2017 AHA/ACC Valvular Heart Disease Focused Update Data Supplement

Table of Contents

Data Supplement 1. Nonrandomized Trials, Observational Studies, and/or Registries of IE (Section 2.4) 2
Data Supplement 2. RCTs for IE (Section 2.4) 3
Data Supplement 3. RCTs Comparing Anticoagulation for AF in Patients With VHD (Section 2.4.3) 4
Data Supplement 4. Nonrandomized Trials, Observational Studies, and/or Registries of Anticoagulation for AF in Patients With VHD (Section 2.4.3) 6
Data Supplement 9. *(Updated From 2014 Guideline)* Choice of Intervention in Symptomatic Adults With Severe AS (Stage D): RCTs of Surgical Versus TAVR or Medical Therapy (Section 3.2.4) 7
Data Supplement 5. Nonrandomized Trials, Observational Studies, and/or Registries of TAVR (Section 3.2.4) 9
Data Supplement 17. *(Updated From 2014 Guideline)* Primary MR—Evidence for Intervention (Section 7.3.3) 9
Data Supplement 18. *(Updated From 2014 Guideline)* Secondary MR—Evidence for Intervention (7.4.3) 12
Data Supplement 20. *(Updated From 2014 Guideline)* Clinical Outcomes With Bioprosthetic and Mechanical Valves (Section 11.1.2) 14
Data Supplement 6. Antithrombotic Therapy for Prosthetic Valves (Section 11.2.2) 22
Data Supplement 21. *(Updated From 2014 Guideline)* Bridging Anticoagulation Therapy for Mechanical Heart Valves (Section 11.3.2) 26
Data Supplement 7. Prosthetic Valve Thrombosis (Section 11.6) 28
Data Supplement 7A. Prosthetic Valve Thrombosis (Section 11.6) 35
Data Supplement 8. Selective Studies of VKA in Patients with Bioprosthetic Valve Thrombosis (Section 11.7.3) 36
Data Supplement 9. Clinical Outcomes With VIV Procedures (Sections 11.7.3 and 11.8.3) 38
Data Supplement 23. *(Updated From 2014 Guideline)* Selective Studies on Surgical and Catheter-based Closure for Paravalvular Regurgitation (Section 11.8.3) 44
Data Supplement 24. *(Updated From 2014 Guideline)* Surgical Outcome in IE (Section 12.2.3) 47
References 54

Abbreviation List:

1° indicates primary; 2°, secondary; ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; AKI, acute kidney injury; AMI, acute myocardial infarction; AP, antibiotic prophylaxis; AS, aortic stenosis; ASA, acetylsalicylic acid; AR, aortic regurgitation; AV, aortic valve; AVA, aortic valve area; AVR, aortic valve replacement; BHV, bioprosthetic heart valve; BPVT, bioprosthetic valve thrombosis; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CT, computed tomography; CTA, computed tomography angiography; CV, cardiovascular; DAPT, dual antiplatelet therapy; dx, diagnosis; EF, ejection fraction; ERO, effective regurgitant orifice; heart failure; HR, hazard ratio; HF, FDA, U.S. Food and Drug Administration; HTN, hypertension; Hx, history; IE, infective endocarditis; INR, international normalized ratio; IV, intravenous; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MAPE, major adverse prosthesis-related events; MCV, Medtronic CoreValve; MDCT, multidetector computed tomography; MHV, mechanical heart valve; MI, myocardial infarction; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; MVR, mitral valve repair; N/A, not available; NICE, National Institute for Health and Care Excellence; NVE, native valve endocarditis; NYHA, New York Heart Association; NS, nonsignificant; NSAID, nonsteroidal anti-inflammatory drug; NOAC, novel anticoagulant; OR, odds ratio; ΔP, mean transaortic pressure gradient; PAP, pulmonary artery pressure; pt, patient; PVL, paravalvular leak; PVR, paravalvular regurgitation; PVT, pulmonary valve thrombosis; RCT, randomized controlled trial; RR, relative risk; Rx, prescription; QoL, quality of life; SAVR, surgical aortic valve replacement; SMR, secondary mitral regurgitation; SPAF, Stroke Prevention in Atrial Fibrillation; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; TEE, transesophageal echocardiography; THV, transcatheter heart valve; TIA, transient ischemic attack; TTE, transthoracic echocardiography; VARC, Valvular Academic Research Consortium; VIV: valve-in-valve; VHD, valvular heart disease; VKA, vitamin K antagonist Vmax; and aortic valve maximum velocity.

Data Supplement 1. Nonrandomized Trials, Observational Studies, and/or Registries of IE (Section 2.4)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (p values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Mackie AS, et al., 2016 (1) 26868840	Study type: Retrospective Size: n=9,431 pts with IE hospitalizations	Inclusion criteria: IE Hospitalizations Exclusion criteria: N/A	1° endpoint: Incidence of IE of hospitalizations per 10 million Results: There was no difference in the rates of hospitalization for IE before and after publication of the revised recommendations	• This retrospective study examined the incidence of IE hospitalizations before and after the 2007 AHA prophylaxis guidelines publication • The rate of IE hospitalizations increased before/after implementation • 2007 AHA recommendations had no impact on incidence rates of hospitalization for IE
Dayer MJ, et al., 2015 (2) 25467569	Study type: Retrospective secular trend study: relationship AP vs. none on IE incidence Size: Cases reported per 10 million people per mo	Inclusion criteria: Single dose IE prophylaxis all pts w/IE dx Exclusion criteria: N/A	1° endpoint: IE dx at discharge/death and number of Rxs of IE prophylaxis Results: • Decrease IE Prophylaxis; • Increase IE incidence	• AP has fallen and incidence of IE has increased since 2008 NICE guidelines
Glenny AM, et al., 2013 (3) 24108511	Study type: Meta-analysis Size: Only 1 study met criteria for inclusion	Inclusion criteria: RCT, cohort, case control Exclusion criteria: Guidelines, editorial discussion	1° endpoint: Development of IE, mortality Results: Only 1 study met criteria	• There remains no evidence to determine whether AP is effective or ineffective
Sherman-Weber S, et al., 2004 (4) 15762934	Study type: Retrospective literature review Size: n=659 pts	Inclusion criteria: Single-center heart transplant hospitalization with IE Exclusion criteria: N/A	1° endpoint: N/A Results: Between 1993-Feb. 2004, 10 pts had endocarditis	• Endocarditis is substantially more common in heart transplant recipients than in general populations. Central venous catheter access and multiple endomyocardial biopsies appear to predispose to infection
Gillinov AM, et al., 2002 (5) 12078774	Study type: Retrospective review Size: n=22 pts	Inclusion criteria: 22 pts with endocarditis of a previously repaired MV Exclusion criteria: N/A	1° endpoint: N/A Results: 15 had repeat MV operations; 7 were treated with antibiotics	N/A
Karavas AN, et al., 2002 (6) 12358402	Study type: Retrospective review of MV repairs Size: n=1,275 pts	Inclusion criteria: MV repairs at a single institution Exclusion criteria: N/A	1° endpoint: Endocarditis (non-recurrent) of previously repaired MV Results: 9 of 1,275 pts developed endocarditis after MV repair: all required excision of the annuloplasty ring	N/A
Duval X, et al.,	Study type: Survey	Inclusion criteria: Pts 25–85 y of age; French	1° endpoint:	• A large no. of pts would need prophylaxis to

2006 (7) 16705565	Size: n=2,805 pts	adults with predisposing cardiac conditions, antibiotics prophylaxis eligible Exclusion criteria: N/A	N/A Results: • The results were extrapolated to general French population. • Risk of developing IE in unprotected procedure: • 1 in 10,700 for prosthetic valve predisposing cardiac conditions and 1 in 54,300 for native valve predisposing cardiac conditions • Risk of developing IE in protected procedures: • 1 in 150,000	avoid 1 case of IE • The results cannot be generalized to general population
Strom BL, et al., 1998 (8) 9841581	Study type: Observational case control Size: n=273 cases (238 native valve infections, 35 prosthetic valve infections)	Inclusion criteria: Subjects with community acquired IE discharged within 3 mo and matched community residents Exclusion criteria: IE due to IV drug abuse, <18 y of age, hospital acquired IE	1° endpoint: N/A Results: • Dental treatment not more common in cases compared to controls (adjusted OR: 0.8, 95% CI: 0.4–1-5) • Cases with Hx of MV prolapse OR: 19.4; congenital heart disease OR: 6.7, valvular surgery OR: 74.6, rheumatic fever OR: 13.4; heart murmur OR: 4.2 • Prophylaxis dental therapy was significantly low (p=0.03) in cases with cardiac lesions as compared to controls.	• Cardiac valvular abnormalities associated with IE more than the dental treatment

Data Supplement 2. RCTs for IE (Section 2.4)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, p values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Mouget FK, et al., 2015 (9) 25758845	Aim: To assess the impact of AP on bacteremia Study type: Double-blind, randomized, placebo-controlled Size: n=290 pts	Inclusion criteria: 2008 cohort urgent care presentation for tooth extraction. Exclusion criteria: <10 teeth antibiotic use within 2 wk. Need for AP based on practice guidelines active viral disease. Immunocompromised, poorly-controlled systemic disease penicillin allergy, fever, cellulitis, chewing/tooth brushing within 1 h.	Intervention: • Tooth brushing (n=98 pts) • Single tooth extraction with AP (n=96 pts) Comparator: Single tooth extraction with placebo	1° endpoint: Bacteremia 32% brushing 33% amoxicillin 60% placebo	• Given frequency of IE causing bacteremia during a tooth brushing; recommend RCT to determine efficacy of prophylaxis for dental procedure; recommend good dental hygiene.
Lockhart PB, et al., 2008 (10) 1851739	Aim: To compare the incidence, duration, type and extent of endocarditis related bacteremia and to determine	Inclusion criteria: Subjects in need for tooth extraction Exclusion criteria:	Intervention: • Tooth brushing group (98) • Extraction with amoxiillin group (96)	1° endpoint: • 32/98 bacterial species identified cause IE. • Cumulative incidence from 6 blood draws	• The results cannot be generalized to general public • Tooth brushing and single tooth-extractions seem to be similar in terms of

	the impact of AP on single tooth extraction. Study type: RCT Size: n=290 pts	Use of systematic antibiotics within previous 2 wk; on AP; active viral disease; immunocompromised; systemic disease with bad prognosis; Hx of penicillin allergy; 100.5°F temp; facial cellulitis; and handling of the gingival tissues within 1 h before the study.	• Extraction with Placebo group (96)	{tooth brushing: 23%, extraction-amoxicillin: 33% and extraction-placebo: 60%; p<0.0001} • Amoxicillin resulted in decrease of positive cultures (p<0.05) 1° Safety endpoint (if relevant): N/A	at risk individuals for IE

Data Supplement 3. RCTs Comparing Anticoagulation for AF in Patients With VHD (Section 2.4.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, p values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
ARISTOTLE Avezum A, et al., 2015 (11) 26106009	Aim: Apixaban vs. warfarin in pts with VHD Study type: Sub-analysis of prospective, multicenter, randomized Size: n=4,808 pts (26.4%) had a Hx of VHD (all types of VHD, except severe MS)	Inclusion criteria: ● Pts with VHD, including AS, AR, mild MS, MR, tricuspid stenosis, tricuspid regurgitation, valve repair, or bioprosthetic valve replacement Exclusion criteria: ● Clinically significant MS ● Indications for oral anticoagulation other than AF ● Planned use of concomitant high-dose ASA (>165 mg/d) or DAPT	Intervention: Apixaban Comparator: Warfarin	1° endpoint: Stroke or systemic embolism Safety endpoint: Major bleeding as defined by the International Society on Thrombosis and Haemostasis	• VHD pts in this subgroup of Aristotle (n=4,808) were older, more prior MI and bleeding; and higher CHADS2 scores • Pts with VHD experienced similar benefit with anticoagulation • Apixaban was associated with less bleeding
ROCKET AF Breithardt G, et al., 2014 (12) 25148838	Aim: Assess outcomes of pts with VHD in ROCKET-AF Rivaroxaban vs. Warfarin Study type: Sub-analysis of prospective, multicenter, randomized Size: n=2,003 pts (14.1%) had VHD	Inclusion criteria: Nonvalvular AF (with no MS, no heart valve prosthesis, and no valvular disease requiring surgery) Exclusion criteria: ● Hemodynamically significant mitral valve stenosis. ● Prosthetic heart valve ● Annuloplasty with or without prosthetic ring ● Planned invasive procedure with potential for uncontrolled bleeding	Intervention: Rivaroxaban Comparator: Warfarin	1° endpoint: Composite of all stroke (both ischaemic and haemorrhagic) and systemic embolism Safety endpoint: Major or non-major bleeding or intracranial hemorrhage	• Risk of stroke is similar to pts without VHD • Efficacy of rivaroxaban vs. warfarin was similar in pts with and without significant valvular disease

NASPEAF Perez-Gomez F, et al., 2004 (13) 15489085	Aim: To evaluate the safety and efficacy of combining antiplatelet and moderate intensity anticoagulation therapy in pts with AF Study type: Multicenter RCT Size: n=1,209 pts, 13 hospitals	Inclusion criteria: Pts with chronic or documented paroxysmal AF Exclusion criteria: ● Low-risk pts according to SPAF III stratification ● Pts <60 y of age ● Mechanical valve prosthesis, ● Stroke in the previous 6 mo ● Serum creatinine over 3 mg/dl, ● Alcoholism or drug addiction, ● Severe uncontrolled HTN ● Diffuse arteriosclerosis, ● Indication for NSAIDs or indication/contraindication for antiplatelet or anticoagulant therapy	Intervention: The high-risk group pts either had anticoagulation (acenocoumarol) with a target INR of 2–3 or the combination therapy with a target INR of 1.4–2.4. Comparator: The intermediate-risk group had 3 arms; oral anticoagulation (acenocoumarol) to a target INR of 2–3; triflusal 600 mg daily, or a combination of both with a target INR of 1.25–2.	1° endpoint: ● Composite of vascular death, TIA, and nonfatal stroke or systemic embolism, (whichever event came first) ● 1° outcome was lower in the combined therapy than in the anticoagulant arm in both the intermediate (HR: 0.33; 95% CI: 0.12–0.91; p=0.02) and the high-risk group (HR: 0.51; 95% CI: 0.27–0.96; p=0.03). Safety endpoint: N/A	● The combination of antiplatelet and anticoagulation therapy significantly decreased vascular events compared to anticoagulation only and was safe in AF pts
RE-LY Sub-analysis Ezekowitz, et al 2016 (14) 27496855	Aim: Compare pts with and without any valve disease and to compare warfarin or dabigatran Study type: Post hoc analysis Size: n=3,950 pts with any VHD	Inclusion criteria: VHD and AF Exclusion criteria: Prosthetic heart valves, significant MS, and VHD requiring intervention	Intervention: Warfarin Comparator: Dabigatran	1° endpoint: The presence of VHD did not influence comparison of dabigatran at either dose with warfarin in terms of stroke or systemic embolism, major bleed, death, or intracranial hemorrhage.	● The baseline characteristics of pts with VHD reflected a higher CV risk than those of pts without VHD

Data Supplement 4. Nonrandomized Trials, Observational Studies, and/or Registries of Anticoagulation for AF in Patients With VHD (Section 2.4.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (p values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Noseworthy PA, et al., 2016 (15) 26896618	Study type: Retrospective analysis of administrative claims data to compare effectiveness and safety of NOACs with warfarin in pts with AF and VHD Size: n=20,158 NOAC-treated pts with VHD	Inclusion criteria: Pts with VHD and AF Exclusion criteria: /A	1° endpoint: N/A Results: N/A	• Combining rheumatic and nonrheumatic MS, NOACs trended toward lower risk of stroke (HR: 0.52 95% CI: 0.15–1.81, p=0.31) and major bleeding (HR: 0.77 95% CI: 0.41–1.43, p=0.40), • Pts with AS or AR or MR both stroke or systemic embolism and major bleeding were significantly lower in NOACs compared to warfarin
Olesen, et al., 2011 (16) 21282258	Study type: Nationwide cohort study Size: n=121,280 pts; 73,538 included in analysis	Inclusion criteria: Nonvalvular AF Exclusion criteria: No previous diagnoses of MV or AV disease, and no MV or AV surgery	1° endpoint: To evaluate the individual risk factors composing the CHADS2 score and the CHA2DS2-VASc score and to calculate the capability of the schemes to predict thromboembolism. Results: • In pts at low risk, 1.67 per 100 person y (95% CI:1.47–1.89) • In pts at intermediate risk, 4.75 per 100 person y (95% CI:4.45–5.07)	• CHA2DS2-VASc performed better than CHADS2 in predicting pts at high risk and low risk
Petty, et al., 2000 (17) 11062286	Study type: Cohort/epidemiological Size: n=729 pts	Inclusion criteria: Echocardiographic dx of MS (n=19), MR (n=528), AS (n=140), and AR (n=106) between 1985 and 1992 Exclusion criteria: N/A	1° endpoint: Rates and determinants of cerebrovascular events in pts with VHD pts. Results: Risk of CVA and death among pts with valve disease was significantly higher than significantly higher than the corresponding age- and sex-adjusted rates for the community	• Independent predictors of CVA were age, AF, and severe AS. • AS was associated with rates of CVA similar to those for MS and was an independent determinant of CVA events after adjustment for age and AF (RR:3.5)

Data Supplement 9. *(Updated From 2014 Guideline)* Choice of Intervention in Symptomatic Adults With Severe AS (Stage D): RCTs of Surgical Versus TAVR or Medical Therapy (Section 3.2.4)

Study	Aim of Study	Study Type	Study Groups (N)	Patient Population	Major Endpoints	Other Results
PARTNER COHORT A (high-surgical risk) Smith et al 2011 21639811 (18) Kodali, et al. 2012 22443479 (19) Mack, et al. 2015 25788234 (20)	To show that TAVR is not inferior to SAVR	RCT	TAVR 348 vs. SAVR 351 TAVR was transfemoral in 244 and transapical in 104	Severe symptomatic calcific AS defined as AVA <0.8 cm^2 plus a $\Delta P \geq 40$ mm Hg or $V_{max} \geq 4.0$ m/s with NYHA class II-IV symptoms. High surgical risk defined as ≥15% risk of death by 30 d after the procedure. An STS score ≥10% was used for guidance with an actual mean STS score of 11.8±3.3% Exclusions were bicuspid aortic valve, AMI, significant CAD, LVEF<20%, aortic annulus <18 or >25 mm, severe AR or MR, TIA within 6 mo, or severe renal insufficiency	All-cause death (intention-to-treat analysis): TAVR / SAVR / p-value 30 d: 3.4% / 6.5% / 0.07 1 y*: 24.2% / 26.8% / 0.44 2 y: 33.9% / 35.0% / 0.78 5 y: 67.8% / 62.4% / 0.76 *(p=0.001 for noninferiority) Composite endpoint at 2 y: all-cause death or stroke: TAVR 37.1% vs. SAVR 36.4% (p=0.85) HR: 0.93; 95% CI: 0.73–1.18; p=0.55	• Stroke or TIA at 2 y: TAVR 11.2 % vs. SAVR 6.5% (p=0.05) • Major vascular complications at 30 d: TAVR 11.0% vs. SAVR 3.2% (p<0.001) • Major bleeding at 30 d: TAVR 9.3% vs. SAVR 19.5% (p<0.001) • New-onset AF at 30 d: TAVR 8.6% vs. SAVR 16.0% (p=0.006).
PARTNER COHORT B (inoperable) Kapadia, et al 2015 25788231 (21) Leon, et al 2010 20961243 (22) Makkar, et al 2012 22443478 (23)	Compare TAVR to medical Rx in inoperable pts with severe symptomatic AS	RCT	TAVR in 179 vs. standard medical therapy in 179 (including BAV in 150 (84%)	Severe symptomatic calcific AS defined as AVA <0.8 cm^2 plus a $\Delta P \geq 40$ mm Hg or $V_{max} \geq 4.0$ m/s with NYHA class II-IV symptoms. Inoperable due to coexisting conditions with predicted ≥50% risk of death within 30 d of intervention or a serious irreversible condition. Exclusions were bicuspid aortic valve, AMI, significant CAD, LVEF<20%, aortic annulus <18 or >25 mm, severe AR or MR, TIA within 6 mo, or severe renal insufficiency	All-cause death at 2 y (Kaplan–Meier): TAVR 43.3% vs. standard therapy 68% HR: with TAVR, 0.58 (95% CI: 0.36–0.92; p=0.02). Repeat hospitalization: TAVR 55% vs. 72.5% standard therapy (p<0.001). Survival benefit of TAVR stratified by STS score: *STS score <5%* HR: 0.37 (95% CI: 0.13–1.01); p=0.04 *STS score 5%–14.9%* HR: 0.58 (95% CI: 0.41–0.81); p=0.002 *STS score ≥15%* HR: 0.77 (95% CI: 0.46–1.28); p=0.31 All-cause death at 5 y: TAVR 71.8% vs. standard therapy 93.6% HR: with TAVR, 0.50 (95% CI: 0.39–0.65; p<0.0001	• Cardiac symptoms (NYHA class III or IV) were present in 25.2% of survivors at 1 y after TAVR vs. 58% with standard therapy (p<0.001). • Major stroke rate at 30 d, was 5.0% with TAVR vs. 1.1% with standard therapy (p=0.06) and remained high at 2 y 13.8% with TAVR vs. 5.5% (p=0.01) • Major vascular complications occurred in 16.2% with TAVR vs. 1.1% with standard therapy (p<0.001).

Core Valve (high surgical risk) Adams, et al 2014 24678937 (24) Deeb et al, 2016 27050187 (25)	Compare TAVR and SAVR in pts at high surgical risk	RCT	TAVR with self-expanding Core Valve prosthesis in 390 vs. SAVR in 357. Mean age 83.2 y. Men 52.7% Mean STS-PROM score 7.4%	Severe symptomatic calcific AS defined as AVA ≤0.8 cm^2, or indexed AVA ≤0.5 cm^2/m^2 and either a ΔP >40 mm Hg or V_{max} >4.0 m/s with NYHA class II-IV symptoms. High surgical risk defined as ≥15% risk of death by 30 d after the procedure and a risk or death or irreversible complications <50% within 30 d of procedure Exclusions were valve sizing mismatch, inadequate access vessels, bicuspid aortic valve, significant CAD, or compliance issues.	All-cause death at 1 y : TAVR 14.2% vs. SAVR 19.1% (p<0.001 for non inferiority and p=0.04 for superiority). All-cause death or stroke at 3 y : TAVR 37.3% vs. SAVR 46.7% (p=0.006).	• Major vascular complications at 1 y: • TAVR 6.2% vs. SAVR 2.0% (p=0.004) • Major bleeding at 1 y: TAVR 29.5% vs. SAVR 36.7% (p=0.03) • AKI: • TAVR 6.0% vs. SAVR 15.1% (p<0.001) • Permanent pacer implantation: • TAVR 22.3% vs. SAVR 11.3% (p<0.001) • New-onset AF at 1 y: TAVR 15.9% vs. SAVR 32.7% (p<0.001)
PARTNER 2 COHORT A Leon, et al. 2016 27040324 (26)	To compare surgical AVR and TAVR in an intermediate risk cohort	RCT	TAVR 1011 pts vs. SAVR 1021 pts TAVR was transfemoral in 76.3% and transapical in 23.7%	Severe symptomatic calcific AS defined as AVA <0.8 cm^2 plus a ΔP≥40 mm Hg or Vmax ≥4.0 m/s with NYHA class II-IV symptoms. Intermediate surgical risk defined as ≥4% risk of death by 30 d after the procedure. An STS score ≥8% was the upper limit of enrolled pts. Pts with an STS score <4% were enrolled if other conditions indicating increased risk. Mean STS score was 5.8%. Exclusions were bicuspid aortic valve, AMI, significant CAD, LVEF<20%, aortic annulus <18 or >25 mm, severe AR or MR, TIA within 6 mo, or severe renal insufficiency	1° endpoint-cause death or disabling stroke at 2 y: HR: 0.89 (95% CI: 0.73–1.09; p=0.25). All-cause death at 2 y: TAVR 16.7% vs. SAVR 18.0% Disabling Stroke TAVR 6.2% vs. SAVR 6.4% Transfemoral TAVR vs SAVR: HR: 0.79; 95% CI: 0.62–1.00; p=0.05 Transthoracic TAVR vs SAVR: HR: 1.21; 95% CI: 0.84–1.74; p=0.31	• Life-threatening bleeding: TAVR 10.4% vs. SAVR 43.4%, p<0.001 • Acute kidney injury: TAVR 1.3% vs. SAVR 3.1%, p=0.006 • New-onset AF: TAVR 9.1% vs. SAVR 26.4%, p<0.001 • Repeat Hospitalization: TAVR 19.6% vs. SAVR 17.3%; p=0.22 • Permanent Pacer within 30 d: TAVR 8.5% vs SAVR 6.9%; p=0.17
NOTION (severe symptomatic AS with low-surgical risk) Thyregod HG, et al. 27005980 (27)	Compare outcomes with TAVR and SAVR in pts at low surgical risk	RCT	TAVR with self-expanding Core Valve prosthesis in 145 vs. SAVR in 135 Mean age: 79.12 y. Men: 53.2% STS-PROM score <4 in 81.8%	Severe symptomatic calcific AS in pts over age 70 y with no significant coronary disease. Severe AS defined as AVA <1.0 cm^2 or indexed AVA ≤0.6 cm^2/m^2 plus a ΔP >40 mm Hg or V_{max} >4.0 m/s with NYHA class II-IV symptoms. Also include asymptomatic severe AS (n=10) if severe LV hypertrophy, decreasing LVEF or new onset AF present. Exclusions were expected survival <1 y, other severe valve disease, significant coronary disease, previous cardiac surgery, MI or stroke within 30 d, severe renal or pulmonary disease.	Composite endpoint: Death from any cause, stroke, or MI at 1 y. TAVR 13.1% vs. SAVR 16.3% (-3.2% absolute difference, p=0.43 for superiority).	Major vascular complications at 30 ds: TAVR 5.6% vs. SAVR 1.5% (p=0.10) Major bleeding at 30 ds: TAVR 29.5% vs. SAVR 36.7% (p=0.03) AKI: TAVR 0.7% vs. SAVR 6.7% (p=0.01) Permanent pacer implantation at 30 d: TAVR 34.13% vs. SAVR 1.6% (p<0.001) New-onset or worsening AF at 30 d: TAVR 16.9% vs. SAVR 57.8% (p<0.001).

Horstkotte, et al 1988 3042404 (28)	Compare outcomes with symptomatic vs. asymptomatic severe AS	Retrospective	n=35 pts	Severe symptomatic AS refused AVR. AVA 0.4–0.8 cm^2	Mean interval from symptom onset to death: 4.5 y for angina (n=18), 2.6 y for syncope (n=13), <1 y for HF (n=20) Mortality reached 100% at: 10 y for angina, 5 y for syncope, 2.4 y for HF	There were 3 sudden deaths before symptom onset

Data Supplement 5. Nonrandomized Trials, Observational Studies, and/or Registries of TAVR (Section 3.2.4)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Popma, et al. 2014 (29) 24657695	Study type: Prospective, multicenter Size: n=506 pts recruited; n=489 pts who underwent attempted treatment with CoreValve THV	Inclusion criteria: Pts with symptomatic sever AS with prohibitive risk for surgery Exclusion criteria: N/A	1° endpoint: All-cause mortality or major stroke at 12 mo, compared to a pre-specified objective performance goal Results: All-cause mortality or stroke was 26.0% vs. 43.0% objective performance goal (p<0.0001)	• TVR with self-expanding bio prosthesis was found to be safe for pts with symptomatic severe AS with prohibitive risk for surgery
Thourani, et al. 2016 (30) 27053442	Study type: Observational Size: n=1,077 pts at 51 sites	Inclusion criteria: Pts receiving TAVR with the SAPIEN 3 valve compared to intermediate risk pts treated with surgical valve replacement in the PARTNER 2A trial. Exclusion criteria: N/A	1° endpoint: All-cause mortality, stroke, reintervention, and aortic valve regurgitation 1 y following plantation. Results: TAVR was noninferior (9·2%; 90% CI: -12.4–6; p<0·0001) and superior (-9·2%, 95% CI: -13.0 – -5·4; p<0·0001) to surgical valve replacement.	• TAVR with SAPIEN 3 was associated with lower all-cause mortality, strokes, and aortic valve regurgitation at 1 y compared with surgical valve replacement of the PARTNER 2A trial.

Data Supplement 17. *(Updated From 2014 Guideline)* Primary MR—Evidence for Intervention (Section 7.3.3)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Outcome
Tribouilloy, et al 1999 (31) 9918527	Assess impact of symptom status on outcome	Retrospective	n=478 pts	Mitral surgery	NYHA class I,II, III, IV	Advanced preoperative symptoms increased operative mortality by 10-fold. Long-term survival also reduced.
Gillinov, et al. 2010 (32) 20667334	Assess impact of symptoms on outcomes	Retrospective propensity-matched	n=4,253 pts	MVR	NYHA all class	Even NYHA class II preoperative symptoms impaired late survival.

Rosenhek, et al. 2006 (33) 16651470	Assess outcome with watchful waiting	Prospective	n=132 pts	Watchful waiting for severe MR	N/A	Survival for watchful waiting identical to age normal population, but triggers for surgery occurred early after enrollment in 50%.
Kang, et al. 2009 (34) 19188506	Assess outcome with watchful waiting	Prospective	n=447 pts	Mitral surgery	Early surgery vs. watchful waiting	Early surgery appeared superior, but several unoperated pts refused surgery despite presence of triggers.
Enriquez-Sarano, et al 1994 (35) 8044955	Assess predictors of outcome	Retrospective	n=409 pts	Mitral surgery	LVEF >60, 50-60, <50	Survival at 10 y, 72% for LVEF >60, 53%, 50–60, 32%, <50.
Tribouilloy, et al. 2009 (36) 19909877	Assess impact of LVESD on outcome	Retrospective	n=739 pts	Mitral surgery	LVESD <40 vs. ≥40	LVESD >40 mm nearly doubled late mortality risk.
Enriquez-Sarano, et al. 2005 (37) 15745978	Assess impact of MR severity	Prospective	n=450 pts	N/A	ERO of different sizes	ERO >0.4 cm^2 nearly tripled mortality, but mortality was reduced by surgery.
Ghoreishi 2011 (38) 21962906	Assess impact of pulmonary HTN on outcome	Retrospective	n=873 pts	Mitral surgery	Preoperative-pulmonary HTN of various degrees	5-y survival 88% for PAP <40 vs. 52% PAP >60.
Goldman, et al. 1987 (39) 3624663	Compare LV function after replace vs. repair	Prospective	n=18 pts	Mitral surgery	Repair vs. replacement	LVEF fell following replacement, but not repair.
David, et al. 1984 (40) 6492840	Compare outcome with and without chordal presentation	Prospective	n=27 pts	Mitral surgery	MV surgery with and without chordal preservation	LVEF decreased without preservation, but was maintained with preservation.
Rozich, et al. 1992 (41) 1451243	Examined LVEF	Retrospective	n=15 pts	Mitral surgery	Chordal preservation vs. destruction	Afterload increased following chordal destruction, but decreases following preservation.
David, et al. 2013 (42) 23459614	Assess long-term Outcome of MV repair	Retrospective	n=804 pts	Mitral repair	Normal population	Predicted Reduced survival for class II pts ; 6% re-op rate at 20 y, 91% freedom from severe MR; 70% freedom from even moderate MR
Tribouiloy, et al 2011 (43) 21821606	Assess predictors of post op LV function	Retrospective	n=355 pts	Mitral surgery	Postoperative EF	Preop EF of 0.64 and an LVESD of <37 mm predicted a normal post-op EF

Suri, et al. 2016 (44) 26846946	Asses Durability of MV repair	Retrospective	n=1,218 pts	Mitral repair	Repair Durability	83% freedom of moderate MR at 10 y; 96% for posterior leaflet disease; 2% need for re-op after 1996
Vassileva, et al. 2013 (45) 23569153	Assess survival after MV surgery	Retrospective	n=47,279 pts	Mitral surgery	Repair vs. replacement	Survival following repair superior to Replacement and not different from a normal population
Suri, et al. 2013 (46) 23942679	Assess watchful waiting vs early surgery	Retrospective	n=2,097 pts	Mitral surgery	Early vs. Triggered MV Surgery	Survival in Propensity Matched Pts was superior in those operated before classic Triggers
Dillon, et al. 2015 (47) 25308120	Assess repair durability in Rheumatic Disease	Retrospective	n=366 pts	Mitral surgery	Repair in Rheumatic vs Nonrheumatic MR	In the 41% of rheumatic MR pts where repair was attempted, results were similar to nonrheumatic pts with an 81% freedom of failure at 10 y
Feldman, et al 2015 (48) 26718672	5-y follow–up of Percutaneous MV repair	Prospective RCT	n=279 pts	Mitral repair	Percutaneous vs Surgical Repair	Initial failure greater in the percutaneous group but failure after 6 mo was identical for percutaneous vs. surgical repair
Grigioni, et al. 2008 (49) 19356418	Outcome of repair vs. replacement	Prospective	n=394 pts	Mitral surgery	Repair vs. replacement vs. nonsurgery	92% 54-y survival for repair; 80% for replacement.
Gillinov, et al. 2008 (50) 18721551	Outcome of repair vs. replacement	Retrospective	n=328 pts	N/A	Repair vs. replacement propensity	5, 10, 15 y survival 95, 87, 68 repair vs. -80, 60, 44 replacement.
Weiner, et al. 2014 (51) 24836989	Assess effect of experience in repair on outcome	Retrospective	n=1,054 pts	Mitral repair	Early experience vs late	As experience improved over time, morbidity and LOS decreased
Enrique Serano, et al. 2015 (52) 25986494	Assess effect of timing of surgical correction of MR on outcome	Retrospective stratification	n=1,512 pts	Mitral surgery correction	Surgical indication class I triggers (HF symptoms, EF <60%, end-systolic diameter ≥40 mm vs. class II (AF or pulmonary HTN) vs. early class III (combination of severe MR and high probability of valve repair).	Operative mortality highest with Class I (1.1% vs. 0% and 0%, p=0.016). Long-term survival was lower with Class I (15-y 42% ± 2%; adjusted HR: 1.89 (95% CI: 1.53, 2.34), p< .0001) and ClassII-CompT (15-y 53% ± 4%, adjusted HR: 1.39 (95% CI: 1.04, 1.84), p=0.027) vs. Class II-EarlyT (15-y 70% ± 3%, p<0.0001).

Suri, et al. 2008 (53) 18692655	Examine early changes in LV size and function after MV repair or replacement	Retrospective	n=861 pts	Mitral repair/replacement	N/A	Rate of valve repair increased from 78% to 92%. At early echocardiography (mean, 5 d postop), significant decreases in LVEF (mean: 28.8) and LVESD (mean, 27.5). Magnitude of early decline in EF was similar in pts who had MVR and MV replacement.
Quintana, et al. 2014 (54) 25173130	Assess predictors and long-term survival of latent LV dysfunction	Retrospective	n=1,705 pts	Mitral repair	Presence vs. absence of early postop LV dysfunction (LVEF <50%)	Pts with absence of LV dysfunction had significant and immediate greater enlargement in systolic dimension and decrease in right ventricular systolic pressure. EF recovered to preop levels (>60%) in only one third of pts with postrepair EF<50% vs. two thirds of those with an EF of ≥50% (p<001).The overall survival at 5, 10, and 15 y of follow-up was 95%, 85%, and 70.8%, respectively. Postop EF <40% conferred a 70% increase in the hazard of late death: adjusted HR: 1.74 (95% CI: 1.03, 2.92), p=0.037
Suri, et al. 2011 (55) 21257316	To assess the tempo of MR progression, predictors of MR progression, incidence of de novo LV dysfunction, and predictors of LV dysfunction	Retrospective observational study	n=142 pts		N/A	• The likelihood of MR progression was higher in those with greater baseline MR grade (mild/mild-moderate 44/124 (31%) vs. moderate/moderate-severe 35/60 (58%) p=0.0008). • LV deterioration occurred even in the absence of MR progression • Multivariable modeling revealed that LVEDD was the only independent predictor OR: 1.15; 95% CI: 1.08, 1.23; p=0.0001 of greater MR progression with time.

Data Supplement 18. *(Updated From 2014 Guideline)* Secondary MR—Evidence for Intervention (7.4.3)

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Outcome
Kang, et al 2006 (56) 16820626	Outcome surgery in moderate-to-severe ischemic MR	Retrospective	n=107 pts	CABG + repair	CABG	Higher operative mortality with CABG and MV repair vs CABG alone (12% vs. 2%) but similar 5 y survival (88% vs87%)
Rossi, et al 2011 (57) 21807656	Impact of on outcome	Retrospective	n=1,256 pts	None	Impact of SMR on HF	After adjusting for LVEF and other factors-SMR increased mortality by 2-fold
Wu, et al 2005 (58) 15680716	Impact of surgery on moderate-severe MR	Retrospective	n=126 pts	Surgery with mitral annuloplasty	Med Rx	No survival advantage to MV annuloplasty

Mihaljevic, et al 2007 (59) 17543639	Impact of mitral surgery moderate- severe on SMR	Retrospective	n=290 pts	CABG+ MV surgery	CABG	1-, 5-, 10-y survival -88, 75, 47 CABG vs. 92, 74, 39 CABG + MV symptoms; (p=NS) functional class improved equally in both groups
Benedetto, et al 2009 (60) 19377377	Impact of MV surgery on SMR	Meta-analysis	n=2,479 pts	CAGB+MV surgery	CABG	No difference in survival or symptomatic status
Fattouch, et al 2009 (61) 19619766	Impact of MV surgery in ischemic MR	Randomize d prospective	n=102 pts	CABG + repair	CABG	No difference in mortality. Repair group had reduced cardiac dimensions and symptoms vs. CABG alone
Deja, et al 2012 (62) 22553307	Impact of repair in ischemic SMR	Randomized to medical Rx vs. surgery	n=104 pts	CABG + repair	CABG	53% mortality CABG, vs. 43% mortality CABG + MVR (p=NS); after adjustment CABG + MVR had better survival
Nombela-Franco, et al. 2014 (63) 26060121	Summarize the effect of TAVR on MR	retrospective	>1,000	TAVR	MR before and after TAVR	Change in MR quite variable
Smith PK, et al. 2014 (64) 25405390	Compare CABG to CABG +	Randomized prospective	n=301 pts	CABG	CABG + Repair	Adding repair increased morbidity but did not improve LV geometry
Michler, et al. 2016 (65) 27040451	Compare CABG to CABG + MV repair in pts with moderated ischemic MR	Randomized prospective	n=301 pts	CABG	CABG + Repair	2-y follow up: In pts with moderate ischemic MR undergoing CABG, the addition of MVR did not lead to significant differences in LV reverse remodeling at 2 y. MVR provided a more durable correction of MR but did not significantly improve survival or reduce overall adverse events or readmissions and was associated with an early hazard of increased neurologic events and supraventricular arrhythmias.
Acker, et al 2014 (66) 24245543	Compare repair to replacement in severe 2° MR	Randomized prospective	n=251 pts	repair	Replacement	There was no significant difference in LV reverse remodeling or survival at 12 mo between pts who underwent MVR and those who underwent MV replacement. Replacement provided a more durable correction of MR, but there was no significant between-group difference in clinical outcomes.
Goldstein, et al 2016 (67) 26550689	Compare repair to replacement in 2° MR	Randomized prospective	n=251 pts	repair	Replacement	High and equal mortality in both groups with greater recurrent in with repair

Data Supplement 20. *(Updated From 2014 Guideline)* Clinical Outcomes With Bioprosthetic and Mechanical Valves (Section 11.1.2)

Author, Year	Study Size	Methods	Patient Population		Follow-Up	Outcomes	Study Limitations
			Inclusion Criteria	Exclusion Criteria			
Hammermeister, et al 2000 (68) 11028464	575 pts undergoing isolated AVR (394) or MVR (181) at 13 VA medical centers (1977–1982)	RCT	Isolated AVR or MVR. Concurrent CABG performed in 39% of AVR and 36% of MVR pts.	Women, contraindications to VKA anticoagulation, requirement for antiplatelet therapy, valve size AVR or endocarditis.	15 y	• AVR, all-cause mortality at 15 y was lower for MHV vs. BHV: (66±3% [mean±SE] vs. 79±3%; p=0.02) No difference for MVR. • 1° valve failure was significantly greater with a BHV vs. MHV valve, both for AVR (23±5% vs. 0±0%; p=0.0001) and MVR (44±8% vs. 5±4%; p=0.0002). 1° valve failure nearly always (93%) occurred in pts <65 y. • AVR reoperation was higher after BHV vs. MHV (29±5% vs. 10±3%; p=0.004). No statistically significant difference for MVR.	Pts receiving mechanical MVR were older and had more HTN than those with a bioprosthetic MVR.
Oxenham, et al. 2003 (69) 12807838	541 pts undergoing MVR (261), AVR (211), or both (61) 1975–1979	RCT	Mean age 53.9 (10.6) y. 56% female.	Additional valve procedures or not eligible for VKA anticoagulation.	20 y	• No difference in overall survival (Bjork-Shiley vs. porcine prosthesis [mean (SEM]): 25.0 (2.7)% vs. 22.6 (2.7)%, log rank test p=0.39. • Combined endpoint of death and reoperation occurred in • 23.5 (2.6)% with BHV vs. 6.7 (1.6)% with MHV (log rank test; p<0.0001). • Major bleeding was more common in pts with MHV (40.7 [5.4]% vs. 27.9 [8.4]% after 20 y; p=0.008), with NS difference in major embolism or endocarditis.	Older generation valve types.
Stassano, et al. 2009 (70) 19892237	310 pts undergoing AVR 1995–2003	RCT	Age 55–70 y	Other valve surgery. Contraindication to VKA anticoagulation	Mean 106±28 mo	• No survival difference at 13 y between BHV and MHV groups. • Valve failures and reoperations were more frequent in the BHV group compared with the MHV group (p=0.0001 and p=0.0003, respectively). • No differences in the linearized rate of thromboembolism, bleeding, endocarditis, and MAPE between the MHV and BHV valve groups.	Power may not be adequate to detect a clinically-meaningful difference at longer follow-up.
Khan, et al 2001 (71) 11479498	Initial AVR in 1389 pts, MVR in 915 pts, 1976–2001 at a single medical center.	Retrospective, observational	Age 64.5±12.9 y for MHV Age 72.0±12.6 y for BHV	Homografts, combined MHV and BHV procedure, any previous valve surgery	20 y	• Freedom from reoperation at 15 y for AVR was 67±4.8% for BHV and 99±0.5% for MVH. For MVR, freedom from reoperation was 52±5.7% for BHV and 93±3.2% for MHV. • Survival at 15 y (BHV vs. MHV, p=NS for all): • AVR in pts <65 y (55±5.9 vs. 61±5.3%), AVR in pts >65 y • (17±3.4 vs. 17±3.8%). • MVR in pts <65 y (32±5.5 vs. 51±5.4%), MVR in pts >65 y • (12±3.5 vs. 18±3.8%)	Not prospective, not randomized. Concurrent CABG in 50%.

Chan, et al. 2006 (72) 16733156	3,063 pts undergoing AVR 1982–1998	Retrospective observational	2,195 BHV and 980 MHV.	Previous cardiac surgery	Average follow-ups in y for the BHV and MHV groups were 7.5±4.7% and 5.9±3.3% (p<0.001), respectively	• Valve-related mortality (per pt-y): BHV 1.0% vs. MHV 0.7% • Valve-related reoperation (per pt-y): BHV 1.3% vs. MHV 0.3% (p<0.001) • Valve-related morbidity: BHV 0.4% vs. MHV 2.1% (p<0.001) • Actual freedom from valve-related reoperation favored MHV for pts <60 y. Actual freedom from valve-related morbidity favored BHV for pts >40 y. Actual freedom from valve-related mortality was similar for BHV vs. MHV >50 y.	Not randomized. AVR only. Concomitant CABG in 43.5% of BHV pts and 26.0% of MHV pts.
Kulik, et al. 2006 (73) 16857373	659 pts age 50–65 y with initial AVR or MVR	Prospective, observational	AVR in 388 (MHV 306, BHV 48). MVR in 236 (MHV 188, BHV 48).	Enrolled only if survived perioperative period. Valve repair excluded.	Mean 5.1±4.1 y; maximum 18.3 y	• Freedom from 1° endpoint MAPE at 10 y (reoperation, endocarditis, major bleeding, or thromboembolism): • AVR MHV 70±4.1% vs. BHV 41.0±30.3% (p=0.55) MVR MHV 53.3±8.8% vs. BHV 61.2±9.2% (p=0.34) • Multivariate analysis did not identify valve type as an independent risk factor for MAPE	Not randomized. Surgeon choice of valve type. Concurrent CABG in 29%.
Ruel, et al., 2007 (74) 17846320	567 pts undergoing AVR or MVR	Retrospective observational	Age <60 y. First heart valve operation.	N/A	Mean survivor follow-up, 24.0±3.1 y	• Survival in AVR: no difference between BHV vs. MHV (HR:0.95, 95% CI: 0.7–1.3); • Survival in MVR: no difference between BHV or MHV (HR: 0.9, 95% CI: 0.5–1.4); • Long-term survival worse in MVR than AVR (HR: 1.4, 95% CI: 1.1–1.8); • Reoperation in 89% of BHV AVR and 84% of BHV MVR (older generation devices) with reoperative mortality 4.3%.	Not randomized or prospective, follow-up available in only 23% of original cohort.
van Geldorp, et al. 2009 (75) 19327512	Bioprosthetic AVR=2,860 (73%) vs. mechanical AVR=1,074 (27%)	Retrospective cohort (1982–2003) Microsimulation used to calculate age-specific pt	Bioprosthetic AVR: mean age=70 y, mean follow-up=6.1 y, CABG=47% vs. Mechanical AVR: mean age=58 y, mean follow-up=8.5 y, CABG=28%	N/A	Bioprosthetic AVR: mean follow-up=6.1 y. Mechanical AVR: mean follow-up=8.5 y.	• Simulated events for a 60-y man undergoing AVR, favors a BP vs. MP: • life-expectancy: 11.9 vs. 12.2 y, • event-free survival: 9.8 vs. 9.3 y, • reoperation-free: 10.5 vs. 11.9 y, • reoperation risk: 25% vs. 3%, • risk of bleeding: 12% vs. 41%	Methodology of microsimulation is dependent on quality of dataset, wide chronological age of prostheses.
Badhwar, et al. 2012 (76) 22364968	172 pts undergoing isolated AVR or MVR (2003–2007)	Prospective, nonrandomized, matched pairs for BP vs. MP	Mean age 56.2±9.6 y (range, 24–72 y).	Limited 5-y survival based on comorbidity	Median follow-up 4.0 y	• At a median 4-y follow-up, thromboembolism was 0.77% for MP and 0.78% for BP (p=NS) • There was a survival benefit of mechanical prostheses at 7.5 y Noninferiority to bioprosthetic AVR for bleeding and thromboembolic complications.	Prosthesis choice by surgeon not randomized. Low INR targets (AVR: 2.0, MVR: 2.5) with home monitoring point- of-care system

Weber, et al. 2012 (77) 22341653	206 pts undergoing AVR (2000–2009)	Retrospective cohort analysis, with propensity matching of 103 BP to 103 MP	Age <60 y. AVR with or without concurrent CABG, aortic root surgery, mitral or	Additional valve replacement.	Median follow- up 33±24 mo (2–120 mo)	• Overall survival was worse with BHV (90.3% vs. MHV=98%, p=0.038; HR:0.243, 0.054–0.923 • Freedom from valve related complication complications was similar: BHV=54.5% vs. MHV=51.6%, p=NS	Concurrent CABG in 49.9%, 14% were reoperations
Chiang YP, et al. 2014 (78) 25268439	4,253 pts s/p AVR with MHV or BHV in New York state (1997-2004) BHV: 1466 pts (34.5%) MHV: 2787 pts (65.5%) Propensity score matching: 1001 pt pairs.	Retrospective with propensity matching	50-69 y of age with 1°, isolated AVR	Out-of-state residency, prior replacement of any valve, concomitant valve replacement, concomitant valve repair, cCABG surgery, or thoracic aortic surgery	Median follow-up time 10.8 y (range, 0 to 16.9 y)	• 15-y survival: BHV: 60.6% (95% CI: 56.3%-64.9%) MHV: 62.1% (95% CI: 58.2%-66.0%) (HR: 0.97 [95% CI: 0.83-1.14]) • 15-y stroke incidence: BHV: 7.7% (95% CI: 5.7%-9.7%); MHV: 8.6% (95% CI: 6.2%-11.0%) HR: 1.04 [95% CI: 0.75-1.43). • 15-y reoperation incidence: BHV: 12.1% [95% CI: 8.8%-15.4%]; MHV: 6.9% [95% CI: 4.2%-9.6%] HR: 0.52 [95% CI: 0.36-0.75]). Bioprostheses were associated with a significantly higher rate of AV reoperation than mechanical prostheses (p=.001) • 15-y major bleeding incidence: BHV: 6.6% [95% CI: 4.8%-8.4%]; MHV: 13.0% [95% CI: 9.9%-16.1%] HR:, 1.75 [95% CI: 1.27-2.43])	Retrospective, single state in US
Kaneko T, et al. 2014 (79) 24079878	768 pts <65 y of age old s/p MVR January 1991 to June 2012 MHV: 627 pts BHV: 141 pts Propensity score matching: 125 matched pairs	Retrospective with propensity matching	Age <65 s/p MVR	MVR performed in pts >65 y; no exclusions were made on gender, race, or other concomitant cardiac surgery.	The median follow-up: 7 y MHV: 8 y BHV: 3 y	• Long- term survival for propensity matched group: MHV: 13.7+/-0.7 y BHV: 11.3+/-1.0 y p<0.004 • MHV 5-, 10-, and 15-y survival of 83.4%, 69.2%, and 62.6%. BHV 5-, 10-, and 15-y survival of 67.3%, 57.6%, and 40.4% in the MVRb group (p=004). • Freedom from stroke and embolic events at 5, 10, and 15 y: • MHV: 95.3%, 93.2%, and 90.7% • BHV: 93.7%, 87.6%, and 87.6%; p=NS after 240 mo • Freedom from major bleeding at 5, 10, and 15 y: MHV 87.2%, 79.2%, and 71.2% • BHV 91.1%, 85.0%, and 77.9%; p=NS • The freedom from reoperation at 5, 10, 15 y: MHV: 97.7%, 96.6%, and 96.1% • BHV: 96.6%, 86.6%, and 75.3% • The risk of reoperation was significantly greater for the BHV patients (p=.003)	Retrospective single-center Relatively short median follow-up

McClure 2014 (80) 24521965	1701 pts aged <65 y who underwent AVR between 1992 and 2011. BHV (2nd generation stented), n=769 MHV (bi-leaflet), n=932	Retrospective Stepwise logistic regression propensity score identified subset of 361 evenly matched pairs	361 matched pairs (Mean age BHV 53.9 y vs. 53.2 y for MHV) "Isolated" stented bioprosthetic or bi-leaflet mechanical AVR Concomitant root and/or ascending aortic repairs included. Prior cardiac surgery included (1701 of 6794 pts who underwent AVR in this time frame met inclusion criteria)	Concomitant valve, coronary or ventricular procedures. Ross procedure Homograft or stentless bioprosthetic AVR	Median follow-up for entire cohort 8 y (14484 pt-y) Median follow-up for matched pairs 6.5 y	• For matched cohort: • 30-d mortality: 1.9% BHV vs. 1.4% MHV (p=0.77) • Survival at 5, 10, 15 and 18 y for BHV vs. MHV: 89% vs. 88%, 78% vs. 79%, 65% vs. 75% and 60% vs 51% (p=0.75). • Freedom from reoperation at 18 y: 55% BHV vs. 95% MHV (p=0.002) • Freedom from major bleeding 78% MHV vs. 98% BHV (p=0.002). • No difference in stroke rates	Single institution Retrospective, observational
Du 2014 (81) 25221895	Pts >65 y of age in Medicare data base who underwent AVR between July 1, 2006 and December 31, 2011. MHV, n=19190 BHV, n=47263	Retrospective analysis. Mixed-effects model adjusting for physician and hospital random effects to estimate ORs of early mortality for MHV vs BHV.	Medicare beneficiaries enrolled in Parts A, B and D for 6 mo before AVR. Age >65 y of age Mean, 77 y of age. 45% of study population underwent concurrent CABG	Medicare Part C beneficiaries. (limited claims data)	Up to 365 d after surgery	• OR death on d of surgery MHV vs. BHV 1.61 (95% CI: 1.27–2.04; p<0.001); RR: 1.60. NNT: 290. • OR death within 30 d surgery MHV vs. BHV 1.18 (1.09–1.28), p<0.001. NNT 121. • No difference between MHV and BHV d 31–365 after surgery • Consistent findings in subgroup analyses of pts undergoing AVR + CABG but not in subgroup undergoing isolated AVR	Retrospective. Administrative data base query. Large mortality hazard for MHV pts on d of surgery not explained. Specific valves utilized not captured.
Bourguignon 2015A (82) 25583467	2,659 pts who underwent AVR with the CE-Perimount BHV valve (1984-2008) at a single center	Retrospective, observational	Mean age 70.7+/-10.4 y of age (range 16–91 y of age) Age <60 y of age: 383 (13%)	Multiple valve replacement	Mean followup 6.7+/- 4.8 y (0–24.6 y)	• Actuarial survival rates 10 y: 52.4% ± 1.2%; 15 y: 31.1% ± 1.4%; 20 y: 14.4% ± 1.7% Freedom from reoperation from structural valve deterioration: 60 y or less:15 y:70.8% ± 4.1%; 20 y:38.1% ± 5.6%, 60-70 y: 15 y:82.7% ± 2.9% ; 20 y: 59.6% ± 7.6% Over 70 y: >15 y:98.1% ± 0.8% • Expected valve durability is 19.7 y for the entire cohort.	Retrospective, not randomized, single center Only 1 type of tissue valve used Pts <60 y received BHV if not good candidates for MHV or personal preference Conflict of interest with

Bourguignon 2014B (83) 24667021	450 pts who underwent MVR with the CE-Perimount BHV valve (1984-2011) at a single center	Retrospective, observational	Mean age 68+/-10.4 y (22-89 y)	Multiple valve replacement	Mean followup 7.2 +/-5.1 y(0 –24.8 y)	• 20 actuarial survival rate including early deaths was 16.9% +/-3.9%. • Valve-related actuarial survival rate was 62.4% ` 9.0% • 20 y actuarial freedom from complications was thromboembolism, 83.9% =/-7.6%; hemorrhage, 80.2% +/-10.8%; endocarditis, 94.8% +/-1.4%; structural valve deterioration, 23.7% +/-6.9%; and explanation for structural valve deterioration, 40.5% +/-8.0%. • The expected valve durability was 16.6 y for the entire cohort (11.4, 16.6, and 19.4 y for pts aged <60, 60 to 70, and >70 y, respectively).	Retrospective, not randomized, single-center study Only 1 type of tissue valve used Pts <60 y of age received BHV if not good candidates for MHV or personal preference Conflict of interest with
Bourguignon 2015C (84) 26187006	373 pts <60 y of age underwent AVR with CE-Perimount BHV valve (1984-2008) at a single center	Retrospective, observational	Mean age 51.0 +/9.2 Median age 54 (47–57.5) Range: 16-60 y	Multiple valve replacement	Mean follow-up was 8.6+/-5.9 y.	• Actuarial survival rates: 78.1% ± 2.6%, 65.6% ± 3.5%, and 46.8% ± 6.0% after 10, 15, and 20 y • Actuarial freedom from reoperation rates attributable to structural valve deterioration at 10, 15, and 20 y: 88.3% ± 2.4%, 70.8% ± 4.1%, and 38.1% ± 5.6%	Retrospective, not randomized, single-center study Only 1 type of tissue valve used Pts received BHV if not good candidates for MHV or personal preference Conflict of interest with
Chikwe, 2015 (85) 25871669	3433 total pts 50-69 y old in New York State who underwent MVR from January 1, 1997, to December 31, 2007. 795 (23.2%) BHV 2638 (76.8%) Propensity matching: 664 pairs	Retrospective, observational	Mean age: Whole group: 60.1 +/5.8 BHV: 61.2 +/-5.9 MHV: 59.7 +/-5.7	Out-of-state residency, prior replacement of any valve, concomitant valve replacement, concomitant valve repair, cCABG surgery, or thoracic aortic surgery	Median duration was 8.2 y(range, 0-16.8 y).	• Actuarial 15-y survival in propensity matched group: • MHV: 57.5% (95% CI: 50.5–64.4%) BHV: 59.9% (95% CI: 54.8–65.0%) HR:0.95 [95% CI: 0.79–1.15], p=0.62; • Stroke 15 yin propensity matched group: • MHV: 14.0%; 95% CI: 9.5–18.6%) BHV: 6.8%; 95% CI: 4.5–8.8%) HR: 1.62 [95% CI: 1.10–2.39], p=0.01 • Bleeding 15 y in propensity matched group: • MHV: 14.9%; 95% (CI: 11.0–18.7%) BHV: 9.0%; 95% CI: 6.4–11.5%) HR: 1.50 [95% CI: 1.05–2.16], p=0.03; • Reoperation at 15 y in propensity matched group: • MHV: 5.0%; 95% CI: 3.1–6.9%) BHV:11.1%; 95% CI: 7.6–14.6% HR: 0.59 [95% CI: 0.37–0.94], p=0.03	Retrospective, single state in US 15-y follow-up was insufficient to fully assess lifetime risks, particularly of reoperation.

Glaser 2015 (86) 26559386	4,545 pts 50–69 y old s/p 1°, isolated AVR in Sweden from January 1, 1997 to December 31, 2013 MHV: 2713 pts BHV: 1832 pts Propensity matching: 1099 pairs	Retrospective, observational	Mean age (y) Whole group: 61.4+/-5.3 MHV: 59.9+/- 5.1 BHV: 63.7 +/- 4.7	Prior cardiac surgery or a concomitant procedures	FU for whole group: Mean: 7.3 +/- 4.7y Max: 17.2 y FU for MHV: Mean 8.8 +/-4.6y Max: 17.2 y FU for BHV: Mean: 5.0+/-3.7 y Max: 17.2 y	• Greater long-term survival in MHV vs. BHV • HR: for bioprostheitic vs. mechanical valves • Overall unadjusted analysis: HR: 1.67; 95% CI: 1.44–1.94 Overall multivariable adjusted model: HR: 1.30; 95% CI: 1.09–1.56) Propensity score-matched cohort: HR: 1.34; 95% CI: 1.09 – 1.66; P ¼ 0.006) • Propensity score-matched pts aged 50–59 y: survival greater in MHV: HR: 1.67; 95% CI: 1.06– 2.61; p=0.026, n=574). • Propensity score-matched pts aged 60–69 y: no survival difference in MHV vs. BHV: HR: 1.08; 95% CI: 0.85 – 1.36; p=0.539, n=1502). • 2° endpoints: Propensity score matched cohort: • MVH: Stroke: 5.8%; Reoperation: 2.2%; Major bleeding: 9.6%; CV death: 5.2% • BHV: HR: biosprosthetic vs. mechanical valves • Stroke : 6.1% HR: 1.04 (95% CI: 0.72–1.50) Reoperation: 5,2% HR: 2.36 95% CI: 1.42–3.94) Major bleeding: 4.9% HR:0.49 (95% CI: 0.34–0.70) CV death: 5.1% HR:1.00 (95% CI: 0.67–1.50) • 2° endpoints: Overall Cohort: • MVH: Stroke: 7.6%; Reoperation: 3.1%; Major bleeding: 9.9%; CV death: 5.4% • BHV: Stroke: 5.1% HR: 0.97 (95% CI: 0.72 –1.31) Reoperation: 4.1 % HR: 2.07 (95% CI: 1.38–3.11). Major bleeding: 4.0% HR: 0.53 (95% CI: 0.39–0.74). CV death: 4.0% HR: 1.26 (95% CI: 0.87–1.81).	Retrospective Relative short follow-up
Isaacs 2015 (87) 25791947	All pts>18 y old who underwent AVR in NIS database. 767,375 implanted valves	Observational	Median age: 74 yfor pts receiving BHV Median age: 67 yfor pts receiving MHV.	Pts who underwent a simultaneous valve annuloplasty, valve repair, or mitral or tricuspid valve replacement were excluded.	All pts aged >18 yin the National Inpatient Sample who received an AVR between 1998 and 2011 were studied	• 767,375 implanted valves. BHV increased from 37.7% in 1998-2001 to 63.6% in 2007-201. • Use of bioprosthetic valves increased across all age groups, most markedly in pts age 55 to 64 y.	Retrospective

De Vincentiis 2008 (88) 18355513	345 consecutive pts who underwent AVR from 5/1991-4/2005 at a single institution BHV: 200 pts (58%) MHV: 145 (42%)	Retrospective	Mean age 82+/1 2 y (range 80-92)	Age <80 y	Mean follow-up was 40 +/-33 mo (range, 1 to 176 mo);	• In hospital mortality: Total group: 7.5% BHV: 8.5% MHV: 6.2% (P-0.536) • Late FU: Total group: 61% at 5 y 21% at 10 y 6% at 14 y • The NYHA functional class improvement • BHV: 3.3 0.7 to 1.2 0.5 (p 0.001) • MVH: 3.2 0.6 to 1.2 0.5 • Survival by type of prosthesis was significantly higher with mechanical prostheses (log- rank p 0.03). • Freedom from cerebrovascular events (thromboembolic/hemorrhagic) at 5 and 10 y: • BHV: 92% and 77% ; MHV: 89% and 62%	Retrospective Very few pts in late followup
Vicchio 2008 (89) 18355512	160 consecutive octogenarians who underwent AVR at a single institution between July 1992-Sept 2006. BHV: 68 pts MHV: 92 pts 121 pts were alive at follow-up and answered the QoL questionnaire BHV: 62 pts MHV: 98 pts	Retrospective	mean age of 82.3 2.3 y of age (range, 80 to 90 y of age) BHV: 82.9 +/12.7 y MHV:81.8+/-1.8 y	Age <80 y	3.4 +/-2.8 y (range, 6 mo to 14.4 y),	• Total hospital mortality: 8.8% • BHV: 10.3%: 7.6% (p=0.75) • Survival at 1, 3, 5 and 8 y: • BHV: 86.4% +/-0.04%, 76.9% +/-0.06%, 58.1% +/-0.1%, and 46.5% +/-0.14% • MHV: 91.3% +/-0.03%, 88.6% +/-0.03%, 81.6% +/-0.05%, and 70% +/-0.67% (p 0.025) • QOL scores comparable between BHV and MHV	Small sample size Bias towards healthier pts receiving MHV Retrospective
Dvir D, et al., 2012 (90) 23052028	202 pts with degenerated bioprosthetic valves from 38 cardiac centers. Bioprosthesis mode of failure was stenosis (n=85, 42%), regurgitation (n=68, 34%) or combined stenosis and regurgitation (n=49, 24%). Implanted devices: Corevalve: n=124 Edwards: n=78	Global valve-in-valve Registry Retrospective collection of data from cases performed before registry initiation, and prospective data collection after that time.	Mean y of age 77.7 +/- 10.4	All pts in the registry were included	Procedural success and 30-d FU 0ne yr FU in 87 pts	• Procedural success: 93.1% cases • Adverse procedural outcomes: Device malposition: 15.3% Coronary obstruction: 3.5% • 30-d FU: All-cause mortality: 8.4% NYHA class I/II: 83.7% • 1 y FU in 87 pts; 85.8% survival	Short-term FU 1-y follow-up in only 87 pts

Dvir D, et al 2014 (91) 25005653	459 pts with degenerated bioprosthetic valves undergoing valve-in-valve implantation between 2007 and May 2013 in 55 centers Modes of BHV failure: Stenosis (n=181[39.4%]) regurgitation(n=139 [30.3%]) Combined (n = 139 [30.3%]).	Multinational valve-in-valve registry from 55 countries Data collected retrospectively for cases performed before registry initiation and prospectively thereafter.	Mean age All: 77.6 +/-9.8 Mean age stenosis:78.8 +/-7.8 Mean age regurgitation: 77.1 +/-10.6 Mean age combined: 76.6 +/-11.1 Mean age self-expandible: 77.6 +/-10 Mean age balloon expandible: 77.6 +/-9.7	All pts in registry included	Survival, stroke, NYHA functional class at 30 ds and 1 y	• 30 d results: 35 (7.6%) pts died, 8 (1.7%) had major stroke, and 313 (92.6%) of surviving pts had good functional status (New York Heart Association class I/II). • 1 y results: The overall Kaplan-Meier survival rate: 83.2% Stenosis group survival: 76.6%; 95% CI: 68.9%-83.1%; Regurgitation group survival: 91.2%; 95% CI: 85.7%-96.7% Combined group survival: 83.9%; 95% CI: 76.8%-91% • Factors associated with 1 yr mortality: Small surgical bioprosthesis (21 mm; HR: 2.04; 95% CI: 1.14–3.67; p=0.02) baseline stenosis (vs. regurgitation; HR: 3.07; 95% CI: 1.33-7.08; p=0.008).	Under-representation of younger pts
McClure RS, et al. 2014 (80) 24521965	n=1,701 pts <65 y referred for isolated AVR (769 received a stented bioprosthetic valve; 932 received a mechanical valve)	Propensity-matched cohort; retrospective single center observational study	Age ≤65 y undergoing an isolated AVR with a bileaflet mechanical or stented bioprosthesis	AVR using a pulmonary autograft, homograft, or stentless bioprostheses.	Up to 18 y of age	• 1° outcome: late survival • At 5, 10, 15, and 18 y, life table estimates for survival: bioprosthetic group: 89% ±2%, 78% ±3%, 65% ±5%, 60% ±6%; mechanical group they were 88% ±2%, 79% ±3%, 75% ±4%, and 51% ±14% (p=0.752). No significant difference in survival up to 18 yin nonelderly (≤65) pts. • 2° outcomes: stroke, major bleeding, and reoperations at late follow-up • No reoperation was significantly better in mechanical prostheses (p=0.002). No major bleeding events significantly better in bioprosthetic valves (p=0.002). NS difference in stroke (p=0.33). Pts with mechanical valve had significantly longer hospital stay (p=0.02). NS difference in 30 d mortality, postoperative stroke, and bleeding NS	Potential underestimation of events due to retrospective study design and questionnaire usage.
Repack 2016 (92) 26389590	N= 146 pts; to assess postoperative QOL in pts with either mechanical or bioprosthetic vales for aortic root repair	Prospective, observational	Pts who underwent aortic root repair with either mechanical (65.1%) or bioprosthetic (34.9) and completed the QoL survey	Pts who did not complete QoL survey	Mean follow-up 32 mo (range 4–56 mo)	• 1° outcome: QoL • No significant differences between mechanical and bioprosthetic valves for any of the QoL aspects, which were scored by the SF-36v2 survey	Postoperative QoL does not differ for pts receiving mechanical or bioprosthetic valves for aortic root repair.

Data Supplement 6. Antithrombotic Therapy for Prosthetic Valves (Section 11.2.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
PROACT Puskas J 2014 (93) 24512654	Aim: To assess the efficacy and safety of less intensive anticoagulation (INR 1.5–2.0) in high-risk pts receiving an On-X AVR Study type: RCT Size: n=375 pts	Inclusion criteria: 1. Indication for AVR; age ≥18 y of age 2. 1 of the following: a. Chronic AF b. EF <0.30 c. LAE (>50 mm) d. LA SEC e. "vascular pathologic features" f. LV or RV aneurysm g. Neurolgic events h. Lack of response to ASA or clopidogrel i. Women receiving estrogen 3. Other cardiac surgery allowed a. CABG b. MV or TV repair c. Ascending aortic replacement d. Maze e. "and so forth" Exclusion criteria: 1. R-sided valve replacement 2. Double valve replacement 3. Active endocarditis	Intervention (test group): Warfarin targeted to INR 1.5-2.0 Comparator (control group): Warfarin targeted to INR 2.0–3.0 All pts received ASA 81 mg Randomization at 3 mo post-operatively All pts were treated with warfarin targeted to INR 2.0–3.0 plus ASA 81 mg daily for first 3 post-operative mo	1° endpoint: The 1° endpoints mandated by the FDA included major bleeding events, minor bleeding events, total bleeding events, TIA, hemorrhagic stroke, nonhemorrhagic stroke, any neurologic event, peripheral TE, any TE, valve thrombosis, TE and thrombosis, major event (major bleeding, any TE, valve thrombosis), death (cardiac, noncardiac, valve-related, and all-cause) Safety endpoint (if relevant): Incorporated in 1° endpoint above Selected Results (test vs. control): 1.Major bleeding rate (%/pt-y) 1.48 vs. 3.31; RR: 0.45; (0.21–0.94, p=0.032) 2. Total bleeding RR: 0.40 (0.24–0.69) p<0.001 3. TE + thrombosis RR: 1.60 (0.82–3.17), p=0.178 3. All events RR: 0.66 (0.44–0.99) p=0.046	• The 2° endpoints included endocarditis, hemolysis, hemolytic anemia, PVL, structural and nonstructural dysfunction, postoperative NYHA class and echocardiographic Hemodynamics. • Comments: TTR 63.6% test group (INR 1.5–2.) vs. 69.8% control group (INR 2.0–3.0) • Mean INR 1.89 +/- 0.50 for test group vs. 2.5±0.64 control group (p<0.0001) 14 (3.7%) of pts had AF • Unblinded
AREVA Acar, et al. 1996 (94) 8901659	Aim: To compare moderate oral anticoagulation (INR 2.0–3.0) to higher intensity anticoagulation (INR 3.0–4.5) following single- MV replacement (Omnicarbon or St. Jude) Study type: RCT Size: n=433 pts (380 pts received treatment)	Inclusion criteria: Pts 18–75 y of age, in sinus rhythm, left atrial diameter ≤50 mm Exclusion criteria: Contraindication to anticoagulant therapy, dialyzed renal failure, hepatic insufficiency, refusal to participate	Intervention: INR of 2.0–3.0 (n= 188 pts) Comparator: INR of 3.0–4.5 (n=192 pts)	1° endpoint: Thromboembolic, hemorrhagic events, mortality, endocarditis, withdrawal from oral anticoagulant therapy Safety endpoint (if relevant): None	• Major and minor bleeding events were significantly lower in the INR 2.0–3.0 group vs. the INR 3.0–4.5 group. • NS difference in thromboembolic event rates in the 2.0–3.0 group compared to the 3.0–4.5 group

Hering 2005 (95) 15653962	Aim: To compare rates of thromboembolism and anticoagulation after MHV replacement. Study type: RCT Size: n=2,735 pts	Inclusion criteria: Pts undergoing St. Jude Medical AVR, MVR or combined AVR/MVR between July 1993 and May 1999 Exclusion criteria: Contraindications to anticoagulation with coumarin, Hx or evidence of coagulation abnormalities, preexisting anticoagulant therapy, and/or valve other than SJM valve.	Intervention and Comparator: • Group A: INR 3.0–4.5 • Group B: INR 2.5–4.0 • Group C: INR 2.0–3.5	1° endpoint: Incidence of moderate and severe TEs and bleeding complications Safety endpoint (if relevant): None	• There was no significant difference in incidence of TEs and bleeding complications among the 3 groups. • Further study is needed of the intensity of anticoagulants in pts with SJM valve.
Torella, 2010 (96) 20598989	Aim: To evaluate the safety of lower intensity oral anticoagulation following isolated mechanical AVR Study type: RCT Size: n=396 pts	Inclusion criteria: low-risk pts following bileaflet mechanical AVR Exclusion criteria: Contraindications to anticoagulant treatment, need for mitral or tricuspid valve replacement, , concomitant nonvalve procedure, dialyzed renal failure, hepatic insufficiency and/or refusal to participate	Intervention: Low- INR 1.5–2.5 Comparator: Conventional- INR 2.0–3.0	1° endpoint: Thromboembolic events, including valve thrombosis, ischemic stroke, TIA, coronary and/or peripheral embolism. 2° endpoint: Bleeding events, including intracranial and spinal bleeding, major and minor extracranial bleeding Safety endpoint (if relevant): None	• The mean INR was 1.94 ± 0.21 in the Low INR group and 2.61±0.25 in the Conventional INR group (p<0.001) • No difference in thromboembolic event rates • Total hemorrhagic events occurred in 6 pts in the low INR group vs. 16 pts in the convention INR group (p=0.04) • The low INR is safe and feasible in low risk pts following bileaflet aortic mechanical valve replacement.
Merie, 2012 (97) 23188028	Aim: To assess the association of warfarin treatment with the risk of thromboembolic complications, bleeding incidents and CV death after bioprosthetic AVR Study type: RCT Size: n=4,075 pts	Inclusion criteria: Pts who had bioprosthetic AVR surgery performed between 1/1/1997 and 12/31/2009 Exclusion criteria: Pts with cardiac surgery or other concomitant surgical procedures	Intervention: Discontinued warfarin treatment Comparator: Continued warfarin treatment: 30 to 89 d 90 to 179 d 180 to 364 d 365 to 729 d and At least 730 d after surgery	1° endpoint: Stroke, thromboembolic events, bleeding incidents and CV death. Incidence rate ratios (IRR) were taken at 30–89 d,90–179 d,180–364 d, 365–729 d and at least 730 d after surgery Safety endpoint (if relevant): None Estimated rates of events per 100 person-y in pts not treated with warfarin compared with those treated with warfarin with comparative absolute risk were 7.00 (95% CI: 4.07-12.06) vs. 2.69 (95% CI: 1.49-4.87; adjusted IRR, 2.46; 95% CI: 1.09-5.55) for strokes; 13.07 (95% CI: 8.76-19.50) vs. 3.97 (95% CI: 2.43-6.48; adjusted IRR, 2.93; 95% CI: 1.54-5.55) for thromboembolic events; 11.86 (95% CI: 7.81-18.01) vs. 5.37 (95% CI: 3.54-8.16; adjusted IRR, 2.32; 95% CI: 1.28-4.22) for bleeding incidents; and 31.74 (95% CI: 24.69-40.79) vs. 3.83 (95% CI: 2.35-6.25; adjusted IRR, 7.61; 95% CI: 4.37-13.26) for CV deaths within 30 to 89 d after surgery; and 6.50 (95% CI: 4.67-	• Discontinuation of warfarin within 3 mo of surgery was associated with significant increases in the risks of stroke, thromboembolism and CV death. • Discontinuation of warfarin within 90 to 179 d after surgery was associated with an increased risk of CV death,

				9.06) vs. 2.08 (95% CI: 0.99-4.36; adjusted IRR, 3.51; 95% CI: 1.54-8.03) for CV deaths within 90 to 179 d after surgery.	
Brennan et al, 2012 (98) 22921973	Aim: To evaluate the risks and benefits of short-term anticoagulation in pts receiving an aortic valve bioprosthesis Study type: STS Adult Cardiac Database analysis Size: n=25,656	Inclusion criteria: Pts >65 y who had bioprosthetic AVR surgery performed between 2004–2006 Exclusion criteria: Pts in whom clinical equipoise for anticoagulation was unlikely, including those with preoperative indication for warfarin, an indwelling mechanical valve, a predischarge contraindication to warfarin, a complication related to anticoagulation or those who died before hospital discharge	Intervention and Comparator: • Group A: ASA only • Group B: ASA and warfarin • Group C: Warfarin only	1° endpoint: Death, repeat hospitalization for embolic events or bleeding Among those receiving ASA-only, 3-mo adverse events were low (death, 3.0%; embolic events, 1.0%; bleeding events, 1.0%). Relative to ASA-only, those treated with warfarin plus ASA had a lower adjusted risk of death (RR: 0.80; 95% CI: 0.66–0.96) and embolic event (RR: 0.52: 95% CI: 0.35–0.76) but a higher risk of bleeding (RR: 2.80; 95% CI: 2.18–3.60). Relative to ASA-only, warfarin-only pts had a similar risk of death (RR: 1.01; 95% CI: 0.80–1.27), embolic events (RR: 0.95; 95% CI: 0.61–1.47), and bleeding (RR: 1.23; 95% CI: 0.85–1.79).	• Death and embolic events were relatively rare in the first 3 mo after bioprosthetic AVR • Compared with ASA-only, ASA plus warfarin was associated with a reduced risk of death and embolic events, but at the cost of an increased bleeding risk.
Egbe AC1, et al. 2015 (99) 26610876	Aim: To determine the diagnostic features of BPVT Study type: Pathology database analysis Size: n=46 pts	Inclusion criteria: 46 of 397 consecutive cases of explanted bioprosthesis in the Mayo Clinic pathology database between 1997–2013 which were diagnosed as BPVT, matched 1:2 for age, sex and bioprosthesis position with pts whose valves were explanted for structural failure Exclusion criteria: Pts whose valves were explanted for structural failure	Intervention and Comparator: BPVT vs. structural deterioration of bioprosthesis	Results: 46 cases of BPVT (11.6%; aortic 29, mitral 9, tricuspid 7, pulmonary 1), mean age 63 y, and 68% were male. 30 (65%) cases occurred >12 mo post-implantation; median bioprosthetic valve longevity was 24 mo (cases) vs. 108 mo (controls) (p<0.001). Independent predictors of BPVT were >50% increase in mean echo-Doppler gradient from baseline within 5 y (OR: 12.7), paroxysmal AF (OR: 5.19), subtherapeutic INR (OR: 7.37), increased cusp thickness (OR: 12.2), and abnormal cusp mobility (OR: 6.94). Presence of all 5 diagnostic features was predictive of BPVT with 76% sensitivity, 93% specificity, 85% positive predictive value, and 89% negative predictive value (p<0.001).	• BPVT is not uncommon and can occur several years after surgery. • A combination of clinical and echocardiographic features can reliably diagnose BPVT
Makkar RR, et al. 2015 (100) 26436963	Aim: To investigate the possibility of subclinical leaflet thrombosis in bioprosthetic AVs after TAVR and the effect of anticoagulation Study type: Analysis of 4D volume rendered CT scans from a clinical trial and 2 registries of TAVR	Inclusion criteria: Pts who had 4D volume rendered CT scans following TAVR implantation in a clinical trial and 2 registry studies Exclusion criteria: Pts with unusable scans (33 in clinical trial and 8 in registry studies)	Intervention and Comparator: • Group A: Initiated or continued anticoagulation • Group B: No anticoagulation	Results: Reduced leaflet motion was noted on CT in 22 of 55 pts (40%) in the clinical trial and 17 of 132 pts (13%) in the 2 registries. Reduced leaflet motion was detected among pts with multiple bioprosthesis types, including transcatheter and surgical bioprostheses. Therapeutic anticoagulation with warfarin, as compared with DAPT, was associated with a decreased incidence of reduced leaflet motion (0% and 55%, respectively, p=0.01 in the clinical trial; and 0% and 29%, respectively, p=0.04 in the pooled registries). In pts reevaluated with follow-up CT,	• Reduced aortic-valve leaflet motion was shown in pts with bioprosthetic AV following TAVR. • The condition resolved with therapeutic anticoagulation.

	implantation Size: n=55 pts in a clinical trial of TAVR and from 2 single-center registries that included 132 pts who were undergoing either TAVR or surgical AV bioprosthesis implantation			restoration of leaflet motion was noted in all 11 pts who were receiving anticoagulation and in 1 of 10 pts who were not receiving anticoagulation (p<0.001).	
Hansson NC et al. 2016 (101) 27580689	Aim: To assess the incidence, potential predictors, and clinical implications of THV thrombosis as determined by contrast-enhanced MDCT after TAVR Study type: Analysis of contrast enhanced MDCT scans from consecutive pts undergoing TAVR Size: n=405 pts	Inclusion criteria: 460 consecutive pts who underwent TAVR at a single center between 2011-2016 Exclusion criteria: 55 pts who did not have contrast enhanced MDCT scans at 1-3 mo following TAVR	Intervention and Comparator: • Group A: Treatment with warfarin • Group B: No treatment with warfarin	Results: MDCT verified THV thrombosis in 28 of 405 (7%) pts. A total of 23 pts had subclinical THV thrombosis, whereas 5 (18%) pts experienced clinically overt obstructive THV thrombosis. The risk of THV thrombosis in pts who did not receive warfarin was higher compared with pts who received warfarin (10.7% vs. 1.8%; RR: 6.09; 95% CI: 1.86–19.84). A larger THV was associated with an increased risk of THV thrombosis (p=0.03). In multivariable analysis, a 29-mm THV (RR: 2.89; 95% CI: 1.44–5.80) and no post-TAVR warfarin treatment (RR: 5.46; 95% CI: 1.68–17.7) independently predicted THV thrombosis. Treatment with warfarin effectively reverted THV thrombosis and normalized THV function in 85% of pts as documented by follow-up TEE and MDCT.	• Incidence of THV thrombosis in this large study was 7%. • A larger THV size may predispose to THV thrombosis, whereas treatment with warfarin appears to have a protective effect.
Pache et al 2016 (102) 26446193	Aim: To evaluate the frequency of early hypo-attenuated leaflet thickening of transcatheter AVs Study type: Analysis of ECG gated dual source CTA angiography following TAVR at median of 5 d after implantation Size: n=156 pts	Inclusion criteria: 249 pts who had TAVR at a single institution between 2014-2015 Exclusion criteria: Pts who had a contraindication for CTA due to acute renal failure, impaired renal function, missing consent, or inability to undergo a CTA examination (93 pts)	Intervention and Comparator: • Group A: Presence of hypo-attenuated leaflet thickening • Group B: Absence of hypo-attenuated leaflet thickening	Results: Hypo-attenuated leaflet thickening was found in 16 pts [10.3% (95% CI: 5.5%–15.0%)]. Hypo-attenuated leaflet thickening was not associated with clinical symptoms, but a small, albeit significant difference in mean pressure gradient at the time of CTA (11.6 ± 3.4 vs. 14.9 ± 5.3 mm Hg, p=0.026). Full anticoagulation led to almost complete resolution of hypo-attenuated leaflet thickening in 13 pts with follow-up CTA.	• Hypo-attenuated leaflet thickening occurred in 10% of pts undergoing TAVR • Early hypo-attenuated leaflet thickening is clinically inapparent and reversible by full anticoagulation

Data Supplement 21. *(Updated From 2014 Guideline)* Bridging Anticoagulation Therapy for Mechanical Heart Valves (Section 11.3.2)

Author, Year	Study Type	Patient Population		Study Size and Comparator (N)	Outcomes	Study Limitations
		Inclusion Criteria	Exclusion Criteria			
Hammerstingl C, et al. 2007 (103) 17578050	Prospective, observational	Pts with MHV undergoing major surgery (n=25) or minor surgery (n=36), pacemaker implantation (n=21), or cardiac cath (n=34)	N/A	116 pts: MVR 31) , AVR (76) or DVR (9) Bridging with enoxaparin in all (renal function dose-adjusted)	No thromboembolic (95% CI: 0–3.1%) complications. 1 major bleeding complication (0.86%; 95% CI: 0.02–4.7%). Minor bleeding in 10 pts (8.6%; 95% CI: 4.2–15.3%) at a mean of 5.4±1.4 d LMWH therapy.	Not randomized, no comparison group, relatively small study group.
Spyropoulos, et al. 2008 (104) 18805116	Observational, prospective, multicenter registry in USA, Canada	Adults undergoing elective surgery or invasive procedure with a mechanical valve on long-term VKA	Enrolled in another bridging study within 30 d.	73 with IV UFH (1,535±532 U/h) vs. 172 with SQ LMWH (76% enoxaparin 1 mg/kg bid, 13% dalteparin 100 U/kg bid, 4% tinzaparin 175 U/kg/d)	Major adverse event rates (5.5% vs. 10.3%; p=0.23) and major bleeds (4.2% vs. 8.8%; p=0.17) were similar in the LMWH and UFH groups, respectively; 1 arterial thromboembolic event occurred in each group. More LMWH-bridged pts were treated as out pts or discharged from the hospital in <24 h (68.6% vs. 6.8%; p <0.0001). Multivariate logistic analysis found no significant differences in major bleeds and major composite adverse events when	Not randomized, bridging therapy chosen by clinician. The LMWH group was less likely to undergo major surgery (33.7% vs. 58.9%; p=0.0002) and cardiothoracic surgery (7.6% vs. 19.2%; p=0.008), and to receive intraprocedural anticoagulants or thrombolytics (4.1% vs. 13.7%; p=0.007)
Pengo, et al. 2009 (105) 19470892	Prospective inception cohort at 22 Italian centers, 2005–2007	Adults undergoing surgical or invasive procedures that required interruption of long-term VKA therapy	Body weight <40 kg. Creatinine >2.0 mg/dL, contraindication to LMWH, need for dual antiplatelet Rx	N=189 MHV valve pts (15% of total study size of 1,262). Bridging with 70 anti-Xa U/kg/bid for high-risk pts.	Intention-to-treat analysis for the entire study population: Thromboembolic events in 5 pts (0.4%; 95% CI: 0.1–0.9), all in high-thromboembolic-risk pts Major bleeding in 15 (1.2%; 95% CI: 0.7–2.0) and minor bleeding in 53 pts (4.2%; 95% CI: 3.2–5.5). Major bleeding was associated with twice-daily LMWH (high-risk pts), but not with the bleeding risk of the procedure.	Only 15% had mechanical valves, no comparison group. Safety in pts with MHV valves has not been conclusively established
Daniels, et al. 2009 (106) 19232682	Retrospective cohort, 1997–2003	MHV on chronic VKA therapy undergoing invasive procedures or surgery	N/A	A total of 580 procedures: 372 AVR, 136 MVR and 48 multivalvular.	E LMWH Only N=243 Thromboembol Major	Any UFH N=99	Not randomized, choice of therapy individualized based on estimated TE and bleeding risk.

				UFH or LMWH bridging used in high-risk pts (older AVR, any MVR, additional risk factors for TE). No bridging in isolated AVR pts.	Minor Bleeding Overall cumulative incidence of TE at 3 mo was 0.9%; all 1 wk of the procedure. No TE events VR with no bridging events occurred within in 93 pts with isolated A 13 (6.1) 13 (5.4) 8 (8.1)	
Bui HT, et al. 2009 (107) 19892063	Retrospective cohort study	173 pts on VKA anticoagulation for MHV (n=90) or for nonvalvular AF undergoing invasive or surgical procedures	Age <18 y, Pregnancy, Hypercoagulable condition, bioprosthetic valve	130 bridging episodes with LMWH were used to compare outcomes in MHV vs. pts with AF.	No deaths or thromboembolic events at 2 mo. Major and minor bleeding rates were similar between the MHV and AF groups (3.2% and 2.9%, 14.5% and 13.2% respectively, p=NS).	Isolated AVR in 43 (48%) of mechanical valve pts. Not randomized. Comparator group of AF may not require bridging. No sample size calculation for power of study.
Biteker, et al. 2012 (108) 22591673	Prospective cohort, single-center	Consecutive pts undergoing noncardiac surgery	Bioprosthetic valves, severe liver or renal disease, contraindication to heparin	140 pts with MHV (77 AVR, 46 MVR, and 17 DVR) receiving enoxaparin 1 mg/kg bid compared to 1,200 pts with native valves (control group) receiving no anticoagulation.	E v e MHV with LMWH N=140 Native valves N=1200 Ble 18.6% 14.2% Thr 3.6% 2% Mor 1.4% 1.3% Car 10.8% 10.7%	Not randomized. Comparison group did not have valve disease. No power calculation with small number of MHV pts.
Weiss, et al. 2013 (109) 23648452	Retrospective, single-center cohort study	Consecutive pts requiring postoperative bridging therapy after cardiac surgery during a 19 mo period	N/A	N=402 receiving LMWH (enoxaparin): comparison of full-dose (FD=1 mg/kg bodyweight bid) to half-dose (HD=0.5 mg/kg bid) with renal function dose adjustment.	E v e n ts / Full dose LMWH Low dose LVWH N=210 N=210 Mor 0.5% 5.5% Thr 5% 9% Ble 11% 5% Hos 15.1±9.3 12.5±8.1	Not randomized, but well matched (first half of cohort received FD, second half HD) Included only 100 (25.9% of total) pts with MHV, also included AF in 83.6%.

(BRIDGE) Douketis, et al. 2015 (110) 26095867	RCT, double-blind, placebo-controlled trial	Pts with chronic AF or flutter receiving warfarin therapy for at least 3 mo undergoing elective surgery	Mechnical heart valve, at least 1 CHADS2 risk factor cardiac, intracranial or intraspinal surgery.	N=1884; 950 with no bridging therapy. 934 assigned to bridging with low-molecular-weight heparin (100 IU of dalteparin per kilogram of body weight) or matching placebo administered subcutaneously twice daily, from 3 d before the procedure until 24 h before the procedure and then for 5 to 10 d after the procedure.	The incidence of arterial thromboembolism was 0.4% in the no-bridging group and 0.3% in the bridging group (risk difference, 0.1 percentage points; 95% CI: −0.6 to 0.8; p=0.01 for noninferiority). The incidence of major bleeding was 1.3% in the no-bridging group and 3.2% in the bridging group (RR: 0.41; 95% CI: 0.20–0.78; p=0.005 for superiority).	Population excluded pts with MHV and was predominantly low risk for thromboembolism.
Pengo, et al. 2007 (111) 17636186	Randomized, prospective, multicenter, pilot study	Inclusion: Consecutive pts having AVR and/or MV replacement with MHVs for the first time.	Exclusion: Need for adjunctive antiplatelet therapy, ASA allergy/ intolerance; combined CABG, emergency surgery, follow-up problems, poor compliance, renal or hepatic insufficiency, life expectancy <12 mo	Pts randomized to 2 groups; Group A (n=94): receiving low-intensity VKA treatment (target INR 2.5) [plus ASA (100 mg/d) for the first 6 mo]; Group B (n=104): receiving standard-intensity (moderate to high) VKA treatment (target INR 3.7).	1° outcomes: • Systemic embolism/thromboembolic complications • Major bleeding/bleeding complications • Vascular death Cumulative 1° outcome incidence: GROUP A - 5.8% (95% CI: 0.9–10.7) GROUP B – 4.3% (95% CI: 0.2–8.4), p=0.6 Low-intensity VKA plus ASA for first 6 mo appears as effective and safe as standard-intensity VKA.	Pts: • Received subcutaneous unfractionated heparin for 2 consecutive d until INR >2.0 • Stratified by: aortic, mitral, double valve replacement • Randomized to Group A or B at first warfarin administration in blocks of 10 • In addition to warfarin, Group B pts received 100 mg ASA from operation to 6 mo. Analysis: • Large trial should involve sample size of 350 pts in each group.

Data Supplement 7. Prosthetic Valve Thrombosis (Section 11.6)

Study Acronym; Author; Year Published	Aim of Study Type/Design; Study Size	Patient Population	Study Intervention (# patients) & Study Comparator (# patients)	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Keuleers S, et al. 2011 (112) 21211605	Aim: to review the outcome of TT vs surgery for obstructive PVT Study type: Single-center retrospective study Size: n=30 pts with mechanical PVT (1 bioprosthesis)	Inclusion criteria: prosthetic valve dysfunction with thrombus present Exclusion criteria: Patient Population: 81% women, mean age 59, NYHA Class IV 42%, all mitral	Intervention: tPA 10 mg then 90 mg over 2 h (13 pts) Comparator: surgery (18 pts)	1° endpoint: Complete clinical response =complete hemodynamic response (normalization of gradient with complete leaflet opening on fluoroscopy) in absence of major complication Results: Complete clinical response 62% partial response in 31% in obstructive. Size of thrombus not related to outcome. Complications: 2 deaths at surgery, recurrence 31% in TT group with 1 death, other TT complications 1 CVA 1	• Conclusion: TT can be given to pts with PVT with outcomes similar to standard surgical therapy • Limitation; single-center study with small number of pts and no standardized approach to treatment • Comments: Authors felt TT is an attractive first line therapy for PVT

				TIA 1 bleed 2 emboli	
Nagy A et al 2009 (113) 19557981	Aim: to assess effect of thrombus size, severity of symptoms and type of valve on success and complication rate of TT for PVT Study type: Single-center retrospective study Size: n=62 episodes in 55 pts identified by TEE	Inclusion criteria: obstructive – restricted leaflet motion with increased gradient, non-obstructive – thrombus on TEE Exclusion criteria: Patient Population: 61% women, mean age 56, NYHA Class III/IV 71% in obstructive, valve type (mitral 62), 52 obstructive 10 nonobstructive. Average thrombus area 1.06 cm2 obstructive and 0.59 cm2 in nonobstructive	Intervention: bolus and continuous infusion of SK, UK up to 72 h Comparator: N/A	1° endpoint: complete clinical response =complete hemodynamic response (normalization of gradient with complete leaflet opening on fluoroscopy) in absence of major complication Results: complete clinical response 73% partial response in 21% in obstructive. Size of thrombus not related to outcome. Complications: 3 deaths after surgery from failed TT, 4 deaths from complications of TT. 5 CVA, 1 TIA, 1 cerebral bleed, 2 major bleed, 2 embolic events.	• Conclusion: Size of thrombus unrelated to success or complication rate. NYHA Class III/IV presentation vs I/II – no difference in success or complication rate of TT • Limitation; single-center study with loss of followup – cannot compare TT mortality vs surgical mortality as 2/3 had surgery after failed TT •Comments: Intention to treat TT mortality 11% and surgical mortality 44% - overall TT mortality 6% and surgical mortality 26%
Lengyel M et al 2001 (114) 11603604	Aim: to compare the efficacy and safety of heparin vs TT vs surgery in pts with both obstructive and nonobstructive PVT Study type: Single-center retrospective study Size: 85 episodes in 59 pts identified by TEE	Inclusion criteria: obstructive – restricted leaflet motion with increased gradient, nonobstructive – thrombus on TEE Exclusion criteria: recurrent PVT or contraindication to TT Patient Population: 58% women, mean age 53, NYHA Class III/IV 90% in obstructive, valve type (mitral 41 aortic 3), 54 obstructive 31 nonobstructive	Intervention: Obstructive - heparin or TT (SK or UK load with continuous infusion until successful) as initial therapy in 30 mitral and 2 aortic obstructive, surgery in 9 mitral and 1 aortic, Nonobstructive-heparin first Comparator: N/A	1° endpoint: complete clinical response =complete hemodynamic response (normalization of gradient with complete leaflet opening on fluoroscopy) in absence of major complication Results: complete clinical response 86% partial response in 9% with TT – heparin ineffective with both obstructive and no obstruction with half leading to obstruction Complications: 1 death heparin, 6 deaths surgery, of 43 TT, 4/43 CVA, 1/43 major bleed	•Conclusion: TT was best in both NYHA class I/II as well as NYHA Cass III/IV due to high risk surgery. Heparin ineffective in both obstructive and nonobstructive •Limitation; single-center without a standard process to decide therapy – cannot compare results of high mortality with surgery (29%) to mortality with TT (6%) as sicker pts in the surgery group •Comments: heparin alone inadequate in 82%. Authors state that TT is treatment of choice for all pts with PVT.
Karthikeyan G et al 2009 (115) 19738134	Aim: to compare the efficacy and safety of an accelerated infusion vs conventional infusion of SK in pts with PVT Study type: Randomized controlled prospective trial Size: 120 pts entered into randomization for PVT	Inclusion criteria: first episode of left sided PVT (immobile or hypomobile leaflets on flouroscopy) Exclusion criteria: recurrent PVT or contraindication to TT Patient Population: 44% women, mean age 33, NYHA Class III/IV 31%, valve type (mitral 79, aortic 30, both 11), all obstructive	Intervention: accelerated 1.5 million units (MU) SK bolus followed by .1 MU/h vs .25 MU bolus followed by .1 MU/h up to 96 h Comparator: N/A	1° endpoint: complete clinical response =complete hemodynamic response (normalization of gradient with complete leaflet opening on fluoroscopy) in absence of major complication Results: complete clinical response 58%, complete hemodynamic response 63%. No difference in the 2 infusions in terms of response or complications Complications: 20 deaths, 6 embolic events, 11 major bleeding with 5 intracranial hemorrhage	•Conclusion: no statistically significant difference in the outcome of the 2 infusion rates, although there was a trend toward more major bleeding in the accelerated infusion group •Limitation: underpowered to show a difference between the 2 groups. TEE was not performed. •Comments: complete clinical response 74 % in NYHA Class I/II and 24% om NYHA Class III/IV. Only randomized trial thus far with TT therapy, showing a lower success rate than prior studies

Caceres-Loriga et al 2006 (116) 16622616	Aim: To determine the efficacy and safety of TT for PVT Study type: Single-center retrospective review Size: 69 consecutive pts with PVT	Inclusion criteria: Consecutive pts presenting with left sided obstructive PVT and no contraindication to TT Exclusion criteria: 2 pts with a contraindication to TT Patient Population: 78% women, mean age 40 y, NYHA Class III/IV 94%, valve type (mitral 50, aortic 9, tricuspid 9) all obstructive	Intervention: bolus and continuous infusion of SK up to 72 h Comparator: N/A	1° endpoint: complete hemodynamic response (normalization of gradient with complete leaflet opening on fluoroscopy) Results: complete hemodynamic response 80.6%, partial response 8.3%, no response 11%. Complications: 4 deaths, 5 embolic complications (3 CVA and 5 TIA), 3 major hemorrhage (2 intracranial bleeding). 16% had recurrence in follow-up.	●Conclusion: TT is effective in 80% of pts but with a high rate of embolism, Recurrence rate is high. ●Limitation: Single-center retrospective study Comments: Authors recommended TT as first line of therapy in all pts
Gupta et al 2000 (117) 11099995	Aim: To determine the short and long-term results of TT for PVT Study type: Single-center retrospective review Size: n=110 consecutive pts with obstructive PVT	Inclusion criteria: All pts presenting with left sided obstructive PVT and no contraindication to TT Exclusion criteria: 6 pts with contraindication to thrombolysis Patient Population: 53% women, mean age 68, NYHA Class III/IV 80%, valve type (mitral 96, aortic 14), all obstructive	Intervention: Bolus and continuous infusion of SK up to 72 h Comparator: N/A	1° endpoint: Complete hemodynamic response (normalization of gradient with complete leaflet opening on fluoroscopy) Results: Complete hemodynamic response 81.8%, partial response 10%, and no response 8.2%. 23% had recurrence in follow up. Complications: 8 deaths, 21 embolic complications (6 CVA and 5 TIA), 9 major hemorrhage (5 intracranial bleeding)	●Conclusion: TT is effective in 80% of pts but with a high rate of embolism, particularly if in AF. Recurrence rate is high. ●Limitation: Single-center study with 10% lost to follow-up. TEE was not done in majority. ●Comments: pts who died were primarily those with severe Class IV HF and 3 died within 2 h of infusion (not enough time for TT to work), of incomplete responders only 3/11 did well
Roudaut et al 2009 (118) 19427604	Aim: To define the efficacy and safety of thrombolysis vs surgery for PVT Study type: Single-center retrospective review Size: n=210 pts; treated by TT (n=127 pts) or surgery (n=136 pts)	Inclusion criteria: All pts at single institution treated for PVT Exclusion criteria: None Patient Population: 66% women, mean age 59, NYHA Class III/IV 66%, valve type (mitral 169, aortic 84, tricuspid 4), obstructive/nonobstructive 148/25	Intervention: SK (49), UK (41), rTPA (37), combination (38) Comparator: surgery with either valve replacement (106) or declotting pannus excision (30)	1° endpoint: Hemodynamic success (complete normalization of hemodynamics by echo and fluoroscopy) Results: Hemodynamic success higher in surgery 89% vs TT group 71% Complications: Mortality similar (10%) both groups, total complications (25% vs 11%) and embolic events (15% vs 0.7%) higher in TT vs surgery group	●Conclusion: Surgery had a higher success rate and lower complication rate than TT ●Limitation: Single-center experience which changed over time – surgery the more preferred therapy with time ●Comments NYHA class at presentation was strongest predictor of late death. Long-term follow-up at 6 y– better outcome in terms of mortality and recurrence with surgery 76% of pts were subtherapeutic on their INR before presentation, 23% had temporary cessation of warfarin

Tong AT et al. 2004 (119) 14715187	Aim: To determine whether thrombus size can predict outcome of thrombolysis therapy for PVT Study type: Registry of TEE performed prior to TT for PVT Size: n=107 pts entered into registry	Inclusion criteria: Pts suspected of PVT obstruction or thrombus formation undergoing TEE prior to TT Exclusion criteria: Patient Population: 107 pts from 14 centers, 71% women, mean age 54, valve type (19 mitral, 13 aortic, 15 tricuspid), NYHA Class III-IV 63%, 99 obstructive vs 14 nonobstructive	Intervention: Slow infusion SK (54%), UK (17%) or tPA (29%) Comparator; N/A	1° endpoint: Complete hemodynamic success (hemodynamics to normal range), partial hemodynamic success (partial improvement in hemodynamics), clinical success (hemodynamic success without complication) Results: Complete hemodynamic success 76%, partial hemodynamic success 8.6%, clinical success 74% Complications: Overall complications in 17.8%. Death 5.6%, left sided embolic rate 14%, major complication of death, CVA, MI, cerebral bleed in 9.3%	•Conclusion: Thrombus area >0.8cm2, Hx of stroke and NYHA Class III/IV was predictive of complications and poor outcome •Limitation Registry study from 14 centers with strict inclusion criteria and differing thrombolytic regimens – a study more of the TEE predictors rather than outcome of thrombolysis •Comments: Soft mass increased success to 91% but still 75% success without soft mass Thrombus size was an important predictor of complication even in Class III/IV pts
TROIA Trial. Ozkan M, et al 2013 (120) 23489534	Aim: To identify the most effective and safest TEE-guided thrombolytic regimen for PVT. Study type: Single-center, non-randomized, prospective Size: 182 consecutive pts with 220 episodes of PVT	Inclusion criteria: Pts with obstructive PVT, nonobstructive PVT with recent thromboembolism, or a thrombus diameter of ≥10 mm Exclusion criteria: Contraindication to TT, nonobstructive PVT with a thrombus diameter of <10 mm and no recent thromboembolism, prosthetic valve obstruction with no thrombus on TEE and normal prosthetic valve leaflet motion Patient population: 182 pts, 71% female, nean age 43, 41% NYHA Class III/IV, valve type (84% mitral, 10% aortic,) 48% obstructive, 52% nonobstructive	Intervention: Different thrombolysis regimens: Group I: Rapid streptokinase (16) Group II: Slow streptokinase (41) Group III: High dose tPA (12) Group IV: Half dose, bolus and slow tPA infusion (27) Group V: low dose, non –bolus and slow tPA infusion (124) Comparator: N/A	1° endpoint: Thrombolytic success Obstructive: Decrease gradient, 75% reduction in thrombus size and clinical improvement (complete all 3, partial <3) Nonobstructive: >75% reduction thrombus size Results: Successful thrombolysis in 83.2% of cases (68.8%, 85.4%, 75.0%, 81.5%, 85.5% respectively; p=0.46) Complications: Overall complication rate of 18.6%. Lower combined complication rate in Group V (10.5%) vs. other groups (24%–38%) Absence of mortality in Group V. The predictors of combined mortality plus nonfatal major complications were any TT regimen other than Group V (OR group 1 through IV: 8.2, 3.8, 8.1 and 4.1 respectively; p<0.05 for each)	•Conclusion: Low-dose nonbolus slow tPA infusion resulted in the highest success rate of thrombolysis and lowest combined complication rate. •Limitation: single-center nonrandomized study with small number of pts in each group. included both obstructive and nonobstructive PVT •Comments: 64 pts who had a contraindication to thrombolysis or failed thrombolysis underwent surgery with a 17% mortality
Ozkum M et al, 2013 (121) 23812180	Aim: To evaluate the safety and efficacy of low-dose, slow infusion tPA activator for the treatment of PVT in pregnant women	Inclusion criteria: Pregnant pts. with obstructive and nonobstructive PVT with recent thromboembolism and thrombus diameter of >5mm and pts with asymptomatic mobile nonobstructive PVT with thrombus	Intervention: Low dose tPA – 25 mg over 6 h, repeat at 24 h Comparator: N/A	1° endpoint: Thrombolytic success Obstructive: Decrease gradient, 75% reduction in thrombus size and clinical improvement (complete all 3, partial <3) Nonobstructive: >75% reduction thrombus size Result: 100% thrombolytic success. (Obstructive PVT group thrombus area, mean, 1.7±1.2 cm^2; range, 0.8–6	• Conclusion: low dose slow infusion of tPA is an effective and safe regiment for PVT in pregnant women • Limitation: single-center nonrandomized trial with small number of pts,: included both obstructive and nonobstructive PVT

	Study type: Single-center, nonrandomized, prospective (subgroup of TROIA trial) Size: 24 consecutive pregnant pts with 28 episodes of PVT (all mitral – 23 mechanical)	diameter of ≥10 mm Exclusion criteria: Pts. with contraindication to TT, asymptomatic non obstructive PVT with a thrombus diameter of <10mm and no recent thromboembolism, pts with imminent abortion or placenta pervia, pts with prosthetic valve obstruction with no thrombus on TEE and normal prosthetic valve leaflet motion Patient population: 24 women during 25 pregnancies and 28 episodes PVT, mean age 29, mean gestational age 19 wk, NYHA class III/IV (50%) obstructive in 15 (all mitral), nonobstructive in 13		cm^2 ; nonobstructive PVT group, mean, 0.9±0.4 cm^2; range, 0.4-1.8 cm^2; p=0.022 . No remaining thrombus after TT on TEE) Complications: no complications in the mother, 20 live births with 1 placental hemorrhage and 1 minor bleeding, 20% miscarraiges	•Comment: this is a subset of the Ozkun 2013 series.
PORMETEE Trial Ozkun M et al 2015 (122) 26299240	Aim: To identify the efficacy and safety of TEE-guided ultraslow infusion of low-dose tPA for PVT. Study type: Single-center, nonrandomized, prospective Size: 114 consecutive pts with120 episodes of PVT (113 mechanical PVT)	Inclusion criteria: Pts with obstructive PVT, nonobstructive PVT with recent thromboembolism, or a thrombus diameter of ≥10 mm Exclusion criteria: Contraindication to TT, nonobstructive PVT with a thrombus diameter of <10 mm and no recent thromboembolism, Prosthetic valve obstruction with no thrombus on TEE and normal prosthetic valve leaflet motion Patient Population: 65% female, mean age 49, NYHA Class III/IV (35%), obstructive in 77 (23 aortic, 48 mitral 4 tricuspid, 2 double valve), nonobstructive in 43 (10	Intervention: Low dose tPA – 25 mg over 6 h, repeat every 24 h Comparator: N/A	1° endpoint: Thrombolytic success Obstructive: Decrease gradient, 75% reduction in thrombus size and clinical improvement (complete all 3, partial <3) Nonobstructive: >75% reduction thrombus size Result: Successful thrombolysis in 90%. Only independent predictor of unsuccessful result was higher NYHA Class. Complications: Total complications in 8 pts (6.7%) – death (0.8%), major complication (3.3%), minor complication (2.5%). – 1 stroke, 1 peripheral embolism and 4 hemorrhage	•Conclusion: Low dose nonbolus slow tPA infusion resulted in the high success rate of thrombolysis (90%) and low combined complication rate (embolism 1.7%, major bleed 1.7% minor bleed 1.7%) •Limitation: single-center nonrandomized study with small number of pts, included both obstructive and nonobstructive PVT. Only 4 pts were in NYHA Class IV •Comments: success rate 20% after first dose and required up to 8 doses, Median number sessions =2, median dose tPA = 64 mg

		aortic, 26 mitral, 7 double valve)			
Barbetseas, et al. 1998 (123) 9809956	Aim: To determine the clinical and echocardiographic parameters to differentiate thrombus from pannus formation for obstructed mechanical prostheses Study type: Prospective observational	Inclusion criteria: 23 pts with 24 obstructed mechanical prostheses (surgical confirmation) Exclusion criteria: N/A	Intervention: 14 pts thrombus Comparator: 10 pts pannus	1° endpoint: 14 pts thrombus vs. 10 pts pannus Results: Pts with thrombus • Shorter duration of symptoms • Lower rate of anticoagulation TEE soft mass • 92% of thrombus • 29% of pannus	• Duration of symptoms and anticoagulation status and ultrasound intensity of mass can differentiate pannus from thrombus
Gunduz, et al. 2015 (124) 26659372	Aim: To determine the utility of MDCT to differentiate thrombus from pannus formation for obstructed mechanical prostheses Study type: Observational	Inclusion criteria: 62 pts with mechanical prosthesis (thrombolysis success or surgical confirmation)	Intervention: N/A Comparator: N/A	1° endpoint: Definitive dx 37 pts: 22 thombus and 17 pannus Attenuation value of Hounsfield Units (HU) differentiated thrombus from pannus HU >145 units for differentiating thrombus from pannus • 87% sensitivity • 95% specificity Safety endpoint: N/A	• 64 slice MDCT is helpful in differentiating pannus from thrombus in pts with mechanical prosthetic obstruction
Cianciulli, et al. 2005 (125) 16245506	Aim: To determine the benefit of cine-flouroscopy for mechanical prosthetic valve dysfunction Study type: Observational	Inclusion criteria: 229 pts with mechanical valve prosthesis underwent Doppler echocardiography and fluoroscopy. n=221 prosthetic valves for analysis Exclusion criteria: LV dysfunction (n=8 pts)	Intervention: N/A Comparator: N/A	1° endpoint: Flouroscopy identified 87 single leaflet and 134 bileaflet prosthesis • Disk motion differentiated between normal and abnormal prosthetic function by opening angle • Normal 74 +/- 13 degree Abnl 49 +/- 18 degree Safety endpoint: N/A	• Flouroscopy is superior to echo in identifying disc motion, while Doppler allows measurement of gradient
Montorsi, et al. 2000 (126) 11078238	Study type: Observational; to evaluate the diagnostic efficacy of cine-flouroscopy, TTE and TEE Size: n=82 pts	Inclusion criteria: consecutive pts with mechanical valves and suspected valve thrombosis Exclusion criteria:	Intervention: N/A Comparator: N/A	1° endpoint: Gp A – positive flouro and positive TTE Gp B – positive flouro and negative TTE Gp C- negative flouro and positive TTE Gp D – negative flouro and negative TEE Results: TEE is not required in Gp A TEE showed thrombus in 33% of Gp B TEE ruled out thrombus in Gp C	• TEE is the gold standard for dx of prosthetic valve thrombosis when either fluoroscopy and TTE are nondiagnostic

				TEE showed thrombus in 14% of Gp D	
Muratori, et al. 2006 (127) 16377291	Study type: Observational; to evaluate the diagnostic accuracy of TTE and TEE for leaflet motion in pts with mechanical prosthesis Size: n=111 pts	Inclusion criteria: Pts with mechanical prosthesis for cardioversion or suspected valve dysfunction Exclusion criteria:	Intervention: N/A Comparator: N/A	1° endpoint: Mitral prosthesis • 18 single disk • 48 bileaflet Aortic prosthesis • 22 single disk • 23 bileaflet Results: Accuracy for leaflet motion Mitral prosthesis • TTE 85% • TEE 100% Aortic prosthesis • TTE 13% • TEE 35%	• TEE is accurate for leaflet motion with MVR and but not for AVR
Suy, et al. 2016 (128) 27096962	Study type: Observational; to evaluate the additive value of cardiac CT in suspected mechanical valve dysfunction Size: n=25 pts	Inclusion criteria: Pts who underwent repeat AVR due to valve dysfunction Exclusion criteria: N/A	Intervention: N/A Comparator: N/A	1° endpoint: CT feasible in 23 pts. Results: In 11 of 13 pts with inconclusive TEE, CT identified pannus. Accuracy for pannus formation – 100% Accuracy for leaflet motion – 61%	• CT was additive to TEE in determination of mechanical valve dysfunction
Symersky P, et al 2009 (129) 19801036	Study type: Observational; to evaluate the additive value of cardiac CT in suspected mechanical valve dysfunction Size: n= 13 pts with 15 prosthetic valves	Inclusion criteria: Pts with prosthetic valves in whom obstruction was suspected but no cause found Exclusion criteria: N/A	Intervention: N/A Comparator: N/A	1° endpoint: CT identified morphologic etiology of obstruction in 8 of 13 pts, confirmed at surgery in 6 pts Results: Findings by CT: • Sub-prosthetic substrate – 8 pts • Leaflet motion restriction - 7 pts	• Multidetector CT scan can identify causes of abnormal prosthesis function which are missed at echocardiography or flouroscopy

Data Supplement 7A. Prosthetic Valve Thrombosis (Section 11.6)

Treatment	Name	Date	Episodes	Obstructive/ Nonobstructive	Complete success (%)	Partial success (%)	Overall Complication Rate (%)	Mortality (%)	Major Bleed (cerebral hemorrhage)(%)	Embolism (CVA/TIA) (%)	Recurrence (%)	Treatment	Type study	Other
TT prior 2013	Gupta	2000	110	110	81	10	27	7.3	9(4.5)	19(8.1)	25	SK	Single center	
TT prior 2013	Lengyl	2001	85	54/31	86	9	17	4.6	2.3	9.3		SK,UK,tPA	Single center	Compare heparin vs TT vs surgery
TT prior 2013	Tong	2004	107	99/14	76	8.6	18	5.6	5.6 (1.9)	14 (5.6)		SK,UK,tPA	Registry	Thrombus size on TEE predictive of outcome
TT prior 2013	Caceres-origa	2006	68	68	80	3.6	22	5.9	4.4 (2.9)	7.4 (4.4)	16	SK	Single center	
TT prior 2013	Roudaut	2009	127	115/12	71	17.3	25	11.8	4.7 (1.6)	15 (11)	24.7	SK,UK,tPA	Single center	Compare with surgery - similar oratily but higher complication rate with TT
TT prior 2013	Karthikeyan	2009	120	120	63		17	7.5	9.1 (4.1)	5.0		Acclerated SK vs conventional SK	Randomized trial	No difference in accelerated dose aside from trend to increased bleeding
TT prior 2013	Nagy	2009	62	52/10	77	21	18	11	4.8 (2)	13(5.8)	11	SK,UK,tPA	Single center	Determine lack of effect of thrombus size on outcome
TT prior 2013	Keuleers	2011	13	13	61	31	38	7.6	7.6	30(15)	31	Conventional tPA	Single center	Compare surgical vs TT
TT prior 2013	Ozkun	2013	220	105/106	83		19	2.7	9 (3.1)	8 (6.8)		5 regimens	Single center	Low dose tPA safest and best
	TT overall before 2013				75 +/- 8	14 +/-8	22+/-6	7+/-3	6.3 +/-2.3(2.8+/-1.0)	13.4 +/- 7.1 (8.1+/-3.4)	21 +/- 7			
Surgery	Deveri	1991	106	106	100			12.3				Surgery	Single center	Overall surgical mortality related to

														NYHA Class I-III(4.75) vs IV(17.5%)
Surgery	Roudaut	2009	136	136	100			10.3		0.7	11.5	Surgery	Single center	Compare surgical vs TT
Surgery	Keuleers	2011	18	18	100			11			11	Surgery	Single center	Compare surgical vs TT
Surgery	Karthikeyan	2013	446	446	100			13.5	1.4	1.6	7.1	Surgery	Literature survey	Surgical outcome from 7 studies
Surgery	Huang	2013	662	662	100			15		6	6	Surgery	Literature survey	Compare surgical vs TT
	Surgical overall				100			12.4 +/- 1.7		2.7 +/-2.3	8.9 +/- 2.4			
TT - low dose	Ozkun	2013	28	15/13	100		0	0	0 (0)	0 (0)	0	Low dose tPA	Single center	Pregnant pts
TT - low dose	Ozkun	2015	114	77/43	90		6.7	0.8	1.7 (0)	1.7 (0.8)	6	Low dose tPA	Single center	Prospective use of low dose tPA

Data Supplement 8. Selective Studies of VKA in Patients with Bioprosthetic Valve Thrombosis (Section 11.7.3)

Author; Year Published	Study Type/Design; Study Size	Patient Population	Endpoints and Results	Comment(s) / Summary/ Conclusion
Jander, et al. 2012 (130) 22000772	Study type: Retrospective Size: n= 6 pts	Inclusion criteria: Pts presenting with obstructive BPV (of all pts who received a single stented bioprosthetic AV); 01/2007-12/2008; single hospital.	Endpoints: MPG Results: • 5 pts were started on phenprocoumon and followed for 114±54 d. • Follow-up MPG 23.5±6 mm Hg (from peak of 57.0±10 mm Hg).	• All 6 pts had received a porcine valve, were hemodynamically stable, and were taking ASA 100 mg/d. • Echocardiography showed an increase in MPG early postoperatively from 23.3±4–57.0±10 mm Hg (p <0.001). • No adverse events were observed with phenprocoumon. • The authors concluded that *'oral anticoagulation with phenprocoumon is a safe and effective treatment in clinically stable pts with obstructive BPVT, thus obviating repeat valve surgery or thrombolysis'.*
Butnaru, et al	Study type:	Inclusion criteria: 9 pts with clinical or	Endpoints: echocardiographic findings (transvalvular gradient, thrombus)	• 5 of the 9 pts presented with HF symptoms at 16±12 mo after implantation.

2013 (131) 23891426	Retrospective Size: n=9 pts	echocardiographic evidence of valve malfunction were identified after screening 149 consecutive pts who underwent MVR with a bioprosthesis; 2002-2011; single center	Results: • Mitral BVPT thrombosis occurred in 9 pts (6%). • Of those, 6 pts received anticoagulation with resolution of the echocardiographic findings (reduction in gradients; complete thrombus resolution).	• The authors concluded that *'surgery should be reserved for those who are not responsive or pts in whom the hemodynamic status does not allow delay'.*
Pislaru, et al 2015 (132) 24829402	Study type: Retrospective Size: n=31 pts	Inclusion criteria: pts diagnosed with BPVT; 1997-2013; single institution	Endpoints: MPG, clinical outcomes (NYHA class, death, stroke, embolic events) Results: • Pts treated initially with VKA group (N = 15) were compared to surgery /thrombolysis (N = 17); [non-randomized]. • VKA and surgery/thrombolysis decreased MPG to a similar extent: VKA group: 13±5–6 ±2 mm Hg in mitral position, 9 ± 3–5 ± 1 mm Hg in tricuspid position and 39±3–24±7 mm Hg in aortic/pulmonary position; non-VKA group: 16 ± 12–5 ± 1 mm Hg in mitral, 10 ± 5–4 ± 1 mm Hg in tricuspid and 57 ± 9–18 ± 6 mm Hg in aortic position (p=0.59 for group effect). • NYHA class improved in 11 of 15 pts in the VKA group and 10 of 17 pts in the non-VKA group (p=0.39). • No deaths, strokes or recognized embolic events in either group.	• Peak incidence of BPVT was 13-24 mo after implantation in both groups. • 1 pt in each group experienced gastrointestinal bleeding requiring transfusion. • The authors concluded that *'VKA therapy resulted in hemodynamic and clinical improvement with minimal risk, and should be considered the first-line therapy in hemodynamically stable pts'.*
Makkar, et al 2015 (100) 26436963	Study type: Retrospective Size: n=187 pts	Inclusion criteria: Study analyzed data from 55 pts in a TAVR clinical trial, and 2 single-center registries of 132 pts undergoing either TAVR or surgical AV bioprosthesis implantation	Endpoints: 4D CT imaging (for reduced leaflet motion detection), clinical outcomes Results: • Therapeutic anticoagulation with warfarin (as compared with DAPT), was associated with lower incidence of reduced leaflet motion (0% and 55%, respectively, p=0.01 in the clinical trial; and 0% and 29%, respectively, p=0.04 in the pooled registries). • In pts reevaluated with follow-up CT: restoration of leaflet motion was noted in all 11 pts who were receiving anticoagulation and only 1 of 10 pts not receiving anticoagulation (p<0.001).	• Sophisticated 4-D volume-rendered CT scan imaging was used to detect reduced leaflet motion • Reduced leaflet motion was noted on CT in 40% in the clinical trial and in 13% in the 2 registries • No differences in stroke or TIA between pts with reduced vs. normal leaflet motion in the clinical trial; a significant difference was detected in the pooled registries, (p=0.007). • The authors concluded: *"Reduced aortic-valve leaflet motion was shown in pts with bioprosthetic aortic valves. The condition resolved with therapeutic anticoagulation".*
Latib, et al. 2015 (133) 25873727	Study type: Retrospective Size: n=26 pts	Inclusion criteria: Pts with THV thrombosis (from a cohort of 4266 pts undergoing TAVR), 01/2008- 09/2013, 12 centers.	Endpoints: frequency/time frame, clinical/ echocardiographic and treatment correlates of THV thrombosis Results: • Echocardiographic findings: elevated MPG (41±14 mm Hg); thickened leaflets or thrombotic apposition of leaflets in 77% of pts, and a thrombotic mass on leaflets in 23% of pts.	• THV thrombosis definition: (1) THV dysfunction 2° to thrombosis diagnosed based on response to anticoagulation therapy, imaging or histopathology; or (2) mobile mass detected on THV suspicious of thrombus, irrespective of dysfunction and in absence of infection. • 26 (0.61%) pts had THV thrombosis after TAVR implantation; median time to thrombosis post-TAVR: 181 d (interquartile range, 45-313); most common clinical presentation: exertional dyspnea (65%).

			• Anticoagulation resulted in a significant decrease in AV MPG in 88% of pts within 2 mo.	• The authors concluded: *'THV thrombosis is a rare phenomenon that was detected within the first 2 y after TAVR and usually presented with dyspnea and increased gradients. Anticoagulation seems to have been effective and should be considered even in pts without visible thrombus on echocardiography.'*
De Marchena, et al. 2015 (134) 2594644	Study type: Retrospective Size: n=4 pts	Inclusion criteria: Pts with THV thrombosis	Endpoints: Pathological/clinical correlates of early thrombosis after TAVR Results: • 2 of the 4 cases had increasing MPG post-TAVR. • 1 case was medically treated with oral anticoagulation with normalization of gradients.	• All 3 pathology cases showed presence of a valve thrombosis in at least 2 bioprosthetic leaflets on autopsy (not previously visualized by echocardiogram) • The authors did a complimentary literature review and found 18 cases of early valve thrombosis after TAVR: in 12 of those, early anticoagulation therapy resolved the thrombus formation and normalized pressure gradients. • The authors concluded: *"Consideration should be given to treatment with dual antiplatelet therapy and oral anticoagulation in pts post-TAVR with increasing mean pressure gradients and maximum aortic valve velocity".*

Data Supplement 9. Clinical Outcomes With VIV Procedures (Sections 11.7.3 and 11.8.3)

Author; Year Published	Study Type/Design; Study Size	Patient Population	Endpoints and Results	Comment(s) / Summary/ Conclusion
Ye J, et al, 2015 (135) 26476608	Study type: registry Size: n=73 pts (of whom 42 had VIV for bioprosthetic AV).	Inclusion criteria: pts with aortic (n=42) and mitral (n=31) bioprosthetic valve dysfunction undergoing transcatheter VIV implantation (2007-2013). Exclusion criteria: N/A	Endpoints: 30-d outcomes; mid/long-term survival, NYHA Results: Overall success rate: 98.6%. At 30 d: All-cause mortality: 1.4%, Disabling stroke 1.4%, Life-threatening bleeding: 4.1%, AKI requiring hemodialysis 2.7%, Coronary artery obstruction requiring intervention 1.4%. At 2-y follow-up, 82.8% of aortic VIV pts were in NYHA functional class I/II. Estimated survival rates were 88.9%, 79.5%, 69.8%, 61.9%, and 40.5% at 1, 2, 3, 4, and 5 y, respectively.	• This has the longest follow-up (Median follow-up: 2.52 ywith a maximum of 8 y) of all registries transcatheter aortic and mitral VIV implantation. • Only Edwards balloon-expandable transcatheter valves (Edwards Lifesciences Inc., Irvine, California) were used. • The small surgical valve size (19 and 21 mm) was an independent risk factor for reduced survival in aortic VIV pts. • Transcatheter VIV procedures can be performed safely with a high success rate and minimal early mortality and morbidity, and provides encouraging mid/long-term clinical outcomes.
Dvir D, et al. 2012 (90) 23052028	Study type: multinational registry (data collected retrospectively and retrospectively)	Inclusion criteria: Either CoreValve or Edwards SAPIEN devices are included Exclusion criteria: N/A	Endpoints: Procedural success; adverse procedural outcomes; post-VIV gradients; 30 d mortality and NYHA I/II; 1-y survival.	• The was the first large, comprehensive evaluation of a transcatheter approach for failed surgically inserted aortic bioprostheses • Pts receiving VIV in the stenosis group had worse 1-y survival (76.6%) in comparison with the regurgitation group (91.2%) and the combined group

	Size: n=202 pts		Results: Procedural success: 93.1% of cases. Adverse procedural outcomes: Initial device malposition in 15.3% of cases. Ostial coronary obstruction in 3.5% of cases. 95% of pts had ≤1 degree of AR. Post-VIV maximum/ mean gradients: 28.4 ± 14.1/ 15.9 ± 8.6 mm Hg, and At 30 d: All-cause mortality: 8.4% of pts; NYHA functional class I/II: 84.1% of pts. 1-y survival: 85.8% survival of treated pts.	(83.9%) (p=0.01). • Having a small surgical bioprosthesis and baseline prosthesis stenosis (vs. regurgitation) were the 2 factors independently associated with 1-y mortality. • The VIV procedure is clinically effective in the vast majority of pts with degenerated bioprosthetic valves. • Safety and efficacy concerns include device malposition, ostial coronary obstruction, and high gradients after the procedure.
(The VIVID Registry) Dvir D, et al. 2014 (91) 25005653	Study type: multinational registry (data retrospectively for cases performed before registry initiation and prospectively) Size: n=459 pts	Inclusion criteria: Pts with degenerated bioprosthetic valves undergoing VIV implantation (2007-2013) Exclusion criteria: VIV procedures performed using other devices than the self-expandable CoreValve (Medtronic) and balloon expandable Edwards SAPIEN devices (Edwards Lifesciences). or implanted in positions other than the aortic position.	Endpoints: Survival, Stroke, and NYHA functional class. [Major clinical endpoints were assessed according to the VARC criteria] Results: • 1-y Kaplan-Meier survival rate: 83.2% (95% CI: 80.8–84.7%). • Within 1 mo: death: 7.6%; major stroke 1.7%; Survivors with NYHA I/II: 92.6%.	• Implanted devices included both balloon- and self-expandable valves. • Pts with at least a moderate degree of both stenosis and regurgitation were included in the combined group. • Pts in the stenosis group had worse 1-y survival (76.6%) in comparison with the regurgitation group (91.2%) and the combined group (83.9%) (p=0.01). • Factors associated with 1-y mortality: small surgical bioprosthesis (≤21 mm) & baseline stenosis (vs. regurgitation).
Webb, et al. 2010 (136) 20385927	Study type: Case series Size: n=24 pts (of whom 10 pts had VIV in the aortic position).	Inclusion criteria: 24 high-risk pts with failed bioprosthetic valves (n=10 were in the aortic position). Exclusion criteria: N/A	Endpoints: Procedural success and complications, 30-d mortality. Results: In the 10 pts with VIV in the aortic position: VIV implantation was uniformly successful with excellent improvement in valve function, no major morbidity. 30 d mortality: 0%.	• Transcatheter VIV implantation is a reproducible option for the management of selected pts with bioprosthetic valve failure. • The aortic, pulmonary, mitral, and tricuspid tissue valves may be amenable to this approach.
Ussia, et al. 2011 (137) 21907949	Study type: Prospective web-based multicenter registry. Size: n=24	Inclusion criteria: Pts treated with the VIV technique for severe PVL following TAVR. Exclusion criteria: N/A	Endpoints: Major adverse cerebrovascular and cardiac events and prosthesis performance at 30 d and midterm follow-up. Results: The VIV technique was used in 3.6% of all 663 TAVR pts.	• The VIV group was a subpopulation from 663 consecutive pts who underwent TAVR with the 18-F CoreValve ReValving System (Medtronic, Inc., Minneapolis, Minnesota) at 14 centers across Italy. • The study demonstrated that transcatheter aortic VIV after TAVR using the 3rd-generation CoreValve ReValving System is feasible, safe, and

			In the transcatheter aortic VIV group: 30 d major adverse cerebrovascular and cardiac events: 0%. 30-d mortality: 0%. 12 mo major adverse cerebrovascular and cardiac events: 14.1%. 12 mo mortality: 13.7%.	efficacious. • Thus, following TAVR, the VIV technique offers a viable therapeutic option in pts with acute significant PVL without recourse to emergent surgery.
Eggebrecht, et al 2011 (138) 22115663	Study type: Retrospective observational study Size: n=45	Inclusion criteria: Pts with degenerated surgically implanted BHVs undergoing aortic VIV procedures Exclusion criteria: N/A	Endpoints: Procedural success, complications, 30-d mortality. Results: • The transcatheter aortic VIV was technically successful in all pts (2 pts requiring bailout implantation of a second TAVR prosthesis for severe regurgitation during the procedure). • Vascular access complications: 13%. • Pacemaker implantation: 11%. • Renal failure requiring dialysis: 9%. • 30-d mortality: 17% (3 of 8 fatalities the result of non-valve-related septic complications).	• Multicenter (n=11) from Germany and Switzerland. • Both transfemoral (n = 25) or transapical (n = 22) approaches. • The transcatheter aortic VIV can be performed with high technical success rates, acceptable post-procedural valvular function, and excellent functional improvement. • In this elderly high-risk pts with multiple comorbidities, transcatheter aortic VIV was associated with 17% mortality, often because of septic complications arising in the post-operative phase.
Begdoni, et al 2011 (139) 22115664	Study type: multicenter registry Size: n=25	Inclusion criteria: High-risk pts with a failed aortic bioprosthesis Exclusion criteria: N/A	Endpoints: Procedural success, 30-d complications, short-term survival, NYHA. Results: Success rate was 100%; no procedural death. At 30 d: Deaths 12%; MI: 8%; Pacemaker implantation: 12%; At a mean follow-up of 6 mo, survival rate of 84%; NYHA functional class improved in all pts to I/II.	• Pts/prostheses were divided in type A (mainly stenotic, n = 9) and type B (mainly regurgitant, n = 16). • VIV was performed using the CoreValve Revalving System (CRS) (Medtronic, Minneapolis, Minnesota) implantation. • The VIV procedure is feasible and effective regardless of the prevalent mode of failure
Toggweiler, 2012 (140) 22625197	Study type: 3-center registry (prospectively collected data). Size: n=21	Inclusion criteria: Pts undergoing aortic balloon-expandable TAVR due toTHV failure with acute severe AR. Exclusion criteria: N/A	Endpoints: Procedural success; 30-d/1-y mortality, mean gradient, PVL. Results: Procedural success: 90%. Mortality at 30 ds and 1 y: 14.3% and 24%, respectively. After successful procedure: • Mean gradient reduced from 37 ± 12 mm Hg–13 ± 5 mm Hg ($p<0.01$); AVA increased from 0.64 ± 0.14–1.55 ± 0.27 cm^2 ($p<0.01$); PVL was none in 4 pts, mild in 13 pts, and moderate in 2 pts. • At 1-y follow-up: 1 pt had moderate and the others had mild/no PVL.	• AR was paravalvular in 18 pts and transvalvular in the remaining 3 pts. • At one-y, the mean transaortic gradient was 15 ± 4 mm Hg, which was higher than in pts undergoing conventional TAVR (11 ± 4 mm Hg, p=0.02). • Transcatheter VIV procedure in a failed THV is feasible and results in satisfactory short- and mid-term outcomes.

Bapat, 2012 (141) 23140962	Study type: single-center case-series Size: n=23	Inclusion criteria: pts undergoing a VIV procedure with the Edwards Sapien valve to treat a failing AV bioprosthesis (2008-201). Exclusion criteria: N/A	Endpoints: procedural success, short-term mortality, gradient. Results: • Procedural success: 100% (1 pt needed a second valve). • Mean gradient was reduced from 31.2 ± 17.06 mm Hg–9.13 ± 4.9 mm Hg. • In-hospital and/or 30-d mortality: 0%.	• 13 pts had predominantly bioprosthetic stenosis, and the remaining had mostly regurgitation. • Most VIV procedures (21/23) were performed via the transapical route. • The transcatheter VIV is a safe and feasible alternative to treat high-risk pts with failing aortic bioprostheses.
Linke, et al 2012 (142) 23048050	Study type: single-center observational study Size: n=27	Inclusion criteria: Consecutive symptomatic pts with failing AV bioprosthesis & aged ≥65 y & logistic EuroSCORE ≥10%; an inner diameter of the previously implanted bioprosthesis: 18.5-27 mm; ascending aorta diameter ≤45 mm above the sinotubular junction; access vessels ≥6 mm. Exclusion criteria: N/A	Endpoints: procedural and short-term outcomes, 30-d mortality Results: No intraprocedural death or MI. Using VARC criteria: • major stroke: 7.4 %. • life-threatening bleeding: 7.4%. • kidney failure stage III: 7.4%. Major access site complication 11.1 %. • 30-d mortality: 7.4%.	• Failure of bioprosthetic valves may be safely corrected by TF implantation of MCV, irrespective of the failure mode and the bioprosthesis valve type. • VIV implantation can be performed completely percutaneously under conscious sedation. • VIV implantation results in marked, instantaneous improvement in hemodynamics, which remains evident at long-term follow-up.
Ihlberg, L et al. 2013 (143) 23998786	Study type: multicenter registry, retrospective. Size: 45	Inclusion criteria: All transcatheter VIV procedures the Nordic countries between 2008 and 2012. Exclusion criteria: N/A	Endpoints: Periprocedural and postoperative outcomes (assessed using the VARC criteria). Results: • No intraprocedural mortality. • Technical success: 95.6%. • All-cause 30-d mortality: 4.4%. • 30-d major complications: stroke: 22%, • Periprocedural MI: 4.4%, • major vascular complication: 2.2%. • At 1 mo, all but 1 pt had either no or mild PVL. • 1 y survival: 88.1%.	• The type of failure was stenosis/ combined in 58% & regurgitation in 42% of cases. • The SAPIEN/XT (Edwards LifeSciences, Irvine, CA) and CoreValve (Medtronic Inc, Minneapolis, Minn) systems were used. • Access (transapical, transfemoral, transaortic, and subclavian). • Mean follow-up: 14.4 mo. • Transcatheter VIV is widely performed in most centers in the Nordic countries. The short-term results were excellent in this high-risk pt population, demonstrating a low incidence of device- or procedure-related complications.
Camboni, et al 2015 (144) 25661576	Study type: prospective single-center registry Size: 31	Inclusion criteria: Pts undergoing VIV procedure at single institution since 2009. Exclusion criteria: TAVR pts not undergoing VIV (608 pts)	Endpoints: Procedural success, 30-d survival, post-VIV regurgitation, Results: • Procedural success: 88%. • Post-procedural regurgitation: trace in 23% and moderate in 13% of pts. • 30-d survival: 77% with a significantly improved NYHA class of 1.79 ± 0.58 (p=0.001).	• Pts were provided with 5 Medtronic CoreValves, 15 Edwards SapienXT, 1 Edwards Sapien 3, 7 Medtronic Engager, and 3 Symetis Acurate TA valves.The left main stem was occluded in 1 pt (Sapien XT 26 in a Mitroflow 25 mm) who underwent emergent • Jeopardizing coronary blood flow was likely in stenotic and calcified bioprostheses, particularly in tubelike aortic sinuses. • The investigators concluded that 'Planning, imaging, and the use of valves

				allowing commissural alignment as well as leaflet capturing seem to reduce the risk'.
Conradi, et al 2015 (145) 26403870	Study type: registry (prospectively-collected data) Size: 75 (of whom 54 pts with VIV in the aortic position)	Inclusion criteria: Consecutive pts receiving VIV procedures from 2008 to 2014 at a single center Exclusion criteria: N/A	Endpoints: procedural success and complications, short-term mortality, trans-AV gradients. Results: Overall VIV success rate: 97.3%. For aortic VIV: • procedural (≤72 h) and all-cause 30-d mortality: 1.9% (1/54) and 5.6% (3/54). • No periprocedural strokes or coronary obstruction. • After aortic VIV, gradients were max/mean 34.1 ± 14:2/20.1 ± 7.1 mm Hg and effective orifice area was 1.5 ± 1.4 cm^2.	• This registry reported a single-center cumulative experience using 6 types of THVs in all anatomic positions. • VIV can be performed in all anatomic positions with acceptable hemodynamic and clinical outcome in high-risk pts
Duncan BF, et al 2015 (146) 26215358	Study type: case series, single center Size: 22	Inclusion criteria: consecutive pts with failing stentless bioprostheses Exclusion criteria: N/A	Endpoints: short-mid-term mortality, procedural complications. Results: • 30-d mortality: 0%. • No cases of MI, tamponade, stroke, severe bleeding, AKI, or major vascular complications. • 3 instances of device migration and 1 device embolization occurred. • Permanent pacing: 14%. • Mild-moderate PVL: 13.6%. • 6 mo and 1 y mortality was 4.8% and 14.3%, respectively.	• 30-d predicted mortality STS score: 14%%, all had severe AR and highly symptomatic, all underwent TAVI with a self-expanding device. • The aortic VIV procedure may be performed in high-risk pts with a degenerate stentless bioprosthesis with low 30-d and 1-y mortality rates.
Erlebach, et al 2015 (147) 26543594	Study type: retrospective single-center observational study Size: 102	Inclusion criteria: All consecutive pts undergoing VIV vs. redo surgical AVR (2001-2014). Exclusion criteria: previous mechanical or transcatheter valves, active endocarditis, concomitant cardiac procedures	Endpoints: post-procedural complications, 30-d mortality, 1-y survival Results: • Postoperative pacemaker implantation and chest tube output were higher in the reoperation surgical group compared to the TAV-in-SAV group [11 (21%) vs. 3 (6%), p=0.042 and 0.9±1.0 vs. 0.6±0.9, p=0.047, respectively]. • NS differences in MI, stroke, dialysis postoperatively, or 30-d mortality. • 1-y survival was significantly lower in the VIV group (83% vs. 96%, p<0.001).	• Pts in the VIV group were significantly older, had a higher logistic EuroSCORE and a lower LVEF. • Both groups, irrespective of different baseline comorbidities, show very good early clinical outcomes. While redo surgery is still the standard of care, a subgroup of pts may profit from the transcatheter VIV procedure.
Ye, et al. 2015 (148) 26476608	Study type: registry Size: 73 (of whom 42 had VIV for bioprosthetic AV).	Inclusion criteria: pts with aortic (n= 42) and mitral (n= 31) bioprosthetic valve dysfunction undergoing transcatheter VIV implantation (2007-2013).	Endpoints: 30-d outcomes; mid/long-term survival, NYHA Results: Overall success rate: 98.6%.	• This has the longest follow-up (Median follow-up: 2.52 y with a maximum of 8 y) of all registries transcatheter aortic and mitral VIV implantation. • Only Edwards balloon-expandable transcatheter valves (Edwards Lifesciences Inc., Irvine, California) were used. • The small surgical valve size (19 and 21 mm) was an independent risk

		Exclusion criteria: N/A	At 30 d: • All-cause mortality: 1.4%, Disabling stroke 1.4%, • Life-threatening bleeding: 4.1%, • AKI requiring hemodialysis 2.7%, • Coronary artery obstruction requiring intervention 1.4%. At 2-y follow-up, 82.8% of aortic VIV pts were in NYHA functional class I/II. Estimated survival rates were 88.9%, 79.5%, 69.8%, 61.9%, and 40.5% at 1, 2, 3, 4, and 5 y, respectively.	factor for reduced survival in aortic VIV pts. • Transcatheter VIV procedures can be performed safely with a high success rate and minimal early mortality and morbidity, and provides encouraging mid/long-term clinical outcomes.
Phan, et al 2016 (149) 26904259	Study type: systematic review Size: n=823 pts (18 studies)	Inclusion criteria: Pts undergoing transcatheter aortic VIV implantation and redo conventional AVR Exclusion criteria: N/A	1° endpoints: • Perioperative/30 d mortality Other endpoints: • PVLs • Stroke • Bleeding • MI • AKI • Vascular complications • Pacemaker implantation • Mean Gradient • Peak Gradient Results: • Perioperative mortality (VIV:7.9% vs. cAVR:6.1%, p=0.35) • PVLs (VIV:3.3% vs. cAVR: 0.4%, p=0.022) • Stroke (VIV:1.9% vs. cAVR:8.8%, p=0.002 • Bleeding (VIV:6.9% vs. cAVR:9.1%, p=0.014) • Mean Gradient (VIV: 38 mm Hg preoperatively to cAVR: 15.2 mm Hg postoperatively, p<0.001) • Peak Gradient (VIV: 59.2 to cAVR: 23.2 mm Hg, p=0.0003).	• Similar hemodynamic outcomes achieved with VIV as compared to redo conventional AVR • Lower risk of strokes and bleeding in VIV compared to redo conventional AVR • Higher PVL rates in VIV compared to redo conventional AVR

*Selective contemporary studies of transcatheter VIV procedures for failed bioprosthetic valves (excluding small studies with <20 pts).

Data Supplement 23. *(Updated From 2014 Guideline)* Selective Studies on Surgical and Catheter-based Closure for Paravalvular Regurgitation (Section 11.8.3)

Study Name, Author, Year	Study Aim	Study Type/Size (N)	Intervention vs. Comparator (n)	Patient Population	Endpoints		Adverse Events/ Comments
				Inclusion/Exclusion Criteria	Primary Endpoint & Results	Secondary and Additional Endpoint & Results	
Orszulak 1983 (150) 6860002	To report outcome with surgical reoperation for PVR	Retrospective N=105	Surgical reoperative repair of prosthetic PVR	Aortic PVR (n=75) and mitral PVR (n=29)	Early mortality for entire cohort: 5.7%. 5-y survival was 94% for aortic PVR pts and 75% for mitral PVR pts.	21 pts required multiple operations for persistent PVR. 85% of survivors at follow-up up to 14 y were NYHA I or II. Murmur of residual or recurrent PVR evident in 21% of pts.	N/A
Miller 1995 (151) 8556176	To identify clinical features that predict occurrence of PVR. Outcome after surgical repair also reported	Retrospective N=30	Surgical reoperative repair of aortic prosthetic PVR	Aortic prosthetic PVR	30-d survival=90%; 5-d survival=73%	Prosthesis replacement in 26, suture repair in 4. Trivial or no residual regurgitation in 16 of 20 with echocardiography in follow-up.	N/A
Akins 2005 (152) 16359061	To examine acute and long-term outcome of surgery for PVR	Retrospective N=136	Surgical reoperative repair of aortic or mitral prosthetic PVR	Mitral PVR in 68% Aortic PVR in 32%	Operative mortality, 6.6% Perioperative stroke, 5.1% 10-y survival, 30%	1° repair in 48%, prosthesis replacement in 52%	N/A
Pate 2006 (153) 16969856	To describe outcome in series of pts undergoing percutaneous repair of PVR	Retrospective N=10 (10 defects)	Percutaneous repair of PVR	Mitral PVR (n=9) and aortic PVR (n=1); 9 were not surgical candidates	7 with successful procedure 3 pts died at 1 y	4 of 10 required second procedure 6 with sustained improvement in symptoms	1 retroperitoneal bleed 1 device dislodgement
Shapira 2007 (154) 17578053	To examine the feasibility and early outcome of percutaneous repair of PVR	Retrospective N=11 (13 defects)	Percutaneous repair of PVR	Mitral PVR (n=8), aortic PVR (n=1), and both aortic and mitral PVR (n=2) Estimated surgical mortality, 17.8%	10 with device deployment 6 with reduction in regurgitation 5 with NYHA improvement by 1 class	Hemolysis improved in 4, worsened in 4, and was unchanged in 2 in early follow-up 3 deaths in follow-up	N/A
Cortes 2008 (155) 18237605	To examine utility of TEE in percutaneous repair of PVR	Retrospective N=27 (27 defects)	TEE before and procedure (n=27) and at follow-up ≥1 mo (n=17)	Mechanical mitral PVR in pts at high risk for surgery	62% with procedure success TEE helped guide procedure and identified variety of complications	N/A	2 stroke 1 cardiac perforation 6 needing blood transfusion for postprocedural anemia
Ruiz 2011 (156) 22078427	To examine feasibility and efficacy of the percutaneous repair of PVR	Retrospective/ N=43 (57 defects)	Percutaneous repair of PVR	Mitral PVR (n=36), aortic PVR (n=9), and both aortic and mitral PVR (n=2)	Device deployment success in 86% of pts and 86% of leaks Survival: 92% at 6 m, 86% at 18 m	12 pts required multiple procedures; reduction in need for transfusions or erythropoietin from 56%–5%; NYHA class improved by ≥1 in	2 device embolizations 1 emergency surgery 1 vascular complication 1 procedural death

						28/35 pts	
Sorajja 2011 (157) 21791673	To examine the feasibility and early outcome of percutaneous repair of PVR	Retrospective N=115 pts (141 defects)	Percutaneous repair of PVR	78% mitral PVR, 22% aortic PVR Average STS risk score=6.9%	Device deployment in 89% Mild or no residual regurgitation in 77% No procedural death	Leaflet impingement in 4.3% Procedure time average 147 min and decreased with case experience	30-d events Death, 1.7% Stroke, 2.6% Emergency surgery,
Sorajja 2011 (158) 22078428	To determine the long-term clinical efficacy of percutaneous repair of PVR	Retrospective N=126 (154 defects)	Percutaneous repair of PVR	79% mitral PVR, 21% aortic PVR Average STS risk score=6.7%	3-y survival, 64% HF accounted to 37% of deaths; noncardiac cause in 30%	Symptom improvement occurred only in pts with mild or no residual regurgitation Hemolytic anemia persisted in 14 of 29 pts	Survival free of death or need for cardiac surgery was 54% at 3 y Need for cardiac surgery related to degree of residual
Nijenhuis 2014 (159) 25097202	To determine the safety and clinical efficacy of transcatheter PVL closure using an open TA approach	Prospective N= 36	Transcatheter PVL closure using an open transapical approach	Consecutive pts (mean age 67±12 y, STS score 7±4%). All had severe symptomatic PVL in the mitral (81%) or aortic (19%) position	Procedure success: 86%.	1-y survival rate: 66%. NYHA class and QoL significantly improved. Survival free of stroke, re-hospitalization, NYHA 3/4, and device-related dysfunction: 49% at 3 mo; 31% at 1 y.	30-d event-free survival: 84%. Moderate to severe residual PVL was associated with all-cause mortality (HR: 3.9; 95% CI: 1.2-12.1).
Taramasso 2014 (160) 24866899	To compare the in-hospital outcomes of pts who underwent surgery and TA closure for PVL	Retrospective N = 139	Surgery vs. TA-closure for PVL	122 pts (87.3%) underwent surgical treatment (68% mitral PVL; 32% aortic PVL) and 17 pts (12.2%) underwent a transcatheter closure via a surgical TA approach. (all the pts had mitral PVL; 1 case had combined mitral and aortic PVLs).	Acute procedural success: 98%. Surgical treatment was a risk factor for in-hospital death (OR: 8, 95% CI: 1.8-13).	Overall actuarial survival at follow-up: 39.8 ± 7% at 12 y; and was reduced in pts who had >1 cardiac re-operation (42 ± 8 vs. 63 ± 6% at 9 y; p=0.009).	In-hospital mortality: 9.3%. No in-hospital deaths in pts treated with a TA approach.
Gafoor 2014 (161) 24038891	To determine the safety and efficacy of percutaneous PVL closure after TAVR	Retrospective n= 5	percutaneous closure of PVL	Pts who received TAVR with self-expandable valves	In all 5 pts, PVL went from moderate-severe to mild-moderate PVL	-	none

Cruz-Gonzales, I (162) 25037539	To analyze the feasibility and efficacy of PVL closure with the Amplatzer Vascular Plug III	Retrospective n= 33	percutaneous closure of PVL	33 pts with 34 PVLs (27 mitral, 7 aortic)	Successful device implantation: 93.9% (in 2 pts, a 2nd planned procedure was needed). Successful closure (defined as regurgitation reduction ≥1 grade): 90.9%	At 90 d: Survival: 100%. Significant clinical improvement: 90.3%.	• Emergency surgery due to disc interference (n=1) • Blood transfusion (n=3) • No procedure-related death, MI, or stroke • 4 pts developed vascular complications (pseudoaneurysm) at 90 d
Millan 2015 (163) 25746018	To assess whether a successful transcatheter PVL reduction is associated with improvement in clinical outcomes	Systematic review/ Meta-analysis n= 362 pts	successful vs. failed transcatheter PVL reductions	12 clinical studies that compared successful and failed transcatheter PVL reductions	Compared with a failed intervention, a successful transcatheter PVL reduction was associated with lower cardiac mortality (OR: 0.08; 95% CI: 0.01–0.90)	A successful transcatheter PVL reduction was associated with: • Superior improvement in functional class or hemolytic anemia, (OR: 9.95; 95% CI: 2.10–66.73). • Fewer repeat surgeries (OR: 0.08; 95% CI: 0.01–0.40).	
Goktekin 2016 (164) 26897292	To evaluate early and midterm outcomes of percutaneous PVL closure utilizing a novel device (Occlutech PVL Device)	Case series n=21		consecutive symptomatic and inoperable pts who had moderate or severe paravalvular prosthetic regurgitation on TEE	≥1 grade reduction in regurgitation was achieved in all pts.	No deaths due to any cause, stroke or surgery for prosthetic impingement, worsening or relapse of PVL occurred at follow-up (90 d and 12 mo)	No in-hospital mortality. 1 case of hemothorax in 1 pt and 1 case of pneumothorax in another

Data Supplement 24. *(Updated From 2014 Guideline)* Surgical Outcome in IE (Section 12.2.3)

Author/ Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Study Intervention	Primary Endpoint	Predictors of Outcome
Jault, 1997 (165) 9205176	Identify significant predictors of operative mortality, reoperation, and recurrent IEs	Retrospective single-center surgical cohort study	247	NVE alone; surgery 100%	Registration of epidemiological and microbiological features, echocardiography data, treatment strategy	Operative mortality was 7.6% (n=19). Overall survival rate (operative mortality excluded) was 71.3% at 9 y. The probability of freedom from reoperation (operative mortality included) was 73.3±4.2% at 8y. The rate of IE of the implanted prosthetic valve was 7%.	Increased age, cardiogenic shock at the time of operation, insidious illness, and greater thoracic ratio (>0.5) were the predominant risk factors for operative mortality; the length of antibiotic therapy appeared to have no influence. Increased age, preoperative neurologic complications, cardiogenic shock at the time of operation, shorter duration of the illness, insidious illness before the operation, and MV endocarditis were the predominant risk factors for late mortality.
Castillo 2000 (166) 10768901	To determine the clinical features and long-term prognosis of IE in pts who were not drug users.	Prospective single-center case series	138	NVE 69%, PVE 31%; surgery 51%	Registration of epidemiological and microbiological features, echocardiography data, treatment strategy	Severe complications (HF, embolic phenomenon, severe valve dysfunction, abscesses, renal failure, and immunologic phenomenon) occurred in 83% of pts. 51% of pts underwent surgery during the active phase (22% was emergency surgery) Inpt mortality was 21%. Overall 10 y survival was 71%	There were no significant differences in survival depending on the type of treatment received during the hospital stay (medical vs. combined medical-surgical) in this observational study.
Alexiou 2000 (167) 10881821	Single-center experience in the surgical treatment of active culture-positive IE and identify determinants of early and late	Retrospective single-center surgical cohort study	118	NVE 70%, PVE 30%; 100% of pts underwent surgery	Registration of epidemiological and microbiological features, echocardiography data, treatment strategy	Operative mortality was 7.6% (9 pts). Endocarditis recurred in 8 (6.7%). A reoperation was required in 12 (10.2%). There were 24 late deaths, 17 of them cardiac. Actuarial freedom from recurrent endocarditis, reoperation, late cardiac death, and long-term survival at 10 y were 85.9%, 87.2%, 85.2%, and 73.1%, respectively.	Predictors of operative mortality: HF, impaired LV function. Predictors of recurrence: PVE. Predictors of late mortality: myocardial invasion, reoperation. Predictors of poor long-term survival: coagulase- negative staphylococcus, annular abscess, long ICU stay.
Wallace, 2002 (193) 12067945	To identify clinical markers available within the first 48 h of admission that are associated with poor outcome in IE	Retrospective single-center cohort study	208	NVE 68%, PVE 32%; surgery 52%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy	Mortality at discharge was 18% and at 6 mo 27%. Surgery was performed in 107 (51%) pts. In-hospital mortality was not influenced by surgery (23% vs. 15% in the nonsurgical group); p=0.3 At 6 mo there was a trend towards increased mortality in the surgical group (33% vs. 20%)	Duration of illness, age, gender, site of infection, organism, and LV function did not predict outcome. Abnormal white cell count, raised creatinine, ≥2 major Duke criteria, or visible vegetation conferred poor prognosis.

Hasbun, 2003 (168) 12697795	To derive and externally validate a prognostic classification system for pts with complicated left-sided native valve IE	Retrospective multicenter cohort study	513	Pts with left-sided NVE with current indication of surgery in 45%`	Registration of clinical information, sociodemographic data, comorbid conditions, previous heart disease, symptoms, physical findings, blood cultures, electrocardiogram, echocardiography, type of surgery performed, and operative findings	In the derivation and validation cohorts, the 6-mo mortality rates were 25% and 26%, respectively. In the derivation cohort, pts were classified into 4 groups with increasing risk for 6-mo mortality: 5%, 15%, 31%, and 59% (p<0.001). In the validation cohort, a similar risk among the 4 groups was observed: 7%, 19%, 32%, and 69% (p<0.001).	5 baseline features were independently associated with 6 mo mortality (comorbidity [p=0.03], abnormal mental status [p=0.02], moderate-to-severe congestive HF [p=0.01], bacterial etiology other than viridans streptococci [p<0.001 except *S. aureus*, p=0.004], and medical therapy without valve surgery [p=0.002])
Vikram, 2003 (169) 14693873	To determine whether valve surgery is associated with reduced mortality in pts with complicated, left-sided native valve IE	Retrospective multicenter cohort study; Propensity analysis	513	Pts with left sided NVE with current surgical intervention in 45%	Registration of clinical information, sociodemographic data, comorbid conditions, previous heart disease, symptoms, physical findings, blood cultures, ECG, echocardiography, type of surgery performed, and operative findings	After adjustment for baseline variables associated with mortality (including hospital site, comorbidity, HF, microbial etiology, immunocompromised state, abnormal mental status, and refractory infection), valve surgery remained associated with reduced mortality (adjusted HR: 0.35; 95% CI: 0.23–0.54; p<0.02). In further analyses of 218 pts matched by propensity scores, valve surgery remained associated with reduced mortality (15% vs. 28%; HR: 0.45; 95% CI: 0.23–0.86; p=0.01). After additional adjustment for variables that contribute to heterogeneity and confounding within the propensity-matched group, surgical therapy remained significantly associated with a lower mortality (HR: 0.40; 95% CI: 0.18-0.91; p=0.03). In this propensity-matched group, pts with moderate- to-severe congestive HF showed the greatest reduction in mortality with valve surgery (14% vs. 51%; HR: 0.22; 95% CI: 0.09–0.53; p=0.001).	Pts with moderate-to-severe HF showed the greatest reduction in mortality with valve surgery. Stratifying the data by congestive HF among propensity- matched pts undergoing surgery revealed that among pts with none to mild HF, valve surgery was not associated with reduced mortality compared with medical therapy (HR: 1.04; 95% CI: 0.43–2.48; p=0.93). Among propensity-matched pts with moderate-to-severe HF, valve surgery was associated with a significant reduction in mortality compared with medical therapy (HR: 0.22; 95% CI: 0.08–0.53; p=0.01).
Habib, 2005 (170) 15958370	To identify prognostic markers in 104 pts with PVE and the effects of a medical vs.surgical strategy outcome in PVE	Retrospective multicenter cohort study	104	100% PVE pts; surgery 49%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy	Overall, 22 (21%) died in hospital. By multivariate analysis, severe HF (OR: 5.5) and *S. aureus* infection (OR: 6.1) were the only independent predictors of in-hospital death. Among 82 in-hospital survivors, 21 (26%) died during a 32 mo follow-up. Mortality was not significantly different between surgical and nonsurgical pts (17% vs. 25%, respectively, not significant). Both in-hospital and long-term mortality were reduced by a surgical approach in high-risk subgroups of pts with staphylococcal PVE and complicated PVE.	Factors associated with in-hospital death were severe comorbidity (6% of survivors vs. 41% of those who died; p=0.05), renal failure (28% vs.45%, p=0.05), moderate- to-severe regurgitation (22% vs. 54%; p=0.006), staphylococcal infection (16% vs. 54%; p=0.001), severe HF (22% vs. 64%; p=0.001), and occurrence of any complication (60% vs. 90%; p=0.05).

Revilla, 2007 (171) 17032690	Describe the profile of pts with left-sided IE who underwent urgent surgery and to identify predictors of mortality	Prospective multicenter cohort study	508	NVE 66%,PVE 34%; surgery studied for the present report	Brucella, Q fever, Legionella, and Mycoplasma. Persistent infection despite appropriate antibiotic treatment (31%).	Of these 508 episodes, 132 (34%) were electively operated on, and 89 pts required urgent surgery (defined as prior to completion of antibiotic course). 1° reasons for urgent surgery in these 89 pts were HF that did not respond to medication (72%) and persistent infection despite appropriate antibiotic treatment (31%). 32 pts (36%) died during their hospital stay. 32% of NVE died vs. 45% of pts with PVE. Late PVE was associated with a higher mortality than early PVE (53% vs. 36%)	Univariate analysis identified renal failure, septic shock, Gram-negative bacteria, persistent infection, and surgery for persistent infection as factors associated with mortality. Multivariate analysis confirmed only persistent infection and renal insufficiency as factors independently associated with a poor prognosis.
Hill, 2007 (172) 17158121	Analyze epidemiology, optimal treatment, and predictors of 6- mo mortality in IE	Prospective single-center cohort study	193	NVE 66%, PVE 34%; surgery 63%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy	43% included staphylococci, 26% streptococci, and 17% enterococci. At least 1 complication occurred in 79% of the episodes and 63% had surgical intervention. 6-mo mortality was 22%: 33% for staphylococci, 24% for enterococci, and 8% for streptococci. 74% of pts with a contraindication to surgery died when compared with 7% with medical treatment without a contraindication and 16% with surgical treatment.	*S. aureus*, contraindication to surgery (present in 50% of deaths).
Remadi, 2007 (173) 17383330	To evaluate the predictors of outcome and to establish whether early surgery is associated with reduced mortality	Prospective multicenter cohort study	116	*S. aureus* IE alone; NVE 83%, PVE 17%; surgery 47%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy. Antibiotic treatment.	In-hospital mortality rate was 26%, and the 36-mo survival rate was 57% Surgical group mortality was 16% vs. 34% in the medically treated group ($p<0.05$) In unadjusted analyses, early surgery performed in 47% of pts was associated with lower in-hospital mortality (16% vs. 34%; $p=0.034$) and with better 36-mo survival (77% vs. 39%; $p<0.001$).	Multivariate analyses identified comorbidity index, HF, severe sepsis, prosthetic valve IE, and major neurologic events as predictors of in-hospital mortality Severe sepsis and comorbidity index were predictors of overall mortality After adjustment of baseline variables related to mortality, early surgery
Akso, 2007 (174) 17205442	To better understand the impact of surgery on the long-term survival of pts with IE	Prospective single-center cohort study with propensity score matching	426	NVE 69%, PVE 19%, "other" 12%; surgery in 29%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy. Pts' propensities for surgery	The fit of the propensity model to the data was assessed using the concordance index with pts who underwent surgery matched to those who did not undergo surgery, using individual propensity scores. The following factors were statistically associated with surgical therapy: age, transfer from an outside hospital, evidence of IE on physical examination, the presence of infection with staphylococci, HF, intracardiac abscess, and hemodialysis without a chronic catheter.	Revealed that surgery was associated with decreased mortality (HR: 0.27; 95% CI: 0.13–0.55). A HX of DM (HR: 4.81; 95% CI: 2.41– 9.62), the presence of chronic IV catheters at the beginning of the episode (HR: 2.65; 95% CI: 1.31– 5.33), and with increased mortality.

Tleyjeh, 2007 (175) 17372170	To examined the association between valve surgery and all-cause 6 mo mortality among pts with left- sided IE	Matched propensity analysis	546	NVE alone; surgery 24%	Propensity score to undergo valve surgery was used to match pts in the surgical and nonsurgical groups. To adjust for survivor bias, the follow-up time was matched so that each pt in the nonsurgical group survived at least as long as the time to surgery in the respective surgically-treated pt.	Death occurred in 99 of the 417 pts (23.7%) in the nonsurgical group vs. 35 deaths among the 129 pts (27.1%) in the surgical group. 18 of 35 (51%) pts in the surgical group died within 7 d of valve surgery.	After adjustment for early (operative) mortality, surgery was not associated with a survival benefit (adjusted HR: 0.92; 95% CI: 0.48–1.76).
Tleyjeh, 2008 (176) 18308866	To examine the association between the timing of valve surgery after IE dx and 6-mo mortality among pts with left-sided IE	Retrospective single-center cohort propensity analysis	546	NVE alone; surgery 24%	The association between time from IE dx to surgery and all-cause 6 mo mortality was assessed using Cox proportional hazards modeling after adjusting for the propensity score (to undergo surgery 0–11 d vs. 11 d, median time, after IE dx).	The median time between IE dx and surgery was 11 d (range 1–30). Using Cox proportional hazards modeling, propensity score and longer time to surgery (in d) were associated with unadjusted HRs of (1.15, 95% CI: 1.04–1.28, per 0.10 unit change; p=0.009) and (0.93; 95% CI: 0.88–0.99, per d; p=0.03), respectively. In multivariate analysis, a longer time to surgery was associated with an adjusted HR: (0.97; 95% CI: 0.90– 1.03). The propensity score and time from dx to surgery had a correlation coefficient of r=20.63, making multicollinearity an issue in the multivariable model.	On univariate analysis, a longer time to surgery showed a significant protective effect for the outcome of mortality. After adjusting for the propensity to undergo surgery early vs. late, a longer time to surgery was no longer significant, but remained in the protective direction.
Thuny, 2009 (177) 19329497	To determine whether the timing of surgery could influence mortality and morbidity in pts with complicated IE	Retrospective single-center cohort propensity analysis	291	NVE 82%, PVE 18%; surgery 100%	The time between the beginning of the appropriate antimicrobial therapy and surgery was used as a continuous variable and as a categorical variable with a cut-off of 7 d to assess the impact of timing of surgery. 2 groups of pts were formed according to the timing of surgery: the "≤1st wk surgery group" and the ">1st wk surgery group". The impact of the timing of surgery on 6 mo mortality, relapses, and PVD was analyzed using PS	1st wk surgery was associated with a trend of decrease in 6-mo mortality in the quintile of pts with the most likelihood of undergoing this early surgical management (quintile 5: 11% vs. 33%, OR: 0.18, 95% CI: 0.04 –0.83; p=0.03). Pts of this subgroup were younger, were more likely to have *S. aureus* infections, congestive HF, and larger vegetations. ≤1st wk surgery was associated with an increased number of relapses or PVD (16% vs. 4%, adjusted OR: 2.9, 95% CI: 0.99–8.40; p=0.05).	Very early surgery (<7 d) associated with improved survival (especially in highest risk pts), but greater likelihood of relapse or post-operative valve dysfunction.

Manne, 2012 (178) 22206953	Describe the morbidity and mortality associated with surgery for IE and compare differences in characteristics, pathogens, and outcomes for pts with NVE and PVE from a large surgery-minded tertiary referral center	Retrospective single-center surgical cohort study	428	NVE 58%, PVE 42%; surgery 100%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography data, and treatment strategy	Overall 90% of pts survived to hospital discharge. When compared with pts with NVE, pts with PVE had significantly higher 30-d mortality (13% vs. 5.6%; p<0.01), but long-term survival was not significantly different (35% vs. 29%; p=0.19).	Pts with IE caused by *S. aureus* had significantly higher hospital mortality (15% vs. 8.4%; p<0.05), 6 mo mortality (23% vs. 15%; p=0.05), and 1 y mortality (28% vs. 18%; p=0.02) compared with non–*S. aureus* IE.
Kang, 2012 (179) 22738096	To compare clinical outcomes of early surgery and conventional treatment in pts with IE	Prospective randomized trial at 2 centers with intention to treat analysis	76	Left-side NVE and high risk of embolism to early surgery (49%) vs. conventional treatment (51%)	Pts were randomly assigned in a 1:1 ratio to the early-surgery group or the conventional-treatment group with the use of a Web-based interactive response system. The protocol specified that pts who were assigned to the early-surgery group should undergo surgery within 48 h after randomization. Pts assigned to the conventional-treatment group were treated according to AHA guidelines, and surgery was performed only if complications requiring urgent surgery developed during medical treatment or if symptoms persisted	The 1° endpoint (composite of in-hospital death and embolic events that occurred within 6 wk after randomization) occurred in 1 pt (3%) in the early surgery group as compared with 9 (23%) in the conventional-treatment group (HR: 0.10; 95% CI: 0.01–0.82; p=0.03). There was no significant difference in all-cause mortality at 6 mo in the early-surgery and conventional- treatment groups (3% and 5%, respectively; HR: 0.51; 95% CI: 0.05–5.66; p=0.59). The rate of the composite en point of death from any cause, embolic events, or recurrence of IE at 6 mo was 3% in the early-surgery group and 28% in the conventional-treatment group (HR: 0.08; 95% CI: 0.01–0.65; p=0.02).	As compared with conventional treatment, early surgery in pts with IE and large vegetations significantly reduced the composite endpoint of death from any cause and embolic events by effectively decreasing the risk of systemic embolism.

Eishi, 1995 (180) 8523887	To establish guidelines for the surgical treatment of pts with IE who have cerebrovascular complications	Retrospective study of 181 pts with cerebral complications among 2523 surgical cases of IE	181 pts	Predominately left sided IE; 37.5% PVE and 62.5% NVE with neurological complicationis of IE	Questionnaire consisting of 2 parts: (1) Each center was asked for a summary of the number and outcome of pts with IE according to the types of IE 1 (active/healed and native valve/prosthetic valve) and the presence of cerebral complications; (2) the other portion inquired about each pt with cerebral complications, asking for details such as age, gender, AF, anticoagulant therapy, diseased valve, organism, effectiveness of antimicrobial therapy, reason for early cardiac operation, interval between the onset of symptoms and the cardiac operation, type of cerebral complication, cerebral aneurysm, prior cerebral surgery, severity, influence of operation on cerebral damage, and outcome.	To study the influence of cardiac surgery on preoperative cerebral complications, we analyzed the interval between the onset of cerebral complications and performance of the cardiac operation, as well as other preoperative variables. The effectiveness of antimicrobial therapy was ranked in 3 grades (1 = ineffective, 2 = effective, and 3 = well controlled). A correlation between the interval and the exacerbation of cerebral complications was evaluated by means of the Spearman rank correlation coefficient. The intervals were then classified in several groups, and variability between the groups for the exacerbation was estimated by Scheffe's F procedure for post-hoc comparisons, according to the Kruskal-Wallis test. To analyze the risk factors affecting exacerbation of cerebral complications, we expressed preoperative variables as mean ± standard error. The difference between the groups with and without exacerbation was tested for significance by the unpaired t test, and incidence was expressed as percentage of pts having the variable compared with the entire group of pts and then compared by $\chi 2$ analysis. Moreover, all variables and incidence (transformed to continuous variables) were estimated by stepwise regression analysis. Statistical significance was accepted at a p level of <0.05. These analyses were done with the Stat View system (Abacus Concepts, Inc., Berkeley, Calif.).	The rate of exacerbation of cerebral complications decreased to 10% in pts who underwent surgical treatment more than 15 d after cerebral infarction and to 2.3% in those operated on more than 4 wk later. Preoperative risk factors were severity of cerebral complications, interval from onset of symptoms to operation, and uncontrolled HF as the indication for cardiac surgery. More than 15 d after cerebral hemorrhage, the risk of the progression of cerebral damage is still significant, and this risk persists even 4 wk later.
Garcia-Cabrera, 2013 (181) 23648777	Assess the incidence of neurological complications in pts with infective endocarditis, the risk factors for their development, their influence on the clinical outcome, and the impact of cardiac surgery	Retrospective analysis of prospectively collected data on a multicenter cohort	1345pts	Consecutive Left sided endocarditis cases from 8 Centers in Spain	Specific variables from registries were analyzed including the date of IE dx; pts age and sex; type of endocarditis (native or prosthetic); location and size of vegetations on echocardiography; infecting microorganism; date, type, and extent of neurological complications; anticoagulant therapy given; date of the start of antimicrobial treatment; date of surgery (if performed); and outcome.	Determine the risk factors associated with the development of all neurological complications	Predictors of neurological complications were vegetation size ≥3 cm (HR: 1.91; 95% CI: 1.07–3.43; p=0.029), S aureus as the cause of IE (HR: 2.47; 95% CI: 1.94–3.15; p<0.001), anticoagulant therapy at IE dx (HR: 1.31; 95% CI: 1.00–1.72; P=0.048), and MV involvement (HR: 1.29; 95% CI: 1.02–1.61; p=0.03). Further analysis showed that elderly pts (≥70 y) had lower complication rates than younger ones, and only hemorrhagic events showed statistical significance (HR: 0.36; 95% CI: 0.16–0.83; p=0.014). Anticoagulant treatment was particularly associated with cerebral hemorrhage (HR: 2.71; 95% CI: 1.54–4.76; p=0.001).

Barsic, B, 2013 (182) 23074311	Examine the relationship between the timing of surgery after stroke and the incidence of in-hospital and 1-y mortalities.	Post-hoc review of the International Collaboration on Endocarditis –Prospective Cohort Study of with definite IE who were admitted to 64 centers June 2000–December 2006	198 pts	198 pts of 857 pts with IE complicated by ischemic stroke who underwent valve replacement surgery post-stroke	Data were obtained from the International Collaboration on Endocarditis–Prospective Cohort Study of 4794 pts with definite IE who were admitted to 64 centers from June 2000 through December 2006. Multivariate logistic regression and Cox regression analyses were performed to estimate the impact of early surgery on hospital and 1-y mortality after adjustments for other significant covariates.	Estimate the impact of early surgery on hospital and 1-y mortality after adjustments for other significant covariates.	After adjustment for other risk factors, early surgery was not significantly associated with increased in-hospital mortality rates (OR: 2.308; 95% CI: .942–5.652). Overall, probability of death after 1-y follow-up did not differ between 2 treatment groups (27.1% in early surgery and 19.2% in late surgery group, p=.328; adjusted HR: 1.138; 95% CI: .802–1.650).

References

1. Mackie AS, Liu W, Savu A, et al. Infective Endocarditis Hospitalizations Before and After the 2007 American Heart Association Prophylaxis Guidelines. Can J Cardiol. 2016;32:942-8.
2. Dayer MJ, Jones S, Prendergast B, et al. Incidence of infective endocarditis in England, 2000-13: a secular trend, interrupted time-series analysis. Lancet. 2015;385:1219-28.
3. Glenny AM, Oliver R, Roberts GJ, et al. Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. Cochrane Database Syst Rev. 2013;10:CD003813.
4. Sherman-Weber S, Axelrod P, Suh B, et al. Infective endocarditis following orthotopic heart transplantation: 10 cases and a review of the literature. Transpl Infect Dis. 2004;6:165-70.
5. Gillinov AM, Faber CN, Sabik JF, et al. Endocarditis after mitral valve repair. Ann Thorac Surg. 2002;73:1813-6.
6. Karavas AN, Filsoufi F, Mihaljevic T, et al. Risk factors and management of endocarditis after mitral valve repair. J Heart Valve Dis. 2002;11:660-4.
7. Duval X, Alla F, Hoen B, et al. Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. Clin Infect Dis. 2006;42:e102-e107.
8. Strom BL, Abrutyn E, Berlin JA, et al. Dental and cardiac risk factors for infective endocarditis. A population-based, case-control study. Ann Intern Med. 1998;129:761-9.
9. Mougeot FK, Saunders SE, Brennan MT, et al. Associations between bacteremia from oral sources and distant-site infections: tooth brushing versus single tooth extraction. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119:430-5.
10. Lockhart PB, Brennan MT, Sasser HC, et al. Bacteremia associated with toothbrushing and dental extraction. Circulation. 2008;117:3118-25.
11. Avezum A, Lopes RD, Schulte PJ, et al. Apixaban in Comparison With Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: Findings From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. Circulation. 2015;132:624-32.
12. Breithardt G, Baumgartner H, Berkowitz SD, et al. Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. Eur Heart J. 2014;35:3377-85.
13. Perez-Gomez F, Alegria E, Berjon J, et al. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. J Am Coll Cardiol. 2004;44:1557-66.
14. Ezekowitz MD, Nagarakanti R, Noack H, et al. Comparison of Dabigatran and Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulant Therapy). Circulation. 2016;134:589-98.
15. Noseworthy PA, Yao X, Shah ND, et al. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and valvular heart disease. Int J Cardiol. 2016;209:181-3.
16. Olesen JB, Lip GY, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ. 2011;342:d124.
17. Petty GW, Khandheria BK, Whisnant JP, et al. Predictors of cerebrovascular events and death among patients with valvular heart disease: A population-based study. Stroke. 2000;31:2628-35.
18. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364:2187-98.
19. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med. 2012;366:1686-95.
20. Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet. 2015;385:2477-84.
21. Kapadia SR, Leon MB, Makkar RR, et al. 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. 2015;385:2485-91.
22. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363:1597-607.
23. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med. 2012;366:1696-704.
24. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med. 2014;370:1790-8.
25. Deeb GM, Reardon MJ, Chetcuti S, et al. Three-Year Outcomes in High-Risk Patients Who Underwent Surgical or Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2016;
26. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2016;
27. Thyregod HG, Steinbruchel DA, Ihlemann N, et al. No clinical effect of prosthesis-patient mismatch after transcatheter versus surgical aortic valve replacement in intermediate- and low-risk patients with severe aortic valve stenosis at mid-term follow-up: an analysis from the NOTION trial. Eur J Cardiothorac Surg. 2016;
28. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. Eur Heart J. 1988;9 Suppl E:57-64.
29. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol. 2014;63:1972-81.
30. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet. 2016;387:2218-25.
31. Tribouilloy CM, Enriquez-Sarano M, Schaff HV, et al. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. Circulation. 1999;99:400-5.
32. Gillinov AM, Mihaljevic T, Blackstone EH, et al. Should patients with severe degenerative mitral regurgitation delay surgery until symptoms develop? Ann Thorac Surg. 2010;90:481-8.

33. Rosenhek R, Rader F, Klaar U, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. Circulation. 2006;113:2238-44.
34. Kang DH, Kim JH, Rim JH, et al. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. Circulation. 2009;119:797-804.
35. Enriquez-Sarano M, Tajik AJ, Schaff HV, et al. Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. Circulation. 1994;90:830-7.
36. Tribouilloy C, Grigioni F, Avierinos JF, et al. Survival implication of left ventricular end-systolic diameter in mitral regurgitation due to flail leaflets a long-term follow-up multicenter study. J Am Coll Cardiol. 2009;54:1961-8.
37. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. N Engl J Med. 2005;352:875-83.
38. Ghoreishi M, Evans CF, deFilippi CR, et al. Pulmonary hypertension adversely affects short- and long-term survival after mitral valve operation for mitral regurgitation: implications for timing of surgery. J Thorac Cardiovasc Surg. 2011;142:1439-52.
39. Goldman ME, Mora F, Guarino T, et al. Mitral valvuloplasty is superior to valve replacement for preservation of left ventricular function: an intraoperative two-dimensional echocardiographic study. J Am Coll Cardiol. 1987;10:568-75.
40. David TE, Burns RJ, Bacchus CM, et al. Mitral valve replacement for mitral regurgitation with and without preservation of chordae tendineae. J Thorac Cardiovasc Surg. 1984;88:718-25.
41. Rozich JD, Carabello BA, Usher BW, et al. Mitral valve replacement with and without chordal preservation in patients with chronic mitral regurgitation. Mechanisms for differences in postoperative ejection performance. Circulation. 1992;86:1718-26.
42. David TE, Armstrong S, McCrindle BW, et al. Late outcomes of mitral valve repair for mitral regurgitation due to degenerative disease. Circulation. 2013;127:1485-92.
43. Tribouilloy C, Rusinaru D, Szymanski C, et al. Predicting left ventricular dysfunction after valve repair for mitral regurgitation due to leaflet prolapse: additive value of left ventricular end-systolic dimension to ejection fraction. Eur J Echocardiogr. 2011;12:702-10.
44. Suri RM, Clavel MA, Schaff HV, et al. Effect of Recurrent Mitral Regurgitation Following Degenerative Mitral Valve Repair: Long-Term Analysis of Competing Outcomes. J Am Coll Cardiol. 2016;67:488-98.
45. Vassileva CM, Mishkel G, McNeely C, et al. Long-term survival of patients undergoing mitral valve repair and replacement: a longitudinal analysis of Medicare fee-for-service beneficiaries. Circulation. 2013;127:1870-6.
46. Suri RM, Vanoverschelde JL, Grigioni F, et al. Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. JAMA. 2013;310:609-16.
47. Dillon J, Yakub MA, Kong PK, et al. Comparative long-term results of mitral valve repair in adults with chronic rheumatic disease and degenerative disease: is repair for "burnt-out" rheumatic disease still inferior to repair for degenerative disease in the current era? J Thorac Cardiovasc Surg. 2015;149:771-7.
48. Feldman T, Kar S, Elmariah S, et al. Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. J Am Coll Cardiol. 2015;66:2844-54.
49. Grigioni F, Tribouilloy C, Avierinos JF, et al. Outcomes in mitral regurgitation due to flail leaflets a multicenter European study. JACC Cardiovasc Imaging. 2008;1:133-41.
50. Gillinov AM, Blackstone EH, Alaulaqi A, et al. Outcomes after repair of the anterior mitral leaflet for degenerative disease. Ann Thorac Surg. 2008;86:708-17.
51. Weiner MM, Hofer I, Lin HM, et al. Relationship among surgical volume, repair quality, and perioperative outcomes for repair of mitral insufficiency in a mitral valve reference center. J Thorac Cardiovasc Surg. 2014;148:2021-6.
52. Enriquez-Sarano M, Suri RM, Clavel MA, et al. Is there an outcome penalty linked to guideline-based indications for valvular surgery? Early and long-term analysis of patients with organic mitral regurgitation. J Thorac Cardiovasc Surg. 2015;150:50-8.
53. Suri RM, Schaff HV, Dearani JA, et al. Determinants of early decline in ejection fraction after surgical correction of mitral regurgitation. J Thorac Cardiovasc Surg. 2008;136:442-7.
54. Quintana E, Suri RM, Thalji NM, et al. Left ventricular dysfunction after mitral valve repair--the fallacy of "normal" preoperative myocardial function. J Thorac Cardiovasc Surg. 2014;148:2752-60.
55. Suri RM, Aviernos JF, Dearani JA, et al. Management of less-than-severe mitral regurgitation: should guidelines recommend earlier surgical intervention? Eur J Cardiothorac Surg. 2011;40:496-502.
56. Kang DH, Kim MJ, Kang SJ, et al. Mitral valve repair versus revascularization alone in the treatment of ischemic mitral regurgitation. Circulation. 2006;114:I499-I503.
57. Rossi A, Dini FL, Faggiano P, et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. Heart. 2011;97:1675-80.
58. Wu AH, Aaronson KD, Bolling SF, et al. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. J Am Coll Cardiol. 2005;45:381-7.
59. Mihaljevic T, Lam BK, Rajeswaran J, et al. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. J Am Coll Cardiol. 2007;49:2191-201.
60. Benedetto U, Melina G, Roscitano A, et al. Does combined mitral valve surgery improve survival when compared to revascularization alone in patients with ischemic mitral regurgitation? A meta-analysis on 2479 patients. J Cardiovasc Med (Hagerstown). 2009;10:109-14.
61. Fattouch K, Guccione F, Sampognaro R, et al. POINT: Efficacy of adding mitral valve restrictive annuloplasty to coronary artery bypass grafting in patients with moderate ischemic mitral valve regurgitation: a randomized trial. J Thorac Cardiovasc Surg. 2009;138:278-85.
62. Deja MA, Grayburn PA, Sun B, et al. Influence of mitral regurgitation repair on survival in the surgical treatment for ischemic heart failure trial. Circulation. 2012;125:2639-48.
63. Nombela-Franco L, Eltchaninoff H, Zahn R, et al. Clinical impact and evolution of mitral regurgitation following transcatheter aortic valve replacement: a meta-analysis. Heart. 2015;101:1395-405.
64. Smith PK, Puskas JD, Ascheim DD, et al. Surgical treatment of moderate ischemic mitral regurgitation. N Engl J Med. 2014;371:2178-88.

65. Michler RE, Smith PK, Parides MK, et al. Two-Year Outcomes of Surgical Treatment of Moderate Ischemic Mitral Regurgitation. N Engl J Med. 2016;374:1932-41.
66. Acker MA, Parides MK, Perrault LP, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. N Engl J Med. 2014;370:23-32.
67. Goldstein D, Moskowitz AJ, Gelijns AC, et al. Two-Year Outcomes of Surgical Treatment of Severe Ischemic Mitral Regurgitation. N Engl J Med. 2016;374:344-53.
68. Hammermeister K, Sethi GK, Henderson WG, et al. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. J Am Coll Cardiol. 2000;36:1152-8.
69. Oxenham H, Bloomfield P, Wheatley DJ, et al. Twenty year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. Heart. 2003;89:715-21.
70. Stassano P, Di Tommaso L., Monaco M, et al. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. J Am Coll Cardiol. 2009;54:1862-8.
71. Khan SS, Trento A, DeRobertis M, et al. Twenty-year comparison of tissue and mechanical valve replacement. J Thorac Cardiovasc Surg. 2001;122:257-69.
72. Chan V, Jamieson WR, Germann E, et al. Performance of bioprostheses and mechanical prostheses assessed by composites of valve-related complications to 15 years after aortic valve replacement. J Thorac Cardiovasc Surg. 2006;131:1267-73.
73. Kulik A, Bedard P, Lam BK, et al. Mechanical versus bioprosthetic valve replacement in middle-aged patients. Eur J Cardiothorac Surg. 2006;30:485-91.
74. Ruel M, Chan V, Bedard P, et al. Very long-term survival implications of heart valve replacement with tissue versus mechanical prostheses in adults <60 years of age. Circulation. 2007;116:I294-I300.
75. van Geldorp MW, Eric Jamieson WR, Kappetein AP, et al. Patient outcome after aortic valve replacement with a mechanical or biological prosthesis: weighing lifetime anticoagulant-related event risk against reoperation risk. J Thorac Cardiovasc Surg. 2009;137:881-5.
76. Badhwar V, Ofenloch JC, Rovin JD, et al. Noninferiority of closely monitored mechanical valves to bioprostheses overshadowed by early mortality benefit in younger patients. Ann Thorac Surg. 2012;93:748-53.
77. Weber A, Noureddine H, Englberger L, et al. Ten-year comparison of pericardial tissue valves versus mechanical prostheses for aortic valve replacement in patients younger than 60 years of age. J Thorac Cardiovasc Surg. 2012;144:1075-83.
78. Chiang YP, Chikwe J, Moskowitz AJ, et al. Survival and long-term outcomes following bioprosthetic vs mechanical aortic valve replacement in patients aged 50 to 69 years. JAMA. 2014;312:1323-9.
79. Kaneko T, Aranki S, Javed Q, et al. Mechanical versus bioprosthetic mitral valve replacement in patients <65 years old. J Thorac Cardiovasc Surg. 2014;147:117-26.
80. McClure RS, McGurk S, Cevasco M, et al. Late outcomes comparison of nonelderly patients with stented bioprosthetic and mechanical valves in the aortic position: a propensity-matched analysis. J Thorac Cardiovasc Surg. 2014;148:1931-9.
81. Du DT, McKean S, Kelman JA, et al. Early mortality after aortic valve replacement with mechanical prosthetic vs bioprosthetic valves among Medicare beneficiaries: a population-based cohort study. JAMA Intern Med. 2014;174:1788-95.
82. Bourguignon T, Bouquiaux-Stablo AL, Candolfi P, et al. Very long-term outcomes of the Carpentier-Edwards Perimount valve in aortic position. Ann Thorac Surg. 2015;99:831-7.
83. Bourguignon T, Bouquiaux-Stablo AL, Loardi C, et al. Very late outcomes for mitral valve replacement with the Carpentier-Edwards pericardial bioprosthesis: 25-year follow-up of 450 implantations. J Thorac Cardiovasc Surg. 2014;148:2004-11.
84. Bourguignon T, El KR, Candolfi P, et al. Very Long-Term Outcomes of the Carpentier-Edwards Perimount Aortic Valve in Patients Aged 60 or Younger. Ann Thorac Surg. 2015;100:853-9.
85. Chikwe J, Chiang YP, Egorova NN, et al. Survival and outcomes following bioprosthetic vs mechanical mitral valve replacement in patients aged 50 to 69 years. JAMA. 2015;313:1435-42.
86. Glaser N, Jackson V, Holzmann MJ, et al. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50-69 years. Eur Heart J. 2015;
87. Isaacs AJ, Shuhaiber J, Salemi A, et al. National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements. J Thorac Cardiovasc Surg. 2015;149:1262-9.
88. De Vincentiis C., Kunkl AB, Trimarchi S, et al. Aortic valve replacement in octogenarians: is biologic valve the unique solution? Ann Thorac Surg. 2008;85:1296-301.
89. Vicchio M, Della CA, De Santo LS, et al. Tissue versus mechanical prostheses: quality of life in octogenarians. Ann Thorac Surg. 2008;85:1290-5.
90. Dvir D, Webb J, Brecker S, et al. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. Circulation. 2012;126:2335-44.
91. Dvir D, Webb JG, Bleiziffer S, et al. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. JAMA. 2014;312:162-70.
92. Repack A, Ziganshin BA, Elefteriades JA, et al. Comparison of Quality of Life Perceived by Patients with Bioprosthetic versus Mechanical Valves after Composite Aortic Root Replacement. Cardiology. 2016;133:3-9.
93. Puskas J, Gerdisch M, Nichols D, et al. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized on-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. J Thorac Cardiovasc Surg. 2014;147:1202-10.
94. Acar J, Iung B, Boissel JP, et al. AREVA: multicenter randomized comparison of low-dose versus standard-dose anticoagulation in patients with mechanical prosthetic heart valves. Circulation. 1996;94:2107-12.
95. Hering D, Piper C, Bergemann R, et al. Thromboembolic and bleeding complications following St. Jude Medical valve replacement: results of the German Experience With Low-Intensity Anticoagulation Study. Chest. 2005;127:53-9.
96. Torella M, Torella D, Chiodini P, et al. LOWERing the INtensity of oral anticoaGulant Therapy in patients with bileaflet mechanical aortic valve replacement: results from the "LOWERING-IT" Trial. Am Heart J. 2010;160:171-8.
97. Merie C, Kober L, Skov OP, et al. Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. JAMA. 2012;308:2118-25.
98. Brennan JM, Edwards FH, Zhao Y, et al. Early anticoagulation of bioprosthetic aortic valves in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. J Am Coll Cardiol. 2012;60:971-7.
99. Egbe AC, Pislaru SV, Pellikka PA, et al. Bioprosthetic Valve Thrombosis Versus Structural Failure: Clinical and Echocardiographic Predictors. J Am Coll Cardiol. 2015;66:2285-94.
100. Makkar RR, Fontana G, Jilaihawi H, et al. Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves. N Engl J Med. 2015;373:2015-24.
101. Hansson NC, Grove EL, Andersen HR, et al. Transcatheter Aortic Valve Thrombosis: Incidence, Predisposing Factors, and Clinical Implications. J Am Coll Cardiol. 2016;68:2059-69.

102. Pache G, Schoechlin S, Blanke P, et al. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. Eur Heart J. 2016;37:2263-71.
103. Hammerstingl C, Tripp C, Schmidt H, et al. Periprocedural bridging therapy with low-molecular-weight heparin in chronically anticoagulated patients with prosthetic mechanical heart valves: experience in 116 patients from the prospective BRAVE registry. J Heart Valve Dis. 2007;16:285-92.
104. Spyropoulos AC, Turpie AG, Dunn AS, et al. Perioperative bridging therapy with unfractionated heparin or low-molecular-weight heparin in patients with mechanical prosthetic heart valves on long-term oral anticoagulants (from the REGIMEN Registry). Am J Cardiol. 2008;102:883-9.
105. Pengo V, Cucchini U, Denas G, et al. Standardized low-molecular-weight heparin bridging regimen in outpatients on oral anticoagulants undergoing invasive procedure or surgery: an inception cohort management study. Circulation. 2009;119:2920-7.
106. Daniels PR, McBane RD, Litin SC, et al. Peri-procedural anticoagulation management of mechanical prosthetic heart valve patients. Thromb Res. 2009;124:300-5.
107. Bui HT, Krisnaswami A, Le CU, et al. Comparison of safety of subcutaneous enoxaparin as outpatient anticoagulation bridging therapy in patients with a mechanical heart valve versus patients with nonvalvular atrial fibrillation. Am J Cardiol. 2009;104:1429-33.
108. Biteker M, Tekkesin AI, Can MM, et al. Outcome of noncardiac and nonvascular surgery in patients with mechanical heart valves. Am J Cardiol. 2012;110:562-7.
109. Weiss A, Brose S, Ploetze K, et al. Half-dose enoxaparin vs. full-dose enoxaparin for postoperative bridging therapy in patients after cardiac surgery: Which dose regimen should be preferred? Clin Hemorheol Microcirc. 2013;
110. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. N Engl J Med. 2015;373:823-33.
111. Pengo V, Palareti G, Cucchini U, et al. Low-intensity oral anticoagulant plus low-dose aspirin during the first six months versus standard-intensity oral anticoagulant therapy after mechanical heart valve replacement: a pilot study of low-intensity warfarin and aspirin in cardiac prostheses (LIWACAP). Clin Appl Thromb Hemost. 2007;13:241-8.
112. Keuleers S, Herijgers P, Herregods MC, et al. Comparison of thrombolysis versus surgery as a first line therapy for prosthetic heart valve thrombosis. Am J Cardiol. 2011;107:275-9.
113. Nagy A, Denes M, Lengyel M. Predictors of the outcome of thrombolytic therapy in prosthetic mitral valve thrombosis: a study of 62 events. J Heart Valve Dis. 2009;18:268-75.
114. Lengyel M, Vandor L. The role of thrombolysis in the management of left-sided prosthetic valve thrombosis: a study of 85 cases diagnosed by transesophageal echocardiography. J Heart Valve Dis. 2001;10:636-49.
115. Karthikeyan G, Math RS, Mathew N, et al. Accelerated infusion of streptokinase for the treatment of left-sided prosthetic valve thrombosis: a randomized controlled trial. Circulation. 2009;120:1108-14.
116. Caceres-Loriga FM, Perez-Lopez H, Morlans-Hernandez K, et al. Thrombolysis as first choice therapy in prosthetic heart valve thrombosis. A study of 68 patients. J Thromb Thrombolysis. 2006;21:185-90.
117. Gupta D, Kothari SS, Bahl VK, et al. Thrombolytic therapy for prosthetic valve thrombosis: short- and long-term results. Am Heart J. 2000;140:906-16.
118. Roudaut R, Lafitte S, Roudaut MF, et al. Management of prosthetic heart valve obstruction: fibrinolysis versus surgery. Early results and long-term follow-up in a single-centre study of 263 cases. Arch Cardiovasc Dis. 2009;102:269-77.
119. Tong AT, Roudaut R, Ozkan M, et al. Transesophageal echocardiography improves risk assessment of thrombolysis of prosthetic valve thrombosis: results of the international PRO-TEE registry. J Am Coll Cardiol. 2004;43:77-84.
120. Ozkan M, Gunduz S, Biteker M, et al. Comparison of different TEE-guided thrombolytic regimens for prosthetic valve thrombosis: the TROIA trial. JACC Cardiovasc Imaging. 2013;6:206-16.
121. Ozkan M, Cakal B, Karakoyun S, et al. Thrombolytic therapy for the treatment of prosthetic heart valve thrombosis in pregnancy with low-dose, slow infusion of tissue-type plasminogen activator. Circulation. 2013;128:532-40.
122. Ozkan M, Gunduz S, Gursoy OM, et al. Ultraslow thrombolytic therapy: A novel strategy in the management of PROsthetic MEchanical valve Thrombosis and the prEdictors of outcomE: The Ultra-slow PROMETEE trial. Am Heart J. 2015;170:409-18.
123. Barbetseas J, Nagueh SF, Pitsavos C, et al. Differentiating thrombus from pannus formation in obstructed mechanical prosthetic valves: an evaluation of clinical, transthoracic and transesophageal echocardiographic parameters. J Am Coll Cardiol. 1998;32:1410-7.
124. Gunduz S, Ozkan M, Kalcik M, et al. Sixty-Four-Section Cardiac Computed Tomography in Mechanical Prosthetic Heart Valve Dysfunction: Thrombus or Pannus. Circ Cardiovasc Imaging. 2015;8:
125. Cianciulli TE, Lax JA, Beck MA, et al. Cinefluoroscopic assessment of mechanical disc prostheses: its value as a complementary method to echocardiography. J Heart Valve Dis. 2005;14:664-73.
126. Montorsi P, De BF, Muratori M, et al. Role of cine-fluoroscopy, transthoracic, and transesophageal echocardiography in patients with suspected prosthetic heart valve thrombosis. Am J Cardiol. 2000;85:58-64.
127. Muratori M, Montorsi P, Teruzzi G, et al. Feasibility and diagnostic accuracy of quantitative assessment of mechanical prostheses leaflet motion by transthoracic and transesophageal echocardiography in suspected prosthetic valve dysfunction. Am J Cardiol. 2006;97:94-100.
128. Suh YJ, Lee S, Im DJ, et al. Added value of cardiac computed tomography for evaluation of mechanical aortic valve: Emphasis on evaluation of pannus with surgical findings as standard reference. Int J Cardiol. 2016;214:454-60.
129. Symersky P, Budde RP, de Mol BA, et al. Comparison of multidetector-row computed tomography to echocardiography and fluoroscopy for evaluation of patients with mechanical prosthetic valve obstruction. Am J Cardiol. 2009;104:1128-34.
130. Jander N, Kienzle RP, Kayser G, et al. Usefulness of phenprocoumon for the treatment of obstructing thrombus in bioprostheses in the aortic valve position. Am J Cardiol. 2012;109:257-62.
131. Butnaru A, Shaheen J, Tzivoni D, et al. Diagnosis and treatment of early bioprosthetic malfunction in the mitral valve position due to thrombus formation. Am J Cardiol. 2013;112:1439-44.
132. Pislaru SV, Hussain I, Pellikka PA, et al. Misconceptions, diagnostic challenges and treatment opportunities in bioprosthetic valve thrombosis: lessons from a case series. Eur J Cardiothorac Surg. 2015;47:725-32.
133. Latib A, Naganuma T, Abdel-Wahab M, et al. Treatment and clinical outcomes of transcatheter heart valve thrombosis. Circ Cardiovasc Interv. 2015;8:

134. De ME, Mesa J, Pomenti S, et al. Thrombus formation following transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2015;8:728-39.
135. Ye J, Cheung A, Yamashita M, et al. Transcatheter Aortic and Mitral Valve-in-Valve Implantation for Failed Surgical Bioprosthetic Valves: An 8-Year Single-Center Experience. JACC Cardiovasc Interv. 2015;8:1735-44.
136. Webb JG, Wood DA, Ye J, et al. Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. Circulation. 2010;121:1848-57.
137. Ussia GP, Scarabelli M, Mule M, et al. Dual antiplatelet therapy versus aspirin alone in patients undergoing transcatheter aortic valve implantation. Am J Cardiol. 2011;108:1772-6.
138. Eggebrecht H, Schafer U, Treede H, et al. Valve-in-valve transcatheter aortic valve implantation for degenerated bioprosthetic heart valves. JACC Cardiovasc Interv. 2011;4:1218-27.
139. Bedogni F, Laudisa ML, Pizzocri S, et al. Transcatheter valve-in-valve implantation using Corevalve Revalving System for failed surgical aortic bioprostheses. JACC Cardiovasc Interv. 2011;4:1228-34.
140. Toggweiler S, Wood DA, Rodes-Cabau J, et al. Transcatheter valve-in-valve implantation for failed balloon-expandable transcatheter aortic valves. JACC Cardiovasc Interv. 2012;5:571-7.
141. Bapat V, Attia R, Redwood S, et al. Use of transcatheter heart valves for a valve-in-valve implantation in patients with degenerated aortic bioprosthesis: technical considerations and results. J Thorac Cardiovasc Surg. 2012;144:1372-9.
142. Linke A, Woitek F, Merx MW, et al. Valve-in-valve implantation of Medtronic CoreValve prosthesis in patients with failing bioprosthetic aortic valves. Circ Cardiovasc Interv. 2012;5:689-97.
143. Ihlberg L, Nissen H, Nielsen NE, et al. Early clinical outcome of aortic transcatheter valve-in-valve implantation in the Nordic countries. J Thorac Cardiovasc Surg. 2013;146:1047-54.
144. Camboni D, Holzamer A, Florchinger B, et al. Single Institution Experience With Transcatheter Valve-in-Valve Implantation Emphasizing Strategies for Coronary Protection. Ann Thorac Surg. 2015;99:1532-8.
145. Conradi L, Silaschi M, Seiffert M, et al. Transcatheter valve-in-valve therapy using 6 different devices in 4 anatomic positions: Clinical outcomes and technical considerations. J Thorac Cardiovasc Surg. 2015;150:1557-65, 1567.
146. Duncan BF, McCarthy PM, Kruse J, et al. Paravalvular regurgitation after conventional aortic and mitral valve replacement: A benchmark for alternative approaches. J Thorac Cardiovasc Surg. 2015;150:860-8.
147. Erlebach M, Wottke M, Deutsch MA, et al. Redo aortic valve surgery versus transcatheter valve-in-valve implantation for failing surgical bioprosthetic valves: consecutive patients in a single-center setting. J Thorac Dis. 2015;7:1494-500.
148. Ye J, Cheung A, Yamashita M, et al. Transcatheter Aortic and Mitral Valve-in-Valve Implantation for Failed Surgical Bioprosthetic Valves: An 8-Year Single-Center Experience. JACC Cardiovasc Interv. 2015;8:1735-44.
149. Phan K, Zhao DF, Wang N, et al. Transcatheter valve-in-valve implantation versus reoperative conventional aortic valve replacement: a systematic review. J Thorac Dis. 2016;8:E83-E93.
150. Orszulak TA, Schaff HV, Danielson GK, et al. Results of reoperation for periprosthetic leakage. Ann Thorac Surg. 1983;35:584-9.
151. Miller DL, Morris JJ, Schaff HV, et al. Reoperation for aortic valve periprosthetic leakage: identification of patients at risk and results of operation. J Heart Valve Dis. 1995;4:160-5.
152. Akins CW, Bitondo JM, Hilgenberg AD, et al. Early and late results of the surgical correction of cardiac prosthetic paravalvular leaks. J Heart Valve Dis. 2005;14:792-9.
153. Pate GE, Al ZA, Chandavimol M, et al. Percutaneous closure of prosthetic paravalvular leaks: case series and review. Catheter Cardiovasc Interv. 2006;68:528-33.
154. Shapira Y, Hirsch R, Kornowski R, et al. Percutaneous closure of perivalvular leaks with Amplatzer occluders: feasibility, safety, and shortterm results. J Heart Valve Dis. 2007;16:305-13.
155. Cortes M, Garcia E, Garcia-Fernandez MA, et al. Usefulness of transesophageal echocardiography in percutaneous transcatheter repairs of paravalvular mitral regurgitation. Am J Cardiol. 2008;101:382-6.
156. Ruiz CE, Jelnin V, Kronzon I, et al. Clinical outcomes in patients undergoing percutaneous closure of periprosthetic paravalvular leaks. J Am Coll Cardiol. 2011;58:2210-7.
157. Sorajja P, Cabalka AK, Hagler DJ, et al. Percutaneous repair of paravalvular prosthetic regurgitation: acute and 30-day outcomes in 115 patients. Circ Cardiovasc Interv. 2011;4:314-21.
158. Sorajja P, Cabalka AK, Hagler DJ, et al. Long-term follow-up of percutaneous repair of paravalvular prosthetic regurgitation. J Am Coll Cardiol. 2011;58:2218-24.
159. Nijenhuis VJ, Swaans MJ, Post MC, et al. Open transapical approach to transcatheter paravalvular leakage closure: a preliminary experience. Circ Cardiovasc Interv. 2014;7:611-20.
160. Taramasso M, Maisano F, Latib A, et al. Conventional surgery and transcatheter closure via surgical transapical approach for paravalvular leak repair in high-risk patients: results from a single-centre experience. Eur Heart J Cardiovasc Imaging. 2014;15:1161-7.
161. Gafoor S, Franke J, Piayda K, et al. Paravalvular leak closure after transcatheter aortic valve replacement with a self-expanding prosthesis. Catheter Cardiovasc Interv. 2014;84:147-54.
162. Cruz-Gonzalez I, Rama-Merchan JC, Arribas-Jimenez A, et al. Paravalvular leak closure with the Amplatzer Vascular Plug III device: immediate and short-term results. Rev Esp Cardiol (Engl Ed). 2014;67:608-14.
163. Millan X, Skaf S, Joseph L, et al. Transcatheter reduction of paravalvular leaks: a systematic review and meta-analysis. Can J Cardiol. 2015;31:260-9.
164. Goktekin O, Vatankulu MA, Ozhan H, et al. Early experience of percutaneous paravalvular leak closure using a novel Occlutech occluder. EuroIntervention. 2016;11:1195-200.
165. Jault F, Gandjbakhch I, Rama A, et al. Active native valve endocarditis: determinants of operative death and late mortality. Ann Thorac Surg. 1997;63:1737-41.
166. Castillo JC, Anguita MP, Ramirez A, et al. Long term outcome of infective endocarditis in patients who were not drug addicts: a 10 year study. Heart. 2000;83:525-30.
167. Alexiou C, Langley SM, Stafford H, et al. Surgery for active culture-positive endocarditis: determinants of early and late outcome. Ann Thorac Surg. 2000;69:1448-54.
168. Hasbun R, Vikram HR, Barakat LA, et al. Complicated left-sided native valve endocarditis in adults: risk classification for mortality. JAMA. 2003;289:1933-40.
169. Vikram HR, Buenconsejo J, Hasbun R, et al. Impact of valve surgery on 6-month mortality in adults with complicated, left-sided native valve endocarditis: a propensity analysis. JAMA. 2003;290:3207-14.
170. Habib G, Tribouilloy C, Thuny F, et al. Prosthetic valve endocarditis: who needs surgery? A multicentre study of 104 cases. Heart. 2005;91:954-9.
171. Revilla A, Lopez J, Vilacosta I, et al. Clinical and prognostic profile of patients with infective endocarditis who need urgent surgery. Eur Heart J. 2007;28:65-71.
172. Hill EE, Herijgers P, Claus P, et al. Infective endocarditis: changing epidemiology and predictors of 6-month mortality: a prospective cohort study. Eur Heart J. 2007;28:196-203.

173. Remadi JP, Habib G, Nadji G, et al. Predictors of death and impact of surgery in Staphylococcus aureus infective endocarditis. Ann Thorac Surg. 2007;83:1295-302.
174. Aksoy O, Sexton DJ, Wang A, et al. Early surgery in patients with infective endocarditis: a propensity score analysis. Clin Infect Dis. 2007;44:364-72.
175. Tleyjeh IM, Ghomrawi HM, Steckelberg JM, et al. The impact of valve surgery on 6-month mortality in left-sided infective endocarditis. Circulation. 2007;115:1721-8.
176. Tleyjeh IM, Steckelberg JM, Georgescu G, et al. The association between the timing of valve surgery and 6-month mortality in left-sided infective endocarditis. Heart. 2008;94:892-6.
177. Thuny F, Beurtheret S, Mancini J, et al. The timing of surgery influences mortality and morbidity in adults with severe complicated infective endocarditis: a propensity analysis. Eur Heart J. 2011;32:2027-33.
178. Manne MB, Shrestha NK, Lytle BW, et al. Outcomes after surgical treatment of native and prosthetic valve infective endocarditis. Ann Thorac Surg. 2012;93:489-93.
179. Kang DH, Kim YJ, Kim SH, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med. 2012;366:2466-73.
180. Eishi K, Kawazoe K, Kuriyama Y, et al. Surgical management of infective endocarditis associated with cerebral complications. Multi-center retrospective study in Japan. J Thorac Cardiovasc Surg. 1995;110:1745-55.
181. Garcia-Cabrera E, Fernandez-Hidalgo N, Almirante B, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. Circulation. 2013;127:2272-84.
182. Barsic B, Dickerman S, Krajinovic V, et al. Influence of the timing of cardiac surgery on the outcome of patients with infective endocarditis and stroke. Clin Infect Dis. 2013;56:209-17.