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

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Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. *N Engl J Med.* 2021 Aug 4. <https://doi.org/10.1056/NEJMoa2103417>

Background: COVID-19 is associated with increased thrombosis and therapeutic anticoagulation has been proposed as a therapeutic strategy to decrease thrombotic events and improve outcomes. The REMAP-CAP, ACTIV-4a, and ATTACC Investigators harmonized their protocols early in the pandemic to perform an integrated, multiplatform, randomized clinical trial to assess the effect of therapeutic dose anticoagulation in critically ill patients who were hospitalized for Covid-19. Patients were randomly assigned to receive therapeutic-dose anticoagulation with unfractionated or low-molecular-weight heparin (for 14 days or recovery) or to receive usual-care pharmacologic thromboprophylaxis in an open-label fashion. The primary outcome was organ support-free days, that combined in-hospital death and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge.

Findings: Data on the primary outcome were available for 1098 patients of whom 536 were randomized to receive therapeutic anticoagulation (mean age 60 years, 72% men, 745 white, 73% from the UK and 15% from the USA, diabetes 32%, chronic respiratory disease 25%, mean body mass index 30 kg/m²,

82% on glucocorticoids, 33% on remdesivir). The median value for organ support-free days was 1 (interquartile range – 1 to 16) for therapeutic anticoagulation vs 4 (interquartile range – 1 to 16) for usual-care pharmacologic thromboprophylaxis. The median adjusted proportional odds ratio for the effect of therapeutic-dose anticoagulation on organ support-free days was 0.83 (95% credible interval, 0.67 to 1.03), yielding a posterior probability of futility of 99.9% and a posterior probability of inferiority of 95.0%. The rate of survival to hospital discharge was not different between the 2 groups (63% vs 65%, posterior probability of inferiority, 89%). Fewer patients in the therapeutic-dose anticoagulation experienced major thrombotic events (6.4% vs 10.4%) but the rate of major thrombotic events or death was similar in the two groups (40.1% and 41.1%) and more patients had major bleeding (3.8% vs 2.3%).

Significance: In this randomized trial of critically ill patients with COVID-19, therapeutic anticoagulation did not increase the probability of survival to hospital discharge or the number of days free of cardiovascular or respiratory organ support (there was a 95% probability of being inferior). While treatment resulted in less thrombotic events it was associated with an 89% probability of decreased survival to hospital discharge. Despite early enthusiasm for anticoagulation in these patients, this data from a large randomized trial does not support the routine use of therapeutic-dose anticoagulation in critically ill patients with COVID-19.

Cardiovascular Biomarkers in the Early Discrimination of Type 2 Myocardial Infarction. *JAMA Cardiol.* 2021;6(7):771–780

Background: The two most common types of myocardial infarction (MI) are type 1 (TIMI), which is

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due to acute plaque rupture, and type 2 (T2MI), which is due to supply demand mismatch. The clinical distinction between both types is crucial as it dictates different treatment pathways. While high-sensitivity cardiac troponin (hs-cTn) is most commonly used to define MI, it lacks the accuracy to distinguish both types. Nestelberger et al. from the University Hospital Basel, Switzerland, performed an international multicenter prospective study with patients presenting to the emergency room with chest pain (12 emergency departments in 5 European countries) to test the quantitative discriminative accuracy of standard cardiac biomarkers of MI (hs-cTnT, hs-cTnI) in addition to 17 new ones to differentiate T1MI vs T2MI. The standard reference was the final diagnosis obtained using all available data (clinical, imaging, biomarkers, etc..) that was adjudicated by two independent cardiologists.

Findings: Among 1106 patients with an adjudicated final diagnosis of MI, 860 (77.8%) had T1MI, and 246 (22.2%) had T2MI. Patients with T2MI had lower concentrations of biomarkers quantifying cardiomyocyte injury (hs-cTnT, hs-cTnI, and cardiac myosin-binding protein C) as compared to those with T1MI ($P < .001$ for all); but higher concentrations of biomarkers quantifying endothelial dysfunction, microvascular dysfunction, and hemodynamic stress (C-terminal proendothelin, mid regional proadrenomedullin, mid regional pro-A-type natriuretic peptide, and growth differentiation factor; $P < .001$ for all). The discriminative accuracy of the biomarkers however, was modest including those specific for myocardial injury (area under the curve [AUC] ranging from 0.67 to 0.71) and the new ones (AUC ranging from 0.66 to 0.77).

Significance: Current and new cardiovascular biomarkers that quantify different pathways (injury, endothelial and microvascular dysfunction and shear stress) have only modest capability to discriminate T2MI from T1MI. The study however included only patients presenting with chest pain to the emergency room; the value of the new biomarkers in other clinical scenarios such as post-operative troponin leak, non-chest pain related presentation, remains to be defined. Furthermore, patients on hemodialysis were excluded from the study. In addition, certain bias cannot be excluded, not to mention possible misclassification as many patients did not undergo coronary angiography or cardiac magnetic resonance imaging that could have provided useful information. Clinical parameters combined with diagnostic imaging remain the current reliable mean to identify patients with T2MI.

Milrinone as Compared with Dobutamine in the Treatment of Cardiogenic Shock. *N Engl J Med* 2021;385:516–25

Background: There is paucity of evidence regarding the use of milrinone vs dobutamine in patients with cardiogenic shock. Mathew et al. from University of Ottawa Heart Institute, Canada conducted a single-center, randomized, double-blinded clinical trial of milrinone vs dobutamine in patients with cardiogenic shock. The primary outcome was the composite of in-hospital death, resuscitated cardiac arrest, cardiac transplant or mechanical circulatory support, nonfatal myocardial infarction, transient ischemic attack or stroke diagnosed by a neurologist, or initiation of renal replacement therapy.

Findings: A total of 192 patients were randomized 1:1 to receive milrinone vs dobutamine (mean age 69 years, 38% women, 90% white, median LVEF 25%, ischemic etiology 69%, atrial fibrillation 51%, chronic kidney disease 40%). A primary outcome event occurred in 49% vs 54% in the milrinone vs dobutamine groups (relative risk 0.90, 95% CI 0.69 to 1.19; $P = .47$). There was no evidence of heterogeneity across multiple subgroups and no difference in a time-to-event analysis. There was no significant difference in any of the secondary outcomes including the components of the primary outcome. Finally, there was no difference in hemodynamics or the occurrence of atrial or ventricular arrhythmia.

Significance: This randomized trial did not find an advantage for using milrinone over dobutamine for the treatment of cardiogenic shock. This trial adds important data for the treatment of this high-risk population. The risk of in-hospital death is still high for patients with cardiogenic shock in the current era (37% vs 43%, relative risk 0.85, 95% CI 0.60 to 1.20). The study is limited by its small size (note the wide confidence intervals) and recruitment from a single center.

Cardiovascular and Kidney Outcomes Across the Glycemic Spectrum Insights From the UK Biobank. *J Am Coll Cardiol* 2021;78:453–64

Background: Dysglycemia in the absence of type 2 diabetes (T2D), termed prediabetes, is more prevalent than diabetes, and associated with subclinical alterations in cardiac structure and function that may lead to cardiovascular and kidney events. Current guidelines focus on risk factor modification, glycemic control and lifestyle changes in prediabetic patients with limited evidence-based strategies for cardiovascular and kidney risk management. Honigberg et al. from Massachusetts

General Hospital, Boston, MA, sought to assess that risk and outcomes across the glycemic spectrum among participants from the United Kingdom Biobank (excluding patients with known type 1 diabetes, known cardiovascular and/or kidney disease). The co-primary study outcomes were: (1) atherosclerotic cardiovascular disease (ASCVD), defined as a composite of coronary artery disease, ischemic stroke, and peripheral artery disease; (2) chronic kidney disease (CKD); and 3) heart failure

Findings: Among 336,709 individuals (mean age: 56 years, 45% male), 46,911 (13.9%) had prediabetes and 12,717 (3.8%) had T2D. Over a median follow-up of 11 years, 13.8% of prediabetic patients developed at least one primary outcome, with only 12% having become frankly diabetic before the outcome. After adjusting for demographic, lifestyle, and cardiometabolic risk factors, prediabetes was an independent predictor of ASCVD (HR 1.11 [1.08 to 1.15]), CKD (HR 1.08 [1.02 to 1.14]), and heart failure (HR 1.07 [1.01 to 1.14]). Similar findings were obtained for patients with T2D but with higher hazard ratios. Using hemoglobin A1c < 5% as reference, adjusted risk for ASCVD, CKD and heart failure increased substantially for A1c > 5.4%, 6.2%, and 7%, respectively.

Significance: Prediabetes was associated with almost 10% increased risk for ASCVD, CKD, and heart failure. Furthermore, the risk for cardiovascular outcomes, CKD and even heart failure were observed across HbA1c levels below the threshold for diabetes. While the study lacked power to assess relationship between HbA1c and different subtypes of cardiomyopathy (ischemic vs non-ischemic) and ejection fraction (preserved vs reduced), and in non-White population, it highlights the importance of recognizing prediabetes as risk for cardiovascular and kidney outcomes, and the need to design risk reduction strategies across the glycemic spectrum. The current dichotomization of patients based on a fixed HbA1c cut-off value may significantly underestimate risk and should be updated

Early Rhythm Control Therapy in Patients with Atrial Fibrillation and Heart Failure. *Circulation* 2021, ahead of print

Background: Despite optimal medical therapy, patients with atrial fibrillation and heart failure, particularly those with preserved ejection fraction (EF), experience cardiovascular outcomes. Kirchhof et al. from the University Heart and Vascular Center UKE Hamburg, assessed the effect of systematic early rhythm control therapy (ERC, using antiarrhythmic drugs or catheter ablation) vs usual care (rate control) in a pre-

specific subanalysis of the randomized EAST-AFNET4 trial (Early Treatment for Atrial Fibrillation for Stroke Prevention Trial). The primary outcome was composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome. Median follow-up time was 5.1 years.

Findings: The study included 785 patients (median age 71 years, 62% male) with 442, 211 and 132 having EF $\geq$ 50%, 40% to 49%, and less than 40%, respectively. Despite similar improvement in EF, quality of life and symptoms in both groups, patients randomized to early rhythm control therapy had 26% lower risk for cardiovascular outcomes (5.7 per 100 patients-years vs 7.9, HR 0.74 [0.56 to 0.97]), with no interaction with heart failure class/status ($P = .3$) and without significant increase in adverse events from the therapy ($P = .33$).

Significance: Among patients with atrial fibrillation and heart failure symptoms, both early rhythm control therapy (antiarrhythmic and/or ablation) within the first year and usual care (rate control or delayed symptom-directed rhythm control therapy) provided equal improvement in quality of life, symptoms and EF. However, early rhythm control therapy significantly reduced cardiovascular outcomes (26% risk reduction as compared to usual care), irrespective of heart failure class or EF, and without increased adverse events. Certain limitations of the study were: (1) the study was not specifically powered for this subanalysis; (2) the intervention was not blinded; (3) and data on EF and quality of life were available for only two years.

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis. *N Engl J Med* 2021;385:493–502

Background: In recent years drugs for ATTR amyloidosis have been introduced that inhibit TTR protein synthesis or stabilize tetrameric TTR. These drugs have been shown to improve symptoms and prolong survival but their use is limited by the need for long-term administration and side effects. Gillmore et al. report the results of a phase 1 study in 6 patients with hereditary ATTR amyloidosis with polyneuropathy using NTLA-2001, an in vivo agent consisting of a lipid nanoparticle delivery system and a single guide RNA that targets human TTR utilizing CRISPR-Cas9-based in vivo gene-editing therapy.

Findings: Preclinical studies in mouse and monkey demonstrated that a single dose of the drug resulted in durable TTR editing and almost complete elimination of serum TTR expression at doses associated with no adverse effects. The 6 patients (46 to 64 years old, 4 men, 3 had received prior diflunisal) had sensory

polyneuropathy but New York Heart Association Class I. NTLA-2001 was administered as a single infusion. There were no serious adverse events but 3 patients had mild adverse events. Increased d-dimer levels were noted in 5 patients which returned to normal by day 7. NTLA-2001 was associated with a dose-dependent reduction in serum TTR (54% for the 0.1mg/kg dose and 87% for the 0.3 mg/kg dose) at day 28.

Significance: Administration of NTLA-2001 to 6 patients with hereditary ATTR amyloidosis with polyneuropathy was associated with a dose-dependent

and sustained reduction in serum TTR protein concentration. These results provide preliminary evidence for the feasibility of in vivo gene editing as a therapeutic strategy for ATTR amyloidosis. Further data is needed in a larger group of patients with longer follow-up for both efficacy and tolerability. Since this constitutes permanent gene editing off-target effects are a legitimate concern.

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