Supplement to
Clinical Cardiology

Volume 24

11'01

Clinical Cardiology™

A Journal for Advances in Cardiovascular Disease

The INternational VErapamil SR/trandolapril STudy (INVEST) – The First Randomized Clinical Trial Evaluating Aggressive Blood Pressure Management (JNC VI) in Patients with CAD

Carl J. Pepine, M.D., MACC, FESC
Guest Editor

November 2001
Foundation for Advances in Medicine and Science, Inc.

Clinical Cardiology™

A Journal for Advances
in Cardiovascular Disease

Guest Editor for this issue:

CARL J. PEPINE
Gainesville, USA

The editorial content of supplements is reviewed by the guest editor and approved by C. Richard Conti, M.D., Editor-in-Chief of the Journal. The findings presented in this supplement are those of the contributors and not necessarily those of the sponsor, the publisher, or the editors of *Clinical Cardiology*.

The Publisher

CLINICAL CARDIOLOGY: A Journal for Advances in Cardiovascular Disease (ISSN 0160-9289) is published monthly and copyrighted © 2001 by the Foundation for Advances in Medicine and Science, Inc., 111 Oweno Road, Mahwah, N.J. 07430. Periodicals postage paid at Mahwah, New Jersey, and additional mailing offices. POSTMASTER: Send address changes to Clinical Cardiology, Box 832, Mahwah, NJ 07430-0832.

Subscription per annum (12 issues plus supplements): Institutional and personal—$80 U.S. and $126.50 foreign; single copy $15.50. Subscriptions calendar year only. Payment for subscriptions should be in U.S. funds drawn on U.S. bank to Clinical Cardiology Publishing Co., Inc., Box 832, Mahwah, N.J. 07430-0832.

This journal is fully refereed and is included in Index Medicus, Current Contents/Clinical Practice, ISI BioMed, Science Citation Index, Index Internacional de Cardiologia, and EMBASE/Excerpta Medica.

Manuscript submission: Refer to last page of Table of Contents for Instructions to Authors page listing.

Printed in USA by Mack Printing Co., Easton, PA

November 2001

Publisher: Tony Bourgholtzer

Executive Editor: Joey Marie Bourgholtzer, Ph.D.

Art Director: John Romano

Circulation Manager: Lillian Conly

Copyreader: Helga Politzer

Advertising rates & information mailed on request.

Contact:
Clinical Cardiology Advertising Department
Box 832, Mahwah, New Jersey 07430-0832
Tel. (201) 818-1010
Telex 220883 TAUR
Fax (201) 818-0086
E-mail: clinicalcardiology@fams.org
Internet: http://www.clinical-cardiology.org/

To implement a change of address, please remove the mailing label affixed to your copy and send it together with your new address to Clinical Cardiology, Box 832, Mahwah, NJ 07430-0832.

The journal is not responsible for replacing missing issues unless the CIrculation Department is notified of nonreceipt within 3 months of issue date for domestic addresses and 6 months for foreign addresses.

Clinical Cardiology™

Supplement V

The INternational VErapamil SR/trandolapril STudy (INVEST) – The First Randomized Clinical Trial Evaluating Aggressive Blood Pressure Management (JNC VI) in Patients with CAD

Carl J. Pepine, M.D., MACC, FESC
Guest Editor

Proceedings from an international symposium held in Istanbul, Turkey on May 12, 2001 among investigators of the INternational VErapamil SR/trandolapril STudy (INVEST). This publication is supported by an unrestricted educational grant from Abbott Laboratories, on behalf of the study sponsors Knoll AG, and the University of Florida.

EDITORIAL BOARD

Clinical Cardiology™

A Journal for Advances in Cardiovascular Disease

Contents • Vol. 24, No. 11, November 2001 (Supplement V)

Clin. Cardiol. Vol. 24 (Suppl. V), A6 (2001)

Introduction: The European INVESTigators Meeting

CARL J. PEPINE, M.D., MACC, FESC

Division of Cardiovascular Medicine, University of Florida, College of Medicine, Gainesville, Florida, USA

Coronary artery disease (CAD) and hypertension are related vascular diseases that often coexist. Approximately one fourth of hypertensive patients have previously established CAD,[1] and depending on the definitions used, more than 50% of patients with CAD have undesirable blood pressures.[2, 3] While antihypertensive agents such as diuretics and beta blockers have been successful at lowering morbidity and mortality rates associated with elevated blood pressure, the reduction in adverse outcomes has been less than anticipated. This finding has led to the suggestion that these agents may adversely impact other cardiovascular risk factors, such as glucose metabolism and lipid profile.[4] Because the prognosis of individuals with hypertension is highly dependent on the presence or absence of CAD, certain antihypertensive agents may not be appropriate for patients with established CAD. Lack of outcome data from randomized controlled trials has lead to questions regarding which antihypertensive agents are optimal for patients with CAD.

Clinical management guidelines of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) recognized the importance of an integrated approach to management of patients with hypertension and CAD.[5] In JNC VI, treatment strategies and blood pressure goals were based on the patient's CAD risk profile and set new target blood pressure goals for those with certain risk factor conditions, such as diabetes.

The INternational VErapamil SR/trandolapril STudy (INVEST) is the first large randomized clinical trial to use the JNC VI guidelines for treatment of hypertension and CAD.[6] This ongoing, prospective, randomized, controlled trial will compare the risk of adverse outcomes, including death, nonfatal myocardial infarction (MI), or nonfatal stroke, in hypertensive patients with established CAD treated with either a calcium antagonist-based strategy or a noncalcium antagonist-based strategy. Patient enrollment for INVEST is 22,599, and, as such, it is one of the largest clinical trials in the world. Thus far, preliminary data suggest that a majority of diabetics and nondiabetics achieved a systolic blood pressure < 140 mmHg. Patients are currently in the follow-up phase.

In addition, INVEST is the first large, randomized clinical trial to be managed entirely over the Internet. In this trial, monitors, sponsors, and investigators have access to certain data in real time, 24 hours a day. The use of special Internet-based technology developed at the University of Florida for this trial has simplified the process of patient enrollment, study drug prescribing, data management, and investigator training, while minimizing errors and reducing costs and time. INVEST will have a substantial impact on clinical trial conduct as a model for future "paperless" trials.

On May 12, 2001, study investigators met in Istanbul, Turkey, to discuss the status of this trial and to review other topics important for its successful conclusion. This supplement contains the insights INVEST's leading researchers presented at that symposium.

Address for reprints:

Carl J. Pepine, M.D.
University of Florida Department of Medicine
Division of Cardiovascular Medicine
P.O. Box 10027
Gainesville, FL 32610, USA

References

1. Sytkowski PA, D'Agostino RB, Belanger AJ, Kannel WB: Secular trends in long-term sustained hypertension, long-term treatment, and cardiovascular mortality. The Framingham Heart Study 1950 to 1990. *Circulation* 1996;93:697–703
2. EUROASPIRE: A European Society of Cardiology survey of secondary prevention of coronary heart disease: Principal results. EUROASPIRE Study Group: European Action on Secondary Prevention through Intervention to Reduce Events. *Eur Heart J* 1997; 18:1569–1582
3. Pepine CJ: Systemic hypertension and coronary artery disease. *Am J Cardiol* 1998;82:21H–24H
4. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL: Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med* 2000;342:905–912
5. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997;157:2413–2446
6. Pepine CJ, Handberg-Thurmond E, Marks RG, Conlon M, Cooper-DeHoff R, Volkers P, Zellig P: Rationale and design of the International Verapamil SR/Trandolapril Study (INVEST): An Internet-based randomized trial in coronary artery disease patients with hypertension. *J Am Coll Cardiol* 1998;32:1228–1237

Clin. Cardiol. Vol. 24 (Suppl. V), V-1–V-5 (2001)

The Vascular Biology of Hypertension and Atherosclerosis and Intervention with Calcium Antagonists and Angiotensin-Converting Enzyme Inhibitors

CARL J. PEPINE, M.D., MACC, FESC, AND EILEEN M. HANDBERG, PH.D.

Division of Cardiovascular Medicine, University of Florida, College of Medicine, Gainesville, Florida, USA

Summary: Recent advances in the understanding of vascular disease genesis suggest that atherosclerosis and hypertension, primary targets of therapy in the INternational VErapamil SR/trandolapril STudy (INVEST), are closely related. A unified model for the development of cardiovascular disease (CVD) is emerging from recent advances related to atherosclerosis and hypertension. The process of vascular disease appears to begin early in life, when signs of endothelial dysfunction first appear. A primary cause of CVD progression is increased oxidative stress in the endothelium caused by multiple risk factor conditions, including heredity, dyslipidemia, smoking, diabetes, and elevated systolic blood pressure (SBP >110 mmHg). The renin-angiotensin and kallikrein-kinin systems are important regulators of blood pressure and atherosclerosis. In the renin-angiotensin system, angiotensin-converting enzyme (ACE) mediates generation of angiotensin II (ang II) at local vascular sites and in the plasma and also degrades bradykinin. Information derived from INVEST will help to identify treatment strategies, such as those containing a calcium antagonist and an ACE inhibitor, that are targeted directly at the vascular disorder responsible for hypertension and atherosclerosis.

Introduction

Recent advances related to the genesis of vascular disease suggest that atherosclerosis and hypertension, primary targets of therapy in the INternational VErapamil SR/trandolapril STudy (INVEST), are closely related. These disorders share similar risk factor conditions and appear to modify vascular function and structure correspondingly. Based on these findings, a unified model for the development of cardiovascular disease (CVD) is emerging. This article will summarize the vascular biology of atherosclerosis and hypertension in the context of a unified model for CVD that is useful for the clinician. In addition, this paper will discuss therapeutic intervention with calcium antagonists and angiotensin-converting enzyme (ACE) inhibitors, focusing on the influence of intervention on vascular function and structure. Some major advances in the area of CVD will be included.

Address for reprints:

Carl J. Pepine, M.D.
Division of Cardiovascular Medicine
University of Florida
P.O. Box 10027
Gainesville, FL 32610, USA

Unifying Model for Cardiovascular Disease

During the development and progression of CVD, a number of risk factor conditions involved with both atherosclerosis and hypertension interact to increase oxidative stress in the vascular wall. These conditions include heredity, dyslipidemia, smoking, diabetes, and elevated systolic blood pressure (SBP ≥110 mmHg) (Fig. 1). The principal site of this increased oxidative stress appears to be the endothelium, the site of nitric oxide (NO) inactivation. In healthy individuals, reactive oxygen species (ROS) and their derivatives are produced and detoxified by antioxidant mechanisms. In the endothelium and other vascular cells, sources of ROS include the xanthine oxidase system, the NADH/NADPH oxidase system, and the endothelial NO synthase (eNOS) system.[1] As oxidative stress increases, CVD develops because the endogenous antioxidant defense systems are overloaded. Emerging evidence suggests that stem cells derived from bone marrow, early precursors of mononuclear cells, may be programmed to interact with ROS within the disordered endothelium. This process may result in sustained functional alterations.

The principal functional alteration is a decrease in bioavailable NO within the arterial wall, principally at the level of the endothelium. When this decrease in bioavailable NO becomes critical, normal endothelial function is altered and endothelial dysfunction results. These functional alterations may include abnormal vascular smooth muscle tone (reduced relaxation and/or increased constriction), vascular smooth muscle growth, abnormalities in blood coagulation (increased activation of platelets and coagulation), and fibrinolysis (reduced release of t-PA and uPA), as well as enhanced inflammation. These

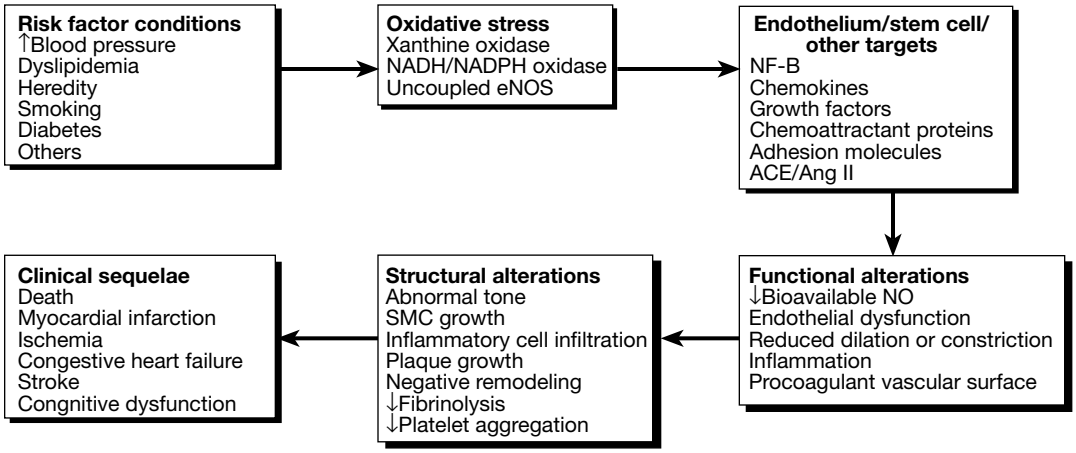

FIG. 1 The progression of cardiovascular disease. ACE = angiotensin converting enzyme, Ang II = angiotensin II, eNOS = endothelial nitric oxide synthase, SMC = smooth muscle cell, NF-B = nuclear factor Kappa B.

functional alterations lead to structural changes in the vessel (e.g., smooth muscle hypertrophy, adverse remodeling, plaque rupture, thrombus formation, and occlusion). In some cases, these functional alterations may result in clinical sequelae, such as death, myocardial infarction, stroke, ischemia, or congestive heart failure.

Renin-Angiotensin and Kallikrein-Kinin Systems

The renin-angiotensin and kallikrein-kinin systems are important regulators of blood pressure and atherosclerosis. Figure 2 shows these systems in detail. Angiotensinogen is abundant in many tissues and the circulating blood. Renin causes angiotensinogen to convert into angiotensin I (ang I) in plasma and tissue. Angiotensin-converting enzyme mediates the generation of angiotensin II (ang II) from angiotensinogen. Ang II can interact with a number of cloned AT receptors. If ang II interacts with the ang I receptor, as stated previously, vasoconstriction results. Other adverse cellular reactions include production of endothelin and superoxide, retention of sodium and water, and cell proliferation.

An angiotensin metabolite, angiotensin-(1-7), has recently been shown to exist in concentrations that are roughly equiva-

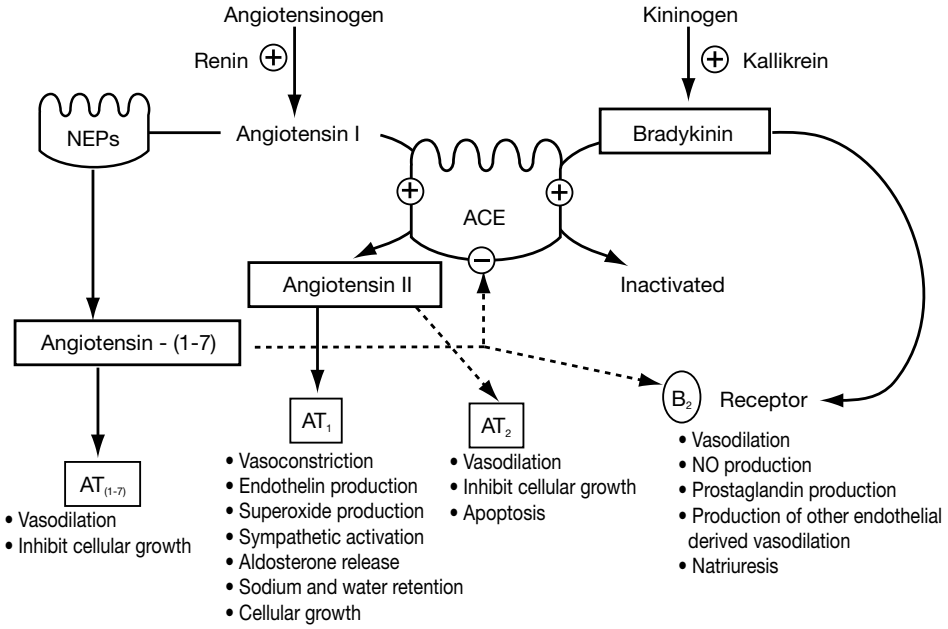

FIG. 2 The renin-angiotensin and kallikrein-kinin systems. ACE = angiotensin converting enzyme, AT_1 = angiotensin II type 1, AT(1-7) = angiotensin 1-7, AT_2 = angiotensin II type 2, NEPs = neutral endopeptidase inhibitors, NO = nitric oxide.

lent to ang II in the plasma and in tissue.[2] The antihypertensive effects of angiotensin-(1-7) suggest that it may counter regulate ang II.[3] The interaction of angiotensin-(1-7) with its receptor site results in vasodilation and growth inhibition.

Considerable evidence suggests that ACE has a greater affinity for bradykinin than for ang I.[4,5] Bradykinin interacts with its beta 2 receptor at the endothelial cell level to cause intense vasodilation and to inhibit cell proliferation. Increasing evidence suggests that bradykinin peptides that are not under the influence of ACE are available to act at the bradykinin I receptor. Therefore, these peptides also cause vasodilation and inhibit cell proliferation. Increasingly, evidence suggests that the angiotensin-renin and kallikrein-kinin systems have crucial roles in the vascular regulation of atherosclerosis and hypertension.

Angiotensin II affects blood vessel tone principally by increasing the concentration of calcium ions available for vascular smooth muscle contraction, resulting in vasoconstriction, and possibly hypertension. It also stimulates cell growth and proliferation by increasing the expression of oncogenes, which increase the number of growth factors. Angiotensin II also promotes oxidation in macrophages and endothelial cells and increases vascular permeability. Each of these reactions has a deleterious effect on blood vessels.

Local Biosynthesis of Angiotensin II

The biosynthesis of ang II from ang I occurs at local vascular sites, tissues, and in the plasma. The microcirculation present in the wall of larger blood vessels and the infiltration of mononuclear cells in the form of macrophages result in the concentration of ang II in vascular sites. Dzau recently hypothesized that ang II provides a positive feedback mechanism to allow these processes to self-perpetuate.[6] For example, increased tissue ang II results in more oxidative stress. Promotion of cytokines, adhesion molecules, smooth muscle tone, growth factors, and vascular inflammation results, causing an infiltration of granulocytes, cathepsin G, mast cells, and monocytes. Ultimately, one result is the increased tissue expression of ang II through upregulation of ACE. This mechanism may account for the perpetuation of vascular disease.

Recent data from a rat model have suggested that many, if not all, components of the renin-angiotensin system (e.g., ACE, angiotensin type 1 and type 2 [AT_1 and AT_2] receptors, and angiotensinogen) appear to be contained in the mononuclear cells and megakaryocytes of bone marrow. Renin, too, has been identified in these megakaryocytes. In addition, megakaryocytes in bone marrow stain richly for angiotensin type I receptors. These receptors activate the expression of adhesion molecules, and therefore the precursors of circulating macrophages, as well as endothelial progenitor cells, are programmed to bind with certain sites in the blood vessel wall. Several experiments suggest that such mononuclear cells in the bone marrow are programmed relative to the upregulation of ACE in the same way that endothelial cells are programmed.

This suggests that abnormal precursor cells may be present in the bone marrow compartment. These precursor cells are programmed very early in life and activated to bind with selected sites of the blood vessel wall. This mechanism, along with other mechanisms previously described, may be responsible for the promotion of vascular disease early in life.

When Does Vascular Disease Begin?

It is now clear that endothelial dysfunction is present early in life. It has been identified in children of patients who have hypertension and in children of households where there is active smoking. Traditional thinking is that foam cells and fatty streaks develop in childhood and result in intermediate type lesions. These lesions then increase in volume with the uptake of oxidized low-density lipoprotein (LDL) in the first three to four decades of a person's life. If large enough to disrupt organ blood flow, these atheroma then have the potential to rupture and produce plaque-related coronary events or cerebrovascular events; if not, they heal and become incorporated into the vessel wall as fibrous plaque.

The question regarding when this process develops recently received considerable attention based upon examination of aortae from aborted fetuses.[7] These aortae reveal considerable macrophage infiltration in the intima—early structural evidence of atherosclerosis. Special histochemistry has also shown oxidation products, revealing that these macrophages are in the earliest stages of atherosclerosis development. Evidence to date suggests that while fetal programming occurs relative to early atherosclerosis, there may also be some early regression in some sites once the child is born. The atherosclerosis process, however, redevelops at sites that may be programmed in utero. Therefore, between the ages of 3 and 10 years, atherosclerosis may be fully developed, with complicated plaque resulting between the ages of 10 and 30 years. Based upon these observations, intervention should occur during early life.

Development of Hypertension

In hypertension, current evidence suggests that endothelial dysfunction is present in early childhood. Panza *et al.* (Fig. 3A) showed that hypertensive adults had reduced blood flow augmentation in response to ascending doses of acetylcholine when compared with normotensive adults, providing evidence of endothelial dysfunction.[8] Children exhibited the same pattern in a study by Taddei *et al.* (Fig. 3B).[9] Children who did not have elevated blood pressure but had a family history of hypertension had a disordered response to acetylcholine early in life when compared with children who had no family history of hypertension. This evidence suggests that blood vessels of genetically susceptible patients may be programmed early in life to develop hypertension.

In addition, Nickenig *et al.* demonstrated the interaction within blood vessels between oxidized lipid (principally oxi-

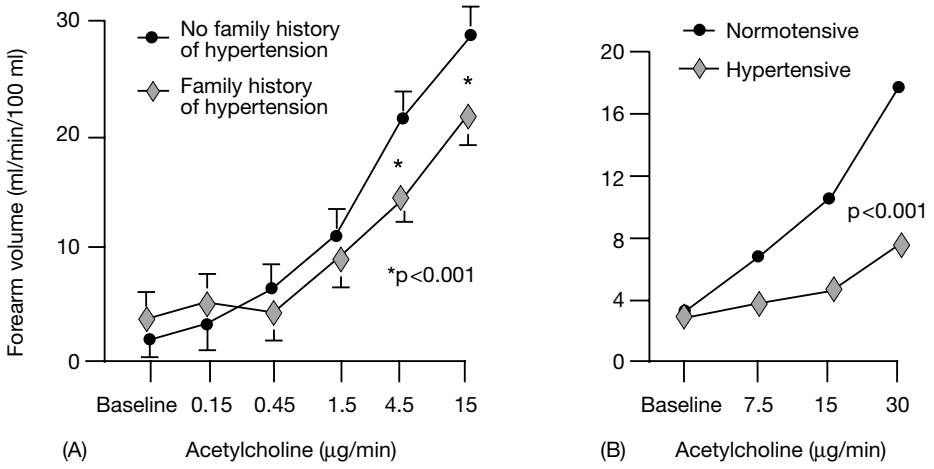

FIG. 3 The blood flow augmentation response of children with a family history of hypertension to elevated levels of acetylcholine (A) appears to mimic the response of adults with established hypertension (B). This suggests that the development of hypertension may begin at an early age. Figures reprinted from Refs. No. 8 and 9 with permission.

dized LDL) and angiotensin.[10] Patients with normal levels of cholesterol (181 ± 11 mg/dl) and patients with hypercholesterolemia (294 ± 10 mg/dl) received increasing doses of ang II, infused intravenously. Hypercholesterolemic patients had a significant increase in SBP when compared with patients with normal levels of cholesterol. When patients with hypercholesterolemia were treated with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) to reduce their cholesterol levels to normal levels and tested again, SBP responses to the same doses of ang II were normalized. The concentrations of ang II used in these studies were physiologic.

In addition, Nickenig *et al.* showed that platelet expression of the ang II type 1 (AT_1) receptor was upregulated and directly correlated to the plasma level of oxidized LDL.[10] Several studies have shown that platelet expression of the AT_1 and AT_2 receptor can be blocked with either ACE inhibitors, AT_1 receptor blockers, or statins.[11] In addition, studies have shown that platelet AT_1 receptor upregulation parallels vascular smooth muscle reactivity. Therefore, oxidized LDL appears to enhance the activity of ang II to increase blood pressure principally through enhanced vascular smooth muscle activation.

Therapeutic Strategies

The endothelium is shown in more detail in Figure 4 to show the role these processes play relative to therapeutic strategies. Regarding eNOS, multiple receptors on the surface of the endothelial cell may act to increase the availability of NO from the amino acid, L-arginine by upregulating eNOS. Nitric oxide is freely diffusible both to the abluminal surface and the luminal surface of the vessel wall. At the abluminal surface, it diffuses across the intimal space to the vascular smooth muscle cells and macrophages residing within the subintimal region. There NO interacts with G-proteins, resulting in relaxation of the vascular smooth muscle and inhibition of mononuclear cell processes.

Sufficient NO may be produced even in disease states, but it is not released in a bioactive form, largely because there is an increased generation of oxygen free radicals. This oxidative

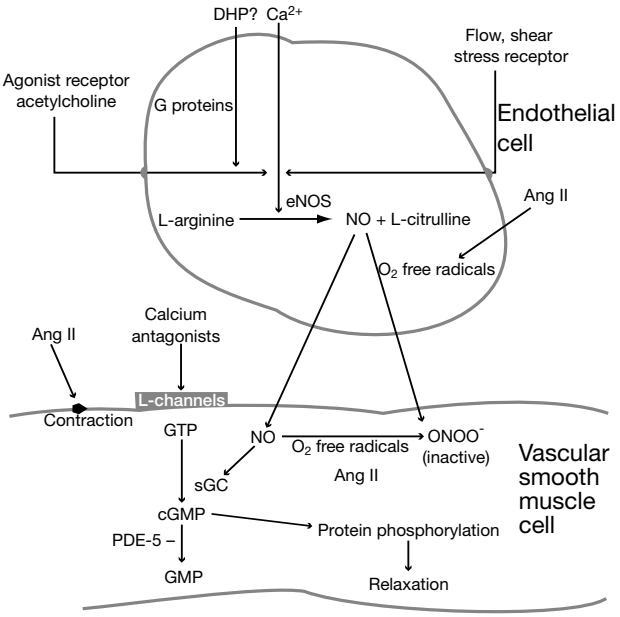

FIG. 4 Dihydropyridine induces vasorelaxation at the level of the endothelial cell via enhancement of endothelial nitric oxide release and at the level of vascular smooth muscle via inhibition of L-type calcium channels. Ang II = angiotensin II, cGMP = cyclic guanosine monophosphate, DHP = dihydropyridine, eNOS = endothelial nitric oxide synthase, GTP = guanosine triphosphate, ONOO- = peroxinitrate, PDE-5 = phosphodiesterase type 5, sGC = soluble guanylyl cyclase.

stress inactivates the NO, thus preventing it from participating in G-protein-coupled reactions. Treatment strategies that increase NO availability, either through production of more NO or reduction of ROS, are likely to have beneficial effects. One strategy is to provide more L-arginine to increase the activity of eNOS. Another is to use an antioxidant to reduce the amount of ROS. Phenolic compounds such as most calcium-channel antagonists (e.g., verapamil) are antioxidants.

Treatment strategies that influence vascular smooth muscle tone may also play a role. Calcium channels on the surface of vascular smooth muscle cells, including L-type, M-type, and others, facilitate calcium movement across the sarcolemma membrane and promote contraction. All of the calcium-channel antagonists block these calcium channels to different degrees. Verapamil, the agent studied in INVEST, has activity at both L channels and M channels. A proposed dihydropyridine calcium receptor at the endothelial cell surface may account for some of the differences reported in outcome studies using short-acting, rapid-release dihydropyridine calcium antagonists, compared with the longer-acting, slow-release, nondihydropyridine calcium antagonists, such as verapamil SR and diltiazem SR.

The angiotensin-renin system (ACE, ang II, and bradykinin) may promote both atherosclerosis and hypertension. Evidence derived from human carotid plaque and human coronary plaque removed during atherectomy has identified an abundance of ACE in plaque, particularly at the shoulders of plaque.[12] These sites may participate in plaque rupture. While ACE is present throughout the plaque and deep in the blood vessel wall, it is highly concentrated in these shoulder areas.

Immunohistochemistry has identified ACE within the macrophages of these plaques. Angiotensin-converting enzyme is responsible for the generation of ang II and the degradation of bradykinin locally. It is upregulated in atherosclerosis and hypertension. Abundant ang II is available locally at the vascular wall, while bradykinin, a potent generator of endothelial-derived vasodilators [NO, endothelium-derived hyperpolarizing factor (EDHF), and prostacyclin (PGI-2)], is reduced. Angiotensin II is believed to be responsible for increasing oxidative stress to inactivate NO. In addition, ang II interacts with the AT_1 receptor and facilitates movement of calcium ions through channels to enhance contraction and increase inflammation. Based upon recent investigations of the involvement of ang II in vascular disease, it would seem prudent to interrupt angiotensin activity and prevent bradykinin breakdown. Therefore, an ACE inhibitor (e.g., trandolapril) would seem prudent as a therapy for atherosclerosis and hypertension. INVEST is testing this hypothesis.

Conclusion

Atherosclerosis and hypertension are the primary targets of treatment in INVEST. Recent advances suggest that these conditions commence very early in human development. New understandings of when vascular disease begins and how it progresses will lead to improved therapeutic strategies.

References

1. Hua C, Harrison DG: Endothelial dysfunction and cardiovascular disease: The role of oxidant stress. *Circ Res* 2000;87:840–844
2. Ferrario CM, Martell N, Yunis C, Flack JM, Chappell MC, Brosnihan KB, Dean RH, Fernandez A, Novikov SV, Pinillas C, Luque M: Characterization of angiotensin-(1-7) in the urine of normal and essential hypertensive subjects. *Am J Hypertens* 1998;11:137–146
3. Iyer SN, Ferrario CM, Chappell MC: Angiotensin-(1-7) contributes to the antihypertensive effects of blockade of the renin-angiotensin system. *Hypertension* 1998;31:356–361
4. Krebs LT, Hanesworth JM, Sardinia MF, Speth RC, Wright JW, Harding JW: A novel angiotensin analog with subnanomolar affinity for angiotensin-converting enzyme. *J Pharmacol Exp Ther* 2000;293:260–267
5. Meng QC, Oparil S: Purification and assay methods for angiotensin-converting enzyme. J *Chromatogr A* 1996;743:105–122
6. Dzau VJ: Theodore Cooper Lecture: Tissue angiotensin and pathobiology of vascular disease: A unifying hypothesis. *Hypertension* 2001;37:1047–1052
7. Napoli C, D'Armiento FP, Mancini FP, Postiglione A, Witztum JL, Palumbo G, Palinski W: Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia. Intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atherosclerotic lesions. *J Clin Invest* 1997;100:2680–2690
8. Panza JA, Quyyumi AA, Callahan TS, Epstein SE: Effect of antihypertensive treatment on endothelium-dependent vascular relaxation in patients with essential hypertension. *J Am Coll Cardiol* 1993;21:1145–1151
9. Taddei S, Virdis A, Mattei P, Arzilli F, Salvetti A: Endothelium-dependent forearm vasodilation is reduced in normotensive subjects with familial history of hypertension. *J Cardiovasc Pharmacol* 1992;20:S193–S195
10. Nickenig G, Baumer AT, Temur Y, Kebben D, Jockenhovel F, Bohm M: Statin-sensitive dysregulated AT1 receptor function and density in hypercholesterolemic men. *Circulation* 1999;100: 2131–2134
11. Wassmann S, Laufs U, Baumer AT, Muller K, Ahlbory K, Linz W, Itter G, Rosen R, Bohm M, Nickenig G: HMG-CoA reductase inhibitors improve endothelial dysfunction in normocholesterolemic hypertension via reduced production of reactive oxygen species. *Hypertension* 2001;37:1450–1457
12. Fukuhara M, Geary RL, Diz DI, Gallagher PE, Wilson JA, Glazier SS, Dean RH, Ferrario CM: Angiotensin-converting enzyme expression in human carotid artery atherosclerosis. *Hypertension* 2000;35:353–359

Clin. Cardiol. Vol. 24 (Suppl. V), V-6–V-8 (2001)

Characteristics of Patients with Coronary Artery Disease and Hypertension: A Report from INVEST

SERAP ERDINE, M.D., EILEEN M. HANDBERG, PH.D.,* BOB KOLB, R.N.*

Istanbul University Cardiology Institute, Istanbul, Turkey; *University of Florida, Gainesville, Florida, USA

Summary: In all, 22,599 patients with coexisting hypertension and coronary artery disease (CAD) from around the world are enrolled in the INternational VErapamil SR/trandolapril STudy (INVEST). As a result, much will be learned regarding the use of treatment strategies using verapamil SR and atenolol with and without trandolapril and/or hydrochlorothiazide in patients with hypertension and CAD, all of whom are at high risk for adverse cardiovascular outcomes. This trial will provide meaningful data on optimal treatment strategies for hypertension, especially among patients who are elderly, have diabetes, have left ventricular hypertrophy, or who are dyslipidemic. This trial will be the first to use Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) guidelines as blood pressure goals to determine the relative benefits of a calcium antagonist versus a beta-blocker strategy in reducing morbidity and mortality. In addition, women and Hispanic patients participating in INVEST will provide the largest controlled experience in the management of hypertensive patients with CAD, facilitating the development of future guidelines.

Key words: antihypertensive agents, baseline characteristics, calcium-channel blockers, coronary artery disease, hypercholesterolemia, hypertension, INVEST, verapamil

Introduction

The INternational VErapamil SR/trandolapril STudy (INVEST) enrolled patients with coexisting hypertension and coronary artery disease (CAD) from around the world. Countries participating in INVEST include the United States, Mexico, Cuba, Guatemala, the Dominican Republic, El Salvador, Panama, Australia, New Zealand, Canada, France, Germany, Hungary, Italy, Spain, and Turkey (countries with patient enrollment are shown in Table I). In all, 862 practitioners in the ambulatory care setting are participating as INVEST site investigators. Patients are randomized to either a calcium antagonist, (verapamil SR)-based, or a beta blocker- (atenolol) based blood pressure control strategy, with or without the addition of trandolapril and/or hydrochlorothiazide, if needed, to meet Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) targets.[1] The primary goal of therapy is the reduction of blood pressure to < 140/90 mmHg, or to < 130/85 mmHg for diabetics and patients with renal disease, in accordance with the targets recommended by the JNC VI.[2] Patient recruitment began in September of 1997 with a pilot phase, and full scale recruitment began in January 1998. Final follow-up visits will take place in December of 2002. Utilizing a web-based system allowed for unlimited enrollment each day. At peak recruitment, 1,792 patients were randomized in 1 month, with a peak of 444 randomizations in 1 week. In all, 22,599 patients with hypertension and CAD were randomized.

Hypertension

Elevated blood pressure is an important risk factor for the occurrence of CAD as well as its adverse outcomes such as death and myocardial infarction (MI), and the risk of these outcomes increases with age in both men and women.[3] Several trials have shown that hypertension is especially problematic among patients > 70 years of age.[4,5] Staessen *et al.*,[5] in a comparison of clinical outcomes trials, suggested that intensive treatment of hypertension in elderly patients could reduce total mortality, cardiovascular mortality, all cardiovascular outcomes, fatal and nonfatal stroke, and fatal and nonfatal MI by 20 to 30%.[5]

Risk Factor Conditions and Hypertension

Of all patients with hypertension, about 40% are obese, 50% have hyperinsulinemia, 40% have cholesterol levels > 240 mg/dl, and 25% have high-density lipoprotein (HDL) levels of <40 mg/dl. Hypercholesterolemia is a strong risk factor for cardiovascular disease (CVD).[6,7] Several epidemiologic studies, such as the Tecumseh Community Health Study[8] and the Framingham Heart Study,[3] established a significant direct relationship between blood pressure levels and

Address for reprints:

Serap Erdine, M.D.
Istanbul University Cardiology Institute
Haseki, Istanbul
Turkey
E-mail: eserdine@superonline.com

TABLE I Patient enrollment by country in the INternational VErapamil SR/trandolapril STudy (INVEST)

Participating country	No. of patients enrolled
Mainland USA	17,154
Mexico	1,496
Cuba	1,872
Caribbean	98
Australia/New Zealand	36
Canada	452
Germany	183
Hungary	333
Italy	134
Turkey	841

serum lipid levels.[9] In INVEST, 100% of the patients have documented CAD, and 53% of the patients had a history of documented dyslipidemia.

Obesity is also an important cardiovascular risk factor.[10] More than three quarters (78%) of the patients enrolled in INVEST had a body mass index (BMI) of > 26, and more than one third (38%) of the patients had a BMI > 30 at entry. Other conditions frequently associated with hypertension and/or obesity include smoking and a sedentary lifestyle. In INVEST, about one half of the patients (46%) reported a history of smoking, and 12% had smoked within the previous 30 days.

Target Organ Damage

Target organ damage, such as left ventricular hypertrophy or renal dysfunction, is also an important determinant of adverse outcome among hypertensive patients. Koren *et al.* showed that left ventricular hypertrophy is an independent determinant of both mortality and other cardiovascular events.[11] Other clinical conditions, such as complications of atherosclerotic vascular disease (e.g., MI, prior revascularization, and congestive heart failure) and stroke are additional factors that predict adverse outcome. Alderman *et al.* reported that prior MI, stroke, and diabetes are primary determinants of future cardiovascular events.[12] All patients in INVEST have documented CAD, making this a high-risk cohort.

Diabetes is another very important coexisting condition that can result in macrovascular and/or microvascular disease. Manifestations of macrovascular disease associated with diabetes include CVD, cerebrovascular disease, peripheral vascular disease, and congestive heart failure. Manifestations of microvascular disease include nephropathy and retinopathy. Several trials have shown that, in diabetic patients, optimal blood pressure control results in decreased risk of all diabetes-related vascular outcomes.[13–15] The risk reduction was correlated with decreased levels of blood pressure, but not type of drug. However, these trials were not conducted using contemporary agents such as angiotensin-converting enzyme (ACE) inhibitors, statins, or JNC VI blood pressure targets. None used a fasting blood sugar >126 mg/dl as the definition of diabetes. At entry, 27% of patients in INVEST had diabetes defined by this newer definition. The subsequent development of diabetes during follow-up is also being captured, and will allow an evaluation of the impact of hypertension treatment on diabetes progression/development.

Recent guidelines, including those from the European Society of Cardiology,[16] the American College of Cardiology/American Heart Association (ACC/AHA),[17] the World Health Organization-International Society of Hypertension (WHO-ISH),[18] and JNC VI[2] emphasize patient assessment according to blood pressure levels and the presence of coexisting conditions. The WHO-ISH guidelines, for example, recommend stratification of patient risk according to blood pressure level and concomitant risk factor conditions, such as gender, total cholesterol, diabetes mellitus, and smoking.[18] INVEST was specifically designed to provide two different treatment strategies that would allow for intensive dose escalation of three study antihypertensive medications if needed. These dose escalations were based on JNC VI guidelines, as well as other literature, but the unique system permitted the physician to customize treatment according to protocol based on an individual patient's risk factors, tolerance of medications, response to therapy, and other factors. In addition, a fourth antihypertensive medication could be added at the investigator's discretion to achieve blood pressure control provided it was not a calcium antagonist if the patient was assigned to beta-blocker strategy, or a beta blocker if the patient was assigned to calcium-antagonist strategy. Unique to INVEST, recommended blood pressure targets are adjusted based on documented risk factors such as diabetes or renal disease. INVEST, using this methodology, will be the first randomized, controlled trial that will evaluate the implementation of JNC VI guidelines and their impact on occurrence of all-cause mortality, nonfatal MI, and nonfatal stroke.

INVEST Patient Characteristics at Entry

The patient characteristics are published in detail elsewhere for the final randomized population (Cooper-DeHoff, *et al.*, in press). Briefly, INVEST will reveal important information regarding treatment of elderly patients with CAD and with hypertension, because the majority are > 65 years of age and over one third of patients are > 70 years of age. Because of the large number of patients in the 50–99 year age range, INVEST will provide considerable data regarding blood pressure treatment strategies for older patients of all ages.

Because patients from many regions of the world are enrolled in INVEST, there is significant racial diversity. Of the patients enrolled, 51% are either black (14%) or Hispanic (37%). Important is the fact that women comprise more than half of the patients enrolled (52%). Women are underrepresented in most hypertensive trials, and randomized trial data on women with hypertension and CAD are even more limited. INVEST will establish whether differences in pharmacologic response to antihypertensive therapies exist between women

and men. In the majority of patients enrolled, cardiovascular comorbidities include prior MI, angina, diabetes, dyslipidemia, and/or smoking history, and a majority of the patients were taking antihypertensive therapy at the time of enrollment.

There has been some speculation regarding the association between dihydropyridine calcium antagonists and the risk of cancer.[19,20] Of the patients enrolled in INVEST, 7% had a medical history that included cancer that was not expected to impair their ability to comply with follow-up. By the end of the trial, there may be sufficient data to clarify whether there is an association between treatment strategy and new cancer development.

Medications

At the time of enrollment, a majority of the INVEST patients were being treated with antihypertensive therapy from a variety of pharmacologic classes, including ACE inhibitors, calcium antagonists, diuretics, alpha blockers, and centrally acting antihypertensives. Only 19% of patients, however, achieved blood pressure control at baseline according to JNC VI guidelines for the total population. Beta-blocker use at the time of enrollment was an exclusion criterion. In addition to treatment for elevated blood pressure, patients were also treated with many other medications for coexisting conditions, including aspirin or other antiplatelet medications, lipid-lowering drugs, oral hypoglycemic agents, insulin, and hormone replacement therapy. Therefore, the INVEST population is very representative of contemporary ambulatory patients with hypertension and CAD. At randomization, 62% of patients were prescribed one study medication, 28% received two, and 10% received three. Preliminary data indicate that larger numbers of patients are prescribed two or three study medications over time. Currently, approximately 70% of patients treated for 1 year receive two or three study medications, indicating that investigators are following the protocol recommendations. Follow-up for the trial will end in December 2002, and results are anticipated in early 2003.

Conclusion

It is clear that certain conditions have an important influence on the adverse outcomes of patients with CAD and established hypertension. While there is general agreement that the treatment of elevated blood pressure is important in the prevention of cardiovascular events, very little evidenced-based medical data exist regarding optimal treatment of blood pressure in terms of reducing adverse outcomes in such patients. INVEST provides global representation of contemporary CAD patients with established hypertension and a plethora of associated risk factor conditions. This trial will provide meaningful data for many subgroups, especially patients who are women, elderly, Hispanic, diabetic, obese, dyslipidemic, or who have left ventricular hypertrophy, prior MI, or have undergone revascularization.

References

1. Pepine CJ, Handberg-Thurmond E, Marks RG, Conlon M, Cooper-DeHoff R, Volkers P, Zellig P: Rationale and design of the International Verapamil SR/Trandolapril Study (INVEST): An Internet-based randomized trial in coronary artery disease patients with hypertension. *J Am Coll Cardiol* 1998;32:1228–1237
2. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997;157:2413–2446
3. Kannel WB, Wilson PW, Zhang TJ: The epidemiology of impaired glucose tolerance and hypertension. *Am Heart J* 1991;121:1268–1273
4. Psaty BM, Furberg CD, Kuller LH, Cushman M, Savage PJ, Levine D, O'Leary DH, Bryan RN, Anderson M, Lumley T: Association between blood pressure level and the risk of myocardial infarction, stroke, and total mortality: The cardiovascular health study. *Arch Intern Med* 2001;161:1183–1192
5. Staessen JA, Wang JG, Thijs L, Fagard R: Overview of the outcome trials in older patients with isolated systolic hypertension. *J Hum Hypertens* 1999;13:859–863
6. Dzau V, Braunwald E: Resolved and unresolved issues in the prevention and treatment of coronary artery disease: A workshop consensus statement. *Am Heart J* 1991;121:1244–1263
7. Law MR, Wald NJ, Thompson SG: By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *Br Med J* 1994;308:367–372
8. Butler WJ, Ostrander LD Jr, Carman WJ, Lamphiear DE: Mortality from coronary heart disease in the Tecumseh study. Long-term effect of diabetes mellitus, glucose tolerance and other risk factors. *Am J Epidemiol* 1985;121:541–547
9. Goode GK, Miller JP, Heagerty AM: Hyperlipidaemia, hypertension, and coronary heart disease. *Lancet* 1995;345:362–364
10. Hulley S, Ashman P, Kuller L, Lasser N, Sherwin R: HDL-cholesterol levels in the Multiple Risk Factor Intervention Trial (MRFIT) by the MRFIT Research Group 1, 2. *Lipids* 1979;14:119–123
11. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH: Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991;114:345–352
12. Alderman MH, Cohen H, Madhavan S: Distribution and determinants of cardiovascular events during 20 years of successful antihypertensive treatment. *J Hypertens* 1998;16:761–769
13. UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J* 1998;317:703–713
14. Tuomilehto J, Rastenyte D, Birkenhager WH, Thijs L, Antikainen R, Bulpitt CJ, Fletcher AE, Forette F, Goldhaber A, Palatini P, Sarti C, Fagard R: Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med* 1999;340:677–684
15. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145–153
16. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention. *Eur Heart J* 1998;19:1434–1503
17. Ryan TJ, Anderson JL, Antman EM, Braniff BA, Brooks NH, Califf RM, Hillis LD, Hiratzka LF, Rapaport E, Riegel BJ, Russell RO, Smith EE Jr, Weaver WD: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol* 1996;28:1328–1428
18. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. *J Hypertens* 1999;17:151–183
19. Pahor M, Furberg CD: Calcium antagonists and cancer: Causation or association? *Cardiovasc Drugs Ther* 1998;12:511–513
20. Grossman E, Messerli FH: Calcium antagonists, ACE inhibitors, and the risk of cancer in hypertensive patients. *J Hum Hypertens* 2000;14:285–286

Clin. Cardiol. Vol. 24 (Suppl. V), V-9–V-11 (2001)

INVEST Substudies: Design and Patient Characteristics

MÁTYÁS KELTAI, M.D., PH.D., JULIE A. JOHNSON, PHARM.D.,* PETER R. KOWEY, M.D.,† L. DOUGLAS RIED, PH.D.,* MICHAEL TUETH, M.D.‡

Hungarian Institute of Cardiology, Budapest, Hungary; *University of Florida College of Pharmacy, Gainesville, Florida; †The Lankenau Hospital and Medical Research Center, Wynnewood, Pennsylvania; ‡University of Florida College of Medicine, Gainesville, Florida, USA

Summary: The INternational VErapamil SR/trandolapril STudy (INVEST) will provide a large database of information. Proposed substudies for analysis include ambulatory blood pressure monitoring (ABPM), depression, genotyping, atrial fibrillation, electrocardiogram (ECG), echocardiography, renal dysfunction, diabetes, and cardiac care cost estimate. This paper reviews the design and status of several of the INVEST substudies. The ABPM substudy will obtain objective blood pressure recordings during daily life masked to both the patient and the investigator. Ambulatory blood pressure monitoring is an especially useful technology because of the role of nocturnal hypertension and circadian blood pressure irregularities in the development of hypertensive disease. The depression substudy, which enrolled 2,393 patients in the United States, will report quality-of-life (QOL) data, including information regarding energy and fatigue. The genotyping substudy will provide genomic DNA samples from approximately 15,000 patients in the United States, including Puerto Rico. Many candidate genes will be examined for polymorphisms that may predict outcomes and/or responses to various treatments.

Key words: ambulatory blood pressure monitoring, atrial fibrillation, depression, INVEST substudies, polymorphisms

Introduction

A considerable amount of new data will be derived from the large INternational VErapamil SR/trandolapril STudy (INVEST) database. This is an important trial and the only one among the antihypertensive treatment trials that has set a blood pressure goal of < 140/90 mmHg or < 130/85 mmHg for special populations, as recommended by the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI).[1] Also, INVEST is the only randomized clinical trial focusing on hypertension treatment in patients with documented coronary artery disease (CAD). In addition to the results of the main study related to optimal treatment strategy (with regard to adverse cardiovascular outcomes), several scientifically important substudies were proposed to the INVEST Steering Committee. Future analyses may include ambulatory blood pressure monitoring (ABPM), patient self report of depressive symptoms, genotype studies, diabetes studies, renal failure studies, cognitive dysfunction studies, and electrocardiogram (ECG) studies. This paper reviews the design of the ongoing ABPM, depression, and genotype substudies.

Address for reprints:

Mátyás Keltai, M.D.
Hungarian Institute of Cardiology
1450 Budapest
P.O. Box 88
Budapest, Hungary

Ambulatory Blood Pressure Monitoring Substudy

Nocturnal hypertension and the absence of circadian blood pressure changes are independent risk factors for adverse outcomes related to cardiovascular disease. Hypertension can be accurately monitored throughout ordinary daily activities using ABPM, an inexpensive and easy-to-use technology that has been available to clinicians for more than 10 years.[2–6] Using this method in a subset of its patients, INVEST will collect data regarding daily control of hypertension that is masked to both the patient and the investigator.

Ambulatory blood pressure monitoring provides the technology for computer-based statistical analysis of blood pressure data. Using this technology, researchers can adjust the time intervals between measurements, and ambulatory blood pressure curves are obtained for individual patients by plotting recorded blood pressure values over time on a graph. This allows changes in blood pressure to be calculated and evaluated for physiologic circadian variation. Long-acting medical regimens are expected to minimize circadian variation, and ABPM provides evidence for the decrease in circadian variation. Also, ABPM compensates for the inflexibility of clinical measurements. While blood pressure measurements recorded in a physician's office are subject to disturbances related to the previous mental and physical activity of the patient, the emo-

tional state of the patient, time of day, and stress related to the visit itself, ABPM does not have these limitations.[5,6]

In a recently published study detailing the use of ABPM, an evaluation of the changes in circadian blood pressure parameters are reported when patients forget to take prescribed daily antihypertensive medication. The authors compared drug regimens containing amlodipine and felodipine, both of which are long-acting medications. Ambulatory blood pressure curves were created and compared between patients taking amlopidine or felodipine who had a 1-day drug holiday. By comparing ambulatory blood pressure curves, differences between two drug regimens might be elucidated. In this report, there was no difference in ambulatory blood pressure curves between patients who regularly took amlodipine and those who took a 1-day holiday. However, in those patients taking felodipine, there were significant differences between patients who regularly took felodipine, and those who took a 1-day holiday. Differences such as these could not be observed without the use of ABPM technology.[7]

Therefore, a study of the changes in circadian blood pressure parameters was proposed to the INVEST Steering Committee by Dr. Csaba Farsang, President of the Hungarian Society of Hypertension. Patients from selected centers in Hungary and the United States have been dually enrolled in INVEST and the ABPM substudy. The ABPM substudy will use Meditech® (Div. Boston Scientific, Maple Grove, Minn., USA) equipment. The Meditech® devices have all been validated according to the standards of the British Hypertension Society. The ABPM evaluation will occur twice—once over a 24-h period at the time of enrollment in INVEST, and again over a 24-h period during the 52nd week of participation in INVEST. This will allow for comparisons of BP assessments both in the physician's office and in the ambulatory setting, and at baseline and after 1 year of antihypertensive therapy according to the randomized strategy from INVEST. Results of the ABPM substudy are expected in 2003.

Depression Substudy (SADD-Sx)

In all, 2,393 INVEST patients in the United States have been enrolled in the Substudy of Antihypertensive Drugs and Depressive Symptoms (SADD-Sx). A relationship between blood pressure levels and depressive symptoms has been established, and the use of beta blockers to treat elevated blood pressure may provoke depression and even suicide.[8–10] Therefore, there may be a difference in depressive symptoms, fatigue, and even the rate of suicide in patients treated with an antihypertensive strategy containing a beta blocker when compared with a strategy containing a calcium antagonist. This substudy uses structured questionnaires to allow patients to self report depressive symptoms. A total of 4 questionnaires was employed: (1) Center for Epidemeologic Studies – The Depression Scale (CESD), (2) Medical Outcomes Study – Short Form 36 (SF36), (3) Instrumental Activities of Daily Living (IADL), and (4) Activities of Daily Living (ADL). Patients who return the survey provide quality-of-life (QOL) data, including information regarding energy and fatigue. Four surveys were mailed to patients over the first year of enrollment. Dr. L. Douglas Ried is the principal investigator of SADD-Sx, and Dr. Michael Tueth is the co-investigator. They provided some preliminary information about the study after the enrollment of 2,393 patients. The investigators recruited a large number of patients in a very short period of time. Of the patients who were sent surveys, 71.5% returned the surveys at baseline, and 61.7% returned them at the 6-week follow-up. It is interesting that 10% more men than women returned the survey. The first survey indicated that 36.9% of the sample returning surveys had high-risk depressive symptoms. At the 6-week follow-up, 36.4% reported high-risk depressive symptoms.

The final results of the SADD-Sx trial are not available, but some baseline information has already been gathered. Characteristics of the patients in SADDS-Sx at baseline were very similar to those of the main trial patients.

Genotyping Substudy

It is well known that there are differences between Blacks and Caucasians in the antihypertensive response to beta blockers.[11,12] The largest studies on this topic suggest that about 40% of Blacks and 60% of Caucasians have a good antihypertensive response to beta blockers. Little is know about how response of Hispanics to beta blockers compares with that of other ethnic populations. Because INVEST is rich with ethnic diversity (37% Hispanic, 14% Black), a substudy to characterize the genetic polymorphisms of a subset of the INVEST population was proposed. Genetic samples from large numbers of Caucasians, Hispanics, and Blacks are being collected. Genetic samples are obtained from buccal mucosal cells obtained after INVEST patients have swished 10 ml of mouthwash up to three times. From these buccal cells, genomic DNA is extracted and stored. Initially, variations in genes encoding the beta receptor will be characterized from the isolated DNA to assess the importance or various polymorphisms in determining antihypertensive effects of beta blockers. In addition, ethnic differences in beta-receptor allele frequency will be assessed and associated to beta-blocker response. Decisions regarding additional candidate genes to evaluate will be determined by the substudy principal investigator, Dr. Julie Johnson, and the INVEST Steering Committee.

Other Substudies

Because of the large number of patients enrolled in INVEST, additional substudy analyses were proposed but are not currently underway. These additional substudies included an economic study, a renal dysfunction substudy, a diabetic substudy, an atrial fibrillation substudy, and an echocardiography substudy. The proposed economic study was designed to evaluate the cost of cardiac care among the enrolled population. Substudies involving renal dysfunction and diabetes were proposed to the INVEST Steering Committee because both

conditions were sufficiently represented in the treatment arms of the main trial to produce scientifically relevant results.

The electrical instability in hypertensive heart disease is a multifactorial phenomenon. Left ventricular hypertrophy (LVH), the vascular and cardiac tissue alteration due to the disease, may evoke arrythmias, and atrial fibrillation is among the most frequent. Conversely, the most frequent cause of atrial fibrillation is hypertension. The treatment strategy may influence the propensity for arrythmias. Experimental evidence suggests that trandolapril (Mavik®) (Abbott Laboratories, Abbott Park, Ill.) or verapamil, or the combination of trandolapril and verapamil (Tarka®) (Abbott Laboratories, Abbott Park, Ill.) may improve the structure of the atria, consequently preventing tachyarrhythmias in the clinical setting of acute ischemia.[13–15]

The purpose of an echocardiography substudy would be to determine whether a strategy using calcium-antagonist treatment could better prevent LVH than the beta-blocker strategy. The effect of angiotensin-converting enzyme (ACE) inhibitors on LVH is established. There is some evidence that use of calcium antagonists (especially verapamil) may prevent LVH more effectively than beta-blocker therapy. Combination therapies (verapamil or a beta blocker combined with an ACE inhibitor), however, probably do not produce large differences in the different arms of the trial.

Conclusions

Several INVEST substudies are underway or proposed. The ABPM trial will provide important information regarding the comparison of blood pressure measurements in the ambulatory setting and the physician's office, and will also provide additional insight into the effects of available medications on the treatment of hypertension. The SADD-Sx trial will provide beneficial information associating the development of depressive symptoms in patients receiving antihypertensive medication regimens that may or may not contain a beta blocker. The genotyping substudy will provide information not yet available, associating response to antihypertensive therapy, ethnic background, and variations in allele frequencies of polymorphisms that are critical to antihypertensive medication response.

References

1. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997;157:2413–2446
2. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guerrieri M, Gatteschi C, Zampi I, Santucci A: Ambulatory blood pressure: An independent predictor of prognosis in essential hypertension. *Hypertension* 1994;24:793–801
3. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J: Predicting cardiovascular risk using conventional vs. ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *J Am Med Assoc* 1999;282:539–546
4. Mancia G, Zanchetti A, Agabiti-Rosei E, Benemio G, De Cesaris R, Fogari R, Pessina A, Porcellati C, Rappelli A, Salvetti A, Trimarco B, Agebiti-Rosei E, Pessino A: Ambulatory blood pressure is superior to clinic blood pressure in predicting treatment-induced regression of left ventricular hypertrophy. SAMPLE Study Group. Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation. *Circulation* 1997;95:1464–1470
5. White WB: Analysis of ambulatory blood pressure data in antihypertensive drug trials. *J Hypertens* 1991;9(suppl):S27-32
6. Barna I, Keszei A, Dunai A: Evaluation of Meditech ABPM-04 ambulatory blood pressure measuring device according to the British Hypertension Society protocol. *Blood Press Monit* 1998;3: 363–368
7. Hu Z: Comparison of the antihypertensive effect and safety of amlodipine and felodipine. *Heart Drug* 2001;1:77–82
8. Ried LD, McFarland BH, Johnson RE, Brody KK: Beta-blockers and depression: The more the murkier? *Ann Pharmacother* 1998; 32:699–708
9. Lindberg G, Bingefors K, Ranstam J, Rastam L, Melander A: Use of calcium channel blockers and risk of suicide: Ecological findings confirmed in population based cohort study. *Br Med J* 1998;316: 741–745
10. Beevers DG: Beta-blockers for hypertension: Time to call a halt. *J Hum Hypertens* 1998;12:807–810
11. Comparison of propranolol and hydrochlorothiazide for the initial treatment of hypertension. II. Results of long-term therapy. Veterans Administration Cooperative Study Group on Antihypertensive Agents. *J Am Med Assoc* 1982; 248:2004–2011
12. Materson BJ, Reda DJ, Cushman WC, Massie BM, Freis ED, Kochar MS, Hamburger RJ, Fye C, Lakshman R, Gottdiener J: Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *N Engl J Med* 1993; 328:914–921
13. Pedersen OD, Bagger H, Kober L, Torp-Pedersen C: Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. *Circulation* 1999;100:376–380
14. Koffi I, Lacolley P, Kirchengaast M, Pomies JP, Laurent S, Benetos A: Prevention of arterial structural alterations with verapamil and trandolapril and consequences for mechanical properties in spontaneously hypertensive rats. *Eur J Pharmacol* 1998;361:51–60
15. Tieleman RG, De Langen C, Van Gelder IC, de Kam PJ, Grandjean J, Bel KJ, Wijffels MC, Allessie MA, Crijns HJ: Verapamil reduces tachycardia-induced electrical remodeling of the atria. *Circulation* 1997;95:1945–1953

Clin. Cardiol. Vol. 24 (Suppl. V), V-12–V-13 (2001)

INVEST: Results of Combined Strategies to Control Blood Pressure

RAINER E. KOLLOCH, M.D.

Gilead Medical Center, University of Münster School of Medicine, Bielefeld, Germany

Summary: The treatment of hypertension continues to be challenging due to the lack of understanding regarding underlying modulators of blood pressure as well as co-existing conditions such as atherosclerosis and diabetes. This has led to uncertainty regarding treatment strategy and intensity. The INternational VErapamil SR/trandolapril STudy (INVEST) is designed to evaluate the relationship between cardiovascular risk and blood pressure modulators. Based on a review of preliminary data, it appears that the treatment regimen used in the INVEST trial has been more successful than other studies at controlling systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure. These preliminary data from INVEST suggest that a high proportion of coronary artery disease (CAD) patients with hypertension should receive combination therapy to achieve contemporary blood pressure targets.

Key words: diastolic blood pressure, hypertension, INVEST, pulse pressure, systolic blood pressure

Introduction

It is difficult to create principles and strategies to achieve target blood pressure levels without a better understanding of underlying blood pressure modulators. Unfortunately, the treatment of hypertension has been confounded by the lack of knowledge regarding factors that modulate blood pressure control. Therefore, physicians often have used an uncertain clinical approach to the treatment of elevated blood pressure. Some clinical trials, however, have reported success at controlling key blood pressure modulators.

Address for reprints:

Rainer E. Kolloch, M.D.
Gilead Medical Center
University of Münster School of Medicine
Krankenanstalten Gilead 1
Burgsteig 13
D-33167 Bielefeld
Germany

Clinical Studies

The Evaluation and Interventions for Systolic Blood pressure Elevation-Regional and Global (EISBERG) project showed that control of diastolic blood pressure (DBP) alone is not sufficient to control overall blood pressure values for some patients.[1] From 1992 to 1997, even though the proportion of patients with a DBP > 90 mmHg decreased, a high proportion of patients did not achieve target blood pressure control. In the EISBERG project, nearly 98% of patients maintained a systolic blood pressure (SBP) of > 140 mmHg. Very few patients improved their SBP in this study.[1] The EUROASPIRE survey also showed poor control of SBP among treated patients. This study, which was conducted among 11,000 patients in France, Germany, Italy, Spain, and the United Kingdom, found that fewer than 13% of treated hypertensive patients reduced their SBP to < 140 mmHg.[2]

Clearly, drug strategies have failed to adequately control SBP. More than 7,000 hypertensive patients in Germany, France, Italy, Spain, and the United Kingdom received different treatments over a period of 2 years to achieve blood pressure targets (S. Julius, personal communication, 2001). Over 2 years, some patients received increased dosage of medication, some had therapies added, and some had therapies changed; however, 84% had unchanged blood pressure, indicating that the therapeutic strategy was not optimal.

The strategy for controlling blood pressure in INternational VErapamil SR/trandolapril STudy (INVEST), however, has been more successful. Almost 70% of patients maintained control of SBP (< 140 mmHg or < 130 mmHg for diabetics and patients with renal dysfunction) 12 months after randomization, a rate higher than that of other trials. In INVEST, almost 90% of patients treated for 12 months achieved control of DBP (< 90 mmHg or < 85 mmHg for diabetics or patients with renal dysfunction). This is also a favorable result compared with other trials and clinical practice. By measuring response rates, as opposed to the mean blood pressure changes for all patients reported by other clinical trials, the proportion of patients who have controlled SBP and DBP can be assessed. Similar to other trials, control of SBP and pulse pressure (a newly identified important indicator of risk for adverse outcome) has been difficult in INVEST. These blood pressure parameters, however, were controlled more successfully in INVEST than in other comparative trials and clinical practice. In the study, control of pulse pressure (to ≤ 55 mmHg, a very high threshold) was achieved in the majority (54%) of pa-

tients. Some current hypotheses suggest that control of pulse pressure can have a positive effect on prognosis.

Alderman provided data regarding the relationship of systolic, diastolic, and pulse pressure to the age-adjusted incidence of coronary vascular events.[3] Their study showed that there is a direct relationship between cardiovascular events and SBP. The relation between DBP and cardiovascular risk was less clear. Some data suggest that for patients with high SBP, an inverse relationship between DBP and cardiovascular events may exist. Therefore, patients with high SBP and low DBP may be at increased risk. This risk would be associated with pulse pressure. Risk increases when pulse pressure is > 60 mmHg. Therefore, pulse pressure should be a new target for antihypertensive therapy. The mechanisms associated with pulse pressure and risk are unknown.

Speculation based on preliminary and indirect evidence suggests that increased pulse pressure may be a sign of organ damage and impaired relaxation of the vessel wall. Elevated pulse pressure is most often observed in high-risk patient groups, such as smokers, obese patients, and diabetics who have frequently elevated SBP with an increased pulse pressure.

The 24-h ambulatory blood pressure measurements (ABPMs) can help clarify the relationship between SBP and cardiovascular events. When SBP, day-time SBP, and 24-h ABPMs are compared, risk is greatest for patients with high nighttime SBP. These patients have the highest incidence of cardiovascular events within 2 years.

Treatment Intensity

Data from many trials suggest that intensive treatment is more effective at reducing cardiovascular risk than less intensive treatment. Some of the trials that used more intensive treatment include the Appropriate Blood Pressure Control in Diabetes (ABCD) trial,[4] the Hypertension Optimal Treatment (HOT) trial,[5] and the United Kingdom Prospective Diabetes Study (UKPDS).[6] These studies analyzed the effect of intensive versus less intensive treatments on the development of coronary artery disease (CAD). These studies showed that patients who receive intensive treatment were less likely to develop CAD. Aggressive treatment also reduced the incidence of stroke.

Specifically, in the HOT study,[5] aggressively treated diabetics were assessed. In this study, patients who were able to achieve a DBP to < 80 mmHg showed reduced cardiovascular risk for adverse outcome by about 50%. In general, a reduction in DBP of 1 mmHg translated into a risk reduction of approximately 6%. A reduction in DBP of 5 mmHg resulted in a reduction of cardiovascular risk of 30%. All reductions in DBP, no matter how small, resulted in an improved prognosis for the patient.

A debate currently exists regarding the best strategy for cardiovascular risk reduction. One meta-analysis[7] involved studies that were similar in design to INVEST. Each study compared treatment consisting of a calcium antagonist with a diuretic or a beta blocker. This meta-analysis included the INSIGHT and the NORDIL studies. When the two treatment regimens were compared, there was no significant difference in cardiovascular risk. So far, no data from large clinical trials exist with regard to the calcium antagonist strategy employed in INVEST.

The same is true with regard to stroke in the comparison between calcium antagonists and beta blockers or diuretics. Some studies suggest that calcium antagonist use may reduce the occurrence of stroke more than beta-blocker or diuretic use in hypertensives. However, none of the studies focused specifically on hypertensive patients with CAD. When the overall cardiovascular rate in both treatment strategies is compared, there is no difference between the treatment strategies. Clearly, more data are needed to evaluate the non-dihydropyridine class of calcium antagonists, such as verapamil.

INVEST is investigating the theory that combination therapy is necessary in a majority of patients in order to achieve the new targets for blood pressure outlined by The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). Preliminary data suggest that the number of patients requiring two or more antihypertensive drugs in order to maintain control of SBP and DBP increases with time. Following 1 year of treatment in INVEST, approximately three quarters of the patients require combination therapy. This is similar to the data obtained with other clinical trials, such as the HOT trial.

Conclusions

Based on a review of preliminary data, it appears that the treatment regimen used in INVEST has been successful at controlling SBP, DBP, and pulse pressure. The data suggest that a majority of patients are receiving combination therapy to achieve blood pressure targets. Data from INVEST suggests that specific therapeutic strategies can successfully control blood pressure. As more data reveal more effective strategies for pharmacologic therapy, improved long-term control of hypertension will be achieved.

References

1. Swales JD: Current clinical practice in hypertension: The EISBERG (Evaluation and Interventions for Systolic Blood pressure Elevation-Regional and Global) project. *Am Heart J* 1999;138:231–237
2. EUROASPIRE I and II Group: Clinical reality of coronary prevention guidelines: A comparison of EUROASPIRE I and II in nine countries. European Action on Secondary Prevention by Intervention to Reduce Events. *Lancet* 2001;357:995–1001
3. Alderman MH: A new model of risk: Implications of increasing pulse pressure and systolic blood pressure on cardiovascular disease. *J Hypertens* 1999;17(suppl 5):S25–S28
4. Schrier RW, Estacio RO: Additional follow-up from the ABCD trial in patients with type 2 diabetes and hypertension. *N Engl J Med* 2000;343:1969
5. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998;351:1755–1762
6. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853
7. Conlin PR, Williams GH: Use of calcium channel blockers in hypertension. *Adv Intern Med* 1998;43:533–562

Clin. Cardiol. Vol. 24 (Suppl. V), V-14–V-16 (2001)

Electronic Prescribing via the Internet for a Coronary Artery Disease and Hypertension Megatrial

RHONDA COOPER-DEHOFF, PHARM.D., EILEEN HANDBERG, PH.D., CAROL HEISSENBERG, R.N., KATHLEEN JOHNSON, R.N.

Division of Cardiovascular Medicine, University of Florida, College of Medicine, Gainesville, Florida, USA

Summary: A unique feature of the International Verapamil SR/Trandolapril Study (INVEST) is the Internet-based, electronic data capture system developed at the University of Florida for this trial. This system allows for direct collection of patient enrollment data, randomization, study drug prescribing, and real-time monitoring of patient data online. In this trial, immediate transmission of patient-specific data occurs using online data collection forms. Investigators only need a personal computer with access to the Internet; no complicated hardware, software systems, or paper storage files are necessary. INVEST is the first large randomized clinical trial to use electronic prescribing systems in the research setting. Electronic prescribing eliminates errors associated with illegible handwriting, inappropriate dosing, and inappropriate medication choice. Because the INVEST protocol allows flexibility of medication choice and dosage range within randomly assigned treatment strategies based on patient tolerance and blood pressure response, physician investigators may use individual practice patterns and preferences. The electronic system provides guidance to physicians relative to the addition of medication or dosage adjustments within the protocol. Electronic tracking and reporting mechanisms have enabled investigators in this complex megatrial to enroll, randomize, and manage patients in real time with great accuracy.

Key words: central drug distribution, clinical trials management, electronic prescribing, enrollment, INVEST, pharmacy, randomization

Address for reprints:

Rhonda Cooper-DeHoff, Pharm.D.
University of Florida Department of Medicine
Division of Cardiovascular Medicine
P.O. Box 100277
Gainesville, FL 32610, USA

Introduction

The rationale and design of the International Verapamil SR/Trandolapril Study (INVEST) has been described,[1] and further information regarding this study can be accessed via the Internet (http://invest.biostat.ufl.edu). Briefly, INVEST is a phase IV, prospective, randomized, open, and blinded endpoint (PROBE) clinical trial comparing a calcium antagonist strategy (verapamil SR) with a beta-blocker strategy (atenolol) for the control of hypertension in 22,599 patients with established coronary artery disease (CAD). A total of 862 physician investigators from around the world enrolled patients, beginning in September 1997 and ending in December 2000. Patient follow-up is scheduled to conclude in December 2002.

Electronic Data Capture—Interaction System

A unique feature of INVEST is the Internet-based, electronic data capture system that allows for completion of patient enrollment, randomization, study drug prescribing, and real-time monitoring of patient data online. All site investigators have direct and continuous access to the system via the World Wide Web. Immediate transmission of patient-specific data is possible with online data collection forms, which allow the administrative coordinating center, the pharmacy coordinating center, the sponsor, and other units (IRB, DSMC, etc.) to receive secure data without delay. Passwords and an encryption system, similar to that used by banks during wire money transfers and automated teller machine transactions, ensures the security of all information during the data-transfer process.

The management of hypertension is complex, especially among patients with coexisting CAD, and often requires multiple medications and aggressive dose escalation to achieve the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) blood pressure control targets. Because the protocol allows flexibility of medication choice and dosage range within the protocol-defined strategy based on patient tolerance and blood pressure response, INVEST physician investigators may use individual practice patterns and preferences. The electronic system can provide guidance to physicians if they need to increase dosage

of a medication or add new medications to compensate for a patient's uncontrolled blood pressure, and helps to assure protocol compliance.

Because INVEST uses an electronic data capture system and commercially available antihypertensive medications, it is uniquely suited for the special electronic prescribing and centralized drug distribution system developed at the University of Florida for this trial. Centralization was difficult because of the international composition of the trial. A centralized system would have required each participating country to comply with the regulations of every other country. As a result, prescribing and dispensing procedures were customized specifically for each participating country. This article describes the prescribing and dispensing procedure developed for the United States (including Puerto Rico), where 17,154 (76%) of all INVEST patients were enrolled.

Electronic Prescribing

Electronic prescribing of medications[2,3] has been approved by about one half of the states in the United States. As a result, pharmacies in those states can legally fill prescriptions that are received electronically from a licensed physician. Using various insurance formularies, electronic prescribing can eliminate errors associated with illegible handwriting, inappropriate dosing, and inappropriate medication choice. Based on these advantages, the Institute for Safe Medication Practices has called for the elimination of handwritten prescriptions by 2003.[4] Despite the obvious advantages, most physicians in the United States do not use electronic prescribing. Use is limited in part because electronic systems are not currently available in many patient care areas and because specialized software systems are required to communicate with particular pharmacies. Furthermore, most U.S. physicians are not familiar with electronic prescribing and, because of this lack of familiarity, would not voluntarily choose an electronic system over the traditional paper mode. Electronic prescribing should increase as hand-held devices become more common, as software systems are developed to interface with them, and as the systems become more user friendly.

Even though electronic prescribing systems have been available for many years, INVEST is the first large, randomized clinical trial to use one in the research setting (Fig. 1). With this system, all site investigators have access to real-time data 24 h a day. Investigators do not need complicated hardware and software packages; the only requirement is access to the Internet via a common web browser and Internet provider. Medications and dosages allowed by the study protocol are programmed into the system so that all prescriptions are necessarily based on the strategy the particular patient is randomized to receive. All prescriptions are automatically adjudicated by the pharmacy upon transmission. Prescriptions printed and archived by the pharmacy are processed immediately, and are legible, appropriate, and delivered direct to the patient's home. At the time of this writing, INVEST site investigators in the United States have issued more than 80,000 electronic prescriptions, all transmitted direct to a central mail-order pharmacy contracted to process the prescriptions for the study. These prescriptions are randomly reviewed in real time by the INVEST pharmacy coordinating center staff for appropriate dose escalation based on blood pressure response and other quality assurance measures.

Centralized Drug Distribution

INVEST offers a total of 41 different dosage regimens to site investigators to control blood pressure in patients enrolled in INVEST. Because of the large number of treatment options, centralized research drug distribution was developed. Without centralized distribution, investigators would have been required to use a large amount of office space to store the treatment options, and many medications would have expired before reaching patients.

A mail-order pharmacy with electronic prescription service capabilities, Express Pharmacy Services (EPS), of Largo, Florida, was selected to process all INVEST prescriptions in the United States. The study sponsor (Abbott Laboratories/Knoll AG) provided EPS with branded study medication (Isoptin SR®, Mavik®, and Tarka®) that was used to fill electronic study prescriptions. Generic brands were utilized for

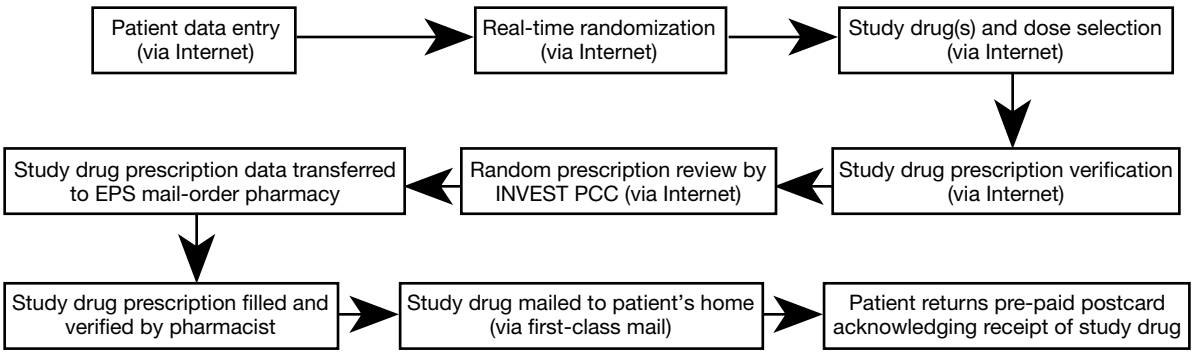

FIG. 1 Electronic prescribing via the Internet in the INternational VErapamil SR/trandolapril STudy (INVEST). *Abbreviations*: EPS = Express Pharmacy Services, PCC = pharmacy coordinating center.

atenolol and hydrochlorothiazide. At the time of this writing, EPS had dispensed approximately 13.6 million tablets of study drug pursuant to the 80,000 electronic prescriptions received for patients in the United States enrolled in INVEST. Rapid and ongoing accountability of study medications is possible because EPS provides daily electronic reporting of all prescriptions that have been filled. Additional tracking of medication occurs at the patient level. Express Pharmacy Services includes a self-addressed, prepaid postcard with each package of study medication sent to a patient's home, so that patients can acknowledge receipt of medications as they are delivered.

Conclusion

The development and use of central study drug distribution and electronic prescribing systems has allowed INVEST to enroll and manage a large number of patients rapidly throughout the world. In the United States and Puerto Rico, the Internet-based, electronic data capture system allows for completion of patient enrollment, randomization, study drug prescribing, and real-time monitoring of patient data online. In addition, electronic tracking and reporting mechanisms have enabled the drug accountability process to occur with great accuracy in real time at many levels. Research physicians and pharmacists can check the accuracy of what was prescribed and dispensed by use of the electronic system, which can then be confirmed by the patient's postcard acknowledgment. This technology has enabled the investigators in this complex megatrial to enroll, randomize, and manage patients in real time with great accuracy.

References

1. Pepine CJ, Handberg-Thurmond E, Marks RG, Conlon M, Cooper-DeHoff R, Volkers P, Zellig P: Rationale and design of the International Verapamil SR/Trandolapril Study (INVEST): An Internet-based randomized trial in coronary artery disease patients with hypertension. *J Am Coll Cardiol* 1998;32:1228–1237
2. Schiff GD, Rucker TD: Computerized prescribing: Building the electronic infrastructure for better medication usage. *J Am Med Assoc* 1998;279:1024–1029
3. Niinimaki J, Forsstrom J: Approaches for certification of electronic prescription software. *Int J Med Inf* 1997;47:175–182
4. Institute for Safe Medication Practices. Available at: http://www.ismp.org. Accessed April 1, 2000.

Clin. Cardiol. Vol. 24 (Suppl. V), V-17–V-23 (2001)

Enhancing Clinical Trials on the Internet: Lessons from INVEST

RONALD MARKS, PH.D., HEATHER BRISTOL, M.S., MICHAEL CONLON, PH.D, CARL J. PEPINE, M.D., MACC, FESC*

Department of Statistics, and *Division of Cardiology, College of Medicine, University of Florida, Gainesville, Florida, USA

Summary: The INternational VErapamil SR/trandolapril STudy (INVEST) is the first long-term, large-scale clinical trial being conducted primarily using Web-based technology. The Web is a powerful tool for enhancing clinical trial management because of its ability to centralize all study information and coordinate multiple trial processes in real time at lower cost. The result is improved efficiency, accuracy, and safety in clinical trials conduct. In Web-based clinical trials, sites are able to focus primarily on medicine and science, rather than on trial administration. Site training, study documentation, subject recruitment, randomization, medication dispensing, and management procedures are simplified by using Web-based software to enhance processes. This paper summarizes the advantages achieved for INVEST investigators, sponsor representatives, monitors, and subjects resulting from the centralization and coordination of multiple tasks through Web-based technology.

Key words: clinical trials management, Internet, INVEST

Introduction

The INternational VErapamil SR/trandolapril STudy (INVEST) is a Phase IV hypertension clinical trial that is unique in its use of the Internet to enhance clinical trials processes. Beginning in the Fall of 1997, INVEST was the first large-scale, truly Web-based clinical trial. Many subsequent clinical trials have used the Internet, primarily for electronic data capture (EDC),[1,2] or for site management, but INVEST is unique in its comprehensive use of the Web to enhance trial processes beyond EDC. Also, having enrolled 22,599 patients at 862 sites in 14 countries, INVEST is considerably larger in Web utilization than any other clinical trial in the world to date. Finally, INVEST is the longest running Web-based clinical trial in the world. Most Web-based trials to date have been of short duration, generally lasting for less than a year. INVEST is now completing its fourth year and patient follow-up will continue until Decemeber 2002.

This paper will summarize the advantages brought to the INVEST sponsor, investigative sites, and subjects through leading edge technology.

The Internet as a Clinical Research Tool

Historically, the clinical trials process has been inefficient, time consuming, and error prone. The sponsor and principal investigators (PIs) did not have timely information regarding clinical trial activity because many activities were decentralized; that is, conducted at many locations with information stored locally at each site, without opportunity for the sponsor or PI to observe directly. Furthermore, disparate trial activities, such as randomization, medication dispensing, and safety monitoring, were conducted independently of each other.

The Web, however, has changed the paradigm for clinical trials management.[3] The Web allows for centralization of information from multiple processes in real time, which leads to immediate oversight and improved coordination of all parties involved. In INVEST, all clinical trial constituents worldwide exchange study information in real time (see Fig. 1). We believe that the Web-based processes used in INVEST will result in increased efficiency, accuracy, and safety in the clinical trials process.

Site Hardware and Software

Many clinical trials require proprietary hardware and software systems generally provided to investigators by the sponsor. To participate in a clinical trial, investigators and their

Statement of financial interest: Michael Conlon, Ronald Marks, and Carl Pepine are inventors of this technology, and Michael Conlon and Ronald Marks also hold equity in MarCon Global Data Solutions, a company commercializing the technology. Drs. Conlon, Marks, and Pepine may benefit from this technology by receiving royalties, and Drs. Conlon and Marks may also benefit from equity growth.

Address for reprints:

Ronald Marks, Ph.D.
University of Florida College of Medicine
Department of Statistics
P.O. Box 100212
Gainesville, FL 32610, USA

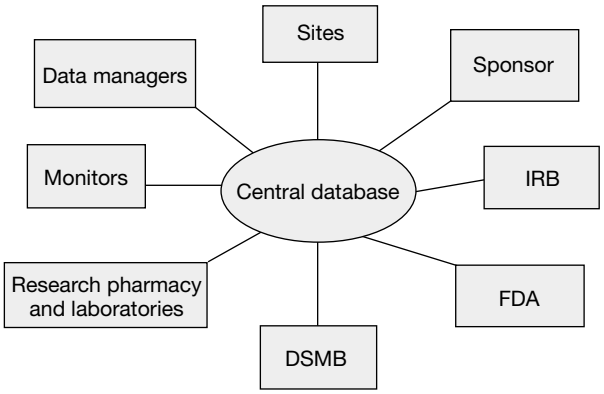

FIG. 1 INVEST trial constitutents who may benefit from the Web-based system. DSMB = Data and Safety Monitoring Board, FDA = Food and Drug Adminstration, IRB = Institutional Review Board.

staffs have needed to learn entirely new computing systems. Physicians wishing to participate in multiple clinical trials from multiple sponsors would require separate computing systems for each study. In addition to being extremely inefficient, this process greatly disrupted clinical practices. Using the Web, however, no proprietary hardware or software is required at the site; only a personal computer (PC) with Internet access is necessary. A unique aspect of INVEST is that investigators received a contemporary computer with Internet access included, which provided a standardized computing environment for investigators. This standardization was required for INVEST because in 1997 and 1998, access to the Web and computing hardware was quite varied. Today, computers with Web access are generally available in most physician offices or can be easily obtained. Web-based clinical trials offer a gain in efficiency because the dependency on proprietary hardware and software systems is eliminated.

Training

Investigator training is also simplified through the Web. INVEST provided training on Institutional Review Board (IRB) issues and case report form (CRF) completion. The Web system documented that each investigator satisfactorily completed the demonstration training program before being allowed to enroll subjects into INVEST. Our experience with Web-based training illustrates the opportunity to eliminate travel to a central location for training and, furthermore, to document the result of a training exercise for each investigator. Using the Web, training can occur at home, at the office, at night, on weekends, all at the convenience of each individual investigator. The investigator's success at learning about the science and protocol of a trial can be documented over the Web. In addition, investigator knowledge regarding the IRB process, informed consent, and principles of good clinical practice (GCP) can be documented over the Web. Online training can ensure that the appropriate knowledge has been obtained before the investigator can begin trial participation.

Monitoring

Monitoring is also a major component of all clinical trials. It is expensive to have monitors visit each site, and there is a complex process for the monitor to supervise trial activity. Using the Web, monitors can observe activities of the trial in real time from anywhere in the world. Subject enrollment, for example, can be monitored from any location as it occurs. In addition, the sponsor, PI, and monitors have real-time access to extensive reports regarding trial conduct.

Utilizing real-time monitoring, site investigators are given the support and continued education they need. This allows issues to be resolved quickly, before becoming major problems. In a Web-based clinical trial, monitors still visit sites but the process changes. In INVEST the monitor knows much about the site's performance before visiting. Each audit is performed more to document what is already known rather than to learn for the first time how the site is performing. The result is a greatly enhanced relationship between site investigators and the monitors, and a vastly improved process.

Randomization

Randomization in INVEST involves assigning an eligible subject to a strategy beginning with either a calcium antagonist or a beta blocker. Either trandolapril or hydrochlorothiazide can be added as necessary. In a clinical trial, randomization of a subject generally requires a minimum of 15 to 20 min, either by opening an envelope with a code for each specific study treatment or, more likely, calling a toll-free phone number and obtaining the randomly assigned group through an interactive voice recognition system (IVRS). In INVEST, randomization is seamlessly integrated into the enrollment process and is completed in about 20 to 30 s. The result of the randomization is automatically stored in the central computer server at the University of Florida. Because randomization is completely automated, no site monitoring is required of this procedure. On-line randomization is an example of an important process improvement for the site, resulting in reduced administrative work and errors committed.

Medication Dispensing

Another unique feature of INVEST is that no medications are managed at the investigative sites in the U.S. Prescriptions are generated electronically and transferred electronically to the mail-order pharmacy. A mail-order pharmacy was contracted for management of INVEST medications. This is a new paradigm for management and distribution of research medications. Because INVEST is a Phase IV clinical trial using only currently marketed medications, a commercial mail-order pharmacy can be used for medication dispensing. A more thorough description of this process is included elsewhere in this supplement.[4]

Briefly, immediately following randomization of a subject in INVEST, a screen of protocol-specific options for dose titration or additional protocol-approved drugs appears on the investigator's computer screen. A specific treatment option is

suggested, according to the titration strategy indicated in the study protocol.[5] The treatment option is determined by software using information regarding the subject's disease state, blood pressure control, and length of time in the study. The investigator may choose to follow the recommendation or to modify it according to his/her clinical judgment. Figure 2 shows an example of the beta-blocker options. A few clicks of the mouse by the site investigator document the medication plan for the subject.

In INVEST, investigators do not receive, manage, or distribute medications at their practice. Investigators do not need to maintain the paperwork associated with the medications. The result is that no monitoring is required for medication management or dispensing. Centralized medication prescribing is another example of an important process improvement for the site, adding efficiency and accuracy by replacing much human administrative effort through technology.

Medical Summary

At the completion of a subject enrollment or follow-up visit in INVEST, a complete medical text summary is provided for all information entered during that clinical visit (Fig. 3). The medical summary also incorporates free text entered by the investigator during the subject visit that is not needed for the science of the clinical trial but is useful to the investigator regarding the subject. Note that in a trial with more regulatory constraints, the free text information may not be permitted. The printed medical summary provides a clear, complete, and correct description of the subject visit. The medical summary is the record of this subject visit and must be printed, signed, and filed. An important note is that the medical summary completely agrees with the research database since the medical summary is generated from information in the database.

Security

Security in clinical trials involves maintaining all study-related information at the investigator sites and at the central site for study coordination. Study information includes volumes of CRFs and related documents that are handled by many individuals, all of whom must understand proper security procedures for managing the information. The Web-based security offered in INVEST greatly simplifies security issues. All access to INVEST data and related information is through the central web site to the server at the University of Florida. Each person accessing information must have an approved unique user identification (ID) and password that identifies information and data they may access, read, and possibly write. Acceptance of the user ID and password by a person indicates

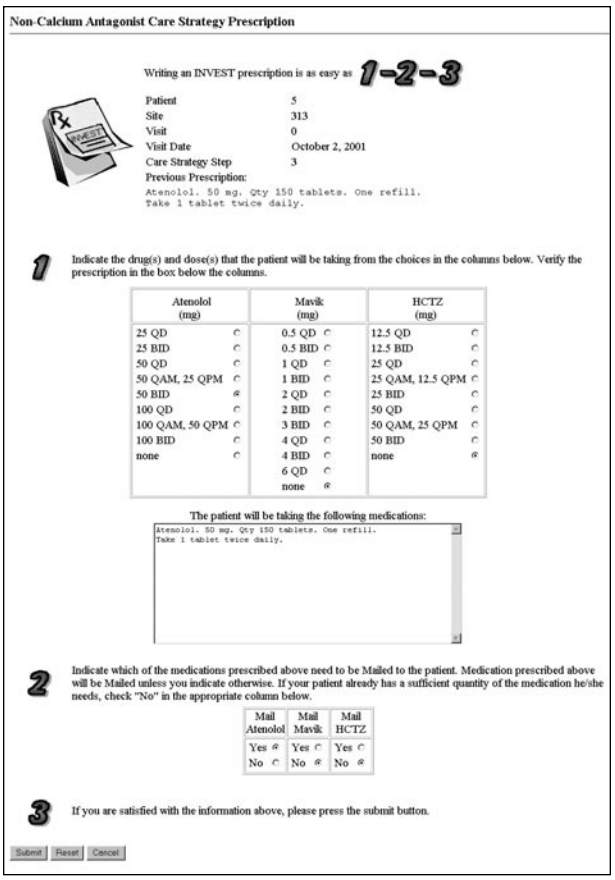

FIG. 2 INVEST non-calcium antagonist care strategy titration form.

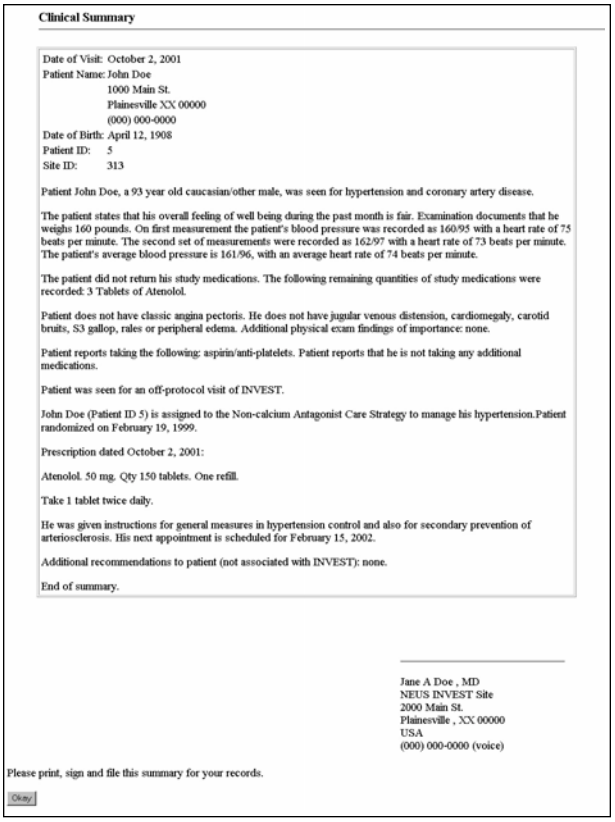

FIG. 3 Medical summary for INVEST subject enrollment.

that they accept responsibility for all information entered under that user ID and password; this serves as their electronic signature for all clinical trial-related activity. All information transferred between the central computer server at the University of Florida and site constituents is fully encrypted using standard RSA 128 bit encryption methods or 40 bit for international transmissions. The result is much greater security for information transfer than that in any previous system.

All data entered into the computer server are automatically identified regarding who provided the information, when, from where, and how. The Web-based system automatically creates an audit trail of all clinical trial activity, in that every keystroke made is preserved in the system. The audit trail allows the study to be recreated for any point in time and prevents unauthorized manipulation of data.

Moving from a clinical trials system that is decentralized with minimal control and supervision to a totally audited centralized process fundamentally changes the relationship of investigators to the clinical trial data and greatly improves the process for all constituents from sites to the sponsor and regulatory agencies.

Reporting Adverse Events

The Web is a great tool for enhancing the reporting of adverse events (AEs). In INVEST, an AE is reported on a standard CRF specific for that purpose. Needed information regarding seriousness of the AE and resolution is requested. When the AE is submitted to the database, the Web-based technology used in INVEST immediately notifies designated safety officials of any serious AE via email. Follow-up by the appropriate safety official occurs more quickly. The result is a more efficient AE-reporting process, leading to improved subject safety in clinical trials.

Site Conduct

The Web greatly reduces the amount of administrative work at the investigative site. In INVEST, a site receives no paperwork after signing a standard paper contract. All needed study information is provided over the Internet. The subject enrollment process is a complete integration of eligibility, medical history, physiologic data, randomization, medication prescribing, and a full textual medical summary of all collected information.

The study protocol is online and can be printed if desired. For each data element on each CRF, there is a link to the needed information for that data element from the protocol by clicking on the "?" appearing before each data element (Fig. 4). Thus, all information is available for the research staff as needed, enhancing study efficiency, accuracy, and saving paper. As described earlier, site efficiencies are also gained by eliminating randomization and medication dispensing from site responsibilities. The result is an improved site operation in terms of efficiency and accuracy of work, in addition to enhanced subject safety.

Site Benefits

In Web-based clinical trials, sites focus on medicine and science and have little administration and bureaucracy to contend with. A major benefit to sites is the tremendous decrease in paper for the conduct of clinical trials. Paper is only generated

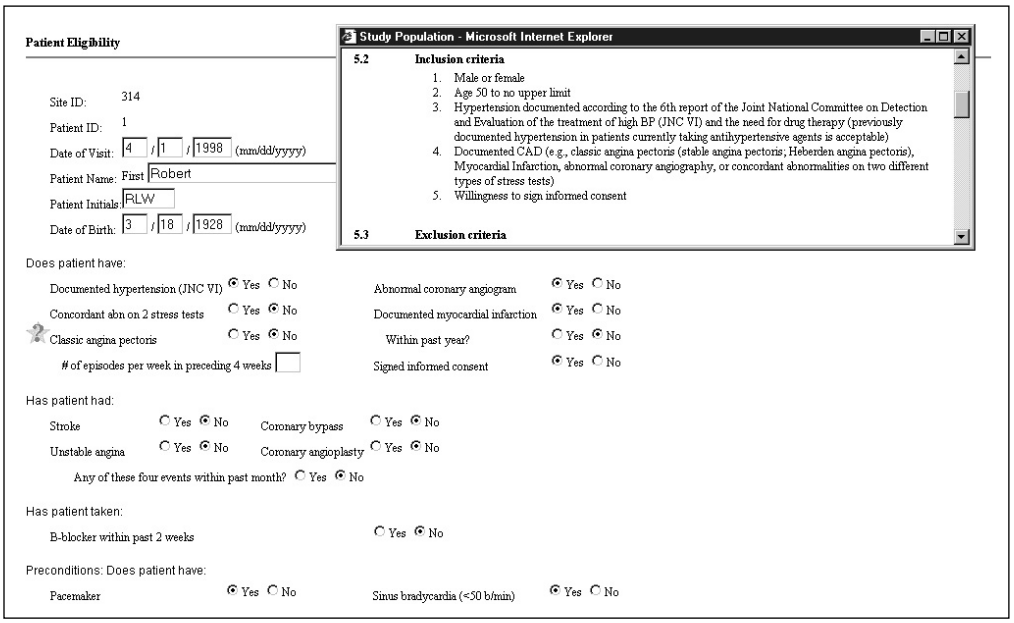

FIG. 4 Online study protocol reference accessible for each data element.

when investigators print out completed CRFs, subject medication prescriptions, medical summaries, and documentation required for events. This reduction in site responsibilities from replacing paper and human processes with Web-based automated processes will encourage more physicians to participate in the clinical trial process. A total of 862 sites are active in INVEST and over 50% were new to clinical research. Process changes leading to gains in site efficiency and accuracy through Web-based technologies allow and will change the paradigm of clinical trials conduct.[3]

In clinical trials, it is typical for the investigator to wait 6 to 8 weeks before the first visit from a trial monitor. With Web-based trials, monitors know how the trial is progressing from the beginning. If the enrollment process or conduct of the trial needs to be modified, investigators can be notified immediately. This allows monitors to be more proactive and supportive of education at sites, rather than reactive to problems that have been discovered. Ultimately, a more professional and positive relationship is facilitated between the investigators and monitors. Also, the number and length of monitor visits are reduced. For sites and sponsors both, efficiency is gained in the capture of clinical data, reporting of adverse events, approval and monitoring of the site, and the sponsor management of the trial.

Sponsor Benefits

An important benefit of Web-based clinical trial management for the trial sponsor is the access to real-time management reports. These reports allow sponsors to monitor sites worldwide, ensuring that the trial progresses in an accurate and efficient manner. Sponsors can identify and resolve queries and problems quickly using Web-managed communications. For example, sponsors in both Ludwigshafen, Germany, and Gainesville, Florida, have access to information regarding screening rates and failures, study enrollment, follow-up rates, study schedule, and medication dispensing. Using this information, sponsors can improve the coordination of the clinical trials process.

Safety Benefits

Web-based clinical trials also enhance the safety of study subjects. In INVEST the IRB is an online trial partner, and can monitor the trial in real time. The IRB has permissions in the Web-based system providing the IRB responsibility to approve a site investigator to participate after all paperwork is in order. Similarly, the IRB has system permissions to remove a site's access to the Web-based system if it identifies any problematic trial behavior. The IRB also conducts its annual renewals via the Internet, bringing much efficiency to the process in this international clinical trial. Using these tools provided via the Internet, the IRB can react quickly to any safety issues that arise in INVEST.

In addition, subject safety is monitored more efficiently because the sponsor and PI have access to all AE information in real time as described earlier.

Results

The web provides an opportunity to monitor the clinical trial in real time in a number of areas through regular reports made available in real time to appropriate study constituents. Table I provides a daily report automatically generated and sent via email to the sponsor and principal investigators. This report documents site activity for November 27, 2000. The main information is the number of enrollments (Visit Number 1) and follow-up visits (2–10). It also identified visits made by telephone and off-protocol visits (Medical Management). Substantial additional information is provided that is useful to those responsible for study conduct.

The goal in INVEST was to accomplish subject enrollments within 20 min and follow-up visits within 10 min. Enrollment combines subject eligibility determination and then collecting the same information at later follow-up visits. Table II provides daily information for the week of November 13, 2000, summarizing eligibility and follow-up visit times for that week. The report provides the mean and median eligibility times, as well as the 75, 90, and 100% eligibility times. It documents for this week that the typical eligibility determina-

TABLE I Report of INVEST daily activity in enrollment and follow-up visits

INVEST Activity Within the Last 24 Hours For 27NOV00

Total number of sites with enrollment permission: 1000

Of those sites:

989 have IRB activation

914 have completed the demo

906 ready to enroll

Total number of sites currently enrolling: 764

Total number of sites with 1 or more enrollments: 866

Total # of successful patient enrollments: 21957

The following new visits occurred:

Visit Number	Number
Phone	2
Medical Management	8
1	11
2	17
3	22
4	5
5	12
6	4
7	3
8	1
9	0
10	1

tion took about 7 min, and 75% of eligibility determinations were completed within the desired 10-min goal. Similar statistics indicate the 10-min goal for follow-up visits is also met using the Web system. Reviewing this report on a weekly basis ensured that the study was meeting time goals for investigators to complete eligibility and follow-up visits.

On a global basis, the sponsor, PIs, and regional directors needed information about study enrollment. Figure 5 illustrates an example of the "drill-down" report available in real time to appropriate study constituents. Experts in CAD and hypertension were recruited as regional directors and, in turn recruited specialists (cardiologists and internists) in their region who, in turn, helped recruit additional site investigators. Figure 5A provides study enrollment figures by defined study regions in the world, with specific names and regions removed for this report. This report would be updated immediately each time a subject was successfully enrolled in INVEST. The result is real-time access to accurate enrollment figures. To follow-up for a specific region, the user would click on the Site ID and Figure 5B would be produced with enrollment figures for that region. Note that this report also indicates the last date a subject was enrolled under each specialist in that region. To follow up on a specific specialist from this report, the user would click on that Site ID, and Figure 5C would be produced. This report summarizes activity for investigators under that specialist and allows easy email access to an individual investigator by clicking on their email address (omitted from this report).

These reports illustrate the type of results that can be produced in real time in Web-based clinical trials. This information indicates the opportunities available to monitor the trial and ensure that enrollment and other study activities remain on schedule.

TABLE II Weekly report of daily eligibility determination and follow-up visit times

Performance Statistics Summary

Eligibility Statistics (minutes)

		N	Mean	Median	75%	90%	100%
2000							
Monday	11/13	89	8	5	9	16	55
	11/14	69	8	7	9	12	25
	11/15	84	7	6	9	14	40
	11/16	74	8	6	8	14	47
	11/17	83	6	6	8	9	31

Visit Statistics (minutes)

		N	Mean	Median	75%	90%	100%
2000							
Monday	11/13	348	10	6	10	19	47
	11/14	337	9	7	10	16	58
	11/15	279	10	7	11	19	63
	11/16	338	10	8	12	20	49
	11/17	370	9	7	11	15	64

Discussion

Clinical trials management has traditionally been inefficient, time consuming, and costly. Data collection typically involved hand recording of information on CRFs, transport by batch of CRFs to the data coordinating center, and single- or double-data entry into the computer system. This was followed by verification and validation of the data. Any data errors or inconsistencies revealed had to be followed up with the investigator and corrected. The process was slow, expensive, and error prone. It required extensive review by monitors, which is one of the most expensive facets of a clinical trial. Site investigators, sponsors, and monitors did not get feedback on trial progress or problems in a timely manner; however,

Regional Director Site ID	Region Code	Region	Last Name	First Name	Specialists	Sites	Sites Enrolling	Patients
					17	93	48	805
					13	53	25	216
					13	94	60	898
					4	29	20	293
					15	100	41	800
					1	3	0	0
					28	163	72	1071
					6	22	13	166
					67	399	207	3577
					1	3	3	20
					1	64	40	3466
					1	1	1	16
					1	46	42	6205
					1	34	18	183
					0	0	0	0
					0	0	0	0
					1	29	21	134
					1	0	0	0
					1	0	0	0
					1	10	5	29
					5	22	12	159
					4	83	40	629
					2	173	84	2082
					4	122	52	676
					1	35	35	841
					1	30	24	333
Total Regional Directors					**Total Specialists**	**Total Sites**	**Total Sites Enrolling**	**Total Patients**
26					**190**	**1608**	**863**	**22599**

(A)

FIG. 5A Trial activity summary by regional director.

Specialist Site ID	Last Name	First Name	Sites	Sites Enrolling	Patients	Last Enrollment
			3	2	115	September 26, 2000 21:48 GMT
			3	2	37	September 18, 2000 22:56 GMT
			4	4	22	October 25, 2000 16:52 GMT
			16	13	188	November 3, 2000 01:07 GMT
			6	5	85	November 7, 2000 18:41 GMT
			4	1	31	February 4, 2000 02:40 GMT
			12	4	5	October 23, 2000 21:01 GMT
			11	7	128	December 13, 2000 16:38 GMT
			8	5	74	June 21, 2000 17:13 GMT
			3	3	22	November 3, 2000 17:25 GMT
			13	7	62	December 5, 2000 13:58 GMT
			5	4	86	October 25, 2000 21:23 GMT
			6	3	43	November 5, 1999 16:37 GMT
Total Specialists			**Total Sites**	**Total Sites Enrolling**	**Total Patients**	
13			**94**	**60**	**898**	

(B)

FIG. 5B Regional director activity summary by specialist for the region.

Site ID	Site Name	Contract Received	Computer Shipped	IRB Approval	Patients	Last Enrolled	User Able to Enter Data	Email	Next Report
		March 23, 1999 04:00 GMT	April 22, 1999 04:00 GMT	April 21, 1999 04:00 GMT	6	August 25, 1999 23:08 GMT	Y		Visit Listing
		September 9, 1998 04:00 GMT			0		N		Visit Listing
		September 1, 1998 04:00 GMT	September 17, 1998 04:00 GMT	October 6, 1998 04:00 GMT	10	April 30, 1999 22:06 GMT	Y		Visit Listing
		April 13, 1999 04:00 GMT	May 6, 1999 04:00 GMT	May 5, 1999 04:00 GMT	58	September 13, 2000 18:29 GMT	Y		Visit Listing
		October 14, 1997 04:00 GMT	October 26, 1997 03:00 GMT	February 3, 1998 04:00 GMT	12	October 25, 2000 21:23 GMT	Y		Visit Listing
Total Sites					Total Patients				
5					86				

(C)

FIG. 5C Specialist enrollment summary by site report.

timely information is essential in a clinical trial, especially in trials where safety and efficacy are major issues.

Subject randomization, prescribing, dispensing of medications, and the reporting of safety information are also prone to inefficiencies and errors. This is particularly true for large, multicenter clinical trials that have added complexities because of geographical dispersion of sites and resources. However, multicenter trials that often cross international boundaries are necessary when a large number of patients is required, such as in INVEST, or when the disease entity being studied is rare.[2,6]

Networked computers and EDC have previously been used to enhance various aspects of multicenter trial operation. Prior to wide availability of the Internet, the European myocardial infarction study, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3),[7,8] had 100 sites connected by modem and had enrolled over 17,000 patients. The system was developed to enhance data entry and checking, data security, and communication between sites. Other studies have used the Internet primarily for EDC,[1,2] and only a few studies to date have documented additional clinical trial activities benefited by the Web.[6,9] INVEST is the first multicenter clinical trial to use the Internet exclusively to coordinate multiple trial activities.

The Web-based system developed at the University of Florida and used to run INVEST was designed to revolutionize the way clinical trials would run.[3] We believe INVEST illustrates the major improvements in efficiency and accuracy that can be achieved compared with traditional paper-based clinical trials. The benefits accrue from the opportunities to centralize all information and coordinate the multiple activities in a clinical trial.

Because of the enhancements brought to the research process through the Web-based system, INVEST has been able to recruit community-based practicing physicians as site investigators. About half of our 862 physician investigators were first-time researchers and are able to participate as effectively as experienced researchers. Because of the more "real-world" physicians involved, INVEST enrolled "real-life" patients more reflective of the general hypertension population. Note that INVEST provides a much better representation of females, Blacks, and Hispanics than other traditional clinical trials.[10]

Conclusions

Web-based clinical trials bring sites, sponsors, and all trial constituents together through online real-time information that is available in a clinical trial such as INVEST. The major paradigm shift involves the centralization of all study information and coordination of the multiple processes associated with clinical trials through improved technology. Clinical investigators should become more interested in clinical research because their focus becomes more on leading-edge medicine and science and much less on administration. The result is a clinical trials process that is safer, more efficient, and more accurate.

References

1. Keim E, Sippel H, Eich HP, Ohmann C: Collection of data in clinical studies via internet. *Stud Health Tech Inform* 1997;43: 57–60
2. Workman R, Beatty E, Workman D: Internet based data collection and analysis. *Stud Health Tech Inform* 1998;51:182–186
3. Marks RG, Conlon M, Ruberg SJ: Paradigm shifts in clinical trials enabled by information technology. *Stat Med* 2001;20:2683–2696
4. Cooper-DeHoff R, Hanberg EM, Heissenberg C, Johnson K: Electronic prescribing via the internet for a coronary artery disease and hypertension megatrial. *Clin Cardiol* 2001;24(suppl 5):V-14–V-16
5. Pepine CJ, Handberg-Thurmond E, Marks RG, Conlon M, Cooper-DeHoff R, Volkers P, Zellig P: Rationale and design of the International Verapamil SR/Trandolapril Study (INVEST): An internet-based randomized trial in coronary artery disease patients with hypertension. *J Am Coll Cardiol* 1998;32:1228–1227
6. Dorman K, Saade G R, Smith H, Moise KJ: Use of the World Wide Web in research: Randomization in a multicenter clinical trial of treatment for twin-twin transfusion syndrome. *Obstet Gynaecol* 2000;96:636–639
7. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994;343: 1115–1122
8. Santoro E, Nicolis E, Franzosi MG, Tognoni G: Internet for clinical trials: Past, present, and future. *Controlled Clin Trials* 1999;20: 194–201
9. Kiuchi T, Ohashi Y, Konishi M, Bandai Y, Kosuge T, Kakizoe T: A world wide web-based user interface for data management systems for use in multi-institutional clinical trials: Development and experimental operation of an automated patient registration and random allocation system. *Controlled Clin Trials* 1996;17:476–493
10. Conti RC, Cooper-DeHoff R: How will INVEST and other hypertension trials change clinical practice? *Clin Cardiol* 2001;24(suppl 5):V-24–V-29

Clin. Cardiol. Vol. 24 (Suppl. V), V-24–V-29 (2001)

How Will INVEST and Other Hypertension Trials Change Clinical Practice?

C. RICHARD CONTI, M.D., MACC, AND RHONDA M. COOPER-DEHOFF, PHARM.D.

Division of Cardiovascular Medicine, University of Florida, College of Medicine, Gainesville, Florida, USA

Summary: Three large, ongoing, international clinical trials will greatly improve our understanding of hypertension management. The trials, which include the INternational VErapamil SR/trandolapril STudy (INVEST), the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), and the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) trial, enrolled a combined total of 81,649 patients over a 7-year period from 18 different countries in North America, South America, Europe, and Australia-Asia. The mean age of all subjects was 66 years, and the mean body mass index (BMI) was 29.5. In addition, 30% of all patients had diabetes and 43% had documented coronary artery disease (CAD). In INVEST, 100% of enrolled patients had documented CAD and 27% had diabetes. Of patients treated for 12 months in INVEST, a systolic blood pressure (SBP) <140 mmHg was achieved by 70% of nondiabetics, and 66% of patients with diabetes achieved that level. Of all the patients enrolled in the three trials, 38% were smokers, 25% had a history of myocardial infarction (MI) or stroke, and 52% had a history of dyslipidemia.

Although these clinical trials are likely to influence treatment guidelines, they may not affect the way medicine is practiced. A survey of primary care physicians found that 41% had not heard of or were not familiar with the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) guidelines. The JNC VI and European guidelines provide management strategies based on severity of coronary risk factors, target organ damage, and blood pressure levels. Primary care physicians have a responsibility to be educated about risk stratification, goals of treatment based on risk, and management strategies for hypertension from available treatment guidelines.

Address for reprints:

C. Richard Conti, M.D.
University of Florida Department of Medicine
Division of Cardiovascular Medicine
P.O. Box 100277
Gainesville, FL 32610, USA

Key words: clinical trials, hypertension, INVEST, practice guidelines, risk stratification, treatment strategies

Introduction

Three large, ongoing, international clinical trials will greatly improve our understanding of hypertension management. The trials, which include the INternational VErapamil SR/trandolapril STudy (INVEST),[1] the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[2] and the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) trial,[3] enrolled a combined total of 81,649 patients over a 7-year period from 18 different countries in North America, South America, Europe, and Australia-Asia. It is likely that these three trials will impact future clinical practice guidelines. In this report, the hypertensive patient will be characterized by assessment of baseline information published from these trials. In addition, guidelines from the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) and the European Societies of Cardiology, Atherosclerosis, and Hypertension, as well as current physician practice patterns will be reviewed. Finally, knowledge gained from recent and ongoing clinical trials will be discussed.

Of patients treated for 12 months in INVEST, preliminary data show that 70% of nondiabetics achieved an SBP <140 mmHg, and 66% of patients with diabetes achieved that level.

ALLHAT

ALLHAT is a randomized, double-blind, active-controlled clinical trial in the United States, Canada, Puerto Rico, and the US Virgin Islands that will compare the effectiveness of newer antihypertensive agents versus traditional antihypertensive treatment with diuretics.[2] Between February 1994 and January 1998, 42,448 patients from 625 sites were enrolled into one of four treatment groups. Patients were randomized into chlorthalidone, amlodipine, lisinopril, and doxazosin treatment groups in a 1.7:1:1:1 ratio, respectively. Based on a

subsequent recommendation from the ALLHAT Data and Safety Monitoring Board (DSMB), the doxazosin scheme (9,067 patients) was discontinued. Reasons for this discontinuation have been detailed previously in the literature.[4] Systolic blood pressure (SBP) treatment goal was < 140 mmHg, and diastolic blood pressure (DBP) goal was < 90 mmHg. The primary outcomes of treatment included nonfatal myocardial infarction (MI) and cardiovascular death.

CONVINCE

The CONVINCE study enrolled 16,602 patients from centers around the world between September 1996 and December 1998. Subjects were randomized in a 1:1 ratio to receive extended-release verapamil or the investigator's choice of atenolol or hydrochlorothiazide. Like ALLHAT, the blood pressure treatment goal for the CONVINCE study was < 140 mmHg for SBP and < 90 mmHg for DBP. The primary outcomes of the CONVINCE study included fatal and nonfatal stroke, fatal and nonfatal MI, and other cardiovascular death. The planned follow-up of this trial, however, was terminated early.

INVEST

INVEST enrolled 22,599 patients with hypertension and coronary artery disease (CAD) from around the world between September 1997 and December 2000. This trial compares the effectiveness of verapamil SR versus atenolol, with or without trandolapril and/or hydrochlorothiazide. Subjects were enrolled into the two treatment arms in a 1:1 ratio. INVEST is the first large, randomized, clinical trial in hypertension to employ JNC VI guidelines as treatment goals. The SBP goal is < 140 mmHg and the DBP goal is < 90 mmHg for patients who do not have diabetes or renal disease, and the SBP goal is < 130 mmHg and the DBP goal is < 85 mmHg for patients who have diabetes and/or renal disease. Because INVEST uses the treatment goals outlined in the JNC VI guidelines and a special Internet electronic data capture and management system, the results of INVEST are likely to impact future guidelines and the way future trials are conducted. The primary outcomes of this trial are nonfatal MI, nonfatal stroke, or death.

Characterizing the Hypertensive Patient

The three large clinical trials—ALLHAT, CONVINCE, and INVEST—combined to enroll 81,649 subjects in North America, South America, Europe, and Australia-Asia. Table I contains highlights of the baseline demographic characteristics from the three studies, and Table II summarizes blood pressure treatment goals and treatment strategies from the three studies. Fifty percent of all patients enrolled in these trials were women. At baseline, the subject population included patients with many CAD risk factors. The mean age of all subjects was 66 years, and the mean body mass index (BMI) was 29.5. In addition, 30% of all patients had diabetes and 43% had documented CAD. In INVEST, 100% of enrolled patients had documented CAD, and 27% had diabetes. Of all the patients enrolled in the three trials, 38% were smokers, 25% had a history of MI or stroke, and 52% had a history of dyslipidemia. At baseline, only 22% of enrolled patients had controlled SBP and DBP (according to individual study-defined BP goals), even though 88% of patients were receiving treatment for hypertension at the time of enrollment.

JNC VI Treatment Guidelines

The JNC VI guidelines used evidence-based medicine and scientific consensus to report on contemporary approaches for the prevention and control of hypertension for use by primary care physicians.[5] The primary goals of JNC VI were to increase awareness of hypertension, to improve the treatment and control of hypertension, and to decrease the morbidity and mortality of stroke and CAD. Primary care physicians and cardiologists, who were not expert hypertensionologists, were the target audience of JNC VI. The JNC VI committee provided guidance regarding major risk factors, target organ damage, and clinical cardiovascular disease (CVD). The major risk factors are well known and include smoking, dyslipidemia, diabetes mellitus, and an age of > 60 years. Men and postmenopausal women are at risk, as are women who are < 65 years and men who are > 55 years who have family history of CVD.

TABLE I Comparison of baseline characteristics of the enrolled populations in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) trial, and the INternational VErapamil SR/trandolapril STudy (INVEST)

	ALLHAT (%)	CONVINCE (%)	INVEST (%)
Female	47	56	52
Black	36	7	14
Hispanic	19	7	37
Documented CAD	26	8	100
Diabetes	36	20	27
Mean age	67	66	66
Mean BMI	30	[a]	29
Prior smoking history	40	23	46
Dyslipidemia	[b]	31	53
Prior stroke	[c]	5	5
Prior MI	[c]	8	32

[a] Not reported.

[b] Reported mean total cholesterol = 5.6 mmol/l.

[c] Reported combined prior MI/stroke = 23%.

Abbreviations: CAD = coronary artery disease, BMI = body mass index, MI = myocardial infarction.

TABLE II Comparison of treatment goals and strategies associated with the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) trial, and the INternational VErapamil SR/trandolapril STudy (INVEST)

	ALLHAT	CONVINCE	INVEST
SBP goal (mmHg)	<140	<140	<140 or <130 for diabetes and renal dysfunction
DBP goal (mmHg)	<90	<90	<90 or <85 for diabetes and renal dysfunction
Treatment strategies	Step 1—double blind, randomized: Chlorthalidone (1.7) vs. amlodipine (1) vs. lisinopril (1) vs. doxazosin (1) Step 2—open label: Reserpine or clonidine or atenolol Step 3—open label: hydralazine	Step 1—double blind, randomized: Controlled onset extended release verapamil (Covera HS; Searle Pharmaceuticals) (1) vs. physician directed choice of hydrochlorothiazide (HCTZ) or atenolol (1) Step 2 and beyond—includes an increase in either dose or number of agents necessary to achieve BP control	Step 1—open label, randomized: Verapamil SR (Isoptin, Knoll AG/ Abbott Laboratories) (1) vs. atenolol (1) Both strategies also contain trandolapril and/or hydrochlorothiazide which may be prescribed at Step 1 as necessary based on patient characteristics Step 2 and beyond—includes an increase in either dose or number of study agents or the addition of nonstudy agents necessary to achieve BP control

Abbreviations: SBP = systolic blood pressure, DBP = diastolic blood pressure, BP = blood pressure.

Target Organ Damage

Target organ damage and clinical CVD include damage associated with left ventricular hypertrophy (LVH), angina pectoris, prior MI, prior revascularization, heart failure, renal disease, nephropathy, peripheral arterial disease, retinopathy, and any kind of vascular accident, stroke, or transient ischemic attack (TIA).

Risk Groups

The JNC VI guidelines divided all patients into one of three categories, labeled A, B, and C. Risk group "A" includes patients who have no major risk factors, no target organ damage, and no clinical evidence of CVD. Patients in risk group "B" must have evidence of at least one major cardiovascular risk factor, without evidence of diabetes, target organ damage, or clinical CVD. Risk group "C" includes patients who are at the highest risk for CVD-related morbidity or mortality. All patients in risk group "C" have target organ damage or clinical evidence of CVD; they may or may not have had diabetes, and they may or may not have additional risk factors.

Management Strategies

The JNC VI guidelines provided initial management strategies for patients according to risk group and blood pressure level (Table III). Because patients in risk group A were at minimal risk, only lifestyle modifications were indicated for

TABLE III Hypertension risk stratification and treatment

Blood pressure stages (mmHg)	Risk group A*	Risk group B†	Risk group C‡
High–normal (130–139/85–89)	Lifestyle modification	Lifestyle modification	Drug therapy‖
Stage 1 (140–159/90–99)	Lifestyle modification (up to 12 mo)	Lifestyle modification§ (up to 6 mo)	Drug therapy
Stages 2 and 3 (≥160/≥100)	Drug therapy	Drug therapy	Drug therapy

* Group A: No risk factors and no target organ disease/clinical cardiovascular disease.
† Group B: At least 1 risk factor not including diabetes and no target organ disease/clinical cardiovascular disease.
‡ Group C: Tagret organ disease/clinical cardiovascular disease and/or diabetes with or without other risk factors.
§ For patients with heart failure, renal insufficiency, or diabetes.
‖ For patients with multiple risk factors, clinicians should consider drugs as initial therapy plus lifestyle modifications.

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Reprinted from Ref. No. 5 with permission.

the group. However, patients in risk group C (maximum risk), who had a blood pressure of 130–139/85–89 mmHg, were advised drug therapy as an initial intervention in addition to lifestyle modification.

For blood pressure levels in the range of 140–159/90–99 mmHg, lifestyle modifications were advised in all three risk groups. In addition, drug therapy was indicated immediately for risk group C. Pharmacologic intervention was also recommended for risk group B, if target blood pressure levels were not achieved within 6 months, and in risk group A, if target blood pressure levels were not achieved within 12 months.

Immediate drug intervention was advised for all patients with a blood pressure level >160/100 mmHg, regardless of risk group.

Drug Choices

JNC VI also suggested some compelling initial drug choices for certain diseases (Table IV). These therapeutic choices were based on the consensus of randomized controlled trials. For heart failure, angiotensin-converting enzyme (ACE) inhibitors and diuretics were recommended as first-line therapy. For MI, beta blockers without intrinsic sympathomimetic activity (ISA) and ACE inhibitors were suggested, particularly in patients with systolic dysfunction. The ACE inhibitors were also recommended by JNC VI for patients with type 1 diabetes mellitus and proteinuria. In older patients with isolated systolic hypertension, diuretics were preferred, and long-acting dihydropyridines and calcium antagonists were also recommended for older patients with this condition.

The guidelines also suggest that if the initial drug choice does not help the patient achieve the target blood pressure of 140/90 mmHg, and the patient experienced no response or troublesome side effects, a drug from a different class should be substituted. If the target blood pressure was not reached but the drug was well tolerated, a second agent should be added. This drug should be a diuretic, if not already used. Treatment of hypertension often requires the use of two drugs, and sometimes three or four. Additional agents from other drug classes should be added as necessary to achieve target blood pressure. Also, referral to a hypertension specialist should be considered.

TABLE IV Initial drug choices for the treatment of hypertension

Uncomplicated hypertension
• Beta blockers
• Diuretics
Compelling indications
• Heart failure
ACE inhibitors
Diuretics
• Myocardial infarction
Beta blockers (nonintrinsic activity)
ACE inhibitors (with systolic dysfunction)
• Diabetes mellitus with proteinuria
ACE inhibitors
• Isolated systolic hypertension (older persons)
Diuretics preferred
Long-acting dihydropyridine calcium antagonists

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Reprinted from Ref. No. 5 with permission.
Abbreviation: ACE = angiotensin-converting enzyme.

Guidelines of the Second European Task Force

The European guidelines were assembled by the Second Joint Task Force of European and other Societies on Coronary Prevention, which was composed of the European Societies of Cardiology, Atherosclerosis, and Hypertension.[6] The purpose of the European guidelines was to reduce the risk of major coronary heart disease or other atherosclerotic disease events, thereby reducing premature disability and mortality and prolonging survival. Primary goals were similar to but not exactly the same as JNC VI. Like JNC VI, the European guidelines included lifestyle modification and a blood pressure level of <140/90 mmHg as primary goals. In addition, goals included a total cholesterol level of 5 mmol/l (193 mg/dl) and a low-density lipoprotein (LDL) level of 3 mmol/l (116 mg/dl). Cholesterol goals were not included in JNC VI, but may be included in JNC VII. The European goals were to be achieved by changes in lifestyle first, and then by addition of pharmacologic therapy if necessary.

Risk stratification in the European guidelines was based on comorbidities and target organ damage, and is very similar to but not exactly the same as the JNC VI guidelines. Like JNC VI, the European guidelines suggest treatment of elevated blood pressure based on the severity of hypertension and cardiac risk, and the degree of target organ damage.

Physician Practice Patterns

In August 2000, Hyman and Pavlik reported the results of a physician survey that was conducted to measure awareness of national hypertension management guidelines.[7] It was surprising that 41% of the physicians who returned the survey had not heard of or were not familiar with the JNC VI guidelines, and 43% reported that they would not treat SBP until it was >160 mmHg. For middle-aged patients with few risk factors, 33% of physicians would not start drug therapy unless the DBP was >95 mmHg, and 43% would not treat unless the SBP was >160 mmHg. Logistic regression showed that familiarity with the guidelines was associated with low treatment thresholds, and physicians familiar with research methods were more likely to use diuretics or beta blockers as first-line agents.

The European Action on Secondary and Primary Prevention through Interventions to Reduce Events (EUROASPIRE) II produced results similar to Hyman and Pavlik's survey. EUROASPIRE II was a survey performed among patients with CHD to assess the use of lifestyle and drug therapies in the management of major risk factors for recurrent CHD.[8]

Between September 1999 and February 2000, 5,500 patients from 15 countries were interviewed after hospitalization for bypass surgery, angioplasty, or new or recurrent MI.

Practice parameters determined that in EUROASPIRE II, 21% of patients were smokers. Forty-eight percent of patients had a BMI between 25 to 30, and BMI was >30 in 31% of patients. Fifty-one percent had an SBP >140 or a DBP >90; 49% of patients with a blood pressure level <140/90 were taking antihypertensive medication; 58% of patients had a total cholesterol level >5 mmol/l (193 mg/dl); and 51% of patients on lipid-lowering medications had a total cholesterol level <5 mmol/l (193 mg/dl). EUROASPIRE II determined that there is a high prevalence of unhealthy lifestyles and modifiable risk factors, and an inadequate use of prophylactic drug therapies found in the patients with CHD throughout Europe. The potential to raise the standards of preventative cardiology in Europe and to reduce coronary mortality and morbidity is considerable.

Blood Pressure Control

Regarding the control of blood pressure, the ALLHAT trial reported that, within 2 years, 61% of patients treated with chlorthalidone reached the target blood pressure of <140/90 mmHg, and 54% of patients treated with doxazosin reached that level. ALLHAT has not yet reported data for the other treatment groups.[4] In the 3-year follow-up report for the CONVINCE trial, 68% of patients reached the target SBP of <140 mmHg, and 91% reached a DBP of <90 mmHg.[3] In INVEST, of those patients treated for 12 months, 70% of nondiabetics achieved an SBP <140 mmHg, and 66% of patients with diabetes achieved that level. Diastolic blood pressure was <90 mmHg in 89% of nondiabetics and 90% of diabetics. Only 39% of patients with diabetes lowered SBP levels to the JNC VI goal of <130 mmHg, but 83% achieved a DBP of <85 mmHg (preliminary unpublished data, 2001).

A meta-analysis of 10 trials evaluated the response of blood pressure to first-line treatment with monotherapy of a beta blocker or a diuretic.[9] This analysis included over 11,000 patients. The response to therapy diuretics was 67%, but response to beta blockers was only 33%.

Lessons from Clinical Trials

Regarding the management of hypertension, many lessons have been gained from clinical trials. The Hypertension Optimal Treatment (HOT) study showed that a DBP level of 80 mmHg is associated with decreased cardiovascular events and mortality.[10] The Nordic Diltiazem (NORDIL) study demonstrated that calcium antagonists were as effective as diuretics and beta blockers in lowering blood pressure and reducing cardiovascular events and mortality.[11] In the SYSTolic hypertension in EURope (SYST-EUR) trial,[12] any decrease in SBP of 20 mmHg was associated with a 42% reduction in total stroke and a 26% reduction in cardiac events. This reduction even included patients in whom SBP was reduced from 170 mmHg to 150 mmHg. Therefore, there are benefits to lowered blood pressure, even when JNC VI target levels are not achieved.

We also know from clinical trials that multidrug therapy is required to achieve blood pressure control. In both CONVINCE[3] and INVEST (preliminary unpublished data, 2001), 75% of patients are taking more than one drug. It is possible in INVEST, using a structured protocol and titration guidelines, to control elevated blood pressure in a majority of the patients treated for 12 months. In Hispanics, blood pressure has been controlled very successfully as well.[13] It is unclear whether this is due to genetics or aggressiveness on the part of physicians caring for the Hispanic patients.

Need for Education

Cardiologists and primary care physicians have a responsibility to be educated about hypertension and coronary disease. In many instances, cardiologists are the primary care physicians for patients with coronary disease. Specialists do not see a large proportion of patients with hypertension and CHD; therefore, primary care physicians must be educated. As Hyman and Pavlik showed, 41% of primary care physicians have never even heard of JNC VI.[7] In addition, patients must be educated about lifestyle modifications and the significance of elevated blood pressure. Patients must know what it means to have high blood pressure and what they can do about it.

Conclusion

Physicians must speculate regarding why patients do not achieve target blood pressure goals. There are many reasons why a patient might not be successful at reaching target blood pressure levels. One reason might be baseline blood pressure levels. A patient who has a blood pressure of 190/110 mmHg might be more difficult to manage than a patient with a level of 150/95 mmHg. This seems true intuitively; however, it must be confirmed by the clinical data. Confirmation might be within INVEST's large database of information. Another reason might be BMI. However, in INVEST, some patients with a low BMI have hypertension. Other reasons blood pressure might be difficult to manage include diabetes, age, race, genetics, and the use of therapy at entry. INVEST is closely exploring the relationship between each of these factors and hypertension.

References

1. Pepine CJ, Handberg-Thurmond E, Marks RG, Conlon M, Cooper-DeHoff R, Volkers P, Zellig P: Rationale and design of the International Verapamil SR/Trandolapril Study (INVEST): An Internet-based randomized trial in coronary artery disease patients with hypertension. *J Am Coll Cardiol* 1998;32:1228–1237
2. Grimm RH Jr, Margolis KL, Papademetriou VV, Cushman WC, Ford CE, Bettencourt J, Alderman MH, Basile JN, Black HR, DeQuattro VV, Eckfeldt J, Hawkins CM, Perry HM Jr, Proschan M: Baseline characteristics of participants in the Antihypertensive

and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Hypertension* 2001;37:19–27

3. Black HR, Elliott WJ, Neaton JD, Grandits G, Grambsch P, Grimm RH Jr, Hansson L, Lacoucière Y, Muller J, Sleight P, Weber MA, White WB, Williams G, Wittes J, Zanchetti A, Fakouhi TD, Anders RJ: Baseline characteristics and early blood pressure control in the CONVINCE Trial. *Hypertension* 2001;37:12–18
4. ALLHAT Collaborative Research Group: Major cardiovascular events in hypertensive patients randomized to doxazosin vs. chlorthalidone: The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *J Am Med Assoc* 2000;283: 1967–1975.
5. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997;157:2413–2446
6. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and other Societies on coronary prevention. *Eur Heart J* 1998;19:1434–1503
7. Hyman DJ, Pavlik VN: Self-reported hypertension treatment practices among primary care physicians: Blood pressure thresholds, drug choices, and the role of guidelines and evidence-based medicine. *Arch Intern Med* 2000;160:2281–2286
8. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries: Principal results from EUROASPIRE II Euro Heart Survey Programme. *Eur Heart J* 2001;22:554–572
9. Messerli FH, Grossman E, Goldbourt U: Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. *J Am Med Assoc* 1998;279:1903–1907
10. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998;351:1755–1762
11. The Nordic Diltiazem Study (NORDIL): A prospective intervention trial of calcium antagonist therapy in hypertension. *Blood Press* 1993;2:312–321
12. Staessen JA, Thijs L, Birkenhager WH, Bulpitt CJ, Fagard R: Update on the systolic hypertension in Europe (Syst-Eur) trial. The Syst-Eur Investigators. *Hypertension* 1999;33:1476–1477
13. Cooper-DeHoff R, Handberg E, Bristol H, Kolb H, Gaxiola E, Cangiano J, Pepine C: Characteristics and blood pressure responses of 6,057 Hispanic hypertensive patients with coronary artery disease enrolled in the INVEST (abstr). *J Am Coll Cardiol* 2001; 37:216A

Clin. Cardiol. Vol. 24 (Suppl. V), V-30 (2001)

Questions and Answers Related to the INternational VErapamil SR/trandolapril STudy (INVEST)

What is INVEST?

The INternational VErapamil SR/trandolapril STudy (INVEST) is an ongoing international, multicenter, prospective, randomized, controlled clinical trial comparing a calcium-antagonist treatment strategy (verapamil SR) with a noncalcium-antagonist treatment strategy (atenolol) for the control of hypertension in a primary care patient population with coronary artery disease (CAD). In this study, 22,599 patients were enrolled between September 1997 and December 2000 by 862 investigators from around the world. The study is in the follow-up phase and should be completed in December of 2002. Further information regarding INVEST can be accessed via the Internet (http://invest.biostat.ufl.edu).

What are the treatment strategies used in INVEST?

The calcium-antagonist-based strategy uses verapamil SR at an initial dose of 240 mg/day. After 6 weeks, an angiotensin-converting enzyme (ACE) inhibitor (trandolapril) may be added at a dose of 1–8 mg/day. If blood pressure remains uncontrolled, a diuretic (hydrochlorothiazide) may also be added at a low dose (12.5–25 mg/day). Physicians may increase the dosage of the verapamil SR/trandolapril combination and the diuretic, as necessary, to control blood pressure. The calcium-antagonist strategy may use trandolapril at any time if required for a special population (diabetes, left ventricular dysfunction, renal insufficiency).

The noncalcium antagonist-based strategy does not contain a calcium antagonist. Hypertension management is initiated with a beta blocker (atenolol) at a dose of 50 mg/day. If blood pressure targets are not achieved, a diuretic (hydrochlorothiazide) may be added at a low dose (12.5–25 mg/day), then the ACE inhibitor (trandolapril) (1–8 mg/day) may be added. In both strategies, physicians are prompted to increase doses of the calcium antagonist, the beta blocker, the diuretic, and/or the ACE inhibitor as necessary to achieve target blood pressure values. Target blood pressures are $<140/<90$ mmHg in general, and $<130/<85$ mmHg for those special populations identified in the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI).

What are the objectives of the study?

The primary objective of this trial is to examine the hypothesis that hypertension treatment with a calcium antagonist-based treatment strategy is equivalent or superior to a noncalcium antagonist-based treatment strategy in terms of the risk for adverse outcomes in hypertensive patients with documented CAD. The primary adverse outcome is a composite of death, nonfatal myocardial infarction, or nonfatal stoke.

The secondary objectives are to determine that these hypertension care strategies are at least equivalent in the control of blood pressure and symptoms of myocardial ischemia, and in the number of major adverse experiences.

What is unique about INVEST's approach to data management?

INVEST uses a specially designed electronic communication and data management system on the Internet; therefore, the study does not require the use of paper. Web-based clinical trials offer many advantages for investigators, monitors, patients, and sponsors. The risks of error are minimized by providing on-screen protocol data entry and randomization information. Monitors, sponsors, and investigators have access to all data in real time, 24 h a day. The system is capable of controlling drug dispensing and modification of prescribed drug and dose. The start-up time of INVEST was minimized because of reduced training times, and no complex hardware or software installations were necessary.

Why is INVEST likely to affect future hypertension management guidelines?

INVEST is the first clinical trial to use the JNC VI guidelines as goals for therapy. The JNC VI guidelines set a blood pressure goal of $<140/90$ mmHg for patients who do not have diabetes or renal failure. For patients with preexisting diabetes or renal failure, the target blood pressure is $<130/85$ mmHg. With 22,599 patients enrolled in the trial, INVEST will reveal much new information regarding the attainability and benefits of the JNC VI guidelines. Furthermore, with this sample size, there are adequate numbers of diabetics, Hispanics, obese patients, and other special populations to draw meaningful conclusions.

Are there any preliminary data available on cardiovascular outcomes that have taken place in the enrolled population?

For the overall trial (both treatment groups), the blood pressure control rates appear excellent when compared with other completed clinical trials and clinical practice. Overall, the cardiac event rate in the study is approximately 2.5% per year among randomized patients. These data are preliminary, but the cardiac event rate is as expected when the study was designed.

Will the Web-based clinical design of INVEST eliminate the need for monitor visits in clinical trials?

Monitoring visits will continue to occur in clinical trials, but the process will likely change. Monitors will still be required to confirm that data in a patient's medical record agree with data entered in a database. In addition, monitors will be required to check informed consent forms and other documents. However, monitoring visits will be fewer in number and more efficient as a result of electronic data entry. Because monitors will have access to site data prior to the visit, they will be more efficient at the site in reviewing source documentation and complete the monitoring visit in an expedited manner.