Heartbeat: Highlights from this issue

Catherine M Otto

Prevention of atrial fibrillation (AF) is an urgent unmet clinical need given its association with a higher risk of stroke, heart failure and death. Known risk factors for AF include age, hypertension, body mass index and diabetes as well as markers of systemic inflammation; all of which likely contribute to the high prevalence of this dysrhythmia in our aging, increasingly obese, population. However, there currently are no established biomarkers to help in assessment of AF risk. Adiponectin is an adipocyte-generated hormone with lower levels seen with increased adiposity. Adiponectin has insulin sensitizing, anti-inflammatory and anti-atherosclerotic effects in experimental studies suggesting that, at least in theory, a lower adiponectin level might increase the likelihood of adverse cardiovascular outcomes, including AF. Paradoxically, previous clinical studies have reported the exact opposite finding for coronary disease, heart failure and all cause mortality, with mixed results for the association between adiponectin levels and AF.

In this issue of *Heart*, Macheret and colleagues (***see page 1368***) hypothesized that these seemingly contradictory findings might be due to a U-shaped relationship between adiponectin and incident AF. To test this hypothesis, they measured adiponectin levels in 3190 older adults (mean age 74±5 years) from the population based Cardiovascular Health Study, who were free of AF, atrial flutter or known cardiovascular disease at study entry. Based on analysis of the 886 incident AF events at 11.4 years of follow-up, with adjustment for both potential cofounders and putative mediators of AF, they did not find the hypothesized U-shaped association. Instead, higher (not lower) adiponectin levels were independently associated with an increased risk of AF (figure 1).

In the accompanying editorial, Barnett and Piccini (***see page 1351***) comment: "The analysis by Macheret and colleagues is the most rigorous study to date to examine the link between adiponectin and AF". Compared to previous publications, the current study "included significantly more incident AF events (n=886) and a more rigorous adjustment for potential confounding variables. Unlike prior studies, the authors controlled for NT-proBNP levels, which are strongly associated with adiponectin. The authors also attempted to estimate the impact of potential mediators of adiponectin, such as inflammatory markers, glycaemic control and lipids". They conclude; "This study adds further insight into the complex associations of this multifaceted hormone. Adiponectin has been paradoxically associated with both positive and adverse clinical outcomes. While linked to a lower risk of diabetes, it is also associated with higher rates of CVD, mortality and, now, AF. The basis for this paradox remains poorly understood. One theory is that adiponectin is driven by opposing factors that lead to a favourable association in healthy populations and an unfavourable association in chronic disease (figure 2)".

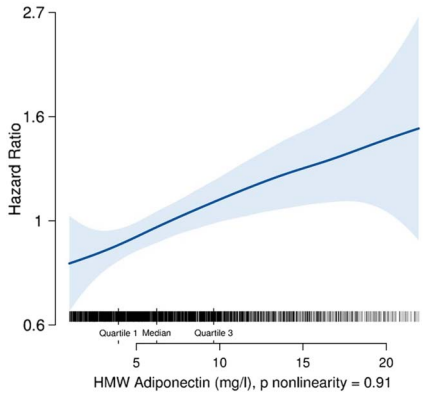

Figure 1 Adjusted cubic spline graph depicting the associations of continuous levels of high-molecular-weight adiponectin with atrial fibrillation. Models are adjusted for age, sex, race, educational status, height, weight, systolic blood pressure, use of antihypertensive medication, smoking, alcohol, self-reported health status and estimated glomerular filtration rate (eGFR). The horizontal band above the X-axis represents individual participants (vertical lines) with corresponding values for adiponectin level (mg/L). Values at the extreme 2.5th percentiles have been removed from the plots.

Management of adults with low-gradient severe aortic stenosis (AS) remains controversial both because of the diagnostic challenges in classifying AS severity and because of limited data on clinical outcomes in this patient group. Kang and colleagues (***see page 1375***) report a cohort of 284 mildly symptomatic patients (mean age 68±10 years) with low-gradient severe AS and a normal left ventricular ejection fraction, defined as an indexed aortic valve area <0.6 cm^2/m^2 with mean gradient <40 mm Hg and stroke volume index ≥ 35 mL/m^2. There was no significant difference in overall mortality or estimated 8 year mortality rates for the 98 patients who underwent early aortic valve

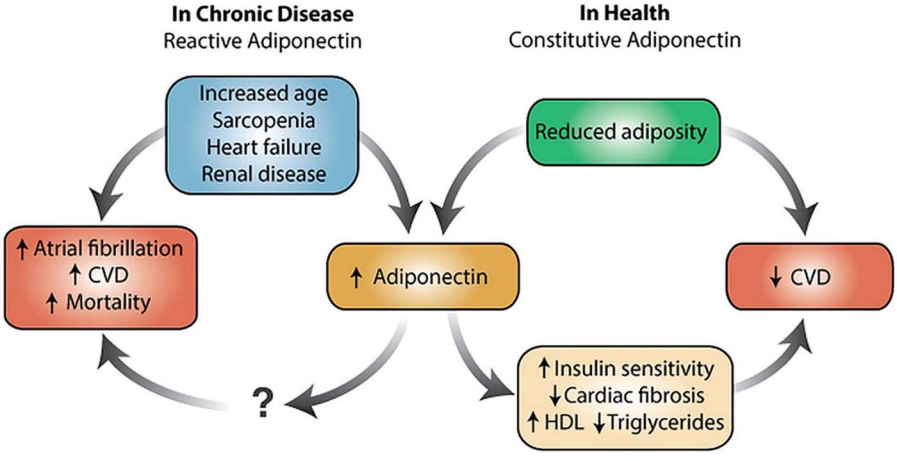

Figure 2 Proposed model for the adiponectin paradox. In healthy populations, adiponectin is a marker of reduced adiposity and leads to improved insulin sensitivity, reduced cardiac fibrosis and improved serum lipids. Thus, in this population, adiponectin is associated with lower rates of cardiovascular disease (CVD). In chronic disease, elevated adiponectin levels may reflect underlying disease processes, such as involuntary weight loss, heart failure and kidney disease. These factors increase the risk of atrial fibrillation, CVD and mortality and may offset adiponectin's potential beneficial effects. HDL; high density lipoprotein.

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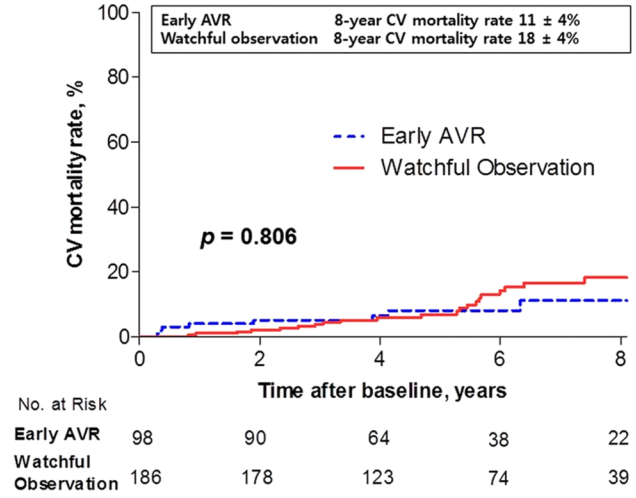

Figure 3 Kaplan–Meier curves for the cumulative probabilities of CV mortality according to treatment group in the overall cohort. AVR, aortic valve replacement; CV, cardiovascular.

replacement (AVR) compared to the 186 patients with watchful observation either in the entire study group or for propensity-score matched pairs. Symptoms at study entry were mild in both groups – all had NYHA Class I/II dyspnea and about 1/3 had angina – and all had a low estimated surgical risk. In the watchful observation group, late AVR was performed in 54% of patients at a median interval of 2.9 years (interquartile range 1.8 to 4.2 years) for progression to high gradient severe AS (figure 3).

In an editorial, Pellikka (***see page 1349***) reminds us that we need to interpret this study with caution. First, it is not clear that all the patients in this study had severe AS given the challenges of this diagnosis when flow rates are low; perhaps many had only moderate AS at study entry. Second, she reminds us that patients with severe AS have a high rate of symptom onset and that many older adults are not referred promptly for valve surgery once symptoms supervene due to concerns about the risk/benefit ratio of surgical AVR (a suboptimal pattern of clinical care that hopefully will change with the availability of transcatheter AVR). In addition, we currently do not have prospective randomized data to guide our management of asymptomatic patients with severe AS. In the meanwhile, she recommends: "Considering all of the evidence until now, we best exercise caution in deferring AVR if we are sure that AS is severe and symptoms, albeit mild, are present".

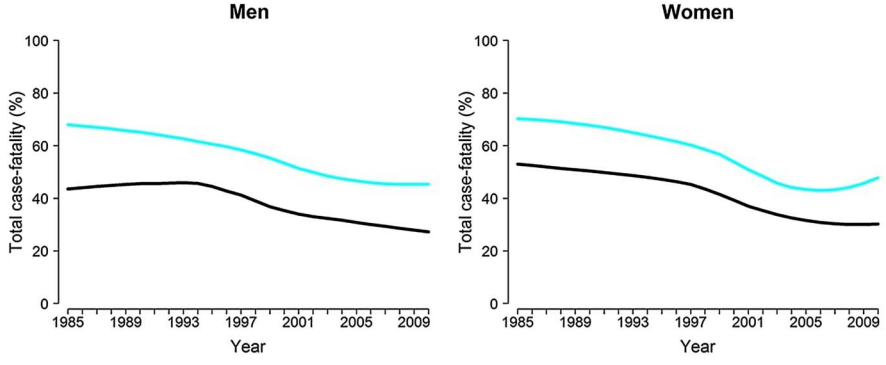

Figure 4 All-population trends in age-standardised acute myocardial infarction total case-fatality during 1985–2010. Results are presented separately for men (left) and for women (right).

Degano and colleagues (***see page 1413***) report epidemiological data showing an overall decline in the attack rates and mortality of acute myocardial infarction (AMI) over the past 25 years in 6 European countries. However, there was considerable variability between countries and in certain population groups. In particular, there was a 4.7% increase in total case fatality for women aged 65 to 74 years over the 5 years from 2005 to 2010 (figure 4).

O'Flaherty, Huffman and Capewell (***see page 1353***) comment that the data reported by Degano and colleagues "and a variety of modeling studies suggest that this mortality fall might reasonably be primarily attributed to improving risk factors (decreasing incidence), with an increasing contribution from acute, evidence-based treatments (to reduce case fatality)". However, they argue that instead of "country-specific preventative policies, tailored to specific age and gender groups", "far larger benefits would be delivered by population-level (structural) interventions." For example, "in the UK, systematic efforts to decrease salt in processed food have achieved a 15% reduction in salt intake of about 1 g in 10 years, saving at least 6000 lives and £1.5 billion annually". "Similarly, large gains could come from stronger tobacco policies, banning trans fat elimination or fiscal strategies to improve diet".

The Education in Heart article in this issue (***see page 1422***) provides a contemporary practical approach when considering transcatheter aortic valve implantation (TAVI) including indications for TAVI, evaluation of the patient before the procedure, and management post TAVI.

The Image challenge (***see page 1412***) shows a rare, but interesting, cause of aortic valve stenosis.

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