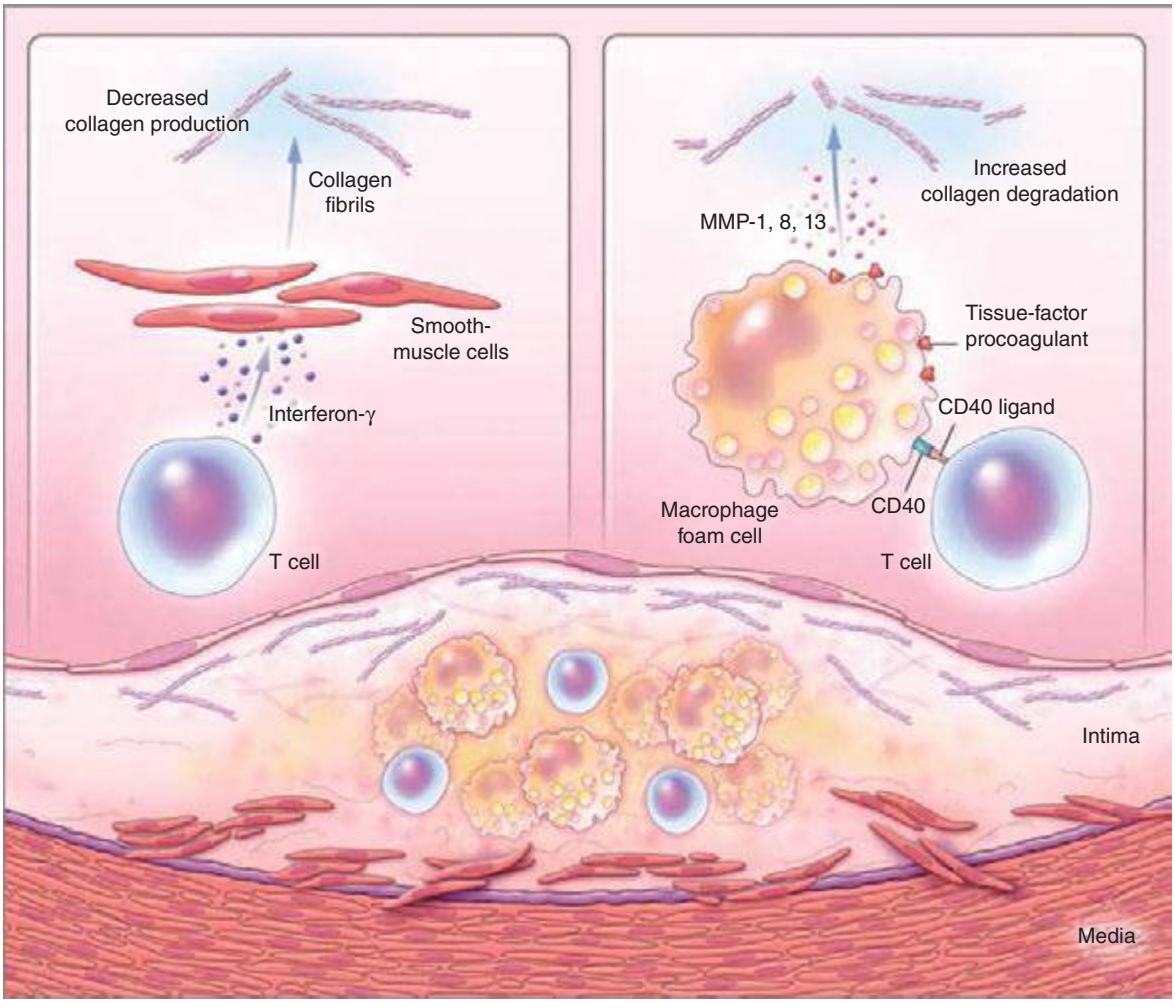

FIGURE 291e-3 Inflammatory pathways that predispose atherosclerotic plaques to rupture and provoke thrombosis. A cross-section of an atheromatous plaque at the bottom of the figure shows the central lipid core that contains macrophage foam cells (*yellow*) and T cells (*blue*). The intima and media also contain arterial smooth-muscle cells (*red*), which are the source of arterial collagen (depicted as triple helical coiled structures). Activated T cells (of the type 1 helper T cell subtype) secrete cytokine interferon γ, which inhibits the production of the new, interstitial collagen that is required to repair and maintain the plaque's protective fibrous cap (*upper left*). The T cells can also activate the macrophages in the intimal lesion by expressing the inflammatory mediator CD40 ligand (CD154), which engages its cognate receptor (CD40) on the phagocyte. This inflammatory signalling causes overproduction of interstitial collagenases (matrix metalloproteinases [MMPs] 1, 8, and 13) that catalyze the initial rate-limiting step in collagen breakdown (*top right*). CD40 ligation also causes macrophages to overproduce tissue-factor procoagulant. Thus, inflammatory signalling puts the collagen in the plaque's fibrous cap in double jeopardy—decreasing synthesis and increasing breakdown—rendering the cap susceptible to rupture. Inflammatory activation also boosts tissue-factor production, which triggers thrombus formation in the disrupted plaque. These mechanisms link inflammation in the plaque to the thrombotic complications of atherosclerosis, including the acute coronary syndromes. *(Adapted from P Libby: N Engl J Med 368:2004, 2013.)*

The 2013 cholesterol guideline focused on 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) rather than other classes of lipid-modulating drugs, including fibric acid derivatives, cholesterol absorption inhibitors such as ezetimibe, and niacin products. The guideline cites the lack of contemporary randomized clinical trial evidence that supports the efficacy of these nonstatin lipid-modifying agents in cardiovascular event reduction. The cholesterol guideline defined four statin benefit groups **(Table 291e-2)**: (1) all individuals who have clinical atherosclerotic cardiovascular disease (ASCVD), therefore considered "secondary prevention"; (2) those with LDL cholesterol ≥190 mg/dL without a secondary cause such as a high intake of saturated or *trans* fats, various drugs, or certain diseases; (3) individuals with diabetes without established cardiovascular disease who are 40–75 years old and have LDL cholesterol of 70–189 mg/dL; and (4) those without established ASCVD without diabetes who are 40–75 years old and who have LDL cholesterol of 70–189 mg/dL and a calculated ASCVD risk ≥7.5%. An online risk calculator based on pooled cohorts was provided to aid clinicians and patients in calculating their risk (*http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp*). Other validated risk calculators that incorporate family history of CAD and a marker of inflammation (high-sensitivity CRP [hsCRP]) that apply to U.S. women and men exist (*http://www.reynoldsriskscore.org*). Downloadable applications for risk calculation on handheld devices are readily available.

The 2013 guideline emphasized a patient-centered approach and recommended that clinicians and patients engage in a risk-benefit conversation before starting statin therapy and not rely solely on calculated risks or arbitrary category assignment. It further emphasizes that medications do not supplant a healthy lifestyle. The guideline also provides some practical suggestions regarding management of muscle symptoms attributed to statins, an issue of considerable concern to many patients and practitioners alike.

In a major departure from prior guidelines, the 2013 guideline eliminates LDL targets as goals of therapy. The panel did so because major clinical trials did not titrate therapy to a goal, but rather used fixed doses of statins. Instead, the new guideline suggests different intensities of statin therapy based on risk category **(Fig. 291e-4)**.

The 2013 guideline focus on statins reflects an extensive body of rigorous evidence that supports the effectiveness of this class of drugs