Scholarship to guide practice and policies to enhance the health of patients and populations are in great demand. Costs of health care continue to escalate, and questions about the effectiveness and value of strategies to prevent and treat cardiovascular disease are growing in volume. In that context, this review highlights important investigations in outcomes research, health services research, and epidemiology published from April 2006 to March 2007. During this period, many prominent contributions have expanded our understanding of the patterns and burdens of cardiovascular disease; deficiencies, challenges, and opportunities in health care delivery and clinical decision-making; and the effect of interventions designed to improve care. Although this review cannot include every high-quality publication, it emphasizes representative work of particular interest or relevance to the topics of safety, effectiveness, equity, efficiency, and epidemiology/prevention.

**Safety**

One of the most important safety issues concerned the failure of pacemakers and implantable cardioverter-defibrillators (ICDs). Given the recent expanding indications for ICD therapy, safety issues regarding devices have growing implications for costs and outcomes. Using annual reports submitted to the U.S. Food and Drug Administration (FDA) by manufacturers from 1990 to 2002, Maisel et al. (1) identified 17,323 device explantations for confirmed malfunctions. Overall, the rates of malfunction replacements were 20.7 per 1,000 implants for ICDs and 4.6 per 1,000 for pacemakers, with 61 deaths attributed to malfunction (30 pacemaker and 31 ICD). Maisel (2) also conducted a meta-analysis of prospective device registries to identify trends in rates of pacemaker and ICD malfunction between 1998 and 2002. The registries revealed malfunctions in 2,981 pacemakers and 384 ICDs. While pacemaker reliability increased steadily over time, ICD malfunction increased 4-fold, reaching a rate of 20-fold that of pacemakers.

Amin et al. (3) used decision analysis to compare the options between maintaining an unreliable device and device replacement. They found that the 2 most important factors influencing the decision were the estimated device failure rate and the likely consequences of device failure. Pacemaker-dependent patients fared better with device replacement if the estimated annual failure rate exceeded 0.3%. In contrast, for primary or secondary prevention ICDs, replacement was favored for annual failure rates of at least 3.0%. For pacemakers used for non–life-threatening conditions, device replacement could expose the patient to greater risks than continued device surveillance.

Statins, among the most popular cardiovascular drugs, have consistently defied safety concerns. In a systematic review of clinical trials of statins, Kashani et al. (4) quantified the risks of musculoskeletal, renal, and hepatic complications. In 35 trials including 74,102 patients, they found low adverse event rates; there was no significant increase in the risks of myalgias, creatine kinase elevations, rhabdomyolysis, or withdrawal of therapy due to possible adverse drug events. The risk of transaminase elevations, however, was significantly higher (by 4.2 per 1,000 patients). Agostini et al. (5) extended this work by examining patients who are under-represented in trials. In a study of 756 community-dwelling veterans age 65 years and older, they found no evidence of adverse effects from statin therapy on muscle strength, cognition, and depressive symptoms. Setoguchi et al. (6), linking data from a large state drug benefit program with a cancer registry and a Medicare database, found no evidence of an impact of statin therapy—either positive or negative—on cancer risks.
In an extension of their earlier work on mis-dosing of IIb/IIIa inhibitors (7), Alexander et al. (8) examined differences in the contribution of mis-dosing to the excess risk of bleeding between women and men. They found that women had a higher risk of bleeding and were more likely to receive excessive doses of IIb/IIIa inhibitors (46.4%) than men (17.2%). The bleeding risk associated with excess dosing events, however, was much greater in men. This study, along with their prior publication, indicates an important area to improve the safety of care for acute coronary syndromes (ACS).

Safety issues can also accrue with the application of therapy to high-risk patient populations that were not included in efficacy trials. In a community-based cohort study of patients hospitalized with heart failure in Ontario, Canada, between 1999 and 2001, Ko et al. (9) found that of the patients prescribed spironolactone, 18% had elevated serum potassium levels (>5 mmol/l) and 23% received concurrent potassium supplementation. Many patients treated with spironolactone had advanced renal insufficiency. The study, concordant with a prior investigation of U.S. patients hospitalized with heart failure (10), identifies a widespread pattern of care posing a risk to patient safety.

The relative safety of strategies for treating patients with ST-segment elevation myocardial infarction (STEMI) who do not respond to initial fibrinolytic therapy is not established. In a meta-analysis, Wijesundera et al. (11) found a paucity of data comparing repeat fibrinolytic therapy with conservative therapy, identifying only 3 studies including 410 patients. Repeat fibrinolytic therapy was associated with a trend toward better survival, but also with a trend toward a higher risk of reinfarction and significantly higher risk of minor bleeding. Overall, the safety and effectiveness of this approach remains questionable. In the 6 trials with 908 subjects undergoing rescue percutaneous coronary intervention (PCI), there was a strong trend toward decreased mortality and readmission and a significantly lower risk of reinfarction. Bleeding and stroke risks were almost 5-fold greater in the rescue PCI group, revealing a mix of benefits and risks with the invasive rescue strategy.

Safety can also be threatened by misdiagnoses. In a retrospective study of 1,684 patients with acute myocardial infarction (AMI) presenting to the emergency department, Masoudi et al. (12) revealed the implications of electrocardiogram (ECG) misinterpretation. In this cohort, 12% had an undetected high-risk ECG abnormality. A missed high-risk feature was associated with worse quality of care and a trend toward higher mortality.

The safety of drug-eluting stents has received considerable attention. In a prospective registry study, Spertus et al. (13) identified a major safety issue for patients who prematurely discontinue thienopyridine therapy after drug-eluting stent placement. Among 500 patients who underwent stent placement for ACS, about 1 in 7 discontinued thienopyridine therapy within 30 days after hospital discharge; these patients had a nearly 10-fold higher risk of death and a 50% increased risk of subsequent hospitalization. This information, in conjunction with recent concerns raised during an FDA advisory panel meeting regarding the potential risks of acute stent thrombosis with drug-eluting stents (14), emphasizes the need for effective strategies to enhance adherence, especially in populations in which non-adherence poses particularly high risks.

**Effectiveness**

Several papers assessed whether variation in hospital performance for AMI and heart failure explains variation in short-term mortality rates at the institutional level (15–17). Although the methods varied, the message from these studies was consistent: variation in performance on process measures explains relatively modest amounts of variation in outcomes. This finding, however, should not be interpreted to undermine the value of the therapies promoted by the measures. Possible reasons for the weak relationship between processes of care and institutional outcomes include: 1) lack of significant variation in some of the process measures; 2) assessment of care at hospital discharge, while relatively few deaths occur over the short term after discharge; and 3) the applicability of process measures only to subgroups of patients (in some cases very small), while mortality is measured for all patients. These studies support the measurement of outcomes as complementary indicators of quality and the expansion of process measures to new areas and larger patient populations whenever possible.

To address the need for statistical models for measures of outcomes suitable for public reporting, 2 studies introduced the evidence to support claims-based, hierarchical models to profile hospitals on their 30-day mortality rates for heart failure and AMI (18,19). For both conditions, claims-based models were highly concordant with those derived from medical records. These models were implemented in the public reporting effort by the Centers for Medicare & Medicaid Services.

Despite the importance of reperfusion therapy for patients with STEMI, gaps in this important process of care persist. Alter et al. (20) determined that 23% of eligible patients presenting with STEMI in Ontario between 1999 and 2001 did not receive reperfusion therapy. Lack of treatment was associated with longer time to presentation, higher cardiovascular risk, and higher intracerebral hemorrhage risk, leaving unresolved whether the decision to forgo therapy results from explicit considerations of the risk-benefit balance by clinicians and whether the best decisions for patients are being made.

Despite the benefits of anticoagulation for atrial fibrillation (AF), many patients still do not receive therapy. Among patients with newly diagnosed AF in a health plan, Glazer et al. (21) found that only 73% used antithrombotic drugs of any type during the 6 months after diagnosis. Among those with a high risk of stroke, only 59% received warfarin, 28% received aspirin, and 24% neither therapy.
Those with transient AF were significantly less likely to be treated, and estimated stroke risk had little association with therapy. These patterns of care conflict with current guidelines (22), which support identical strategies of antithrombotic therapy for both paroxysmal and persistent AF as well as therapy that is calibrated to the patient’s risk for stroke.

Elkayam et al. (23), using data from ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness), studied the association between the use of vasodilators and inotropes and the 6-month risk of all-cause mortality and rehospitalization among patients with acute decompensated heart failure. Treatment site was a stronger correlate of inotropes or vasodilator use than any patient factor, suggesting that treatment choice was influenced more by institutional culture than the patients’ clinical condition. Overall, inotropes with or without concomitant vasodilators were associated with a higher risk of death, possibly accounting for some of the national hospital-level variation in heart failure mortality.

In GRACE (Global Registry of Acute Coronary Events), Steg et al. (24) showed that patients with an AMI participating in randomized controlled trials had a lower baseline risk and experienced lower mortality than non-enrolled patients, even among those nonenrolled patients who were eligible for the treatments. The mortality difference was not entirely explained by differences in baseline risk, use, and type of reperfusion therapy, and/or delays in presentation. This study increases concerns about the degree to which existing clinical trials can be extrapolated to larger populations. Systems can have a powerful effect on improving the effectiveness of treatments. Roumie et al. (25) performed a trial demonstrating that an intervention to improve blood pressure control that included a patient education component resulted in better blood pressure control than those including only provider education. More studies are needed to understand how nonpharmacologic adjunctive interventions can improve effectiveness and which components of multifaceted interventions achieve the best results.

Several studies advanced our knowledge about door-to-balloon times for patients undergoing primary PCI for STEMI. In the NRMI (National Registry of Myocardial Infarction) -3 and -4 cohorts, McNamara et al. (26) found a strong relationship between door-to-balloon times and risk of mortality; patients whose PCI was delayed had a nearly 50% greater odds of dying than those treated within the recommended 90 min. Pinto et al. (27), using data from 192,509 patients at 645 NRMI hospitals, reported that the mortality advantage of primary PCI over fibrinolysis decreased with increasing delays in PCI, and that the “break-even” point, where there was no advantage to primary PCI, differed substantially based on patient age and infarct location.

An understanding of the importance of reducing the time of primary PCI for STEMI, however, does not provide insights into how to improve this time. Bradley et al. (28–30) published a series of articles that identified factors associated with faster primary PCI times. These process strategies included having emergency medicine physicians activate the catheterization laboratory, having a single call to a central page operator activate the laboratory, having the emergency department activate the catheterization laboratory while the patient is en route to the hospital, expecting staff to arrive in the catheterization laboratory within 20 min of being paged, having an attending cardiologist always on site, and providing real-time data feedback. A national campaign, sponsored by the American College of Cardiology, is underway to promote faster times in part based on the implementation of a number of these strategies (31).

Lack of adherence can also diminish effectiveness of proven therapies. Kramer et al. (32) examined health plan records from 17,035 members of 11 health plans who had an AMI in 2001, survived at least 1 year, and maintained insurance coverage. At 1 year, only 45% were adherent to beta-blockers, with the biggest decline between 30 and 90 days. Ho et al. (33) reported that by 1 year after AMI, more than 10% of patients had discontinued aspirin, beta-blockers, and statins, and almost another 15% discontinued at least 1 of the medications. Overall, discontinuations were associated with an increased risk of mortality. The need for an understanding of effective strategies to improve adherence was addressed in a randomized trial by Lee et al. (34) that found a positive impact of an intensive pharmacy care program on medication adherence, medication persistence, and blood pressure levels. The evidence of the effectiveness of the intervention was bolstered by the finding that after discontinuation of the program, adherence declined. This finding, however, also suggests that even after an intensive intervention, sustainability cannot be assumed. Whether such intensive interventions are realistic on a large scale remains unknown.

Equity

Many studies documented a gap in black–white life expectancy; Harper et al. (35) reported that between 1993 and 2003, the life expectancy gap declined by 1 year, but remains substantial (4.5 years less in blacks). For women, heart disease was the most important contributor, accounting for about 30% of the gap in 1983, 1993, and 2003. For men, heart disease became most important in 2003, accounting for 21% of the gap. The authors thus identify the importance of targeting cardiovascular disease as a means of reducing racial inequalities in mortality.

Environmental stressors have been suggested as exacerbating factors in hypertension, particularly among racial minorities. Brown et al. (36), with data from SWAN (Study of Women’s Health Across the Nation), investigated the impact of perceived unfair treatment, including perceived racism, sexism, and ageism on blood pressure. While perceived unfair treatment was reported by substantial proportions of racial and ethnic minorities, including 65% of...
African Americans, 60% of Chinese, 36% of Japanese, and 27% of Hispanics, this factor was not correlated with elevated blood pressure levels.

The relationship between socioeconomic status and outcomes in patients with cardiovascular disease was the focus of several studies. Rathore et al. (37), in a national study of Medicare patients hospitalized with heart failure, reported that lower socioeconomic status was associated with a 10% higher risk of mortality and an 8% higher risk of readmission in the year after discharge, independent of patient baseline characteristics. A Canadian study of 5,622 patients presenting to emergency departments with an AMI similarly found that the importance of socioeconomic status as a predictor of mortality was not substantially attenuated by adjustment for baseline patient factors and hospital factors (38). However, the effect of socioeconomic status was largely confined to patients who were not revascularized. In contrast, in a study of 2,142 patients with AMI at 19 U.S. centers, Bernheim et al. (39) showed that low socioeconomic status was associated with worse clinical status on admission and poorer quality of care. These differences, particularly clinical factors, explained much of their higher risk of mortality. A clearer understanding of the mediators of adverse outcomes would provide perspective on the optimal policy strategies for improving outcomes in patients of low socioeconomic status; economic policies to alleviate poverty would likely have an important effect.

Avendano et al. (40), in a longitudinal study of 10 Western populations during the 1990s, determined that lower socioeconomic status was associated with a higher risk of mortality from ischemic heart disease. The disparities were largest in the Scandinavian countries and England/Wales and less pronounced in the southern European countries, reflecting the distribution of cardiovascular risk factors in Europe. In a study of 4 National Health and Nutrition Examination Surveys, Kanjilal et al. (41) found that socioeconomic gaps in risk factors in the U.S. have not changed substantially or have even worsened from 1971 to 2002. While the prevalence of risk factors declined in all education and income groups, reductions in cholesterol and smoking were more pronounced in the higher education and income groups. Meanwhile, increases in diabetes disproportionately affected those with low incomes and education.

Albert et al. (42) studied the relationship between socioeconomic status and both traditional and novel risk factors for cardiovascular events over 10 years of follow-up in the Women's Health Study. At baseline, median total cholesterol, low-density lipoprotein, triglyceride, C-reactive protein, intercellular adhesion molecule-1, fibrinogen, and homocysteine levels decreased progressively, and high-density lipoprotein levels increased with increasing education and income levels. The risk of incident cardiovascular events decreased with increasing education and income. For income, cardiovascular event rates were largely explained by differences in risk factors; however, this was not true for education, perhaps suggesting that different pathways mediate the relationships between income, education, and cardiovascular events. The strength of the associations in this study was notable given that the subjects were all health care professionals. In sum, several studies published during the year suggest that effective preventive efforts would substantially reduce the burden of cardiovascular disease that disproportionately affects patients with lower socioeconomic status.

Hospitals in the Veterans Affairs (VA) system provide an opportunity to examine disparities in a system designed to provide equal access. Groeneveld et al. (43) found that VA hospitals with larger proportions of black patients had larger racial differences in cardiovascular procedure use. In contrast, Kressin et al. (44) found similar subsequent procedure rates and functional status after positive nuclear myocardial perfusion tests regardless of patient race in a study of 5 VA hospitals. These studies seem to suggest that while race influences procedure use in the VA, once patients receive diagnostic testing that indicates high risk, they are treated similarly and have similar outcomes. There is still much to understand about the consequences of differences in diagnosis and treatment by gender and race.

**Efficiency**

Unbridled growth in the cost of health care in the U.S. has increased the scrutiny of the utilization of cardiovascular care, particularly of diagnostic and therapeutic procedures. In an assessment of the use of cardiovascular services in fee-for-service Medicare beneficiaries between 1999 and 2004, Hayes et al. (45) found an average annual change in volume of 6.7% per beneficiary for all cardiovascular services. The annual growth in utilization was greatest for nuclear medicine (16.1%) and echocardiography (10.5%). The decline in bypass surgeries (−4.0%) was offset by an increase in angioplasty (7%). The sustainability of this growth in cardiovascular services in the future is questionable.

The striking rise in the utilization of cardiovascular imaging has generated greater pressures for professional accountability. During the year, the American College of Cardiology published appropriateness criteria for imaging in the areas of cardiovascular computed tomography/magnetic resonance imaging, transthoracic echocardiography, and transesophageal echocardiography (46, 47). These documents, reflecting expert consensus, identify clinical scenarios where the use of a specific imaging modality is considered appropriate, inappropriate, or of uncertain appropriateness. How these criteria can be integrated into clinical care, and whether their use will result in a meaningful decrement in the inappropriate utilization of cardiovascular imaging are issues for further study.

Policies and programs to constrain costs have proliferated in response to the alarming growth in the costs of medical care. Hsu et al. (48) determined the effect of caps on annual drug benefits for Medicare beneficiaries. Compared with beneficiaries without drug benefit caps, those with caps had
substantially lower pharmacy costs (by 31%); total medical costs, however, were only 1% lower. Those with caps were 9% more likely to visit the emergency department, 13% more likely to experience a non-elective hospitalization, and 22% more likely to die. This may have been mediated, in part, by lower adherence to drug therapy for hypertension, dyslipidemia, and diabetes among the patients with limited benefits. Indeed, blood pressure, cholesterol levels, and glycated hemoglobin levels were higher in the group with caps.

Rahimi et al. (49) determined the relationship between financial barriers to care and medications in a cohort of 2,498 survivors of a hospitalization for AMI. The prevalence of self-reported financial barriers to health care services or medications was 18.1% and 12.9%, respectively, and barriers were relatively common even among insured patients with annual incomes exceeding $70,000. Financial barriers were associated with more angina, poorer quality of life, and higher risk of rehospitalization in the year after hospitalization. The policy implication is that possessing health insurance alone does not necessarily address the deleterious effects of financial barriers to care.

Soumerai et al. (50) assessed rates of non-adherence related to drug costs in a national sample of 13,835 non-institutionalized Medicare beneficiaries. Overall, about 1 in every 9 men and 1 in every 7 women reported cost-related medication non-adherence. Among disabled enrollees with 4 or more comorbidities, rates were markedly higher, exceeding 50% among those without drug coverage and 25% among those with coverage.

Several cost-effectiveness analyses have assessed the economic attractiveness of electrophysiologic interventions. Chan et al. (51) found that catheter ablation of AF was not favored for patients with a relatively low risk of stroke (~1.4% annually). It may be economically attractive for patients with moderate risk (at least 3.0% annually); however, this assumes an 80% overall success rate at achieving sinus rhythm and a reduction in the risk of stroke of 42% by catheter ablation. Because such success rates and benefits have not been firmly established, it remains unclear whether catheter ablation for AF will be a cost-effective strategy in any population.

Several studies focused on the economic implications of ICDs. Using data from the industry-sponsored MADIT (Multicenter Automatic Defibrillator Implantation Trial)-II over 3.5 years, Zwanziger et al. (52) found that the average gain in the defibrillator arm of the trial was 0.167 years (2 months) at an estimated additional cost of $39,200. This translated into an incremental cost-effectiveness ratio of $235,000 per year of life saved, which is markedly more costly than what is traditionally considered economically attractive. Although a 12-year time horizon resulted in better cost-effectiveness ratios, even under best-case assumptions, the incremental cost-effectiveness ratio per year of life saved was still relatively high ($78,000). Mark et al. (53), in the economic analyses from the industry-sponsored SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), reported that relative to medical therapy, ICD therapy was associated with a lifetime cost-effectiveness ratio of $41,530 per quality-adjusted life-year. This calculation assumed, however, that the benefits of ICD therapy seen in SCD-HeFT extended to 8 years after implantation.

Microvolt T-wave alternans (MTWA) testing has been proposed as a strategy to identify patients with left ventricular systolic dysfunction who will benefit from ICD therapy. Although MTWA testing is covered by the Centers for Medicare & Medicaid Services, its cost-effectiveness is not clear. In an economic analysis in a population similar to that of MADIT-II, Chan et al. (54) found that MTWA screening followed by ICD therapy in the MTWA non-negative population rendered ICD therapy cost-effective, in contrast to an ICD-for-all-patients approach, which was not cost-effective (similar to the findings of Zwanziger [52]). However, because a screening strategy will miss a small number of patients who would benefit from ICD therapy, the challenge for society is to determine the value of saving a life.

Yao et al. (55) assessed the economics of cardiac resynchronization therapy for patients with heart failure and cardiac dyssynchrony. Compared with medical therapy and with a lifetime perspective for a patient age 65 years, cardiac resynchronization therapy had an estimated cost-effectiveness ratio of €7,538 per quality-adjusted life-year gained. Adding an ICD to the cardiac resynchronization device had a substantially less attractive incremental cost-effectiveness ratio of €47,909 per quality-adjusted life-year gained. Although these findings suggest the economic attractiveness of resynchronization therapy, the overall cost will be high, as many people are eligible.

The cost-effectiveness of guidelines has rarely been evaluated. Manuel et al. (56) compared the effectiveness and efficiency of different national guidelines for the use of statins for preventing deaths from coronary artery disease. Although the guideline developers were exposed to the same science, each national guideline provided somewhat different recommendations. The Australian and British guidelines were estimated to save the most lives, but the New Zealand guideline prevented almost as many deaths while treating about a third less patients (12.9% vs. 17.3%). The U.S. guideline recommended treating about twice as many people as the New Zealand guideline with no substantial increase in the number of deaths averted.

Several articles raised concerns about conflicts of interest, which also introduce inefficiencies into the health care system. Jørgensen et al. (57), in a comprehensive Cochrane review, determined that industry-supported reviews of drugs were less transparent, had fewer reservations about methodological limitations of the included trials, and had more favorable conclusions than Cochrane reviews of the same topics. Ridker and Torres (58), in a review of 324 superiority trials of cardiovascular medicines, found that studies funded by for-profit organizations more often reported positive
findings than trials funded by not-for-profit organizations. Ross et al. (59) evaluated laws in Vermont and Minnesota intended to promote transparency in payments from industry to physicians, finding substantial gaps in reporting and evidence of payments in excess of American Medical Association guidelines.

Epidemiology and Prevention

Epidemiological studies continue to expand our understanding of the importance of both novel and established cardiovascular risk factors and the distribution and outcomes of cardiovascular disease in the population. Ogden et al. (60) from the Centers for Disease Control and Prevention estimated the prevalence and trends in overweight and obesity from 1999 to 2004. They reported that in 2003 to 2004, 17.1% of U.S. children and adolescents were overweight and 32.2% of adults were obese. In children and adolescents, obesity prevalence rose from 14.0% to 18.2% in male children and adolescents and from 13.8% to 16.0% in female children and adolescents. Among adult men, the rate of obesity increased from 27.5% to 31.1%, while in women, although the prevalence was stable, obesity affected 1 in 3.

The consequences of the obesity epidemic for rates of diabetes are profound. In the Framingham Heart study, Fox et al. (61) found a doubling of the incidence of type 2 diabetes over the past 30 years. They also found that most of the absolute increase occurred in people with a body mass index (BMI) of 30 kg/m² or more. The impact of obesity on cardiovascular outcomes is also substantial. Adams et al. (62) assessed the association between obesity and risk of death in a study of 527,265 men and women in a National Institutes of Health-American Association of Retired Persons cohort, finding a strong association with risk of death in both men and women, in all racial and ethnic groups, and at all ages. After taking into account other health conditions and smoking, they found an increased risk even with moderately higher BMI. Compared with people who, at age 50, had a BMI between 23.5 and 24.9 kg/m², those who were overweight had a 50% higher risk and those who were obese had between 2- and 3-fold greater risk.

Although the benefits of structured exercise are documented, the effects of energy expenditures during free-living activity on outcomes have not been characterized. In a study of high-functioning, community-dwelling older adults, Manini et al. (63) identified a strong association between free-living activity energy expenditure and mortality. Every standard deviation increase in energy expenditure—the equivalent of about 75 min of activity such as everyday chores or non-sitting work daily—was associated with a 32% lower risk of death.

Several important diet articles were published this year. A comprehensive meta-analysis of 89 randomized and observational studies found little evidence to support the routine use of omega-3 fats to reduce risks of death or cardiovascular events (64). Results were similar with long chain versus short chain and dietary advice versus supplements. The results of individual studies varied widely; an analysis of observational studies alone suggested benefits, raising questions about the influences of confounders in this subgroup of studies. In a study of the benefits of antioxidant supplements for primary and secondary prevention by the Cochrane Collaboration (65), evidence emerged that beta carotene, vitamin A, and vitamin E may increase mortality. The effects of vitamin C and selenium were less certain.

The PREMIDED (Prevención con Dieta Mediterránea) study (66) provided some support for the Mediterranean diet. Investigators assigned 772 subjects to 1 of 2 Mediterranean diets or a low-fat diet. The subjects in the Mediterranean diet groups received nutritional education and either free virgin olive oil, or 1 liter per week of free nuts. At 3 months, subjects in the 2 Mediterranean diet groups had more favorable plasma glucose levels, systolic blood pressures, and cholesterol to high-density lipoprotein cholesterol ratios. Further, the Mediterranean diet with olive oil reduced C-reactive protein levels by 0.54 mg/l (95% confidence interval 1.04 to 0.03 mg/l) compared with the low-fat diet. The impact of these changes in risk factor profiles resulting from Mediterranean diets on cardiovascular outcomes, however, remains unclear. In a parallel-design trial of garlic in 192 adults, there were no benefits on low-density lipoprotein levels (67). In another trial, McMillan-Price et al. (68) randomized 129 overweight and obese young adults to 1 of 4 reduced fat, high-fiber diets with varying glycemic indexes. Weight loss over 12 weeks did not differ as a function of glycemic index, but the superior diet for cardiovascular risk reduction was high carbohydrate and low glycemic index. In a comparison of 4 popular diet programs, Gardner et al. (69) found the greatest weight loss with the Atkins diet compared with similar weight losses with the Ornish, LEARN, and Zone diets. Metabolic effects were also most favorable with the Atkins diet. Based on observational data from the Nurses Health Study, Halton et al. (70) found no evidence of an excess risk associated with a low carbohydrate diet over 20 years of follow-up, while a high glycemic load was associated with a higher risk of heart disease. A low carbohydrate diet with vegetable sources of fat and protein appeared associated with lower risk.

Several important studies of trends were published, including 2 on AF from Olmsted County. One study revealed an increase in the age-adjusted incidence of AF, with a relative increase of 21% over 21 years (71). Based upon this trajectory, the authors estimate that there may be 15.9 million Americans with AF by 2050. In another article in the same timeframe (72), the early (4 month) mortality risk of AF was almost 10-fold higher for those with newly diagnosed AF. Although AF was associated with a persistently higher mortality in longer-term follow-up, the magnitude of this risk was substantially lower. Over 21 years of the study, that risk remained unchanged. In another important trend study from Olmsted County, Gerber et al. (73)
showed that cardiovascular mortality declined markedly in the community, with a shift toward deaths that occurred out of the hospital and due to non-coronary causes. In a study of Medicare beneficiaries hospitalized with AMI in 4 U.S. states between 1992 and 2001, Masoudi et al. (74) found substantial increases in the burden of comorbidity in this elderly population. Although the quality of care with aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors improved significantly during the time of the study, diminishing proportions of patients met eligibility criteria for these evidence-based therapies. Unadjusted mortality increased over time, but adjusted mortality improved during the time of the study. These trends likely reflected both the marked increase in disease severity and simultaneous improvements in care over time.

Several studies focused upon the relationship between depressive symptoms and cardiovascular disease. Sherwood et al. (75), based on a study of 204 patients with heart failure, found that patients with depressive symptoms had a worse prognosis, with a 56% increased risk of death or cardiovascular hospitalization. Paradoxically, antidepressant use was associated with a 75% higher risk of death or cardiovascular hospitalization after adjusting for the severity of the depressive symptoms. The benefits of antidepressant therapy in patients with heart failure thus remain debatable.

Ruo et al. (76) reported in a prospective, longitudinal study of 2,675 women with coronary disease that depressive symptoms had an effect on self-rated health over 3 years that rivaled the impact of major cardiac events. In a registry study, Mallik et al. (77) found that the prevalence of depressive symptoms is particularly high in younger women after an AMI, with a prevalence of 40% in women age 60 years and younger. In another study from this registry, the same investigators showed that depressive symptoms after an AMI, whether they persist, subside, or develop in the first month after hospitalization, are associated with worse outcomes after the AMI (78). Further studies of effective interventions to reduce the adverse impact of depression on cardiovascular disease outcomes are clearly needed.

Conclusions

The past year has witnessed substantial advances in our understanding of the patterns of cardiovascular diseases and the care and outcomes of these conditions in the population. The increasing volume of high-quality studies reflects growing appreciation of the need to develop approaches to identify populations at risk for cardiovascular disease; intervene with effective strategies to prevent cardiovascular events; improve the care of those who have events despite our best efforts; and to do so efficiently, safely, and equitably. While much more must be done, the year provided clinicians with a wealth of information and tools to achieve the central goal of providing better care to patients.


34. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. JAMA 2006;296:2563–71.


