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

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Received Mar 14, 2019; accepted Mar 14, 2019
doi:10.1007/s12350-019-01696-x

Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. *N Engl J Med*.2019;380:752-62

Background: Inflammation is a causal factor in the development and progression of coronary artery disease (CAD). Low-dose methotrexate (LDM) is an inexpensive and effective anti-inflammatory agent that is widely used for the treatment of rheumatoid arthritis and other inflammatory diseases. Ridker et al from the Brigham and Women's Hospital, Boston randomized in a double-blind fashion after a run-in period, 4786 patients with diabetes mellitus or metabolic syndrome who have prior myocardial infarction or multivessel to LDM or placebo. All participants received 1 mg of folate daily. The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina.

Findings: At the end of the trial (median follow-up of 2.3 years) 21% of the LDM group and 22% of placebo group had permanently discontinued study drug. The primary outcome was not different between the LDM and placebo groups (incidence rate 4.13 vs 4.31 per 100 person-years; hazard ratio, 0.96; 95% CI 0.79-1.16). There was no difference in any of the pre-specified outcomes. LDM was associated with greater increases in serum aspartate aminotransferase and alanine aminotransferase and decreases in white-cell counts but no change in C-reactive protein (CRP) levels or other markers of inflammation compared to placebo. Rates of serious adverse events, including bleeding and infection, were similar in the two groups. Rates of cancer, primarily non-basal cell skin cancer, were higher in the LDM group.

Significance: In this large randomized study LDM was not associated with improved outcomes in patients with prior myocardial infarction or multivessel disease who also have diabetes or metabolic syndrome. These results contrast with the recently reported Canakinumab Antiinflammatory Thrombosis Outcomes Study (CANTOS) in which canakinumab, a monoclonal antibody that selectively neutralizes interleukin-1β, resulted in lower cardiovascular events than placebo in patients with CAD and elevated CRP levels. In contrast, the median level of CRP in this trial was not elevated (1.6 mg/L) and, importantly, LDM did not lower CRP levels. Further trials using other anti-inflammatory agents that have been shown to reduce inflammation in patients with CAD are needed.

Sudden Cardiac Death in Women. Causes of Death, Autopsy Findings, and Electrocardiographic Risk Markers. *Circulation* 2019;139:1012–1021

Background: Despite medical progress in preventive and therapeutic medicine, sudden cardiac death (SCD) remains a major cause of death. Although the incidence is lower among women, it remains significant. Haukilahti et al from the University Hospital of Oulu, Finland, sought to determine the causes of SCD among women using a large autopsy data of subjects from Northern Finland collected between 1998 and 2017 (N = 5869). Previously recorded ECGs were available and analyzed in 1101 subjects (18.8% of total population; and in 25.3% of women).

Findings: The majority of SCD (85%) were unwitnessed; they occurred more indoors and during the night while sleeping for women, vs outdoors and during exercise for men. Female subjects with SCD were significantly older than men (70.1 ± 13.1 years vs

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J Nucl Cardiol 2019;26:701–3.
1071-3581/$34.00

63.5 ± 11.8 years, $P < 0.001$), and had more abdominal fat. Ischemic heart disease was the most frequent identified cause of SCD in both women (71.7%) and men (75.7%); however, the proportion of ischemic SCD decreased for both sexes from late 1990s to 2017. Women were more likely to have non-ischemic cause of SCD (28.3% vs 24.3%, $P = 0.005$), and more primary myocardial fibrosis (5.2% vs 2.6%, $P < 0.001$). Also, female subjects with SCD were more likely to have normal prior ECG tracings (22.2% vs 15.3%, $P < 0.001$), particularly among non-ischemic subjects. However, ECG markers of left ventricular hypertrophy, with or without repolarization abnormalities, were more common among women.

Significance: In this large autopsy database of subjects from Finland, ischemic SCD was the most common cause of SCD, although it has significantly declined since 1998. Still, considerable differences between genders were identified pertaining to causes of SCD, autopsy and ECG findings. In particular, women were more likely to die at night and indoors, were older at the time of SCD, had more commonly non-ischemic causes and primary fibrosis. One-third of females with SCD had normal ECGs prior to SCD, but more women had ECG markers of left ventricular hypertrophy. The lack of specific time of symptom occurrence prior to SCD, missing ECG, and variability of timeframe of ECG recordings are limitations of the study. A strength of the study is that its population contains nearly all subjects with SCD from Northern Finland because of the high autopsy rate in the country, which decreases the risk of selection bias.

Impact of Abnormal Coronary Reactivity on Long-Term Clinical Outcomes in Women *JACC* 2019;73:684-93

Background: Abnormal coronary reactivity (CR) is commonly found among women with non-obstructive coronary artery disease (CAD) and suspected myocardial ischemia. Albadri et al from University of Emory, Atlanta, Georgia, prospectively evaluated the impact of CR on long-term major adverse cardiovascular outcomes (MACE) among women with and without obstructive CAD in the National Heart and Lung and Blood Institute sponsored WISE (Women's Ischemia Syndrome Evaluation) study. Non-endothelium dependent microavascular CR was assessed in 224 women by measuring coronary blood flow and flow reserve with intracoronary adenosine challenge. Endothelium and non-endothelium dependent epicardial CR were tested using intracoronary acetylcholine and nitroglycerine, respectively.

Findings: After 10 years of follow-up, 129 events occurred. After adjustment for cardiovascular risk factors, reduced coronary flow reserve was associated with increased MACE (HR 1.06 [1.01-1.12], $P = 0.02$); while reduced coronary blood flow was associated with increased mortality (HR 1.12, $P = 0.038$) and MACE (HR 1.11, $P = 0.006$). Increased epicardial coronary constriction with intracoronary acetylcholine was associated with increased risk of angina-related hospitalization (HR 1.05, $P < 0.0001$), while intracoronary dilation with nitroglycerin did not predict outcomes.

Significance: In the absence of obstructive CAD, abnormal CR in women with ischemia symptoms predicts long-term outcomes. Early identification of microvascular disease can help risk stratify this cohort. The cohort consisted of patients pre-selected to undergo coronary angiography; CR testing was done at one time point only, and variability with time could not be factored in; the majority of patients were not treated medically, and medication use with time might have varied. Future research should be invested in non-invasive cost-effective imaging strategies such as cardiac CT with fractional flow reserve and other modalities to assess CR.

Association of Left Ventricular Ejection Fraction and Symptoms With Mortality After Elective Noncardiac Surgery Among Patients With Heart Failure. *JAMA*2019;321(6):572-579

Background: Heart failure (HF) is a known risk factor for post-operative mortality. However, the degree to which a reduction in left ventricular ejection fraction (LVEF) and HF symptoms contribute to post-operative risk is not known. Lerman et al from Stanford, California reported on the post-operative mortality of 609,735 patients (47,997 with HF and 561,738 without HF) who underwent elective, non-cardiac surgery in the Veterans Affairs Surgical Quality Improvement Project database from 2009 through 2016. Patients were classified as having HF if they had ≥ 1 inpatient admission or ≥ 2 outpatient clinic visits with a diagnosis of HF within 3 years of surgery. HF patients were further subdivided by LVEF and symptom status. The primary outcome of this study was all-cause, 90-day, post-operative mortality.

Findings: Of the patients with HF 59.9% had preserved LVEF (HFpEF). The majority of patients with

HF did not have HF symptoms (90.1, 86.4, 82.9, and 79.2% for HFpEF, mildly, moderately, and severely reduced LVEF, respectively). The crude 90-day post-operative mortality was higher among patients with HF (5.49% vs 1.22%, adjusted odds ratio 1.67, 95% CI 1.57-1.76). The risk of post-operative mortality progressively increased with decreasing systolic function (P for trend < 0.001). Patients with HF who had symptoms were at higher risk than those without symptoms (10.11% vs 4.84% at 90 days, adjusted odds ratios of 1.53, 95% CI 1.44-1.63 for asymptomatic and 2.37 95% CI 2.14-2.63 for symptomatic compared to those without HF).

Significance: In this large retrospective cohort study patients with HF including those with HFpEF and those with or without symptoms were at higher risk of 90-day mortality after non-cardiac surgery compared to those without HF. Multivariate adjustment greatly attenuated the risk associated with HF indicating that HF is associated with multiple comorbidities contributing to post-operative risk, but HF itself remained an independent predictor even after adjustment. The major limitations of this study include selection bias (all patients underwent surgery) and generalizability outside of the veteran population.

Prospective Validation of the Emergency Heart Failure Mortality Risk Grade for Acute Heart Failure. The ACUTE Study. *Circulation* 2019;139:1146–1156

Background: The majority of patients with heart failure (HF) who present to the emergency department are admitted to the hospital. Lee et al from University of Toronto, Canada prospectively validated the previously derived Emergency Heart failure Mortality Risk Grade (EHMRG7) and EHMRG30-ST for prediction of 7-day and 30-day risk, respectively, in 1983 patients presenting to the emergency department with HF at 9 hospitals in Ontario, Canada from 2010 to 2015.

Findings: Among the study cohort, 79% were admitted to the hospital. There were 39 deaths at 7 days and 138 deaths at 30 days. Compared with physician-estimated risk, EHMRG7 improved discrimination for mortality at 7 days. Addition of physician estimates did not significantly improve model discrimination for 7-day or 30-day mortality. There were no deaths at 7-days or 30-days for the 2 lowest risk groups of EHMRG7 and EHMRG30-ST, respectively.

Significance: This study prospectively validated the use of EHMRG for prediction of 7-day and 30-day mortality risk of HF patients presenting to the emergency department. Importantly, these risk score were superior to physician estimates and resulted in improved reclassification. The main limitation of the study is that the tested score was not used to alter decision-making and this should be tested in future trials.

Fractional flow-reserve vs angiographically-guided coronary artery bypass grafting. *JACC* 2018;72:2732-43

Background: The value of fractional flow reserve (FFR) in guiding percutaneous coronary re-vascularization is well established; however, there are limited data evaluating its role in guiding decision for bypass grafting. Thuesen et al from the Odense University Hospital, Denmark, performed a randomized clinical trial of patients referred for coronary artery bypass grating (CABG). Patients were randomized to FFR-guided CABG (N = 49), where lesions with FFR > 0.8 were deferred; and angiography-guided CABG (N = 48) where FFR values were obtained but blinded to the surgeon. The primary endpoint was graft failure after 6 months follow-up.

Findings: Follow-up data were available for 72 patients There was no difference between the FFR-guided and angiography-guided groups with regards to primary endpoint (graft failure rate was 16% vs 12% at 6 months, $P = 0.97$). Similarly, there was no difference in death, myocardial infarction, stroke, freedom from angina, or need for re-vascularization before the 6-months follow-up, between the groups. In regards to the deferred lesions (n = 24), there was significant drop in mean FFR from 0.89 to 0.82 ($P = 0.002$), and with 9 (37%) deferred lesions having follow-up FFR < 0.80.

Significance: FFR-guided CABG was associated with same rate of graft failure and clinical outcomes as compared to angiography-guided therapy. While significant number of lesions were spared and deferred in FFR-guided group, there was significant drop in FFR on follow-up, with more than a third of the lesions becoming physiologically flow-limiting (i.e., FFR < 0.80). Still, freedom from angina was similar between the two groups. The relatively small sample size, short duration of the study, the significant loss of follow-up of a quarter of the cohort, and failure of the surgeon to comply with graft plan in 12% of cases, are significant limitations. This remains a hypothesis generating study that needs further validation and testing in larger multicenter cohorts.

Disclosure

Dr. Hage reports research grant support from Astellas pharma and GE Healthcare.