Conclusions—The Cardiovascular Research Network represents a new paradigm in the approach to cardiovascular quality of death nationally and is increasingly internationally. Both large, diverse populations will yield novel insights into contemporary disease and risk factor surveillance, management, outcomes, and costs. The Cardiovascular Research Network aims to become the national research partner of choice for efforts to improve the prevention, diagnosis, treatment, and outcomes of cardiovascular diseases.

Key Words: cardiovascular disease ■ risk factors ■ outcomes ■ epidemiology ■ quality of care

Despite recent advances in its prevention and treatment, cardiovascular disease (CVD) remains the leading cause of death nationally and is increasingly internationally. Both the American Heart Association and Healthy People 2010 have set bold goals to reduce the risks of heart disease, stroke, and other CVD conditions in the next decade. However, current surveillance systems in the United States are severely restricted in their ability to systematically track progress...
toward these goals. Present efforts to discern the burden of CVD and trends in CVD epidemiology, treatment, and associated outcomes have been based on a patchwork of data sources of varying study designs, sample sizes, sociodemographic diversity, and data quality.

In 2004, the National Heart, Lung, and Blood Institute (NHLBI) convened a working group to provide guidance on priorities for CVD outcomes research. Priority areas identified included (1) assessing national trends in CVD risk factors and clinical events; (2) evaluating the degree to which evidenced-based CVD preventive strategies and treatments are used in clinical practice and various patient subgroups; (3) gaining a better understanding about how well estimates of efficacy or safety with therapies observed in randomized trials translate when applied to community-based populations at risk; (4) assessing the effectiveness and cost-effectiveness of new models of CVD care delivery; and (5) creating a national framework to respond rapidly to evolving research and public health priorities. The workgroup also identified aspects of the current CVD research infrastructure that limit the ability to achieve these aims. Current surveillance systems and existing cohort studies that describe CVD treatment practices and outcomes are relatively limited in scope, clinical detail, follow-up, and generalizability. Furthermore, currently established national registries have important limitations, in that they generally focus on hospitalized patients or a single disease or procedure, and they rely on voluntary hospital participation. Thus, these registries lead to self-selected sites and data collection that is typically cross-sectional and deidentified, precluding longitudinal assessment. Finally, whereas randomized trials use the most rigorous method to answer a specific therapeutic question, findings from trials may have limited generalizability because enrolled patients are often not representative of patients treated in clinical practice with regard to age, gender, race/ethnicity, or comorbidity burden; existing trials also currently answer only a limited number of clinical questions. Although the NHLBI has invested enormous resources to identify safe and effective CVD therapies, it is clear that better approaches are needed to “close the loop” from research results to clinical care. Therefore, a consensus recommendation of the working group was for an investment by the NHLBI to create a national surveillance program for evaluating CVD epidemiology, care, and outcomes.

In response, the NHLBI sponsored formation of a CVD research network that would leverage health care systems as a platform for advancing clinical and population CVD outcomes research. Although many opportunities exist to improve clinical practice and health care delivery, it became clear that a multifaceted network of health systems had great potential for expanding data collection and research topics on CVD prevention, treatment, and outcomes. Furthermore, this could be accomplished for much less than the cost required to establish such a system de novo. After an open competition, the HMO Research Network (HMORN) brought together its broad cardiovascular expertise, diverse health plans and populations, and integrated data systems to create the Cardiovascular Research Network (CVRN) (www.cvrn.kaiser.org). The CVRN is establishing a framework to help answer critical CVD questions within large community-based populations where the majority of clinical care is delivered. Its overall goals are to:

- provide robust longitudinal surveillance of CVD risk factors and conditions across diverse populations and settings;
- promote rigorous research on clinical practice and quality of care;
- assess adoption and clinical impact of new diagnostic and therapeutic technologies;
- evaluate adherence to guidelines and their impact on CVD incidence, prevalence, clinical care, and outcomes;
- promote research on determinants of disease for uncommon disease phenotypes; and
- create collaborative research opportunities for non-CVRN investigators and other research networks.

Overview of the CVRN

Participating Sites

The HMORN, founded in 1993, is a consortium of 15 geographically diverse US health plans with integrated research divisions that care for ~11 million health plan members. The CVRN includes all HMORN member sites and brings together methodological and content expertise for nearly all CVD areas and relevant disciplines such as epidemiology, health services research, outcomes and quality of care assessment, qualitative methods, biostatistics, health economics, and clinical trials (Figure 1; Table 1). CVRN sites represent a variety of health care delivery system and provider group structures, with several plans using group or staff model delivery systems and a substantial number of enrollees receiving care through network, individual practice association, or point of service models (Table 2). Most sites provide care through commercial, Medicare, Medicaid, and state-specific “gap” insurance programs, reflecting essentially all health service and finance options in the United States. The population size within each CVRN site ranges from ~140 000 to ~3 300 000, with low annual disenrollment rates (3% to 4%) among older persons and those with any chronic medical condition. The cumulative population within the CVRN has substantial age, gender, socioeconomic, racial, and ethnic diversity (Table 3). Thus, the CVRN provides a rare opportunity to study the impact of clinical questions for nearly all demographic groups and insurance relationships within a unified health services delivery and health information systems framework.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Data Sources

All CVRN sites have invested in advanced information technology that routinely captures the majority of their membership’s care and outcomes through multiple electronic databases that are readily accessible to their researchers (Table 4). All sites use unique medical record numbers to track individuals across their databases, with detailed records on membership and resource utilization. A unique aspect of the CVRN is the availability of clinical and administrative
data through inpatient and outpatient diagnoses and procedures, detailed pharmacy prescription drug data, and laboratory test results. At nearly all sites, ≥90% of members have a pharmacy benefit requiring only modest copayments to purchase medications. Patients with a pharmacy benefit have a strong financial incentive to fill prescriptions through their health plan insurance which in turn yields nearly comprehensive data on prescription drug exposure. Finally, 14 of 15 sites have implemented an electronic medical record that allows for highly efficient and rich data-only studies as well as unique interventions involving electronic medical record systems.

Data Standardization and the Virtual Data Warehouse
Development and implementation of cardiovascular-related data standards across participating sites is a major goal. CVRN projects adhere to standardized methods for defining cardiovascular and other data elements along with development of future data capacities in conjunction with ongoing NHLBI (eg, CardioVascular Research Grid) and other national efforts (eg, National Cancer Institute’s CaBIG). This approach to standardize data elements increases the quality and efficiency of research within the CVRN and will foster productive partnerships between CVRN and non-CVRN investigators interested in collaborative research using nonnetwork data resources.

Electronic data systems created by each CVRN site for internal operations represent valuable data sources for research. Information from these disparate health plan data systems have been restructured into a common, standardized format in a “virtual data warehouse” (VDW) within each individual health plan that facilitates combining data sets across sites to conduct large-scale clinical research studies (Figure 2). The VDW, originally developed through the National Cancer Institute–sponsored HMORN Cancer Research Network, serves as the source of standardized data within each site. This includes demographic characteristics, inpatient and ambulatory diagnoses and procedures, medications, laboratory and pathology results, vital signs, membership, insurance and pharmacy benefit status, and selected socioeconomic indicators. Importantly, all person-level information is linked by a unique identifier across the various data sources. Essentially, the VDW comprises (1) a series of data sets stored behind separate security firewalls at participating sites that include variables with identical names, formats, and specifications and identical variable definitions, labels, coding, and definitions; (2) informatics tools that facilitate data storage, retrieval, processing, and management; and (3) regularly updated documentation of all data elements.

Access to CVRN site databases occurs through each site’s research team and use for research requires approval by the respective institutional review boards. All sites implement currently accepted methods for protection of data and confidentiality.

CVRN Organizational Structure
The CVRN governance and operational approaches are based, in part, on successful components from prior and existing HMORN collaborations as well as from CVRN investigators’ experience with other multicenter collaborations (Figure 3).
The Executive Committee provides overall leadership for the CVRN and is the primary liaison with the NHLBI, the External Collaborations and Advisory Committee, outside organizations and funders, as well as other HMORN collaborators.

The Steering Committee is composed of members of the Executive Committee, site principal investigators, and a representative from the NHLBI. The Steering Committee has established guidelines and policies that facilitate multisite collaboration within and outside the CVRN, oversees development of special interest groups focused on targeted cardio-

| Table 1. Research Centers and Lead Investigators Among CVRN Sites |
|-----------------|------------------|------------------|------------------|------------------|
| CVRN Principal Investigators | Research Center/Parent Organization/Location | Center Began | Investigators |
| Alan S. Go, MD (Director) | Division of Research | Kaiser Permanente Northern California/Calif | 1961 | 41 |
| David J. Magid, MD, MPH (Co-Director) | Institute for Health Research | Kaiser Permanente Colorado/Colo | 1990 | 15 |
| Jerry H. Gurwitz, MD (Co-Director) | Meyers Primary Care Institute | Fallon Community Health Plan/Mass | 1996 | 13 |
| Robert D. Langer, MD, MPH | Center for Health Research | Geisinger Health System/Pa | 2003 | 14 |
| Katherine M. Newton, PhD | Group Health Center for Health Studies | Group Health/Wash | 1983 | 30 |
| Tracy A. Lieu, MD, MPH | Department of Ambulatory Care and Prevention | Harvard Pilgrim Health Care and Harvard Medical School/Mass | 1992 | 38 |
| Karen L. Margolis, MD, MPH | HealthPartners Research Foundation | HealthPartners/Minn | 1989 | 66 |
| Andrea E. Cassidy-Bushrow, PhD | Department of Biostatistics and Research Epidemiology and Center for Health Services Research | Henry Ford Health System/Mich | 1979 | 150 |
| Rachel Novotny, PhD, RD | Center for Health Research | Kaiser Permanente Hawaii/Hawaii | 1999 | 4 |
| David H. Smith, RPh, MHA, PhD | Center for Health Research | Kaiser Permanente Northwest/Ore | 1964 | 42 |
| Douglas W. Roblin, PhD | Center for Health Research | Kaiser Permanente Southeast/Ga | 1998 | 3 |
| Suma Vupputuri, PhD | Center for Health Research | Kaiser Permanente Southeast/Ga | 1998 | 3 |
| Kristi Reynolds, PhD, MPH | Department of Research and Evaluation | Kaiser Permanente Southern California/Calif | 1975 | 14 |
| Robert E. White, MD, MPH | Lovelace Clinic Foundation | Lovelace Health Systems/NM | 1990 | 10 |
| Glen H. Murata, MD | Lovelace Clinic Foundation | Lovelace Health Systems/NM | 1990 | 10 |
| Robert T. Groenlee, PhD, MPH | Marshfield Clinic Research Foundation | Marshfield Clinic/Wis | 1959 | 25 |
| Catherine A. McNeal, MD, MPH | Division of Research & Education | Scott and White/Tex | 1960 | 163 |

| Table 2. Provider and Infrastructure Characteristics Among CVRN Sites (as of December 2007) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| KPNK | KPCO | FCHP | GH | GHS | HFHS | HPHC | HPRF | KPH | KPNW | KPSE | KPSC | LSHS | MCRF | S&W |
| Staff physicians | 7000 | 700 | 246 | 893 | 720 | 800 | 380* | 829* | 400 | 700 | 221 | 6246 | 250 | 741 | 606 |
| Contracted physicians | ... | 1734 | 2300 | 2400 | 14 000 | 4300 | 37 000* | 24 924* | ... | ... | 525 | ... | 3000 | 726 | 719 |
| Primary care providers | 2098 | 267 | 960 | 518 | 3 250 | 1672 | 8 000* | 10 651* | 210 | 326 | 79 | 1584 | 115 | 530 | 427 |
| Clinic sites | 59 | 17 | 20 | 39 | 41 | 25 | >500* | 650 | 17 | 27 | 15 | 130 | 20 | 41 | 35 |
| Hospitals | 17 | 3 | 1 | 0 | 3 | 8 | 135 | 3 | 1 | 9 | 3 | 12 | 5 | >12 | 19 |

KPNK indicates Kaiser Permanente of Northern California; KPCO, Kaiser Permanente Colorado; FCHP, Fallon Community Health Plan; GH, Group Health; GHS, Geisinger Health System; HFHS, Henry Ford Health System; HPHC, Harvard Pilgrim Health Care; HPRF, HealthPartners Research Foundation; KPH, Kaiser Permanente Hawaii; KPNW, Kaiser Permanente Northwest; KPSE, Kaiser Permanente Southeast; KPSC, Kaiser Permanente Southern California; LSHS, Lovelace Sandia Health Systems; MCRF, Marshfield Clinical Research Foundation; S&W, Scott and White.

*Including affiliated hospitals and providers.
Multiple proven antihypertensive agents exist for controlling hypertension. Nearly 1 in 4 American adults have hypertension, and the prevalence is expected to increase to 30% by 2025. Recent data demonstrate relatively poor awareness among patients with hypertension. Only two thirds of patients with recognized hypertension are treated, and only one third receive treatment and achieve recommended blood pressure goals. Thus, >40 million adults have uncontrolled hypertension in the United States.

Vascular topics, and reviews and approves proposals for new projects and manuscripts. Efforts are underway to streamline multicenter project reviews by site institutional review boards and to create efficient methods for sharing data across CVRN sites while maintaining appropriate protections for individual subjects and health plans.

The CVRN has also established an External Collaborations and Advisory Committee composed of distinguished researchers with core expertise in epidemiology, outcomes research, health policy, trials, community-based interventions, genetics, health disparities, patient safety, nutrition, CVD registries, health information technology, statistics, and econometrics. Committee members participate actively within the infrastructure of the CVRN by providing input on strategic direction, providing additional methodological and content expertise on projects, and facilitating collaborations with external investigators and institutions.

**CVRN Research Studies**

The CVRN is initially conducting 3 projects that showcase its ability to address research questions with high clinical and public health relevance through the efficient combination of its cardiovascular expertise, diverse populations, and electronic databases.

**Hypertension Recognition, Treatment, and Control in Community Practice**

Nearly 1 in 4 American adults have hypertension, and the prevalence is expected to increase to 30% by 2025. Multiple proven antihypertensive agents exist for controlling hypertension and reducing cardiovascular morbidity and mortality. However, recent data demonstrate relatively poor awareness among patients with hypertension. Only two thirds of patients with recognized hypertension are treated, and only one third receive treatment and achieve recommended blood pressure goals. Thus, >40 million adults have uncontrolled hypertension in the United States.

Optimal delivery of hypertension care remains a major challenge, and we need a better understanding of hypertension treatment over time and its management in routine practice (eg, how providers respond to elevated blood pressures or how well patients adhere to antihypertensive therapy).

This project evaluates contemporary hypertension management across 3 CVRN sites involving >850,000 subjects with recognized and unrecognized hypertension. The analytic data set includes all blood pressure measurements, associated treatments, and other patient characteristics over an extended period of time (2002 to 2006). The study (1) identifies factors associated with overall hypertension recognition, treatment, and control; (2) quantifies the relationship of patient, provider, and clinic characteristics to hypertension care received at each encounter; (3) delineates predictors of appropriate provider treatment intensification when blood pressure targets are not met; and (4) characterizes factors linked to patient medication adherence. The findings of the study will inform future interventions to improve hypertension care and reduce the morbidity and mortality associated with uncontrolled hypertension.
Community-Based Control and Persistence of Warfarin Therapy and Associated Rates and Predictors of Adverse Clinical Events in Atrial Fibrillation and Venous Thromboembolism

The oral vitamin-K antagonist, warfarin, is highly effective for the prevention of thromboembolism across a variety of conditions such as atrial fibrillation and venous thromboembolism. However, warfarin is a narrow therapeutic index drug that requires frequent monitoring to avoid both overanticoagulation (which increases the risk of bleeding) and underanticoagulation (which increases the risk of thromboembolism). Recent analyses reveal that warfarin is a leading cause of serious preventable adverse drug events, particularly among the growing elderly population in the United States, highlighting the importance of better understanding the risks and benefits of this therapy.

Relatively little insight exists into the contemporary quality of care and associated risks and benefits of warfarin therapy among large, diverse populations in clinical practice. This project addresses these issues among a multicenter cohort of anticoagulated patients from 5 CVRN sites by characterizing...
their longitudinal exposure to warfarin therapy and associated anticoagulation intensity, comorbidity, other medication exposure, and clinical outcomes. The study (1) provides a “real world” assessment of the quality of control (ie, proportion of time spent at a therapeutic anticoagulation intensity) and persistence of warfarin therapy for patients with atrial fibrillation and venous thromboembolic disease in a large community-based network of clinical practices; (2) precisely determines the rates of thromboembolism and major bleeding in persons exposed to warfarin therapy, overall and associated with initiation of treatment; and (3) identifies patient-related predictors of anticoagulation control, long-term persistence of therapy, and associated clinical outcomes.

Implantable Cardioverter Defibrillators for Primary Prevention in Community Practice—Clinical Characteristics, Outcomes, Resource Utilization, and Cost

Implantable cardioverter defibrillators (ICDs) reduced the risk of sudden cardiac death in selected high-risk patients with left ventricular systolic dysfunction in the setting of randomized trials. However, little is known about the patterns of use and outcomes of ICDs for primary prevention in typical practice, which often bears little resemblance to the clinical trial environment. The broadening of ICD eligibility criteria to the population with left ventricular systolic dysfunction has resulted in a dramatic rise in the number of patients considered eligible for preventive ICD therapy. Despite the broader indications for ICD therapy, use varies across important demographic groups, the devices are extremely expensive, procedural complications may limit their benefits, and they may not be cost-effective in some patient populations. These factors highlight the urgent need to understand community-based patterns of ICD use, outcomes, and costs after implantation.

This project identifies a cohort of patients across 4 CVRN sites who receive an ICD for primary prevention and uniquely links individual-level longitudinal data from health plan databases and from the National Cardiovascular Registry for ICDs (NCDR ICD registry), which includes detailed baseline patient and ICD procedure information. Additional information on occurrence of appropriate and inappropriate ICD shocks will also be accessible through medical records. The study (1) assesses the extent to which patients receiving ICD therapy for primary prevention in community-based settings meet guideline-based recommendations for implantation; (2) determines real world rates of morbidity, mortality, procedural complications, and cost after ICD implantation; and (3) delineates the patient and provider factors associated with these longitudinal outcomes in a large, broadly representative community-based population to improve decision making for the use of ICD therapy for primary prevention.

Beyond these 3 initial studies, the CVRN is actively pursuing and implementing additional research projects across the spectrum of CVD care and outcomes.

Emerging Research Issues in CVD

Advances in our understanding of CVD pathophysiology and molecular mechanisms, along with the development of an expanding array of new technologies have, in some instances, led to approval and rapid uptake of new treatments that are subsequently shown to have serious side effects that were not appreciated when these treatments were first introduced. Examples include the increased risk of CVD events associ-
ated with COX-2 inhibitors\textsuperscript{30–34} and the possible differential risk of late cardiac events and stent thrombosis for drug-eluting compared with bare metal stents.\textsuperscript{35–39} To date, researchers have relied primarily on meta-analyses or pooled analyses of randomized trials to examine expected and unexpected risks. Occasionally, surveillance is expanded after introduction of new treatments or therapeutic strategies into the marketplace through phase IV trials. However, it is well known that trials often severely underrepresent important demographic groups (eg, women, children, and the elderly)\textsuperscript{40} as well as those with comorbid conditions (eg, chronic kidney disease),\textsuperscript{41} which may alter the balance of risks and benefits of specific therapies.

Because of its many advantages, the CVRN is well positioned to address rapidly emerging CVD research issues in both adults and youth, especially about the safety of cardiovascular therapies delivered under usual clinical care circumstances. The CVRN will work closely with the NHLBI, the CVRN External Collaborations and Advisory Committee as well as other NIH Institutes and federal agencies (eg, Food and Drug Administration, Centers for Disease Control), the NIH-sponsored Clinical and Translational Science Awards consortium, and professional societies (eg, American Heart Association, American College of Cardiology, Heart Rhythm Society) to identify high-priority emerging research issues that are in need of timely data to inform clinical or policy decision making.

**Challenges**

Implementing the CVRN brings several challenges. Ongoing efforts are required to ensure that the data used in CVRN studies are complete, accurate, and comparable across participating sites. Clinical data are not typically collected with the same rigor as protocol-driven research data, so measurements may have greater variability both within and across sites, and missing data may introduce biases. CVRN research projects will help to mitigate this through targeted validation efforts and application of statistical methods to determine the potential influence of missing data. Because of the differences in data availability, certain projects might not involve all 15 sites, although many research questions can be answered without inclusion of all sites’ populations. Given the variability in data structures and availability in other types of networks and populations (eg, Medicare, Veterans Affairs), additional efforts will be needed to facilitate future collaborative research projects between CVRN and non-CVRN researchers that involve disparate data sources. Streamlining the administrative and financial aspects of research collaborations within the CVRN and with outside researchers, optimizing communication across geographically distributed teams, and increasing the speed of multicenter project implementation are also significant hurdles that are currently being addressed. Finally, given that CVRN sites care primarily for insured populations, study results will be most generalizable to those individuals with health insurance.

**Discussion**

Attaining the American Heart Association\textsuperscript{3} and Healthy People 2010\textsuperscript{4} goals of reducing the population burden of CVD in the United States is a serious challenge that requires novel approaches. To achieve these goals requires an understanding of the current status and temporal trends in the epidemiology, diagnosis, and management of CVDs and risk factors. Novel, large-scale efforts are also needed to assess the degree to which information from clinical trials of proven CVD therapies and strategies are translated into contemporary practice and the associated clinical outcomes, resource utilization, and costs these practices incur among typical patient populations.

The CVRN establishes a new paradigm that uses an integrated and comprehensive approach to support the vision of the NHLBI in developing a community-based research network to address these challenges. Strengths of the CVRN include a diverse set of experienced cardiovascular researchers with expertise working with a large, geographically diverse sample of patients that reflects community-based care and that is not currently available through any other network or research consortium. Although other large health care entities exist nationally (eg, Veterans Affairs) and internationally (eg, UK National Health Service), they are not focused primarily on CVD and have other limitations with regard to the diversity of their populations, available clinical data sources, and/or completeness of follow-up for various clinical outcomes. CVRN site populations are insured through commercial programs as well as Medicare, Medicaid, state-specific gap programs, and other financing arrangements, so it will be able to address clinical and health policy questions relevant to every market segment through which insured Americans receive health care. CVRN member health plans provide care to relatively stable populations that are remarkably diverse across age, gender, and race/ethnicity. The long-term retention of its members is particularly high among those who are older and/or have chronic illnesses. This provides a key opportunity for longitudinal research with systematic follow-up and assessment of many different exposures and CVD outcomes, as well as a potential starting point for collaborative efforts on very large-scale epidemiology studies.\textsuperscript{42} In addition, the CVRN has the potential to leverage capabilities to streamline the conduct of randomized clinical trials within community-based settings.\textsuperscript{43} Finally, the combination of these attributes along with the rich clinical data resources, approach to data standardization and integration, and multiple local and national avenues of rapid dissemination of study findings will facilitate the CVRN’s ability to close the loop between research results and clinical care to improve CVD outcomes.

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