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

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Long-term leisure-time physical activity intensity and all-cause and cause-specific mortality: a prospective cohort of US adults. Circulation. 2022;146:0000. DOI:https://doi.org/10.1161/CIRCULATIONAHA.121.058162

Background: Current guidelines recommend at least 150 to 300 min/wk of moderate physical activity (MPA), 75 to 150 min/wk of vigorous physical activity (VPA), or combination of both. There is concern that higher intensity leisure-time activity, such as running a marathon, may be associated with harm. Lee et al. from Harvard T.H. Chan School of Public Health, Boston conducted a study using 2 large prospective cohorts (Nurses’ Health Study and Health Professionals Follow-up Study; total of 116,221 adults with a mean age of 66 years, 63% women, mean BMI 26 kg/m²), with up to 15 repeated measures of self-reported leisure-time physical activity over 30 years of follow-up to examine the association of physical activity and mortality.

Findings: During a median follow-up of 26 years there were 47,596 deaths. Compared to those without leisure-time VPA, those with 75-149 min/wk of VPA had 19% lower all-cause mortality, 31% lower CVD mortality, and 15% lower non-CVD mortality. Those with 150-299 min/wk VPA had further lower mortality but benefits leveled off after ≥ 300 min/wk VPA. Compared to those with no long-term leisure-time MPA, those with 50-224 and 225-299 min/wk of MPA had 20% to 21% lower all-cause mortality, 22% to 25% lower CVD mortality, and 19% to 20% lower non-CVD mortality. Those with 300-599 min/wk MPA had further reductions in mortality. MPA ≥ 600 min/wk showed associations with mortality similar to 300 to 599 min/wk of MPA. A strong inverse association between VPA and mortality was found among those who had MPA < 150 min/wk but weaker associations for higher MPA. Importantly, there was no association between VPA and mortality in those with MPA ≥ 300 min/wk.

Significance: In this large study with repeated measures of self-reported leisure-time physical activity with long follow-up, lowest mortality was observed among individuals who reported ≥ 150 to 300 min/wk of long-term leisure-time VPA or 300 to 600 min/wk of long-term leisure-time MPA. Higher levels of activity were not associated with increased benefits or harm. Individuals with > 300 min/wk of MPA did not derive further benefits from VPA. Main limitations of this large study include the self-report of physical activity, potential residual confounding, and the lack of generalizability of this data to non-white and non-health professionals.

Diagnosis of heart failure with preserved ejection fraction among patients with unexplained dyspnea. JAMA Cardiol. 2022; doi:https://doi.org/10.1001/jamacardio.2022.1916.

Background: While various clinical models have been proposed to diagnose heart failure with preserved ejection fraction (HFpEF), they have not been validated in trials against gold-standard references. Reddy Y et al. from Mayo Clinic, Rochester, MN, sought to validate two clinical scoring model algorithms (H2FPEF and HFA-PEEF) in patients with unexplained dyspnea from a large, multicenter, international cohort, with case-control status that was ascertained using the gold standard of an elevated pulmonary capillary wedge pressure (PCWP) during exercise. Logistic regression was used to
evaluate the accuracy of HFA-PEFF and H2FPEF scores to discriminate patients with HFpEF from controls.

**Findings:** There were 736 patients (76% with HFpEF) that were identified from 6 centers (US, Europe, and Australia) between 2016 and 2022. Patients with HFpEF were older, had more co-morbidities and worse echocardiographic parameters. Both H2FPEF and HFA-PEFF scores discriminated patients with HFpEF from controls, but the H2FPEF score had significantly greater area under the curve (0.845 [0.810–0.875] vs. 0.710 [0.659–0.756], P value for difference < 0.001). While the specificity was similar for both, HFA-PEFF had more than double the false negative rate of H2FPEF score. Finally, the use of an alternative criterion, the PCWP/cardiac output slope, led to potential misclassification in 20% of patients.

**Significance:** Among ambulatory patient with unexplained dyspnea, the H2FPEF score provided superior diagnostic performance to discriminate patients with HFpEF from controls, despite fewer input variables. The study did not include patients from South America, Asia or Africa where prevalence of obesity and other co-morbidities differ; hence, the study’s results may not be generalizable to these regions. Furthermore, the lack of central core laboratory to interpret the hemodynamic waveforms, as well as the potential referral bias, are some of the limitation of the study.

**Long-term outcomes and risk stratification of patients with heart failure with recovered ejection fraction. Am J Cardiol 2022;173:80-87.**

**Background:** Patients with heart failure with recovered ejection fraction (HFrecEF) are those with HF with reduced ejection fraction (HFrEF) who subsequently normalize their left ventricular ejection fraction (LVEF). Perry et al. from University of Washington School of Medicine, Seattle, Washington retrospectively identified 133 patients (median age 66 years, 38% female, 77% White, 30% ischemic etiology, diabetes 29%, atrial fibrillation 41%) with HFrecEF (< 40% to ≥ 53% LVEF on sequential echocardiograms). The primary outcome was all-cause mortality.

**Findings:** During a median follow-up of 3.1 years, there were 34 deaths, 2 heart transplants, and 1 LVAD implantation. The median survival was > 9.5 years. The median time to first hospitalization was 1.37 years. A decrease in LVEF to < 40% was 20% at 1-year and 28% at 3 years. On multivariate analyses, furosemide dose and BNP were independent predictors of mortality while furosemide dose, BNP, and cessation of b-blocker therapy were significantly associated with future hospitalization.

**Significance:** Patients with HFrecEF have better outcome than those with HFrEF but worse than the general population. Furosemide dose and BNP at time of LVEF recovery are the most important predictors of mortality and future hospitalizations. A significant proportion of patients with HFrecEF will experience a drop in LVEF on follow-up. Important limitations of this study include its retrospective nature, the cohort derived from a single center, and the relatively small sample size.

**Presenting pattern of atrial fibrillation and outcomes of early rhythm control therapy. J Am Coll Cardiol 2022;80:283-295.**

**Background:** The impact of atrial fibrillation (AF) pattern (first-diagnosed within 7 days, paroxysmal, or persistent) and timing of AF therapy on the effectiveness of early rhythm control is not well-known. Goette A et al. from St. Vincenz Hospital, Paderborn, Germany extracted data from the Early treatment of atrial fibrillation for stroke prevention randomized trial (EAST-AFNET 4). The authors then compared the effectiveness of early rhythm control among patients with first-diagnosis AF (n = 1098, 48% female), paroxysmal AF (n = 994, 50% female), and persistent AF (n = 743, 38% female) (overall mean age 70 years). The first primary outcome was composite endpoint of cardiovascular death, stroke, and hospitalization for heart failure and acute coronary syndrome; the second primary outcome was number of nights spent in hospital per year. The secondary outcome was change in health-related quality of life using the EQ-5D questionnaire.

**Findings:** While early rhythm control reduced the first composite cardiovascular endpoint for all 3 subgroups, patients with first-diagnosis of AF had the highest hospitalization for acute coronary syndrome (incidence rate ratio 1.50, P interaction 0.032). Similarly, the same group spent more nights in the hospital (incidence rate ratio 1.38, P interaction 0.004). While patients with paroxysmal and persistent AF had improved health-related quality of life scores, patients with first-diagnosis of AF did not have any benefit (P = 0.19).

**Significance:** In this pre-specified analysis of the EAST-AFNET 4 trial, early rhythm control reduced composite endpoint in patients with first-diagnosis (within 7 days), paroxysmal and persistent AF. However, patients with first-diagnosis of AF that were managed with early rhythm control strategy had significantly higher risks of prolonged hospitalization and acute coronary syndrome, and without any improvement of quality of life. The lack of benefit and potential harm in this subgroup requires further investigation to better
risk-stratify patients. Notably, the trial was not powered to perform subgroup analysis, could not rule out asymptomatic episodes of AF prior to presentation among those classified as first-diagnosis of AF, nor did it include or quantify AF burden.

**Trends in 10-Year outcomes among medicare beneficiaries who survived an acute myocardial infarction. JAMA Cardiol. 2022;7(6):613-622.**

**Background:** Although the rates of all-cause 30 day mortality and readmission for acute myocardial infarction (AMI), 1 year mortality for AMI, and 1 year recurrent AMI have decreased, the long-term outcomes are not well-established. Wang Y et al. from Yale University, New Haven, evaluated the trends in 10-year all-cause mortality and hospitalization for recurrent AMI among almost 4 million AMI survivors (49% female, mean age 78 years) from 1995-2019 using the national Medicare fee-for-service-database.

**Findings:** The 10-year mortality and recurrent AMI rates were 72.7% and 27.1%, with corresponding adjusted annual reductions of 1.5% and 2.7%, respectively. Mortality within 10 years after the initial AMI was higher for patients with a recurrent AMI versus those without recurrence (80% vs. 72.4%; \(P < 0.001\)). Furthermore, recurrent AMI was associated with almost double the risk of 10-year mortality (HR 1.89 [1.88-1.90]). Finally, men, Black patients, and dual Medicare-Medicaid-eligible patients had higher risks of adverse outcomes (hazard ratio 1.05 [1.05-1.06], 1.08 [1.07-1.09], and 1.21 [1.20-1.21], respectively).

**Significance:** In this 25-year national study of Medicare fee-for-service beneficiaries who survived 30 days post AMI, both 10-year mortality and hospitalization for recurrent AMI decreased steadily over time. However, there were marked differences in outcomes and trends across demographic subgroups, particularly among men, black patients and those eligible with dual Medicare-Medicaid, hence emphasizing the need for prioritization of efforts to reduce inequities in long-term outcomes among these subgroups. The current database included patients age 66 years of age or greater; therefore the results may not be generalizable to younger cohort. Furthermore, relevant data with known impact on outcomes including troponin levels, secondary prevention medications, and post-acute care information on medication adherence, nursing home stays, home health services, and physician office visits were not available, and therefore could not be incorporated in the analysis.

**Myosin inhibition in patients with obstructive hypertrophic cardiomyopathy referred for septal reduction therapy. J Am Coll Cardiol 2022;80:95-108.**

**Background:** Patients with obstructive hypertrophic cardiomyopathy (HCM) with intractable symptoms despite medical therapy are referred for septal reduction therapy (SRT). Mavacamten, a novel small molecule modulator of beta-cardiac myosin, has been shown to improve LVOT gradient and physical functioning in HCM patients. Desai et al. from the Cleveland Clinic, Ohio used data from VALOR-HCM (a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial) to test whether addition of mavacamten to maximally tolerated medical therapy will improve patients sufficiently to no longer meet guideline criteria or choose to not undergo SRT. The primary endpoint was the composite of eligibility for SRT or a patient decision to proceed with SRT after 16 weeks of treatment.

**Findings:** The study enrolled 112 patients with symptomatic HCM (mean age 60 years, 51% men, 93% with \(\geq\) NYHA class 3, resting LVOT gradient 49 \(\pm\) 31 mm Hg). The primary endpoint was reached in 77% of those on placebo vs. 18% on mavacamten (treatment difference 59%, 95% CI 44%-74%; \(P < 0.001\)). 2 of 56 patients on mavacamten had LVEF \(\geq\) 50% resulting in temporary drug discontinuation.

**Significance:** This study demonstrated that mavacamten may allow the deferral of SRT in symptomatic patients with HCM after 16 weeks of treatment. A main limitation is that the primary endpoint was driven exclusively by reduction in guideline eligibility for SRT, not by the decision of patients not to undergo SRT, and the short duration of the study. Concern remains regarding the effect of mavacamten on systolic function necessitating close monitoring during treatment.

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