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

Fadi G. Hage, MD, MASNC,[a,b] and Wael AlJaroudi, MD, FASNC[c]

[a] Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL
[b] Section of Cardiology, Birmingham Veterans Affairs Medical Center, Birmingham, AL
[c] Division of Cardiovascular Medicine, Clemenceau Medical Center, Beirut, Lebanon

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Long-Term Survival Following Multivessel Revascularization in Patients With Diabetes. The FREEDOM Follow-On Study. J Am Coll Cardiol 2019; https://doi.org/10.1016/j.jacc.2018.11.001

Background: The FREEDOM trial showed that in patients with diabetes and multivessel CAD, CABG is associated with a reduction in major adverse cardiovascular and cerebrovascular events compared to PCI. Farkouh et al. from the University of Toronto, Canada reported on the long-term outcomes from FREEDOM.

Findings: Of the original 1900 patients in FREEDOM, long-term follow-up (7.5 years, interquartile range 5 to 9 years) was available on 943 (49.6%). Mortality at 8 years in the PCI group was 24.3% compared to 18.3% in CABG group (hazard ratio 1.36, 95% CI 1.07 to 1.74, $P = .01$). The survival benefit of CABG versus PCI was more evident in younger patients (≤ 63 year), in those that ever smoked, and in those from centers in North America.

Significance: In patients with diabetes and multivessel CAD and without left main disease, CABG is superior to PCI with regard to all-cause mortality during long-term follow-up. A major limitation of this data is that long-term follow-up was available for only half of the participants in the randomized study.

Reprint requests: Fadi G. Hage, MD, MASNC, Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL; Section of Cardiology, Birmingham Veterans Affairs Medical Center, Birmingham, AL; *fadihage@uab.edu*

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Myocardial and Systemic Inflammation in Acute Stress-Induced (Takotsubo) Cardiomyopathy. *Circulation* 2018 Nov 11. https://doi.org/10.1161/circulationaha.118.037975. [Epub ahead of print].

Background: Acute stress-induced cardiomyopathy (takotsubo) can result in long-term heart failure phenotype with persistent symptoms, subclinical cardiac dysfunction, and with prognosis similar to myocardial infarction. Scally et al. from the University of Aberdeen, United Kingdom, hypothesized that inflammatory pathways are central to the pathophysiology and natural history of takotsubo cardiomyopathy; they enrolled 55 patients with takotsubo cardiomyopathy and 51 age-, sex-, and co-morbidity-matched control subjects. Myocardial inflammation was assessed with USPIO (ultrasmall superparamagnetic particles of iron oxide)-enhanced cardiac magnetic resonance (CMR) for detection of inflammatory macrophages in the myocardium; myocardial edema was assessed with native T1 mapping, and myocardial energetics using 31-P CMR spectroscopy. Blood monocyte subpopulations and serum cytokines were assessed as measures of systemic inflammation. Matched controls underwent investigation at a single time point, while patients with takotsubo at time of event and 5 months of follow-up.

Findings: Compared to control subjects, patients with takotsubo cardiomyopathy had greater USPIO enhancement in both ballooning and non-ballooning left ventricular myocardial segments ($P < .001$ and .02, respectively), and higher T1 values ($P < .001$ for both) that resolved at 5 months of follow-up. Resting myocardial energetics was significantly reduced in acute takotsubo with partial recovery at follow-up. Serum interleukin-6, chemokine ligand 1 concentrations, and classical CD14++ CD16− monocytes were increased on presentation and on follow-up.

Significance: In this multicenter, prospective, case-control, mechanistic investigation study, acute takotsubo

cardiomyopathy was shown to have macrophage-mediated myocardial inflammation with increased systemic pro-inflammatory cytokines for at least 5 months, serving as a potential therapeutic target. Both native and post-USPIO myocardial T2* values, however, could have been affected by other concomitant pathology such as myocardial edema, hemorrhage, rather than pure inflammation. Also, there was a lack of biopsy to correlate with the USPIO-T2* findings with tissue histology. Still, this is one of the first studies that evaluates in depth the pathophysiology of acute takotsubo and serves as a platform for further research and treatment.

Association of the Hospital Readmissions Reduction Program With Mortality Among Medicare Beneficiaries Hospitalized for Heart Failure, Acute Myocardial Infarction, and Pneumonia. *JAMA* 2018;320(24):2542–2552.

Background: The Hospital Readmissions Reduction Program (HRRP), which was established under the Affordable Care Act, required that the Centers for Medicare & Medicaid Services (CMS) impose financial penalties starting in 2012 on hospitals with higher-than-expected 30-day readmission rates for patients with heart failure, acute myocardial infarction, and pneumonia. Although HRRP resulted in significant declines in readmission rates, its effect on mortality is not clear. Wadhera et al. from Beth Israel Deaconess Medical and Harvard Medical School, Boston performed a retrospective analysis of 8.3 million Medicare beneficiaries who were hospitalized with heart failure, acute myocardial infarction, or pneumonia across 4 time periods from 2005 to 2015 to determine the relationship of HRRP with mortality.

Findings: The mean age of the study population was 80 years. Readmission rates within 30 days declined significantly following the announcement and implementation of HRRP. 30-day mortality rate increased following the announcement and implementation of HRRP for heart failure (0.49% and 0.52%) and pneumonia (0.26% and 0.44%). These differences were explained by an increase in death in patients who were not readmitted within 30 days. For acute myocardial infarction, the mortality rate slightly decreased (0.008%) after announcement of HRRP but did not significantly change after its implementation.

Significance: The announcement and implementation of the HRRP was associated with increased mortality for Medicare beneficiaries admitted with heart failure or pneumonia but not acute myocardial infarction. These findings are worrisome in that attention and resources aimed at reducing readmission rates may have unintended adverse effects on mortality. These results should be interpreted with caution given the observational study design and that 45-day mortality rates were not different.

Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. *N Eng J Med* 2018;379:2297–306.

Background: Secondary mitral regurgitation due to left ventricular (LV) dysfunction is associated with poor clinical outcomes. Whether percutaneous repair of severe secondary mitral regurgitation improves outcomes beyond optimal medical therapy has been debated with conflicting results. Obadia JF et al. from Hôpital Cardiovasculaire Louis Pradel, France, performed a multicenter, randomized, open-label controlled phase 3 trial, enrolling in a 1:1 ratio of 304 patients (severe secondary mitral regurgitation, LV ejection fraction 15 to 40%, symptomatic, not candidate for surgery) to undergo percutaneous mitral valve repair on top of medical therapy versus optimal medical therapy alone (152 in each arm). All the echocardiograms were reviewed at an independent central laboratory in accordance with European Association of Echocardiography guidelines. The primary efficacy outcome was a composite of death from any cause or unplanned hospitalization for heart failure at 12 months.

Findings: The majority of patients (95%) had a reduction of mitral regurgitation by at least one grade, and 76% mild (or less) residual regurgitation in the repair arm. At one-year follow-up, there was no significant difference in the primary outcomes between the intervention and medical treatment arms (54.6% vs 51.3%, odds ratio 1.16 [0.73 to 1.84], $P = .53$). Similarly, there was no difference in the rate of all-cause death (hazard ratio 1.11 [0.69 to 1.77]), cardiac death (HR 1.09 [0.67 to 1.78]), or unplanned hospitalization (HR 1.13 [0.81 to 1.56]). The results were similarly not significant in pre-specified subanalysis subgroups such as age greater than 75 years, NYHA III to IV, LVEF less than 30%, and without any interaction with treatment.

Significance: Among patients with severe secondary mitral regurgitation with LV dysfunction (EF 15 to 40%) and symptomatic heart failure, percutaneous mitral valve repair on top of medical therapy did not improve the rate of death or unplanned hospitalization for heart failure at 1 year compared to optimal medical therapy alone. The lack of benefit could be due to a late presentation and repair of the mitral valve given the significant baseline LV dysfunction, and the optimal medical therapy that included the new class of angiotensin receptor–neprilysin inhibitor drugs. There are several limitations to the study. First, the trial was

limited to centers in France. Second, the follow-up time was relatively short at 1 year. Third, there was a considerable amount of missing follow-up data for the assessments of echocardiography, functional status, natriuretic peptide, and quality of life.

Transcatheter Mitral Valve Repair in Patients with Heart Failure *N Eng J Med* 2018;379:2307–18.

Background: Surgical repair or replacement of the mitral valve in severe secondary regurgitation failed to improve outcomes and confers significant risk of complication. Whether transcatheter mitral valve repair in patients with left ventricular dysfunction and severe mitral regurgitation improves outcomes has been debated. Stone GW et al. from Columbia University Medical Center, New York, NY, performed a multicenter randomized clinical trials at 78 sites in the United States and Canada, randomized patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy to transcatheter mitral valve repair (N = 302) or medical therapy alone (N = 312). The primary end point was hospitalizations for heart failure within 2 years of follow-up. The primary safety end point was freedom from device-related complications at 1 year

Findings: In the device group, the mean number of clips implanted per patient was 1.7 ± 0.7 (range 1 to 4). The majority of patients had significant reduction in the severity of regurgitation and 82% had 1+ or less residual regurgitation at discharge. At 2 years of follow-up, transcatheter mitral valve repair was associated with significant reduction in the annualized rate of all hospitalizations for heart failure (35.8% vs 67.9% per patient-year, hazard ratio 0.53 [0.40 to 0.70], $P < .001$), and death from any cause (HR 0.62 [0.46 to 0.82], $P < .001$). The rate of freedom from device-related complications at 1 year was 96.6%.

Significance: Among patients with grade 3 to 4+ secondary mitral regurgitation and symptomatic heart failure despite the use of maximal doses of guideline-directed medical therapy, transcatheter mitral valve repair resulted in a lower rate of hospitalization for heart failure and all-cause death at 2 years and had low complication rate. While the lower rate of hospitalization for heart failure with the device-based treatment emerged within 30 days after treatment, the lower all-cause mortality was delayed and did not emerge until more than 1 year after treatment. Unlike the negative results of a very similar randomized trial published in the same issue of the journal (presented above), and that limited the follow-up to 1-year, the current trial extended it to 2 years and was able to detect mortality benefit. This could be due to the fact that reverse LV remodeling, which impacts survival benefit, takes time to improve after correction of a chronic severe volume overload state. Further, patients included in this trial had more severe mitral regurgitation and smaller left ventricular volume than those in the negative trial above. Still, there are several limitations to the study. First, the investigators were not blinded to the trial group as the MitralClip device was visible on chest-x-ray images. Second, the median follow-up was longer in the device group than in the control group, in part because of the lower mortality in the device group. Third, medications that affect the renin–angiotensin system were more frequently used in the device group.

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia *N Eng J Med* 2019;380:11–22.

Background: Patients with cardiovascular disease and elevated triglyceride levels are at increased risk despite treatment with statins. Bhatt et al. from Brigham and Women's Hospital, Boston performed a multicenter, randomized, double-blind, placebo-controlled trial of 8179 patients with established cardiovascular disease or diabetes and an additional risk factor, who had a fasting triglyceride level of 150 to 499 mg/dL and LDL of 41 to 100 mg/dL and were already on statins. The patients were randomized to receive 2 g of icosapent ethyl twice daily or placebo. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina.

Findings: The median change in triglyceride level after 1 year was a decrease of 18.3% in the treatment group vs an increase of 2.2% in the placebo group $P < .001$). After a median follow-up of 4.9 years, the primary outcome occurred in 17.2% in the treatment group vs 22.0% in the placebo group (hazard ratio 0.75, 95% CI 0.68 to 0.83, $P < .001$). Treatment benefit was consistent across selected pre-specified subgroups and baseline triglyceride levels had no influence on the efficacy of treatment. The rate of cardiovascular death was lower in the treatment arm (4.3% vs 5.2%, hazard ratio 0.80; 95% CI 0.66 to 0.98, $P = .03$). The rate of atrial fibrillation and serious adverse bleeding events were higher in the treatment group.

Significance: In this trial, treatment of patients with established cardiovascular disease or those with diabetes and a risk factor already on a statin and elevated triglyceride level with icosapent ethyl resulted in significant reduction in triglycerides and improvement in outcomes. The number needed to treat to prevent a primary outcome was 21. These results are surprising

given the multiple negative trials reported with $n - 3$ fatty acids. The mechanism of action is unclear given that results were independent of baseline or achieved triglyceride level.

Disclosure

Dr. Aljaroudi reports no conflicts of interest. Dr. Hage reports grant support from Astellas Pharma and GE Healthcare.