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YEAR IN CARDIOLOGY SERIES

The Year in Epidemiology, Health Services Research, and Outcomes Research

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Epidemiology, health services research, and outcomes research have commanded a growing presence in the medical literature and have had an increasing impact on practice and policy. Summarizing the important contributions in this literature requires a review of a broad spectrum of sources and investigators, because the highest-impact work typically results from multidisciplinary collaboration. This overview highlights findings from prominent epidemiology, health services research, and outcomes research publications from April 2005 through March 2006. Although the limited space of this review does not permit inclusion of every high-quality publication in this area, we have highlighted representative work of particular interest or relevance consistent with the core domains of health care, as articulated by the National Academy of Sciences Institute of Medicine—safety, effectiveness, equity, efficiency, timeliness, and patient-centeredness. Additional categories for quality and epidemiology are also included.

SAFETY

Two prominent articles addressed the issue of incorrect medication dosing. Mehta et al. (1) found that approximately 5% of the subjects in the ASSENT-2 (Assessment of the Safety and Efficacy of a New Thrombolytic-2) trial received the incorrect dose of fibrinolytic agent. Because this occurred within the context of a randomized trial, it likely underestimates rates of incorrect dosing in practice. Older patients, women, black patients, those with low body weight and systolic blood pressure, and those with a higher Killip class had a higher risk for incorrect dosing. Overdose and underdose were associated with higher mortality, not only for the fibrinolytic agent but also for placebo, indicating that baseline patient characteristics and/or concomitant deficiencies in quality of care likely played a role in these differences. Alexander et al. (2), assessing the dosing of antiplatelet and antithrombin agents for ST-segment elevation myocardial infarction (STEMI), found that 42% of patients received at least 1 dose of antithrombotic agents that was higher than recommended. This mistake was particularly common with glycoprotein IIb/IIIa inhibitors (27%) and unfractionated heparin (33%). Again, older age, female gender, and low body weight, along with renal insufficiency, diabetes, and heart failure, were risk factors for inappropriate medication dosing. Excess dosing was associated with greater risks of bleeding and death.

Meta-analyses also examined safety issues associated with chronic anticoagulation. In a meta-analysis of 10 randomized trials, Rothberg et al. (3) reported that the use of warfarin plus aspirin after an acute myocardial infarction (AMI) was associated with a 250% increase in the risk of bleeding compared with aspirin alone. It was also associated with a 44% reduction in the risk of a subsequent AMI, a 54% reduction in stroke, and a 20% reduction in revascularization procedures, findings that indicate a need for safer approaches to anticoagulation therapy. This topic was addressed by Heneghan et al. (4) in a meta-analysis of self-monitoring of oral anticoagulation. In 14 trials, they found that self-monitoring was associated with a 55% reduction in the odds of thromboembolic events, a 39% reduction in mortality, and a 35% reduction in major bleeding. The combination of self-monitoring and self-adjustment showed even more impressive reductions in thromboembolic events and mortality, but not in major bleeding.

Several studies addressed the safety of statins, including rosuvastatin, the newest high-potency agent. In a postmarketing analysis, Alsheikh-Ali et al. (5) reviewed statin-associated events reported to the Food and Drug Administration during rosuvastatin's first year of approval. The adverse event reports per million (composite of event reports occurring at moderate doses of rosuvastatin for rhabdomyolysis, proteinuria, nephropathy, or renal failure) were higher for rosuvastatin than for atorvastatin, simvastatin, or pravastatin. Interestingly, the adverse events for rosuvastatin tended to be reported earlier after the initiation of therapy.

The possible risks of cancer from statins were also investigated. In a meta-analysis of 26 studies, Dale et al. (6)

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were unable to identify an increased risk of cancer incidence or mortality. In a prospective meta-analysis using individual data for 90,056 subjects in 14 trials, the Cholesterol Treatment Trialists' Collaborators also concluded that there was no evidence showing that statins increased the risk of all cancer or site-specific malignancies (7). In a case-control study, Poynter et al. (8) found that statins may reduce the risk of colorectal cancer, although these findings should be considered hypothesis-generating because of the study design.

Concerns that angiotensin receptor blockers might increase risk for an AMI were refuted by 2 articles. McDonald et al. (9), in a systematic review of 19 trials including 31,569 patients, found no strong evidence of a hazard with angiotensin receptor blockers. In an analysis of the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) studies, Demers et al. (10) reported a reduction in AMI risk in patients with heart failure treated with candesartan.

Several other articles with strong safety implications in clinical practice were noteworthy. Masoudi et al. (11) reported dramatic increases in the use of spironolactone in patients with heart failure at high risk for hyperkalemia after the publication of RALES (Randomized Aldactone Evaluation Study). In a prospective, observational study, Iakovou et al. (12) reported a 1.3% 9-month rate of acute stent thrombosis after drug-eluting stent (DES) placement, more frequent than rates reported in randomized trials. An important risk factor was premature discontinuation of antiplatelet therapy. Mangano et al. (13), in an observational study, reported that aprotinin in patients undergoing cardiac surgery was associated with double the risk of renal failure.

EFFECTIVENESS

Systematic reviews investigated issues of treatment effectiveness that individual studies have been unable to address. In an important systematic review, Katritsis and Ioannidis (14) compared percutaneous coronary intervention (PCI) with medical therapy in patients with stable angina. They found that PCI did not reduce the risk of death, AMI, or the need for subsequent revascularization.

Many other reviews were notable. A meta-analysis of 22 studies of perioperative beta-blockade for noncardiovascular surgery found only a nominally significant reduction in the risk of the composite of cardiovascular mortality, nonfatal AMI, and nonfatal cardiac arrest while conferring a significantly higher risk of bradycardia or hypotension requiring therapy, raising questions about the widespread use of beta-blockade around the time of noncardiovascular surgery (15). A comparison of studies of routine invasive strategy compared with a selective invasive strategy for acute coronary syndromes (ACS) found that the routine invasive approach reduced the risk of AMI, severe angina, and rehospitalization, but was associated with an early hazard of death and a longer-term trend toward a mortality reduction (16). In a study of acute reperfusion strategies for STEMI, Keeley et al. (17) compared standard PCI with facilitated PCI (i.e., administration of a medication before planned immediate PCI to improve preprocedural coronary patency). They found that despite higher rates of early TIMI (Thrombolysis in Myocardial Infarction)-3 flow in the infarct vessel, the facilitated strategy resulted in a higher risk of death, nonfatal reinfarction, urgent target vessel revascularization, and major bleeding. The investigators concluded that facilitated PCI should not be used outside of randomized trials. In a meta-analysis of first-line antihypertensive therapy, Lindholm et al. (18) found that beta-blockers were associated with a 16% higher risk of stroke compared with other active agents and conferred less of a benefit on stroke than would be expected based on other antihypertensive trials. The investigators suggest that beta-blockers should be considered inferior—and thus inappropriate—comparators for future hypertension trials.

The relationship between procedural volume and outcomes was the focus of several studies. In a study of PCI in the stent era in New York, Hannan et al. (19) found that lower hospital (at least 400 cases annually as a cut point) and operator (at least 75 cases annually) volumes were important correlates of worse in-hospital outcomes, including mortality (for hospital volume), and same-day bypass surgery (for both hospital and operator volume). In a national study of Medicare patients, Schelbert et al. (20) found that institutional volume of valve replacement procedures was associated with the use of bioprosthetic valves for older patients, an approach consistent with recent guidelines. Al-Khatib et al. (21) reported that physician procedure volumes for implantable cardioverter-defibrillator (ICD) placement were related to outcomes. A physician volume threshold below 11 implants annually was associated with significantly higher risks of mechanical complications, and a threshold below 18 was associated with higher risks of device infection. These results have potential implications for competency statements and policy, although substantial variations in the relationship between volume and outcomes suggest that volume criteria alone are inadequate barometers, and may still misclassify physicians and institutions when used as a surrogate for direct measurement of quality.

In a post-hoc analysis of CHARM, Granger et al. (22) found that adherence to medications was associated with better outcomes even among placebo-treated subjects. The implication is that behaviors associated with adherence have important effects on prognosis, and raise questions about the specific mediators of this effect.

An examination of RITA-3 (Randomised Intervention Trial of Unstable Angina-3) shows the importance of understanding the time horizon in testing the value of treatments (23). Among patients with non-STEMI randomized to an intervention strategy (routine angiography followed by revascularization) or a conservative strategy (ischemia-driven or symptom-driven angiography), rates of

death and nonfatal AMI were similar at 1 year, but were lower in the routine angiography group by 5 years of follow-up (16.6% vs. 20.0%). Although the 1-year results may have limited enthusiasm for an early invasive strategy, the longer-term results will likely increase support for an early invasive strategy for ACS.

Another study raised questions about a controversial intervention in critical care. The ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial investigators found that the use of pulmonary artery catheterization to guide therapy for patients hospitalized with severe heart failure did not improve outcomes but resulted in more adverse events (24).

Three trials found major benefits from relatively straightforward interventions in care delivery. In a study of 1,518 outpatients with heart failure, investigators from Argentina reported lower risks of death or admission for heart failure and better quality of life with a simple telephone intervention to provide education, counseling, and monitoring (25). Barnfather et al. (26) reported a 17% improvement in smoking quit rates with a 10-min point-of-care test for salivary nicotine metabolites. An unrestricted visiting policy in the intensive care unit reduced cardiovascular complications and patient complications without an increased risk of major infection (27).

The international PRESTO (Prevention of Restenosis With Tranilast and its Outcomes) trial provided an opportunity to assess differences in the effectiveness of PCI across countries. Patients in the U.S. had higher rates of target vessel revascularization (18% vs. 11%) and angiographic restenosis (65% vs. 48%) than in other countries, differences not entirely accounted for by the higher risk profile of U.S. patients (28). The finding suggests that issues beyond patient selection, such as procedural techniques, may explain these differences.

EQUITY

The assessment of health differences and disparities in treatment and outcomes of cardiovascular diseases by race, gender, and socioeconomic status remains an active area of investigation. In an observational study of patients with ACS, Spertus et al. (29) found that black patients had a higher prevalence of angina, worse quality of life, and worse physical function than white patients 1 year after their event, although the underlying explanations for this finding remain unclear. Two studies investigated temporal trends in race and gender differences in cardiovascular care. Among Medicare beneficiaries from 1992 through 2001, Jha et al. (30) found that differences in procedure use by race persisted through the decade. Vaccarino et al. (31) found that rates of reperfusion therapy and procedures varied according to race and gender, and the differences did not change from 1994 through 2002. They also noted that in-hospital mortality was significantly higher for black women than for white women or for all men.

A central insight this year expanded on race differences in treatment and outcomes among hospitals and regions. Skinner et al. (32) found that black patients with an AMI may have worse outcomes because they are more commonly admitted to hospitals with higher mortality rates. Barnato et al. (33) also showed that race differences in treatment for patients with AMI were largely explained by the hospitals to which the patients were admitted. Lucas et al. (34) determined that higher crude mortality rates among black patients for 4 cardiovascular surgical procedures were not substantially changed after adjustment for patient-level characteristics, but were no longer present after accounting for hospital factors. These 3 studies suggest that racial disparities might be most effectively addressed by interventions directed at the performance of hospitals that disproportionately serve this population. In addition to the accumulating evidence of the role of the hospital in differences and disparities in care, Rathore et al. (35) identified substantial national variation in racial differences by geographic region, with the greatest variation in the South.

Data from NHANES (National Health and Nutrition Examination Survey) provided insights into racial disparities in the prevalence and management of high blood pressure. Hertz et al. (36) found that the prevalence of hypertension increased in black subjects from 35.8% in 1988 to 1994 to 41.4% in 1999 to 2002. Rates for white subjects also increased, but were only 28.1% in the latter period. Black subjects were much less likely than white subjects to have had their blood pressure controlled (51% of black subjects vs. 40% of white subjects).

A few important studies assessed differences in care and outcomes by socioeconomic status. Investigators from the Worcester Heart Attack Study showed that patients living in high-poverty areas had a 30% greater risk of dying compared with those in the wealthiest areas (37). Shishehbor et al. (38) determined that impaired functional capacity and abnormal heart rate were more common in patients with low socioeconomic status, and these abnormal responses explained a major proportion of the association between socioeconomic status and mortality. In a Canadian observational study of patients with AMI, Alter et al. (39) showed that the excess mortality risk associated with low socioeconomic status was largely explained by risk factors present at the time of the event.

Spertus et al. (40) found that the benefit of clinical revascularization strategies varied depending on the patient's ability to afford health care, showing that those who had difficulty paying for health care had better outcomes with surgical revascularization. This study leads to the uncomfortable conclusion that the financial burden of health care might affect the benefit of particular strategies.

Gender differences in angina treatment also received some attention. Hemingway et al. (41) reported in a prospective cohort study that the age-standardized annual incidence of angina (based on treatment with nitrates or a positive invasive or noninvasive test result) was similar in

women and men, as were prognoses. Daly et al. (42) found that women with stable angina were less likely than men to be referred for stress tests or coronary angiography or to be treated with antiplatelet and statin therapy. Women with confirmed coronary disease were also twice as likely to die or have a nonfatal AMI in the 1 year of follow-up.

COSTS

Spiraling health care costs are directing more attention toward the economics of health care. A recent report from the Centers for Medicare and Medicaid Services found that health spending in the U.S. increased by 7.9% to $1.9 trillion in 2004 (43). This amount translates to $6,280 per person and 16% of the gross domestic product. The increase in spending slowed in 2004, with the percent of gross domestic product increasing only by 0.1%, mostly as a result of above-average economic growth.

Contributing to rapidly rising costs, the use of cardiovascular diagnostic tests and treatments proliferated rapidly in the U.S. and Canada. In the U.S., imaging stress testing increased nearly 3-fold between 1993 and 2001 to a rate of 82 tests per 1,000, without contemporaneous declines in the rate of nonimaging stress tests (44). Rates of PCI doubled and rates of bypass surgery remained relatively stable. In Canada, where financial incentives to perform tests and procedures are less pronounced, the use of diagnostic tests and reperfusion therapy still increased significantly between 1992 and 2001, with annual increases of 6% for echocardiography, 7% for perfusion stress testing, 12% for PCI, and 4% for bypass surgery (45).

Expensive interventions with demonstrated efficacy, such as ICDs, are a natural focus for economic analyses. Sanders et al. (46) assessed the cost-effectiveness of ICD in primary prevention studies that enrolled patients with left ventricular systolic dysfunction but without a history of life-threatening ventricular arrhythmias. In this analysis, ICD therapy had a cost-effectiveness range of $34,000 to $70,200 per quality-adjusted life-year (QALY) gained. Goldberger et al. (47) investigated 3 approaches to ICD therapy among patients without a clear indication for a dual-chamber device: universal single-chamber ICD implantation with subsequent upgrade as indicated, universal dual-chamber device implantation, and device selection determined by electrophysiological testing. The strategy of universal dual-chamber ICD implantation was least costly as long as the need for upgrades exceeded 10%.

In a study of in-home automated defibrillators, Cram et al. (48) found that for adults older than 60 years with an annual probability of sudden death <4% (e.g., patients with prior AMI but without left ventricular systolic dysfunction), the estimated cost-effectiveness of automated external defibrillators exceeds $100,000 per QALY and should be considered relatively expensive. Among those with 6% annual sudden death rates (e.g., those with ischemic cardiomyopathy), the incremental cost-effectiveness was $88,000 per QALY (48).

Resynchronization therapy is another effective but expensive strategy for treating patients with symptomatic heart failure caused by left ventricular systolic dysfunction. Feldman et al. (49) evaluated the cost effectiveness of this strategy among patients in the COMPANION (Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure) trial. Cardiac resynchronization therapy reduced the risk of death and hospitalization in patients with left ventricular systolic dysfunction, advanced symptoms (New York Heart Association functional class III or IV), and intraventricular conduction delays. Hospital costs were reduced by 29% for those who received resynchronization via a pacemaker-defibrillator and by 37% for those who received therapy via a pacemaker compared with those receiving optimal pharmacological therapy alone. The cost effectiveness ratio was <$50,000 per QALY for either resynchronization strategy approach.

Among other cost effectiveness analyses, one focusing on stents was notable. Kaiser et al. (50) assessed the economic attractiveness of DES in a real-world setting. They found that although the DES strategy reduced the need for target lesion revascularization, it was associated with a substantial incremental cost per QALY of $67,015 to $90,036. However, in subgroups with relatively high restenosis risks, such as high-risk elderly patients with 3-vessel disease, those with multiple lesions, long lesions, or small vessels, the strategy was more cost-effective or even cost-saving. In another cost-effectiveness analysis in a community-based population, Bagust et al. (51) found that even when restricting the number of DES per patient, only a small minority (4%) of DES were economically attractive, and that 90% rates of substitution of DES for bare-metal stents, the current U.S. practice, could only be justified with modest price premiums for DES ($212 for sirolimus-eluting and $167 for paclitaxel-eluting stents).

QUALITY

Several important articles addressed quality of care. Alexander et al. (52) found that older patients with ACS were less likely to be treated with early aspirin and beta-blockers than younger patients. Interestingly, above age 65 there was not a substantial increase in underuse. Ko et al. (53) compared the quality of heart failure care and mortality between the U.S. and Ontario, Canada. Patients in both countries received similar treatment as measured by quality indicators, but those in the U.S. had a lower adjusted risk of mortality within the first 30 days after hospitalization. By 1 year after discharge, however, the survival difference disappeared. The convergence in longer-term mortality may result from differences in the quality of outpatient follow-up, but the study was not able to test this hypothesis.

Historically, the preponderance of studies of guideline adherence has been cross-sectional. Newby et al. (54)

assessed the persistence of use of guideline-based medications after hospital discharge in patients with coronary artery disease, finding that their subsequent medication use was often inconsistent and many failed to continue evidence-based therapy over time. Watkins et al. (55) examined trends in mortality and treatment between 1987 and 2000 in the ARIC (Atherosclerosis Risk in Communities) study. They found a marked improvement in 30-day mortality and associated improvements in treatment, suggesting a meaningful relationship between measures of care quality and health outcomes.

Appropriate calibration of the intensity of therapy with patient risk remains an issue of significant concern, highlighted by Lee et al. (56) in a study of evidence-based heart failure therapy according to baseline mortality risk. The likelihood of prescribing angiotensin-converting enzyme inhibitors and beta-blockers was inversely related to patients' risk of dying, even though the highest-risk patients would derive the greatest treatment benefit. The means of improving the alignment between treatment intensity and patient risk remains an important area of investigation.

Beyond descriptions of patterns of care, studies of the implementation of quality improvement interventions are occurring with greater frequency. Moscucci et al. (57) found that a regional quality improvement initiative in Michigan improved processes and outcomes for patients undergoing PCI. Zhang et al. (58) evaluated the effect of data feedback and clinical process improvement in 38 hospitals, reporting significant improvements in AMI process measures after implementation. Investigators for the NC ACE (North Carolina Achieving Cardiac Excellence) project reported improvements in angiotensin-converting enzyme inhibitor and beta-blocker use for patients with heart failure enrolled in managed care Medicaid and Medicare (59). Butler et al. (60) reported improved inpatient heart failure care after the institution of a computerized physician order entry system.

Not all such studies were positive, however. Australian investigators, in a cluster-randomized trial, found that much-heralded medical emergency teams, which respond to unstable patients before they progress to an arrest, did not reduce the risk of the combined end point of cardiac arrest, unexpected death, or unplanned intensive care unit admission (61). Beck et al. (62) found that a one-time hospital report card for AMI patients was ineffective in improving care. These negative results highlight the importance of subjecting quality improvement interventions to the rigors of clinical study to prove (or disprove) their impact.

Several studies specifically addressed factors associated with acute reperfusion time for STEMI. McNamara et al. (63) showed that there has been little recent improvement in time-to-reperfusion nationwide. Nallamothu et al. (64) emphasized the particularly long times for patients who are transferred from one institution to another for primary PCI. Magid et al. (65) reported that the time of day and day of the week were related to door-to-balloon times but not door-to-drug times. Curtis et al. (66) showed that prehospital electrocardiography was associated with much faster times. Finally, Bradley et al. (67) reported on qualitative research from top performers, indicating key characteristics associated with success.

Despite growing interest in interventions and quality, there is some disappointing evidence about the speed with which physicians adopt quality improvements. Audet et al. (68) reported on a national physician survey conducted in 2003 and sponsored by the Commonwealth Fund that evaluated the use of quality improvement methods. Only one-third of respondents reported receiving feedback of information about the quality of care that they provided. Moreover, only one-third reported engaging in redesign efforts to improve the systems of care in their practice. Interestingly, more than two-thirds thought that the public should probably not or definitely not have access to physician performance data.

Several studies addressed the impact of public reporting. A study by Hibbard et al. (69) found that public reporting of hospital performance in Wisconsin was associated with improvements in the report areas, concluding that public performance information may stimulate improvements in care. The news about public reporting, however, was not all positive. In a study of patient selection for PCI, Moscucci et al. (70) found that in New York, which has public reporting, there was a tendency to avoid high-risk cases compared with Michigan, where public reporting is not practiced. Looking forward, it will be important to consider both the positive and negative consequences of the implementation of policies for public reporting of performance.

PATIENT-CENTEREDNESS

Several studies support the integration of formal health status assessments into clinical heart failure care. In an analysis of VAL-HeFT (Valsartan Heart Failure Trial), Rector et al. (71) assessed the correlates of quality of life in patients with heart failure. Although dyspnea was strongly associated with quality of life, traditional measures of heart failure severity, including ejection fraction, B-type natriuretic peptide levels, jugular venous distension, peripheral edema, systolic blood pressure, creatinine, and hemoglobin, were not strongly related to symptoms or quality of life. Similarly, in a study of outpatients with heart failure, Luther et al. (72) found no correlation between B-type natriuretic peptide levels and health status. These studies show that physiologic measures of heart failure severity and health status represent distinct domains, and measuring one does not necessarily provide meaningful information with respect to the other. Additional evidence supports the prognostic importance of health status in heart failure independent of physiologic measures. Heidenreich et al. (73) found that in an outpatient population with heart failure, poor health status was a strong, independent predictor of death and hospitalization after adjustment for clinical covariates, 6-min walk distance, and B-type natriuretic peptide levels.

Investigators also characterized health status outcomes in other patient populations. McCrindle et al. (74) assessed health status in children after the Fontan procedure, finding deficits in physical and psychological function that represent potential targets for future intervention in this population. Sleeper et al. (75) found that survivors of cardiogenic shock treated with emergency revascularization achieved better functional status and quality of life than those receiving initial medical stabilization, and perhaps more surprisingly achieved functional outcomes similar to those of historical controls without shock undergoing elective intervention. These findings add further support to the use of an early interventional strategy in many patients with shock complicating AMI despite persistently high mortality.

EPIDEMIOLOGY

Progress in epidemiology during the year included several studies focused on the relationship between diet and cardiovascular disease. In one of the most publicized reports of the year, Howard et al. (76) presented the results of the WHI (Women's Health Initiative) Randomized Controlled Dietary Modification Trial, which found that in postmenopausal women, a dietary intervention of intensive behavioral modification designed to reduce dietary fat intake and increase consumption of vegetables, fruits, and grains over more than 8 years did not significantly reduce the risk of coronary heart disease, stroke, or the composite of the two. Experts are still trying to understand these findings that so strikingly contradict conventional wisdom. In another contribution from WHI, Howard et al. (77) reported that a low-fat diet was not associated with weight gain, contrary to the concerns raised by advocates of low-carbohydrate diets. Appel et al. (78), in another randomized trial, found that although 3 diets low in saturated fats were effective at lowering estimated cardiovascular risk, diets substituting protein or monounsaturated fat for carbohydrate calories exerted more favorable effects on blood pressure, lipid levels, and overall cardiovascular risk.

Two greatly anticipated randomized trials of the cannabinoid-1 receptor blocker rimonabant were published (RIO [Rimonabant in Obesity Lipids]-North America and RIO-Europe) (79,80). Both showed that in addition to a calorie-restricted diet, treatment for 1 year with 20 mg daily of rimonabant resulted in significantly greater weight loss (>4.5 kg in both studies), greater decline in waist circumference, and improvements in triglyceride and high-density lipoprotein cholesterol levels. In RIO-North America, however, discontinuation of therapy after 1 year resulted in gain of weight, and dropout rates in both studies in all treatment arms were substantial, highlighting the persistent challenges of sustaining any approach to weight loss (79).

Other studies further defined the relationship between obesity and cardiovascular events. The prospective Uppsala Longitudinal Study of Adult Men found that measures of insulin resistance accounted for the relationship between obesity and the risk of heart failure, suggesting that insulin resistance may be a central mechanism whereby obesity increases heart failure risk (81). In a provocative analysis from the multinational case-control INTERHEART study, Yusuf et al. (82) compared measures of obesity as markers of risk. Body mass index (BMI), the current standard measure, was not associated with increased risk of AMI after adjustment for waist-to-hip ratio and other traditional risk factors. In contrast, waist-to-hip ratio maintained an independent graded relationship with obesity after multivariable adjustment including BMI, suggesting that waist-to-hip ratio is a clinically more informative measure of obesity, at least with respect to the risk of AMI.

Addressing the effects of dietary supplements, WHI investigators found that 600 IU of vitamin E, although significantly reducing cardiovascular death, did not reduce the risk of cardiovascular events, cancer, or all-cause mortality, further diminishing any remaining enthusiasm for vitamin E supplementation as a preventive measure (83). Another trial with unexpected findings raised controversy about the proposed antiarrhythmic properties of omega-3 polyunsaturated fatty acids. In a randomized controlled trial of patients with ICDs and recent ventricular tachyarrhythmias, Raitt et al. (84) found that patients treated with 1.8 g/day of fish oil did not have a lower risk of ventricular tachycardia (VT)/ventricular fibrillation (VF) than patients receiving placebo. More surprisingly, however, patients who qualified for study enrollment because of VT had a significantly higher likelihood of receiving ICD therapy for VT/VF, and the overall risk of recurrent VT/VF was higher in patients treated with fish oils (84).

Poor physical fitness also remains an important problem as well as a potential opportunity for intervention. In NHANES, Carnethon et al. (85) found that more than one-third of U.S. adolescents had low fitness as defined by their maximal oxygen consumption (Vo_{2max}). Low fitness levels were not surprisingly associated with cardiovascular risk factors, including more obesity, higher blood pressure, and lower high-density lipoprotein cholesterol levels, providing perspective on the population impact of poor physical fitness. Another study provided some hope about effective strategies to ameliorate the adverse consequences of physical inactivity. In a randomized trial of patients with stable coronary artery disease, Blumenthal et al. (86) assigned patients to usual medical care, supervised aerobic exercise (35 min, 3 times weekly), or formal stress management training (1.5 h weekly) for 16 weeks. Patients in both treatment arms had lower emotional distress and improved physiological markers of cardiovascular risk compared with those receiving standard therapy. The widespread dissemination of effective strategies, however, remains an important challenge.

The past year revealed greater insights into cardiovascular changes with aging. In a community cohort free of clinical heart disease followed up for almost 8 years in the Baltimore Longitudinal Study of Aging, investigators found that

declines in peak oxygen consumption with age were not linear, but rather accelerated substantially with each decade of age, particularly among men (87). Moreover, the decline was seen across all quartiles of baseline reported physical activity. In a cross-sectional study from Olmsted County, age was strongly associated with increased vascular stiffness, in subjects both with and without established cardiovascular disease, and the increase was significantly greater in women (88). The investigators speculate that this gender difference may explain the consistent preponderance of women in populations with heart failure and preserved left ventricular systolic function.

Several studies further examined traditional risk factors. Smoking continues to be an important health threat. Ezzati et al. (89) estimated that more than 1 in 10 of all cardiovascular deaths worldwide—or more than 1.6 million—in the year 2000 were attributable to smoking. An analysis of NHANES data between 1960 and 2000 showed significant declines in the prevalence of hyperlipidemia (21%), hypertension (18%), and smoking (12%) (90). Declines in hyperlipidemia prevalence were particularly marked in patients with high BMI, and overall changes in risk factor prevalence were associated with higher rates of use of lipid-lowering and antihypertensive medications, particularly among obese persons. Carroll et al. (91) examined contemporary trends in serum lipid and lipoprotein levels in NHANES. They found that between the 1999 to 1994 and 1999 to 2002 surveys, there were significant declines in total and low-density lipoprotein cholesterol but no significant change in high-density lipoprotein cholesterol, and a nonsignificant increase in triglyceride levels. These encouraging changes, most prominent in men older than 50 years and women older than 60 years, were attributed to expanded use of lipid-lowering medications. In a report using the Minnesota Heart Survey, Arnett et al. (92) found downward trends in cholesterol levels between 1980 and 2002 that were more pronounced in middle-aged and older adults and correlated with higher treatment rates. However, substantial proportions of the population in 2002 had hyperlipidemia, and the majority of these were unaware of their lipid levels. Thus, despite recent gains in addressing traditional cardiovascular risk factors, ongoing efforts to modify these factors remain likely to have important public health benefits.

Although risk factor profiles may be improving in some countries, they are emerging in others. In a cross-sectional survey in China, Gu et al. (93) reported that the age-standardized prevalence of metabolic syndrome among adults age 35 to 70 years was 9.8% in men and 17.8% in women, and the prevalence of BMI of at least 25 kg/m^2 was 26.9% in men and 31.1% in women. The prevalence was higher in urban areas.

Risk models can be powerful tools for guiding decisions about the use of therapeutic interventions. Investigators from the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial developed and validated a risk score to predict mortality after primary PCI (94). In order of importance, left ventricular ejection fraction, renal insufficiency, higher Killip class, poor postprocedure TIMI grade flow, older age, anemia, and 3-vessel disease contributed to a risk score predicting mortality with good discrimination at both 30 days (c-index = 0.81) and at 1 year (c-index = 0.78). With the New York state PCI database, Wu et al. (95) developed a risk score predicting in-hospital mortality for PCI. Patient age, gender, hemodynamic state, left ventricular ejection fraction, preprocedure AMI, peripheral artery disease, heart failure, renal failure, and left main disease all contributed to a risk score with excellent discrimination (c-index = 0.89). British investigators, using data from 7,311 patients in a multicenter trial, developed a risk score for predicting death, AMI, and stroke among stable outpatients with angina and normal left ventricular systolic function (96). The 16-variable score identified deciles of risk ranging from 4% to 35%. Euro Heart investigators developed a score predicting outcomes in patients with stable angina (97). Six readily available clinical factors (comorbidity, diabetes, shorter symptom duration, increasing severity of symptoms, ST-segment depressions, or T-wave inversions on the electrocardiogram, and abnormal ventricular function) contributed to a risk score with predicted outcomes ranging from about 1% to 45% with reasonable discrimination (c-index = 0.74). Looking beyond the widely accepted 10-year time frame, Framingham investigators developed an approach to predict lifetime risk of incident cardiovascular disease for persons age 50 years. Not surprisingly, individuals without risk factors had lower lifetime risks of developing cardiovascular disease. The magnitude of the estimated differences in median survival between these 2 groups (11 years in men and 8 years in women) was particularly striking, again emphasizing the potential impact of aggressive early risk factor control (98).

CONCLUSIONS

The year witnessed a strong group of studies with direct relevance to the prevention, diagnosis, and treatment of cardiovascular disease. There is a growing interest and focus on studies that challenge conventional wisdom and produce insights that can improve practice and policy. The translation of this newly developed knowledge into practice and the generation of effective strategies for delivering discoveries into patient care remain central challenges for future investigation.

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