Review of Cardiovascular Literature

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Nonobstructive Coronary Artery Disease and Risk of Myocardial Infarction

Background: There are limited data about cardiovascular events among patients with nonobstructive coronary artery disease (CAD). In this retrospective cohort of all US veterans without prior known CAD undergoing elective coronary angiogram between 2007 and 2012, Maddox et al[1] from University of Colorado school of medicine sought to compare myocardial infarction (MI) and mortality rates between patients with nonobstructive (stenosis $\geq$ 20%, but <70%), obstructive (any stenosis $\geq$ 70% or left main $\geq$ 50%), and no CAD (no stenosis $\geq$ 20%). The primary endpoint was 1-year hospitalization for nonfatal MI. Secondary endpoints were 1-year all-cause death and composite endpoint of 1-year death or MI.

Findings: There were 37,646 patients, 8,363 (22.3%) had no CAD, 8,384 (22.3%) had nonobstructive CAD, and 20,899 (55.4%) had obstructive CAD. At 1 year, 845 patients died and 385 were hospitalized for MI. Relative to patients without CAD and after multivariate adjustment, patients with 1-vessel nonobstructive CAD had a hazard ratio (HR) for 1-year MI of 2.0 (95% CI 0.8-5.1); 2-vessel nonobstructive HR 4.6 (95% CI 2.0-10.5), 3-vessel nonobstructive HR 4.5 (95% CI 1.6-12.5). Patients with obstructive CAD had HR for 1-year MI of 9.0 (4.2-19), 16.5 (8.1-33.7), and 19.5 (9.9-38.2) for 1, 2, or 3-vessel/left main disease. Similarly, 1-year mortality and composite endpoint were associated with increasing extent of CAD and number of involved vessels.

Significance: In this multicenter retrospective study, nonobstructive CAD compared with no apparent CAD was associated with increased 1-year risk of MI and death, and with incremental increase with the number of vessels involved. These findings are quite interesting and further reinforce the need for aggressive medical therapy in such cohorts at high risk for events. Only 60% of patients with 3-vessel nonobstructive CAD received statins. The study is representative of US veterans only, predominately male, and spans 5 years through which optimal medical therapy has greatly changed since 2007. A prospective multicenter large study with greater representation of females and optimal medical therapy is warranted to further validate these findings.

Twelve or 30 Months of Dual Antiplatelet Therapy After Drug-Eluting Stents

Background: After placement of a drug-eluting stent, treatment with dual antiplatelet therapy is recommended for 6-12 months. Risk of stent thrombosis has been shown to extend beyond this period. Mauri et al[2] from the Brigham and Women's Hospital, Boston conducted an international, multicenter, randomized, placebo-controlled trial to determine the benefits and risks of continuing dual antiplatelet therapy beyond 1 year in patients who received a drug eluting stent.

Findings: Out of 25,682 patients who had received a stent and enrolled in the study 9961 patients were randomized at 1 year to receive aspirin plus placebo vs dual antiplatelet therapy for another 18 months. Continued treatment with thienopyridine, as compared with placebo, decreased the rates of stent thrombosis by 71% (0.4% vs 1.4%), the composite outcome of death, myocardial infarction or stroke by 29% (4.3% vs 5.9%),

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and myocardial infarction by 53% (2.1% vs 4.1%, all P values <.001) and increased the rate of moderate or severe bleeding by 61% (2.5% vs 1.6%, $P = .001$).

Significance: In this large study, continuation of dual antiplatelet therapy beyond 1 year after placement of a drug-eluting stent significantly reduced the risk of stent thrombosis and major adverse events at the expense of increased risk of bleeding. Importantly, the risk of cardiovascular death was comparable between the 2 groups but the risk of non-cardiovascular death was significantly higher in the dual antiplatelet therapy group (1.0% vs 0.5%, $P = .002$). It is notable that myocardial infarction that was not related to stent thrombosis accounted for 55% of the treatment benefit on myocardial infarction indicating that this population is at high risk of ischemic events irrespective of stent placement. This data suggests that patients receiving drug-eluting stents who are at high risk of ischemic events and low risk of bleeding may benefit from treatment with dual antiplatelet therapy beyond 1 year.

Effect of Screening for CAD Using CT Angiography on Mortality and Cardiac Events in High-Risk Patients with Diabetes: The FACTOR-64 RCT

Background: Coronary artery disease (CAD) is a leading cause of morbidity and mortality in patients with diabetes, and is often asymptomatic. Muhlestein et al[3] from Intermoutain Medical Center Heart Institute, Murray, Utah, sought to assess whether routine CAD screening by coronary computed tomography angiography (CCTA) in asymptomatic high risk patients with diabetes mellitus (type 1 or 2) followed by CCTA-directed therapy would result in lower cardiovascular events. In a multicenter randomized clinical trial, patients with diabetes were randomized to CCTA-directed therapy versus standard of care.

Findings: After a mean follow-up of 4 ± 1.7 years, the primary endpoint, a composite of all-cause mortality, nonfatal myocardial infarction, or hospitalization for unstable angina, occurred in 62 patients (6.9%) with no significant difference between groups (6.2% for CCTA and 7.6% for control, Hazard ratio 0.80 [95% CI 0.49-1.32], $P = .38$). Similarly, there was no difference between groups in the secondary endpoint which was a composite of CAD death, nonfatal myocardial infarction or unstable angina (HR 1.15 [0.60-2.19], $P = .68$).

Significance: Among asymptomatic high risk patients with diabetes, routine screening with CCTA with targeted therapy did not confer any survival benefit or a decrease in cardiovascular major adverse events. These results are in line with the DIAD trial where screening asymptomatic patients with diabetes using stress myocardial perfusion imaging was not superior to standard of care. Interestingly, the event rate was low in both trials. This highlights the powerful impact of optimal medical therapy and aggressive risk factor management on reducing event rates but leaves open the possibility that screening for CAD may be beneficial in higher risk patients with diabetes.

Left Ventricular Ejection Fraction Normalization in Cardiac Resynchronization Therapy and Risk of Ventricular Arrhythmias and Clinical Outcomes: Results from MADIT-CRT Trial

Background: Patients who receive cardiac resynchronization therapy (CRT) experience improvement in left ventricular ejection fraction (LVEF). Ruwald et al[4] from University of Rochester, NY studied 752 patients in the MADIT-CRT trial who were randomized to receive CRT-D (CRT with a defibrillator) who had echocardiograms at baseline and at 12 months to determine the risk of ventricular arrhythmias in those who experienced LVEF normalization with CRT.

Findings: 7.3% of patients experienced LVEF normalization (LVEF > 50%) while 79% achieved an LVEF of 36%-50% at follow-up. Factors associated with LVEF normalization included female gender, no prior myocardial infarction, left bundle branch block, baseline LVEF > 30%, small LV end systolic volume and left atrial volume. During 3 years of follow-up, ventricular tachyarrhythmias requiring ICD shock was seen in 16% of those with LVEF ≤ 35%, 6% of those with LVEF 36%-50%, and none of those with LVEF normalization. Heart failure or death was seen in 28%, 12% and 5% of patients, respectively, while inappropriate ICD therapy was seen in 20%, 8% and 7%, respectively.

Significance: Patients who experience normalization of LVEF after placement of a CRT-D have a low risk of ventricular tachyarrhythmias and have an excellent prognosis with a low incidence of heart failure or death during 3-year follow-up. If this provocative data can be confirmed over longer follow-up, it suggests that patients with LVEF normalization at time of generator change may safely receive a CRT without a defibrillator.

Impact of Lifelong Exercise ''Dose'' on Left Ventricular Compliance and Distensibility

Background: Left ventricular (LV) and arterial vasculature stiffening are often the result of aging and sedentary lifestyle, and play a key role in the pathophysiology of cardiovascular disease. Exercise training, however, is thought to retain LV compliance and distensibility. Bhella et al[5] from Texas Health Presbyterian Hospital, Dallas, TX, sought to assess whether moderate lifelong exercise training retains LV compliance and distensibility among 102 healthy seniors (age ≥ 65 years). Subjects were stratified according to frequency of exercise training average over at least 20 years:

sedentary (<2 sessions·week^{-1}), casual (2-3), committed (4-5), and competitive (6-7), and were matched according to age, gender and co-morbidities. Frank-Starling curves were generated using invasive and non-invasive hemodynamic measurements to calculate LV compliance and distensibility.

Findings: With increasing doses of lifelong exercise training, there was an incremental increase in peak oxygen consumption, stroke volume index, and a decrease in heart rate and body mass index. Sedentary and casual training were associated with significant decrease in LV compliance and distensibility, while committed and competitive lifelong exercise training prevented such changes.

Significance: At least 30 minutes of dynamic exercise per session, 4-5 times a week, is associated on the long-term with preserved LV compliance and distensibility, and prevention of LV stiffening which is implicated in cardiovascular disease. The cross-sectional nature and potential recall bias are some of the limitations of the study. However, this paper presents interesting data on the minimal exercise dose needed to prevent or delay aging-related LV deconditioning.

How Cardiologists Present the Benefits of Percutaneous Coronary Interventions to Patients with Stable Angina. A Qualitative Analysis

Background: There is no evidence that percutaneous coronary intervention (PCI) reduces risk of death or myocardial infarction (MI) in patients with stable coronary artery disease (CAD). Prior studies demonstrated that patients with stable CAD believe that PCI will reduce their risk of MI and death. Goff et al[6] from Tufts University School of Medicine performed qualitative content analysis of 40 encounters between cardiologists and patients with stable CAD regarding angiogram and PCI.

Findings: An abnormal stress test result was the most common reason for advocating for angiogram and PCI. When optimal medical therapy was discussed, it was presented as inferior to PCI. In only 5% of encounters, cardiologists explicitly stated that PCI may improve symptoms but would not reduce risk of death or MI. Explicit overstatements of the benefits of PCI were made in 13% of encounters and implicit overstatements were very common including references that PCI will fix the problem in 35% of encounters. Discussion of risk was limited and when offered was rarely quantitative and usually offered in non-numerical terms. Communication styles that may discourage participation in decision making, such as use of technical language or not listening to the patient were present in 75% of encounters.

Significance: This study suggests that cardiologists may contribute to patients' misperceptions of benefits of PCI in stable CAD through explicit or implicit overstatement of benefits, understatement of risks, and communication styles that discourage patient participation in decision-making. In this small sample, the majority of cardiologists did not inform the patients using evidence-based statements regarding the benefits and risks of PCI in stable CAD. This study has limitations including its qualitative analysis and its inability to ascertain whether further informed consent discussions were made outside of the studied encounters.

References

1. Maddox TM, Stanislawski MA, Grunwald GK, Bradley SM, Ho PM, Tsai TT, et al. Nonobstructive coronary artery disease and risk of myocardial infarction. J Am Med Assoc 2014;312:1754–63.
2. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155–66.
3. Muhlestein JB, Lappe DL, Lima JA, Rosen BD, May HT, Knight S, et al. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: The FACTOR-64 Randomized Clinical Trial. JAMA 2014;312:2234–43.
4. Ruwald MH, Solomon SD, Foster E, Kutyifa V, Ruwald AC, Sherazi S, et al. Left ventricular ejection fraction normalization in cardiac resynchronization therapy and risk of ventricular arrhythmias and clinical outcomes: Results from the MADIT-CRT trial. Circulation 2014. doi:10.1161/CIRCULATIONAHA.114.011283.
5. Bhella PS, Hastings JL, Fujimoto N, Shibata S, Carrick-Ranson G, Palmer MD, et al. Impact of lifelong exercise ''dose'' on left ventricular compliance and distensibility. J Am Coll Cardiol 2014;64:1257–66.
6. Goff SL, Mazor KM, Ting HH, Kleppel R, Rothberg MB. How cardiologists present the benefits of percutaneous coronary interventions to patients with stable angina: a qualitative analysis. JAMA Int Med 2014;174:1614–21.