Clinical Research in Cardiology
https://doi.org/10.1007/s00392-019-01571-2

ORIGINAL PAPER

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

Felix Hofer[1] · Christian Hengstenberg[1] · Georg Goliasch[1] · Marek Grygier[2] · Julia Mascherbauer[1] · Jolanta M. Siller-Matula[1,3]

Received: 15 September 2019 / Accepted: 6 November 2019

Abstract

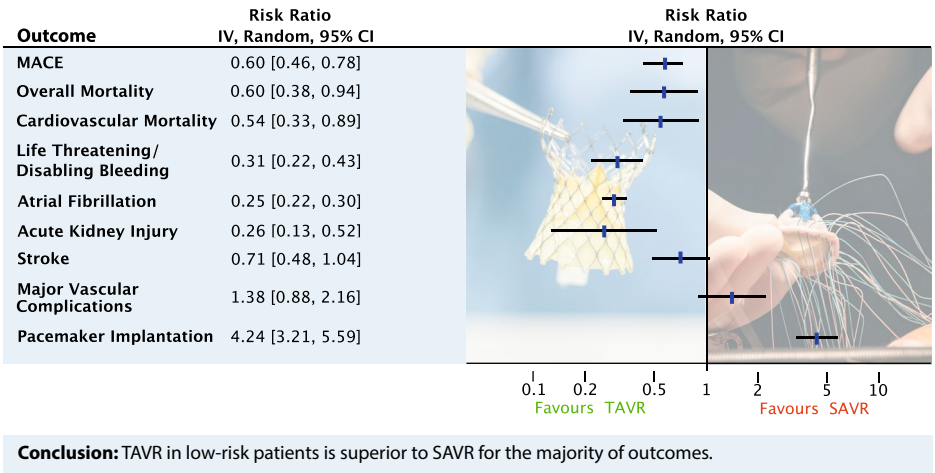
Background Transcatheter aortic valve replacement (TAVR) has emerged as a treatment option for severe aortic stenosis in patients at intermediate or high surgical risk. However, until recently there was insufficient evidence regarding the outcomes of TAVR compared to surgical aortic valve replacement (SAVR) for patients at low risk.

Methods We conducted a meta-analysis and systematic review of all randomized trials comparing the efficacy and safety of TAVR versus SAVR in patients at low surgical risk. Risk ratios (RR) and 95% confidence intervals (CIs) were calculated, using fixed- or random-effects model.

Results Four trials were eligible for analysis and comprised a total of 2887 patients (1497 allocated to TAVR and 1390 allocated to SAVR group). TAVR was associated with a 39% relative risk reduction (RRR) of major adverse cardiac events (MACE) (absolute risk reduction ARR of 3.7%; RR 0.61; 95% CI 0.47–0.79); 39% RRR of overall mortality (ARR of 1.4%; RR 0.61; 95% CI 0.39–0.96) and 45% RRR of cardiovascular mortality (ARR of 1.3%; RR 0.55; 95% CI 0.33–0.90), 69% RRR of life threatening or disabling bleeding (ARR of 7.0%; RR 0.31; 95% CI 0.22–0.44), 73% RRR of new-onset atrial fibrillation (ARR of 29%; RR 0.27; 95% CI 0.20–0.35) and 73% RRR of acute kidney injury (ARR of 2.1%; RR 0.27; 95% CI 0.14–0.56) as compared with SAVR. In contrast, TAVR was associated with a 4.7-fold increased risk of new pacemaker (PM) implantation (RR 4.72; 95% CI 1.83–12.15), which was driven by use of self-expanding valves.

Conclusion TAVR in low-risk patients is superior to SAVR for the majority of outcomes.

Graphical abstract



Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00392-019-01571-2) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

Published online: 20 December 2019

Keywords TAVR · SAVR · Aortic stenosis · Low surgical risk

Abbreviations

AF	Atrial fibrillation
AKI	Acute kidney injury
ARI	Absolute risk increase
ARR	Absolute risk reduction
AS	Aortic stenosis
CIs	Confidence intervals
CV	Cardiovascular
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac events
NNH	Number needed to harm
NNT	Number needed to treat
PM	Pacemaker
PPI	Permanent pacemaker implantation
RCT	Randomized-controlled trials
RR	Relative risk
RRI	Relative risk increase
RRR	Relative risk reduction
STS-PROM	Society of thoracic surgeons predicted risks of mortality
SAVR	Surgical valve replacement
TAVR	Transcatheter aortic valve replacement

Background

Transcatheter aortic valve replacement (TAVR) has emerged as a treatment option for severe aortic stenosis in patients who are at intermediate or high risk for complications or death from surgery. Previous randomized trials founded a basis for the guideline recommendation for TAVR in patients at intermediate or high surgical risk, by showing that TAVR with both balloon-expandable and self-expanding valves was either superior or non-inferior to surgical valve replacement (SAVR) [1–9]. To be able to use TAVR by default in young patients at low operative risk, it requires sufficient evidence of safety and effectiveness, which is given by aortic-valve surgery in relatively young, healthy patients. However, until recently there was insufficient evidence regarding the outcomes of TAVR compared to surgery for patients at low risk, for whom SAVR is the standard of care [10, 11]. Recently published randomized trials (as PARTNER 3 and EVOLUT LOW RISK) investigated the efficacy and safety of TAVR as compared with SAVR, and reported positive findings.

Due to successful TAVR results in intermediate-to-high surgical risk patients, technical advancements of TAVR devices and increased operator experience, the next logical aim was an expansion of TAVR in low-surgical risk patients [12]. To further contribute to the ongoing debate on the benefit-risk of TAVR in low-risk patients, we performed a systematic review and meta-analysis that comprises large randomized trials. We focused on 30 days and 1 year clinical outcomes [10, 11, 13, 14].

Methods

This systematic review and meta-analysis was performed according to established methods. We searched PubMed and web of science using predefined search terms ("transcatheter aortic valve replacement", "TAVR", "surgical aortic valve replacement", "SAVR", "TAVI", "SAVI", AND "low risk") from 2010 until April 2019. Title and abstract of suspected relevant citations were screened for eligibility and full-text was acquired for further evaluation if the citation was deemed pertinent. References of retrieved meta-analyses and reviews were also checked for additional trials.

Included studies had to be randomized-controlled trials (RCT). The target patient collective comprised patients with severe aortic stenosis at low surgical risk [Society of Thoracic Surgeons Predicted Risks of Mortality (STS-PROM) score < 4% or EuroScore < 4%]. Due to the superiority of the STS score compared to the EuroScore, the STS score was predominantly used in the majority of trials. The EuroScore was only used in the absence of the STS score. Two reviewers independently and in duplicate applied the selection criteria (F.H. and J.M.S.-M.).

The primary endpoint was the composite of major adverse cardiovascular events defined by each study differently. Major vascular complications, permanent pacemaker implantation, life-threatening/disabling bleeding, stroke, TIA, myocardial infarction, coronary obstruction, endocarditis, atrial fibrillation (AF), acute kidney injury (AKI), cardiovascular death and all-cause death were defined as secondary endpoints.

Subgroup analyses comparing self- vs balloon-expandable bioprostheses were performed for primary and secondary outcomes.

This systematic review analyzed outcomes at 12 months after procedure (except for AKI, where the follow-up was 1 month). The STACCATO trial, was not included in this meta-analysis due to lack of follow-up data and premature termination [15].

Statistical analysis

Variables are reported as number or percentages as appropriate. Risk ratios (RR) were calculated from individual studies and pooled according to the inverse variance model with 95

percent confidence intervals (95% CI) and reported as relative risk reduction or increase, respectively (RRR/RRI). The statistical inconsistency test (I^2) was used to assess heterogeneity between studies. If the I^2 value was low ($I^2 < 25\%$), a fixed-effect model was additionally calculated. The following sensitivity analyses were performed: (1) comparison of the results of the fixed vs random effect model; and (2) the influence of each study was assessed by testing whether, deleting each in turn, would have significantly changed the pooled results of the meta-analysis; (3) effect size and direction for balloon vs self-expandable valves. Absolute risk reduction or increase (ARR/ARI) and number needed to treat/harm (NNT/NNH) were calculated per 1 year of treatment. A two-tailed p value of < 0.05 was considered significant. Review Manager (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2019) was used for statistical computations.

Results

Study selection

Our search identified 251 references of which four studies met our inclusion criteria (Fig. 1); all studies reported rates of events during a 30-day follow-up and at 1-year follow-up. Additionally, retrieved reviews and meta-analyses were thoroughly examined to identify further trials. Four trials were eligible for analysis and comprised a total of 2887 patients, 1497 allocated to TAVR and 1390 allocated to SAVR group. Three trials used a self-expandable bioprostheses (EVOLUT low risk, SURTAVI and NOTION), and one trial utilized a balloon-expandable valve (PARTNER 3). The majority of TAVR procedures were performed via transfemoral access. All included trials were performed as multicenter studies. The characteristics of the included studies are presented in Table 1.

Outcomes

MACE

All studies reported rates of MACE (Fig. 2) [10, 11, 13, 14]. In the TAVR group, 5.6% of patients (84/1497) experienced MACE compared to 9.4% in the SAVR group (130/1390) over a mean follow-up of 1 year. TAVR therefore resulted in RRR of MACE by 39% (RR 0.61; 95% CI 0.47–0.79); $p < 0.0002$; $I^2 = 0\%$; Fig. 2). The annual ARR was 3.7%, which corresponded to a NNT of 27 (Table 2). If 1000 patients would be treated with TAVR instead of SAVR, 37 MACE events could be prevented within 1 year of intervention (Table 2).

Ischemic stroke

There was no significant difference between both groups regarding ischemic stroke, but a trend toward reduction of stroke with TAVR was apparent (Fig. 1S in the supplemental file). During a mean follow-up period of 1 year, 3% of patients (45/1497) experienced an ischemic stroke in the TAVR group compared to 4.2% in the SAVR group (59/1390; RR 0.72; 95% CI 0.49–1.06; $p = 0.10$; $I^2 = 0\%$).

Mortality

TAVR was associated with a RR of overall death: 2.1% of patients (31/1497) allocated to TAVR died within 1 year of intervention as compared to 3.5% of patients (48/1390) allocated to SAVR, resulting in a RRR of overall death of 39% by TAVR (RR 0.61; 95% CI 0.39–0.96;

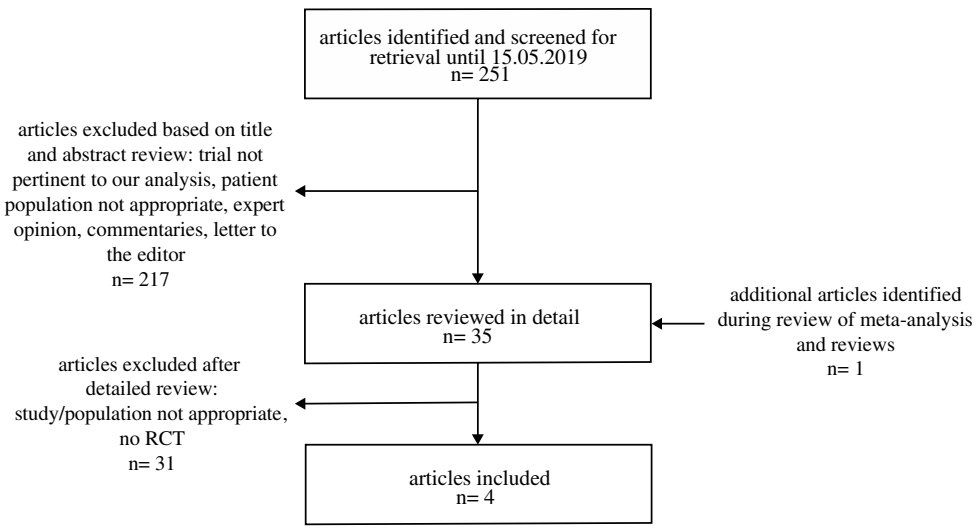


Fig. 1 Workflow of studies included in the meta-analysis

Table 1 Characteristics of included studies: definition of outcomes, inclusion and exclusion criteria, lost to follow-up, period of recruitment, delivery route, valve types

Study	Outcomes	Inclusion criteria	Exclusion criteria	Lost to follow-up (%)	Period of recruitment	Delivery route	Valve types	Mean Age TAVR	Mean STS-score
Mack et al. PARTNER 3 trial	Primary endpoint: composite of death from any cause, stroke, or rehospitalization	Severe calcific aortic stenosis, STS-PROM score of less than 4%	Patients with clinical frailty (as determined by the heart team), bicuspid aortic valves, or other anatomical features that increased the risk of complications associated with either TAVR or surgery	0	03/2016–10/2017	Transfemoral	Balloon expandable valve (Sapien 3)	73.3 ± 5.8	1.9 ± 0.7
Popma et al. EVOLUT LOW RISK trial	Primary endpoint: composite of death from any cause or disabling stroke	Severe aortic-valve stenosis with suitable anatomy for TAVR or surgery and no more than a predicted 3% risk of death by 30 days with surgery	Patients with clinical frailty, bicuspid aortic valves, or other anatomical features that increased the risk of complications associated with either TAVR or surgery	0.14	03/2016–11/2017	Transfemoral; subclavian; direct aortic	Self-expanding valve (CoreValve, Evolut R, or Evolut PRO; Medtronic)	74.1 ± 5.8	1.9 ± 0.7
Serruys et al. SURTAVI low risk population	Primary endpoint: composite of death from any cause or disabling stroke	Severe calcified aortic stenosis and STS-Prom score of less that 4%	Contraindication to all anticoagulation/antiplatelet regimens; ongoing sepsis; symptomatic carotid or vertebral artery disease; cardiogenic shock, recent cerebrovascular accident; any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to randomization	0	06/2012–06/2016	Transfemoral; subclavian; direct aortic	Self-expanding valve (CoreValve and Evolut R)	75.1 ± 6.5	2.4 ± 0.6

Table 1 (continued)

Study	Outcomes	Inclusion criteria	Exclusion criteria	Lost to follow-up (%)	Period of recruitment	Delivery route	Valve types	Mean Age TAVR	Mean STS-score
Thyregod et al. NOTION trial	Primary endpoint: composite rate of death from any cause, stroke, or myocardial infarction	Patients > 70 years of age with severe degenerative aortic valve stenosis referred for SAVR and also candidates for TAVR were eligible for inclusion with low operative risk	Another severe heart valve disease or coronary artery disease requiring intervention, previous cardiac surgery, myocardial infarction or stroke within 30 days, severe renal failure requiring dialysis, or pulmonary failure with a forced expiratory volume within 1 s or diffusion capacity < 40% of expected	0	12/2009–04/2013	Transfemoral; subclavian	Self-expanding valve (CoreValve)	79.2 ± 4.9	2.9 ± 1.9

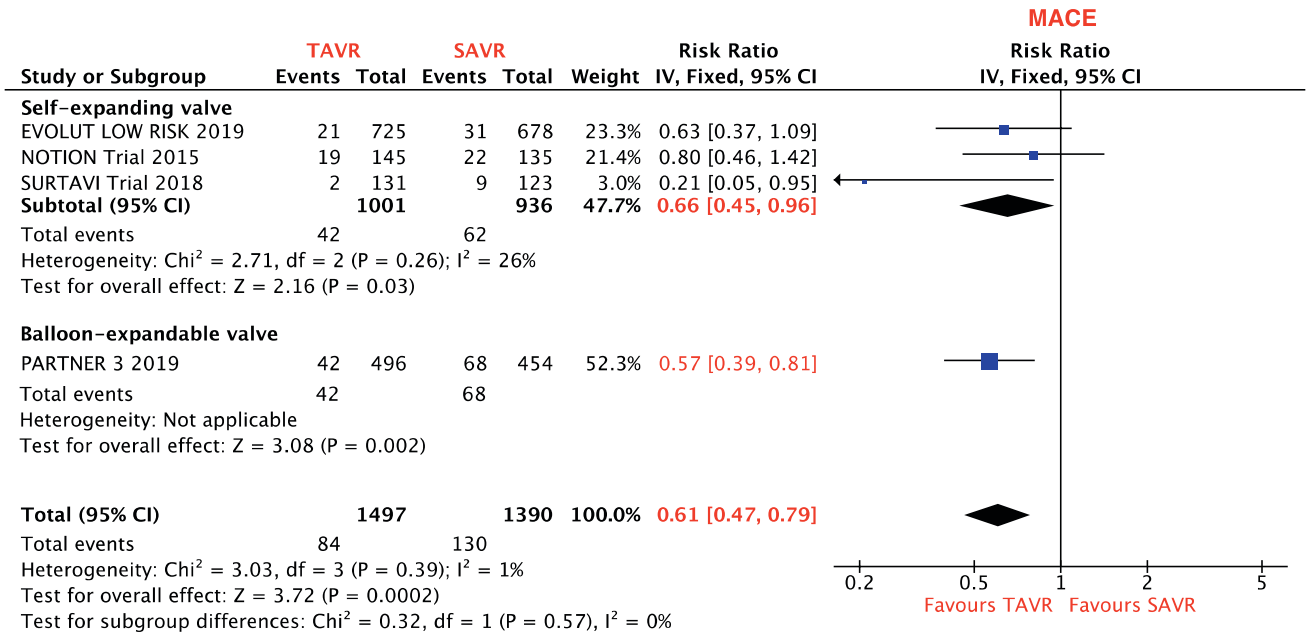


Fig. 2 Forest plots depicting the risk ratio (RR) of major adverse cardiovascular events (MACE)

Table 2 Absolute risk reduction (ARR) or increase (ARI) and number-needed-to-treat/harm (NNT/NNH) for the primary and secondary endpoints over a period of 1 year

Event	Incidence TAVR	Incidence SAVR	ARR	ARI	NNT	NNH	N of events reduced with TAVR per 1000 treated patients	N of events caused with TAVR per 1000 treated patients	*p* value
MACE	0.06	0.09	0.04		27		37		0.0002
Overall-death	0.02	0.03	0.01		72		14		0.03
Cardiovascular-death	0.02	0.03	0.01		74		13		0.02
Ischemic stroke	0.03	0.04	0.01		81		12		0.05
Life threatening/disabling bleeding	0.03	0.1	0.07		14		70		< 0.00001
Major vascular complication	0.03	0.02	0.01		NA		NA		0.25
Pacemaker implantation	0.17	0.04		0.13		8		133	0.001
New-onset atrial fibrillation	0.1	0.39	0.29		3		293		< 0.00001
Acute kidney injury	0.01	0.03	0.02		48		21		0.0003
Myocardial infarction	0.02	0.02	0.00		NA		NA		0.37
Coronary obstruction	0.01	0.01	0.00		NA		NA		0.99
Endocarditis	0.01	0.01	0.00		NA		NA		0.58

NA none applicable

$p = 0.03$; $I^2 = 0\%$; Fig. 3a). The annual ARR of overall death was 1.4% and the NNT 72 (Table 2). There was also a significant difference in the risk of cardiovascular (CV) death between the TAVR (1.6%, 24/1497) and the SAVR groups (2.9%, 41/1390): TAVR reduced the relative risk of CV death by 45% (RR 0.55; 95% CI 0.33–0.90; $p = 0.02$; $I^2 = 0\%$; Fig. 3b). The annual ARR of cardiovascular death was 1.3% and the NNT 74 (Table 2). If 1000 patients would be treated with TAVR, 14 patients more would survive the first year after the procedure as compared to patients treated with SAVR (Table 2).

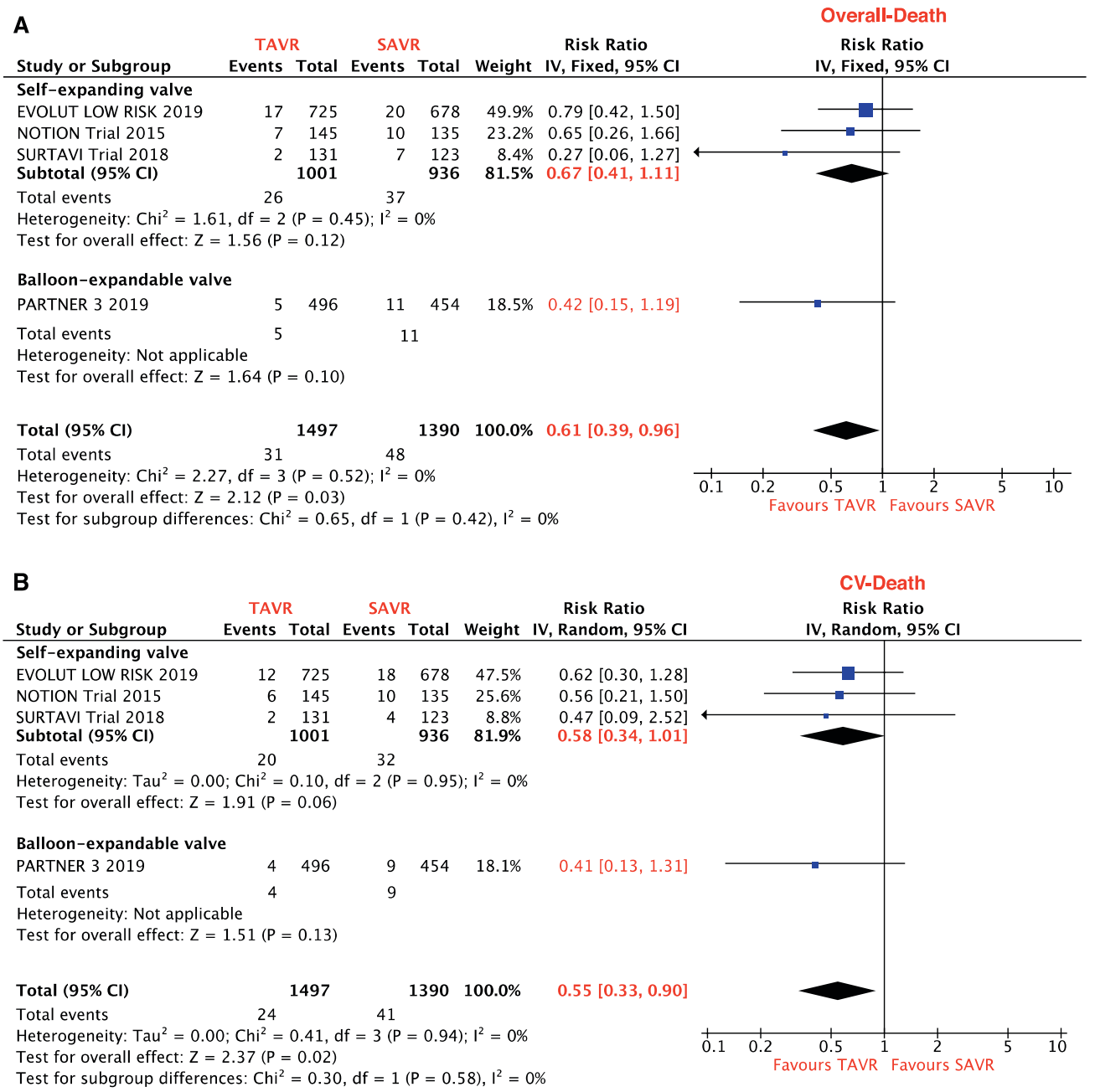


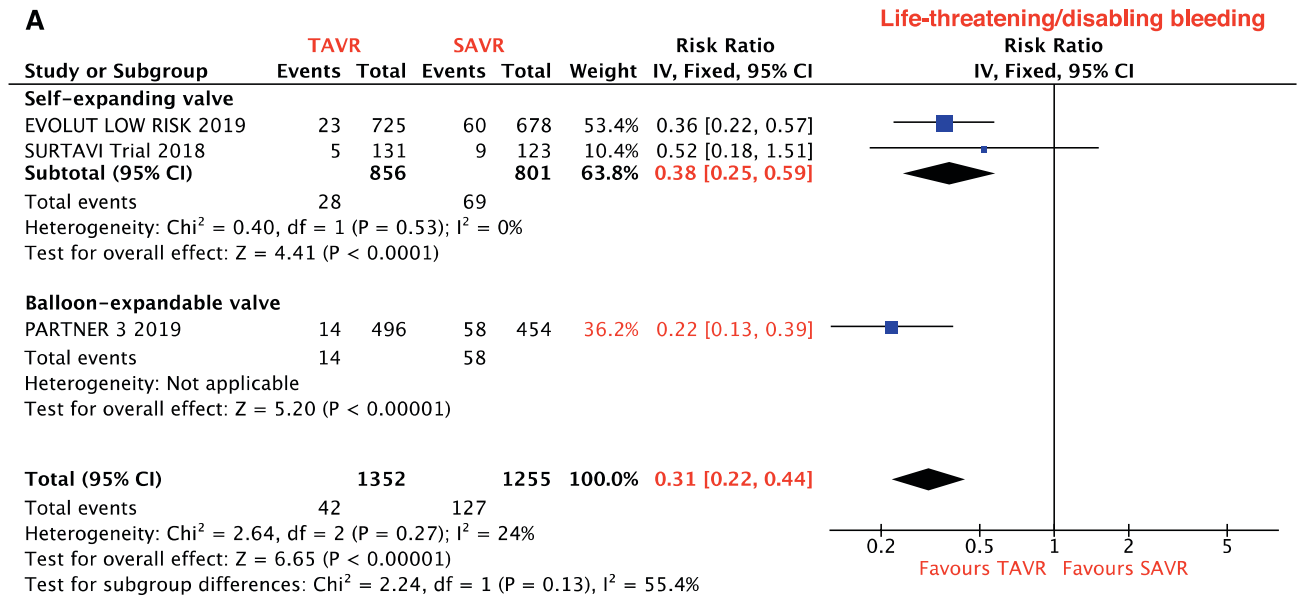
Fig. 3 Forest plot showing the risk ratio (RR) of (**a**) overall-death and (**b**) cardiovascular death

Bleeding events

Three studies, including a total of 2607 patients, reported on the rate of life threatening/disabling bleeding within 1 year [10, 11, 13]. Life threatening/disabling bleeding occurred in 3.1% of patients (42/1352) treated with TAVR compared to 10.1% of patients (127/1255) in the SAVR group. TAVR therefore was associated with a RRR of life threatening/disabling bleeding by 69% (RR 0.31; 95% CI 0.22–0.44; $p < 0.00001$; $I^2 = 24\%$; Fig. 4a). The annual ARR was 7.0% and the NNT to avoid one life threatening/disabling bleeding was 14 (Table 2). If 1000 patients would be treated with TAVR instead of SAVR, 70 life-threatening/disabling bleeding could be prevented (Table 2).

Major vascular complications

Major vascular complications, which were reported in three studies [10, 11, 13], did not show a significant difference between both groups (RR 1.31; 95% CI 0.83–2.06; $p = 0.25$;



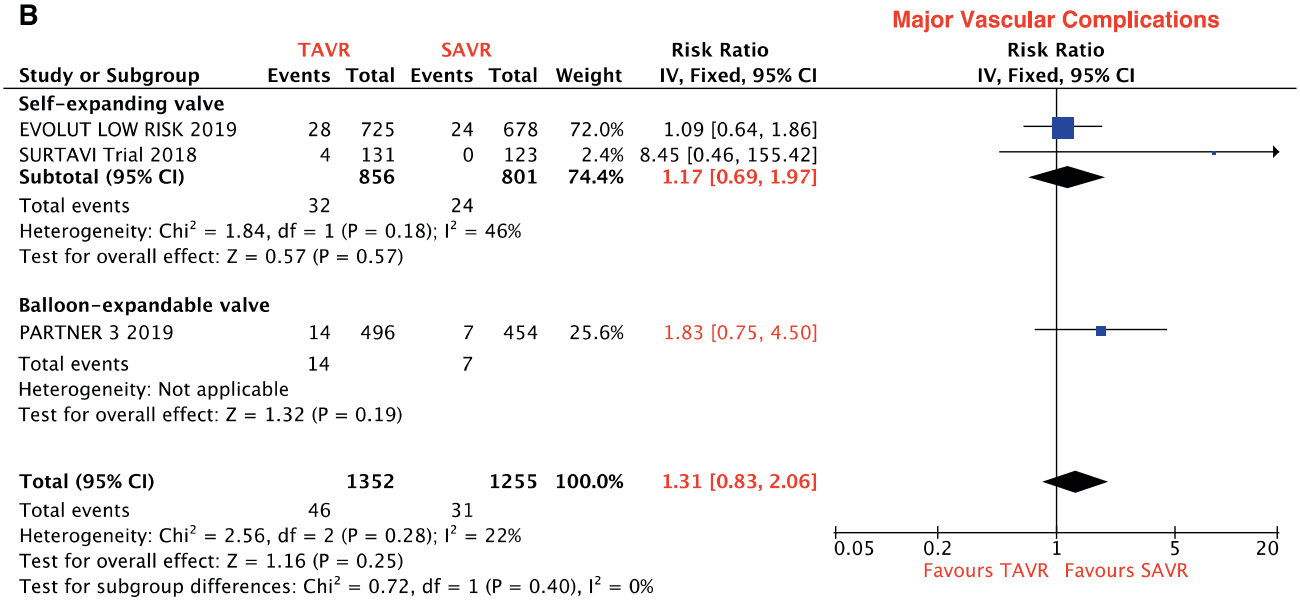


Fig. 4 Forest plot showing the risk ratio (RR) of (**a**) a life threatening/disabling bleeding and (**b**) major vascular complications

$I^2 = 22\%$; Fig. 4b). Major vascular complications occurred in 3.4%/year (46/1352) in patients treated with TAVR compared to 2.5%/year (31/1255) in patients treated with SAVR.

Pacemaker implantation

There was a significant increase of pacemaker implantation rates (RR 4.72; 95% CI 1.83–12.15; $p < 0.00001$; Fig. 5a) in patients who underwent TAVR compared with SAVR. In the TAVR group, 17.4% of patients (260/1497) received a permanent pacemaker compared to 4.1% in the SAVR group (57/1390) over a mean follow-up of 1 year. The annual ARI was 13.3% and the NNH was 8 (Table 2). If 1000 patients would be treated with TAVR instead of SAVR, 133 additional patients would receive a permanent pacemaker within 1 year of procedure.

New-onset atrial fibrillation

In the TAVR group, 10% of patients (150/1497) suffered from new-onset atrial fibrillation compared to 39% in the SAVR group (547/1390) over a mean follow-up of 1 year (Fig. 5b). TAVR was therefore associated with a 73% RRR of atrial fibrillation within 1 year (RR 0.27; 95% CI 0.20–0.35;

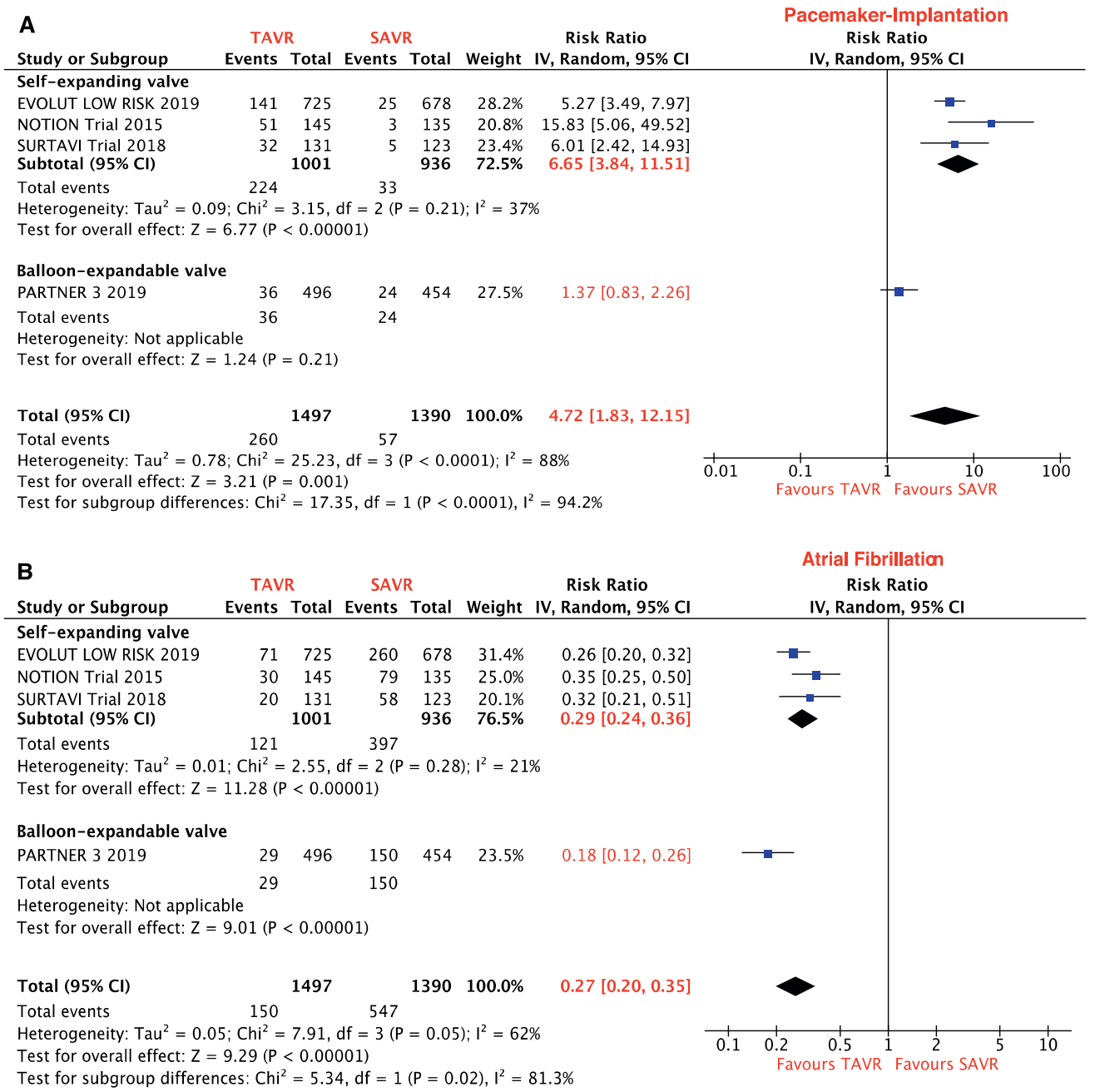


Fig. 5 Forest plot showing the risk ratio (RR) of (**a**) pacemaker implantation and (**b**) atrial fibrillation

$p < 0.00001$; $I^2 = 62\%$). The annual ARR was 29% and the NNT 3 (Table 2). If 1000 patients would be treated with TAVR instead of SAVR, 293 new-onset atrial fibrillation events could be prevented within 1 year of procedure.

Acute kidney injury

Three studies, including a total of 2633 patients, reported on the rate of acute kidney injury within a month [10, 11, 14]. 0.7% of patients (10/1366) allocated to TAVR suffered from AKI after the procedure compared to 2.8% of patients (36/1267) allocated to SAVR. TAVR therefore was associated with a 73% RRR of an acute kidney injury within a month of procedure (RR 0.27; 95% CI 0.14–0.56; $p < 0.0003$; $I^2 = 0\%$; Fig. 6). NNT was 47 and the ARR 2.1% (Table 2). If 1000 patients would be treated with TAVR instead of SAVR, 21 acute kidney injuries could be prevented.

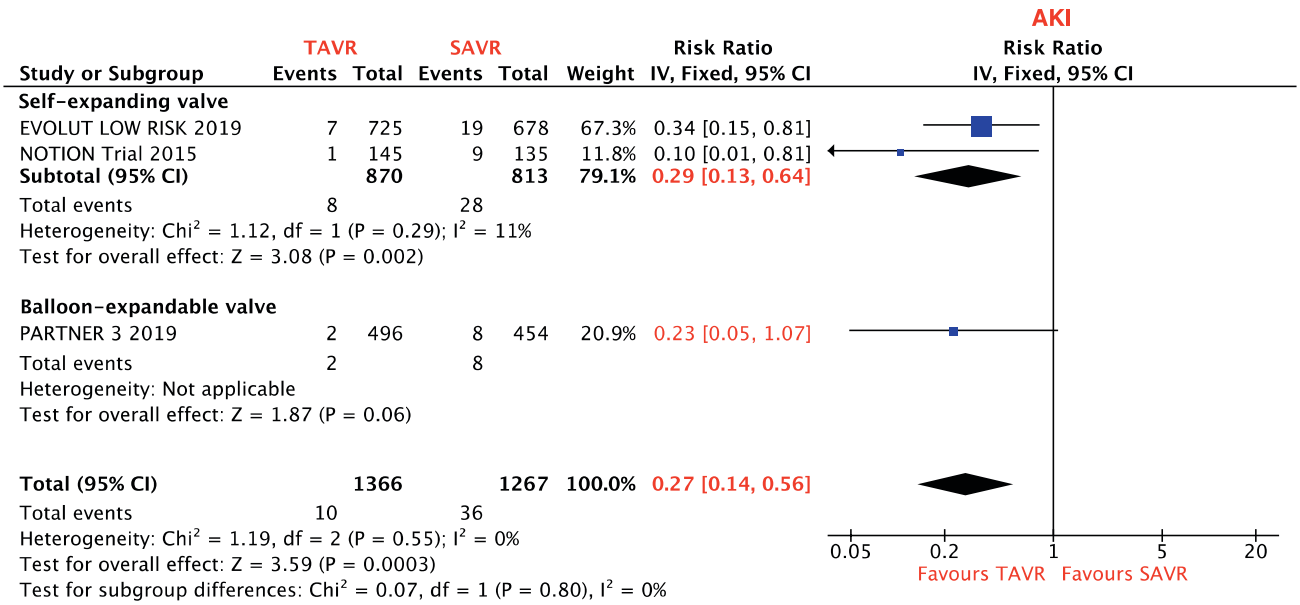


Fig. 6 Forest plots depicting the relative risk (RR) of acute kidney injury (AKI)

Myocardial infarction

There was no significant difference between both groups regarding rates of myocardial infarction (RR 0.78; 95% CI 0.46–1.34; $p = 0.37$; $I^2 = 0\%$; Fig. 2Sa in the supplementary file). During a mean follow-up period of 1 year, 1.7% of patients (25/1497) experienced a myocardial infarction in the TAVR group compared to 2.1% in the SAVR group (29/1390).

Coronary obstruction

Coronary obstruction, which was reported in three studies [10, 11, 13], did also not show a significant difference between TAVR compared to SAVR (RR 1.01; 95% CI 0.15–6.65; $p = 0.99$; $I^2 = 53\%$; Fig. 2Sb in the supplementary file). In the TAVR group, 0.7% of patients (8/1221) experienced coronary obstruction compared to 0.5% in the SAVR group (6/1132) over a mean follow-up of 1 year.

Endocarditis

There was no significant difference between both groups regarding endocarditis (RR 0.73; 95% CI 0.24–2.20; $p = 0.58$; $I^2 = 0\%$). In the TAVR group, 0.4% of patients (6/1497) suffered from endocarditis compared to 0.6% in the SAVR group (8/1390) over a mean follow-up of 1 year (Figure S3 in the supplementary file).

Sensitivity analyses

Reporting bias/small study effects

Visual inspection of funnel plots indicated a minor asymmetry. Therefore, reporting bias and small study effects cannot be excluded (funnel plots not shown).

Random versus fixed-effect estimates

A comparison of the results revealed by a random and fixed-effect model showed no significant differences (Table 3).

Excluding single studies

By sequentially excluding one single study from the analysis it was shown that the direction of the effect and the magnitude of the effect remained unchanged.

Balloon vs self-expandable valves

Sensitivity analysis assessing the valve type showed that the direction of the effect for the majority of outcomes remained unchanged. For the PM implantation, the significance level and the effect size differed between the valve types: while the balloon-expandable valve did not result in a statistically significant increase of newly implanted PM (RR 1.37; 95% CI 0.83–2.26; $p = 0.21$; Fig. 6a), self-expanding valves did result in a statistically significant increase. TAVR with a self-expanding valve was associated with a 6.65-fold RRI of

Table 3 Random-effect and fixed-effect models calculated for primary and secondary endpoints

Event	Random-effect model				Fixed-effect model			
	RR	95% CI	*p*	I^2 (%)	RR	95% CI	*p*	I^2 (%)
MACE	0.86	0.47–0.79	< 0.0002	1	0.86	0.47–0.79	0.0002	1
Ischemic stroke	0.68	0.43–1.07	0.10	17	0.72	0.49–1.06	0.10	17
Overall death	0.61	0.39–0.96	0.03	0	0.61	0.39–0.96	0.03	0
Cardiovascular death	0.55;	0.33–0.90	0.02	0	0.55	0.33–0.90	0.02	0
Life threatening/disabling bleeding	0.31	0.21–0.48	< 0.00001	24	0.31	0.22–0.44	< 0.00001	24
Major vascular complication	1.41	0.77–2.55	0.26	22	1.31	0.83–2.06	0.26	22
Pacemaker implantation	4.72	1.83–12.15	0.001	88	3.65	2.73–4.88	< 0.00001	88
Atrial fibrillation	0.72	0.20–0.35	< 0.00001	62	0.26	0.22–0.31	< 0.00001	62
Acute kidney injury II/III	0.27	0.14–0.56	0.003	0	0.27	0.14–0.56	0.003	0
Myocardial infarction	0.78	0.46–1.34	0.37	0	0.78	0.46–1.34	0.37	0
Coronary obstruction	1.01	0.15–6.65	0.99	53	1.01	0.15–6.65	0.99	53
Endocarditis	0.73	0.24–2.20	0.58	0	0.73	0.24–2.20	0.58	0

new pacemaker implantation (RR 6.65; 95% CI 3.84–11.51; $p < 0.00001$; $I^2 = 37\%$; Fig. 6a).

When assessing the risk reduction of life threatening/disabling bleeding and new-onset atrial fibrillation with TAVR vs SAVR, the magnitude of the effect tended to be greater with the balloon-expandable valve as compared to the self-expanding valves (RR 0.22 vs. 0.38; RR 0.18 vs. 0.29; respectively).

Discussion

The current meta-analysis in almost three thousand patients undergoing TAVR is to our knowledge one of the largest one to investigate the safety and efficacy of TAVR compared to SAVR in low-risk patients. The main finding of this meta-analysis and systematic review is that TAVR was superior to SAVR for the majority of outcomes in low-risk patients. We could reveal that TAVR was associated with significantly lower risks of MACE (RRR of 39%; ARR of 3.7%); overall mortality (RRR of 39%; ARR of 1.4%) and cardiovascular mortality (RRR of 45%; ARR of 1.3%), life threatening or disabling bleeding (RRR of 69%; ARR of 7.0%), new-onset atrial fibrillation (RRR of 73%; ARR of 29%) and acute kidney injury (RRR of 73%; ARR of 2.1%) as compared with SAVR. As expected, TAVR was associated with a 4.7-fold higher risk of new PM implantation as compared with SAVR.

Another recently published meta-analysis by Siontis et al. also showed that TAVI was superior to SAVR for the majority of outcomes. However, in contrast to Siontis et al. our study deals with outcomes at 1 year and focuses exclusively on low-risk patients [16].

Until now, TAVR was not used in younger patients with severe aortic stenosis (AS) at low surgical risk. Previous data that supported the use of TAVR in low-risk patients are limited due to their mostly retrospective character [17–20]. Therefore, surgical intervention for those deemed low surgical-risk is still recommended. However, due to an increasing experience and technical advancement, the expansion of TAVR to younger and healthier patients was a next logical step [9]. To consider extending TAVR to younger patients, excellent safety and effectiveness data form the basis for the guideline recommendations.

In our meta-analysis, the majority of included patients were at median younger than 75 years of age [10, 11, 13, 14]. If TAVR would be extended to younger AS patients, the treatment of bicuspid aortic valves would be an increasing part of clinical practice, especially in those patients under 75 years. However, until now large randomized trials excluded patients with AS and bicuspid valves. Therefore, long-term data of this specific cohort are until now still limited but will become essential, because the majority of AS patients at a younger age suffer from a bicuspid aortic valve (30–50%) [21].

Another important concern regarding the extension of TAVR indication to younger patients with longer life-expectancy is the issue of TAVR durability. It has been postulated that TAVR devices, similar to biological surgical valves might have a limited durability. In 2016, there were some concerns that TAVR has a poor long-term durability, which would limit its usefulness in younger patients [22]. However, these concerns were based on data with older valve generations and criteria for valve dysfunction were only defined by echocardiography [22]. On the contrary, 5 year follow-up data of several studies including the NOTION trial, showed stable valve durability with low rates of hemodynamic valve dysfunction and/or re-intervention after TAVR procedures in several studies [1, 23–25]. However, the most appropriate procedure type and valve type for re-do procedure after

TAVR are still a matter of debate. The only large randomized study currently comparing TAVR with SAVR in younger patients (≤ 75 years of age at low surgical risk, not excluding bicuspid valves) is the NOTION 2 trial (ClinTrials.Gov: NCT02825134). This randomized trial should provide the required clinical evidence for the applicability of TAVR in young AS patients at low surgical risk.

We included four trials into our meta-analysis, which share some common characteristics, but also have some differences. The NOTION, the SURTAVI low-risk population and the EVOLUT LOW RISK trials used the Medtronic self-expanding prostheses whereas the PARTNER 3 trial tested the balloon-expandable Edwards Sapien 3 valve. Importantly, and in contrast to other low-risk trials, the NOTION trial included low-risk patients, who were oldest across the four studies included in our meta-analysis (median 79) compared to other three trials (median age in the PARTNER 3 trial: 73, the EVOLUT LOW RISK trial: 74, the SURTAVI low risk population: 75) [11, 14].

An important issue associated with the use of invasive procedures is the length of hospital stay, as this has major financial consequences. Patients treated with SAVR had a longer post procedural hospital stay, [11, 13, 14] as compared with TAVR, which is due to the more invasive nature of SAVR [2, 6].

In our meta-analysis, we found an increased risk of permanent pacemaker implantation (PPI) in the TAVR group compared to the SAVR group (17.4% vs. 4.1%), but the increase was only statistically significant with self-expanding supraannular bioprostheses. The NNH was high resulting in 1 of 8 patients receiving a PPI if treated with TAVR. Recently, there has been accumulating evidence on the prognostic implications of PPI. Patients with PPI are at increased risk of rehospitalization due to heart failure and higher rates of the combined endpoint of mortality or rehospitalization for heart failure [26]. Furthermore, PPI was associated with lesser improvement in left ventricular ejection fraction (LVEF) over time, particularly in patients with reduced LVEF before TAVR [26]. Although, valve interface may recover over time and lead to lower rates of PPI, further data on long-term outcomes of TAVR are needed [10, 11, 27]. Nevertheless, despite higher risk of PPI, the majority of patients would have chosen TAVR due to the risk reduction of other events.

It is a crucial point to note that TAVR was associated with a remarkable reduction of the incidence of newly-onset AF (absolute reduction of 29%) in our-meta-analysis, translating to a NNT of 3. This estimate indicates that treating patients with TAVR instead of SAVR, would prevent new-onset AF in one patient of three during a time frame of 1 year after the procedure. This is probably the most relevant finding in our meta-analysis as AF implicates an indication for oral anticoagulation in this patient population, which in turn increases bleeding risks [28]. Furthermore, AF is an independent predictor of morbidity and mortality, and a leading cause of heart failure [29–33]. As AF is likely to dominate the next era in cardiovascular disease epidemiology, in terms of prevalence, incidence, morbidity and mortality [34–36], reduction of AF incidence after TAVR might have a large impact on healthcare expenditure.

Importantly, our meta-analysis indicates that TAVR despite the use of contrast media is associated with a lower risk of AKI as compared with SAVR, translating to a NNT of 48. This finding is of great relevance, as AKI itself is an independent predictor of higher mortality. Mortality at 30 days post-TAVR varied between 10–30% in patients with AKI, compared to 2–15% in those patients without AKI [37–40]. Even 1 year post-TAVR, mortality rates were significantly higher in patients with AKI than without AKI (10–70% vs. 3–40%) [37–40]. Furthermore, AKI showed to be a predictor of sepsis, which itself is also independently associated with increased mortality and length of stay [37–40].

Finally, it is noteworthy to critically analyze the impact of the procedure type on postprocedural life-threatening bleeding events. TAVR was associated with a 7% ARR of life-threatening bleeding events as compared to SAVR in our meta-analysis. Taking into consideration that puncture-side bleeding complications occur frequently in TAVR procedures, one would expect a lower difference in the bleeding risks between TAVR vs SAVR. Nevertheless, our data clearly indicate that TAVR is safer than SAVR: major bleeding could be prevented in one patient of 14 if TAVR will be performed. The increased number of major bleeding, which was associated with SAVR translates to worse clinical prognosis. These patients might require re-operation for bleeding or blood transfusions, which are independent predictors of mortality [15]. As blood transfusions prolonged hospital—and intensive care unit stay [15], the risk reduction of bleeding events after TAVR might directly correspond to the improvement of the quality of life and an improved survival. This has been also shown in our meta-analysis, indicating that SAVR is associated with an increased risk of overall and cardiovascular death. In 1000 patients treated with TAVR instead of SAVR, 14 additional deaths could be prevented within 1 year of intervention as compared to SAVR. These results give rise to the extension of TAVR to patients with low operative risk.

Limitations

The main limitation of our meta-analysis is that the definition of the primary endpoint (MACE) slightly differed between studies. Moreover, the included studies comprised only two valve types: self-expanding Medtronic Corevalve and Evolut series and Edwards S3. Randomized data

regarding patients' outcomes using other valve types as Portico and Acurate Neo are lacking.

Conclusion

Our meta-analyses in low-risk patients with severe aortic stenosis indicate that TAVR is superior to SAVR regarding MACE, all-cause- and cardiovascular death, life-threatening/disabling bleeding and new-onset atrial fibrillation. In contrast, TAVR showed an increased risk of permanent pacemaker implantation due to higher rates of conduction abnormalities. As the majority of low-risk patients are younger than 75 years of age, the issue of valve durability and the valve type choice for the future valve-in-valve procedures must be clarified in future studies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

1. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, Hermiller J Jr, Hughes GC, Harrison JK, Coselli J, Diez J, Kafi A, Schreiber T, Gleason TG, Conte J, Buchbinder M, Deeb GM, Carabello B, Serruys PW, Chenoweth S, Oh JK (2014) Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol 63(19):1972–1981. https://doi.org/10.1016/j.jacc.2014.02.556
2. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J Jr, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK (2014) Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Medi 370(19):1790–1798. https://doi.org/10.1056/NEJMoa1400590
3. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PW, Kappetein AP, Investigators S (2017) Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med 376(14):1321–1331. https://doi.org/10.1056/NEJMoa1700456
4. Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, Kleiman NS, Chetcuti S, Hermiller JB Jr, Heiser J, Merhi W, Zorn GL 3rd, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte JV, Mumtaz M, Oh JK, Huang J, Adams DH (2018) 5-Year outcomes of self-expanding transcatheter versus surgical aortic valve replacement in high-risk patients. J Am Coll Cardiol 72(22):2687–2696. https://doi.org/10.1016/j.jacc.2018.08.2146
5. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S (2010) Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 363(17):1597–1607. https://doi.org/10.1056/NEJMoa1008232
6. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ (2011) Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 364(23):2187–2198. https://doi.org/10.1056/NEJMoa1103510
7. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG (2016) Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 374(17):1609–1620. https://doi.org/10.1056/NEJMoa1514616
8. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A (2017) 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 70(2):252–289. https://doi.org/10.1016/j.jacc.2017.03.011
9. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Munoz D, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL (2017) 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 38(36):2739–2791. https://doi.org/10.1093/eurheartj/ehx391
10. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR (2019) Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 380(18):1695–1705. https://doi.org/10.1056/NEJMoa1814052
11. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, Askew J, Sorajja P, Rovin J, Chetcuti SJ, Adams DH, Teirstein PS, Zorn GL 3rd, Forrest JK, Tchetche D, Resar J, Walton A, Piazza N, Ramlawi B, Robinson N, Petrossian G, Gleason TG, Oh JK, Boulware MJ, Qiao H, Mugglin AS, Reardon MJ (2019) Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med 380(18):1706–1715. https://doi.org/10.1056/NEJMoa1816885
12. Waksman R, Rogers T, Torguson R, Gordon P, Ehsan A, Wilson SR, Goncalves J, Levitt R, Hahn C, Parikh P, Bilfinger T, Butzel D, Buchanan S, Hanna N, Garrett R, Asch F, Weissman G, Ben-Dor I, Shults C, Bastian R, Craig PE, Garcia-Garcia HM, Kolm P, Zou Q, Satler LF, Corso PJ (2018) Transcatheter aortic valve replacement in low-risk patients with symptomatic severe aortic stenosis. J Am Coll Cardiol 72(18):2095–2105. https://doi.org/10.1016/j.jacc.2018.08.1033
13. Serruys PW, Modolo R, Reardon M, Miyazaki Y, Windecker S, Popma J, Chang Y, Kleiman NS, Lilly S, Amrane H, Boonstra PW, Kappetein AP, Onuma Y, Sondergaard L, van Mieghem N (2018) One-year outcomes of patients with severe aortic stenosis and an STS PROM of less than three percent in the SURTAVI trial. Eurointerv J EuroPCR Collab Work Group Interv

Cardiol Eur Soc Cardiol 14(8):877–883. https://doi.org/10.4244/eij-d-18-00460
14. Thyregod HG, Steinbruchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engstrom T, Clemmensen P, Hansen PB, Andersen LW, Olsen PS, Sondergaard L (2015) Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. J Am Coll Cardiol 65(20):2184–2194. https://doi.org/10.1016/j.jacc.2015.03.014
15. Nielsen HH, Klaaborg KE, Nissen H, Terp K, Mortensen PE, Kjeldsen BJ, Jakobsen CJ, Andersen HR, Egeblad H, Krusell LR, Thuesen L, Hjortdal VE (2012) A prospective, randomised trial of transapical transcatheter aortic valve implantation vs. surgical aortic valve replacement in operable elderly patients with aortic stenosis: the STACCATO trial. Eurointerv J EuroPCR Collab Work Group Interv Cardiol Eur Soc Cardiol 8(3):383–389. https://doi.org/10.4244/eijv8i3a58
16. Siontis GCM, Overtchouk P, Cahill TJ, Modine T, Prendergast B, Praz F, Pilgrim T, Petrinic T, Nikolakopoulou A, Salanti G, Søndergaard L, Verma S, Jüni P, Windecker S (2019) Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. Eur Heart J 40(38):3143–3153. https://doi.org/10.1093/eurheartj/ehz275
17. Rosato S, Santini F, Barbanti M, Biancari F, D'Errigo P, Onorati F, Tamburino C, Ranucci M, Covello RD, Santoro G, Grossi C, Ventura M, Fusco D, Seccareccia F (2016) Transcatheter aortic valve implantation compared with surgical aortic valve replacement in low-risk patients. Circ Cardiovasc Interv 9(5):e003326. https://doi.org/10.1161/circinterventions.115.003326
18. Schymik G, Heimeshoff M, Bramlage P, Herbinger T, Wurth A, Pilz L, Schymik JS, Wondraschek R, Suselbeck T, Gerhardus J, Luik A, Gonska BD, Tzamalis P, Posival H, Schmitt C, Schrofel H (2015) A comparison of transcatheter aortic valve implantation and surgical aortic valve replacement in 1141 patients with severe symptomatic aortic stenosis and less than high risk. Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv 86(4):738–744. https://doi.org/10.1002/ccd.25866
19. Bekeredjian R, Szabo G, Balaban U, Bleiziffer S, Bauer T, Ensminger S, Frerker C, Herrmann E, Beyersdorf F, Hamm C, Beckmann A, Mollmann H, Karck M, Katus HA, Walther T (2019) Patients at low surgical risk as defined by the Society of Thoracic Surgeons Score undergoing isolated interventional or surgical aortic valve implantation: in-hospital data and 1-year results from the German Aortic Valve Registry (GARY). Eur Heart J 40(17):1323–1330. https://doi.org/10.1093/eurheartj/ehy699
20. Finkelstein A, Rozenbaum Z, Halkin A, Banai S, Bazan S, Barbash I, Segev A, Fefer P, Maor E, Danenberg H, Planner D, Orvin K, Assa HV, Assali A, Kornowski R, Steinvil A (2019) Outcomes of transcatheter aortic valve implantation in patients with low versus intermediate to high surgical risk. Am J Cardiol 123(4):644–649. https://doi.org/10.1016/j.amjcard.2018.11.010
21. Roberts WC, Ko JM (2005) Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. Circulation 111(7):920–925. https://doi.org/10.1161/01.cir.0000155623.48408.c5
22. Dvir D (2016) First look at long-term durability of transcatheter heart valves: assessment of valve function up to 10-years after implantation. In: Paper presented at the EuroPCR, Paris
23. Kapadia SR, Leon MB, Makkar RR, Tuzcu EM, Svensson LG, Kodali S, Webb JG, Mack MJ, Douglas PS, Thourani VH, Babaliaros VC, Herrmann HC, Szeto WY, Pichard AD, Williams MR, Fontana GP, Miller DC, Anderson WN, Akin JJ, Davidson MJ, Smith CR (2015) 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet (London, England) 385(9986):2485–2491. https://doi.org/10.1016/s0140-6736(15)60290-2
24. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ, Svensson LG (2015) 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet (London, England) 385(9986):2477–2484. https://doi.org/10.1016/s0140-6736(15)60308-7
25. Gerckens U, Tamburino C, Bleiziffer S, Bosmans J, Wenaweser P, Brecker S, Guo J, Linke A (2017) Final 5-year clinical and echocardiographic results for treatment of severe aortic stenosis with a self-expanding bioprosthesis from the ADVANCE Study. Eur Heart J 38(36):2729–2738. https://doi.org/10.1093/eurheartj/ehx295
26. Chamandi C, Barbanti M, Munoz-Garcia A, Latib A, Nombela-Franco L, Gutierrez-Ibanez E, Veiga-Fernandez G, Cheema AN, Cruz-Gonzalez I, Serra V, Tamburino C, Mangieri A, Colombo A, Jimenez-Quevedo P, Elizaga J, Laughlin G, Lee DH, Garcia Del Blanco B, Rodriguez-Gabella T, Marsal JR, Cote M, Philippon F, Rodes-Cabau J (2018) Long-term outcomes in patients with new permanent pacemaker implantation following transcatheter aortic valve replacement. JACC Cardiovasc Interv 11(3):301–310. https://doi.org/10.1016/j.jcin.2017.10.032
27. Sondergaard L, Steinbruchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Ngo AT, Olsen NT, Chang Y, Franzen OW, Engstrom T, Clemmensen P, Olsen PS, Thyregod HG (2016) Two-Year outcomes in patients with severe aortic valve stenosis randomized to transcatheter versus surgical aortic valve replacement: the all-comers nordic aortic valve intervention randomized clinical trial. Circ Cardiovasc Interv. https://doi.org/10.1161/circinterventions.115.003665
28. Siller-Matula JM, Pecen L, Patti G, Lucerna M, Kirchhof P, Lesiak M, Huber K, Verheugt FWA, Lang IM, Renda G, Schnabel RB, Wachter R, Kotecha D, Sellal JM, Rohla M, Ricci F, De Caterina R (2018) Heart failure subtypes and thromboembolic risk in patients with atrial fibrillation: the PREFER in AF-HF substudy. Int J Cardiol 265:141–147. https://doi.org/10.1016/j.ijcard.2018.04.093
29. Anter E, Jessup M, Callans DJ (2009) Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. Circulation 119(18):2516–2525. https://doi.org/10.1161/CIRCULATIONAHA.108.821306
30. Cuadrado-Godia E, Ois A, Roquer J (2010) Heart failure in acute ischemic stroke. Curr Cardiol Rev 6(3):202–213. https://doi.org/10.2174/157340310791658776
31. Maisel WH, Stevenson LW (2003) Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 91(6A):2D–8D
32. Zakeri R, Chamberlain AM, Roger VL, Redfield MM (2013) Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study. Circulation 128(10):1085–1093. https://doi.org/10.1161/CIRCULATIONAHA.113.001475
33. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L (2009) A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. Eur J Heart Fail 11(7):676–683. https://doi.org/10.1093/eurjhf/hfp085
34. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X (2013) Estimates of current and future incidence and prevalence of atrial fibrillation in the US adult population. Am J Cardiol 112(8):1142–1147. https://doi.org/10.1016/j.amjcard.2013.05.063

35. Kotecha D, Piccini JP (2015) Atrial fibrillation in heart failure: what should we do? Eur Heart J 36(46):3250–3257. https://doi.org/10.1093/eurheartj/ehv513
36. Guha K, McDonagh T (2013) Heart failure epidemiology: European perspective. Curr Cardiol Rev 9(2):123–127
37. Thongprayoon C, Cheungpasitporn W, Srivali N, Kittanamongkolchai W, Greason KL, Kashani KB (2016) Incidence and risk factors of acute kidney injury following transcatheter aortic valve replacement. Nephrology (Carlton, Vic) 21(12):1041–1046. https://doi.org/10.1111/nep.12704
38. Thongprayoon C, Cheungpasitporn W, Srivali N, Harrison AM, Gunderson TM, Kittanamongkolchai W, Greason KL, Kashani KB (2016) AKI after transcatheter or surgical aortic valve replacement. J Am Soc Nephrol JASN 27(6):1854–1860. https://doi.org/10.1681/asn.2015050577
39. Barbanti M, Gulino S, Capranzano P, Imme S, Sgroi C, Tamburino C, Ohno Y, Attizzani GF, Patane M, Sicuso R, Pilato G, Di Landro A, Todaro D, Di Simone E, Picci A, Giannetto G, Costa G, Deste W, Giannazzo D, Grasso C, Capodanno D, Tamburino C (2015) Acute kidney injury with the renalguard system in patients undergoing transcatheter aortic valve replacement: the PROTECT-TAVI trial (PROphylactic effecT of furosEmide-induCed diuresis with matched isotonic intravenous hydraTion in Transcatheter aortic valve implantation). JACC Cardiovasc Interv 8(12):1595–1604. https://doi.org/10.1016/j.jcin.2015.07.012
40. Barbash IM, Ben-Dor I, Dvir D, Maluenda G, Xue Z, Torguson R, Satler LF, Pichard AD, Waksman R (2012) Incidence and predictors of acute kidney injury after transcatheter aortic valve replacement. Am Heart J 163(6):1031–1036. https://doi.org/10.1016/j.ahj.2012.01.009
41. Silva Junior JM, Rezende E, Amendola CP, Tomita R, Torres D, Ferrari MT, Toledo DO, Oliveira AM, Marques JA (2012) Red blood cell transfusions worsen the outcomes even in critically ill patients undergoing a restrictive transfusion strategy. Sao Paulo Med J (Revista paulista de medicina) 130(2):77–83

Affiliations

Felix Hofer[1] · Christian Hengstenberg[1] · Georg Goliasch[1] · Marek Grygier[2] · Julia Mascherbauer[1] · Jolanta M. Siller-Matula[1,3]

✉ Jolanta M. Siller-Matula
Jolanta.siller-matula@meduniwien.ac.at

[1] Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria

[2] 1st Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland

[3] Department of Experimental and Clinical Pharmacology, Centre for Preclinical Research and Technology (CEPT), Medical University of Warsaw, Warsaw, Poland