Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

REVIEW

Inflammation in Atherosclerosis:
Transition From Theory to Practice

Peter Libby, MD; Yoshihisa Okamoto, MD, PhD*;
Viviane Z. Rocha, MD; Eduardo Folco, PhD

Inflammation drives the formation, progression, and rupture of atherosclerotic plaques. Experimental studies have demonstrated that an inflammatory subset of monocytes/macrophages preferentially accumulate in atherosclerotic plaque and produce proinflammatory cytokines. T lymphocytes can contribute to inflammatory processes that promote thrombosis by stimulating production of collagen-degrading proteinases and the potent procoagulant tissue factor. Recent data link obesity, inflammation, and modifiers of atherosclerotic events, a nexus of growing clinical concern given the worldwide increase in the prevalence of obesity. Modulators of inflammation derived from visceral adipose tissue evoke production of acute phase reactants in the liver, implicated in thrombogenesis and clot stability. Additionally, C-reactive protein levels rise with increasing levels of visceral adipose tissue. Adipose tissue in obese mice contains increased numbers of macrophages and T lymphocytes, increased T lymphocyte activation, and increased interferon-γ (IFN-γ) expression. IFN-γ deficiency in mice reduces production of inflammatory cytokines and inflammatory cell accumulation in adipose tissue. Another series of in vitro and in vivo mouse experiments affirmed that adiponectin, an adipocytokine, the plasma levels of which drop with obesity, acts as an endogenous antiinflammatory modulator of both innate and adaptive immunity in atherogenesis. Thus, accumulating experimental evidence supports a key role for inflammation as a link between risk factors for atherosclerosis and the biology that underlies the complications of this disease. The recent JUPITER trial supports the clinical utility of an assessment of inflammatory status in guiding intervention to limit cardiovascular events. Inflammation is thus moving from a theoretical concept to a tool that provides practical clinical utility in risk assessment and targeting of therapy. (*Circ J* 2010; **74:** 213–220)

Key Words: Adaptive immunity; Adiponectin; Atherosclerosis; Inflammation; Obesity

Inflammation in Atherosclerosis

Over the past few years an understanding of the importance of inflammation during all stages of atherosclerosis, from its inception through its progression and its final complication of thrombosis, has greatly increased. No longer do we view atherosclerosis merely as a cholesterol storage disease that obstructs arteries.[1] Our therapeutic goals now reach beyond addressing flow-limiting stenoses by invasive revascularization procedures. Much of the plaque's peril lies in its thrombogenic potential, not just the degree of stenosis it causes. Inflammatory processes govern many of the aspects of the biology of plaques that determine their clinical destiny.[2–5]

Under normal conditions, the endothelial cells of the arterial wall resist adhesion and aggregation of leukocytes and promote fibrinolysis. When activated by stimuli such as hypertension, smoking, an unhealthy diet, obesity, insulin resistance or inflammation, the endothelial cells express a series of adhesion molecules that selectively recruit various classes of leukocytes. Blood monocytes, the most numerous of the inflammatory cells that populate plaques, adhere to the dysfunctional endothelial surface by binding to leukocyte adhesion molecules not expressed by normal endothelial cells, but induced by mediators associated with risk factors such as proinflammatory cytokines, angiotensin II, and oxidized lipoproteins (**Figure 1**). Once the monocytes adhere to the activated endothelium, proinflammatory proteins known as chemokines provide a chemotactic stimulus that induces them to enter the intima. Within the intima, the monocytes mature into macrophages, which express scavenger receptors that allow them to engulf modified lipoprotein particles. The cytoplasm becomes engorged with lipid particles, giving the macrophages the typical microscopic frothy appearance of the foam cells found in atherosclerotic lesions. The macrophages proliferate within the intima, sustaining and amplifying the inflammatory process by releasing several growth factors and cytokines, including enzymes that can destroy the arterial extracellular matrix, such as metalloproteinases (MMPs) and

Received November 11, 2009; accepted November 26, 2009; released online January 9, 2010
Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, *Department of Bioregulation, Nippon Medical School, Kawasaki, Kanagawa, Japan
Mailing address: Peter Libby, MD, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, 77 Avenue Louis Pasteur NRB 741 Boston, MA 02115, USA. E-mail: plibby@rics.bwh.harvard.edu
ISSN-1346-9843 doi:10.1253/circj.CJ-09-0706

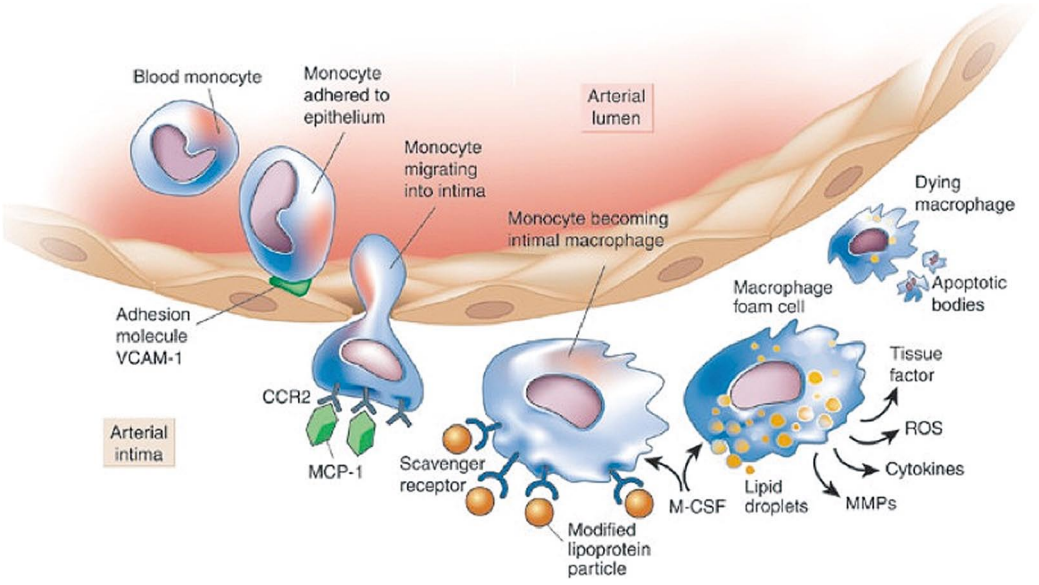

Figure 1. Mononuclear phagocytes in atherogenesis.

the procoagulant tissue factor (TF).[2–5]

Examples of specific mediators involved in initiation of atherosclerotic plaques include vascular cell adhesion molecule-1 (VCAM-1).[6,7] The chemoattractant cytokine monocyte chemoattractant protein-1 (MCP-1) interacts with the monocyte chemokine receptor CCR2, recruiting the monocytes to the arterial endothelium and facilitating their entry between endothelial cells by diapedesis.[8,9] One key mediator of monocyte maturation into macrophages within the intima, macrophage colony-stimulating factor, increases in experimental and human atherosclerotic lesions and can induce scavenger receptor expression.[10,11]

Monocyte Heterogeneity

Like endothelial cells and smooth muscle cells, monocytes/macrophages exhibit heterogeneity, falling into 2 distinct subsets.[12,13] Mice with normal blood cholesterol have approximately equal numbers of circulating monocytes bearing low or high levels of the marker Ly-6C. When fed a high-fat Western diet, apolipoprotein-E deficient (apoE$^{-/-}$) mice have a striking increase in monocytes with high levels of this marker (Ly-6C^{hi}), but no change in the numbers of monocytes with low levels of Ly-6C. Ly-6C^{hi} monocytes adhere preferentially to activated endothelium, accumulate in atherosclerotic plaques, and rapidly become lesional macrophages.[13,14] In comparison with Ly-6C^{lo} cells, Ly-6C^{hi} monocytes have heightened proinflammatory properties, producing higher levels of proinflammatory cytokines, myeloperoxidase, and some proteinases. An et al demonstrated that Ly-6C^{hi} monocytes produce higher levels of P-selectin glycoprotein ligand-1 (PSGL-1) than Ly-6C^{lo} monocytes, which contributes to their homing to and rolling on the arterial endothelium prior to penetrating into the intima.[15] Although human monocytes do not express Ly-6C, data from the same study indicate that high expression of PSGL-1 may identify a proinflammatory population of monocytes in humans. Taken together, these studies support a particular role for proinflammatory monocytes in the inflammatory process that takes place in atherosclerotic plaques.

In addition to macrophages, the prototypical cells of innate immunity, atheromata contain a smaller population of T lymphocytes. Although numerically a minority of the leukocytes in plaque, these master cells of the adaptive immune response appear to exert decisive regulatory roles by instructing the more abundant monocytic effectors of the innate immune response. Thus, the relationship of the T cells to the mononuclear phagocytes may be like the conductor of an orchestra or the general of an army.[16] The T cells in the plaque also display heterogeneity of functions. Some subsets appear to be proinflammatory (eg, Th1 cells), while others tend to mute inflammation (eg, Treg and Th2 cells). The putative antigens that activate the plaque T cells, and the regulation of the balance between the T cell subsets, remain areas of active investigation.[16–20] B lymphocytes, the key cells in the humoral arm of the adaptive immune response, seem to have a net inhibitory effect on atherogenesis, a property being explored in the development of vaccines to mitigate atherosclerosis.[21]

Inflammation and Thrombosis

Fracture of the plaque's fibrous cap and subsequent thrombosis cause most cases of fatal myocardial infarction (MI).[22,23] Inflammation regulates the fragility of the fibrous cap, as well as the thrombogenic potential of the plaque.[2–5] In addition to macrophages, T lymphocytes play an important role in the inflammatory process leading to thrombosis. T lymphocytes enter the intima by binding to VCAM-1 and in response to the interferon-γ (IFN-γ)-inducible chemokine ligands (CXCLs), IFN-γ-inducible protein-10 (IP-10), monokine induced by IFN-γ (MIG), and IFN-γ-inducible T-cell α-chemoattractant (I-TAC).[24–26] These chemokines bind to the chemokine receptor CXCR3, expressed on T lymphocytes in the plaque. When activated in the intima, the T lymphocytes produce pro-

Table. Secreted Adipose Tissue Factors That Can Cause Inflammation

Adipose tissue products	Status in obesity	Comments
Leptin	↑	Inhibits food intake; obesity characterized by resistance to leptin
Adiponectin	↓	Insulin sensitizer; antiinflammatory actions
Resistin	↑	Induces IR; in humans secreted by macrophages
RBP4	↑	Might promote IR
Visfatin	↑	Insulin-mimetic action
Omentin	↓	Insulin sensitizer; likely secreted by SVC rather than adipocytes
TNF-α	↑	Induces IR
IL-6	↑	Induces IR
IL-1β	↑	With IL-6, predicts risk for T2DM
MCP-1	↑	Induces IR and promotes macrophage infiltration
CRP	↑	Proinflammatory: increases risk of CV events
MIF	↑	Proinflammatory
PAI-1	↑	Fibrinolysis inhibitor: increases risk of CV events

IR, insulin resistance; RBP4, retinol-binding protein 4; SVC, stromal vascular cells; TNF, tumor necrosis factor; IL, interleukin; T2DM, type 2 diabetes mellitus; MCP-1, monocyte chemoattractant protein-1; CRP, C-reactive protein; CV, cardiovascular; MIF, macrophage migration inhibitory factor; PAI-1, plasminogen activator inhibitor-1.

inflammatory cytokines, including the CD40 ligand, CD154. Ligation of CD40 by CD154 induces production of extracellular matrix-degrading MMPs, and the potent procoagulant TF.[27,28] TF initiates the coagulation cascade, enhancing the thrombogenicity of the plaque's lipid core.

Inflammation also influences the metabolism of collagen, the key extracellular matrix molecule that confers strength and stability on the fibrous cap. IFN-γ produced by T lymphocytes in the plaque inhibits production of collagen by smooth muscle cells.[29] T lymphocytes also promote degradation of collagen indirectly by local production of cytokines, including CD40L, that boost the elaboration of MMPs by neighboring macrophages.[27] Thus, inflammation contributes to all phases of atherosclerosis, from its initiation to its ultimate complication of thrombosis.

Obesity, Inflammation, and Vascular Risk

An epidemic of obesity is sweeping the world, led by the United States, in which approximately 65% of adults are overweight or obese.[30] Obesity may itself heighten risk of cardiovascular disease (including in Japanese people[31]), and certainly promotes the development of diabetes mellitus (DM), a condition complicated by augmented risk of both macrovascular and microvascular disease. An emerging understanding of the proinflammatory nature of adipose tissue and its connection to atherosclerosis provides new insight into the mechanisms of these important associations.[32]

Inflammatory Mediators in Adipose Tissue

In contrast with classical views, adipose tissue not only provides a depot for fat storage but can serve as a factory for manufacturing bioactive molecules (adipocytokines), including proinflammatory cytokines.[33] Adipose tissue can elaborate numerous modulators of inflammation (**Table**).[34] Visceral adipose tissue that accumulates in the abdomen drains directly through the portal circulation to the liver, where the proinflammatory cytokines (in particular interleukin (IL)-6) modulate hepatic protein synthesis by evoking an acute phase response. Some acute phase reactants clearly participate in the causal pathway of thrombogenesis and thrombus formation and stability; for example, the clotting factor fibrinogen and plasminogen activator inhibitor-1 (PAI-1), an important inhibitor of fibrinolysis.[35,36]

The liver also synthesizes acute phase reactants that, while not indubitably linked to causal pathways, may nonetheless serve as useful markers of inflammation; for example, C-reactive protein (CRP) or serum amyloid-A.[37] Blood levels of these markers reflect an individual's overall inflammatory status. Along with several other studies, the Quebec Heart Study showed that obesity is associated with systemic inflammation by demonstrating a relationship between the amount of visceral adipose tissue and the CRP level.[38] The same study also showed that CRP levels increase as waist circumference increases.

The Adaptive Immune Response in Adipose Tissue

Considerable recent data support the participation of adipose tissue in innate immunity.[39,40] As in the atheroma, T lymphocytes may provide important regulatory input to innate immunity in the form of proinflammatory Th1 cytokines, such as IFN-γ, and Th2 cytokines, such as IL-10, that may mute inflammation.[41,42] Moreover, recent studies have demonstrated an essential role of $CD8^+$ T lymphocytes and T regulatory cells in the regulation of adipose tissue inflammation, further supporting the importance of the adaptive arm of immunity in obesity.[43,44] We recently tested the conjecture that adaptive immunity also participates in the inflammatory network in adipose tissue.[45] In this study, male C57BL/6 mice consumed a standard low-fat diet until they reached 6 weeks of age, and then were switched to a high-fat diet for 15 or 21 weeks. Lean controls remained on a low-fat diet. Flow cytometry showed that visceral adipose tissue from the obese mice contained more macrophages than that from the lean mice. Visceral adipose tissue from obese mice also contained more $CD4^+$ and $CD8^+$ T lymphocytes than that from lean mice ($P<0.05$) (**Figure 2**). Quantitative immunohistochemistry yielded similar findings.

Immunohistochemical examination also demonstrated significantly more cells expressing the mouse class II major histocompatibility complex antigen $I\text{-}A^b$ in visceral adipose tissue from obese mice than in adipose tissue from lean mice

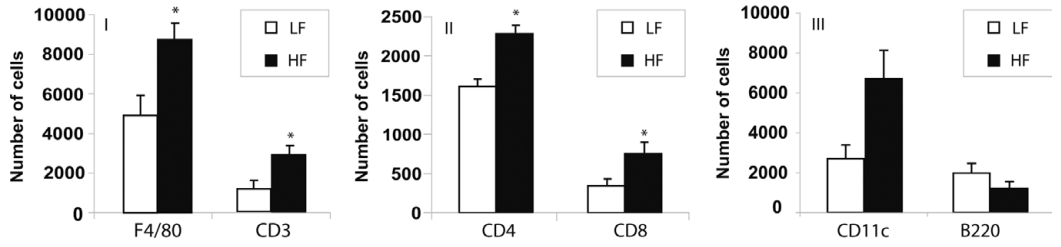

Figure 2. Visceral adipose tissue (VAT) from obese mice contains more inflammatory cells than VAT from lean counterparts. LF, low-fat diet; HF, high-fat diet.

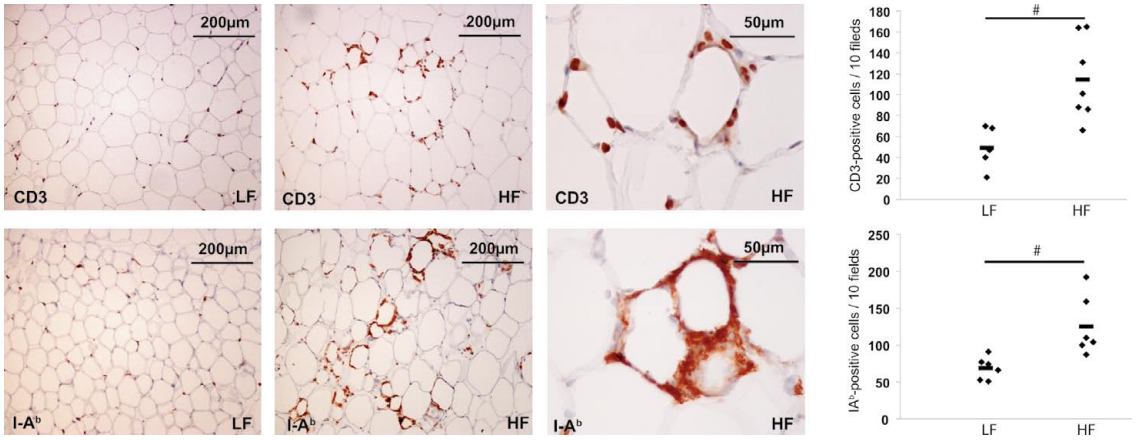

Figure 3. Accentuated major histocompatibility complex class II levels (I-A^b) in visceral adipose tissue of obese mice indicate local T lymphocyte activation. LF, low-fat diet; HF, high-fat diet.

(P<0.05) (**Figure 3**). This finding indicates local T lymphocyte activation in adipose tissue of obese mice. IFN-γ expression in visceral adipose tissue from obese mice increased significantly compared with lean mice (P<0.04), as demonstrated by reverse transcription-quantitative polymerase chain reaction that measured levels of IFN-γ over glyceraldehyde 3-phosphate dehydrogenase mRNA.[45]

The presence of T lymphocytes and IFN-γ in adipose tissue suggests activity of T lymphocyte chemoattractants. Therefore, we performed a transcriptional profiling analysis of differentiated murine 3T3-L1 adipocytes stimulated with IFN-γ in vitro. The IFN-γ stimulated cells had increased levels of 5 gene families: those responsible for lipid metabolism, glucose metabolism, fatty acid metabolism, inflammatory responses, and chemokines. We focused on the chemokines because of their contribution to the recruitment of the mononuclear inflammatory cells that populate adipose tissue and produce the cytokines that evoke the acute phase response in the liver. The IFN-γ stimulated adipocytes exhibited significantly increased production of several chemokines from the CC and CXC families and chemokine receptors (P<0.05). The increase in CXCR3 expression held particular interest, as this chemokine receptor selectively binds the chemokines IP-10, MIG, and I-TAC and is only expressed on activated T lymphocytes. These 3 chemokines increased significantly in the IFN-γ-stimulated cells compared with the untreated cells (P<0.05), suggesting that IFN-γ selectively regulates inflammatory gene expression in adipocytes.

Our previous studies had shown that CD4$^+$ T lymphocytes that accumulate in human atherosclerotic plaques express CXCR3.[24] In the recent studies, incubation of mouse perigonadal adipose tissue with IFN-γ significantly increased the secretion of IP-10 and MIG, confirming the role of IFN-γ in stimulating expression of these chemokine genes.[45]

Studies in C57BL6 wild-type (WT) and IFN-γ-deficient mice have extended these in vitro results in vivo.[45] The mice consumed regular chow for 5 weeks, and then some of the WT and IFN-γ-deficient (n=6) mice were switched to a high-fat diet while the rest of the WT and IFN-γ-deficient mice remained on the low-fat diet for 15 weeks, at which point tissues from all of the mice were harvested. In white adipose tissue, the expression of both MCP-1 and regulated on activation, normal T cell expressed and secreted (RANTES) fell significantly in the IFN-γ-deficient mice on the high-fat diet relative to WT mice on the high-fat diet. Glucose tolerance curves showed that IFN-γ deficiency had a systemic influence on mice fed a high-fat diet. Whereas IFN-γ-deficient and WT mice on a low-fat diet had similar glucose tolerance curves, IFN-γ-deficient mice on a high-fat diet had greater glucose tolerance than WT mice fed a high-fat diet. Assessment of macrophage content in the adipose tissue of these animals

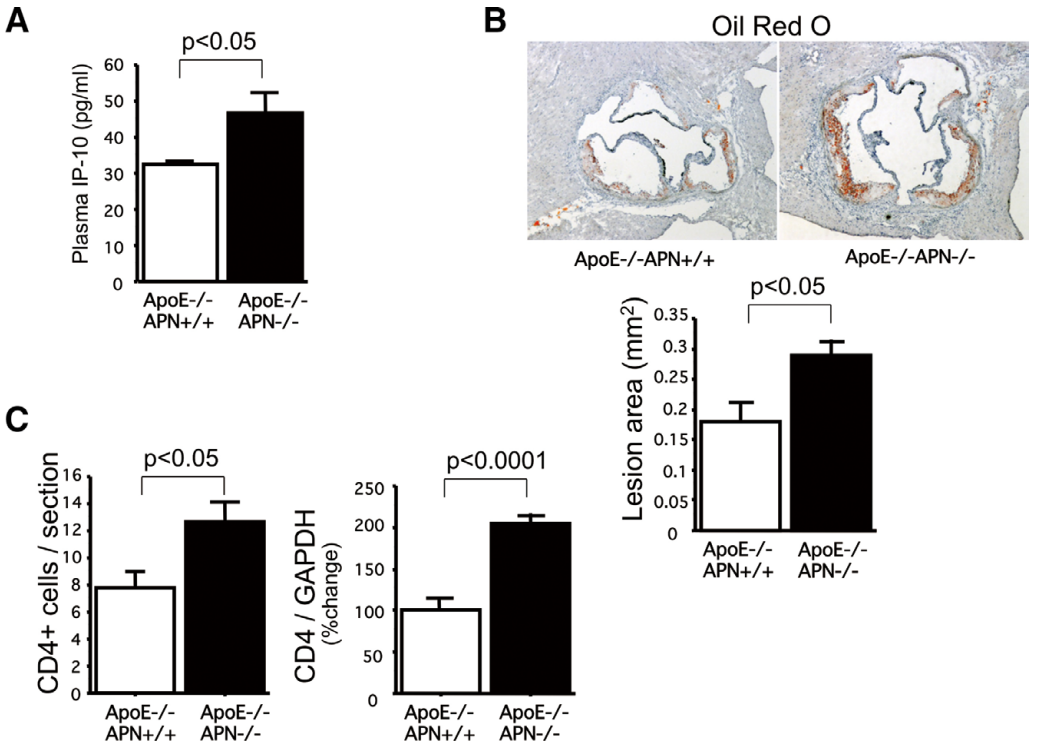

Figure 4. Adiponectin deficiency increases plasma inducible protein-10 (IP-10) levels, accelerates T lymphocyte accumulation in atherosclerotic lesions, and promotes the development of atherosclerosis in apolipoprotein-E (apoE) deficient mice.

showed that high-fat-fed IFN-γ-deficient mice had reduced numbers of Mac-3-positive cells compared with high-fat-fed WT mice (P<0.05). These findings indicate that IFN-γ deficiency reduces inflammatory cytokines and accumulation of macrophages in adipose tissue, and improves glucose tolerance in mice in vivo. This study supports an important role for T lymphocytes and IFN-γ in the regulation of the inflammatory response that accompanies obesity, and establishes a novel mechanism by which mediators of adaptive immunity can contribute to the metabolic complications of obesity.

Adiponectin as a Modulator of Adaptive Immunity

Adipose tissue produces a number of adipocytokines, among the most abundant of which is adiponectin.[46–49] Obese mice and humans have lower plasma levels of adiponectin than their lean counterparts.[46,50,51] We studied the antiinflammatory actions of adiponectin to clarify its role in regulating atherogenesis through the T lymphocyte chemoattractant pathway.[52] Human monocyte-derived macrophages were cultured with or without recombinant human adiponectin for 24 h, then underwent stimulation with lipopolysaccharide (LPS) for 6 h. Transcriptional profiling showed that LPS markedly induced expression of IP-10, I-TAC, and MIG in cells not exposed to adiponectin. Preincubation with adiponectin strongly inhibited LPS-induced expression of IP-10 (–99.1%, P<0.01), I-TAC (–97.1%, P<0.01), and MIG (–90.7%, P<0.05), compared with non-adiponectin-treated controls. Adiponectin inhibited expression of these chemokines at both the mRNA and protein levels in a concentration-dependent manner.

In vivo studies in apolipoprotein-E-deficient and adiponectin double-deficient (apoE$^{-/-}$ APN$^{-/-}$) mice showed that at 30 weeks, plasma levels of IP-10, the sentinel IFN-γ inducible T lymphocyte chemokine, were 44% higher in apoE$^{-/-}$ APN$^{-/-}$ mice than in apoE$^{-/-}$ APN$^{+/+}$ mice (P<0.05) (Figure 4). The apoE$^{-/-}$ APN$^{-/-}$ mice also developed 61% larger atherosclerotic lesions (P<0.05) and had 63% more CD4^{+} T lymphocytes within the lesions in aortic root than apoE$^{-/-}$ APN$^{+/+}$ mice (P<0.05), indicating that adiponectin retards the recruitment of T lymphocytes to evolving atheromata.

This study supports a role for adiponectin as an endogenous antiinflammatory mediator involved in adaptive as well as innate immunity. Not only do these findings show that adiponectin reduces the production of CXCR3 chemokine ligands by human macrophages, but they suggest the existence of a new mechanism by which adiponectin may mitigate inflammation during atherogenesis by modulating adaptive immunity.

The JUPITER Trial: A Clinical Application of Inflammation Biology

As noted earlier, blood levels of the marker of inflammation CRP (measured with a high-sensitivity assay denoted hsCRP) can predict future clinical cardiovascular events.[37,38] Posthoc analysis of the AFCAPS/TExCAPS study suggested that apparently well people with some inflammation (indicated by above median CRP) but below median levels of low-density lipoprotein (LDL) could nonetheless benefit from statin therapy.[53] Yet until recently, we lacked prospective evidence that CRP-guided therapy improves outcomes in those with LDL levels at or below targets for primary prevention of cardio-

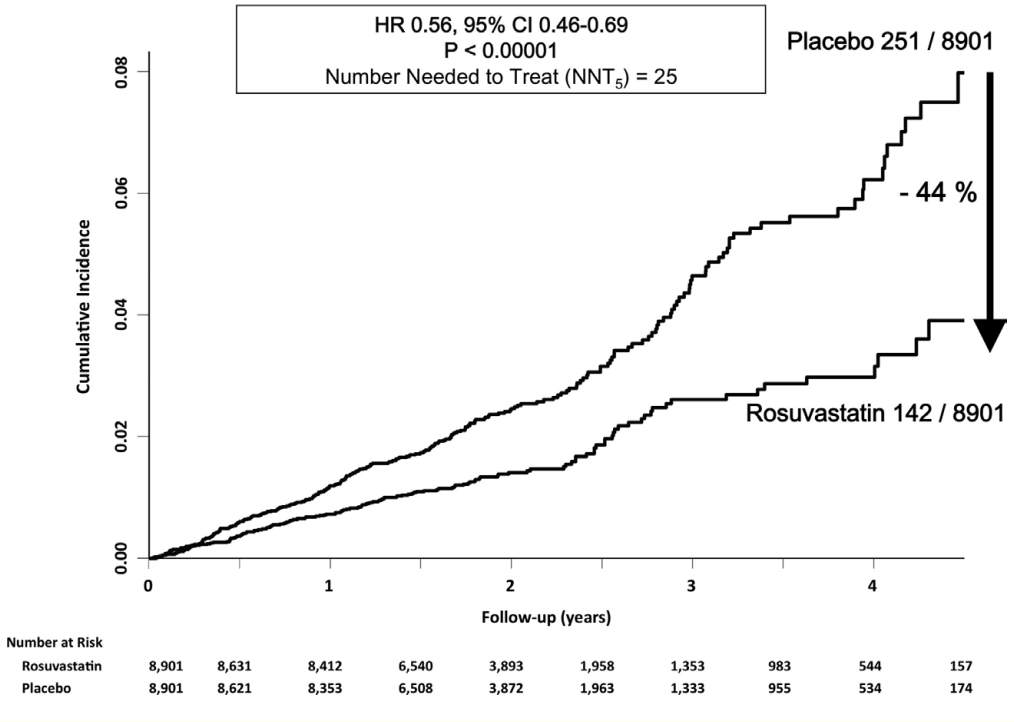

Figure 5. Jupiter trial primary endpoint: myocardial infarction, stroke, unstable angina/revascularization, cardiovascular death.

vascular events. For this reason, Dr Paul Ridker designed the JUPITER trial to test this hypothesis prospectively in a large-scale randomized placebo-controlled clinical trial.[54] Subjects with no history of coronary artery disease, LDL-cholesterol <3.4 mmol/L, and CRP >19.0 nmol/L randomly received treatment with rosuvastatin 20 mg daily (n=8,901) or placebo (n=8,901). The primary endpoint included occurrence of a major cardiovascular event, defined as MI, non-fatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes. The secondary endpoints included the components of the primary endpoint analyzed individually and death from any cause. The trial design called for 2 interim efficacy analyses, but the trial was terminated on the recommendation of the independent academic data safety monitoring committee almost 2 years prematurely, because of the unequivocal evidence of benefit with rosuvastatin therapy.

Baseline characteristics did not differ between the 2 treatment groups. The median age was 66 years and 38% of the subjects were female. Caucasians represented 71% of subjects; the remaining subjects were black (12.5%) or Hispanic (12.7%). Approximately 16% of subjects were smokers, 41% had metabolic syndrome, approximately 11.5% had a family history of cardiovascular disease, and 16.6% used aspirin. The median systolic blood pressure was 134 mmHg and the median diastolic blood pressure was 80 mmHg. The median body mass index was 28.3. In both groups, the median LDL-cholesterol level was 2.8 mmol/L, the median high-density lipoprotein (HDL) cholesterol level was 1.3 mmol/L, and the median triglyceride level was 1.3 mmol/L. The CRP levels were 40.0 and 40.9 nmol/L in the rosuvastatin and placebo groups, respectively.

At the time of study termination (median follow-up 1.9 years; maximum follow-up 5.0 years), 142 major cardiovascular events had occurred in the rosuvastatin group, compared with 251 events in the placebo group, representing a highly significant 44% reduction in the cumulative incidence of cardiovascular events with rosuvastatin therapy (hazard ratio 0.56, 95% confidence interval 0.46–0.69; P<0.00001) (**Figure 5**). The cumulative incidence of "hard" endpoints (MI, stroke, or cardiovascular death) fell by 47% in the rosuvastatin group compared with the placebo group (P<0.00001) (**Figure 6**). Participants in the rosuvastatin group underwent 47% fewer arterial revascularization procedures or hospitalizations for unstable angina than those receiving placebo (P< 0.00001). Rosuvastatin treatment also significantly reduced occurrence of the individual components of the primary endpoint, and the pre-specified endpoints of stroke and venous thromboembolism.[54,55]

Subgroup analysis of the primary endpoint showed that all of the pre-specified groups gained benefit from rosuvastatin therapy. The magnitude of benefit was the same for men and women, Caucasians and non-Caucasians, obese and non-obese subjects, and those with low and high Framingham risk scores. JUPITER provides the largest data set supporting the efficacy of statins in women and in non-Caucasians. Asian individuals were not included in JUPITER.

Even though the design of the study did not anticipate power to evaluate mortality, the efficacy analysis did show a statistically significant reduction in all-cause mortality of 20% in the rosuvastatin group (n=198/8,901) compared with the placebo group (n=247/8,901) (HR 0.80, 95%CI 0.67–0.97; P=0.02). This reduction in all-cause mortality, the "holy grail" of clinical trials, helps put to rest traditional concerns regarding the efficacy of lipid-lowering therapy in this regard.

The clinical benefit in JUPITER came at little cost in terms of unwanted effects. The only statistically significantly increased adverse events in the rosuvastatin group were

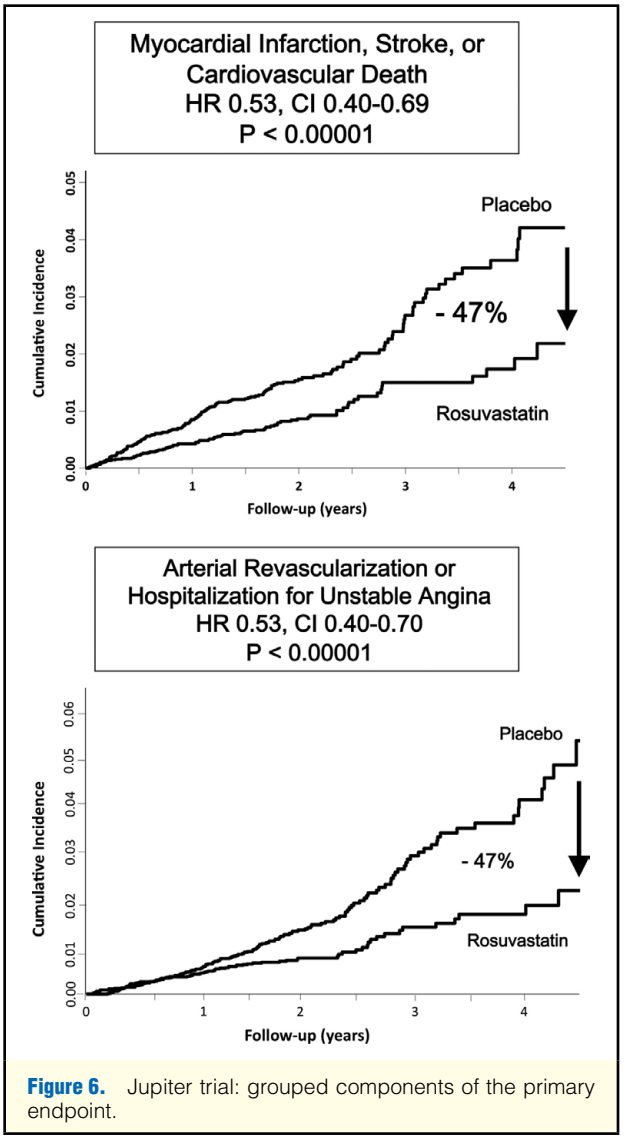

Figure 6. Jupiter trial: grouped components of the primary endpoint.

elevated HbA_{1c} (P=0.01) and physician-reported incident DM (P=0.01). Notably, the reports of myalgia were the same in the rosuvastatin and placebo groups of this double-blind trial.

The JUPITER study showed that statin therapy reduced the incidence of major cardiovascular events even in subjects with LDL levels well below the threshold for treatment according to current guidelines. The reduction in the hazard for cardiovascular events in this trial, with enrollment based on elevated hsCRP levels rather than elevated LDL-cholesterol levels, exceeded the relative benefit observed in most previous statin trials. Importantly, more than 6,000 of the subjects enrolled in this trial had CRP >2 mg/L as their only risk factor. Additional results on the cost benefits, cost effectiveness, and other analyses of JUPITER are forthcoming.

Further pre-specified analyses of JUPITER furnish insight regarding the mechanism of benefit of the statin intervention. Following similar analyses of trials of statin therapy in patients with acute coronary events, the JUPITER investigators stratified outcomes by in-trial achieved levels of CRP and LDL. These data provide further evidence that reduction in cardiovascular events by statin treatment derives from both LDL lowering and an LDL-independent antiinflammatory effect. These concordant findings from intervention trials in both primary and secondary prevention support the practical clinical importance of inflammation in atherosclerosis.

Conclusions

The studies described in this review contribute to our understanding of the pathophysiology of atherosclerosis. Studies in mice and in humans show that inflammation drives all phases of atherosclerosis, including initiation, progression, and thrombotic complications of the lesion. Inflammation provides a common link between many risk factors for atherosclerosis and altered arterial biology. Modification of these risk factors can exert a clinical benefit by reducing inflammation and its effects. Emerging evidence from clinical trials supports the use of inflammatory status as a guide to therapy that can reduce cardiovascular events in apparently healthy people who would otherwise evade detection as standing to benefit from treatment. Indeed, the concept of inflammation in atherosclerosis has emerged from the realm of theory and laboratory investigation to assume a promising role as a useful tool in the clinic to aid the prevention and management of cardiovascular disease.

Acknowledgement

We thank Ms. Mary Mosely and Ms. Sara Karwacki for editorial assistance.

References

1. Libby P. Atherosclerosis: The new view. *Sci Am* 2002; **286:** 46–55.
2. Libby P. Inflammation in atherosclerosis. *Nature* 2002; **420:** 868–874.
3. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002; **105:** 1135–1143.
4. Mestas J, Ley K. Monocyte-endothelial cell interactions in the development of atherosclerosis. *Trends Cardiovasc Med* 2008; **18:** 228–232.
5. Rader DJ, Daugherty A. Translating molecular discoveries into new therapies for atherosclerosis. *Nature* 2008; **451:** 904–913.
6. Cybulsky MI, Gimbrone Jr MA. Endothelial expression of a mononuclear leukocyte adhesion molecule during atherogenesis. *Science* 1991; **251:** 788–791.
7. Li H, Cybulsky MI, Gimbrone MA Jr, Libby P. Inducible expression of vascular cell adhesion molecule-1 (VCAM-1) by vascular smooth muscle cells in vitro and within rabbit atheroma. *Am J Pathol* 1993; **143:** 1551–1559.
8. Gu L, Okada Y, Clinton S, Gerard C, Sukhova G, Libby P, et al. Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low-density lipoprotein-deficient mice. *Mol Cell* 1998; **2:** 275–281.
9. Boring L, Gosling J, Cleary M, Charo IF. Decreased lesion formation in CCR2–/– mice reveals a role for chemokines in the initiation of atherosclerosis. *Nature* 1998; **394:** 894–897.
10. Clinton S, Underwood R, Sherman M, Kufe D, Libby P. Macrophage-colony stimulating factor gene expression in vascular cells and in experimental and human atherosclerosis. *Am J Pathol* 1992; **140:** 301–316.
11. Rosenfeld M, Ylä-Herttuala S, Lipton B, Ord V, Witztum J, Steinberg D. Macrophage colony-stimulating factor mRNA and protein in atherosclerotic lesions of rabbits and humans. *Am J Pathol* 1992; **140:** 291–300.
12. Tacke F, Alvarez D, Kaplan TJ, Jakubzick C, Spanbroek R, Llodra J, et al. Monocyte subsets differentially employ CCR2, CCR5, and CX3CR1 to accumulate within atherosclerotic plaques. *J Clin Invest* 2007; **117:** 185–194.
13. Libby P, Nahrendorf M, Pittet MJ, Swirski FK. Diversity of denizens of the atherosclerotic plaque: Not all monocytes are created equal. *Circulation* 2008; **117:** 3168–3170.
14. Swirski FK, Libby P, Aikawa E, Alcaide P, Luscinskas FW, Weissleder R, et al. Ly-6Chi monocytes dominate hypercholesterolemia-associated monocytosis and give rise to macrophages in atheromata. *J Clin Invest* 2007; **117:** 195–205.

15. An G, Wang H, Tang R, Yago T, McDaniel JM, McGee S, et al. P-selectin glycoprotein ligand-1 is highly expressed on Ly-6Chi monocytes and a major determinant for Ly-6Chi monocyte recruitment to sites of atherosclerosis in mice. *Circulation* 2008; **117:** 3227–3237.
16. Hansson GK, Libby P. The immune response in atherosclerosis: A double-edged sword. *Nat Rev Immunol* 2006; **6:** 508–519.
17. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; **352:** 1685–1695.
18. Schulte S, Sukhova GK, Libby P. Genetically programmed biases in Th1 and Th2 immune responses modulate atherogenesis. *Am J Pathol* 2008; **172:** 1500–1508.
19. Mor A, Planer D, Luboshits G, Afek A, Metzger S, Chajek-Shaul T, et al. Role of naturally occurring CD4+ CD25+ regulatory T cells in experimental atherosclerosis. *Arterioscler Thromb Vasc Biol* 2007; **27:** 893–900.
20. Han SF, Liu P, Zhang W, Bu L, Shen M, Li H, et al. The opposite-direction modulation of CD4+CD25+ Tregs and T helper 1 cells in acute coronary syndromes. *Clin Immunol* 2007; **124:** 90–97.
21. Binder CJ, Horkko S, Dewan A, Chang MK, Kieu EP, Goodyear CS, et al. Pneumococcal vaccination decreases atherosclerotic lesion formation: Molecular mimicry between *Streptococcus pneumoniae* and oxidized LDL. *Nat Med* 2003; **9:** 736–743.
22. Kume T, Okura H, Yamada R, Kawamoto T, Watanabe N, Neishi Y, et al. Frequency and spatial distribution of thin-cap fibroatheroma assessed by 3-vessel intravascular ultrasound and optical coherence tomography: An ex vivo validation and an initial in vivo feasibility study. *Circ J* 2009; **73:** 1086–1091.
23. Kashiwagi M, Tanaka A, Kitabata H, Tsujioka H, Matsumoto H, Arita Y, et al. Relationship between coronary arterial remodeling, fibrous cap thickness and high-sensitivity C-reactive protein levels in patients with acute coronary syndrome. *Circ J* 2009; **73:** 1291–1295.
24. Mach F, Sauty A, Iarossi AS, Sukhova GK, Neote K, Libby P, et al. Differential expression of three T lymphocyte-activating CXC chemokines by human atheroma-associated cells. *J Clin Invest* 1999; **104:** 1041–1050.
25. Heller EA, Liu E, Tager AM, Yuan Q, Lin AY, Ahluwalia N, et al. Chemokine CXCL10 promotes atherogenesis by modulating the local balance of effector and regulatory T cells. *Circulation* 2006; **113:** 2301–2312.
26. van Wanrooij EJ, de Jager SC, van Es T, de Vos P, Birch HL, Owen DA, et al. CXCR3 antagonist NBI-74330 attenuates atherosclerotic plaque formation in LDL receptor-deficient mice. *Arterioscler Thromb Vasc Biol* 2008; **28:** 251–257.
27. Mach F, Schoenbeck U, Bonnefoy JY, Pober J, Libby P. Activation of monocyte/macrophage functions related to acute atheroma complication by ligation of CD40: Induction of collagenase, stromelysin, and tissue factor. *Circulation* 1997; **96:** 396–399.
28. Mach F, Schönbeck U, Sukhova GK, Bourcier T, Bonnefoy JY, Pober JS, et al. Functional CD 40 Ligand is expressed on human vascular endothelial cells, smooth muscle cells, and macrophages: Implications for CD40-CD40 ligand signaling in atherosclerosis. *Proc Natl Acad Sci USA* 1997; **94:** 1931–1936.
29. Amento EP, Ehsani N, Palmer H, Libby P. Cytokines and growth factors positively and negatively regulate intersitial collagen gene expression in human vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol* 1991; **11:** 1223–1230.
30. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *JAMA* 2004; **291:** 2847–2850.
31. Shiraishi J, Kohno Y, Sawada T, Nishizawa S, Arihara M, Hadase M, et al. Relation of obesity to acute myocardial infarction in Japanese patients. *Circ J* 2006; **70:** 1525–1530.
32. Oda E. CRP may be superior to anthropometric markers of obesity [Letter]. *Circ J* 2007; **71:** 1332; author reply 1332–1333.
33. Maeda K, Okubo K, Shimomura I, Mizuno K, Matsuzawa Y, Matsubara K. Analysis of an expression profile of genes in the human adipose tissue. *Gene* 1997; **190:** 227–235.
34. Rocha VZ, Libby P. The multiple facets of the fat tissue. *Thyroid* 2008; **18:** 175–183.
35. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation [Review]. *N Engl J Med* 1999; **340:** 448–454 [published erratum appears in *N Engl J Med* 1999; **340:** 1376].
36. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: Is interleukin-6 the link? *Atherosclerosis* 2000; **148:** 209–214.
37. Libby P, Ridker PM. Novel inflammatory markers of coronary risk: Theory versus practice. *Circulation* 1999; **100:** 1148–1150.
38. Lemieux I, Pascot A, Prud'homme D, Almeras N, Bogaty P, Nadeau A, et al. Elevated C-reactive protein: Another component of the atherothrombotic profile of abdominal obesity. *Arterioscler Thromb Vasc Biol* 2001; **21:** 961–967.
39. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003; **112:** 1796–1808.
40. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* 2003; **112:** 1821–1830.
41. Wu H, Ghosh S, Perrard XD, Feng L, Garcia GE, Perrard JL, et al. T-cell accumulation and regulated on activation, normal T cell expressed and secreted upregulation in adipose tissue in obesity. *Circulation* 2007; **115:** 1029–1038.
42. Kintscher U, Hartge M, Hess K, Foryst-Ludwig A, Clemenz M, Wabitsch M, et al. T-lymphocyte infiltration in visceral adipose tissue: A primary event in adipose tissue inflammation and the development of obesity-mediated insulin resistance. *Arterioscler Thromb Vasc Biol* 2008; **28:** 1304–1310.
43. Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A, et al. Lean, but not obese, fat is enriched for a unique population of regulator T cells that affect metabolic parameters. *Nat Med* 2009; **15:** 930–939.
44. Nishimura S, Manabe I, Nagasaki M, Eto K, Yamashita H, Ohsugi M, et al. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat Med* 2009; **15:** 914–920.
45. Rocha VZ, Folco EJ, Sukhova G, Shimizu K, Gotsman I, Vernon AH, et al. Interferon-gamma, a Th1 cytokine, regulates fat inflammation: A role for adaptive immunity in obesity. *Circ Res* 2008; **103:** 467–476.
46. Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. *J Biol Chem* 1996; **271:** 10697–10703.
47. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem* 1995; **270:** 26746–26749.
48. Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). *Biochem Biophys Res Commun* 1996; **221:** 286–289.
49. Shibata R, Ouchi N, Murohara T. Adiponectin and cardiovascular disease. *Circ J* 2009; **73:** 608–614.
50. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999; **257:** 79–83.
51. Okamoto Y, Kihara S, Funahashi T, Matsuzawa Y, Libby P. Adiponectin, a key adipocytokine in metabolic syndrome. *Clin Sci (Lond)* 2006; **110:** 267–278.
52. Okamoto Y, Folco EJ, Minami M, Wara AK, Feinberg MW, Sukhova GK, et al. Adiponectin inhibits the production of CXC receptor 3 chemokine ligands in macrophages and reduces T-lymphocyte recruitment in atherogenesis. *Circ Res* 2008; **102:** 218–225.
53. Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001; **344:** 1959–1965.
54. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. *N Engl J Med* 2008; **359:** 2195–2207.
55. Glynn RJ, Danielson E, Fonseca FAH, Genest J, Gotto AM Jr, Kastelein JJP, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism: The JUPITER Trial. *N Engl J Med* 2009; **360:** 1851–1861.