

AJC Editor's Consensus: Psoriasis and Coronary Artery Disease

Vincent E. Friedewald, MD^{a,*}, Jennifer C. Cather, MD^b, Joel M. Gelfand, MD, MSCE^c,
Kenneth B. Gordon, MD^d, Gary H. Gibbons, MD^e, Scott M. Grundy, MD, PhD^f,
Michael T. Jarratt, MD^g, James G. Krueger, MD^h, Paul M. Ridker, MDⁱ, Neil Stone, MD^j, and
William C. Roberts, MD^k

Acknowledgment

This CME activity is supported by an educational grant from Amgen, Thousand Oaks, California.

Disclosure

Dr. Friedewald has received honoraria for speaking from Novartis, East Hanover, New Jersey. Dr. Cather has received honoraria for speaking, consulting, and board membership from Amgen; Abbott Laboratories, Abbott Park, Illinois; Astellas, Tokyo, Japan; and Genentech, South San Francisco, California. Dr. Gelfand has received consulting fees from Amgen; Genentech; Pfizer, New York, New York; Celgene, Summit, New Jersey; and Centocor, Horscham, Pennsylvania. Dr. Gelfand is a grants investigator for Amgen, Centocor, and Pfizer. Dr. Gordon has received honoraria for consulting and research grants from Abbott and Centocor and honoraria for consulting from Amgen. Dr. Gibbons has received honoraria for speaking from Merck, Whitehouse Station, New Jersey; and Novartis. Dr. Grundy is a consultant for Merck; Merck/Schering-Plough, Kenilworth, New Jersey; Kos, Abbott Park, Illinois; Pfizer; Eli

Lilly, Indianapolis, Indiana; GlaxoSmithKline, Research Triangle Park, North Carolina; Abbott Laboratories; Fournier, Chenôve, France; Bristol-Myers Squibb, Plainsboro, New Jersey; Sankyo, Santa Clara, California; AstraZeneca, Wilmington, Delaware; and Sanofi-Aventis, Bridgewater, New Jersey. Dr. Grundy is a research grants investigator for Merck, Abbott, and Kos. Dr. Jarratt is a research grants investigator for Abbott, Amgen, and Genentech. Dr. Krueger has no relevant financial relationships to disclose. Dr. Ridker has received investigator-initiated research grants from the National Heart, Lung, and Blood Institute, Bethesda, Maryland; the National Cancer Institute, Bethesda, Maryland; AstraZeneca; Novartis; Merck; Sanofi-Aventis; the Donald W. Reynolds Foundation, Las Vegas, Nevada; and the Leducq Foundation, Paris, France. Dr. Ridker is a consultant for AstraZeneca; Merck/Schering-Plough; Dade Behring, Deerfield, Illinois; and Isis Pharmaceuticals, Carlsbad, California. Dr. Ridker is listed as a co-inventor on patents held by the Brigham and Women's Hospital, Boston, Massachusetts, that relate to the use of inflammatory biomarkers in the detection and treatment of cardiovascular disease. Dr. Stone is a consultant for Abbott; Merck; Schering-Plough; and Unilever, Rotterdam, The Netherlands (donated to American Heart Association). Dr. Stone has received honoraria for educational activities from Abbott, Merck, Pfizer, and Unilever. Dr. Roberts has received honoraria for speaking from Merck/Schering-Plough, AstraZeneca, and Novartis.

^aAssistant Editor, *The American Journal of Cardiology*, Clinical Professor, Department of Internal Medicine, The University of Texas Medical School at Houston, Houston, Texas, and Research Professor, University of Notre Dame, Notre Dame, Indiana; ^bCo-Director, Graft vs. Host Clinic, and Co-Director, Cutaneous Lymphoma Clinic, Baylor University Medical Center, and Medical Director, Modern Dermatology, Dallas, Texas; ^cMedical Director, Clinical Studies Unit, Assistant Professor of Dermatology, and Associate Scholar, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; ^dAssociate Professor of Dermatology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois; ^eDirector, Cardiovascular Research Institute, and Professor of Medicine, Morehouse School of Medicine, Atlanta, Georgia; ^fProfessor of Medicine and Distinguished Chair in Human Nutrition, The University of Texas Southwestern Medical Center, Dallas, Texas; ^gClinical Associate Professor of Dermatology, Baylor College of Medicine, Houston, Texas, and Principal Investigator, DermResearch, Austin, Texas; ^hD. Martin Carter Professor in Clinical Investigation, The Rockefeller University, New York, New York; ⁱEugene Braunwald Professor of Medicine, Harvard Medical School, and Director, Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, Boston, Massachusetts; ^jProfessor of Clinical Medicine, Feinberg School of Medicine, Northwestern University, and Medical Director, Center for Vascular Disease, Bluhm Cardiovascular Institute, Northwestern Memorial Hospital, Chicago, Illinois; and ^kEditor-in-Chief, *The American Journal of Cardiology* and *Baylor University Medical Center Proceedings*, Dean, A. Webb Roberts Center for Continuing Medical Education of Baylor Health Care System, and Executive Director, Baylor Heart and Vascular Institute of Baylor University Medical Center, Dallas, Texas.

*Corresponding author: Tel: 512-264-1611; fax: 512-264-7034.

E-mail address: vfriedew@nd.edu (V.E. Friedewald).

Objectives

Upon reading this activity, the reader should be able to:

1. Inform patients with moderate to severe psoriasis that they may be at increased risk for coronary artery disease (CAD) and other forms of atherosclerotic cardiovascular (CV) disease.
2. Assess patients with moderate to severe psoriasis for their risk factors for CAD.
3. Prescribe appropriate lifestyle and pharmacologic therapies for patients with psoriasis who are at increased risk for CAD.
4. Consult in the diagnosis and management of coronary risk factor modification when a dermatologist or other health care provider with primary responsibility for psoriasis treatment cannot assume this responsibility.

Needs Assessment

The need for this activity for cardiologists and other health care specialists in CV medicine is based on the following premises:

1. Psoriasis is a common disease involving >125 million patients worldwide and 7 million patients in the United States.
2. Patients with moderate to severe psoriasis have an increased prevalence of CAD and an increased risk for myocardial infarction.
3. Patients with psoriasis have an increased prevalence of risk factors for CAD.
4. Physicians and patients with psoriasis are generally unaware of the link between psoriasis and CAD.

Target Audience: This activity is designed for cardiologists and all other health care specialists caring for patients with CAD and for dermatologists, primary care physicians, and all other health care professionals caring for patients with psoriasis.

CME Credit: The A. Webb Roberts Center for Continuing Medical Education of Baylor Health Care System, Dallas, designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit*.™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

The A. Webb Roberts Center for Continuing Medical Education of Baylor Health Care System, Dallas, Texas, is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Privacy Policy: A. Webb Roberts Center for CME of Baylor Health Care System observes privacy and confidentiality of CME information and personal information of CME participants. Third parties receive only aggregated data about CME activities that are relevant to their interests and/or the activities they support.

CME Instructions: After reading this article, go online at www.AJConline.org to register, complete a post-test with a minimum score of 80%, complete an evaluation, and print a certificate.

Combination of Media: Print and Internet
 Computer Requirements: Windows 2000, Pentium 3 or greater, 512 ram, 80 gigabytes storage
 Estimated Time to Complete: 1 hour
 Release Date: December 2008
 Termination Date: December 2009

Overview of Psoriasis

Psoriasis is a common disease, affecting an estimated 125 million patients worldwide (2% to 3% of the global population).¹ In the United States, about 7.5 million patients have psoriasis, including about 2.5% of European Americans and 1.3% of African Americans. Psoriasis is common in certain ethnic groups, affecting 12% of individuals in Arctic Kasach'ye,² and is uncommon in other populations (e.g., only 0.3% of individuals in China³). Psoriasis may begin at any age and has 2 peak periods of onset: (1) at 15 to 25 years of age and (2) at 50 to 60 years of age. Psoriasis causes significant disability in many individuals, especially women and young patients.⁴ About 80% of patients with psoriasis report that the disease has a negative impact on

their lives for a variety of reasons, including physical symptoms, embarrassing physical appearance (particularly because it begins at <30 years of age in 60% of cases), helplessness, frustration, anger, anxiety, depression, and increased use of alcohol.⁵

The cause of psoriasis is unknown, and its pathogenesis is not fully understood.⁶ Psoriasis has a complex genetic predisposition with a complex inheritance pattern,² plus an environmental component.⁷ Recent studies implicate smoking and obesity as modifiable risk factors for psoriasis. *Psoriasis vulgaris* is the most common form of psoriasis (90% of cases), manifested by papulosquamous plaques that are well delineated from normal skin. The main histologic features of the psoriatic plaque are epidermal hyperplasia, dilated dermal vasculature, and dermal inflammation with leukocyte infiltration.³ The dermal plaques tend to be symmetrical and are most often located on extensor surfaces of elbows and knees, the scalp, lumbosacral spine, and umbilicus. New lesions sometimes appear at sites of trauma or pressure, termed the *Koebner phenomenon*. Psoriatic arthritis occurs in up to 25% of patients and precedes skin manifestations in 10% of cases. Psoriasis is associated with several other disorders, including Crohn's disease, diabetes mellitus, the metabolic syndrome, cancer, and CAD.⁸⁻¹⁰

The pathophysiology of psoriasis is incompletely understood but appears primarily due to a cell-mediated adaptive immune response involving cytokines of Th1 and Th17 pathway.^{3,11,12} The leukocyte infiltrate in psoriatic skin lesions contains mainly T cells positive for clusters of CD-4 and CD-8.

Psoriasis treatment is based on 4 broad therapeutic categories, dictated mainly by disease severity¹³:

1. *Topical agents* are the first-line therapy for most patients. Agents are applied once or twice daily and require significant effort in many patients. The agents include emollients, corticosteroids, vitamin A analogues, vitamin D analogues, calcineurin inhibitors, coal tar, and dithranol.
2. *Phototherapy* and *photochemotherapy* are usually limited to patients with moderate and severe psoriasis, not mild forms, and include broadband ultraviolet B light, narrowband ultraviolet B light, psoralens and ultraviolet A radiation (topical and systemic), and lasers.
3. *Systemic drugs* are generally used for more severe forms of psoriasis and are less often prescribed since the advent of biologic agents. They include methotrexate (MTX), cyclosporine, and acitretin.
4. *Systemic biologics* are recombinant molecules designed to target specific steps in immune pathways involved in the pathogenesis of psoriasis. Many agents in this class are under investigation. Biologic drugs currently approved in the United States for the treatment of psoriasis include T-cell inhibitors (alefacept [Amevive; Astellas Pharma US, Inc., Deerfield, Illinois] and efalizumab [Raptiva; Genentech, Inc., South San Francisco, California]) and tumor necrosis factor (TNF)- α inhibitors (etanercept [Enbrel; Immunex Corporation, Thousand Oaks, California], infliximab [Remicade; Centocor Pharmaceuticals, Hor-

sham, Pennsylvania], and adalimumab [Humira; Abbott Laboratories, Abbott Park, Illinois]).

4. The underdiagnosis and undertreatment of CAD risk factors because of attention required to treat psoriasis, and
5. Shared genetics of psoriasis and CAD.

Association of Psoriasis With Coronary Artery Disease

Evidence: A possible association between psoriasis and atherosclerotic CAD was first suggested in 1961.¹⁴ Many subsequent observational studies detected an increased prevalence of CAD and its risk factors in patients with psoriasis, but these studies were inconclusive in establishing a connection between the diseases because most of these studies involved only hospitalized patients and generally did not control for confounding factors.^{15–23}

The largest study of nonhospitalized patients with psoriasis and CAD to date, by Gelfand et al,²⁴ used the General Practice Research Database (GPRD) in Great Britain. The objective of the GPRD study was “to determine if within a population-based cohort psoriasis is an independent risk factor for myocardial infarction.” The study population involved 130,976 patients with psoriasis, of whom 3,827 (2.9%) had severe psoriasis, mostly treated with MTX. There were 556,995 control patients. The mean follow-up period was 5.4 years. The GPRD study found an increased incidence of acute myocardial infarction (AMI) in patients with psoriasis compared with the control patient population, and the AMI rate was highest in patients with severe psoriasis. The *relative* risk for AMI was highest in younger patients, and the increased relative risk, but not *absolute* risk, lessened with age. The study investigators concluded that the “results suggest that psoriasis is an independent risk factor for AMI.”

An analysis of 2 large health plan databases in the United States further confirmed the findings of earlier studies that the prevalence of CV disease and risk factors in the overall psoriasis population is increased, even in patients with mild psoriasis.²⁵ Another study of the GPRD, separate from Gelfand et al’s²⁴ GPRD study, also found an increased *cumulative* incidence of CV risk factors, AMI, and other vascular diseases in patients with psoriasis.²⁶

A study of 32 patients with psoriasis found a prevalence of coronary artery calcium of 59%, compared with 28% in control patients ($p = 0.015$), and an Agatston coronary artery calcium score of 3.7 in patients with psoriasis, compared with 0 in control subjects ($p = 0.019$).²⁷ CAD also was more severe in patients with psoriasis than in controls. The investigators concluded that psoriasis was “likely” an independent risk factor for coronary artery calcium on the basis of multiple linear regression calculations in the study population, which had been controlled for CV risk factors.

Possible mechanisms responsible for the association of psoriasis with CAD include²⁸

1. Sharing and possibly increased prevalence of common CAD risk factors,
2. Antipsoriatic medications (cyclosporine, acitretin) increasing CV risk through the promotion of adverse CAD risk profiles (e.g., elevation of blood pressure and adverse effects on serum levels of lipids and lipid subfractions),
3. Inflammation,

Cardiovascular Risk Factors and Psoriasis

Patients with severe psoriasis have a 3- to 4-year average decrease in their life expectancy, comparable with the estimated reduction in the longevity of patients with severe hypertension.²⁹ This shortened lifespan is likely due in part to increased prevalence of CAD, which is the most common cause of death in patients with psoriasis. Conditions that are known contributors to CAD—dyslipidemia, obesity, hypertension, and diabetes mellitus—are more prevalent in patients with psoriasis than in the general population and patients with other dermatologic disorders.^{18,28,30–34}

Obesity: Obesity is common in patients with psoriasis, occurring up to 2 times more often than in the general population.^{18,35} Obesity is a component of the metabolic syndrome, which also is common in patients with psoriasis,^{36–39} and is closely related to chronic inflammation.^{30,40,41} The metabolic syndrome is a strong contributor to other CAD risk factors, including type 2 diabetes mellitus, abnormal serum lipids, and systemic arterial hypertension.^{42–46} However, unlike the *decreased* prevalence of obesity typically found in populations of patients with other severe forms of chronic inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease, the prevalence of obesity in patients with psoriasis *increases* with disease severity.^{47,48} In Gelfand et al’s GPRD study, the adjusted odds ratio (OR) for obesity was increased in patients with psoriasis compared with controls (OR 1.79, 95% confidence interval [CI] 1.55 to 2.05) and in patients with severe psoriasis compared with mild psoriasis (OR 1.47, 95% CI 1.32 to 1.63).³³

Cigarette smoking: In Gelfand et al’s GPRD study, cigarette smoking was more common in patients with psoriasis than in the general population (OR 1.31, 95% CI 1.3 to 2.01).³³ Approximately 80% of patients with psoriasis had smoked cigarettes *before* the onset of psoriasis.³⁵ Cigarette smoking, which increases markers of inflammation,⁴⁹ also may trigger psoriasis and contribute to its severity.^{30,50}

Serum lipids: Elevated low-density lipoprotein (LDL) cholesterol is common in patients with psoriasis, and the degree of elevation generally correlates with the severity of psoriasis.³² High-density lipoprotein (HDL) cholesterol, which is negatively correlated with CAD, tends to be lower in patients with psoriasis. Low HDL cholesterol is the only detectable lipid abnormality in some patients with mild psoriasis.³¹ Other proatherogenic lipid abnormalities also may be present, including elevated levels of serum triglycerides, very low density lipoprotein cholesterol, lipoprotein(a), and apolipoprotein B.⁵² Lipid abnormalities often can be detected at the onset of psoriasis, suggesting that they may be genetically acquired.^{32,51} Increased lipid oxidant stress and decreased antioxidant capacity are associated with psoriasis.⁵²

Hypertension: Hypertension is 2 times more common in patients with psoriasis than in the general population.^{18,19} In Gelfand et al's²⁴ GPRD study, hypertension was present in 20% of patients with severe psoriasis, 15% of patients with mild psoriasis, and 12% of controls.

Age: The *relative* increased incidence of CAD in younger patients with psoriasis decreases with age, but there is an *absolute* increased age-related CAD incidence,²⁴ consistent with the fact that advancing age is the strongest risk factor for CAD. The pattern of age-related CV risk in the population with psoriasis suggests accelerated CV risk in younger patients.

Family history of premature CAD: There are no reports on the frequency of family history of premature CAD in patients with psoriasis.

Diabetes mellitus and insulin resistance: Gelfand et al's²⁴ GPRD study found a strong association between diabetes mellitus (independent of obesity) and severe psoriasis, consistent with other reports.^{51,53,54} Patients with psoriasis without overt diabetes mellitus often exhibit evidence of insulin resistance.⁵⁵

Plasma homocysteine: Epidemiologic studies suggest a connection between atherosclerosis and elevated plasma levels of homocysteine in patients with psoriasis.^{56–59} Whether hyperhomocysteinemia is an independent risk factor for atherosclerosis, however, is unproved.⁶⁰

Physical inactivity: There are no reports on the effect of exercise or sedentary lifestyles on the prevalence of CAD or its risk factors in patients with psoriasis.

Major depression: Depression and depressive symptoms occur with increased frequency in patients with psoriasis.^{61–63} Major depression is a significant predictor of CV disease, may be an independent risk factor for death >12 months after sustaining an AMI,^{64,65} and may increase the risk for first-time CAD.^{66,67} There appears to be an association between depressive symptoms and serum inflammatory markers.⁶⁸ The prevalence of CAD in patients with major depression is unknown.

Inflammation

Inflammation may be an important link between psoriasis and CAD.^{69–71} Inflammation may be defined as a *physiologic state in which elevated levels of circulating inflammatory cytokines provoke localized inflammation in susceptible organs throughout the body*, such as the gums (periodontitis), joints (rheumatoid arthritis and osteoarthritis), and intestines (inflammatory bowel disease). Inflammation is important in the pathophysiology of psoriasis, with a central role of cytokines,⁷² especially T helper 1 and T helper 17.¹² Inflammation has emerged as a possible independent risk factor for atherosclerosis⁷³ and may contribute to plaque rupture in acute coronary syndromes.^{74–79}

Cytokines and C-reactive protein (CRP): Cytokines are low-molecular-weight soluble proteins that regulate cell activity.⁸⁰ Cytokines are produced by many different cell types, most often T helper cells and macrophages in the

body's response to immune stimuli.⁸¹ The role of cytokines is to mediate and regulate immunity, inflammation, and hematopoiesis. More than 20 different cytokines have been identified. CRP is the most commonly measured inflammatory biomarker in the blood and is measured by the high-sensitivity assay hs-CRP.⁸² CRP is manufactured mainly in the liver and is released by the liver in response to increased levels of circulating cytokines, especially interleukin (IL)-6.⁸³ Plasma hs-CRP levels are elevated in many patients with psoriasis,^{72,84–87} and although they decrease during periods of treatment-induced remission, they usually do not return to normal levels.⁷²

Inflammation as a cardiovascular risk factor: Elevated plasma hs-CRP is associated with AMI and unstable angina pectoris^{88,89} and is a predictor of future hypertension, AMI, and stroke,^{90–92} independent of serum levels of total cholesterol and HDL cholesterol.⁹³ Some investigators suggest that CRP itself, beyond serving as a biomarker, may be an active anti-inflammatory protein with a role in endothelial cell dysfunction and vascular remodeling.^{83,94,95} The erythrocyte sedimentation rate, chemokines, and cytokines including IL-6, IL-8, IL-10, IL-18, TNF- α , and monocyte chemoattractant protein-1 are also implicated in acute coronary syndromes.^{96–98} Acute coronary events are increased in patients with other chronic inflammatory diseases, including rheumatoid arthritis,⁹⁹ periodontitis,^{100,101} systemic lupus erythematosus,^{102,103} and some types of infections, mainly those involving the respiratory and urinary tracts.¹⁰⁴

Arterial inflammation, along with arterial stiffness and remodeling, is likely a factor in systemic arterial hypertension, particularly in obese patients.^{105–124} Elevated plasma hs-CRP is also a predictor of future hypertension.⁹² Aldosterone may induce vascular inflammation and angiotensin II appears to be an essential factor in the relation between vascular inflammation and hypertension.^{92,125–130}

Although future therapies for atherosclerosis may target inflammation, the *precise* role of inflammation as a *causative* factor in atherogenesis and in the complications of atherosclerosis is not established.^{95,131,132}

Anti-inflammatory therapies: MTX is an important anti-inflammatory drug for the treatment of patients with rheumatoid arthritis and psoriasis.¹³ One epidemiologic retrospective study of 7,615 outpatients with psoriasis and 6,707 patients with rheumatoid arthritis showed that MTX treatment was related to a significantly reduced incidence of CAD,¹³³ although MTX increases plasma homocysteine blood levels. The decreased incidence of CAD was even greater in patients with psoriasis receiving folic acid, possibly because of its suppression of plasma homocysteine. In a study involving only patients with rheumatoid arthritis, MTX treatment produced a 70% reduction in CV deaths, which the investigators attributed to improved physical activity and/or decreased inflammation.¹³⁴

Aspirin, a nonsteroidal anti-inflammatory drug (NSAID), is proved to prevent acute cardiac events, possibly because of its anti-inflammatory effects in addition to its proved antiplatelet effects.^{91,135} Cyclooxygenase-2 inhibitors (selective NSAIDs) and nonselective NSAIDs, however, do not show beneficial effects in preventing CAD, and several

drugs in this class are associated with varying rates of *increases* in CAD event rates,^{136–139} which has led to a US Food and Drug Administration requirement that *all* selective and nonselective prescription-strength NSAIDs carry an identical black-box warning for CV risk.

Statins, whose primary effect is to reduce serum levels of LDL cholesterol, also have anti-inflammatory effects and consistently lower plasma hs-CRP levels in the general population.^{140–143} One trial found that patients with rheumatoid arthritis treated with atorvastatin had a 50% reduction in plasma hs-CRP and a “modest” reduction in inflammation-related symptoms, such as morning stiffness and joint swelling.¹⁴⁴ The anti-inflammatory effects of statins also may be beneficial in inflammatory disorders involving the skin, including psoriasis.^{145,146} Drugs in the antihypertensive classes, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers, whose principle mechanism of action is to suppress the renin-angiotensin-aldosterone system, also appear to have anti-inflammatory effects through their negative effects on angiotensin II.^{109,110} Niacin, which lowers total and LDL cholesterol and triglycerides and increases HDL cholesterol, lowers CV disease risk when used alone and when used in conjunction with statins. It also has an anti-inflammatory effect.¹⁴⁷ Niacin reduced plasma hs-CRP by 24% in 1 study when used in combination with a statin¹⁴⁸ and by up to 20% in another study when used alone.¹⁴⁹

Whether CRP is a true risk factor (i.e., plays a *causative* role in atherogenesis or its complications) or is only a risk marker is unresolved.¹⁵⁰ Thus, the role of lipid-lowering medications and renin-angiotensin-suppressing antihypertensive agents in treating and preventing CV disease in the general population via their anti-inflammatory effects is unproved and the focus of considerable ongoing investigation. Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), for example, showed favorable effects of statins in subjects with LD cholesterol <130 mg/dl and plasma hs-CRP levels >2 mg/dl.¹⁵¹

Recommendations

(Note: Many of the following recommendations are based on psoriatic disease severity, which by convention has been designated as “mild,” “moderate,” or “severe.” This classification, however, can be confusing to nondermatologists, who should not assign disease severity for the purpose of assessing psoriasis-related CV risk factor based solely on the type of treatment used for individual patients. For example, a patient with psoriasis confined to the palms and feet, and thus not carrying a large psoriatic burden and perhaps insignificant psoriatic-related CV risk, nonetheless has a very lifestyle limiting form of skin involvement that may benefit from aggressive treatment strategies such as systemic agents. Thus, communication between dermatologists and the physicians responsible for CV treatments are essential.)

Epidemiologic data support the contention that there is an association of psoriasis, especially *severe* psoriasis, with several major risk factors for CV disease. Furthermore, there is evidence that inflammation may serve as a common

link between the 2 conditions. Precisely how these interrelations affect the clinical care of patients with psoriasis, which is the primary objective of this consensus document, is especially challenging because of uncertainty whether psoriasis *itself* is a risk factor. Until there is better understanding of the psoriasis-CAD link, physicians managing CV risk factors in patients with psoriasis should adhere to standard atherosclerosis prevention and treatment guidelines, particularly those of the National Cholesterol Education Program Adult Treatment Panel (ATP) III,¹⁵² the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7),¹⁵³ and the scientific statement on the diagnosis and management of the metabolic syndrome of the American Heart Association and the National Heart, Lung, and Blood Institute,⁴⁶ from which many of the following recommendations are derived. Although these standard guidelines are intended for *all* populations, certain populations, such as patients with diabetes mellitus or previous CV events, are targeted at high risk, and therefore, treatment recommendations are more aggressive for these populations. Patients with psoriasis (and other inflammatory conditions except the metabolic syndrome) are not currently given special attention in standard guidelines, but if future data further advance the notion that psoriasis is an independent risk factor for CV disease, it is anticipated that these recommendations for risk factor modification will be modified accordingly.

One important issue that generated considerable attention by the panel is the fact that many dermatology practices cannot alone carry out recommendations for CAD risk assessment and treatment because of time and/or facility constraints. In those instances, the panel recommends that at a minimum, patients with moderate and severe forms of psoriasis be advised of possible increased CAD risk and encouraged to undergo CAD risk assessment by their primary care physicians. In view of the current general lack of physicians’ awareness of the psoriasis-CAD relation, dermatologists also should provide explanations to primary care physicians of the reason for recommendations for CAD risk assessment. Conversely, physicians caring for patients with psoriasis who have established CAD (or other forms of atherosclerotic CV disease) or who have significantly increased CV risk factors should communicate their treatment strategies to those patients’ dermatologists or other health care professionals managing their psoriasis.

The recommendation scales are defined in Table 1.

I. Patient Information

- A. Recommendation: ***Patients with moderate to severe psoriasis should be informed that they may be at increased risk for CAD and that they should undergo appropriate medical evaluations.***

Confidence level: 2B

- B. Recommendation: ***Patients with mild forms of psoriasis and apparent increased CAD risk factors such as abdominal obesity or increased blood pressure should be informed that they may be at increased risk for CAD and should undergo medical evaluations.***

Confidence level: 3D

Table 1
Confidence and evidence codes

Confidence	Description
1	Very confident
2	Confident
3	Marginally confident
4	Not confident
Type of evidence	Description
A	Well-designed randomized controlled clinical trials conducted in patients who have reported adverse experiences
B	Single randomized controlled clinical trial with a highly statistically significant result
C	Well-conducted retrospective case-control studies with adverse experiences as primary end points
	Managed care claims database analysis with a highly statistically significant result
	Reports to regulatory agencies judged to exceed population averages and reporting bias
D	Multiple case studies with nonblinded dechallenge and rechallenge
	Strong trends, not reaching statistical significance, for safety issues in large randomized controlled clinical trials
	Well-conducted prospective cohort study, giving a result that is statistically well above population average
	Metabolic or clinical surrogate studie
U	Undocumented opinion of experienced research investigators and clinicians
	Poorly controlled or uncontrolled studies
	Nondefinitive evidence from regulatory agency reporting systems or managed care claims databases
	Unknown, no appropriate evidence, or evidence considered subject to bias

II. Medical Evaluation

- A. Recommendation: *Patients with moderate to severe psoriasis should undergo medical histories assessing for CAD risk, including past CAD events, and family histories evaluating for premature CAD or sudden cardiac death, diabetes mellitus, hypertension, or dyslipidemia.*

Confidence level: 2D

- B. Recommendation: *Patients with moderate to severe psoriasis should undergo complete physical examinations and annual measurements of blood pressure at rest (seated for 5 minutes with feet on the floor and attention to appropriate blood pressure cuff size).*

Confidence level: 2D

- C. Recommendation: *Patients with moderate to severe psoriasis should undergo blood lipid profiles (total cholesterol, LDL cholesterol, HDL cholesterol, and fasting triglycerides) and blood glucose measurements. A plasma hs-CRP determination is optional, because some authorities believe that elevated plasma hs-CRP may have added value by helping determine how aggressively standard risk factors should be treated, especially the encouragement of lifestyle changes.*

Confidence level: 2D

III. Risk Factor Treatment: Abnormal Lipids

- A. Recommendation: *Patients with psoriasis and ≥ 1 abnormal serum lipid level and/or elevated plasma hs-CRP should follow a multifaceted lifestyle approach to reduce CAD risk according to ATP III guidelines.¹⁵²*

Confidence Level: 1C

Consistent with ATP III guidelines, emphasis on weight loss and physical activity to enhance weight reduction in patients with elevated serum LDL cholesterol should be undertaken. Goals for

LDL cholesterol levels are based on CAD risk assessment:

- For 1 CAD risk factor and LDL cholesterol >160 mg/dl, the target LDL cholesterol level is <160 mg/dl.
- For ≥ 2 CV risk factors and LDL cholesterol >130 mg/dl, the target LDL cholesterol level is <130 mg/dl. An optional target is LDL cholesterol <100 mg/dl if factors such as age, metabolic syndrome, abnormal plasma hs-CRP, and abnormal coronary calcium score (75th percentile) are present.
- If CV disease is present or there are CAD risk equivalents, such as diabetes mellitus, the target LDL cholesterol level is <100 mg/dl or an optional target of <70 mg/dl if CV disease is present *and* there are high-risk features, such as diabetes mellitus, the metabolic syndrome, or heavy cigarette smoking, or if the patient presents with an acute coronary syndrome.

Lifestyle changes that should be undertaken include the following:

- The intake of saturated fats should be reduced (to <7% of total calories), and low levels of trans fats and dietary cholesterol (<200 mg/day) should be consumed.
- Therapeutic options for enhancing LDL lowering, such as plant stanols and sterols (2 g/day) and increased viscous (soluble) fiber (10 to 25 g/day), should be considered.
- Weight should be reduced.
- Physical activity should be increased.
- Alcohol ingestion should be moderated. Patients with psoriasis often drink alcohol excessively. Used in moderation ("Moderation is defined as the consumption of up to one drink per day for women and up to two drinks per day for men. Twelve fluid ounces of regular

beer, 5 fluid ounces of wine, or 1.5 fluid ounces of 80-proof distilled spirits count as one drink for purposes of explaining moderation. This definition of moderation is not intended as an average over several days but rather as the amount consumed on any single day¹⁵⁴), alcohol does not add to CAD risk and may convey some protective effect against future CAD events. Patients needing to lose weight should be cautioned, however, that alcohol is high in caloric content. Patients who do not drink alcohol should not be advised to begin drinking alcohol for the purpose of CAD risk modification, because the other risks of alcohol consumption, such as higher frequencies of accidents and medical illnesses, outweigh CV benefits.

B. Recommendation: *Drug therapy for elevated LDL cholesterol should be prescribed in patients with psoriasis in whom target LDL cholesterol levels are not achieved with lifestyle changes.*

Confidence level: 2D

In patients with psoriasis, the following are of particular importance:

- *Statins* are contraindicated in patients with active or chronic liver disease, and therefore, *they should be used with caution in patients who have received MTX until hepatic status is determined by blood liver function tests.*
- *Statins* also may have a favorable effect on plaque psoriasis¹⁴⁵ and on plasma hs-CRP.¹⁴⁴
- The effect of *niacin* on lipids makes this drug particularly effective in patients with diabetes mellitus, which is common in patients with psoriasis. Niacin preparations must be used with caution in patients with diabetes mellitus, however, because they increase blood glucose levels.
- *Niacin* is contraindicated in patients with severe gout and chronic liver disease and therefore *must be used with caution in patients who have been treated with MTX until hepatic status and serum uric acid are determined.* If there are concerns regarding liver disease, sustained-release niacin is best avoided, and the use of short-acting or intermediate-release niacin is favored.¹⁵⁵
- The perception that niacin cannot be taken by patients with psoriasis because of secondary flushing is false.¹⁵⁶ Many patients, regardless whether they have psoriasis, who take niacin develop flushing, which is mediated primarily by prostaglandin D₂ and can be significantly lessened by pretreatment with aspirin.¹⁵⁷ In most patients, the bothersome itching and flushing that initially occur decrease with continued use.
- *Fibrates* are contraindicated in patients with severe renal disease and severe hepatic disease, so *they must be used with caution in patients*

who have been treated with previous MTX or cyclosporine therapy until renal and hepatic status are determined.

- The fibrate *gemfibrozil* has been linked to exacerbations of psoriasis in rare instances.¹⁵⁸

IV. Risk Factor Treatment: Cigarette Smoking

A. Recommendation: *All cigarette smokers with psoriasis should discontinue this habit.*

Confidence Level: 1C

Cigarette smoking is a major risk factor for CV disease and also may contribute to the severity of psoriasis.³⁵

V. Risk Factor Treatment: Hypertension

JNC-7¹⁵³ defines hypertension as follows:

- *Prehypertension*: systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg.
- *Stage 1 hypertension*: systolic blood pressure of 140 to 159 mm Hg or diastolic blood pressure of 90 to 99 mm Hg.
- *Stage 2 hypertension*: systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg.

A. Recommendation: *All patients with psoriasis should have elevated blood pressures treated to target levels as defined by the JNC-7.*¹⁵³

Confidence Level: 1C

Using JNC-7 recommendations,¹⁵³ the target blood pressures in patients with psoriasis are as follows:

- <140/90 mm Hg in all patients with psoriasis and ≤2 major risk factors for CAD, and
- <130/80 mm Hg in patients with previous CV disease, diabetes mellitus, chronic renal disease, or ≥3 major risk factors.

B. Recommendation: *All patients with psoriasis and elevated blood pressure should undertake lifestyle changes.*

Confidence Level: 1A

Blood pressure can be significantly decreased by lifestyle changes, including

- Weight reduction in individuals who are overweight (systolic blood pressure reduction of 5 to 20 mm Hg),
- A diet high in potassium and calcium (the American Heart Association Dietary Approaches to Stop Hypertension diet; systolic blood pressure reduction of 8 to 4 mm Hg),
- A diet low in sodium (systolic blood pressure reduction of 2 to 8 mm Hg),
- Physical activity (systolic blood pressure reduction of 4 to 9 mm Hg), and
- Moderation of alcohol intake (systolic blood pressure reduction of 2 to 4 mm Hg).

In addition to lowering blood pressure, lifestyle modifications also increase the efficacy of antihypertensive drug therapy and decrease the risk for CAD.

- C. Recommendation: **All patients with psoriasis and elevated blood pressure not controlled to target levels with lifestyle changes should be treated with pharmacologic therapy.**

Confidence Level: 2D

The following drug classes are approved for the initial treatment of hypertension:

- Thiazide-type diuretics,
- Angiotensin-converting enzyme inhibitors,
- Angiotensin receptor blockers,
- Direct renin inhibitors,
- β blockers, and
- Calcium channel blockers.

There is no evidence at the present time that any of the approved classes of drugs for hypertension are more or less efficacious in treating hypertension in patients with psoriasis compared with the general population. Beta blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, however, may in rare instances precipitate psoriatic flare-ups.^{159–161} Patients receiving these drugs should be monitored for exacerbations of psoriasis.

VI. Risk Factor Treatment: The Metabolic Syndrome

- A. Recommendation: **Patients meeting criteria for the metabolic syndrome should be identified, and all risk factors for CAD should be treated, beginning with lifestyle changes aimed at weight reduction.**

Confidence level: 1D

The metabolic syndrome is closely linked to insulin resistance and is a secondary target of lipid therapy because the risk factors for the metabolic syndrome are highly concordant and, in aggregate, enhance the risk for CAD at any serum level of LDL cholesterol.⁴⁶ Many patients with psoriasis, especially moderate to severe forms, meet criteria for the metabolic syndrome. Because systemic inflammation is a common feature of psoriasis and the metabolic syndrome, it may be particularly important to identify patients who meet these criteria for CAD prevention strategies.

The metabolic syndrome is diagnosed when ≥ 3 of the following features are present⁴⁶:

1. Increased waist circumference ≥ 40 in (≥ 102 cm) in men and ≥ 35 in (≥ 88 cm) in women;
2. Elevated serum triglycerides ≥ 150 mg/dl (1.7 mmol/L) or receiving drug treatment for elevated triglycerides (most commonly fibrates and nicotinic acid);
3. Reduced serum HDL cholesterol < 40 mg/dl (1.03 mmol/L) in men and < 50 mg/dl (1.3 mmol/L) in women or receiving drug treatment for reduced HDL cholesterol (most commonly fibrates and/or nicotinic acid);
4. Elevated blood pressure ≥ 130 mm Hg systolic and/or ≥ 85 mm Hg diastolic or antihypertensive drug treatment in patients with histories of hypertension; and

5. Elevated fasting glucose ≥ 100 mg/dl or drug treatment for elevated glucose.

VII. Psoriasis Treatment and CAD Risk: MTX

- A. Recommendation: **Patients taking statins, nicotinic acid, and/or fibrates should have close monitoring of liver function when receiving MTX to avoid toxicity.**

Confidence level: 1D

Statins, nicotinic acid, and fibrates are metabolized in the liver. Thus, particular attention should be paid to liver function when prescribing these drugs in patients receiving MTX, which may cause liver toxicity.

- B. Recommendation: **MTX should not be prescribed for the primary purpose of reducing CV risk.**

Confidence level: 2D

Additional data, ideally from controlled trials, are necessary to determine the risk-benefit profile with respect to CV outcomes and the treatment of psoriasis with potentially cardioprotective therapies such as MTX.

VIII. Psoriasis Treatment and CAD Risk: Cyclosporine

- A. Recommendation: **Blood pressure and serum lipids should be monitored in patients receiving cyclosporine.**

Confidence level: 3D

The primary effect of cyclosporine on CAD risk is blood pressure elevation.¹⁶² Cyclosporine also elevates serum LDL cholesterol.¹⁶³ Given the relatively short treatment courses with cyclosporine and the reversibility of cyclosporine-induced hypertension and serum lipid changes, however, neither elevated blood pressure nor serum lipid abnormalities are contraindications for carefully monitored cyclosporine treatment.

IX. Psoriasis Treatment and CAD Risk: Topical Corticosteroids

- A. Recommendation: **Patients with established hypertension and/or other CV risk factors should have regular blood pressure monitoring when applying high-strength topical corticosteroids to large areas of psoriatic skin.**

Confidence level: 3D

Topical corticosteroids, when used in sufficient strength (i.e., clobetasol propionate > 50 g/week) and applied over large areas of psoriatic skin disease, may reach significant levels of absorption and in theory could elevate blood pressure, but this effect has not been reported.

X. Psoriasis Treatment and CAD Risk: Acitretin

- A. Recommendation: **Patients who have elevated serum cholesterol and/or triglycerides should not receive acitretin unless necessary (relative contraindication), and those who take the drug, including patients taking lipid-modifying agents, should undergo monitoring of serum lipid levels.**

Confidence level: 1C

In patients with psoriasis receiving acitretin, it is reported that 66% develop elevated triglycerides and 33% have elevations in total serum cholesterol.¹⁶⁴ Acitretin also may cause hepatotoxicity, so patients receiving statins, fibrates, and nicotinic acid should be monitored carefully when taking this drug.

XI. Psoriasis Treatment and CAD Risk: Ultraviolet Phototherapies

A. Recommendation: *Patients can receive ultraviolet treatment for psoriasis without regard to CAD risk.*

Confidence level: 1D

There are no reported studies of the effect of ultraviolet therapy on CAD risk factors, but there is no physiologic basis for withholding this treatment from patients at increased CAD risk. Several CV medications can be photosensitizing, and therefore it is important to notify the treating dermatologist if a change in medications is to be made while a patient is receiving phototherapy.

XII. Psoriasis Treatment and CAD Risk: Biologics

A. Recommendation: *Patients can be treated with biologics for psoriasis without regard to CAD risk. Anti-TNF- α drugs, however, should be used with caution in patients with congestive heart failure.*

Confidence level: 3D

There are no reports of adverse effects of biologic agents on CAD risk factors. However, there have been no long-term studies regarding the safety of biologic agents related to CAD or its risk factors. There are case reports that brief treatment with anti-TNF- α agents might induce new cases and exacerbate previous cases of heart failure.¹⁶⁵ However, in 1 series of patients with rheumatoid arthritis, heart failure appeared to be ameliorated in patients treated with anti-TNF- α agents,¹⁶⁶ and in 2 other studies, they were well tolerated by patients with heart failure.^{167,168} Although risk in patients with heart failure is currently challenged by some authorities,¹⁶⁹ *clinicians are advised to consult prescribing information for specific anti-TNF- α agents when considering their use in patients with histories of congestive heart failure or existing heart failure or who or at increased risk for heart failure.*

XIII. Special Considerations in the Treatment of CV Disease in Patients With Psoriasis

There are no studies that have determined whether patients with psoriasis with acute or chronic CV disease should be treated differently from the general population, with the following exceptions.

A. Recommendation: *Patients with psoriasis prescribed β blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers for any indication should be monitored for worsening of psoriasis.*^{160,170}

Confidence level: 2C

B. Recommendation: *Patients with psoriasis receiving cyclosporine who are prescribed diuretics for any*

indication should be monitored for increased risk for cyclosporine-induced renal toxicity.

Confidence level: 2C

C. Recommendation: *Patients with psoriasis receiving cyclosporine who are taking statins should be monitored closely for signs of rhabdomyolysis.*

Confidence level: 2C

D. Recommendation: *Patients with psoriasis receiving MTX or acitretin who are prescribed the lipid-modifying agents statins, fenofibrate, and/or nicotinic acid should be monitored for hepatic dysfunction.*

Confidence level: 2C

E. Recommendation: *Patients with heart failure who are receiving anti-TNF- α drugs for psoriasis should be carefully monitored for worsening of heart failure.*

Confidence level: 1C

Recommendations for Future Research

The association between CAD and psoriasis is a relatively new observation and largely limited to retrospective analyses of large patient data sets. Additional research is needed to (1) provide better guidance in reducing the risk for CAD in patients with psoriasis and (2) provide better insight into the mechanisms underlying this association. The panel believes that the following avenues of research will help meet these objectives.

1. A national, controlled registry or prospective cohort should be formed, with epidemiologic follow-up of patients with all grades of psoriasis severity. Patients being treated in nonacademic settings should be included in the study. Among the questions that should be addressed are the following:
 - How large is the true risk for CAD in patients with psoriasis, and does that risk vary by psoriasis treatment status, gender, race, and the presence of other concomitant risk factors?
 - Is the increased risk for CAD in patients with psoriasis independent of established risk factors?
 - What is the role of psoriasis activity in CAD risk?
 - Are there clinical markers other than standard CAD risk factors that can help discern patients with psoriasis who are at increased risk?
 - Is it cost effective for *all* patients with psoriasis to have their CAD risk factors measured, or only patients with moderate to severe psoriasis (as recommended in this document)?
 - Do standard consensus guidelines (i.e., JNC-7, ATP III, etc.) apply equally to patients with psoriasis judged to be at increased risk for CAD as in the general population, or should some or all factors be treated more aggressively, analogous to recommendations for patients with diabetes mellitus?
 - What is the role of CRP as a *marker* for CAD in patients with psoriasis?
 - What is the role of CRP as a *target* of risk factor modification in patients with psoriasis?
 - How do lipid profiles in patients with psoriasis compare with those in the general population? (For

example, HDL cholesterol appears to be lower in patients with psoriasis.)

- Is there a link between the genetic predisposition to psoriasis and the genetic predisposition to CAD?
 - Are lifestyle-related CAD risk factors such as obesity and type 2 diabetes mellitus caused by altered eating behavior in patients with psoriasis?
 - Are lifestyle-related CAD risk factors such as obesity and type 2 diabetes precipitating factors for psoriasis or, in patients who have psoriasis, factors that add to the severity of psoriasis?
 - How can lifestyle changes be optimized in patients with psoriasis? What is the effect of standard psoriasis therapeutic regimens, if any, on CAD risk factors?
 - What is the effect, if any, of biologics on lipids and other CAD risk factors? (The effects of anti-TNF- α and anti-IL-6 drugs are of special interest given the possible role of TNF- α and IL-6 in atherogenesis.)
 - Does the presence of psoriatic arthritis add to CAD risk?
 - Does therapeutic reduction of psoriasis lower CAD risk independent of treatment modality?
2. Other important questions that should be considered for research include the following:
- What is the role of inflammation as a link between psoriasis and CAD?
 - What are the roles of obesity, adipose tissue per se, and insulin resistance as possible causative or exacerbating factors in psoriasis?
 - What are the roles of T cells, angiotensin II, and inflammation in patients with psoriasis with hypertension, and can more knowledge of these interrelations in psoriasis add to our understanding of the role of cellular immunity and vascular biology?
 - What is the effect of psoriasis on lipid synthesis and metabolism? (A specific area of interest is the role of keratinocytes, which have a high rate of proliferation in psoriasis and produce large amounts of lipid.)
 - Do TNF- α blockers improve endothelial function and reduce vascular inflammation?
 - To what degree, and in which patients with psoriasis, are β blockers contraindicated in patients for whom there may be CV indications?
3. An international, Internet-based “clearinghouse” compilation of new publications and select past publications relevant to this topic should be created. A significant problem that emerged in writing this document was the multiplicity of disciplines that do not ordinarily interact but provide data important to the advancement of our collective understanding of the complex interrelations among CV medicine, immunology, dermatology, rheumatology, gastrointestinal disease, periodontal disease, infectious disease, cell physiology, and pharmacology (especially biologic agents). In addition to being a repository of information, this site also could serve as an international forum for open dialogue on specific topics of interest in which academic and nonacademic health care researchers and practitioners could openly exchange ideas and make specific inquiries about new information as it is posted.
1. National Psoriasis Foundation. About psoriasis: statistics. Available at: <http://www.psoriasis.org/about/stats>. Accessed September 1, 2008.
 2. Schon MP, Boehncke W-H. Psoriasis. *N Engl J Med* 2005;352:1899–1912.
 3. Griffiths CE, Barker JNW. Pathogenesis and clinical features of psoriasis. *Lancet* 2007;360:263–271.
 4. Gelfand JM, Feldman SR, Stern RS, Thomas J, Rolstad T, Margolis DJ. Determinant of quality of life in patients with psoriasis: a study from the US population. *J Am Acad Dermatol* 2004;51:704–708.
 5. Mease PJ, Menter MA. Quality-of-life issues in psoriasis and psoriatic arthritis: outcome measures and therapies from a dermatological perspective. *J Am Acad Dermatol* 2006;54:685–704.
 6. Van de Kerkhof PCM. The evolution of the psoriatic lesion. *Br J Dermatol* 2007;157:4–15.
 7. Krueger JG, Bowcock A. Psoriasis pathophysiology: current concepts of pathogenesis. *Ann Rheum Dis* 2005;64:ii30–ii36.
 8. Christophers E. Comorbidities in psoriasis. *Clin Dermatol* 2007;25:529–534.
 9. Kimball AB, Gladman D, Gelfand JM, Gordon K, Horn EJ, Korman NJ, Korver G, Krueger GG, Strober BE, Lebwohl MG, et al. National psoriasis foundation clinical consensus on psoriasis comorbidities and recommendations for screening. *J Am Acad Dermatol* 2008;58:1031–1042.
 10. Gottlieb AB, Chao C, Dann F. Psoriasis comorbidities. *J Dermatol Treat* 2008;19:5–21.
 11. Schlaak JF, Buslau M, Jochum W, Hermann E, Girmdt M, Gallati H, Meyer zum Büschelfelde KH, Fleischer B. T cells in psoriasis vulgaris belong to the Th1 subset. *J Invest Dermatol* 1994;102:145–149.
 12. Lowes MA, Kikuchi T, Fuentes-Duculan J, Cardinale I, Zaba LC, Haider AS, Bowman EP, Krueger JG. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. *J Invest Dermatol* 2008;128:1207–1211.
 13. Menter A, Griffiths EM. Current and future management of psoriasis. *Lancet* 2007;370:272–284.
 14. Reed WB, Becker SW, Rhode R, Heiskell CL. Psoriasis and psoriatic arthritis. A clinicopathologic conference. *Arch Dermatol* 1961;99:86.
 15. McDonald CJ, Calabresi P. Complication on psoriasis. *JAMA* 1973;224:629.
 16. McDonald CJ, Calabresi P. Occlusive vascular disease in psoriatic patients. *N Engl J Med* 1973;288:912.
 17. Ena P, Madeddu P, Glorioso N, Cerimele D, Rappelli A. High prevalence of cardiovascular diseases and enhanced activity of the renin-angiotensin system in psoriatic patients. *Acta Cardiol* 1985;40:199–205.
 18. Henseler T, Christophers E. Disease concomitance in psoriasis. *J Am Acad Dermatol* 1995;32:982–986.
 19. Lindgard B. Diseases associated with psoriasis in a general population of 159,200 middle-aged, urban, native Swedes. *Dermatologica* 1986;172:298–304.
 20. Krueger GG, Duvic M. Epidemiology of psoriasis: clinical issues. *J Invest Dermatol* 1994;102:14S–18S.
 21. Poikolainen K, Karvonen J, Pukkala E. Excess mortality related to alcohol and smoking among hospital-treated patients with psoriasis. *Arch Dermatol* 1999;135:1490–1493.
 22. Mallbris L, Akre O, Granath F, Yin L, Lindelof B, Ekblom A, Stahle-Backdahl M. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. *Eur J Epidemiol* 2004;19:225–230.
 23. McDonald CJ, Calabresi P. Psoriasis and occlusive vascular disease. *Br J Dermatol* 1978;99:469–475.
 24. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA* 2006;296:1735–1741.
 25. Kimball AB, Robinson D, Wu Y, Guzzo C, Yeilding N, Paramore C, Fraeman K, Bala M. Cardiovascular disease and risk factors among psoriasis patients in two US healthcare databases, 2001–2002. *Dermatology* 2008;217:27–37.
 26. Kaye JA, Li L, Jick SS. Incidence of risk factors for myocardial infarction and other vascular diseases in patients with psoriasis. *Br J Dermatol* 2008;159:895–902.
 27. Ludwig RJ, Herzog C, Rostock A, Ochsendorf FR, Sollner TM, Thaci D, Kaufmann R, Vogl TJ, Boehncke W-H. Psoriasis: a possible risk factor for development of coronary artery calcification. *Br J Dermatol* 2007;156:272–276.

28. Kremers HM, McEvoy MT, Dann FJ, Gabriel SE. Heart disease in psoriasis. *J Am Acad Dermatol* 2008;58:347–352.
29. Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, Margolis DJ, Strom BL. The risk of mortality in patients with psoriasis. *Arch Dermatol* 2007;143:1493–1499.
30. Wakke M, Thio HB, Prens EP, Sijbrands EJG, Neumann HAM. Unfavorable cardiovascular risk profiles in untreated and treated psoriasis patients. *Atherosclerosis* 2007;190:1–9.
31. Dratelin CR, Martinez-Abundis E, Balcázar-Muñoz BR, Bustos-Saldaña R, González-Ortiz M. Lipid profile, insulin secretion, and insulin sensitivity in psoriasis. *J Am Acad Dermatol* 2003;48:882–885.
32. Rocha-Pereira P, Santos-Silva A, Rebelo I, Figueiredo A, Quintanilha A, Teixeira F. Dyslipidemia and oxidative stress in mild and in severe psoriasis as a risk for cardiovascular disease. *Clin Chim Acta* 2001;303:33–39.
33. Neimann AI, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. *J Am Acad Dermatol* 2006;55:829–835.
34. Mallbris L, Ritchlin CT, Ståhle M. Metabolic disorders in patients with psoriasis and psoriatic arthritis. *Curr Rheumatol Rep* 2006;5:355–363.
35. Herron MD, Hinckley M, Hoffman MS, Papenfuss J, Hansen CB, Callis KP, Krueger GC. Impact of obesity and smoking on psoriasis presentation and management. *Arch Dermatol* 2005;141:1527–1534.
36. Sommer DM, Jenisch S, Suchan M, Christophers E, Weichenthal M. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. *Arch Dermatol Res* 2006;298:321–328.
37. Cohen AD, Gilutz H, Henkin Y, Zaher D, Shapiro J, Bonne DY, Vardy DA. Psoriasis and the metabolic syndrome. *Acta Derm Venereol* 2007;87:506–509.
38. Cohen AD, Sherf M, Vidavsky L, Vardy DA, Shapiro J, Meyerovitch J. Association between psoriasis and the metabolic syndrome. A cross-sectional study. *Dermatology* 2008;216:152–155.
39. Gisondi P, Tessari G, Conti A, Piaserico S, Schianchi S, Peserico A, Giannetti A, Girolomoni G. Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case-control study. *Br J Dermatol* 2007;157:68–73.
40. Wellen KE, Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. *J Clin Invest* 2003;112:1785–1788.
41. Panagiotakos DM, Pitsavos C, Yannakoulia M, Chrysohoou C, Stefanadis C. The implication of obesity and central fat on markers of chronic inflammation: the ATTICA study. *Atherosclerosis* 2005;183:308–315.
42. Meigs JB, Wilson PWF, Nathan DM, D'Agostino RB, Williams K, Haffner SM. Prevalence and characteristics of the metabolic syndrome in the San Antonio heart and Framingham offspring studies. *Diabetes* 2003;52:2160–2167.
43. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB, Wilson PWF. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham offspring study. *Circulation* 2004;110:380–385.
44. Olijhoek JK, Van der Graaf Y, Banga J-D, Algra A, Rabelink TJ, Visseren FLJ. The metabolic syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm. *Eur Heart J* 2004;25:342–348.
45. Lau DC, Dhillon B, Yan H, Szmítok PE, Verma S. Adipokines: molecular links between obesity and atherosclerosis. *Am J Physiol* 2005;288:H2031–H2041.
46. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, et al. Diagnosis and management of the metabolic syndrome. *Circulation* 2005;112:2735–2752.
47. Escalante A, Haas RW, del Rincon I. Paradoxical effect of body mass index on survival in rheumatoid arthritis. *Arch Intern Med* 2005;165:1624–1629.
48. Sterry W, Strober BE, Menter A. Obesity in psoriasis: the metabolic, clinical and therapeutic implications. *Br J Dermatol* 2007;157:649–655.
49. Wannamethee G, Lowe GDO, Shaper AG, Rumley A, Lennon L, Whincup PH. Association between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. *Eur Heart J* 2005;26:1765–1773.
50. Fortes C, Mastroeni S, Leffondrè K, Sampogna F, Melchi F, Mazzotti E, Pasquini P, Abeni D. Relationship between smoking and the clinical severity of psoriasis. *Arch Dermatol* 2005;141:1580–1584.
51. Mallbris L, Granath F, Hamsten A, Ståhle M. Psoriasis is associated with lipid abnormalities at the onset of skin disease. *J Am Acad Dermatol* 2006;54:614–621.
52. Kural BV, Örem A, Cimsit G, Yandi YE, Calapoglu M. Evaluation of the atherogenic tendency of lipids and lipoprotein content and their relationships with oxidant-antioxidant system in patients with psoriasis. *Clin Chim Acta* 2003;328:71–82.
53. Shapiro J, Cohen AD, David M, Hodak E, Chodik G, Viner A, Kremer E, Heymann A. The association between psoriasis, diabetes mellitus, and atherosclerosis in Israel: a case-control study. *J Am Acad Dermatol* 2007;56:629–634.
54. Cohen AD, Dreher J, Shapiro Y, Vidavsky L, Vardy DA, Davidovici B, Meyerovitch J. Psoriasis and diabetes: a population-based cross-sectional study. *J Eur Acad Dermatol Venereol* 2008;22:585–589.
55. Boehncke S, Thaci D, Beschmann H, Ludwig RJ, Ackermann H, Badenhoop K, Boehncke W-H. Psoriasis patients show signs of insulin resistance. *Br J Dermatol* 2007;157:1249–1251.
56. Kural BV, Örem A, Cimsit G, Uyda HA, Yandi YE, Alver A. Plasma homocysteine and its relationship with atherothrombotic markers in psoriatic patients. *Clin Chim Acta* 2003;332:23–30.
57. Malebra M, Gisondi P, Radaeli A, Sala R, Calzavara Pinton PG, Girolomoni G. Plasma homocysteine and folate levels in patients with chronic plaque psoriasis. *Br J Dermatol* 2006;155:1165–1169.
58. Malinow MR, Bostom AG, Krauss RM. Homocyst(e)ine, diet, and cardiovascular diseases. *Circulation* 1999;99:178–182.
59. Mayer EL, Jacobsen DW, Robinson K. Homocysteine and coronary atherosclerosis. *J Am Coll Cardiol* 1996;27:517–527.
60. Kaul S, Zadeh AA, Shah PK. Homocysteine hypothesis for atherothrombotic cardiovascular disease. *J Am Coll Cardiol* 2006;48:914–923.
61. Wu Y, Mills D, Bala M. Psoriasis: cardiovascular risk factors and other disease comorbidities. *J Drugs Dermatol* 2008;7:373–377.
62. Nasreen S, Ahmed I, Effendi S. Frequency and magnitude of anxiety and depression in patients with psoriasis vulgaris. *J Coll Physicians Surg Pak* 2008;18:397–400.
63. Friedewald VE, Cather JC, Gordon KB, Kavanaugh A, Ridker PM, Roberts WC. The editor's roundtable: psoriasis, inflammation, and coronary artery disease. *Am J Cardiol* 2008;101:1119–1126.
64. Vaccarino V, Johnson BD, Sheps DS, Reis SE, Kelsey SF, Bittner V, Rutledge T, Shaw LJ, Sopko G, Bairey CN. Depression, inflammation, and incident cardiovascular disease in women with suspected coronary ischemia. *J Am Coll Cardiol* 2007;50:2044–2050.
65. Carney RM, Blumenthal JA, Catellier D, Freedland KE, Berkman LF, Watkins LL, Czajkowski SM, Hayano J, Jaffe AS. Depression as a risk factor for mortality after acute myocardial infarction. *Am J Cardiol* 2003;92:1277–1281.
66. Barth J, Schumacher M, Hermann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med* 2004;66:802–813.
67. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom Med* 2003;65:201–210.
68. Stewart JC, Janicki-Deverts D, Muldoon MF, Kamarck TW. Depressive symptoms moderate the influence of hostility on serum interleukin-6 and C-reactive protein. *Psychosom Med* 2008;70:197–204.
69. Michowitz Y, Goldstein E, Roth A, Afek A, Abashidze A, Gal YB, Keren G, George J. The involvement of tumor necrosis factor-related apoptosis-inducing ligand (trail) in atherosclerosis. *J Am Coll Cardiol* 2005;45:1018–1024.
70. Zhang L, Poppel K, Sivashanmugam P, Orman ES, Brain L, Exum ST, Freedman NJ. Expression of tumor necrosis factor receptor-1 in arterial wall cells promotes atherosclerosis. *Arterioscler Thromb Vasc Biol* 2007;27:1087–1094.
71. Ridker PM, Rifai N, Pfeffer M, Sacks F, Lepage S, Braunwald E. Elevation of tumor necrosis factor- α and increased risk of recurrent coronary events after myocardial infarction. *Circulation* 2000;101:2149–2153.
72. Piertzak AT, Zalewska A, Chodorowska G, Krasowska D, Michalak-Stoma A, Nockowski P, Osemłak P, Paszkowski T, Rolinski JM. Cytokines and anticytokines in psoriasis. *Clin Chim Acta* 2008;394:7–21.
73. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med* 1999;340:115–126.
74. Spagnoli LG, Bonanno E, Sangiorgi G, Mauriello A. Role of inflammation in atherosclerosis. *J Nucl Med* 2007;48:1800–1815.

75. Libby P. What have we learned about the biology of atherosclerosis? The role of inflammation. *Am J Cardiol* 2001;88(suppl):3J–6J.
76. Forrester JS. Prevention of plaque rupture: a new paradigm of therapy. *Ann Intern Med* 2002;137:823–833.
77. Newby AC. Metalloproteinases and vulnerable atherosclerosis plaques. *Trends Cardiovasc Med* 2007;17:253–258.
78. Shah PK. Mechanisms of plaque vulnerability and rupture. *J Am Coll Cardiol* 2003;41:15S–22S.
79. Friedewald VE, Ambrose JA, Roberts WC, Stone GW, Willerson JT. The editor's roundtable: the vulnerable plaque. *Am J Cardiol*. In press.
80. Delves PJ, Roitt IM. The immune system. *N Engl J Med* 2008;343:37–49.
81. Jiang H, Chess L. Regulation of immune responses by T cells. *N Engl J Med* 2006;354:1166–1176.
82. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation* 2003;107:363–369.
83. Marnell L, Mold D, Du Clos TW. C-reactive protein: ligands, receptors and role in inflammation. *Clin Immunol* 2005;117:104–111.
84. Rocha-Pereira P, Santos-Silva A, Rebelo I, Figueiredo A, Quintanilhas A, Teixeira F. The inflammatory response in mild and in severe psoriasis. *Br J Dermatol* 2004;150:917–928.
85. Sergeant A, Markygerogou A, Chan WC, Thorrat A, Burden D. C-reactive protein in psoriasis. *Br J Dermatol* 2008;158:417–419.
86. Ohtsuka T. The relation between high-sensitivity C-reactive protein and maximum body mass index in patients with psoriasis. *Br J Dermatol* 2008;158:1141–1143.
87. Chodorowska G, Wojnowska D, Juszkiwicz-Borowiec M. C-reactive protein and α_2 -macroglobulin plasma activity in medium-severe and severe psoriasis. *J Eur Acad Dermatol Venereol* 2004;18:180–183.
88. Beer FC, Hind CR, Allan RM, Maseri A, Pepys MB. Measurement of serum C-reactive protein concentration in myocardial ischaemia and infarction. *Br Heart J* 1982;47:239–243.
89. Berk Bradford C, Weintraub WS, Alexander RW. Elevation of C-reactive protein in "active" coronary artery disease. *Am J Cardiol* 1990;65:168–172.
90. Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, Curhan GC, Rifai N, Cannuscio CC, Stampfer MJ, et al. Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med* 2004;351:2599–2610.
91. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;336:973–979.
92. Sesso HD, Buring JE, Rafai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. *JAMA* 2003;290:2945–2951.
93. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation* 1998;97:2007–2011.
94. Yeh ETH. CRP as a mediator of disease. *Circulation* 2004;109:II-11–II-14.
95. Scirica BM, Morrow DA. Is C-reactive protein an innocent bystander or proatherogenic culprit? *Circulation* 2006;113:2128–2151.
96. Armstrong EJ, Morrow DA, Sabatine MS. Inflammatory biomarkers in acute coronary syndromes. *Circulation* 2006;113:72–75.
97. Inoue T, Komoda H, Nonaka M, Kameda M, Uchida T, Node K. Interleukin-8 as an independent predictor of long-term clinical outcome in patients with coronary artery disease. *Int J Cardiol* 2008;124:319–325.
98. Natali A, L'Abbate, Ferrannini E. Erythrocyte sedimentation rate, coronary atherosclerosis, and cardiac mortality. *Eur Heart J* 2003;24:639–648.
99. Roman MJ, Moeller E, Davis A, Paget SA, Crow MK, Lockshin MD, Sammaritano L, Devereux RB, Schwartz JE, Levine DM, et al. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. *Ann Intern Med* 2006;144:249–256.
100. Buhlin K, Gustafsson A, Pockley G, Frostefård, Klinge B. Risk factors for cardiovascular disease in patients with periodontitis. *Eur Heart J* 2003;24:2099–2107.
101. Chen Y-W, Umeda M, Nagasawa T, Takeuchi Y, Huang Y, Inoue Y, Iwai T, Izumi Y, Ishikawa I. Periodontitis may increase the risk of peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2008;35:153–158.
102. Asanuma Y, Oeser A, Shintani AK, Turner E, Olsen N, Fazio S, Linton MF, Raggi P, Stein CM. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;349:2407–2415.
103. McMahon M, Hahn BH. Atherosclerosis and systemic lupus erythematosus- mechanistic basis of the association. *Curr Opin Immunol* 2007;19:633–639.
104. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004;351:2611–2618.
105. Marchesi C, Paradis P, Schiffrin EL. Role of the renin-angiotensin system in vascular inflammation. *Trends Pharmacol Sci* 2008;29:367–374.
106. Sahar S, Dwarakanath RS, Reddy A, Lanting L, Todorov I, Natarajan R. Angiotensin II enhances interleukin-18 mediated inflammatory gene expression in vascular smooth muscle cells. *Circ Res* 2005;96:1064–1071.
107. Katarina K, Perola M, Terwilliger J, Kaprio J, Koskenvuo M, Syvänen A-C, Vartiainen E, Peltonen L, Kontula K. Evidence for involvement of the type 1 angiotensin II receptor locus in essential hypertension. *Hypertension* 1999;33:844–849.
108. Pedrinelli R, Dell'Omo G, Di Bello V, Pellegrini G, Pucci L, Del Prato S, Penno G. Low-grade inflammation and microalbuminuria in hypertension. *Arterioscler Thromb Vasc Biol* 2004;24:2414–2419.
109. Ferrario CM, Strawn WB. Role of renin-angiotensin-aldosterone system and proinflammatory mediators in cardiovascular disease. *Am J Cardiol* 2006;98:121–128.
110. Sironi L, Nobili E, Gianella A, Gelosa P, Tremoli E. Anti-inflammatory properties of drugs acting on the renin-angiotensin system. *Drugs Today (Barc)* 2005;41:609–622.
111. Schillaci G, Pirro M. C-reactive protein in hypertension significance and predictive value. *Nutr Metab Cardiovasc Dis* 2006;16:500–508.
112. Lim HS, Lip GYH. Interleukin-15 in hypertension: further insights into inflammation and vascular disease. *Am J Hypertens* 2005;18:1017–1018.
113. Hjeistuen A, Anderssen SA, Holme I, Seljeflot I, Klemdsal TO. Markers of inflammation are inversely related to physical activity and fitness in sedentary men with treated hypertension. *Am J Hypertens* 2006;19:669–677.
114. Kampus P, Muda P, Kals J, Ristimäe T, Fischer K, Teesalu R, Zilmer M. The relationship between inflammation and arterial stiffness in patients with essential hypertension. *Int J Cardiol* 2006;122:46–51.
115. Takase H, Nakazawa A, Yamashita S, Toriyama T, Sato K, Ueda R, Dohi Y. Pioglitazone produces rapid and persistent reduction of vascular inflammation in patients with hypertension and type 3 diabetes mellitus who are receiving angiotensin II receptor blockers. *Metab Clin Exp* 2007;56:559–564.
116. Karthikeyan VJ, Lip GYH. Alpha 1-microglobulin: a further insight to inflammation in hypertension? *Am J Hypertens* 2007;20:1022–1023.
117. Aznaouridis KA, Stefanadis CI. Inflammation and arterial function. *Artery Res* 2007;1:32–38.
118. Mahmud A, Feely J. Arterial stiffness is related to systemic inflammation in essential hypertension. *Hypertension* 2005;46:1118–1122.
119. Setty AR, Curhan G, Chou HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women. *Arch Intern Med* 2007;167:1670–1675.
120. Virdis A, Schiffrin EL. Vascular inflammation: a role in vascular disease in hypertension? *Curr Opin Nephrol Hypertens* 2003;12:181–187.
121. Engström G, Janzon L, Berglund O, Lind P, Stavenow L, Hedblad B, Lindgärde F. Blood pressure increase and incidence of hypertension in relation to inflammation-sensitive plasma proteins. *Arterioscler Thromb Vasc Biol* 2002;22:2054–2058.
122. August P, Suthanthiran M. Transforming growth factor β signaling, vascular remodeling, and hypertension. *N Engl J Med* 2006;354:2721–2723.
123. Ghanem FA, Movahed A. Inflammation in high blood pressure: a clinician perspective. *J Am Soc Hypertens* 2007;1:113–119.
124. Lakoski SG, Herrington DM, Siscovick DM, Hulley SB. C-reactive protein concentration and incident hypertension in young adults. *Arch Intern Med* 2006;166:345–349.
125. Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, Goronzy J, Weyand C, Harrison DG. Role of the T-cell in the genesis of angiotensin II-induced hypertension and vascular dysfunction. *J Exp Med* 2007;204:2449–2460.
126. Brown NJ. Aldosterone and vascular inflammation. *Hypertension* 2008;51:161–167.

127. Savoia C, Schiffrin EL. Reduction of c-reactive protein and the use of anti-hypertensives. *Vasc Health Risk Manag* 2007;3:975–983.
128. Ruiz-Ortega M, Esteban V, Rupérez M, Sánchez-López E, Rodríguez-Vita J, Carvajal G, Egido J. Renal and vascular hypertension-induced inflammation: role of angiotensin II. *Curr Opin Nephrol Hypertens* 2006;15:159–166.
129. Ishibashi M, Hiasa K, Zhao Q, Inoue S, Ohtani K, Kitamoto S, Tsuchihashi M, Sugaya T, Charo IF, Kura S, et al. Critical role of monocyte chemoattractant protein-1 receptor CCR2 on monocytes in hypertension-induced vascular inflammation and remodeling. *Circ Res* 2004;94:1203–1210.
130. Recinos A, Lejeune W, Sun H, Lee CY, Tieu BC, Lu, Hou T, Boldogh I, Tilton RG, Brasier AR. Angiotensin II induces IL-6 expression and the Jak-stat2 pathway in aortic adventitia of LDL receptor-deficient mice. *Atherosclerosis* 2007;194:125–133.
131. Libby P, Ridker PM. Inflammation and atherothrombosis. *J Am Coll Cardiol* 2006;48:A33–A46.
132. Granger DN, Vowinkel T, Petnehazy T. Modulation of the inflammatory response in cardiovascular disease. *Hypertension* 2004;43:924–931.
133. Prodanowich S, Ma F, Taylor R, Pezon C, Fasihi T, Kirsner RS. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. *J Am Acad Dermatol* 2005;52:262–267.
134. Choi HK, Hernán MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002;359:1173–1177.
135. Ikonomidis I, Andreotti F, Economou E, Stefanadis C, Toutouzas P, Nihoyannopoulos P. Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin. *Circulation* 1999;100:793–798.
136. White WB, West CR, Borer JS, Gorelick PB, Lavange L, Pan SX, Weiner E, Verburg KM. Risk of cardiovascular events in patients receiving celecoxib: a meta-analysis of randomized clinical trials. *Am J Cardiol* 2007;99:91–98.
137. Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoefft A, Parlow JL, Boyce SW, Verburg KM. Complications of the COX-2-inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005;352:1081–1091.
138. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanasa A, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;353:1092–1102.
139. Solomon SD, McMurray JJV, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;353:1071–1080.
140. Schönbeck U, Libby O. Inflammation, immunity, and HMG-CoA reductase inhibitors. *Circulation* 2004;109:II-18–II-26.
141. Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, Gotto AM. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001;26:1959–1965.
142. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. *Circulation* 2004;109:II-2–II-10.
143. Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels. *JAMA* 2001;286:64–70.
144. McCarey DW, McInnes IB, Madhok R, Hampson R, Scherbakova O, Ford I, Capell HA, Sattar N. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomized placebo controlled trial. *Lancet* 2004;363:2015–2021.
145. Shirinsky IV, Shirinsky VS. Efficacy of simvastatin in plaque psoriasis: a pilot study. *J Am Acad Dermatol* 2007;57:529–531.
146. Namazi MR. Statins: novel additions of the dermatologic arsenal? *Exp Dermatol* 2004;13:337–339.
147. Yu B-L, Zhao S-P. Anti-inflammatory effect is an important property of niacin on atherosclerosis beyond its lipid-altering effects. *Med Hypotheses* 2007;69:90–94.
148. Kashyap ML, McGovern ME, Berra K, Guyton JR, Kwitterovich PO, Harper WL, Toth PD, Favrot LK, Kerzner B, Nash SD, et al. Long-term study and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia. *Am J Cardiol* 2002;89:672–678.
149. Grundy SM, Vega GL, McGovern ME, Tullock BR, Kendall DM, Fitz-Patrick D, Ganda OP, Rosenson RS, Buse JB, Robertson DD, et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes. *Arch Intern Med* 2002;162:1568–1576.
150. Friedewald VE, Grundy S, Gotto AM, Haffner S, Denke MA, Hollander P, Roberts WC. The editor's roundtable: the metabolic syndrome. *Am J Cardiol* 2007;99:382–389.
151. Ridker PM, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, Khurmi NS, Koenig W, Libby P, Lorenzatti AJ, Nordestgaard BG, et al. Baseline characteristics of participants in the Jupiter trial, a randomized placebo-controlled primary prevention trial of statin therapy among individuals with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. *Am J Cardiol* 2007;100:1659–1664.
152. Grundy SM, Cleeman JI, Mertz CN, Brewer HB, Clark LT, Hunninghake DB, Pasternak RC, Smith SC, Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227–239.
153. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206–1252.
154. United States Department of Agriculture. Dietary guidelines for Americans 2005. Available at: <http://www.health.gov/DIETARYGUIDELINES/dga2005/document/html/chapter9.htm>. Accessed October 28, 2008.
155. McKenney J. New perspective on the use of niacin in the treatment of lipid disorders. *Arch Intern Med* 2004;164:697–705.
156. Guyton JR, Bays HE. Safety considerations with niacin therapy. *Am J Cardiol* 2007;99:22C–31C.
157. Cheng K, Wu TJ, Sturino C, Metters K, Gottesdiener K, Wright SD, Wang Z, O'Neill G, Lai E, Waters MG. Antagonism of the prostaglandin D₂ receptor 1 suppresses nicotine-induced vasodilation in mice and humans. *Proc Natl Acad Sci U S A* 2006;103:6682–6687.
158. Wolf R, Schiavo AL, Russo A, de Angelis F, Ruocco V. Effects of gemfibrozil on in vitro cultured normal human skin explants. *Int J Dermatol* 1999;38:65–69.
159. Fry L, Baker BS. Triggering psoriasis: the role of infections and medications. *Clin Dermatol* 2007;25:606–615.
160. Kawamura AI, Ochiai T. Candesartan cilexetil induced pustular psoriasis. *Eur J Dermatol* 2003;13:406–407.
161. Wakefield PE, Berger TG, James WD. Atenolol-induced pustular psoriasis. *Arch Dermatol* 1990;126:968–969.
162. Coroas, ASPS, de Oliveira JGG, Magina S, Santos J, Pestana M, de Almeida MDV. Cyclosporine enhances salt sensitivity of body water composition as assessed by impedance among psoriatic patients with normal renal function. *J Ren Nutr* 2004;14:226–232.
163. Rayyes OA, Wallmark A, Florén C-H. Cyclosporine inhibits catabolism of low-density lipoproteins in hepg2 cells by about 25%. *Hepatology* 1996;24:613–619.
164. Katz HI, Waalen J, Leach EE. Acitretin in psoriasis: an overview of adverse effects. *J Am Acad Dermatol* 1999;41:S7–S12.
165. Kwon HJ, Coté TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. *Ann Intern Med* 2003;138:807–811.
166. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effects of anti-tumor necrosis factor therapy. *Am J Med* 2004;116:305–311.
167. Bozhurt B, Torre-Amione G, Warren MS, Whitmore J, Soran OZ, Feldman AM, Mann DL. Results of targeted anti-tumor necrosis factor therapy with etanercept (Enbrel) in patients with advanced heart failure. *Circulation* 2001;103:1044–1047.
168. Listing J, Strangfeld A, Kekow J, Schneider M, Kapelle A, Wassenberg S, Zink A. Does tumor necrosis factor α inhibition promote or prevent heart failure in patients with rheumatoid arthritis? *Arthritis Rheum* 2008;58:667–677.
169. Danila MI, Patkar NM, Curtis JR, Saag KG, Teng GG. Biologics and heart failure in rheumatoid arthritis: are we any wiser? *Curr Opin Rheumatol* 2008;20:327–333.
170. Wolf R, Tamir A, Brenner S. Psoriasis related to angiotensin-converting enzyme inhibitors. *Dermatologica* 1990;181:51–53.