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

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MYOCARDIAL INJURY IN SEVERE COVID-19 COMPARED WITH NON-COVID-19 ACUTE RESPIRATORY DISTRESS SYNDROME. CIRCULATION. 2021;143:553-565.

Background: Myocardial injury is common in patients hospitalized with COVID-19. Metkus et al. from Johns Hopkins University, Baltimore, MD performed a retrospective cohort study of 243 patients intubated with COVID-19 with troponin levels assessed and compared them to 506 patients with acute respiratory distress syndrome (ARDS) from pneumonia without COVID-19. The primary outcome was in-hospital mortality.

Findings: The mean age of the COVID-19 cohort was 63 years and the majority (87%) received vasopressors. Half of the patients (51%) had troponin levels above the upper limits of normal and 16% had levels more than tenfold the upper limits of normal. Mortality was higher for those with abnormal vs normal troponin (61.5% vs 22.7%, $P < 0.001$; hazard ratio 2.31, 95% CI 1.47-3.65). The association between troponin levels and mortality was not significant after multivariate adjustment for age, sex, creatinine, bilirubin, Pao₂/Fio₂ ratio, vasopressor use, and lactate levels. The rate of myocardial injury in the control group of ARDS without COVID-19 was similar (50%; odds ratio 1.09, 95% CI 0.78-1.44, $P = 0.72$). After multivariate adjustment, COVID-19 was associated with *lower* odds of myocardial injury compared with ARDS (odds ratio 0.55, 95% CI 0.36-0.84, $P = 0.005$). In unadjusted analysis,

COVID-19 patients with myocardial injury had the highest mortality (P -interaction 0.012) but this was no longer significant after multivariate adjustment (P -interaction 0.082).

Significance: In this study, myocardial injury was common in intubated patients with COVID-19 and it was associated with increased mortality. However, this association was not significant after multivariate adjustment suggesting that the risk of myocardial injury is related to baseline factors and underlying multi-organ dysfunction. Importantly, myocardial injury was less common in COVID-19 than in ARDS from pneumonia after adjustment for confounders. These findings suggest that the adverse prognosis associated with myocardial injury in COVID-19 is a function of multisystem organ involvement, similar to ARDS from pneumonia.

ABSOLUTE CORONARY BLOOD FLOW MEASURED BY CONTINUOUS THERMODILUTION IN PATIENTS WITH ISCHEMIA AND NONOBSTRUCTIVE DISEASE. J AM COLL CARDIOL 2021;77:728-41

Background: Ischemia with non-obstructive coronary artery disease (INOCA) is a well-defined entity involving coronary endothelial and vasomotor dysfunction, and commonly associated with angina. Still, the association between absolute coronary flow, resistance and anginal symptoms is not well defined in this cohort of patients. Konst R et al. from Radboud University Medical Center, Nijmegen, the Netherlands, explored this relationship in 84 patients with INOCA (87% women, mean age 57 years) using intracoronary continuous thermodilution with saline-induced hyperemia which is a novel technique to quantify absolute coronary flow (Q) and resistance (R), and compared it to conventional coronary function testing, including acetylcholine provocation

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testing, and adenosine testing (coronary flow reserve [CFR]/index of microvascular resistance [IMR])

Findings: The vast majority of patients with INOCA had coronary vasospasm (87% with positive acetylcholine provocation testing) and 38% had abnormal CFR/IMR (adenosine testing). The absolute resistance R was significantly higher among those with abnormal adenosine testing ($P = 0.04$); however, there was no significant difference in either Q or R among those with and without coronary vasospasm. Finally, reduced Q and increased R were predictive of severe angina symptoms (odds ratio 3.1 [1.2-8.3], $P < 0.03$; and 2.6 [1.0-6.8], $P = 0.05$, respectively) with corresponding area under the curves of 0.60 and 0.58, respectively.

Significance: Among patients with INOCA, reduced Q and increased R with intracoronary continuous thermodilution were associated with two-to-threefold increased odds of developing severe angina, with an intermediate area under the curve. While increased R was significantly higher among those with abnormal CFR/IMR, there was no difference among those with/without coronary vasospasm. Continuous thermodilution is an accurate, reproducible, easy to use method with promising clinical value in patients with INOCA. The prognostic value of this new method as compared to conventional CFR needs to be determined in follow-up outcome studies. Also, reference values for Q and R need to be validated.

CARDIAC MYOSIN ACTIVATION WITH OMECANTIV MECARBIL IN SYSTOLIC HEART FAILURE. N ENGL J MED 2021;384:105- 16.

Background: Omecamtiv mecarbil is a cardiac myosin activator that improves myocardial function by directly augmenting cardiac sarcomere function. Teerlink et al. from the San Francisco Veterans Affairs Medical Center, San Francisco, CA report the results of the GALACTIC-HF study, a phase 3 trial that randomized 8256 patients (mean age 64.5 years, 21% female, 78% White, ischemic heart failure 53%) with symptomatic chronic heart failure (left ventricular ejection fraction $\leq 35\%$) to receive oral omecamtiv mecarbil or placebo on top of standard heart-failure therapy. The primary outcome was a composite of a first heart-failure event (hospitalization or urgent visit for heart failure) or death from cardiovascular causes.

Findings: During a median follow-up of 21.8 months the primary outcome occurred in 37.0% in the omecamtiv mecarbil group vs 39.1% in the placebo group (hazard ratio 0.92; 95% CI 0.86-0.99; $P = 0.03$). Cardiovascular deaths was not different between the 2 groups (19.6% vs 19.4%, 1.01; 0.92-1.11; $P=0.86$). Similarly,

there was no difference in all-cause death or first hospitalization for heart failure. Omecamtiv mecarbil was discontinued in 20.6% and placebo in 21.9%. Major cardiac ischemic events occurred in 4.9% in the omecamtiv mecarbil group and in 4.6% in the placebo group.

Significance: In this randomized, placebo-controlled trial, a first-in-class medication, omecamtiv mecarbil, was associated with a lower risk of the composite primary outcome of a heart-failure event or death from cardiovascular cause. However, the effect was rather modest (absolute risk reduction of 2.1%) compared to the rate of events with no detectable effect on hard outcomes or any secondary outcome. Although there is a concern for myocardial ischemia with myosin activation, there was no difference in ischemic events in this randomized study.

EFFECT OF A RESTRICTIVE VS LIBERAL BLOOD TRANSFUSION STRATEGY ON MAJOR CARDIOVASCULAR EVENTS AMONG PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND ANEMIA. THE REALITY RANDOMIZED CLINICAL TRIAL. JAMA. 2021;325(6):552-560.

Background: Anemia is common in patients with acute myocardial infarction (AMI) and is associated with worse outcomes. Prior randomized studies in patients with gastrointestinal bleeding and those undergoing surgical procedures have generally favored a restrictive rather than a liberal blood transfusion strategy but these trials have excluded patients with AMI. Ducrocq et al. from the Université de Paris, France randomized 668 patients (median age 77 years, 58% men, 50% diabetes) with myocardial infarction and hemoglobin level between 7 and 10 g·dL in an open-labeled fashion to a restrictive (transfusion triggered by hemoglobin ≤ 8 g·dL) or a liberal (transfusion triggered by hemoglobin ≤ 10 g·dL) transfusion strategy. The primary outcome was a composite of all-cause death, nonfatal stroke, nonfatal recurrent myocardial infarction, or emergency revascularization prompted by ischemia at 30 days.

Findings: Most patients ~ 80% underwent coronary angiography and two thirds underwent myocardial revascularization. Most patients received dual antiplatelet therapy. Almost all patients in the liberal group (99.7%) received at least 1 transfusion compared to 35.7% in the restrictive group. At discharge, the hemoglobin level was lower in the restrictive group (9.7 vs 11.1 g·dL, -1.4 , 95% CI -1.6 to -1.2). The primary outcome occurred in 11.0% in the restrictive group vs 14.0% in the liberal group, relative risk 0.79 [1-sided 97.5% CI 0.00-1.19] meeting the pre-specified margin for non-inferiority but not of superiority. Recurrent myocardial infarction occurred in 2.1% vs 3.1% of patients in the 2 groups.

Significance: This trial demonstrated that in patients with AMI and anemia a restrictive transfusion strategy is non-inferior to a liberal strategy. It is noted that the restrictive strategy was not statistically superior to the liberal strategy and the margin for non-inferiority was relatively large and included the potential for significant harm. While larger studies are needed for definitive conclusions, this study demonstrates that a restrictive transfusion strategy may be safe in some patients with AMI and anemia.

CRYOABLATION OR DRUG THERAPY FOR INITIAL TREATMENT OF ATRIAL FIBRILLATION. N ENGL J MED 2021;384:305- 15.

Background: Pulmonary vein isolation in patients with atrial fibrillation is more effective in maintaining normal sinus rhythm than anti-arrhythmic therapy; yet, current guidelines recommend ablation only after a failed trial of at least one anti-arrhythmic therapy. Andrade J et al. from Vancouver General Hospital and the University of British Columbia, performed a randomized controlled trial of 303 symptomatic patients with untreated paroxysmal atrial fibrillation to first-line treatment with catheter ablation cryotherapy (n = 154) or a trial of anti-arrhythmic drug therapy (n = 149). All patients underwent an implantable cardiac monitoring device, with the primary outcome being the first documented recurrence of any atrial tachyarrhythmia between 91 and 365 days after catheter ablation or the initiation of an antiarrhythmic drug.

Findings: After a median follow-up of 12 months, patients randomized to anti-arrhythmic therapy first had significantly higher rate of recurrence of tachyarrhythmia compared to those who underwent cryoablation as first-line therapy (67.8% vs 42.9%, hazard ratio 2.08, $P < 0.001$), and similarly more symptomatic atrial tachyarrhythmia (26% vs 11%, hazard ratio 2.6 [1.5-4.5]). There was no significant difference in serious adverse events between the two groups

Significance: In symptomatic untreated patients with paroxysmal atrial fibrillation, cryoablation as a first line therapy, as compared to antiarrhythmic therapy, was safe and associated with significantly lower rate of recurrence (more than half) of atrial fibrillation including symptomatic episodes and overall burden as assessed by continuous cardiac rhythm monitoring. Future studies are needed to assess hard cardiovascular endpoints and evaluate other non-cryoablation techniques with longer follow-up time.

SCREENING FOR ATRIAL FIBRILLATION IN THE OLDER POPULATION A RANDOMIZED CLINICAL TRIAL. JAMA CARDIOL 2021 AHEAD OF PRINT

Background: Atrial fibrillation (AF) is common in the elderly population and a major risk factor for stroke. There are limited data regarding value of screening for AF in this cohort. Gladstone D et al. from the University of Toronto, ON, randomized 856 hypertensive patients without known AF and age ≥ 75 years from 48 different primary care practices between 2015 and 2019 (57% women, mean age 80 years) to two groups: (1) control group (n = 422) that received standard care (routine clinical follow-up with pulses check and heart auscultation at baseline and 6 month); and (2) screening group (n = 434) that received in addition to standard care, a 2-weeks continuous ECG patch recording at baseline and 3 months, and automated home blood pressure machine with oscillometric AF screening capability to use twice-daily. The primary outcome was AF detected by ECG monitoring or clinically within 6 months. Secondary outcomes included anticoagulant use, device adherence, and AF detection by BP monitors.

Findings: Using intention to treat analysis, AF was detected in a significantly higher proportion of screened individuals as compared to the control group (5.3% vs 0.5%, relative risk 11.2, $P = 0.001$). The median total time spent in AF and longest duration of AF were 6.3 and 5.7 hours, respectively. Almost three-quarters of patients with detected AF were started on anticoagulation, resulting in more than fourfold higher relative risk of being on anticoagulation in the screening group (4.1% vs 0.9%, RR 4.4, $P = 0.007$). Finally, twice daily screening for AF using the home blood pressure monitoring device had sensitivity, specificity, positive and negative predictive values of 35%, 81%, 9%, and 96%, respectively.

Significance: Among hypertensive elderly patients without known AF, screening with 2 weeks ECG monitoring at baseline and 3 months was associated with more than tenfold higher detection rate of AF and resulted into a fourfold higher rate of use of anticoagulant. Intermittent oscillometric screening with a blood pressure monitor was an inferior screening strategy and with suboptimal diagnostic accuracy. Additional data are needed to assess other screening methods such as smart watch devices, as well as short and long-term cardiovascular endpoints, particularly stroke, as well as incidence of bleeding. Also, a cost-effective analysis is needed to further explore risk/benefit of screening for AF.

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