Introduction

Given the increasing life expectancy, improvement in cardiovascular disease prevention and therapy, and technological advancements, the number of individuals with treatable structural heart or complex obstructive epicardial coronary artery disease (CAD) is rapidly expanding. Epidemiological studies support this notion, as evidenced by the following: (I) a prevalence of moderate or severe valvular heart disease estimated to be 23% in tertiary-care referral settings, of which 40% have concurrent CAD; (II) the prevalence of valve disease increases from 17% in those <45 years old to 28% of patients aged >75 years; (III) nearly half of patients are treated conservatively due to perceived or realized surgical risks; and (IV) despite a decrease in overall CAD burden in the United States over the past two decades, the rate of myocardial infarction and necessity for aggressive secondary prevention has remained steady (1-5).

This year's major societal scientific sessions exemplified the research and efforts underway to study and apply less invasive methods of valvular and complex coronary interventions to the aforementioned populations, in hopes of improving patient outcomes and expanding treatment indications. Transcatheter aortic valve replacement (TAVR), percutaneous mitral and tricuspid valve therapy, and complex coronary interventions, were the focus of important clinical trials and registry data. Herein, we provide a select and concise review of the most pivotal studies presented.

Keywords: Percutaneous coronary intervention (PCI); COAPT; MitraClip; PARTNER; transcatheter aortic valve replacement (TAVR)
A prospective, randomized, controlled, multicenter study to establish the safety and effectiveness of the SAPIEN 3 transcatheter heart valve in low risk patients who have severe, calcific, aortic stenosis requiring aortic valve replacement (PARTNER 3 Trial)

Over the last decade, TAVR has surpassed SAVR as the treatment of choice for severe symptomatic aortic stenosis (AS) in intermediate and high-risk patients (1,2). However, a majority of patients with severe symptomatic AS have a low surgical risk (Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score ≤4%) and evidence of TAVR benefit in this patient population is extrapolated from intermediate and high-risk studies, and registry data.

The PARTNER 3 trial addressed this issue by randomizing 1,000 low surgical risk patients with severe AS (STS <4%) to undergo TAVR (n=503) with a balloon-expandable SAPIEN 3 valve (Edwards Lifesciences; Irvine, CA, USA) or bioprosthetic SAVR (n=497) (6). Patients with bicuspid aortic valves (BAV), complex CAD, and severe multivalve disease were excluded. The mean age and STS score of the patients was 73 years and 1.9%, respectively, and 30.7% were women. Primary statistical analysis was used in the as-treated population with non-inferiority hypothesis (margin 6%), followed by superiority if the non-inferiority threshold was met.

The primary composite end point of death, stroke, or rehospitalization at 1 year was significantly lower in the TAVR group compared with SAVR (HR 0.54; 95% CI: 0.37-0.79; P=0.001). At 30 days, TAVR was associated with decreased rates of stroke (P=0.02), death or stroke (P=0.01), and new-onset atrial fibrillation (P<0.001), and a shorter hospital length of stay (3 vs. 7 days, P<0.001). Moderate or severe paravalvular was present in 0.6% in TAVR group vs. 0.5% in SAVR group at 1 year (P=1.00). No significant differences between the approaches in vascular complications or permanent pacemaker implantations were observed. In low-risk patients with severe symptomatic AS, TAVR reduced the 1-year primary endpoint of death, stroke, or rehospitalization by 46%.

The main limitations of PARTNER 3 are the short-term follow-up that precludes insight into TAVR prosthesis thrombosis and degeneration, and incomplete echocardiographic follow-up data. Nevertheless, this trial indicates that TAVR is likely to become the preferred treatment strategy in low-risk surgical patients with severe AS. Long-term follow up outcomes will continue up to 10 years.

Evolut surgical replacement and transcatheter aortic valve implantation in low risk patients

Similar to the PARTNER trials utilizing a balloon-expandable valve, the self-expandable valve system has also been shown to have superior outcomes in patients with severe AS at high or prohibitive surgical risk, and non-inferior outcomes in the intermediate-risk population (7,8). The objective of this trial was to compare the outcomes between TAVR and SAVR in patients with severe symptomatic AS at low surgical risk using a self-expanding valve system.

The Evolut low-risk investigators performed a randomized noninferiority trial involving 1,403 low surgical risk patients with severe symptomatic AS (STS-PROM score ≤3%) allocated to undergo TAVR (n=725) or SAVR (n=678) (9). The TAVR were performed with one of three self-expanding bioprostheses (CoreValve, Evolut R, or Evolut PRO; Medtronic, Minneapolis, MN, USA). The primary efficacy and safety composite outcomes were death from any cause or disabling stroke at 24 months. The mean age of the patients was 74 years, 34.9% were women, and the mean STS-PROM score measured 1.9%.

The primary composite outcome occurred in 5.3% in the TAVR group vs. 6.7% in the SAVR group (P<0.05 for noninferiority; P>0.05 for superiority). At 30 days, patients in the TAVR group had a lower incidence of stroke (0.5% vs. 1.7%), bleeding complications (2.4% vs. 7.5%), acute kidney injury (0.9% vs. 2.8%), and atrial fibrillation (7.7% vs. 35.4%) compared with SAVR. TAVR patients were also found to have a higher incidence of moderate or severe paravalvular regurgitation (3.5% vs. 0.5%) and pacemaker implantation (17.4% vs. 6.1%). Hemodynamic parameters of prosthetic valve function at 12 months were superior in patients having undergone TAVR vs. SAVR (mean transvalvular gradient: 8.6 vs. 11.2 mmHg; effective orifice area: 2.3 vs. 2.0 cm²). Both groups had similar functional improvement at 12 months. Of note, patients with BAV were excluded from the trial.

In low surgical risk patients with severe symptomatic AS, TAVR with the self-expanding CoreValve was noninferior to SAVR with respect to hard clinical endpoints; however, TAVR patients had a higher incidence of significant paravalvular regurgitation and permanent pacemaker implantation. This latter point is salient, as these conditions are associated with increased morbidity and mortality (10,11).
Outcomes of TAVR with a Balloon-Expandable Sapien 3 valve in bicuspid aortic stenosis: an analysis of the Society of Thoracic Surgeons/American College of Cardiology (STS/ACC) transcatheter valve therapies (TVT) registry

The objective of this study was to compare the outcomes of TAVR for severe AS with a balloon-expandable SAPIEN 3 valve in BAV (n=2,726) vs. tri-leaflet aortic valves (TAV) (n=79,096) as reported in the STS/ACC TVT Registry (12). A 1:1 propensity-matched analysis was performed in a cohort of 5,382. The median age was 74 years, mean STS-PROM score measured 5.0%, and 39.1% were women. The primary composite outcomes were 30-day and 1-year mortality and stroke; secondary outcomes included procedural complications, valve hemodynamics, and quality-of-life assessment.

In the adjusted analysis, all-cause mortality at 30 days (2.6% vs. 2.5%; HR 1.04; 95% CI: 0.74–1.47) and 1-year (10.5% vs. 12.0%; HR 0.90; 95% CI: 0.73–1.10) was not significantly different between patients with BAV vs. TAV. The rate of moderate or severe paravalvular leak (3.2% vs. 2.5%) and improvement in quality of life score (KCCQ score: −2.4 vs. −5.1; P=0.08) at 1-year were also similar. However, there was a greater prevalence of stroke (2.4% vs. 1.6%; P=0.02), pacemaker implantation (9.1% vs. 7.5%; P=0.03), conversion to surgery (0.9% vs. 0.4%; P=0.03), and aortic annular rupture (0.3% vs. 0.0%; P=0.02) in BAV.

The outcomes of TAVR in BAV are improving when compared to prior observational studies (13,14). TAVR appears effective, however, there exists a higher risk of stroke, pacemaker implantation, and aortic trauma amongst patients with BAV. Randomized trials are needed to discern the true risk vs. benefit of TAVR in BAV, with risk stratification and treatment approach individualized for each patient.

Randomized comparative effectiveness study of complete versus culprit-only revascularization strategies to treat multi-vessel disease after early percutaneous coronary intervention for ST-segment elevation myocardial infarction (COMPLETE Trial)

Percutaneous coronary intervention (PCI) is the gold standard of myocardial revascularization and reperfusion for patients with ST-elevation myocardial infarction (STEMI) (15,16). Non-culprit lesion stenting vs. conservative management with guideline directed medical therapy (GDMT) alone is a common dilemma; published data suggests a possible reduction in clinical events with complete myocardial revascularization (17-20).

The COMPLETE trial randomized 4,041 patients to a strategy of complete (n=2,016) vs. culprit-lesion-only (n=2,025) revascularization in the setting of STEMI and multivessel CAD (20). Clinically significant non-culprit lesions were diagnosed if at least 70% of the vessel diameter on visual estimation was stenosed, or with 50% to 69% stenosis accompanied by a fractional flow reserve measurement ≤0.80. The main exclusion criteria were pre-randomization planning for non-culprit lesion stenting or surgical revascularization, or previous coronary artery bypass graft (CABG) surgery. Randomization was performed no later than 72 hours after the index PCI, and complete revascularization was mandated within 45 days of discharge in the culprit-lesion-only PCI group. Dual antiplatelet therapy with aspirin and ticagrelor for at least 1 year was recommended.

Mean age was 61 years, 20% were females, and 20% had diabetes mellitus. At discharge 99% were on aspirin, 64% on ticagrelor, and 25% on clopidogrel, with excellent adherence to GDMT for secondary prevention. At a mean follow up of 36.2 months the first co-primary outcome of death from cardiovascular (CV) causes or new myocardial infarction (MI) occurred in 7.8% vs. 10.5% of the complete vs. culprit lesion-only PCI groups (HR 0.74; 95% CI: 0.60–0.91; P=0.004). The second coprimary composite outcome of death from CV causes, new MI, or ischemia driven revascularization was also significantly decreased in the complete revascularization group (8.9% vs. 16.7%; HR 0.51; 95% CI: 0.43–0.61; P<0.001). Landmark analyses revealed that the early clinical benefit of complete revascularization was driven by decreased ischemia-driven revascularization, while late benefit was centered on attenuated risks for CV mortality and MI.

Despite having non-blinded inclusion criteria in regards to the timing of non-culprit lesion PCI and angiographic findings, the COMPLETE trial provides strong evidence that total myocardial revascularization both at index hospitalization or within a short-term follow-up period after STEMI, improves morbidity and mortality in this high-risk population.
Synergy between PCI with TAXUS and cardiac surgery: extended survival (10-Year) follow-up of the multicenter randomized controlled SYNTAX trial (SYNTAXES study)

The SYNTAX Extended Survival Study (SYNTAXES) presents the 10-year outcomes from the SYNTAX trial, which compared PCI (n=903) using first-generation Paclitaxel-eluting stents with CABG (n=897) in patients with three-vessel or left main CAD (21,22). The mean age was 65 years, 22% were female, mean SYNTAX score measured 29, left main CAD was present in 40%, and 60% had three-vessel CAD. At 10 years post-revascularization, all-cause mortality was observed in 27% of the PCI group vs. 24% of the CABG group (HR 1.17; 95% CI: 0.97–1.41; P=0.092). In landmark analyses, patients with three-vessel CAD had a higher mortality when treated with PCI as compared with CABG (28% vs. 21%; HR 1.41; 95% CI: 1.10–1.80), while no difference was observed in left main CAD (26% vs. 28%; HR 0.90; 95% CI: 0.68–1.20). Additionally, there was no treatment interaction between PCI and CABG in diabetic patients (P=0.66) or in mild (SYNTAX score ≤22) to moderately complex (SYNTAX score 23–31) CAD; in patients with CAD and SYNTAX score ≥33, CABG may be the preferable option (10-year all-cause mortality: PCI 34% vs. CABG 26%; HR 1.41; 95% CI: 1.05–1.89).

An important limitation to the present data is the lack of details regarding the primary endpoint of all-cause death; the study did not differentiate between non-cardiac and cardiac mortality, the latter of which can result from myocardial infarction, stent thrombosis, or bypass graft occlusion. An additional caveat was the use of first-generation Paclitaxel-eluting stents for PCI, which have been surpassed with regards to clinical outcomes by the current durable polymer intracoronary stents (23,24). Nevertheless, the SYNTAXES study provides impressive 10-year follow-up which showed a survival benefit with CABG in patients with three-vessel disease, but not in patients with isolated left main CAD.

Percutaneous repair or medical treatment for secondary mitral regurgitation: reconciling the 2-year outcomes of the COAPT and MITRA-FR trials

Secondary mitral regurgitation (MR) is a consequence of left ventricular (LV) remodeling and papillary muscle displacement, which results in mitral valve leaflet tethering and incomplete systolic closure (25–27). The mainstay of treatment is GDMT and neurohormonal blockade for heart failure (HF) with reduced ejection fraction (28,29). While surgical mitral valve replacement provides a more durable correction of secondary MR as compared with repair, to date neither approach has been shown to significantly impact survival (30,31).

The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial compared percutaneous edge-to-edge mitral valve repair (MitraClip system, Abbott Vascular, Chicago, IL, USA) plus GDMT (n=302) vs. GDMT alone (n=312) for moderate to severe secondary MR (32). The mean age, MR effective regurgitant orifice area (EROA), LV end-diastolic volume index, and LV ejection fraction were 72 years, 0.4 cm², 193 mL, and 31%. At 24-month follow-up, MitraClip plus GDMT was associated with decreased all-cause mortality (29% vs. 46%; HR 0.62; 95% CI: 0.46–0.82; P<0.001) and HF hospitalizations (36% vs. 68%; HR 0.53; 95% CI: 0.4–0.7; P<0.001) when compared with GDMT alone. These outcomes were observed out to a 36-month preliminary analysis; additionally, patients crossing over from GDMT only to MitraClip treatment at 24 months had a 57% reduced risk of mortality or heart failure hospitalization in the subsequent 12 months post-intervention (33).

Conversely, the smaller Multicentre Randomized Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation (MITRA‐FR) trial enrolled 304 patients in a 1:1 fashion to receive MitraClip plus GDMT vs. GDMT alone (n=152 each) (34). The mean age, EROA, LV end-diastolic volume index, and LV ejection fraction were 70 years, 0.31 cm², 101 mL/m², and 33%, respectively. At 24-month follow-up, there was no difference in all-cause mortality (34.9% vs. 34.2%; HR 1.02; 95% CI: 0.70–1.50) or HF hospitalizations (55.9% vs. 61.8%; HR 0.97; 95% CI: 0.72–1.30) between the MitraClip plus GDMT vs. GDMT only groups (35).

The COAPT and MITRA‐FR trials were divergent, however, they reconciled each study’s main findings. Firstly, the cohort enrolled in COAPT had more severe MR and less remodeled left ventricles at the time of intervention when compared with MITRA‐FR. The extent of LV remodeling at baseline and its persistence after mitral valve intervention are powerful predictors of outcomes (36,37). The prevalence of a baseline EROA <0.3 cm² was far lower in COAPT (14% vs. 52%), and importantly, the COAPT
subgroup that did not experience a benefit with MitraClip had a similar extent of LV remodeling and MR severity as MITRA-FR (EROA <0.3 cm² + LV end-diastolic volume index >96 mL/m²) (38). Secondly, GDMT was maximally tolerated in COAPT enrollees but continually adjusted according to practice guidelines in MITRA-FR. Patients in MITRA-FR may have benefited from up-titration of their neurohormonal blockade during the trial period, which influences the severity of MR based on its close dependence to LV function, hemodynamics, and volume load (39,40). Finally, a substantial amount of echocardiographic analyses and quality-of-life metrics were missing from the final MITRA-FR analysis, imparting an important selection and attrition bias when interpreting the data.

In summary, the COAPT and MITRA-FR trials complementarily showed that in addition to GDMT, the MitraClip system decreases morbidity and mortality in carefully selected patients with symptomatic heart failure, moderate to severe secondary MR, and without a markedly dilated LV. The core echocardiography laboratory integrative grading algorithm used in COAPT, which includes three different tiers of hemodynamically significant MR diagnosed by multiparametric inclusion criteria, allows for selection of candidates most likely to benefit from MitraClip (41). Given the large heart failure and valvular heart disease population not represented in this subset, these trials provide impetus for continued study and development of percutaneous therapies.

International study of comparative health effectiveness with medical and invasive approaches (ISCHEMIA Trial)

Prior randomized trials (i.e., COURAGE, BARI 2D, ORBITA) have suggested that in the current era of GDMT, routine coronary revascularization for stable ischemic heart disease (SIHD) does not improve clinical outcomes compared with GDMT alone (42-44). However, in fractional flow reserve-guided PCI trials and large meta-analyses myocardial revascularization in SIHD may decrease cardiovascular morbidity and mortality, commensurate to the extent of ischemia (45,46). The international ISCHEMIA trial randomized 5,179 patients with SIHD to lifestyle modification and GDMT vs. PCI or CABG plus GDMT (47). The mean age was 64 years, 83% had moderate-to-severe inducible ischemia on stress testing, 79% had multi-vessel CAD, 19% had a prior myocardial infarction, and 41% were diabetic.

At a follow-up of 3.3 years, there was no significant difference in the primary composite endpoint of CV death, MI, hospitalization for unstable angina or heart failure, or cardiac arrest (HR 0.93; 95% CI: 0.80–1.08; P=0.34), nor in the individual secondary endpoints of all-cause mortality (6.5% vs. 6.4%; P=0.67) and CV death or MI (13.9% vs. 11.7%; P=0.21) between the GDMT only vs. myocardial revascularization plus GDMT groups. No heterogeneity in treatment effect was observed amongst important subgroups, including by severity or extent of ischemia and CAD. Similarly, no benefit to invasive treatment of SIHD was observed in the complementary ISCHEMIA-CKD trial of 777 patients with an estimated glomerular filtration rate <30 mL/min/1.73 m² or on permanent hemodialysis (48).

Patients were excluded from the ISCHEMIA trial if they had ≥50% obstructive CAD of the left main coronary artery, an LV ejection fraction ≤35%, or New York Heart Association functional class III or IV heart failure, limiting the generalizability of the findings to these high-risk groups. In summary, an invasive strategy with PCI or CABG for patients with SIHD, moderate to severe ischemia, and mild to moderate LV dysfunction did not attenuate cardiovascular morbidity and mortality at mid-term follow-up.

Randomized comparison of early surgery versus conventional treatment in very severe aortic stenosis (RECOVERY Trial)

Aortic valve replacement is the only effective treatment for severe asymptomatic AS; it remains unknown if patients with very severe asymptomatic AS benefit from early intervention (49,50). The RECOVERY trial randomized 145 patients with very severe AS, defined as an aortic valve area ≤0.75 cm², and either a peak transaortic velocity ≥4.5 m/s or a mean transaortic gradient ≥50 mmHg, in a 1:1 open-label protocol to early SAVR (n=73) or conservative therapy (n=72) (51). Individuals with an LV ejection fraction <50%, significant aortic regurgitation or mitral valve disease, prior cardiac intervention, and age >80 years were excluded.

Mean age was 64 years and LV ejection fraction measured 65%, 51% were females, and 60% of patients had BAV. At 4 years, operative or CV mortality occurred in 1% vs. 6% of patients treated with early surgery vs. conservative therapy. At 8 years, early surgery was associated with a lower prevalence of operative or CV mortality (1% vs. 26%; P=0.003) all-cause mortality (10% vs. 32%; P<0.05), and heart failure hospitalization (0% vs. 11%; P<0.05), when
compared with a conservative approach.

The results RECOVERY signal that early SAVR for patients with asymptomatic very severe AS improves survival up to 8 years post-operatively when compared with conservative management. It is important to note that RECOVERY patients were low-surgical risk candidates with a mean EuroSCORE II of 0.9%, had preserved LV systolic function, and a low prevalence of obstructive CAD.

A randomized multicentre trial to evaluate the utilization of revascularization or optimal medical therapy for the treatment of chronic total coronary occlusions (EUROCTO Trial)

Coronary chronic total occlusions (CTO) are found in up to 25% of patients with SIHD and when revascularized, may improve angina and health status (52,53). The EUROCTO trial evaluated the benefit of PCI plus GDMT compared with GDMT alone among patients with stable angina and CTO, in whom multivessel non-CTO lesions were revascularized electively at least 4 weeks prior to allocation (54).

A total of 396 patients were randomized to PCI with a Biolimus-eluting stent plus GDMT (n=259) vs. GDMT alone (n=137); mean age was 65 years, 16% were females, and 27% had diabetes mellitus. PCI was successfully performed in 87% of the allocated intervention group, and 7.3% of those treated with GDMT only crossed over and received PCI. At 3-year follow-up, CTO-revascularization plus GDMT was associated with greater resolution of angina (71.6% vs. 57.8%; P=0.008) and less ischemia-driven revascularization (2% vs. 6.7%; P=0.04), when compared with GDMT alone. Importantly, there was no difference in the hard endpoints of CV mortality or MI (5% vs. 2.9%; P=0.32), or in adverse cardiovascular and cerebrovascular events (5.2% vs. 6.7%; P=0.55) between PCI plus GDMT vs. GDMT alone.

Interpretation of these outcomes must be placed within the context of two earlier studies of CTO intervention. In Drug-Eluting Stent Implantation vs. Optimal Medical Treatment in Patients trial (DECISION-CTO), while no benefit was observed with CTO revascularization, non-occlusive CAD was not routinely addressed and there was a nearly 20% cross-over rate, introducing powerful confounders (55). In the sham-PCI Objective Randomized Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina Trial (ORBITA), no difference in outcomes including angina and health status were reported between PCI plus GDMT vs. GDMT only (plus sham PCI). While EUROCTO adds to our knowledge regarding optimal treatment strategies of CTO lesions, a multi-disciplinary heart team approach is critical.

The transcatheter tricuspid valve therapies (TriValve) registry: percutaneous treatment of severe symptomatic tricuspid regurgitation

It is well established that clinically significant tricuspid regurgitation (TR) increases cardiovascular morbidity and mortality (56,57). Unfortunately, TR is underdiagnosed and undertreated; less than 5% of patients with indications for tricuspid valve surgery have intervention due to a high operative risk and lack of definitive long-term benefit (58,59). Given the less invasive percutaneous options available which may decrease risk and improve outcomes, the TriValve registry prospectively enrolled and closely follows 472 international patients who underwent transcatheter tricuspid valve intervention (TTVI) between 2016 to 2018 (60).

A propensity-matched study of 536 patients with moderate or greater TR and managed with TTVI vs. medical therapy was constructed using the TriValve TTVI registry and a separate cohort of patients under conservative treatment. Patients were paired based on age, Euroscore II, and systolic pulmonary artery pressure. The mean age and LV ejection fraction were 77 years and 50%, respectively, with >90% having secondary/functional TR. At 1-year follow-up, TTVI was associated with lower mortality (23% vs. 36%; P=0.001) and rehospitalization (26% vs. 47%; P<0.0001), and greater combined survival and freedom from HF rehospitalization (HR 0.60; 95% CI: 0.46–0.79; P=0.003). These outcomes remained significant despite adjustment for sex, HF severity, right ventricular dysfunction, atrial fibrillation, and presence of MR or pacemaker/defibrillator.

The promising results of TTVI when compared with conservative medical management for severe TR create the potential for a treatment option in a high-risk subset of the valvular heart disease population. Ongoing randomized trials of leaflet and annular-based tricuspid valve therapies for primary and secondary TR are eagerly awaited.

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