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

Fadi G. Hage, MD, MASNC,[a,b] and Wael AlJaroudi, MD, FASNC[c]

[a] Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL
[b] Section of Cardiology, Birmingham Veterans Affairs Medical Center, Birmingham, AL
[c] Division of Cardiovascular Medicine, Clemenceau Medical Center, Beirut, Lebanon

Received Sep 19, 2019; accepted Sep 20, 2019
doi:10.1007/s12350-019-01909-3

Trends in Cardiometabolic Mortality in the United States, 1999-2017 *JAMA 2019;322:780-2*

Background: Cardiovascular disease (CVD) is the leading cause of death in the USA. From 2000 to 2014, CVD death rates declined by 36%. Shah et al. from Northwestern University in Chicago, IL examined CVD and cardiometabolic disease death rates from 1999 to 2017. Mortality rates were age-adjusted.

Findings: In 1999, age-adjusted death rates per 100,000 were 266.5, 61.6, 25.0, and 6.2 for heart disease, stroke, diabetes, and hypertension, respectively. The corresponding numbers for 2017 were 165.0, 37.6, 21.5, and 9.0, respectively. The heart disease death rate exhibited an inflection point in 2010. Prior to 2010, there were 8.3 fewer deaths per 100,000 people per year, while after 2010, there were 1.8 fewer deaths per 100,000 people per year. Both stroke and diabetes showed declining death rates prior to 2010, while the rates after 2010 were stable. The death rate from hypertension increased less rapidly after 2003. When examined by race, black individuals had higher death rates compared to whites.

Significance: The data indicate that the rate of decline in CVD death rates that we have been experiencing for several decades is slowing down. Furthermore, the mortality rates for stroke and diabetes have now plateaued and are still increasing for hypertension (although at a slower rate). Further interventions are needed to reinvigorate the fight against CVD and cardiometabolic disease in the USA.

Reprint requests: Fadi G. Hage, MD, MASNC, Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL , USA; *fadihage@uab.edu*
J Nucl Cardiol 2019;26:1796–9.
1071-3581/$34.00

Complete Revascularization with Multivessel PCI for Myocardial Infarction *N Eng J Med;* https://doi.org/10.1056/nejmoa1907775.

Background: In patients with ST-elevation myocardial infarction (STEMI), randomized trials have shown that non-culprit lesion PCI strategy resulted in reduced composite outcomes driven mainly by reduction in revascularization, while the impact on cardiovascular death or non-fatal MI remains debatable. Mehta et al. from McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada performed a randomized study of complete revascularization strategy of angiographically significant non-culprit lesion versus no further revascularization of patients with STEMI and multivessel coronary artery disease who had undergone successful culprit-lesion PCI. Patients who were randomly assigned to the complete revascularization strategy were to have routine staged PCI, regardless of whether there were residual clinical symptoms or evidence of ischemia. Randomization was stratified according to either during or after the index hospitalization. The first primary outcome was the composite of cardiovascular death or MI; the second was the composite of cardiovascular death, MI, or ischemia-driven revascularization.

Findings: The median time to non-culprit lesion PCI was 1 day (interquartile range 1 to 3) for the 1285 patients with intended revascularization during hospitalization and 23 days (12.5 to 33.5) for those shortly after discharge. After a median follow-up of 3 years, complete revascularization resulted in 26% and 49% reduction in the first and second co-primary composite endpoints (7.8% vs 10.5%, hazard ratio 0.74 [0.60-0.91], $P = 0.0004$; and 8.9% vs 16.7%, HR 0.51 [0.43-0.61], $P < 0.001$, respectively). The benefit of complete revascularization was consistently observed regardless

of the intended timing of non-culprit-lesion PCI (interaction P value = 0.62 and P = 0.27 for the first and second co-primary outcomes, respectively).

Significance: Among patients with STEMI and multivessel coronary artery disease status post PCI of the culprit lesion, complete revascularization was superior to culprit-lesion-only PCI in reducing the risk of cardiovascular death or MI, as well as the risk of cardiovascular death, MI, or ischemia-driven revascularization. This remained true whether PCI was performed during the same hospitalization or shortly after discharge, irrespective of whether patient had subsequent symptoms or ischemia. Unlike other randomized trials, the COMPLETE trial showed that the reduction in composite endpoint was driven by a 32% reduction of new, non-fatal MI. However, there was no difference in cardiovascular death between strategies. The high percentage of patients on optimal medical therapy and limited cross over (less than 5%) are obvious strength of the study. However, patients who had PCI of the non-culprit lesion at the same time of the culprit lesion were excluded. Finally, there were no patients with STEMI and cardiogenic shock; hence, the current findings cannot be extrapolated to this cohort.

Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease *N Engl J Med 2019;* https://doi.org/10.1056/nejmoa1904143

Background: The long-term anti-platelet/anticoagulant treatment regimen (beyond 12 months) of patients with atrial fibrillation who undergo coronary revascularization or those with stable CAD is not clear. Yasuda et al. from Osaka Police Hospital, Japan performed a multicenter, randomized, open- label, parallel-group trial in which they randomized 2236 patients (mean age 74 years, 79% men) with atrial fibrillation who had undergone PCI (71%) or CABG (11%) more than 1 year earlier or who had angiographically confirmed stable CAD not requiring revascularization to receive monotherapy with rivaroxaban or combination therapy with rivaroxaban plus a single anti-platelet agent (70% aspirin). The primary efficacy endpoint was the composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause. The primary safety endpoint was major bleeding, as defined according to the criteria of the International Society on Thrombosis and Hemostasis.

Findings: During a median follow-up of 24 months, the incidence rates for the monotherapy vs. combination therapy groups were 4.14% and 5.75% per patient-year, respectively (hazard ratio, 0.72; 95% CI, 0.55 to 0.95; $P < 0.001$ for noni-nferiority, P = 0.02 for superiority). The incidence of the primary safety end point was lower in the monotherapy group than that in the combination therapy group (1.62% vs 2.76% per patient-year; hazard ratio, 0.59; 95% CI, 0.39 to 0.89; P = 0.01). All-cause mortality was lower in the monotherapy group;:1.85% and 3.37% per patient-year (hazard ratio, 0.55; 95% CI 0.38 to 0.81) due to a lower incidence of both cardiovascular and non-cardiovascular deaths.

Significance: This trial demonstrated the non-inferiority of rivaroxaban monotherapy, as compared with combination therapy with rivaroxaban plus anti-platelet therapy (mainly aspirin or clopidogrel), for the composite of cardiovascular events or death from any cause and the superiority of this approach with regard to bleeding. The lower incidence of all-cause mortality adds further emphasis to the superiority of this approach. This randomized data support the current guidelines for the treatment of this challenging population of patients.

Effectiveness of Polypill for Primary and Secondary Prevention of Cardiovascular Diseases (PolyIran): A Pragmatic, Cluster-Randomized Trial *Lancet 2019; 394:672-83*

Background: A fixed-dose combination therapy (polypill strategy) has been proposed as an effective method to reduce the burden of cardiovascular disease and outcomes, particularly in low- and middle-income countries. Rochandel et al. from Shariati Hospital, Tehran conducted a two-group, pragmatic, cluster 1:1 randomized trial of participants aged 40-75 years to receive either non-pharmacological intervention alone (education training, N = 3417) or together with a once-daily polypill (aspirin 81 mg, atorvastatin 20 mg, hydrochlorothiazide 12.5 mg, and either enalapril 5 mg or valsartan 40 mg; N = 3420) for primary and secondary prevention of cardiovascular disease. The primary outcome was a composite of hospitalization for acute coronary syndrome, fatal myocardial infarction, sudden death, heart failure, coronary artery revascularization procedures, and non-fatal or fatal stroke. The primary outcome was adjudicated by a follow-up team that was blinded to the allocation status.

Findings: Half of the cohort included women, and the median adherence to the polypill was 80%. After 5 years of follow-up, the polypill strategy resulted in reduced cardiovascular events (5.9% vs 8.8%, HR 0.66 [0.55-0.80]), irrespective of the presence or absence of prior cardiovascular disease (p interaction = 0.19). Among those with high adherence, the polypill achieved greater risk reduction (HR 0.43 [0.33-0.55]). There was no significant difference in adverse events between groups.

Significance: The PolyIran study is the first large-scale randomized clinical trial that assessed the benefit of a fixed combination therapy on primary and secondary prevention. The polypill strategy resulted in 24% risk reduction of major cardiovascular events (number needed to treat 34), and more so among participants with higher adherence (57% risk reduction, NNT 21), without increase in adverse events. While more than half of the participants were normotensive, the use of low-dose antihypertensive medications in the polypill did not result in significant drop in blood pressure or hypotension; still, there was significant reduction in cardiovascular disease burden and outcomes. Hence, the polypill strategy could be considered as an additional effective component in controlling cardiovascular diseases, especially in low- and middle-income cohorts. While recent trials showed that aspirin should not be used for primary prevention because of high risk of bleeding that counterbalances the reduction in cardiac adverse events, the polypill did include aspirin and did not result in increased risk of bleeding, most likely because patients at high risk of bleeding were excluded. The study was done in rural population, the majority of which were Turkmen, and less than 5% were smokers; hence, this strategy cannot be generalized to all cohorts. Hypothetically speaking however, the polypill risk reduction might be even greater in cohorts that include higher percentage of smokers. Different fixed-dose combination polypills could be considered for primary and secondary prevention and a longer follow-up is needed to assess the impact on mortality.

Association Between Use of Primary Prevention Implantable Cardioverter-Defibrillators and Mortality in Patients with Heart Failure: A Prospective Propensity-Score Matched Analysis from the Swedish Heart Failure Registry *Circulation* https://doi.org/10.1161/circulationaha.119.043012.

Background: Implantable cardioverter defibrillator (ICD) has been shown to reduce sudden cardiac death in patients with heart failure with reduced ejection fraction (HFrEF) in randomized controlled trials. Whether the findings from these trials which were conducted more than 20 years ago still apply today is not clear. Schrage et al. from Karolinska Institute, Sweden investigated the association between ICD use and all-cause mortality in the patients with HFrEF who are eligible for a primary prevention ICD in the contemporary Swedish HF Registry.

Findings: Of the 16,702 patients who were eligible for a primary prevention ICD, only 1,599 (10%) had an ICD. These patients were matched 1:1 to non-ICD recipients using propensity scores. One-year mortality for ICD vs non-ICD recipients was 12.7% vs 16.9% (hazard ratio 0.73, 95% CI 0.60-0.90) and 5-year risk was 47.4% vs. 49.5% (0.88, 0.78-0.99), respectively. The results were consistent when the analysis was conducted for the overall cohort adjusting for propensity scores. There was no significant interaction between ICD use and important subgroups such as age (< 75 vs. ≥ 75 years), gender, cardiac revascularization therapy use, ejection fraction ($< 30\%$ vs. 30-39%), NYHA class (II vs. III/IV), etc.

Significance: The data support the use of ICD for primary prevention in HFrEF in contemporary practice despite advances in clinical management and the change in risk of sudden death over time. More importantly, the data highlight the low utilization of ICDs in patients who are eligible and who may derive benefits (at least in this Swedish cohort).

Presenting Symptoms in Men and Women Diagnosed With Myocardial Infarction Using Sex-Specific Criteria *J Am Heart Assoc. 2019;8:e012307.*

Background: While the Universal definition of myocardial infarction (MI) recommends the use of sex-specific criteria, the impact of such criteria on clinical features and presentation by gender remains poorly defined. Ferry et al. from the University of Edinburgh, United Kingdom performed a prospective trial of patient-reported symptoms in 1941 patients (39% women) with suspected acute coronary syndrome that presented to the emergency room of a tertiary care center. Chest pain was defined as typical or atypical using the Greenslade definition, based on pain nature, location, radiation, and additional symptoms. Diagnosis of MI was made using a high-sensitivity cardiac troponin I assay with sex-specific thresholds (> 16 ng/L women, > 34 ng/L men). The final diagnosis was adjudicated by two physicians.

Findings: Type 1 MI was diagnosed in 16% of men and 12% of women. Chest pain was the main presenting symptom in almost 90% of either gender, although typical symptoms were more common in women (77% vs 59%; $P = 0.007$) and were more predictive of type 1 MI (positive likelihood ratio 1.18 [1.04-1.31]) in women. In addition, the presence of ≥ 3 typical features was associated with a positive likelihood ratio for the diagnosis of MI in women (positive likelihood ratio, 1.18; 95% CI, 1.03-1.31) but not in men. On the other hand, radiation of pain was predictive of MI in men (positive LR 1.39 [1.22-1.56] but not women. Finally, the use of a high-sensitivity cardiac troponin I assay and sex-specific diagnostic thresholds increased the number of patients diagnosed with type 1 MI and reclassified 30% of women and 5% of men.

Significance: Contrary to previous assumptions, typical symptoms of angina are more common and have higher predictive value of type 1 MI in women than in men irrespective of whether sex-specific criteria were used. The use of high-sensitivity troponin with sex-specific thresholds resulted in significant reclassification of patients with additional 30% of women having type 1 MI. Women with MI remain at risk of under-diagnosis and under-treatment if the correct symptom and presentation are not recognized. The current study highlights the importance of proper history taking and to avoid being biased by gender. There were several strengths in its design; this was a prospective study and data were collected directly from patients through an interview in the emergency room by an independent well-trained research team; the symptoms were classified using standardized definition; high-sensitivity troponin with sex-specific thresholds were used; and 2 cardiologists adjudicated the final diagnosis. Still, the cohort was limited to a tertiary center and included predominately white population; hence there is a need to validate it in different and more diverse cohorts.