

The Effect of Inflammation and Infection on Lipids and Lipoproteins

Kenneth R Feingold, MD

Professor of Medicine, University of California- San Francisco, San Francisco VA Medical Center, Metabolism 111F, VA Medical Center, 4150 Clement St, San Francisco, CA 94121

kenneth.feingold@ucsf.edu

Corresponding author.

Carl Grunfeld, MD, PhD

Professor of Medicine, University of California- San Francisco; Chief of the Metabolism and Endocrine Section and Associate Chief of Staff for Research and Development-San Francisco VA Medical Center, Metabolism 111F, VA Medical Center, 4150 Clement St, San Francisco, CA 94121

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ABSTRACT

Chronic inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and psoriasis and infections, such as periodontal disease and HIV, are associated with an increased risk of cardiovascular disease. Patients with these disorders also have an increase in coronary artery calcium measured by CT and carotid intima media thickness measured by ultrasound. Inflammation and infections induce a variety of alterations in lipid metabolism that may initially dampen inflammation or fight infection, but if chronic could contribute to the increased risk of atherosclerosis. The most common changes are decreases in serum HDL and increases in triglycerides. The increase in serum triglycerides is due to both an increase in hepatic VLDL production and secretion and a decrease in the clearance of triglyceride rich lipoproteins. The mechanisms by which inflammation and infection decrease HDL levels are uncertain. There is also a consistent increase in lipoprotein (a) levels due to increased apolipoprotein (a) synthesis. LDL levels are frequently decreased but the prevalence of small dense LDL is increased due to cholesterol ester transfer protein (CETP) mediated exchange of triglycerides from triglyceride rich lipoproteins to LDL followed by triglyceride hydrolysis. In addition to affecting serum lipid levels, inflammation also adversely effects lipoprotein function. LDL is more easily oxidized as the ability of HDL to prevent the oxidation of LDL is diminished. Moreover, there are a number of steps in the reverse cholesterol transport pathway that are adversely affected during inflammation. The greater the severity of the underlying inflammatory disease, the more consistently these abnormalities in lipids and lipoproteins are observed. Treatment of the underlying disease leading to a reduction in inflammation results in the return of the lipid profile towards normal. The changes in lipids and lipoproteins that occur during inflammation and infection are part of the innate immune response and therefore are likely to play an important role in protecting the host. The guidelines for the management of lipid disorders and the standard risk calculators for predicting cardiovascular disease (ACC/AHA, Framingham, etc.) underestimate the risk in patients with inflammation. It has been recommended to increase the calculated risk by approximately 50% in patients with severe inflammatory disorders. The treatment of lipid disorders in patients with inflammatory disorders is similar to patients without inflammatory disorders. Of note statins, fibrates, and fish oil have anti-inflammatory properties and have been reported to have beneficial effects on many of these inflammatory disorders.

INTRODUCTION

A number of chronic inflammatory diseases, including rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, Sjögren's syndrome, polymyalgia rheumatica, inflammatory bowel disease, and psoriasis are associated with an increased risk of cardiovascular disease (1-9). For example, in a meta-analysis of twenty-four studies comprising 111,758 patients with 22,927 cardiovascular events it was observed that there was a 50% increased risk of CVD death in patients with rheumatoid arthritis (10). Patients with rheumatoid arthritis have a similar risk for a cardiovascular event as patients with diabetes (11). Similarly, women with systemic lupus erythematosus in the 35- to 44-year age group were over 50 times more likely to have a myocardial infarction than were women of similar age in the Framingham Offspring Study (12). As a final example, a meta-analysis of 14 studies reported that in individuals with severe psoriasis the risk for cardiovascular mortality was 1.37, the risk for myocardial infarction was 3.04, and the risk for stroke was 1.59 times higher than the general population (13). It should be noted that the pathology in psoriasis is localized to the skin but

nevertheless even this disorder, by inducing systemic inflammation, is associated with an increased risk of cardiovascular disease.

Further, supporting the link of rheumatoid arthritis, systemic lupus erythematosus, and psoriasis with atherosclerosis are studies showing that patients with these disorders have an increase in coronary artery calcium measured by CT and carotid intima media thickness measured by ultrasound (14-20). Finally, even children and adolescents with systemic lupus erythematosus have an increase in carotid intimal-medial thickness (21). Thus, it is clear that patients with a number of different chronic inflammatory diseases have an increased risk of atherosclerotic cardiovascular complications.

In addition, chronic infections are also associated with an increased risk of atherosclerosis (22-24). Since the development of effective anti-viral agents, it has been widely recognized that a major cause of morbidity and mortality in HIV infected patients is due to cardiovascular disease (25). Moreover, numerous studies have demonstrated an association of periodontal infections with an increased risk of atherosclerotic vascular disease (26). Additionally, carotid intima-media thickness is increased in patients with periodontal disease (27-30). The link between various chronic infections, such as HIV, dental infections, *Helicobacter pylori*, chronic bronchitis, and urinary tract infections with cardiovascular disease is presumably due to the chronic inflammation that accompanies these infections (31). For certain infections such as chlamydia pneumonia and cytomegalovirus it is possible that the association with cardiovascular disease is due to a direct role in the vessel wall.

To definitively link inflammation with cardiovascular disease studies determining the effect of anti-inflammatory drugs on cardiovascular events have been carried out. The Cantos study has provided data supporting a link between inflammation and cardiovascular disease (32). In this trial 10,061 patients with a previous myocardial infarction and a hsCRP level of 2 mg/L or more were randomized to canakinumab, a monoclonal antibody targeting interleukin-1 β , or placebo. At 48 months canakinumab did not reduce lipid levels from baseline but did reduce hsCRP levels by approximately 30-40% indicating a decrease in inflammation. Most importantly, canakinumab administration led to a significantly lower rate of recurrent cardiovascular events than placebo. These results support the hypothesis that inflammation increases the risk of cardiovascular events. In contrast, a recent trial using methotrexate to inhibit inflammation failed to reduce cardiovascular event (33). However, in this trial methotrexate did not reduce levels of interleukin-1 β , interleukin-6, or C-reactive protein raising the possibility that methotrexate did not effectively inhibit inflammation and therefore did not reduce cardiovascular events. Clearly further studies determining the effect of drugs that reduce inflammation on cardiovascular events are required.

The mechanisms by which chronic inflammation and infection increase the risk of atherosclerotic cardiovascular disease are likely multifactorial. As will be discussed below inflammation and infection induce a variety of alterations in lipid and lipoprotein metabolism that could contribute to the increased risk of atherosclerosis.

LIPID AND LIPOPROTEIN ABNORMALITIES IN PATIENTS WITH INFLAMMATORY DISORDERS AND INFECTIONS

Rheumatoid Arthritis

The most consistent abnormality in patients with rheumatoid arthritis is a decrease in HDL cholesterol and apolipoprotein A-I levels (9,34-37). In particular, small HDL particles are decreased in patients with rheumatoid arthritis (38). Patients with more severe rheumatoid arthritis have the greatest reductions in HDL cholesterol levels (34-37,39). There is an inverse correlation of CRP levels with HDL cholesterol levels (i.e. higher CRP levels are associated with lower HDL cholesterol levels). With regards to total cholesterol and LDL cholesterol, there is more variability with many studies showing a decrease, other studies showing no change, and some studies showing an increase in patients with rheumatoid arthritis (34-37,39). The more severe the rheumatoid arthritis the greater the likelihood that the LDL cholesterol levels will be decreased. Serum triglyceride levels and small dense LDL levels tend to be increased in patients with rheumatoid arthritis (34-37,39,40). Levels of lipoprotein (a) are characteristically elevated in patients with rheumatoid arthritis and correlate with CRP levels (41-43).

Systemic Lupus Erythematosus

The changes in serum lipids and lipoproteins seen in patients with systemic lupus erythematosus are very similar to those observed in patients with rheumatoid arthritis (44-46). Specifically, there is a decrease in HDL cholesterol levels and an increase in serum triglyceride levels. LDL cholesterol levels are variable and maybe increased, normal, or low but small dense LDL levels tend to be increased. Lipoprotein (a) levels are also increased (47). Similar to rheumatoid arthritis the more severe the disease state the greater the alterations in serum lipid levels.

Psoriasis

A large number of studies have compared serum lipid levels in controls and patients with psoriasis (48). However, many of these studies included only a small number of subjects and the results have therefore been extremely variable with some studies showing alterations in serum lipid levels in patients with psoriasis and other studies showing no changes. In general, there is a tendency for an increase in serum triglycerides and a decrease in HDL cholesterol levels in patients with psoriasis (49-53). Additionally, a number of studies showed an increase in LDL cholesterol and lipoprotein (a) levels in patients with psoriasis (49,50,52). Small dense LDL levels and oxidized Lp(a) are also increased in psoriasis (40) (54). This variability between studies is most likely due to differences in the severity of the psoriasis with more severe disease demonstrating more robust alterations in lipid levels. The prevalence of other abnormalities that affect lipid metabolism such as obesity and abnormalities in glucose metabolism could also account for the variability in results.

Other Inflammatory Disease

Decreased HDL cholesterol levels have also been observed in patients with inflammatory bowel disease, Sjögren's syndrome, and ankylosing spondylitis (55-58). LDL cholesterol and triglyceride levels varied but LDL cholesterol levels tended to be decreased and triglyceride levels increased.

Periodontal Disease

Differences exist between studies but in general patients with periodontitis tend to have increased LDL cholesterol and triglyceride levels and decreased HDL cholesterol levels (59-63). Additionally, the prevalence of small dense LDL is increased in patients with periodontitis (62,64). The severity of the periodontitis correlated with the changes in the lipid profile with patients with increased periodontal disease having higher triglyceride levels, lower HDL cholesterol levels, and smaller LDL particle size (65). Moreover, treatment of periodontitis improved the dyslipidemia, with the HDL cholesterol levels increasing and the LDL cholesterol levels decreasing (62,66,67).

Acute Infections

Patients with a variety of different infections (gram positive bacterial, gram negative bacterial, viral, tuberculosis) have similar alterations in plasma lipid levels. Specifically, total cholesterol, LDL cholesterol, and HDL cholesterol levels are decreased while plasma triglyceride levels are elevated or inappropriately normal for the poor nutritional status (31,68-74). As expected apolipoprotein A-I, A-II, and B levels are reduced (68,73,74). While LDL cholesterol levels were decreased, the concentration of small dense LDL has been found to be increased during infections (75-77). That plasma cholesterol levels decrease during infection has been known for many years as it was described by Denis in 1919 in the Journal of Biological Chemistry (JBC 29: 93, 1919). The alterations in lipids correlate with the severity of the underlying infection i.e. the more severe the infection the more severe the alterations in lipid and lipoprotein levels (78,79). The decreases in plasma cholesterol levels can be quite profound and a recent case report described HDL cholesterol levels < 10mg/dl and LDL cholesterol levels < 3mg/dl in sepsis (80).

Of note studies have demonstrated that the degree of reduction in total cholesterol, HDL cholesterol, and apolipoprotein A-I are predictive of mortality in patients with severe sepsis (81-85). Moreover, epidemiologic studies have suggested that low cholesterol, LDL cholesterol, and HDL levels increase the chance of developing an infection (86-89). During recovery from the infection plasma lipid and lipoprotein abnormalities return towards normal. The changes in lipid and lipoproteins that occur during infection can be experimentally reproduced in humans and animals by the administration of endotoxin and lipoteichoic acid (31,90).

Summary

Thus, in these different inflammatory disorders and infectious diseases, the alterations in plasma lipid and lipoprotein levels are very similar with decreases in plasma HDL being consistently observed. Also of note is the consistent increase in lipoprotein (a) levels and small dense LDL (31,91). There is also a tendency for plasma triglyceride levels to be elevated and LDL cholesterol levels decreased. The greater the severity of the underlying disease the more consistently these abnormalities in lipids are observed. Additionally, treatment of the underlying disease leading to a reduction in inflammation results in a return of the lipid profile towards normal. This is best illustrated in periodontal disease where intensive dental hygiene can reverse the abnormalities in the lipid profile (66,67).

Table 1.

Effect of Inflammation and Infection on Lipid and Lipoprotein Levels

Triglycerides- Tend to be increased
HDL cholesterol- Decreased
LDL cholesterol- Variable but with more severe inflammation or infection they are decreased
Small dense LDL- Increased
Lp(a)- Increased

EFFECT OF ANTI-INFLAMMATORY DRUGS ON LIPID LEVELS

As noted above, treatments that reduce inflammation will return the lipid profile towards normal resulting in an increase in plasma HDL levels and a decrease in triglyceride levels. If LDL levels were reduced at baseline, treatment that reduces inflammation will also result in an increase in LDL levels (i.e. a return towards “normal” levels) (92-94). Many of the drugs used for the treatment of rheumatoid arthritis, systemic lupus erythematosus, and psoriasis decrease inflammation and have been shown to increase both HDL and LDL levels (9,92,93,95). The increase in HDL tends to be more robust. In a few instances, drugs used to treat inflammatory disorders have effects on lipid metabolism that are independent of the reduction in inflammation. For example, high dose glucocorticoid treatment results in an increase in serum triglyceride and LDL levels due to the increased production and secretion of VLDL by the liver (96-98) and hydroxychloroquine has been reported to lower total cholesterol, LDL, and triglycerides in patients with rheumatoid arthritis and systemic lupus erythematosus (99-101).

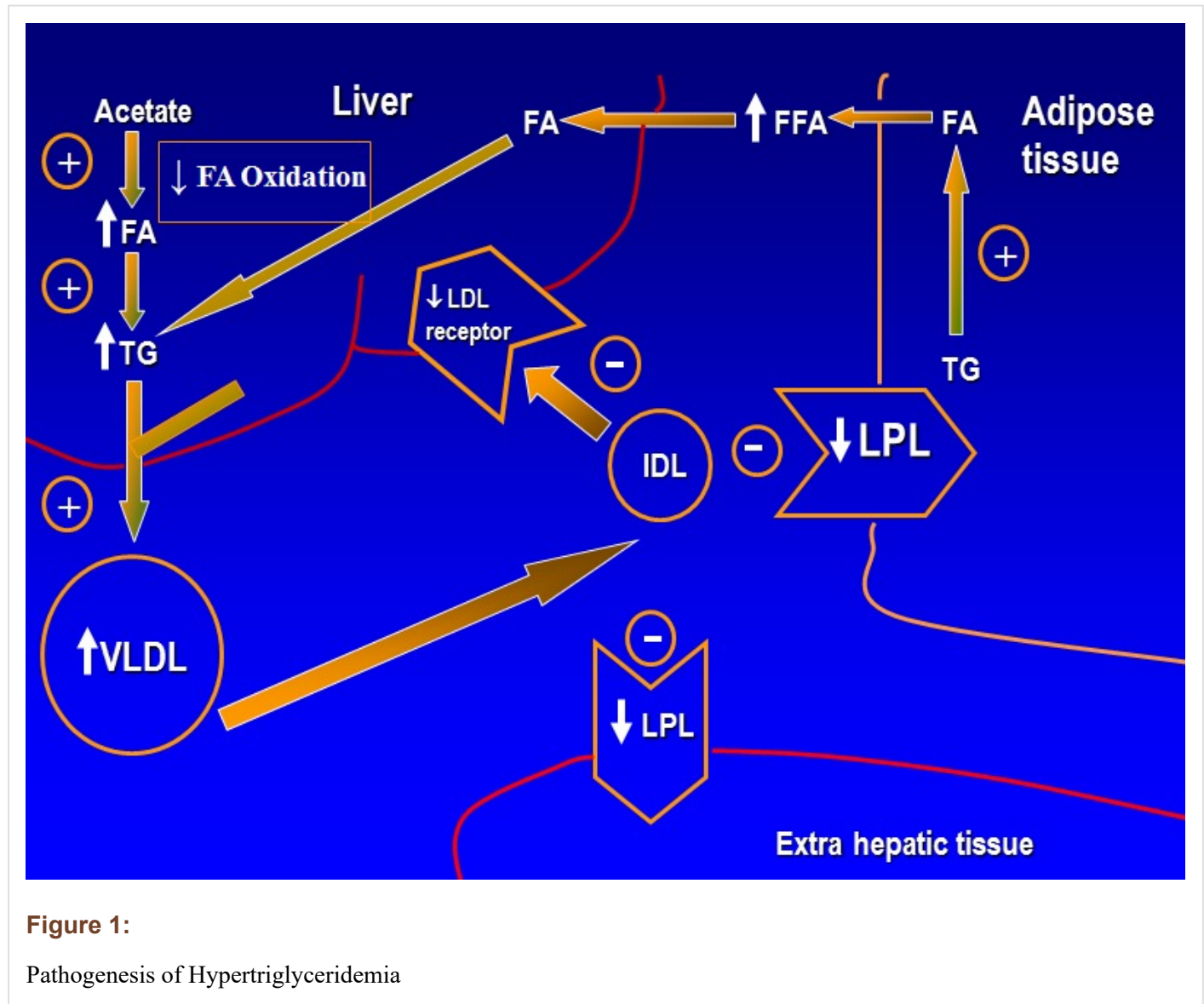
PATHOPHYSIOLOGY OF THE DYSLIPIDEMIA OF INFLAMMATION AND INFECTION

Inflammation and infections increase the production of a variety of cytokines, including TNF, IL-1, and IL-6, which have been shown to alter lipid metabolism (31). Many of the changes in plasma lipids and lipoproteins that are seen during chronic inflammation and infections are also observed following the acute administration of cytokines (31).

Increased Triglyceride Levels

Multiple cytokines increase serum triglyceride and VLDL levels (TNF, IL-1, IL-2, IL-6, etc.) (31). Following a single administration of a cytokine or LPS (a model of gram-negative infections), which stimulates cytokine production, an increase in serum triglyceride and VLDL levels can be seen within 2 hours and this effect is sustained for at least 24 hours. The increase in serum triglycerides is due to both an increase in hepatic VLDL production and secretion and a decrease in the clearance of triglyceride rich lipoproteins (figure 1) (31). The increase in VLDL production and secretion is a result of increased hepatic fatty acid synthesis, an increase in adipose tissue lipolysis with the increased transport of fatty acids to the liver, and a decrease in fatty acid oxidation in the liver. Together these changes provide an increased supply of fatty acids in the liver that stimulate an increase in hepatic triglyceride synthesis (31). The increased availability of triglycerides leads to the increased formation and secretion of VLDL. The decrease in the clearance of triglyceride rich lipoproteins is due to a decrease in lipoprotein lipase, the key enzyme that metabolizes triglycerides in the circulation (31). A variety of cytokines have been shown to decrease the synthesis of lipoprotein lipase in adipose

and muscle tissue (31). Studies have also shown that inflammation also increases angiopoietin like protein 4, an inhibitor of lipoprotein lipase activity, which would further block the metabolism of triglyceride rich lipoproteins (102). In systemic lupus erythematosus, antibodies to lipoprotein lipase have been reported and are associated with increased triglyceride levels (103,104).



Production of Small Dense LDL and HDL

The elevation in triglyceride rich lipoproteins in turn has effects on other lipoproteins (31). Specifically, cholesterol ester transfer protein (CETP) mediates the exchange of triglycerides from triglyceride rich VLDL and chylomicrons to LDL and HDL. The increase in triglyceride rich lipoproteins *per se* leads to an increase in CETP mediated exchange, increasing the triglyceride content of both LDL and HDL. The triglyceride on LDL and HDL is then hydrolyzed by hepatic lipase and lipoprotein lipase leading to the increased production of small dense LDL and HDL. The affinity of Apo A-I for small HDL particles is reduced leading to the disassociation of Apo A-I and the consequent accelerated clearance and breakdown of Apo A-I by the kidneys. These changes, along with other factors described below, result in a reduction in the levels of Apo A-I and HDL in patients with inflammation.

Decreased HDL Levels

In addition to a decrease in HDL, inflammation can also lead to structural changes in this lipoprotein (31). During inflammation HDL particles tend to be larger with a decrease in cholesterol ester and an increase in free cholesterol,

triglycerides, and free fatty acids. Furthermore, there are marked changes in HDL associated proteins and the enzymes and transfer proteins involved in HDL metabolism and function (figure 2 and 3).

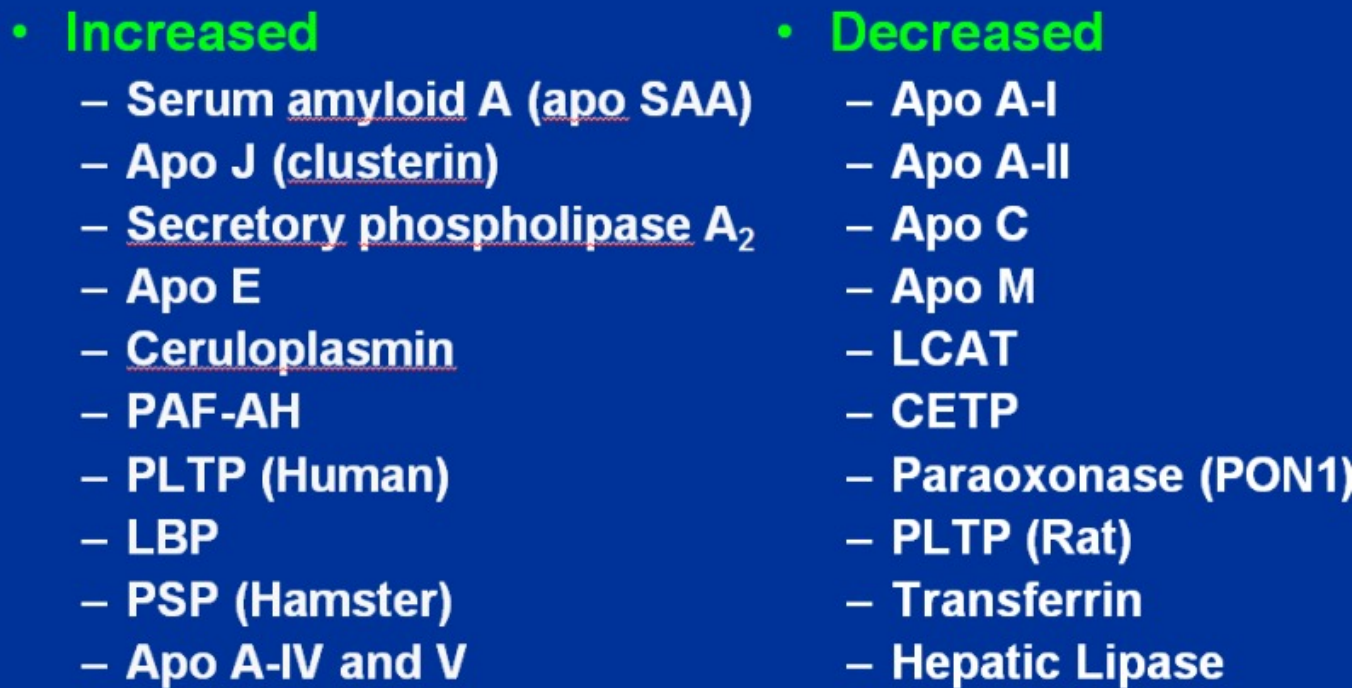
- 
- **Increased**
 - Serum amyloid A (apo SAA)
 - Apo J (clusterin)
 - Secretory phospholipase A₂
 - Apo E
 - Ceruloplasmin
 - PAF-AH
 - PLTP (Human)
 - LBP
 - PSP (Hamster)
 - Apo A-IV and V
 - **Decreased**
 - Apo A-I
 - Apo A-II
 - Apo C
 - Apo M
 - LCAT
 - CETP
 - Paraoxonase (PON1)
 - PLTP (Rat)
 - Transferrin
 - Hepatic Lipase

Figure 2:

Changes in HDL Protein Composition During Inflammation

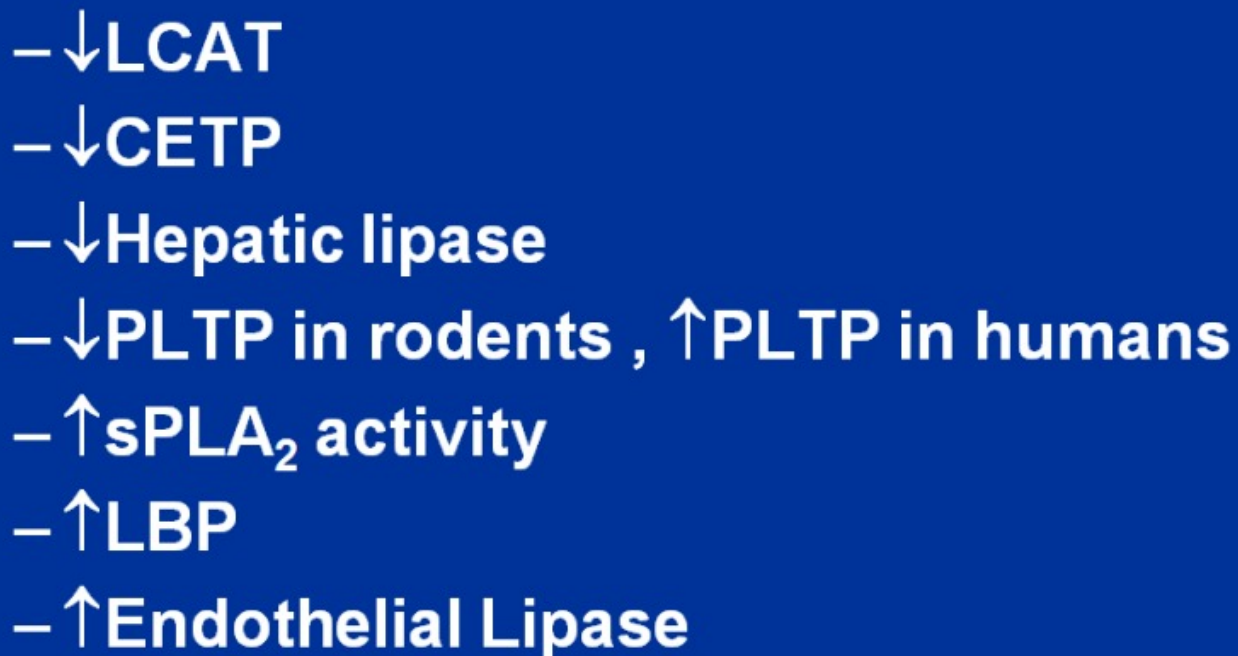
- 
- ↓ LCAT
 - ↓ CETP
 - ↓ Hepatic lipase
 - ↓ PLTP in rodents , ↑ PLTP in humans
 - ↑ sPLA₂ activity
 - ↑ LBP
 - ↑ Endothelial Lipase

Figure 3:

Changes in Enzymes and Transfer Proteins During Inflammation

The precise mechanism by which inflammation and infection decrease HDL levels is uncertain and is likely to involve multiple mechanisms (31). Decreases in apolipoprotein A-I synthesis in the liver occur during inflammation and would result in the decreased formation of HDL. However, in acute infection and inflammation HDL decreases faster than would be predicted from decreased synthesis of apolipoprotein A-I. Increased serum amyloid A (SAA) production by the liver and other tissues occurs during inflammation and infection and the SAA binds to HDL displacing apolipoprotein A-I, which can accelerate the clearance of HDL. However, the overexpression in SAA in the absence of the acute phase response does not result in a decrease in HDL levels (105). Inflammation results in a decrease in LCAT leading to decreased cholesterol ester formation, which would prevent the formation of normal HDL, leading to decreased cholesterol carried in HDL. Elevations in triglyceride rich lipoproteins that accompany inflammation and infection can lead to the enrichment of HDL with triglycerides that can accelerate the clearance of HDL. Finally, cytokine induced increases in enzymes such as secretory phospholipase A2 (sPLA2) and endothelial cell lipase, which metabolize key constituents of HDL, could alter the stability and metabolism of HDL. Given the complexity of HDL metabolism it is not surprising that multiple pathways could be affected by inflammation, which together may account for the decrease in HDL levels.

Increased Lipoprotein (a)

The mechanism accounting for the increase in lipoprotein (a) (Lp(a)) during inflammation is likely due to increased apolipoprotein (a) synthesis, as apolipoprotein (a) is a positive acute phase protein whose expression is up-regulated during inflammation (31,106). The apolipoprotein (a) gene contains several IL-6 responsive elements that enhance transcription (107). Tocilizumab an antibody against IL-6, that is used to treat rheumatoid arthritis, has been shown to decrease Lp(a) levels (108) .

FUNCTIONAL CHANGES IN LIPOPROTEINS THAT INCREASE THE RISK OF ATHEROSCLEROSIS

LDL

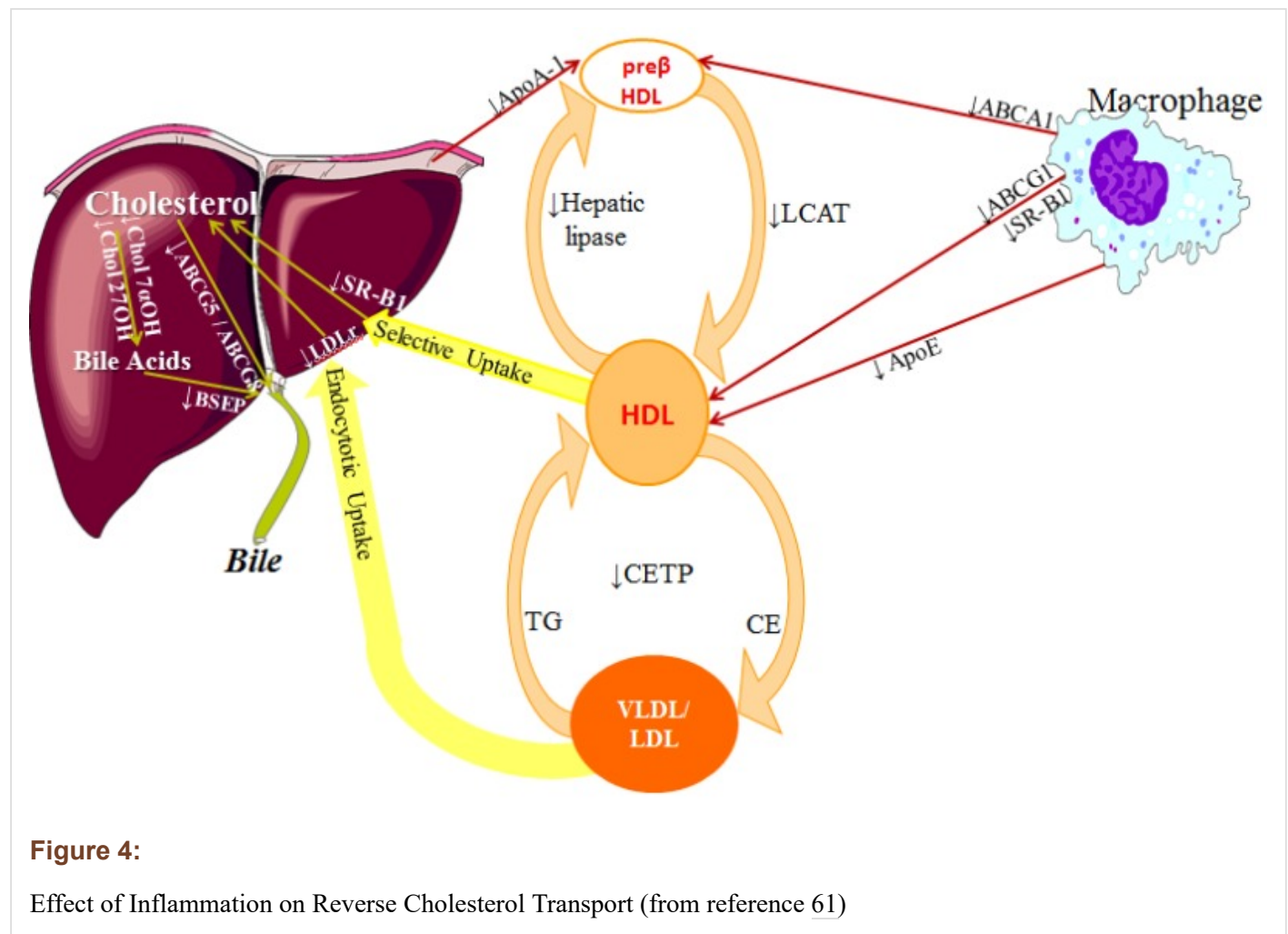
While the levels of LDL do not consistently increase and may even decrease with inflammation and infection, many studies have indicated that inflammation and infection are associated with small dense LDL (31). These small dense LDL particles are believed to be more pro-atherogenic for a number of reasons (109). Small dense LDL particles have a decreased affinity for the LDL receptor resulting in a prolonged period of time in the circulation. Additionally, they more easily enter the arterial wall and bind more avidly to intra-arterial proteoglycans, which traps them in the arterial wall. Finally, small dense LDL particles are more susceptible to oxidation, which could result in an enhanced uptake by macrophages (110).

Several markers of lipid peroxidation, including conjugated dienes, thiobarbituric acid-reactive substances, malondialdehyde, and lipid hydroperoxides are increased in serum and/or circulating LDL during inflammation and infection (31,65,111-113). Moreover, LDL isolated from LPS-treated animals is more susceptible to oxidation in vitro (31). Oxidized LDL is taken up very efficiently by macrophages and is thought to play a major role in foam cell formation in the arterial wall (114). Additionally, antibodies to oxidized LDL are present in patients with systemic lupus erythematosus and could facilitate the uptake of an antibody LDL complex via the Fc-receptor in macrophages (111). Finally, studies have shown that LDL isolated from patients with periodontal disease leads to enhanced uptake of cholesterol esters by macrophages (65)

HDL

In addition to a decrease in serum HDL, inflammation and infection affects the anti-atherogenic properties of HDL (31,115,116). Reverse cholesterol transport plays a key role in preventing cholesterol accumulation in macrophages thereby reducing atherosclerosis. Most steps in the reverse cholesterol transport pathway are adversely affected during inflammation and infection (figure 4 and 5) (39,117). First, cytokines induced by inflammation and infection decrease the production of Apo A-I, the main protein constituent of HDL. Second, pro-inflammatory cytokines decrease the

expression of ABCA1, ABCG1, SR-B1, and apolipoprotein E in macrophages, which will lead to a decrease in the efflux of phospholipids and cholesterol from the macrophage to HDL. Third, the structurally altered HDL formed during inflammation is a poor acceptor of cellular cholesterol and in fact may actually deliver cholesterol to the macrophage (39,55,117-124). HDL isolated from patients with rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, psoriasis, ankylosing spondylitis, periodontal disease, and acute sepsis are poor facilitators of cholesterol efflux (55,118-123,125). Similarly, the experimental administration of endotoxin to humans also results in the formation of HDL that is a poor facilitator of the efflux of cholesterol from macrophages (126). Of note treatments that reduce inflammation in patients with rheumatoid arthritis, psoriasis, or periodontitis can restore towards normal the ability of HDL to remove cholesterol from cells (123,127-129). Fourth, pro-inflammatory cytokines decrease the production and activity of LCAT, which will limit the conversion of cholesterol to cholesterol esters in HDL. This step is required for the formation of a normal spherical HDL particle and facilitates the ability of HDL to transport cholesterol. Fifth, pro-inflammatory cytokines decrease CETP levels, which will decrease the movement of cholesterol from HDL to Apo B containing lipoproteins, an important step in the delivery of cholesterol to the liver. Sixth, pro-inflammatory cytokines decrease the expression of SR-B1 in the liver. SR-B1 plays a key role in the uptake of cholesterol from HDL particles into hepatocytes. Finally, inflammation and infection decrease both the conversion of cholesterol to bile acids and the secretion of cholesterol into the bile, the two mechanisms by which cholesterol is disposed of by the liver.



Macrophages	Plasma	Liver
Decreased ABCA1	Decreased Apo A1	Decreased SR-B1
Decreased ABCG1	Decreased LCAT	Decreased <u>LDLr</u>
Decreased SR-B1	Decreased CETP	Decreased CYP 7A
Decreased Apo E	Decreased Hepatic Lipase	Decreased CYP 27
	Abnormal HDL	Decreased ABCG5/8

Figure 5.

Effect of Inflammation on the Factors Involved in Reverse Cholesterol Transport (from reference 61)

Another important function of HDL is to prevent the oxidation of LDL. Oxidized LDL is more easily taken up by macrophages and is pro-atherogenic (114). Paraoxonase is an enzyme that is associated with HDL and plays a key role in preventing the oxidation of LDL. Inflammation and infection decrease the expression of paraoxonase 1 in the liver resulting in a decrease in circulating paraoxonase activity (31). Plasma paraoxonase levels are decreased in patients with patients rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and infections (130-138). Studies have shown that HDL isolated from patients with rheumatoid arthritis and systemic lupus erythematosus have a diminished ability to protect LDL from oxidation and in fact may facilitate LDL oxidation (115). Moreover, in patients with rheumatoid arthritis, reducing inflammation and disease activity with methotrexate treatment restored HDL function towards normal (139). Additionally, treatment with atorvastatin 80mg improved the function of HDL in patients with rheumatoid arthritis (140).

Thus, it should be recognized that in patients with inflammatory disorders and infections the absolute levels of lipids and lipoproteins may not be the only factor increasing the risk of atherosclerosis (31,48,112,115-117). Rather functional changes in LDL and HDL maybe pro-atherogenic and thereby contribute to the increased risk of atherosclerosis in inflammatory disorders and infections. Additionally, the increase in lipoprotein (a) may also play a role.

Table 2.

Pro-Atherogenic Changes During Inflammation

Increased triglycerides
Decreased HDL
Increased small dense LDL
Increased Lp(a)
Oxidized LDL
Dysfunctional HDL

BENEFICIAL EFFECTS OF LIPIDS DURING INFECTIONS AND INFLAMMATION

The changes in lipids and lipoproteins that occur during inflammation and infection are part of the innate immune response and therefore are likely to play an important role in protecting from the detrimental effects of infection and inflammatory stimuli (31,141-143). Some of the potential beneficial effects are listed in Table 3. Thus, the changes in lipid and lipoprotein metabolism that occur during inflammation may initially be protective but if chronic can increase the risk of atherosclerosis.

Table 3.

Beneficial Effects of Lipoproteins

Redistribution of nutrients to immune cells that are important in host defense
Lipoproteins bind endotoxin, lipoteichoic acid, and other biological agents and prevent their toxic effects
Lipoproteins bind urate crystals
Lipoproteins bind and target parasites for destruction
Apolipoproteins neutralize viruses
Apolipoproteins lyse parasites

LIPID MANAGEMENT IN A PATIENT WITH AN INFLAMMATORY DISEASE

Deciding When to Treat

As noted earlier, patients with inflammatory disorders are at an increased risk for atherosclerosis and this is not totally accounted for by standard lipid profile measurements and other risk factors (1-3,9). Some authors have advocated considering inflammatory disorders as a cardiovascular risk equivalent similar to diabetes; however many of the guidelines and risk calculators commonly used for deciding on lipid lowering therapy do not take into account this increased risk in patients with inflammatory disorders (3,144). For example, both the 2013 American College of Cardiology/American Heart Association and National Lipid Association recommendations do not specifically address this patient population (145,146). In the 2018 American College of Cardiology/American Heart Association recommendations, the presence of inflammatory disease is included as a risk factor, which can influence decisions on whether to initiate treatment (147). Additionally, the standard risk calculators for predicting cardiovascular disease (ACC/AHA and Framingham) underestimate the risk in this population (148-152). Even the Reynolds Risk Calculator (<http://www.reynoldsriskscore.org/Default.aspx>), which uses measurements of hsCRP levels, a marker of inflammation, underestimates the risk of cardiovascular events in patients with inflammatory disorders (148-152). Thus, if one follows the standard protocols one will undertreat patients with inflammatory disorders. It should be noted that the QRISK calculator (<http://qrisk.org/>) does factor in the presence of rheumatoid arthritis when calculating risk (153).

A reasonable approach is to use the standard approach and calculators but increase the calculated risk by approximately 50% in patients with severe inflammatory disorders. For example, if a patient with rheumatoid arthritis has a 5% ten-year risk and 40% lifetime risk one might increase the ten-year risk to 7.5% and lifetime risk to 60%. This approach has been recommended by an expert committee who advocated introducing a 1.5 multiplication factor (i.e. 50% increase) in patients with rheumatoid arthritis (9). Alternatively, one could carry out imaging studies such as obtaining a coronary artery calcium score to better define risk. Whatever the approach taken, it is crucial to recognize that patients with inflammatory diseases have an increased risk of cardiovascular disease and therefore one needs to be more aggressive.

Recent guidelines from the American College of Cardiology and American Heart Association are summarized in table 4 (147).

Table 4.

ACC/AHA Guidelines

In patients with clinical ASCVD initiate high intensity statin therapy or maximally tolerated statin therapy. High intensity statin therapy is atorvastatin 40-80mg per day or rosuvastatin 20-40mg per day.

In very high-risk ASCVD, use an LDL cholesterol > 70 mg/dL (1.8 mmol/L) to consider addition of non-statins (ezetimibe or PCSK9 inhibitors). Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

In patients with LDL cholesterol ≥ 190 mg/dL (≥ 4.9 mmol/L) begin high-intensity statin therapy. If the LDL-C level remains ≥ 100 mg/dL (≥ 2.6 mmol/L), adding ezetimibe is reasonable.

In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥ 70 mg/dL (≥ 1.8 mmol/L) start a moderate-intensity statin if the 10-year ASCVD risk is $\geq 7.5\%$. Moderate intensity therapy is atorvastatin 10-20mg, rosuvastatin 5-10mg, simvastatin 20-40mg, pravastatin 40mg.

It should be noted that the ACC/AHA guidelines do not emphasize LDL cholesterol or non-HDL cholesterol goals while other organizations such as the National Lipid Association and American Association of Clinical Endocrinologists do provide LDL cholesterol and non-HDL cholesterol goals in their recommendations (Figures 6 and 7) (145,154). Our approach is to combine these approaches. In patients who have pre-existing cardiovascular disease we initiate intensive statin therapy. In patients 40-75 years of age without pre-existing cardiovascular disease we calculate the 10-year risk of developing cardiovascular disease and initiate moderate statin therapy if the 10-year risk is > 7.5% (note we adjust the results by multiplying by 1.5 to account for the effects of inflammation). In patients < 40 years of age we calculate both the 10-year risk and lifetime risk and discuss with the patients the various options. In the presence of a high 10-year risk or lifetime risk we tend to recommend therapy. In patients >75 years of age we examine the 10-year risk and the patient's functional status. If there is uncertainty, we will often obtain a cardiac calcium scan to help decide the best course of action. A zero calcium indicates a very low 10-year risk.

Table 6 Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Treatment Goals				
Risk category	Risk factors ^a /10-year risk ^b	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	<ul style="list-style-type: none"> Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH History of premature ASCVD (<55 male, <65 female) 	<55	<80	<70
Very high risk	<ul style="list-style-type: none"> Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% Diabetes or CKD 3/4 with 1 or more risk factor(s) HeFH 	<70	<100	<80
High risk	<ul style="list-style-type: none"> ≥ 2 risk factors and 10-year risk 10-20% Diabetes or CKD 3/4 with no other risk factors 	<100	<130	<90
Moderate risk	≤ 2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Abbreviations: ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not recommended; UKPDS = United Kingdom Prospective Diabetes Study.

^a Major independent risk factors are high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure $\geq 140/90$ mm Hg or on hypertensive medication), low HDL-C (<40 mg/dL), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), chronic renal disease (CKD) stage 3/4, evidence of coronary artery calcification and age (men ≥ 45 ; women ≥ 55 years). Subtract 1 risk factor if the person has high HDL-C.

^b Framingham risk scoring is applied to determine 10-year risk.

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Figure 6.

American Association of Clinical Endocrinologists LDL-C, Non-HDL-C, and Apo B Treatment Goals (154)

Table 3 Criteria for ASCVD risk assessment, treatment goals for atherogenic cholesterol, and levels at which to consider drug therapy

Risk category	Criteria	Treatment goal	Consider drug therapy
		Non-HDL-C mg/dL LDL-C mg/dL	Non-HDL-C mg/dL LDL-C mg/dL
Low	<ul style="list-style-type: none"> 0–1 major ASCVD risk factors Consider other risk indicators, if known 	<130	≥190
		<100	≥160
Moderate	<ul style="list-style-type: none"> 2 major ASCVD risk factors Consider quantitative risk scoring Consider other risk indicators* 	<130	≥160
		<100	≥130
High	<ul style="list-style-type: none"> ≥3 major ASCVD risk factors Diabetes mellitus (type 1 or 2)[†] <ul style="list-style-type: none"> 0–1 other major ASCVD risk factors and No evidence of end organ damage Chronic kidney disease stage 3B or 4[‡] LDL-C ≥190 mg/dL (severe hypercholesterolemia)[§] Quantitative risk score reaching the high-risk threshold 	<130	≥130
		<100	≥100
Very high	<ul style="list-style-type: none"> ASCVD Diabetes mellitus (type 1 or 2) <ul style="list-style-type: none"> ≥2 other major ASCVD risk factors or Evidence of end-organ damage[¶] 	<100	≥100
		<70	≥70

For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high-intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

Figure 7.

National Lipid Association LDL-C and Non-HDL-C Treatment Goals (145)

Eight to twelve weeks after initiating statin therapy we obtain a lipid panel to determine if the LDL and non-HDL cholesterol levels are at goal. In patients with pre-existing cardiovascular disease our goal is an LDL cholesterol < 70mg/dl and a non-HDL cholesterol < 100mg/dl. In patients with cardiovascular disease that is progressive or who have multiple risk factors a goal LDL cholesterol of < 55mg/dl and a non-HDL c < 80mg/dl should be strongly considered as suggested by the American Association of Clinical Endocrinologists (154). In patients without pre-existing cardiovascular disease our goal is an LDL cholesterol < 100mg/dl and a non-HDL cholesterol < 130mg/dl. On occasion in patients without pre-existing cardiovascular disease but either a high ten-year risk or multiple risk factors we will aim for an LDL cholesterol < 70mg/dl and a non-HDL cholesterol < 100mg/dl. If the LDL cholesterol or non-HDL cholesterol levels are not at goal, we either adjust the statin dose or consider adding additional medications.

Treatment Approach

As in all patients with lipid abnormalities the initial approach is lifestyle changes. Dietary recommendations are not unique in patients with inflammatory disorders. Exercise is recommended but depending upon the clinical situation the ability of patients with certain inflammatory disorders to participate in an exercise regimen may be limited. Exercise programs will need to be tailored for each patient's capabilities. Treatment of the underlying disease to decrease inflammation is likely to be beneficial (9). Studies have shown that increased disease activity is associated with a greater risk of cardiovascular disease while lower disease activity is associated with a lower risk (9,155-161). Moreover, treatments that reduce disease activity can decrease cardiovascular risk (9).

Drug Therapy

This section on drug therapy will focus solely on the studies that are unique to patients with inflammatory diseases. Detailed information on the use of these drugs can be found in the chapters on cholesterol lowering drugs and triglyceride lowering drugs (162,163).

STATIN THERAPY

As expected, studies have demonstrated that statins lower LDL cholesterol levels in patients with inflammatory disorders to a similar degree as patients without inflammatory disorders. For example, in a randomized trial in 116 patients with rheumatoid arthritis with a mean LDL cholesterol level of 125mg/dl, the effect of atorvastatin 40mg was compared to placebo (164). Atorvastatin reduced LDL cholesterol by 54mg/dl vs. 3mg/dl in the placebo group (164). Similarly in the IDEAL trial there was a small subgroup of patients with rheumatoid arthritis (165). The IDEAL trial compared the ability of atorvastatin 80mg vs. simvastatin 20-40mg to reduce cardiovascular events. The lowering of LDL cholesterol with either simvastatin or atorvastatin was similar in the patients with and without rheumatoid arthritis (165). Finally, a combined analysis of the IDEAL, Treat to New Target (TNT), and CARDS trials reported that the decrease in LDL cholesterol levels with statin therapy was similar in patients with or without psoriasis (166). Studies have shown similar reductions in LDL cholesterol levels with statin therapy in patients with systemic lupus erythematosus (see below). The effects of statin treatment on other lipid parameters were also similar in patients with and without inflammatory diseases. Thus, as expected statins improve the lipid profile in patients with inflammatory disorders. In some studies, the incidence of statin associated side effects have been increased in the patients with inflammatory disorders. Specifically, in the IDEAL trial rheumatoid arthritis patients reported myalgia more frequently than patients without rheumatoid arthritis (10.4% and 7.7% in rheumatoid arthritis patients vs 1.1% and 2.2% in non-rheumatoid arthritis patients receiving simvastatin and atorvastatin respectively) (165). Note that this does not necessarily indicate that statins induce myalgias more frequently in patients with rheumatoid arthritis as there was not a placebo group in the IDEAL trial. Rather it is likely that patients with rheumatoid arthritis have an increased prevalence of myalgias.

A key question is whether statin therapy will reduce cardiovascular events in patients with inflammatory diseases. A number of studies have looked at surrogate markers for events such as changes in carotid intima-media thickness or changes in cardiac calcium scores in patients treated with statins. The results have varied with some studies showing benefits and other studies showing no effects. Rollefstad et al measured changes in carotid plaque size in 86 patients with inflammatory joint disease treated with rosuvastatin for 18 months (167). The LDL cholesterol levels decreased from 155mg/dl to 66mg/dl and plaque height was significantly reduced (167). Similarly, Mok et al treated 72 patients with systemic lupus erythematosus with rosuvastatin 10mg or placebo for 12 months and reported that carotid intima-media thickness appeared to decrease (168). Moreover, Plazak et al treated 60 patients with systemic lupus erythematosus with atorvastatin 40mg or placebo for 1 year and measured changes in coronary calcium score (169). They observed an increase in coronary calcium in the placebo group while there was no change in the patients treated with statin therapy (169). In contrast, Petri et al treated 200 patients with systemic lupus erythematosus with atorvastatin 40mg or placebo for 2 years and measured both carotid intima-media thickness and coronary calcium score (170). In this study no beneficial effects of statin therapy were observed (170). Similarly, Schanberg et al treated 221 children with systemic lupus erythematosus with atorvastatin 10-20mg or placebo for 36 months and did not observe a beneficial effect of statin treatment on carotid intima-media thickness (171). Thus, the effect of statin therapy in patients with inflammatory disorders on these surrogate markers of atherosclerosis is uncertain.

There are no large randomized controlled trials evaluating the impact of statin therapy on cardiovascular disease outcomes in patients with inflammatory disease. A subgroup analysis of a small number of patients with systemic lupus erythematosus in the ALERT study has been reported (172). The ALERT study was a randomized placebo-controlled trial examining the effect of fluvastatin 40-80mg on cardiovascular events after kidney transplantation. In this trial fluvastatin therapy reduced the risk of cardiovascular events by 74% in the patients with systemic lupus erythematosus (172). Additionally, a post hoc analysis of patients with inflammatory arthritis in the IDEAL and TNT trial has been reported (173). The IDEAL trial compared atorvastatin 80mg vs simvastatin 20-40mg and the TNT compared atorvastatin 80mg vs. atorvastatin 10mg. In these trials, statin therapy resulted in a decrease in lipid levels in the patients with inflammatory arthritis to a similar degree as patients without inflammatory arthritis (173). Moreover, there was an approximate 20% reduction in the risk of cardiovascular events in patients treated with atorvastatin 80mg compared to moderate dose statin therapy in patients with and without inflammatory arthritis (173). Similarly, a post hoc analysis of the IDEAL and TNT trials reported a similar reduction in cardiovascular events with high dose statin therapy compared to low dose statin therapy in patients with psoriasis (166). A trial that focused solely on patients with rheumatoid arthritis was initiated (TRACE RA) but was terminated early after a median of 2.5 years (Kitas GD, et al. Trial of atorvastatin for the primary prevention of cardiovascular events in patients with rheumatoid arthritis [abstract]. Arthritis

Rheumatol 2015;67 Suppl 10; available from: <http://acrabstracts.org/abstract/trial-of-atorvastatin-for-the-primary-prevention-of-cardiovascular-events-in-patients-with-rheumatoid-arthritis/>). In this trial 2,986 patients with RA were randomized to atorvastatin 40mg/day vs. placebo. As expected, the reduction in LDL cholesterol levels was significantly greater in the atorvastatin group compared to placebo (-42mg/dL vs. -5mg/dL, $p<0.001$). There was a 34% (unadjusted) risk reduction for major cardiovascular events in the atorvastatin group compared to placebo that was not statistically significant. Of note, the decrease in events was in the range expected based on the Cholesterol Treatment Trialists' Collaboration meta-analysis of the effect of statins in other populations. The number and type of adverse events were similar in the atorvastatin and placebo groups. Taken together these results suggest that patients with inflammatory diseases will have a reduction in cardiovascular events with statin therapy but clearly further studies are indicated.

It is well recognized that statins have anti-inflammatory properties and studies have consistently demonstrated a decrease in CRP levels in patients treated with statins. Two meta-analyses have explored the effect of statin therapy on disease activity in patients with rheumatoid arthritis. A meta-analysis by Ly et al included 15 studies with 992 patients and reported that statin therapy decreased erythrocyte sedimentation rate, CRP, tender joint count, swollen joint count, and morning stiffness (174). Similarly, a meta-analysis by Xing et al included 13 studies with 737 patients (175). They reported that statin therapy decreased erythrocyte sedimentation rate, CRP, tender joint count, and swollen joint count (175). Additionally, the disease activity score 28 (DAS28), which focuses on joint pathology, decreased significantly in the patients treated with statin therapy and the patients with the most active disease benefited the most (175,176).

In contrast to the beneficial effects seen in patients with rheumatoid arthritis, in randomized placebo controlled trials in patients with systemic lupus erythematosus studies by Plazak et al and Petri et al failed to show a decrease in disease activity with statin therapy (169,170). In psoriasis treatment with statins has produced mixed results with some studies showing a decrease in skin abnormalities and others showing no significant effect or even an increase in disease activity (177). Finally, treatment with statins has been shown to improve periodontal disease and reduce inflammation (178-180). Thus, statins can decrease the clinical manifestations of rheumatoid arthritis, periodontitis, and perhaps psoriasis but have no effect on the clinical manifestations of systemic lupus erythematosus. These differences could be due to the relative severity of the inflammatory response and/or the specific pathways that induce inflammation in these different disorders.

The effect of statins on outcomes in patients with sepsis has been extensively studied. Numerous observational studies have shown that patients treated with statins have a marked reduction in morbidity and mortality (181,182). For example, in a meta-analysis by Wan et al of 27 observational studies with 337,648 patients, statins were associated with a relative mortality risk of 0.65 (CI 0.57-0.75) (182). However, in randomized placebo controlled clinical trials statin administration has not been shown to reduce mortality or improve outcomes (181-183). For example in a meta-analysis by Wan et al of 5 randomized controlled trials with 867 patients the relative risk was 0.98 (182). Similarly, a meta-analysis by Pertzov et al of fourteen randomized trials evaluating 2628 patients also did not observe any benefits of statin therapy in patients with sepsis (184). Additionally, a recent study examining the effect of rosuvastatin on sepsis associated acute respiratory distress also failed to demonstrate a benefit of statin therapy (185). Thus, while observational data suggested that statins may be beneficial the more rigorous randomized placebo-controlled trials have not provided evidence of benefit.

FIBRATE THERAPY

Fibrates, gemfibrozil and fenofibrate, are used to lower triglycerides and raise HDL cholesterol levels. However, fibrates, by activating PPAR alpha, are well known to have anti-inflammatory effects. Several studies have shown that fibrate therapy improves the clinical manifestations in patients with rheumatoid arthritis. For example Shirinsky et al treated 27 patients with rheumatoid arthritis with fenofibrate and reported a significant reduction in disease activity score (DAS28) (186). A recent review described 4 randomized trials and 2 observation trials of fibrates in patients with rheumatoid arthritis and in general these studies showed that fibrate therapy decreased disease activity in patients with rheumatoid arthritis (187). There have been no clinical trials of fibrate therapy in patients with sepsis, psoriasis, systemic lupus erythematosus, and periodontal disease. Thus, there is a suggestion that the anti-inflammatory properties of fibrates may beneficially impact disease activity, but clearly further studies are required.

BILE ACID SEQUESTRANT THERAPY

Bile acid binders are used to lower LDL cholesterol levels. While there are no studies of the effect of bile acid binders in patients with either rheumatoid arthritis, systemic lupus erythematosus, or periodontal disease, there are two studies in patients with psoriasis. Both Roe and Skinner et al reported that the treatment of patients with psoriasis with bile acid binders improved the skin condition (188,189). The mechanism for this beneficial effect is unknown.

EZETIMIBE THERAPY

Ezetimibe is used to lower LDL cholesterol levels. There is a single six week trial in 20 patients with rheumatoid arthritis that demonstrated that ezetimibe treatment decreased total cholesterol, LDL cholesterol, and CRP levels (190). Moreover, ezetimibe treatment reduced disease activity (190). The mechanism for this beneficial effect is unclear.

FISH OIL THERAPY

Fish oil is widely used to reduce serum triglyceride levels and is recognized to have anti-inflammatory properties. There are numerous studies examining the effect of fish oil therapy on inflammatory diseases. A meta-analysis of 17 randomized controlled trials by Goldberg and Katz of the effect of omega-3-polyunsaturated fatty acids in patients with rheumatoid arthritis reported that treatment with omega-3-fatty acids reduced joint pain intensity, morning stiffness, number of painful and/or tender joints, and the use of non-steroidal anti-inflammatory medications (191). Similarly, meta-analyses by Lee et al and Gioxari et al also demonstrated that fish oil had beneficial effects in patients with rheumatoid arthritis (192,193). In psoriasis, a recent review of 15 trials reported that overall there was a moderate benefit of fish oil supplements with 12 trials showing clinical benefit and 3 trials showing no benefit (194). In contrast, Gamret et al evaluated fish oil treatment in patients with psoriasis in 20 studies (12 randomized controlled trials, 1 open-label nonrandomized controlled trial, and 7 uncontrolled studies) (195). They reported that most of the randomized controlled trials showed no significant improvement in psoriasis, whereas most of the uncontrolled studies showed benefit when fish oil was used daily. In systemic lupus erythematosus four randomized trials have demonstrated clinical benefit with fish oil therapy, while three trials failed to show disease improvement (196-202). Finally, there are data suggesting that treatment with fish oil reduces periodontal disease (203-205). A major limitation of the studies in patients with periodontal disease is that in these trials the experimental group treated with fish oil also was simultaneously treated with aspirin making it difficult to be sure that the beneficial effects were solely due to fish oil supplementation (203,204). Taken together these studies indicate that in addition to lowering serum triglyceride levels, fish oil therapy may have beneficial effects on the underlying inflammatory disorder in some instances.

NIACIN THERAPY

Niacin is used to lower LDL cholesterol levels and triglycerides and raise HDL cholesterol levels. There are no reported clinical trials of niacin in patients with rheumatoid arthritis, systemic lupus erythematosus, psoriasis, or periodontal disease.

PCSK9 INHIBITORS

PCSK9 inhibitors are used to lower LDL cholesterol level. In addition, PCSK9 inhibitors also lower Lp(a) levels. There are no reported clinical trials of PCSK9 inhibitors in patients with rheumatoid arthritis, systemic lupus erythematosus, psoriasis, or periodontal disease.

Treatment Strategy

The first priority in treating lipid disorders is to lower the LDL cholesterol levels to goal, unless triglycerides are markedly elevated (> 500-1000mg/dl), which increases the risk of pancreatitis. LDL cholesterol is the usual first priority because the database linking lowering LDL cholesterol with reducing cardiovascular disease is extremely strong and we now have the ability to markedly decrease LDL cholesterol levels in the vast majority of patients. Dietary therapy is the initial step but, in many patients, will not be sufficient to achieve the LDL cholesterol goals. If patients are willing and able to make major changes in their diet it is possible to achieve remarkable reductions in LDL cholesterol levels but

this seldom occurs in clinical practice (for details see the chapter on the effect of lifestyle changes on lipids and lipoproteins) (206).

Statins are the first-choice drugs to lower LDL cholesterol levels and many patients with inflammatory disorders will require statin therapy. Currently four statins are available as generic drugs, lovastatin, pravastatin, atorvastatin, and simvastatin, and these statins are relatively inexpensive. The choice of statin will depend on the magnitude of LDL cholesterol lowering required and whether other drugs that the patient is taking might alter statin metabolism thereby increasing the risk of statin toxicity. For example, cyclosporine affects the metabolism of many of the statins and in patients taking cyclosporine fluvastatin appears to be the safest statin (207).

If a patient is unable to tolerate statins or statins as monotherapy are not sufficient to lower LDL cholesterol to goal the second-choice drug is either ezetimibe or a PCSK9 inhibitor. Ezetimibe can be added to any statin. PCSK9 inhibitors can also be added to any statin and are the drugs of choice if a large decrease in LDL cholesterol is required to reach goal (PCSK9 inhibitors will lower LDL cholesterol levels by 50-60% when added to a statin, whereas ezetimibe will only lower LDL cholesterol by approximately 20%). Bile acid sequestrants are an alternative particularly if a reduction in A1c level is also needed. Ezetimibe, PCSK9 inhibitors, and bile acid sequestrants additively lower LDL cholesterol levels when used in combination with a statin, because these drugs increase hepatic LDL receptor levels by different mechanisms, thereby resulting in a reduction in serum LDL cholesterol levels. Niacin and the fibrates also lower LDL cholesterol levels but are not usually employed to lower LDL cholesterol levels

The second priority should be non-HDL cholesterol (non-HDL cholesterol = total cholesterol – HDL cholesterol), which is particularly important in patients with elevated triglyceride levels (>150mg/dl). Non-HDL cholesterol is a measure of all the pro-atherogenic apolipoprotein B containing particles. Numerous studies have shown that non-HDL cholesterol is a strong risk factor for the development of cardiovascular disease. The non-HDL cholesterol goals are 30mg/dl greater than the LDL cholesterol goals. For example, if the LDL goal is <100mg/dl then the non-HDL cholesterol goal would be <130mg/dl. Drugs that reduce either LDL cholesterol or triglyceride levels will reduce non-HDL cholesterol levels.

The third priority in treating lipid disorders is to decrease triglyceride levels. Initial therapy should focus on lifestyle changes including a decrease in simple sugars and ethanol intake. Fibrates, niacin, statins, and omega-3-fatty acids all reduce serum triglyceride levels. Typically, one will target triglyceride levels when one is trying to lower non-HDL cholesterol levels to goal. Patients with very high triglyceride levels (> 500-1000 mg/dl) are at risk of pancreatitis and therefore lifestyle and triglyceride lowering drug therapy should be initiated early. Note that there is limited evidence demonstrating that lowering triglyceride levels reduces cardiovascular events. With a recent study demonstrating that adding omega-3-fatty acids (EPA) to statins in patients with elevated triglyceride levels reduces cardiovascular events one can anticipate an increased use of omega-3-fatty acids in patients with elevated triglyceride levels and a non-HDL cholesterol level above goal (208). In addition, the potential beneficial effects of fish oil on disease activity in many patients with inflammatory diseases make the use of omega-3-fatty acids an attractive choice in patients with inflammatory diseases and elevated triglyceride levels.

The fourth priority in treating lipid disorders is to increase HDL cholesterol levels. There is strong epidemiologic data linking low HDL cholesterol levels with cardiovascular disease, but whether increasing HDL levels with drugs reduces cardiovascular disease is unknown and studies have not been encouraging (209). Life style changes are the initial step and include increased exercise, weight loss, and stopping cigarette smoking. The role of recommending ethanol, which increases HDL levels, is controversial but in patients who already drink moderately there is no reason to recommend that they stop. The most effective drug for increasing HDL levels is niacin, but studies have not demonstrated a reduction in cardiovascular events when niacin is added to statin therapy (210,211). Fibrates and statins also raise HDL cholesterol levels but the increases are modest (usually less than 15%). Additionally, the ACCORD-LIPID trial failed to demonstrate that adding fenofibrate to statin therapy reduces cardiovascular disease (212). Unfortunately, given the currently available drugs, it is very difficult to significantly increase HDL cholesterol levels and in many of our patients we are unable to achieve HDL cholesterol levels in the recommended range. Furthermore, whether this will result in a reduction in cardiovascular events is unknown.

Note that there is very limited evidence that adding fibrates or niacin to lower triglyceride levels and/or increase HDL cholesterol levels will reduce cardiovascular events. However, the recent studies of fibrates or niacin in combination

with statins did not specifically target patients with high triglycerides, high non-HDL cholesterol, and low HDL cholesterol levels. The only drugs in combination with statin therapy that has been shown to further reduce cardiovascular events beyond statins alone is ezetimibe, PCSK9 inhibitors, and EPA, an omega-3-fatty acid.

Many patients with inflammatory diseases have multiple lipid abnormalities. As discussed above life style changes are the initial therapy. If life style changes are not sufficient in patients with both elevations in LDL cholesterol levels and triglycerides (and elevations in non-HDL cholesterol) one approach is to base drug therapy on the triglyceride levels (Figure 8). If the serum triglycerides are very high (greater than 500- 1000mg/dl), where there is an increased risk for pancreatitis and hyperviscosity syndromes, initial pharmacological therapy is directed at the elevated triglycerides and the initial drug choice is either a fibrate or high dose fish oil (3 grams EPA/DHA per day). After lowering triglyceride levels to < 500mg/dl statin therapy should be initiated if the LDL cholesterol and/or non-HDL cholesterol is not at goal. If the serum triglycerides are less than 500mg/dl, statin therapy to lower the LDL cholesterol levels to goal is the initial therapy (see Figure 8). Studies have clearly demonstrated that statins are effective drugs in lowering triglyceride levels in patients with elevated triglycerides. In patients with low triglyceride levels statins do not greatly affect serum triglyceride levels. If the non-HDL cholesterol levels remain above goal after one reaches the LDL cholesterol goal one should then consider combination therapy to lower triglyceride levels which will lower non-HDL cholesterol levels.

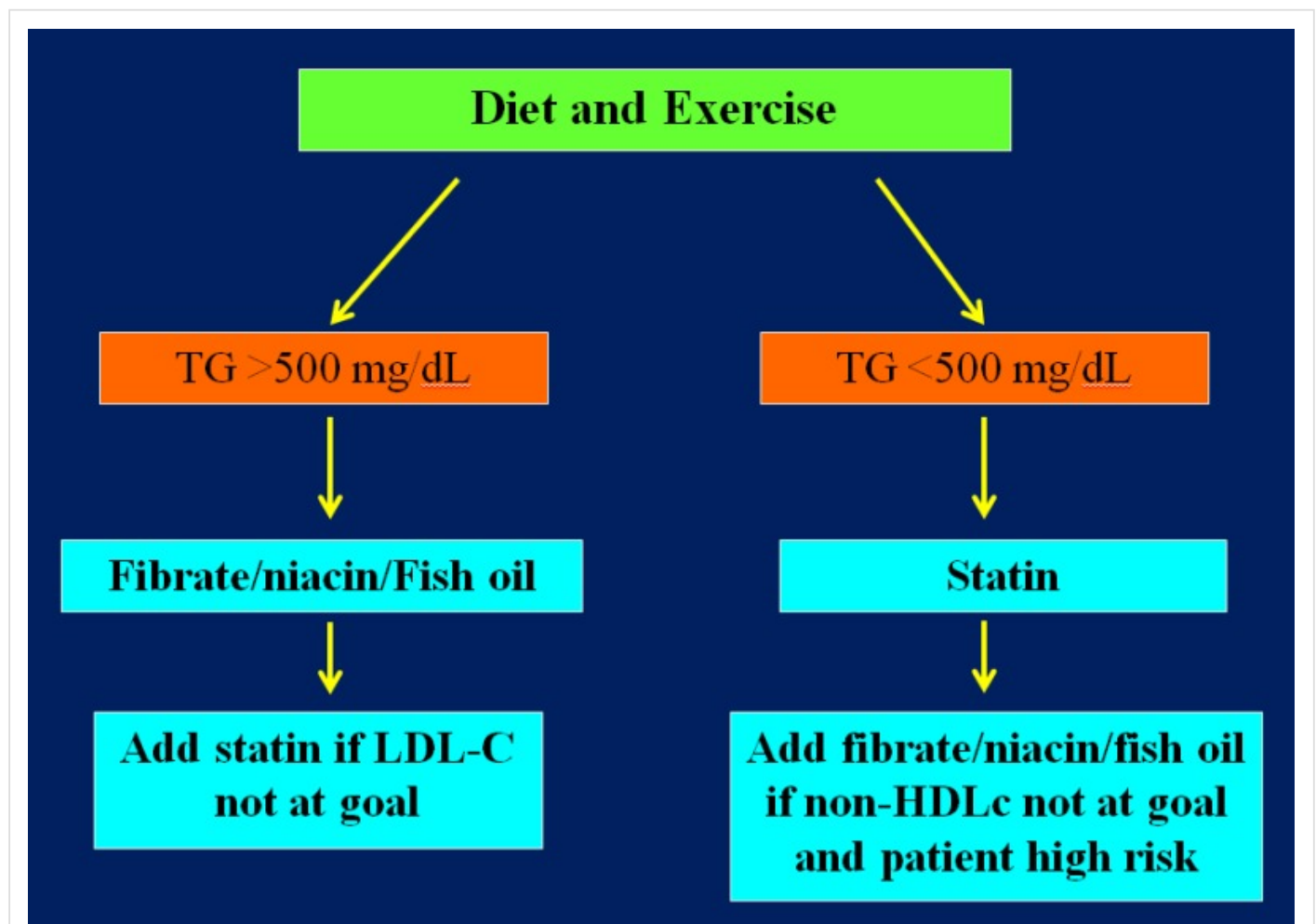


Figure 8.

Combined Hyperlipidemia. Increased LDL and TG

Often monotherapy is not sufficient to completely normalize the lipid profile. For example, with statin therapy one may often lower the LDL cholesterol to goal but the non-HDL cholesterol and triglycerides remain in the abnormal range. Currently, there are no randomized controlled trials demonstrating that combination therapy with fibrates or niacin

reduces cardiovascular disease to a greater extent than statin monotherapy. In fact three recent outcome studies adding either niacin or fenofibrate to statin therapy failed to demonstrate additional benefit (210-212). In contrast, adding EPA to statin therapy did reduce cardiovascular events (208). Despite the limited data based on randomized outcome trials many experts believe that further improvements in the lipid profile will be beneficial and that the studies completed so far should not be considered definitive as they had flaws such as not treating patients with the appropriate lipid profile.

When using combination therapy, one must be aware that the addition of either fibrates or niacin to statin therapy may increase the risk of myositis. The increased risk of myositis is greatest when gemfibrozil is used in combination with statins. Fenofibrate has a much more modest risk and the FDA approved the use of fenofibrate in combination with moderate doses of statins. Additionally, in the ACCORD LIPID trial the combination of simvastatin and fenofibrate was well tolerated (212). The increased risk with niacin appears to be modest. In the AIM-HIGH trial the risk of myositis was not increased in patients on the combination of Niaspan and statin, whereas in the HPS2-Thrive trial myopathy was increased in the group treated with the combination of niacin and statin (210,211). The absolute risks of combination therapy are relatively modest if patients are carefully selected; in many patients at high risk for cardiovascular disease combination therapy may be appropriate. Table 5 indicates the type of patient that one should consider the use of combination therapy. As with many decisions in medicine one needs to balance the benefits of therapy with the risks of therapy and determine for the individual patient the best approach. In deciding to use combination therapy a key focus is the non-HDL cholesterol level. When the LDL cholesterol is at goal but the non-HDL cholesterol is still markedly above goal it may be appropriate to resort to combination therapy in patients at high risk.

Table 5.

When to Use Combination Therapy

Clinical Evidence of Arteriosclerosis
High Risk Patient
Hypertension
Family History of CAD
Cigarettes
Proteinuria
Microalbuminuria
Central Obesity
Inactivity
Elevated CRP
No Contraindications
Renal or Liver Disease
Non-compliant patient
Use of other drugs that effect statin metabolism
Other medical disorders that increase risk of toxicity

In summary, modern therapy of patients with inflammatory diseases demands that we aggressively treat lipids to reduce the high risk of cardiovascular disease in this susceptible population and in those with very high triglycerides to reduce the risk of pancreatitis. Furthermore, treatment with lipid lowering drugs in some instances may improve the underlying inflammatory disorder.

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