Cardiovascular disease in the literature: A selection of recent original research papers

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Transcatheter Aortic-Valve Replacement with a Balloon Expandable Valve in Low-Risk Patients. N Engl J Med 2019;380:1695-705.

Background: Transcatheter aortic-valve replacement (TAVR) has been shown to be equivalent or superior to surgical aortic-valve replacement (SAVR) in patients who are at intermediate or high risk for SAVR. Mack et al. from Baylor Scott and White Health Heart Hospital, Texas report on the PARTNER 3 study, a mulitcenter randomized trial of transfemoral third-generation balloon expandable SAPIEN 3 TAVR vs. SAVR in 1000 patients with severe calcific aortic stenosis at low surgical risk (Society of Thoracic Surgeons Predicted Risk of Mortality STS-PROM score $< 4\%$). The primary end point was a composite of death from any cause, stroke, or rehospitalization at 1 year after the procedure.

Findings: The primary endpoint was met in 8.5% for TAVR and 15.1% for SAVR ($p < 0.001$ for non-inferiority and $p = 0.001$ for superiority). There was no heterogeneity for subgroup analysis based on age, gender, STS-PROM score, LVEF, NYHA class, atrial fibrillation, or KCCQ score (an assessment of physical limitation and wellbeing). TAVR was associated with shorter length of index hospitalization (3 vs. 7 days, $p < 0.001$), a lower rate of new-onset atrial fibrillation, a lower rate of death or disabling stroke at 1 year, and a higher rate of discharge to home or self-care than SAVR. While the rate of moderate or severe paravalvular aortic regurgitation was similar, mild paravalvular aortic regurgitation at 1 year was higher with TAVR (29.4% vs. 2.1%). Asymptomatic valve thrombosis was also more common with TAVR (5 cases vs. 1 case with SAVR).

Significance: In this trial, TAVR was superior to SAVR at 1 year for the composite of death, stroke, or rehospitalization in low-risk patients. The shorter hospital stay, lower rate of atrial fibrillation, and higher likelihood of discharge to self-care with TAVR are expected but very important for patients and will likely influence the use of this procedure going forwards. While this trial is expected to revolutionize the use of TAVR for the treatment of aortic stenosis, important questions remain regarding the durability of TAVR especially in younger patients. The higher rates of paravalvular aortic regurgitation and valve thrombosis with TAVR are concerning.

Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med 2019;380:1706-15.

Background: TAVR using self-expanding valves has been shown to be equivalent or superior to SAVR in patients who are at intermediate or high risk for SAVR. Pompa et al. from Beth Israel Deaconess Medical Center, Boston conducted a multinational, randomized clinical trial of self-expanding supraannular TAVR vs. SAVR in 1468 patients with severe aortic stenosis with suitable anatomy for TAVR who have a predicted risk of death with SAVR of 3% or less at 30 days. The primary endpoint was a composite of death from any cause or disabling stroke at 24 months. This report is for the interim analysis which was completed after 850 patients completed 12 months of follow-up with outcomes imputed to 24 months based on a prespecified statistical model.

Findings: The incidence of the primary outcome at 24 months was 5.3% for TAVR and 6.7% for SAVR

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(criterion for non-inferiority was met but not for superiority). The rate of disabling stroke with TAVR was lower at 30 days (0.5% vs. 1.7%) and 1 year (0.8% vs. 2.4%). The rate of valve thrombosis was similar for the 2 groups but the rate of permanent pacemaker implantation (17.4% vs. 6.1%) and moderate or severe aortic regurgitation (3.5% vs. 0.5%) at 30 days was higher for TAVR.

Significance: This study demonstrates that TAVR using a self-expanding suprannular bioprosthesis was non-inferior to SAVR in patients at low risk for surgery. It is important to note that non-inferiority was achieved despite the very good outcomes seen with SAVR. A major limitation of this study is the imputed outcomes since the majority of patients had not completed 24 months of follow-up at the time of this interim analysis. The higher rate of permanent pacemaker implantation and aortic regurgitation with TAVR is concerning.

Randomized trial evaluating percutaneous coronary intervention for the treatment of chronic total occlusion. Circulation 2019;139:1674-83.

Background: The success rate of percutaneous coronary intervention (PCI) of chronic total occlusion lesions (CTO) has improved in recent years with more interventionalists aiming at complete revascularization; still, the impact of PCI of CTO lesions on cardiovascular outcomes remains limited to small clinical trials or observational studies. Lee et al. from the University of Ulsan College of Medicine, Seoul, Korea performed an open-label multicenter randomized non-inferiority clinical trial where patients with CTO lesions and eligible for PCI were randomized to PCI versus no-PCI. Other lesions that were not CTO were intervened upon at the discretion of the physician. Of 1284 patients that were supposed to be recruited, only 834 were enrolled within 6 years and the study enrollment was stopped prematurely due to slow recruitment. The primary endpoint was a composite of death, myocardial infarction, stroke, or any revascularization. Secondary endpoints included health-related quality of life.

Findings: There were 417 patients (CTO-PCI) and 398 (no CTO-PCI) that were enrolled. 20% of patients in the no CTO-PCI group crossed over. The success rate of CTO-PCI was 91% with a very low serious complication rate of 0.7%. After a mean follow-up period of 4 years, there was no significant difference in primary outcomes between groups (22% for each group, HR 1.03, $p = 0.86$) and similar improvement in quality of life up to 36 months.

Significance: CTO-PCI is feasible with high success rate and very low major complication risk; however, it did not confer any survival benefit or improvement in major cardiovascular events or quality of life compared to conservative treatment. The high cross over rate and the under powered study (enrollment prematurely terminated due to slow recruitment) were significant limitation of the study. The lack of assessment of myocardium at risk/viability in many patients and the open-label study design without sham-control or blinding are additional limitations. Further data from randomized clinical trials are needed before routine PCI of CTO lesions can be recommended.

Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. N Engl J Med 2019;380:1509-24.

Background: Patients who have an acute coronary syndrome (ACS) and/or undergo percutaneous coronary intervention (PCI) and have atrial fibrillation are indicated to receive dual anti-platelet therapy (DAPT) and anticoagulation. The combination of triple therapy increases the risk of bleeding. Lopes et al. from the Duke Clinical Research Institute, Durham, North Carolina conducted the AUGUSTUS trial, a two-by two factorial, randomized, controlled clinical trial to compare the safety and efficacy of standard-dose apixaban vs. vitamin K antagonist and low-dose aspirin vs. placebo, on a background of concomitant P2Y12 inhibitor therapy for 6 months in 4614 patients with atrial fibrillation within 14 days of having ACS and/or PCI. The primary outcome was major or clinically relevant bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH).

Findings: The median CHA2DS2-VASc score was 4 and 49% had been on anticoagulation prior to the study. Clopidogrel was the main P2Y12 inhibitor used (92.6%). The primary outcome at 6 months was significantly lower in apixaban vs. vitamin K antagonist group (10.5% vs. 14.7%, $p < 0.001$ for non-inferiority and superiority) and significantly higher for aspirin vs. placebo (16.1% vs. 9.0%, $p < 0.001$). There was no significant interaction between the 2 randomization factors. Ischemic events were not different between apixaban and vitamin K antagonist groups (6.7% vs. 7.1%) and aspirin and placebo groups (6.5% vs. 7.3%). The hazard ratios for myocardial infarction [0.81 (0.59–1.12)], stent thrombosis [0.52 (0.25–1.08)], and urgent revascularization [0.79 (0.51–1.21)] were all non-significant but in favor of aspirin.

Significance: In this population of patients with atrial fibrillation and recent ACS and/or PCI receiving P2Y12 inhibitor therapy (primarily clopidogrel), apixaban was associated with a lower risk of bleeding and hospitalization at 6 months than a vitamin K antagonist,

while aspirin was associated with a higher risk of bleeding with similar hospitalization rate. While the risk of ischemic events was not different between the groups, the study was powered for bleeding events and not for ischemic events and there was a strong signal for lower ischemic events in the aspirin vs. placebo group. The time in the therapeutic range for the patients who received a vitamin K antagonist was lower than in other studies (59%). More studies are needed before a definitive recommendation can be made for treatment of this difficult population.

Lifestyle, Glycosylated Hemoglobin A1c, and Survival Among Patients with Stable Ischemic Heart Disease and Diabetes. JACC 2019;73:2049-58.

Background: Among patients with stable ischemic heart disease (SIHD) and diabetes mellitus (DM), the impact of glycosylated hemoglobin A1c control among other traditional risk factors on survival is not well established. In a subgroup study of the COURAGE trial, Mancini et al. from the University of British Columbia, Vancouver evaluated 690 patients with SIHD and DM who had 7 prespecified risk factors ascertained at baseline and 1-year follow-up: systolic blood pressure < 130 mm hg; low-density lipoprotein < 70 mg/dl; non-smoking; physical activity of ≥ 150 min; diet adherence to AHA step 2 diet; body mass index < 25 kg/m2, and A1c < 7. The primary endpoint was all-cause death.

Findings: After a mean follow-up time of 7 years, 186 patients died (4.5%/year). The strongest predictors of survival on multivariate analysis were no smoking, regular physical activity, dietary adherence, and A1c control. Compared with achievement of 0-1 goals, there was a graded reduction in mortality with higher number of goals achieved reaching 65% among those attaining at least 3 goals (hazard ratio 0.35 [0.15-0.83]), and 87% among those achieving 6-7 goals (HR 0.13 [0.05-0.40]).

Significance: Among diabetic patients with SIHD, control of at least 3 risk factors at 1 year was associated with significant long-term survival, with highest impact including non-smoking, physical activity, diet, and A1c control. The study underlines the importance of risk factor modification and reaching goals and its impact on mortality. The major limitations of the study were lack of data on changes in risk factors beyond 1 year, introduction of new medications, non-fatal cardiovascular events, and other potential confounders.

Systemic inflammation and cardio-renal organ damage biomarkers in middle age are associated with physical capabilities up to 9 years later. Circulation 2019;139:1988-99.

Background: Poor physical performance is associated with cardiovascular outcomes. Using data from the oldest British birth control cohort, Kuh D et al. from the University College London tested the association between biomarkers of heart and kidney damage (cystatin C, NT-proBNP, interleukin 6, and E-selectin) at age 60-64 years and physical performance at age 69 years among 1736 subjects. Mutual adjustment for risk factors was performed as well as other traditional risk factors.

Findings: NT-proBNP, cystatin C, and interleukin 6 (but not E-selectin) were inversely associated with all outcomes after adjustment for gender, height, and body mass index. A one standard deviation increase in log-NT-proBNP was associated with weaker handgrip ($-$ 0.63 kg [$-$ 0.99 to $-$ 0.025], and similarly for cystatin C and interleukin-6. On multivariate adjustment, lower NT-proBNP and interleukin 6 were independently associated with better physical capability (a key component of healthy aging) up to 9 years later.

Significance: Elevated NT-proBNP and interleukin 6 in midlife could help risk stratify patients and identify those set to have poor physical performance as they age. Whether these biomarkers are capturing early end-organ damage or cumulative stressor pathways that lead to poor aging needs to be further tested in future studies.