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

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Natural History of Patients With Ischemia and No Obstructive Coronary Artery Disease. The CIAO-ISCHEMIA Study. *Circulation*. 2021;144:1008–1023

Background: Patients with ischemia and non-obstructive coronary artery disease (INOCA) are often symptomatic and have adverse cardiovascular events. Reynolds et al. from New York University Grossman School of Medicine, New York, conducted the CIAO-ISCHEMIA (Changes in Ischemia and Angina over One Year in ISCHEMIA Trial Screen Failures With INOCA), a 5-year international cohort registry conducted between 2014 and 2019, to assess natural history of INOCA in 208 patients. Inclusion criteria included patients with angina and positive stress echocardiogram (images interpreted in an echocardiography core laboratory by blinded readers) without obstructive lesions on cardiac CT angiography who were excluded from the ISCHEMIA trial. The primary outcome was the correlation between changes in ischemic burden on follow-up stress echocardiogram and angina frequency and score (Seattle angina questionnaire). The cohort was compared to that of ISCHEMIA participants, i.e., those with ischemia and obstructive coronary artery disease.

Findings: INOCA participants in CIAO were more often female (66% vs 26%), younger, more likely to have depression but less likely to have diabetes as compared to ISCHEMIA participants. Still, both cohorts had similar ischemic burden on stress echocardiogram

(82% underwent exercise stress in both cohorts). In addition, there was no correlation between ischemic burden and angina score at enrollment in either cohort. After 1 year, the ischemic burden resolved in half of CIAO participants, while 23% had at least 3 ischemic segments. The change in ischemic burden, however, did not correlate with angina score that improved in 43% and worsened in 14% of participants.

Significance: Ischemia and non-obstructive coronary artery disease is becoming a well-recognized entity, attributed in part to microvascular disease, endothelial dysfunction, among others. Still, the pathophysiology of angina remains enigmatic in many aspects, particularly that ischemic burden does not necessarily correlate with symptoms. Therefore, ischemic burden on stress echocardiography is not a surrogate for symptoms in patients with or without obstructive coronary artery disease. It is worthwhile to note that of the original 345 CIAO participants, 137 patients were excluded leaving 208 only for analysis. It will be interesting to assess whether the results are also valid for exercise and pharmacological stress myocardial perfusion imaging.

Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. *N Engl J Med* 2021;385:1078–90.

Background: The safety and tolerability of COVID-19 vaccines have been documented in clinical trials. However, these trials are limited by the relatively small number of participants making it hard to detect rare side-effects. To date, almost 3.4 billion doses of vaccine have been administered world-wide. Barda et al. used data from the largest health care organization in Israel which insures 52% of the population of the country to evaluate the safety of the BNT162b2 mRNA (Pfizer–BioNTech) vaccine. The study includes individuals 16 years and older who had not had prior

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COVID and excluded residents of long-term care facilities and healthcare workers. Vaccinated individuals were matched to eligible controls who had not been previously vaccinated. The study included 42 days of follow-up, which provided 21 days of follow-up after each of the first and second vaccine doses. The study also estimated the effects of COVID infection on these same adverse events.

Findings: The vaccinated cohorts included a mean of 884,828 persons (median age 38 years, 48% female) matched 1:1 to a control group and the COVID-infected cohorts included 173,106 persons (median age 24 years, 54% female) matched 1:1 to a control group. The risk of vaccination compared to control group was higher for myocarditis (risk ratio 3.24, 95% CI 1.55-12.44, risk difference 2.7 events per 100,000 persons, 95% CI 1.0-4.6), lymphadenopathy (2.43; 78.4 per 100,000 persons), appendicitis (1.40; 5.0 per 100,000), and herpes zoster infection (1.43; 15.8 per 100,000). The incidence of myocarditis was mainly after the second dose of the vaccine. COVID infection increased the risk of myocarditis (18.28; 11.0 per 100,000), acute kidney injury (14.83; 125.4 per 100,000 persons), pulmonary embolism (12.14; 61.7 per 100,000), intracranial hemorrhage (6.89; 7.6 per 100,000), pericarditis (5.39; 10.9 per 100,000), myocardial infarction (4.47; 25.1 per 100,000), deep vein thrombosis (3.78; 43.0 per 100,000), and arrhythmia (3.83; 166.1 per 100,000).

Significance: Using data from a large population in Israel matched to controls, the BNT162b2 mRNA vaccine was associated with an increased risk of myocarditis (2.7 events per 100,000 persons), appendicitis, lymphadenopathy, and herpes zoster infection. To place these numbers in perspective, the study also showed a substantially higher risk of myocarditis with COVID infection (11.0 events per 100,000 persons) in addition to other adverse events such as pericarditis, myocardial infarction, and arrhythmia which are not increased with the vaccine. The main limitation of the study is that the participants were matched to a control group and not randomized.

Prevalence of Subclinical Coronary Artery Atherosclerosis in the General Population. Circulation. 2021;144:916-929

Background: In an effort to improve on prevention strategies, Bergström et al. from the University of Gothenburg, Sweden, sought to assess the prevalence of subclinical coronary artery atherosclerosis in the general Swedish population. A random 30,154 individuals (age 50-64 years), asymptomatic, without known coronary artery disease (CAD) underwent a high-quality cardiac CT angiography and coronary artery calcium (CAC)

score and were enrolled in the Swedish Cardiopulmonary Bioimage study (SCAPIS).

Findings: Subclinical coronary atherosclerosis was common and involved 42% of the cohort, while significant stenosis ($\geq 50\%$) and critical disease were found in 5.2% and 1.9% of the cohort, respectively. The disease onset was delayed on average by 10 years in women and was driven by age and cardiovascular risk factors. Almost half of patients with CAC score greater than 400 had significant stenosis. Finally, 5.5% of patients with CAC score of zero had atherosclerosis (i.e., non-calcified plaques) and 0.4% had significant stenosis.

Significance: In this Swedish registry of middle-age general population, subclinical atherosclerosis is quite prevalent. While the majority of patient had no or mild disease, more than 5% had significant disease. Also, while CAC score of zero is associated with very low probability of disease, it does not exclude it. This reiterates prior data showing up to 5% of patients presenting with acute myocardial infarction have CAC score of zero. The current registry will be very helpful to design high-risk screening and cost-effective preventive strategies and will add to the data from the MESA registry among others. With the evolving technology with new-generation CT scanner allowing faster scanning with much lower radiation, we should expect positive dynamic changes in preventive medicine.

Side Effect Patterns in a Crossover Trial of Statin, Placebo, and No Treatment. J Am Coll Cardiol 2021;78:1210-1222.

Background: Many patients on statins experience side-effects and a significant proportion of them discontinue treatment. Howard et al. from National Heart and Lung Institute, Imperial College London, United Kingdom, evaluated 60 patients (mean age 65.5 ± 8.6 years, 42% female, 90% White, 77% primary prevention, median number of statins tried was 2, median previous statin treatment duration was 1 year) who had side-effects severe enough to require abandonment of statin therapy within 2 weeks of starting therapy using a multiple cross-over, 3-arm, double-blind, placebo-controlled study. Participants were randomized into 12 treatment periods each for 1 month (4 months of statin—atorvastatin 20 mg, 4 months of placebo, 4 months with no treatment). Participants used an app to submit their symptom burden on a daily basis (0 no symptoms to 100 worst imaginable symptoms). Participants could stop taking medications at any time if symptoms were intolerable but were asked to retry every month. The primary outcome was the nocebo ratio = (symptom intensity on placebo—symptom intensity on no tablets)/(symptom intensity on statins—symptom intensity on no tablets).

Findings: The most common symptom causing statin abandonment before enrollment was muscle ache (60%) followed by fatigue (15%) and cramps (10%). The mean symptom score for no-tablet months was 8.0 (95% CI 4.7–11.3), for placebo months 15.4 (12.1–18.7, $P < 0.001$ vs no-tablet), and for statin months 16.3 (13.0–19.6, $P < 0.001$ vs no-tablet and $P = 0.39$ vs placebo months). The nocebo ratio calculated using individual patient data was 2.2 and using pooled patient data was 0.90. 31 of 60 patients stopped at least 1 tablet month early (26 stopped statin and 23 stopped placebo, not statistically significant). Neither the intensity of symptom onset nor the magnitude of symptom relief predicted whether the tablet was statin or placebo. At 6 months after completion of the trial, 30 of the 60 patients had successfully restarted statin therapy after a discussion of their individualized trial results (10 of which had stopped taking study drug during the trial due to intolerable side-effects).

Significance: Most side-effects attributed to statin therapy are nocebo effects. In this randomized, blinded, cross-over trial, cessation of treatment was as frequent for placebo as it was for statin and the intensity of side-effects was similar (and higher than no treatment). Even symptoms that start with treatment and quickly resolve after stopping the drug could be caused by placebo and this pattern may not be used clinically as evidence of statins causing the symptoms. Why statins induce a high-level of nocebo effect should be further evaluated. Encouragingly, when patients were shown their own data, half of the patients who originally abandoned statin therapy successfully restarted treatment.

Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension. *N Engl J Med* 2021;385;14:1268–79

Background: The ideal target for systolic blood pressure (SBP) control in elderly patients with hypertension for cardiovascular risk reduction remains controversial. Zhang et al. from FuWai Hospital, Peking Union Medical College, Beijing, China, performed a randomized clinical trial of Chinese patients, aged 60 to 80 years, to an intensive treatment cohort (SBP 110–129 mm Hg, $N = 4243$) and standard treatment cohort (SBP 130–149 mm Hg, $N = 4268$). Patients with prior stroke were excluded. The primary outcome was a composite of stroke, acute coronary syndrome (acute myocardial infarction and hospitalization for unstable angina), acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes.

Findings: The mean SBP at 1-year follow-up was lower among patients assigned to intensive treatment group (127.5 mm Hg vs 135.3 mm Hg). After a median follow-up period of 3.3 years, aggressive SBP control was associated with 26% reduction in the primary endpoint (3.5% vs 4.6%, HR 0.74 [0.60–0.92], $P = 0.0007$). The benefit was seen in most individual components of the primary outcome, with a favorable trend, but driven mainly by significant reduction in acute decompensated heart failure (HR 0.27), stroke (HR 0.67), and acute coronary syndrome (HR 0.67). There was no significant difference in safety endpoints and renal outcomes between the two groups, but higher incidence of hypotension in the intensive group (3.4% vs 2.6%, HR 1.3, $P = 0.03$).

Significance: Intensive treatment of blood pressure among Chinese aged 60–80 years to achieve SBP 110–129 mm Hg was associated with significant reduction in cardiovascular outcomes, driven mainly by reduction in acute heart failure, stroke, and acute coronary syndrome, with good safety profile except for mild increase in incidence of hypotension. The large sample size of the cohort as well as using home blood pressure monitoring are some of the strengths of the paper. The study however excluded patients with prior stroke (ischemic and hemorrhagic) and therefore the findings cannot be generalized to this cohort. Additional studies to assess the impact of such intensive SBP control in a non-Chinese cohort as well as those with age greater than 80 years are warranted.

Myocardial Viability Assessment Before Surgical Revascularization in Ischemic Cardiomyopathy. *J Am Coll Cardiol* 2021;78:1068–1077

The most common cause of heart failure is ischemic heart disease. This could be caused by scar formation in the myocardium and/or areas of dysfunctional but viable myocardium. Identifying patients with dysfunctional but viable myocardium is important since they can recover function with appropriate treatment, especially revascularization with coronary artery bypass grafting. Panza, Chrzanowski, and Bonow review the literature on this important topic and provide insights on myocardium viability assessment. The paper reminds us that some patients with ischemic heart disease who do not meet the dichotomous imaging endpoint for ‘viability’ may also benefit from revascularization even if they do not experience an improvement in left ventricular systolic function since revascularization also provides functional and electric stability to the myocardium. In addition to prolonging life, revascularization may also improve

quality of life and exercise capacity. The paper provides a useful algorithm for the use of imaging for assessment of myocardial viability in which the focus is not on whether the patient has substantial amount of viable myocardium per se, but rather if the distribution of viable myocardium is concordant with vessels suitable for revascularization on angiography. The decision for or against revascularization integrates findings from viability imaging and angiography in addition to upfront

risk of revascularization. This later point should be stressed in clinical practice since it is vital for deriving benefit from the use of imaging to guide revascularization in these patients and is hard to assess in clinical trials.

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