Syncope in High-Risk Cardiomyopathy Patients With Implantable Defibrillators: Frequency, Risk Factors, Mechanisms, and Association With Mortality: Results From the Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy (MADIT-RIT) Study

Syncope is a frequent event in heart failure patients with implantable cardioverter defibrillators (ICDs). Recently it was shown that ICD programming to high-rate cutoff or prolonged monitoring did not increase the likelihood of syncope compared with conventional programming. In the present report, we further explore the specific cause and mechanism of syncope in relation to ICD programming and the impact of both arrhythmogenic syncope and nonarrhythmogenic syncope on death. Syncope caused by arrhythmias is responsible for 40%, whereas 60% of all syncopal events are caused by nonarrhythmic events, such as orthostatic hypotension syncope or vasodepressor reflex syncope. ICD programming to high-rate cutoff or prolonged monitoring algorithms did not increase the risk of syncope caused by ventricular tachyarrhythmias, and particularly slow ventricular tachyarrhythmias (in the range of 170–199 bpm) are rare causes of arrhythmogenic syncope. These results indicate that high-risk heart failure patients with moderate to severe heart failure symptoms and reduced ejection fraction are able to tolerate rather long durations of fast ventricular tachycardias, whereas slow ventricular tachycardias, for practical purposes, do not result in a loss of consciousness. In the Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy (MADIT-RIT), both arrhythmogenic and nonarrhythmogenic syncope were significantly associated with increased risk of death. These findings suggest that syncope in heart failure patients with ICDs is a significant marker of high risk, despite the cause of the syncopal event. See p 545.

Discordance of Low-Density Lipoprotein (LDL) Cholesterol With Alternative LDL-Related Measures and Future Coronary Events

US guidelines recommend measuring a standard lipid panel in adults and targeting therapy based on levels of low-density-lipoprotein (LDL) cholesterol. Non–high-density lipoprotein (HDL) cholesterol, the cholesterol carried by LDL and very low-density lipoprotein (VLDL) particles (apolipoprotein B particles), is calculated as total cholesterol minus HDL cholesterol and is a secondary target of therapy in individuals with hypertriglyceridemia. Non-HDL cholesterol, apolipoprotein B, and LDL particle number are 3 alternative measures of LDL-related risk; however, the clinical utility of these measures may only become apparent among individuals for whom levels are inconsistent (discordant) with LDL cholesterol. Discordance was defined as LDL-C greater than or equal to the median and the alternative measure less than the median, or vice versa. In this prospective study of 27,533 apparently healthy women (median follow-up 17 years), we observed that the prevalence of discordance defined according to median concentrations of LDL cholesterol with either non-HDL cholesterol, apolipoprotein B, or LDL particle number was common, reaching up to 25%. Among discordant individuals, coronary risk was either underestimated or overestimated by LDL cholesterol. These data support the concept that for most individuals with concordant levels of LDL cholesterol and an alternative LDL-related measure (non-HDL cholesterol, apolipoprotein B, or LDL particle number), the clinical utility of these measures is similar. However, among the subgroup of individuals (up to a quarter of this population) with discordance of LDL cholesterol with another LDL-related measure, risk may be overestimated or underestimated when LDL-C alone is used. See p 553.

Spatial Association Between Ambient Fine Particulate Matter and Incident Hypertension

Mounting evidence now links millions of cardiovascular deaths worldwide to ambient air pollutants, especially fine particulate matter (particles with an aerodynamic diameter ≤2.5 μm (PM_{2.5})). There is also growing evidence associating long-term exposure to PM_{2.5} with the incidence of myocardial infarction, stroke, and other clinical events that typically occur at the later stages of the vascular disease processes. However, far less is known about the possible effect of air pollution at the earlier stages of the disease. This study extends the detrimental actions of air pollution to include an augmented risk for the development of hypertension, one of the most important risk factors for cardiovascular disease and the leading cause of global mortality. By following 35,303 adults who lived across Ontario, Canada, between 1996 and 2010, this study found that long-term exposures to low levels of PM_{2.5} were associated with increased incidences of hypertension, especially among individuals with diabetes mellitus. Given that billions of people worldwide are exposed to higher concentrations of PM_{2.5}, these findings may have serious global public health implications. For healthcare providers, these results emphasize that patients with or at high risk for cardiovascular diseases should be educated about the potential harmful health effects posed by air pollution. From the public health perspective, these observations add further support to the continuing public efforts to improve overall air quality, even considering present-day low levels of PM_{2.5} in locations such as Ontario. See p 562.

Racial/Ethnic Differences in Dyslipidemia Patterns

Our analysis offers insight on racial/ethnic differences in dyslipidemia, a major cardiovascular risk factor. Given the rapid increase in minority groups within the United States, especially the Hispanic/Latino and Asian American populations, a better understanding of these differences in dyslipidemia is crucial in tailoring optimal strategies in management and prevention, both at the individual and population levels. Despite known heterogeneity in cardiovascular risk and outcomes, no studies have comprehensively examined the prevalence of dyslipidemia subtypes and treatment across the major racial/
explored as potential adjunctive glucose-lowering agents. Sodium-glucose cotransporter (SGLT) 2 inhibitors are being developed because of their insulin-independent mechanism of action.

Diabetes Mellitus

Renal Hemodynamic Effect of Sodium-Glucose Cotransporter 2 Inhibition in Patients With Type 1 Diabetes Mellitus

Because of their insulin-independent mechanism of action, sodium-glucose cotransporter (SGLT) 2 inhibitors are being explored as potential adjunctive glucose-lowering agents. Trials should consider combining these 2 drug classes to potentially augment renal protection. Ultimately, prospective clinical trials are required to determine whether changes in renal hyperfiltration with SGLT2 inhibition translate into long-term renal protection.

Implantable cardioverter-defibrillators (ICDs) improve survival in patients at high risk of sudden cardiac death, and their use has increased over time. In conjunction with a coverage expansion in 2006 to cover primary prevention, the ICD Registry was developed to capture the characteristics and in-hospital outcomes of ICD recipients. A major goal of the registry is to provide feedback to hospitals that can be used for quality improvement efforts, and as the largest database of US ICD recipients to date, it provides a unique opportunity to examine quality metrics. The purpose of our study was to examine trends in 3 quality metrics known to be associated with long-term outcomes in patients receiving ICDs: Adverse in-hospital events (procedural complications or mortality), prescription of optimal medical therapy as defined by receipt of angiotensin-converting enzyme inhibitor and β-blocker in eligible patients at discharge, and use of cardiac resynchronization therapy in eligible patients. We found that from April 2006 to March 2010, there was significant improvement in all 3 quality metrics: Adverse events declined (from 3.7% to 2.8%, P<0.0001), and use of optimal medical therapy and cardiac resynchronization therapy increased (optimal medical therapy, from 69.0% to 74.3%, P<0.001; cardiac resynchronization therapy, from 80.5% to 84.2%, P<0.001). After adjustment for patient characteristics in each year, these trends persisted. However, we found that among hospitals, there was little correlation in trends in the 3 metrics known to be associated with long-term outcomes in patients receiving ICDs: Adverse in-hospital events, prescription of optimal medical therapy, and use of optimal medical therapy and cardiac resynchronization therapy. In the context of experimental work in animals showing reductions in hyperfiltration, proteinuria, and histological nephropathy, our results provide further evidence that SGLT2 inhibitors may exert short-term renal protective effects in humans. Our results may also have implications for primary renal disease prevention in patients with type 1 diabetes mellitus, because the use of angiotensin-converting enzyme inhibitors has failed to show clinical benefit in normotensive, normalalbuminuric individuals. Moreover, because different racial/ethnic groups may be at higher risk for developing certain dyslipidemias, clinicians will be able to provide culturally competent recommendations on prevention and management.

Temporal Trends in Quality of Care Among Recipients of Implantable Cardioverter-Defibrillators: Insights From the National Cardiovascular Data Registry

Implantable cardioverter-defibrillators (ICDs) improve survival in patients at high risk of sudden cardiac death, and their use has increased over time. In conjunction with a coverage expansion in 2006 to cover primary prevention, the ICD Registry was developed to capture the characteristics and in-hospital outcomes of ICD recipients. A major goal of the registry is to provide feedback to hospitals that can be used for quality improvement efforts, and as the largest database of US ICD recipients to date, it provides a unique opportunity to examine quality metrics. The purpose of our study was to examine trends in 3 quality metrics known to be associated with long-term outcomes in patients receiving ICDs: Adverse in-hospital events (procedural complications or mortality), prescription of optimal medical therapy as defined by receipt of angiotensin-converting enzyme inhibitor and β-blocker in eligible patients at discharge, and use of cardiac resynchronization therapy in eligible patients. We found that from April 2006 to March 2010, there was significant improvement in all 3 quality metrics: Adverse events declined (from 3.7% to 2.8%, P<0.0001), and use of optimal medical therapy and cardiac resynchronization therapy increased (optimal medical therapy, from 69.0% to 74.3%, P<0.001; cardiac resynchronization therapy, from 80.5% to 84.2%, P<0.001). After adjustment for patient characteristics in each year, these trends persisted. However, we found that among hospitals, there was little correlation in trends in the 3 metrics known to be associated with long-term outcomes in patients receiving ICDs: Adverse in-hospital events, prescription of optimal medical therapy, and use of optimal medical therapy and cardiac resynchronization therapy. In the context of experimental work in animals showing reductions in hyperfiltration, proteinuria, and histological nephropathy, our results provide further evidence that SGLT2 inhibitors may exert short-term renal protective effects in humans. Our results may also have implications for primary renal disease prevention in patients with type 1 diabetes mellitus, because the use of angiotensin-converting enzyme inhibitors has failed to show clinical benefit in normotensive, normalalbuminuric individuals. Moreover, because different racial/ethnic groups may be at higher risk for developing certain dyslipidemias, clinicians will be able to provide culturally competent recommendations on prevention and management.

Role of Extracellular RNA in Atherosclerotic Plaque Formation in Mice

Atherosclerosis remains the number one cause of death in the Western world, and the therapeutic options currently available are limited. Regarded as a chronic inflammatory disease of the vessel wall, monocytes/macrophages, inflamed smooth muscle cells, and several cytokines, proteases, and other molecular players, as well, contribute to disease development. Based on our previous studies concerning extracellular RNA (eRNA) as a novel alarm signal and potent cofactor in inflammation and thrombosis, we here investigated the contribution of the eRNA/RNase system during atherogenesis. In the experimental model of high-fat diet–induced atherosclerosis in low-density lipoprotein receptor–deficient and apolipoprotein E–deficient mice, eRNA accumulated in atherosclerotic plaques in a time-dependent manner, but was also released from activated cells, yielding increased plasma levels after arterial injury. In fact, eRNA functioned to promote inflammatory gene expression in macrophages and smooth muscle cells. Importantly, eRNA-degrading RNase1, administered via minipumps, significantly reduced plaque formation, monocyte recruitment, and vascular inflammation after injury. These data provide evidence for a major role of the eRNA/RNase system in atherogenesis and identify eRNA as an important trigger of inflammatory processes that fuel atherosclerotic lesion growth. These novel data extend our previous findings in which RNase1 was found to reduce infarction size in acute stroke. Thus, our study may harbor great potential for the establishment of RNase1 administration as a novel interventional strategy for the therapy of cardiovascular diseases. Because RNase1 is a thermostable, nontoxic enzyme, it bears several features that are applicable as a new interventional regimen against atherothrombotic disease.