2014 Valvular Heart Disease Guideline Data Supplements

(Section numbers correspond to the full-text guideline.)

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Data Supplement 1. Outcomes in Adults With Low-Flow/Low-Gradient Aortic Stenosis With Reduced Left Ventricular Ejection Fraction (stage S1) (Sections 3.2.1.1 and 3.2.3)

Study	Aim of Study	Study Type	Study Size	Definition of LFLG Severe AS With rLVEF	Exclusion Criteria	Stress Findings/Clinical Outcomes	Comments
DeFillippi, 1995 (1) 7810504	To determine if DSE can distinguish severe fixed AS from flow-dependent AS	Prospective	24	AVAi ≤0.5 cm^2/m^2 ΔP_{mean} ≤30 mm Hg LVEF ≤45% All symptomatic	Too ill AF	**IA**. (n=7, 39%) No change in AVA with ≥20% improvement in LVEF (contractile reserve). **IB**. (n=5, 28%) ↑AVA ≥0.3 cm^2 and contractile reserve. **II**. (n=6, 33%) No contractile reserve.	**IA.** 4 underwent AVR with improved symptoms (1 perioperative death). **IB.** 4 medical Rx and alive at 1 y. 1 CAD death. **II.** 3 deaths and 3 persistent CHF.
Connolly, 1997 (2) 9170402	Determine outcome after AVR for severe AS with LG and low LVEF	Retrospective surgical database	154	LVEF ≤35% Undergoing AVR	Other valve disease	Baseline mean AVA 0.6±0.2 cm^2, Mean cardiac output 4.1±1.5 L/min, Perioperative (30 d) mortality 9%, Postoperative LVEF improved in 76% of pts.	Study group had low LVEF, but not all had LG or LF.
Pereira, 2002 (3) 11955855	Evaluate outcome with AVR vs. medical Rx in LFLG severe AS	Retrospective, propensity score matched	68	AVA ≤0.75 cm^2 ΔP_{mean} ≤30 mm Hg LVEF ≤35%	Other valve disease.	In propensity matched pts, survival at 4 y was 78% with AVR vs.15% with medical Rx (p<0.0001).	Multivariate predictors of survival were AVR, age, and renal function.
Nishimura, 2002 (4) 12176952	Diagnostic value of invasive hemodynamics with dobutamine stress	Prospective, comparison with surgical findings	32	AVA <1.0 cm^2 ΔP_{mean} <40 mm Hg LVEF <40%	N/A	With dobutamine, final AVA ≤1.2 cm^2 with a ΔP_{mean} >30 mm Hg in 21 pts; severe AS confirmed at surgery. In 15 pts with CR, mortality was 7% (1 death) with medical therapy.	CR defined as ↑SV ≥20% with dobutamine.
Monin, 2003 (5) 12835219	Assess prognostic value of DSE in LFLG AS	Prospective, multicenter	136	AVA ≤1.0 cm^2 Cardiac index ≤3 $L/min/m^2$ ΔP_{mean} ≤40 mm Hg	Other valve disease, severe comorbidities	Operative mortality 5% with CR vs. 32% without CR (p=0.0002). Predictors of long-term survival were AVR and CR.	CR defined as ↑SV ≥20% on DSE.
Quere, 2006 (6) 16585393	Determine relationship between CR on DSE and postoperative LVEF	Prospective, multicenter	66	AVA ≤1.0 cm^2 ΔP_{mean} ≤40 mm Hg LVEF ≤40% All symptomatic	Excluded operative deaths	**I**. CR in 70%; post-AVR LVEF improved ≥10 LVEF units in 83%. **II**. No contractile reserve in 30%; post-AVR LVEF improved ≥10 LVEF units in 65%.	Symptoms improved by ≥2 classes after AVR in 58%. Mean LVEF increased from 29±6% to 47±11% after AVR.
Blais, 2006 (7) 16461844	Improve differentiation of true from pseudo severe AS on DSE	In vitro model and prospective pt group	23	AVAi ≤0.6 cm^2/m^2 LVEF ≤40% ΔP_{mean} ≤40 mm Hg All symptomatic undergoing AVR	Other valve disease AF or paced rhythm	Projected effective orifice area at a normal transvalvular flow rate was accurate for identifying true vs. pseudo severe AS in comparison to surgical findings.	No outcome data.
Bergler-Klein, 2007 (8) 15117847	Relationship between BNP and outcome in LFLG AS	Prospective, multicenter	69	AVAi <0.6 cm^2/m^2 ΔP_{mean} ≤40 mm Hg LVEF ≤40%	Other valve disease, AF, or paced rhythm	BNP was higher with true-severe AS compared to pseudo-severe AS (p=0.12). 1-y survival 47±9% with BNP ≥550 pg/mL vs. 97±3% with BNP <550 pg/mL (p=0.0001).	Classified as severe AS if DSE showed AVA ≤1.0 cm^2 at projected flow rate of 250 mL/s; pseudo-severe if AVA >1.0 cm^2 projected at 250 mL/s.

Study	Aim of Study	Study Type	Study Size	Definition of LFLG Severe AS With rLVEF	Exclusion Criteria	Stress Findings/Clinical Outcomes	Comments
Pai, 2008 (9) 19021976	Surgical outcome with low-gradient AS	Retrospective surgical database	362	AVA ≤0.8 cm^2 *AND* ΔP_{mean} ≤30 mm Hg *OR* LVEF ≤35%	N/A	In 194 pts with LVEF ≤35%, 5-y survival was 50% with AVR vs. 23% without AVR (p<0.0001). In 168 pts with ΔP_{mean} ≤30 mm Hg, 5-y survival was 80% with AVR vs. 22% without AVR (p<0.0001).	Univariate predictors of mortality were older age, lower LVEF, renal insufficiency, and lack of AVR.
Levy, 2008 (10) 18402902	Evaluate perioperative mortality with LFLG severe AS	Surgical series AVR for LGLF AS	217	AVA <1 cm^2 LVEF ≤35% ΔP_{mean} ≤30 mm Hg	Other valve disease	Perioperative mortality 16% overall (decreased from 20% in 1990s to 10% after 2000). 5-y survival was 49±4%.	Predictors of perioperative mortality were very LG, multivessel CAD, and absence of CR on DSE.
Clavel, 2010 (11) 20975002	Compare outcomes after TAVR vs. SAVR with low LVEF severe AS	Prospective comparison of echo data	200 SAVR; 83 TAVR	AVA ≤1 cm^2 LVEF ≤50%	No LVEF by echo	LVEF improved more with TAVR compared to SAVR (ΔLVEF, 14±15% vs. 7±11%; p=0.005). At 1 y, LVEF was normal in 58% of TAVR compared to 20% SAVR pts.	Treatment not randomized.
Tribouilloy, 2009 (12) 19442886	Effect of AVR on outcomes in LFLG severe AS without contractile reserve	Prospective, multicenter	81	AVA <1 cm^2 LVEF ≤40% ΔP_{mean} ≤40 mm Hg No contractile reserve	N/A	Survival at 5 y was higher with AVR compared to medical therapy (54±7% vs. 13±7%; p=0.001). Operative mortality was 22% (n=12).	Contractile reserve defined as ↑SV ≥20% on DSE. Multivariate predictors of mortality were associated bypass surgery (p=0.007) and ΔP_{mean} ≤20 mm Hg (p=0.035).
Gotzmann, 2012 (13) 21805576	Outcomes after TAVR with low LVEF and LG AS	Prospective CoreValve TAVR	202	LVEF groups >50% or ≤50% ΔP_{mean} groups >40 or ≤40 mm Hg	N/A	1 y mortality: *LVEF >50%* vs. *LVEF ≤50%* *ΔP_{mean} >40*: 14% (n=86) vs. 27% (n=45) *ΔP_{mean} ≤40*: 22% (n=27) vs. 39% (n=44)	1-y mortality after TAVR was higher with LG, low LVEF severe AS. Severe AS defined as AVA ≤1.0 cm^2. All pts were high surgical risk.
Fougeres, 2012 (14) 22733832	Outcome of pseudo-severe AS without AVR	Multicenter registry of severe symptomatic LFLG AS	107	AVA ≤1 cm^2 or AVAi ≤0.6 cm^2/m^2 LVEF ≤40% ΔP_{mean} ≤40 mm Hg Cardiac index ≤3.0 L/min/m^2	Severe comorbidities, Other valve disease, AF	**IA**: 43 with true-severe AS **IB:** 29 with pseudo-severe AS defined as CR with final AVA ≥1.2 cm^2 and ΔP_{mean} ≤40 mm Hg **II:** 23 with no CR (↑SV <20%)	74 deaths (69%) at a median interval of 10 m. Outcomes with pseudo-severe AS (Group IB) were similar to pts with HF without AS. Multivariate predictors of mortality in Group 1B were CAD (HR: 1.88; 95% CI: 1.35–2.63) and ΔP_{mean} <20 mm Hg (HR: 1.55; 95% CI: 1.07–02.23).
Herrmann 2013 (15) 23661722	Surgical vs. transcatheter AVR for in operable pts with LFLG severe AS with	Subgroup analysis of RCT	42 randomized to TAVR vs.	AVA ≤0.8 cm^2 or AVAi <0.5 cm^2/m^2 LVEF <50%	N/A	Mortality at 2 y was 80.0% with medical therapy vs. 47.1% with TAVR (HR: 0.43; 95% CI: 0.19–0.98; p=0.040)	No difference in 2-y outcomes in the 105 pts with LFLG severe AS with low LVEF randomized to SAVR vs.

Study	Aim of Study	Study Type	Study Size	Definition of LFLG Severe AS With rLVEF	Exclusion Criteria	Stress Findings/Clinical Outcomes	Comments
	reduced LVEF		medical Rx	$\Delta P_{mean} \leq 40$ mm Hg SVi < 35 mL/m^2			TAVR (42.9% vs. 37.1%; HR: 1.25, 95% CI: 0.66–2.36; p=0.50).

AF indicates atrial fibrillation; AS, aortic stenosis; AVA, aortic valve area; AVAi, aortic valve area indexed to body surface area; AVR, aortic valve replacement; BNP, brain natriuretic peptide; CAD, coronary artery disease; CHF, congestive heart failure; CR, contractile reserve; DSE, dobutamine stress echocardiography; HF, heart failure; LFLG, low-flow/low-gradient; LF, low flow; LG, low gradient; N/A, nonapplicable; ΔP_{mean}, mean transaortic systolic pressure gradient; pts, adult patients; Rx, prescription; rLVEF, left ventricular reduced ejection fraction; ΔP_{mean} , mean transaortic pressure gradient; SAVR, surgical aortic valve replacement; SV, stroke volume; SVi, stroke volume indexed to body surface area; and TAVR, transcatheter aortic valve replacement.

Data Supplement 2. Hemodynamic Progression of Aortic Stenosis in Adult Patients (stages B and C) (Section 3.2.1.3)

First Author, Year	N	Type of Study	Entry Criteria	Mean Follow-up (y)	Increase in ΔP_{mean} (mmHg/y) (mean± SD)	Increase in V_{max} (m/s/y) (mean± SD)	Decrease in AVA (cm^2/y) (mean± SD)
Otto, 1989 (16) 2918158	42	Prospective	Asymptomatic; V_{max} >2.5 m/s	1.7	8 (-7–23)	0.36±0.31	0.1
Roger, 1990 (17) 2301222	112	Retrospective	AS on echo	2.1	N/A	0.23±0.37	N/A
Faggiano, 1992 (18) 1626512	45	Prospective	AS on echo	1.5	N/A	0.4±0.3	0.1±0.13
Peter, 1993 (19) 8404089	49	Retrospective	AS on echo	2.7	7.2	N/A	N/A
Brener, 1995 (20) 7829781	394	Retrospective	AS on echo	6.3	N/A	N/A	0.14
Otto, 1997 (21) 9142003	123	Prospective	Asymptomatic, V_{max} >2.5 m/s	2.5	7±7	0.32±0.34	0.12±0.19
Bahler, 1999 (22) 10569661	91	Retrospective	AS on echo	1.8	2.8	0.2	0.04
Palta, 2000 (23) 10831524	170	Retrospective	AS on echo	1.9	N/A	N/A	0.10±0.27
Rosenhek, 2000 (24) 10965007	128	Prospective	V_{max} >4.0m/s	1.8	Slow	0.14±0.18	N/A
					Rapid	0.45±0.38	N/A
Rosenhek, 2004 (25) 14972419	176	Retrospective	V_{max} 2.5–3.9 m/s	3.8	N/A	0.24±0.30	N/A
Rossebo, 2008 (26) 18765433	1,875	Prospective	V_{max} 2.5–4 m/s	4.3	Statin Rx	0.15±0.01	0.03±0.1
					Placebo	0.16±0.01	0.03±0.1

AS indicates aortic stenosis; AVA, aortic valve area; echo, echocardiography; N/A, not applicable; ΔP_{mean}, mean transaortic pressure gradient; V_{max}, maximum velocity.

Data Supplement 3. Exercise Stress Testing in Asymptomatic Adults With Aortic Stenosis (stages B and C) (Sections 3.2.1.5 and 3.2.3)

Study	Aim of Study	Study Type	Study Size	Inclusion Criteria	Exclusion Criteria	Exercise Findings/Clinical Outcomes	Comments
Nylander, 1986 (27) 3707789	Describe hemodynamics, clinical features, noninvasive findings in elderly pts with suspected severe symptomatic AS	Observational, exercise test	76 (37 in NHYA class III/IV)	Suspected symptomatic severe AS, Mean age 65 y	N/A	Inadequate BP increase with exercise in 82%. ETT was at variance with reported NYHA class in 25%. Exercise tolerance was <80% expected for age.	ETT stopped for low BP in 36% and chest pain in 29%. No clinical outcome data. Most pts were symptomatic at baseline.
Clyne, 1991 (28) 1746429	Evaluate exercise response	ETT, Thallium perfusion imaging, MUGA	14	Asymptomatic AS	N/A	AS pts had decreased exercise tolerance and VO_{2max} vs. controls	ST depression >1 mm flat or downsloping in 71%. Reversible perfusion defect in 21%. ↓BP >10 mm Hg in 7%. No clinical outcome data.
Otto, 1992 (29) 1401617	Measure physiologic response to exercise	Prospective, Bruce protocol ETT, Doppler echo	28	Asymptomatic AS	N/A	Exercise duration 6.7±4.3 min V_{max} ↑3.99±0.93 to 4.61±1.12 m/s (p<0.0001) ΔP_{mean} ↑39±20 to 52±26 mm Hg (p<0.0001) Stroke volume ↓98±29 to 89±32 mL (p=0.01) Q_{max} ↑422±117 to 523±209 mL/s (p<0.0001) SEP ↓0.33±0.04 to 0.24±0.002 (p<0.0001) Cardiac output ↑6.5±1.7 to 10.2 4.4 L/min (p<0.0001) AVA 1.17±0.45 to 1.28±0.65 (p=NS)	↓BP >10 mm Hg in 11%. ST depression >1 mm flat or downsloping in 75%. Occasional PVCS in 39%. Asymptomatic 3-beat VT in 4% (1 pt.). No clinical outcome data.
Otto, 1997 (21) 9142003	Identify predictors of clinical outcome	Prospective, clinical, echo, and ETT data	104 pts 274 exercise tests	Asymptomatic AS (V_{max} >2.5 m/s)	Unable to walk on treadmill	Univariate predictors of clinical outcome (AVR or death) included a smaller exercise ↑AVA, BP, and cardiac output and ↓stroke volume with exercise. Multivariate predictors of outcome were resting V_{max}, the rate of change in V_{max} (m/s/y), and functional status score; exercise variables did provide additive prognostic information.	No complication in 85%. ↓BP >10 mm Hg in 9%. ST depression >1 mm flat or downsloping in 69%. ST depression >2 mm flat or downsloping persisting >5 m in recovery in 2%.
Amato, 2001(30) 11559673	To determine prognostic value of exercise testing	Prospective	66 Mean age 49.5 y, 67% men	Severe AS (AVA ≤1.0 cm^2)	CAD, arrhythmias, abnormal baseline ECG, comorbid disease	Main outcome measure of sudden death (6%) or symptom onset (52%). Positive ETT in 67%: symptoms in 35%, BP rise <20 mm Hg in 20%, ST changes alone in 12%, ventricular arrhythmia in 7%. Event free survival at 2 y was 19% with a positive ETT and 85% with a negative ETT.	Dizziness during ETT in 12%, no other complications of ETT. The 66 pts were derived from a cohort of 853 consecutive pts. These data may not apply to all AS pts.
Alborino, 2002 (31)	Risk stratification of asymptomatic pts with	Prospective	30 Mean age	Asymptomatic AS	N/A	Abnormal ETT in 18 (60%) with: Fall in BP (3), angina (1), ECG ST changes (3), dyspnea	At 1 y: All 12 pts with a normal ETT

Study	Aim of Study	Study Type	Study Size	Inclusion Criteria	Exclusion Criteria	Exercise Findings/Clinical Outcomes	Comments
12000161	moderate-severe AS		62±14 y			(11)	remained symptom free. 10/18 with abnormal ETT required AVR
Das, 2005 (32) 15820999	Accuracy of stress testing to predict symptom onset at 12 mo	Prospective	125	Asymptomatic AS AVA <1.4 (mean 0.9±0.2) cm^2/m^2 Normal LVEF	Other valve disease. Regional wall motion.	At 1-y follow-up, 36 (29%) developed symptoms. ETT provoked symptoms in 26 (72%) of these pts. Abnormal BP response or ST changes did not improve accuracy of ETT for predicting symptom onset.	Symptoms provoked by ETT had a PPV of 57% and NPV of 87% for onset of symptoms within 1 y. Accuracy was higher in pts under 70 y of age.
Lancellotti, 2005 (33) 16159850	Role of quantitative exercise Doppler	Prospective	69	Asymptomatic AS AVA <1.0 cm^2	Other valve disease, AF, AVR within 2 mo	Abnormal exercise response in 26 (38%) including symptoms, ST depression, failure of BP rise.	Cardiac events (n=18) at 15±7 mo follow-up were predicted by an exercise $\uparrow\Delta P_{mean}$ ≥18 mm Hg, an abnormal exercise test or an AVA <0.75 cm^2.
Marechaux, 2010 (34) 20308041	Assess if exercise hemodynamics provide incremental prognostic value to standard ETT data	Prospective, multicenter	186	Moderate-severe AS Normal LV (LVEF ≥50%)	Symptoms Other valve disease CAD AF/flutter	In the 73% with a normal ETT, 67 had an event (AVR or CV death) at 20±14 mo follow-up. The 27% with an abnormal ETT (symptoms limiting exercise, fall in BP below baseline or complex ventricular arrhythmias) were excluded from analysis.	Adverse events associated with age 65 y, diabetes mellitus, LVH, resting ΔP_{mean} 35 mm Hg, exercise $\uparrow\Delta P_{mean}$ >20 mm Hg.
Rajani, 2010 (35) 11479246	Test if exercise symptoms are due to changes in LV function	Prospective	38	Asymptomatic AVA <1.5 cm^2	N/A	ETT revealed symptom in 10 (26%) which was associated with a lower cardiac index, stroke index, and VO_{2max} compared to those without symptoms.	The only independent predictor of peak cardiac index was the log BNP level (p<0.001; r=0.71)

AF indicates atrial fibrillation, AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; BNP, brain natriuretic peptide; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular, echo; echocardiography; ECG, electrocardiogram; ETT, exercise treadmill test; LV, left ventricular, LVEF, left ventricular ejection fraction; LVH; left ventricular hypertrophy; MUGA; multi gated acquisition scan; N/A, nonapplicable; NS, nonsignificant; NPV, negative predictive value; NYHA, New York Heart Association; ΔP_{mean}, mean transaortic systolic pressure gradient ; PPV, positive predictive value; pt(s), patients; PVCs, premature ventricular contractions; Q_{max}, maximum flow rate; SEP, systolic ejection period; VO_2max, maximal oxygen consumption.

Data Supplement 4. Clinical Trials of Lipid Lowering Therapy in Adults With Asymptomatic Mild to Moderate Aortic Stenosis (stage B (Section 3.2.2)

Study Name, First Author, Year	Type of Study, Mean Follow-Up (y)	N	Entry Criteria	Exclusion Criteria	Treatment Group	Serum LDL on Rx (% change from baseline)	Increase in V_{max} (m/s/y) or ΔP_{mean} (mm Hg/y)	Decrease in AVA (cm^2/y)	Other Endpoints	Clinical Endpoints	Study Limitations and Adverse Events
SALTIRE Cowell, 2005 (36) 15944423	Randomized, double-blind, Placebo controlled 2.1 y	134	V_{max} >2.5 m/s Aortic valve Ca^{++} Age >8 y Asymptomatic	Severe MS, AR, or MR LVEF <35% Statin Rx or indication Cholesterol <150 mg/dL Pacer or ICD Child bearing potential Liver disease Alcohol or drug abuse history	Atorvastatin 80 mg/d (n=77)	63±23 mg/dL (↓53%)	V_{max} 0.2±0.21	0.08±0.11	CT valve Ca^{++} ↑22.3±21.0 %/y	Primary endpoints were hemodynamics and valve Ca^{++}	Study drug discontinued in 5% of placebo and 9% of treatment groups. Study not powered for clinical outcomes.
					Placebo (n=78)	130±30 mg/dL (0%)	0.2±0.21 (p=NS)	0.08±0.11 (p=NS)	CT valve Ca^{++} ↑21.7±19.8 %/y		
RAAVE Moura, 2007 (37) 17276178	Open-label, prospective. 1.4 y	121	AVA 1.0–1.5 cm^2 Asymptomatic	CAD, rheumatic mitral valve disease, BAV, liver disease, elevated creatinine, comorbidities	Rosuvastatin 20 mg/d (n=61)	93±21 mg/dL (↓42%)	V_{max} 0.04±0.38	0.05±0.12	Inflammatory markers showed ↓CRP in statin group; ↓IL-6 and ↓sCD4OL in both groups	Endpoints were cholesterol levels and AS severity	Pts with LDL >130 mg/dL at baseline were treated, those with LDL <130 received placebo
					No statin (n=60)	118±29 mg/dL (0%)	0.24±0.30 (p=0.007)	0.1±0.09 (p=0.041)			
ASTRONOMER Chan, 2010 (38) 20048204	Randomized, double-blind, Placebo controlled 3.5 y	269	V_{max} 2.5–4.0 m/s Age 18–82 y Asymptomatic Trileaflet or bicuspid (49%) valve	Clinical indication for statin including CAD, CVD, PVD	Rosuvastatin 40 mg/d (n=134)	1.45 mmol/L (↓54%)	ΔP_{mean} 3.8±4.4	0.08±0.21	7 cardiac deaths 55 AVR	No difference in survival or AVR between groups.	Primary endpoint was AS progression. Composite clinical outcome was secondary outcome.
					Placebo (n=135)	1.61 mmol/L (↑1.8%)	3.9 ±4.9 (p=NS)	0.07±0.15 (p=NS)			
SEAS Rossebø, 2008 (26) 18765433	Randomized, double-blind, Placebo controlled 5.4 y	1,873	V_{max} 2.5–4.0 m/s Age 45–85 y Asymptomatic	CAD, PVD, CVD, DM Clinical indication for statin	Simvastatin 40 mg plus ezetimibe 10 mg/d (n=944)	53±23 mg/dl (↓61%)	V_{max} 0.15±0.01	0.03±0.01	333 composite outcome of CV death, AVR, CHF, and CAD events	No difference for aortic valve related events HR: 1.00; 95% CI: 0.84–1.18	Noncardiac deaths occurred in 5.9% of treatment group and 4.75 of placebo group (p=0.26)
					Placebo (n=929)	139±35 mg/dL (0%)	0.16±0.01 (p=NS)	0.03±0.01 (p=NS)	335 composite outcome (p=NS)		

AR indicates aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; BAV, bicuspid aortic valve; CA++, calcium; CAD, coronary artery disease; CHF, congestive heart failure; CI, 95% confidence interval; CRP,C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; ICD, implantable cardioverter defibrillator; IL-6; interleukin-6; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MS, mitral stenosis; NS, non-significant; ΔP_{mean}, mean transaortic systolic pressure gradient; PVD, peripheral vascular disease; pt(s), patient(s); Rx, prescription; sCD4OL soluble CD40 ligand; Vmax, maximum transvalvular aortic velocity.

Data Supplement 5. Clinical Outcomes in Asymptomatic Adults With Aortic Stenosis (stages B and C) of Known Hemodynamic Severity (Section 3.2.3)

Author, Year	Study Size (N)	Patient Population Inclusion Criteria	Exclusion Criteria	Pt. Age (y)	% Male	Follow-Up (mo)	AS Severity at Entry	Event-Free Survival	Cardiac Events	Multivariate Predictors of Clinical Outcome
Kelly, 1988 (39) 3337000	51	V_{max} ≥3.5 m/s Asymptomatic	Other valve disease	63±19	75%	17±0	ΔP 68±19 mm Hg	60% at 2 y	21 AS symptom onset 8 deaths (2 cardiac)	N/A
Pellikka, 1990 (40) 2312954	113	V_{max} ≥4.0 m/s Age≥40 y Asymptomatic	Other valve disease CAD Prior valve procedure Early aortic intervention	70 (40–94)	67%	20	V_{max} 4.3 (4–6) m/s	62% at 2 y	37 AS symptoms (20 with AVR) 14 deaths (6 cardiac)	V_{max} ≥4.5 m/s; RR: 4.9 (1.64–14.6) LVEF <50%; RR: 2.93 (0.84–10.2)
Kennedy, 1991 (41) 1991886	66	AVA 0.7–1.2 cm^2 at cath	Other valve disease Previous valve surgery	67±10	77%	35	AVA 0.92±0.13cm^2	59% at 4 y	21 AVR (13 for symptoms) 14 deaths due to AS	LVEF <50%; RR: 1.94 (0.86–4.41). LV-end diastolic pressure >18 mm Hg RR: 2.71 (1.23–5.97). AVA index <0.5 cm^2 RR: 1.93 (0.89–4.23).
Otto, 1997 (21) 9142003	123	V_{max} >2.6 m/s Asymptomatic	Severe comorbid disease	63±16	70%	30	V_{max} <3 m/s V_{max} 3–4 m/s V_{max} >4 m/s	84% at 2 y 66% at 2 y 21% at 2 y	48 AVR for symptoms 8 deaths	V_{max} Functional status score Rate of change in V_{max}
Rosenhek, 2000 (24) 10965007	128	V_{max} ≥4.0 m/s Asymptomatic	Other valve disease	60±18	54%	22±18	V_{max} 5.0±0.7 m/s	67% at 1 y 56% at 2 y 33% at 4 y	59 AVR for symptoms 8 deaths	Extent of valve calcification RR: 4.6 (1.6–14.0).
Rosenhek, 2004 (25) 14972419	176	V_{max} 2.5–3.9 m/s LVEF >50% No AS symptoms	Other valve disease	58±19	59%	48±19	V_{max} 3.1±0.4 m/s	95% at 1 y 75% at 2 y 60% at 5 y	33 AVR for symptoms 34 deaths	Severe valve calcification RR: 2.0 (1.3–3.3). V_{max} ≥3 m/s RR: 1.6 (1.04–2.8). CAD RR: 1.7 (1.2–2.7).
Pellikka, 2005 (42) 15956131	622	V_{max} ≥4.0 m/s No AS symptoms	Other valve disease CAD	72±11	62%	65±48	V_{max} 4.4 ±0.4 m/s	82% at 1 y 67% at 2 y 33% at 5 y	297 AS symptoms (AVR in 207 of these) 103 deaths without AVR or AS symptoms	AVA HR: 0.33 for a 1 cm^2 increase (95%CI: 0.15–0.71). LVH by ECG HR: 1.39 (95% CI: 1.02–1.89).
Rossebo, 2008 (26) 18765433	1,873	V_{max} 2.5 m/s to 4.0 m/s	CAD, CHF, diabetes mellitus, CVA, PVD, and other valve disease	68±9	59%	52 (median)	V_{max} 3.1±0.55	65% at 5 y	668 (36%) Major CV events (death, AVR, CHF, coronary events, and ischemic stroke)	No effect of statin therapy on major CV events.
Lancellotti, 2010 (43) 20483891	163	AVAi ≤0.6 cm^2/m^2 No AS symptoms LVEF ≥55%	Nonsinus rhythm Other valve disease	70±10	65%	20±19	≤0.6 cm^2/m^2	50% at 2 y 44% at 4 y	11 symptoms, but no AVR 57 AVR 6 deaths	V_{max} ≥4.4 m/s, LV longitudinal deformation ≤15.9%, valvulo-arterial impedance ≥4.9 mm Hg/m^2, LA area

Author, Year	Study Size (N)	Patient Population Inclusion Criteria	Exclusion Criteria	Pt. Age (y)	% Male	Follow-Up (mo)	AS Severity at Entry	Event-Free Survival	Cardiac Events	Multivariate Predictors of Clinical Outcome
										≥12.2 cm^2/m^2
Kang, 2010 (44) 20308614	95	AVA 0.75 cm^2 plus V_{max} ≥4.5 m/s or ΔP_{mean} ≥50 mm Hg No AS symptoms	LVEF <50% Other valve disease Age >85 y Malignancy Known CAD	63±12	46%	50	V_{max} 4.9±0.4	71±5% at 2 y 47±5% at 4 y 28±6% at 6 y	18 cardiac deaths 10 noncardiac deaths 46 AVR for symptoms	V_{max} ≥5 m/s age, male sex, EuroScore, degree of valve calcification.
Stewart, 2010 (45) 20513730	183	V_{max} >3 m/s LVEF >50% No AS symptoms	Other valve disease, ACS in previous 6 mo, LVOT obstruction, Respiratory disease, Renal dysfunction	70	65%	31 (median)	AVA 0.81 (IQR: 0.62–1.01) cm^2 V_{max} 3.8 (IQR: 3.3–4.4) m/s	Probability of symptom free survival at 3 y (95% CI) V_{max} <3.5 m/s 0.72 (0.61–0.84). V_{max} 3.5–4.0 m/s 0.46 (0.30–0.62). V_{max} >4.0 m/s 0.32 (0.20–0.44).	103 AS symptoms 3 sudden death	V_{max} HR: 1.43 for each 0.5 m/s increase (95% CI: 1.25–1.64). AVA HR: 1.23 for each -0.1 cm^2 (95% CI: 1.12–1.35).
Rosenhek, 2010 (46) 20026771	116	V_{max} ≥5.0 m/s No AS symptoms	Other valve disease	67±15	49%	41 (median)	V_{max} 5.0–5.5 m/s V_{max} ≥5.5 m/s	43% at 2 y 25% at 2 y	90 AVR 6 cardiac deaths	$V_{max,}$ but not AVA predicted outcome
Jander, 2011 (47) 21321152	435	Low gradient "severe" AS: AVA <1 cm^2 with ΔP_{mean} ≤40 mm Hg	CAD, CHF, diabetes, CVA, PVD, and other valve disease (SEAS substudy)	70±9	45%	46±14	V_{max} 3.3±0.5 m/s ΔP_{mean} 26±7 mm Hg AVA 0.82±0.13 cm^2	No difference in event rates between groups	183 AVR 17 HF 34 CV death	Low gradient "severe" AS defined as an AVA <1 cm^2 with ΔP_{mean} ≤40 mm Hg was **NOT** a predictor of clinical outcome
	184	Moderate AS: AVA 1–1.5 cm2, ΔP_{mean} 25–40 mmHg		67±9	73%		V_{max} 3.6±0.3 m/s ΔP_{mean} 31±4 mm Hg AVA 1.19±0.13 cm^2		82 AVR 4 HF 9 CV death	
Saito, 2012 (48) 22497679	103	AVA <1.0 cm^2 No AS symptoms	Hx CAD Other valve disease HCM	72±11	45%	36±27	AVAi <0.6 cm^2/m^2 AVAi ≥0.6 cm^2/m^2	41% at 3 y 86% at 3 y	31 AVR 20 cardiac deaths	AVAi <0.6 cm^2/m^2 (HR: 2.6; 95% CI: 11.1–6.3). V_{max} >4.0 m/s (HR: 2.6; 95% CI: 1.2–5.8). (AVA<0.75 cm^2 did not predict outcome) (Mean BSA 1.50±0.15 m^2).

ACS indicates acute coronary syndrome; AS, aortic stenosis; AVA, aortic valve area; AVAi, indexed AVA; AVR, aortic valve replacement; BSA; body surface area; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; CVA, cerebral vascular accident; HCM, hypertrophic cardiomyopathy; HF, heart failure; Hx, history; HR, hazard ratio; IQR, interquartile range; LA, left atrium; LV, left ventricular, LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; N/A, not available; ΔP_{mean}, mean transaortic systolic pressure gradient; pt(s), patient(s); PVD, peripheral vascular disease; RR, relative risk; SEAS, Simvastatin Ezetimibe in Aortic Stenosis study; $V_{max,}$ maximum velocity.

Data Supplement 6. Incidence of Sudden Death in Asymptomatic Adults With Aortic Stenosis (stages B and C) (Section 3.2.3)

First Author	N	Follow-Up (mo)*	V_{max} at Entry (m/s)	AVA at Entry (cm^2)	Sudden Deaths (n)	Sudden Deaths (% per y)
Kelly, 1988 (39) 3337000	51	18	≥3.5	N/A	0	0
Faggiano, 1992 (18) 1626512	37	24	N/A	0.85±015	0	0
Otto, 1997 (21) 9142003	114	30	3.6±0.6	N/A	0	0
Rosenhek, 2000 (24) 10965007	128	22	≥4.0	N/A	1	0.4
Amato, 2001(30) 11559673	66	15	N/A	≤1.0	4	4.8
Das, 2005 (32) 15820999	125	12	N/A	≤1.4	0	0
Pellikka, 2005 (42) 15956131	270	65	≥4.0	N/A	11	0.75
Rossebø, 2008 (26) 18765433	1,873	52	2.5–4.0	N/A	40	0.5
Monin, 2009 (49) 19546391	211	22	≥3.0	≤1.5	2	0.5
Lancellotti, 2010 (43) 20483891	163	20	N/A	≤0.6 cm^2/m^2	3	1.1
Kang, 2010 (44) 20308614	95	59	≥4.5	≥0.75	9	1.9
Marechaux, 2010 (34) 20308041	135	20	N/A	≤1.5	1	0.4
Rosenhek, 2010 (46) 20026771	116	41	≥5.0	N/A	1	0.3
Total	3,384	31*	N/A	N/A	72	0.8

*Mean follow-up duration.
AVA indicates aortic valve area; N/A, not applicable; and V_{max}, maximum aortic velocity
From Rosenhek R et al., (50). (PERMISSION NEEDED)

Data Supplement 7. Clinical Outcomes in Symptomatic Adults With Aortic Stenosis of Known Hemodynamic Severity (Section 3.2.3)

Author, Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Primary Endpoint	Predictors of Mortality or AVR	Comments
Frank, 1973 (51) 4685905	Outcomes with AS of known hemodynamic severity	Observational	15	Isolated AS. Not referred for AVR Symptomatic (10) or asymptomatic (5) No other valve disease	Mortality from symptom onset: 15% at 2 y 36% at 3 y 52% at 5 y 90% at 10 y	Overlap in hemodynamic parameters between 5 asymptomatic and 10 symptomatic pts	Indexed AVA ranged from 0.26–0.63 cm^2/m^2. Transaortic gradient ranged from 30–90 mm Hg.
Chizner, 1980 (52) 7189084	Outcomes with AS of known hemodynamic severity	Observational	32	Symptomatic AS Not referred for AVR	Mortality from symptom onset: 25% at 1 y 57% by 3 y 64% by 5 y 80% by 8 y	Mortality was no different with "moderate" (AVA 0.71–1.1 cm^2, peak ΔP <70 mm Hg) compared to "severe" AS (AVA 0.7 cm^2, peak ΔP >70 mm Hg).	Time from symptom onset to death: Angina 1.4 (0.25–3.3) y Syncope 0.8 (0.25–2.0) y CHF 2.0 (0.3–3.0) y
Lombard & Selzer, 1987 (53) 3800187	Describe clinical findings in pts with AS of known hemodynamic severity	Retrospective	397	Undergoing cardiac cath for AS Mean age 61 y AVA <1 cm^2 in 87% No other valve disease	Early symptoms (angina and syncope) correlated with AS severity, but not LV function. Late symptoms (HF) correlated with LV dysfunction.	N/A	No outcome data
Turina, 1987 (54) 3609042	Determine prognostic value of hemodynamic and clinical variables	Observational	N/A	Referred for cardiac cath. No AVR due to disease severity or pt refusal	Survival without AVR by AS severity; Severe AS (AVA <0.9 cm^2): 60% at 1 y, 9% at 10 y Moderate AS (AVA 0.95–1.4 cm^2): 97% at 1 y, 35% at 10 y Mild AS (AVA >1.5 cm^2): 85% at 10 y	Survival without AVR by symptom status with severe AS: Symptomatic AS 27% at 2 y 12% at 5 y Asymptomatic AS: 100% at 2 y 75% at 5 y	AS was more severe in severely symptomatic vs. oligosymptomatic pts: ΔP_{mean} 69 vs. 57 mm Hg (p=NS), AVA 0.56 vs. 0.76 cm^2 (<0.01), Cardiac index 2.6 vs. 3.3 L./min/m^2 (p<0.01), LVEDP 17 mm Hg vs.12 mm Hg (p<0.05).
Horstkotte, 1988 (55) 3042404	Compare outcomes with symptomatic vs. asymptomatic severe AS	Retrospective	35	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
Kelly, 1988 (39) 3337000	Compare outcomes with symptomatic vs. asymptomatic severe AS	Prospective	39	Referred for echo for systolic murmur with Doppler $\Delta P \geq 50$ mm Hg cardiac symptoms, but did not undergo AVR. No other valve disease.	Death in 15 (38%) with a mean follow-up of 12 mo. Compared to 8 (%) deaths in 51 initially asymptomatic pts (See Table 6).	N/A	Study group represents 19% of all surgical candidates for AVR for severe symptomatic AS. Surgery refused by 26/39 pts; symptoms judged not severe in 13 by referring clinician.

Author, Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Primary Endpoint	Predictors of Mortality or AVR	Comments
				Other valve disease.			No difference in Doppler AS severity between these 39 symptomatic and 51 asymptomatic pts during the same time interval.
Otto, 1988 (56) 3143323	Identify echo criteria for AVR with symptomatic AS	Prospective, split sample decision analysis	103	Symptomatic pts undergoing cardiac cath for suspected AS Clinical outcome defined as AVR as determined by clinical cardiologist without knowledge of echo data or death	Decision model recommended AVR in 73 with: V_{max} >4.0 m/s, or V_{max} 3 m/s-4 m/s and AVA<1.0 cm^2 or V_{max} 3 m/s-4 m/s, AVA >1.0 and 2-3+AR	AVR in 68, 2 noncardiac death, 2 nonsurgical candidates, 1 refused	Overall diagnostic accuracy for clinical outcome 94%
					AVR not recommended in 30 with: V_{max} <3.0 m/s or V_{max} 3-4 m/s with AVA ≥1.7 cm^2 or V_{max} 3-4 m/s, AVA 1.1-1.6 cm^2 and 0-1+ AR	No AVR in 28. AVR for severe AR in 2 pts confirmed absence of severe AS by surgical inspection	
Oh, 1988 (57) 3366997	Compare echo and cath data	Prospective	100	Symptomatic AS undergoing cardiac cath	Severe AS at cath defined as (Gorlin AVA ≤0.75 cm^2)	No outcome data	V_{max} >4.5 m/s predicted severe AS at cath with 60% accuracy–specificity 93%, but sensitivity 44% Doppler velocity ratio <0.25 had sensitivity of 92% for severe AS
Galan, 1991 (58) 2018003	Identify echo predictors of AVR	Observational, retrospective	510	Consecutive AS pts undergoing Doppler echo	Comparison with diagnosis of critical AS at cath, defined as Gorlin AVA ≤0.75 cm^2	In 160 pts with V_{max} >4.5 m/s or Doppler AVA ≤0.75 cm^2, 109 underwent AVR No long-term outcome data	V_{max} >4.5 m/s or Doppler AVA ≤0.75 cm^2 was 97% specific for critical AS at cath (n=105) V_{max} ≤4.5 m/s or Doppler AVA >0.75 cm^2 was 95% specific for noncritical AS at cath (n=133)
Otto, 1994 (59) 8313553	Outcomes after aortic balloon dilation	Registry	674	Severe symptomatic AS undergoing aortic balloon dilation V_{max} 4.4±0.8 (2.3–6.6) m/s AVA 0.6 ±0.2 (0.1–1.4) cm^2	Overall survival was 55% at 1 y, 35% at 2 y, and 23% at 3 y, with 70% of deaths classified as cardiac	Multivariate predictors of outcome were functional status, LV systolic function, renal function, sex, cardiac output, and MR	All pts underwent aortic balloon dilation in this registry so outcomes may be worse with no intervention.

AS indicates aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; cath, catheterization; CHF, congestive heart failure, echo, echocardiography; HF, heart failure; LV, left ventricular; LVEDP, left ventricular end diastolic pressure; MR, mitral regurgitation; N/A, not applicable; NS, nonsignificant; ΔP_{mean}, mean transaortic systolic pressure gradient; pt(s), patient(s); and V_{max}, maximum velocity.

Data Supplement 8. Outcomes in Adults With Low-Flow/Low-Gradient Aortic Stenosis With Preserved Left Ventricular Ejection Fraction (stage S2) (Section 3.2.3)

Study	Aim of Study	Study Type	Study Size	Definition of LFLG severe AS	Exclusion Criteria	Clinical Outcomes	Comments
Hachicha, 2007 (60) 17533183	Determine prevalence, mechanisms and clinical relevant of LFLG severe AS with pLVEF	Retrospective, consecutive pts with severe AS (AVA_i ≤0.6 cm^2 and LVEF ≥50%)	512 pts, mean age 70±14 y, 43% women	181 (35%) LFLG severe AS pLVEF: SV_i ≤35 mL/m^2 **and** AVA_i ≤0.6 cm^2 **and** LVEF≥50% 331 (65%) with normal flow (SV_i >35 mL/m^2) despite AVA_i ≤0.6 cm^2 and LVEF≥ 50%	LVEF <50%	76% survival at 3 y with LFLG severe AS 86% survival at 3 y with normal flow severe AS (p=0.006) Multivariate predictors of overall death were older age, valvulo-arterial impedance ≥5.5 mm Hg/mL/m^2, and medical (vs. surgical) treatment	In LFLG severe AS group: Average BSA 1.8±0.2 m^2 Average AVA 0.76±0.23 cm^2 Average V_{max} 3.5±0.9 m/s LFLG severe AS typically associated with small LV with restrictive physiology
Jander, 2011 (47) 21321152	Evaluate outcome of LG severe AS	Prospective (SEAS substudy)	435 with LG severe AS vs. 184 with moderate AS	AVA <1.0 cm^2 and ΔP_{mean} ≤40 mm Hg (Moderate AS defined as AVA 1.0–1.5 cm^2, ΔP_{mean} 25–40 mm Hg)	See SEAS study in Table 4	Aortic valve events (CV death, AVR,HF due to AS) at 46 mo were no different in pts with LG severe AS vs. those with moderate AS (48.5% vs. 44.6%; p=0.37)	In 223 pts with LFLG severe AS pLVEF (SV_i ≤35 mL/m^2) aortic valve events were no different compared to pts with a normal SVi (46.2% vs. 50.9%; p=0.53).
Tarantini, 2011 (61) 21619977	Investigate outcome after AVR for LFLG severe AS with pLVEF	Retrospective surgical series	73 AVR 29 medical Rx	AVA ≤1.0 cm^2 LVEF >50% ΔP_{mean} ≤30 mm Hg	Age <18 y Other valve disease Previous valve surgery	Overall mortality 37% at mean 42 mo follow-up. Cardiac death in 13 (18%) AVR and 15 (52%) medical Rx pts (p=0.001) AVR was a predictor of survival on multivariate analysis, even in the 78 pts with an AVA between 0.8 and 1.0 cm^2.	Low SVi present in 20 (27%) AVR and 6 (21%) medical Rx pts with no difference in outcome for normal vs. low SVi Retrospective database of 2,055 pts with an AVA ≤1.0 cm^2; LVEF <50% in 25% and LFLG severe AS pLVEF in 5% of pts
Clavel, 2012 (62) 22657269	Compare outcome in AS with normal LVEF with 1) LFLG severe AS, 2) high mean gradient (>40 mm Hg) severe AS, and 3) moderate AS (AVA >1.0 cm^2)	Case match study	187 with LFLG severe AS matched to 187 moderate AS and 187 high-flow severe AS	ΔP_{mean} <40 mm Hg SV_i <35 mL/m^2 and AVA ≤1.0 cm^2	LVEF <50%	Survival at 1 and 5 y: LFLG severe AS pLVEF 89±2% and 64±4% High-gradient severe AS 96±1% and 82±3% Moderate AS 96±1% and 81±3%	AVR associated with improved survival for high-gradient severe AS (HR: 0.18; p=0.001) and LFLG severe AS pLVEF (HR: 0.50; p=0.04), but not for moderate AS
Lancellotti, 2012 (63) 22240128	Evaluate clinical course in AS pts stratified by SVi and ΔP_{mean}	Prospective	150 consecutive pts with asymptomatic severe AS (AVA <1.0 cm^2) referred for ETT	LF: SVi <35 mL/m2 LG: ΔP_{mean} <40 mm Hg (all had AVA <1.0 cm^2)	LVEF <55%, other valve disease, AS, pulmonary disease, inability to exercise	Event free survival at 2 y (p<0.0001): Normal flow (SV_i ≥35 mL/m^2) vs. Low-flow (SV_i <35 mL/m^2) High-gradient ΔP_{mean} ≥40 mm Hg: 44±6% (n=78) vs. 30±12% (n=15) Low-gradient ΔP_{mean} <40 mm Hg: 83±6% (n=46) vs. 27±13% (n=11) Predefined endpoints were CV death in 6 and AVR in 70 pts	

Study	Aim of Study	Study Type	Study Size	Definition of LFLG severe AS	Exclusion Criteria	Clinical Outcomes	Comments
Herrmann 2013 (15) 23661722	Evaluate outcomes with TAVR compared to medical therapy with LG severe AS	Subgroup analysis of RCT	52 inoperable symptomatic pts with LFLG severe AS with normal LVEF	ΔP_{mean} <40 mm Hg SV_i <35 mL/m^2 and AVA <0.8 cm^2 or AVAi <0.5 cm^2/m^2	LVEF <50%	In 52 inoperable pts with LFLG severe AS with preserved LVEF, 1-y mortality was 66% with TAVR compared to 35% with medical therapy (HR: 0.38; p=0.02). In 87 pts at high risk for surgery, there was no difference between TAVR and SAVR (39.0% vs. 38.3%; HR: 0.91; 95% CI: 0.57–1.45; p=0.69.	
Le Ven 2013 (64) 23770162	Evaluate effect of LV EF and gradient on outcomes after TAVR	Retrospective analysis of registry data	639 severe AS undergoing TAVR	Low flow (SVi <35 mL/m^2) with a normal EF (>50%) was present in 86 (13%) of pts	---	Low flow (but not low EF) was an independent predictor of 30-day mortality (odds ratio: 1.94, p=0.026), cumulative all-cause mortality (hazard ratio: 1.27 per 10 mL/m² SVi decrease, p=0.016), and cumulative cardiovascular mortality (hazard ratio: 1.29 per 10 mL/m² decrease, p=0.04).	
Mehrotra 2013 (65) 23533186	Compare clinical characteristics and outcomes in AS subgroups	Retrospective echocardiographic database	LFLG severe AS in 38 pts, compared to 75 normal flow low gradient and 70 moderate AS pts.	AVA ≤1.0 cm2 with LVEF≥ 55%, mead gradient <40 mm Hg and SVi <35 mL/m^2.	Mitral valve disease, aortic regurgitation, poor quality study. Severe AS with mean gradient >40 mm Hg.	Survival at 3 years was significantly lower in LF LG compared with NF LG (p=0.006) and moderate AS (p=0.002), but not different between NF LG and moderate AS (p=0.49).	
Ozkan 2013 (66) 23812184	Compare outcomes of LG severe AS with AVR or medical therapy	Prospective follow-up of symptomatic severe LG AS	260 pts with symptomatic severe AS (AVAi ≤0.6 cm^2/m^2) and mean gradient <40 mm Hg	Normal flow present in 125; low flow (SVi ≤35 mL/m^2) in 135.	Mitral disease, aortic regurgitation	At 28 ±24 mos follow-up, 105 pts died (40%): 32 (30%) in the AVR group and 73 (70%) in the medical treatment group. AVR (hazard ratio, 0.54; 95% confidence interval, 0.32–0.94; p<0.001) was independently associated with outcome and remained a strong predictor of survival after adjustment for propensity score. The protective effect of AVR was similar in 125 pts with normal flow (stroke volume index >35 mL/m^2; p=0.22).	
Eleid 2013 (67) 24048203	Evaluate impact of stroke volume with normal EF on outcomes with severe AS	Echocardiographic database.	1,704 consecutive pts with severe AS (AVA <1.0 cm^2) and LVEF≥50%	Low flow = SVi ≤35 mL/m^2 Low gradient <40 mm Hg. LFLG present in 53 pts (3%) compared to normal flow LG (n=352, 21%) and to high gradient severe AS.	Prosthetic valve, congenital or other native valve disease	AVR was associated with a 69% mortality reduction (HR 0.31 (0.25, 0.39) p<0.0001) in LF/LG and NF/HG, with no survival benefit associated with AVR in NF/LG and LF/HG.	

AS indicates aortic stenosis; AVAi, aortic valve area indexed to body surface area; AVR, aortic valve replacement; BSA, body surface area; CV, cardiovascular; ETT, exercise treadmill testing; HG, high gradient; HF, heart failure; LFLG, low-flow low-gradient; LF, low-flow; LG, low-gradient; LV, left ventricular; NF, normal flow; pLVEF, preserved left ventricular ejection fraction; ΔP_{mean}, mean transaortic systolic pressure gradient; RCT, randomized controlled clinical trial; Rx, prescription; SEAS, Simvastatin Ezetimibe in Aortic Stenosis study; SVi, stroke volume index; TAVR, transcatheter aortic valve replacement; and $V_{max,}$ maximum velocity.

Data Supplement 9. Choice of Intervention in Symptomatic Adults With Severe Aortic Stenosis (stage D): Surgical Versus Transcatheter Aortic Valve Replacement (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) (68) 21639811 (69) 22443479	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 mean 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. 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 *(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) (70) 22443478 (71) 20961243	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 mean ΔP ≥40 mm Hg or V_{max} ≥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	**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).

AF indicates atrial fibrillation; AMI, acute myocardial infarction; AS, aortic stenosis; AR, aortic regurgitation; AVA, aortic valve area; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; ΔP, mean transaortic pressure gradient; pt(s), patient(s); RCT, randomized controlled trial; Rx, prescription; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack; and V_{max}, aortic valve maximum velocity.

Data Supplement 10. Clinical Outcomes of Asymptomatic Patients With Chronic Aortic Regurgitation (Sections 4.3.1.1 and 4.3.3)

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Details	Outcomes	Comments, Limitations
Bonow, 1983 (72) 6872164	Determine clinical outcome of asymptomatic pts with chronic AR and normal LV systolic function	Prospective, observational series; consecutive pts enrolled 1973-1982; single institution	77	4.1	Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 37 y (range 17–67) Serial echo and radionuclide angiographic studies 63 pts had 3+–4+ AR on aortic root angiography, and the other 14 pts had pulse pressures >70 mm Hg Endpoints: death, symptoms, LV systolic dysfunction	No pt died 12 pts underwent AVR because of symptoms (n=11) or asymptomatic LV dysfunction (n=1) Progression to symptoms or LV dysfunction: less than 4%/y No perioperative deaths in pts who underwent AVR	Percent of pts who did not need surgery was 90±3% (±SE) at 3 y, 81+6% at 5 y, and 75±7% at 7 y. Outcome associated with LVESD, LVEDD, FS, change in LVEF with exercise
Scognomiglio, 1986 (73) 3720042	Determine factors predictive of progression to LV systolic dysfunction	Observational series; single institution	30	4.7	38 initially asymptomatic pts with chronic AR, 30 of whom had normal LV fractional shortening Mean age 26±10 y Serial echo studies Endpoints: death, symptoms, subnormal LV fractional shortening	No pt died Progression to symptoms or LV dysfunction: 2.1%/y Progression to asymptomatic LV dysfunction: 2.1%/y	3 pts developing asymptomatic LV dysfunction had lower initial PAP/ESV ratios and trend toward higher LVESD and LVEDD and lower fractional shortening
Siemienczuk, 1989 (74) 2930091	Determine clinical outcome of asymptomatic pts with chronic AR and normal LV function.	Observational series derived from screening for randomized clinical trial; single institution	50	3.7	Pts included those receiving placebo and medical dropouts in a randomized drug trial of hydralazine therapy; included some pts with NYHA II symptoms. Mean age 48±16 y Serial echo and radionuclide LV angiographic studies	No pt died Progression to symptoms or LV dysfunction: 4.0%/y Progression to asymptomatic LV dysfunction: 0.5%/y	Outcome associated with LVESV, EDV, change in LVEF with exercise, and end-systolic wall stress
Bonow, 1991 (75) 1914102	Determine outcomes of asymptomatic pts with chronic AR; extension of Bonow, 1983	Prospective, observational series; consecutive pts enrolled 1973-1988; single institution	104	8.0	Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 37 y (range 17–67) Serial echo (average 7.5 per pt) and radionuclide LV angiographic (average 5.0 per pt) studies Endpoints: death, symptoms, LV systolic dysfunction	2 pts died suddenly Progression to symptoms or LV dysfunction: 2.1%/y Progression to asymptomatic LV dysfunction: 2.1%/y	Outcome associated with age, LVESD, LVEDD, change in LVEF with exercise, and rate of change in LVESD and LVEF at rest with time Initial LVESD >50 mm was associated with risk of death, symptoms, and/or LV dysfunction of 19% per y
Scognomiglio, 1994 (76) 8058074	Effect of nifedipine on outcomes of pts with severe AR and normal LV function	Randomized clinical drug trial (see Data Supplement 11); single institution	74	6.0	Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 36±12 y Serial echo studies Endpoints: death, symptoms, LV systolic dysfunction	No pt died Progression to death, symptoms or LV dysfunction: 5.7%/y Progression to asymptomatic LV dysfunction: 3.4%/y	This table include only the pts who received digoxin as part of a randomized trial See Data Supplement 11 for outcomes in those receiving active drug (nifedipine, n=69)

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Details	Outcomes	Comments, Limitations
Tornos, 1995 (77) 7631617	Determine clinical outcome of asymptomatic pts with chronic AR and normal LV systolic function	Prospective, observational series; consecutive pts beginning in 1982; single institution	101	4.6	Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 41±14 y Serial echo and radionuclide LV angiographic studies Endpoints: death, symptoms, LV systolic dysfunction	No pt died Progression to symptoms or LV dysfunction: 3.0%/y Progression to asymptomatic LV dysfunction: 1.3%/y	Outcome associated with pulse pressure, LVESD, LVEDD, and LVEF at rest Initial LVESD >50 mm was associated with risk of death, symptoms, and/or LV dysfunction of 7% per y
Ishii, 1996 (78) 8759822	Clinical outcome and LV response to chronic AR	Prospective, observational series; consecutive pts 1970-1990; single institution	27	14.2	94 consecutive pts followed for ≥6 mo; the 27 asymptomatic pts with normal LV function are included here Mean age 42±12 y LV function assessed by echo	No pt died Progression to symptoms or LV dysfunction: 3.6%/y	Development of symptoms associated with systolic BP, LVESD, LVEDD, mass index, and wall thickness. LV function not reported in all pts
Borer, 1998 (79) 9494022	Determine clinical outcome of asymptomatic pts with chronic AR and normal LV systolic function	Prospective, observational series; consecutive pts beginning in 1979; single institution	104	7.3	Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 46±15 y 20% of pts in NYHA II initially Serial echo and radionuclide LV angiographic studies Endpoints: death, symptoms, LV systolic dysfunction	4 pts died suddenly Progression to symptoms or LV dysfunction: 6.2%/y Progression to asymptomatic LV dysfunction: 0.9%/y	Change in LVEF from rest to exercise, normalized for change in end-systolic stress from rest to exercise was strongest predictor of any endpoint or of sudden cardiac death alone Outcome also associated with initial NYHA II symptoms, change in LVEF with exercise, LVESD, and LVFS
Tarasoutchi, 2003 (80) 12706927	Clinical outcome of asymptomatic pts with chronic AR and normal LV systolic function	Prospective, observational series; consecutive pts beginning in 1979; single institution	72	10	Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 28±9 y Serial echo and radionuclide LV angiographic studies Endpoints: death, symptoms, LV systolic dysfunction	No pt died Progression to symptoms or LV dysfunction: 4.7%/y Progression to asymptomatic LV dysfunction: 0.1%/y	AR of predominant rheumatic etiology LV function not reported in all pts Development of symptoms associated with LVESD and LVEDD Initial LVESD >50 mm was associated with risk of symptoms and/or LV dysfunction of 7.6%/y
Evangelista, 2005 (81) 16192479	Effect of nifedipine versus enalapril on outcomes of pts with severe AR and normal LV function	Randomized clinical drug trial (see Data Supplement 11); single institution	31	7	Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 42±15 y Serial echo studies Endpoints: death, symptoms, LV systolic dysfunction	1 pt died from HF Progression to death, symptoms or LV dysfunction: 3.6%/y	Pts reported here were in the control (placebo) group of this clinical trial See Data Supplement 11 for pts receiving active drugs nifedipine (n=32) and enalapril (n=31)

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Details	Outcomes	Comments, Limitations
Detaint, 2008 (82) 19356398	Predictive value of quantitative measures of AR severity and LV volumes in asymptomatic pts with chronic AR and normal LV systolic function	Prospective, observational series; consecutive pts enrolled from 1991–2003; single institution.	251	8	Initially asymptomatic pts with chronic AR and normal LV systolic function Mean age 60±17 y Serial echo studies to assess severity of AR (ROA and RV) as well as LV dimensions and volumes Endpoints: death, HF, AF, surgery	33 pts died Progression to death or surgery: 5.0%/y Survival at 10 y: Mild AR: 92±4% Moderate AR: 75±6% Severe AR: 69±9% Survival free from AVR at 10 y: Mild AR: 92±4% Moderate AR: 57±6% Severe AR: 20±5%	Surgical indications included symptoms (n=38), LV dysfunction or enlargement (n=17), aortic aneurysm (n=11), IE (n=3, and clinician and/or pt preference [n=11]) Cardiac events (defined as cardiac death, HR, or new onset of AF) associated with RV and ROA as well as ESV index, which superseded M-mode LV dimensions Mortality rate in this series is highest of all series Pts in this series older than all others; only 1 death in pts <50 y in this series
Pizzaro, 2011 (83) 21982316	Predictive value of BNP and quantitative measures of AR severity and LV volumes in asymptomatic pts with chronic AR and normal LV systolic function	Prospective, observational series; consecutive pts enrolled from 1991–2003; single institution	294	3.5	Initially asymptomatic pts with chronic AR and normal LV systolic function The first 160 consecutive pts were analyzed as the derivation set of data (mean age 51±9 y) The next 134 consecutive pts were analyzed as the validation set (mean age 53±10 y) BNP and serial echo studies to assess severity of AR (ROA and RV) as well as LV dimensions and volumes	5 pts died Progression to symptoms or LV dysfunction: 10%/y Progression to asymptomatic LV dysfunction: 2.8%/y	Outcome associated with BNP >130 pg/mL Outcome also associated with RV, ROA, LVESD index, LVEDD index, ESV index, and EDV index
Olsen, 2011 (84) 21414568	Predictive value of speckle-tracking echo in asymptomatic pts with chronic AR and normal LV systolic function	N/A	35	1.6	35 initially asymptomatic pts with chronic AR and normal LV systolic function were followed sequentially Mean age 56±14 y Serial echo studies Endpoints: symptoms, increase in LVEDV >15%, or decrease in LVEF >10% 29 additional pts who underwent AVR at the outset are not reported here	No pts died Progression to death, symptoms, increase in LVEDV or decrease in LVEF: 14.3%/y	Disease progression defined as symptoms, increase in LVEDV >15%, or decrease in LVEF >10% Disease progression associated with reduced myocardial systolic strain, systolic strain rate, and early diastolic strain rate

AF indicates atrial fibrillation; AR, aortic regurgitation; AVR, aortic valve replacement; BNP; brain natriuretic peptide; BP, blood pressure; EDV, end-diastolic volume; ESV, end-systolic volume; HF, heart failure; Hx, history; LV, left ventricular; LVEDD, end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic volume; IE, infective endocarditis; N/A, not applicable; NYHA, New York Heart Association; PAP, pulmonary artery pressure; pt(s), patient(s); ROA, regurgitant orifice area; RV, regurgitant volume; and SE, standard error.

Data Supplement 11. Vasodilator Therapy in Asymptomatic Patients With Chronic Aortic Regurgitation (Section 4.3.2)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Study Comparator	Endpoints	Results
				Inclusion Criteria	*Exclusion Criteria*			*Primary Endpoint & Results*	
Evangelista, 2005 (81) 16192479	Effects of vasodilator therapy on LV function and time to AVR	RCT/95	Intervention: open-label nifedipine-32 pts (20 mg every 12 h) or open label enalapril-32 pts (20 mg every 12 h) vs. Comparator: no treatment-31 pts	Asymptomatic, chronic, severe AR and normal LV function	LVEF <50%., other valve disease. Hypertension, AF, CAD, aortic aneurysm	Open-label nifedipine (20 mg every 12 h) or open-label enalapril (20 mg/d)	No treatment	LVEF Time to AVR	Rate of AVR was similar among the groups: Control group 39% Enalapril group 50% Nifedipine group 41%; p=0.62) No significant group differences in AR severity, LV size or LVEF. Follow-up mean 7 y
Scognomiglio, 1994 (76) 8058074	Assess whether vasodilator therapy reduces or delays the need for AVR	RCT/143	Intervention: Nifedipine (20 mg twice daily)-69 pts vs. Comparator: Digoxin (0.25 mg twice daily)-74 pts	Asymptomatic chronic severe AR with normal LV function	LVEF <50%, recent or worsening AR, hypertension, CAD, AS, other valve disease.	Nifedipine	Digoxin	Time to AVR	AVR in 34%+6% of pts on digoxin versus 15%+3% of pts on nifedipine pts (p<0.001) at 6 y follow-up

AF indicates atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; CAD, coronary artery disease; LV, left ventricular; LVEF, left ventricular ejection fraction; pts, patients; and, RCT, randomized controlled trial.

Data Supplement 12. Determinants of Outcome After Surgery for Chronic Aortic Regurgitation (Section 4.3.3)

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Outcome Assessed	Outcomes	Comments, Limitations
Forman 1980 (85) 7377109	Determinants of survival after AVR	Retrospective, observational series; pts undergoing AVR 1972–1978; single institution	90	3	Indications for AVR not specified; age not specified Preoperative angiography Lillehei-Kastor, Starr Edwards model 2400, and Bjork-Shiley mechanical valves and first generation porcine bioprostheses Endpoint: survival	3-y survival: Overall 79±6% LVEF ≥50% 93±4% LVEF <50% 64±10% p<0.02 CI: ≥2.5 L/m/m^2 93±4% CI: <2.5 L/m/m^2 63±10% p<0.02	High-risk group identified by preoperative angiographic LVEF <50% and/or CI: <2.5 L/m/m^2
Henry 1980 (86) 7353236	Determinants of survival after AVR	Prospective, observational series; consecutive pts undergoing AVR 1972–1977; single institution	50	3.7	Indications for AVR; symptoms Mean age 46 y (range 19–68 y) Preoperative echo and hemodynamics Endpoint: survival	4-y survival: Overall 61% LVESD <55 mm 75% LVESD ≥55mm 38% p=0.006	High-risk group identified by preoperative echocardiographic LVFS <25% and/or LVESD >55 mm
Cunha 1980 (87) 7351849	Determinants of survival after AVR	Retrospective, observational series; consecutive pts undergoing AVR 1973–1977; single institution	86	2.4 (range 1–5.4)	79 symptomatic pts, 7 asymptomatic Mean age 49.6 y (range 17–82 y) Preoperative echo (all pts) and hemodynamics (37 pts) Endpoint: survival	3-y survival: LVFS >35% 100% LVFS 31-35% 91% LVFS ≤30% 78% p<0.05 LVEF ≥60% 100% LVEF <60% 77% p<0.05	High-risk group identified by preoperative echocardiographic LVFS <30%. Mortality also significantly associated with preoperative LVESD. Among pts with FS <30%, mortality higher in NYHA III-IV than in I-II.
Bonow 1980 (88) 6777072	Determinants of survival and LV function after AVR	Prospective, observational series; pts undergoing AVR 1972-1978; single institution	45	3.2	Symptomatic pts undergoing AVR Mean age 44 y (range 20-68 y) Studied with echo, radionuclide LV angiography, and graded treadmill testing Good exercise capacity defined as >stage 1 of NIH protocol Endpoints: survival and LV function	Among 32 pts with subnormal LVFS, those with good vs. poor exercise capacity had: Better survival (100% vs. 47%, p<0.01). Lower postoperative LVEDD (56±8 vs. 68±11 mm, p<0.005) Higher exercise LVEF (5±15 vs. 42±8%, p<0.01)	Exercise capacity imprecise in assessing preoperative LV function in symptomatic pts with AR, but useful in predicting long-term survival after AVR and reversibility of LV dilatation and systolic dysfunction
Borow 1980 (89) 7377221	Determinants of LV function after AVR	Retrospective, observational series; pts undergoing AVR starting 1971; single institution	20	2.0 (range 0.5–5.8)	NYHA: II (20%), III (70%), IV (10%) Preoperative hemodynamics and angiography; postoperative echo Endpoint: LV function (LVFS)	Preoperative LVESVi correlated with postoperative LVFS (r=0.77) The 3 postoperative deaths occurred in pts with preoperative LVESVi 0.60 mL/m^2	In symptomatic pts with AR, preoperative LVESV is an important determinant of postoperative LV systolic function

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Outcome Assessed	Outcomes	Comments, Limitations
Greves 1981 (90) 6451163	Determinants of survival after AVR	Retrospective, observational series; pts undergoing AVR 1973–1979; single institution	42	3.7 (range 0.2–6.6)	38 symptomatic pts, 4 asymptomatic Mean age 45 (range 14–74) Preoperative hemodynamics and angiography Endpoint: survival	5-y survival: Overall 65.3±7.8% (SE) LVEF ≥45% 86.6±6.2% LVEF <45% 53.6±20.1% p=0.04 Cardiac index: ≥2.5L/m/m^2 92±6% Cardiac index: <2.5L/m/m^2 66±16.1% p<0.02	High-risk group identified by preoperative angiographic LVEF <45% and/or cardiac index: <2.5 L/m/m^2 Among pts with LVEF <45%, mortality higher in NYHA III-IV than in I-II.
Kumpuris 1982 (91) 6461239	Determinants of survival, LV function, symptoms after AVR	Prospective, observational series; consecutive pts undergoing AVR 1973–1979; single institution	43	0.67	43 pts with chronic AR and 14 pts with acute AR; only the pts with chronic AR reported here Mean age 46 y (range 18–72 y) Pre- and postoperative echos Endpoint: survival, HF, LV function	Prediction of persistent LV dilatation after AVR (LVEDD >58 mm): Index — Accuracy LVEDD 72 mm — 77% LVESD 50 mm — 86% FS 28% — 70% Mean R/Th 2.5 — 93% MWS 300 mm Hg — 88% ESS 235 mm Hg — 91%	Persistent LV dilatation after AVR predicted by preoperative LVESD, R/Th ratio, mean and end-systolic wall stress; greater precision than LVFS or LVEDD. All deaths occurred in pts with persistent LV dilatation.
Gaasch 1983 (92) 6219153	Determinants of LV function, symptoms after AVR	Prospective, observational series; pts undergoing AVR 1975–1980; single institution	32	Range 1–6	Group A: 25 pts with normal LVEDD after AVR (mean age 45 y, range 18–63 y) Group B: 7 pts with LVEDD >33 mm/m^2 after AVR (mean age 58 y, range 23–74 y) 24 symptomatic pts, 9 asymptomatic (8 in Group A) Pre- and serial postoperative echos Endpoint: symptoms, LV function	Preoperative data, Group A vs. Group B (p<0.001): —LVEDD 69±6 mm vs. 79±6 mm —LVESD 46±7 mm vs. 58±7 mm —LVFS 34±6% vs. 27±6% —R/Th 3.4±0.4 vs. 4.1±0.3 More postoperative symptoms in Group B	Persistent LV dilatation after AVR predicted by echocardiographic LVESD >2.6 cm/m^2 and R/Th ratio >3.8. Trend toward worse survival in Group B (but only 2 deaths in each group at 4 y). Note: Group B was also 12 y older than Group A and more symptomatic.
Fioretti 1983 (93) 6847800	Determinants of LV function after AVR	Retrospective, observational series; consecutive pts undergoing AVR 1972–1980; single institution	47	3.4 (range 0.5–6.3)	All pts symptomatic Group A: 27 pts with LVESD <55 mm (45 y of age, range 22-75 y) Group B: 20 pts with LVESD ≥55 mm (49 y of age, range 22-65 y) NYHA III-IV: Group A 26%, Group B 65% Preoperative echo and angiographic data; postoperative echo at 3 mo and 36 mo Endpoint: LV function	Preoperative data, Group A vs. Group B (p<0.001): —LVEDD 67±7 vs. 82±6 mm —LVFS 33±6 vs. 24±6% —LVEDV 147±43 vs. 247±42 mL/m^2 —LVEF 54±7 vs. 42±9% Postoperative data, Group A vs. Group B: —LVEDD 53±8 vs. 63±7 mm (p<0.001)	Persistent LV dysfunction predicted by preoperative LVEDD ≥75 mm and/or LVESD ≥55 mm. Note greater preoperative symptoms in Group B than Group A

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Outcome Assessed	Outcomes	Comments, Limitations
Stone 1984 (94) 6707364	Determinants of LV function after AVR	Prospective, observational series; consecutive pts undergoing AVR 1962–1977; single institution.	113	4.6±3.3	108 pts symptomatic Mean age 51 y (range 25–77 y) Hemodynamics and angiography in all pts; echo in 44 pts 20 pts with pre- and postoperative echos Endpoint: survival (all pts) and LV function (20 pts)	43 pts died after AVR (8 from HF), no predictors of death Predictors of postoperative LVEDD ≤57 mm: LVESD, LVFS, R/Th ratio Predictors of postoperative LVESD ≤40 mm: LVESD, LVEDD, LV mass	No preoperative variable predicted postoperative LV function. Normal LV size after AVR most likely in pts with preoperative LVFS >26%, LVESD <55 mm, and LVEDD <80 mm
Bonow 1985 (95) 4064269	Determinants of survival and LV function after AVR	Prospective, observational series; consecutive pts undergoing AVR 1976–1983; single institution.	80	3.75 (range 0.5–7.5)	96 consecutive pts; 16 with CAD excluded Group A: 30 pts with normal LVEF Group B: 50 pts with subnormal LVEF Mean age 44 y (range 15–74 y) Preoperative and postoperative echo and radionuclide angiography; preoperative exercise testing Endpoint: Survival, LV function	5 y survival was 83±5%, significantly better than pts undergoing AVR from 1972–1976 (62±9%) Preoperative determinants of postoperative survival: LVEF and FS (both p<0.001) and LVESD (p<0.01) 5 y survival: 96±3% in Group A, 63±12% in Group B (p<0.001)	High-risk group identified by subnormal LVEF at rest. Pts in Group B with poor exercise tolerance and prolonged duration of LV dysfunction were the highest-risk group (5 y survival 52±11) and had greater LVEDD and lower LVEF (both p<0.001) than the others.
Daniel 1985 (96) 3156010	Determinants of survival, symptoms and LV function after AVR	Retrospective, observational series; pts undergoing AVR 1975–1983; single institution.	84	2.5	Consecutive series of pts with high-quality echos Preoperative symptoms not specified Age 46±11 y (range 18–71) Pts with CAD excluded Endpoint: Survival, symptoms, LV function	Survival at 2.5 y: 90.5% in pts with LVFS >25% and LVESD ≤55 mm, but only 70% with LVESD >55 mm and LVFS ≤25%. Survival at 2.5 y: 79% in pts with LVESD >55 mm or LVFS ≤25%.	Outcome after AVR predicted by preoperative LVFS and LVESD. Pts with preoperative LVFS ≤25% had greater postoperative LVEDD compared to those with LVFS >25%: 62±10 vs. 54±7 mm (p<0.05)
Cormier 1986 (97) 3727677	Determinants of survival after AVR	Prospective, observational series; consecutive pts undergoing AVR 1968–1983; single institution.	73	4.9±0.8 (range 0.3–14)	All pts in NYHA FC I-II (26 FC I, 47 FC II) Age 46±11 y (range 14–76 y) Echo in 58 pts (LVEDD 70±12 mm; hemodynamics and angiography in 62 pts) (LVEDV 222±55 mL/m^2) Pts with CAD excluded Endpoint: Survival	84% survival at 8 y There were only 2 determinants of survival after AVR: LVEF (p<0.05) and LVESD (p<0.05)	Overall survival good in asymptomatic/mildly symptomatic pts High-risk group identified by preoperative LVEF <40% and LVESD ≥55 mm.
Sheiban 1986 (98) 3727678	Determinants of survival after AVR	Retrospective, observational series; consecutive pts undergoing AVR 1973–1982; single institution.	84	6.5 (range 3–10)	NYHA: I (12%), II (33%), III (45%), IV (10%) Mean age 42 y (range 20–68) Echo, hemodynamics, and angiography Endpoint: Survival	10-y survival (p<0.01): NYHA I 100%, II 86%, III 70%, IV 0% 5-y survival (p<0.01): —82% in LVESD ≤55 mm; —37% in LVESD <55 mm —81% in LVEF ≥50% ; 62% in LVEF <50%	High-risk group identified by preoperative LVEF <50% and LVESD >55 mm. Severity of preoperative symptoms associated with late survival

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Outcome Assessed	Outcomes	Comments, Limitations
Carabello 1986 (99) 3779916	Determinants of LV function after AVR in pts with preoperative LV dysfunction	Retrospective, observational series; pts undergoing AVR 1980–1987; single institution.	14	1.9±0.67 (range 0.5–6)	Pts with isolated severe AR and LVEF <55% Mean age 49±6 y Pts with CAD excluded Preoperative hemodynamic and echo data; postoperative radionuclide angiography Endpoint: LV function	Preoperative LVESD 57±3 mm Correlation with postoperative LVEF: —LVEDD r=-0.47; p<0.05 —LVEF r=0.55; p<0.05 —R/Th r=-0.56; p<0.05 —LVESV r=-0.62; p<0.05 —LVFS r=0.71; p<0.01 —LVESD r=-0.91; p<0.001	Postoperative LVEF correlated with preoperative LVESD, FS, LVEDD, R/Th ratio Postoperative LVEF most strongly associated with preoperative LVESD
Taniguchi 1987 (100) 3624657	Determinants of survival after AVR	Retrospective, observational series; consecutive pts undergoing AVR 1978–1985; single institution.	62	3.8±2.2	Age 43±12 y (range 18–64) Group A: LVESV <200 mL/m^2 (n=48), Group B: LVESV >200 mL/m^2 (n=12) Pts with CAD excluded Preoperative hemodynamic and angiographic data Postoperative catheterization in 29 pts Endpoint: Survival and LV function	7-y survival 83±5% Preoperative LVESV index was most important indicator of postoperative death (p<0.001) 6.5 y survival: 92±4% in Group A, 51±16% in Group B (p<0.001) Postoperative data, Group A vs. Group B (p<0.001) —LVEF: 62±7 vs. 42±8% —LVEDV: 98±19 vs. 124±58 mL/m^2	High-risk group identified by preoperative LVESV index >200 mL/m^2 and/or LVEF <40%. No cardiac deaths in Group A
Bonow 1988 (95) 4064269	Factors influencing short- and long-term changes in LV function after AVR	Prospective, observational series; pts undergoing AVR 1976–1983; single institution.	80	Range 3-7	Mean age 43 y (range 19–72 y) Pts with CAD excluded Echo and radionuclide angiography before, 6–8 mo after AVR and 3–7 y after AVR; preoperative exercise testing Endpoint: LV function	Preoperative to early postoperative changes (p<0.001): —LVEDD 75±6 to 56±9 mm —LVEF 43±9 to 51±16% —LVPSS 247±50 to 163±42 dynes/cm^2 Early to late postoperative: no change in LVEDD or PSS, but further increase in LVEF to 56±19% (p<0.001)	Short- and long-term LV function after AVR predicted by preoperative LVEF, FS, LVESD. Among pts with subnormal preoperative LVEF, those with poor exercise tolerance or prolonged duration of LV dysfunction are at highest risk for persistent LV dysfunction
Michel 1995 (101) 8563993	Determinants of long-term survival after AVR	Retrospective, observational series; consecutive pts undergoing AVR 1980–1994; single institution.	286	6	NYHA: I (19%), II (34%), III (44%), IV (3%) Age 52±13 y (range 17–76 y) Pts with CAD excluded Hemodynamic and echo data Endpoint: Postoperative LV dysfunction defined as clinical HF or LVEF <40% Group A: no postoperative LV dysfunction (n=247); Group B: postoperative LV dysfunction (n=28)	5- and 10-y survival 80% and 60%, respectively Preoperative data, Group A vs. Group B (p<0.001): —LVEF: 48±9 vs. 37±5% —LVFS: 29±7 vs. 21±5% —LVEDD: 69±7 vs. 76±7 mm —LVESD: 49±7 vs. 61±5 mm —NYHA: 44% vs. 82%	Postoperative LV dysfunction predicted by severity of preoperative symptoms and preoperative LVEF, FS, LVESD, LVEDD. On multivariate analysis, preoperative symptoms (p<0.01), LVESD (p<0.03) and LVEF (p<0.04) were significant factors. Determinants of survival not presented.

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Outcome Assessed	Outcomes	Comments, Limitations
Klodas 1996 (102) 8606280	Impact of LV function on survival after AVR	Retrospective, observational series; consecutive pts undergoing AVR 1980–1989; single institution	219	5-y and 10-y survival data reported	Group A: preoperative LVEDD <80 mm (n=188, age 55±16 y) Group B: preoperative LVDD ≥80 mm (n=31, age 50±15 y) NYHA III-IV symptoms: Group A 37%, Group B 29% Includes pts with CAD: Group A 37%, Group B 29% Endpoint: Survival	Preoperative data, Group A vs. Group B (p<0.001): —LVEF: 53±11 vs. 43±12% —LVEDD: 67±8 vs. 84±4 mm —LVESD: 45±9 vs. 63±8 mm —LVESS: 96±39 vs. 147±39 dynes x 105/s Postoperative survival, Group A vs. Group B (p=NS): —5 y: 89±3% vs. 87±6% —10 y: 73±5% vs. 71±9% Postoperative survival, LVEF ≥50% vs. <50% (p<0.01): —10 y: 80±5% vs. 63±7%	Extreme LV dilatation associated with LV systolic dysfunction Preoperative LVEF, not degree of LV dilatation, associated with survival
Klodas 1997 (103) 9283535	Impact of symptom severity on survival after AVR	Retrospective, observational series; consecutive pts undergoing AVR 1980–1989; single institution	289	5-y and 10-y survival data reported	Group A: NYHA I-II (n=161, age 50±16 y, 86% men) Group B: NYHA III-IV (n=128, age 61±14 y, 70% men) Includes pts with CAD: Group A 11%, Group B 35%; including AVR plus CABG: Group A 8%, Group B 32% (both p<0.0001) Echo data in 249 pts Endpoint: survival	Preoperative data, Group A vs. Group B (p<0.05): —LVEF: 5 3±11 vs. 49±14% 10-y survival, Group A vs. Group B (p<0.001) —Total: 78±7% vs.45±4% —LVEF ≥50%: 82% vs. 40% —LVEF <50%: 73% vs. 40% —Men: 80% vs. 55% —Women: 73% vs. 21% —CAD: 76% vs. 39% —No CAD: 79% vs. 48%	High-risk group identified by symptom severity and preoperative LVEF <50% Survival in Group A equivalent to normal age/sex matched population Note higher frequency of CAD and CABG surgery (and other comorbidities) in the more symptomatic Group B
Turina 1998 (104) 9852889	Determinants of survival after AVR	Retrospective, observational series; consecutive pts undergoing AVR 1970–1983; single institution	192	18.7 (range 13–26)	Mean age 44 y Endpoint: Survival	Survival rates 76% at 10 y, 55% at 20 y. 83% of long-term survivors in NYHA I-II. Multivariate predictors of late survival: age, LVESV, NYHA, previous IE. LVEF significant in univariate analysis.	High-risk group identified by symptom severity, low LVEF, and elevated ESV.
Chaliki 2002 (105) 12438294	Survival after AVR in pts with normal versus reduced LV function	Retrospective, observational series; consecutive pts undergoing AVR 1980–1995; single institution	450	8.1 (median)	Group A (273 pts, age 56±16) with LVEF ≥50% Group B (134 pts, age 58±15) with LVEF 35%–50% Group C (43 pts, age 58±14) with LVEF <35% LVEF measured by left ventriculography	Operative mortality, Group A vs. B vs. C: 3.7%, 6.7%, 14% (p=0.02) 10-y mortality, Group A vs. B vs. C: 30%, 44%, 59% (p<0.001) 10-y HF rate, Group A vs. B vs. C: 9%, 17%, 25% (p<0.003) Postoperative change in LVEF, Group A vs.	Pts with markedly low LVEF incur have high rates of short- and long-term mortality and HF after AVR. However, postoperative LVEF improves significantly, and most pts survive without recurrence of HF. Thus they should not be denied benefits

Study, Year	Aim of Study	Study Type	Study Size (n)	Mean Follow-Up (y)	Inclusion Criteria, Outcome Assessed	Outcomes	Comments, Limitations
					and/or echo Endpoint: Survival	B vs. C: -2.3%, 4%, 4.9% (p<0.01)	of AVR.
Tornos 2006 (106) 16516086	Determinants of survival after AVR	Prospective, observational series; consecutive pts undergoing AVR 1982–2002; single institution	170	10±6 (range 1–22)	Group A (60 pts age 47±15) mild symptoms (NYHA II), mild LV dysfunction (LVEF 45–50%) or LVESD 50–55 mm Group B (110 pts age 53±14) with NYHA III-IV symptoms or more severe LV dysfunction (LVEF <45% or LVESD >55 mm) Echo data Endpoint: Survival	Cardiac deaths: 5 (9%) in Group A, 28 (28%) in Group B (p=0.002). Survival Group A vs. Group B (p=0.009): 90% vs. 75% at 5 y, 86% vs. 64% at 10 y, 78% vs. 53% at 15 y	Early AVR as defined in the 2006 ACCF/AHA guidelines improves long-term survival in pts with chronic AR. Delaying AVR until more severe symptoms or more severe LV dysfunction decreases postoperative survival.
Bhudia 2007 (107) 17397676	Survival after AVR in pts with marked LV dysfunction compared to normal LV function or mild LV dysfunction	Prospective, observational series; consecutive pts undergoing AVR 1972–1999; single institution	724	8.3±6.5	Group A (88 pts, age 56±12) with severe LV dysfunction (LVEF <30%) Group B (636 pts, age 50±15) with either less severe LV dysfunction or normal LV function Endpoint: Survival	Survival diminished in Group A (severe LV dysfunction) compared to Group B (p=0.04): 81% vs. 92% at 1 y, 68% vs. 81% at 5 y, 46% vs. 62% at 10 y, 26% vs. 41% at 15 y, 12% vs. 24% at 20 y	In propensity matched pts since 1985, these survival trends persisted, but were not significant between pts in Groups A and B (p=0.9): 92% vs. 96% at 1 y, 79% vs. 83% at 5 y, 51% vs. 55% at 10 y

AR indicates aortic regurgitation; AVR, aortic valve replacement; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; echo, echocardiography; ESS, end-systolic stress; ESV, end-systolic volume; FS, fractional shortening; HF, heart failure; IE, infective endocarditis; LV, left ventricular; LVEDD, left ejection end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVESV (i), left ejection end-systolic volume (indexed to body surface area); LVFS, left ventricular fractional shortening; LVPSS, left ventricular peak systolic wall stress; MWS, mean wall stress; NIH, National Institute of Health; NYHA , New York Heart Association; PSS, peak systolic wall stress; pts, patients; and, R/Th, radius to wall thickness ratio.

Data Supplement 13. Hemodynamic Effects Percutaneous Mitral Balloon Commissurotomy (PMBC) Compared to Surgical Closed Commissurotomy (CC) or Open Commissurotomy (OC) (Section 6.2.3)

Author, Year	Mean Follow-Up	Procedure	No. of Patients	Age, y	Average Morphology Score*	Mitral Gradient (mm Hg)		Mitral Valve Area (cm^2)		Restenosis (%)	Freedom From Reintervention (%)	NYHA I (%)
						Pre	Post	Pre	Post			
Patel 1991 (108) 1918709	Immediate	PMBC	23	30±11	6.0	12±4	4±3	0.8±0.3	2.1±0.7†	N/A	N/A	91
		CC	22	26±26	6.0	12±5	6±3	0.7±0.2	1.3±0.3	N/A	N/A	N/A
Turi 1991 (109) 2013139	7 mo	PMBC	20	27±8	7.2	18±4	10±2	0.8±2	1.6±0.2	N/A	N/A	N/A
		CC	20	28±1	8.4	20±6	12±2	0.9±0.4	1.7±0.2	N/A	N/A	N/A
Arora 1993 (110) 8465732	22 mo	PMBC	100	19±5	N/A	N/A	N/A	0.8±0.3	2.3±0.1	5	N/A	N/A
		CC	100	20±6	N/A	N/A	N/A	0.8±0.2	2.1±0.4	4	N/A	N/A
Reyes 1994 (111) 8084354	3 y	PMBC	30	30±9	6.7	N/A	N/A	0.9±0.3	2.4±0.4†	10	N/A	72
		CC	30	31±9	7.0	N/A	N/A	0.9±0.3	1.8±0.4	13	N/A	57
Ben Farhat 1998 (112) 9462525	7 y	PMBC	30	29±12	6.0	N/A	N/A	0.9±0.2	1.8±0.4	N/A	90	87
		OC	30	27±9	6.0	N/A	N/A	0.9±0.2	1.8±0.3	N/A	93	90
		CC	30	28±10	6.0	N/A	N/A	0.9±0.2	1.3±0.3	N/A	50	33
Cotrufo 1999 (113) 10386411	38 mo	PMBC	111	47±14	7.6	N/A	N/A	1.0±0.2	1.8±0.3	28	88	67
	50 mo	OC	82	49±10	8.2	N/A	N/A	1.0±0.2	2.3±0.3	18	96	84

*Wilkins echocardiographic mitral valve morphology score, the sum of a 0 to 4 score for each of 4 characteristics: eaflet mobility, thickness, calcification and chordal involvement .
†Significant difference ($p<0.05$) in increased mitral valve area by PMBC compared with surgical commissurotomy.
CC indicates closed commissurotomy; N/A, not available; NYHA, New York Heart Association; OC, open commissurotomy; Post, postprocedure; PMBC, percutaneous mitral balloon commissurotomy; and, Pre, preprocedure.
Adapted from Bonow et al. (114).
Bhudia SK, McCarthy PM, Kumpati GS, et al. Improved outcomes after aortic valve surgery for chronic aortic regurgitation with severe left ventricular dysfunction. J Am Coll Cardiol. 2007;49;1465-71.

Data Supplement 14. Echocardiographic Prediction of Outcome of Percutaneous Balloon Mitral Commissurotomy (Section 6.2.3)

Author, Year	Mean Follow-Up, mo	Echo Criteria	Number of Patients	Age (y±SD)	Survival (%)	Survival Free of Events (%)	Events
Cohen et al., 1992 (115) 1406834	36±20	Score ≤8 Score >8	84 52	N/A	N/A	68% at 5 y 28% at 5 y	Death, MVR, repeat PMBC
Palacios et al., 1995 (116) 7828292	20±12	Score ≤8 Score >8	211 116	48±14 64±11	98% at 4 y 39% at 4 y	98% at 4 y 39% at 4 y	Death, MVR, NYHA III-IV symptoms
Dean et al., 1996 (117) 8917257	38±16	Score ≤8 Score 8–12 Score >12	272 306 24	49±13 58±15 58±15	95% at 4 y 83% at 4 y 24% at 4 y	N/A	Death
Iung et al., 1996 (118) 8557913	32±18	Group 1 Group 2 Group 3	87 311 130	46±13	N/A	89% at 3 y 78% at 3 y 65% at 3 y	Death, MVR, repeat PMBC, FC III-IV symptoms
Cannan et al., 1997 (119) 8996311	22±10	Com Ca- Com Ca+	120 29	N/A	N/A	86% at 3 y 40% at 3 y	Death, MVR, repeat PMBC
Palacios et al., 2002 (120) 11914256	50±44	Score >8 Score <8	278 601	63+14 51+14	82% at 12 y 57% at 12 y	38% at 12 y 22% at 12 y	Death, MVR, repeat PMBC

Echo score based on scoring system of Wilkins et al. (121) mitral valve morphology score, the sum of a 0 to 4 score for each of 4 characteristics: leaflet mobility, thickness, calcification and chordal involvement. Echo groups defined as 1, 2, or 3 based on valve flexibility, chordal fusion and valve calcification (Iung, et al. (112)).

Com Ca indicates commissural calcification; echo, echocardiographic; MVR, mitral valve replacement; N/A, not available; NYHA, New York Heart Association; and, PMBC, percutaneous mitral balloon commissurotomy.

Data Supplement 15. Randomized Trials of Percutaneous Mitral Balloon Commissurotomy Versus Surgery for Mitral Stenosis (Section 6.2.3)

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Study Comparator	Results
				Inclusion Criteria	*Exclusion Criteria*			
Patel 1991 (108) 1918709	Compare PMBC by single catheter technique versus CC	RCT/45	Intervention: 23 PMBC vs. comparator: 22 CC	Symptomatic NYHA II or III, tight MS	Mitral valve calcification or left atrial thrombus on 2D echo, more than mild MR or AR, history of systemic embolism within 3 mo of presentation	PBMC	Closed surgical valvotomy	PBMC: MVA increased from 0.8±0.3 cm^2 to 2.1±0.7 cm^2 (p<0.001) CC: MVA increased from 0.7±0.2 cm^2 to 1.3±0.3 cm^2 (p<0.001)
Ben 1998 (112) 9462525	Compare the early invasive and long-term (7 y) clinical and echo follow-up results of PBMC with those of OC and CC for the treatment of tight pliable rheumatic MS	RCT/90	Intervention: PBMC vs. comparator: CC; OC	Rheumatic tight rheumatic mitral valve stenosis (MVA <1.3 cm^2),	Other valve disease, previous thromboembolism, mitral valve calcification, and left atrium thrombus, AF, severe pulmonary hypertension or mild-to-moderate TR	PBMC	CC or OC	Increase in Gorlin MVA : PBMC (from 0.9±0.16 to 2.2±0.4 cm^2), OC (from 0.9±0.2 to 2.2±0.4 cm^2), CC (from 0.9±0.2 to 1.6±0.4 cm^2). Residual MS (MVA <1.5 cm^2): 0% after PBMC or OC and 27% after CC. No early or late mortality or thromboembolism among the 3 groups. At 7-y follow-up, echo MVA was similar and greater after PBMC and OC (1.8±0.4 cm^2) than after CC (1.3±0.3 cm^2; p<0.001). Restenosis (MVA <1.5 cm^2) rate was 6.6% after PBMC or OC vs. 37% after CC. Residual ASD in 2 pts and 3+ MR in 1 pt in the PBMC group. NYHA class I in 87% of pts after PBMC and 90% of pts after OC vs. CC 33% (p<0.0001) Freedom from reintervention 90% after PBMC, 93% after OC, and 50% after CC.
Turi 1991 (109) 2013139	Compare PBMC with surgical CC	RCT/40	Intervention: 20 PBMC vs. Comparator: 20 CC	Pts deemed acceptable as candidates for both procedures	N/A	PBMC	Surgical CC	No differences between groups in pulmonary artery wedge pressures, mitral valve gradients, and MVA at 1 wk and at 8 mo. (all p>0.4).
Arora 1993 (110) 8465732	Compare the immediate and long-term results of PBMC vs. CMC	RCT/200	Intervention: 100 vs. Comparator: 100	Symptomatic pts with moderate-to-severe MS	Pts with more than minimal mitral valve calcification AF, or >2+ MR	PBMC	CC	Both procedures resulted in significant and similar increases in MVA (PBMV: 0.85±0.28 to 2.39±0.94 cm^2; CC: 0.79±0.21 to 2.2±0.85 cm^2; p=NS). MR developed in 14 pts after PBMC and in 12 pts after CC. Restenosis (defined as a loss of >50% of the achieved

Study Name, Author, Year	Study Aim	Study Type/ Size (N)	Intervention vs. Comparator (n)	Patient Population		Study Intervention	Study Comparator	Results
				Inclusion Criteria	*Exclusion Criteria*			
								increase in MVA) was seen in 4 (5%) pts after PBMV and in 3 (4%) after CC.
Reyes 1994 (111) 8084354	Compare PBMC to OC for treatment of rheumatic MS	RCT/60	Intervention: 30 vs. Comparator: 30	Severe rheumatic MS, in sinus rhythm, no severe subvalvular disease/ calcification or more than mild MR	Coexisting other cardiac or valve disease, stroke, severe pulmonary hypertension, low body weight, Lutembacjer's syndrome, and pt decision not to be randomized	PBMC	Open surgical commissurotomy	MVA at 3 years was larger after PBMC (2.4±0.6 cm^2) vs. OC (1.8±0.4 cm^2). NYHA class I at 3 years in 72% or PBMC pts and 57% of OC pts
Cotrufo 1999 (113) 10386411	Compare PPMC vs. OC	RCT/193	Intervention: PBMC 111 vs. Comparator: OC 82	N/A	N/A	PBMC	OC	Survival, event free analysis, recurrent restenosis No hospital mortality in both groups (p=0.3) Hospital complications: 4/111 PBMC vs. 1/82 OC (p=0.3)

2D indicates 2-dimensional; AF, atrial fibrillation; AR, aortic regurgitation; ASD, atrial septal defect; CC, closed commissurotomy; echo, echocardiography; MR, mitral regurgitation, MS, mitral stenosis; MVA, mitral valve area; N/A, not applicable; NS, nonsignificant; NYHA, New York Heart Association; OC, open commissurotomy; PMBC; percutaneous mitral balloon commissurotomy; pts, patients; RCT, randomized controlled trial; and, TR, tricuspid regurgitation.

Data Supplement 16. Preoperative Predictors of Surgical Outcome in Mitral Regurgitation (Section 7.3.3)

Study, Year	Study Design	Type of Surgery	Number of Patients	Outcome Assessed	Findings
Schuler 1979 (122) 436214	Retrospective	MVR	20	LV function	12 pts with average LVEF 0.70 had normal postoperative LVEF; 4 pts with average LVEF 0.58 had postoperative LVEF 0.25.
Phillips 1981 (123) 7282546	Retrospective	MVR	105	Survival	LVEF <0.50 predicted poor survival.
Zile 1984 (124) 6693615	Prospective	MVR	16	HF, LV function	LVESD index >2.6 cm/m^2 (45 mm) and LVFS <0.32 predicted poor outcome.
Crawford 1990 (125) 2317900	Prospective	MVR	48	Survival, LV function	LVEF <0.50 predicted reduced survival; ESV >50 mL/m^2 predicted persistent LV dilatation.
Wisenbaugh 1994 (126) 8012639	Registry	MVR MVR-CP	26 35	Survival, LV function	LVESD, LVEDD, and FS predicted poor survival and LV function; only LVESD significant in multivariate analysis.
Enriquez-Sarano 1994 (127) 8044955	Retrospective	MVR Repair	214 195	Survival	LVEF <0.60 predicted poor survival whether MVR or CP was preformed; LVEF estimated by echo FS or visual analysis.
Enriquez-Sarano 1994 (128) 7930287	Retrospective	MVR Repair	104 162	LV function	LVEF, LVESD, LV diameter/thickness ratio and end-systolic wall stress predicted outcome; LVEF estimated by echo FS or visual analysis.

CP indicates chordal preservation procedure; ESV, end-systolic volume; FS, fractional shortening; HF, heart failure; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVFS, left ventricular fractional shortening; MVR, mitral valve replacement; PAWP, pulmonary artery wedge pressure; and, pts, patients.

Data Supplement 17. Primary Mitral Regurgitation—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 1999 (129) 9918527	Assess impact of symptom status on outcome	Retrospective	478	Mitral surgery	NYHA class I,II, III, IV	Advanced preoperative symptoms increased operative mortality by 10 fold. Long-term survival also reduced.
Gillinov 2010 (130) 20667334	Assess impact of symptoms on outcomes	Retrospective propensity-matched	4,253	MVR	NYHA all class	Even NYHA class II preoperative symptoms impaired late survival.
Rosenhek 2006 (131) 16651470	Assess outcome with watchful waiting	Prospective	132	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 2009 (132) 19188506	Assess outcome with watchful waiting	Prospective	447	Mitral surgery	Early surgery vs. watchful waiting	Early surgery appeared superior, but several unoperated pts refused surgery despite presence of triggers.
Enriquez-Sarano 1994 (127) 8044955	Assess predictors of outcome	Retrospective	409	Mitral surgery	LVEF >60, 50-60, <50	Survival at 10 y, 72% for LVEF >60, 53%, 50–60, 32%, <50.
Tribouilloy 2009 (133) 19909877	Assess impact of LVESD on outcome	Retrospective	739	Mitral surgery	LVESD <40 vs. ≥40	LVESD >40 mm nearly doubled late mortality risk.
Enriquez-Sarano 2005 (134) 15745978	Assess impact of MR severity	Prospective	450	N/A	ERO of different sizes	ERO >0.4 cm^2 nearly tripled mortality, but mortality was reduced by surgery.
Ghoreshi 2011 (135) 21962906	Assess impact of pulmonary HTN on outcome	Retrospective	873	Mitral surgery	Preoperative-pulmonary HTN of various degrees	5 y survival 88% for PAP <40 vs. 52% PAP >60.
Goldman 1987 (136) 3624663	Compare LV function after replace vs. repair	Prospective	18	Mitral surgery	Repair vs. replacement	LVEF fell following replacement, but not repair.
David 1984 (137) 6492840	Compare outcome with and without chordal presentation	Prospective	27	Mitral surgery	MV surgery with and without chordal preservation	LVEF decreased without preservation, but was maintained with preservation.
Rozich 1992 (138) 1451243	Examined LVEF	Retrospective	15	Mitral surgery	Chordal preservation vs. destruction	Afterload increased following chordal destruction, but decreases following preservation.
Grigioni 2008 (139) 19356418	Outcome of repair vs. replacement	Prospective	394	Mitral surgery	Repair vs. replacement vs. nonsurgery	92% 54 y survival for repair 80% for replacement.

Study Name, Author, Year	Aim of Study	Study Type	Study Size (N)	Study Intervention Group (n)	Study Comparator Group (n)	Outcome
Gillinov 2008 (140) 18721551	Outcome of repair vs. replacement	Retrospective	328	N/A	Repair vs. replacement propensity	5, 10, 15 y survival 95, 87, 68 repair vs. -80, 60, 44 replacement.

ERO indicates effective regurgitant orifice; HTN, hypertension; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation; MV, mitral valve; MVR, mitral valve repair; N/A not applicable; NYHA, New York Heart Association; PAP, pulmonary artery pressure; and, pts, patients.

Data Supplement 18. Secondary Mitral Regurgitation—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 2006 (141) 16820626	Outcome surgery in moderate-to-severe ischemic MR	Retrospective	107	CABG + repair	CABG	Higher operative mortality with CABG and MV repair vs CABG alone (12% vs 2%) but similar 5 year survival (88% vs 87%)
Rossi 2011 (142) 21807656	Impact of SMR on outcome	Retrospective	1,256	None	Impact of SMR on HF	After adjusting for LVEF and other factors-SMR increased mortality by 2-fold
Wu 2005 (143) 15680716	Impact of surgery on moderate-severe MR	Retrospective	126	Surgery with mitral annuloplasty	Med Rx	No survival advantage to mitral valve annuloplasty
Mihaljevic 2007 (144) 17543639	Impact of mitral surgery moderate-severe on SMR	Retrospective	290	CABG+ MV surgery	CABG	1-, 5-, 10-y survival -88, 75, 47 CABG vs. 92, 74, 39 CABG + MV Sx; (p=NS) functional class improved equally in both groups
Benedetto 2009 (145) 19377377	Impact of MV surgery on SMR	Meta-analysis	2,479	CAGB+MV surgery	CABG	No difference in survival or symptomatic status
Fattouch 2009 (146) 19619766	Impact of MV surgery in ischemic MR	Randomized prospective	102	CABG + repair	CABG	No difference in mortality. Repair group had reduced cardiac dimensions and symptoms vs. CABG alone
Deja 2012 (147) 22553307	Impact of repair in ischemic SMR	Randomized to medical Rx vs. surgery	104	CABG + repair	CABG	53% mortality CABG, vs. 43% mortality CABG + MVR (p=NS); after adjustment CABG + MVR had better survival

CABG indicates coronary artery bypass graft; HF, heart failure; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MV, mitral valve, MVR, mitral valve repair; NS, nonsignificant; pts, patients; Rx, prescription; SMR, secondary mitral regurgitation; and, Sx, symptoms.

Data Supplement 19. Functional Tricuspid Regurgitation: Outcomes Following Tricuspid Valve Surgery (Sections 8.2.3 and 8.4.3)

Study, Year	Aim of Study	Study Type	Study Size, Details	Outcomes	Comments, Limitations
Dreyfus, 2005 (148) 15620928	Determine benefit of TV annuloplasty based on intraoperative measurement of TA size	Prospective, observational series 1989–2001; single surgeon	311 pts undergoing MVR for chronic severe MR. 163 pts with TA <70 mm received isolated MVR (Group 1); 148 pts with TA ≥70 mm received MVR + TVR (Group 2). 88% of pts had 0-1+ TR preoperatively. No pts in Group 1 had >2+ TR; 2 pts in Group 2 had 3+ TR.	Postoperative TR grade 2.1±1.0 Group 1 vs. 0.4±0.6 Group 2; (p<0.001). TR severity increased >2 grades in 48% of Group 1 pts vs. 2% of Group 2 pts. Progressive TR occurred independent of residual MR, LVEF, and PA pressures. No differences between groups in 10-y actuarial survival or cardiac event-free survival.	No echo core lab. Time at which postoperative echo obtained not specified. Median y of follow-up not specified. Predictors of worsening TR not reported.
Chan, 2009 (149) 19766809	Determine the effects of TR and TV repair on clinical and TTE outcomes in pts undergoing MV replacement.	Retrospective, observational, single center, 1990–2005	624 pts undergoing MV replacement. 231 with ≥2+TR; 125 received TVR, 106 did not. Mean follow-up 6.8±4.8 y.	TVR was associated with a reduction in TR grade and HF symptoms. No difference in survival between groups. Trend for worsening TR in pts with ≤1+TR but dilated TA.	Study spans 15 y Multiple annuloplasty techniques used. 22% of pts had suture annuloplasty.
Calafiore, 2009 (150) 19231373	Evaluate clinical outcomes of pts undergoing TV annuloplasty for ≥moderate TR at time of MVR for functional MR.	Retrospective, observational, single center, 1988–2003	110 pts with ≥moderate TR undergoing MVR for functional MR. 51 pts underwent TV annuloplasty (treated). 59 pts did not have TV annuloplasty (untreated). Midterm propensity score analysis.	Adjusted 5-y survival was 45.0±6.1% in untreated group and 74.5±5.1% in treated group (p=0.004). Untreated ≥moderate TR a risk factor for lower midterm survival (HR: 2.7; 95% CI: 1.3–5.4) and survival in NYHA class I or II (HR: 1.9; 95% CI: 1.1–3.4). Follow-up functional TR progression rate (3+/4+) was 5% in treated group vs. 40% in untreated group (p<0.001). The progression of functional TR grade at follow-up was a risk factor for worse survival and the possibility to be alive in NYHA class I or II.	Study span 15 y. DeVega annuloplasty in all pts. All pts had functional MR. Incomplete TTE follow-up.
Di Mauro, 2009 (4) (151) 19233670	Evaluate impact of ≥moderate TR on midterm outcomes of pts undergoing surgery for functional MR	Retrospective, observational, single center 1988–2003	165 pts with functional MR and untreated TR 102 pts with 0-1+TR 63 pts with 2-3+TR	5-y survival and NYHA class better for pts with 0-1+TR. Negative impact on survival of untreated moderate or more TR (HR: 3.1; 95% CI: 1.8–5.1; p<0.001). TR grade initially declined after MV surgery, but then progressed in pts with 2-3+ preoperative TR.	Study span 15 y. Incomplete TTE follow-up. No information on success of MV surgery. Same pt cohort as reported by Calafiore 2009.
Van de Veire, 2011 (152) 20832082	Determine if TV annuloplasty in pts with TA dilatation undergoing MVR prevents progression of TR and RV remodeling	Retrospective, observational, single center series, 2 separate cohorts: 2002 and 2004	2002: 13 pts with 3-4+ TR underwent TV annuloplasty at time of MVR 2004: 21 pts with 3-4+TR and 43 pts with TA ≥40 mm underwent TV annuloplasty at time of MVR	2002 cohort: no evidence of RV reverse remodeling; TR grade unchanged. For 23 pts without 3-4+ TR but with TA dilatation, TR grade worse and RV size larger at 2 y. 2004 cohort: RV reverse remodeling with reduction in TR grade in 43 pts with TA dilatation who underwent TV annuloplasty.	Limited clinical data. Reason for choice of these 2 observational pt cohorts not provided.
Yilmaz, 2011 (153) 21277597	Examine clinical and TTE outcomes of pts with "clinically silent" TR undergoing isolated MVR for prolapse	Retrospective, observational, single center, 1995–2006	n=699 pts with MVP Preoperative TR grade was 1-2+ in ≥80% of pts. Pts with right HF or primary TR excluded.	Overall TR grade decreased significantly at 1 y. Independent risk factors for worsening TR included female sex, preoperative AF, diabetes mellitus. In pts with <moderate preoperative TR (mean grade, 1.6 [0.49]), mean TR grade remained stable and increased only slightly after 5-y follow-up (mean, 2.0 [0.86]; p<0.01).	TA measurements not provided. All pts had MVP. Other, but not all investigators have reported that the incidence of TR after MVR may be dependent on the etiology of

Study, Year	Aim of Study	Study Type	Study Size, Details	Outcomes	Comments, Limitations
				In pts with at least moderate preoperative TR, mean TR grade decreased significantly from preoperative values after MVR (p<0.001 at hospital discharge, <1 y, and 1–3 y). Mean TR grade trended down at 3 and 5 y after surgery (p=0.18 after 3 y; p=0.33 after 5 y). Degree of preoperative TR was not associated with early or late mortality.	MR. Effect of recurrent TR on survival not reported.
Calafiore, 2011 (154) 21163499	Determine benefit of TV annuloplasty for TR based on TA diameter	Retrospective, observational, single center 2006–2008	298 pts with ≥1+ TR undergoing MV surgery. 167 underwent TVR, 108 with ≥moderate TR and 59 with TA >24 mm. 137 did not have TVR, 16 with ≥moderate TR and 81 with TA >24 mm.	In pts who did not undergo TVR, TA >24 mm was a risk factor for increasing TR grade during follow-up (HR: 2.4; 95% CI: 1.4–5.1; p=0.020).	DeVega annuloplasty used in all pts with TA <28 mm. Small cohort sizes.
Navia, 2012 (155) 22093694	Identify factors associated with TVR; assess safety and efficacy of TVR	Retrospective, observational, single center series 1997–2008	91(5%) of 1,724 pts with 2+ TR undergoing left-sided heart valve surgery. Propensity analysis performed for 91 matched pairs. Pts nonrandomly selected for TVR had more severe indices of RV remodeling with TV tethering.	In propensity-matched groups, prevalence of early postoperative TR grades 0 and 1 was 83% after TVR vs. 46% in the no-repair group 11% of the repair group had persistent grade 2+ TR after TVR, compared with 39% of the no-repair group. Worse TR on was present in 7% of the TVR group, vs. 15% of the no-repair group (p<0.0001). Differences in TR grade for matched pts were sustained at over 3 y. TVR did not add significant in-hospital morbidity or mortality. Long-term survival of propensity matched pts did not differ.	Multiple TVR techniques used Limited long-term outcome and TTE data. Matched pairs differed significantly.
Kim, 2012 (156) 21930721	Assess clinical and TTE outcomes of TVR in pts with mild-to-moderate TR at time of MV replacement	Retrospective, observational, single center, 1997-2008	236 pts with mild-moderate TR undergoing mechanical MV replacement for rheumatic disease. 123 pts underwent TVR. 113 pts did not undergo TVR.	Freedom from moderate-severe TR at 5 y 92.9±2.9% in repair group vs. 60.8+/16.9% in nonrepair group (p<0.001). Approximately 10% of pts with mild TR who did not have repair progressed to ≥moderate TR over 10 y. No differences between groups in mortality, need for TV reoperation, or HF. Postoperative moderate-severe TR an independent predictor of poorer event-free survival (HR: 2.90; p=0.038).	All pts had rheumatic MV disease. Groups significantly unbalanced at baseline. Limited TTE follow-up information, especially regarding MV prosthesis function, PA pressures, etc.
Benedetto 2012 (157) 22244561	Determine if TV annuloplasty in pts with TA dilatation and ≤moderate TR prevents TR progression after MV surgery	Randomized, prospective, single institution, 2008-2009	44 pts undergoing MV surgery with ≤2+ TR and TA ≥40 mm on preoperative TTE. Randomized 1:1 to TV annuloplasty with a flexible ring or no TV annuloplasty. Primary endpoint: ≥3+ TR at 1 y.	≥3+ TR at 1 y 0% in TV annuloplasty group vs. 28% in no annuloplasty group (p=0.02). Compared with no annuloplasty, TV annuloplasty resulted in significant RV reverse remodeling. Distance during 6-min walk test greater in the TV annuloplasty group (p=0.008).	Small sample size. Nonblinded endpoint assessment.

AF indicates atrial fibrillation; echo, echocardiography; HF, heart failure; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MV, mitral valve; MVP, mitral valve prolapse; MVR, mitral valve repair; NYHA, New York Heart Association; PA, pulmonary artery; pt(s), patients; RV, right ventricle; TA, tricuspid annulus; TR, tricuspid regurgitation; TTE, transthoracic echocardiography TV, tricuspid valve; and, TVR, tricuspid valve repair.

Data Supplement 20. 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 2000 (158) 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 ≤19 mm AVR or ≤25 mm MVR, active 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. Primary 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). Primary 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 hypertension than those with a bioprosthetic MVR.
Oxenham, 2003 (159) 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 no significant difference in major embolism or endocarditis.	Older generation valve types.
Stassano 2009 (160) 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 2001 (161) 11479498	Initial AVR in 1389 pts, MVR in 915 pts, 1976–2001 at	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	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.	Not prospective, not randomized. Concurrent CABG in

Author, Year	Study Size	Methods	Patient Population		Follow-Up	Outcomes	Study Limitations
			Inclusion Criteria	Exclusion Criteria			
	a single medical center.			valve surgery		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%)	50%.
Chan 2006 (162) 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 2006 (163) 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 primary 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 2007 (164) 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 2009 (165) 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%,	Methodology of microsimulation is dependent on quality of dataset, wide chronological age of prostheses.

Author, Year	Study Size	Methods	Patient Population		Follow-Up	Outcomes	Study Limitations
			Inclusion Criteria	Exclusion Criteria			
		outcome after AVR				• risk of bleeding: 12% vs. 41%	
Badhwar 2012 (166) 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 2012 (167) 22341653	206 pts undergoing AVR (2000–2009)	Retrospective, with propensity matching of 103 BP to 103 MP AVR	Age <60 y. AVR with or without concurrent CABG, aortic root surgery, mitral or tricuspid valve repair.	Additional valve replacement.	Median follow-up 33±24 mo (2–120 mo)	Overall survival was worse with BP (90.3% vs. MP=98%, p=0.038; HR:0.243, 0.054–0.923 Freedom from valve related complication complications was similar: BP=54.5% vs. MP=51.6%, p=NS	Concurrent CABG in 49.9%, 14% were reoperations

AVR indicates aortic valve replacement; BHV, bioprosthetic heart valve; CABG, coronary artery bypass graft; HTN, hypertension; INR, international normalized ratio; MAPE, major adverse prosthesis-related events; MHV, mechanical heart valve; MVR, mitral valve replacement; N/A, not applicable; NS, nonsignificant; RCT, randomized controlled trial; pts, patients; VA, Veterans Affairs; and, VKA, vitamin K antagonist.

Data Supplement 21. 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 2007 (168) 17578050	Prospective, observational	Pts with MHV undergoing major surgery (n=25) or minor surgery (n=36), pacer 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 2008 (169) 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 outpts or discharged from the hospital in <24 hours (68.6% vs. 6.8%; p <0.0001). Multivariate logistic analysis found no significant differences in major bleeds and major composite adverse events when adjusting for cardiothoracic or major surgery between groups.	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 2009 (170) 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

Author, Year	Study Type	Patient Population		Study Size and Comparator (N)	Outcomes	Study Limitations
		Inclusion Criteria	Exclusion Criteria			
Daniels 2009 (171) 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. UFH or LMWH bridging used in high-risk pts (older AVR, any MVR, additional risk factors for TE). No bridging in isolated AVR pts.	**Events at 3 mo N (%)** / **No Heparin N=213** / **LMWH Only N=243** / **Any UFH N=99** Thromboembolism 1 (0.5) / 2 (0.8) / 2 (3.1) Major Bleeding 5 (2.4) / 9 (3.7) / 6 (6.1) Minor Bleeding 13 (6.1) / 13 (5.4) / 8 (8.1) Overall cumulative incidence of TE at 3 mo was 0.9%; all events occurred within 1 wk of the procedure. No TE events in 93 pts with isolated AVR with no bridging.	Not randomized, choice of therapy individualized based on estimated TE and bleeding risk. Most frequent procedures were GI endoscopy (19.1%), urologic procedures (14.0%), angiography or transcatheter interventions (10.5%), and orthopedic surgery (10.3%).
Bui HT 2009 (172) 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 2012 (173) 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.	**Events (3 mo) N (%)** / **MHV with LMWH N=140** / **Native valves N=1200** / **p-value** Bleeding 18.6% / 14.2% / NS Thromboembolism 3.6% / 2% / NS Mortality 1.4% / 1.3% / NS Cardiovascular events 10.8% / 10.7% / NS	Not randomized. Comparison group did not have valve disease. No power calculation with small number of MHV pts.
Weiss 2013 (174) 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.	**Events (by hospital discharge) N (%)** / **Full dose LMWH N=210** / **Low dose LVWH N=210** / **p-value** Mortality 0.5% / 5.5% / 0.003 Thromboembolism 5% / 9% / 0.277 Bleeding 11% / 5% / 0.126 Hospital stay (d) 15.1±9.3 / 12.5±8.1 / 0.003	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%.

AF indicates atrial fibrillation; AVR, aortic valve replacement; DVR, double-valve replacement; FD, dull dose; GI, gastrointestinal; HD, half dose; LMWH, low molecular weight heparin; MHV, mechanical heart valve; MVR, mitral valve replacement; N/A, not available; NS, nonsignificant; pt(s), patient(s); TE, thromboembolism; UFH, unfractionated heparin; USA, United States of America; and, VKA, vitamin K antagonist.

Data Supplement 22. Fibrinolytic Therapy for Prosthetic Valve Thrombosis (Section 11.6.2)

Author, Year	Study Type	Patient Population		Intervention vs. Comparator (n)	Outcomes	Study Limitations
		Inclusion Criteria	Exclusion Criteria			
Deviri 1991 (175) 1993782	Observational, single center, surgical treatment for PVT, 1980–1989	n=100 (32 male) aged 5 mo–82 y (median 32 y) with PVT (n=61) or pannus (n=7), or both (n=44)	N/A	Only included pts undergoing surgery for PVT or pannus. AVR in 51 (48%), MVR in 49 (46%), and both in 6 (6%)	Early mortality 12.3% (n=13) Perioperative mortality higher in pts with NYHA IV (17.5%) vs. NYHA I-III (4.7%) symptoms, p<0.05 Same outcome between valve replacement vs. declotting	Older generation mechanical PHV, chart-recovered data, various diagnostic approaches.
Tong 2004 (176) 14715187	International registry of pts with suspected PVT, 1985–2001	107 pts (71 females; age 24 to 86 y) from 14 centers (6 in the U.S.) MVR=79, AVR=13, TVR=15	N/A	Only included pts with suspected PVT who underwent TEE and were treated with FT	Hemodynamic success rate 85% Overall complications rate 17.8% Death in 5.6% Independent predictors of complications: 1) thrombus area >0.8cm^2 (OR: 2.41 per cm^2, CI: 1.12–5.19) and 2) Hx of stroke (OR: 4.55, CI: 1.35–15.380) Presentation with shock was associated with clinical failure 10.7% vs. 0%; p=0.0032	Not all pts had PHV obstruction, thrombolysis criteria not standardized. Goal of study was to assess role of TEE measurement of thrombus burden.
Roudaut 2009 (177) 19427604	Observational, nonrandomized single center over 20 y, 1978–2001	n=263 episodes in 210 pts (98% left sided valves)	Decision for surgical vs. FT made by each clinician.	Surgery=136 Fibrinolysis=127	**Outcomes** / **Surgery N=136** / **FT N=127** / **p-value ….** Restored valve fx: 89% / 70.9% / <0.001 Mortality (6 y): 26% / 48% / 0.002 Thromboembolism: 0.7% / 15% / <0.001 Major Comp.: 11.1% / 25.2% / 0.05 Recurrent PVT: 11% / 25% / 0.021	Not randomized (standard clinical practice). Use of FT decreased over study interval. Older generation valves.
Karthikeyan 2009 (178) 19738134	Randomized, controlled, single Indian center	120 pts with first episode of left sided PVT	Contraindications to FT, symptom duration >2 wk, recurrent PVT	Accelerated infusion of streptokinase vs. conventional infusion	Complete clinical response: Accelerated=38/59 (64.4%) vs. Conventional=32/60 (53.3%), HR: 1.6, 95% CI: 0.9-2.5, p=0.055. Overall success rate 59%, with lower success rate (24%) in pts with NYHA III/IV symptoms. Composite secondary outcome (death, major bleeding, embolic stroke, systemic TE): HR: 1.4%,95% CI: 0.5–3.5; p=0.50 Major bleeding: HR: 2.2, 95% CI: 0.6–7.7, p=0.24	No surgical comparison group. Low success rate with both types of therapy.
Keuleers 2011	Retrospective,	n=31 PVT:	Contraindications	Surgery (n=18) compared	Surgery: 2 (11%) perioperative deaths,	Small numbers, no data on

Author, Year	Study Type	Patient Population		Intervention vs. Comparator (n)	Outcomes	Study Limitations
		Inclusion Criteria	Exclusion Criteria			
(179) 21211605	nonrandomized, single center, 1988–2008	MVR=17 (55%), AVR=8 (26%), TVR=6 (19%).	to FT	to FT (n=13)	FT: 2 (11%) recurrent PVT (follow-up 76 mo) 8 (61%) with restoration of normal valve function. 4 (31%) recurrent PVT (follow-up 18 mo) 4 (31%) major complications (death, stroke, TIA, or bleeding requiring surgery)	thrombus size
Özkan 2013 (66) 23489534	Observational , single center clinical experience, 1993–2009	TEE-guided FT in 182 consecutive pts with 220 episodes of PVT in 220 different episodes (156 women; mean age, 43.2±13.06 y).	Contraindications to FT, asymptomatic PVT with normal valve hemodynamics and no TE or with, thrombus size <10 mm.	FT regimen adjusted over study duration with Groups: **I**–Slow streptokinase **II**–Rapid streptokinase **III**–tPA 100 mg (bolus) **IV**–tPA 50 mg 6 h infusion **V**–tPA 25 mg 6 h infusion	**Outcomes** / **I** / **II** / **III** / **IV** / **V** / **p-value** **N** 16 41 12 27 124 Overall success 68.8% 85.4% 75% 81.5% 85.5% 0.46 Major nonfatal comp. 12.5% 12.2% 8.3% 11.1% 4.8% NS Death 12.5% 2.4% 16.7% 3.7% 0% 0.01 Multivariate predictors of mortality plus major nonfatal complications: Any thrombolytic therapy regimen other than Group V and a history of stroke/TIA.	
Karthikeyan 2013 (180) 23329151	Meta-analysis	Published articles on left-sided PVT with at least 5 pts each treated with surgery and FT	Lack of data on primary outcome (restoration of normal valve function)	7 studies with 690 episodes of left sided PVT, 446 treated with surgery, and 244 with FT.	**Outcomes** / **Surgery** N=446 / **FT** N=244 / **OR** / **p-value** Restored valve Fx 86.5% 69.7% 2.53, 95% CI: 0.94–6.78 0.066 Death 13.5% 9% 1.95, 95% CI: 0.63–5.98 0.244 Thromboembolism 1.6% 16% 0.10, 95% CI: 0.04–0.24 <0.001 Major Bleeding 1.4% 5% 0.27, 95% CI: 0.08–0.98 0.046 Recurrent PVT 7.1% 25.4% 0.25, 95% CI: 0.08–0.74 0.013	

AVR indicates aortic valve replacement; FT, fibrinolytic therapy; fx, function; Hx, history; MVR, mitral valve replacement, N/A, not available; NS, nonsignificant; NYHA, New York Heart Association; PHV, prosthetic heart valves; pts, patients; PVT, prosthetic valve thrombosis; TE, thromboembolism, TEE, transesophageal echocardiography; TIA, transient ischemic attack (stroke); TVR, tricuspid valve replacement; and, U.S., United States.

Data Supplement 23. 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
				Inclusion/Exclusion Criteria	Primary Endpoint & Results	Secondary Endpoint & Results	
Orszulak 1983 (181) 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 (182) 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 (183) 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%	Primary repair in 48%, prosthesis replacement in 52%	N/A
Pate 2006 (184) 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 (185) 11479246	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 (186) 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 (187) 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 EPO from 56–5% NYHA class improved by ≥1 in 28/35 pts	2 device embolizations 1 emergency surgery 1 vascular complication 1 procedural death
Sorajja 2011	To examine the feasibility and	Retrospective	Percutaneous repair of	78% mitral PVR, 22% aortic	Device deployment in 89%	Leaflet impingement in 4.3%	30-d events

Study Name, Author, Year	Study Aim	Study Type/Size (N)	Intervention vs. Comparator (n)	Patient Population	Endpoints		Adverse Events
				Inclusion/Exclusion Criteria	Primary Endpoint & Results	Secondary Endpoint & Results	
(188) 21791673	early outcome of percutaneous repair of PVR	N=115 pts (141 defects)	PVR	PVR Average STS risk score=6.9%	Mild or no residual regurgitation in 77% No procedural death	Procedure time average 147 min and decreased with case experience	Death, 1.7% Stroke, 2.6% Emergency surgery, 0.9%, Bleeding=5.2%
Sorajja 2011 (189) 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 regurgitation

EPO indicates erythropoietin; HF, heart failure; N/A, not applicable; NYHA, New York Heart Association; pts, patients; PVR, paravalvular regurgitation; STS, Society of Thoracic Surgeons; and, TEE, transesophageal echocardiography.

Data Supplement 24. Surgical Outcome in Infective Endocarditis (Section 12)

Author/ Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Study Intervention	Primary Endpoint	Predictors of Outcome
Jault, 1997 (190) 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 8 y. 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 mitral valve endocarditis were the predominant risk factors for late mortality. Risk factors for reoperation were younger age and aortic valve endocarditis.
Castillo, 2000 (191) 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 (192) 10881821	Single center experience in the surgical treatment of active culture-positive IE and identify determinants of early and late outcome	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 (194)	To derive and externally validate a prognostic	Retrospective multicenter cohort study	513	Pts with left-sided NVE with current	Registration of clinical information, sociodemographic data, comorbid conditions, previous heart disease,	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	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

Author/ Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Study Intervention	Primary Endpoint	Predictors of Outcome
12697795	classification system for pts with complicated left-sided native valve IE			indication of surgery in 45%`	symptoms, physical findings, blood cultures, electrocardiogram, echocardiography, type of surgery performed, and operative findings	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).	[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 (195) 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 (196) 15958370	To identify prognostic markers in 104 pts with PVE and the effects of a medical versus 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,	Describe the profile	Prospective	508	NVE 66%,	Brucella, Q fever, Legionella, and	Of these 508 episodes, 132 (34%) were electively	Univariate analysis identified renal failure, septic shock,

Author/ Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Study Intervention	Primary Endpoint	Predictors of Outcome
2007 (197) 17032690	of pts with left-sided IE who underwent urgent surgery and to identify predictors of mortality	multicenter cohort study		PVE 34%; surgery studied for the present report	Mycoplasma. Persistent infection despite appropriate antibiotic treatment (31%).	operated on, and 89 pts required urgent surgery (defined as prior to completion of antibiotic course). Primary 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%)	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 (198) 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 (199) 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.	The 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 remained associated with reduced overall mortality.
Aksoy, 2007 (200) 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 history of diabetes mellitus (HR: 4.81; 95% CI: 2.41–9.62), the presence of chronic intravenous catheters at the beginning of the episode (HR: 2.65; 95% CI: 1.31–5.33), and with increased mortality.
Tleyjeh,	To examined the	Matched	546	NVE alone;	Propensity score to undergo valve	Death occurred in 99 of the 417 pts (23.7%) in the	After adjustment for early (operative) mortality, surgery

Author/ Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Study Intervention	Primary Endpoint	Predictors of Outcome
2007 (201) 17372170	association between valve surgery and all-cause 6 mo mortality among pts with left-sided IE	propensity analysis		surgery 24%	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. Valve surgery was used as a time-dependent covariate in different Cox models.	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.	was not associated with a survival benefit (adjusted HR: 0.92; 95% CI: 0.48–1.76).
Tleyjeh, 2008 (202) 18308866	To examine the association between the timing of valve surgery after IE diagnosis 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 diagnosis 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 diagnosis).	The median time between IE diagnosis 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 diagnosis 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 versus late, a longer time to surgery was no longer significant, but remained in the protective direction.
Thuny, 2009 (203) 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 analyses.	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 (204)	Describe the morbidity and mortality associated	Retrospective single-center surgical	428	NVE 58%, PVE 42%; surgery 100%	Registration of epidemiological, clinical, microbiological and other laboratory features, echocardiography	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%;	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%

Author/ Year	Aim of Study	Study Type	Study Size (N)	Patient Population	Study Intervention	Primary Endpoint	Predictors of Outcome
22206953	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	cohort study			data, and treatment strategy	p<0.01), but long-term survival was not significantly different (35% vs. 29%; p=0.19).	vs. 18%; p=0.02) compared with non–*S. aureus* IE.
Kang, 2012 (205) 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 the AHA guidelines, and surgery was performed only if complications requiring urgent surgery developed during medical treatment or if symptoms persisted after the completion of antibiotic therapy.	The primary 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.

AHA indicates American Heart Association; HF, heart failure; ICU, intensive care unit, IE, infective endocarditis; NVE, native valve endocarditis; pts, patients; PVE, prosthetic valve; and *S. aureus,* Staphylococcus aureus.
Table modified from Prendergast BD and Tornos P. Surgery for infective endocarditis: who and when? Circulation 2010, 121:1141-1152.

Data Supplement 25.Outcomes in Pregnant Women With a Mechanical Prosthetic Valve Treated with Warfarin or Unfractionated Heparin (UFH) (Section 13.3.2)

Author, Year	Study Aim	Study Size (N)	Patient Population	Study Type	Type of Anticoagulation	Endpoints		Summary	Study Limitations
						Maternal	*Fetal*		
Chan, 2000 (206) 10647757	Systematic review anticoagulation mechanical valves	1,234 pregnancies in 976 women	All pts with mechanical prosthesis–40 articles–treated with differing anticoagulation regimens 1966–1997	Systematic review of literature	1. Warfarin throughout 2. UFH 1st trimester, then warfarin 3. UFH throughout pregnancy 4. No AC	Maternal Death 1. 1.8% 2. 4.2% 3. 15% 4. 4.7% Thromboembolic 1. 3.9% 2. 9.2% 3. 33% 4. 24%	Fetal anomalies 1. 6.4% 2. 3.4% 3. 0% 4. 3.3% Fetal wastage 1. 33% 2. 26% 3. 43% 4. 20%	Reduction of thromboembolic events for mother greatest with warfarin throughout pregnancy, worse maternal outcome with heparin throughout pregnancy. Heparin in 1st trimester reduces risk of fetopathic effects, but with increased risk of thromboembolic embolic events.	Retrospective systematic review–prior to LMWH use
Meschengieser, 1999 (207) 10377303	Single center experience anticoagulation mechanical valves	92 pregnancies in 59 women	Consecutive unselected pregnancies between 1986–1997	Observational	1. Warfarin throughout pregnancy 2. UFH 1st trimester, then warfarin 3. UFH throughout pregnancy 4. No A/C	Thromboembolic 1. 0.3 episodes/100 pt mo 2. 4.9 episodes/100 pt mo	Fetal wastage 1. 25% 2. 19%	Reduction of thromboembolic events for mother greatest with warfarin throughout pregnancy. No maternal deaths or valve thrombosis occurred in this study.	Retrospective review of small number pts–prior to LMWH use
Vitale, 1999 (208) 10334435	Single center experience anticoagulation mechanical valves	58 pregnancies in 43 pts	Consecutive unselected pregnancies between 1987–1997	Observational	Warfarin throughout pregnancy: A. Dose ≤5 mg vs. B. Dose >5 mg	Maternal Death None Valve thrombosis 2 pts	Fetal complications A. 4 SA and 1 GR (28/32 healthy babies) vs. B: 2 WE, 18 SA, 1 SB, 1 VSD (3/25 healthy babies)	First to show that fetal complications are dose-dependent, relatively safe if dose ≤5 mg	Retrospective review–only warfarin throughout was used
Salazar, 1996 (209) 8636556	Single center experience anticoagulation mechanical valves	40 pregnancies in 37 pts	Single center experience of a prospective protocol using UFH SQ during the 1st trimester	Prospective cohort trial	All pts had SQ UFH from 6–12 wk and then during the last 2 wks of gestation	2 cases of massive thrombosis of a MVR tilting disk. 1 death from GI bleeding during warfarin.	37% spontaneous abortion 2.5% neonatal death No embryopathy	UFH is a poor anticoagulant and does not prevent massive thrombosis	Trial stopped after 2 events occurred
Sbarouni, 1994 (210) 8130033	Questionnaire to all cardiac centers in Europe	214 pregnancies in 182 pts (133 with	Questionnaire sent 1994 to all cardiac centers in Europe	Questionnaire data	N/A	6 maternal deaths (4 valve thrombosis, 1 cerebral embolism, 1 pulmonary edema)	No embryopathies in 36 women on warfarin	Heparin is neither effective or safe for both fetus and mother with increased risk thromboembolism and bleeding	No detailed information on level of anticoagulation

Author, Year	Study Aim	Study Size (N)	Patient Population	Study Type	Type of Anticoagulation	Endpoints		Summary	Study Limitations
						Maternal	***Fetal***		
		mechanical prosthesis)				13 valve thrombosis–10/13 on heparin, 12/13 MVR 8 embolic events–5/8 heparin	Fetal outcome similar for warfarin vs. heparin–22% abortion and 10% stillbirths		dose. Selection bias of those who responded to the questionnaire
Al-Lawati 2002 (211) 12142189	Single center experience anticoagulation mechanical valves from country of Oman	63 pregnancies in 21 pts	Consecutive unselected pregnancies between 1983–1997	Observational	1. Warfarin throughout 2. UFH 1st trimester, then Warfarin	Thrombosis of valves 1. None 2. 2 pts	Fetal complications 1. 74% live babies 2. 71% live babies Spontaneous abortion 1. 26% 2. 14% No embryopathy (2 pts with 6 mg, rest with ≤5 mg)	Role of warfarin embryopathy overstated. Warfarin recommended, especially with low dose of warfarin. Valve thrombosis occurred only in pts with UFH during 1st trimester–none with warfarin.	Retrospective review—only warfarin throughout was used
Sadler 2000 (212) 10688509	Historical cohort of women with mechanical, bioprosthetic and homograft valves from New Zealand	147 pregnancies in 79 pts	All women in New Zealand who had valve replacement 1972–1992 and had subsequent pregnancy	Observational	1. Warfarin throughout pregnancy 2. Warfarin for 6 wk then subq UFH 3. Warfarin for 28 wk then subq UFH	Valve thrombosis 1. 0% 2. 20% 3. 0% Embolic events 1. 0% 2. 20% 3. 25% Hemorrhage 1. 3% 2. 30% 3. 25%	Pregnancy loss 1. 70% 2. 22% 3. 33%	Warfarin had high rate of fetal loss High rate of thromboemboli on heparin (29%) Bioprosthesis or homografts were associated with successful pregnancies	Retrospective review of small number pts—prior to LMWH use
De Santo 2005 (213) 15999035	Single center experience of all pts who had mechanical prosthesis and became pregnant	48 pregnancies in 37 pts	All women from a single center who had MVR 1975 to 2002 and had subsequent pregnancy	Observational	1. Warfarin throughout A. Dose ≤5 mg B. Dose >5 mg 2. 2 pts with UFH	2/2 pts with UFH had valve thrombosis No pt with warfarin had adverse cardiac or valve related event	1A. 2/23 (8.6%) adverse fetal event 1B. 17/21 (81%) adverse fetal event	If continue warfarin throughout pregnancy, there are no maternal events Adverse fetal events mainly if dose >5 mg	Retrospective review of small number pts—prior to LMWH use

AC indicates anticoagulation; GI, gastrointestinal; GR, growth retardation; LMWH, low molecular weight heparin; MVR, mitral valve replacement; N/A, not available; pts, patients; SA, spontaneous abortion; SB, still birth; SQ subcutaneous; UFH, unfractionated heparin; VSD, ventricular septal defect; and, WE, warfarin embryopathy.

Data Supplement 26. Outcomes in Pregnant Women With a Mechanical Prosthetic Valve Treated With Low Molecular Weight Heparin (LMWH) (Section 13.3.2)

Author, Year	Study Aim	Study Size (N)	Type of Anticoagulant	Patient Population	Study Type	Endpoints		Summary	Study Limitations
						Maternal	***Fetal***		
Rowan 2001 (214) 11568791	Examine pregnancy outcomes in women with mechanical prosthesis treated with LMWH throughout pregnancy	14 pregnancies in 11 women	LMWH throughout pregnancy	All pts with mechanical prosthesis treated with LMWH single center—1997–1999—fixed dose LMWH	Observational	One valve thrombosis 14.3% hemorrhage	9 live births 3 miscarriages 2 terminations	Can achieve successful pregnancy using LMWH throughout pregnancy, but risk of valve thrombosis	Use fixed dose LMWH with mean anti-Xa level 0.46 pre- and 0.89 post dose. Retrospective review of small number pts.
James, 2006 (215) 16966122	Examine pregnancy outcomes in women with mechanical prosthesis treated with LMWH throughout pregnancy	76 pregnancies	LMWH throughout pregnancy	Medline search of 73 cases 1966–2006 and 3 of single center using LMWH throughout pregnancy	Meta-analysis	22% thrombotic events 4% maternal mortality	No congenital anomalies 8 spontaneous abortions	Use of LMWH during pregnancy associated with high risk of life threatening thrombosis	No anti X-a levels performed. Meta-analysis only
Abildgaard, 2009 (216) 19162303	Examine pregnancy outcomes in women with mechanical prosthesis treated with LMWH throughout pregnancy	12 pregnancies in 12 women	LMWH throughout pregnancy	All pts with mechanical prosthesis treated with LMWH throughout pregnancy in country Norway—1997–2008—use anti-Xa levels	Observational	1 systemic embolism and 1 valve thrombosis (both subtherapeutic doses) Pooled risk of thromboembolism 7.1% vs. prior data 25% with UFH	13 healthy babies	If use anti-Xa levels, successful in 10/12 pregnancies, risk lower than UFH by retrospective comparison	Retrospective review of small number pts
Oran, 2004 (217) 15467905	Meta-analysis of pregnancy outcomes in women with mechanical prosthesis treated with differing anticoagulation regimens, including LMWH	10 reports (2 prospective) 81 pregnancies in 75 women	LMWH 1st trimester, then warfarin vs. LMWH throughout pregnancy	Medline search of studies in pts with prostheses receiving LMWH from 1989–2004	Meta-analysis	12% had thromboemboli–all MVR–all with LMWH throughout–9/10 did not have anti-Xa monitoring. Valve thrombosis 8.6%	Spontaneous abortion in 7.4% Stillbirth in 1.2% 87% live births	All thromboemboli occurred in pts with mitral prosthesis who had LMWH throughout pregnancy. Anti Xa levels were not monitored in 90% of thromboembolic events.	Meta-analysis only
McLintock, 2009 (218) 19681850	Examine pregnancy outcomes in women with mechanical prosthesis treated with differing anticoagulation regimens including LMWH	47 pregnancies in 31 women	Warfarin throughout pregnancy vs. LMWH 1st trimester, then warfarin vs. LMWH throughout pregnancy	All pts with mechanical prosthesis treated with differing anticoagulation regimens including LMWH—2 centers—1997–2008—use anti-Xa levels	Observational	Thromboembolism 7 total–5 (10.6%) LMWH Antepartum bleeding 10.6% LMWH Postpartum bleeding 12.7% LMWH	96% live births with LMWH vs. 75% live births with warfarin	Poor compliance or subtherapeutic anti-Xa levels were present in all valve thrombosis on LMWH	Retrospective review of small number pts

Author, Year	Study Aim	Study Size (N)	Type of Anticoagulant	Patient Population	Study Type	Endpoints		Summary	Study Limitations
						Maternal	***Fetal***		
Yinon, 2009 (219) 19840573	Examine pregnancy outcomes in women with mechanical prosthesis treated with LMWH throughout pregnancy	23 pregnancies in 17 women	LMWH throughout pregnancy	All pts with mechanical prosthesis treated with LMWH—single center 1998–2008—use anti-Xa levels	Observational	1 (4%) maternal thrombosis died 5 (22%) pulmonary edema, arrhythmias, and endocarditis 13% postpartum hemorrhage	19 live births 2 first trimester miscarriages 2 intrauterine deaths	Even with careful monitoring of anti X-a levels thrombosis may occur, even with low risk AVR	Retrospective review of small number pts
Quinn, 2009 (220) 19880782	Examine pregnancy outcomes in women with mechanical prosthesis treated with LMWH throughout pregnancy	12 pregnancies in 11 women	LMWH throughout pregnancy	All pts with mechanical prosthesis treated with LMWH—single center—2001–2007—use anti-Xa levels	Observational	3 major bleeds 3 minor bleeds BS MVR thrombosis 1 pt (Xa level not done and later subtherapeutic)	11/12 live births	Increasing dose LMWH during pregnancy necessary Only valve thrombosis occurred in pt with subtherapeutic level Xa	Retrospective review of small number pts

AVR indicates aortic valve replacement; BS, Bjork-Shiley; GI, gastrointestinal; LMWH, low molecular weight heparin; MVR, mitral valve replacement; N/A, not available; pts, patients; UFH, unfractionated heparin; and, SES, socioeconomic status.

Data Supplement 27. Outcomes With the Maze Procedure for Atrial Fibrillation in Patients With Valvular Heart Disease (Section 14.2.2)

Author, Year	Aim of Study	Study Type	Study Size (N)	Study "Intervention" Group (n)	Study Comparator Group (n)	Outcomes
Prognostic Significant of AF at Time of Surgery						
Eguchi et al 2005 (221) 15845559	Examine impact of preoperative AF on outcome of MV repair for 1° MR	Retrospective observational	283 pts with moderate-to-severe MR who underwent MV repair between 1991 and 2002	129 in AF Age 59±13 y 60% male	154 in NSR Age 52±14 y 67% male	5 y outcomes were better in pts in NSR vs. AF for: survival (96±2.1 vs. 87±3.2%; p=0.002) and freedom from cardiac events (96±2.0 vs. 75±4.4%; p<0.001)
Alexiou 2007 (222) 17280837	Impact of preoperative AF on early and late outcome after MV repair	Retrospective observational	349 pts undergoing MV repair for primary MR	152 (44%) in AF	197 (56%) in NSR	Kaplan-Meier survival at 7 y was 75±6% for AF pts vs. 90±3% (p=0.005) for SR pts.
Ngaage 2006 (223) 17643612	Prognostic significance of preoperative AF at the time of AVR	Retrospective observational, cohort comparison	381 AVR 1993 and 2002 matched for age, gender, and LVEF	Preoperative AF (n=129)	Preoperative NSR (n=252)	Pts with preoperative AF had had worse late survival (RR for death=1.5; p=0.03) with 1-, 5-, and 7-y survival rates of 94%, 87%, and 50%, respectively, for those in AF vs. 98%, 90%, and 61% for pts in SR preoperatively. Pts with AF more frequently developed HF (25% vs. 10%; p=0.005) and stroke (16% vs. 5%; p=0.005). By multivariable analysis, preoperative AF was an independent predictor of late adverse cardiac and cerebrovascular events, but not late death.
Predictors of Return of Sinus Rhythm After Valve Surgery						
Chua 1994 (224) 8302059	Determine frequency of reversion to NSR after MV repair among pts with preoperative AF	Retrospective, observational	323 consecutive pts who underwent surgical MV valvuloplasty for MR from 1980–1991	97 in AF before surgery	216 in NSR before surgery	At late follow-up (mean 2.6 y, range 3 mo–10 y), AF was present in 5% pts with preoperative NSR, 80% pts with preoperative chronic AF, and 0% pts with preoperative recent onset AF (p<0.01)
Obadia 1997 (225) 9270633	Determine predictors for return to NSR after MVR	Retrospective, observational	191 pts undergoing surgery for MVR	Preoperative AF in 96 (50%)	Preoperative NSR in 95 (40%)	The probability of return to stable NSR was 93.7% when NSR was already present before the operation and 80% when AF was intermittent or of less than 1 y duration; probability of postop NSR declined abruptly for preoperative duration of AF >1 y
Jessurun 2000 (226) 10814915	Outcome analysis of arrhythmias after MV surgery	Retrospective, observational	162 consecutive pts undergoing MV surgery between 1990 and 1993	Preoperative chronic AF in 74 (46%) and paroxysmal AF in 29 (18%)	Preoperative NSR in 59 (36%)	NSR present postop in 40 of 57 (70%) pts with preop NSR. AF present postop in 58 of 68 (85%) of pts with preop chronic AF (>1 y). NSR present postop in 10 of 29 (34%) pts with preoperative paroxysmal AF.
Outcomes With Surgical Maze for AF						
Deneke 2002 (227) 11922646	Efficacy of a modified maze procedure in pts with chronic AF undergoing MVR	Prospective randomized	30 consecutive pts undergoing MVR	Modified maze at time of MVR	MVR alone	After 12 mo, NSR was present significantly more often in pts undergoing modified maze (cumulative rate NSR=0.800) compared to pts with MV replacement alone (0.267) (p<0.01)

Author, Year	Aim of Study	Study Type	Study Size (N)	Study "Intervention" Group (n)	Study Comparator Group (n)	Outcomes
Akpinar 2003 (228) 12895612	Assess the feasibility and effectiveness of irrigated RF modified maze procedure through a port access approach during MV surgery	Prospective randomized	67 pts with chronic AF eligible for port access MV surgery	33 irrigated RF modified Maze procedure	34 valve procedure alone	100% of pts who underwent RF modified maze were free of AF at the end of the operation (76% NSR, 24% pacemaker) compared with 41% of those who underwent MV repair alone. At 6 and 12 mo freedom from AF was 87.2 and 93.6% for those undergoing RF maze and 9.4% (p=0.0001) for those undergoing MVR alone
Jessarun 2003 (229) 12627066	Assess outcome of combining the Maze III procedure with MV surgery	Prospective. randomized (2.5:1 ratio)	35 pts with AF undergoing MVR. Mean age 64 y	Maze III in 25	MVR along in 10	Freedom from AF in the maze + MVR group was 56% at discharge and 92% at 12 mo. MVR alone group, freedom from AF was 0% at discharge and 20 at 1 y. Group differences at discharge p=0.002 and at 1 y p=0.0007.
Abreu Filho 2005 (230) 16159816	Evaluate effectiveness of maze procedure for permanent AF in pts with rheumatic MV disease	Prospective randomized	70 consecutive pts (2002−03) with rheumatic MV disease and permanent AF	MV surgery plus Maze III procedure saline-Irrigated cooled-tip RF ablation	MV surgery alone	Cumulative rates of NSR were 79.4% for those undergoing maze and 26.9% for those undergoing mitral surgery alone (p=0.001). Group differences were significant at discharge (p=0.002), after 12 mo (p=0.0007).
Doukas 2005 (231) 16278360	To determine whether intraoperative RF ablation increases the long-term restoration of NSR and improves exercise capacity	Randomized, double-blind trial	97 pts referred for MV surgery with AF for at least 6 mo	MV surgery plus RF left atrial ablation	MV surgery alone	At 12 mo NSR was present in 20 (44.4%) of 45 RFA pts and in 2 (4.5%) of 44 controls, RR: 9.8; 95% CI: 2.4–86.3; p<0.001
Von Oppell 2009 (232) 19233678	Evaluate the effect of maze procedure on postop AF in pts undergoing MV surgery	Prospective randomized	49 pts undergoing MV surgery with AF of more than 6 mo duration in 2004−06	MV surgery plus RF maze procedure (n=24)	MV surgery plus intensive rhythm control strategy (n=25).	At discharge, 3 and 12 mo follow-up, more pts in the maze group returned to NSR compared to control (29%, 57% and 75% vs. 20%, 43% and 39%; p=0.030).
Cheng 2010 (233) 22437354	To determine if surgical maze ablation for AF improves clinical outcomes and resource utilization	Meta-analysis	4647	Adults with persistent and permanent AF undergoing maze surgical ablation at the time of cardiac surgery	Persistent or permanent AF undergoing cardiac surgery without maze procedure	The number of pts in NSR was significantly improved at discharge in the surgical AF ablation group (68.6%) versus the surgery alone group (23.0%) in RCTs (OR: 10.1, 95% CI: 4.5-22.5) and non-RCTs (OR: 7.15, 95% CI: 3.42-14.95). Meta-analysis includes both coronary bypass and valve surgery (numbers not stated).
Long-Term Outcomes After Surgical Maze Procedure						
Bando 2003 (234) 12928631	Identify risk factors for mortality and stroke after mechanical MVR	Retrospective	812 pts undergoing MVR between 1977−2001. Chronic AF present in 630 (78%)	In addition to MVR: 493 (61%) had LV appendage closure 148 (18%) had LA plication 185 (23%) had maze procedure 348 (43%) had tricuspid	Endpoints were early and late mortality and freedom from stroke	At 8 y, freedom from stroke was significantly greater in pts with MVR plus maze (99%) compared to MVR alone (89%, p<0.001) Of 72 pts with late stroke, 65 (90%) were in AF and 47 (65%) had LA appendage closure. Multivariate analysis show that late AF (OR: 3.39; 95% CI: 1.72–6.67; p=.0001) and omission of the maze procedure (OR: 3.40; 95% CI: 1.14–10.14; p=0.003) were significant risk factors for

Author, Year	Aim of Study	Study Type	Study Size (N)	Study "Intervention" Group (n)	Study Comparator Group (n)	Outcomes
				annuloplasty.		late stroke.
Bum Kim 2012 (235) 22456472	Evaluate long-term benefits of the maze procedure in pts with chronic AF undergoing mechanical MVR	Retrospective, observational	569 pts undergoing mechanical MVR between 1997−2010	317 with MVR plus a concomitant maze procedure	252 with MVR alone	Pts who had undergone the maze procedure were at similar risks of death (HR: 1.15; 95% CI: 0.65–2.03; p=0.63) and the composite outcomes (HR: 0.82; 95% CI: 0.50–1.34; p=0.42), but a significantly lower risk of thromboembolic events (HR: 0.29; 95% CI: 0.12–0.73; p=0.008) compared with those who underwent valve replacement alone
Malaisrie 2012 (236) 22808837	Determine the impact of concomitant AF ablation in pts undergoing AVR	Retrospective, observational	124 pts (mean age 74±12 y) with pre-existing AF undergoing AVR	80 (65%) had concomitant surgical AF ablation	44 had AVR alone	Postop freedom from AF when not receiving anti-arrhythmic drugs occurred in 58 pts (82%) in the ablation group, compared to 8 (36%) in the nonablation group (p<0.001)
Liu 2010 (237) 20573636	Compare pulmonary vein isolation versus maze procedure for treatment of permanent AF	Prospective randomized	99 with rheumatic heart disease and permanent AF	49 with valve surgery plus circumferential pulmonary vein isolation	50 with valve surgery plus maze procedure for AF	After one procedure, pts undergoing the maze procedure had a significantly higher freedom from atrial arrhythmias (82% vs. 55.2%, p<0.001). At 15–20 mo follow-up, cumulative rates of sinus rhythm were 71% vs. 88% (p<0.001).

1° indicates primary; AF, atrial fibrillation; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; LA, left atrial; LV, left ventricle; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MV, mitral valve; MVR, mitral valve replacement; NSR, normal sinus rhythm; preop, preoperative; postop, postoperative; pts, patients; RCT, randomized clinical trial; RF, radiofrequency; RFA, radiofrequency ablation; and, SR, sinus rhythm.

Data Supplement 28. Noncardiac Surgery in Patients With Valvular Heart Disease (Section 15.3)

Study Name, Author, Year	Aim of Study	Study Type	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Endpoints		Predictors of Adverse Outcomes	Study Limitations
					Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint (Efficacy) and Results*	*Secondary Endpoint and Results*		
Aortic Stenosis										
Agarwal 2013 (238) 23481524	Compared outcomes with noncardiac surgery in pts with moderate vs. severe AS.	Retrospective surgical and echocardiographic database	634 pts with AS; 244 with severe AS and 390 with moderate AS	2,536 controls without AS propensity matched for 6 revised cardiac risk index criteria plus age and sex.	Severe AS defined as valve area <1 cm^2. Moderate AS as valve area 1.0–1.5 cm^2	Emergency surgery.	Combined primary endpoint of 30-d mortality plus MI occurred in 4.9% of pts with AS vs. 2.1% in controls (p<0.001)	30-d mortality was 2.1% for pts with AS vs. 1.0% in non-AS controls (p=0.036). Post-op MI occurred in 3.0% of AS vs 1.1% of controls (p=0.001).	Predictors of adverse outcomes in AS were symptomatic severe AS, MR, coronary disease.	Some pts with AS were symptomatic. Not an RCT.
Calleja 2010 (239) 20381670	Evaluate post-op outcomes of pts with asymptomatic, severe AS	Retrospective	30 pts with asymptomatic severe AS undergoing noncardiac surgery.	60 pts with mild-moderate AS age and sex matched.	Noncardiac surgery, intermediate risk severe AS vs. mild or moderate AS=77% vs. 83%, ASA 3=63% vs. 62%, general anesthesia=73% vs. 82%.	AR >moderate, symptomatic AS.	Composite endpoint (hospital mortality, MI, HF, arrhythmia, and hypotensive requiring vasopressors) in severe AS: 10/30 (33%) vs. 14/60 (23%) in those with mild to moderate AS; p=0.06; MI: 3% in both groups; p=0.74	Hypotension AS severe: 9/30 (30%) vs. AS mild/moderate: 10/60 (17%); p=0.11.	For severe AS: Hypotension OR: 2.5, CI: 0.8–7.6; p=0.11, MI OR: 0.63, CI: 0.04–10; p=0.74.	Use of composite endpoint. Majority of pts underwent intermediate (not high) risk noncardiac surgery.
Leibowitz 2009 (240) 19287130	Outcome of pts with AS undergoing hip fracture repair	Retrospective	Pts with AS (n=32)	Age-matched control (n=88)	Elderly pts >70 y, with AVA <1 cm^2	N/A	30-d mortality AS=6.2%, control=6.8%	Cardiac event rate (death, ACS, pulmonary edema): AS=18.7%, control=11.8%	N/A	Retrospective, 50% of anesthetics were regional techniques
Zahid 2005 (241) 16054477	Evaluate the perioperative risk of noncardiac surgery in pts with AS	Retrospective Based on National Hospital Discharge Survey	AS=5,149	AS-no=10,284 age/surgical risk matched	Noncardiac surgery (1996–2002)	Cardiac surgery	The presence of AS is not a significant predictor for mortality after adjusting for all significant univariate predictor of in-hospital death.	The presence of AS increased the likelihood of AMI (3.86% in AS vs. 2.03% in controls, p<0.001): OR: 1.55, 95% CI: 1.27–1.9; p<0.001	N/A	Pts with AS more likely to have concomitant CAD and CHF, controls more likely to have DM and HTN.
Torsher 1998	Outcomes of pts with AS	Retrospective	Severe AS=19	N/A	Noncardiac	N/A	In selected pts with severe AS, the risk of noncardiac	N/A	N/A	Coexisting mild AR=9, moderate

Study Name, Author, Year	Aim of Study	Study Type	Study Intervention Group (n)	Study Comparator Group (n)	Patient Population		Endpoints		Predictors of Adverse Outcomes	Study Limitations
					Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint (Efficacy) and Results*	*Secondary Endpoint and Results*		
(242) 9485135	undergoing noncardiac surgery						surgery is acceptable: Death=2, hypotension was frequent (14 pts)			AR=4, mild MR=12, balloon aortic valvuloplasty=2
Mitral Regurgitation										
Lai 2007 (243) 17383316	Perioperative outcome of pts with MR undergoing noncardiac surgery	Retrospective	84 pts with moderate-severe MR	NA	Undergoing noncardiac surgery	Tracheal intubation prior to noncardiac surgery	Intraoperative course had frequent (31%) minor complications: controllably hypotension and bradycardia	Post-op complications were serious: Death=11.9%, MI=0, Vtach/fib=4.8%, pulmonary edema=23.8%	For post-op complications: AF OR: 3.058, CI: 1.02–9.14, intermediate surgical risk=5.12, CI: 1.28–20.4, low LVEF: 0.96, CI: 0.92–0.99	N/A
Aortic Regurgitation										
Lai 2010 (244) 19930243	Perioperative outcome of chronic, moderate-severe AR who undergo noncardiac surgery	Retrospective (1999–2006)	Chronic, moderate-severe AR=167	Case-matched=167	Chronic moderate-severe AR	N/A	Prolonged intubation and acute pulmonary edema: 16.2% vs. 5.4%; p=0.003, Death: AR=9% vs. 1.8%; p=0.008	LVEF, renal dysfunction, high surgical risk and no cardiac meds predictors of in-hospital death in pts with AR intraoperative hypotension and bradycardia were similar between groups	N/A	N/A

ACS indicates acute coronary syndrome; AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; ASA, aspirin; AVA, aortic valve area; CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; N/A, not applicable; pts, patients; and, post-op, postoperative.

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