RESEARCH DRIVING EVIDENCE BASED CLINICAL PRACTICE SYMPOSIUM 2011

Saturday 1st October 2011 @ Medical Sciences Lecture Theatre, University of Tasmania, Liverpool St, Hobart

START	FINISH	DURATION	SPEAKER	TITLE
08:00		30	Registration	
08:30	08:40	10	*Diane Lim*	Intravitreal Ranibizumab Treatment for Neovascular AMD in a Regional Clinical Setting.
08:40	08:50	10	*Steven van der Werf*	A Study on the Pre-operative Fasting Plasma Glucose levels and Glycated Haemoglobin and the Post-operative Outcome of Elective Surgery
08:50	09:10	20	*Alton Ma*	Pineal Germinoma Case Study
09:10	09:40	30	*James Sharman*	Blood Pressure: What are you measuring and why?
09:40	10:25	45	*Raymond Playford*	Mechanisms of Intestinal Repair & Growth Factors in Inflammatory Bowel Disease
10:25		25	Morning Coffee Break	
10:50	11:25	35	*Yahya Shehabi*	Use of Procalcitonin as a Biomarker of Infection and Sepsis
11:25	11:55	30	*Matthew Jose*	Towards a Better Understanding of Uraemic Molecules
11:55	12:25	30	*Phil Roberts-Thomson*	Debigatran in Atrial Fibrillation
12:25	13:05	40	*Joseph McConnell*	Cardiovascular Risk Profiling (Part 1)
13:05		50	Lunch	
13:55	14:35	40	*Joseph McConnell*	Cardiovascular Risk Profiling (Part 2)
14:35	14:45	10	*Michael Thompson*	A Primer on Epigenetics
14:45	15:15	30	*Kate Burbury*	Epigenetics – The Changing Landscape
15:15	15:55	40	*Kazu Kotani*	The Potential of Oxidised Lipoproteins as an Atherosclerolic Biomarker
15:55	16:35	40	*Hari Sharma*	Role of Angiogenesis in Airway Remodelling during Asthma and COPD
16:35		20	Afternoon Tea Break & Grand Final Update	
16:55	17:35	40	*Shanthi Kamatham*	Laboratory Physicians' Perspective Of Plasma Cell Dyscrasias – the Indian Scenario
17:35	18:15	40	*Swapan Sinha*	Hematological Aberrations in HIV/AIDs Patients in NE India
18:15	18:30	15	CLOSING REMARKS	

Check Website for Latest Details www.medlabstats.com/CME2011

SPEAKER PROFILES AND ABSTRACTS

Kate Burbury, Consultant Haematologist, Peter MacCallum Cancer Centre

Profile : Kate is a Tasmania graduate and completed her training and fellowship at John Radcliffe Hospital in the UK and Peter MacCallum Cancer Centre Melbourne, where she currently works as a Clinical Haematologist. She received her DPhil from Oxford University in 1999. She has a very active research and clinical program with an interest in epigenetics, the haemostatic dysfunction associated with malignancy, myeloproliferative disorders and flow cytometry in MDS – and is part of the European Leukaemia Network Flow Cytometry Working Party.

Topic : Epigenetics – The Changing Landscape

Epigenetics ("over or upon genetics") is one of the most promising and expanding fields in biomedical research, with implications in both normal and disease biology. It refers to the variability in gene expression, without underlying modification in the actual genetic sequence, but with these alterations being heritable through mitosis and potentially meiosis. This capacity for alteration in gene expression plays a fundamental role in normal development and differentiation, from conception to lineage commitment, as well as maintenance of tissue-specific gene expression patterns, biological and phenotypic diversity, and evolution. It offers an explanation for why genetic variations sometimes do not lead to phenotypic changes and equally why genes, without modification, can yield variable phenotypes. But more importantly the disruptions of epigenetic processes, through global dysregulation of gene function and expression profiles, are a hallmark of initiation and progression of cancer. Recent advancements in the rapidly evolving field of cancer epigenetics have shown extensive reprogramming of every component of the epigenetic machinery in cancer, including DNA methylation, histone modifications, nucleosome positioning and non-coding RNAs, specifically microRNA expression. The reversible nature of epigenetic aberrations has led to the emergence of the promising arena of epigenetic therapy. I will discuss the epigenetic landscape, various mechanisms of regulation and dysregulation, the progress in the field of cancer research, in terms of biomarkers of the disease and pharmacological strategies.

Matthew Jose, Professor of Medicine, University of Tasmania, Consultant Nephrologist, Royal Hobart Hospital

Profile : Matthew Jose qualified with FRACP as a renal physician in 1999 and awarded his doctorate (PhD) through Monash University in 2003 with a thesis titled "Macrophages in acute renal allograft dysfunction". He worked as a clinical nephrologist and physician-in-charge of transplantation at Monash Medical Centre, then was appointed Director of Renal Services for the Northern Territory and between 2004-2006 was responsible for the care of all people with kidney disease in the Northern Territory.
A change in career direction occurred in 2006 with a move to Hobart for family reasons where he was the Head of the Renal Unit at the Royal Hobart Hospital from 2007 to July 2011 and a member of the Menzies Research Institute Tasmania. In July 2011 he was appointed as Professor of Medicine at the University of Tasmania.

Current international standing:

- He is the current Honorary Executive Officer for the Australian and New Zealand Society of Nephrology (ANZSN)
- Member of council for the Australian and New Zealand Society of Nephrology (ANZSN),
- Member of the steering committee of the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA)
- Convener of the Indigenous working group of the Australian and New Zealand Dialysis and Transplant Registry
- Australian coordinator for the International Society of Nephrology Renal Disaster Relief Taskforce
- Subject editor for international journal *Nephrology*
- Member of the Kidney Health Australia Chronic Kidney Disease education committee (KCAT).

Previous: In 2009 he was chair of the local organising committee of the 41st annual scientific meeting of ANZSN, was the ANZSN representative to the 2nd International CKD summit and an Australian representative to the International Society of Nephrology education tour of Indonesia. In 2010 he was the ANZSN representative to the Australian Creatinine Consensus Committee. In January 2011 he was the Australian representative for the International Society of Nephrology / Cross-regional exchange and education visit to Yangon, Myanmar.

Topic : Towards a Better Understanding of Uraemic Molecules

Chronic kidney disease (CKD) affect nearly 2 million Australians causing premature death. The treatment for end stage kidney failure (ESKF) is around $70,000 per patient each year on dialysis and unfortunately, the number of patients is increasing each year.
Although improvements in dialysis procedure can improve the quality and quantity of life among the patients, still half of the patients die within 3 years while they are under modern dialysis treatment. The main reason which causes premature mortality is cardiovascular disease. There are some toxins which aren't removed even with modern dialysis procedure and those molecules contribute to cardiovascular disease.
Among all chromatographic methods developed for the recognition of uremic molecules, capillary electrophoresis (CE) is very suitable for analysis of highly polar and charged compounds (most of metabolites). As metabolites often don't have UV absorbance, hyphenation of CE with MS has provided a strong tool for their analysis and provides us higher sensitivity. In addition, MS can provide structural information of unknown metabolites. The other advantage of CE is small sample and organic solvent requirement.
In this work, some of our efforts towards developing a robust and reproducible CE-MS method for monitoring low-molecular weight metabolites in serum samples of some patients will be presented.

Dr. Shanthi Kamatham, Consultant Clinical Biochemist and Head of Department of Laboratory Medicine at CARE Hospital, Institute of Medical Sciences, Hyderabad, India,

Profile : Shanthi graduated from medical college in 1979. Her specialization was in Clinical Biochemistry at Madras Medical College and obtained MD in 1983.

Her experience in diagnostics is widely varied. Over the past 2 decades, has been involved in the diagnostic laboratories in Kidwai Memorial Institute of Oncology, Bangalore, a premier state government tertiary care hospital – Nizam's Institute of Medical Sciences, Hyderabad and at CARE Hospital since the past 9 years. Though a clinical biochemist has established and runs a haemostasis laboratory, which is looked on as referral laboratory in the state of Andhra Pradesh.

She has been awarded a number of citations towards her contribution to teaching and diagnostics.

She has been an active member of the clinical chemistry bodies of India especially the Association of Medical Biochemists of India and is a member of the Indian Society of Nephrology and Haematology. She is a member of the Technical Committee and a Lead Assessor of National Accreditation Board for Calibration and Testing Laboratories (NABL), India, for accreditation process to the standard ISO 15189:2007.

Topic : Laboratory Physicians' Perspective Of Plasma Cell Dyscrasias – the Indian Scenario

A plasma cell dyscrasias (monoclonal gammopathies) involves the laboratory in fields of hematology and biochemistry to clinch the diagnosis.

At our hospital, a tertiary referral centre, the maximum number of references are from nephrology and cardiology divisions followed by intensive care and neurology, the latter two being in the elderly age group. The median age in the referrals is 60 years and there is a male predominance. Over the past couple of years a younger age group between 40 to 50 years is presenting to the laboratory for a complete workup for plasma cell dyscrasias.

The initial laboratory evaluation is either serum protein electrophoresis or immunofixation electrophoresis and over the past 2 years serum light chain assay. Urine electrophoresis is mandatory when amyloidosis or free light chain disease is suspected. Non secretory tumours which do not show significant laboratory evaluation are subject for a trephine biopsy to yield tissue diagnosis with immunohistochemistry stains. Radiological evaluation also plays a major role in evaluation. The clinical presentations which we encounter are mainly renal impairment, anemia, electrolyte imbalance, hypercalcemia and cardiomyopathy. Monoclonal Gammopathy of Undetermined Significance is prominent in our records followed by IgG kappa and IgG lambda.

Though of late, serum light chain have been of prognostic and diagnostic significance, the belief that it can do away with electrophoresis and bone marrow studies is not very strong at this centre at present. A lot of assays have shown a ratio alteration but no tissue or radiological findings or electrophoresis have shown a monoclonal protein and hence these patients are subject to follow up at regular intervals. The belief in our centre is that serum protein electrophoresis, immunofixation electrophoresis, serum light chains and bone

marrow evaluation along with radiology should form an initial evaluation when ever plasma cell dyscrasias is thought of.

Kazuhiko Kotani, MD, PhD; Research head, Department of Clinical Laboratory Medicine, Jichi Medical University, Japan.

Profile : Kotani is one of the lead researchers about the measurements of oxidised lipoproteins in Japan. He was graduated from Jichi Medical University, which has a mission to improve the rural medicine in Japan, so he conducted the community medicine for postgraduate 10 years. He has also worked in lipid and metabolism clinics, and have learned basic and clinical science in Research Institute of Diabetes and Metabolic Disease, National Hospital Organization Kyoto Medical Centre (as a Visiting Director, Japan), and Tottori University (as a Lecturer, Japan), as well as Glycation, Oxidation and Disease Laboratory, Toro University-California, (as a Visiting Prof., USA). He has worked in Clinical Laboratory Medicine, Jichi Medical University, since 2008. To date, he has developed various oxidized lipoprotein markers, and shown the clinical significance of these markers. He was awarded several prizes on this topic (Japanese Society of Laboratory Medicine, Japan Society of Clinical Chemistry, American Association for Clinical Chemistry, etc.).

Topic : The Potential of Oxidised Lipoproteins as an Atherosclerolic Biomarker

Cardiovascular disease (CVD), one of the atherosclerotic diseases, occurs frequently and remains the most common cause of death in the world; therefore, a deeper understanding of the pathophysiology of CVD, more sensitive and easier measurements of CVD risks in the clinical settings, and better development of preventive strategies, are necessary in order to control the development of CVD. In addition to the quantitative levels of low-density lipoprotein (LDL) cholesterol, much attention has been drawn to the qualitative features of LDL particles as a risk factor for CVD. Whereas oxidative modification of LDL, a crucial step in atherogenesis, occurs in the arterial sub-intimal space and oxidized LDL (oxLDL) is observed chiefly in arterial lesions, it has also been shown to exist in the circulation, where it can become a surrogate marker of CVD. Serum amyloid A**-**LDL (SAA-LDL) complex is currently considered as a novel oxLDL marker. There have been prior reports using SAA-LDL measurements in patients with dyslipidemia, the metabolic syndrome and coronary artery disease. These reports have shown that there are higher circulating SAA-LDL levels in the aforementioned disease status and that a reduction in the levels can be achieved by intervention treatments including lifestyle modifications and drugs such as highly purified eicosapentaenoic acid. Data also suggest a prognostic value of SAA-LDL on cardiac events in patients with coronary artery disease. We will summarize the current data that indicates the usefulness of SAA-LDL measurements as a potential biomarker for CVD. If possible, we will talk about the other new types of oxidized lipoprotein markers.

Alton Ma, Senior Radiation Therapist, Holman Clinic, Hobart

Topic : Pineal Germinoma Case Study

Purpose:

This presentation aims to share knowledge on radiation treatment planning and delivery using intensity modulated radiation therapy (IMRT) for a patient with a pineal germinoma. This tumour has incidence of 0.4%-3.4% of all intra-cranial tumours and is rarely seen in an adult.

Methodology:

This patient was planned for IMRT using Philips Pinnacle^3 (Version 8.0m) treatment planning system with direct machine parameter optimization (DMPO). The treatment plan consisted of two phases, nine 6MV fields for phase I and five 6MV fields for phase II with 13 and 12 increments respectively, treating 1.80Gy per increment in both phases.

The patient was treated with Varian Clinac iX with On-Board Imaging (OBI) version 1.4. The current departmental imaging protocol is daily kV imaging (2D/2D).

Result/Discussion:

Though the shape of target volume in Phase I was very irregular, 9-field IMRT was capable of shaping the isodose to conform to the CTV and limiting doses to critical structures as per table below:

The evenly spaced 9 fields beam arrangement resulted in a very homogeneous target dose distribution whilst minimizing dose to hair follicles (maximum dose 20.6Gy). The patient was reviewed at least weekly by a radiation oncologist/registrar. Mild headache, tiredness and loss of appetite were side effects reported by the patient. The patient experienced some alopecia.

Conclusion:

This case has proven that IMRT is capable of generating very conformal dosimetry while minimizing dose to adjacent tissues.

Alternate beam arrangements might be considered such as non-coplanar technique which may further lower the doses to the critical structures.
Though the maximum dose of hair follicle was low in this plan, the patient still experienced some hair loss. The dose tolerance of hair follicles is questionable.

Joseph McConnell, Laboratory Director, Chief Medical Officer, and Co-founder of Health Diagnostic Laboratory (HDL) Inc., in Richmond Virginia.

Profile : Dr. McConnell is currently the Laboratory Director, Chief Medical Officer, and Co-founder of Health Diagnostic Laboratory (HDL) Inc., in Richmond Virginia. Health Diagnostic Laboratory is a national clinical reference laboratory committed to personalized disease management with focus on identifying and reversing the health risks associated with cardiovascular diseases, diabetes, metabolic syndrome and fatty liver disease.

Until November of 2009, Dr. McConnell was an assistant professor in the Department of Laboratory Medicine at Mayo Clinic. In that role he served for 12 years as the Director of Cardiovascular Laboratory Medicine, and was the Chair of the Clinical Chemistry Fellowship Program at Mayo. He also held a joint appointment in the Cardiovascular Diseases Section of the Division of Internal Medicine. Dr. McConnell graduated high school *Magna Cum Laude*, received his Bachelors degree in Biology (with honors) from the University of Michigan in 1987, and completed Medical Technology training and certification (MT: ASCP) in 1988. Dr. McConnell received his M.S. degree in Chemistry and Ph.D. degree in Clinical Chemistry from Cleveland State University in 1990 and 1993 respectively. Dr. McConnell participated in the Clinical Chemistry Postdoctoral Training Program at Mayo Clinic from 1993 to 1995 and upon completion joined the faculty at Indiana University School of Medicine, where he served as associate director of the Special Coagulation Laboratory at Indiana University Medical Center. He was recruited back to the Mayo Clinic in 1998 to serve as Director of Cardiovascular Laboratory Medicine. He was on the faculty of the Mayo Graduate School of Medicine until November of 2009 when he left Mayo to establish Health Diagnostic Laboratory, Inc. in Richmond Virginia.

Dr. McConnell has been active in the American Association for Clinical Chemistry (AACC), participating as Chair of the Lipoproteins and Vascular Diseases Division in 2006 and 2007 and as past chair in 2008 and 2009. He has been a delegate to the Midwest section for 4 years and served as the Chair for the AACC House of Delegates in 2009. He has also participated as a member of several other AACC committees.

Dr. McConnell's primary research interest is in the field of atherosclerosis, specifically the use of novel risk factors to identify individuals at increased risk for developing cardiovascular disease and events, with a focus on prevention. Dr. McConnell has co-authored more than 80 manuscripts in the peer-reviewed scientific literature.

Topic : Cardiovascular Risk Profiling

Prof. Raymond Playford, Dean of the Faculty of Health Science, University of Tasmania.

Profile : Ray has recently joined UTas as Dean of the Faculty of Health Science. He was previously Vice Principal for NHS liaison and external relations at Queen Mary University of London in addition to being Professor of Medicine at Barts and the London Hospital. His previous roles include being Head of Gastroenterology Section at Imperial College London and also formally Professor of Gastroenterology, University of Leicester, UK 1996-2000. He was awarded the British Society of Gastroenterology Sir Francis Avery Jones Research Medal 1995 and has also been a member of BSG Council. His main clinical interests are Berrett's oesophagus, peptic ulceration and inflammatory bowel disease. Main research interests are importance of growth factors in gut health and disease and the use of bioactive natural products to prevent and treat gut injury.

Topic : Mechanisms of Intestinal Repair & Growth Factors in Inflammatory Bowel Disease

Peptide growth factors are a fascinating group of molecules with diverse effects. Recent developments have allowed us to gain much greater into their pathophysiological functions. In addition, the development of recombinant peptide technology, monoclonal antibody production and artificial small molecule receptor agonists and inhibitors now allows us to use these factors for the treatment of multiple conditions including gastrointestinal malignancy (particularly colonic carcinoma) , short bowel syndrome (where factors such as growth hormone, EGF and glucagon like peptide 2 show particular promise), and inflammatory bowel disease. This presentation provides a broad overview of where research in this area is heading and the pitfalls that need to be considered

Dr Phil Roberts-Thomson, Director of Cardiology, Royal Hobart Hospital.

Profile : Phil is a staff specialist in cardiology at the Royal Hobart Hospital. He is a graduate of the University of Tasmania and trained in cardiology in Adelaide before completing a PhD at Flinders University. He undertook further research and clinical training at the University of Iowa before returning to Hobart in 1999 to a conjoint appointment with the Royal Hobart Hospital, the University of Tasmania and the newly collocated Hobart Private Hospital. He is an interventional cardiologist and has been involved in clinical research that has included studies on AF, acute and chronic coronary artery disease, and heart failure.

Topic : Dabigatran in Atrial Fibrillation

Atrial Fibrillation (AF) is a frequent and often challenging problem for clinicians and their patients. The symptoms of AF are highly variable and consequently management needs to be individualised according to the patient's symptoms and comorbidities. AF has an adverse prognosis which is largely related to the presence of specific comorbidities, many of which contribute to the aetiology of AF. Thromboembolic complications of AF, in particular stroke, are a major part of the adverse prognosis of AF; and are a stochastic effect. Risk calculators for stroke complicating AF are in common use. Anticoagulant strategies can reduce the risk of stroke but inevitably carry a risk of bleeding. Bleeding complications in turn are a random event, the risk of which can be estimated. Several of the risk factors for stroke in AF are also risk factors for bleeding. Large studies provide information to guide the use and effectiveness of stoke prevention in AF with aspirin and warfarin. Alternative oral agents are now available for anticoagulation in AF, and have been studied in large clinical trials. Dabigatran is the first of these to become available in Australia. It is also the first agent to show superior effectiveness over warfarin in a trial of stroke prevention in AF. Aspects of the drug and its use will be discussed.

Dr Hari S. Sharma, PhD, DSc, Institute for Cardiovascular Research, VUMC, University Medical Centre, Amsterdam, The Netherlands

Profile : Hari Shankar Sharma, born at Kunwerpur in India obtained High School diploma in 1974 (with Distinction) and further studied Biological Sciences at A.M. University, Aligarh and obtained BSc (with Honours) and MSc in Biochemistry (with First Division). In 1980, he then joined V.P. Chest Institute, Delhi University and received MPhil and PhD degrees in Biochemistry. After a short working experience as a Biochemist at the Armed Forces Transfusion Centre, Delhi, he moved to Germany in 1985 to the prestigious Max-Planck Institute (MPI) for Biophysical Chemistry, Göttingen as a Post Doctoral fellow. In 1988, he accepted a junior group leader position at the MPI for Experimental Cardiology in Bad Nauheim where he worked for 5 years prior to move to the Netherlands in 1993 as a faculty at the Erasmus University Medical Centre, Rotterdam and established a research group on Cardiopulmonary Molecular Biology. Currently, he is the senior staff member at the Free University Medical Centre, Amsterdam. He is a visiting Professor to the Leuven University, Belgium and CSM Medical University, Lucknow, India. In 2005, he has been awarded DSc degree for his work on 'Angiogenesis and Tissue Remodeling in the Heart and Lung Diseases'. Dr. Sharma's area of research include: 'Role of growth factors/cytokines/vasoactive agents (FGF, PDGF, TGF ß, ET-1, ANG-II, VEGF, IL-1ß, serotonin etç in the pathogenesis of cardio-pulmonary diseases. Dr. Sharma has obtained a number of research grants, published 136 papers and cloned several genes including porcine VEGF and FGF-1. He has teaching experience of more than 20 years for Molecular and Cell Biology, Pharmacology and Laboratory Techniques to medical/Master/PhD students. He has supervised 10 MD/MSc and 9 PhD students for their theses. He has organized 17 international conferences/symposia and delivered 168 invited lectures worldwide. Dr. Sharma has been bestowed with numerous awards/medals including young Investigator Award of the International Society of Hypertension, Distinguished Service Award of Heart Care Foundation of India, Medal of Merit of the International Academy of Cardiovascular Sciences and Masters of Indo-European Intervention Council. Dr. Sharma serves as editor, editorial board member and referee for many reputed journals and funding agencies. He is a member of several Indian, European and International scientific societies.

Topic: Role of Angiogenesis in Airway Remodelling during Asthma and COPD

Chronic lung diseases, such as asthma and COPD are associated with airway remodeling, caused by epithelial shedding, airway smooth muscle (ASM) hyperplasia and hypertrophy and vascular changes. We have shown that different growth factors and cytokines result in differential gene expression and secretion of various proinflammatory cytokines and vascular endothelial growth factor (VEGF), an angiogenic molecule in cultured human ASM cells. To assess the role of airway smooth muscle (ASM) in bronchial angiogenesis and remodeling, we investigated the production of VEGF in ASM cells in relation to mediators of asthma, such as,

IL-1β, TNF-α, TGF-β, ANG II and ET-1. Time dependent release of VEGF protein in the conditioned medium was observed which in its turn induced proliferation and growth of pulmonary artery endothelial cells. We further investigated the effects of nitric oxide (NO) pathway on the pro-inflammatory cytokine; Interleukin-1β (IL-1β) induced expression and secretion of VEGF and PlGF from cultured porcine airway smooth muscle cells (PASMC). PASMC cultures were generated by enzymatic digestion of bronchial smooth muscle and maintained in DMEM. Serum deprived (for 48h) PASMC were stimulated with IL-1β (5 ng/ml), IL-1β + N^{w}-nitro-L-arginine methyl ester (L-NAME, 2 mM), IL-1β + L-arginine (10 mM) and IL-1β + L-NAME + L-arginine for 4 and 24 h. NO synthase inhibitor (L-NAME) was used 1h prior to IL-1β incubation in all experiments. IL-1β induced expression (1.8 fold vs control) of VEGF mRNA (quantitative RT-PCR) was attenuated by L-NAME (1.1 fold vs serum deprived control cells) and augmented by L-arginine (3.8 fold vs control) at 4h. L-NAME inhibited the secretion of VEGF (1208 vs 723 pg/ml) and PlGF (25 vs 5 pg/ml) (assessed by ELISA) in conditioned media of IL-1β treated PASMC at 4 and 24 h, respectively. Treatment of PASMC with IL-1β and L-arginine resulted in further increase in VEGF (1816 vs 783 pg/ml) but not of PlGF in conditioned media. By restoring NO pathway (L-arginine treatment) in L-NAME treated cells led to elevated (2.2 fold) expression of VEGF.

In another set of experiments, we employed cyclical strain using a Flexer Strain Unit (0.5 seconds stretch and 0.5 seconds relaxation; frequency 1Hz) to the human ASMC cultured on a collagen coated BioFlex plates. Protein profile using cytokine antibody arrays revealed enhanced stretch induced release of direct/indirect angiogenic molecules; vascular endothelial growth factor (VEGF), Angiogenin, interleukin (IL)-6 and IL-8 (2-5 fold) from cultured HASM cells. VEGF secretion, assessed by ELISA, was significantly higher after 8h ($p<0.02$) and 24h ($p<0.001$) as compared to controls. Western blot analysis showed robust phosphorylation of ERK1/2 after 15 min and Akt; P-Thr-Akt ($p<0.001$) and P-Ser-Akt ($p<0.004$) after 30 min of cyclical stretch. Respective blockers for Akt, ERK1/2 and Rho pathways revealed significant inhibition of VEGF release only with ERK1/2 inhibitor, U0261 after 8 h. Furthermore, cyclical stretch induced significant release of IL-6 ($p<0.05$) and IL-8 ($p<0.01$) after 24 h, which was blocked by inhibitors of ERK1/2 and RhoA/ROCK pathways at 8h.

Taken together, our findings suggest that a cytokine cascade involving mainly IL-6, IL-8 and VEGF operates in hyper contractile human ASM cells where NO pathway may modulate VEGF signaling during airway inflammation and subsequently contributing to bronchial angiogenesis and airway remodeling in patients with asthma and COPD.

James Sharman, Senior Research Fellow and Head, Blood Pressure Research Group, Menzies Research Institute Tasmania.

Profile : Jim completed his undergraduate and Honours degree at the University of Tasmania. His PhD was at The University of Queensland, with most studies conducted at the Wales Heart Research Institute, Cardiff, UK. He holds an NH&MRC Biomedical Career Development Award to investigate the clinical application of arterial pressure waveform analysis and has published >70 research papers in the field of blood pressure.

Topic : Blood Pressure : What are you measuring and why ?

The most common method to assess blood pressure is with inflation of a cuff at the upper arm. This method was introduced more than 100 years ago and is used to diagnose hypertension and determine the effect of therapy. Blood pressure values acquired by this method are used to indicate the pressure load experienced by the organs. However, recent evidence does not support this assumption, and the consequences of this may include inappropriate assessment of risk related to blood pressure. The aim of this presentation is to provide a detailed explanation of the pitfalls and problems, as well as the underlying physiology, associated with measuring arm cuff blood pressure. New methods to assess blood pressure control will also be presented.

Assoc Prof. Yahya Shehabi, Associate Professor, School of Medicine, University New South Wales, Medical Director, Acute Complex and Community Care Clinical Services Program and Director Intensive Care Services & Research, Prince of Wales Hospital, Sydney.

Profile : Yahya graduated in 1979 with his MBBS from the University of Jordan In 1988 he was awarded Fellowship from the Australian and New Zealand College of Anaesthesia and became a Fellow of the Faculty of Intensive Care in 1989. He is Foundation Fellow of the recently formed College of Intensive Care Medicine. He has an Executive Masters of Business Administration from the University of Technology Sydney (2003)

and a Graduate Diploma of the Australian Institute of Company Directors (2007). He is currently the Chairman of the Intensive Care Foundation of ANZ.

Topic : Use of Procalcitonin as a Biomarker of Infection and Sepsis

Systemic infections and sepsis are a leading cause of mortality in critically ill intensive care patients worldwide. Whilst it is essential that antibiotics are started early in this patient population, the indiscriminate and inappropriate lengthy use of antibiotics is unwarranted. Antimicrobials are one of the most common types of drugs prescribed for patients admitted intensive care. The daily defined dose (DDD) of antimicrobials in the Western Intensive Care population in 2008 – 2009 was 1650 DDD per 1000 occupied bed days much higher than that in hospital words. Beside the cost associated with the use of antimicrobials and the potential for patients to develop side effects due to their use, there is also a particular concern that widespread antibiotic use is contributing to the emergence of higher levels of antibiotic resistance and hospital acquired infections.

Clinicians are used to the conventional indicators of bacterial infection and sepsis to decide when to start and when to stop antibiotic therapy. Conventional biomarkers, such as white cell count, C-reactive protein (CRP) and systemic inflammatory response are very unhelpful. More targeted biomarkers like Tumour Necrosis Factor (TNF) and the Interleukins, IL6 and IL10, are neither independently sensitive nor specific for diagnosing infection.

Procalcitonin (PCT) has recently been utilized as a biomarker for bacterial infections and sepsis. PCT has fast kinetics and can be measured as soon as 2 hours after the onset of infection, has a half-life of 20-24 hours and highly stable in serum or plasma in vivo, and therefore daily blood sampling is adequate. It has a very high negative predictive value and reasonable positive predictive value.

Recently a number of studies have looked at the utilization of PCT measurements to guide antibiotic therapy compared with conventionally guided antibiotic therapy. These studies show that the patients randomized to have PCT guided therapy had less chance of being prescribed antibiotics, received antibiotics for a shorter time with shorter ICU stay and a reduced cost of care compared to those who received conventionally guided antibiotic therapy with no increased risk for adverse outcomes.

While a randomized controlled studies are currently underway in Europe and Australasia evaluating the efficacy of PCT in reducing antibiotic usage in ICU. A PCT guided decision making algorithm may improve the accuracy and appropriateness of antibiotic prescribing which may lead to a potential reduction in inappropriate antibiotic usage, and possible reduction in hospital acquired infections (HAI) including multi-resistant micro organisms (MRO's). It could also be of significant cost benefit.

Swapan Sinha, Calcutta Medical College, University of Calcutta.

Profile : Professor and Head Dept of Pathology since 1995. Chairman of PG Council for Pathology, Assessor Medical Council of India since 2004, Assessor of National Accrediatation Board for Laboratories since 2006. Member selection board for recruitment of Professors/Assoc Professors & Consultants in Pathology since 1999
Chaired and delivered CME lectures on atleast 100 scientific conferences, published more than 65 papers in indexed journal, written six chapters in four books on Medical Sciences; taken more than 80 PG(MD) examinations in Pathology; giuded/coguided/adjudicated more than 250 thesis. Worked as Consultant Haematologist at PMGH, PNG and Gabourne State General Hospital Gabourne and attended Hemophilia Conference at Goldcoast Australia in Oct, 1995 and received training in coagulation disorders at RBH Brisbane under J Rowell in Oct, 1995 .Awarded Fellow in Pathology at AFMC Pune in 2004 and Fellow Ind Soc of Hematology and TM at JIPMER 2008.

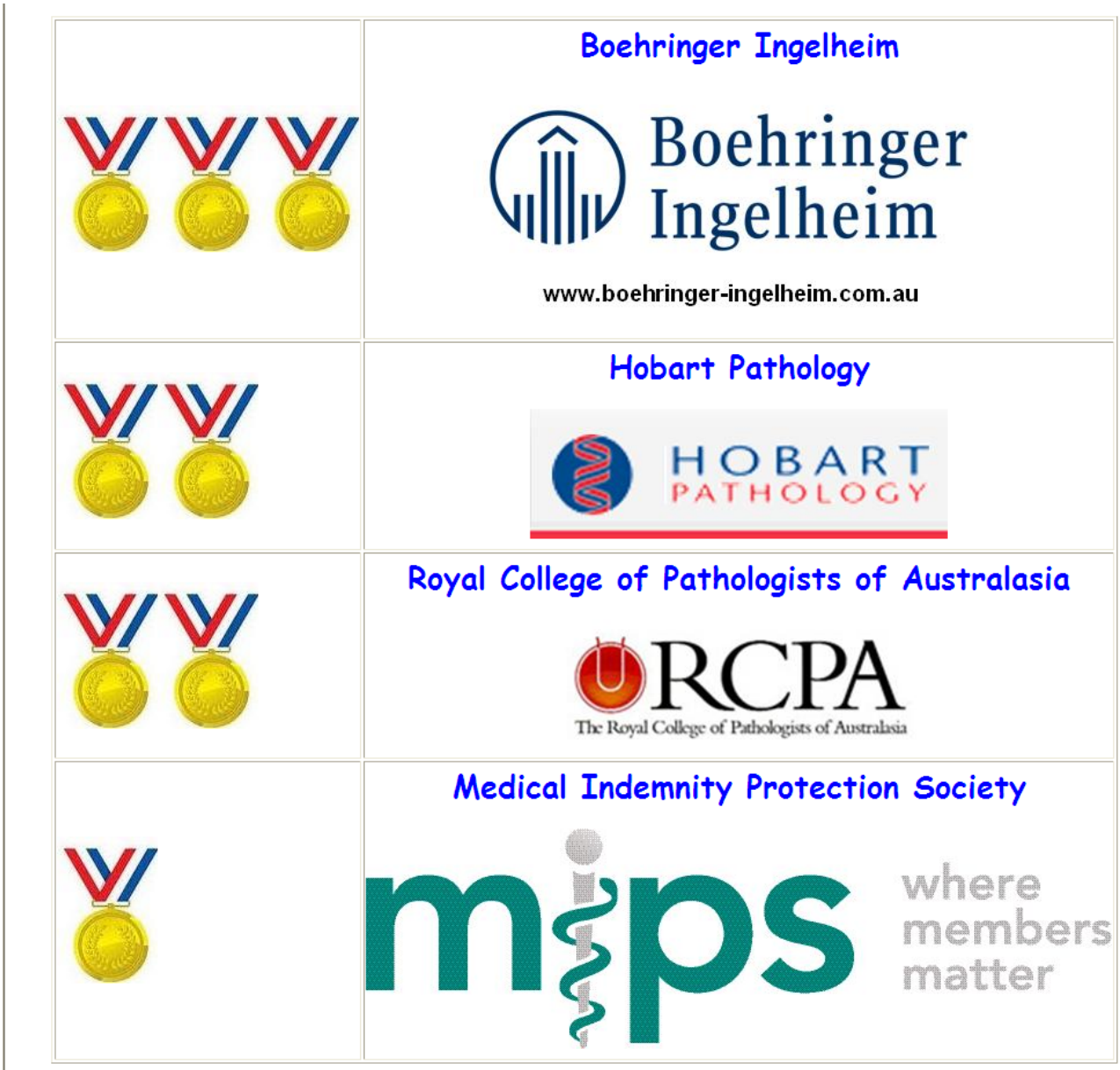
Topic : Hematological Aberrations in HIV/AIDs Patients in NE India

Haematological aberrations are quite common in HIV/AIDS patients. Primary marrow failure, Cytomegalovirus infection, B19 parvo virus, deranged iron metabolism, B12 deficiency, haemolysis may lead to anaemia. Neutropenia is relatively common in HIV infection. Lymphocytopenia due to enhanced apoptosis of CD4 and CD8 cells. Thrombocytopenia may be due decreased survival, immune destruction, and primary marrow failure. HIV infected endothelial cells may lead to thrombotic thrombocytopenic purpura.

117 HIV seropositive patients were subjected to haematological evaluation at ART Centre, N.B.Medical Collage, Darjeeling. 106 (90.6%) fulfilled CDC criterion of AIDS. Age ranged from 3-64 yrs; 75 males and 42 females. Their clinical, radiological and serological status of HBV, HCV, VDRL, Mantoux test, CD4 count was collected. EDTA samples were taken for haemogram, Reticulocyte% and ESR.

The results showed anemia in 47(43.9%), Leukocytopenia in 14 (13.1%), Thrombocytopenia in 8(7.5%), Pancytopenia in 3(2.8%), Neutropenia in 3 (2.8%), Eosinophilia in 10(8.5%) and raised ESR in 95(81.2%).

Anaemia (Hb<10gms/dl), Neutropenia (ANC<1,000/cu/.mm), Thrombocytopenia (50,000/cu.mm.) are poor prognostic parameter.



STUDENT PRESENTATIONS

Diane Lim

Profile : Diane is a final year medical student at the University of Tasmania. She is based at the Launceston Clinical School, where she has been actively carrying out research on age-related macular degeneration under the supervision of Clinical A/Prof Brendan Vote.

Topic : Intravitreal Ranibizumab Treatment for Neovascular AMD in a Regional Clinical Setting.

Michael Thompson

Profile : Michael is 4th Year Medical Student.

Topic : A Primer on Epigenetics

The study of genetics is revolutionising medical care, with targeted molecular therapies and use of genetic tests to determine an individual's predisposition to disease becoming increasingly prevalent. Genetic research

involves investigation of how changes in the DNA sequence, or genotype, affect gene expression and cell fate. Recently parallel field of research, epigenetics, has emerged as a vital determinant of cell phenotype and cellular fate. Epigenetics, literally “above genetics,” is the study of how hereditable, non-genetic alterations may bring about changes in gene expression. Such phenotype changes without a correspond genotypic modification are fundamental to the development of multicellular organisms, where every hepatocyte and neuron share a common genetic code, yet are each specialised to a specific function. Following development epigenetic modifications continue to play a fundamental role in human health with well recognised involvement in the process of carcinogenesis. Furthermore, medications targeted against epigenetic modifications have proven value as chemotherapeutic agents. This introductory level presentation will cover the basic mechanisms of epigenetic modification, their relevance to human disease and clinical application.

Steven van der Werf

Topic : A Study on the Pre-operative Fasting Plasma Glucose levels and Glycated Haemoglobin and the Post-operative Outcome of Elective Surgery

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 10, 2008 VOL. 358 NO. 15

Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events

The ONTARGET Investigators*

ABSTRACT

BACKGROUND

In patients who have vascular disease or high-risk diabetes without heart failure, angiotensin-converting–enzyme (ACE) inhibitors reduce mortality and morbidity from cardiovascular causes, but the role of angiotensin-receptor blockers (ARBs) in such patients is unknown. We compared the ACE inhibitor ramipril, the ARB telmisartan, and the combination of the two drugs in patients with vascular disease or high-risk diabetes.

METHODS

After a 3-week, single-blind run-in period, patients underwent double-blind randomization, with 8576 assigned to receive 10 mg of ramipril per day, 8542 assigned to receive 80 mg of telmisartan per day, and 8502 assigned to receive both drugs (combination therapy). The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

RESULTS

Mean blood pressure was lower in both the telmisartan group (a 0.9/0.6 mm Hg greater reduction) and the combination-therapy group (a 2.4/1.4 mm Hg greater reduction) than in the ramipril group. At a median follow-up of 56 months, the primary outcome had occurred in 1412 patients in the ramipril group (16.5%), as compared with 1423 patients in the telmisartan group (16.7%; relative risk, 1.01; 95% confidence interval [CI], 0.94 to 1.09). As compared with the ramipril group, the telmisartan group had lower rates of cough (1.1% vs. 4.2%, P<0.001) and angioedema (0.1% vs. 0.3%, P=0.01) and a higher rate of hypotensive symptoms (2.6% vs. 1.7%, P<0.001); the rate of syncope was the same in the two groups (0.2%). In the combination-therapy group, the primary outcome occurred in 1386 patients (16.3%; relative risk, 0.99; 95% CI, 0.92 to 1.07); as compared with the ramipril group, there was an increased risk of hypotensive symptoms (4.8% vs. 1.7%, P<0.001), syncope (0.3% vs. 0.2%, P=0.03), and renal dysfunction (13.5% vs. 10.2%, P<0.001).

CONCLUSIONS

Telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefit. (ClinicalTrials.gov number, NCT00153101.)

The members of the writing committee (Salim Yusuf, D.Phil., Koon K. Teo, Ph.D., Janice Pogue, M.Sc., Leanne Dyal, M.Sc., and Ingrid Copland, Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada; Helmut Schumacher, Ph.D., Boehringer Ingelheim, Ingelheim, Germany; Gilles Dagenais, M.D., Laval University Heart and Lung Institute, Laval Hospital, Quebec, QC, Canada; Peter Sleight, D.M., Oxford University, Oxford, United Kingdom; and Craig Anderson, Ph.D., George Institute for International Health, University of Sydney, Sydney) assume responsibility for the overall content and integrity of the article. Address reprint requests to Dr. Yusuf at the Population Health Research Institute, Hamilton Health Sciences and McMaster University, 237 Barton St. East, Hamilton, ON L8L 2X2, Canada, or at yusufs@mcmaster.ca.

*The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) investigators are listed in the Appendix.

This article (10.1056/NEJMoa0801317) was published at www.nejm.org on March 31, 2008.

N Engl J Med 2008;358:1547-59.

RANDOMIZED, CONTROLLED TRIALS involving about 150,000 patients have convincingly demonstrated that angiotensin-converting–enzyme (ACE) inhibitors reduce rates of death, myocardial infarction, stroke, and heart failure among patients with heart failure,[1] left ventricular dysfunction,[2-4] previous vascular disease alone,[5-7] or high-risk diabetes.[8] ACE inhibitors do not block the production of all angiotensin II, so direct receptor blockade might be more effective. ACE inhibitors reduce bradykinin degradation, which enhances vasodilatation, but increase the rates of angioedema and cough. In patients with heart failure, angiotensin II levels may increase and symptoms worsen, despite the use of ACE inhibitors.[9] The use of an angiotensin-receptor blocker (ARB), as compared with placebo, reduced the rate of death or hospitalization for heart failure in patients with a low ejection fraction and heart failure who either could not tolerate an ACE inhibitor[10] or were already receiving one.[11,12] As compared with beta-blockers, ARBs also reduced vascular events in high-risk patients with hypertension and left ventricular hypertrophy.[13] Nevertheless, in other high-risk populations, the role of ARBs as an alternative or in addition to ACE inhibitors to prevent cardiovascular outcomes is not known.

We evaluated whether the ARB telmisartan was not inferior to the ACE inhibitor ramipril and whether a combination of the two drugs was superior to ramipril alone as a treatment to prevent vascular events in high-risk patients who had cardiovascular disease or diabetes mellitus but did not have heart failure. We used a dose of ramipril that had previously been shown to be effective for this outcome.

METHODS

STUDY DESIGN

The design of the study has been described previously.[14] We enrolled patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage. Patients who could not tolerate ACE inhibitors were randomly assigned to receive either telmisartan or placebo in a parallel trial.[14] Detailed eligibility criteria have also been described previously[14] (for details, see the Supplementary Appendix, available with the full text of this article at www.nejm.org). The primary objectives of our study were to determine the effectiveness of 80 mg of telmisartan daily, as compared with 10 mg of ramipril daily. If the noninferiority of telmisartan was demonstrated, we would test the superiority of telmisartan over ramipril. We would also determine whether the combination of the two drugs was more effective than ramipril alone in reducing the composite outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

The main secondary outcome was a composite of death from cardiovascular causes, myocardial infarction, or stroke, which was the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial.[5] Other secondary outcomes were new heart failure, diabetes mellitus, atrial fibrillation, dementia or cognitive decline, nephropathy, and revascularization procedures. Other outcomes were death from any cause or from noncardiovascular causes, angina, transient ischemic attack, development of left ventricular hypertrophy, microvascular complications of diabetes, changes in blood pressure or in the ankle-to-arm ratio of blood pressure, and new cancers.

National coordinators and clinical monitors supervised the recruitment of patients at 733 centers in 40 countries. The trial was coordinated and data were gathered and analyzed by the Population Health Research Institute at McMaster University and Hamilton Health Sciences, with coordinating suboffices at Oxford University and the University of Auckland. The steering committee designed and oversaw the trial. An operations committee, with representatives from the three coordinating centers and the sponsor (Boehringer Ingelheim), met regularly to evaluate progress.

All main study outcomes (death according to any cause, myocardial infarction, stroke, and hospitalization for heart failure) were adjudicated by a central committee whose members were unaware of study-group assignments, with the use of standard criteria.[14] All serious adverse events were reviewed by an independent data and safety monitoring board.

The initial draft of the manuscript was written by Dr. Yusuf and the writing committee, who vouch for the data, with input from the steering committee. The protocol was approved by regulatory authorities and the ethics review committee at each participating institution.

RUN-IN PERIOD AND RANDOMIZATION

After written informed consent was obtained, patients entered a single-blind run-in period in which

they received 2.5 mg of ramipril once daily for 3 days, followed by 40 mg of telmisartan and 2.5 mg of ramipril once daily for 7 days and then 5 mg of ramipril plus 40 mg of telmisartan for 11 to 18 days. Of the 29,019 patients who entered the run-in period, 3399 (11.7%) were excluded from the study: 1123 (3.9%) had poor compliance, 597 (2.1%) withdrew from the study, 492 (1.7%) had symptomatic hypotension, 223 (0.8%) had an elevated potassium level, 64 (0.2%) had an elevated creatinine level, 872 (3.0%) had other reasons for exclusion, and 27 (0.1%) died.

A total of 25,620 patients underwent randomization and were stratified according to site with the use of permuted blocks through a central automated telephone service. For the first 2 weeks after randomization, 8542 patients were assigned to receive 80 mg of telmisartan once daily, 8576 were assigned to receive 5 mg of ramipril once daily, and 8502 were assigned to receive a combination of the two drugs (combination therapy). After 2 weeks, the dose of ramipril was increased to 10 mg per day. Follow-up visits occurred at 6 weeks, at 6 months, and then every 6 months until the last scheduled visit.

INTERIM ANALYSIS AND DATA MONITORING

An independent data and safety monitoring board of cardiologists, statisticians, and clinical-trial experts met twice yearly; three formal interim analyses were conducted when 25%, 50%, and 75% of the events accrued. A modified Haybittle–Peto approach[15] guided decisions (i.e., a boundary of 4 SD in the first half of the trial and 3 SD in the second half for efficacy; for safety, if boundaries of 3 SD and 2 SD, respectively, were crossed in a second analysis 4 to 6 months later, it would trigger consideration of stopping).

STATISTICAL ANALYSIS

The number of patients was based on the rate of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure associated with ramipril in the HOPE trial, in which the Kaplan–Meier estimate for the primary outcome was 0.0397 per year. A determination of noninferiority required a hazard ratio for telmisartan as compared with ramipril that was below a predefined margin, with most of ramipril's effect, as compared with placebo, retained by telmisartan.

The margin was determined by the results of the HOPE trial, in which the hazard ratio with 10 mg of ramipril, as compared with placebo, was 0.775 for a composite outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure; this was similar to the hazard ratios in other studies comparing ACE inhibitors with placebo.[6,7] We chose the 40th percentile (0.794) as a more robust reference to describe the effect of ramipril. The relative risk was translated into an excess risk for placebo as compared with ramipril of 1.26. Thus, a margin of 1.13 ensured that telmisartan retained at least half the effect of ramipril, if the upper limit of the one-sided 97.5% confidence interval for the hazard ratio was less than this value. We also evaluated whether the combination of telmisartan plus ramipril was superior to ramipril alone.

We tested both hypotheses using group sequential tests with a one-sided type I error of 0.025, with three planned interim analyses. If one of the two comparisons did not reject the null hypothesis, the other comparison needed an alpha of 0.0125. The original planned sample size of 7800 patients who were followed for a mean of 4.5 years provided a power of 93% for the superiority hypothesis, if the hazard ratio was 0.87. For noninferiority, the expected power was 89%, for a hazard ratio of 1.00.

The primary analysis used a time-to-event approach, counting the first occurrence of any component of the composite outcome, and included all randomized patients. All reported P values (other than for noninferiority) are two-sided. Consistency of treatment effects in prespecified subgroups was explored by the Cox regression model, with tests for interaction.[16,17] We performed a sensitivity analysis according to the protocol by censoring data from patients who took the study drugs for less than 50% of the study period.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Characteristics of the 25,620 patients who underwent randomization were similar in the three study groups (Table 1); 27% were women, 85% had cardiovascular disease, 69% had hypertension, and 38% had diabetes. A high proportion of patients had previously received proven therapies: statins (61.6% at baseline, increasing to 70.6% by the end of the study), antiplatelet therapy (80.9% and 77.5%, respectively), beta-blockers (56.9% and 56.9%), and diuretics (28.0% and 32.5%).

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)
Age — yr	66.4±7.2	66.4±7.1	66.5±7.3
Blood pressure — mm Hg†	141.8±17.4/82.1±10.4	141.7±17.2/82.1±10.4	141.9±17.6/82.1±10.4
Heart rate — beats/min	67.9±12.2	68.0±12.3	67.7±12.2
Body-mass index‡	28.1±4.5	28.1±4.6	28.0±4.5
Cholesterol — mmol/liter			
Total	4.9±1.1	4.9±1.1	5.0±1.2
LDL	2.9±1.0	2.9±1.0	2.9±1.0
HDL	1.3±0.4	1.3±0.4	1.3±0.4
Triglycerides — mmol/liter	1.7±1.1	1.7±1.l	1.7±1.1
Glucose — mmol/liter	6.7±2.6	6.7±2.5	6.7±2.6
Creatinine — μmol/liter	93.5±22.8	93.8±22.8	93.8±22.8
Potassium — mmol/liter	4.4±0.4	4.4±0.4	4.4±0.5
Female sex — no. (%)	2331 (27.2)	2250 (26.3)	2250 (26.5)
Ethnic group — no. (%)§			
Asian	1182 (13.8)	1172 (13.7)	1167 (13.7)
Arab	102 (1.2)	106 (1.2)	106 (1.2)
African	206 (2.4)	215 (2.5)	208 (2.4)
European	6273 (73.1)	6213 (72.7)	6222 (73.2)
Native or aboriginal	747 (8.7)	756 (8.9)	728 (8.6)
Other ethnic group	64 (0.7)	77 (0.9)	69 (0.8)
Missing data	2 (<0.1)	3 (<0.1)	2 (<0.1)
Clinical history — no. (%)			
Coronary artery disease	6382 (74.4)	6367 (74.5)	6353 (74.7)
Myocardial infarction	4146 (48.3)	4214 (49.3)	4189 (49.3)
Angina pectoris			
Stable	3039 (35.4)	2958 (34.6)	2960 (34.8)
Unstable	1257 (14.7)	1296 (15.2)	1264 (14.9)
Stroke or transient ischemic attacks	1805 (21.0)	1758 (20.6)	1779 (20.9)
Peripheral artery disease	1136 (13.2)	1161 (13.6)	1171 (13.8)
Hypertension	5918 (69.0)	5862 (68.6)	5827 (68.5)
Diabetes	3146 (36.7)	3246 (38.0)	3220 (37.9)
Left ventricular hypertrophy	1085 (12.7)	1120 (13.1)	1082 (12.7)
Microalbuminuria¶	929 (13.1)	923 (13.2)	929 (13.3)
Previous procedures — no. (%)			
Coronary-artery bypass grafting	1862 (21.7)	1920 (22.5)	1893 (22.3)
Percutaneous transluminal coronary angioplasty	2527 (29.5)	2476 (29.0)	2434 (28.6)
Smoking status — no. (%)			
Current smoker	1062 (12.4)	1062 (12.4)	1101 (12.9)
Past smoker	4463 (52.0)	4468 (52.3)	4345 (51.1)

Table 1. (Continued.)

Characteristic	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)
Medication — no. (%)			
Statin	5234 (61.0)	5294 (62.0)	5255 (61.8)
Beta-blocker	4847 (56.5)	4860 (56.9)	4876 (57.4)
Aspirin	6473 (75.5)	6469 (75.7)	6461 (76.0)
Clopidogrel or ticlopidine	927 (10.8)	966 (11.3)	931 (11.0)
Antiplatelet agent	6903 (80.5)	6926 (81.1)	6898 (81.1)
Diuretic	2454 (28.6)	2359 (27.6)	2351 (27.7)
Calcium-channel blocker	2821 (32.9)	2787 (32.6)	2864 (33.7)

* Plus–minus values are means ±SD. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.
† A total of 13,386 patients had a systolic blood pressure of more than 140 mm Hg.
‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Ethnic group was self-reported.
¶ The percentage is based on 21,074 patients who underwent baseline urinary analysis: 7073 patients in the ramipril group, 7013 patients in the telmisartan group, and 6988 patients in the combination-therapy group.

FOLLOW-UP AND ADHERENCE

A total of 25,577 patients (99.8%) were followed until a primary event occurred or until the end of the study (median, 56 months). Among patients in the ramipril group, 92.2% were taking an ACE inhibitor and 1.0% were taking an ARB at 1 year, with respective proportions of 89.4% and 1.8% at 2 years, 87.5% and 2.0% at 3 years, 86.6% and 2.4% at 4 years, and 84.7% and 3.3% at the end of the study. Among patients in the telmisartan group, 93.9% were taking an ARB and 2.6% were taking an ACE inhibitor at 1 year, with respective proportions of 91.2% and 4.2% at 2 years, 89.3% and 4.6% at 3 years, 87.7% and 5.0% at 4 years, and 85.6% and 6.4% at the end of the study. Among patients in the combination-therapy group, 85.5% received both drugs, 2.8% received an ACE inhibitor only, and 3.5% received an ARB only at 1 year; the respective proportions were 81.5%, 4.2%, and 4.8% at 2 years; 78.7%, 4.5%, and 5.4% at 3 years; 76.8%, 4.7%, and 5.7% at 4 years; and 73.6%, 6.0%, and 6.4% at the end of the study.

The proportion of patients receiving the full dose of ramipril at 2 years was 81.7% in the ramipril group and 75.3% in the combination-therapy group. The proportion of patients receiving the full dose of telmisartan at 2 years was 88.6% in the telmisartan group and 84.3% in the combination-therapy group. The study drug was discontinued by 2029 patients (23.7%) in the ramipril group and 1796 (21.0%) in the telmisartan group. In the combination-therapy group, 1929 patients (22.7%) discontinued both drugs, and an additional 566 (6.7%) stopped taking one drug.

The most important reasons for permanent discontinuation of a study drug are summarized in Table 2. More patients discontinued ramipril (either as monotherapy or with telmisartan) because of cough or angioedema than discontinued telmisartan alone. In the combination-therapy group, an increased number of patients stopped taking a study drug because of hypotensive symptoms, syncope, diarrhea, or renal impairment, as compared with the ramipril groups.

BLOOD PRESSURE, POTASSIUM, AND CREATININE

Before the run-in period, the mean blood pressure was 141.8/82.1 mm Hg. At 6 weeks, the mean blood pressure was reduced by 6.4/4.3 mm Hg in the ramipril group, by 7.4/5.0 mm Hg in the telmisartan group, and by 9.8/6.3 mm Hg in the combination-therapy group. Patients in the telmisartan group and the combination-therapy group continued to have slightly lower blood-pressure levels throughout the study period (average reductions, 0.9/0.6 mm Hg and 2.4/1.4 mm Hg, respectively) than did patients in the ramipril group. The numbers of patients who had a doubling of the creatinine level were similar in the three groups (159 in the ramipril group, 170 in the telmisartan group, and 180 in the combination-therapy group). The numbers of patients who had an increase in the potassium level of more than 5.5 mmol per liter were similar in the ramipril group (283 pa-

Table 2. Discontinuation of Study Medications and Selected Reasons for Permanent Discontinuation.*

Variable	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)	Telmisartan vs. Ramipril		Combination Therapy vs. Ramipril	
				Relative Risk	P Value	Relative Risk	P Value
		number (percent)					
Total no. of discontinuations†	2099 (24.5)	1962 (23.0)	2495 (29.3)	0.94	0.02	1.20	<0.001
Reason for permanent discontinuation							
Hypotensive symptoms	149 (1.7)	229 (2.7)	406 (4.8)	1.54	<0.001	2.75	<0.001
Syncope	15 (0.2)	19 (0.2)	29 (0.3)	1.27	0.49	1.95	0.03
Cough	360 (4.2)	93 (1.1)	392 (4.6)	0.26	<0.001	1.10	0.19
Diarrhea	12 (0.1)	19 (0.2)	39 (0.5)	1.59	0.20	3.28	<0.001
Angioedema	25 (0.3)	10 (0.1)	18 (0.2)	0.4	0.01	0.73	0.30
Renal impairment	60 (0.7)	68 (0.8)	94 (1.1)	1.14	0.46	1.58	<0.001

* There were no predefined criteria for each of the adverse events listed. Reasons listed are those provided by the investigator for the discontinuation of study drug.

† A patient could have multiple discontinuations, since patients were encouraged to restart study medications whenever possible after discontinuation.

tients) and the telmisartan group (287 patients), but the number was significantly higher in the combination-therapy group (480 patients, P<0.001 for the comparison between the combination-therapy group and the ramipril group).

PRIMARY OUTCOMES AND DEATH

The primary outcome occurred in 1412 patients (16.5%) in the ramipril group, in 1423 patients (16.7%) in the telmisartan group, and in 1386 patients (16.3%) in the combination-therapy group (Fig. 1 and 2 and Table 3). The upper boundary of the confidence interval (1.09) for the relative risk of the primary outcome in the telmisartan group as compared with the ramipril group was significantly lower than the predefined noninferiority boundary of 1.13 (P=0.004). However, the lower boundary of the confidence interval (0.94) indicates that telmisartan was not superior to ramipril. The secondary outcome — death from cardiovascular causes, myocardial infarction, or stroke — occurred in 1210 patients (14.1%) in the ramipril group and in 1190 patients (13.9%) in the telmisartan group (relative risk, 0.99; 95% confidence interval [CI], 0.91 to 1.07; P=0.001 for noninferiority). The results were consistent for all components of the primary outcome. Combination therapy was not significantly better than ramipril alone (relative risk, 0.99; 95% CI, 0.92 to 1.07). Adjustments for the small differences in blood pressure did not materially alter the results for the primary outcome (relative risk for telmisartan vs. ramipril, 1.02; 95% CI, 0.95 to 1.10; relative risk for combination therapy vs. ramipril, 1.00; 95% CI, 0.93 to 1.07).

There was no significant difference in the total number of deaths between the ramipril group and the telmisartan group (1014 deaths and 989 deaths, respectively; relative risk in the telmisartan group, 0.98; 95% CI, 0.90 to 1.07); the number of deaths was higher in the combination-therapy group than in the ramipril group (1065 deaths vs. 1014 deaths; relative risk in the combination-therapy group, 1.07; 95% CI, 0.98 to 1.16), but the difference was not siginificant. Analyses of the cause of death did not indicate significant differences with respect to any particular cause (data not shown).

SECONDARY AND OTHER OUTCOMES

There were no significant differences in the rates of secondary outcomes (Table 4), except for renal dysfunction, which occurred in 871 patients (10.2%) in the ramipril group, 906 patients (10.6%) in the telmisartan group, and 1148 patients (13.5%) in the combination-therapy group. As compared with the ramipril group, the telmisartan group had a similar relative risk of renal impairment (1.04), whereas the combination-therapy group had a significant increase in the relative risk (1.33,

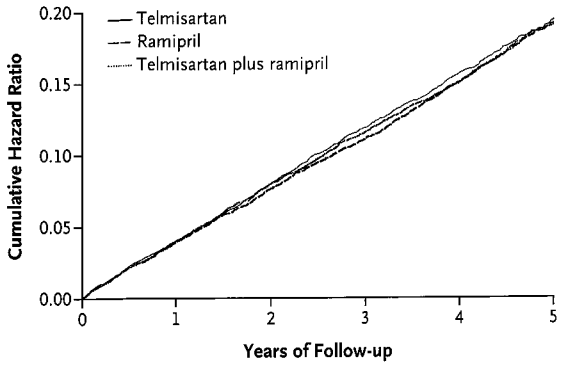
P<0.001). The rate of renal dialysis was the same in the ramipril group and the telmisartan group, with 48 patients (0.6%) and 52 patients (0.6%), respectively, undergoing dialysis, whereas the rate was increased in the combination-therapy group, with 65 patients (0.8%) undergoing dialysis (P=0.10 for the comparison with the ramipril group).

SUBGROUP ANALYSES

Comparisons of key subgroups showed similar results between the ramipril group and the telmisartan group (Fig. 3A) and between the ramipril group and the combination-therapy group (Fig. 3B). The results for both comparisons were also consistent in analyses that were adjusted for the patients' use of various concomitant drugs (e.g., statins, antiplatelet agents, beta-blockers, diuretics, and calcium-channel blockers) (data not shown).

PER-PROTOCOL ANALYSIS

For the primary outcome with telmisartan as compared with ramipril, the per-protocol analysis showed a relative risk of 1.00 (95% CI, 0.92 to 1.09; P=0.006 for noninferiority). Analyses comparing combination therapy with ramipril showed results similar to those of the intention-to-treat analysis (relative risk, 0.98; 95% CI, 0.90 to 1.07).



No. at Risk						
Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan plus ramipril	8502	8133	7738	7375	7022	1718

Figure 1. Kaplan–Meier Curves for the Primary Outcome in the Three Study Groups.

The composite primary outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

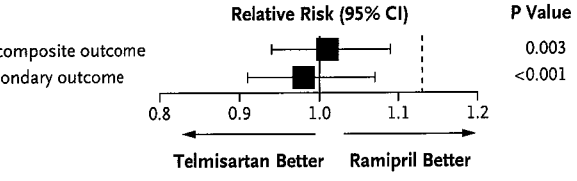


Figure 2. Relative Risk of the Primary Outcome and of the Main Secondary Outcome.

The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. The main secondary outcome was death from cardiovascular causes, myocardial infarction, or stroke, which was used as the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial.[5] The P value is for the comparison with the noninferiority margins.

DISCUSSION

ACE inhibitors have been convincingly shown to reduce rates of death, myocardial infarction, stroke, heart failure, and revascularization among patients with previous cardiovascular disease and high-risk diabetes. Therefore, to provide clinically relevant information, trials evaluating ARBs in these patients must include proven doses of an ACE inhibitor, either as background therapy or as a comparator.

In our study, we evaluated both approaches in a population similar to the one studied in the HOPE trial. Telmisartan was clearly not inferior to ramipril for both the prespecified primary outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure and for the primary outcome in the HOPE trial (death from cardiovascular causes, myocardial infarction, or stroke). Similarities in the telmisartan group and the ramipril group in the proportions of patients who had heart failure, underwent revascularization, or had renal dysfunction (outcomes that were reduced by ramipril in the HOPE trial) and the high rates of adherence to both drug regimens provided additional confidence in establishing the noninferiority of telmisartan. As compared with the ramipril group, the telmisartan group had significantly fewer episodes of cough or angioedema, but this benefit was partially offset by higher rates of hypotensive symptoms (but not syncope). Higher rates of hypotension-related symptoms are consistent with the slightly lower blood-pressure levels associated with telmisartan, although the lower levels did not lead to further benefit. The

Table 3. Incidence of the Primary Outcome, Its Components, and Death from Any Cause.

Outcome	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)	Telmisartan vs. Ramipril	Combination Therapy vs. Ramipril
	number (percent)			*risk ratio (95% CI)*	
Death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure*	1412 (16.5)	1423 (16.7)	1386 (16.3)	1.01 (0.94–1.09)	0.99 (0.92–1.07)
Death from cardiovascular causes, myocardial infarction, or stroke†	1210 (14.1)	1190 (13.9)	1200 (14.1)	0.99 (0.91–1.07)	1.00 (0.93–1.09)
Myocardial infarction‡	413 (4.8)	440 (5.2)	438 (5.2)	1.07 (0.94–1.22)	1.08 (0.94–1.23)
Stroke‡	405 (4.7)	369 (4.3)	373 (4.4)	0.91 (0.79–1.05)	0.93 (0.81–1.07)
Hospitalization for heart failure‡	354 (4.1)	394 (4.6)	332 (3.9)	1.12 (0.97–1.29)	0.95 (0.82–1.10)
Death from cardiovascular causes	603 (7.0)	598 (7.0)	620 (7.3)	1.00 (0.89–1.12)	1.04 (0.93–1.17)
Death from noncardiovascular causes	411 (4.8)	391 (4.6)	445 (5.2)	0.96 (0.83–1.10)	1.10 (0.96–1.26)
Death from any cause	1014 (11.8)	989 (11.6)	1065 (12.5)	0.98 (0.90–1.07)	1.07 (0.98–1.16)

* Patients could have multiple events in this category. The numbers of events were 2058 (24.0%) in the ramipril group, 2042 (23.9%) in the telmisartan group, and 2000 (23.5%) in the combination-therapy group. The differences were not significant (P=0.83 for telmisartan vs. ramipril, and P=0.38 for combination therapy vs. ramipril).
† This composite was the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial.[5]
‡ Patients could have multiple events in this category. The category includes both fatal and nonfatal events.

Table 4. Secondary and Other Outcomes.

Outcome	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)	Telmisartan vs. Ramipril	Combination Therapy vs. Ramipril
	number (percent)			*relative risk (95% CI)*	
Revascularization	1269 (14.8)	1290 (15.1)	1303 (15.3)	1.03 (0.95–1.11)	1.04 (0.97–1.13)
Hospitalization for angina	925 (10.8)	954 (11.2)	952 (11.2)	1.04 (0.95–1.14)	1.04 (0.95–1.14)
Worsening or new angina	567 (6.6)	536 (6.3)	538 (6.3)	0.95 (0.84–1.07)	0.96 (0.85–1.08)
New diagnosis of diabetes*	366 (6.7)	399 (7.5)	323 (6.1)	1.12 (0.97–1.29)	0.91 (0.78–1.06)
Any heart failure	514 (6.0)	537 (6.3)	478 (5.6)	1.05 (0.93–1.19)	0.94 (0.83–1.07)
New atrial fibrillation†	570 (6.9)	550 (6.7)	537 (6.5)	0.97 (0.86–1.09)	0.96 (0.85–1.07)
Renal impairment‡	871 (10.2)	906 (10.6)	1148 (13.5)	1.04 (0.96–1.14)	1.33 (1.22–1.44)§
Renal failure requiring dialysis	48 (0.6)	52 (0.6)	65 (0.8)	1.09 (0.74–1.61)	1.37 (0.94–1.98)

* The numbers of patients included in this analysis were 5427 in the ramipril group, 5294 in the telmisartan group, and 5280 in the combination-therapy group.
† This category includes only patients who did not have atrial fibrillation at baseline: 8296 in the ramipril group, 8259 in the telmisartan group, and 8218 in the combination-therapy group.
‡ No specific definitions were used. A determination of renal impairment was based on the clinical investigator's report of an event that led to the discontinuation of a study drug.
§ P<0.001.

benefits of ARBs are being evaluated in three other placebo-controlled trials that are expected to be completed in 2008.[14,18,19]

Our results parallel the findings of the Valsartan in Acute Myocardial Infarction Trial (VALIANT),[20] which established the noninferiority of valsartan, as compared with captopril, in patients with left ventricular dysfunction or heart failure after myocardial infarction. The upper boundaries of the confidence intervals and the noninferiority margins were almost identical in the two studies, even though they enrolled different patient populations. The side effects in our study were similar to those in the VALIANT study,

which showed lower rates of cough and angioedema in the valsartan group than in the captopril group but higher rates of hypotension-related symptoms. There were more dose reductions (but not discontinuations) because of renal complications in the valsartan group than in the captopril group, an association that was not observed in our study.

In order to establish noninferiority, a rigorous trial design is required that includes a patient population similar to that in the reference trial, a similar drug regimen, high adherence rates, outcomes that the comparator is known to affect, and high statistical power to exclude clinically important differences. All these criteria were satisfied in our study. The entry criteria for our study and the event rates in the ramipril group were similar to those in the HOPE trial, with high follow-up rates in both trials. Moreover, the adherence rate was higher in the ramipril group (89.4% at 2 years and 84.7% at the end of the study among patients receiving either ramipril or an open-label ACE inhibitor) than that in the HOPE trial (85.0% and 78.8%, respectively). A sensitivity analysis that was restricted to patients who adhered to their allocated drug regimen for more than 50% of the study period showed the consistency of our results and confirmed the robustness of noninferiority.

In our study, we confirmed the statistical noninferiority of telmisartan, as compared with ramipril, since the upper boundary of the 97.5% confidence interval (1.09) was lower than the predefined margin of 1.13 for both the primary outcome ($P=0.004$) and the primary outcome used in the HOPE trial ($P=0.001$). Telmisartan preserved about 95% (95% CI, 83.2 to 106.3) of the benefits of ramipril over placebo with respect to the primary outcome and preserved 105% (95% CI, 91.6 to 119.0) of the benefits with respect to the outcome of death from cardiovascular causes, myocardial infarction, or stroke that were observed in the HOPE trial. Use of the method of Hasselblad and Kong[21] to impute effects of telmisartan versus placebo (based on the benefits of ramipril over placebo in the HOPE trial) indicates a relative risk of 0.79 (95% CI, 0.70 to 0.89) for the primary outcome. The number of patients who discontinued therapy was significantly smaller in the telmisartan group than in the ramipril group, although the absolute difference in the discontinuation rate was modest, because we used an active run-in phase that selected patients for randomization only if they tolerated both medications. After randomization, we vigorously reinforced adherence and encouraged patients who stopped medications to restart them. In clinical practice, the rates of discontinuation might be higher.

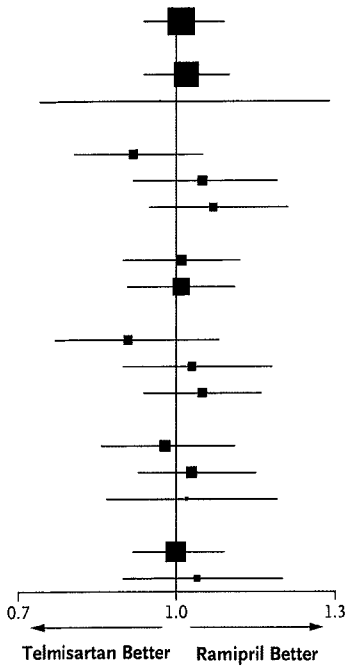
We also evaluated whether the combination of telmisartan and ramipril (with both drugs targeted to the full dose) would be superior to ramipril alone. Surprisingly, despite a reduction in systolic blood pressure of 2 to 3 mm Hg in the combination-therapy group, as compared with the ramipril group — a decrease that should have translated into a risk reduction of 4 to 5% — no significant benefit was seen in the primary outcome among patients receiving the two-drug therapy. However, combination therapy significantly increased the risk of hypotension, syncope, renal dysfunction, and hyperkalemia, with a trend toward an increased risk of renal dysfunction requiring dialysis. These results are similar to the analysis of the combined effects of an ARB and an ACE inhibitor, as compared with an ACE inhibitor alone, in four previous trials.[22] Therefore, even though combination therapy had a larger biologic effect (as suggested by greater blood-pressure lowering and changes in potassium), dual blockade did not produce any additional clinical benefit in this population.

In this regard, our results are also similar to those of the VALIANT study, in which the combination of a full dose of captopril plus valsartan (the latter at a dose of 80 mg per day, which was lower than the 160 mg per day used in the valsartan-only group) did not significantly reduce the occurrence of the primary outcome but did increase hypotension.[20] Taken together, these two studies showed no additive effect for an ARB in conjunction with a full dose of a proven ACE inhibitor.

However, our findings contrast with those of two other studies. In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study,[12] which involved patients who had symptomatic heart failure and had been hospitalized in the previous 6 months, candesartan, when added to existing therapy with any ACE inhibitor used at variable doses (with less than half the patients receiving full doses), was superior to placebo in reducing death or hospitalization for heart failure. Similarly, a reduction

A

Subgroup	No. of Patients	Incidence of Primary Outcome in Ramipril Group (%)	P Value for Interaction
Primary composite	17,118	16.5	
Cardiovascular disease			0.79
Yes	15,627	16.8	
No	1,486	13.1	
Systolic blood pressure			0.10
≤134 mm Hg	5,704	16.2	
>134 to ≤150 mm Hg	6,042	14.9	
>150 mm Hg	5,352	18.4	
Diabetes			0.97
Yes	6,391	20.7	
No	10,722	14.0	
HOPE risk score			0.21
≤3.677	5,751	10.1	
>3.677 to ≤4.090	5,620	15.0	
>4.090	5,747	24.4	
Age			0.65
<65 yr	7,319	13.0	
≥65 to <75 yr	7,310	17.3	
≥75 yr	2,489	24.2	
Sex			0.68
Male	12,537	16.7	
Female	4,581	15.8	



B

Subgroup	No. of Patients	Incidence of Primary Outcome in Ramipril Group (%)	P Value for Interaction
Primary composite	17,078	16.5	
Cardiovascular disease			0.82
Yes	15,589	16.8	
No	1,484	13.1	
Systolic blood pressure			0.64
≤134 mm Hg	5,714	16.2	
>134 to ≤150 mm Hg	6,019	14.9	
>150 mm Hg	5,329	18.4	
Diabetes			0.15
Yes	6,365	20.7	
No	10,708	14.0	
HOPE risk score			0.97
≤3.677	5,676	10.1	
>3.677 to ≤4.090	5,570	15.0	
>4.090	5,832	24.4	
Age			0.75
<65 yr	7,362	13.0	
≥65 to <75 yr	7,177	17.3	
≥75 yr	2,539	24.2	
Sex			0.82
Male	12,497	16.7	
Female	4,581	15.8	

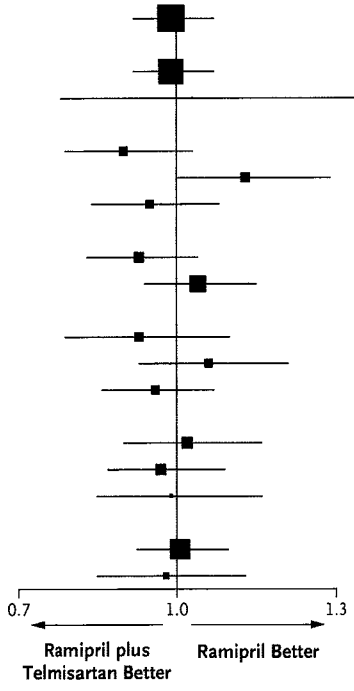


Figure 3 (facing page). Relative Risks in Prespecified Subgroups.

Shown are the comparisons between the telmisartan group and the ramipril group (Panel A) and between the combination-therapy (telmisartan plus ramipril) group and the ramipril group (Panel B). The risk score from the Heart Outcomes Prevention Evaluation (HOPE) trial[5] ranges from 2.350 to 5.928, with higher scores indicating higher risk. The sizes of the squares are proportioned to the numbers of events.

in hospitalization for heart failure was observed in the Valsartan Heart Failure Trial,[11] which compared valsartan with placebo in patients with heart failure, with about 90% of patients receiving background therapy with ACE inhibitors at variable doses. Both trials differed from both our study and the VALIANT study in that decisions regarding the dose and choice of an ACE inhibitor were left to individual physicians, and there was no attempt to titrate the ACE inhibitor to the maximum dose. Furthermore, patients had symptomatic heart failure despite receiving an ACE inhibitor.

The lack of an additional benefit of a substantial lowering of blood pressure is puzzling, both in our study and in the VALIANT study. These results may have been due to previous successful treatment of patients with other drugs so that little further clinical benefit was possible with the addition of full doses of multiple drugs that block the renin–angiotensin system. Alternatively, some harm from combined therapy with ACE inhibitors and ARBs used at full doses may offset any potential gains. Further information is expected regarding the role of ARBs as compared with placebo in patients after stroke,[18] in high-risk patients with vascular disease who are unable to tolerate an ACE inhibitor,[14] and in patients with atrial fibrillation.[19]

In conclusion, our data show that in patients who have vascular disease or high-risk diabetes but do not have heart failure, telmisartan is an equally effective alternative to ramipril and is less likely to cause angioedema. The choice between the two agents will depend on the preferences of patients and physicians and the individual patient's susceptibility to specific adverse events. There is no additional advantage (and there is some harm) from the combination of telmisartan and ramipril used in full doses in this population, as compared with ramipril alone.

Supported by a grant from Boehringer Ingelheim, the Heart and Stroke Foundation of Ontario, and a Senior Scientist Award from the Canadian Institutes of Health Research (to Dr. Yusuf).

Dr. Yusuf reports receiving consulting and lecture fees and research grants from Boehringer Ingelheim, AstraZeneca, Sanofi-Aventis, Servier, Bristol-Myers Squibb, and GlaxoSmith-Kline; Dr. Teo, receiving consulting and lecture fees and grant support from Boehringer Ingelheim; Dr. Schumacher, being an employee of Boehringer Ingelheim; Dr. Dagenais, receiving consulting and lecture fees from Boehringer Ingelheim and Sanofi-Aventis and grant support from Sanofi-Aventis; Dr. Sleight, receiving consulting and lecture fees from Boehringer Ingelheim and lecture fees from AstraZeneca and Sanofi-Aventis; and Dr. Anderson, receiving consulting fees from Boehringer Ingelheim, Servier, Novo Nordisk, and AstraZeneca, lecture fees from Boehringer Ingelheim, Servier, AstraZeneca, and Sanofi-Aventis, and grant support from Boehringer Ingelheim. No other potential conflict of interest relevant to this article was reported.

We thank Judy Lindeman for her secretarial assistance.

APPENDIX

Current members of the Operations Committee are denoted by an asterisk. Previous members of the Operations Committee are denoted by a dagger. NC denotes National Coordinator, and NL National Leader. **Steering Committee:** S. Yusuf (Chair and Principal Investigator),* P. Sleight,* C. Anderson,* K. Teo,* I. Copland,* B. Ramos,† L. Richardson,* J. Murphy,* M. Haehl,* L. Hilbrich,† R. Svaerd,* K. Martin,† D. Murwin,* T. Meinicke,† A. Schlosser,* G. Schmidt,† R. Creek,* H. Schumacher,* M. Distel,† B. Aubert, J. Pogue, L. Dyal, R. Schmieder, T. Unger, R. Asmar, G. Mancia, R. Diaz, E. Paolasso, L. Piegas, A. Avezum, G. Dagenais, E. Cardona Munoz, J. Probstfield, M. Weber, J. Young, R. Fagard, P. Jansky, J. Mallion, J. Mann, M. Böhm, B. Eber, N.B. Karatzas, M. Keltai, B. Trimarco, P. Verdecchia, A. Maggioni, F.W.A. Verheugt, N.J. Holwerda, L. Ceremuzynski, A. Budaj, R. Ferreira, I. Chazova, L. Rydén, T.L. Svendsen, K. Metsärinne, K. Dickstein, G. Fodor, P. Commerford, J. Redon, T.R. Luescher, A. Oto, A. Binbrek, A. Parkhomenko, G. Jennings, L.S. Liu, C.M. Yu, A.L. Dans, R. Shah, J.-H. Kim, J.-H. Chen, S. Chaithiraphan. **Data and Safety Monitoring Board:** J. Cairns (Chair), L. Wilhelmsen, J. Chalmers, J. Wittes, M. Gent, C.H. Hennekens. **Adjudication Committee:** G. Dagenais (Chair), N. Anderson, A. Avezum, A. Budaj, G. Fodor, M. Keltai, A. Maggioni, J. Mann, A. Parkhomenko, K. Yusoff, P. Auger, V. Bernstein, E. Lonn, A. Panju, I. Anand, J.T. Bigger, P. Linz, J. Healey, C. Held, C. McGorrian, M. Rokoss, J. Villar. **Substudies/Publication Committee:** P. Sleight (Chair), C. Anderson, R. Creek, A. Dans, R. Diaz, R. Fagard, J. Probstfield, R. Svaerd, K. Teo, T. Unger, S. Yusuf. **Coordinating Centers:** *Hamilton* — K. Teo, I. Copland, B. Ramos, A. McDonald, J. Pogue, L. Dyal, R. Afzal, F. Zhao, S. Yusuf; *Oxford* — P. Sleight, L. Richardson; *Auckland* — C. Anderson, J. Murphy. **Sites and Principal Investigators by Country:** *Argentina* — R. Diaz (NC), E. Paolasso (NL), R.A. Ahuad Guerrero, M. Amuchastegui, H.P. Baglivo, M. Bendersky, J. Bono, B. Bustos, A. Caccavo, L.R. Cartasegna, C.R. Castellanos, M.A. Cipullo, P. Crunger, C.A. Cuneo, M. Focaccia, J.J. Fuselli, E. Hasbani, M.A. Hominal, J. Humphreys, F. Inserra, C.R. Killinger, E. Kuschnir, C.R. Majul, O.D. Manuale, G. Martinez, E.M. Marzetti, R. Nordaby, A.D. Orlandini, J.C. Pomposiello, G.M. Rodríguez, J. Salas, O.A. Salomone, R.A. Sanchez, C. Serra, M.L. Vico; *Australia* — G.L.R. Jennings (NC), J.V. Amerena, L.F. Arnolda, G.M. Aroney, P.E. Aylward, C.F. Bladin, J.C. Bridgeman, B.R. Chambers, A.J. Corbett, D.S. Crimmins, D.B. Cross, L. Davies, S.M.

Davis, G.A. Donnan, D.S. Eccleston, J.H. Frayne, R. Hendriks, G.K. Herkes, A.T. Hill, I.M. Jeffery, J.A. Karrasch, G. Koshy, T.H. Marwick, D.A. Owensby, M.W. Parsons, D.M. Rees, A. Russell, R. Schwartz, B. Singh, P.L. Thompson, J.H. Waites, W.F. Walsh, D.L. Walters, R.W. Watts, A.P. Whelan; *Austria* — M. Böhm (NC), B.E. Eber (NL), J.B. Bonelli, P. Dolliner, J.H. Hohenecker, G.S. Steurer, W.W. Weihs; *Belgium* — R. Fagard (NC), I. Bekaert, C. Brohet, P. Chaumont, P. Cheron, V. Crasset, J.-P. Degaute, P. Dendale, K. Dujardin, S. Elshot, S. Hellemans, M. Herssens, G. Heyndrickx, P. Laloux, H. Lesseliers, P. Noyens, M. Quinonez, F. Stammen, H. Striekwold, J. Thoeng, W. Van Mieghem, G. Vanhooren, G. Vervoort, M. Vrolix, B. Wollaert; *Brazil* — L. Piegas (NC), A. Avezum (NL), J. A.M. Abrantes, D. Armaganijan, J.C. Ayoub, L.C. Bodanese, A.C. Carvalho, M. Coutinho, J.P. Esteves, R.J.S. Franco, P.C.B.V. Jardim, J.F. Kerr Saraiva, P.E. Leães, L.N. Maia, J.A. Marin-Neto, R.L. Marino, D. Mion, Jr., J.R. Moreira, Jr., W. Oigman, R.C. Pedrosa, E.A. Pelloso, F.L. Plavnik, C.A. Polanczyk, Á. Rabelo, Jr., S. Rassi, G. Reis, A.B. Ribeiro, J.M. Ribeiro, J.C. Rocha, P.R.F. Rossi, R.D. Santos, J.C.E. Tarastchuk, M.N. Villalón; *Canada* — K. Teo (NC), G. Dagenais (NC), B. Abramson, M. Arnold, T. Ashton, P. Auger, I. Bata, K. Bayly, J. Beauchef, A. Bélanger, V. Bernstein, R. Bhargava, A.W. Booth, S. Bose, M. Boulianne, M. Cameron, Y.K. Chan, C. Constance, P. Costi, D. Dion, J. Douketis, D. Fell, J.P. Giannoccaro, A. Glanz, G. Gosselin, D. Gould, S. Goulet, F. Grondin, M. Gupta, G. Gyenes, J.W. Heath, V.A. Heath, A. Hess, J.G. Hiscock, G. Hoag, G. Honos, J. Imrie, R. Kuritzky, C. Lai, A. Lalani, A. Lamy, P. LeBouthillier, H. Lochnan, E. Lonn, B. Lubelsky, A. Mackey, M. Meunier, A. Milot, L.B. Mitchell, S. Nawaz, M. Omichinski, A. Panju, C. Pilon, D. Pilon, P. Polasek, G. Proulx, T. Rebane, A.J. Ricci, D.W. Rupka, É. Sabbah, D. Savard, N.K. Sharma, D. Shu, R. St. Hilaire, F. St. Maurice, R. Starra, B. Sussex, T. Szaky, P. Talbot, K.-W. Tan, T.B. To, S. Tobe, R. Tytus, R. Vexler, P. Whitsitt, V. Woo; *China* — L. Liu (NC), X. Bai, X. Chen, J. Feng, S. Fu, Y. Ge, L. Gong, Z. He, J. Huang, Y. Jiang, L. Li, Q.H. Li, Y. Liao, Z. Lu, F. Lu, S. Ma, F. Niu, C. Pan, F. Qian, X. Shi, N. Sun, M. Sun, G. Sun, J. Wang, S. Wang, Y. Wang, Z. Wu, X. Yan, X. Yang, H. Yang, X. Ye, S. Yuan, T. Zhang, C. Zhang, F. Zhang, S. Zhang, D. Zhao, B. Zheng, H.Y. Zhou, S. Zhou, J. Zhu; *Czech Republic* — P. Janský (NC), V. Dedek, J. Dvorák, R. Holaj, J. Kotouš, E. Pederzoliová, M. Polák, J. Povolný, K. Smetana, J. Špác; *Denmark* — T.L. Svendsen (NC), L. Götzsche, H.F. Juhl, K. Koelendorf, P. Lund, F. Pedersen, O.L. Perdersen, T. Pindborg, L.H. Rasmussen, S.L. Rasmussen, K. Thygesen, C. Tuxen; *Finland* — K. Metsärinne (NL), R. Antikainen, M. Jääskivi, I. Kantola, M. Kastarinen, P. Kohonen-Jalonen, A. Koistinen, E. Lehmus, R. Nuuttila, M.-L. Tuominen, H. Ylihärsilä; *France* — J. Mallion (NC), N. Abenhaim, J. Allix, L. Boucher, M. Bourgoin, A. Boye, N. Breton, D. Cadinot, A. Campagne, J. Churet, G. Constantin, E. De Sainte Lorette, A. El Sawy, G. Etchegarray, S. Farhat, F. Lacoin, T. Latte, C. Magnani, D. Pineau-Valenciennes, M. Pithon, A. Quéguiner, J. Sicard, G. Sorbe, D. Taminau, H. Vilarem, J.Y. Vogel; *Germany* — H.H. Ebert, S. Genth-Zotz, N. Hermanns, C. Holzer, J. Minnich, D. Schimkus, M. Boehm (NC), J. Mann (NC), B. Brado, G. Claus, U. Dietz, R. Griebenow, T. Haak, K. Hahn, R. Hampel, H. Heitzer, G. Holle, T. Horacek, J. Jordan, C. Klein, R. Kolloch, S. Ludewig, W. Motz, T. Muenzel, H.P. Nast, M. Nauck, H. Nebelsieck, K. Rybak, H. Samer, T. Schaefer, J. Scholze, B. Schulze, Schleppinghoff, R. Schmieder, B. Schwaab, U. Sechtem, W. Sehnert, E. Steinhagen-Thiessen, G. Stenzel, P. Trenkwalder, B. Wedler, J. Zippel; *Greece* — N. Karatzas (NC), A. Achimastos, E. Diamantopoulos, A. Efstratopoulos, M. Elisaf, H. Karvounis, D. Mentzikof, D. Mytas, D. Papadogiannis, V. Pyrgakis, C. Stefanadis, D. Symeonidis, A. Tsoukas, I. Vogiatzis, S. Voyaki, C. Zamboulis; *Hong Kong* — C.-M. Yu (NC), C.K.H. Chan, L. Lam, Y.K. Lau, J. Sanderson, J. Wong, E.B. Wu, C.S. Yue; *Hungary* — M. Keltai (NC), I. Czuriga, I. Édes, C.S. Farsang, Á. Kalina, K. Karlócai, K. Keltai, M. Kozma, Z. László, V. Nagy, A. Papp, G.Y. Polák, I. Préda, A. Rónaszéki, M. Sereg, K. Simon, S. Sonkodi, J. Szegedi, S. Timár, K. Tóth, G.Y. Vándorfi, A. Vértes; *Ireland* — J. Feely, V.M.G. Maher, A.V. Stanton, P. Sullivan; *Italy* — B. Trimarco (NC), P. Verdecchia (NC), A. Maggioni (NL), E. Agabiti Rosei, G.B. Ambrosio, M. Bentivoglio, A. Branzi, P. Cavallo Perin, M. Chiariello, V. Cirrincione, R. Ferrari, R. Gattobigio, E. Giovannini, D. Giugliano, A. Lacchè, R. Lauro, G. Lembo, G. Marchetti, L. Moretti, L. Pancaldi, L. Partemi, S. Pede, G. Pettinati, G. Reboldi, R. Ricci, G. Rosiello, F. Rozza, M.G. Sardone, E.V. Scabbia, G. Selvetella, L. Tavazzi, P. Terrosu, A. Venco, A. Vetrano, M. Volpe, G. Zilio; *Malaysia* — T. Ismail, R.P. Shah, M. Singaraveloo, W.A. Wan Ahmad, Z. Yusof, K. Yusoff, I. Zainal Abidin, R. Zambahari; *Mexico* — E. Cardona Munoz (NC), L. Alcocer Diaz, S. Pascoe-Gonzalez, R. Arriaga Nava, G. De La Peña Topete, L.A. Elizondo Sifuentes, H.R. Hernández García, J. Illescas-Diaz, M.A. Macías Islas, J.A. Noriega Arellano, R. Olvera Ruiz, J.Z. Parra Carrillo, G. Velasco Sánchez, M. Vidrio Velásquez; *the Netherlands* — F.W.A. Verheugt (NC), N.J. Holwerda (NL), D.C.G. Basart, A.J.M. Boermans, H.A. Bosker, K.P. Bouter, C.P. Buiks, W.A. de Backer, J. J. de Graaf, J.H.M. Deppenbroek, F.D. Eefting, F.C.N.M. Gunneweg, H.R. Michels, D. Poldermans, G. Schrijver, M.I. Sedney, T. Slagboom, J.G. Smilde, G.E.M.G. Storms, R.M. Tjon, P.F.M.M. van Bergen, G.J.M. van Doesburg, L.H.J. van Kempen, H.F.C.M. van Mierlo, A. Veerman, F.A.A.M. Vermetten, A. Wester; *New Zealand* — W. Bagg, J. Benatar, R.J. Coxon, R.N. Doughty, D.H. Friedlander, R.A. Luke, P.L. Nairn, Y. Ratnasabapathy, A.M. Richards, G.P. Singh, R.A.H. Stewart, R.W. Troughton, H.D. White, M. Williams, S.P. Wong; *Norway* — K. Dickstein (NL), N. Bogale, J.O. Lier, J.E. Otterstad, P.K. Rønnevik, S. Skeie, P.O. Walle; *Philippines* — A.L. Dans (NC), M.T.B. Abola, J.C. Añonuevo, J.M. Jaro, D.R. Marañon, V.L. Mendoza, D.R. Morales, E.P. Pacheco, E.B. Reyes, A.A. Roxas, M.B. Sedurante; *Poland* — L. Ceremuzynski (NC), A. Budaj (NC), Z. Binio, M. Bronisz, P. Buszman, T. Czerski, M. Dalkowski, J. Gessek, A. Gieroba, K. Janik, M. Janion, T. Kawka-Urbanek, R. Klabisz, M. Krauze-Wielicka, S. Malinowski, P. Miekus, J. Mormul, M. Ogorek, G. Opolski, M. Skura, M. Szpajer, M. Tendera, T. Waszyrowski, M. Wierzchowiecki, B. Zalska; *Portugal* — R. Ferreira (NC), R. Capucho, C. Correia, L. Cunha, J.M. Ferro, V. Gama Ribeiro, V. Gil, P. Marques da Silva, M. Oliveira Carrageta, R. Sebra Gomes, M. Veloso Gomes; *Russia* — I. Chazova (NC), F. Ageev, Y. Belenkov, A. Ivleva, Y. Karpov, M. Shestakova, E. Shlyakhto, S. Shustov, B. Sidorenko; *Singapore* — H.M. Chang, B. Kwok; *Slovakia* — G. Fodor (NC), A. Dukát, J. Gonsorcík, M. Hranai, J. Lietava, D. Pella, R. Rybar, L. Ruffini; *South Africa* — P. Commerford (NC), F. Bonnici, B. Brown, A.J. Dalby, G.J. Gibson, L. Herbst, J. King, E. Klug, M. Middle, D. P. Naidoo, M. Pretorius, G. Podgorski, N. Ranjith, K. Silwa-Hahnle, H. Theron; *South Korea* — J.H. Kim (NC), S.C. Chae, N.S. Chung, K.P. Hong, M.H. Jeong, H.J. Kang, J.J. Kim, M.H. Kim, H.S. Seo, E.K. Shin; *Spain* — J. Redón (NC), J. Abellán, P. Aranda, V. Barrios, C. Calvo, M. De La Figuera, E. De Teresa, R. Durá, F. Escobar, F. Fernandez-Cruz, E. Galve, J. Garcia-Puig, B. Gil-Extremera, R. Gomis, O. Gonzalez-Albarran, J.R. González-Juanatey, A. Llacer, L. López-Bescós, J. Oliván, A. Picó, A. Pose, A. Roca-Cusachs, L.M. Ruilope; *Sweden* — L. Rydén (NC), A. Alvång, P.-Å. Boström, M. Dellborg, U.-B. Ericsson, J. Herlitz, T. Juhlin, K. Pedersen, B. Sträng, B. Sundqvist, B.-O. Tengmark, G. Ulvenstam, B. Westerdahl, L. Winberg; *Switzerland* — T.R. Luescher (NC), I. Baumgartner, P. Dubach, A. Gallino, T. Moccetti, G. Noll, A. Nordmann, H. Rickli, H. Schläpfer, K. Weber; *Taiwan* — J.-H. Chen (NC), T.H. Chao, C.Y. Chen, J.J. Cheng, H.C. Chiou, C.C. Fu, M. Fu, W.T. Lai, Y.H. Li, L.M. Lien, C.D. Tsai, J.H. Wang, P.S. Yeh; *Thailand* — S. Chaithiraphan (NC), T. Chantadansuwan, K. Jirasirirojanakorn, R. Krittayaphong, P. Laothavorn, N. Mahanonda, S. Sitthisook, S. Tanomsup, S. Tansuphaswadikul, P. Tatsanavivat, S. Yamwong; *Turkey* — A. Oto (NC), M. Akin, N.T. Caglar, A. Ergin, H. Müderrisoglu, A. Oguz, Z. Ongen, V. Sansoy, T. Tetiker, A. Uysal; *Ukraine* — A. Parkhomenko (NC), E. Amosova, O. Cherkasova, Y. Dykun, G. Dzyak, A. Galystska, O. Grishyna, O. Jaremenko, L. Kononenko, E. Koval, V. Kovalenko, V. Netyazhenko, T. Pertseva, A. Prokhorov, G. Radchenko, Y.U. Rudyk, Y. Sirenko, A. Skarzhevsky; *United Arab Emirates* — A.S. Binbrek (NC), A.A.R. Al Hajiri, E. Al Hatou, A.A.S. Al-Sousi, M. Alomairi, I. Maqsood Wajib; *United Kingdom* — P. Sleight (NC), A.A.J. Adgey, R. Andrews, S.G. Ball, D.H. Barer, A.H. Barnett, A.B. Bridges, V. Bryson, A.S. Cowie, A.J. De Belder, R. Donnelly, C.M. Francis, J. Furnace, S.K. Glen, N. Gough, A.M. Heagerty, P.R. Jackson, S.H.D. Jackson, E. Joyce, D.J. McEneaney, A.J. Moriarty, D.L. Murdoch, J.P. O'Hare, W.J. Penny, C.J. Reid, J. Tilley, J.P. Vora, J. Webster, B. Wil-

liams; *United States* — J. Probstfield (NC), M. Weber (NC), J. Young (NC), I. Ahmed, I.S. Anand, J.L. Anderson, J.S. Aponte Pagán, J. Barzilay, J.N. Basile, P.F. Bass III, S.S. Blumenthal, W.J. Bommer, D.F. Brautigam, C.D. Brown, N. Brown, J.D. Byrum, A.A. Carr, J. Chinn, D. Chiu, N.R. Cho, J.O. Ciocon, P.J. Colón-Ortíz, J.B. Cruz, W.D. Dachman, G.M. Dolson, S.G. Dorfman, W. Drummond, C. East, F. Eelani, H.S. Ellison, J.V. Felicetta, M.H. Fishbach, R.W. Force, S.J. Giddings, M.C. Goldberg, S. Goldman, R. Gomez Adrover, S.L. Goss, S.P. Graham, C.B. Granger, M.M. Greenspan, R.H. Grimm, G.B. Habib, M.R. Hagen, P.D. Hart, T.J. Hartney, M.A. Henriquez, J.J. Holland, B.J. Hoogwerf, M. Hossfeld, A.K. Jacobson, M.J. Jelley, T.V. Jones, R.A. Kaplan, D.G. Karalis, L.A. Katz, D.J. Kereiakes, M. Khan, R.M. Kipperman, M.J. Kozinn, J.G. Kozlowski, E.W. Lader, C. Landau, J.S. Landzberg, D. Laughrun, S.J. Lewis, C.S. Liang, M.C. Limacher, P.E. Linz, T.S. Lo, F. Lopez-Arostegui, R.R. Maddox, P.R. Mahrer, M.S. Maurer, D.K. McGuire, A.D. Mercando, J.H. Mersey, M. Meyer, A.N. Mooss, P. Narayan, S. Oparil, D.N. Padhiar, A.L. Phillips, M. Prisant, N. Qureshi, M.P. Raghuwanshi, R.R. Randall, T.M. Retta, R.E. Ringrose, A.A. Rizvi, M.D. Rizvi, M.G. Saklayen, S. Sastrasinh, I.K. Savani, A. Schlau, H.S. Schultz, M.J. Schweiger, R.D. Smith, M. Sosa-Padilla, D. Streja, T.P. Stuver, D.C. Subich, F.C. Sulak, W.A. Swagler III, M. Taitano, J.A. Tavarez-Valle, E.M. Taylor, M.L. Tuck, W.B. White, W.J. Wickemeyer, T.B. Wiegmann, P.A. Zee, X.Q. Zhao.

REFERENCES

1. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.
2. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement trial. N Engl J Med 1992; 327:669-77.
3. Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. Lancet 2003; 361:1843-8.
4. Flather MD, Yusuf S, Køber L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet 2000; 355:1575-81.
5. Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting–enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342: 145-53. [Errata, N Engl J Med 2000;342: 784, 1376.]
6. Fox KM, EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003;362:782-8.
7. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. Lancet 2006; 368:581-8.
8. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253-9. [Erratum, Lancet 2000;356:860.]
9. McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study. Circulation 1999;100:1056-64.
10. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003; 362:772-6.
11. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667-75.
12. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362: 767-71.
13. Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995-1003.
14. Teo K, Yusuf S, Sleight P, et al. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. Am Heart J 2004; 148:52-61.
15. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 1977;35:1-39.
16. Cox DR. Regression models and life-tables. J R Stat Soc [B] 1972;34:187-220.
17. Cox DR, Oakes D. Analysis of survival data. London: Chapman & Hall, 1984.
18. Diener HC, Sacco R, Yusuf S. Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: the Prevention Regimen for Effectively Avoiding Second Strokes Trial (PRoFESS). Cerebrovasc Dis 2007;23:368-80.
19. The ACTIVE Steering Committee. Rationale and design of ACTIVE: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events. Am Heart J 2006;151:1187-93.
20. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349:1893-906. [Erratum, N Engl J Med 2004;350:203.]
21. Hasselblad V, Kong DF. Statistical methods for comparison to placebo in active-control trials. Drug Inf J 2001;35:435-49.
22. Phillips CO, Kashani A, Ko DK, Francis G, Krumholz HM. Adverse effects of combination angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors for left ventricular dysfunction: a quantitative review of data from randomized clinical trials. Arch Intern Med 2007;167:1930-6.

Original Paper

Results of Treatment With Telmisartan-Amlodipine in Hypertensive Patients

Thomas W. Littlejohn, III, MD;[1] Claudio R. Majul, MD;[2] Rafael Olvera, MD;[3] Mary Seeber, MD;[4] Maureen Kobe, MSc;[5] Robert Guthrie, MD;[6] Wille Oigman, MD;[7] On behalf of the study investigators

This randomized 4×4 factorial study determined the efficacy and safety of telmisartan (T) plus amlodipine (A) in hypertensive patients. Adults (N=1461) with stage 1 or 2 hypertension (baseline blood pressure [BP]: 153.2[12.1]/101.7[4.3] mm Hg) were randomized to 1 of 16 treatment groups with T 0, 20, 40, 80 mg and A 0, 2.5, 5, 10 mg for 8 weeks. In-clinic BP reductions were greater with combination therapy than respective monotherapies. The greatest least-square mean systolic/diastolic BP reductions were observed with T80 mg plus A10 mg (−26.4/−20.1 mm Hg; P<.05 compared with both monotherapies). BP control was also greatest in the T80-mg plus A10-mg group (76.5% [overall control] and 85.3% [diastolic BP control]), and BP response rates >90% with this combination. Peripheral edema was most common in the A10-mg group (17.8%); however, this rate was notably lower when A was used in combination with T: 11.4% (T20/A10), 6.2% (T40/A10), and 11.3% (T80/A10). J Clin Hypertens (Greenwich). *2009;11:207–213.* ©*2009 Wiley Periodicals, Inc.*

From Piedmont Medical Research Associates, Winston-Salem, NC;[1] the Hospital Santojanni, Buenos Aires, Argentina;[2] the Clinica de Estudios Medicos SC, Mexico City, México;[3] the Mediclinic Heart Hospital, Pretoria City, South Africa;[4] the Department of Cardiovascular and CNS Medicine, Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT;[5] Ohio State University, Columbus, OH;[6] and Rio de Janeiro State University, Rio de Janeiro, Brazil[7]
Address for correspondence:
Maureen Kobe, MSc, Department of Cardiovascular Medicine, Medical Affairs, Boehringer Ingelheim Pharmaceuticals Inc, 900 Ridgebury Road, Ridgefield, CT 06877
E-mail: maureen.kobe@boehringer-ingelheim.com
Manuscript received August 11, 2008;
revised January 22, 2009; accepted January 30, 2009.

doi: 10.1111/j.1751-7176.2009.00098.x

The majority of hypertensive patients, especially those with target organ damage, are likely to require multiple drug therapy in order to reach blood pressure (BP) targets and reduce their risk of adverse vascular outcomes.[1,2] The rationale for combination therapy with agents that block the renin-angiotensin-aldosterone system (RAAS) and a calcium channel blocker (CCB) or diuretic is well founded.[2–5] Recent landmark studies, such as the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) and the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA), have demonstrated the antihypertensive benefits associated with angiotensin-converting enzyme (ACE) inhibitor/CCB combinations.[6,7] More recently, the combination of an angiotensin receptor blocker (ARB), such as valsartan or olmesartan and amlodipine have been introduced and tested in stage 1 and 2 hypertensive patients as well as those not controlled by monotherapy.[6,8–10] Besides the increased antihypertensive efficacy, the addition of an RAAS blocker has been shown to reduce the incidence of amlodipine-related edema.

Telmisartan has a different pharmacokinetic profile when compared with other ARBs,[11] and there are few studies examining telmisartan/CCB combinations in hypertensive patients.[12]

Against this background, the aim of the current study was to determine the clinical and safety profile of telmisartan (20–80 mg) plus amlodipine (2.5–10 mg) in stage 1 or 2 hypertension, and to establish the optimal doses using a rigorous factorial design involving 9 telmisartan-amlodipine combinations.

METHODS

Study Design

This was an 8-week, randomized, double-blind, double-dummy, placebo-controlled, international, multicenter, parallel-group, 4×4 factorial design trial that evaluated the efficacy and safety of telmisartan 20, 40, or 80 mg plus amlodipine 2.5, 5, or 10 mg in adults with hypertension (trial registration: NCT00281580). Patients were recruited from 150 centers in the United States, South Africa, Mexico, Argentina, and Brazil. The trial was conducted in accordance with the Declaration of Helsinki (1996), and was approved by each participating country's health authority and institutional review board or an independent ethics committee.

Following screening and a 21- to 28-day, single-blind, placebo run-in period, eligible patients were randomized to 1 of 16 treatment groups involving either telmisartan 20, 40, 80 mg or telmisartan placebo and/or amlodipine 2.5, 5, 10 mg or amlodipine placebo for 8 weeks. All patients randomized to a treatment group containing amlodipine 10 mg started with amlodipine 5 mg for the first 2 weeks and were then up-titrated to the higher dosage. Trial drug was taken orally as 3 tablets and 2 capsules with water at 8 AM (±1 hour). If a dose was missed, the patient was instructed to take the next dose as scheduled.

Participants and Medication Restrictions

Patients were men and women aged 18 years and older with stage 1 or 2 hypertension according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) diastolic BP ranges[13] (diastolic BP ≥95 mm Hg and ≤119 mm Hg) at baseline. Diastolic BP was chosen as this was the standard inclusion criteria used for drug approvals at the time the trial commenced. Consequently, change in diastolic BP was chosen as the primary end point. There were no inclusion criteria relating to systolic BP, and a change in systolic BP was included as a secondary end point as per protocol. All patients provided written informed consent prior to participation. Patients with prespecified renal or hepatic disorders, congestive heart failure (New York Heart Association class III or IV), clinically relevant cardiac arrhythmias (as determined by the investigator's clinical judgment on a patient-by-patient basis), severe obstructive coronary artery disease, unstable diabetes (glycated hemoglobin A_{1c} ≥10%), or any other condition that would not allow for safe completion of the protocol were excluded, as were nightshift workers, pregnant or nursing women, and women of childbearing potential not using medically approved means of contraception. Patients with known hypersensitivity to any component of the trial drugs, prior angioedema due to an ACE inhibitor or ARB, or those with a history of drug or alcohol dependency within the 6 months prior to signing the informed consent, were also excluded. Any antihypertensive or concomitant medications known to affect BP were not permitted during the study.

Assessments

Seated cuff BP and pulse rate were measured in the clinic prior to randomization, after 2 weeks of treatment, and then periodically until the end of the study. BP was recorded to the nearest 2 mm Hg using standard equipment, and the mean of 3 readings (taken 2 minutes apart) was used for the final measurement. Pulse rate was recorded during the 2-minute interval between the second and third BP recording. The primary end point was change in the in-clinic seated trough diastolic BP (ie, the diastolic BP measured 20–30 hours after the last drug dose from baseline to end of study [week 8]). Secondary efficacy end points included change from baseline in the in-clinic seated trough systolic BP, the percentage of patients achieving a diastolic BP response (defined as diastolic BP <90 mm Hg or a decrease in diastolic BP ≥10 mm Hg) or a systolic BP response (defined as systolic BP <140 mm Hg or a decrease in systolic BP ≥15 mm Hg) after 8 weeks of treatment, and the percentage of patients achieving BP control (defined as diastolic BP <90 mm Hg and systolic BP control <140 mm Hg) and diastolic BP control (<90 mm Hg) following treatment.

All adverse events that occurred after the first dose of randomized study drug until the follow-up visit, and adverse events that occurred up to 1 day after treatment discharge were defined as on-treatment. Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) Version 10. Laboratory tests were con-

ducted at screening, baseline, and end-of-study visits. Twelve-lead electrocardiography was performed at screening and at the end-of-study visit, and a physical examination was performed at screening. In addition, orthostatic changes in BP (defined as a decrease in diastolic BP >10 mm Hg and/or a decrease in systolic BP >20 mm Hg from a seated to standing position) were documented. Drug compliance was assessed by physical count of returned trial medication at each visit.

Statistical Analysis

The statistical models were adjusted (1) for telmisartan-by-amlodipine interaction (this first analysis was designed to show whether there were significant differences across the dosages of telmisartan or amlodipine, but was not a comparison between the 2 agents); (2) by dosage, country/region, and baseline BP as a covariate; and (3) for all combination treatment groups vs respective monotherapies. Least square means were used to quantify treatment effects, and the mean squared error was used to evaluate differences between combination therapy and the respective monotherapies. Analysis of covariance using the 3 statistical models was also performed on the secondary end point of the change from baseline in systolic BP. Responder rates were evaluated using the Mantel-Haenszel test. A 2-sided significance level of 0.05 was used when evaluating the primary and all secondary end points.

The efficacy analyses were performed on the full analysis set, which consisted of all treated patients with at least 1 trough BP measurement at the baseline and at the target dosage. For the primary analysis, the last observation following titration to the randomized target dosage was used in evaluating the change from baseline. The safety analyses were performed on all patients who received at least 1 dose of active treatment. The incidence of peripheral edema in the amlodipine 10-mg monotherapy group was compared with the 4 key combinations of telmisartan 40 mg or 80 mg plus amlodipine 5 mg or 10 mg in a post hoc analysis.

RESULTS

Population

A total of 2607 patients were enrolled in the study between April 2006 and November 2006, and 1461 were randomized and treated for up to 8 weeks. The baseline demographics are shown in Table I. A total of 1344 (92%) patients completed the 8-week trial. The efficacy analyses were performed on all patients with a baseline value and at least 1 efficacy measurement at target dose (n=1423). The safety analysis was performed on all patients who received at least 1 dose of study medication (n=1461). Compliance with study medication was 98.4% with no appreciable differences between the treatment groups. A total of 117 patients (8%) prematurely discontinued the study; the main reasons were adverse events (n=38), consent withdrawn (n=27), lack of efficacy (n=16), noncompliance (n=13), lost to follow-up (n=10), and other (n=13).

Table I. Baseline Demographics and Clinical Characteristics of Randomized Population

Variables	Total (N=1461)
Age, y	53.1±11.1
Males	737 (50.4)
Blood pressure, mm Hg	
Systolic	153.2±12.1
Diastolic	101.7±4.3
Pulse rate, beats per minute	74.4±9.3
Race	
Caucasian	1160 (79.4)
Black	237 (16.2)
Asian	64 (4.4)
Body mass index, kg/m^2	31.3±6.4
Duration of hypertension	
<1 year	211 (14.4)
1–5 years	444 (30.4)
>5 years	806 (55.2)
Previous antihypertensives used	
0	307 (21.0)
1	531 (36.3)
≥2	623 (42.6)
Diabetes	238 (16.3)
Renal impairment[a]	12 (0.8)

Values are expressed as mean ± standard deviation or No. (%). [a]Renal impairment was defined as serum creatinine >3.0 mg/d.

Efficacy Assessments

Both telmisartan (irrespective of amlodipine dosage; P<.0001) and amlodipine (irrespective of telmisartan dosage; P<.0001) significantly lowered the in-clinic trough diastolic BP, without evidence of counterproductive telmisartan-by-amlodipine interaction at any dosage (not involving patients treated with placebo; P=.1777).

As expected, the greatest least-square mean reductions in in-clinic diastolic and systolic BP were observed with combination therapy compared with respective monotherapies (Figure 1). The greatest overall reduction in BP was observed with the telmisartan 80-mg plus amlodipine 10-mg combination (mean reduction in systolic BP/diastolic BP: −26.4/−20.1 mm Hg; P<.05 vs both monothera-

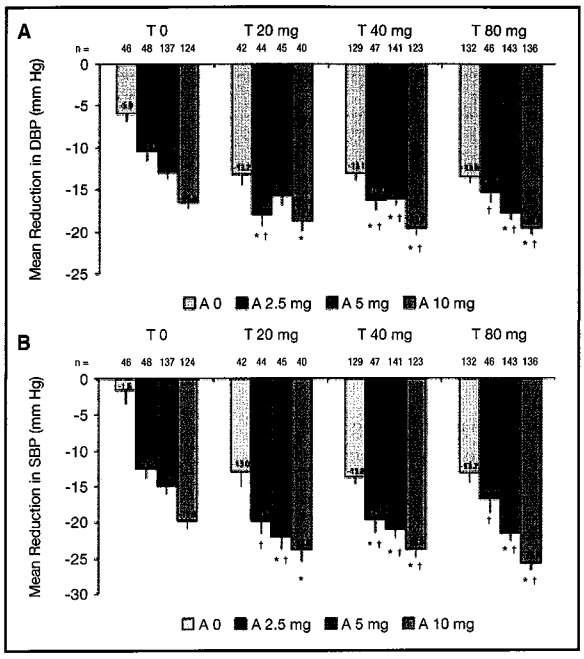


*Figure 1. Effect of 8 weeks of treatment with telmisartan (T) 0, 20, 40, 80 mg plus amlodipine (A) 0, 2.5, 5, 10 mg on the change from baseline in the in-clinic seated trough (A) diastolic blood pressure (DBP) (mm Hg) or (B) systolic blood pressure (SBP) (mm Hg). *P<.05 vs T monotherapy. †P<.05 vs A monotherapy. Data are least-square mean (SE) values adjusted for dosage, country/region, and baseline blood pressure.*

pies). When the mean reductions in diastolic or systolic BP were analyzed according to baseline categories, the 4 key combinations (telmisartan 40 mg or 80 mg plus amlodipine 5 mg or 10 mg) were all shown to consistently reduce BP even in patients with high baseline diastolic BP (≥110 mm Hg) (Figure 2A) and in patients with high baseline systolic BP (>160 mm Hg), achieving BP drops of more than 20 mm Hg diastolic BP and more than 30 mm Hg systolic BP with the combinations of telmisartan 40 mg or 80 mg and amlodipine 10 mg (Figure 2B).

The proportion of patients with BP control (diastolic BP <90 mm Hg and systolic BP <140 mm Hg) after 8 weeks of treatment is summarized in Table II. More than 50% of all patients treated with combination therapy achieved BP control, with the highest percentages (76.5% [overall control] and 85.3% [diastolic BP control]) being achieved by patients treated with telmisartan 80 mg plus amlodipine 10 mg. There was a clear relationship between dose and responder rate (Table II). Diastolic BP response and systolic BP response was achieved by 91.2% and 90.4% of patients in the telmisartan 80-mg plus amlodipine 10-mg group, respectively.

Safety Assessments

A total of 545 (37.3%) patients reported at least 1 adverse event during the 8-week study. When analyzed by treatment groupings, the percentage of patients reporting adverse events on specific treatment was comparable: placebo (39.1%, n=18), telmisartan monotherapy (36.8%, n=113), amlodipine monotherapy (36.1%, n=115), and combination therapy (37.9%, n=299) groups. The most commonly reported adverse events were headache (5.4%, n=79) and peripheral edema (4.4%, n=65). Headache was more frequent in the placebo group (10.9%, n=5) compared with the telmisartan monotherapy (5.9%, n=18), amlodipine monotherapy (6.0%, n=19), and combination therapy (4.7%, n=37) groups. The incidence of peripheral edema was highest in the amlodipine 10-mg group (17.8%, n=23); however, this rate was lower when amlodipine was used in combination with telmisartan: 11.4% (telmisartan 20 mg/amlodipine 10 mg), 6.2% (telmisartan 40 mg/amlodipine 10 mg), and 11.3% (telmisartan 80 mg/amlodipine 10 mg) (Figure 3). A total of 6 patients (2 in the amlodipine 10-mg group and 4 in the amlodipine 10-mg combination groups) discontinued the trial as a consequence of peripheral edema.

Drug-related adverse events were reported in 167 (11.4%) patients. These were lower in the telmisartan monotherapy group (6.5%, n=20) than in the placebo (13.0%, n=6), amlodipine monotherapy (12.2%, n=39), and combination therapy (12.9%, n=102) groups. The most frequent drug-related adverse events were peripheral edema (3.4%, n=50) and headache (2.1%, n=31). Adverse events associated with excessive BP lowering were reported at low rates in the placebo, telmisartan monotherapy, amlodipine monotherapy, and combination therapy groups; hypotension was reported in 0.0%, 0.0%, 0.0%, and 0.6%, respectively. There was no evidence of any dose-related trends in orthostatic changes (data not shown).

Serious adverse events were reported in 8 (0.5%) patients. Only one of the events (chest pain) in a patient in the telmisartan 80-mg plus amlodipine 2.5-mg group was considered related to study drug. There was one fatality (respiratory choking while eating dinner) during the study, which occurred in a patient who had been using telmisartan 80 mg. This was not considered drug-related and was not associated with any other condition. There were no clinically relevant changes on the electrocardiogram, in pulse rate, or in routine laboratory test results from baseline to end of study.

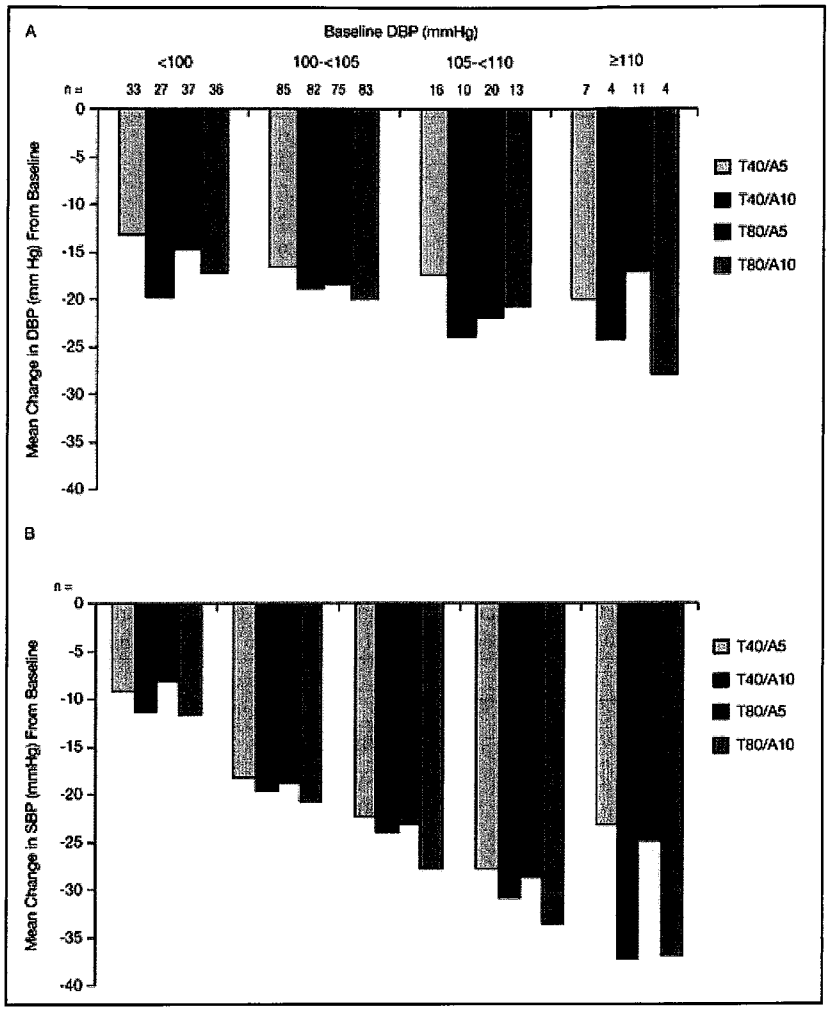


Figure 2. Effect of 8 weeks of treatment with the combinations of telmisartan 40 mg (T40) or 80 mg (T80) plus amlodipine 5 mg (A5) or 10 mg (A10) on the unadjusted mean change from baseline in the in-clinic trough (A) diastolic blood pressure (DBP) (mm Hg) or (B) systolic blood pressure (SBP) (mm Hg) according to baseline blood pressure categories.

DISCUSSION

As anticipated, significant in-clinic BP reductions were observed following 8 weeks of treatment with telmisartan plus amlodipine in this randomized population of 1461 patients with stage 1 and 2 hypertension. Statistically significant reductions in both in-clinic systolic BP and diastolic BP were observed with the combinations of most clinical interest (ie, telmisartan 40 mg or 80 mg plus amlodipine 5 mg or 10 mg). There was evidence of a dose effect as the greatest reduction in systolic BP/diastolic BP (−26.4/−20.1 mm Hg; $P<.05$ compared with each monotherapy) was observed with telmisartan 80 mg plus amlodipine 10 mg. This also resulted in the greatest percentage of patients achieving BP control (76.5%) and diastolic BP control (85.3%). Diastolic BP and systolic BP responses were also high in the telmisartan 80-mg plus amlodipine 10-mg group (91.2% and 90.4%, respectively).

These results are consistent with other factorial studies where combination therapy with an ARB (valsartan or olmesartan) and amlodipine were more effective than respective monotherapies, in lowering BP. Philipp and colleagues[14] report findings from 2 valsartan/amlodipine studies in which 1911 and 1250 patients were randomized to the different treatments for 8 weeks. These studies showed that both monotherapies contributed to the overall efficacy of the combination and the biggest reductions were attained with the highest dose (valsartan 320 mg/amlodipine 10 mg). Similar reductions of more than 25 mm Hg in systolic BP and more than 18 mm Hg in diastolic BP were

Table II. Effect of 8 Weeks of Treatment With Telmisartan Plus Amlodipine on Blood Pressure Response and Control Rates (N=1423)

Treatment	DBP Response, %[a]	SBP Response, %[a]	Control, %[b]	DBP Control, %[c]
Telmisartan 0 mg/amlodipine 0 mg	39.1	32.6	19.6	30.4
Telmisartan 20 mg/amlodipine 0 mg	64.3	64.3	40.5	54.8
Telmisartan 40 mg/amlodipine 0 mg	69.8	63.6	42.6	53.5
Telmisartan 80 mg/amlodipine 0 mg	78.0	65.2	41.7	60.6
Amlodipine 2.5 mg/telmisartan 0 mg	52.1	47.9	25.0	33.3
Amlodipine 5 mg/telmisartan 0 mg	67.9	73.0	42.3	52.6
Amlodipine 10 mg/telmisartan 0 mg	85.5	82.3	62.9	73.4
Telmisartan 20 mg/amlodipine 2.5 mg	90.9	84.1	52.3	75.0
Telmisartan 20 mg/amlodipine 5 mg	80.0	77.8	51.1	64.4
Telmisartan 20 mg/amlodipine 10 mg	92.5	87.5	70.0	85.0
Telmisartan 40 mg/amlodipine 2.5 mg	87.2	83.0	66.0	72.3
Telmisartan 40 mg/amlodipine 5 mg	80.9	88.7	58.9	71.6
Telmisartan 40 mg/amlodipine 10 mg	91.9	91.9	75.6	82.1
Telmisartan 80 mg/amlodipine 2.5 mg	73.9	76.1	56.5	69.6
Telmisartan 80 mg/amlodipine 5 mg	88.8	83.9	65.7	74.8
Telmisartan 80 mg/amlodipine 10 mg	91.2	90.4	76.5	85.3

[a]Diastolic blood pressure (DBP) <90 mm Hg or ≥10 mm Hg reduction; systolic blood pressure (SBP) <140 mm Hg or ≥15 mm Hg reduction. [b]Trough DBP <90 mm Hg; trough SBP <140 mm Hg. [c]DBP <90 mm Hg.

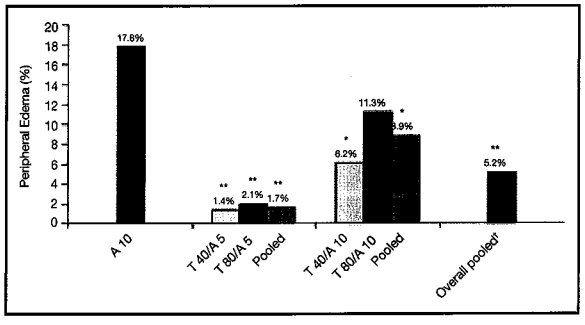


*Figure 3. Incidence of peripheral edema (%) in the amlodipine 10-mg (A10) group compared with combinations (telmisartan 40 mg [T40] or 80 mg [T80] plus amlodipine 5 mg [A5] or 10 mg). *P<.05. **P<.0001 vs A10. †Pooled for key combinations.*

observed by Chrysant and colleagues,[10] with the highest dose of olmesartan and amlodipine (40 mg/10 mg, respectively) in an 8-week factorial study in 1940 patients with higher baseline BP values.

The ACCOMPLISH study, which compared 2 different approaches of combination therapy suggests that the combination of an ACE inhibitor with amlodipine may provide better cardiovascular protection than an ACE inhibitor and diuretic at similar levels of BP control.[8,15] Although cumulative, mounting evidence supports the therapeutic equivalence between ARBs and ACE inhibitors, there are no studies to date that report the cardiovascular benefits of the combination of an ARB and a CCB. Nevertheless, the favorable tolerability profile of an ARB alone or in combination makes them an appealing alternative to ACE inhibitors.

The safety analysis showed that the number of patients experiencing an adverse event was comparable between combination therapy (37.9%) and the telmisartan (36.8%) and amlodipine (36.1%) monotherapies. Retention and drug adherence were high (92% and 98.4%, respectively). However, as expected, amlodipine 10 mg was associated with a high incidence of peripheral edema (17.8%) compared with all dosages of telmisartan monotherapy (range: 0.0%–0.8%). When telmisartan (all dosages) was used in combination with amlodipine 10 mg, the incidence of peripheral edema was notably reduced: 6.2% (telmisartan 40 mg/amlodipine 10 mg) and 11.3% (telmisartan 80 mg/amlodipine 10 mg). Although CCB-induced edema is not a new finding, the underlying mechanism is still not fully understood. It may involve pronounced vasodilation in precapillary vessels, which could result in abnormal intracapillary pressure or it could be linked to interference in local vasodilator control.[16,17] RAAS blockade is known to attenuate this effect, possibly via normalization of intracapillary pressure. However, the attenuation of edema has not been observed with some other combinations such as amlodipine plus hydrochlorothiazide.[18]

CONCLUSIONS

In conclusion, the findings in our study suggest that the combination of telmisartan plus amlodipine is associated with significant BP lowering after 8 weeks. The results of this factorial design study

are in line with the observations from factorial studies of other ARB/amlodipine combinations. However, head-to-head studies are needed to determine if the different pharmacokinetic profile of the individual ARBs, eg the longest half-life of telmisartan, are translated into clinically different pharmacodynamic effects among the 3 ARB/amlodipine combinations.

Overall, among the different combinations of telmisartan and amlodipine, it is clear that telmisartan 80 mg plus amlodipine 10 mg is the most effective combination and when treatment decisions have to take into consideration not only the antihypertensive efficacy but also the peripheral edema rates, the telmisartan and amlodipine combinations offer a very effective and tolerable option particularly in susceptible patients that require combination therapy.

Acknowledgments and disclosures: The authors would like to thank all study personnel who participated in the study, especially the Principal Investigators: H. Baglivo, M. Bendersky, E. Kuschnir, P. Rodriguez, A. Villamil (Argentina); J. Felicio, P. Jardim, O. Kohlman, D. Mion Jr (Brazil); M. Alpizar, R. Alvarado, J. Illescas, A. Meaney, J. Parra, R. Peralta, I. Rodriguez, H. Sanchez, S. Trevethan (Mexico); D. Bernhardi, A. Briel, S. Chetty, E. Janari, J. Jurgens, C. Kahanowitz, D. Lakha, H. Makan, I. Mitha, P. Nel, P. Patel, Z. Vawda, N. Wellington, (South Africa); J. Agaiby, J. Anderson, G. Balaji, H. Bays, N. Bertini, W. Bestermann Jr, K. Blaze, A. Borge, J. Boscia III, T. Brobyn, J. Brodnan, V. Brown, T. Cavalieri, C. Chappel, A. Chen, D. Cheung, S. Christensen, S. Chrysant, C. Cooper, T. Copeland, C. De Busk, D. DeSantis, B. Douglas, J. Ervin, P. Fiacco, T. Fiel, J. George, L. Gilderman, R. Gilman, R. Glover III, A. Goetsch, R. Graf, A. Graff, M. Graves, J. Gutmann, C. Hall, W. Harper, D. Henry, H. Hidalgo Jr, J. Holland, D. Honeycutt, C. Johnson, A. Khan, B. Khan, P. Klaassen, M. Kozinn, S. Kreis, K. Layne, J. Lee, A. Lewin, C.-S. Liang, L. Ligon, T. Linder, R. Lipetz, M. Lucas, R. Marple, J. Meli, C. Mello, R. Middleton, S. Mion-Bet, K. Mootoo, A. Murray, J. Naidu, P. Narayan, J. Navarro, J. Neutel, A. Niederman, R. Noble, A. Patron, F. Phillips, W. Pleskow, H. Punzi, G. Raad, T. Raoof, P. Raskin, A. Razzetti, L. Reed, H. Resnick, J. Schmidt, R. Schreiman, D. Schumacher, M. Seidner, K. Self, G. Serfer, W. Shapiro, J. Silverfield, S. Slabic, R. Sockolov, J. Sparks, R. Struble, C. Thompson, P. Toth, T. Treimer, P. Vrooman, D. Webster, G. Willis, S. Willsie, D. Wright, S. Yates (USA). The authors would also like to thank Karen Shannon (Trial Data Manager, Boehringer Ingelheim), Steven Koval (Trial Statistician, Boehringer Ingelheim), and Ashish Singh (Director, Boehringer Ingelheim). Writing assistance was provided by PAREXEL MMS, and was funded by Boehringer Ingelheim. The work was funded and sponsored by an educational grant from Boehringer Ingelheim. M. Kobe is an employee of Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT.

References

1 Wang YR, Alexander GC, Stafford RS. Outpatient hypertension treatment, treatment intensification, and control in Western Europe and the United States. *Arch Intern Med.* 2007;167:141–147.
2 Tedesco MA, Natale F, Calabro R. Effects of monotherapy and combination therapy on blood pressure control and target organ damage: a randomized prospective intervention study in a large population of hypertensive patients. *J Clin Hypertens.* 2006;8:634–641.
3 Weir MR. Targeting mechanisms of hypertensive vascular disease with dual calcium channel and renin-angiotensin system blockade. *J Hum Hypertens.* 2007;21:770–779.
4 Egan BM. Combination therapy with an angiotensin-converting enzyme inhibitor and a calcium channel blocker. *J Clin Hypertens.* 2007;9:783–789.
5 Epstein M, Bakris G. Newer approaches to antihypertensive therapy. Use of fixed-dose combination therapy. *Arch Intern Med.* 1996;156:1969–1978.
6 Weber MA, Bakris GL, Dahlöf B, et al. Baseline characteristics in the Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial: a hypertensive population at high cardiovascular risk. *Blood Press.* 2007;16:13–19.
7 Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet.* 2005;366:895–906.
8 Kjeldsen SE, Jamerson KA, Bakris GL, et al. Predictors of blood pressure response to intensified and fixed combination treatment of hypertension: the ACCOMPLISH study. *Blood Press.* 2008;17:7–17.
9 Allemann Y, Fraile B, Lambert M, et al. Efficacy of the combination of amlodipine and valsartan in patients with hypertension uncontrolled with previous monotherapy: the Exforge in Failure After Single Therapy (EX-FAST) study. *J Clin Hypertens.* 2008;10:185–194.
10 Chrysant SG, Melino M, Karki S, et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. *Clin Ther.* 2008;30:587–604.
11 Costa FV. Telmisartan standing out in a crowded contest? *High Blood Press Cardiovasc Prev.* 2006;13:85–94.
12 Fogari R, Derosa G, Zoppi A, et al. Effect of telmisartan-amlodipine combination at different doses on urinary albumin excretion in hypertensive diabetic patients with microalbuminuria. *Am J Hypertens.* 2007;20:417–422.
13 Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *JAMA.* 2003;289:2560–2572.
14 Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. *Clin Ther* 2007;29:563–580.
15 Jamerson KA, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med.* 2008;359:2417–2428.
16 Fogari R, Zoppi A, Derosa G, et al. Effect of valsartan addition to amlodipine on ankle oedema and subcutaneous tissue pressure in hypertensive patients. *J Hum Hypertens.* 2007;21:220–224.
17 Schrader J, Salvetti A, Calvo C, et al. The combination of amlodipine/valsartan 5/160 mg produces less peripheral oedema than amlodipine 10 mg in hypertensive patients not adequately controlled with amlodipine 5 mg. *Int J Clin Pract.* 2009;63:217–225.
18 Neldam S, Edwards C, ATHOS Study Group. Telmisartan plus HCTZ vs. amlodipine plus HCTZ in older patients with systolic hypertension: results from a large ambulatory blood pressure monitoring study. *Am J Geriatr Cardiol.* 2006;15:151–160.

Erratum

• *The Journal of Clinical Hypertension (Greenwich).* 2009;11(4):207–213.

Results of Treatment With Telmisartan-Amlodipine in Hypertensive Patients

Thomas W. Littlejohn, III, MD; Claudio R. Majul, MD; Rafael Olvera, MD; Mary Seeber, MD; Maureen Kobe, MSc; Robert Guthrie, MD; Wille Oigman, MD; On behalf of the study investigators

Section B of Figure 2 appearing on page 211 was missing Baseline SBP (mm Hg) data on the *x*-axis. The correct figure is printed below:

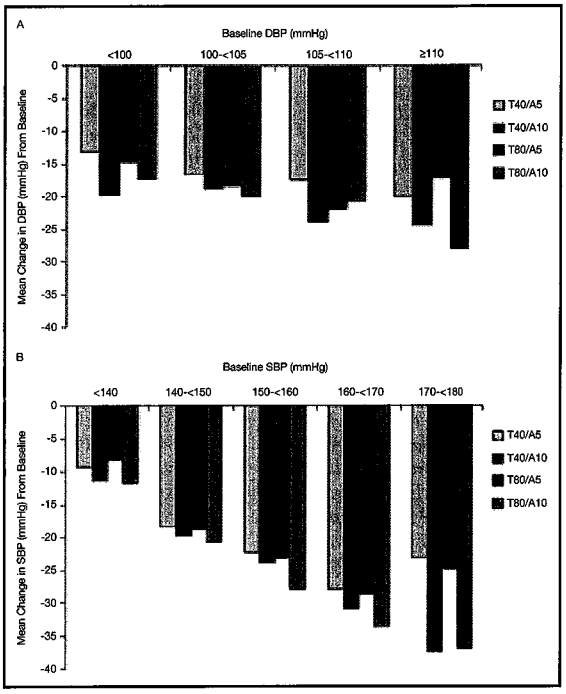


Figure 2. Effect of 8 weeks of treatment with the combinations of telmisartan 40 or 80 mg plus amlodipine 5 or 10 mg on the change from baseline in the in-clinic trough [A] diastolic blood pressure (mm Hg) or [B] systolic blood pressure (mm Hg) according to baseline blood pressure categories. DBP, diastolic blood pressure; SBP, systolic blood pressure; A5, amlodipine 5 mg; A10, amlodipine 10 mg; T40, telmisartan 40 mg; T80, telmisartan 80 mg.

doi: 10.1111/j.1751-7176.2009.00178.x

Effects of telmisartan and amlodipine in combination on ambulatory blood pressure in stages 1–2 hypertension

William B. White[a], Thomas W. Littlejohn[b], Claudio R. Majul[c], Willie Oigman[d], Rafael Olvera[e], Mary Seeber[f], Helmut Schumacher[g] and Giuseppe Mancia[h]

Background **Evaluation of combination therapy with antihypertensive agents by clinic blood pressure (BP) measurements may yield results that differ from out-of-office BP readings. This is of clinical relevance because out-of-office BP values are of prognostic importance. We studied the effects of combining telmisartan and amlodipine on ambulatory BP in patients with stages 1–2 hypertension.**

Methods **We conducted an 8-week, placebo-controlled, double-blind, 4 × 4 factorial design trial in which 562 patients with clinic diastolic BP at least 95 and 119 mmHg or less were randomized to receive telmisartan (0, 20, 40, or 80 mg) and/or amlodipine (0, 2.5, 5, or 10 mg). Ambulatory BP monitoring was performed at baseline and after 8 weeks of treatment; the end points of interest were the changes from baseline in 24-h systolic and diastolic BP. Secondary end points included the proportion of responders (≥ 10 mmHg BP reduction from baseline and/or <130/80 mean 24-h BP) and controlled patients (<130/80 mmHg mean 24-h BP).**

Results **Combination therapies of telmisartan and amlodipine lowered 24-h BP to a larger extent than the corresponding monotherapies at all doses. Mean reductions from baseline in 24-h BP for the combination of the highest doses of telmisartan (80 mg) and amlodipine (10 mg) were −22.4/−14.6 versus −11.9/−6.9 mmHg for amlodipine (10 mg) and −11.0/−6.9 mmHg for telmisartan (80 mg) ($P<0.0001$ for each comparison). In addition, BP response and control rates (24-h BP <130/80 mmHg) were significantly higher with the combination therapy versus the monotherapy groups.**

Conclusion **These findings show that telmisartan and amlodipine in combination provide substantial 24-h BP efficacy that is superior to either monotherapy in patients with stages 1 and 2 hypertension. *Blood Press Monit* 15:205–212 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Blood Pressure Monitoring 2010, 15:205–212

Keywords: ambulatory blood pressure monitoring, amlodipine, factorial design trial, telmisartan

[a]Division of Hypertension and Clinical Pharmacology, Pat and Jim Calhoun Cardiology Center, University of Connecticut School of Medicine, Farmington, Connecticut, [b]Piedmont Medical Research Associates, Winston-Salem, North Carolina, USA, [c]Hospital Santojanni, Buenes Aires, Argentina, [d]Rio de Janeiro State University, Rio de Janeiro, Brazil, [e]Clinica de Estudios Medicos SC, Guadalajara, Jalisco, Mexico, [f]Medi-Clinic Heart Hospital, Gauteng, South Africa, [g]Boehringer Ingelheim GmbH & Co. KG, Ingelheim am Rhein, Germany and [h]University Milano-Bicocca, San Gerardo Hospital, Monza, Milan, Italy

Correspondence to William B. White, MD, Division of Hypertension and Clinical Pharmacology, Pat and Jim Calhoun Cardiology Center, University of Connecticut School of Medicine, 263 Farmington Avenue, Farmington, CT 06030, USA
Tel: +1 860 679 2104; fax: +1 860 679 1250;
e-mail: wwhite@nso1.uchc.edu

Received 26 April 2010 **Accepted** 28 April 2010

Introduction

Since the publication of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) [1] in 2008 and the Anglo-Scandanavian Cardiac Outcomes Trials Blood Pressure Lowering Arm (ASCOT-BPLA) [2], the benefits of combined renin–angiotensin system blockade with a calcium antagonist have become an attractive combination therapy for patients with hypertension who have cardiovascular comorbidities. The clinical benefit of the combining of a renin–angiotensin system blocker and calcium channel blocker includes additive BP control, protection from both cardiac and cerebrovascular events, and an excellent safety and tolerability profile [1].

Telmisartan, a long-acting angiotensin receptor blocker (ARB) that has shown superior BP lowering effects in trials of patients with hypertension [3,4], is effective and used widely in the management of hypertension alone and in combination with other classes of antihypertensive therapies. In addition, telmisartan is approved in the US for the reduction of cardiovascular risk in patients with vascular disease who are intolerant of the angiotensin-converting enzyme inhibitors and by the European regulatory agencies for the reduction of cardiovascular morbidity in patients with manifest atherothrombotic, cardiovascular disease, or type 2 diabetes mellitus with documented target organ damage. Amlodipine, a dihydropyridine calcium antagonist with a long pharmacodynamic action is also effective in the treatment of hypertension and it has been extensively studied in both hypertension control and cardiovascular outcome studies [2,5].

This study evaluated the combinations of telmisartan and amlodipine at various dose levels to determine whether

1359-5237

DOI: 10.1097/MBP.0b013e32833c5722

the BP lowering effects of the combination therapy would be superior to either monotherapy and to evaluate the effects according to age, race, and baseline BP levels. The focus of efficacy in this study was 24-h ambulatory BP in approximately 40% of the patients from a larger, parent trial [6] to more fully evaluate the combination of the two therapies [7–9].

Methods

Study design

The trial was a randomized, double-blind, double-dummy, placebo-controlled, 4×4 factorial design trial (Trial Registration: NCT00281580), which evaluated telmisartan 20, 40, or 80 mg in combination with amlodipine 2.5, 5, and 10 mg for 8 weeks of treatment. Following a 3–4 week, single-blind, placebo run-in period, eligible patients with hypertension were randomized to one of 16 treatment groups for 8 weeks. The groups consisted of placebo, monotherapies of telmisartan 20, 40, and 80 mg, and amlodipine 2.5, 5, and 10 mg, and each of the nine combination therapies of telmisartan and amlodipine doses. All patients randomized to a treatment group containing 10 mg of amlodipine started with amlodipine 5 mg for the first 2 weeks and were then uptitrated to the higher dosage. Final assessments were performed 8 weeks after randomization.

Patients

Patients were recruited from 108 centers in Argentina, Mexico, South Africa and the US. Before initiation of the study, all patients were informed of the details of the study and signed consent forms approved by regional institutional review boards. Approximately the first 50% of the randomized patients in the parent study [6] underwent ambulatory BP monitoring (ABPM) evaluating the effects of trial medication over the 24-h dosing interval at baseline and end-of-study visits using a tracking system through the sponsor. Men and women with hypertension were included if their clinic diastolic BP was at least 95 and 119 mmHg or less. Exclusion criteria included: patients with known or suspected secondary hypertension, clinically significant renal, metabolic, hepatic, or psychiatric disorders, clinically relevant or unstable cardiovascular diseases, unstable diabetes mellitus ($HbA_{IC} \geq 10\%$ for over 3 months). In addition, night-shift workers, pregnant or nursing women, and women of childbearing potential not using medically approved means of contraception were excluded from study participation. Any antihypertensive or concomitant medications known to affect BP were not permitted during the study.

Blood pressure monitoring assessments

Ambulatory BP and heart rate measurements were obtained with the Spacelabs 90207 monitor (Issaquah, Washington, USA). Quality criteria used for an acceptable ambulatory BP recording included (i) a minimum of 18 hourly means available within 24 h after monitor hookup, (ii) no more than three consecutive hours of missing data. If these criteria were not met, the patient was asked to repeat the procedure within 3 days. If the repeat study failed to meet the quality control criteria, the ambulatory BP data were considered nonevaluable.

During the 24-h ambulatory monitoring study, BP and heart rate were measured every 20 min. Monitoring hook-up was initiated at $8:00 \pm 1$ h.

Statistical analyses

In the ABPM substudy, the primary end point for assessing efficacy was the change from baseline in the 24-h diastolic BP after 8 weeks of treatment. Secondary end points were the changes from baseline in 24-h systolic BP and changes from baseline in 24-h systolic and diastolic BP in the various treatment groups according to age (< 65 vs. ≥ 65 years) and race (Black vs. non-Black).

The primary analysis compared treatment effects on the primary efficacy end point using an analysis of covariance that included treatment as the main effect with baseline diastolic BP as a covariate. This analysis involved all 16 treatment groups and used the mean squared error for all treatment comparisons.

Assuming a standard deviation of 7 mmHg for the changes from baseline in 24-h mean DBP, a sample size of 50 patients per group would deliver approximately 80% power if there was a difference of 4 mmHg between combination and monotherapy treatment arms.

Results

Study population

Of the 1461 patients who participated in the main study, 562 (38.5%) were included in this ABPM substudy. The baseline characteristics of the patients and the number of patients participating in each study drug combination arm are shown in Table 1. Of the 562 patients included in the ABPM substudy, 403 (71.7%) had stage 2 hypertension (clinic diastolic BP ≥ 100 mmHg). The mean age of the patients was 53.0 years (range 22–84 years); most of the patients were non-Black (84.0%), and over half of the patients were male (54.3%). Safety assessments and adverse-event profile for the total study population have been reported elsewhere [6].

Effects on 24-h blood pressure

There were 742 patients enrolled into the ABPM substudy; 180 (24.3%) were excluded from this analysis because of missing or invalid data at either baseline or at the end of study. Reductions in 24-h mean BP are shown in Table 2 for all patients and Table 3 for patients with stage 2 hypertension. In both the categories of patients, combination treatments of telmisartan 20–80 mg plus amlodipine 2.5–10 mg resulted in additive reductions compared with their respective monotherapies. Trends relating changes from baseline in ambulatory BP according to dose was observed with both telmisartan and

Table 1 Baseline characteristics and number of patients participating in the various treatment arms

Number of patients, *n*	562
Age (years)	
Mean (SD)	53.0 (10.6)
Range	22–84
Age group, *n* (%)	
<65 years	492 (87.5)
65 to <75 years	60 (10.7)
≥ 75 years	10 (1.8)
Sex, *n* (%)	
Male	305 (54.3)
Female	257 (45.7)
Race, *n* (%)	
Caucasian	472 (84.0)
Black	75 (13.3)
Asian	15 (2.7)
Body mass index (kg/m^2)	
Mean (SD)	31.5 (6.4)
Range	18.4–61.7

	Amlodipine placebo	Amlodipine 2.5 mg	Amlodipine 5 mg	Amlodipine 10 mg	Total study
Telmisartan placebo	16	21	52	58	147
Telmisartan 20 mg	16	16	18	19	69
Telmisartan 40 mg	50	16	57	57	180
Telmisartan 80 mg	43	15	56	52	166
All patients	125	68	183	186	562

Table 2 Changes from baseline in 24-h systolic and diastolic blood pressure (all patients)

	Placebo	Amlodipine 2.5 mg	Amlodipine 5 mg	Amlodipine 10 mg
Changes from baseline in SBP/DBP (SD) mmHg				
Placebo	−1.4 (9.3)/−0.3 (6.0)	−7.4 (8.5)/−4.3 (5.1)	−9.3 (8.6)/−5.4 (5.3)	−11.9 (9.6)/−6.9 (6.8)
Telmisartan 20 mg	−7.4 (8.1)/−5.4 (5.0)	−11.1 (11.5)/−5.8 (6.4)	−15.9 (10.7)/−9.6 (4.9)	−14.0 (11.7)/−9.7 (7.0)
Telmisartan 40 mg	−8.4 (10.5)/−5.4 (6.8)	−13.7 (11.7)/−9.3 (5.8)	−17.3 (10.4)**,†††/−11.0 (7.2)***,†††	−20.5 (13.9)***,†††/−13.2 (7.7)***,†††
Telmisartan 80 mg	−11.0 (9.5)/−6.9 (6.1)	−15.8 (9.3)/−11.0 (6.5)	−19.5 (11.6)**,†††/−12.8 (7.4)**,†††	−22.4 (9.8)***,†††/−14.6 (6.9)***,†††

DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.
**$P<0.001$.
***$P<0.0001$ vs. telmisartan alone.
†††$P<0.0001$ vs. amlodipine alone.

Table 3 Changes from baseline in 24-h systolic and diastolic blood pressure (SD) in patients with stage 2 hypertension (diastolic blood pressure >100 mmHg)

	Amlodipine placebo	Amlodipine 2.5 mg	Amlodipine 5 mg	Amlodipine 10 mg
Changes from baseline in SBP/DBP (SD), mmHg				
Telmisartan placebo	−3.0 (12.1)/−1.3 (7.5)	−8.1 (8.0)/−5.2 (4.6)	−9.6 (8.5)/−5.0 (5.4)	−12.2 (9.8)/−7.3 (7.1)
Telmisartan 20 mg	−7.9 (9.0)/−6.2 (5.5)	−12.6 (13.0)/−6.0 (7.2)	−17.9 (10.6)/−10.5 (5.0)	−15.5 (13.2)/−11.9 (8.0)
Telmisartan 40 mg	−7.4 (11.0)/−5.1 (7.1)	−18.3 (12.7)/−11.0(6.7)	−16.7 (11.3)***,†/−11.0 (7.7)***,†††	−20.8 (14.1)***,††/−13.6 (8.0)***,†††
Telmisartan 80 mg	−11.3 (9.3)/−6.9 (6.0)	−14.9 (9.8)/−9.4 (6.6)	−20.9 (11.0)**,†††/−13.6 (7.1)**,†††	−22.7 (9.9)***,†††/−15.3 (7.0)***,†††

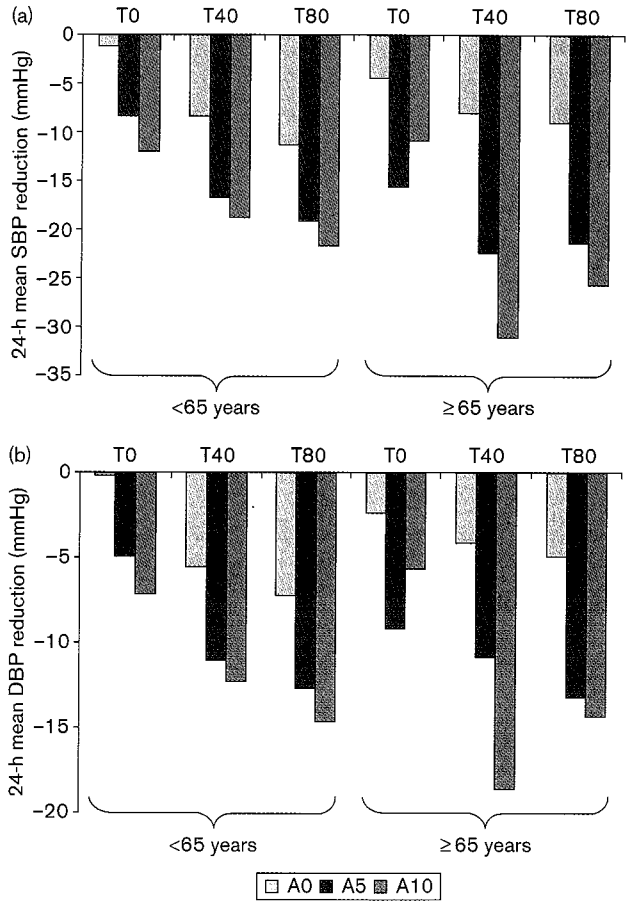
DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.
**$P<0.001$.
***$P<0.0001$ vs. telmisartan alone.
†$P<0.01$.
††$P<0.001$.
†††$P<0.0001$ vs. amlodipine alone.

amlodipine (Figs 1 and 2). The largest reductions in 24-h mean BP were observed with the combination of telmisartan 80 mg and amlodipine 10 mg when compared with their respective monotherapies ($P < 0.0001$ in each comparison): telmisartan 80 mg and amlodipine 10 mg (−22.4/−14.6 mmHg), telmisartan 80 mg (−11.0/−6.9 mmHg) and amlodipine 10 mg (−11.9/−6.9 mmHg) (Table 2). This effect was also seen in the stage 2 subgroup (Table 3). Greater BP reductions were also observed for the combinations of lower doses of telmisartan (40 mg) and amlodipine (5 mg) in combination compared with the components (Table 2).

In older patients (≥ 65 years), substantial reductions in 24-h BP were observed for the telmisartan and amlodipine combinations (Fig. 1). Reductions from baseline in systolic BP on the combination arms were generally larger in the older subgroup versus the younger population (< 65 years) and similar for the diastolic BP between age groups.

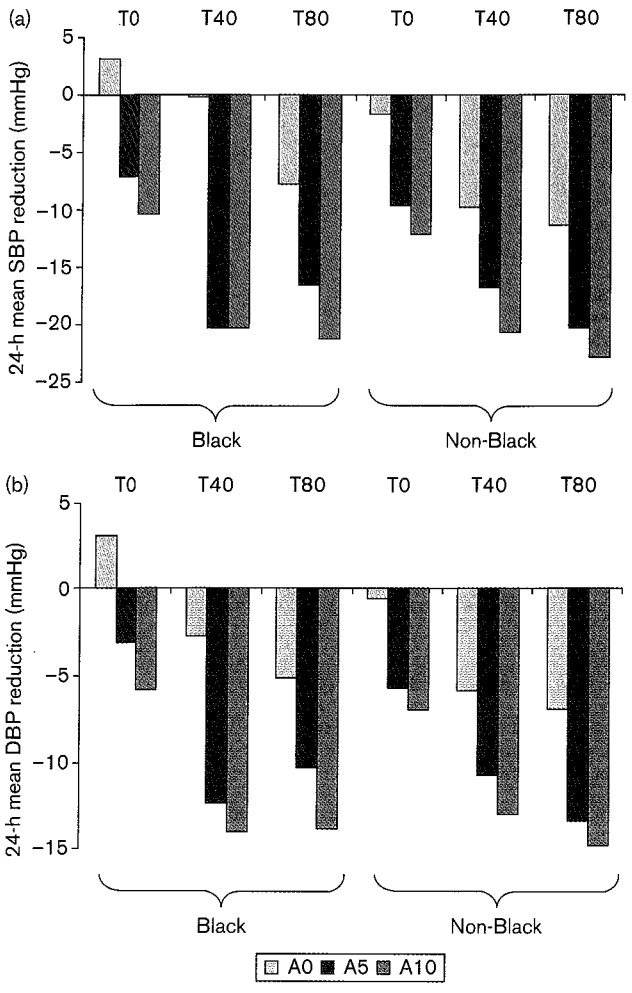
The effects of treatment according to race are shown in Fig. 2. Changes from baseline on telmisartan monotherapy was less in Blacks ($n = 75$) versus non-Blacks ($n = 487$). However, changes from baseline in the combination groups were similar for the two race groups (Fig. 2).

Fig. 1



Mean reduction from baseline in 24-h (a) systolic blood pressure (SBP) and (b) diastolic blood pressure (DBP) according to age. A5, amlodipine 5 mg; A10, amlodipine 10 mg; T80, telmisartan 80 mg; T40, telmisartan 40 mg

Fig. 2



Mean reduction from baseline in 24-h (a) systolic blood pressure (SBP) and (b) diastolic blood pressure (DBP) according to race. A5, amlodipine 5 mg; A10, amlodipine 10 mg; T80, telmisartan 80 mg; T40, telmisartan 40 mg.

Mean reductions in daytime, night-time, and final 6 h of dosing interval blood pressure

Changes from baseline in BP for each of the four key combination therapies (telmisartan 40 and 80 mg and amlodipine 5 and 10 mg) and their respective individual monotherapies are shown in Table 4. Combination therapies resulted in larger changes from baseline in BP than either of their respective individual monotherapies throughout the daytime, night-time, and in the last 6 h of the 24 h dosing period.

Blood pressure control and response rates

The effects of 8 weeks of treatment on 24-h ABPM response and control rates for the higher dose combinations of telmisartan and amlodipine are shown in Table 5 and compared to the respective monotherapy regimens. For the telmisartan 40 or 80 mg and amlodipine 10 mg combination, more than 80% of patients achieved 24-h diastolic BP control (< 80 mmHg) while 92% achieved 24-h diastolic BP control, 86.5% achieved 24-h systolic BP control (< 130 mmHg) and 82.7% achieved 24-h BP control (< 130/80 mmHg) in the telmisartan 80 mg and amlodipine 10 mg group. For the telmisartan 40 or 80 mg and amlodipine 10 mg combination, more than 90% of patients achieved 24-h diastolic BP response (< 80 mmHg or reduction of ≥ 10 mmHg) while 98% achieved diastolic BP response in the telmisartan 80 mg and amlodipine 10 mg group. In addition, 73.7–86.5% of patients achieved 24-h systolic BP control (< 130 mmHg) on the Telmisartan and Amlodipine 10 mg dose combinations. Similar trends with lower rates of BP responses and control rates were seen for the lower doses of telmisartan and Amlodipine 5 mg (Table 5).

Twenty-four hour hourly blood pressure profiles

The mean hourly systolic and diastolic BP curves at baseline and end of study for telmisartan 40 mg and

Table 4 Changes from baseline in daytime, night-time and last 6 h of dosing interval blood pressure for combination therapies of telmisartan and amlodipine compared with respective monotherapies

	Daytime (mmHg)	Night-time (mmHg)	Last 6 h (mmHg)
Placebo	−1.5/−0.2	−1.0/−0.5	1.1/1.2
Telmisartan 40 mg	−8.0/−5.1	−8.8/−5.5	−8.9/−6.0
Telmisartan 80 mg	−11.6/−7.2	−9.6/−5.5	−9.9/−6.2
Amlodipine 5 mg	−10.3/−5.6	−8.1/−4.7	−8.4/−5.5
Amlodipine 10 mg	−12.1/−7.1	−11.5/−6.4	−12.9/−7.9
Telmisartan 40 + Amlodipine 5 mg	−17.4***,††/−11.4***,†††	−16.9***,††/−10.4***,††	−16.2*,†/−10.2*,†
Telmisartan 40 + Amlodipine 10 mg	−21.3***,†††/−14.3***,†††	−18.9***,††/−10.9***,††	−18.7***,†/−10.9***,†
Telmisartan 80 + Amlodipine 5 mg	−20.7***,†††/−13.5**,†††	−16.8*,††/−11.2*,†	−16.5*,†/−10.6†
Telmisartan 80 + Amlodipine 10 mg	−23.2***,†††/−15.5***,†††	−20.8***,†††/−12.8***,†††	−22.6***,†††/−14.7***†††

Data are mean changes (mmHg) relative to baseline.
*$P<0.05$.
**$P<0.001$.
***$P<0.0001$ vs. telmisartan alone.
†$P<0.05$.
††$P<0.001$.
†††$P<0.0001$ vs. amlodipine alone.

Table 5 Effect of 8 weeks of treatment with key combinations of telmisartan plus amlodipine on blood pressure response* and control rates† ($n=562$)

Treatment	Diastolic BP response§ (%)	Systolic BP response§ (%)	Diastolic BP control$ (%)	Systolic BP control$ (%)	BP control¥ (%)	Daytime BP control# (%)	Nighttime BP control¶ (%)
Placebo	50.0	31.3	43.8	18.8	18.8	18.8	25.0
Telmisartan 40 mg	40.0	42.0	34.0	40.0	30.0	26.0	32.0
Telmisartan 80 mg	55.8	62.8	55.8	48.8	44.2	48.8	30.2
Amlodipine 5 mg	63.5	61.5	53.9	53.9	38.5	42.3	26.9
Amlodipine 10 mg	63.8	69.0	50.0	56.9	37.9	46.6	32.8
Telmisartan 40 mg + Amlodipine 5 mg	86.0***,†	79.0***,†	73.7***	64.9*	54.4	54.4*	38.6
Telmisartan 40 mg + Amlodipine 10 mg	91.2***,††	84.2***	80.7***††	73.7**	68.4***,†	75.4***,†	57.9*,†
Telmisartan 80 mg + Amlodipine 5 mg	80.4*	87.5*,†	62.5	66.1	53.6	62.5	42.9
Telmisartan 80 mg + Amlodipine 10 mg	98.1***,†††	96.2***,††	92.3***,†††	86.5***,††	82.7***†††	86.5***,†††	63.5*,†

DBP diastolic blood pressure; SBP, systolic blood pressure.
§24-h mean DBP <80 mmHg or reduction ≥ 10 mmHg; SBP <130 mmHg or reduction ≥ 15 mmHg.
$24-h mean DBP <80 mmHg; SBP < 130 mmHg.
¥24-h mean SBP/DBP <130/<80 mmHg.
#Daytime mean SBP/DBP <135/<85 mmHg.
¶Night-time mean SBP/DBP <120/<70 mmHg.
*$P<0.01$.
**$P<0.001$.
***$P<0.0001$ vs. telmisartan alone.
†$P<0.01$.
††$P<0.001$.
†††$P<0.0001$ vs. amlodipine alone.

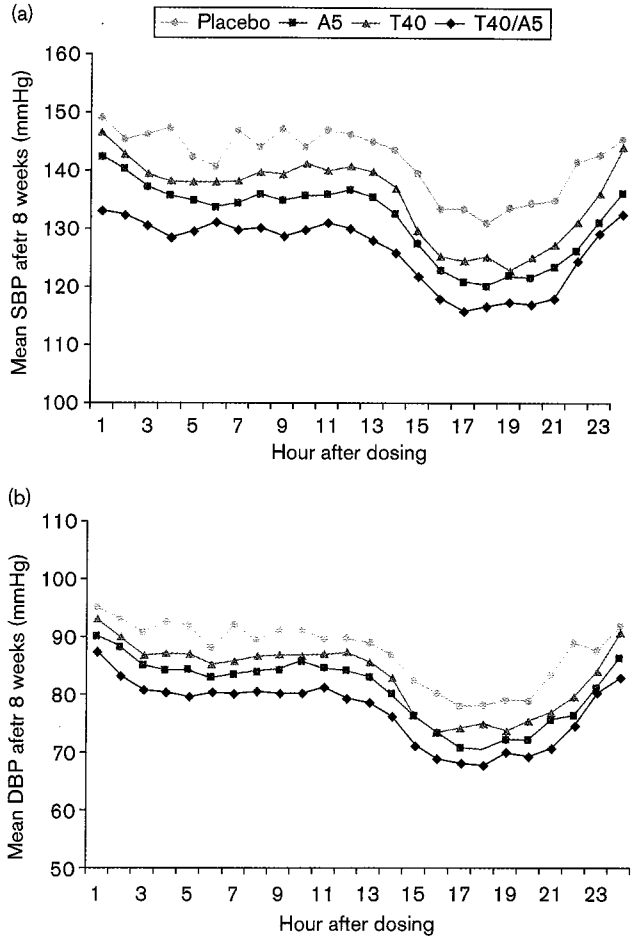
telmisartan 80 mg plus amlodipine 5 or 10 mg are compared with the monotherapies in Figs 3–6. Reductions with combination therapy were consistently greater than the respective monotherapies throughout the 24-h dosing period (mean 24 h reductions from baseline, $P < 0.0001$ versus either monotherapy for both systolic and diastolic BP).

Discussion

In this large factorial design clinical trial, the combination of telmisartan and amlodipine lowered ambulatory BP in an additive fashion as compared with the effects of the combination components in monotherapy. This was the case regardless of the age and race of the patients. The combination showed additive reductions in 24-h BP of 9–11/6–8 mmHg (systolic/diastolic) versus telmisartan alone, and of 9–11/6–8 mmHg versus amlodipine alone, at the doses of 40/5, 40/10, 80/5, and 80/10 mg, which are those that are now registered and available in several countries around the world. The additive effect is presumably because of the different pharmacological effects of ARBs and calcium antagonists [6,10], as these agents cause a dilation of vascular smooth muscle, with a reduction in the elevated systemic vascular resistance typical of hypertension through complementary mechanisms [11,12].

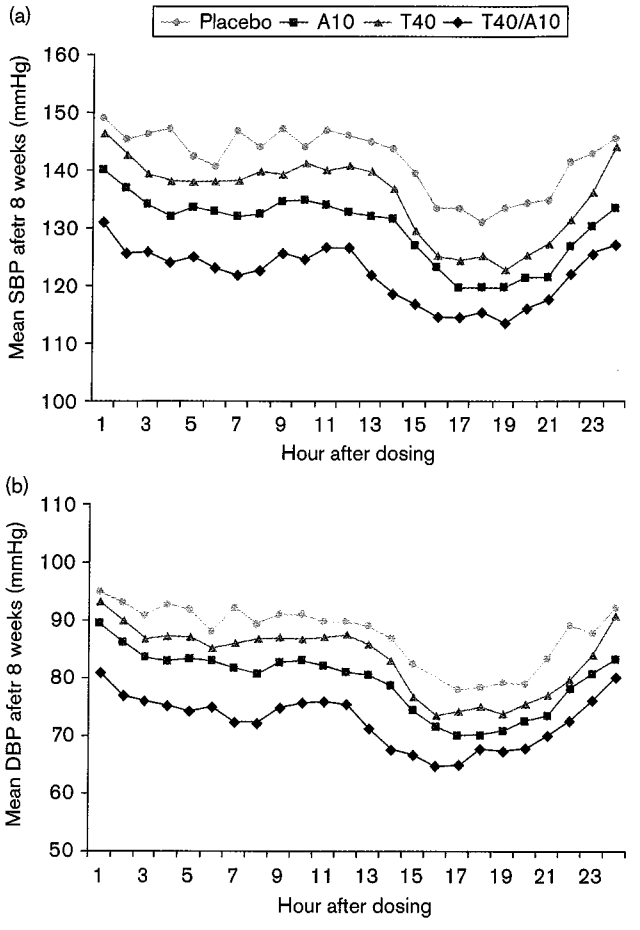
The greater BP-lowering effects of the telmisartan/amlodipine combination were manifest throughout the 24 h, including the last 6 h postdosing. This ensures that its substantial therapeutic effect lasts throughout the dosing interval. The present results on 24 h ambulatory BP are consistent with the findings obtained in earlier studies that the telmisartan/amlodipine combination additively lowered clinic BP versus telmisartan or amlodipine monotherapy [6]. The changes in clinic BP from baseline with telmisartan 80 mg plus amlodipine 10 mg were −26/−20 mmHg while the corresponding changes in 24-h BP from baseline were −22/−15 mmHg.

Fig. 3



Twenty-four hour profile of mean hourly blood pressure (BP) for placebo, telmisartan (T) 40 mg, amlodipine 5 mg (A5), and the combination T40 + A5. (a) Systolic BP (SBP), (b) diastolic BP (DBP). Mean 24-h BP reductions for combination therapy were significantly greater than either monotherapy ($P<0.0001$).

Fig. 4



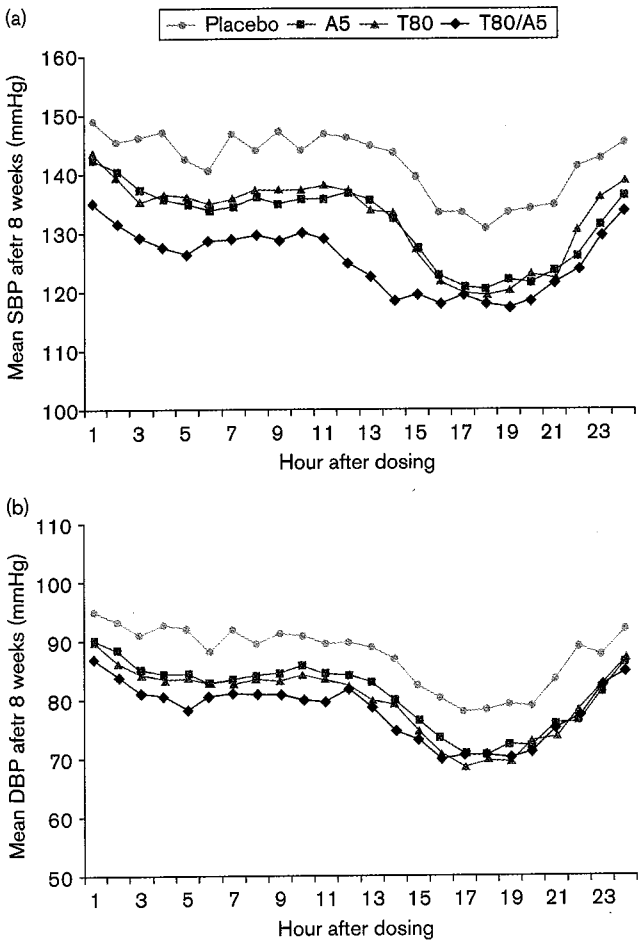
Twenty-four hour profile of mean hourly blood pressure (BP) for placebo, telmisartan (T) 40 mg, amlodipine 10 mg (A10), and the combination T40 + A10. (a) Systolic BP (SBP), (b) diastolic BP (DBP). Mean 24-h BP reductions for combination therapy were significantly greater than either monotherapy ($P<0.0001$).

The effects of antihypertensive treatment based on ambulatory BP are nearly always less than measurements made in the clinic; indeed a meta-analysis of studies in which the effects of treatment on the two BPs were compared in the same individuals has shown that an approximate 30% difference could be expected [13]. This can be explained in part, by the fact that 24 h includes sleep time, when lower baseline BP values reduce the magnitude of the antihypertensive effect [13] and the observer bias [14–16] and the placebo effect, which are known to affect clinic to a much greater degree than ambulatory BP [17,18]. This phenomenon was probably playing a role for the data herein as the change in clinic diastolic values seen in the placebo group was −5.9 mmHg, whereas the 24-h diastolic BP change was only −0.3 mmHg.

The combination therapy showed substantial reductions in ambulatory systolic BP in the older patient subgroup, which may enhance the combined effect of two powerful arteriolar vasodilators such as telmisartan and amlodipine [19,20]. It is also possible that the two drug combination favors a reduction of arterial stiffness, which is a major determinant of the elevated systolic BP seen in elderly patients [21].

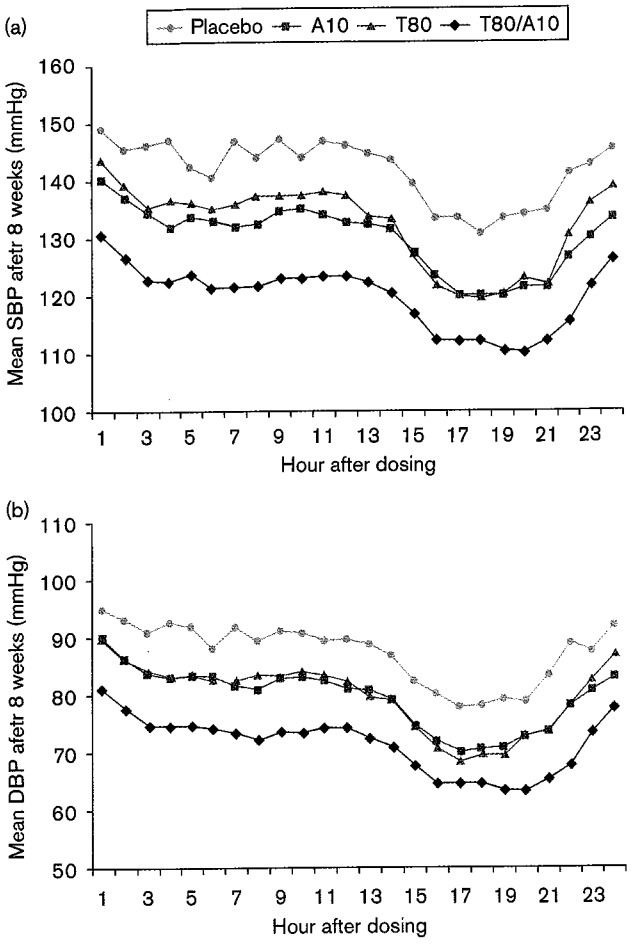
There was also evidence that combining telmisartan and amlodipine was as effective in Black patients with hypertension as in non-Black patients with hypertension (Fig. 2). Lack of efficacy of renin–angiotensin blocking agents is well known in African–American patients with hypertension [22] and confirmed in this study by the small effect of telmisartan alone on ambulatory BP (Fig. 2). When amlodipine was combined with telmisartan, the magnitude of reduction in ambulatory BP was quite similar to that seen with the telmisartan/amlodipine combination in the

Fig. 5



Twenty-four hour profile of mean hourly blood pressure (BP) for placebo, telmisartan (T) 80 mg, amlodipine 5 mg (A5), and the combination T80 + A5. (a) Systolic BP (SBP), (b) diastolic BP (DBP). Mean 24-h BP reductions for combination therapy were significantly greater than either monotherapy ($P<0.0001$).

Fig. 6



Twenty-four hour profile of mean hourly blood pressure (BP) for placebo, telmisartan (T) 80 mg, amlodipine 10 mg (A10), and the combination T80 + A10. (a) Systolic BP (SBP), (b) diastolic BP (DBP). Mean 24-h BP reductions for combination therapy were significantly greater than either monotherapy ($P<0.0001$).

non-Black patient subgroup. Of note, similar findings have been obtained when a thiazide diuretic was added to telmisartan in standard clinical doses [23].

Conclusion

This large factorial design study that used 24-h ABPM to evaluate the effects of telmisartan alone, amlodipine alone, and the combination of the agents has shown that telmisartan lowers BP to a similar extent to amlodipine, and that telmisartan added to amlodipine has significant additive BP lowering effects. Response and control rates (Table 5) were also substantially greater for the combination of these agents at their clinically registered doses. The benefits related to BP control in hypertension are well known [24], as are the advantages of using combination treatment, which provides a greater BP lowering effect than monotherapies and improved compliance by patients [11,12]. For the combination of an ARB and calcium antagonist, enthusiasm has increased substantially based on the results of the ACCOMPLISH Study [1] and the ASCOT BP lowering study in patients with high-risk hypertension [1,2].

Acknowledgements

Funding was provided by Boehringer-Ingelheim GMBH, Ingelheim, Germany. Editorial assistance was provided by Anne Jacobson, PhD, Parexel, UK.

References

1 Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, *et al.* Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008; **359**:2417–2428.

2 Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, *et al.*; ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandanavian

cardiac outcomes trial –blood pressure lowering arm (ASCOT-BPLA): a multicentre randomized controlled trial. *Lancet* 2005; **366**:895–906.
3 White WB, Lacourciere Y, Davidai G. Effects of the angiotensin II receptor blockers telmisartan versus valsartan on the circadian variation of blood pressure. *Am J Hypertens* 2004; **17**:347–353.
4 Lacourciere Y, Krzesinski JM, White WB, Davidai G, Schumacher H. Sustained antihypertensive activity of telmisartan compared with valsartan. *Blood Press Monit* 2004; **9**:203–210.
5 Punzi HA, Noveck R, Weiss RJ, Graf R, Ruff DA, Hutchinson HG, White WB. Are there differences in the effects of long-acting calcium antagonists on ambulatory blood pressure? Extended release nisoldipine versus amlodipine as a model. *Blood Press Monit* 1998; **3**:267–272.
6 Littlejohn T, Majul CR, Olvera R, Seeber M, Kobe M, Guthrie G, Oigman W. Results of treatment with telmisartan–amlodipine in hypertensive patients. *J Clin Hypertens* 2009; 11:207–213.
7 Staessen J, Thijs L, Fagard F, O'Brien E, Clement D, De Leeuw PW, *et al.* Predicting cardiovascular risk using conventional vs. ambulatory blood pressure in older patients with systolic hypertension. *JAMA* 1999; **282**:539–546.
8 Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population. Follow-Up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) Study. *Circulation* 2005; **111**:1777–1783.
9 Williams B. The year in hypertension. *J Am Coll Cardiol* 2006; **48**:1698–1711.
10 Wilson TW, Lacourciere Y, Barnes CC. The antihypertensive efficacy of losartan and amlodipine assessed with office and ambulatory blood pressure monitoring. *CMAJ* 1998; **159**:469–476.
11 Mancia G, De Backer G, Dominiczak D, Cifkova R, Fagard R, Germano G, *et al.* 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25**:1105–1187.
12 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, *et al.*; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *JAMA* 2003; **289**:2560–2572.
13 Mancia G, Parati G. Office compared with ambulatory blood pressure in assessing response to antihypertensive treatment: a meta-analysis. *J Hypertens* 2004; **22**:435–445.
14 White WB, Pitt B, Preston RA, Hanes V. Antihypertensive effects of drospirenone with 17-beta estradiol, a novel hormone treatment in postmenopausal women with stage 1 hypertension. *Circulation* 2005; **112**:1979–1984.
15 Ghuman N, Campbell P, White WB. Role of ambulatory and home blood pressure recording in clinical practice. *Curr Cardiol Reports* 2009; **11**:414–421.
16 White WB, Giles T, Bakris GL, Neutel JM, Davidai G, Weber MA. Measuring the efficacy of antihypertensive therapy by ambulatory blood pressure monitoring in the primary care setting. *Am Heart J* 2006; **151**:176–184.
17 Mancia G, Omboni S, Parati G, Ravogli A, Villani A, Zanchetti A. Lack of placebo effect on ambulatory blood pressure. *Am J Hypertens* 1995; **8**:311–315.
18 Mancia G, Sega R, Grassi G, Cesana G, Zanchetti A. Editorial: defining ambulatory and home blood pressure normality: further considerations on data from PAMELA Study. *J Hypertens* 2001; **19**:995–999.
19 White WB. Comparative effects of telmisartan in the treatment of hypertension. *J Clin Hypertens (Greenwich)* 2002; **4 (Suppl 1)**:20–25.
20 Lund-Johansen P, Omvik P, White W, Digranes O, Helland B, Jordal O, Stray T. Long-term haemodynamic effects of amlodipine at rest and during exercise in essential hypertension. *Cardiology* 1992; **80 (Suppl 1)**:37–45.
21 O'Rourke MF, Mancia G. Arterial stiffness. *J Hypertens* 1999; **17**:1–4.
22 Saunders E, Gavin JR. Blockade of the renin–angiotensin system in African-Americans with hypertension and cardiovascular diseases. *J Clin Hypertens* 2003; **5 (Suppl 1)**:12–17.
23 White WB, Murwin D, Chyrsant SG, Koval SE, Davidai G, Guthrie R. Effects of the angiotensin II receptor blockers telmisartan versus valsartan in combination with hydrochlorothiazide: a large, confirmatory trial. *Blood Press Monit* 2008; **13**:21–27.
24 Blood Pressure Lowering Treatment Trialist' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomized trials. *Lancet* 2003; **362**:1527–1535.

Wolters Kluwer Health | Lippincott Williams & Wilkins

Reprints provided by

Wolters Kluwer Pharma Solutions
Level 4 / 333 George Street, Sydney NSW 2000
T: +61 (0)2 9276 6667 | F: +61 (0)2 9231 5086
E-mail: PS-asiapacific.reprints@wolterskluwer.com

ELS1OL2872

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

ABSTRACT

BACKGROUND

Warfarin reduces the risk of stroke in patients with atrial fibrillation but increases the risk of hemorrhage and is difficult to use. Dabigatran is a new oral direct thrombin inhibitor.

METHODS

In this noninferiority trial, we randomly assigned 18,113 patients who had atrial fibrillation and a risk of stroke to receive, in a blinded fashion, fixed doses of dabigatran — 110 mg or 150 mg twice daily — or, in an unblinded fashion, adjusted-dose warfarin. The median duration of the follow-up period was 2.0 years. The primary outcome was stroke or systemic embolism.

RESULTS

Rates of the primary outcome were 1.69% per year in the warfarin group, as compared with 1.53% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.91; 95% confidence interval [CI], 0.74 to 1.11; P<0.001 for noninferiority) and 1.11% per year in the group that received 150 mg of dabigatran (relative risk, 0.66; 95% CI, 0.53 to 0.82; P<0.001 for superiority). The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the group receiving 110 mg of dabigatran (P=0.003) and 3.11% per year in the group receiving 150 mg of dabigatran (P=0.31). The rate of hemorrhagic stroke was 0.38% per year in the warfarin group, as compared with 0.12% per year with 110 mg of dabigatran (P<0.001) and 0.10% per year with 150 mg of dabigatran (P<0.001). The mortality rate was 4.13% per year in the warfarin group, as compared with 3.75% per year with 110 mg of dabigatran (P=0.13) and 3.64% per year with 150 mg of dabigatran (P=0.051).

CONCLUSIONS

In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. (ClinicalTrials.gov number, NCT00262600.)

Reprinted from THE NEW ENGLAND JOURNAL OF MEDICINE
(ISSN 0028-4793) Vol. 361:1139-1151 (September 17, 2009).

Printed in the U.S.A. Fax: (781) 893-8103 www.nejm.org

From the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada (S.J.C., S.Y., J.E., J.P., E.T.); Lankenau Institute for Medical Research and the Heart Center, Wynnewood, PA (M.D.E., A.P.); Uppsala Clinical Research Center, Uppsala, Sweden (J.O., L.W.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (P.A.R., J.V., S.W.); Working Group on Cardiovascular Research the Netherlands, Utrecht, the Netherlands (M.A.); St. John's National Academy of Health Sciences, Bangalore, India (D.X.); FuWai Hospital, Beijing (J.Z.); Estudios Clínicos Latinoamérica, Rosario, Argentina (R.D.); Lady Davis Carmel Medical Center, Haifa, Israel (B.S.L.); Vivantes Klinikum Neukölln, Berlin (H.D.); University Duisburg-Essen, Essen, Germany (H.-C.D.); and Sunnybrook Health Sciences Centre, Toronto (C.D.J.). Address reprint requests to Dr. Connolly at the Population Health Research Institute, 237 Barton St. E., Hamilton, ON L8L 2X2, Canada, or at connostu@phri.ca.

*Members of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Study Group are listed in the Appendix and the Supplementary Appendix, available with the full text of this article at NEJM.org.

Drs. Connolly, Ezekowitz, Yusuf, and Wallentin contributed equally to this article.

This article (10.1056/NEJMoa0905561) was published on August 30, 2009, and updated on September 16, 2009, at NEJM.org.

N Engl J Med 2009;361:1139-51.

Atrial fibrillation increases the risks of stroke and death. Vitamin K antagonists, such as warfarin, reduce the risks of stroke and death but increase the risk of hemorrhage as compared with control therapy.[1] Therefore, warfarin is recommended for patients who have atrial fibrillation and are at risk for stroke.[2]

Vitamin K antagonists are cumbersome to use, because of their multiple interactions with food and drugs, and they require frequent laboratory monitoring. Therefore, they are often not used, and when they are, rates of discontinuation are high.[3,4] Many patients receiving warfarin still have inadequate anticoagulation.[5] Thus, there is a need for new anticoagulant agents that are effective, safe, and convenient to use.

Dabigatran etexilate is an oral prodrug that is rapidly converted by a serum esterase to dabigatran, a potent, direct, competitive inhibitor of thrombin. It has an absolute bioavailability of 6.5%, 80% of the given dose is excreted by the kidneys, its serum half-life is 12 to 17 hours, and it does not require regular monitoring.[6] Dabigatran has been evaluated in a pilot trial involving patients with atrial fibrillation and in a study for the prevention of venous thromboembolism, in which doses of 150 mg twice daily and 220 mg once daily, respectively, were promising.[7,8] We performed a large, randomized trial comparing the use of dabigatran, at doses of 110 mg twice daily and 150 mg twice daily, with warfarin.

METHODS

TRIAL DESIGN

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) was a randomized trial designed to compare two fixed doses of dabigatran, each administered in a blinded manner, with open-label use of warfarin in patients who had atrial fibrillation and were at increased risk for stroke. The design of this study has been described previously.[9]

The study was funded by Boehringer Ingelheim and was coordinated by the Population Health Research Institute (Hamilton, ON, Canada), which independently managed the database and performed the primary data analyses. An operations committee, with assistance from an international steering committee and with participation by the sponsor, was responsible for the design, conduct, and reporting of the study. The study was approved by all appropriate national regulatory authorities and ethics committees of the participating centers. All the authors vouch for the accuracy and completeness of the data and the analyses.

STUDY PARTICIPANTS

Patients were recruited from 951 clinical centers in 44 countries. In brief, patients were eligible if they had atrial fibrillation documented on electrocardiography performed at screening or within 6 months beforehand and at least one of the following characteristics: previous stroke or transient ischemic attack, a left ventricular ejection fraction of less than 40%, New York Heart Association class II or higher heart-failure symptoms within 6 months before screening, and an age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease. Reasons for exclusion were the presence of a severe heart-valve disorder, stroke within 14 days or severe stroke within 6 months before screening, a condition that increased the risk of hemorrhage, a creatinine clearance of less than 30 ml per minute, active liver disease, and pregnancy. (Detailed inclusion and exclusion criteria are available in Tables 1 and 2 of the Supplementary Appendix, available with the full text of this article at NEJM.org.)

PROCEDURES

After providing written informed consent, all trial participants were randomly assigned to receive one of two doses of dabigatran, or to receive warfarin, by means of a central, interactive, automated telephone system. Dabigatran was administered, in a blinded fashion, in capsules containing either 110 mg or 150 mg of the drug, to be taken twice daily. Warfarin was administered, in an unblinded fashion, in tablets of 1, 3, or 5 mg and was adjusted locally to an international normalized ratio (INR) of 2.0 to 3.0, with the INR measured at least monthly. The time that the INR was within the therapeutic range was calculated with the use of the method of Rosendaal et al.,[10] excluding INRs from the first week and after discontinuation of the study drug. These data were reported back to the participating centers with advice for optimal INR control. Concomitant use of aspirin (at a dose of <100 mg per day) or other antiplatelet agents was permitted. Quinidine use was

permitted until 2 years after the trial started, when the protocol was amended to prohibit its use, because of its potential to interact with dabigatran.

Follow-up visits occurred 14 days after randomization, at 1 and 3 months, every 3 months thereafter in the first year, and then every 4 months until the study ended. Liver-function testing was performed monthly during the first year of the follow-up period. On the basis of a prespecified evaluation of liver-function tests in at least 6000 patients in the dabigatran group after they had been followed for 6 months or more, the data safety monitoring board recommended that the frequency of liver-function testing be reduced, with such testing performed only at the regular visits.

OUTCOMES

The primary study outcome was stroke or systemic embolism. The primary safety outcome was major hemorrhage. Secondary outcomes were stroke, systemic embolism, and death. Other outcomes were myocardial infarction, pulmonary embolism, transient ischemic attack, and hospitalization. The primary net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major hemorrhage. Stroke was defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery and categorized as ischemic, hemorrhagic, or unspecified. Hemorrhagic transformation of ischemic stroke was not considered to be hemorrhagic stroke. Intracranial hemorrhage consisted of hemorrhagic stroke and subdural or subarachnoid hemorrhage. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ, documented by means of imaging, surgery, or autopsy. Major bleeding was defined as a reduction in the hemoglobin level of at least 20 g per liter, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. Life-threatening bleeding was a subcategory of major bleeding that consisted of fatal bleeding, symptomatic intracranial bleeding, bleeding with a decrease in the hemoglobin level of at least 50 g per liter, or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or necessitating surgery. All other bleeding was considered minor.

An international team of adjudicators reviewed documents in local languages after blinding, or documents were translated by an independent group and were centrally blinded. Each primary and secondary outcome event was adjudicated by two independent investigators who were unaware of the treatment assignments. All transient ischemic attacks were reviewed to ensure that strokes had not been missed. To detect possible unreported events, symptom questionnaires were regularly administered to patients, and adverse-event and hospitalization reports were scrutinized for unreported primary or secondary outcomes.

STATISTICAL ANALYSIS

The primary analysis was designed to test whether either dose of dabigatran was noninferior to warfarin, as evaluated with the use of Cox proportional-hazards modeling. To satisfy the noninferiority hypothesis, the upper bound of the one-sided 97.5% confidence interval for the relative risk of an outcome with dabigatran as compared with warfarin needed to fall below 1.46. This noninferiority margin was derived from a meta-analysis of trials of vitamin K antagonists as compared with control therapy in patients with atrial fibrillation, with the margin defined according to the upper bound of the 95% confidence interval for the relative risk of the primary outcome in the control group versus the warfarin group.[11] The margin of 1.46 represents half the 95% confidence interval of the estimated effect of control therapy over warfarin. To account for testing of both dabigatran doses against warfarin, we planned to determine whether the higher of the two one-sided P values for the two doses was less than 0.025, in which case both treatments would be declared to be noninferior. If the higher of the two one-sided P values was 0.025 or greater, the lower of the two was required to be less than 0.0125 to permit a claim of statistical significance. All analyses were based on the intention-to-treat principle. After noninferiority of both doses of dabigatran was established, all subsequent P values were reported for two-tailed tests of superiority. Cox regression was used to calculate relative risks, confidence intervals, and P values. Chi-square testing was used to compare rates of medication discontinuation and adverse events.

We planned to enroll 15,000 patients, an enrollment that we estimated would provide 84% power to evaluate the noninferiority of each dose

of dabigatran. Two protocol changes were made by the operations committee during the enrollment period, without knowledge of emerging treatment effects. These were the enforcement of balanced enrollment of patients who had not received long-term therapy with a vitamin K antagonist (i.e., had a total lifetime use of <61 days) and those who had (i.e., had a total lifetime use of ≥61 days), and an increase in the sample size to 18,000 patients to maintain the statistical power in case of a low event rate. An independent data safety monitoring board reviewed the unblinded study data and performed two prespecified interim analyses of efficacy, with a plan to recommend study termination if the benefit of dabigatran exceeded 3 SD from unity of the parameter estimate and if that benefit persisted on repeat analysis 3 months later.

RESULTS

CHARACTERISTICS OF THE STUDY PATIENTS

A total of 18,113 patients were enrolled between December 22, 2005, and December 15, 2007. The three treatment groups were well balanced with respect to baseline characteristics (Table 1). The mean age of the patients was 71 years, and 63.6% were men. Half the patients had received long-term therapy with vitamin K antagonists. The mean $CHADS_2$ score was 2.1 (Table 1).

FOLLOW-UP DATA

Final follow-up visits occurred between December 15, 2008, and March 15, 2009. The median duration of the follow-up period was 2.0 years, and complete follow-up was achieved in 99.9% of patients, with 20 patients lost to follow-up. The rates of discontinuation for 110 mg of dabigatran, 150 mg of dabigatran, and warfarin were 14.5%, 15.5%, and 10.2%, respectively, at 1 year and 20.7%, 21.2%, and 16.6% at 2 years. Aspirin was used continuously during the treatment period in 21.1%, 19.6%, and 20.8% of patients receiving 110 mg of dabigatran, 150 mg of dabigatran, and warfarin, respectively. In the warfarin group, the mean percentage of the study period during which the INR was within the therapeutic range was 64%.

PRIMARY OUTCOME

Stroke or systemic embolism occurred in 182 patients receiving 110 mg of dabigatran (1.53% per year), 134 patients receiving 150 mg of dabigatran (1.11% per year), and 199 patients receiving warfarin (1.69% per year) (Table 2 and Fig. 1). Both doses of dabigatran were noninferior to warfarin (P<0.001). The 150-mg dose of dabigatran was also superior to warfarin (relative risk, 0.66; 95% confidence interval [CI], 0.53 to 0.82; P<0.001), but the 110-mg dose was not (relative risk, 0.91; 95% CI, 0.74 to 1.11; P=0.34). Rates of hemorrhagic stroke were 0.38% per year in the warfarin group, as compared with 0.12% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.31; 95% CI, 0.17 to 0.56; P<0.001) and 0.10% per year in the group that received 150 mg of dabigatran (relative risk, 0.26; 95% CI, 0.14 to 0.49; P<0.001).

OTHER OUTCOMES

Rates of death from any cause were 4.13% per year with warfarin, as compared with 3.75% per year with 110 mg of dabigatran (relative risk with dabigatran, 0.91; 95% CI 0.80 to 1.03; P=0.13) and 3.64% per year with 150 mg of dabigatran (relative risk, 0.88; 95% CI, 0.77 to 1.00; P=0.051). The rate of myocardial infarction was 0.53% per year with warfarin and was higher with dabigatran: 0.72% per year in the 110-mg group (relative risk, 1.35; 95% CI, 0.98 to 1.87; P=0.07) and 0.74% per year in the 150-mg group (relative risk, 1.38, 95% CI, 1.00 to 1.91; P=0.048).

BLEEDING

The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.80; 95% CI, 0.69 to 0.93; P=0.003) and 3.11% per year in the group that received 150 mg of dabigatran (relative risk, 0.93; 95% CI, 0.81 to 1.07; P=0.31) (Table 3). Rates of life-threatening bleeding, intracranial bleeding, and major or minor bleeding were higher with warfarin (1.80%, 0.74%, and 18.15%, respectively) than with either the 110-mg dose of dabigatran (1.22%, 0.23%, and 14.62%, respectively) or the 150-mg dose of dabigatran (1.45%, 0.30%, and 16.42%, respectively) (P<0.05 for all comparisons of dabigatran with warfarin). There was a significantly higher rate of major gastrointestinal bleeding with dabigatran at the 150-mg dose than with warfarin.

The net clinical benefit outcome consisted of major vascular events, major bleeding, and death. The rates of this combined outcome were 7.64% per year with warfarin and 7.09% per year with 110 mg of dabigatran (relative risk with dabiga-

Table 1. Baseline Characteristics of the Study Participants, According to Treatment Group.*

Characteristic	Dabigatran, 110 mg	Dabigatran, 150 mg	Warfarin
Age — yr	71.4±8.6	71.5±8.8	71.6±8.6
Weight — kg	82.9±19.9	82.5±19.4	82.7±19.7
Blood pressure — mm Hg			
Systolic	130.8±17.5	131.0±17.6	131.2±17.4
Diastolic	77.0±10.6	77.0±10.6	77.1±10.4
Male sex — no./total no. (%)	3865/6015 (64.3)	3840/6076 (63.2)	3809/6022 (63.3)
Type of atrial fibrillation — no./total no. (%)			
Persistent	1950/6011 (32.4)	1909/6075 (31.4)	1930/6021 (32.0)
Paroxysmal	1929/6011 (32.1)	1978/6075 (32.6)	2036/6021 (33.8)
Permanent	2132/6011 (35.4)	2188/6075 (36.0)	2055/6021 (34.1)
$CHADS_2$ score†	2.1±1.1	2.2±1.2	2.1±1.1
0 or 1 — no./total no. (%)	1958/6014 (32.6)	1958/6076 (32.2)	1859/6022 (30.9)
2 — no./total no. (%)	2088/6014 (34.7)	2137/6076 (35.2)	2230/6022 (37.0)
3–6 — no./total no. (%)	1968/6014 (32.7)	1981/6076 (32.6)	1933/6022 (32.1)
Previous stroke or transient ischemic attack — no./total no. (%)	1195/6015 (19.9)	1233/6076 (20.3)	1195/6022 (19.8)
Prior myocardial infarction — no./total no. (%)	1008/6015 (16.8)	1029/6076 (16.9)	968/6022 (16.1)
Heart failure — no./total no. (%)	1937/6015 (32.2)	1934/6076 (31.8)	1922/6022 (31.9)
Diabetes mellitus — no./total no. (%)	1409/6015 (23.4)	1402/6076 (23.1)	1410/6022 (23.4)
Hypertension — no./total no. (%)	4738/6015 (78.8)	4795/6076 (78.9)	4750/6022 (78.9)
Medications in use at baseline — no./total no. (%)			
Aspirin	2404/6013 (40.0)	2352/6075 (38.7)	2442/6017 (40.6)
ARB or ACE inhibitor	3987/6013 (66.3)	4053/6075 (66.7)	3939/6017 (65.5)
Beta-blocker	3784/6013 (62.9)	3872/6075 (63.7)	3719/6017 (61.8)
Amiodarone	624/6013 (10.4)	665/6075 (10.9)	644/6017 (10.7)
Statin‡	2698/6013 (44.9)	2667/6075 (43.9)	2673/6017 (44.4)
Proton-pump inhibitor	812/6013 (13.5)	847/6075 (13.9)	832/6017 (13.8)
H_2-receptor antagonist	225/6013 (3.7)	241/6075 (4.0)	256/6017 (4.3)
Long-term VKA therapy	3011/6015 (50.1)	3049/6076 (50.2)	2929/6022 (48.6)

* Plus-minus values are means ±SD. ARB denotes angiotensin-receptor blocker, and ACE angiotensin-converting enzyme.

† The $CHADS_2$ score is a measure of the risk of stroke in which congestive heart failure, hypertension, an age of 75 years or older, and diabetes mellitus are each assigned 1 point and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient.[12]

‡ Statins are defined here as 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors.

§ Long-term therapy with a vitamin K antagonist (VKA) denotes a total lifetime use of a VKA of 61 or more days.

tran, 0.92; 95% CI, 0.84 to 1.02; P=0.10) and 6.91% per year with 150 mg of dabigatran (relative risk, 0.91; 95% CI, 0.82 to 1.00; P=0.04).

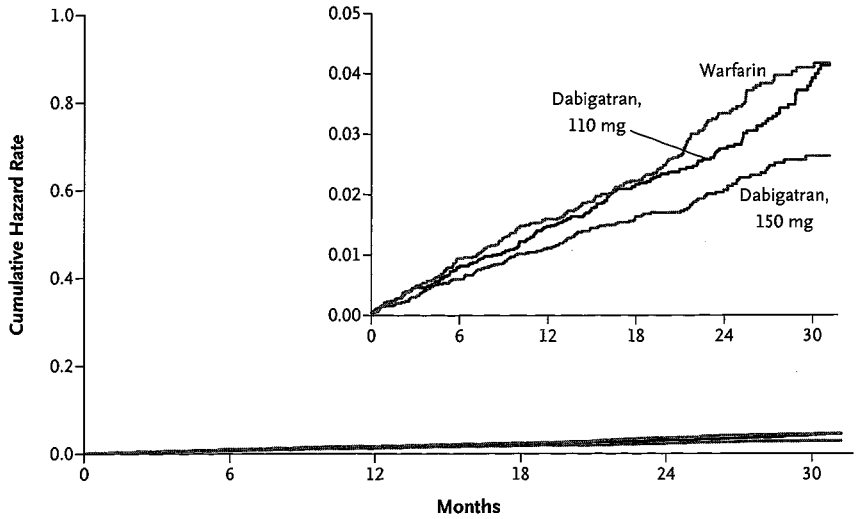
COMPARISON OF DABIGATRAN DOSES

As compared with the 110-mg dose, administration of the 150-mg dose of dabigatran reduced the risk of stroke or systemic embolism (P=0.005). This difference was driven mostly by a decrease in the rate of stroke with ischemic or unspecified cause, whereas rates of hemorrhagic stroke were similar in the two dabigatran groups. There was no significant difference in the rates of death from either vascular causes or any cause between the two doses. On the other hand, as compared with the 110-mg dose, the 150-mg dose of dabigatran

Table 2. Efficacy Outcomes, According to Treatment Group.

Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*						
Stroke or systemic embolism*	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	<0.001 for noninferiority, 0.34	0.66 (0.53–0.82)	<0.001 for noninferiority, <0.001	0.73 (0.58–0.91)	0.005
Stroke	171	1.44	122	1.01	185	1.57	0.92 (0.74–1.13)	0.41	0.64 (0.51–0.81)	<0.001	0.70 (0.56–0.89)	0.003
Hemorrhagic	14	0.12	12	0.10	45	0.38	0.31 (0.17–0.56)	<0.001	0.26 (0.14–0.49)	<0.001	0.85 (0.39–1.83)	0.67
Ischemic or unspecified	159	1.34	111	0.92	142	1.20	1.11 (0.89–1.40)	0.35	0.76 (0.60–0.98)	0.03	0.69 (0.54–0.88)	0.002
Nondisabling stroke	60	0.50	44	0.37	69	0.58	0.86 (0.61–1.22)	0.40	0.62 (0.43–0.91)	0.01	0.72 (0.49–1.07)	0.10
Disabling or fatal stroke	112	0.94	80	0.66	118	1.00	0.94 (0.73–1.22)	0.65	0.66 (0.50–0.88)	0.005	0.70 (0.53–0.94)	0.02
Myocardial infarction	86	0.72	89	0.74	63	0.53	1.35 (0.98–1.87)	0.07	1.38 (1.00–1.91)	0.048	1.02 (0.76–1.38)	0.88
Pulmonary embolism	14	0.12	18	0.15	11	0.09	1.26 (0.57–2.78)	0.56	1.61 (0.76–3.42)	0.21	1.27 (0.63–2.56)	0.50
Hospitalization	2311	19.4	2430	20.2	2458	20.8	0.92 (0.87–0.97)	0.003	0.97 (0.92–1.03)	0.34	1.06 (1.00–1.12)	0.04
Death from vascular causes	289	2.43	274	2.28	317	2.69	0.90 (0.77–1.06)	0.21	0.85 (0.72–0.99)	0.04	0.94 (0.79–1.11)	0.44
Death from any cause	446	3.75	438	3.64	487	4.13	0.91 (0.80–1.03)	0.13	0.88 (0.77–1.00)	0.051	0.97 (0.85–1.11)	0.66

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. P values are for superiority, unless otherwise indicated. The modified Rankin scale (on which scores can range from 0 [no neurologic disability] to 5 [severe disability], with 6 indicating a fatal stroke) was used to categorize stroke: nondisabling stroke was defined by a score of 0 to 2, and disabling or fatal stroke, a score of 3 to 6.



No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

was associated with a trend toward an increased risk of major bleeding (P=0.052) and also with increased risks of gastrointestinal, minor, and any bleeding. The net clinical benefit was almost identical for the two doses.

ADVERSE EVENTS AND LIVER FUNCTION

The only adverse effect that was significantly more common with dabigatran than with warfarin was dyspepsia (Table 4). Dyspepsia occurred in 348 patients (5.8%) in the warfarin group and in 707 patients (11.8%) and 688 patients (11.3%) in the 110-mg and 150-mg dabigatran groups, respectively (P<0.001 for both comparisons) (Table 4). Elevations in the serum aspartate aminotransferase or alanine aminotransferase level of more than 3 times the upper limit of the normal range did not occur more frequently with dabigatran, at either dose, than with warfarin.

SUBGROUP ANALYSES

For the subgroups shown in Figure 2, no significant interaction was seen with the treatment effect of dabigatran (at either dose). There was no significant interaction between the treatment effect of dabigatran and presence or absence of long-term therapy with a vitamin K antagonist. Although 80% of the dabigatran dose is renally excreted, there was no significant interaction in the treatment effect of dabigatran across levels of the baseline calculated creatinine clearance.

DISCUSSION

We compared two fixed-dose regimens of dabigatran (110 mg twice daily and 150 mg twice daily), administered in a blinded fashion, with adjusted-dose warfarin, administered in an unblinded fashion, in patients who had atrial fibrillation and were at risk for stroke. Both dabigatran doses were noninferior to warfarin with respect to the primary efficacy outcome of stroke or systemic embolism. In addition, the 150-mg dose of dabigatran was superior to warfarin with respect to stroke or systemic embolism, and the 110-mg dose was superior to warfarin with respect to major bleeding.

Previous studies seeking to identify a safe and effective alternative to warfarin for patients with atrial fibrillation have all had specific limitations. The combination of clopidogrel and aspirin was more effective than aspirin alone[13] but less effective than warfarin.[14] Subcutaneous idraparinux was more effective than warfarin but was associated with a substantially higher risk of bleeding.[15]

Table 3. Safety Outcomes, According to Treatment Group.*

Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	%/yr	*no. of patients*	%/yr	*no. of patients*	%/yr						
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31	1.16 (1.00–1.34)	0.052
Life threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001	0.81 (0.66–0.99)	0.04	1.19 (0.96–1.49)	0.11
Non–life threatening	198	1.66	226	1.88	208	1.76	0.94 (0.78–1.15)	0.56	1.07 (0.89–1.29)	0.47	1.14 (0.95–1.39)	0.17
Gastrointestinal†	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43	1.50 (1.19–1.89)	<0.001	1.36 (1.09–1.70)	0.007
Minor bleeding	1566	13.16	1787	14.84	1931	16.37	0.79 (0.74–0.84)	<0.001	0.91 (0.85–0.97)	0.005	1.16 (1.08–1.24)	<0.001
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.97)	0.002	1.16 (1.09–1.23)	<0.001
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001	1.32 (0.80–2.17)	0.28
Extracranial bleeding	299	2.51	342	2.84	315	2.67	0.94 (0.80–1.10)	0.45	1.07 (0.92–1.25)	0.38	1.14 (0.97–1.33)	0.11
Net clinical benefit outcome‡	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10	0.91 (0.82–1.00)	0.04	0.98 (0.89–1.08)	0.66

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. Hemorrhagic stroke was a subcategory of stroke in the efficacy analysis and in the safety analysis is also counted as major, life-threatening bleeding and as part of intracranial bleeding.
† Gastrointestinal bleeding could be life threatening or non–life threatening.
‡ The net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding.

Table 4. Discontinuation of the Study Drug, Adverse Events, and Liver Function According to Treatment Group.*

Variable	Dabigatran, 110 mg (N=6015)	Dabigatran, 150 mg (N=6076)	Warfarin (N=6022)
	number of patients (percent)		
Study-drug discontinuation			
Discontinued at 1 yr†	862 (15)	935 (16)	608 (10)
Discontinued at 2 yr†	1161 (21)	1211 (21)	902 (17)
Reason for discontinuation			
Patient's decision	440 (7.3)	474 (7.8)	375 (6.2)
Outcome event	192 (3.2)	164 (2.7)	130 (2.2)
Serious adverse event‡	163 (2.7)	166 (2.7)	105 (1.7)
Gastrointestinal symptoms§	134 (2.2)	130 (2.1)	38 (0.6)
Gastrointestinal bleeding	58 (1.0)	80 (1.3)	54 (0.9)
Adverse events¶			
Dyspepsia‡‖	707 (11.8)	688 (11.3)	348 (5.8)
Dizziness	486 (8.1)	506 (8.3)	568 (9.4)
Dyspnea	557 (9.3)	580 (9.5)	586 (9.7)
Peripheral edema	473 (7.9)	478 (7.9)	468 (7.8)
Fatigue	399 (6.6)	401 (6.6)	372 (6.2)
Cough	344 (5.7)	348 (5.7)	364 (6.0)
Chest pain	312 (5.2)	377 (6.2)	357 (5.9)
Back pain	316 (5.3)	314 (5.2)	337 (5.6)
Arthralgia	270 (4.5)	335 (5.5)	346 (5.7)
Nasopharyngitis	337 (5.6)	330 (5.4)	336 (5.6)
Diarrhea	377 (6.3)	397 (6.5)	346 (5.7)
Atrial fibrillation	330 (5.5)	357 (5.9)	349 (5.8)
Urinary tract infection	273 (4.5)	289 (4.8)	335 (5.6)
Upper respiratory tract infection	288 (4.8)	285 (4.7)	313 (5.2)
Liver function			
ALT or AST >3× ULN	124 (2.1)	117 (1.9)	132 (2.2)
ALT or AST >3× ULN with concurrent bilirubin >2× ULN	13 (0.2)	13 (0.2)	21 (0.3)
Hepatobiliary disorder**			
Serious adverse event	33 (0.5)	34 (0.6)	33 (0.5)
Non–serious adverse event	101 (1.7)	109 (1.8)	112 (1.9)

* ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.
† Rates of discontinuation at 1 and 2 years were higher with dabigatran than with warfarin (P<0.001). The rates are based on Kaplan–Meier estimates.
‡ P<0.001 for the comparison of either dose of dabigatran with warfarin.
§ Gastrointestinal disorders included pain, vomiting, and diarrhea.
¶ The adverse events listed are those that were reported in more than 5% of patients in any of the three treatment groups.
‖ Dyspepsia was defined to include the coding terms abdominal pain upper, abdominal pain, abdominal discomfort, and dyspepsia.
** Hepatobiliary disorders were classified as serious adverse events if they consisted of clinical or biochemical liver dysfunction requiring hospitalization, most frequently cholelithiasis or cholecystitis. Hepatobiliary disorders classified as adverse events were most frequently cholelithiasis, cholecystitis, abnormal hepatic function, and jaundice.

Ximelagatran, an earlier direct thrombin inhibitor, appeared to be similar to warfarin with respect to efficacy and safety but was found to be hepatotoxic.[16] In our serial measurement of liver function, we did not find evidence of hepatotoxicity with dabigatran.

The rate of myocardial infarction was higher with both doses of dabigatran than with warfarin. An explanation might be that warfarin provides better protection against coronary ischemic events than dabigatran, and warfarin is known to reduce the risk of myocardial infarction.[17] However, rates of myocardial infarction were similar between patients with atrial fibrillation who were receiving warfarin and those who were receiving ximelagatran, another direct thrombin inhibitor.[16] The explanation for this finding is therefore uncertain.

The most devastating complication of warfarin therapy is intracranial hemorrhage, especially hemorrhagic stroke. As compared with aspirin, warfarin doubles the risk of intracranial hemorrhage.[1] Thus, our finding that the rate of this complication with both doses of dabigatran was less than one third the rate with warfarin, without a reduction in the efficacy against ischemic stroke, suggests an important advantage of dabigatran. The rate of major bleeding with warfarin was higher in our study than in some previous trials.[11,13,14] This is partly explained by the more inclusive definition of major bleeding in our study. There was an increase in the rate of gastrointestinal bleeding with the higher dabigatran dose, despite the overall lower rates of bleeding at other sites. To enhance absorption of dabigatran, a low pH is required. Therefore, dabigatran capsules contain dabigatran-coated pellets with a tartaric acid core. This acidity may partly explain the increased incidence of dyspeptic symptoms with both dabigatran doses and the increased risk of gastrointestinal bleeding with the 150-mg dose.

The benefit of dabigatran may be explained in part by the twice-daily dosing regimen. Since dabigatran has an elimination half-life of 12 to 17 hours, twice-daily dosing reduces variability in the anticoagulation effect, especially as compared with the anticoagulation effect of warfarin, which is difficult to control. Warfarin broadly inhibits coagulation (inhibiting factors II, VII, IX, and X and proteins C and S). By selectively inhibiting only thrombin, dabigatran may have antithrombotic efficacy while preserving some other hemostatic mechanisms in the coagulation system and thus potentially mitigating the risk of bleeding.

Figure 2 (facing page). Relative Risk of the Primary Outcome of Stroke or Systemic Embolism with Dabigatran versus Warfarin, According to Subgroup.

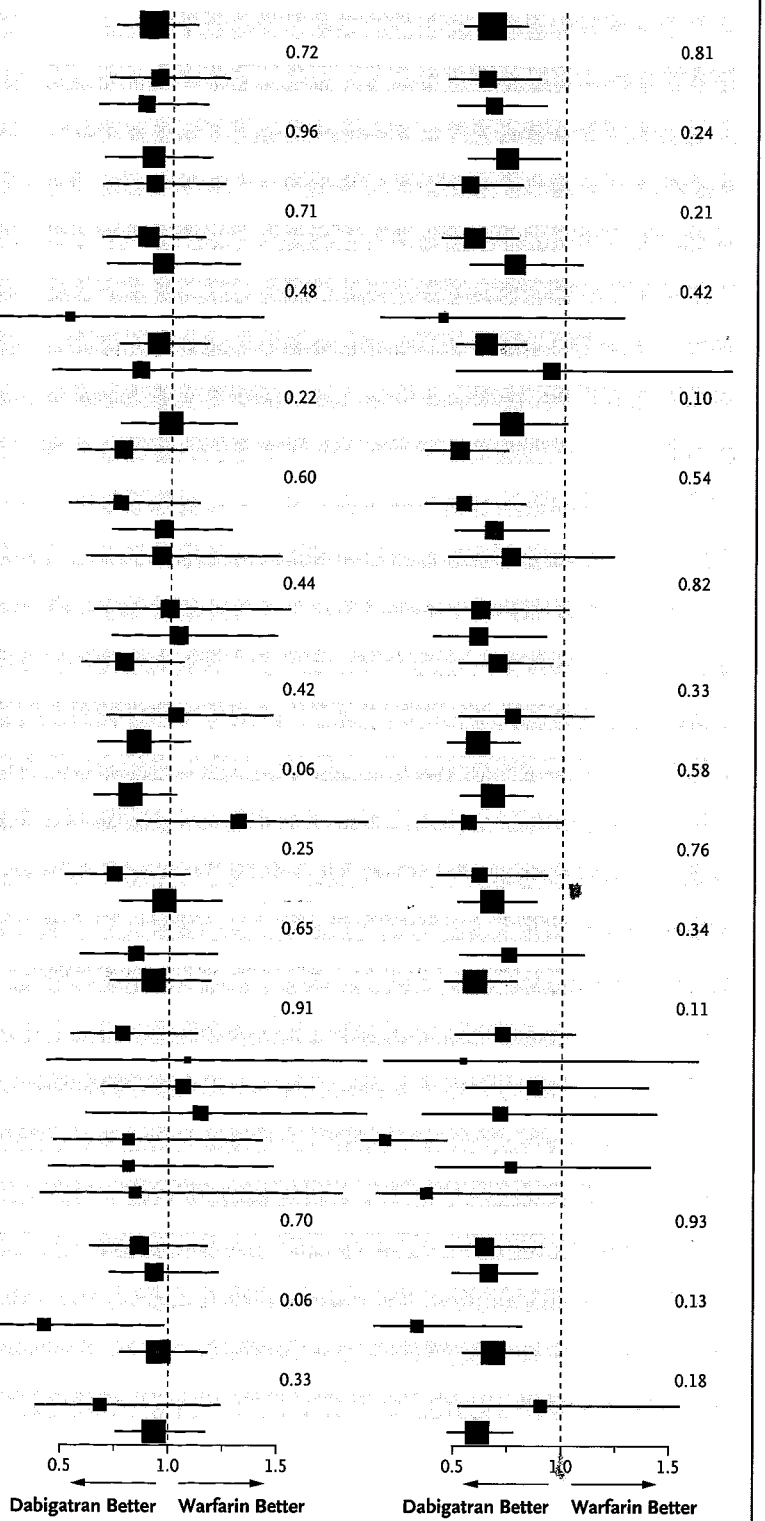
Ethnic group was self-reported. Long-term therapy with a vitamin K antagonist (VKA) denotes a total lifetime use of a VKA of 61 days or more. The body-mass index is the weight in kilograms divided by the square of the height in meters. The $CHADS_2$ score is a measure of the risk of stroke in which congestive heart failure, hypertension, an age of 75 years or older, and diabetes mellitus are each assigned 1 point and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient.[12] Creatinine clearance was calculated according to the Cockcroft–Gault method. The squares with horizontal lines are hazard ratios and corresponding 95% confidence intervals; the sizes of squares are proportional to the sizes of the subgroups. PPI denotes proton-pump inhibitor.

The use of open-label warfarin could have introduced a bias in the reporting or adjudication of events. This risk was reduced by the implementation of several validated procedures, including blinded evaluation of outcome events. The unexpectedly different rates of myocardial infarction and gastrointestinal bleeding among the three treatment groups support an absence of bias. Control of anticoagulation with warfarin in our study was similar to that in previous international clinical trials, even though half our patients had not previously had extensive treatment with warfarin.[10,17]

The net clinical benefit outcome, which is a measure of the overall benefit and risk, was similar between the two doses of dabigatran, owing to the lower risk of ischemia with the 150-mg dose and the lower risk of hemorrhage with the 110-mg dose. These findings suggest that the dose of dabigatran could potentially be tailored to take into consideration the risk characteristics of a specific patient, although this concept was not specifically tested in our trial.

In conclusion, we compared two doses of dabigatran with warfarin in patients who had atrial fibrillation and who were at risk for stroke. As compared with warfarin, the 110-mg dose of dabigatran was associated with similar rates of stroke and systemic embolism and lower rates of major

Subgroup	Patients *total no.*	Dabigatran 110 mg *% per yr*	Dabigatran 150 mg *% per yr*	Warfarin *% per yr*	Hazard Ratio with Dabigatran, 110 mg (95% CI)	P Value for Interaction	Hazard Ratio with Dabigatran, 150 mg (95% CI)	P Value for Interaction
All patients	18,113	1.53	1.11	1.69				
Long-term VKA therapy						0.72		0.81
No	9,123	1.57	1.07	1.67				
Yes	8,989	1.49	1.15	1.70				
Sex						0.96		0.24
Male	11,514	1.35	1.10	1.49				
Female	6,598	1.86	1.14	2.03				
Body-mass index						0.71		0.21
<28	9,131	1.78	1.17	2.01				
≥28	8,962	1.28	1.04	1.34				
Weight						0.48		0.42
<50 kg	376	2.58	2.24	5.04				
50–99 kg	14,629	1.66	1.14	1.77				
≥100 kg	3,099	0.80	0.87	0.94				
Ethnic group						0.22		0.10
European or Arab	12,679	1.35	1.03	1.35				
Other	5,433	1.97	1.32	2.52				
Creatinine clearance						0.60		0.54
<50 ml/min	3,505	2.15	1.52	2.78				
50–79 ml/min	8,766	1.70	1.20	1.76				
≥80 ml/min	5,826	0.94	0.75	0.98				
$CHADS_2$ score						0.44		0.82
0 or 1	5,775	1.06	0.65	1.05				
2	6,455	1.43	0.84	1.38				
≥3	5,882	2.12	1.88	2.68				
Symptomatic heart failure						0.42		0.33
Yes	4,904	1.90	1.44	1.85				
No	13,203	1.40	1.00	1.63				
Hypertension						0.06		0.58
Yes	14,283	1.46	1.20	1.78				
No	3,829	1.79	0.78	1.36				
Diabetes						0.25		0.76
Yes	4,221	1.76	1.46	2.32				
No	13,891	1.46	1.01	1.50				
Stroke or TIA						0.65		0.34
Yes	3,623	2.32	2.07	2.74				
No	14,489	1.33	0.87	1.43				
Region						0.91		0.11
North America	6,533	1.19	1.11	1.51				
South America	1,134	1.82	0.91	1.68				
Western Europe	3,941	1.53	1.26	1.43				
Central Europe	2,829	1.22	0.78	1.06				
South Asia	1,134	3.35	0.84	4.00				
East Asia	1,648	1.87	1.77	2.28				
Other	1,072	1.95	0.88	2.27				
Aspirin use at baseline						0.70		0.93
Yes	7,198	1.66	1.26	1.92				
No	10,910	1.44	1.03	1.53				
Amiodarone use at baseline						0.06		0.13
Yes	1,933	0.66	0.54	1.55				
No	16,174	1.63	1.18	1.70				
PPI use at baseline						0.33		0.18
Yes	2,491	1.22	1.63	1.77				
No	15,616	1.58	1.03	1.67				



hemorrhage; the 150-mg dose of dabigatran was associated with lower rates of stroke and systemic embolism but with a similar rate of major hemorrhage.

Supported by a grant from Boehringer Ingelheim.

Dr. Connolly reports receiving consulting fees, lecture fees, and grant support from Boehringer Ingelheim; Dr. Ezekowitz, consulting fees, lecture fees, and grant support from Boehringer Ingelheim and Aryx Therapeutics, consulting fees from Sanofi-Aventis, and lecture fees and grant support from Portola Pharmaceuticals; Dr. Yusuf, consulting fees, lecture fees and grant support from Boehringer Ingelheim and consulting fees from AstraZeneca, Bristol-Myers Squibb, and Sanofi-Aventis; Dr. Eikelboom, consulting fees, lecture fees, and grant support from Boehringer Ingelheim, AstraZeneca, Sanofi-Aventis, and GlaxoSmithKline, consulting fees and lecture fees from Eisai Pharmaceuticals, Eli Lilly, and McNeil, and consulting fees from Bristol-Myers Squibb, Corgenix Medical Corporation, and Daiichi-Sankyo; Dr. Oldgren, consulting fees, lecture fees, and grant support from Boehringer Ingelheim and lecture fees from AstraZeneca; and Drs. Parekh and Xavier, grant support from Boehringer Ingelheim. Drs. Reilly, Varrone, and Wang report being employees of Boehringer Ingelheim. Drs. Alings and Zhu report receiving consulting fees and grant support from Boehringer Ingelheim; Dr. Diaz, consulting fees from GlaxoSmithKline, lecture fees from Sanofi-Aventis, GlaxoSmithKline, and Boehringer Ingelheim, and grant support from Boehringer Ingelheim; Dr. Lewis, consulting fees from Sanofi-Aventis, Bristol-Myers Squibb, and Boehringer Ingelheim and grant support from Boehringer Ingelheim; Dr. Darius, consulting fees, lecture fees, and grant support from Boehringer Ingelheim, consulting fees from Sanofi-Aventis and Bayer Schering Pharma, and lecture fees from the Medicines Company and Eli Lilly; Dr. Diener, consulting fees and lecture fees from Boehringer Ingelheim, Abbott, AstraZeneca, Bayer, Bristol-Myers Squibb, CoAxia, D-Pharm, Fresenius, GlaxoSmithKline, Janssen Cilag, Merck Sharp and Dohme, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Sankyo, Servier, Solvay, Thrombogenics, Wyeth and Yamaguchi and grant support from Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline, Novartis, Janssen-Cilag, and Sanofi-Aventis; Dr. Joyner, grant support from Boehringer Ingelheim, AstraZeneca, Sanofi-Aventis, and Bristol-Myers Squibb; and Dr. Wallentin, consulting fees, lecture fees, and grant support from Boehringer Ingelheim, consulting fees from Regado and Athera, lecture fees from Boehringer Ingelheim, AstraZeneca, and Eli Lilly, and grant support from AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, and Schering Plough. No other potential conflict of interest relevant to this article was reported.

APPENDIX

Members of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Study Group are as follows (a full list of investigators is included in the Supplementary Appendix): **Operations Committee:** S.J. Connolly (principal investigator), M.D. Ezekowitz (principal investigator), S. Yusuf (chair, steering committee), J. Eikelboom, J. Oldgren, A. Parekh, P.A. Reilly, E. Themeles, J. Varrone, S. Wang, E. Palmcrantz-Graf, M. Haehl, L. Wallentin (chair, steering committee). **Steering Committee:** A.M.W. Alings, J.V. Amerena, A. Avezum, I. Baumgartner, J. Brugada, A. Budaj, V. Caicedo, L. Ceremuzynski, J.H. Chen, P.J. Commerford, S.J. Connolly, A.L. Dans, H. Darius, G. Di Pasquale, R. Diaz, C. Erol, M.D. Ezekowitz, J. Ferreira, G.C. Flaker, M.D. Flather, M.G. Franzosi, R. Gamboa, S.P. Golitsyn, J.A. Gonzalez Hermosillo, D. Halon, H. Heidbuchel, S.H. Hohnloser, M. Hori, K. Huber, P. Jansky, G. Kamensky, M. Keltai, S. Kim, C.P. Lau, J.Y.F. Le Heuzey, B.S. Lewis, L.S. Liu, J. Nanas, J. Oldgren, P.S. Pais, A.N. Parkhomenko, K.E. Pedersen, L.S. Piegas, D. Raev, O. Razali, T.A. Simmers, P.J. Smith, M. Talajic, R.S. Tan, S. Tanomsup, L. Toivonen, D. Vinereanu, L. Wallentin, D. Xavier, S. Yusuf, J. Zhu. **Core Adjudication–Stroke Advisory Committee:** H.C. Diener (cochair), C.D. Joyner (cochair), A. Diehl, G. Ford, M. Robinson (core adjudication only), J. Silva. **Data Safety Monitoring Board:** P. Sleight (cochair), D.G. Wyse (cochair), J. Collier, D. De Mets, J. Hirsh, E. Lesaffre, L. Ryden, P. Sandercock. **Investigators who recruited at least 12 patients:** *Argentina:* A. Caccavo, L. Cartasegna, C.A. Cuneo, M.V. Elizari, A.J. Gabito, M.A. Hominal, A.D. Hrabar, I.J. Mackinnon, M.A. Rodriguez, A.S. Sanchez, D.R. Vogel; *Australia:* D.M. Colquhoun, R.G. Lehman, B.B. Singh, J.H. Waites; *Austria:* F. Gazo, A. Podczeck, P. Siostrzonek; *Belgium:* J.L. Boland, A. de Meester, L. De Wolf, D. Dilling-Boer, M. Goethals, P. Goethals, O. Gurne, S. Hellemans, B. Ivan, M. Jottrand, I. Kersschot, F. Provenier, W. van Mieghem, Y. Vandekerckhove; *Brazil:* J.C.F. Braga, J.F. Kerr Saraiva, A.M. Lorga-Filho, L.N. Maia, C.S. Melo, D.B. Precoma, S. Rassi, P.R. Rossi; *Bulgaria:* E.S. Baldjiev, I.G. Filibev, N.N. Gotcheva, A.R. Goudev, D.T. Guenova, E.I. Manov, A.L. Radoslavov, D.A. Spirova, V.M. Tsanova, M.L. Tzekova; *Canada:* A.I. Bakbak, J.C. Berlingieri, K. Blackburn, A.W. Booth, S. Bose, P. Boucher, C. Constance, P. Costi, B. Coutu, M.S. Green, J. Habot, S. Kouz, A.V. Lalani, A.S. Lam, P.T.S. Ma, L.B. Mitchell, C.A. Morillo, G. O'Hara, A.S. Pandey, Y. Pesant, C.N. Powell, T.M. Rebane, D. Savard, S. Schulman, M.J. Sehl, D. Shu, L.D. Sterns, R. St-Hilaire, G.S. Syan, P. Talbot, I. Teitelbaum, S.A. Vizel; *China:* X.J. Bai, W. Gao, Z.S. He, Q. Hua, L. Li, W.M. Li, G.P. Lu, S. Lv, N.L. Sun, N.F. Wang, Y.M. Yang, F. Zhang, L. Zhang; *Czech Republic:* J. Belohlavek, M. Cernohous, M. Choura, V. Dedek, B. Filipensky, K. Kovarova, Z. Poklopova, H. Skalicka, J. Spinar; *Denmark:* K.K. Dodt, K. Egstrup, S. Husted, K.K. Klarlund, S. Lind Rasmussen, T.M. Melchior, M.E. Olsen, N. Ralfkiaer, L.H. Rasmussen, K. Skagen; *Finland:* K.E. Airaksinen, H.V. Huikuri, M. Mänttäri, J.H. Melin, K. Peuhkurinen, V.K. Virtanen, A. Ylitalo; *France:* L. Boucher, A. Boye, P. Igigabel, C. Magnani, M. Martelet, J.E. Poulard; *Germany:* K.F. Appel, C.E.H. Dempfle, A. Dormann, J. Harenberg, W.L. Haverkamp, T. Horacek, D. Koudonas, J. Kreuzer, A. Müegge, T.F. Munzel, P.B. Salbach, W. Schoels, R. Veltkamp, E. Von Hodenberg; *Greece:* M.I. Anastasiou-Nana, K. Karamitsos, C. Lappas, A. Manolis; *Hong Kong (China):* W.K. Chan, H.F. Tse, P.T. Tsui, C.M. Yu; *Hungary:* A. Jánosi, A. Kadar, P. Karpati, K. Keltai, J. Rapi, L.I. Regos, I. Szakal; *India:* R.K. Aggarwal, A. Bharani, J.S. Bhuvaneswaran, R.B. Byrapaneni, J.B. Gupta, K.K. Haridas, J. Hiremath, A.S. Jain, J. Joseph, A.M. Naik, R.B. Panwar, J.P.S. Sawhney, N. Sinha, A. Srinivas, P.S. Vadagenalli; *Israel:* J. Benhorin, N.M. Bornstein, B. Brenner, A. Butnaru, A. Caspi, M. Elias, E. Grossman, S. Hamoud, R. Ilia, E.I. Klainman, M. Lishner, C. Lotan, A. Marmor, M. Motro, L.H. Reisen, E. Schwammenthal, M. Shochat, B. Strasberg, Y. Turgeman, A.T. Weiss, D.H. Wexler, R. Wolff, D. Zeltser, R. Zimlichman; *Italy:* G. Argiolas, M. Barbiero, A. Fraticelli, M. Mennuni, L. Moretti, L. Mos, S. Pirelli; *Japan:* J. Furuya, S. Hara, M. Hiroe, S. Kakinoki, N. Miyamoto, M. Yokochi; *Malaysia:* K.H. Chee, A.F.Y. Fong, O. Ismail, S. Jeyaindran; *Mexico:* J. Carrillo, P.A. Fernandez Bonetti; *the Netherlands:* G.L. Bartels, T.A. Bruning, R. Ciampricotti, L. Cozijnsen, H.J. Crijns, M.C.G. Daniels, D.E.P. de Waard, F.R. den Hartog, W.F. Heesen, P.A. Hoogslag, A. Huizenga, J.A. Kragten, G.C. Linssen, D.J. Lok, H.R. Michels, J. Plomp, L. Pos, P.G. Postema, R. Salomonsz, I. Stoel, J.G. Tans, H.J. Thijssen, A.J.M. Timmermans, H.A. van de Klippe, C. van der Zwaan, I.C. van Gelder, L.H. van Kempen, H.A. van Kesteren, P. van Rossum; *Norway:* O. Breder, P.A. Sirnes, A. Tveit; *Peru:* W. Cabrera, J.M. Heredia, M.E. Horna, P.M. Salazar; *Philippines:* M.T.B. Abola, J.C. Anonuevo, D.D. Morales, G.G. Rogelio, A.A. Roxas, Jr.; *Poland:* B. Bacior, J. Grodecki, Z.F. Kalarus, P. Miekus, F. Monies, J. Rekosz, M. Szpajer, A. Wasilewska-Piepiorka, B. Zaborska; *Portugal:* L. Cunha, L.A. Providencia; *Romania:* M.A. Cinteza; *Russia:* I.G. Gordeev, A.Y. Ivleva, T.N. Novikova, E.P. Panchenko, E.V. Shlyakhto, S.B. Shustov, B.A. Sidorenko, V. Sulimov, A.L. Syrkin, D.A. Zateyshchikov; *Singapore:* D. Foo; *Slovak Republic:* V. Bugan, J. Dúbrava, G. Kaliska, M. Masarovicova, D. Pella, J. Sedlák, R. Uhliar; *South Africa:* J.M. Engelbrecht, D. Jankelow,

R.J. Routier, F.A. Snyders, H.D. Theron; *South Korea:* T.J. Cha, J.G. Cho, I.S. Choi, K.J. Choi, K.S. Kim, Y.N. Kim, M.H. Lee, M.Y. Lee, D.J. Oh, T.H. Rho; *Spain:* L. Cano, A. Martinez-Rubio, L. Mont; *Sweden:* S. Bandh, C.M. Blomstrom Lundqvist, P. Cherfan, E. Fengsrud, J. Herlitz, T. Juhlin, F. Maru, O.R. Nilsson, F. Ronn, M. Rosenqvist; *Taiwan:* H.H. Hu, C.J. Jack, W.T. Lai, C.H. Liu, H.L. Po, S.J. Ryu, C.D. Tsai, C.D. Tseng, J.H. Wang, S.P. Yang; *Thailand:* S. Kiatchoosakun, R. Krittayaphong, S. Kuanprasert, T. Simtharakaew; *Turkey:* A. Usal; *Ukraine:* K.M. Amosova, O.I. Karpenko, O. Kuryata, L. Martynova, S.S. Pavlyk, L.V. Rudenko, V. Tseluyko, N. Usan, L.G. Voronkov, O.J. Zharinov; *United Kingdom:* J.G. Cleland, A.T. Cohen, P. Davey, J. Davies, H.H. Kadr, G.H. Lip, G.T. McInnes, A.J. Moriarty, M. Pye, S.H.L. Thomas, P.R. Wilkinson; *United States:* Z.A. Abbud, K.V. Adams, I.S. Ahmed, R. Arora, G.R. Aycock, A.J. Bartkowiak, Jr., B. Bean, N.W. Bedwell, A.D. Belber, D.R. Bensimhon, R.E. Benton, O. Ben-Yehuda, B.D. Bertolet, S.D. Bilazarian, D.E. Bolster, J. Bomba, C.R. Bricker, R.I. Brock, K.F. Browne, F. Cardona, T. Carlson, K.W. Carr, W.R. Cashion, Y.S. Chandrashekar, J.H. Chappell, Y. Chen, J.H. Cieszkowski, D.M. Clark, J.F. Cole, S.F. Cossu, D.M. Denny, V.S. Desai, N.J. Deumite, L. Dewey, D.W. Dunning, C. East, W.A. Edmiston, H.S. Ellison, M. Elshahawy, G. Emlein, B. Ewing, P.W. Farrell, P.G. Fattal, J.A. Fialkow, R.H. Fields, M.S. Finkel, G.J. Fishbein, F.J. Fleischhauer, M.A. Frais, D.C. Friedman, M.D. Gelernt, H.C. Genovely, E.L. Gillespie, R.K. Goldberg, D.A. Goldscher, M. Goldstein, A.J. Greenspon, T.C. Hack, S.W. Halpern, C. Hamburg, G.S. Hamroff, G.D. Hanovich, E.J. Haskel, W.H. Haught, S.E. Hearne, J.A. Hemphill, C.H. Henes, P.R. Hermany, W.R. Herzog, T.C. Hilton, M.B. Honan, D.A. Hotchkiss, V.N. Howard, R.K. Ison, A.K. Jacobson, N.F. Jarmukli, D.B. Joyce, P.L. Judson, S. Kaatz, K.J. Kaplan, H.B. Karunaratne, R.N. Khant, M.J. Koren, E.J. Kosinski, P. Kosolcharoen, J.H. Kramer, S.J. Kulback, A. Kumar, J.S. Landzberg, D.T. Lang, T.K. Lau, J.K. Lee, R.M. Levy, D. Linzer, L. Maletz, M.F. McGough, W.P. McGuinn, M.D. McMillen, C.A. McPherson, M.E. Meengs, W.L. Meengs, A.W. Meholick, M.B. Melucci, S.K. Meymandi, R.H. Miller, S.T. Minor, M. Modi, J.F. Moloney, S.K. Mukherjee, V.K. Nadar, M. Nallasivan, J.P. Navas, E.N. Nsah, J.L. Nunamaker, D.J. O'Dea, B. Olliff, P.G. O'Neill, J.R. Onufer, R.C. Orchard, P. Pandey, S. Pezzella, D. Phillips, S.G. Pollock, S.D. Promisloff, J.T. Rittelmeyer, T.A. Rocco, Jr., D. Rosenbaum, D.M. Salerno, K.A. Saxman, R.M. Schneider, K.H. Sheikh, N.K. Shemonsky, W.G. Short, N. Singh, R. Sperling, A.D. Steljes, D.P. Suresh, S.M. Teague, J.M. Teixeia, R.W. Terry, J.A. Trippi, J.E. Usedom, R.M. Vicari, N. Vijay, K.N. Vora, R.B. Vranian, J.L. Walker, R.L. Walsh, S. Weiner, R.J. Weiss, W. Wera-Archakul, J.H. Whitaker, R.H. White, J.N. Whitehill, M.L. Williams, V.E. Wilson, W.W. Wilson, C.W. Wulff, K.A. Yousuf, B.G. Zakhary, P. Zimetbaum, R. Zoble, P.L. Zwerner.

REFERENCES

1. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67.
2. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation — executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Arial Fibrillation). J Am Coll Cardiol 2006;48:854-906. [Erratum, J Am Coll Cardiol 2007;50:562.]
3. Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. Stroke 2006;37:1070-4.
4. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation 2007;115:2689-96.
5. Connolly SJ, Pogue J, Eikelboom J, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation 2008;118:2029-37.
6. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. Clin Pharmacokinet 2008;47:285-95.
7. Ezekowitz MD, Reilly PA, Nehmiz G, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol 2007;100:1419-26.
8. Eriksson BI, Dahl OE, Rosencher N, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomized, double-blind, non-inferiority trial. Lancet 2007;370:949-56. [Erratum, Lancet 2007;370:2004.]
9. Ezekowitz MD, Connolly SJ, Parekh A, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J 2009;157:805-10.
10. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69:236-9.
11. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 1999;131:492-501.
12. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864-70.
13. The ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360:2066-78.
14. ACTIVE Writing Group of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006;367:1903-12.
15. Amadeus Investigators, Bousser MG, Bouthier J, et al. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. Lancet 2008;371:315-21. [Erratum, Lancet 2008;372:2022.]
16. Deiner HC, Executive Steering Committee of the SPORTIFF III and V Investigators. Stroke prevention using the oral direct thrombin inhibitor ximelagatran in patients with non-valvular atrial fibrillation: pooled analysis from the SPORTIF III and V studies. Cerebrovasc Dis 2006;21:279-93.
17. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;347:969-74.

Newly Identified Events in the RE-LY Trial

TO THE EDITOR: We wish to update our article about the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (Sept. 17, 2009, issue).[1] After the database was locked on August 15, 2009, we identified several additional primary efficacy and safety outcome events during routine clinical site closure visits. These events included two systemic embolic events and nine major hemorrhages. Subsequently, after discussions with the Food and Drug Administration, the primary and secondary efficacy and safety data were checked for consistency, and the study database was reevaluated for possible underreporting of events. To achieve this, all free text, outcomes, and adverse events in the database were searched with the use of multiple algorithms to identify any symptom that might suggest the possibility of any primary or secondary event or bleeding. This included an examination of all decreases in the hemoglobin level by more than 2 g per deciliter between visits, other markers of potential bleeding, new pathologic Q waves on routine electrocardiography (ECG), and any report of weakness or other symptoms that might be potentially related to a stroke. This process resulted in the identification of 81 new events in 80 patients. These included 1 stroke, 1 systemic embolic event, 4 clinical myocardial infarctions, 1 pulmonary embolism, 5 transient ischemic attacks, and 69 major hemorrhages.

Although silent myocardial infarction, defined as the new appearance of pathologic Q waves on ECG, was part of the RE-LY definition of myocardial infarction, no cases of silent myocardial infarction were reported by investigators during the course of the study. However, review of the routine ECG reports revealed 28 cases fulfilling the criteria for silent myocardial infarction.

All these newly identified events were adjudicated in a blinded fashion and in accordance with the study protocol. Two rounds of data entry were performed for all data on the international normalized ratio (INR), for purposes of validation. This resulted in a change in the mean percentage of the study period in which the warfarin INR was within the therapeutic range, from 64.2% to 64.4%.

Inclusion of the newly identified events did not

Table 1. Published and Revised Data for Primary Efficacy and Safety Outcomes and Myocardial Infarction, According to Treatment Group.*

Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*				
Stroke or systemic embolism										
Published	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	0.34	0.66 (0.53–0.82)	<0.001
Revised	183	1.54	134	1.11	202	1.71	0.90 (0.74–1.10)	0.30	0.65 (0.52–0.81)	<0.001
Major bleeding										
Published	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31
Revised	342	2.87	399	3.32	421	3.57	0.80 (0.70–0.93)	0.003	0.93 (0.81–1.07)	0.32
Myocardial infarction										
Published	86	0.72	89	0.74	63	0.53	1.35 (0.98–1.87)	0.07	1.38 (1.00–1.91)	0.048
Revised	98	0.82	97	0.81	75	0.64	1.29 (0.96–1.75)	0.09	1.27 (0.94–1.71)	0.12

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. P values are for superiority. CI denotes confidence interval.

Reprinted from THE NEW ENGLAND JOURNAL OF MEDICINE
(ISSN 0028-4793) Vol. 363:1875-1876 (November 4, 2010).

Printed in the U.S.A. Fax: (781) 893-8103 www.nejm.org

materially change the study results, as shown in Table 1 (more detailed tables are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org). The study conclusions remain unchanged.

Stuart J. Connolly, M.D.
McMaster University
Hamilton, ON, Canada

Michael D. Ezekowitz, M.B., Ch.B., D.Phil.
Lankenau Institute for Medical Research
Wynnewood, PA

Salim Yusuf, M.D., D.Phil.
McMaster University
Hamilton, ON, Canada

Paul A. Reilly, Ph.D.
Boehringer Ingelheim Pharmaceuticals
Ridgefield, CT

Lars Wallentin, M.D., Ph.D.
Uppsala Clinical Research Center
Uppsala, Sweden

for the Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators

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

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361:1139-51.

A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease

Donald P. Tashkin, M.D., Bartolome Celli, M.D., Stephen Senn, Ph.D., Deborah Burkhart, B.S.N., Steven Kesten, M.D., Shailendra Menjoge, Ph.D., and Marc Decramer, M.D., Ph.D., for the UPLIFT Study Investigators*

ABSTRACT

BACKGROUND

Previous studies showing that tiotropium improves multiple end points in patients with chronic obstructive pulmonary disease (COPD) led us to examine the long-term effects of tiotropium therapy.

METHODS

In this randomized, double-blind trial, we compared 4 years of therapy with either tiotropium or placebo in patients with COPD who were permitted to use all respiratory medications except inhaled anticholinergic drugs. The patients were at least 40 years of age, with a forced expiratory volume in 1 second (FEV_1) of 70% or less after bronchodilation and a ratio of FEV_1 to forced vital capacity (FVC) of 70% or less. Coprimary end points were the rate of decline in the mean FEV_1 before and after bronchodilation beginning on day 30. Secondary end points included measures of FVC, changes in response on St. George's Respiratory Questionnaire (SGRQ), exacerbations of COPD, and mortality.

RESULTS

Of a total of 5993 patients (mean age, 65±8 years) with a mean FEV_1 of 1.32±0.44 liters after bronchodilation (48% of predicted value), we randomly assigned 2987 to the tiotropium group and 3006 to the placebo group. Mean absolute improvements in FEV_1 in the tiotropium group were maintained throughout the trial (ranging from 87 to 103 ml before bronchodilation and from 47 to 65 ml after bronchodilation), as compared with the placebo group ($P<0.001$). After day 30, the differences between the two groups in the rate of decline in the mean FEV_1 before and after bronchodilation were not significant. The mean absolute total score on the SGRQ was improved (lower) in the tiotropium group, as compared with the placebo group, at each time point throughout the 4-year period (ranging from 2.3 to 3.3 units, $P<0.001$). At 4 years and 30 days, tiotropium was associated with a reduction in the risks of exacerbations, related hospitalizations, and respiratory failure.

CONCLUSIONS

In patients with COPD, therapy with tiotropium was associated with improvements in lung function, quality of life, and exacerbations during a 4-year period but did not significantly reduce the rate of decline in FEV_1. (ClinicalTrials.gov number, NCT00144339.)

From the David Geffen School of Medicine at the University of California, Los Angeles (D.P.T.); Caritas St. Elizabeth's Medical Center, Boston (B.C.); Glasgow University, Glasgow, Scotland (S.S.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (D.B., S.K., S.M.); and the University of Leuven, Leuven, Belgium (M.D.). Address reprint requests to Dr. Tashkin at the David Geffen School of Medicine, University of California, Los Angeles, 10833 Le Conte Ave., Los Angeles, CA 90095-1690, or at dtashkin@mednet.ucla.edu.

*Investigators in the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial are listed in Supplementary Appendix 1, available with the full text of this article at www.nejm.org.

This article (10.1056/NEJMoa0805800) was published at www.nejm.org on October 5, 2008.

N Engl J Med 2008;359:1543-54.

Reprinted from THE NEW ENGLAND JOURNAL OF MEDICINE
(ISSN 0028-4793) Vol. 359:1543-1554 (October 9, 2008).

Printed in the U.S.A. Fax: (781) 893-8103 www.nejm.org

PROSPECTIVE STUDIES TESTING EFFECTS on the progression of chronic obstructive pulmonary disease (COPD) through the evaluation of the slope of the forced expiratory volume in 1 second (FEV_1) have not shown that inhaled short-acting anticholinergic drugs, inhaled corticosteroids, or *N*-acetylcysteine alter this marker of disease progression.[1-7] To date, only smoking cessation has prospectively been shown to alter the rate of decline of FEV_1 in patients with COPD.[2]

Tiotropium is a once-daily, inhaled anticholinergic drug that provides at least 24-hour improvements in airflow and hyperinflation in patients with COPD.[8-10] Clinical trials lasting 6 weeks to 12 months have shown improvements in exercise tolerance, health-related quality of life, and rates of dyspnea and exacerbations.[8-13] A retrospective analysis of 1-year, placebo-controlled trials indicated that tiotropium had the potential to slow the rate of decline in FEV_1.[14]

Given previous favorable clinical outcomes, we designed this trial to prospectively extend these observations to 4 years.[15] In the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial, we tested whether tiotropium would reduce the rate of decline in FEV_1 in patients with COPD who were permitted therapy other than other inhaled anticholinergic drugs, according to current COPD guidelines. We evaluated the long-term effects of tiotropium therapy on the clinically important outcomes of health-related quality of life, exacerbations, related hospitalizations, and mortality.

METHODS

STUDY DESIGN

Details of the study design were reported previously by Decramer et al.[15] and are summarized below. The protocol is provided in Supplementary Appendix 2, available with the full text of this article at www.nejm.org.

The study was a 4-year, randomized, double-blind, placebo-controlled, parallel-group trial involving patients with moderate-to-very-severe COPD.[15] The two coprimary end points were the yearly rate of decline in the mean FEV_1 before the use of a study drug and short-acting bronchodilators in the morning (prebronchodilator) and after the use of a study drug (postbronchodilator) from day 30 (steady state) until completion of double-blind treatment. Secondary outcome measures included the rate of decline in the mean forced vital capacity (FVC) and slow vital capacity (SVC); health-related quality of life, as measured by the total score on St. George's Respiratory Questionnaire (SGRQ), in which scores range from 0 to 100, with lower scores indicating improvement and a change of 4 units or more considered to be clinically meaningful; exacerbations of COPD (as defined below) and related hospitalizations; and the rate of death from any cause and from lower respiratory conditions. Details regarding secondary end points are provided in Supplementary Appendix 3.

Patients received either 18 μg of tiotropium or a matching placebo once daily, delivered through the HandiHaler inhalation device (Boehringer Ingelheim). All respiratory medications, except other inhaled anticholinergic drugs, were permitted during the trial. Smoking cessation programs were offered to all patients before randomization, and self-reported smoking behavior was recorded at each visit. At the end of the study, all patients were provided with and asked to take 40 μg of ipratropium (two inhaler actuations) four times daily and to return for a final assessment 30 days later.

PATIENTS

Patients were recruited at 490 investigational centers in 37 countries. Criteria for participation included a diagnosis of COPD, an age of 40 years or more, a smoking history of at least 10 pack-years, a postbronchodilator FEV_1 of 70% or less of the predicted value, and an FEV_1 of 70% or less of the FVC (after supervised administration of 80 μg of ipratropium [four actuations], followed by 400 μg of albuterol [four actuations] 60 minutes later).[16] Key exclusion criteria were a history of asthma, a COPD exacerbation or respiratory infection within 4 weeks before screening, a history of pulmonary resection, use of supplemental oxygen for more than 12 hours per day, and the presence of a coexisting illness that could preclude participation in the study or interfere with the study results. The protocol was approved by the ethics committee at each center, and all patients provided written informed consent.

PROCEDURES

After a screening period, eligible patients were randomly assigned in a 1:1 ratio to receive either tiotropium or placebo with the use of centralized randomization in blocks of four, stratified according to site. After randomization, clinic visits oc-

curred at 1 month and 3 months and then every 3 months throughout the 4-year study period.

Spirometry was performed according to American Thoracic Society guidelines[17] at randomization, at the 1-month visit, at visits every 6 months throughout the study period, and at a follow-up visit approximately 30 days after the end of the study. Before spirometry testing, respiratory medications were withheld according to the following schedule: study drug, 24 hours; morning dose of inhaled corticosteroids, 12 hours; short-acting beta-agonists, 8 hours; short-acting (twice-daily or four-times-daily) theophyllines and long-acting beta-agonists (including fixed combination with inhaled corticosteroids), 24 hours; and once-daily theophyllines, 48 hours. Prebronchodilator spirometry was performed initially, followed immediately by the blinded administration of a study drug. Immediately thereafter, all patients received 80 μg of ipratropium (four inhaler actuations), followed 60 minutes later by 400 μg of albuterol (four inhaler actuations). Thirty minutes after the administration of albuterol, spirometry was again performed. Sites were provided with identical spirometry equipment and study-specific software. A centralized quality-assurance review of all spirometry data was performed during the study.[15]

Health-related quality of life was measured with the use of the SGRQ before prebronchodilator spirometry testing at baseline and every 6 months.[18] Reports of adverse events were collected at each visit.

Exacerbations were defined as an increase in or the new onset of more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, or dyspnea) lasting 3 days or more and requiring treatment with an antibiotic or a systemic corticosteroid. Data regarding exacerbations and related hospitalizations were collected on study-specific case-report forms at every visit. An independent data and safety monitoring committee reviewed data throughout the trial (for details, see Supplementary Appendixes 2 and 4).

STUDY OVERSIGHT

The design of the trial, the monitoring of the trial conduct, the approval of the statistical analyses, the review and interpretation of the data, the writing of the manuscript, and the decision to publish the manuscript involved a joint advisory committee composed of four academic researchers (three investigators and a statistician), three researchers employed by Boehringer Ingelheim, and a representative of Pfizer (see Supplementary Appendix 4). The first draft of the manuscript was written by an academic investigator, and the final content of the manuscript was developed collaboratively by all authors. Statistical analyses were performed by employees of Boehringer Ingelheim. All authors had full access to the data and vouch for the accuracy and completeness of the data and the analyses.

STATISTICAL ANALYSIS

The number of patients needed for the study was based on the assumption of a standard deviation of 90 ml in the rate of decline in the mean FEV_1 during the 4-year period[2] to detect a difference of 15 ml between the tiotropium group and the placebo group, with a power of more than 90% at a significance level of 5% with the use of a two-sided test. The sample size was also based on an assumption that it would not be possible to perform a complete evaluation of 35% of patients because of early discontinuation. The sample size was chosen to be sufficiently large to undertake subgroup analyses of the primary end point in smokers, who were assumed to comprise about 40% of enrolled patients. The other planned subgroup analyses included the variables of age, sex, severity of COPD, region, reversibility, body-mass index, and concomitant use of medication. In addition, we conducted a post hoc subgroup analysis comparing patients in each study group who were or were not receiving inhaled corticosteroids or long-acting beta-agonists at baseline.

The two coprimary end points were analyzed with the use of a normal random-effects model in which the mean FEV_1 changed linearly after day 30 for each patient, the intercepts and slopes among patients were assumed to be random with an arbitrary covariance matrix, and the treatment effect was fixed.[19] The same model was used for the secondary end points of FVC and SVC (from day 30 until study completion) and the total score on the SGRQ (from 6 months until study completion). All patients who underwent randomization and received a study drug and who had at least three post-randomization data points (at least two for the SGRQ) were included in the analyses. We used likelihood-based methods to handle missing data for the random coefficient regression analysis, and therefore no imputation was deemed necessary. A sensitivity analysis was conducted for the rate of decline in the mean FEV_1, with adjustment for baseline FEV_1, smoking

status, age, sex, and height. Analyses of heterogeneity of subgroups were assessed by testing for interaction between study-group slope and each baseline factor. The yearly rates of decline from baseline to 30 days after the discontinuation of a study drug were analyzed using the Wilcoxon rank-sum test. The mean effects at various visits were compared in the two study groups with the use of repeated-measures analysis of covariance without imputation of missing values. SGRQ data from Turkey were excluded owing to incorrect validation of the questionnaire.

The times to the first exacerbation and associated hospitalization in the two study groups were compared with the use of log-rank tests and were prespecified as the key secondary analyses. Cox regression was used to derive hazard ratios. Kaplan–Meier curves of the probability of no exacerbation and related hospitalization were calculated. The number of events and event days were compared between study groups with the use of Poisson regression with correction for treatment exposure and overdispersion.[20]

All patients who received a study drug were included in the analysis of safety and discontinuations. Incidence rates were computed as the number of patients with events divided by the time at risk. Time-to-event analyses were performed with the use of the log-rank test; hazard ratios were calculated with the use of Cox regression.

Analyses were performed with the use of SAS software, version 8.2 (SAS Institute). All reported P values are two-sided and were not adjusted for multiple testing. The scientific steering committee (Joint Advisory Committee) added a number of secondary end points and updated the analyses during the course of the trial while its members were unaware of study-group assignments. Details of the statistical analysis plan are provided in Supplementary Appendix 3.

RESULTS

STUDY POPULATION

Patients were recruited from January 2003 through March 2004; the study ended in February 2008. Of the 8020 patients who were recruited, 5993 underwent randomization (Fig. 1). Of these patients, 4383 (73%) completed 2 years, 3891 (65%) completed 3 years, and 3569 (60%) completed at least 45 months. The median duration of treatment was 1436 days in the tiotropium group and 1435 days in the placebo group. A higher proportion of patients did not complete at least 45 months of treatment in the placebo group (44.6%) than in the tiotropium group (36.2%, P<0.001) (Fig. 2A). The majority of discontinuations were due to adverse events.

Baseline characteristics and concomitant use of respiratory medications were similar in the two study groups (Table 1). The mean age was 65±8 years among the patients, of whom 75% were men and 30% were current smokers. The mean prebronchodilator FEV_1 was 1.10±0.40 liters (39% of the predicted value), and the mean postbronchodilator FEV_1 was 1.32±0.44 liters (48% of the predicted value). The mean increase in FEV_1 after maximal bronchodilation was 23±18%.[21] Patients whose disease was classified as stage II, III, or IV, according to criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), comprised 46%, 44%, and 9% of patients, respectively.[1] The mean baseline prebronchodilator FEV_1 was lower in patients who discontinued a study drug than in those who completed the study period (37% vs. 41% of the predicted value, P<0.001). More than 90% of patients were receiving respiratory medications at baseline.

During the study period, 26% of patients changed their smoking behavior. On at least one clinic visit, 74% of patients reported having received inhaled corticosteroids, 72% long-acting beta-agonists, and 46% a fixed combination of the two.

RATE OF DECLINE IN LUNG FUNCTION

The rate of decline in the mean postbronchodilator FEV_1 was greater in patients who prematurely discontinued a study drug (55±4 ml per year in the tiotropium group and 57±4 ml per year in the placebo group), as compared with those who completed the study period (38±1 ml per year in the tiotropium group and 40±1 ml per year in the placebo group).

There were no significant differences between study groups in the rate of decline in the mean values for FEV_1 and FVC either before or after bronchodilation from day 30 to the end of study-drug treatment (Table 2; for SVC measures, see Supplementary Appendix 5). In the tiotropium group, the mean values for FEV_1 and FVC before and after bronchodilation showed significant improvements that were maintained at all time points after randomization (Fig. 2B and 2C). Mean improvements in FEV_1 in the tiotropium group,

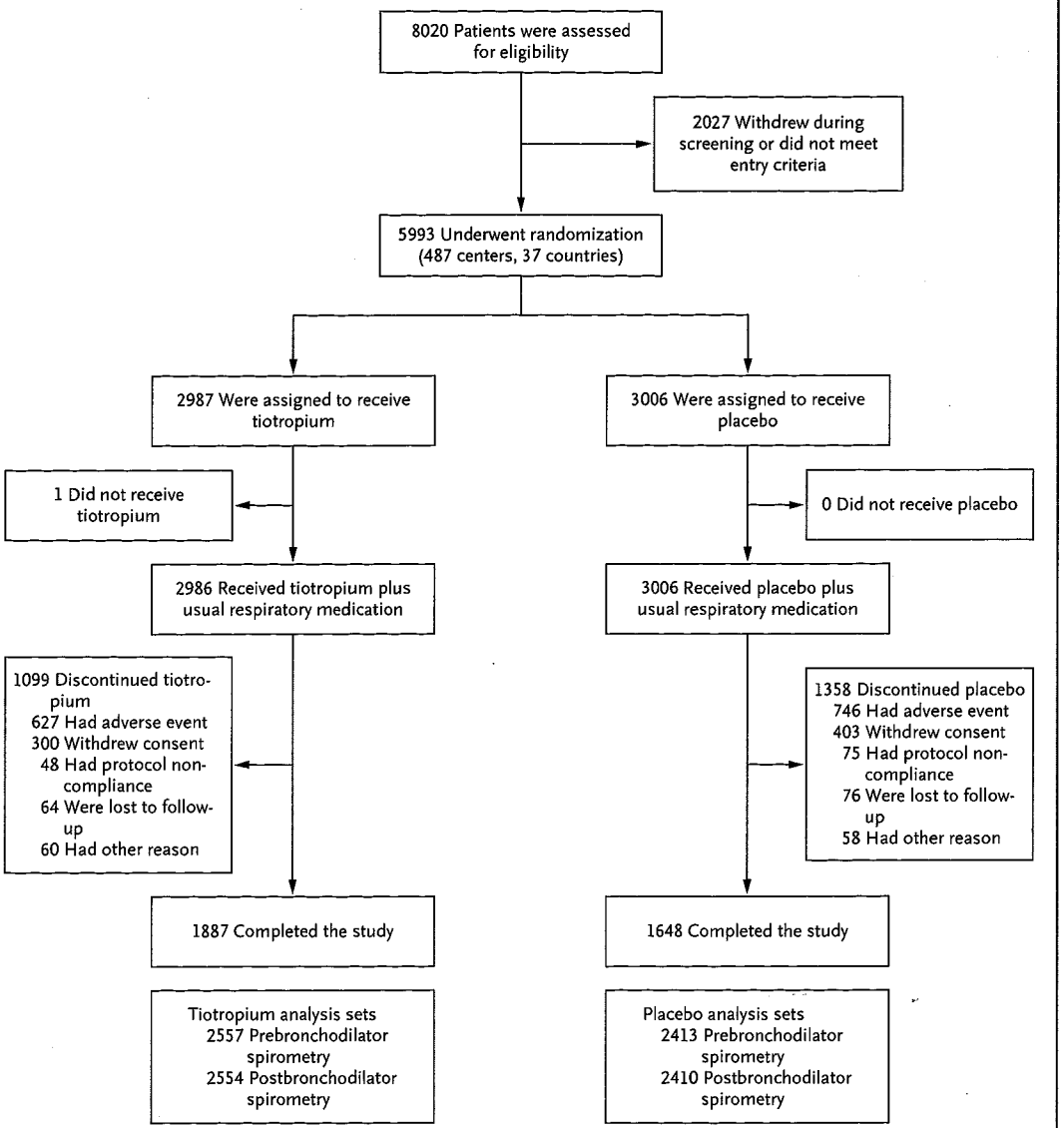


Figure 1. Enrollment and Outcomes.

Patients with three or more measurements of pulmonary function after day 30 were included in the analysis of lung function. Patients in the study were permitted to use all respiratory medications except other inhaled anticholinergic drugs. After the initial assessment, one patient underwent randomization twice.

as compared with the placebo group, ranged from 87 to 103 ml before bronchodilation and from 47 to 65 ml after bronchodilation ($P<0.001$). Adjustments for baseline FEV_1, smoking status, age, sex, and height had similar results.

The prespecified subgroup analyses revealed no significant heterogeneity in the effect of tiotropium according to the baseline variables examined (Supplementary Appendix 6). In a post hoc analysis, between-group differences in the rate of decline in postbronchodilator FEV_1 were observed in favor of tiotropium, as compared with placebo (40±3 ml in the tiotropium group and 47±3 in the placebo group, $P=0.046$) in the subgroup of 1554 patients who were not receiving either inhaled corticosteroids or long-acting beta-agonists at baseline.

Among 3421 patients from baseline until 30 days after treatment discontinuation, the median rate of decline in prebronchodilator FEV_1 did not differ significantly between the tiotropium group (15 ml per year) and the placebo group (17 ml per

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Tiotropium (N=2986)	Placebo (N=3006)
Male sex (%)	75.4	73.9
Age (yr)	64.5±8.4	64.5±8.5
Body-mass index	26.0±5.1	25.9±5.1
Smoking status		
Current smoker (%)	29.3	29.9
Smoking history (pack-yr)	49.0±28.0	48.4±27.9
Duration of COPD (yr)	9.9±7.6	9.7±7.4
Baseline spirometry		
Before bronchodilation		
FEV_1 (liters)	1.10±0.40	1.09±0.40
FEV_1 (% of predicted value)	39.5±12.0	39.3±11.9
FVC (liters)	2.63±0.81	2.63±0.83
Ratio of FEV_1 to FVC	42.4±10.5	42.1±10.5
After bronchodilation		
FEV_1 (liters)	1.33±0.44	1.32±0.44
FEV_1 (% of predicted value)	47.7±12.7	47.4±12.6
FVC (liters)	3.09±0.86	3.09±0.90
Ratio of FEV_1 to FVC	43.6±10.8	43.3±10.7
GOLD stage (%)†		
II	46	45
III	44	44
IV	8	9
SGRQ total score (units)‡	45.7±17.0	46.0±17.2
Respiratory medication (%)		
Any	93.4	93.1
Inhaled anticholinergic§		
Short-acting	44.9	44.1
Long-acting	2.0	1.6
Inhaled β_2-agonist§		
Short-acting	68.5	68.1
Long-acting	60.1	60.1
Corticosteroid		
Inhaled§	61.6	61.9
Oral	8.4	8.3
Theophylline compound	28.4	28.5
Mucolytic agent	7.4	6.9
Leukotriene-receptor antagonist	3.3	3.1
Supplemental oxygen	2.3	1.9

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. FEV_1 denotes forced expiratory volume in 1 second, FVC forced vital capacity, and SGRQ St. George's Respiratory Questionnaire.

† Data were missing in this category for 2% of patients. The enrollment of three patients with stage I disease, according to criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), represented a protocol violation, but data from these patients were included in the study.

‡ Data are for 2888 patients in the tiotropium group and 2909 patients in the placebo group. Scores on the SGRQ range from 0 to 100, with lower scores indicating improvement; a change of 4 units or more is considered to be clinically meaningful.

§ This medication was used either alone or as a fixed combination.

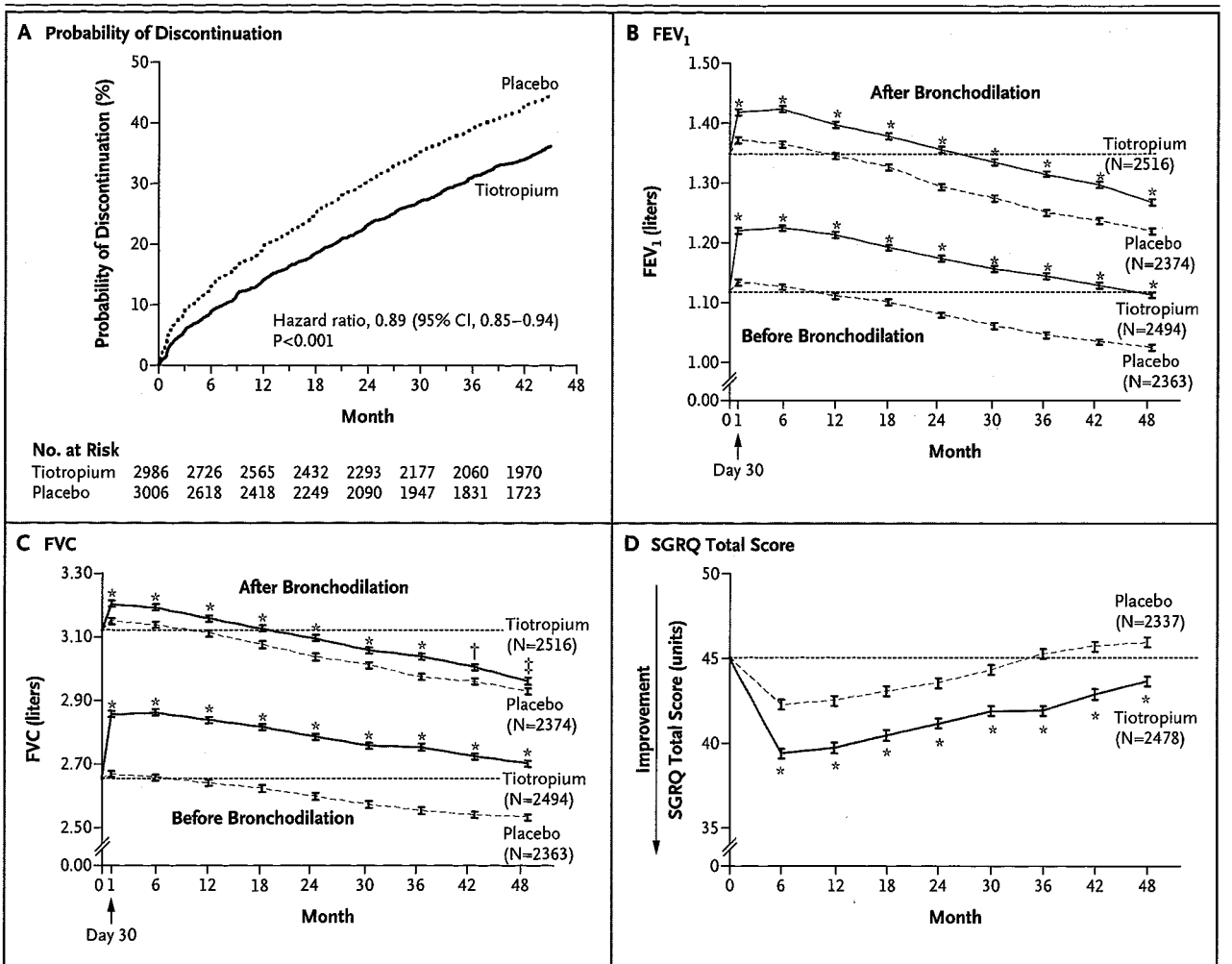


Figure 2. Probability of Treatment Discontinuation, Mean FEV_1 and FVC before and after Bronchodilation, and Scores for Health-Related Quality of Life.

Panel A shows the probability of treatment discontinuation in the tiotropium group and the placebo group. Panel B shows the estimated mean forced expiratory volume in 1 second (FEV_1) before and after bronchodilation from day 30 to the end of the study. Before bronchodilation, the annual rates of decline were the same in the tiotropium group and the placebo group: 30±1 ml per year. After bronchodilation, the annual rate of decline was 40±1 ml per year in the tiotropium group, as compared with 42±1 ml per year in the placebo group. Panel C shows the mean forced vital capacity (FVC) before and after bronchodilation from day 30 to the end of the study. Before bronchodilation, the annual rate of decline was 43±3 ml per year in the tiotropium group and 39±3 in the placebo group. After bronchodilation, the annual rates of decline were the same in the tiotropium group and the placebo group: 61±3 ml per year. Panel D shows the health-related quality-of-life score from month 6 to the end of the study, as measured on St. George's Respiratory Questionnaire (SGRQ), which ranges from 0 to 100, with lower scores indicating improvement. The annual rate of change was 1.25±0.09 units per year in the tiotropium group, as compared with 1.21±0.09 units in the placebo group. Repeated-measure analysis of variance was used to estimate means. Means are adjusted for baseline measurements. For FEV_1 and FVC, patients with three or more acceptable pulmonary-function tests after day 30 and no missing baseline values were included in the analysis. For the SGRQ total score, patients with two or more acceptable scores after month 6 and no missing baseline values were included in the analysis. The I bars represent standard errors, and the horizontal dashed lines represent baseline levels. Asterisks denote P<0.001, the dagger P=0.002, and the double dagger P=0.04.

2. Annual Rates of Decline in FEV_1 and FVC before and after Bronchodilation and Scores on Health-Related Quality of Life.*

ble	Tiotropium		Placebo		Difference between Tiotropium and Placebo (95% CI)	P Value†
	Patients	Mean Decline	Patients	Mean Decline		
	no.	*ml/yr*	*no.*	*ml/yr*		
efore bronchodilation	2557	30±1	2413	30±1	0±2 (−4 to 4)	0.95
fter bronchodilation	2554	40±1	2410	42±1	−2±2 (−6 to 2)	0.21
efore bronchodilation	2557	43±3	2413	39±3	4±4 (−4 to 12)	0.30
fter bronchodilation	2554	61±3	2410	61±3	1±4 (−7 to 9)	0.84
SGRQ score‡	2505	1.25±0.09	2362	1.21±0.09	0.04±0.13 (−0.2 to 0.3)	0.78

-minus values are means ±SE. Values for the rate of decline in forced expiratory volume in 1 second (FEV_1) and forced vital capacity) are expressed as milliliters per year. Values were measured from day 30 until the end of the study (including 30 days after the discontion of treatment). Patients with three or more measurements after day 30 were included in the analysis of lung function.
ues are unadjusted.
s for the health-related quality-of-life score on St. George's Respiratory Questionnaire (SGRQ) are expressed in units per year. Scores on GRQ range from 0 to 100, with an increase in the score indicating a decline in quality of life; a change of 4 units or more is considered to nically meaningful. Patients with two or more measurements after month 6 were included in the analysis of the SGRQ.

year) (P=0.25). However, among 3418 patients who had technically acceptable postbronchodilator spirometry, there was a significant difference in favor of tiotropium in the median rate of decline in postbronchodilator FEV_1 (27 ml per year in the tiotropium group, as compared with 32 ml per year in the placebo group; P=0.01).

HEALTH-RELATED QUALITY OF LIFE

Significant differences in favor of tiotropium were observed at all time points for the mean absolute change in the SGRQ total score (ranging from 2.3 to 3.3 units, P<0.001), although the differences on average were below what is considered to have clinical significance (Fig. 2D). The overall mean between-group difference in the SGRQ total score at any time point was 2.7 (95% confidence interval [CI], 2.0 to 3.3) in favor of tiotropium (P<0.001). A higher proportion of patients in the tiotropium group than in the placebo group had an improvement of 4 units or more in the SGRQ total scores from baseline at 1 year (49% vs. 41%), 2 years (48% vs. 39%), 3 years (46% vs. 37%), and 4 years (45% vs. 36%) (P<0.001 for all comparisons). There were no significant between-group differences in the rate of decline in SGRQ scores from 6 months to the end of the study (Table 2).

EXACERBATIONS

Tiotropium was associated with a significant delay in the time to the first exacerbation, with a median of 16.7 months (95% CI, 14.9 to 17.9) in the tiotropium group and 12.5 months (95% CI, 11.5 to 13.8) in the placebo group. Tiotropium was also associated with a significant delay in the time to the first hospitalization for an exacerbation. Since hospitalizations for exacerbations occurred in less than 50% of patients, a median time to the first event cannot be calculated. In the tiotropium group, the associated hazard ratios were 0.86 (95% CI, 0.81 to 0.91) and 0.86 (95% CI, 0.78 to 0.95), respectively. Tiotropium was also associated with a reduction in the mean number of exacerbations of 14% (P<0.001) (Fig. 3A and Supplementary Appendix 7). The mean numbers of exacerbations leading to hospitalizations were infrequent and did not differ significantly between the two study groups (Table 3).

MORTALITY

Data regarding vital status were systematically requested for patients who prematurely discontinued study participation on a recorded date determined as 4 years from the first day of administration of a study drug. Data regarding deaths extending beyond 4 years (up to and beyond 1470 days) were not systematically collected but were occasionally received. Every effort was made to ensure that vital-status data were full and complete up to 4 years, as described. Vital-status information (at least 45 months of follow-up, including patients who discontinued treatment) was known

for 98% of patients in the tiotropium group and 97% in the placebo group. During a period of 4 years plus 30 days (1470 days) included in the intention-to-treat analysis, 941 patients died: 14.9% in the tiotropium group and 16.5% in the placebo group (hazard ratio, 0.89; 95% CI, 0.79 to 1.02) (Fig. 3B). For the 4-year, protocol-defined study period up to day 1440, among patients for whom vital-status information was available, 921 patients died: 14.4% in the tiotropium group and 16.3% in the placebo group (hazard ratio, 0.87; 95% CI, 0.76 to 0.99).

ADVERSE EVENTS

Safety was monitored through the collection of reports of adverse events, serious adverse events, and fatal events while patients were receiving a study drug (including the last day of a study drug plus 30 days). Adverse events were reported by 92.6% of the tiotropium group and 92.3% of the placebo group. The proportions of serious adverse events were 51.6% in the tiotropium group and 50.2% in the placebo group. Fatal events occurred in 381 patients (12.8%) in the tiotropium group and 411 (13.7%) in the placebo group (hazard ratio, 0.84; 95% CI, 0.73 to 0.97).

In the tiotropium group, as compared with the placebo group, the most common adverse events were due to lower respiratory causes, including COPD exacerbations (64.8% and 66.1%, respectively; relative risk, 0.84; 95% CI, 0.79 to 0.89), pneumonia (14.5% and 13.9%; relative risk, 0.96; 95% CI, 0.84 to 1.10), and dyspnea (12.2% and 14.7%; relative risk, 0.75; 95% CI, 0.65 to 0.86). Respiratory failure developed in 88 patients in the tiotropium group and in 120 in the placebo group (relative risk, 0.67; 95% CI, 0.51 to 0.89). Myocardial infarction developed in 67 patients in the tiotropium group and 85 in the placebo group (relative risk, 0.73; 95% CI, 0.53 to 1.00), and stroke developed in 82 in the tiotropium group and 80 in the placebo group (relative risk, 0.95; 95% CI, 0.70 to 1.29). Adverse events consistent with the known safety profile of tiotropium, such as dry mouth and constipation, were observed.[22,23]

Serious adverse events reported by more than 1% of patients in either study group were either cardiac or respiratory in nature (Table 4). The incidence of such serious adverse events was lower in the tiotropium group than in the placebo group, including a reduced risk of congestive heart failure, COPD exacerbation, dyspnea, or respiratory failure. Serious adverse events according to organ system and adverse events that were reported by more than 3% of patients in either of the study groups are provided in Supplementary Appendix 8.

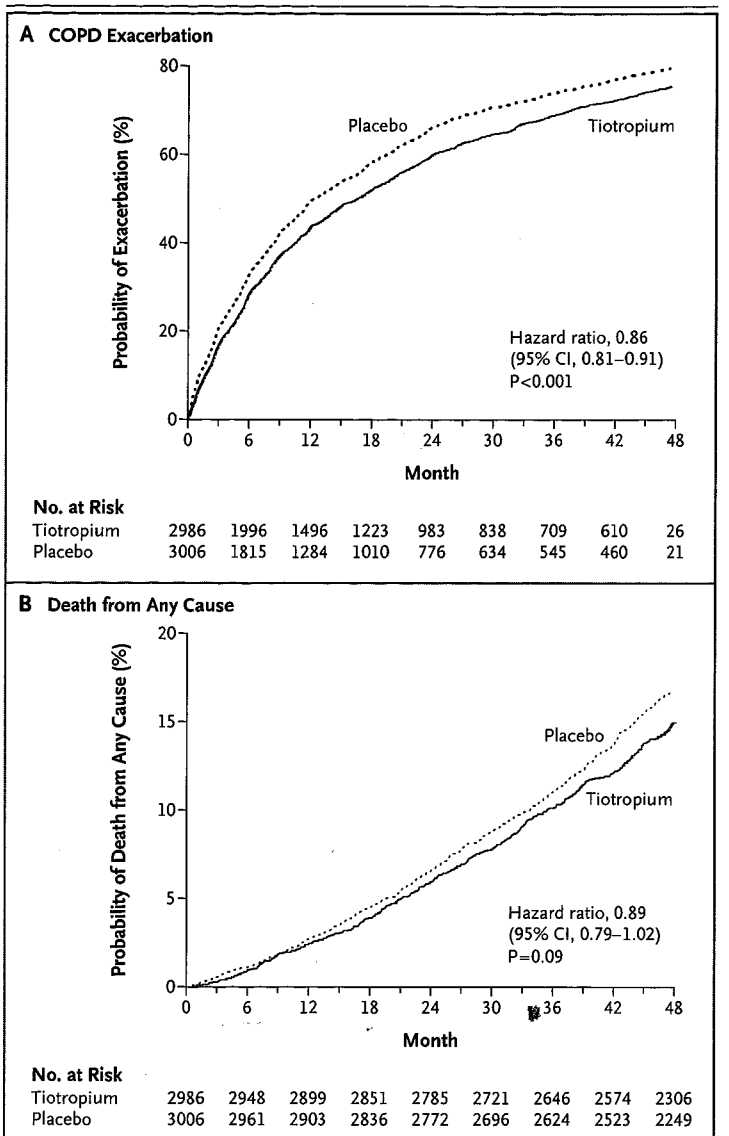


Figure 3. Kaplan–Meier Estimates of the Probability of COPD Exacerbation and Death from Any Cause.

Kaplan–Meier curves show the cumulative incidence estimate of the probability of COPD exacerbation (Panel A) and of death from any cause at day 1470 for all patients for whom data were available regarding vital status (Panel B). The numbers of patients who continued to receive a study drug (including those at 30 days after the last dose) are listed for each time point, with the study period truncated at 48 months. All patients who received at least one dose of a study drug were included in the analysis. P values were calculated with use of the log-rank test.

Table 3. Exacerbations of COPD and Related Hospitalizations.*

Variable	Tiotropium	Placebo	Relative Risk for Tiotropium vs. Placebo (95% CI)	P Value
Exacerbation†				
Per patient-year — no.	0.73±0.02	0.85±0.02	0.86 (0.81–0.91)	<0.001
Leading to hospitalization — no. per patient-year	0.15±0.01	0.16±0.01	0.94 (0.82–1.07)	0.34
Days per patient-year	12.11±0.32	13.64±0.35	0.89 (0.83–0.95)	0.001
Hospitalization days per patient-year	3.17±0.17	3.13±0.17	1.01 (0.87–1.18)	0.86
Patients with exacerbation — no. (%)‡				
Total	2001 (67.0)	2049 (68.2)	NA	0.35
Leading to hospitalization	759 (25.4)	811 (27.0)	NA	0.18

* Plus–minus values are means ±SE. NA denotes not applicable.
† The relative risks in this category were calculated with the use of Poisson regression corrected for treatment exposure and overdispersion.
‡ The comparisons in this category were calculated with the use of Fisher's exact test.

DISCUSSION

In our study, we showed that in the presence of freely prescribed respiratory medications (i.e., inhaled long-acting beta-agonists, inhaled corticosteroids, and theophyllines) other than another inhaled anticholinergic agent, tiotropium (at a dose of 18 μg once daily) did not alter the rate of decline in the mean FEV_1 in patients with COPD. However, lung function was significantly better than in the placebo group throughout the trial, and there were improvements in health-related quality of life and the rate of exacerbations.

As compared with results of previous long-term, prospective studies, the yearly rate of decline in FEV_1 that we observed was numerically lower than the rates of decline reported previously.[2-6] Prospective interventional studies that were designed to examine the decline in FEV_1 — such as the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease (EUROSCOP), the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) trial, the Lung Health Study II, and the Bronchitis Randomized on NAC [*N*-acetylcysteine] Cost–Utility Study (BRONCUS) — showed a decline in postbronchodilator rates ranging from 44 to 57 ml per year in the active-treatment groups and 47 to 69 ml per year in the placebo groups.[3-6] In our study, the decline in lung function averaged 30 ml per year before bronchodilation and 41 ml per year after bronchodilation in the two study groups, a change that is less than that in any of the previous studies. The values for the decline in FEV_1 are also smaller than those observed in the post hoc analysis of lung function in the Towards a Revolution in COPD Health (TORCH) trial (ClinicalTrials.gov number, NCT00268216).[24]

There are several potential explanations for the discrepancies in the rate of decline in our study, as compared with those in previous studies. First, our study design allowed for prescription of all respiratory therapies at the discretion of physicians, with the exception of another inhaled anticholinergic agent. It is therefore possible that the medical care that patients received during our study, including both short-acting and long-acting inhaled respiratory medications and aggressive treatment of exacerbations, differed from that in earlier trials and, as a whole, contributed to the generally lower rates of decline. However, such factors have not been definitively shown. Second, in our study, a higher proportion of patients with sustained abstinence from smoking tobacco may have resulted in a lower mean rate of decline. In our study, self-reports of smoking behavior indicated that only 30% of patients were current smokers at baseline, as compared with 38 to 90% in other studies.[3-6] Third, other factors, such as differences in study design, selection of patients, and regional factors, could also account for discrepancies. In interpreting the results of our study, one should consider that the rates of decline in our study are similar to those reported for healthy nonsmokers and sustained quitters with mild-to-moderate COPD.[2]

Similar, low rates of decline in lung function were seen in the two study groups. A possible

Table 4. Incidence Rate of Serious Adverse Events per 100 Patient-Years.*

Adverse Event	Tiotropium (N=2986)	Placebo (N=3006)	Relative Risk for Tiotropium vs. Placebo (95% CI)
Cardiac	3.56	4.21	0.84 (0.73–0.98)†
Angina	0.51	0.36	1.44 (0.91–2.26)
Atrial fibrillation	0.74	0.77	0.95 (0.68–1.33)
Cardiac failure	0.61	0.48	1.25 (0.84–1.87)
Congestive heart failure	0.29	0.48	0.59 (0.37–0.96)†
Coronary artery disease	0.21	0.37	0.58 (0.33–1.01)
Myocardial infarction	0.69	0.97	0.71 (0.52–0.99)†
Lower respiratory	11.32	13.47	0.84 (0.77–0.92)†
Bronchitis	0.37	0.31	1.20 (0.73–1.98)
COPD exacerbation	8.19	9.70	0.84 (0.76–0.94)†
Dyspnea	0.38	0.62	0.61 (0.40–0.94)†
Pneumonia	3.28	3.46	0.95 (0.81–1.11)
Respiratory failure	0.90	1.31	0.69 (0.52–0.92)†

* Listed are the incidence rates of serious adverse events (excluding lung cancer) that were reported by more than 1% of patients in either study group, according to organ class during the study period (from the first day of administration of a study drug until the last day plus 30 days).
† $P<0.05$.

explanation for this finding is that tiotropium does not influence the decline in lung function over time. There are other potential explanations. Current management of COPD could affect the decline in lung function so that a ceiling effect occurs and further improvements are not seen in the absence of an intervention that repairs or regenerates lung tissue. This possibility is supported by the high rate of prescriptions for concomitant respiratory medications in our study and by the differences between tiotropium and placebo in the rate of decline in postbronchodilator FEV_1 in patients who did not use inhaled corticosteroids or long-acting beta-agonists. Another potential reason is the higher rate of discontinuation in the placebo group. Data from our study and other trials suggest that patients who discontinue treatment have a more rapid decline in lung function than those who do not discontinue treatment.[25] Since patients who discontinued treatment had, on average, significantly more severe airflow obstruction at baseline, those in the placebo group who completed the trial probably represent "healthy survivors." The possibility of a healthy-survivor effect may not be adequately addressed with the prespecified analysis presented here.[25,26]

Tiotropium improved measures of airflow obstruction and vital capacity that were performed 24 hours after daily study-drug administration during the 4-year study period. Tiotropium also improved lung function, as compared with placebo, beyond the improvement resulting from serial administration of maximal doses of salbutamol and ipratropium. These improvements in lung function were accompanied by improvements in some of the clinical outcomes measured. Scores regarding health-related quality of life improved relative to placebo during the entire 4-year study period. In the tiotropium group, there were significant delays in the onset of exacerbations and associated hospitalizations. These outcomes appeared in the presence of substantial use of concomitant COPD therapies.

The results of our study are consistent with the published pooled safety analysis[23] and indicate a reduction in cardiac adverse events associated with tiotropium. The reduced risk of respiratory failure was also observed in the previous pooled safety analysis of tiotropium, in which the relative risk of respiratory failure in the tiotropium group, as compared with the placebo group, was 0.59 (95% CI, 0.26 to 1.34).[23] However, our study had significantly more power to detect such differential event reporting because of a larger and longer exposure to tiotropium.

Our data show that among patients with COPD who were receiving other classes of respiratory medications during the study period, the addition of 18 μg of tiotropium once daily for up

to 4 years did not result in changes in the rate of decline in lung function. However, there were important lung-function benefits associated with tiotropium that were maintained during the 4 years, as well as positive effects on health-related quality of life and a reduced risk of exacerbations and exacerbation-related hospitalizations consistent with a relevant effect on the clinical course of COPD. Finally, tiotropium reduced respiratory morbidity (including a decreased risk of respiratory failure) and reduced cardiac morbidity.

Supported by Boehringer Ingelheim and Pfizer.

Dr. Tashkin reports receiving consulting fees from AstraZeneca, Boehringer Ingelheim, Dey Laboratories, and Schering, lecture fees from AstraZeneca, Boehringer Ingelheim, and Dey Laboratories, and grant support from Almirall, AstraZeneca, Boehringer Ingelheim, Dey Laboratories, GlaxoSmithKline, Ivax, MediciNova, Nabi Biopharmaceuticals, Novartis, Pfizer, and Sepracor; Dr. Celli, receiving consulting fees from Almirall, AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline, lecture fees from Almirall, AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline, and grant support from Boehringer Ingelheim, Forrest, and GlaxoSmithKline; Dr. Senn, receiving consulting fees from Bayer, Boehringer Ingelheim, Chiesi, Eisai, GlaxoSmithKline, INOT, Novartis, Pfizer, Servier, and Takeda, lecture fees from Amgen, Alcon, and Unilever, and grant support from Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and Novartis, having an equity interest in Novartis, and serving as an expert witness for GlaxoSmithKline; Ms. Burkhart, Dr. Kesten, and Dr. Menjoge, being employees of Boehringer Ingelheim; and Dr. Decramer, receiving consulting fees from Boehringer Ingelheim, Pfizer, GlaxoSmithKline, and Nycomed, lecture fees from Boehringer Ingelheim and Pfizer, and grant support from AstraZeneca. No other potential conflict of interest relevant to this article was reported.

We thank the UPLIFT trial team and clinical monitors; Dr. Dacheng Liu and Dr. Inge Leimer of Boehringer Ingelheim for their statistical support; Terry Keyser (funded by Boehringer Ingelheim) for editorial and technical support in the preparation of this manuscript; and Dr. Romain Pauwels, who contributed to the design of the study and was a key member of the UPLIFT Joint Advisory Committee before his death in 2005.

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Bethesda, MD: National Heart, Lung, and Blood Institute, April 2001 (revised 2007). (Accessed September 16, 2008, at http://www.goldcopd.org.)

2. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1: the Lung Health Study. JAMA 1994; 272:1497-505.

3. The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med 2000;343:1902-9.

4. Pauwels RA, Löfdahl CG, Laitinen LA, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. N Engl J Med 1999;340: 1948-53.

5. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320:1297-303.

6. Decramer M. Rutten-van Mölken M, Dekhuijzen PN, et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. Lancet 2005;365:1552-60. [Erratum, Lancet 2005;366:984.]

7. Soriano JB, Sin DD, Zhang X, et al. A pooled analysis of FEV_1 decline in COPD patients randomized to inhaled corticosteroids or placebo. Chest 2007;131:682-9.

8. Casaburi R, Mahler DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J 2002;19: 217-24.

9. O'Donnell DE, Flüge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. Eur Respir J 2004;23:832-40.

10. Maltais F, Hamilton A, Marciniuk D, et al. Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. Chest 2005;128:1168-78.

11. Vincken W, van Noord JA, Greefhorst APM, et al. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. Eur Respir J 2002; 19:209-16.

12. Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax 2003;58:399-404. [Erratum, Thorax 2005;60:105.]

13. Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator. Ann Intern Med 2005;143: 317-26.

14. Anzueto A, Tashkin D, Menjoge S, Kesten S. One-year analysis of longitudinal changes in spirometry in patients with COPD receiving tiotropium. Pulm Pharmacol Ther 2005;18:75-81.

15. Decramer M, Celli B, Tashkin DP, et al. Clinical trial design considerations in assessing long-term functional impacts of tiotropium in COPD: the UPLIFT trial. COPD 2004;1:303-12.

16. Quanjer PH. Standardised lung function testing: report of the European Community for Coal and Steel. Bull Eur Physiopathol Respir 1983;19:Suppl:7-28.

17. American Thoracic Society. Standardization of spirometry: 1994 update. Am J Respir Crit Care Med 1995;152:1107-36.

18. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992;145: 1321-7.

19. Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics 1982;38:963-74.

20. Suissa S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006;173:842-6.

21. Tashkin DP, Celli B, Decramer M, et al. Bronchodilator responsiveness in patients with COPD. Eur Respir J 2008;31:742-50.

22. Spiriva HandiHaler. Ingelheim, Germany: Boehringer Ingelheim Pharma GmbH, 2008 (package insert).

23. Kesten S, Jara M, Wentworth C, Lanes S. Pooled clinical trial analysis of the safety of tiotropium. Chest 2006;130: 1695-703.

24. Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. Am J Respir Crit Care Med 2008;178:332-8.

25. Calverley PM, Spencer S, Willits L, Burge PS, Jones PW. Withdrawal from treatment as an outcome in the ISOLDE study of COPD. Chest 2003;124:1350-6.

26. Kesten S, Plautz M, Piquette CA, Habib MP, Niewoehner DE. Premature discontinuation of patients: a potential bias in COPD clinical trials. Eur Respir J 2007;30: 898-906.