Atherosclerosis Reviews

Edited by Rodolfo Paoletti and Antonio M. Gotto, Jr.

Volume 2

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Editors

Rodolfo Paoletti, M.D.
Director and Professor
Institute of Pharmacology and Pharmacognosy
University of Milan
Milan, Italy

Antonio M. Gotto, Jr., M.D., D.Phil.
Professor and Chairman
Department of Medicine
and
Scientific Director
National Heart and Blood Vessel Research and Demonstration Center
The Methodist Hospital
Baylor College of Medicine
Houston, Texas

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Contributors

N. Battistini
Neurological Clinic
University of Siena
Siena, Italy

Edwin L. Bierman
Division of Metabolism, Endocrinology, and Gerontology
Department of Medicine
University of Washington School of Medicine
Seattle, Washington 98195

Alberico Catapano
Center E. Grossi Paoletti for the Study of Metabolic Diseases and Hyperlipidemias
Department of Pharmacology and Pharmacognosy
University of Milan
Milan, Italy

M. D'Ettorre
Neurological Clinic
University of Siena
Siena, Italy

Harriet P. Dustan
Research Division
The Cleveland Clinic Foundation
Cleveland, Ohio 44106

T. C. Evans, Jr.
Cardiovascular Research Unit
Mayo Clinic
Rochester, Minnesota 55901

C. Fieschi
Neurological Clinic
University of Siena
Siena, Italy

Yuichiro Goto
Department of Medicine
Keio University School of Medicine
Tokyo, Japan

J. F. Greenleaf
Cardiovascular Research Unit
Mayo Clinic
Rochester, Minnesota 55901

Noboru Kimura
Kurume University School of Medicine
Kurume, Japan

B. A. Kottke
Cardiovascular Research Unit
Mayo Clinic
Rochester, Minnesota 55901

David Kritchevsky
The Wistar Institute of Anatomy and Biology
Philadelphia, Pennsylvania 19104

Henry C. McGill, Jr.
Department of Pathology
The University of Texas Health Science Center
San Antonio, Texas 78284
and
The Southwest Foundation for Research and Education
San Antonio, Texas 78284

Haruo Nakamura
Department of Medicine
Keio University School of Medicine
Tokyo, Japan

M. Nardini
Neurological Clinic
University of Siena
Siena, Italy

Genju Ooneda
Second Department of Pathology
School of Medicine
Gunma University
Maebashi, Japan

Rodolfo Paoletti
Center E. Grossi Paoletti for the Study of Metabolic Diseases and Hyperlipidemias
Department of Pharmacology and Pharmacognosy
University of Milan
Milan, Italy

Basil M. Rifkind
Lipid Metabolism Branch
Division of Heart and Vascular Disease
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland 20014

Russell Ross
Department of Pathology
University of Washington School of Medicine
Seattle, Washington 98195

G. Scollo-Lavizzari
Neurological Clinic
University of Basel
Basel, Switzerland

Takio Shimamoto
Japan Arteriosclerosis Research Institute;
Prof. Em. Tokyo Ika-Shika National University Medical School;
and
Prof. Tokai University Medical School
Tokyo, Japan

Cesare R. Sirtori
Center E. Grossi Paoletti for the Study of Metabolic Diseases and Hyperlipidemias
Department of Pharmacology and Pharmacognosy
University of Milan
Milan, Italy

F. Volante
Neurological Clinic
University of Siena
Siena, Italy

R. Wüthrich
Neurological Clinic
University of Basel
Basel, Switzerland

Yoji Yoshida
Second Department of Pathology
School of Medicine
Gunma University
Maebashi, Japan

E. Zanette
Neurological Clinic
University of Siena
Siena, Italy

Introduction

Antonio M. Gotto, Jr. and Michael E. DeBakey

Cardiovascular disease is the major health problem facing Western society today. Most cardiovascular disease is related to the arteries. Over the past 50 years there has been a considerable shift in emphasis in cardiovascular disease from infectious etiologies such as luetic and rheumatic heart disease to the variety caused by arteriosclerosis or atherosclerosis. Revolutionary changes have been achieved during the past century in cardiovascular surgery. What were hopeless cases of congenital heart disease a hundred years ago are now corrected daily in many medical centers. Reconstruction of major arteries has become commonplace. The coronary bypass operation, reviewed in *Volume 1* of *Atherosclerosis Reviews*, is the most commonly performed cardiovascular operation in the world today.

There is no way of innoculating an individual against the development of atherosclerosis and its complications, as can be done against communicable diseases. Nonetheless, in our society, with the recognition of significant coronary risk factors, implemented by widespread programs of public education, the responsibility for an individual's care and protection has become more and more a personal matter. Because many conflicting views are now being publicized in the popular press, in medical publications, and in the scientific literature, *Atherosclerosis Reviews* has undertaken the formidable task of providing up-to-date information to the practitioner on subjects relating to atherosclerosis. Some of the articles will be controversial; there will not be agreement about all of the questions addressed.

Recently, skepticism has been growing as to whether or not anything can be done to prevent atherosclerosis, particularly coronary artery disease death. Conflicting viewpoints abound. A seven-year secondary prevention trial with four drugs in the United States, the Coronary Drug Project, yielded negative results. In this study, there was no decrease in overall mortality in groups receiving nicotinic acid and clofibrate, as compared with those receiving the placebo. There was a decrease in the incidence of nonfatal myocardial infarctions from about 12% to 9% in the nicotinic acid group as compared with the control group. No such difference was observed with clofibrate. The lowering of cholesterol was not impressive with any of the drugs. Clofibrate reduced cholesterol by about 4% and triglycerides by 22%. The comparable values with nicotinic acid were approximately 9% and 22%. The numbers of the individuals in the groups were too small to have detected significant changes in cardiovascular mortality for the extent of cholesterol-lowering achieved and the extensiveness of the atherosclerosis present. Perhaps with a younger group of patients, with a more effective cholesterol-lowering drug and with attention to other risk factors, there might have been a more favorable

outcome. At the present time it cannot be stated that there is definitive scientific evidence to prove that normalization or treatment of risk factors will stop or reverse the progression of atherosclerosis. The benefits are presumed rather than proven.

At least three major and other secondary risk factors have been identified. The best established of the risk factors are hypercholesterolemia, hypertension and cigarette smoking. In addition, diabetes mellitus, stress, personality type, lack of exercise, and obesity may all contribute to what is, undoubtedly, a multifactorial disease. In the treatment of a risk factor, the age of a subject, the severity or extensiveness of atherosclerosis, the degree of abnormality, and the risk versus benefit of treatment must be carefully considered.

Although there is not a definitive experiment establishing the efficacy of risk factor intervention in man, a number of authoritative groups (including committees of the American Medical Association, the National Academy of Science of the United States, the American Heart Association, the Inter-Society Commission on Heart Disease, the Royal College of Physicians in the United Kingdom, and the British Cardiac Society) have nonetheless recommended that the general population follow a diet with a reduced intake of saturated fat and cholesterol. All groups caution against an excessive consumption of calories, and one group recommends a reduced intake of refined sugar.

The National Heart, Lung and Blood Institute (NHLBI) of the United States is currently sponsoring a number of multi-center trials, several of which deal with risk factors. One of these, the Lipid Research Clinics Program, involves a network of 12 clinics in the United States and Canada. This trial is concerned exclusively with reduction of hyperbetalipoproteinemia, i.e., with elevations of LDL-cholesterol, or the type II hyperlipoproteinemia phenotype. This is primarily a prevention trial in that participants are free of clinically overt coronary artery disease. All participants are given a diet to follow and are randomized in a double-blind trial with cholestyramine or a placebo. This trial is projected to last from five to seven years. Another trial sponsored by the NHLBI intervenes on hypertension, while a third will treat hypercholesterolemia, hypertension, and cigarette smoking. Still another trial involves the use of anti-platelet agents. It is hoped that the results from these studies will be conclusive enough to give some firm guidelines to the practicing physician as to the benefit of risk factor intervention.

The past decade has witnessed a tremendous increase in the use of coronary bypass surgery, a subject discussed in *Volume 1* of *Atherosclerosis Reviews*. The consensus at the present time is that many patients with severe angina pectoris have relief of symptoms and an improvement in the quality of life following the operation. The effects of the operation on mortality and survival are not known.

Heart transplantations are still being performed by Dr. Norman Shumway's group at Stanford University. The program of immunologic rejection remains

a major deterrent to the widespread application of transplantation in addition to the unavailability of adequate donors.

Development of an artificial heart requires further research and appears to be a number of years away. At present, the focus of activity is on various short-term cardiac assist devices. A joint project between the USSR and the United States is underway in this area.

A promising note is the report on coronary mortality rates for 1974, released by the National Center for Health Statistics in the United States. These data show an overall decrease of 13 to 37% (varying with age, sex, and race) in the death rate from coronary heart disease in the United States between 1968 and 1974 (Table 1). The reasons for the decline are uncertain and it is not possible

TABLE 1. *Percent change in heart attack death rates in the United States, 1968–1974 by age, sex, and race. Based on death rates per 100,000 population, 8th Revision, Codes 410–413*

	White		Non-white	
Age group	Male	Female	Male	Female
35–44	−20.6	−20.1	−30.7	−36.8
45–54	−13.3	−14.4	−15.7	−22.4
55–64	−14.6	−15.0	−17.9	−26.3
65–74	−14.4	−20.3	−25.7	−30.3

to pinpoint a single factor to credit it for the reduction. There may have been a greater attention to diet and to reduction of obesity, hypercholesterolemia, and hypertriglyceridemia. There has been a more effective detection and treatment of hypertension. Smoking is declining, particularly among males, but not in young females. Also, there has probably been an increase in the number of people on exercise programs. In terms of numbers, the reduction in coronary mortality rate between 1968 and 1974 means that approximately 67,000 fewer deaths occurred in the United States in 1974 than if the rate had remained constant. These results are very encouraging and it is hoped that this trend will continue.

Our belief is that much of the confusion about the etiology, diagnosis, treatment, and prevention of atherosclerosis is caused by the failure to recognize this disease complex which represents several different entities with various manifestations. More than 25 years of experience in observing patients with cardiovascular disease at The Methodist Hospital has led us to conclude that there are several clinical patterns of presentation of atherosclerosis. It is not possible at the present time to relate these patterns to any single risk factor or combination thereof. Hypertension is particularly important as a risk factor for the development of cerebrovascular disease, especially cerebral hemorrhage. A number of reports claim that certain of the lipoprotein phenotypes are associated with an increased likelihood of either coronary or periph-

eral arterial disease. Such studies await further confirmation. Patients with familial hypercholesterolemia often do have extensive atherosclerosis, but the pathological features of the lesions do not appear significantly different from lesions in other patients with atherosclerosis. The pathological lesions in "Familial Broad Beta Disease" (type III hyperlipoproteinemia phenotype) do, however, appear to have unique characteristics. An understanding of the patterns of atherosclerosis may be of importance in determining individual susceptibility to the disease. It is possible that the clinical patterns may influence the response to treatment with diet, drugs, or surgical intervention.

The Editors and International Advisory Board of *Atherosclerosis Reviews* are very pleased with the response to this new series and take pride in the quality and variety of the manuscripts prepared for Volume 2 by busy experts in the atherosclerosis field. Doctor Harriet P. Dustan, President Elect of the American Heart Association, has contributed an extremely helpful and clear-cut manuscript concerning the mechanisms, recognition, and control of hypertension. Doctor Henry McGill's paper on the pathogenesis of atherosclerosis is a very carefully written, comprehensive review of this controversial area. Doctor Basil Rifkind, Director of the Lipid Research Clinic Program of the National Heart, Lung and Blood Institute, presents an authoritative review of the current status of clinical trials supported by that Institute that affect reduction of plasma lipids. Doctors Bierman and Ross, in writing about aging and atherosclerosis, highlight their theory of the pathogenesis of atherosclerosis which is currently gaining widespread attention. The chapter by Professors Sirtori, Catapano, and Paoletti will be useful to the clinician in providing information about the current drugs available for lowering plasma lipids and for treating atherosclerosis. Doctors Fieschi, Battistini, Nardini, D'Ettorre, Volante, and Zanette have contributed an interesting and practical approach to the clinical management of cerebrovascular disease. Doctors Scollo-Lavizzari and Wüthrich have prepared an appendix to this chapter describing computerized axial tomography, a technique that is revolutionizing the diagnosis of neurological disease. Doctor David Kritchevsky has contributed a concise, informative article on dietary fiber, a subject that is written about exhaustively in the lay press. Doctors Greenleaf, Kottke, and Evans discuss advances in the important area of early diagnosis and detection of atherosclerosis; they describe scientific bases for such approaches.

Professor Goto of Keio University in Tokyo has put together a chapter by four groups of collaborators to illustrate studies of atherosclerosis in Japan. The section written by Doctors Goto and Nakamura presents an overview of the research currently underway in Japan that deals with lipid metabolism and atherosclerosis. Professor Kimura of Kurume University School of Medicine has provided an excellent paper on epidemiological studies of atherosclerotic disease in Japan. The frequent occurrence of hypertension and death from cerebrovascular accidents in Japan has fascinated epidemiologists for many years. Professor Kimura gives particular attention to the Japanese farm and

the fishing village in the pathogenesis of hypertension; he points out the potential protection against ischemic heart disease provided by low serum cholesterol values and calls attention to the possibility that protein malnutrition may be a contributing factor in addition to hypertension to the high frequency of cerebrovascular disease. The chapter by Professors Ooneda and Yoshida describes pathological studies of atherosclerosis in Japan. It is the thesis of these investigators that hypertensive intracerebral hemorrhage is caused by necrosis of small arteries rather than by the usual forms of atherosclerosis. Finally, Dr. Shimamoto has written a section on "Prevention and Enhancement of Regression of Human Atherosclerosis by Modifying Local Factors." The contraction of endothelial cells is postulated to regulate the flux of substances into the arterial wall. Shimamoto proposes that in the development of the arterial lesion there is a decrease in the concentration of cyclic AMP and that one approach to reversing atherosclerosis would be to increase the arterial concentration of this substance. He suggests this as a rationale for various drugs which are then tested. The drug about which the greatest amount of information is available is pyridinolcarbamate. The more recently developed drug phthalazinol is also discussed. Professor Shimamoto refers to unpublished studies by Terry et al. on femoral atherosclerosis and by Mishima et al. on ischemic ulcers which, to the best of our knowledge, represent the first double-blind evaluations of pyridinolcarbamate. (We acknowledge with thanks these authors making their manuscripts available to us prior to publication.) There are other studies that have not reported positive results with pyridinolcarbamate. Professor Shimamoto and his colleagues conclude that further study and carefully controlled clinical trials are needed with both drugs in order to establish efficacy with hard scientific evidence.

We believe that the articles contained in this volume will be of interest both to the practicing physician and to workers in the field of atherosclerosis. It may stimulate new thinking and further discussion of what are often very controversial areas.

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Vascular Diseases of Hypertension: Mechanisms, Recognition, and Control

Harriet P. Dustan

Research Division, The Cleveland Clinic Foundation, Cleveland, Ohio 44106

Over the last 25 years hypertension has progressively come to be recognized as a major public health problem. It affects 10–15% of the adult American population, and because of its associated vascular diseases it causes premature death and disability. These vascular diseases are of two main types: arteriolar and arterial. Arteriolar disease can result in hypertensive encephalopathy, retinal disease and blindness, cardiac failure, and renal failure. The arterial disease is atherosclerosis. It causes myocardial infarction, cerebral thrombosis, and intermittent claudication. Hypertension is important to diagnose and control because reducing the pressure to normal or near normal eliminates the arteriolar complications and may in the long run be similarly beneficial against atherosclerotic complications.

The purpose of this discussion is twofold: to present the current guidelines for evaluating and treating hypertension from the point of view that it is a cardiovascular disease of varied etiology that can best be understood and treated through application of basic principles of cardiovascular physiology and pharmacology (1) and to present the evidence linking hypertension with atherosclerosis and its complications.

EVALUATION AND THERAPY OF HYPERTENSION

Evaluation

The purposes of this exercise are to determine: (a) the severity of the arteriolar and arterial disease that results from high intra-arterial pressure; and (b) whether there is a definable cause for hypertension.

The *medical interview* should obviously include questions directed toward both purposes. In regard to severity of arteriolar disease these relate to cerebral, retinal, cardiac, and renal manifestations; and in regard to arterial disease, to symptoms of atherosclerosis. The search for causes includes questions directed toward age of onset of hypertension, family history of

hypertension, and symptoms of renal and adrenal diseases. Results of the medical interview help determine the need for specific studies. For example, knowing the age of onset of hypertension immediately suggests certain types of hypertension (Table 1). A little child is almost certain to have a definable cause for hypertension, as is a patient who becomes hypertensive after age 50, while in a 40-year-old the most likely diagnosis is essential hypertension. A positive family history of hypertension supports the diagnosis of essential hypertension in a middle-aged patient but does not establish it because an inherited inability to regulate pressure within the normal range may predispose to development of hypertension from known causes. Finally, in regard to history-taking, it cannot be overemphasized that practically all patients with pheochromocytoma have characteristic symptoms; because of this, routine measurement of urinary catecholamine metabolites has long since been abandoned.

Because gross signs are not the rule in hypertensive patients (except, of course, for the abnormal arterial pressure level), the importance of the *physical examination* has unfortunately been underemphasized. However, this examination provides information concerning the extent of vascular disease, the presence of known causes of hypertension, and an opportunity to assess the direct physiologic determinants of the elevated pressure (Table 2)—whether the hypertension results from high cardiac output with inadequate adjustment of peripheral resistance, a mixture of high flow and high resistance, high resistance alone, or increased impedance. With few exceptions the physical examination gives no information on the indirect determinants of arterial pressure (Table 2), which are neural activity, extracellular fluid volume, the renal pressor system, and electrolyte-active steroids.

The funduscopic examination provides reasonably reliable information about the arterioles generally. This gives indications of the severity of arteriolar disease as well as the degree of vasoconstriction, i.e., peripheral resistance. For example, retinal hemorrhages and exudates, with or without papilledema, tell of a serious vascular disease that requires prompt treatment; severe vasoconstriction suggests a high-resistance hypertension; arteriolar tortuosity without vasoconstriction indicates a high-output type; marked arteriovenous crossing defects tell of severity and long duration of hypertension.

Examination of the heart provides answers to two questions: Has the heart suffered from sustained high pressure? Is a hyperdynamic heart "contributing" to the hypertension? Obviously if heart failure is present, hypertensive heart disease is severe. However, long before that one can tell much about the heart by its size, whether apex impulse is sustained, and by the presence of S_4. When the heart is enlarged, the impulse is sustained and S_4 is heard, and cardiac output is usually either normal or decreased. In contrast, a normal-sized heart with a quick, "tapping" apex impulse, with or without S_4, usually indicates a hyperdynamic circulation and increased cardiac output. Murmurs are not characteristic of particular types of hypertension, except of course for the late systolic parasternal murmur of coarctation. However, as a result of

TABLE 1. *Diagnostic possibilities for hypertension according to age of onset*

Age of onset[a]	Diagnostic possibility
Up to 10 yrs	Likely
	Renal arterial stenosis, nonatherosclerotic
	Renal parenchymal disease
	Aortic coarctation
	Adrenogenital syndrome
	Adrenal enzyme defects
	Possible
	Pheochromocytoma
	Primary aldosteronism
	Unlikely
	Essential hypertension
	Hyperdynamic circulation
10–20 years	Likely
	Renal arterial stenosis, nonatherosclerotic
	Renal parenchymal disease
	Aortic coarctation
	Adrenal enzyme defects
	Possible
	Pheochromocytoma
	Primary aldosteronism
	Essential hypertension
	Hyperdynamic circulation
	Unlikely
	Aortic coarctation
20–35 years	Likely
	Renal arterial stenosis, nonatherosclerotic
	Renal parenchymal disease
	Hyperdynamic circulation
	Contraceptive drugs
	Possible
	Primary aldosteronism
	Pheochromocytoma
	Essential hypertension
35–50 years	Likely
	Essential hypertension
	Possible
	Renal arterial stenosis, atherosclerotic and nonatherosclerotic
	Pheochromocytoma
	Primary aldosteronism
	Hyperdynamic circulation
	Estrogen therapy
	Unlikely
	Renal parenchymal disease
Over 50 years	Likely
	Renal arterial stenosis, atherosclerotic
	Possible
	Pheochromocytoma
	Primary aldosteronism
	Essential hypertension
	Estrogen therapy
	Unlikely
	Renal parenchymal disease
	Hyperdynamic circulation

[a]This is not to be confused with age of detection; it relates only to the age at which hypertension develops.

TABLE 2. *Physiologic determinants of arterial pressure, normal and elevated*

Direct	Cardiac output
	Vascular resistance
	Aortic impedance
	Diastolic arterial volume
Indirect	Neural activity
	Extracellular fluid volume
	Renal pressor system
	Adrenal steroids

hypertension, two murmurs occur: an aortic diastolic murmur caused by a dilated aortic ring which sometimes accompanies long-standing severe hypertension, and a rough, late systolic murmur signifying papillary muscle dysfunction as a reflection of coronary atherosclerosis.

Examination for peripheral pulse disparities allows diagnosis not only of atherosclerosis but also of aortic coarctation. Coarctation is the only type of hypertension that can be surely diagnosed by physical examination, and the diagnosis should never be missed.

Bruits should be listened for over all peripheral arteries as indicators of atherosclerosis and in the abdomen as a sign of renal arterial stenosis. In addition to listening for bruits of renovascular hypertension, the abdomen should be examined for enlarged polycystic kidneys, and the costolumbar angles for the tenderness sometimes produced by pyelonephritis.

Finally, a word should be said about measuring both supine and standing arterial pressure because the nervous system maintains pressure in response to orthostasis, and determining standing pressure provides an indication of deficient or excessive neural control. Normally mean pressure (diastolic + one-third the pulse pressure) changes ± 10 mm Hg; mild orthostatic hypotension (asymptomatic) is not uncommon in severe hypertension and pheochromocytoma, while orthostatic hypertension is often found in mild or moderately severe hypertension (2). It is in these latter patients that catecholamine levels are also modestly elevated (3).

The *basic laboratory examination* of hypertensives is simple and relatively inexpensive (4). It is directed toward determining the extent of vascular disease and identifying known causes. It includes a measure of renal excretory function (BUN or serum creatinine, urinalysis) to indicate renal parenchymal disease; serum potassium concentration as an indicator of hyperaldosteronism; a chest x-ray; and an electrocardiogram. Serum uric acid, blood glucose, and serum cholesterol concentrations have also been recommended, not as indicators of extent of vascular disease or any of the known causes of hypertension but because they are often either slightly elevated in hypertensive patients or adversely influenced by treatment.

Special, detailed examinations for known causes of hypertension are indi-

cated in patients with hypokalemia, evidence of renal parenchymal disease or arterial stenosis, and symptoms suggestive of pheochromocytoma, as well as in those whose hypertension begins before age 30 or after age 50 years.

Do these guidelines ensure that all patients with definable causes of hypertension are identified? The answer is obviously no, but most are; and for those very few who are not, subsequent responses to treatment and continued medical care allow proper diagnosis.

Treatment

The goals of therapy, whether medical or surgical, are: (a) to reduce arterial pressure to normal or as near normal levels as possible; (b) to stop the advance of arteriolar disease; and (c) to slow the progression of atherosclerosis. Antihypertensive drugs can be classified into three groups: diuretics, sympatholytics, and vasodilators (Table 3). This wide variety speaks to the multifactorial nature of hypertension and is particularly impressive when viewed in relation to the direct and indirect determinants of pressure as listed in Table 2. The goal, of course, is to use the drug that best vitiates the mechanism(s) operating in each patient; i.e., treatment should be rational. However, most treatment is still empirical because it is rarely possible to determine precise mechanisms in each patient and because we have failed to apply broadly to therapeutics what we have learned concerning the pathophysiology of various types of hypertension. In the following sections the empirical and rational uses of antihypertensive drugs are presented; the discussion of rational therapy is based on the principles of cardiovascular physiology and pharmacology.

TABLE 3. *Classification of antihypertensive drugs*

Type of drug	Examples
Diuretics	
Chloruretic thiazides	Chlorothiazide, hydrochlorothiazide
Potent types	Furosemide, ethacrynic acid
Potassium-sparing agents	Triamterene, spironolactone
Other	Chlorthalidone, quinethazone, metalozone
Sympatholytics	
Predominant central action	Clonidine
Peripheral action	Guanethidine, ganglioplegics
Central and peripheral action	Reserpine, methyldopa
Receptor blockers	Phentolamine, phenoxybenzamine, (? prazosin), propranolol
Vasodilators	
Predominant arteriolar action	Diazoxide, hydralazine, minoxidil,[a] guancydine[a]
Arteriolar *and* venous action	Nitroprusside, nitroglycerin

[a]Investigational drugs.