

July 15, 2002

Diabetes Mellitus Interagency Coordinating Committee

Macrovascular Disease and Diabetes: Translation Issues

**NIH Campus, Building 31c, 6th Floor, Room 6
Bethesda, Maryland**

Meeting Summary

Introduction

Dr. Sanford Garfield, Executive Secretary, DMICC, opened the meeting and introduced Dr. Allen Spiegel, Director of the NIDDK and Chairman of the Diabetes Mellitus Interagency Coordinating Committee (DMICC). Citing data which indicates an increased relative risk of cardiovascular disease (CVD) for those individuals who have been diagnosed with diabetes or pre-diabetes, Dr. Spiegel defined the purpose of the meeting: To determine the means and methods for translating the current scientific data from clinical trials and epidemiological studies to diabetic patients and the general public. Dr. Spiegel also took the opportunity to introduce Dr. Claude Lenfant, Director of the National Heart, Lung and Blood Institute (NHLBI), who further emphasized the need for translation efforts involving CVD and diabetes.

Diabetes and Macrovascular Disease: Scope of the Problem

Dr. Hertzell Gerstein, Professor of Clinical Epidemiology and Biostatistics and Medicine at McMaster University, examined the increased relative risk of a macrovascular event in subjects with diabetes. CVD must be considered as a risk factor for people with diabetes, since 70 percent of diabetic subjects die of cardiovascular causes, and CVD represents more than two-thirds of the greater than \$100 billion per year diabetes costs in the U.S. alone.

Data from clinical studies show that diabetes in men increases the relative risk of a CVD event two- to three-fold; in women the risk is increased from two- to five-fold. The OASIS database indicates that having diabetes at the time of admission for unstable angina predicts a higher risk of mortality. Even having experienced a previous myocardial infarction (MI) presents less risk than does having diabetes alone.

The absolute risk of a cardiovascular event in people with diabetes is difficult to accurately predict. Although less than ideal, the best data is obtained from clinical trial databases. Dr. Hertzler summarized data from the HOPE, RENAAL, IDNT, IRMA, and HPS studies, concluding that a person with diabetes and no previous CV event may have a risk equivalent to a non-diabetic subject who has experienced a CV event.

Blood glucose levels of >133 mg/dl and elevated hemoglobin A1c are consistently predictive of CV risk, independent of diabetes. Since these risk factors extend well below the diabetes threshold, Dr. Gerstein asserted that the prevalence of metabolic problems in the general public foretells a much larger epidemic of CVD.

Recent Clinical Trials: Projected Benefits

Dr. Steven M. Haffner, Professor of Internal Medicine at the University of Texas Health Science Center in San Antonio, Texas, reviewed recent clinical trials in the area of CVD and diabetes translation research. Dr. Haffner recommended that the focus of NIH strategy be on the primary prevention of diabetes for two reasons: 1) diabetic subjects have a high mortality rate within 1 year of their first MI, and 2) diabetics develop CVD at twice the rate of those individuals who are never diagnosed with diabetes.

Current clinical trials such as the ACCORD, LOOKAHEAD, and BARI studies are examining hemoglobin A1c, blood pressure, LDL, HDL, and smoking as risk factors. Clearly, data from these trials show that these conventional risk factors predict CV risk within diabetic subjects. Data further suggests that ACEs, ARBs, statins, and antihypertensive agents are particularly promising pharmacologic interventions.

The heterogeneity of the risk in diabetics for CVD is evidenced by data indicating that subjects with metabolic syndrome have an intermediate risk of CVD. Eighty-five percent of diabetic subjects have metabolic syndrome and a subsequent two-fold risk for CVD than do diabetics without metabolic syndrome.

Dr. Haffner emphasized that a multifactorial approach in clinical trials will be necessary to halt the CVD epidemic, one which addresses the prevention of type 2 diabetes, as well as the improvement and treatment of the disease, including examination of improved glycemic control, risk factor management, and special interventions.

Economics of the Problem

Dr. Vinkat Narayan, Chief of the Epidemiology Section at the Centers for Disease Control and Prevention (CDC), addressed the economics of diabetes and CVD translational research and application. The interaction of diabetes and CVD has a huge impact on the cost of health service

in the U.S. Direct costs of diabetes are estimated at \$44 billion per year, and CVD at \$8 billion; of that, 56 percent of deaths and 55 percent of lost productivity are attributed to CVD. At all ages, the impact of CVD is substantial. Although the direct costs of diabetes in terms of medical expenses is but a small component, the indirect costs (i.e., mortality costs) are substantial. Among people with diabetes, macrovascular complications account for a large percentage of total costs.

Total lifetime costs of diabetes are probably underestimated at \$82,000. This figure decreases with age, since younger individuals have longer lifetime exposure to risk of complications, and argues for better screening for diabetes at younger age levels.

QALY, which incorporates mortality, morbidity, and quality of life, is an important measurement tool. Data from the UKPDS study among others show that, per \$1.00 of investment, blood pressure control is a clearly superior investment, although glycemic control may be more beneficial in younger age groups. Dr. Narayan suggested that other interventions, such as ACE inhibitors and aspirin use, should be more closely evaluated.

Diabetes Translation: The Challenge for Primary Care

Dr. Evan Benjamin of the Bayside Medical Center, Springfield, Massachusetts, identified safety in health care as one of the challenges of providing comprehensive health care to patients. Misuse, underuse, and overuse of treatment are components that ought to be addressed in the health care system.

Although ultimately we ought to seek to prevent diabetes, our immediate goal must be to get treatment to patients with diabetes. Aggressive goals for blood pressure, LDL, hemoglobin A1c, aspirin, and anti-platelet therapies are laudable, but are not widely or consistently attained among diabetic patients, let alone the general population. In a Massachusetts General Hospital study, 92 percent of patients diagnosed with diabetes had A1c determined and 99 percent had blood pressure readings taken. However, only 76 percent had their cholesterol tested and just 61 percent had a fasting lipid profile for LDL. Of those tested, the majority were above the target levels, reflecting an underuse of testing for risk factors in diabetic subjects.

The message regarding aggressive treatment regarding blood pressure and lowered lipid levels has been well received by both physicians and patients. However, problems in translation persist in the areas of knowledge and attitude among physicians, systems issues, and patient adherence to treatment plans. Without clear guidelines for health care providers, physicians must rely on computerized systems or diabetes registries for standards. Alternatively, patients must be directly instructed by the health care system as to how to recognize the standards and demand the necessary treatment for high quality diabetes care.

Dr. Benjamin cited the diabetes clinic approach used by the Indian Health Service and Kaiser

Permanente, which focuses on diabetes, glycemic control, blood pressure, lipid levels, standards of care, and secondary prevention related to diabetes as well as CVD, as being an effective tool that all health care systems ought to consider.

The Drug Industry and Its Role in Translation

Dr. Fred Fiedorek, Vice President of the Metabolics, Clinical Development, and Life Cycle Management Division, Pharmaceutical Research Institute at Bristol-Myers Squibb, related the current focus of the drug industry as the determination of surrogates which will lead to event reduction in clinical trials and clinical practice.

The drug industry is focusing on the metabolic syndrome because of concern that these are the events that most impact not only patients with diabetes, but those in the 10- to 15-year period prior to diagnosis. Those in the drug industry recognize a balance of benefit and costs associated with risk is an important consideration where patients taking multiple medications are concerned.

To that end, Dr. Fiedorek suggests that two approaches be followed: 1) to do innovative science to understand core mechanisms underlying diabetes and how it is linked to CVD, and 2) to investigate “killer applications” (research of the use of multiple medications as effective treatment).

The drug industry grants the importance of prevention as well as drug therapy such as Metformin, Pravastatin, aspirin-drug combinations; the investigation of metabolic syndrome; and the need for translation. However, the past emphasis on glycemic ranges may need to be downplayed, since diabetes does not involve simply a problem with sugar, but more precisely relates to an increased risk of CVD, together with its inherent health hazards.

The Managed Care Perspective

Dr. Joseph V. Selby, physician, health services researcher, and Director of the Division of Research at Kaiser Permanente in Northern California, presented the managed care perspective on diabetes, macrovascular disease, and translation. The prevalence of diabetes within the Kaiser Permanente population has risen 33 percent in the past 5 years, while coronary heart disease and congestive heart failure rates have remained stable.

Although hospitalization costs for diabetic patients have decreased slightly over the past 5 years, the current focus on lowering blood pressure and lipid levels has contributed to a significant rise in laboratory testing and pharmaceuticals, keeping overall costs relatively neutral. Still, health care costs for diabetic patients are significantly greater than for non-diabetics. Dr. Selby emphasized the importance of good disease management in reducing health care costs, and recommended a systems approach to identify populations; to provide decision support, monitoring, and feedback on performance and outcomes; and to ensure that the highest risk patients receive the most intensive efforts.

The high co-occurrence rates of hypertension and dyslipidemia among diabetic patients suggests the benefit in risk-stratifying populations of diabetic patients lies in being able to identify subgroups having an increased risk of metabolic syndrome and accompanying complications. Using a multivariate model, Kaiser Permanente has identified three predictors that a patient with no previous event would suffer a major micro/macrovascular, infectious, or metabolic event within 12 months: 1) elevated serum creatinine levels, 2) use of two blood pressure medications, and 3) use of insulin.

Kaiser Permanente is currently expanding the training and responsibilities of diabetes nurse care managers to include CVD risk factor management, and plans to re-design risk stratification algorithms to incorporate findings from the risk predictor study. Future and ongoing research will evaluate trends in CAD and stroke incidence over time, with a particular focus on possible increases in end-stage renal disease (ESRD) as macrovascular disease rates decline.

Agency Overviews on Macrovascular Disease/Diabetes and Translation

National Diabetes Education Program (NDEP)

Dr. Judith Fradkin, Director of Diabetes, Endocrinology and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), presented an update on the National Diabetes Education Program with regard to cardiovascular issues.

The NDEP is committed to expanding the glucocentric message to include more comprehensive care for patients with diabetes, with a particular focus on cardiovascular disease. The NDEP's ABC (A1c, blood pressure, and cholesterol) Campaign targets patients, and is therefore complementary to the American Diabetes Association's (ADA) Make The Link Program, which is primarily aimed at health care providers.

A joint press conference with ADA emphasizing that two-thirds of patients with diabetes are unaware that CVD is the major source of mortality for diabetics generated a fair amount of publicity. Information is being disseminated through a variety of media, including the NDEP website, community publications, and television and radio news broadcasts.

Most recently, NDEP has turned its efforts toward sub-populations, such as African Americans, Asian Americans, and women.

National High Blood Pressure Education Program (NHBPEP)

Dr. Jeffrey Cutler discussed the translation efforts of the National High Blood Pressure Education Program. The NHBPEP, overseen by a coordinating committee comprised of

approximately 45 members representing professional and volunteer organizations, as well as government agencies, has recommended aggressive treatment of high blood pressure among patients with diabetes. While lifestyle changes, weight control, and increased physical activities are interventions which have been promoted for many years, new emphasis has been applied to the prevention of hypertension and diabetes.

Previously, treatment goals for hypertensive diabetic patients were determined strictly on risk considerations, and lacked a basis in trial data. However, more recent trials have provided evidence of the improved effectiveness of beta blockers over earlier drug interventions, and have identified diabetic patients as the high risk level, resulting in the recommendation of immediate drug treatment initiation for those patients.

Most information regarding hypertension guidelines is shared internationally, and a broad awareness of the principles are apparent, even if their implementation is less clear.

Since the benefits from the treatment and control of high blood pressure seem to be leveling off, the NHBPEP is concentrating efforts in a new direction, including work with the National Committee on Quality Assurance, to adopt a HETIS or control standard aimed at the CVD high risk populations. NHBPEP is also involved in contracts with the community-based consortia, or dissemination-utilization center, whose goal is to provide for CVD high risk populations.

National Cholesterol Education Program (NCEP)

Dr. James Cleeman, Coordinator of the NCEP, discussed the translational efforts of the program with respect to diabetes. Dr. Cleeman explained that science must first be translated into guidelines for professionals before those guidelines can be extended into useful tools for health care professionals, patients, and the public.

The Adult Treatment Panel III (ATP III) Study regards diabetes as a CHD risk equivalent. Within the study's statin trials, over 20 percent of those subjects in the placebo group suffered an MI plus coronary death within a 10-year period. In comparison, 15 to 25 percent of diabetic patients are at risk of developing CHD.

Data from the Heart Protection Study, which examined the effects of therapeutic lifestyle changes and the LDL level at which drug therapy ought to be considered, is currently being evaluated.

ATP III derived therapeutic objectives for metabolic syndrome, including the reduction of underlying causes (i.e., obesity and a sedentary lifestyle). The study produced an executive summary published by JAMA and a Quick Desk Reference (the ATP III At-A-Glance, which provides treatment instructions). These reference materials have been augmented by a NHLBI website, patient brochures, kits sent to 65,000 physicians, a palm device program, and

implementation of National Cholesterol Education Month, all of which emphasize diabetes as a coronary disease equivalent.

Centers for Medicare and Medicaid Services (CMS)

Dr. Steve Phurrough, Director, Division of Medical and Surgical Services of the Coverage and Analysis Group, addressed the translation efforts of CMS. Medicare was authorized by Congress to pay for the diagnosis and treatment of injury and disease, covering 34 million Americans at an annual cost of \$300 million. While coverage originally excluded screening or prevention, over the past decade, Congress has approved some limited screening procedures.

For diabetic patients, coverage has generally been available for secondary prevention in macrovascular care, since secondary prevention is considered the treatment of a primary disease. Coverage has recently been expanded to include nutritional counseling, selected foot exams, and a 10-hour diabetes education program. Medical benefits may also be covered in the future. However, translation at CMS remains an issue of coverage.

Currently, CMS publishes several pamphlets and manuals made available to both health care providers and patients. The agency is investigating the level and causes of disparities in diabetes treatment between gender, racial, and ethnic groups.

Indian Health Service (IHS)

Dr. Kelly Acton, Director of the National Diabetes Program at the IHS, spoke about the agency's approach to macrovascular disease and transition activities in terms of risk factors. CVD and cerebrovascular disease mortality rates in American Indians and Alaska Natives, although variable between tribes, exceed all other races in the U.S. combined. The Strong Heart Study, an NHLBI-funded, longitudinal study of CVD in 13 American Indian tribes, produced data showing diabetes is second only to age as the strongest determinant of CVD.

IHS updates its standards for care every 2 years, and has recently instituted the CVD Risk Factor Report, a subreport from the agency's annual diabetes care and outcome audit which calculates CV risk status for individual facilities, as well as for regions. Data from this report shows a substantial increase in the number of people within the population who are tobacco-free. Aspirin use has increased over the past 2 years as a result of changes in IHS standards of care. Levels of glycemic control, blood pressure, LDL and HDL, triglycerides, and albuminuria, while increasingly favorable, still present an area for improvement. The population continues to show a significant problem with obesity.

IHS targets the highest risk individuals, utilizing a systems approach with diabetes clinics in nearly every facility, electronic registries, and standards of care. Currently, IHS is gathering age-specific diabetes prevalence data.

Veterans Administration (VA)

Dr. Leonard Pogach, National Program Director for Diabetes for the Veterans Health Administration and Chief of Endocrinology for the VA Health Care System, offered information regarding cardiovascular prevalence, risk factors, and outcomes in the VA health care system. The VA health care system is a nationwide system which includes clinical reminders and an emphasis on prevention, care coordination, and chronic disease management. It provides health care services for a relatively challenged population, 40 percent of whom have known CVD.

To improve quality of care for its patients, the VA instituted the Quality Enhancement Research Initiative (QUERI) program in 1999, using health services research in its system for translation, feedback, and evaluation. Primarily, effort has been focused on ongoing organizational improvements and integration with existing tools, especially using the VA's electronic databases, with the goal of inducing behavioral changes within the population.

Aspirin use and maximal hypertension therapy (defined as three or more medications) interventions have shown promising results in lowering the incidence of hypertension among VA patients. Health care providers using the VA computer system are presented with reminders for blood pressure and lipid levels. Pilot data indicates clinicians are responding by entering data and making an appropriate intervention.

Centers for Disease Prevention (CDC)

Dr. Frank Vinicor, Director of Diabetes Translation at CDC, suggested that the diabetes epidemic may cause a neutralization of the benefits of lowering blood pressure and lipid levels, together with a corresponding increase in CVD associated with diabetes.

Dr. Vinicor stressed the importance of science in underpinning public health translation approaches, since absent the essential scientific basis, controversies regarding treatment and programs will arise.

Dr. Vinicor raised the issue that discussion of CVD ought to focus on the large percentage of time patients spend away from their doctors or health care professionals, and that rather than making the best treatment available to a small number of diabetic patients, it would be better to make a good treatment available to many, at least insofar as CVD is concerned.

At CDC, the focus is currently on 1) collection of data from national sources such as the Diabetes Quality Improvement Program, 2) examination of the issue of proper CVD care for diabetics through systems of care and the development of health care workers as an essential part

of the health care team, and 3) comprehensive diabetes control programs concerned with health systems changes, community interventions, and health communications. Future CDC endeavors include establishing a better definition of diabetes and examination of the metabolic syndrome.

Following the presentations by invited speakers, Dr. Garfield invited representatives from various agencies and associations to share current translational efforts.

Dr. Daniel Stryer, Center for Outcomes and Effectiveness Research, Agency for Healthcare Research and Quality (AHRQ), informed the group that AHRQ is conducting studies examining the impact of diabetes policies, disparities in diabetes, and systems level changes, including disease management programs, and the use of diabetic clinics and automated telephone assessment and reminder systems. Implementation research includes TRIP studies (translating research into practice), such as the impact of opinion leaders, academic detailing, and patient empowerment tools. AHRQ's National Guidelines Clearinghouse puts guidelines into the public domain, making the information easily accessible. Data networks and surveys are also available.

Dr. Robert Misbin, Medical Officer of the Division of Endocrine and Metabolic Products, Center for Drug Evaluation and Research at the Food and Drug Administration, highlighted studies being conducted by the pharmaceutical industry regarding the benefit of treating insulin resistance with respect to hard endpoints.

Dr. Nathaniel Clark, National Vice President of Clinical Affairs at the American Diabetes Association, stressed the need for consistent, evidence-based, and achievable guidelines. Current projects involve issues of optimal lipid levels in children, and the construction of guidelines for children with type 1 diabetes.

Dr. Robert Eckel, of the American Heart Association, expressed his association's goal that by 2010 morbidity and mortality from heart disease and stroke be reduced by 25 percent, and risk factors for heart disease and stroke also be reduced by 25 percent. To accomplish their goal, the AHA has placed a very high priority on understanding the connection between obesity and diabetes. Information from research and the agency's progress has culminated in several Prevention conferences.

Panel Discussion

During the Panel Discussion, the following questions were raised:

- What, if any, are the public health responsibilities of agencies that are not public health agencies?
- How will the health care of patients with more than one chronic disease be effectively coordinated?
- How can agencies coordinate efforts on translation research in order to perform larger, more efficient studies?
- How can patients be risk stratified so that translation efforts can be made more immediately usable?
- Would a trial research network be feasible?
- Given the accessibility to care and medications, why are patients not achieving goals?
- If interventions are effective, are they additive or subadditive?

Summary

Participants reached a general consensus in recognizing that primary prevention research in the areas of diabetes and CVD will provide the greatest benefit for translation efforts. Future research in the following areas is therefore warranted:

I. Interventions

- Examination of pharmacologics, particularly ACEs, ARBs, statins, and antihypertensive agents
- Determination of the benefits of glycemic control versus CV risk reduction
- Investigation of multiple drug therapy and its metabolic effects
- Identification of the underuse and misuse of pharmacologic therapies
- Assessment of the effects of underuse of specific patient exams, such as A1cs, eye exams, and foot exams

II. Health Care Costs/Economics

- Institution of incentives for health care providers
- Promotion of earlier screening for younger subjects, in an effort to reduce lifetime costs
- Examination of costs over a finite time period versus lifetime costs
- Prospective data collection of costs in clinical trials

It was strongly emphasized that extensive research efforts are demanded in the area of metabolic syndrome and its connection to diabetes and cardiovascular disease, especially since there is no clearly science-based definition of metabolic syndrome. Additionally, disparity issues between gender, race, and ethnicity must be addressed.

The traditional emphasis on blood pressure control and lowering of cholesterol levels, while certainly effective to some degree, has created a narrowly glucocentric focus for diabetes research and application. In order to go beyond the current levels of prevention and increase the effectiveness of treatment, the message must be expanded to include CV risk reduction.

It was noted that not all failure of individuals to achieve target levels is due to faults in the health care system or providers. The piecemeal approach to investigating the epidemiology of diabetes as a CV risk factor and providing care to patients with the disease has been largely ineffective. Research efforts directed at promoting a system approach may correct the current paucity of databases available, as well as facilitate large outcome trials. Clinical reminders (i.e., those promoting aspirin use) are relatively easy to implement, and have shown a good measure of success with respect to health care provider and patient use. As the message to be portrayed is more clearly defined, tools such as Quick References and websites ought to be put into place. Doing so will not only impart diagnostic and treatment data to health care professionals, but perhaps more importantly will place information in the hands of patients and the general public.