AMERICAN GERIATRICS SOCIETY

INTEGRATING GERIATRICS INTO COMPARATIVE EFFECTIVENESS RESEARCH (CER) CONFERENCE

JOINTLY SPONSORED BY:
THE GERIATRICS-FOR-SPECIALISTS INITIATIVE
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SUPPORTED BY A GENEROUS GRANT FROM
THE JOHN A. HARTFORD FOUNDATION, INC.

NOVEMBER 2 -3, 2010

BETHESDA NORTH MARRIOTT HOTEL & CONFERENCE CENTER
5701 MARINELLI ROAD, BETHESDA, MD 20852

ROOM - BROOKSIDE A & B

CONFERENCE GOALS

1. Define CER and its relevance to clinical geriatrics research
2. Explore issues in CER pertaining to older persons, determine where, and where not, CER has been successfully applied in clinical geriatrics research
3. To identify knowledge gaps and barriers in CER for older people
4. To identify ways to address knowledge gaps and barriers in CER for older people
5. To foster discussion amongst geriatricians and the geriatric workforce about CER and its relevance to the field

CONFERENCE AGENDA

Tuesday, November 2, 2010

TIME	SPEAKER	SESSION TITLE
11:30 AM	**Jeffrey Silverstein, MD** Director of Geriatric Anesthesia, Mount Sinai	Welcome and Introductions
12:00 PM	**Richard Hodes, MD** Director of the National Institute on Aging **Carolyn M. Clancy, MD** Director of the Agency for Healthcare Research and Quality (AHRQ) **Michael S. Lauer, MD** Director of the Division of Prevention and Population Science at the NHLBI	Keynote Speakers
1:00 PM	**LUNCH: Brookside Foyer**	
2:00 PM	**Harold C. Sox, MD, MACP** Chair, Institute of Medicine Committee on Comparative Effectiveness Research Priorities	A View from the IOM Priority-Setting Report
2:30 PM	**Marcel Salive, MD** Health Scientist Administrator, Division of Geriatrics and Clinical Gerontology, NIA	The Importance of CER from the Perspective of Both NIA & CMS
3:00 PM	**Stephanie Studenski, MD, MPH** Professor, Department of Medicine & Staff Physician, VA Pittsburgh GRECC	Integrating Geriatrics into CER: What is the Role of CER in Patients with Multiple Chronic Conditions?
3:30 PM	**BREAK**	
3:45 PM	**Charles E. Boult, MD, MPH, MBA** Director of the Roger C. Lipitz Center for Integrated Health Care in the Department of Health Policy & Management at Johns Hopkins Bloomberg School of Public Health	Successful Models of Comprehensive Care
4:15 PM	**Andrea LaCroix, PhD, MPH** Fred Hutchinson Cancer Research Center, University of Washington	Integrating Geriatrics into CER: View from an Aging Epidemiologist
4:45 PM	**Peter Peduzzi, PhD** Professor, Biostatistics, Yale University, Director of the Yale Center for Analytical Sciences	CER Trials in the Elderly: Methodological & Practical Considerations
5:15 PM	**Jeffrey Silverstein, MD** Director of Geriatric Anesthesia, Mount Sinai	Work Group Process and Wrap-up
6:00 PM- 8:30 PM	**Reception & Cocktails: Foyer A** **Dinner: Salon A**	

Wednesday, November 3, 2010

7:00 AM	**BREAKFAST: Brookside Foyer**	
7:30 AM	Group 1 - Glen Echo Meeting Room **George Kuchel, MD** Director, UConn Center on Aging Chief, Division of Geriatric Medicine Group 2 – Oakley Meeting Room **Jeffrey Silverstein, MD** Director of Geriatric Anesthesia, Mount Sinai Group 3 – Brookside Meeting Room **Ken Schmader, MD** Chief, Division of Geriatrics, Duke University Medical Center	**Breakout Session:** Key Issues in CER – Critical Review of Landmark Studies In preparation for this small work group discussion, please read the article: *The Effects of Guided Care on the Perceived Quality of HealthCare for Multi-morbid Older Persons: 18-Month Outcomes from a Cluster-Randomized Controlled Trial (See page 20)*
8:45 AM	**Stephanie Studenski, MD** Professor, Department of Medicine & Staff Physician, VA Pittsburgh GRECC	Work Group Presentations and Discussion
10:00 AM	Group 1 - Glen Echo Meeting Room **George Kuchel, MD** Director, UConn Center on Aging Chief, Division of Geriatric Medicine Group 2 - Oakley Meeting Room **Jeffrey Silverstein, MD** Director of Geriatric Anesthesia, Mount Sinai Group 3 - Brookside Meeting Room **Ken Schmader, MD** Chief, Division of Geriatrics, Duke University Medical Center	**Breakout Session:** CER and the ACCORD Trials In preparation for this small work group discussion, please read the articles: • *Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial: Design and Methods (See page 28)* • *Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus (See page 41)*
11:30	**Kevin High, MD** Program Director, Translational Science Institute; Director, General Clinical Research Center; Section Head, Infectious Diseases; Professor, Infectious Diseases; Comprehensive Cancer Center Sticht Center on Aging	Work Group Presentations and Discussion
12:45 PM	**LUNCH: Brookside Foyer**	
1:30 PM	**Jeffrey Silverstein, MD**	Large Group Discussion: Follow-Up from morning Work Groups Sessions
3:00 PM	**BREAK**	
3:15 PM	**Jeffrey Silverstein, MD**	Wrap-Up and Next Steps
4:00 PM	**ADJOURN**	

AMERICAN GERIATRICS SOCIETY (AGS)
COMPARATIVE EFFECTIVENESS RESEARCH (CER) CONFERENCE

November 2-3, 2010

FUNDED BY THE JOHN A. HARTFORD FOUNDATION, INC.

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Michael S. Lauer, MD

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COMPARATIVE EFFECTIVENESS RESEARCH (CER) CONFERENCE

DAY TWO BREAKOUT SESSION GROUPS

Group 1 Phase of Research Assignments: Design; Missing Data; Analysis
George Kuchel, Group Leader

Barbara Alving
Marie Bernard
Cynthia Boyd
Martin Brown
Vicky Cahan
William Dale J
Stacie Deiner
Elizabeth Haney
Joe Hanlon
Richard Hodes
Teresita Hogan
Ula Hwang
Mary Kerr
Lenore Launer
Una Makris
Peter Peduzzi
Subashan Perera
Taylor Riall
James Rudolph
Dorry Segev
Harold Sox
William Tse
Molly Wagster
Susan Zieman

Group 2 Phase of Research Assignments: Research Question; Design; Sample
Jeff Silverstein, Group Leader

Heather Allore
James Appleby
Robin Barr
Ann Bonham
Charles Boult
John Burton
Carolyn Clancy
Basil Eldadah
Jerry Gurwitz
Jennie Chin Hansen
Susan Hardy
Kevin High
Frances McFarland Horne
Chryen Hunter
Lyndon Joseph
Walter Koroshetz
Laura Lee
Chung Lim
Joan McGowan
Supriya Mohile
Neil Segal
Benjamin Sun
Richard Suzman
Heather Whitson

Group 3 Phase of Research Assignments: Outcome Measures; Independent/Predictor Measures; Intervention/Control groups
Ken Schmader, Group Leader

Jonathon Bean
Warren Chow
Jovier Evans
Evan Hadley
Matthew Ho
Andrea LaCroix
Christopher Langston
Michael Lauer
Rohit Loomba
Nancy Miller
Arvind Nana
George Niederehe
Sharmilee Nyehuis
Iris Obrams
Kathie Reed
Judy Salerno
Marcel Salive
Mara Schonberg
Nina Silverberg
Gwen Sterns
Stephanie Studenski
Jennifer Tija
Ravi Varadhan
Heidi Wald

KEY ISSUES IN CER INVOLVING OLDER ADULTS

CRITICAL REVIEW OF LANDMARK STUDIES

Phase of research	Strengths	Limitations
Research Question		
Design		
Participant Sample		
Outcome Measures		
Independent or Predictor Measures		
Missing Data Assessment		
Analysis		

Use the review above to identify key issues in CER involving older adults

Key issues identified by critical review of a landmark study
Gaps in knowledge
Barriers to use/implementation
Next steps

Table 1. Overview of Strategies to Promote Participation of Older Adults in Clinical Trials

Phase of research	Main Strategies
Research Question	• Explore options to enhance generalizability • Maximize benefit to burden ratio • Maximize use of primary data through ancillary pilots and sub-studies • Incorporate less burdensome alternatives to invasive gold standard tests
Design	• Identify opportunities for benefit for all participants including controls • Consider frequency, site and duration of participation. • Plan for flexibility in schedules, sites and protocols. • Build in and budget for retention activities.

Participant Sample	• Minimize exclusion criteria. • Consider the needs of non-participants involved in the study, such as family members and health care providers.
Outcome Measures	• Select easily accessible primary outcome measures • Use universal rather than organ specific outcomes • Pre-specify alternate data collection strategies to use when the primary strategy fails • Consider alternatives to a single fixed time point for outcome assessment
Independent or Predictor Measures	• Prioritize order of collection • Plan for participant inability to perform tests, and code reasons why
Intervention	• For all study arms, particularly control groups, identify opportunities for participants to benefit from the research activities • Minimize the burdens on participants: travel, time, effort, risk, and cost
Pilot Studies	• Use pilot studies to assess the potential magnitude of missing data. • Use this experience to modify design and plans.
Implementation	• Promote a sense of belonging with stable staff, personal attention, and rewards for participation that promote study membership • Provide feedback when possible to enhance participation and retention • Provide transportation if needed • Maximize convenience and flexibility of scheduling • Have protocols for identifying participants at risk of missing data • Have protocols for back up data collection alternatives

	• Operationalize complex interventions through pilot studies
Data Tracking	• Plan for ongoing tracking and reporting of retention and missing data.
	• Be prepared to implement enhanced efforts if problems arise.
Missing Data	• Quantify amount of missing data (problems minor when < 5%)
Assessment	• Characterize missing data rates by items, waves, and participants
	• Understand the reasons and mechanisms for missing data
Analysis	• Know the analytic problems that result from missing data or nonparametric outcome measures
	• Know the appropriate use, advantages, and disadvantages of various analytic strategies for missing data
	• Plan and implement analytic strategies for multi-component interventions

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From: Stephanie Studenski, Luigi Ferrucci and Neil M. Resnick. Geriatrics. In Clinical and Translational Science. Elsevier, 2009; chapter 32, p 477-495

in scope, the recommendations may be more influential than they might otherwise have been, but the report is unlikely to quell the controversy surrounding CER.

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Mr. Iglehart is a national correspondent for the *Journal*.

1. Institute of Medicine. Initial national priorities for comparative effectiveness research. Washington, DC: Institute of Medicine, 2009.
2. Iglehart JK. Health insurers and medical-imaging policy — a work in progress. N Engl J Med 2009;360:1030-7.
3. Avorn J. Debate about funding comparative-effectiveness research. N Engl J Med 2009;360:1927-9.
4. Garber AM, Tunis SR. Does comparative-effectiveness research threaten personalized medicine? N Engl J Med 2009;360:1925-7.
5. Wilensky GR. Developing a center for comparative effectiveness information. Health Aff (Millwood) 2006;25:w572-w585.

Comparative-Effectiveness Research — Implications of the Federal Coordinating Council's Report

Patrick H. Conway, M.D., M.Sc., and Carolyn Clancy, M.D.

Despite a plethora of diagnostic and treatment options, practical information that can guide health care choices for an individual patient are often elusive, and the resultant clinical uncertainty is an important factor driving regional variations in clinical practice. Clinicians and patients need to know not only that a treatment works on average but also which interventions work best for specific types of patients. Comparative patient-centered information is essential to translating new discoveries into better health outcomes, accelerating the application of beneficial innovations, and delivering the right treatment to the right patient at the right time.[1]

The American Recovery and Reinvestment Act (ARRA) provided support for comparative-effectiveness research (CER), which has recently been referred to as "patient-centered outcomes research."[2] The purpose of CER is to provide information that helps clinicians and patients choose the options that best fit the individual patient's needs and preferences. CER is already conducted by the Agency for Healthcare Research and Quality (AHRQ), the National Institutes of Health (NIH), the Department of Veterans Affairs (VA), and others, but the ARRA substantially increased the federal investment in CER, providing $400 million for the Office of the Secretary in the Department of Health and Human Services (DHHS), $400 million to the NIH, and $300 million to the AHRQ. It also established the Federal Coordinating Council for Comparative Effectiveness Research to foster optimal coordination of CER conducted or supported by the federal government. On June 30, the Council released a report to President Barack Obama and the Congress on its recommendations for CER funding priorities for the Office of the Secretary.[3] This report, along with one from the Institute of Medicine (described by Iglehart on pages 325–328), will inform the operational plan of the secretary of health and human services for $1.1 billion in CER funds. We serve as the Council's executive director and the director of AHRQ, but the report reflects public input and contributions of all Council members and many others.

The Council's vision is to lay the foundation and build the infrastructure for CER to develop and prosper so it can inform decisions made by patients and clinicians. The Council specifically identified high-priority research gaps and one-time investments in infrastructure that would accelerate the conduct of CER by multiple researchers. We set three main objectives: to develop a definition, establish prioritization criteria, create a strategic framework, and identify priorities for CER; to foster optimal coordination of CER conducted or supported by federal departments; and to formulate recommendations for investing the $400 million provided to the Office of the Secretary.

To establish a transparent, collaborative process for making recommendations, the Council sought public input through three public listening sessions and extensive commenting on its public Web site. The Council heard from hundreds of diverse stakeholders and received feedback on draft documents.

We defined CER as the conduct and synthesis of research comparing the benefits and harms

Threshold and Prioritization Criteria Outlined by the Federal Coordinating Council for Comparative Effectiveness Research.*

Minimum threshold criteria for projects (must be met for a project to be considered)
- Inclusion within statutory limits of ARRA and the Council's definition of CER
- Potential to inform decision making by patients, clinicians, or other stakeholders
- Responsiveness to expressed needs of patients, clinicians, or other stakeholders
- Feasibility of research topic

Prioritization criteria for scientifically meritorious research and investments
- Potential impact (e.g., prevalence of condition, burden of disease, variability among outcomes, costs)
- Potential for evaluating comparative effectiveness among diverse populations and engaging communities in research
- Addressing of uncertainty within the clinical and public health communities regarding management decisions and variability in practice
- Addressing of a need or gap unlikely to be addressed through other organizations
- Potential for multiplicative effect (e.g., laying of a foundation for future CER, such as data infrastructure and methods development and training, or generating of additional investment outside government)

* ARRA denotes the American Recovery and Reinvestment Act, and CER comparative-effectiveness research.

of various interventions and strategies for preventing, diagnosing, treating, and monitoring health conditions in real-world settings. The purpose of this research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision makers about which interventions are most effective for which patients under specific circumstances. The Council established explicit threshold and prioritization criteria to guide recommendations for funding priorities (see table). The Council also developed a strategic framework for categorizing current CER activity, identifying gaps, and informing our recommendations for priorities. The framework supports immediate decisions and provides the foundation for longer-term strategic decisions on CER priorities and related infrastructure.

CER investments and activities can be grouped into four major categories: research, human and scientific capital (e.g., training of new researchers or development of methods), data infrastructure (e.g., distributed data networks, registries, or linked longitudinal administrative data), and dissemination and translation into practice. Investments in cross-cutting "themes," including high-priority populations, conditions, or types of interventions, could span more than one category of activity, and investments should be leveraged for additional uses (e.g., data-infrastructure work that also supports research on high-priority populations).

In making recommendations, the Council aimed to respond to the needs of patients and clinicians, balance the achievement of near-term results with the building of longer-term opportunities, and capture the unique role that the ARRA funds could play in filling gaps and building the foundation for future CER. The Council recommended that the primary area of investment for this funding be data infrastructure, which could include projects such as the linking of current data sources to enable researchers to answer comparative-effectiveness questions or the development of distributed electronic-data networks, patient registries, or partnerships with the private sector.

Recommendations for secondary investments include the dissemination and translation of CER findings and investment in cross-cutting projects focused on high-priority populations or interventions. The specific populations identified by the Council were racial and ethnic minorities, persons with disabilities, persons with multiple chronic conditions (including coexisting mental illness), the elderly, and children. CER will be an important tool for informing decisions that affect these populations and reducing health disparities. High-priority interventions include medical and assistive devices, procedures or surgery, behavioral changes, prevention, and delivery systems. For example, behavioral changes and prevention have the potential to decrease the rates of obesity and smoking and boost adherence to medical therapies. Delivery-system research, such as studies comparing various processes for hospital discharge or differing community-based care models or studies testing the health effects of various medical-home models, have substantial potential to drive better health outcomes.

The Office of the Secretary's funds may also play a supporting role in research and human and scientific capital. Because the Council anticipates that the AHRQ, the NIH, and the VA will contin-

ue to play major roles in these essential CER activities, the Secretary's funding would probably focus on gaps in their portfolios.

The expansion of CER, or patient-centered outcomes research, has at least three major implications. First, the results of such research will better inform a broad array of health care decisions. Second, the ARRA's provision for CER represents a significant investment in one of the translational steps toward improving the quality and value of health care for all.[4] Health services research, of which CER is only a part, has been estimated to account for 1.5% of total biomedical research expenditures and 0.1% of total U.S. expenditures on health care,[5] but the ARRA funding may reflect a trend toward increased investment in these translational building blocks for improving health. This investment creates the potential for training a new cadre of researchers, invigorating current researchers, and improving health outcomes.

Third, CER has the potential to drive high-value innovation and to enable the practice of more personalized medicine based on subgroups of patients. The goal of randomized efficacy trials is often to prove that a treatment is superior to placebo. But more important questions may be whether the intervention is better than other available interventions for specific populations and whether we can identify the subgroups of patients who will benefit the most from (or are the most likely to be harmed by) specific interventions. CER must focus on informing the care of people who are often excluded from trials (e.g., those with multiple chronic conditions) and identifying subgroups of patients (e.g., the elderly, racial and ethnic minorities, or people with a particular genetic marker) whose response to a given therapy or intervention may be different from that of the "average" patient in a trial.

This unique opportunity to invest in a major component of the scientific infrastructure for improving health care delivery will be indispensable for achieving a health care system that delivers affordable, high-quality care for all Americans. Physicians and patients deserve the best patient-centered evidence regarding what works, so that Americans can receive care of the highest quality and the best possible outcomes can be achieved.

The views expressed in this article are those of the authors and do not represent official policy of the DHHS or the AHRQ.

The entire Federal Coordinating Council and staff contributing to the Council report include Peter Delaney, Ezekiel Emanuel, Jesse Goodman, Garth Graham, Anne Haddix, Deborah Hopson, David Hunt, Michael Kilpatrick, Joel Kupersmith, Michael Marge, Elizabeth Nabel, James Scanlon, Neera Tanden, Tom Valuck, Cecilia Rivera Casale, Kelley Brix, Margaret Cary, Rosaly Correa-de-Araujo, Elisabeth Handley, Lynn Hudson, Michael Millman, Kate Goodrich, Lauren Hunt, John Poelman, Daria Steigman, Caroline Taplin, and Jordan VanLare.

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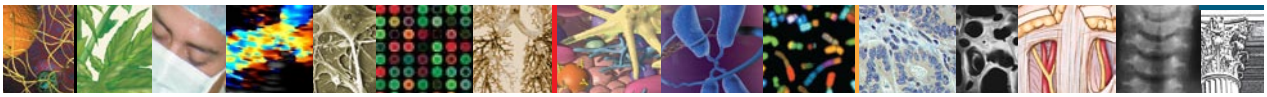

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Perspective

Five Next Steps for a New National Program for Comparative-Effectiveness Research

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The American Recovery and Reinvestment Act appropriated $1.1 billion to fund comparative-effectiveness research (CER) — unprecedented generosity for a program for evaluating health care practices. The legislation established the Federal Coordinating Council for Comparative Effectiveness Research and charged it with advising the secretary of health and human services on the allocation of CER funds. It also mandated an Institute of Medicine (IOM) study to recommend initial national priorities for CER. Both the Federal Coordinating Council and the IOM reported to Congress on June 30, 2009.

Both organizations solicited input from stakeholders. The IOM committee issued an open solicitation asking the public to nominate research topics. It received 1546 nominations, which it narrowed to 100 highest-priority research questions. The Federal Coordinating Council hosted three public listening sessions to identify priorities and posted drafts of its work on its Web site for public comment. By establishing a national CER agenda with input and support from diverse stakeholders, the two reports moved the United States closer to creating a sustained national CER program.[1,2]

Both reports recognized the need for a robust CER enterprise. The IOM made 10 recommendations for its development (see box). The Federal Coordinating Council's report included a definition of CER, a strategic framework, priority-setting criteria, and recommendations for investing the $400 million that Congress allocated to the Department of Health and Human Services for CER. Both reports recommended creating CER data networks and conducting research on practitioners' adoption of changes based on CER findings.[3]

Federal agencies and Congress appear willing to implement these recommendations. The National Institutes of Health, the Agency for Healthcare Research and Quality (AHRQ), and the secretary of health and human services have begun to allocate their Recovery Act funds and coordinate their efforts. The AHRQ has requested proposals for studying the IOM's high-priority research questions that fit within its own priorities,[4] and the secretary of health and human services has asked for proposals to begin building a stronger data infrastructure for CER. Recommendations from the two reports also appear in the health care reform bills passed

Institute of Medicine's Recommendations for a National System of Comparative-Effectiveness Research (CER).

1. Prioritization of CER topics should be a sustained and continuous process, recognizing the dynamic state of disease, interventions, and public concern.
2. Public participation (including participation by consumers, patients, and caregivers) in the priority-setting process is imperative for ensuring that the process is transparent and that the public has input into the delineation of research questions.
3. Consideration of CER topics requires the development of robust, consistent topic briefs providing background information, an understanding of current practice, and assessment of the research status of the condition and relevant interventions.
4. Regular reporting of the activities and recommendations of the prioritizing body is necessary for evaluating the portfolio's distribution, its effect on discovery, and its translation into clinical care in order to provide a process for continuous quality improvement.
5. The secretary of HHS [Health and Human Services] should establish a mechanism — such as a coordinating advisory body — with the mandate to strategize, organize, monitor, evaluate, and report on the implementation and impact of the CER program.
6. The CER program should fully involve consumers, patients, and caregivers in key aspects of CER, including strategic planning, priority setting, research-proposal development, peer review, and dissemination.
7. The CER program should devote sufficient resources to research and innovation in CER methods, including the development of methodologic guidance for CER study design — for instance, on the appropriate use of observational data and approaches to designing more informative, practical, and efficient clinical trials.
8. The CER program should help to develop large-scale clinical and administrative data networks to facilitate better use of data and more efficient ways of collecting new data to inform CER.
9. The CER program should develop and support the workforce for CER to ensure that the country has the capacity to carry out the CER mission.
10. The CER program should promote rapid adoption of recommendations based on CER findings and conduct research to identify the most effective strategies for disseminating new and existing CER findings to health care professionals, consumers, patients, and caregivers and for helping them to implement changes based on these results in daily clinical practice.

by the House and Senate, which call for a national CER program financed through a trust fund or appropriated dollars potentially sufficient to support an annual budget of more than $600 million.[5] Regardless of the specific outcome of the health care reform effort, CER will probably account for an increasing portion of the U.S. research enterprise and should build on the reports of the Federal Coordinating Council and the IOM and the successes of the National Institutes of Health, the AHRQ, and others.

The complex, long-term agenda outlined by the IOM and the Federal Coordinating Council will require sustained, mission-focused leadership. The program must build durable public support while implementing the "enterprise" recommendations of the IOM and the Federal Coordinating Council and supporting decades of research on the 100 priority topics and others that are sure to arise and claim high priority.

Stakeholder direction is critically important to establishing — and sustaining — the CER program's leadership mandate. The CER program's leaders will need stakeholder input into the initial steps in developing the CER enterprise. Deciding how to translate the IOM's priorities into a portfolio of specific research projects is a critical first step.

Even with its substantial funding, the national program cannot support research on all 100 IOM topics simultaneously. Moreover, it needs some early successes on which to build public support. Deciding which research questions to address first is complex, because the priority topics vary widely in their potential impact on health care costs and outcomes, target population, and the most suitable research methods and their costs. We propose a five-step process.

First, the national CER program must develop an overall funding strategy. It could follow the traditional biomedical research model by inviting proposals on any of the 100 high-priority topics and awarding grants to the scientifically strongest proposals. However, the research interests of individual investigators would then define the national priorities. Instead, we believe that the national CER program should decide on a coordinated portfolio consisting of research on priority topics, infrastructure enhancement, and studies of translation and adoption. This approach places priority-setting responsibility on the organization that the public will hold accountable for results.

So far, the public — through representatives from academia, industry, provider organizations, and patient-advocacy groups, as well as individuals — has tangibly influenced the recommendations of the IOM and the Federal Coordinating Council for CER. Public involvement in formulating the agenda is the best assurance that CER will support real-

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world decisions that matter to patients. But in the end, someone must allocate the available funding to a portfolio of research projects that will deliver results. Who sets priorities among the IOM's high-priority topics is an important strategic question. We cast our vote for the CER program and its stakeholder advisory board — not the research community.

Second, the CER program should establish an initial list of priority topics and evaluate the current state of knowledge about each. For the first of these tasks, it should build on the priority-setting work of the IOM committee. It could develop a portfolio chosen from the top 25 IOM topics by applying the already-published prioritization criteria of the IOM (see Table 1) and the Federal Coordinating Council (see Table 2). Next, the program must decide what type of evidence to obtain, identifying evidence gaps by conducting systematic literature reviews and performance gaps using data from insurance claims or electronic health records. This process will identify gaps in comparative-effectiveness evidence for some topics, indicating a need for primary research. For other topics, the evidence of comparative effectiveness will be solid but poorly translated into practice — grounds for funding studies that compare strategies for changing practice.

Third, the CER program, with the help of expert advisory committees and the research community, should choose the research methods that will fill gaps in the evidence for a specific topic. In an investigator-initiated research program, the grant applicant typically chooses the methods. The cost of studies using the methods of CER (whether clinical trial, observational study, or qualitative research) varies widely. To achieve a portfolio that stays within budget but has maximal impact, the CER program should take responsibility for matching research methods to the research question. Defining the desired future state — a desired patient care outcome, reduced harms, or a change in clinical practice — is a key step in defining research objectives and refining the research question, which in turn drive the choice of methods and the projected research costs.

Modeling potential population-level effects can help the CER program to decide which research questions to fund. Modelers will need to estimate the likelihood of various study results, implementation strategies, and possible shifts in practice and policy.

Table 1. Institute of Medicine's Prioritization Criteria for Comparative-Effectiveness Research (CER).*

Condition-level criteria
Prevalence
Mortality
Morbidity
Cost
Practice variability
Priority topic–level criteria
Appropriateness of topic for CER
Information gaps and duplication
Gaps in translation

* Condition-level criteria are used to assess the importance of a disease or problem. Priority topic–level criteria are used to assess the relative importance of specific research questions.

Table 2. Federal Coordinating Council's Prioritization Criteria for Comparative-Effectiveness Research (CER).

Minimum threshold criteria
Inclusion within statutory limits of Recovery Act and the Council's definition of CER
Potential to inform decision making by patients, clinicians, or other stakeholders
Responsiveness to expressed needs of patients, clinicians, or other stakeholders
Feasibility (including time necessary for research)
Prioritization criteria for scientifically meritorious research and investments
Potential impact (based on prevalence of condition, burden of disease, variability in outcomes, costs, potential for increased patient benefit or decreased harm)
Potential for evaluating comparative effectiveness in diverse populations and patient subgroups and engaging communities in research
Uncertainty within the clinical and public health communities regarding management decisions and variability in practice
Identified need or gap unlikely to be addressed through other organizations
Potential for multiplicative effect, such as laying the foundation for future CER (e.g., data infrastructure and methods development and training) or generating additional investment from outside government

When considering policy shifts, the modeler must envision the standard of evidence necessary to convince key decision makers. Some questions will require a definitive randomized, controlled trial, whereas weaker forms of evidence, such as nested case–control studies or well-designed cohort studies, may answer some questions with sufficient certainty for decision makers and may be more applicable to real-world settings. This conceptualization of policymaking means that the end users of research results must identify their requirements for certainty in decision making and communicate them to the CER program as input into the design of a research portfolio.

Fourth, the program should strive for a balanced portfolio of high-impact research topics. Although it could simply rank topics in order of importance and fund them in ranked order until the money ran out, we recommend developing a portfolio that addresses a balanced distribution of topics, outcomes, and target populations, as well as keeping the total portfolio cost within budget and producing a body of evidence sufficient to influence health care decisions. Accordingly, the portfolio may need to include several complementary studies of each high-priority research question in order to ensure a strong body of new and existing evidence that decision makers can act on.

Fifth, the CER program should evaluate progress and report to the public. To meet this obligation, it should do large-scale, ongoing observational research and evaluation to measure CER's effects on clinical practices and patient outcomes. Public investment in health information technology and data infrastructure — including patient registries and distributed data networks of hospitals and clinicians — can facilitate ongoing surveillance. Moreover, with changes in the environment — such as new technology or changes in the health care system, providers' behavior, or patients' needs — the CER program should periodically update its list of high-priority topics.

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The Effects of Guided Care on the Perceived Quality of Health Care for Multi-morbid Older Persons: 18-Month Outcomes from a Cluster-Randomized Controlled Trial

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BACKGROUND: The quality of health care for older Americans with chronic conditions is suboptimal.

OBJECTIVE: To evaluate the effects of "Guided Care" on patient-reported quality of chronic illness care.

DESIGN: Cluster-randomized controlled trial of Guided Care in 14 primary care teams.

PARTICIPANTS: Older patients of these teams were eligible to participate if, based on analysis of their recent insurance claims, they were at risk for incurring high health-care costs during the coming year. Small teams of physicians and their at-risk older patients were randomized to receive either Guided Care (GC) or usual care (UC).

INTERVENTION: "Guided Care" is designed to enhance the quality of health care by integrating a registered nurse, trained in chronic care, into a primary care practice to work with 2–5 physicians in providing comprehensive chronic care to 50–60 multi-morbid older patients.

MEASUREMENTS: Eighteen months after baseline, interviewers blinded to group assignment administered the Patient Assessment of Chronic Illness Care (PACIC) survey by telephone. Logistic and linear regression was used to evaluate the effect of the intervention on patient-reported quality of chronic illness care.

RESULTS: Of the 13,534 older patients screened, 2,391 (17.7%) were eligible to participate in the study, of which 904 (37.8%) gave informed consent and were cluster-randomized. After 18 months, 95.3% and 92.2% of the GC and UC recipients who remained alive and eligible completed interviews. Compared to UC recipients, GC recipients had twice greater odds of rating their chronic care highly (aOR=2.13, 95% CI=1.30–3.50, p=0.003).

CONCLUSION: Guided Care improves self-reported quality of chronic health care for multi-morbid older persons.

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INTRODUCTION

A recently published research agenda emphasized the need to develop and evaluate more effective models of health care, recognizing that the often fragmented, uncoordinated, and inefficient current delivery system does not meet the needs of older Americans who require complex care for multiple chronic conditions[1–3]. Putative remedies such as disease-specific guidelines, care management, and disease management programs may be ineffective or impractical[4,5]. As a result, many chronically ill patients and their families experience suboptimal quality of care, many primary care physicians are dissatisfied, and Medicare incurs unnecessarily high expenses[6]. Multimorbid older patients seek and need individualized, patient-centered, easily accessible care, supported by a single coordinator, and associated with a clearly communicated health plan[7].

The Chronic Care Model (CCM) postulates that achieving this goal will require redesign of the current delivery system, enhancement of decision support, improvement of clinical information systems, encouragement for self-management, and access to community resources[8]. In accordance with the CCM, we developed "Guided Care" (GC)[9]. GC is comprehensive care that incorporates evidence-based processes and patient preferences to attempt to improve outcomes for patients 65 years or older with chronic conditions and complex health-care needs[9]. GC is provided by a practice-based registered nurse who works closely with two to five primary care physicians and other members of the practice staff. This team provides comprehensive, coordinated, chronic health care to a panel of 50–60 of the practice's high-risk older patients. Results of a pilot study of Guided Care conducted during 2003–2004 suggested that Guided Care may improve the patient-reported quality and efficiency of chronic care[10,11].

GC was designed to improve several outcomes including patients' health-related quality of life and functional independence, as well as the quality and efficiency of their health care. The purpose of the present analysis is to measure the effect of

18 months of GC on patients' perceptions of the quality of the care they receive for their chronic conditions. We used the Patient Assessment of Chronic Illness Care (PACIC) instrument to measure patient-reported quality of chronic care[12]. The PACIC is associated with use of self-management resources, self-management behaviors, and quality of life[13]. Preliminary data from the first 6 months of this cluster-randomized controlled trial(cRCT) of GC indicated that the odds of rating overall chronic care as "high-quality" were twice as high in patients who had received GC compared to patients who had received usual care (aOR=2.03, p=0.006)[14].

In the present analysis, we test the hypothesis that, compared to usual care, 18 months of GC is associated with higher perceived quality of chronic care among multi-morbid older patients with complex health-care needs. We explore whether the effect of GC is consistent across patients with high and low pre-intervention PACIC scores.

METHODS

In 2006, we launched a cRCT of GC in eight community-based primary care practices in urban and suburban neighborhoods in the Baltimore-Washington DC metropolitan area. Three practices were operated by Kaiser Permanente, a group-model managed care organization; four were operated by Johns Hopkins Community Physicians, a statewide network of community-based practices; one was operated by Medstar Physician Partners, a multi-site group practice. Additional study details have been published previously[14] (Clinical Trials.gov ID# NCT00121940). The study was approved by the Institutional Review Boards of the Johns Hopkins Bloomberg School of Public Health, Kaiser-Permanente Mid-Atlantic States, and MedStar Physician Partners.

Recruitment of Physicians

Teams of primary care physicians were eligible if they cared for at least 650 patients age 65 years or older, expressed willingness to participate, and agreed to provide an on-site office for a Guided Care Nurse (GCN). Fourteen eligible teams were invited and agreed to participate. Individual primary care physicians (board-certified internists and family physicians) were eligible to participate if they worked at least 70% time on these teams. All eligible physicians were informed about the requirements of the study; all gave written informed consent to participate (n=49).

Recruitment of Nurses

To recruit nurses for the GCN role, we placed advertisements in local newspapers, human resources websites of participating delivery systems, and a regional nursing journal. To be eligible, applicants had to be licensed registered nurses with at least 3 years of practice experience. Applicants with strong communication skills, flexible approaches to complex problem-solving, cultural competence, comfort with interdisciplinary team care, experience in geriatric and community nursing, and enthusiasm for coaching patients and caregivers in self-management were preferred. Successful applicants gave written informed consent to serve as research subjects as well as providers of health care (n=7).

Recruitment of Patient Participants

Patients of the participating physicians were eligible for initial screening if they were 65 years or older and covered by fee-for-service Medicare Parts A and B, a Kaiser-Permanente Medicare health plan, or TriCare/USFHP (a Medicare-like insurance plan for military retirees). Potential participants' insurance claims for health care during the previous 12 months were screened by their insurers using the Hierarchical Condition Category (HCC) predictive model[15,16], which estimates a person's risk for incurring high health-care costs during the coming year. Patients were considered "high-risk" if their HCC risk ratios were in the highest quartile of the population of older patients covered by their primary health-care insurer.

Beginning in December 2005, high-risk patients received introductory letters advising them that they might be eligible for the study and offering them the opportunity to "opt out" by returning a card in a pre-addressed, stamped envelope. Beginning in February 2006 and ending in March 2007, a professional interviewer attempted to telephone each person who did not "opt out" to describe the study, answer questions, and offer an in-home meeting to provide additional information. Potential participants were deemed ineligible for the study if they did not have a telephone, did not speak English, were planning extended travel during the following 2 1/2 years, or failed a brief cognitive screen and did not have a proxy who could provide informed consent. The cognitive screen involved asking potential participants to spell their names and state their addresses and ages. If there were any mistakes, the interviewer probed to allow an opportunity for correction. If the potential participant was unable to do this successfully, a proxy was sought. Proxies were accepted if they were legal guardians or close family relatives.

Professional interviewers then visited the homes of eligible patients to describe the study in detail, answer questions, offer participation, and obtain written informed consent. Patients who provided consent then completed in-home baseline interviews.

Randomization

Within the 8 participating practices, we identified 14 teams, each of which consisted of 2–5 primary care physicians and their consenting high-risk patients. The study's statistician, blinded to the identities of the teams, randomly allocated each team of physician and their high-risk patients to either GC (7 teams) or UC (7 teams).

Intervention

Before joining their assigned teams in May 2006, the GCNs completed an educational curriculum designed to prepare them to provide the clinical services of GC. During the following 6–8 months, each GCN established a case load of 50–60 patients and provided them with eight clinical services: a comprehensive assessment at home, creation and maintenance of an evidence-based "Care Guide" (care plan) and an "Action Plan" (patient's self-care plan), monthly monitoring, coaching for self-management, smoothing transitions into and out of hospitals, coordinating all providers of care, educating and supporting family caregivers, and accessing community resources[9].

To track the nurses' performance of the essential activities of GC, such as completing monthly monitoring and coaching

calls and facilitating patients' transitions from hospitals, the study team produced monthly reports of the GCNs' documented performance of these activities. Throughout the study, members of the study team, nurse managers and the GCN's met monthly to review and discuss these performance reports and to troubleshoot challenges in implementing the GC model.

Measures

Face-to-face interviews were conducted to assess participants' baseline socio-demographic characteristics, health and functional status, chronic conditions, satisfaction with health care[14]. Included in the baseline and 18-month interviews was the Patient Assessment of Chronic Illness Care (PACIC) instrument, which assesses patients' perceptions of the quality of the care they have received for their chronic conditions. The 18-month interviews were conducted by telephone by rigorously trained, supervised professional interviewers who were masked to group assignment, used computer-assisted interviewing technology, and underwent 10% reliability testing.

The PACIC is a validated measure of patients' experience of chronic care[12]. It consists of 20 questions that inquire about important elements of chronic care received by a patient from his or her health-care team, e.g., being asked about one's health habits, being given a list of things to do to improve one's health, having one's health care well organized, receiving a copy of one's treatment plan, and being asked for one's ideas when making a treatment plan. Respondents indicate how often, during the past 6 months, they have experienced each of the 20 elements: "almost always" (5), "most of the time" (4), "sometimes" (3), "generally not" (2), or "almost never" (1). The 20 items constitute an aggregate scale and five subscales: goal setting, coordination of care, decision support, problem solving, and patient activation.

Analysis

As described in detail previously, we imputed values for missing baseline interview responses[14]. We computed all scale scores as recommended by the originators of the scales and analyzed all data according to the "intention-to-treat" principle. To the extent possible, we used site-stratified testing procedures to evaluate baseline differences between the GC and UC groups. For very rare (ethnicity) or very common (insurer) baseline factors, we used unstratified testing procedures.

To test our hypothesis, i.e., that the quality of care for people who received GC exceeds the quality of care for people who received UC, we compared the two groups' 18-month PACIC scores. From each respondent's raw PACIC data, we computed a continuous score for each subscale and for the aggregate PACIC instrument by summing responses to individual items and dividing by the number of items in the subscale or instrument. To create corresponding categorical outcome variables, we recoded continuous scores as "high-quality" (score = 4–5), "medium-quality" (score $\geq$3 or <4.0), or "low-quality" (score <3). To compare with our previous analysis of PACIC outcomes at 6 months, we also created dichotomous variables for "high-quality" (score = 4–5) and "low to medium quality" (score <4) chronic care.

To estimate the effect of group assignment (i.e., GC or UC) on quality of care, we constructed multivariate linear and logistic regression models of 18-month PACIC aggregate and subscale scores. Included in these models were covariates that adjusted for characteristics that we defined *a priori* as possible confounders: socio-demographic characteristics (i.e., age, race, sex, educational level, financial status, habitation status), health status (i.e., HCC score), functional ability (i.e., Short Form-36 physical component and mental component summary scores), subscale specific baseline PACIC scores, and satisfaction with health care. The models also included site indicators to account for clustering, i.e., for patients' tendency to resemble more closely patients at their site than those at other sites.

To determine whether the effects of GC varied according to the quality of care patients were receiving at baseline, we stratified the study participants and constructed multivariate linear regression models of 18-month PACIC subscale and aggregate scores. One set of models was based on data from patients who had rated the quality of their care at baseline as "low" (i.e., <3.0) and the other on data from patients who had rated the quality of their care at baseline as "medium or high" (i.e., 3.0–5.0). Low quality was defined for each domain and for aggregate score. Logistic regression models were also constructed to estimate the effect of the intervention on quality of care among the subgroup of patients who rated the quality of their care as low at baseline for each domain of the PACIC and overall. All analyses were performed on Stata Version 9® statistical software (StataCorp, College Station, TX).

RESULTS

We screened the insurance claims of 13,534 older patients of the participating physicians to identify 3,692 (27.3%) at high risk for incurring high health-care costs during the following year. Of these, 2,391 were alive, accessible, and eligible; 904 (37.8%) consented to participate. After 18 months, 96.5% and 94.2% of the GC and UC participants who were alive and eligible to participate responded to follow-up interviews: 12.7% of patients died, 3.2% refused to continue their participation in the study, 2.3% could not be located, 6.4% were ineligible because they were no longer receiving care from a participating practice, and 1.2% declined the interview.

The two treatment groups had similar demographic characteristics and chronic disease burdens at baseline, but they differed in marital status, finances, self-rated health and functional status, quality of care, satisfaction with care, insurer, and risk of incurring high health-care costs during the following year (Table 1).

Eighteen months after baseline, the mean quality of care scores of the GC recipients were higher than the mean scores of the UC recipients in the aggregate and on all five PACIC subscales. In linear regression models that adjusted for multiple covariates, five of these six differences were statistically significant at the $p<0.05$ level (Table 2).

Eighteen months after baseline, the odds that a GC recipient rated his or her aggregate quality of care as "high-quality" were twice as great (aOR=2.13, 95% CI=1.30, 3.50, p=0.003) (Table 3). Similarly, GC recipients had significantly greater odds of rating two specific elements of their care as "high-quality": coordination of care (aOR=1.80, 95% CI=1.12, 2.90, p=0.016) and decision support (aOR=1.49, 95% CI=1.05, 2.11, p=0.025). Although not statistically significant at the $p<0.05$ level, GC recipients also

Table 1. Characteristics of Participants (n=904) at Baseline

	Guided Care (n=485)	Usual care (n=419)	p value
Socio-demographic factors			
Age, mean years (range)	77.2 (66–106)	78.1 (66–96)	0.46
Sex (% female)	54.2	55.4	0.39
Race (%)			
Caucasian	51.1	48.9	0.924
African- American	45.6	46.3	
Other	3.3	4.8	
Ethnicity (% Hispanic)	1. 9	1.4	0.26[a]
Marital status (%)			
Married	46.0	48.5	<0.001
Divorced/separated	11.6	10.7	
Widowed	37.9	37.0	
Never married	4.5	3.8	
Education (% with >12 years)	46.4	43.4	0.24
Finances at end of month (%)			
Some money left over	57.9	51.1	0.004
Just enough money left over	32.8	34.2	
Not enough money left over	9.3	14.7	
Habitation status (% living alone)	32.0	30.6	0.94
Type of Medicare insurance (%)			
HMO-A	26.2	16.0	0.001[a]
Fee-for-service	31. 7	36.5	0.90[a]
HMO-B	42.1	47.5	Ref
Health and functional status			
HCC score, mean (SD) range	2.07 (1.07) 0.8–7.8	1.96 (1.05) 0.8–9.7	<0.001
Self-rated health (%)			
Excellent	2.5	3.1	<0.001
Very good	20.0	13.6	
Good	37.7	36.5	
Fair	30.1	32.2	
Poor	9.7	14.6	
Number of self-reported conditions, mean (range)	4.3 (0–13)	4.3 (0–12)	0.12
Self-reported diseases / conditions (%)			
Hypertension	79.2	81.4	0.64
Angina	28.7	27.2	0.77
Congestive heart failure	18.6	19.3	0.33
Myocardial infarction	23.9	22.7	0.73
Other heart problems	39.6	42.7	0.23
Stroke	20.0	21.2	0.46
Chronic obstructive pulmonary disease	22.3	19.3	0.48
Arthritis	70.1	70.2	0.08
Sciatica	19.4	14.8	0.28
Diabetes	48.4	50.4	0.17
Cancer	26.6	29.1	0.18
Osteoporosis	20.0	17.0	0.33
Hip fracture	8.0	5.5	0.56
Alzheimer's disease	3.9	5.3	0.35
Falls in the last 6 months	0.8	0.7	0.22
Difficulty with 1+ ADL (%)	32.2	30.6	0.27
Difficulty with 2+ IADL (%)	23.5	29.6	0.03
Receives help from a person (%)	45.2	54.9	0.003
SF-36 score, mean (SD) range			
Physical component summary	38.7 (10.5) 13.8–63.0	38.1 (10.8) 6.7–63.1	<0.001
Mental component summary	50.3 (11.8) 6.4–70.0	48.7(12.3) 13.7–71.9	0.005
Cognition, mean SPMS (SD) range	0.9 (1.1) 0–6	1.0 (1.3) 0–7	0.07
% with high-quality health care on the PACIC[b]			
Aggregate score	5.9	2.9	<0.001
Patient activation subscale	15.1	10.1	0.10
Decision support subscale	24.9	21.5	0.33
Goal-setting subscale	9.0	5.0	<0.001
Problem-solving subscale	19.2	12.1	0.26
Coordination subscale	5.0	4.2	<0.001
Satisfaction with health care			
From regular care team (%)			
Very satisfied	57.0	48.5	0.008
Satisfied	35.2	42.0	
Unsatisfied	3.7	3.8	
Very unsatisfied	4.2	5.8	

Table 1. (continued)

	Guided Care (n=485)	Usual care (n=419)	p value
From all care providers (%)			
Very satisfied	47.0	43.7	0.12
Satisfied	45.6	45.6	
Unsatisfied	3.9	5.0	
Very unsatisfied	3.5	5.7	

SPMS = Short Portable Mental Status, range = 0 (no errors) to 10 (10 errors)
HCC = hierarchical condition category, 1 = average risk of high future health-care costs
ADL = Activities of Daily Living
IADL = Instrumental Activities of Daily Living
SF-36 = Short-Form 36, range = 0 (poor function) to 100 (excellent function)
PACIC = Patient Assessment of Chronic Illness Care
[a]*Comparisons between the groups' ethnicity and type of insurance were unstratified*
Multinomial regression used to compare race, marital status, and type of insurance; ordinal regression used to compare finances at end of month; self-rated health and satisfaction with health care
[b]*High-quality health care: % with PACIC scale score of 4–5 (who reported on the PACIC survey that care process occurred "most of the time" or "almost always")*

tended to have greater odds of rating their care as "high-quality" in goal setting (aOR=1.53, 95% CI=0.99, 2.37), problem solving (aOR=1.33, 95% CI=0.90, 1.95), and patient activation (aOR= 1.28, 95% CI=0.87, 1.89).

Within each of the two subgroups of participants (low baseline quality, medium or high baseline quality), the effect of GC on the aggregate 18-month quality of care was significantly positive ($p<0.05$) (Table 4). Of the participants with low scores at baseline, those receiving GC had nearly twice greater odds to rate the aggregate quality of their care as medium or high compared to those receiving UC (aOR 1.98, 95%CI= 1.27–3.07).

DISCUSSION

The results of this study support the hypothesis that GC improves important dimensions of the quality of chronic health care experienced by multi-morbid older persons. Health-care processes that were improved significantly as measured by patient report include goal setting, coordination of care, problem solving, and patient activation. In general, these effects were consistent among patients who rated their pre-study chronic care as "medium to high quality" and those who rated their pre-study chronic care as "low quality."

Tools for evaluating the quality of chronic illness care for older adults with multi-morbidity are still under development and discussion. The limited applicability of disease-specific guidelines and tools for measuring the quality of health care for older adults with several chronic illnesses has been previously described[4]. Patients with morbidity similar to those enrolled in this cRCT of GC are often excluded from the denominators of quality standards for specific diseases, thus excluding their care from measurement and, perhaps, from improvement[17,18]. Yet, such multi-morbid patients experience the negative effects of a fragmented chronic care system at high rates, suggesting that evaluating their care with process measures not linked to specific diseases is especially important[2,19,20].

In this study, we employed the PACIC because it is a validated measure based on important elements of the CCM and because it is relevant to all chronically ill patients, regardless of their specific diagnoses and levels of co-morbidity. Higher PACIC scores indicate that elements of chronic care occur more often. The mean aggregate PACIC score at 18 months of 3.14 in the GC group indicates that, on average, goal setting, coordination of care, decision support, problem solving, and patient activation occurred "sometimes" to "most of the time." The mean aggregate PACIC score of 2.85 in the UC group indicates that, on average, these elements "generally did not occur" or occurred "sometimes." To our knowledge,

Table 2. Effect of Guided Care on Patient-Reported Quality of Chronic Illness Care (PACIC) Scores After 18 Months

PACIC scales	Guided care (mean)	Usual care (mean)	Crude treatment effect (β)[a]	95% CI	Adjusted treatment effect[a] (β)[a]	95% CI	p value (adjusted effect)
Goal setting (n=649)	2.94	2.68	0.28	0.10, 0.45	0.19	0.03, 0.35	0.02
Coordination of care (n=645)	2.96	2.57	0.37	0.20, 0.54	0.34	0.18, 0.50	<0.001
Decision support (n=655)	3.66	3.51	0.18	0.03, 0.33	0.09	-0.05, 0.24	0.21
Problem solving (n=641)	3.25	2.92	0.33	0.15, 0.52	0.22	0.04, 0.39	0.01
Patient activation (n=656)	3.10	2.83	0.29	0.11, 0.47	0.20	0.02, 0.37	0.02
Aggregate quality (n=642)	3.14	2.85	0.29	0.15, 0.44	0.20	0.07, 0.33	0.002

[a]*β = beta coefficients from unadjusted and adjusted linear regression models. Adjusted for participants' baseline socio-demographic characteristics, i.e., age, race, sex, educational level, financial status, habitation status, HCC score, functional ability (i.e., SF-36 physical component summary and mental component summary scores), subscale-specific baseline PACIC score, satisfaction with health care, and practice site*
CI = Confidence interval
HCC = hierarchical condition category, 1 = average risk of high future health-care costs
SF-36 = Short-Form 36, range = 0 (poor function) to 100 (excellent function)

Table 3. Effect of Guided Care on Patient Reported "High-Quality" Health Care After 18 Months

PACIC scales	Guided Care (%)	Usual care (%)	Crude odds ratio	95% CI	Adjusted odds ratio[a]	95% CI	p value (adjusted odds ratio)
Goal setting (n=649)	23.1	15.3	1.65	1.09, 2.49	1.53	0.99, 2.37	0.05
Coordination of care (n=645)	19.8	12.7	1.68	1.08, 2.61	1.80	1.12, 2.90	0.01
Decision support (n=655)	45.1	36.2	1.54	1.11, 2.14	1.49	1.05, 2.11	0.02
Problem solving (n=641)	32.4	23.6	1.52	1.06, 2.18	1.33	0.90, 1.95	0.14
Patient activation (n=656)	28.7	22.6	1.40	0.97, 2.01	1.28	0.87, 1.89	0.20
Aggregate quality (n=642)	20.3	11.0	2.03	2.28, 3.21	2.13	1.30, 3.50	0.003

[a]*Adjusted for participants' baseline age, race, sex, educational level, financial status, habitation status, HCC score, functional ability (i.e., SF-36 physical component summary and mental component summary scores), subscale-specific baseline PACIC score, satisfaction with health care, and practice site*
PACIC = Patient Assessment of Chronic Illness Care
CI = Confidence interval
HCC = hierarchical condition category, 1 = average risk of high future health-care costs
SF-36 = Short-Form 36, range = 0 (poor function) to 100 (excellent function)

however, no published research has established the magnitude of difference between mean PACIC scores that can be regarded with confidence as clinically significant. While higher levels of these elements of chronic care have been shown to be related to better health outcomes, it also remains unclear how frequently these elements must be provided to improve these outcomes. We currently do not have data to measure the association of perceived quality of care and other indicators of quality of care. Future analyses of GC insurance claims may provide some insight into this relationship.

To help quantify the effects of GC, we compared the proportions of the GC and UC groups that received elements of high-quality care "almost always" or "most of the time." The resulting multiple logistic regression model suggests that recipients of GC had 2.13 times the odds as UC recipients to report high-quality care (Table 3). Importantly, compared to the UC group, a significantly greater proportion of patients in the GC group who rated the quality of their care as "low" before the intervention reported a higher quality of care score 18 months later.

The GC model was designed to provide comprehensive, coordinated, patient-centered care. Possibly one of the most important components of this model is the accessibility of the nurse. A caseload of 50–60 patients allows the nurse to devote the time necessary to patients. As an example of this improved accessibility, GC patients were 70% more likely to rate the time they had to wait for an appointment when sick as "excellent" or "good" compared to usual care patients. Similarly, they were 50% more likely to rate the ability to get phone advice as "excellent" or "good."

There are several limitations to the study. First, only 38% of the patients who were high-risk consented to participate. A portion of these patients opted out of the study initially, and others declined an in-home visit to provide consent when contacted by telephone. For privacy reasons, we were unable to collect any health or demographic information on people who

Table 4. Effect of Guided Care on Patient Reported Quality of Chronic Illness Care (PACIC) Scores After 18 Months Stratified by Baseline Reports of Quality

PACIC scales	n	Guided Care mean	Usual care mean	Adjusted treatment effect (β)[a]	95% CI	p value
"Low" quality of care reported at baseline						
Goal setting	456	2.64	2.48	0.15	-0.05, 0.35	0.13
Coordination	454	2.67	2.33	0.30	0.11, 0.49	0.002
Decision support	222	3.22	3.15	0.06	-0.23, 0.35	0.67
Problem solving	347	2.84	2.60	0.32	0.06, 0.58	0.01
Patient activation	413	2.73	2.63	0.12	-0.11, 0.35	0.29
Aggregate quality	437	2.83	2.65	0.18	0.02, 0.35	0.02
"Medium to high" quality of care reported at baseline						
Goal setting	193	3.59	3.22	0.26	-0.03, 0.55	0.08
Coordination	191	3.60	3.20	0.42	0.10, 0.74	0.01
Decision support	433	3.85	3.74	0.11	-0.06, 0.29	0.20
Problem solving	294	3.66	3.38	0.14	-0.10, 0.38	0.25
Patient activation	243	3.64	3.25	0.26	-0.03, 0.56	0.07
Aggregate quality	205	3.68	3.40	0.25	0.03, 0.48	0.03

[a]*β = beta coefficients from linear regression models adjusted for participants' baseline socio-demographic characteristics, i.e., age, race, sex, educational level, financial status, habitation status, HCC score, functional ability (i.e., SF-36 physical component summary and mental component summary scores), subscale-specific baseline PACIC score, satisfaction with health care, and practice site*
PACIC = Patient Assessment of Chronic Illness Care
CI = Confidence interval
HCC = hierarchical condition category, 1 = average risk of high future health-care costs
SF-36 = Short-Form 36, range = 0 (poor function) to 100 (excellent function)

refused to participate and who could not be located. It is likely that refusers had worse health than consenters, so the generalizability of the results reported here may be limited.

Second, the provision of GC to patients in one team within a practice could have "contaminated" the care provided to patients in the UC team within the practice. Although we saw no evidence that this occurred, it has the potential to reduce the measured differences between the GC and UC groups throughout the study. Theoretically, the unblinded design of the study also could have influenced the quality of the health care provided to the participants, although this is unlikely to have had a significant influence on the teams' health-care processes.

The range in participants' HCC risk ratios is the result of differences in the completeness with which practices entered diagnoses on their insurance claims. Less complete entry produced lower HCC risk ratios. In order to identify the patients with highest quartile of HCC risk ratios in practices where this was done, we had to include some patients with HCC ratios of less than 1.0. This may have led to the inclusion of some healthier people in our sample than we originally anticipated, among control and experimental participants.

We accepted proxies' ratings of some participants' quality of health care (5% at baseline, 11% at 18 months). Although the concordance between patients' and proxies' PACIC scores has not been reported, most of the proxies in this study were family caregivers who were well positioned to report the frequency with which the PACIC's 20 elements of chronic care had occurred.

Our analyses assumed a common treatment effect across teams within each practice. While some teams may have implemented GC more effectively than others, this study was not powered to evaluate such heterogeneity. Strengths of this study include its enrollment of a large, diverse group of multi-morbid older adults who received care in different health-care delivery systems and were covered by three different health insurance plans, as well as its high rate of follow-up and its rigorous data collection and analytic methods.

In conclusion, these findings add support for the expanded use of GC to improve important elements of the quality of chronic health care for older people with multi-morbidity. Previously published papers have suggested that GC may produce short-term improvements in the quality of chronic care[21], reductions in family caregivers' strain[22], and net cost savings for health insurers[23]. Future work will study longer term health and cost outcomes.

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Conflict of Interest: *Dr. Boyd received an honorarium for speaking on multimorbidity at a conference jointly sponsored by AHRQ, Center for HealthCare Strategies, and Schaller Anderson in 2006. Ms. Frey received an honorarium for speaking at a conference in Spain on multidisciplinary heart failure programs sponsored by the Grupo Menarini. Dr. Marsteller has stock and stock options in Freddie Mac (husband's employer). Dr. Karm is employed by the Mid-Atlantic Permanente Group (for profit), which is the exclusive partner of Kaiser Permanente (not for profit). Ms. Groves is employed by the not-for-profit Kaiser Health Plan, which has an exclusive contract with the Mid-Atlantic Permanente Group.*

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Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial: Design and Methods

The ACCORD Study Group*,†

Most patients with type 2 diabetes mellitus develop cardiovascular disease (CVD), with substantial loss of life expectancy. Nonfatal CVD contributes greatly to excess healthcare costs and decreased quality of life in patients with diabetes. The current epidemic of obesity has raised expectations that CVD associated with type 2 diabetes will become an even greater public health challenge. Despite the importance of this health problem, there is a lack of definitive data on the effects of the intensive control of glycemia and other CVD risk factors on CVD event rates in patients with type 2 diabetes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is a randomized, multicenter, double 2 × 2 factorial design study involving 10,251 middle-aged and older participants with type 2 diabetes who are at high risk for CVD events because of existing CVD or additional risk factors. ACCORD is testing the effects of 3 medical treatment strategies to reduce CVD morbidity and mortality. All participants are in the glycemia trial, which is testing the hypothesis that a therapeutic strategy that targets a glycosylated hemoglobin (HbA_{1c}) level of <6.0% will reduce the rate of CVD events more than a strategy that targets an HbA_{1c} level of 7.0%–7.9%. The lipid trial includes 5,518 of the participants, who receive either fenofibrate or placebo in a double-masked fashion to test the hypothesis of whether, in the context of good glycemic control, a therapeutic strategy that uses a fibrate to increase high-density lipoprotein cholesterol and lower triglyceride levels together with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) to lower low-density lipoprotein cholesterol will reduce the rate of CVD events compared with a strategy that uses a statin plus a placebo. The blood pressure trial includes the remaining 4,733 participants and tests the hypothesis that a therapeutic strategy that targets a systolic blood pressure of <120 mm Hg in the context of good glycemic control will reduce the rate of CVD events compared with a strategy that targets a systolic blood pressure of <140 mm Hg. The primary outcome measure for all 3 research questions is the first occurrence of a major CVD event, specifically nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Upon the expected completion of participant follow-up in 2009, the ACCORD trial should document for the first time the benefits and risks of intensive glucose control, intensive blood pressure control, and the combination of fibrate and statin drugs in managing blood lipids in high-risk patients with type 2 diabetes. **(Am J Cardiol 2007;99[suppl]:21i-33i)**

Type 2 diabetes mellitus is a complex disease characterized by hyperglycemia, insulin resistance, and variable degrees of insulin deficiency. Patients with type 2 diabetes have a high rate of cardiovascular disease (CVD) mortality, nonfatal myocardial infarction (MI), and stroke.[1] This CVD risk is related in part to a high prevalence of other CVD risk factors, such as elevated blood pressure and dyslipidemia. Epidemiologic analyses suggest that the risk for CVD in patients with diabetes increases in a graded fashion with increases in glycosylated hemoglobin (HbA_{1c}), blood pressure, low-density lipoprotein (LDL) cholesterol, and triglycerides and with a decrease in high-density lipoprotein (HDL) cholesterol.[2]

The prevalence of diagnosed diabetes in the United States has increased substantially over time, increasing >4-fold over the past 50 years, with a particularly steep increase

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Table 1
Action to Control Cardiovascular Risk in Diabetes (ACCORD): the protocol-specified double 2 × 2 design*

	BP Trial		Lipid Trial†		
Glycemia Trial	SBP <120 mm Hg	SBP <140 mm Hg	Group A	Group B	Total
HbA_{1c} <6.0%	1,050	1,050	1,450	1,450	5,000
HbA_{1c} 7.0%–7.9%	1,050	1,050	1,450	1,450	5,000
	2,100	2,100	2,900	2,900	
Total	4,200		5,800		10,000

BP = blood pressure; HbA_{1c} = glycosylated hemoglobin; SBP = systolic BP.
* All numbers represent planned sample sizes.
† Treatment group assignments are blinded until the end of the trial.

Table 2
Action to Control Cardiovascular Risk in Diabetes (ACCORD): observed distribution of participants

	BP Trial		Lipid Trial*		
Glycemia Trial	SBP <120 mm Hg	SBP <140 mm Hg	Group A	Group B	Total
HbA_{1c} <6.0%	1,178	1,193	1,383	1,374	5,128
HbA_{1c} 7.0%–7.9%	1,184	1,178	1,370	1,391	5,123
	2,362	2,371	2,753	2,765	
Total	4,733		5,518		10,251

BP = blood pressure; HbA_{1c} = glycosylated hemoglobin; SBP = systolic BP.
* Treatment group assignments are blinded until the end of the trial.

over the past 5–10 years. The Centers for Disease Control and Prevention (CDC) estimates that in 2005, 14.6 million individuals in the United States were diagnosed with diabetes, and an additional 6.2 million went undiagnosed.[3] It is predicted that by 2050 the number of individuals in the United States with diagnoses of diabetes will have climbed to 39 million.[4]

Coupled with the increases in the prevalence and incidence of diabetes is the increasing burden of death and disability associated with diabetes. Patients with diabetes exhibit CVD at 2–4 times the rate of those without diabetes; women with diabetes are disproportionately affected and exhibit a similar age-adjusted risk for CVD to that of men with diabetes.[5] CVD is the most common cause of death and the single biggest driver of healthcare costs in patients with diabetes. The healthcare costs of diabetes are staggering,[6] with direct medical costs in 2002 estimated at $92 billion and an additional $40 billion in indirect costs due to disability, work loss, and premature mortality. This estimated $132 billion price tag is certainly an underestimate, because it omits costs incurred in undiagnosed individuals, the cost of unreimbursed care, and certain healthcare costs such as care by optometrists and dentists.[7] Although control of CVD risk factors has improved in the United States over the past 30 years,[8] estimates suggest that <5% of patients with diabetes in the United States in 2000 achieved all 5 targets included routinely in guidelines aimed at controlling cardiovascular and microvascular risk (control of blood pressure, LDL cholesterol, and glycemia; smoking cessation; and daily aspirin use).[9]

Clinical trials completed to date have shown that CVD risk can be reduced in patients with diabetes. However, in so doing, they highlight the critical gap in knowledge regarding the relative CVD benefits of intensively targeting normal glucose, blood pressure, and lipid status.[10] As a result, since 1997, scientists on 3 different panels sponsored by the National Institutes of Health (NIH) have concluded that a major randomized clinical trial was needed to determine the effects on CVD of intensive glycemic control, as well as strategies for lipid and/or blood pressure treatments in patients with type 2 diabetes. As a consequence, a number of such trials are under way.[11] The purpose of this report is to present the design of one of these, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. A fuller discussion of the rationale for conducting the ACCORD trial is presented elsewhere in this supplement.[12]

Study Overview

The overall goal of the ACCORD trial is to determine whether CVD event rates can be reduced in patients with type 2 diabetes who are at high risk for CVD events by intensively targeting 3 important CVD risk factors: hyperglycemia, dyslipidemia, and elevated blood pressure. Tables 1 and 2 present the overall design of the ACCORD trial, which is a randomized, double 2 × 2 factorial design conducted at 77 clinical centers across the United States and Canada. Table 1 lists the original planned distribution of 10,000 randomized participants across the 8 treatment groups. Table 2 presents the realized distribution of the

Table 3
Timetable of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial

Phase	No. of Months	Calendar Dates	Trial Activities
1	10	10/99–7/00	Protocol development
2	2	8/00–9/00	Procedure finalization and training
3	3	10/00–12/00	Vanguard startup and screening
4	24	1/01–1/03	Vanguard recruitment, follow-up, review, and protocol revision
5	34	2/03–10/05	Main trial recruitment and follow-up
6	40	11/05–2/09	Follow-up only
7	4	3/09–6/09	Participant close-out
8	9	7/09–4/10	Analysis and reporting

10,251 participants actually randomized. Whereas the final observed number of participants in the blood pressure trial is 13% greater than originally planned, the number of participants in the lipid trial is 5% less. This shortfall was anticipated a year before the end of recruitment, and revised power estimates reviewed by the investigators and the ACCORD Data and Safety Monitoring Board (DSMB) showed that there was still more than sufficient power to address the lipid hypothesis.

Participants will be treated and followed for 4–8 years (approximate mean, 5.6 years). The primary outcome measure for all 3 research questions is the first occurrence of a major cardiovascular event, specifically a composite outcome of nonfatal MI, nonfatal stroke, or cardiovascular death. Secondary outcomes include other cardiovascular outcomes, total mortality, diabetic microvascular disease (retinopathy, nephropathy, and neuropathy), health-related quality of life, and cost-effectiveness.

All participants were randomized to either intensive or standard glycemic goals in the open-label glycemia trial. Participants randomized to the intensive glycemia treatment group have an HbA_{1c} target of <6.0%. Participants randomized to the standard glycemia treatment group have an HbA_{1c} target of 7.0%–7.9%, with an expectation that the median HbA_{1c} level will be approximately 7.5%. Treatment algorithms using metformin, sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, insulin, and insulin analogues, coupled with lifestyle intervention, have been developed for the 2 groups. Exenatide was added to the available formulary in April 2007. Details of the approaches to glycemia therapy are presented elsewhere in this supplement.[13]

Among the 10,251 randomized participants, 5,518 with moderate levels of dyslipidemia were also randomized to either fenofibrate or matching placebo in a double-masked fashion, in addition to open-label background simvastatin therapy administered in accordance with current guidelines (20–40 mg/day, depending on observed LDL cholesterol values and whether the participant has had a clinical CVD event).[14] This is the only masked intervention in ACCORD. Details regarding the evolution of the lipid protocol are also presented elsewhere in this supplement.[14] Briefly, the standard dose of the masked fenofibrate or identical placebo used in ACCORD is 160 mg/day (or the bioequivalent doses of previous formulations). However, if the estimated glomerular filtration rate (GFR), using the observed serum creatinine level and the abbreviated Modification of Diet in Renal Disease (MDRD) equation,[15] is ≥30 and <50 mL/min per 1.73 m^2, the participant would be given a reduced dose of 54 mg/day (or the bioequivalent dose) of fenofibrate or placebo. If during follow-up the GFR decreases to consistently <30 mL/min per 1.73 m^2, the masked medication is discontinued.[14]

Finally, the other 4,733 participants in ACCORD were further randomized to either an intensive or a standard systolic blood pressure target, <120 or <140 mm Hg, respectively. Most currently available antihypertensive drug classes are available for use in the 2 groups, and they are administered in an open-label fashion. Details regarding the blood pressure treatment strategies are presented elsewhere in this supplement.[16]

As background treatment, all participants receive nutrition and physical activity counseling, as well as a recommendation to use aspirin daily. For participants with histories of MI, congestive heart failure, nephropathy, or ≥1 additional risk factor for CVD, treatment with an angiotensin-converting enzyme inhibitor is recommended, independent of blood pressure level or assigned treatment group. Current smokers receive smoking cessation counseling. All participants receive glucose-lowering therapy by protocol, as well as either lipid-modifying therapy or blood pressure–lowering therapy by protocol. Participants with high blood pressure assigned to the lipid study do not have their blood pressure managed through the study; similarly, participants with dyslipidemia assigned to the blood pressure study do not have their lipids managed through the study. However, information on current guidelines for lipids and blood pressure treatment is provided by the study to participants' personal physicians.

Table 3 presents the timeline of the study. Protocol development, external review, and training occurred over an initial 12-month period beginning in October 1999. Randomization into the vanguard phase began in January 2001, with a recruitment goal of 1,000 participants. The purpose of the vanguard phase was to assess the feasibility of recruitment, achievement of glycemia and blood pressure treatment goals, and achievement of an acceptable level of adherence in the masked lipid trial. On the

basis of the outcomes of these measures in the 1,174 recruited vanguard participants, protocol changes were proposed, reviewed, and approved in the winter of 2002. Main trial recruitment started in February 2003. The ACCORD recruitment goal of 10,000 participants was reached on September 30, 2005, with the inclusion of the vanguard and main trial participants. The last patient was randomized on October 29, 2005. The final visit for the last randomized participant is planned for June 30, 2009, with final study reports expected in the spring of 2010.

Eligibility and Baseline Characteristics

The ACCORD inclusion and exclusion criteria are presented in Table 4. These criteria were established to identify a trial population with type 2 diabetes and at high risk for CVD events, with expected event rates for sufficient statistical power with the proposed sample size while balancing generalizability and safety.[17] To be eligible, a volunteer needed to fulfill the glycemia eligibility criteria as well as criteria for either the blood pressure or the lipid trial. If a screenee was not eligible for either the blood pressure or the lipid trial, he or she was not eligible for the ACCORD trial at all. If a screenee was eligible for both the blood pressure and the lipid trials, a computerized randomization process assigned the participant to either the lipid or the blood pressure trial. Patients aged >79 years were excluded from the main trial because of increased rates of hypoglycemia in that age group in the vanguard phase. The Protocol Review Committee, appointed by the National Heart, Lung, and Blood Institute (NHLBI), approved the study protocol. Each ACCORD participant has provided written informed consent using procedures reviewed and approved by each clinical site's local institutional review board and based on a template provided by the study group that was approved and subsequently centrally monitored by the Coordinating Center and the NHLBI. The portion of the informed consent document describing the genetics component of ACCORD uses the multilevel approach recommended by the NHLBI.[18]

Specific targets were set to recruit ≥50% women, 33% racial and ethnic minorities, and 50% secondary prevention participants (ie, those with histories of clinical CVD). A full description of the recruitment planning, results, and lessons learned from the vanguard portion of ACCORD is presented elsewhere in this supplement.[17]

Table 5 presents baseline characteristics for the ACCORD trial. As expected, the treatment groups were balanced on these characteristics. Overall, there was an excess of men recruited into ACCORD (61% vs 39%), largely driven by the preponderance of men within US Department of Veterans Affairs (VA) centers. The proportion of participants with clinical CVD at baseline (35.2%) did not reach the 50% target, although sensitivity analyses indicate that this will not substantially affect the overall power of the study.

Hurricane Katrina had a significant impact on the ACCORD clinic in New Orleans, at the Tulane University Health Sciences Center. A total of 193 participants were randomized at this site. Final edits of the baseline data and decisions regarding the handling of any missing participants and data will be made when complete information is available on each of the Tulane participants. Consequently, the data in Table 5 may be modified slightly in the future.

Measurements

A wide range of interview, physical examination, and laboratory data are being collected (Table 6), with the frequency of measurement varying by treatment assignment, but at least at baseline, every 2 years, and at the end of the trial. Blood and urine samples are also stored for future measurements. White blood cells are stored for future DNA extraction for genetic studies in patients who consented to such studies.

Data are collected in 2 substudies of the trial participants to examine visual and cognitive effects of the interventions. In the ACCORD Eye Study (ACCORD-EYE), with 3,537 participants, retinal photographs are obtained and read centrally to determine the effects of the interventions on the incidence and progression of retinopathy. In the ACCORD Memory in Diabetes Study (ACCORD-MIND), with 2,977 participants, cognitive functioning is assessed by a battery of cognitive neuropsychological tests. In a subset of ACCORD-MIND, 630 participants are undergoing serial brain magnetic resonance imaging (MRI) scanning to examine potential intervention effects on cognitive functioning and brain anatomy. These 2 substudies are the subject of other reports in this supplement.[19,20]

Outcomes

The primary end point for ACCORD is the composite of nonfatal MI, nonfatal stroke, or CVD death. Cardiovascular causes of death include fatal MI, congestive heart failure, documented arrhythmia, death after invasive cardiovascular interventions, death after noncardiovascular surgery, fatal stroke, unexpected death presumed to be due to ischemic CVD occurring <24 hours after the onset of symptoms, and death due to other vascular diseases (eg, pulmonary emboli, abdominal aortic aneurysm rupture). The diagnosis of MI is based on the occurrence of a compatible clinical syndrome associated with diagnostic elevation of cardiac enzymes (ie, an increase in troponin T or troponin I to a level indicating myonecrosis and/or an increase in creatine kinase–myocar-

Table 4
Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial major inclusion and exclusion criteria

A. Overall inclusion criteria
   1. Type 2 diabetes mellitus defined according to the 1997 ADA criteria for ≥3 mo
   2. An HbA_{1c} level (obtained <3 mo before anticipated date of randomization) of
      a. 7.5%–11%: (i) If on insulin <1 U/kg and on 0 or 1 oral agent or (ii) If not on insulin, and on 0, 1, or 2 oral agents
      b. 7.5%–9%: (i) If on insulin <1 U/kg and on 2 oral agents, (ii) If on insulin >1 U/kg and 0 oral agents, or (iii) If not on insulin and on 3 oral agents
   3. Stable diabetes therapy for >3 mo
   4. Age at randomization
      a. 40–79 yr (inclusive) for anyone with a history of clinical CVD, or
      b. 55–79 yr (inclusive) for anyone without a history of clinical CVD (the age eligibility was modified on the basis of the results of the vanguard phase, so some participants were aged ≥80 yr at randomization)
   5. At high risk for CVD events, defined as
      a. Presence of clinical CVD (prior MI, stroke, arterial revascularization, angina with ischemic changes on ECG at rest, changes on a graded exercise test, or positive cardiac imaging test results,
      b. If no clinical CVD, evidence in the past 2 yr suggesting high likelihood of CVD (1 risk factor: microalbuminuria, ankle-brachial index <0.9, left ventricular hypertrophy by ECG or echocardiography, or >50% stenosis of a coronary, carotid, or lower extremity artery), or
      c. Presence of ≥2 of the following factors that increase CVD risk: LDL-C >130 mg/dL (1 mg/dL = 0.02586 mmol/L) treated with lipid-lowering medication or untreated, low HDL-C (<40 mg/dL for men and <50 mg/dL for women), systolic BP >140 mm Hg or diastolic BP >95 mm Hg treated with BP-lowering medication or untreated, current cigarette smoking, or BMI >32
   6. In addition, all participants must be eligible for either the BP trial or the lipid trial

B. Overall exclusion criteria
   1. History of hypoglycemic coma/seizure within past 12 mo
   2. Hypoglycemia requiring third-party assistance in past 3 mo, with concomitant glucose <60 mg/dL (3.3 mmol/L)
   3. History consistent with type 1 diabetes
   4. Unwilling to do frequent capillary blood glucose self-monitoring or unwilling to inject insulin several times a day
   5. BMI >45
   6. Serum creatinine >1.5 mg/dL (132.6 μmol/L) obtained within the previous 2 mo
   7. Transaminase >2 times the upper limit of normal or active liver disease
   8. Any ongoing medical therapy with known adverse interactions with the glycemic interventions (eg, corticosteroids, protease inhibitors)
   9. Cardiovascular event or procedure (as defined for study entry) or hospitalization for unstable angina within past 3 mo
   10. Current symptomatic heart failure, history of NYHA class III or IV congestive heart failure at any time, or ejection fraction (by any method) <0.25
   11. A medical condition likely to limit survival to <3 yr or a malignancy other than nonmelanoma skin cancer within the past 2 yr
   12. Any factors likely to limit adherence to interventions
   13. Failure to obtain informed consent from participant
   14. Currently participating in another clinical trial
   15. Living in the same household as an already randomized ACCORD participant
   16. Any organ transplantation
   17. Weight loss >10% in past 6 mo
   18. Pregnancy, currently trying to become pregnant, or of child-bearing potential and not practicing birth control
   19. Participants with recurrent requirements for phlebotomy or transfusion of red blood cells

C. Additional lipid trial criteria (for entry into lipid trial)
   1. Inclusion criteria: (a) Lipids measured within the previous 12 mo with (i) Estimated LDL-C off statin therapy of 60–180 mg/dL, and (ii) HDL-C <55 mg/dL for women or African Americans or HDL-C <50 mg/dL for all other sex and race groups, and triglycerides <750 mg/dL (1 mg/dL = 0.01129 mmol/L) on no therapy or <400 mg/dL on treatment with lipid-lowering drugs
   2. Exclusion criteria for lipid intervention include known hypersensitivity to statins or fibrates; requirements for use of erythromycin, clarithromycin, cyclosporine, systemic azole antifungals, or nefazodone or trazodone (all of which have reported interactions with either statins or fibrates); refusal to stop current lipid-lowering drugs; history of pancreatitis; untreated or inadequately treated thyroid disease; breastfeeding; documented previous occurrence of myositis/myopathy; preexisting gallbladder disease

D. Additional BP trial criteria (for entry into blood pressure trial)
   1. To be eligible, systolic BP can be
      a. 130–160 mm Hg, inclusive, if the participant is on 0, 1, 2, or 3 antihypertensive medications,
      b. 161–170 mm Hg, inclusive, if the participant is on 0, 1, or 2 antihypertensive medications, or
      c. 171–180 mm Hg, inclusive, if the patient is on 0 or 1 antihypertensive medication
   2. The dipstick protein in a spot urine test must be <2+, the protein/creatinine ratio in a spot urine test must be <700 mg/g creatinine, and the 24-hr protein excretion must be <1.0 g/24 hr
   3. For screenees who are not currently on BP-lowering medication, there must be documentation of systolic BP ≥130 mm Hg on ≥2 occasions

ADA = American Diabetes Association; BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; ECG = electrocardiography; HbA_{1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NYHA = New York Heart Association.

Table 5
Baseline description of randomized Action to Control Cardiovascular Risk in Diabetes (ACCORD) participants

Characteristic	Overarching Glycemia Trial (n = 10,251)	BP Trial (n = 4,733)	Lipid Trial (n = 5,518)
Mean age (yr)	62.2	62.2	62.3
Women (%)	38.6	47.7	30.7
Race/ethnicity			
White (%)	64.8	60.5	68.4
Black (%)	19.3	24.1	15.1
Hispanic (%)	7.2	7.0	7.4
Highest level of education			
Less than high school (%)	14.8	16.3	13.6
High school graduate (%)	26.4	26.9	26.0
Some college (%)	32.8	32.4	33.1
College graduate or more (%)	26.0	24.5	27.3
Cigarette smoker			
Current (%)	14.0	13.3	14.6
Former (%)	44.4	42.1	46.3
Never (%)	41.6	44.6	39.0
Secondary prevention (%)	35.2	33.6	36.6
Mean HbA_{1c} (%)	8.3	8.3	8.3
Median HbA_{1c} (%)	8.1	8.1	8.1
Mean fasting serum glucose, mg/dL (mmol/L)	175.3 (9.7)	174.7 (9.7)	175.8 (9.8)
Median duration of diabetes (yr)	10	10	9
Mean weight, lb (kg)	206.2 (93.5)	202.8 (92.0)	209.1 (94.8)
Mean body mass index	32.2	32.2	32.3
Mean waist circumference, in (cm)	42.0 (106.6)	41.6 (105.6)	42.4 (107.7)
Mean systolic BP (mm Hg)	136.4	139.2	133.9
Mean diastolic BP (mm Hg)	74.9	76.0	74.0
Use of any antihypertensive (%)	85.4	87.3	83.8
Use of ACE inhibitor (%)	52.9	52.0	53.6
Use of β-blocker (%)	29.2	25.4	32.5
Mean LDL-C, mg/dL (mmol/L)	104.9 (2.71)	110.0 (2.84)	100.6 (2.60)
Mean HDL-C, mg/dL (mmol/L)			
Women	47.0 (1.22)	51.3 (1.33)	41.4 (1.07)
Men	38.6 (1.00)	41.7 (1.08)	36.6 (0.95)
Mean total cholesterol, mg/dL (mmol/L)	183.3 (4.74)	192.8 (4.99)	175.2 (4.53)
Median triglyceride, mg/dL (mmol/L)	155 (1.74)	147 (1.65)	162 (1.81)
Use of statins (%)	59.3	61.1	57.7
Mean potassium (mmol/L)	4.5	4.5	4.5
Mean serum creatinine, mg/dL (μmol/L)	0.9 (80)	0.9 (80)	0.9 (80)

ACE = angiotensin-converting-enzyme; BP = blood pressure; HbA_{1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; statin = 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor.

dial band to a level more than twice the upper limit of normal). Q-wave MI is defined as the development of new significant Q waves. Silent MI is diagnosed when new (compared with the previous 12-lead electrocardiogram) significant Q waves are detected by surveillance electrocardiography performed every 2 years and at study end in all participants. Stroke is diagnosed by a focal neurologic deficit that lasts >24 hours, associated with evidence of brain infarction or hemorrhage by computed tomography, MRI, or autopsy.

The secondary end points are (1) an expanded macrovascular outcome, specifically the combination of the primary end point plus any revascularization and hospitalization for congestive heart failure; (2) total mortality; (3) cardiovascular mortality; (4) major coronary artery disease events, specifically fatal events, nonfatal MI, and unstable angina; (5) total stroke (combined fatal and nonfatal); (6) congestive heart failure death or hospitalization for heart failure (with documented clinical and radiologic evidence); (7) the main microvascular outcome of ACCORD and the primary outcome of ACCORD-EYE, namely, the combined outcome of progression of diabetic retinopathy of ≥3 stages on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, photocoagulation, or vitrectomy for diabetic retinopathy, which will be determined only in the 3,537 participants in ACCORD-EYE[19]; (8) a second composite microvascular end point, to be examined in the entire ACCORD population, namely, fatal or nonfatal renal failure or retinal photocoagulation or vitrectomy for diabetic retinopathy; and (9) outcomes related to health-related quality of life and cost-effectiveness.[21]

Table 6
Measures

1. Questionnaires
   a. Sociodemographics: age, ethnicity, sex, level of education, persons living with participants, and US zip code/Canadian postal code; Social Security number, Medicare number, Canadian Social Insurance number, or Provincial Health Insurance number was collected for tracking purposes
   b. Medical history: detailed initial medical history; follow-up abbreviated interval history focused on eligibility criteria, allergies, CVD, smoking status, and diabetes mellitus
   c. Concomitant medications: all standing therapies, with the emphasis placed on concurrent antihypertensive, glycemic, and lipid-lowering therapy, as well as background risk reduction (eg, aspirin) therapy
   d. Diet*
   e. Physical activity*
   f. Health-related quality of life substudy*
   g. Cost-effectiveness substudy*
   h. ACCORD Eye Study* (ACCORD-EYE)
   i. ACCORD Memory in Diabetes Study* (ACCORD-MIND)
2. Physical examination measures
   a. Anthropometric measurements: standing height, weight, and waist circumference
   b. BP and pulse
   c. Systems physical examination: general survey, skin, head, ears, eyes, nose, throat, neck, chest, heart, abdomen, musculoskeletal/extremities, pulse assessment, and neurologic (including lower extremity)
   d. Visual acuity
3. Laboratory measures
   a. HbA_{1c}
   b. Electrocardiogram
   c. Fasting serum glucose
   d. Potassium, creatinine
   e. Fasting lipid panel
   f. Alanine transaminase, creatine phosphokinase*
   g. Urine albumin–creatinine ratio
   h. Stored samples: serum, urine, WBCs for DNA extraction (the latter only with participant consent)

ACCORD = Action to Control Cardiovascular Risk in Diabetes; BP = blood pressure; CVD = cardiovascular disease; HbA_{1c} = glycosylated hemoglobin; WBC = white blood cell.

* Measured in subsets of patients.

Analysis Plan

The primary ACCORD hypotheses are as follows: In middle-aged or older patients with type 2 diabetes who are at high risk for having a CVD event,

1. Does a therapeutic strategy that targets an HbA_{1c} level of $<6.0\%$ reduce the rate of CVD events more than a strategy that targets an HbA_{1c} level of 7.0%–7.9% (with the expectation of achieving a median level of 7.5%)?
2. In the context of good glycemic control, does a therapeutic strategy that uses a fibrate to increase HDL cholesterol and lower triglyceride levels together with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) to lower LDL cholesterol reduce the rate of CVD events compared with a strategy that uses a statin plus a placebo?
3. In the context of good glycemic control, does a therapeutic strategy that targets a systolic blood pressure level of <120 mm Hg reduce the rate of CVD events compared with a strategy that targets a systolic blood pressure level of <140 mm Hg?

Analyses of each primary hypothesis will be conducted within separate models to test each intervention as a comparison of the marginal (main) effect for each of the 3 research hypotheses separately, not as comparisons among the individual cells of the double 2×2 design. The 1,174 participants entered during the vanguard phase are included in all the planned analyses along with the 9,077 entered during the main trial phase, yielding the total number of 10,251 participants. All of these participants will be included in the analysis for the glycemia hypothesis. Primary analyses will be performed according to the intention-to-treat principle (ie, all randomized participants will be analyzed according to their intervention assignment at randomization, regardless of adherence). Each hypothesis will be tested using a 2-sided probability of type 1 error of 0.05. The main analyses will be based on survival analysis methods, with failure time measured from the time of randomization. Proportional hazards models will be used,[22] incorporating adjustment for the prespecified covariates listed below.

Glycemia hypothesis: The glycemia hypothesis will be tested in all 10,251 randomized participants. The model to be fit will contain separate indicator variables that identify participants (1) in the blood pressure trial, (2) in the blood pressure trial and randomized to the intensive blood pressure control intervention, (3) in the lipid trial, (4) in the lipid trial and randomized to fibrate, and (5) randomized to intensive glycemic control.

In addition to these variables, indicator variables will be included that identify secondary prevention participants (variable 6) and clinical center networks (CCNS) (variable 7). The main comparison in this model will be based on the χ^2 statistic from a likelihood ratio test obtained from proportional-hazards models with or without variable 5.

Lipid hypothesis: The lipid hypothesis will be tested in the 5,518 lipid trial participants. The model to be fit will contain variables 4, 5, 6, and 7. This hypothesis will be tested using a likelihood ratio test for models with or without variable 4.

Blood pressure hypothesis: The blood pressure hypothesis will be tested in the 4,733 participants in the blood pressure trial. The model to be fit will contain the variables 2, 5, 6, and 7. This hypothesis will be tested using a likelihood ratio test for models with or without variable 2.

Kaplan-Meier[23] estimates of survival will be obtained for the intervention and control groups for each hypothesis. Estimates of the proportion of participants who remain

event free at prespecified time points, and the associated confidence intervals, will be constructed.[24] The hazard functions will be assessed for proportionality using log/log plots of survival and Schoenfeld residuals. Unadjusted analyses (ie, log-rank tests) will also be performed.

All of the secondary outcomes and the 2 substudies (ACCORD-MIND and ACCORD-EYE) also will be analyzed as marginal (main) effects, with the glycemia, lipid, and blood pressure trials analyzed separately. Two subgroup hypotheses for the glycemia intervention are to determine whether the effects of glycemic control on the primary outcome are the same across baseline levels of HbA_{1c} and if the effects of glycemic control on the primary outcome are independent of effects due to the blood pressure and lipid interventions. Three subgroup hypotheses for the lipid intervention are to determine whether the benefits of fibrate (in the context of desirable levels of LDL cholesterol and good glycemic control) are equal across levels of LDL cholesterol, HDL cholesterol, and triglycerides measured before the initiation of fibrate therapy. The consistency of the effects for the glycemia, lipid, and blood pressure interventions will also be examined in subgroups defined by sex, age, race or ethnicity, and the presence of clinical CVD at baseline (ie, primary and secondary prevention participants), and the presence or absence of the other interventions.

The ACCORD study was designed to have 89% power to detect a 15% treatment effect of intensive glycemic control compared with standard glycemic control, 87% power to detect a 20% treatment effect of lipid treatment with fibrate compared with placebo (on a background of statin treatment for LDL cholesterol), and 94% power to detect a 20% treatment effect of intensive blood pressure control compared with standard blood pressure control. The original sample size and power determinations for each intervention were made under the assumption that the other 2 interventions would produce the effect sizes for which they were powered. The ACCORD clinic investigators are masked to all CVD outcome measurements until the end of the trial, when data analysis is complete.

Management

The ACCORD organizational structures and responsibilities are similar to those of other large, multicenter clinical trials sponsored by government or industry. Seven CCNs and the Coordinating Center are contracted by the NHLBI to work together through the Steering Committee to successfully design and conduct the trial. In addition, the Central Chemistry Laboratory and the ECG Reading Center are subcontracted by the Coordinating Center. The Drug Distribution Center is funded by a governmental interagency agreement. Each CCN comprises a network of collaborating clinical sites, which include medical facilities and/or individual practices that enroll and treat participants in the trial. In all, there are 77 such active clinical sites located across the United States and Canada.

The ACCORD Steering Committee provides the overall leadership for the trial and establishes scientific and administrative policy. It is composed of voting members (the principal investigators from the 7 CCNs, the principal investigator from the Coordinating Center, and the NHLBI project officer) and the chairs of the 3 major intervention working groups (glycemia, lipid, and blood pressure), the Steering Committee chair, and the Steering Committee vice chair. Nine standing subcommittees of the Steering Committee are specified in the protocol: Design and Analysis, Medical Interventions, Recruitment and Retention, Measurement Procedures and Quality Control, Morbidity and Mortality, Publications and Presentations, Health-Related Quality of Life/Cost-Effectiveness, Laboratory and Ancillary Studies, and Operations. The Executive Committee acts as the operational arm of the Steering Committee and makes decisions on behalf of the Steering Committee on day-to-day operational issues requiring immediate action as well as study processes and assignments.

The independent Protocol Review Committee, appointed by the director of the NHLBI, reviewed the originally proposed protocol (in mid-2000) and recommended to the NHLBI that a vanguard phase of 1,000 participants be conducted and evaluated before mounting the full-scale trial. The independent DSMB, also appointed by the director of the NHLBI, monitors data and oversees patient safety, meeting twice annually to advise the NHLBI. ACCORD receives contributed resources from industry, including some medications and some supplies. However, the scientific decisions and governance of the trial are determined solely by the Steering Committee.

The ACCORD investigators established a conflict-of-interest policy to meet public standards of conduct and to ensure unbiased and fully informed decision making. To meet these goals, the study obtains full disclosure by all key members of the study regarding their own and their immediate family members' financial relationships with all pharmaceutical and biomedical companies judged to have active or potential interests in the conduct and outcome of the study. Members with significant financial conflicts of interest are required to recuse themselves from voting on issues related to the conflict.

ACCORD is an Internet-based trial, with its home page located at http://www.accordtrial.org. In addition to the public section of the Web site, which contains general information regarding ACCORD, there is a password-protected section used by the CCNs and clinical sites to randomize participants and to enter data. All study documents are found in the password-protected section of the Web site, including the protocol, the manual of procedures, training materials, forms, special notices, Steering Committee minutes, the study directory, quality-control reports, and overall and site-specific reports related to the achievement of recruitment and treatment goals. The current protocol is

posted on the public Web site. It should be recognized that the protocol is a dynamic document that may change over time.

Conclusion

By addressing several important and currently unanswered questions regarding the prevention of CVD in patients with type 2 diabetes, the results of the ACCORD trial should provide substantial direction regarding appropriate targets and techniques of risk factor management in patients with type 2 diabetes for many years to come.

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ORIGINAL ARTICLE

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

ABSTRACT

BACKGROUND

There is no evidence from randomized trials to support a strategy of lowering systolic blood pressure below 135 to 140 mm Hg in persons with type 2 diabetes mellitus. We investigated whether therapy targeting normal systolic pressure (i.e., <120 mm Hg) reduces major cardiovascular events in participants with type 2 diabetes at high risk for cardiovascular events.

METHODS

A total of 4733 participants with type 2 diabetes were randomly assigned to intensive therapy, targeting a systolic pressure of less than 120 mm Hg, or standard therapy, targeting a systolic pressure of less than 140 mm Hg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years.

RESULTS

After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive-therapy group and 133.5 mm Hg in the standard-therapy group. The annual rate of the primary outcome was 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group (hazard ratio with intensive therapy, 0.88; 95% confidence interval [CI], 0.73 to 1.06; P=0.20). The annual rates of death from any cause were 1.28% and 1.19% in the two groups, respectively (hazard ratio, 1.07; 95% CI 0.85 to 1.35; P=0.55). The annual rates of stroke, a prespecified secondary outcome, were 0.32% and 0.53% in the two groups, respectively (hazard ratio, 0.59; 95% CI, 0.39 to 0.89; P=0.01). Serious adverse events attributed to antihypertensive treatment occurred in 77 of the 2362 participants in the intensive-therapy group (3.3%) and 30 of the 2371 participants in the standard-therapy group (1.3%) (P<0.001).

CONCLUSIONS

In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events. (ClinicalTrials.gov number, NCT00000620.)

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Diabetes mellitus increases the risk of cardiovascular disease by a factor of two to three at every level of systolic blood pressure.[1] Because cardiovascular risk in patients with diabetes is graded and continuous across the entire range of levels of systolic blood pressure, even at prehypertensive levels, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommended beginning drug treatment in patients with diabetes who have systolic blood pressures of 130 mm Hg or higher, with a treatment goal of reducing systolic blood pressure to below 130 mm Hg.[1-3] There is, however, a paucity of evidence from randomized clinical trials to support these recommendations. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial (ACCORD BP)[4] tested the effect of a target systolic blood pressure below 120 mm Hg on major cardiovascular events among high-risk persons with type 2 diabetes. We present here the main results of the ACCORD BP trial.

Methods

Study Design

ACCORD was a randomized trial conducted at 77 clinical sites organized into seven networks in the United States and Canada (for a full list of participating institutions and investigators, see Section 1 in Supplementary Appendix 1, available with the full text of this article at NEJM.org). The trial enrolled 10,251 high-risk participants with type 2 diabetes mellitus.[5] All participants were randomly assigned to either intensive or standard glycemic control (the ACCORD glycemia trial). In addition, 5518 of the ACCORD participants were also randomly assigned (in a 2-by-2 factorial design) to either simvastatin plus fenofibrate or simvastatin plus placebo (the ACCORD lipid trial), and the remaining 4733 participants were also randomly assigned (in a 2-by-2 factorial design) to either intensive or standard blood-pressure control (the ACCORD blood-pressure trial). Details of the randomization are provided in Section 3 of Supplementary Appendix 1. The trial was sponsored by the National Heart, Lung, and Blood Institute (NHLBI). The protocol was approved by the institutional review board or ethics committee at each center and by an independent protocol review committee appointed by the NHLBI. The main results of the ACCORD glycemia trial have been published previously,[6] and the main results of the ACCORD Lipid trial are published elsewhere in this issue of the *Journal*.[7] The ACCORD trial protocol and amendments are available in Supplementary Appendix 2.

Eligibility Criteria and Recruitment

Inclusion criteria for the glycemia trial are described in detail elsewhere.[5] In brief, participants were eligible if they had type 2 diabetes mellitus and a glycated hemoglobin level of 7.5% or more and were 40 years of age or older with cardiovascular disease or 55 years of age or older with anatomical evidence of a substantial amount of atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, smoking, or obesity). Exclusion criteria included a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 45, a serum creatinine level of more than 1.5 mg per deciliter (132.6 μmol per liter), and other serious illness. Participants with a systolic blood pressure between 130 and 180 mm Hg who were taking three or fewer antihypertensive medications and who had the equivalent of a 24-hour protein excretion rate of less than 1.0 g were also eligible for the blood-pressure trial (see Section 4 in Supplementary Appendix 1).[8] All participants provided written informed consent.

Recruitment occurred during two noncontiguous periods: 491 participants in the blood-pressure trial were recruited from January 2001 through early June 2001 during a "vanguard" phase, and the remaining 4242 participants were recruited from January 2003 through October 2005 during the main trial phase. An upper age limit of 79 years was added to the eligibility criteria for the main trial recruitment.

Trial Procedures

The ACCORD BP trial was a nonblinded trial in which participants were randomly assigned to intensive therapy that targeted systolic blood pressures of less than 120 mm Hg or standard therapy that targeted systolic blood pressures of less than 140 mm Hg. Treatment strategies that are currently available in clinical practice were used to lower blood pressure. Randomization was per-

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formed centrally on the study's Web site with the use of permuted blocks to maintain concealment of future study-group assignments.

The approach to the management of blood pressure has been described elsewhere.[4] The schedules of visits for the assessment and management of blood pressure differed according to treatment group. For participants in the intensive-therapy group, visits to assess blood pressure were scheduled once a month for 4 months and every 2 months thereafter; for participants in the standard-therapy group, visits were scheduled at months 1 and 4 and every 4 months thereafter. Additional visits were scheduled as needed in both groups to monitor and ensure appropriate implementation of the study intervention strategies. In both blood-pressure groups, participants who were assigned to intensive glycemic therapy had more frequent contacts for the management of glycemia, but blood pressure was not monitored at these additional visits.

The ACCORD BP trial was a study of a treatment strategy to achieve specific systolic blood-pressure goals, rather than an evaluation of any specific drug regimen. However, all the antihypertensive regimens were to include drug classes that had been shown to result in a reduction in cardiovascular events among participants with diabetes. Details of the assessment of blood pressure, the adjustment of medication doses, and antihypertensive drug regimens are provided in Sections 8 and 9 in Supplementary Appendix 1. Antihypertensive drugs were donated by Abbott Laboratories, AstraZeneca Pharmaceuticals, GlaxoSmithKline Pharmaceuticals, King Pharmaceuticals, Sanofi-Aventis U.S., and Novartis Pharmaceuticals. Sphygmomanometers were donated by Omron Healthcare. The companies that donated the drugs and devices had no role in the design of the study, the accrual or analysis of the data, or the preparation of the manuscript.

At the 4-month visits that both treatment groups were scheduled to attend, information on study outcomes and adverse events was ascertained, blood samples were obtained, and clinical examinations were performed. The occurrence of self-reported symptoms of swelling or of dizziness on standing during the previous month was assessed as part of a standardized symptom checklist that was administered at baseline and at 1, 3, and 4 years after randomization to a random sample of 969 participants who were assessed for health-related quality of life.

TRIAL OUTCOMES

The primary outcome for all three ACCORD trials was the first occurrence of a major cardiovascular event, which was defined as the composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Prespecified secondary outcomes included the combination of the primary outcome plus revascularization or hospitalization for congestive heart failure (termed the "expanded macrovascular outcome"); the combination of a fatal coronary event, nonfatal myocardial infarction, or unstable angina (termed "major coronary disease events"); nonfatal myocardial infarction; fatal or nonfatal stroke; nonfatal stroke; death from any cause; death from cardiovascular causes; and hospitalization or death due to heart failure. Definitions of each prespecified end point and information regarding methods of ascertainment are included in Section 6 in Supplementary Appendix 1.

Since all the antihypertensive medications used in the trial were approved by the Food and Drug Administration and were used according to approved labeling, we limited detailed data collection on serious adverse events to those attributed by investigators to antihypertensive medications (see Section 7 in Supplementary Appendix 1). Clinical and laboratory variables, including serum potassium and creatinine levels and estimated glomerular filtration rate,[9] were also examined as potential adverse effects.

STATISTICAL ANALYSIS

With a planned sample size of 4200 participants, the ACCORD BP trial was designed to have 94% power to detect a 20% reduction in the rate of the primary outcome for participants in the intensive-therapy group, as compared with those in the standard-therapy group, assuming a two-sided alpha level of 0.05, a primary-outcome rate of 4% per year in the standard-therapy group, and a planned average follow-up of 5.6 years for participants who did not have an event. Since ACCORD was a factorially designed trial, the targeted number of participants and the determination of sample size were made under the assumption that the intensive glucose-lowering intervention would produce a 15% benefit.[5]

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Overall (N=4733)	Intensive Therapy (N=2362)	Standard Therapy (N=2371)	P Value
Age — yr	62.2±6.9	62.2±6.8	62.2±6.9	0.82
Female sex — no. (%)	2258 (47.7)	1128 (47.8)	1130 (47.7)	0.95
Race or ethnic group — no. (%)†				
Non-Hispanic white	2864 (60.5)	1455 (61.6)	1409 (59.4)	0.13
Black	1142 (24.1)	561 (23.8)	581 (24.5)	0.56
Hispanic	330 (7.0)	159 (6.7)	171 (7.2)	0.53
Education — no./total no. (%)				0.18
Less than high school	771/4729 (16.3)	404/2359 (17.1)	367/2370 (15.5)	
High-school graduate or GED	1271/4729 (26.9)	606/2359 (25.7)	665/2370 (28.1)	
Some college	1530/4729 (32.4)	776/2359 (32.9)	754/2370 (31.8)	
College degree or higher	1157/4729 (24.5)	573/2359 (24.3)	584/2370 (24.6)	
Previous cardiovascular event — no. (%)	1593 (33.7)	804 (34.0)	789 (33.3)	0.58
Previous heart failure — no./total no. (%)	203/4683 (4.3)	109/2338 (4.7)	94/2345 (4.0)	0.28
Cigarette-smoking status — no./total no.(%)				0.94
Current	626/4728 (13.2)	314/2358 (13.3)	312/2370 (13.2)	
Former	1981/4728 (41.9)	992/2358 (42.1)	989/2370 (41.7)	
Never	2121/4728 (44.9)	1052/2358 (44.6)	1069/2370 (45.1)	
Weight — kg	92.0±18.6	92.1±19.4	91.8±17.7	0.57
Body-mass index	32.1±5.6	32.2±5.7	32.1±5.4	0.58
Blood pressure — mm Hg‡				
All participants				
Systolic	139.2±15.8	139.0±16.1	139.4±15.5	0.47
Diastolic	76.0±10.4	75.9±10.6	76.0±10.2	0.87
Participants taking no medication at screening				
Systolic	139.4±14.3	139.8±15.0	139.1±13.7	0.53
Diastolic	77.5±9.4	77.5±9.5	77.4±9.4	0.86
Participants taking at least one medication at screening				
Systolic	139.2±16.0	138.9±16.3	139.4±15.8	0.34
Diastolic	75.7±10.5	75.7±10.7	75.8±10.3	0.87
Duration of diabetes — yr				0.86
Median	10	9	10	
Interquartile range	5–15	5–15	5–15	
Glycated hemoglobin — %	8.3±1.1	8.4±1.1	8.3±1.1	0.08
Fasting plasma glucose — mg/dl	174.7±57.7	176.1±57.7	173.2±57.7	0.09
Cholesterol — mg/dl				
Total	192.8±44.7	194.1±45.1	191.4±44.3	0.04
Low-density lipoprotein	110.0±36.7	111.1±37.4	108.8±36.0	0.03
High-density lipoprotein				
Women	51.3±13.8	51.3±13.4	51.3±14.3	0.99
Men	41.7±11.8	41.4±11.2	42.0±12.4	0.17

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Table 1. (Continued.)

Characteristic	Overall (N=4733)	Intensive Therapy (N=2362)	Standard Therapy (N=2371)	P Value
Plasma triglycerides — mg/dl				0.71
Median	147	147	147	
Interquartile range	98–226	98–227	98–224	
Potassium — mg/dl	4.5±0.7	4.5±0.5	4.5±0.8	0.73
Serum creatinine — mg/dl	0.9±0.2	0.9±0.2	0.9±0.2	0.98
Estimated GFR — ml/min/1.73 m^2	91.6±28.8	91.6±30.3	91.7±27.1	0.93
Ratio of urinary albumin (mg) to creatinine (g)				0.64
Median	14.3	14.6	14.0	
Interquartile range	6.9–44.8	7.0–43.7	6.9–45.8	

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. To convert the values for glucose to millimoles per liter, multiply by 0.055551. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for potassium to millimoles per liter, multiply by 0.2558. To convert the values for creatinine to micromoles per liter, multiply by 88.4. GED denotes general equivalency diploma, and GFR glomerular filtration rate.
† Race or ethnic group was self-reported, and participants could check multiple categories.
‡ Data were available for 4733 participants in the total cohort, 599 who were taking no medication at screening and 4134 who were taking one or more medications at screening.

Statistical analyses were conducted at the coordinating center with the use of S-Plus software, version 8.0 (Insightful) or SAS software, version 9.1 (SAS Institute). Baseline characteristics and key safety outcomes were compared between the two study groups with the use of the chi-square test, Fisher's exact test, Wilcoxon rank-sum test, and the two-sample t-test.

Analyses of primary and secondary outcomes were performed with the use of time-to-event methods according to the intention-to-treat principle. Event rates are expressed as the percentage of events per follow-up year, taking into account the censoring of follow-up data. Kaplan–Meier estimates were used to calculate the proportion of participants who had an event during follow-up.

Occurrences of primary and secondary outcomes in the two study groups were compared with the use of hazard ratios and 95% confidence intervals. Two-sided P values were calculated with the use of likelihood-ratio tests from Cox proportional-hazards regression analyses. The Cox models contained a term representing study-group assignments plus terms accounting for the following prespecified stratifying variables: assignment to the intensive glucose-lowering intervention, each of the seven clinical-center networks, and the presence or absence of a previous cardiovascular event. Using the log of follow-up time as a time-dependent covariate, we found no evidence of important departures from the assumption of proportionality.[10] We examined the consistency of the intervention effect on the primary outcome among nine prespecified subgroups using statistical tests of interaction between the treatment effect and the subgroup within the Cox models.

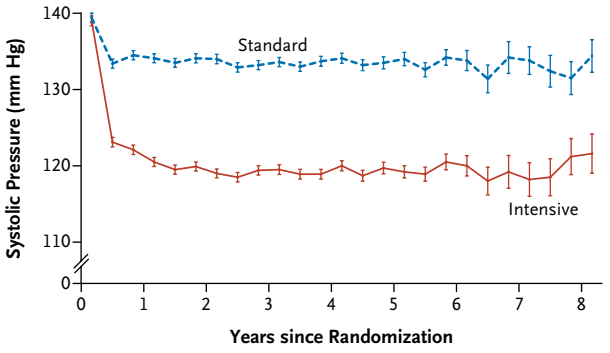
During the trial, an independent data and safety monitoring committee appointed by the NHLBI monitored the primary outcome (11 times) and total rate of death (7 times) with the use of O'Brien–Fleming boundaries determined by the Lan–DeMets approach. For these two outcomes, P values were adjusted to account for the number, timing, and results of interim analyses. All other P values for secondary outcomes and for subgroup analyses are nominal and have not been adjusted for multiple comparisons.

All analyses are based on observed data with the assumption that missing data were missing completely at random. For the longitudinal analysis of systolic blood pressure, a sensitivity analysis with the use of maximum-likelihood methods, under the assumption that the missing data were missing at random, is presented in Section 13 in Supplementary Appendix 1.

RESULTS

STUDY PARTICIPANTS

A total of 4733 participants were enrolled in the ACCORD BP trial. Of these, 2362 were randomly



Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3
No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201

Figure 1. Mean Systolic Blood-Pressure Levels at Each Study Visit.
I bars indicate 95% confidence intervals.

assigned to intensive blood-pressure control and 2371 were assigned to standard therapy. Baseline characteristics were generally similar between the two groups (Table 1). The mean age of the participants was 62.2 years; 47.7% were women and 33.7% had cardiovascular disease at baseline. The mean systolic and diastolic blood pressures of the participants at baseline were 139.2 mm Hg and 76.0 mm Hg, respectively.

At the end of the trial (June 2009), vital status was known for 95.1% of the randomly assigned participants. The mean duration of follow-up for the rate of death was 5.0 years, or 98.4% of the potential person-years of follow-up that would have been available if all surviving participants had been followed until the end of the trial. The mean duration of follow-up for the primary outcome was 4.7 years (94.8% of the potential follow-up). At the final follow-up visit, the rate of current smoking was 8.5% in the intensive-therapy group and 7.5% in the standard-therapy group (P=0.44).

BLOOD PRESSURE

The two therapeutic strategies quickly resulted in different systolic blood-pressure levels (Fig. 1). After the first year of therapy, the average systolic blood pressure at the 4-month protocol visits that both groups attended was 119.3 mm Hg (95% confidence interval [CI], 118.9 to 119.7) in the intensive-therapy group and 133.5 mm Hg (95% CI, 133.1 to 133.8) in the standard-therapy group, resulting in an average between-group difference of 14.2 mm Hg (95% CI, 13.7 to 14.7). The corresponding mean diastolic blood pressures were 64.4 (95% CI, 64.1 to 64.7) and 70.5 (95% CI, 70.2 to 70.8), for an average difference of 6.1 mm Hg (95% CI, 5.7 to 6.5) (Section 14 in Supplementary Appendix 1).

The lower blood pressure in the intensive-therapy group was associated with a greater exposure to drugs from every class (Fig. 1, and Section 11 in Supplementary Appendix 1). The mean number of medications after the first year was 3.4 (95% CI, 3.4 to 3.5) in the intensive-therapy group and 2.1 (95% CI, 2.1 to 2.2) in the standard-therapy group.

ADVERSE EVENTS

As compared with the standard-therapy group, the intensive-therapy group had significantly higher rates of serious adverse events attributed to antihypertensive treatment, as well as higher rates of hypokalemia and elevations in serum creatinine level (Table 2). The mean estimated glomerular filtration rates were significantly lower in the intensive-therapy group than in the standard-therapy group at the last visit. There were significantly more instances of an estimated glomerular filtration rate less than 30 ml per minute per 1.73 m^2 of body-surface area in the intensive-therapy group than in the standard-therapy group (99 vs. 52 events, P<0.001), although only 38 participants in the intensive-therapy group and 32 in the standard-therapy group had two or more instances of that rate (P=0.46). The frequency of macroalbuminuria at the final visit was significantly lower in the intensive-therapy group than in the standard-therapy group, and there was no between-group difference in the frequency of end-stage renal disease or the need for dialysis. In the random sample of 969 participants who were assessed for health-related quality of life, the frequency of symptoms of orthostatic hypotension was similar between the groups.

CLINICAL OUTCOMES

The primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes occurred in 445 participants. The rate was 1.87% per year in the intensive-therapy group as compared with 2.09%

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Table 2. Serious Adverse Events and Clinical Measures after Randomization.*

Variable	Intensive Therapy (N=2362)	Standard Therapy (N=2371)	P Value
Serious adverse events — no. (%)†			
Event attributed to blood-pressure medications	77 (3.3)	30 (1.27)	<0.001
Hypotension	17 (0.7)	1 (0.04)	<0.001
Syncope	12 (0.5)	5 (0.21)	0.10
Bradycardia or arrhythmia	12 (0.5)	3 (0.13)	0.02
Hyperkalemia	9 (0.4)	1 (0.04)	0.01
Angioedema	6 (0.3)	4 (0.17)	0.55
Renal failure	5 (0.2)	1 (0.04)	0.12
End-stage renal disease or need for dialysis	59 (2.5)	58 (2.4)	0.93
Symptoms affecting quality of life — no./total no. (%)‡			
Hives or swelling	44/501 (8.8)	41/468 (8.8)	1.00
Dizziness when standing	217/501 (44.3)	188/467 (40.3)	0.36
Adverse laboratory measures — no. (%)			
Potassium <3.2 mmol/liter	49 (2.1)	27 (1.1)	0.01
Potassium >5.9 mmol/liter	73 (3.1)	72 (3.0)	0.93
Elevation in serum creatinine			
>1.5 mg/dl in men	304 (12.9)	199 (8.4)	<0.001
>1.3 mg/dl in women	257 (10.9)	168 (7.1)	<0.001
Estimated GFR <30 ml/min/1.73 m^2	99 (4.2)	52 (2.2)	<0.001
Clinical measures§			
Glycated hemoglobin — %	7.6±1.3	7.5±1.2	0.13
Fasting plasma glucose — mg/dl	147.1±56.6	148.1±57.5	0.58
Plasma LDL cholesterol — mg/dl	98.7±40.3	96.8±37.8	0.10
Plasma HDL cholesterol — mg/dl	46.7±14.0	47.8±14.9	0.02
Plasma triglycerides — mg/dl			0.001
Median	138	131	
Interquartile range	97–210	92–197	
Potassium — mg/dl	4.3±0.5	4.4±0.5	0.17
Serum creatinine — mg/dl	1.1±0.4	1.0±0.5	<0.001
Estimated GFR — ml/min/1.73 m^2	74.8±25.0	80.6±24.8	<0.001
Ratio of urinary albumin (mg) to creatinine (g)			<0.001
Median	12.6	14.9	
Interquartile range	6.4–41.7	7.0–56.8	
Microalbuminuria — no./total no. (%)	656/2174 (30.2)	712/2205 (32.3)	0.13
Macroalbuminuria — no. /total no. (%)	143/2174 (6.6)	192/2205 (8.7)	0.009
Weight — kg	93.3±21.2	92.5±20.2	0.20

* Plus–minus values are means ±SD. To convert the values for glucose to millimoles per liter, multiply by 0.055551. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for potassium to millimoles per liter, multiply by 0.2558. To convert the values for creatinine to micromoles per liter, multiply by 88.4. GFR denotes glomerular filtration rate, HDL high-density lipoprotein, and LDL low-density lipoprotein.

† Serious adverse events are events that are life-threatening, cause permanent disability, or necessitate hospitalization (see Section 7 in Supplementary Appendix 1).

‡ Symptoms were assessed at 12, 36, and 48 months after randomization in a random sample of 969 participants who were assessed for health-related quality of life.

§ Data are from the last visit at which assessments were made for each participant.

Table 3. Primary and Secondary Outcomes.

Outcome	Intensive Therapy (N=2363)		Standard Therapy (N=2371)		Hazard Ratio (95% CI)	P Value
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03
Death						
From any cause	150	1.28	144	1.19	1.07 (0.85–1.35)	0.55
From cardiovascular cause	60	0.52	58	0.49	1.06 (0.74–1.52)	0.74
Primary outcome plus revascularization or nonfatal heart failure	521	5.10	551	5.31	0.95 (0.84–1.07)	0.40
Major coronary disease event†	253	2.31	270	2.41	0.94 (0.79–1.12)	0.50
Fatal or nonfatal heart failure	83	0.73	90	0.78	0.94 (0.70–1.26)	0.67

* The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.

† Major coronary disease events, as defined in the protocol, included fatal coronary events, nonfatal myocardial infarction, and unstable angina.

per year in the standard-therapy group, with no significant between-group difference (hazard ratio with intensive therapy, 0.88; 95% CI, 0.73 to 1.06; P=0.20) (Table 3 and Fig. 2).

There were 294 deaths from any cause and 118 deaths from cardiovascular causes (Table 3). Rates of death from any cause were 1.28% per year in the intensive-therapy group and 1.19% in the standard-therapy group (hazard ratio with intensive therapy, 1.07; 95% CI, 0.85 to 1.35; P=0.55). Rates of death from cardiovascular causes were 0.52% per year in the intensive-therapy group and 0.49% in the standard-therapy group (hazard ratio, 1.06; 95% CI, 0.74 to 1.52; P=0.74).

The two study groups did not differ significantly with respect to most of the other secondary outcomes. Nominally significant differences were seen in the rate of total stroke (0.32% per year in the intensive-therapy group vs. 0.53% per year in the standard-therapy group; hazard ratio, 0.59; 95% CI, 0.39 to 0.89; P=0.01) and in the rate of nonfatal stroke (0.30% per year in the intensive-therapy group vs. 0.47% per year in the standard-therapy group; hazard ratio, 0.63; 95% CI, 0.41 to 0.96; P=0.03). There were no significant interactions among prespecified subgroups (see Section 17 in Supplementary Appendix 1).

DISCUSSION

Intensive antihypertensive therapy in the ACCORD BP trial did not significantly reduce the primary cardiovascular outcome or the rate of death from any cause, despite the fact that there was a significant and sustained difference between the intensive-therapy group and the standard-therapy group in mean systolic blood pressure. There was also no significant benefit with respect to most of the secondary trial outcomes. At a significance level of less than 0.05, intensive blood-pressure management did reduce the rate of two closely correlated secondary outcomes — total stroke and nonfatal stroke. Assuming that this finding was real, the number needed to undergo intensive blood-pressure management to prevent one stroke over the course of 5 years was 89. These effects would be consistent with the findings of two meta-analyses of the effect of a reduction of 10 mm Hg in systolic blood pressure on the incidence of stroke[11,12]; the meta-analyses showed a

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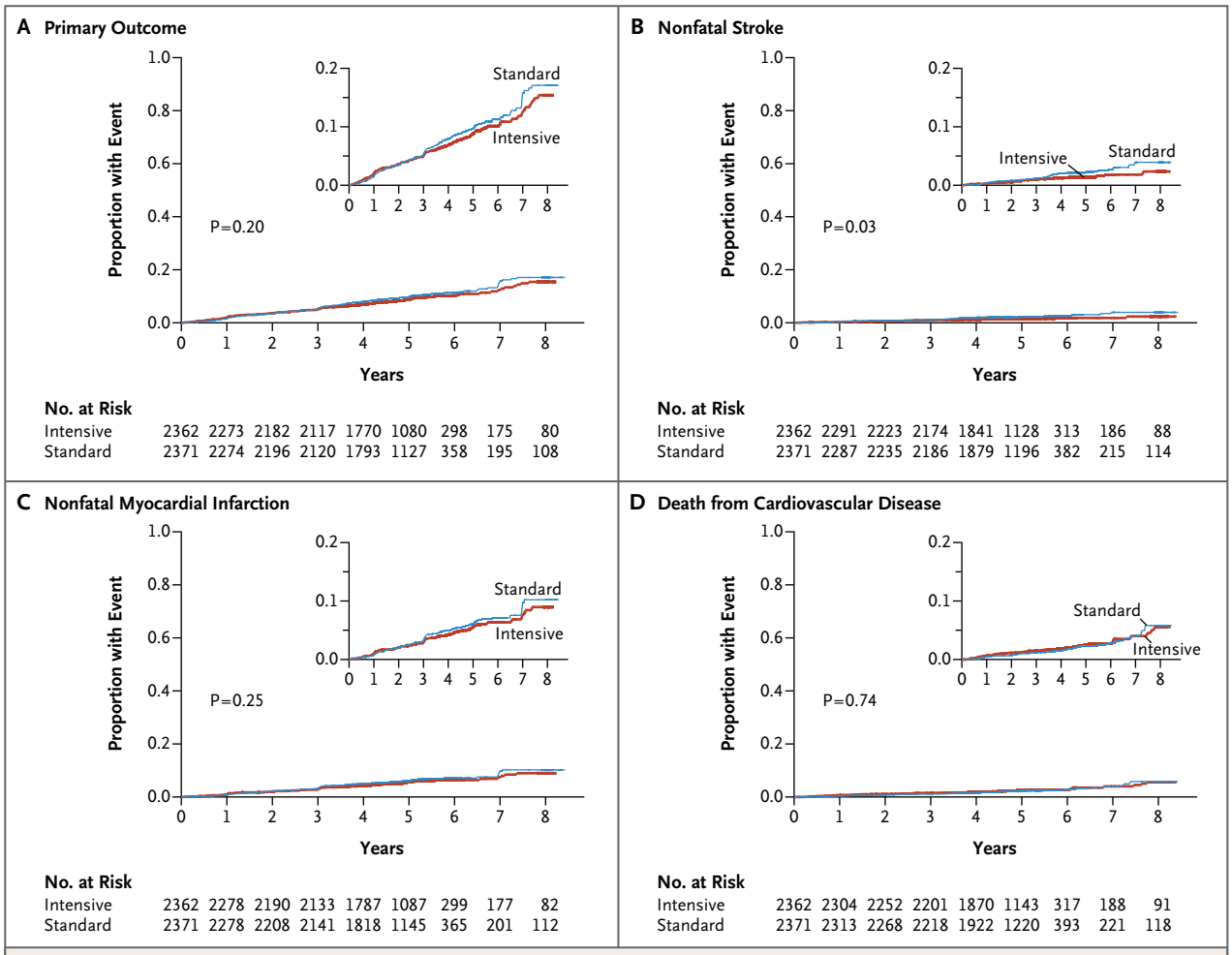

Figure 2. Kaplan–Meier Analyses of Selected Outcomes.

Shown are the proportions of patients with events for the primary composite outcome (Panel A) and for the individual components of the primary outcome (Panels B, C, and D). The insets show close-up versions of the graphs in each panel.

relative risk with blood-pressure reduction of 0.64 with the use of data from observational studies and of 0.59 with the use of data from drug-treatment trials.[12]

The interpretation of the ACCORD BP results is complicated by the fact that the event rate observed in the standard-therapy group was almost 50% lower than the expected rate. This result may have been a consequence of the frequent use of statins and of inclusion criteria that directed participants with dyslipidemia into the ACCORD lipid trial, leaving participants who were at lower risk in the blood-pressure trial.[5] The reduced power was reflected in the relatively wide confidence interval that does not exclude a 27% benefit for the primary end point.

There were some signals of possible harm associated with intensive blood-pressure control, including a rate of serious adverse events that was significantly higher in the intensive-therapy group than in the standard-therapy group. Both the estimated glomerular filtration rate and macroalbuminuria were reduced, but the implications of these changes on cardiovascular and renal outcomes are uncertain.

The United Kingdom Prospective Diabetes Study[13,14] and a post hoc subgroup analysis of the Hypertension Optimal Treatment (HOT) trial[15,16]

showed reductions in cardiovascular events with antihypertensive therapy among patients with type 2 diabetes mellitus, but the participants in their intensively treated groups had much higher mean systolic blood-pressure levels (144 mm Hg in both cases) than did the participants in either group of our trial. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial (ADVANCE; ClinicalTrials.gov number, NCT00145925),[17] active treatment with an angiotensin-converting–enzyme inhibitor and a thiazide-type diuretic reduced the rate of death but did not significantly reduce a composite macrovascular outcome. However, the ADVANCE trial had no specified blood-pressure goals, and the mean systolic blood pressure in the intensive group (135 mm Hg) was not as low as the mean systolic blood pressure even in the ACCORD standard-therapy group. It is possible that lowering systolic blood pressure from the mid-130s to approximately 120 mm Hg does not further reduce most cardiovascular events or the rate of death, and most of the benefit from lowering blood pressure is achieved by targeting a goal of less than 140 mm Hg. Alternatively, it is possible that 5 years is not long enough to see significant cardiac benefits from the normalization of systolic blood pressure among persons with diabetes who have good control of glycemia, especially when other effective treatments, such as statins and aspirin, are used frequently.

There are several limitations of the ACCORD BP trial. First, the trial had an open-label design, a design that was not likely to have affected blood-pressure goals or measurement or the blinded ascertainment of the outcomes but may have affected the reporting of adverse events; second, the rate of cardiovascular events was lower than the expected rate in the standard-therapy group; and third, patients younger than 40 years of age were not included in the study and patients older than 79 years of age were not included after the vanguard phase. In addition, although it was not the intent of this trial to test the blood-pressure goal of 130 mm Hg that was recommended in the JNC 7 (a recommendation that was made after the ACCORD trial was initiated), it would be difficult to argue that such a target would be better than a target of 140 mm Hg, since even a blood-pressure goal of 120 mm Hg did not confer benefit.

In conclusion, the ACCORD BP trial evaluated the effect of targeting a systolic blood pressure of 120 mm Hg, as compared with a goal of 140 mm Hg, among patients with type 2 diabetes at high risk for cardiovascular events. The results provide no evidence that the strategy of intensive blood-pressure control reduces the rate of a composite of major cardiovascular events in such patients.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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