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

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A New Index for Pre-Operative Cardiovascular Evaluation. ***J Am Coll Cardiol* 2019;73:3067-78**

Background: The most commonly used risk models for pre-operative cardiovascular evaluation prior to non-cardiac surgery are the Revised Cardiac Risk index (RCRI) and the National Surgical Quality Improvement Program (NSQIP) risk calculator. Dakik et al from the American University of Beirut Medical Center, Beirut, Lebanon derived and validated a cardiovascular risk index (CVRI) to stratify cardiovascular risk in patients undergoing non-cardiac surgery. The derivation cohort was from a prospective study of 3284 patients from a single center and the validation cohort was from the NSQIP database of more than a million patients from $>$ 200 hospitals. The primary outcome of the study was the occurrence of death, myocardial infarction, or stroke at 30 days after surgery.

Findings: In the derivation cohort, 38 patients (1.2%) had a cardiovascular event in the first 30 days after surgery. The identified predictors that were included in the CVRI (each assigned a value of 1) were age $\geq$ 75 years, history of heart disease, symptoms of angina or dyspnea, hemoglobin $<$ 12 mg·dL^{-1}, vascular surgery, and emergency surgery. 48%, 30%, 14%, 5% and 3% had a score of 0, 1, 2, 3, and $>$ 3, respectively. The corresponding rate of the primary outcome was 0%, 0.5%, 2.0%, 5.6%, and 15.7%, respectively. The discriminatory power of CVRI was comparable to NSQIP and better than RCRI (area under the ROC curve of 0.9, 0.89, 0.78, respectively). The CVRI was similarly predictive in the validation cohort with an area under the ROC curve of 0.82.

Significance: This study derived a novel index for risk stratification of cardiovascular events in patients undergoing non-cardiac surgery. This index, which is simple to calculate during clinical care, provided similar discriminatory power to the more complicated NSQIP score and was better than the more widely used RCRI score. An important finding from this study is the identification of a large proportion of patients who are at low risk of events and would likely not require any work-up. Strengths of this report include the use of a large validation cohort and the inclusion of symptoms and emergency surgery in the model. Limitations include the derivation of the index in a single medical center and the absence of comparison of the three scores in the validation data set.

Natural History, Quality of Life, and Outcome in Cardiac Transthyretin Amyloidosis. ***Circulation* 2019;140:16-26**

Background: Transthyretin cardiac amyloidosis (ATTR-CM) is a common cause of heart failure in the growing elderly population. Using the UK National Amyloidosis Center, Lane T et al from the University College London, United Kingdom, evaluated 1094 patients with confirmed ATTR-CM between 2000 and 2017 including wild type (n = 771), hereditary with V122l mutation (n = 205), and hereditary with non-V122l mutation (n = 118). Prospective evaluation was performed to assess cardiovascular parameters, 6-minute walk-test, quality of life using standardized questionnaire, hospitalization, and survival.

Findings: There was a significant delay in the diagnosis of ATTR-CM with more than 4 years in the

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wild-type variant (42% had cardiac symptoms). Patients with the hereditary V122I mutation were more functionally impaired ($P < .001$), had worse measure of cardiac involvement ($P < .001$) and higher mortality ($P < .0001$) compared to the two other subgroups. Using multivariate analysis, age (hazard ratio [HR] 1.037 [1.01-1.07] per year), advanced ATTR stage (HR 2.05 [1.35-3.10] for stage II and 3.70 [2.31-5.93] for stage III, using stage I as reference), V122I mutation (HR 2.07 [1.41-3.0]), LVEF (HR 0.98 [0.96-0.99]), and 6-minute walk-test (HR 0.88 [0.83-0.99] per 50 m increase) were independent predictors of patient survival.

Significance: While ATTR-CM is more commonly recognized, greater efforts in establishing the diagnosis early on are needed in order to start early treatment and improve quality of life and survival. Improved awareness, wider availability, and use of validated and standardized diagnostic modalities are hence crucial. Global longitudinal strain, myocardial contraction fraction, and other highly sensitive parameters were not readily available for many patients given they were introduced later throughout the enrollment period. Also, many new therapeutic strategies were not available early on which affected survival rate. Still, the current cohort is one of the largest ones available and highlights the importance of recognizing this cardiomyopathy and encourages new research in this field.

Stress-Associated Neurobiological Pathway Linking Socioeconomic Disparities to Cardiovascular Disease. ***J Am Coll Cardiol*** **2019;73:3243-55**

Background: Socioeconomic status (SES) is an important predictor of cardiovascular events and longevity. Tawakol et al from Massachusetts General Hospital and Harvard Medical School, Boston studied 509 patients without known cardiovascular disease who underwent clinically indicated whole body FDG PET to test the hypothesis that stress-associated metabolic activity in the amygdala (AmygA) mediates the link between lower SES and cardiovascular events. Major adverse cardiovascular events (MACEs) were a composite of cardiac death, myocardial infarction, unstable angina, cerebrovascular accident, peripheral artery disease with revascularization, or heart failure.

Findings: SES was inversely associated with AmygA and arterial inflammation even after adjusting for cardiovascular risk factors. During a median of 4 years, 40 individuals experienced MACE. SES was independently associated with MACE. AmygA was associated with MACE even after adjusting for SES and in cohorts with high SES stress (low income, high crime). AmygA associated with both hematopoietic tissue activity and arterial inflammation and all three associated with MACE. Mediation analysis demonstrated that the two pathways: ↓SES to ↑AmygA to ↑hematopoietic tissue activity to ↑arterial inflammation to ↑ MACE and ↓SES to ↑AmygA to ↑arterial inflammation to ↑ MACE significantly mediated the association of SES with MACE and together accounted for 28% of the total effect of SES on risk of MACE.

Significance: This study demonstrated that SES associates with MACE via a biological pathway that involves the amygdala, hematopoietic tissues, and arterial inflammation. This study may help identify targets for intervention to help ameliorate the adverse effect of SES on cardiovascular health. A major limitation of the study is that the FDG PET studies were performed for clinical indications and therefore the findings may not be generalizable. Also, the study did not demonstrate causation which will need to be demonstrated in a future study that involves an intervention that targets the proposed pathway.

Magnetic Resonance Perfusion or Fractional Flow Reserve in Coronary Disease. ***N Engl J Med*** **2019;380:2418-28**

Background: Among patients with stable angina, the decision to guide revascularization is often based on ischemic burden from perfusion imaging, or fractional flow reserve (FFR) assessment from an invasive coronary angiography. Nagel et al from the University Hospital Frankfurt, Germany, performed a multicenter, unblinded, clinical-effectiveness non-inferiority trial, where 918 patients with stable angina and at least 2 risk factors or a positive treadmill stress test were randomized to stress-perfusion cardiac MRI strategy (n = 454) vs invasive coronary angiogram with FFR (n = 464) strategy. Revascularization was performed if the ischemic burden was at least 6% of the left ventricular myocardium (semi-quantified from the MRI perfusion) or if the FFR was ≤ 0.8. The primary endpoint was a composite of death, non-fatal myocardial infarction, or target vessel revascularization at 1 year.

Findings: Revascularization was recommended in both MRI and FFR groups to similar extent (41% vs 46%, $P = .11$), but were less performed in the former group (36% vs 45%, $P = .005$). There was no difference in the primary outcome between the two strategies (3.6% vs 3.7%, respectively, with risk difference − 0.2% meeting the non-inferiority threshold) with hazard ratio for MRI strategy 0.96 (95% CI 0.47-1.94, $P = .91$). Similarly, there was no difference among patients free from angina at 1 year between both strategies ($P = .21$).

Significance: Among patients with stable angina symptoms, stress-perfusion cardiac MRI strategy was

associated with lower incidence of downstream coronary revascularization as compared to invasive FFR strategy, but with similar major cardiovascular endpoints at 1 year, and was therefore non-inferior. The study cohort was relatively large, well randomized, and with similar optimal medical treatment at 1-year follow-up. However, the incidence of MACE was lower than predicted which affected the non-inferiority margins. Also, the patient population was predominately white male; optimization of antianginal therapy prior to enrollment was not done systematically; and follow-up time was relatively short. While the study focused on comparing cardiac MRI and invasive FFR in guiding revascularization, other strategies involving stress myocardial perfusion imaging with positron emission tomography and coronary flow reserve vs cardiac CT angiography with CT-FFR are worth evaluating in future prospective studies.

Effect of Systolic and Diastolic Blood Pressure on Cardiovascular Outcomes. ***N Engl J Med*** **2019;381:243-51**

Background: Current risk prediction tools consider systolic blood pressure (SBP) but not diastolic BP (DBP). Further, the newest American guidelines have defined two treatment thresholds of 130/80 and 140/90 mmHg depending on the level of risk. Flint et al from Kaiser Permanente Northern California, Oakland, CA used $>$ 36 million outpatient BP measurements from 1.3 million adults in a large integrated health care system to examine the relationship between BP and cardiovascular events. The primary outcome was a composite of the first episode of myocardial infarction, ischemic stroke, or hemorrhagic stroke.

Findings: During 8 years of follow-up more than 44,000 events occurred. 18.9% and 43.5% of the cohort had a BP $>$ 140/90 and 130/80 mmHg, respectively. Increasing SBP was associated with increased events, whereas there was a J-shaped relationship between DBP and outcomes with increased risk seen with both low and high DBP. This relationship was partially explained by age and other covariates. In multivariable Cox regression model, both the burden of systolic hypertension ($\geq$ 140 mmHg, hazard ration per unit increase in z score 1.18; 95% CI 1.17 to 1.18; $P < .001$ and diastolic hypertension ($\geq$ 90 mmHg, 1.06; 95% CI 1.06 to 1.07; $P < .001$) were independently associated with outcomes. Similar results were obtained with the lower threshold of 130/80 mmHg. Lastly, DBP continued to be associated with outcomes in patients with normal SBP (defined at both thresholds).

Significance: This study demonstrated in a large contemporary cohort that both SBP and DBP independently associated with increased cardiovascular events and that these associations were not altered by the choice of threshold used. These findings seem to support the recent guideline shift to lower BP targets for high-risk individuals. Although SBP had a greater association with outcomes than DBP, both were independently prognostic and should be considered in clinical care.

Application of High-Sensitivity Troponin in Suspected Myocardial Infarction. ***N Engl J Med*** **2019;380:2529-40**

Background: The value of high-sensitivity troponin levels in predicting probability of myocardial infarction and subsequent 30-day outcomes among patients presenting to the emergency room with anginal symptoms is not well established. Neumann et al from the University Heart Center Hamburg, Germany, pooled data from 15 international cohorts, comprising 22,651 patients (9,604 in the derivation data set and 13,047 in the validation data set). All patients had clinical suspicion of myocardial infarction (MI) and were evaluated in the emergency room with high-sensitivity troponin and for many with serial dynamic testing. A risk-assessment tool was developed to estimate the risk of MI at presentation and subsequent 30-day risk for death or MI.

Findings: The prevalence of MI was 15.3% in the entire cohort. Lower concentrations of high-sensitivity troponin (less than 6 $ng \cdot L^{-1}$) and smaller absolute change during serial sampling (less than 4 $ng \cdot L^{-1}$ after 45-120 minutes) were found in more than half of the cohort and were associated with very low likelihood of MI (negative predictive value 99.5%) and reduced short-term risk of major cardiovascular adverse event (0.2% at 30 days). On the other hand, patients with a high-sensitivity troponin (at least 100 $ng \cdot L^{-1}$) or an absolute change of at least 12 $ng \cdot L^{-1}$ within 120-210 minutes had significant high likelihood of MI (positive predictive value of 76.5%) and increased 30-day outcomes (14.7%). These results were tested in the validation cohort. Finally, patients in the emergency room who were ruled out to have MI but still had high-sensitivity troponin greater than 10 $ng \cdot L^{-1}$ had increased long-term risk of death or MI (4.8% at 1 year and 8.1% at 2 years vs general population risk of 1.4% and 3.4%, respectively).

Significance: Using high-sensitivity troponin and its dynamic change, a risk-assessment calculator was developed and validated among patients presenting to the emergency room with anginal symptoms to predict likelihood of MI on presentation and 30-day cardiovascular outcomes. In the subset of patients in whom MI was ruled out but had positive troponin, long-term

outcomes were also predicted by this new tool. The major limitations included (1) lack of standardized adjudication tool for the diagnosis of MI among the different cohorts, and (2) different pre-test probabilities among the different cohorts.

Disclosure

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