring implantation with Myval. Symptomatic patients with a significant increase in trans-prosthetic gradient or severe regurgitation, who were deemed to be too high-risk for surgical valve replacement based on Heart Team decision, were considered as potential candidates for transcatheter valve-in-valve or valve-in-ring implantation.	Myval (n=97; aortic valve-in-valve 33, mitral valve-in-valve or valve-in-ring 64)	N/A	Not in scope: main analysis compares aortic valve-in-valve with mitral valve-in-valve (incorrect population). Single-arm cohort (all treated with Myval) making determination of incremental benefit difficult. Longer follow-up for single arm was included in the original EAG report (for example Moscarella et al. 2024). However, this study does present evidence of Myval in valve-in-valve procedures (not explicitly contraindicated in this population, but not explicitly indicated either).
29.	Okuno (JACC Cardiovasc Inter, 2023; 429-440) [Swiss TAVI Registry, NCT01368250] Switzerland (N=1)	Prospective cohort (n=723); with propensity score matching (n=342) calculated using multivariable logistic regression model based on 33 variables that may affect valve-type selection). Given potentially difference in outcome by generation of device, 83 patients treated with older generation devices were matched independently from the overall cohort, using 1:1 greedy nearest neighbour with caliper of 0.02.	Between January 2012 and June 2021.	*Inclusion:* Consecutive patients with severe aortic stenosis, with aortic valve annulus area (<430 mm2) undergoing TAVI with CoreValve Evolut or Sapien. *Exclusion:* Patients who underwent TAVI for degenerated surgical or transcatheter aortic bioprosthesis, TAVI for pure native aortic valve regurgitation.	Balloon-expanding (Sapien XT, Sapien 3, Sapien 3 Ultra) Self-expanding (CoreValve, Evolut R, Evolut Pro, Evolut Pro+)	Technical success, composite outcome, discharge: No statistical difference between arms. New permanent pacemaker implantation, 30 days: higher in self-expanding arm (20.6% compared with 8.3%, HR: 2.68 (1.46 to 4.93), p=0.002). Disabling stroke: no difference in arms at 30 days, but lower in balloon expanding at 1 year (0.6% compared	In scope but evidence not considered key evidence: Mixed old and new generation in both arms; although majority new generation (93.6%). Difference in post-dilation reported between groups: 32.2% in self-expanding group compared with 19.9% in balloon-expandable group. Authors acknowledged potential bias caused by unmeasured or unrecognised confounding; limitation of all observational studies.

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
		Follow-up: 5 years Funder: NR				with 5.4%, HR 9.07 (1.12 to 73.23), p0.038), and 5 years (0.6% compared with 6.6%, HR 10.01 (1.25 to 80.01), p=0.030) <u>All-cause mortality, life-threatening or major bleeding, NYHA functional class III or IV</u>: no difference in each outcome between arms at 30 days, 1 year, 5 years <u>MI, structural valve deterioration, unplanned repeat aortic valve intervention (including valve-in-series, surgical revision, and aortic valve treatment):</u> no difference in each outcome between arms at 1 or 5 years.	
30.	Pellegrini (EuroIntervention, 2023; e1077-e1087) [SCOPE II subanalysis; overlap with Tamburino et al. 2020 – see later in addendum] Europe (N=23)	Subgroup analysis of as-treated population from an non-inferiority RCT (n=796) Subgroup 1: patients with no previous pacemaker were analysed for PPI at 30 days (n=648) Subgroup 2: patients without previous left bundle branch block (LBBB) were analysed for LBBB at 30 days (n=426) Follow-up: up to 1 year Funder: Sponsored by CERIC (Center for European Research Initiatives in Cardiovascular Medicine) with support from a dedicated research grant from Symetis SA (Ecublens, Switzerland) [EAG note that Boston Scientific acquired Symetis]	NR (assumed the same as reported by Tamburino between April 2017 and April 2019)	*Inclusion:* As-treated population from SCOPE II trial (considering treatment actually received by the participants, regardless of adherence to randomisation assignment), only patients who survived to 30 days or with known pacemaker status at 30 days were included. *Exclusion*: Subgroup 1: patients with prior pacemaker. Subgroup 2: patients with missing or uninterpretable ECG at baseline, discharge or 30 days, and prior LBBB.	Subgroup 1: ACURATE neo (n=333) and CoreValve Evolut (n=315) Subgroup 2: ACURATE neo (n=217) and CoreValve Evolut (n=209)	<u>Permanent pacemaker implantation, 30 days</u>: Lower for ACURATE neo, 12.3% compared with 21.0%, p=0.004. Multivariable analysis reported lower risk with ACURATE neo, OR 0.50 (95%CI 0.31 to 0.81). p=0.005 (when valve used, RBBB, left bundle branch block, moderate to severe aortic calcification, moderate to severe LVOT calcification, pre-dilatation were included in the logistic regression model). <u>LBBB, 30 days</u>: lower for ACURATE neo, 5.5% compared with 13.4%, p=0.007. No multivariable analysis reported.	<u>In scope but evidence not considered key evidence</u>: Subanalysis of Tamburino et al. 2020 (reported in addendum), older generations of devices in comparator arm. Differences in baseline characteristics between TAVI devices across subgroups. In subgroup 1 (PPI at 30 days) differences in baseline first degree atrio-ventricular block, aortic annulus perimeter, pre-dilatation and post-dilatation reported (adjusted for in multivariable analysis). In subgroup 2 (LBBB at 30 days) differences in baseline first degree atrio-ventricular block, aortic annulus area, aortic annulus perimeter, pre-dilatation and post-dilatation reported.
31.	Rheude (Am J Cardiol, 2021; 92-99) Setting: NR	Meta-analysis (N=20 studies, which included 5 RCT and 15 observational studies; n=12,128 patients) Funder: NR	Between 2007 and 2018 [Literature search between January 2010 to December 2019]	*Inclusion:* • Reports of bioprosthetic valve thrombosis in patients treated with TAVI, • Availability of data for at least 1 outcome of interest: subclinical leaflet thrombosis, clinical valve thrombosis. • Publication as full-length manuscript. *Exclusion:* • Duplicated publication data; • Outcomes of interest not clearly reported or impossibility to extract or calculate them from the published results.	Mixture of TAVI devices including self and balloon expanding, including Biovalve, Centera, CoreValve, Evolut, Evolut R, Direct Flow, JenaValve, Lotus, Portico, Sapien, Sapien XT, Sapien 3, Symetis, Symetis ACURATE.	N/A	<u>Not in scope</u>: All TAVI devices aggregated together, no device comparison.
32.	Rück (EuroIntervention, 2024, e781-e782) Sweden (N=1)	Cohort (n=452)	Between October 2015 and	*Inclusion:* Consecutive patients who underwent TAVI with first generation ACURATE neo. *Exclusion:* NR	ACURATE neo (n=452)	N/A	<u>Not in scope:</u> single-arm cohort making determination of incremental benefit difficult. Follow-up up to 7 years was reported in

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
		Follow-up: echocardiographic median 39 months (3.25 years) up to 69 months (5.75 years) Funder: Boston Scientific	December 2018				original EAG report (for example: Siqueira et al. 2021).
33.	Sanchez-Luna (EuroIntervention, 2023; 580-588) Europe, US and Asia-Pacific region (N=17)	Retrospective cohort (n=113) Follow-up: 1 year Funder: NR	From January 2019 (end date NR)	*Inclusion:* Consecutive patients with symptomatic severe non-calcified aortic regurgitation, with comorbidities that would preclude SAVR according to Heart Team at each centre. undergoing TAVI with Myval. *Exclusion:* Patients with aortic stenosis (peak aortic jet velocity on continuous-wave Doppler >2.5 m/s).	Myval (n=113)	N/A	Not in scope: incorrect population (regurgitation), single-arm cohort making determination of incremental benefit difficult
34.	Schofer (Clin Res Cardiol, 2022; 934-943) Germany (N=NR)	Retrospective non-randomised cohort from German administrative claims database (n=21,430) Funder: Open Access funding enabled and organized by Projekt DEAL.	Between January 2017 and December 2019	*Inclusion:* Patients aged 20 years or older, insured by the Allegemeine Ortskrankenkasse (provides healthcare insurance for 30% of German population), who received endovascular TAVI. *Exclusion:* Primary diagnosis of endocarditis, aortic valve insufficiency or received other valve interventions.	Balloon-expandable and self-expanding (devices used not reported).	N/A	Not in scope: main analysis was 30 day outcomes for different risk categories, no analysis comparing devices reported. EAG note that expansion type was only available for 14,777 patients (69%) from 2018 and 2019; no additional information on devices used reported.
35.	Senguttuvan (Front Cardiovasc Med, 2023; 1130354) [CRD42020181190] Setting: NR	Systematic review and meta-analysis (N=6 RCTs, n=2,935 patients) Primary endpoint varied across studies and included device success, post-procedural aortic regurgitation assessed by MRI, primary composite safety and efficacy outcome, haemodynamics, composite efficacy outcome only. Included 1 RCT with post-hoc analysis. Funder: No commercial funding reported	Across 6 studies patients recruited between earliest of March 2012 and latest February 2019.	High-risk patients with severe native aortic stenosis undergoing transfemoral TAVI. *Inclusion:* • Randomized controlled trials (RCTs) in patients with severe native AS undergoing TAVI. • RCTs or post hoc analysis of RCTs comparing valve platforms into BE vs. SE or an RCT with pre-specified analysis by valve platforms. If a trial included MEV platform in either study arm (SEV or BEV), then it had to be <5% for inclusion in the current study. • Study should report all-cause mortality at 30 days as either primary or secondary outcome. *Exclusion:* NR	• Abdel-Wahab (2014): Sapien XT compared with CoreValve. • Kooistra (2020): Sapien 3 compared with CoreValve. • Lanz (2019): Sapien 3 compared with ACURATE neo. • Linke et al. (2017): Sapien XT, Sapien 3 compared with CoreValve, Evolut (other non-balloon expanding valves were used in 5 patients). • Makkar (2020b); Sapien 3 compared with Evolut R, Evolut Pro, Portico. • Thiele (2020); Sapien 3 compared with Evolut R.	All-cause mortality balloon expanding associated with lower risk, RR: 0.51, 95%CI 0.31 to 0.82; p<0.006, compared to self-expanding. Implantation of more than 1 device balloon expanding associated with lower risk when compared to self-expanding, RR: 0.15, 95%CI 0.07 to 0.31; p<0.00001. Moderate/severe aortic regurgitation or paravalvular leak balloon expanding associated with lower risk compared to self-expanding, RR: 0.29, 0.17 to 0.48; p<0.00001.	In scope but evidence not considered key evidence: Study included older generation of devices (for example: Sapien XT, CoreValve, ACURATE neo); technology changes between these and those listed in the Final Scope (see Table 3 of the EAR) therefore cannot assume equivalence. Comparator arm included SEV from multiple manufacturers and some devices were recapturable; this makes determination of the incremental benefit difficult. SR included mechanically expandable valve (MEV) in; acknowledging MEV had to be <5% for inclusion in SR. SR restricted to RCTs reporting all-cause mortality at 30 days as a primary or secondary outcome. Authors acknowledge that “Some studies also excluded patients with heavy calcification in the aortic annulus, left ventricular outflow tract (LVOT) or sinotabular junction, limiting the interpretation of these findings to those subgroups”. Authors assessed risk of bias using the Cochrane risk-of-bias tool for randomized trials version 2 (RoB 2); 4 were considered to have low risk of bias, 1 some concern, and 1 high risk of bias.
36.	Tamburino (Circulation, 2020; 2431-2442) [SCOPE II trial; NCT03192813] Denmark, France, Germany, Italy, Spain, UK (N=23 centres, including 2 from UK)	RCT, non-inferiority (n=796). Powered based on composite primary end point (all-cause death, any stroke at 1 year) predicted as 12% in comparator arm and assumed non-inferiority margin of 6%.	Between April 2017 and April 2019	Symptomatic patients aged ≥75 years, with severe aortic stenosis with an indication of transfemoral TAVI. *Inclusion:* • Patient with severe symptomatic aortic stenosis defined by a mean aortic gradient > 40 mmHg or peak jet velocity > 4.0 m/s or an aortic valve area (AVA) < 1cm2 or AVA	Comparison of ACURATE neo (n=398) with CoreValve Evolut R and Pro (n=398)	Primary composite endpoint at 1 year was 15.8% in ACURATE neo arm and 13.9% in CoreValve Evolut arm; p=0.0549 for non-inferiority. Inconsistent results between ITT and per-protocol analyses, therefore the authors stated that non-inferiority of ACURATE neo was not established for the primary end point.	In scope but evidence not considered key evidence: Older generations of devices in comparator arm. Authors acknowledge that centres contributing to the trial had different levels of experience with the devices, and the proportion where Evolut Pro was used (which included an external pericardial wrap) was not recorded.

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
		Follow-up: 1 year Funder: This trial was sponsored by the Center for European Research Initiatives in Cardiovascular Medicine with support by a dedicated research grant from Symetis SA (Ecublens, Switzerland). [The EAG note that Symetis was acquired by Boston Scientific]		indexed to body surface area (BSA) of <0.6 cm2/m2 • Patient is symptomatic (NYHA functional class > I, angina or syncope) • Patients are considered at high risk for mortality with conventional surgical aortic valve replacement as assessed by a Heart Team consisting of a cardiologist and surgeon or as confirmed by a logistic EuroSCORE I >20% and / or STS score >10%. • Aortic annulus dimensions suitable for both valve types (diameter range: 21-26 mm and perimeter rage from 66 – 81.7 mm), based on ECG-gated multi-slice computed tomographic measurements. • Findings of transthoracic echocardiography (TTE), Transesophageal echocardiography (TEE) and conventional aortography should be integrated in the anatomic assessment. • Arterial aorto-iliac-femoral axis suitable for transfemoral access as assessed by conventional angiography and/or multidetector computed tomographic angiography (access vessel diameter ≥ 6mm). • Patient understands the purpose, the potential risks as well as benefits of the trial and is willing to participate in all parts of the follow-up. • Patient age 75 years or older. • Patient has given written consent to participate in the trial. *Exclusion:* • Severely reduced left ventricular (LV) function (ejection fraction <20%). • Pre-existing prosthetic heart valve in aortic and/or mitral position. • Participation in another trial, which would lead to deviations in the preparation or performance of the intervention or the post-implantation management from this protocol. • Severe coagulation conditions. • Inability to tolerate anticoagulation therapy. • Contraindication to contrast media or allergy to nitinol. • Active infection, including endocarditis. • Congenital aortic stenosis or unicuspid or bicuspid aortic valve. • Non-valvular aortic stenosis. • Hypertrophic obstructive cardiomyopathy. • New or untreated echocardiographic evidence of intracardiac mass, thrombus, or vegetation. • Non-calcific acquired aortic stenosis. • Severe eccentricity of calcification. • Anatomy not appropriate for transfemoral implant due to size, disease and degree of calcification or tortuosity of the aorta or iliofemoral arteries. • Severe mitral regurgitation.		<u>New permanent pacemaker at 30 days</u> occurred in 10.5% in ACURATE neo and 18.0% in CoreValve Evolut; p=0.0027. <u>Cardiac death at 30 days</u> occurred in 2.8% in ACURATE neo and 0.8% in CoreValve Evolut; p=0.03. <u>Cardiac death at 1 year</u> occurred in 8.4% in ACURATE neo and 3.9% in CoreValve Evolut; p=0.01.	

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
37.	Tamm (pre-publication) [AIC] [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Not in scope: [redacted]
38.	Tarantini (Catheter Cardiovasc Interv, 2021; 876-884) SOURCE 3 10 European countries (N=80)	Prospective post-market registry (n=1,694) Follow-up: 4 years Funder: Edwards Lifesciences	Between July 2014 and October 2015.	*Inclusion:* Patients with severe, symptomatic, calcific AS who were at high risk for surgery in real-world practice for 5 years, receiving the Sapien 3 valve (23, 26, 29 mm) via transfemoral route, in line with Sapien 3 indications for us. *Exclusion:* NR	Sapien 3 (n=1,694)	N/A	Not in scope: single-arm cohort making determination of incremental benefit difficult. Focus of analysis was comparison of outcomes between males and females.
39.	Tebar (Catheter Cardiovasc Interv, 2024; 1015-1022) PRECISA [NCT03846557] Spain (number of centres not known: study narratively reports 5 medical centres, 7 medical centres, and trial registry reports 10 centres)	Prospective cohort (n=296) Follow-up: 1 year. Funder: NR	Between January 2019 and September 2021 (ACURATE neo used between January 2019 to September 2020; ACURATE neo2 from October 2020 to September 2021)	*Inclusion:* Consecutive adult (aged 18 years or older) with severe aortic stenosis, requiring aortic valve prosthesis implantation. Both tricuspid and non-tricuspid anatomies, and various access routes were considered for inclusion). *Exclusion:* None.	ACURATE neo2 (n=118) ACURATE neo (n=178)	*Primary outcome* Device success (absence of procedural mortality, accurate positioning of single prosthetic valve, absence of prosthesis-patient mismatch, mean aortic gradient <20mmHg, absence of moderate or severe prosthetic valve regurgitation), at discharge: Higher in ACURATE neo than ACURATE neo2: 18% compared with 9.3%, p=0.04 (p=0.01 from propensity score analysis adjusting for predictor variables) Moderate or severe paravalvular aortic regurgitation: Higher in ACURATE neo arm at discharge (9.8% compared with 5%, p=0.03) at 30 days (4% compared with 2.5%, p=0.04) and 1 year (21.9% compared with 13.6%, p=0.047). Mean aortic valve gradient ≥20 mmHg: no difference between arms at discharge, higher in ACURATE neo at 30 days (4% compared with 2.5%; p=0.04) and no difference at 1 year. Cardiac tamponade, at time of valve implantation: higher in ACURATE neo2, 3.4% compared with 0% for ACURATE neo; p=0.02.	In scope but evidence not considered key evidence: Larger cohort included in original EAG report (for example: Kim et al. 2022c). Historical comparator group. No statistical differences in baseline characteristics reported, however difference in post-dilation were reported: 47.2% with ACURATE neo and 12.7% in ACURATE neo2 group; p<0.0001, and differences in post-dilation balloon diameter, 22.9 (2.0) in ACURATE neo compared with 24.0 (0.9) in the ACURATE neo2 group, p=0.02. Propensity score analysis not reported for all outcomes, predictor variables used in this analysis not reported. Short term outcomes. Confusion over reporting of primary outcome reported in methods section as device success, but values reported in Table 4 and breakdown of the primary outcome appear device failure. Authors acknowledge the tendency to use ACURATE neo2 valve predominantly in women with small aortic annulus, that differences in post-dilation between arms, and differences in access approach may have influenced outcomes.
40.	Thiele (Eur Heart J, 2020a; 1890-1899)[SOLVE-TAVI trial; NCT02737150] [Additional detail regarding study design reported in Thiele (Circulation, 2020b; 1437-1447)] Germany (N=7)	RCT; 2x2 factorial (n=447) Comparison of general anaesthesia and local anaesthesia with conscious sedation, and also comparison of self-expandable with balloon-expandable. Powered for equivalence in primary endpoint (all-cause mortality, stroke, moderate or severe PVL, and permanent pacemaker implantation at 30-day follow-up) Follow-up: 30 days	Between April 2016 and April 2018	*Inclusion:* Patients with symptomatic aortic valve stenosis, age ≥75 years, at high risk for conventional SAVR (logistic EuroSCORE ≥20%, or STS ≥10%, or other high risk criteria as deemed by heart team consensus), a native aortic valve annulus size (between 18 and 29 mm) appropriate for the available valve sizes, suitable for transfemoral vascular access. *Exclusion:* Contraindication for specific valve type, cardiogenic shock or haemodynamic instability, history of or active endocarditis, active infection requiring antibiotic treatment, life expectancy <12 months, active peptic ulcer or upper GI bleeding <3 months, hypersensitivity or contraindication to aspirin, heparin or clopidogrel, participation in another trial.	Evolut R (n=225) compared with Sapien 3 (n=222)	*Primary endpoint* Composite (all-cause mortality, stroke, moderate or severe PVL, permanent pacemaker) at 30 days: equivalent between groups 28.4% in Evolut R compared with 25.9% Sapien 3; p=0.04 for equivalence. All-cause mortality, 30 days: similar between Evolut R and Sapien 3, 3.2% and 2.3% respectively, p<0.0001 for equivalence. Stroke, 30 days: similar between Evolut R and Sapien 3, 0.5% and 4.7% respectively, p=0.003 for equivalence.	Key evidence 2x2 factorial design, but no interactions was assumed to be clinically plausible but no exploration of this was reported. Statistical difference in the contrast agent used between TAVI device arms (higher with Evolut R, p<0.001). In self-expanding TAVI arm, 2 participants electively crossed over to balloon-expanding, and other valves were used in 2 additional participants. In the balloon-expanding device arm, 1 participant electively crossed over to the self-expanding arm. A per protocol analysis was conducted that adjusted for this and had similar findings to the intention to treat analysis.

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
		Funder: German Heart Research Foundation and the Leipzig Heart Institute Germany		The EAG note that additional exclusion criteria were listed in Thiele et al. 2020b, including: mode of anaesthesia or for TAVI procedure, clear patient-specific clinical reasons to prefer 1 form of anaesthesia over the other.		Moderate to severe PVL, 30 days: similar between Evolut R and Sapien 3, 3.4% and 1.5% respectively, p=0.0001 for equivalence. Permanent pacemaker, 30 days: significantly higher for Evolut R than Sapien 3, 23.0% and 19.2% respectively, p=0.06 for equivalence.	Authors acknowledge that the RCT was powered to show equivalence in treatment groups on composite clinical endpoint only; not component endpoints, and that "valve choice should take into account individual factors in which a specific valve type might be favoured (for example severe calcification, bicuspid anatomy, horizontal aorta, or the requirement of uncomplicated coronary access).
41.	Ubben (J Clin Med, 2024; 3163) Germany (N=6)	Retrospective cohort (n=402) Follow-up: until discharge Funder: Meril Life Sciences via research grant for investigator-sponsored trials.	Between 01 March and 31 August 2020.	*Inclusion:* Consecutive patients who underwent TAVI for severe symptomatic aortic valve stenosis with Myval or Sapien 3 or Sapien 3 Ultra. *Exclusion:* pre-existing prosthetic heart valves in aortic position and patients who underwent an emergent TAVI or TAVI with mechanical circulatory support.	Myval (n=134) Sapien 3/3 Ultra (n=268)	Major vascular complication, at discharge: higher in Myval (9%) compared with Sapien 3/3 Ultra (5%), p=0.02 All-cause mortality, cardiac mortality, stroke, disabling stroke, new pacemaker implantation, annular rupture, new onset AF, cerebrovascular events, AKI, bleeding (type 3), endocarditis, MI, minor vascular complications, at discharge: No difference between arms.	In scope but evidence not considered key evidence: Short term outcomes, studies with longer follow-up for Myval were included in original EAG report (for example: Baumbach et al. 2024) Unclear whether the intervention included both Myval and Myval Octacor (latest iteration). Reported baseline characteristics of cohorts not statistically different but no formal matching of patient characteristics reported. Authors acknowledge that the analysis includes learning curve of the Myval device.
42.	Ueyama (Am J Cardiol, 2021; 104-111) Setting: NR	Network meta-analysis (N=10 RCTs, n=9,388) [Note N=3 studies directly compared balloon expanding and self-expanding TAVI devices, 4 compared self-expanding TAVI with SAVR and 3 compared balloon-expanding TAVI with SAVR] Follow-up: up to 5 years Funder: NR	NR (Literature search between database inception to 06 February 2021)	*Inclusion:* RCTs comparing TAVI and SAVR or balloon-expanding and self-expanding in patients with severe aortic stenosis, reporting at least 1 of the pre-specified outcomes (structural valve deterioration, moderate to severe aortic regurgitation, aortic valve reintervention at the longest available follow-up), study reported outcome at follow-up of at least 1 or more years, published in peer-reviewed journal or presented in international academic conferences. *Exclusion:* None.	Balloon-expandable included Sapien, Sapien XT, Sapien 3 (all combined, n=2,562). Self-expanding included: CoreValve, Evolut R, Evolut Pro, ACURATE neo (all combined, n=2,863) SAVR (n=3,963)	Structural valve deterioration, 5 years: Self-expanding valves lower risk than balloon-expanding; HR 0.14 (0.07 to 0.27) Moderate to severe aortic regurgitation, 5 years: Self-expanding valves associated with high risk than balloon; HR 1.78 (95% CI 1.03 to 3.07). Aortic valve re-intervention, 5 years: No statistical difference between balloon and self-expanding valves. Mean gradient, mmHg, 5 years: Lower with self-expanding versus balloon-expanding, mean difference: -5.13 (95%CI -6.21 to -4.04); p<0.001. EOA, cm2, 5 years: higher with self-expanding compared with balloon-expanding, mean difference: 0.25 (0.15 to 0.35), p<0.001.	In scope but evidence not considered key evidence: Different device manufacturers and models combined to directly/indirectly compare self-expanding with balloon expanding; unable to determine incremental benefit of devices. EAG note that it is unclear whether all RCTs were statistically powered to detect differences in the outcomes extracted. Authors acknowledge that definition of outcomes was not consistent across studies, and that there was heterogeneity in surgical risk and device generation in studies included.
43.	Van Belle (Circulation, 2020; 243-259) [NCT01777828] France (N=48)	Prospectively cohort, registry, FRANCE-TAVI (n=12,141). Includes both propensity score matching on 25 clinical and anatomical variables (n=7,820 after matching) and inverse probability of treatment weighting (n=12,141). Follow-up: 30 days, up to 2 years.	Between 02 January 2013 and 31 December 2015. (Sapien XT used between January 2013 to last quarter 2014, Sapien 3 used from	*Inclusion:* All patients included in the FRANCE-TAVI registry. *Exclusion:* Patients with previous SAVR (including those referred for valve-in-valve procedures), those treated with different valve design (Lotus, Boston Scientific, Direct Flow, JenaValve).	CoreValve (n=4,103; n=3,910 after matching) compared with Sapien XT/3 (n=8,038; n=3,910 after matching)	Mortality, in-hospital: Higher in CoreValve than Sapien XT/3, confirmed by propensity matching (5.6% compared with 4.2%, p=0.01) and IPTW cohorts (5.6% compared with 3.8%, p=0.001). Moderate or severe paravalvular leak, at discharge: Higher in CoreValve than Sapien XT/3, confirmed by propensity matching (15.5% compared with 8.3%; p<0.0001) and	In scope but evidence not considered key evidence: Older generation devices in both intervention and comparator arm; no longer available in NHS. EAG note that 4 sizes were available for each device, but different sizing (CoreValve: 23, 26, 29, 31mm; Sapien 3: 20, 23, 26, 29mm). Combination of generations in the Sapien (balloon expanding) arm; which may influence results.

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
		Funder: The registry was established by the French Society of Cardiology and French Working Group of Interventional Cardiology with the participation of the French Society of Thoracic and Cardiovascular Surgery and with support from Edwards Lifesciences and Medtronic.	last quarter 2014 to December 2015).			IPTW cohorts (15.6% compared with 7.5%; p<0.0001). Second valve used, at discharge: higher with CoreValve than Sapien XT/3, confirmed by propensity matching (3.7% compared with 1.0%, p<0.0001) and IPTW cohorts (3.7% compared with 0.8%, p<0.0001). Permanent pacemaker, at discharge: higher with CoreValve than Sapien XT/3, 22.3% compared with 11.0%, p<0.0001. Mean gradient, post-procedure: lower with CoreValve than Sapien XT/3, confirmed by propensity matching (mean difference: -0.21 (-0.24 to -0.19); p<0.0001) and IPTW cohorts (mean difference: -0.23 (-0.25 to -0.21), p<0.001). Hospitalisation for acute cardiac event (including acute coronary syndrome or heart failure), 2 years: Increased risk associated with self-expanding compared to balloon-expanding in propensity matched cohort (HR 1.26 (1.06 to 1.48); p=0.001) and with IPTW cohort (HR: 1.28 (1.10 to 1.54); p=0.0001). Aortic valve re-intervention, 2 years: No statistical difference between arms confirmed by propensity matched and IPTW cohorts. Stroke, 2 years: No statistical difference between arms confirmed by propensity matched and IPTW cohorts. All-cause mortality, 2 years: higher for CoreValve than Sapien XT/3 confirmed by propensity matched (HR 1.17 (1.06 to 1.28); p=0.002) and IPTW cohorts (HR: 1.18 (1.08 to 1.29); p<0.0001). Proportional hazard assumption was not satisfied because excess mortality risk of CoreValve compared to Sapien XT/3 only observed for the first 3-month period (HR: 1.37, (1.16 to 1.60), p=0.0001.	
44.	Welle (Catheter Cardiovasc Interv, 2021; 895-902) US (N=1)	Retrospective cohort identified from registry (n=260) Follow-up: 30 days. Funder: NR	Between July 2018 and July 2019 Sapien 3 Ultra available option from	*Inclusion:* Consecutive patients undergoing TAVI for severe aortic stenosis. Valve selection was collaboratively chosen by Heart Team. *Exclusion:* off-label TAVI, conversion to SAVR strategy prior to TAVI, those receiving self-expanding TAVI, aortic valve-in-valve procedure, died prior to discharge of index hospitalisation.	Sapien 3 Ultra (n=101) Sapien 3 (n=159)	PVL, 30 days: Proportion with mild PVL less in Sapien 3 Ultra arm compared with Sapien 3, 10.8% compared with 36.5%; p<0.0001. Proportion with moderate also less in Sapien 3 Ultra arm, 0% compared with 5.8% (p=NR). Univariate analysis showed TAVI device was associated	In scope but evidence not considered key evidence: No adjustment for population differences between arms; statistical differences in male sex, annular area, perimeter and diameter, aortic valve calcium score, proximal left anterior descending stenosis, valve size, access site observed and not adjusted for. Valve size of 29mm not

#	Author (journal, year; pages); Setting (N centres)	Study design (n number of patients); Funder	Recruitment period	Population	Intervention/Comparator	Key findings	EAG comment and consideration of study limitations.
			February 2019 onwards.			with mild PVL, but TAVI device not associated with moderate PVL. LVEF and aortic valve mean gradient, 30 days: No difference between arms.	available in Sapien 3 Ultra. Comparator arm also includes historical comparator group (July 2018 to February 2019 Sapien 3 Ultra was not available). Larger studies with matching between Sapien 3 and Sapien 3 Ultra already included in EAG report (e.g. Nazif et al. 2021, Cannata et al. 2023).

Abbreviations: AKI, Acute Kidney Injury; AVA, Aortic Valve Area; BE, Balloon Expanding; CAD, Coronary artery disease; CVA, Cerebrovascular accident; CVT, Clinical valve thrombosis; ECG, Electrocardiogram; GFR, Glomerular Filtration Rate; HALT, Hypo attenuated leaflet thickening; iEOA, indexed effective orifice area; IPTW, inverse probability of treatment weighting; IQR, Interquartile Range; LBBB, left bundle branch block; LV, Left ventricular; LVEF, Left ventricular ejection fraction; LVOT, Left ventricular outflow tract; MA, meta-analysis; MDCT, Multi-detector CT; MDT, Multidisciplinary team; MI, Myocardial infarction; N/A, Not applicable; NR, Not reported; NYHA, New York Heart Association; PPI, Permanent pacemaker implantation; ; PPMI, Permanent pacemaker implantation; PVL, Paravalvular leak; PVR, Paravalvular regurgitation; RCT, Randomised controlled trial; SE, Self-expanding expansion type; SLT, Subclinical leaflet thrombosis; STS, The Society of Thoracic Surgeons; SUCRA, Surface Under the Cumulative Ranking; SVD, Structural valve deterioration; TAPSE, Tricuspid annular plane systolic excursion; TAVI, Transcatheter aortic valve implantation; TAVR, Transcatheter aortic valve replacement; TEE, Transoesophageal echocardiogram; THV, Transcatheter Heart Valve; TIA, Transient ischaemic attack; TTE, Transthoracic echocardiogram; VARC-2, Valve Academic Research Consortium-2; VARC-3, Valve Academic Research Consortium-3;