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Themed Section: Targeting Inflammation to Reduce Cardiovascular Disease Risk

REVIEW ARTICLE

Current and future therapies for addressing the effects of inflammation on HDL cholesterol metabolism

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Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide. Inflammatory processes arising from metabolic abnormalities are known to precipitate the development of CVD. Several metabolic and inflammatory markers have been proposed for predicting the progression of CVD, including high density lipoprotein cholesterol (HDL-C). For ~50 years, HDL-C has been considered as the atheroprotective 'good' cholesterol because of its strong inverse association with the progression of CVD. Thus, interventions to increase the concentration of HDL-C have been successfully tested in animals; however, clinical trials were unable to confirm the cardiovascular benefits of pharmaceutical interventions aimed at increasing HDL-C levels. Based on these data, the significance of HDL-C in the prevention of CVD has been called into question. Fundamental *in vitro* and animal studies suggest that HDL-C functionality, rather than HDL-C concentration, is important for the CVD-preventive qualities of HDL-C. Our current review of the literature positively demonstrates the negative impact of systemic and tissue (i.e. adipose tissue) inflammation in the healthy metabolism and function of HDL-C. Our survey indicates that HDL-C may be a good marker of adipose tissue health, independently of its atheroprotective associations. We summarize the current findings on the use of anti-inflammatory drugs to either prevent HDL-C clearance or improve the function and production of HDL-C particles. It is evident that the therapeutic agents currently available may not provide the optimal strategy for altering HDL-C metabolism and function, and thus, further research is required to supplement this mechanistic approach for preventing the progression of CVD.

LINKED ARTICLES

This article is part of a themed section on Targeting Inflammation to Reduce Cardiovascular Disease Risk. To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v174.22/issuetoc and http://onlinelibrary.wiley.com/doi/10.1111/bcp.v82.4/issuetoc

Abbreviations

Apo-A1, apolipoprotein A1; Apo-A2, apolipoprotein A2; AT, adipose tissue; CETP, cholesterol ester transfer protein; CRP, C-reactive protein; CVD, cardiovascular disease; FA, fatty acid; LCAT, lecithin cholesterol acyltransferase; LPL, lipoprotein lipase; PLTP, phospholipid transfer protein; RA, Rheumatoid arthritis; RCT, reverse cholesterol transport; sC5b-9, serum complement membrane attack complex generated by the assembly of C5 through C9 complements; SR-B1, scavenger receptor class B type 1; SREBP-1c, sterol regulatory element binding protein-1c; TG, triglyceride; VLDL-TG, very LDL triglyceride

DOI:10.1111/bph.13743

Tables of Links

TARGETS	
Other protein targets[a]	**Enzymes**[e]
IL-1β	5-LOX
TNF-α	Caspase 1
Nuclear hormone receptors[b]	Cathepsin B
PPAR-α	COX-1
PPAR-β/δ	COX-2
PPAR-γ	JNK
LXR-α	MMP3
LXR-β	MMP7
RAR-α	MMP9
Catalytic receptors[c]	MMP12
NLRP3	MPO
Transporters[d]	P38 MAPK
ABCA1	PCSK9
ABCG1	$sPLA_2$
ABCB11	tPA

LIGANDS	
Adiponectin	Methotrexate
Aspirin	Metformin
C3	MCP-1 (CCL2)
Canakinumab	Montelukast
Etanercept	Niacin
Fibrinogen	Pioglitazone
FLAP	Rosiglitazone
ICAM-1	SAA (serum amyloid A)
IFN-γ	Sildenafil
IL-6	Tocilizumab
IL-10	Tofacitinib
IL-18	Theophylline
Leptin	Thromboxane A_2
LTB_4	VCAM-1

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 ([a,b,c,d,e]Alexander *et al.*, 2015a,b,c,d,e).

Introduction

There have been several sharp turns in the evidence trail marking the atheroprotective role of high density lipoproteins (HDLs). Very early studies on dyslipidaemia highlighted the positive correlation between total triglycerides (TGs) with the risk of developing cardiovascular disease (CVD). Since the mid-1970s, numerous epidemiological and animal studies, including the Framingham Study (Gordon *et al.*, 1977), reported that HDL cholesterol (HDL-C) has the strongest inverse relationship with the development of CVD of the known serum lipid factors (Badimon *et al.*, 1990; Rubin *et al.*, 1991; Liu *et al.*, 1994; Plump *et al.*, 1994). This association is underpinned by reverse cholesterol transport (RCT) – a process by which HDL-C transfers the cholesterol from peripheral cells, for example, lipid-laden foam cells, to the liver for secretion into bile and faeces. The promotion of RCT is considered a major anti-atherogenic function of HDL-C (Gofman *et al.*, 1966; Miller and Miller, 1975; Rhoads *et al.*, 1976). Based on these findings, interventions to increase the levels of HDL-C were developed but found to be ineffective for preventing cardiovascular outcomes in several large clinical trials (Brousseau *et al.*, 2004; McKenney *et al.*, 2006; Barter *et al.*, 2007; Boden *et al.*, 2011; Lüscher *et al.*, 2012; Schwartz *et al.*, 2012). Given these results, the importance of HDL-C for preventing CVD has been questioned and revisited. An expert panel from the National Lipid Association concluded that although 'HDL-C is not a therapeutic target at the present time', 'rigorous research into the biology and clinical significance of low HDL-C should continue' and that 'the development of novel drugs designed to modulate the serum levels and functionality of HDL particles should also continue' (Toth *et al.*, 2013), a recommendation which has been echoed by other experts in the field (Brown *et al.*, 2014; Toth *et al.*, 2014). In our opinion, the key issue in this matter is the functionality of HDL-C, which can be affected by adipose tissue (AT) and low-grade systemic inflammation (Brewer, 2007; Rader and Daugherty, 2008; Rosenson, 2010; Zhang *et al.*, 2010; Chung *et al.*, 2011). Here, we discuss the data available illustrating the effect of inflammation on the functionality of HDL particles and potential therapeutic interventions that can help reverse these effects and, thus, prevent the development of metabolic abnormalities leading to the progression of CVD and associated co-morbidities.

Mechanism of the synthesis of mature or functional HDL-C

Currently, the most important known function of HDL-C is to provide the successful transfer of cholesterol from peripheral tissues to the liver for extraction (i.e. RCT). The HDL-C particles that can effectively accomplish this task are the functionally mature ones, which are rich in apolipoprotein A1 (Apo-A1) and cholesterol (Rader and Daugherty, 2008). Several apolipoproteins, enzymes and transfer proteins participate in formation and function of these mature HDL-C particles. The first step in the formation of HDL-C requires Apo-A1 and ATP-binding cassette transporter A1 (ABCA1) (Lee and Parks, 2005; Zannis *et al.*, 2006). ABCA1 mediates the efflux of phospholipids and free cholesterol from AT to Apo-A1, a step that is necessary for the initial lipidation of Apo-A1 and formation of nascent HDL-C particles (Verghese

et al., 2007; Phillips, 2014). The next step is the maturation of HDL-C particles, which involves several enzymes – lipoprotein lipase (LPL), phospholipid transfer protein (PLTP) and lecithin cholesterol acyltransferase (LCAT). LPL hydrolyzes circulating very LDL triglyceride (VLDL-TGs), while PLTP transfers phospholipids and free cholesterol from the surface of VLDL-TG to HDL-C (Tall *et al.*, 1985; Rinninger *et al.*, 1998; 2001; Ji *et al.*, 2014). Thereafter, LCAT esterifies cholesterol, rendering it more hydrophobic and amenable for efficient packaging and transport by HDL-C to the liver (Rader, 2009; Dobiásová and Frohlich, 1999; Asztalos *et al.*, 2007). Finally, the transporter ABCG1 mediates cholesterol efflux from the surface of cells and macrophages to mature HDL-C particles (Kennedy *et al.*, 2005). The mature particles are subject to cholesterol ester transfer protein (CETP)-mediated exchange of cholesteryl esters with TGs from VLDL or LDL, which subsequently binds to LDL receptors in the liver (Bruce *et al.*, 1998). Successful completion of this exchange process and binding of HDL-C to scavenger receptor class B type I (SR-B1) receptors in the liver allows for elimination of cholesterol in the liver, thereby preventing the deposition of cholesterol in the endothelium and the development of atherosclerosis.

In addition to playing a major role in RCT, the HDL-C particles have been shown to (a) have anti-inflammatory, anti-oxidative and anti-apoptotic properties; (b) contribute to innate immunity, the modulation of glucose metabolism and platelet function; and (c) influence stem cells and embryogenesis (Gordon *et al.*, 2011). The changes in the functionality of HDL-C particles are discussed throughout this review article; however, our review is mainly focused on the effect of inflammatory processes on the functionality and atheroprotective properties of HDL-C particles. The functional diversity of HDL-C particles is related to their compositional complexity and heterogeneity. As an example, mature cholesterol and Apo-A1-rich HDL-C particles have been shown to be successful at RCT, while the smaller, cholesterol-poor, TG- and Apo-A2-rich HDL-C particles degrade easily and are unable to contribute to RCT. The published data suggest that the differences in HDL-C functionality depend on the composition of the HDL-C particles (Asztalos *et al.*, 2011).

Several assays have been proposed to assess the functionality of HDL-C. Some assays are designed to measure the anti-inflammatory and anti-oxidative properties of HDL-C, while others evaluate HDL-C RCT efflux (Navab *et al.*, 1991; 2001; Zhang *et al.*, 2003; Annema *et al.*, 2010; Suzuki *et al.*, 2010; Khera *et al.*, 2011). Furthermore, electrophoretic and NMR methods have been developed to estimate HDL-C particle size and composition. Thus far, there has been no consensus regarding the superiority of one method versus another for HDL-C characterization, and attempts to standardize the various nomenclature systems of HDL-C are a work in progress (Asztalos *et al.*, 2011). Further research is needed to elucidate the relationship between HDL-C particle heterogeneity and function (Gordon *et al.*, 2011).

Effect of inflammatory processes on HDL-C metabolism

Several factors and conditions, including genetic (i.e. familial disorders) and acquired (e.g. decreased cholesterol efflux, inflammation, hypertriglyceridaemia and AT dysfunction), affect the concentration and functionality of HDL-C. Here, we will focus on mechanisms related to inflammation, which have been depicted in detail in Figure 1.

Adipose tissue lipid kinetics. Cholesterol efflux occurs in several tissues, including the liver, intestine and AT (Basso *et al.*, 2003; Sahoo *et al.*, 2004; Lee and Parks, 2005; Timmins *et al.*, 2005; Singaraja *et al.*, 2006; Zannis *et al.*, 2006; Verghese *et al.*, 2007; Chung *et al.*, 2011; Ji *et al.*, 2012; Phillips, 2014). Regarding the role of AT, *in vitro* and animal studies demonstrated that cholesterol efflux from adipocytes plays a significant role in the initial lipidation of Apo-A1 and the formation of mature and functional HDL-C particles (Zhang *et al.*, 2010; Chung *et al.*, 2011). These results are supported by studies demonstrating that hepatic cholesterol efflux was essential but insufficient to correct HDL-C deficiency in hepatic ABCA1$^{-/-}$ knockout mice, illustrating that extrahepatic ABCA1 expression and cholesterol metabolism are critical for the formation of mature HDL-C particles (Singaraja *et al.*, 2006). Others showed that individuals with compensated liver cirrhosis have higher levels of IL-6 and NF-κB but lower levels of HDL-C and Apo-A1 (Trieb *et al.*, 2016). Thus, it appears that although the liver plays a significant role, it is not isolated in its contribution to the formation of mature HDL-C particles.

With the development of AT inflammation, several pathways are activated leading to the impairment of HDL-C metabolism. AT inflammation has been shown to suppress the expression and function of cholesterol transfer proteins (e.g. ABCA1) leading to decreased efflux of cholesterol from AT (De Haan *et al.*, 2014; Figure 1). This results in the formation of immature rather than mature HDL-C particles, which fail to successfully transfer cholesterol to the liver (Rashid and Genest, 2007). In our recent clinical study, we used a deuterium labelling approach to estimate the fractional synthesis of triglycerides (f_{TG}) in AT in humans with differing degrees of obesity. Our results demonstrated that f_{TG} is inversely associated with the markers of insulin sensitivity (Tuvdendorj *et al.*, 2013). Furthermore, f_{TG} is associated with the total concentration of HDL-C and the fractional contribution of large HDL-C particles (Tuvdendorj *et al.*, 2016). Based on the principles of the stable isotope tracer labelling approach (synthesis-breakdown/lipolysis = net balance; Turner *et al.*, 2003; Wolfe and Chinkes, 2005; Tuvdendorj *et al.*, 2013, 2016) and the reports that AT TG efflux directly correlates with the efflux of cholesterol (Le Lay *et al.*, 2003; Verghese *et al.*, 2007), we assumed that the f_{TG} represented AT cholesterol efflux in these individuals. Taken together, these data suggest that inflammation in AT is one of the principal factors affecting HDL-C functionality (Figure 1A). Thus, these data suggest that metabolically healthier people have high cholesterol efflux and higher levels of circulating total and functional HDL-C particles that are able to fulfil their atheroprotective role. Notably, our data describing the association between AT lipid flux and HDL-C metabolism were true for women but not for men, supporting the sex-dependent nature of lipid metabolism (Hazzard and Applebaum-Bowden, 1990; Williams, 1997).

An additional factor in reduced HDL-C functionality arises from AT dysfunction and chronic inflammation

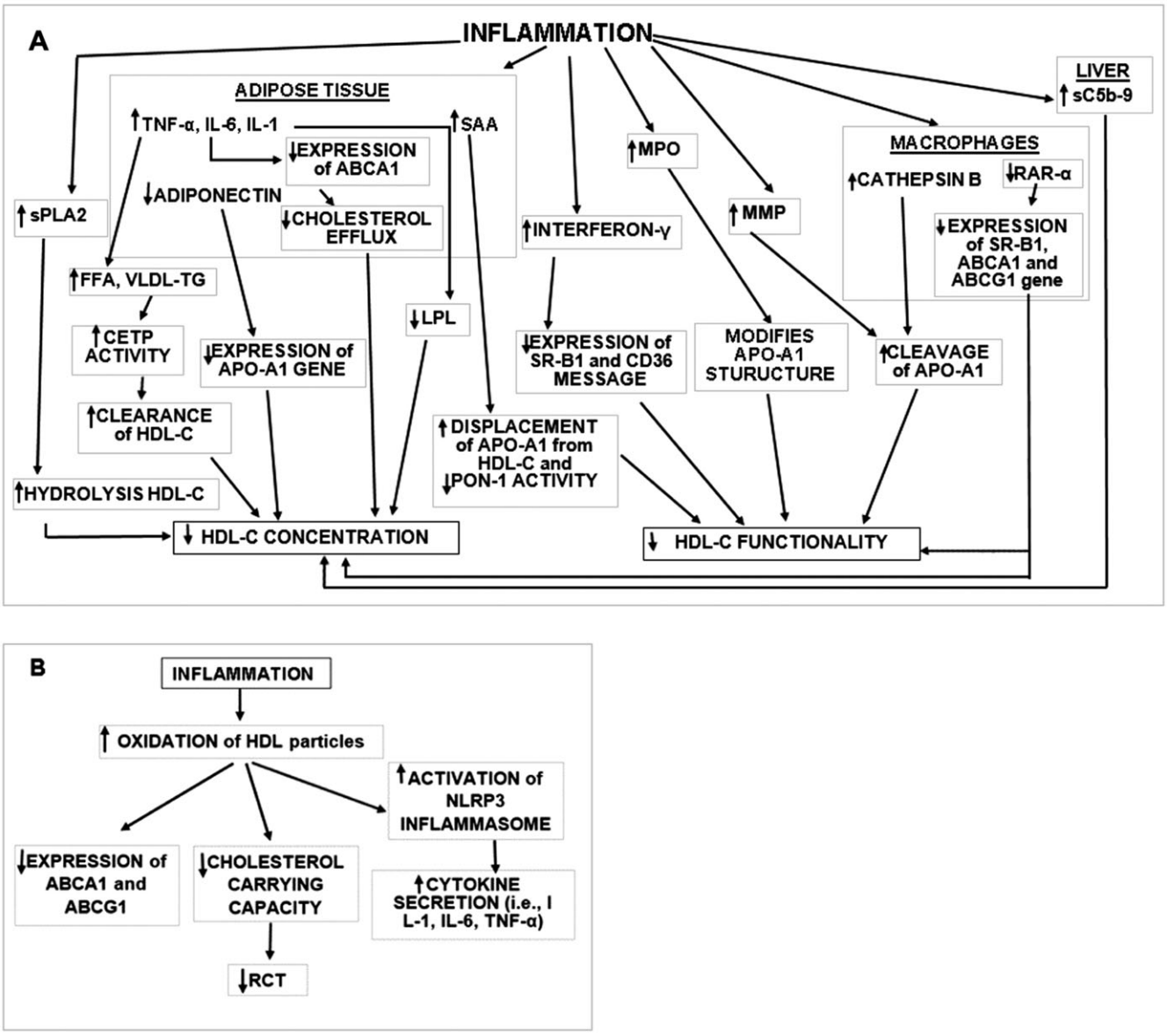

Figure 1

Schematic presentation of the mechanisms causing decreased HDL-C concentration or function due to inflammation. (A) The majority of mechanisms that affect HDL-C metabolism are associated with AT inflammation and function. Increased levels of FFA and VLDL-TG can enhance the activity of CETP resulting in TG-enriched HDL-C particles. These particles are prone to higher liver clearance rates. Decreased adiponectin levels affect the expression of the Apo-A1 gene. Inflammatory markers have been shown to affect LPL and ABCA1 gene expression impeding maturation of HDL-C. Other mechanisms which affect HDL-C concentration include (a) enhanced $sPLA_2$ activity causing increased hydrolysis of HDL-C; (b) increased secretion of complement sC5b-9 from liver; and (c) decreased expression of RAR-α in macrophages. The later mechanism also affects HDL-C function and results in (a) increased production of SAA in AT which displaces Apo-A1 from HDL-C and decreases PON-1 activity; (b) interferon-γ secretion which decreases the expression of SR-B1 and CD36; (c) MPO expression which modifies Apo-A1 structure; and (d) MMP and macrophage cathepsin B-induced cleavage of Apo-A1. (B) Mechanisms associated with the modification of HDL-C particles. Inflammatory environments induce HDL oxidation activating NLRP3 inflammasome pathways and the secretion of cytokines while decreasing ABCA1 and ABCG1 expression and the cholesterol carrying capacity of HDL-C via RCT. FFA, free fatty acid; RAR-α, retinoic acid receptor-α.

hindering the ability of adipocytes to take up excess dietary calories. As a result, the concentration of circulating fatty acids (FAs) is increased. Because FAs are used in the liver for the synthesis of triglycerides and VLDL-TG, a concomitant increase in the overall concentration of circulating lipids occurs (Figure 1A). As a result, CETP modulates the increased exchange of TGs for cholesteryl esters in HDL-C particles. These TG-enriched HDL-C particles are vulnerable to clearance resulting in a decreased concentration of HDL-C (Rashid *et al.*, 2002; Figure 1A).

Inflammatory markers. As depicted in Figure 1A, from a cell signalling perspective, AT inflammation is associated with increased activation of pro-inflammatory pathways resulting in enhanced secretion of inflammatory cytokines [i.e. TNF-α, IL-6, IL-1β, C-reactive protein (CRP) and serum amyloid A (SAA; Mortensen, 2001; Ryden *et al.*, 2002; Berg and Scherer, 2005; Stienstra *et a*l., 2012; Rodríguez-Hernández *et al.*, 2013)]. These cytokines increase the activity of downstream factors (e.g. transcription factor activator protein 1, NF-κB and INF regulatory factor), thus up-regulating the gene expression of inflammatory mediators (Figure 1A). Notably, TNF-α plays a central role in this inflammatory process. It promotes the secretion of other pro-inflammatory cytokines and decreases the production of the anti-inflammatory cytokine adiponectin (Hotamisligil *et al.*, 1993; Kern *et al.*, 2001; Ryden *et al.*, 2002; Xu *et al.*, 2003). Animal, but not human, studies have shown that decreased production of adiponectin results in decreased expression of mRNA for Apo-A1 and ABCA1, resulting in decreased levels of Apo-A1 and HDL-C (Arita *et al.*, 1999; Hotta *et al.*, 2000, 2001; Kondo *et al.*, 2002; Oku *et al.*, 2007). Additionally, all these cytokines suppress the activity of LPL, which also leads to decreased levels of both the Apo-A1 and HDL-C (Hotamisligil *et al.*, 1993; Kern *et al.*, 2001; Ryden *et al.*, 2002; Dusanov *et al.*, 2016; Jung *et al.*, 2016; O'Reilly *et al.*, 2016; Ottobelli *et al.*, 2016) (Figure 1A).

Impaired HDL-C metabolism is also associated with inflammation-induced macrophage migration to AT (Figure 1A). Macrophages cause cell-mediated modifications of Apo-A1, such as chlorination, nitration, oxidation and proteolysis. *In vitro* studies demonstrated that macrophages limit the ability of Apo-A1 to solubilize lipids and promote ABCA1-dependent cholesterol efflux. The proteolytic mechanism identified is C-terminal cleavage of Apo-A1 at Ser ^{228} by cathepsin B, which diminishes the functionality of Apo-A1 and HDL-C (Figure 1A). Cathepsins are proteases that are secreted by inflammatory macrophages (Brehm *et al.,* 2014; Abd-Elrahman *et al.,* 2016; Yan *et al.,* 2016). In point of fact, this cathepsin B-promoted cleavage process is inhibited by the lipidation of Apo-A1, which causes the C-terminal region of Apo-A1 to become more α-helical, thereby providing cleavage protection (Dinnes *et al.*, 2016).

In chronic inflammation, adipocytes secrete SAA (Poitou *et al.*, 2005; Sjöholm *et al.*, 2005), which has a high affinity for HDL-C and is known to displace apolipoproteins from HDL-C (Figure 1A). When SAA is attached to HDL-C, LCAT-mediated esterification of HDL-C is reduced affecting the formation of mature HDL-C particles. SAA also inhibits the activity of HDL-associated antioxidant enzyme paraoxonase (PON-1) resulting in HDL-C being unable to prevent the oxidation of LDL. Thus, SAA affects both the synthesis of mature HDL-C and its anti-oxidative properties (Clifton *et al.*, 1985; Malle *et al.*, 1993; Kappelle *et al.*, 2011). Interestingly, patients with rheumatoid arthritis (RA) have been shown to have increased levels of SAA and low levels of HDL-C (van Eijk *et al.*, 2009) along with higher rates of cardiovascular complications (Lehtinen, 1993; Lautermann and Braun, 2002; Peters *et al.*, 2004). Interventions to ameliorate inflammation in patients with RA have been shown to decrease SAA (van Eijk *et al.*, 2009; McInnes *et al.*, 2013) and improve HDL-C metabolism (van Eijk *et al.*, 2009; Charles-Schoeman *et al.*, 2016), which is discussed below (see subsection 'Methotrexate and Etanercept').

Other factors affecting HDL-C metabolism. Complement systems 3 and 4 (C3 and C4 respectively) play a significant role in inflammation, dyslipidaemia and metabolic syndrome. They have been shown to increase the levels of CRP, TG and fibrinogen. Increased plasma levels of circulating sC5b-9 complex have been shown to be inversely correlated with the concentration of HDL-C (Pasqui *et al.*, 2000; 2002; Onat *et al.*, 2005; Liu *et al.*, 2016); Figure 1A). Inflammation also results in increased secretion of secretory PLA_2 (sPLA2) from various tissues. $sPLA_2$ increases the hydrolysis of HDL-C particles, breaking down the phospholipids from HDL-C and thus decreasing the HDL-C concentration (Tietge *et al.,* 1999; Rye and Duong, 2000). The above factors affect the concentration and, consequently, the functionality of HDL-C (Figure 1A).

Several other agents have also been shown to directly affect the functionality of HDL-C. Low-grade systemic inflammation causes a down-regulation in the expression of retinoic acid receptor-α and alters its binding to the promoters of SR-B1 and ABCA1 (Maitra and Li, 2013). This leads to decreased expression of SR-B1, ABCA1 and ABCG1 in macrophages and thus decreased RCT (Figure 1A). Matrix metalloproteinases (MMPs) are expressed during inflammation and modulate the function of inflammatory cytokines. MMP3, MMP7 and MMP12 have been shown to cleave Apo-A1 at its carboxyl terminus (Lindstedt *et al.*, 1999). Furthermore, INF-γ, another inflammatory cytokine, has been shown to induce activation of macrophages and to decrease the expression of SR-B1 and messaging associated with CD36 (Zuckerman *et al.*, 2000; Imachi *et al.*, 2001; Bujold *et al.,* 2009). Additionally, the conditional acute phase reactant myeloperoxidase (MPO) uses chloride ions and cell-generated hydrogen peroxide to create hypochlorous acid that damages Apo-A1 (Smith, 2010; Figure 1A), thus altering the structure and function of HDL-C. Plasma Apo-A1 is a selective target for MPO-mediated protein modification which results in high levels of covalent modifications. All of these mechanisms have been shown to reduce the capacity of HDL-C to take up cholesterol and thus inhibit HDL-C function (i.e. RCT). HDL-C particles become oxidized during acute inflammation and present an additional source of impaired transport (Figure 1B). The oxidized HDL-C particles exacerbate inflammation by activating the NLRP3 inflammasome and thereby impacting HDL-C and the inflammatory environment by (1) activating downstream cytokines and caspase 1; (2) inducing the secretion of IL-18 and IL-1β; and (3) decreasing ABCA1 and ABCG1 activity (Figure 1B), thus further impairing HDL-C (van Lenten *et al.*, 1995; Nakajima *et al.*, 2000; He *et al.*, 2013; Li *et al.*, 2016).

Anti-inflammatory interventions and HDL-C metabolism

The essential question at this time is whether interventions to suppress inflammation and inflammatory markers can influence HDL-C levels and improve HDL-C functionality. The CETP inhibitors and other established pharmaceuticals are known to affect HDL-C metabolism; however, these drugs do not affect inflammatory processes; therefore, we will not

Table 1

Effects of pharmaceutical agents on inflammation and HDL-C metabolism

Pharmaceutical agents	Effect on		References
	Inflammation	HDL-C metabolism	
Aspirin	Inhibits NF-κB and MAPK	Increases expression of ABCB11 in the liver leading to increased bile acid excretion and RCT	Amann and Peskar, 2002 Demetz *et al.*, 2014
	Decreases inflammatory cytokines	Increases SR-B1 expression leading to increased cholesterol transport.	Tancevski *et al.*, 2006 Herová *et al.*, 2014
	–	Increases LCAT and PON-1 activity	Jafarnejad *et al.*, 2008
Salsalates	Inhibits NF-κB	Increases adiponectin and expression of ABCA1 and AMPK leading to increased cholesterol efflux to Apo-A1 and HDL-C	Fullerton *et al.*, 2015 Fakhri *et al.*, 2014 Goldfine *et al.*, 2013a Goldfine *et al.*, 2013b
Metformin	Decreases NF-κB, CRP and IL-6	Increases PON-1 enzyme activity and the anti-oxidative function of HDL-C	Camps *et al.*, 2016 Yoshifumi, 2016 Goldberg *et al.*, 2016
Statins	Decreases NF-κB(at high dose). Also decrease MMP9 and CRP	Increases the expression of Apo-A1 gene by activating PPAR-α Decreases VLDL-TG, TGs and CETP activity and raises HDL-C concentration	Kim *et al.*, 2007; Singh *et al.*, 2008; Bonnet *et al.*, 2008; van de Ree *et al.*, 2003 Martin *et al.*, 2001 Schaefer and Asztalos, 2006
Extended release niacin	Decreases NF-κB, TNF-α and IL-6	Decreases clearance of HDL-C by decreasing CETP activity. Increases Apo-A1 and adiponectin mRNA expression raising HDL-C concentration	Si *et al.*, 2014 Yadav *et al.*, 2015 Digby *et al.*, 2010
–	–	May increase anti-ApoA1 antibody formation that reduces HDL-C anti-oxidative function	Batuca *et al.*, 2016
Methotrexate	Decreases MMP-1, TNF-α, IL-6, IL-1 and IFN-γ	Increases expression of ABCA1 leading to enhanced RCT	Coomes *et al.*, 2011 Cutolo *et al.*, 2001 Reiss *et al.*, 2008 Chan and Cronstein, 2010
PPAR-α agonists	Decrease NF-κB, CRP and IL-6	Increase Apo-A1 and adiponectin leading to increase HDL-C concentration. Increase ABCA1, ABCG1 and SR-B1 activity in macrophages leading to enhanced RCT	Ogata *et al.*, 2009 Mahdy *et al.*, 2012 Colin *et al.*, 2015 Wagner *et al.*, 2010
–	PPAR-α agonists did not decrease inflammation in rodents with renal crystal formation. Fenofibrate did not decrease inflammatory markers in one study	–	Taguchi *et al.*, 2016 Hogue *et al.*, 2008
PPAR-γ agonists	Suppresses IFN-γ and increases M2 macrophages	Increase adiponectin and ABCA1 leading to higher HDL-C concentration. Enhance cholesterol efflux and increase expression of SR-B1	Colin *et al.*, 2015 Zuckerman *et al.*, 2000 Bujold *et al.*, 2009
Biological agents (IL-6 inhibitor, JAK inhibitor and TNF-α inhibitor)	Modulate immune response Decrease inflammatory cytokines	Improve HDL-C concentration and metabolism	Souto *et al.*, 2015; Genovese *et al.*, 2008 Mathieu *et al.*, 2010 Kawashiri *et al.*, 2011 Ghoreschi *et al.*, 2011 van Eijk *et al.*, 2009

continues

Table 1 (Continued)

Pharmaceutical agents	Effect on Inflammation	Effect on HDL-C metabolism	References
			McInnes *et al.*, 2013 Charles-Schoeman *et al.*, 2016
–	–	Etanercept may cause hypertriglyceridaemia	Haroon and Devlin, 2009
LXR agonists	Decrease TNF-α, IL-6, IL-1β, MMP-9 and IFN-γ	Increase HDL concentration and function by increasing ABCA1, ABCG1 and RCT	Joseph *et al.*, 2003 Wang *et al.*, 2006 Jamroz-Wisniewska *et al.*, 2007 Jiang *et al.*, 2003 Miao *et al.*, 2004 Repa *et al.*, 2000b Naik *et al.*, 2006
–	–	May cause increase in TGs, VLDL and LDL by inducing SREBP-1c	Repa *et al.*, 2000a Schultz *et al.*, 2000 Grefhorst *et al.*, 2002
Sildenafil	Decrease NF-κB, TNF-α and IL-1	Increase HDL-C function by unknown mechanism	Nunes *et al.*, 2015
HDL-C reconstituted therapy Apo-A1 Milano	Decrease MMP-9	Increase HDL-C function by increasing ABCA1 activity	Uehara *et al.*, 2015 Nasr *et al.*, 2015
4F mimetic peptide	Decrease inflammatory cytokines	Increase RCT	Bloedon *et al.*, 2008 Smythies *et al.*, 2010
5-Lipoxygenase inhibitors	Decrease adipose tissue inflammation, SAA, CRP and MPO levels	Improve HDL-C metabolism	Horrillo *et al.*, 2010 Bäck *et al.*, 2007 Allayee *et al.*, 2007

be discussing them in this review. In this section, we will discuss interventions that alter HDL-C metabolism *via* inflammatory pathways, including several pharmaceutical and non-pharmaceutical interventions that have been shown to ameliorate inflammation and potentially improve HDL-C metabolism, as well as others which are currently being evaluated. A summary of these interventions, including positive and negative treatment outcomes, is presented in Table 1.

Pharmaceutical approaches

Current therapies

Aspirin and salsalates. Aspirin is one of the oldest drugs in use and its effects in treating inflammation are widely known. It inhibits COX-1 and COX-2 and thus the synthesis of prostaglandins and thromboxane (Spite and Serhan, 2010). In terms of CVD treatment, aspirin has been shown to reduce the risk of first myocardial infarction in men in direct correlation with initial CRP levels (Ridker *et al.*, 1997). Aspirin does not, however, appear to reduce inflammation via pathways which impact CRP levels, as aspirin has been shown to be minimally effective in reducing CRP levels in at-risk diabetic populations (Hovens *et al.*, 2008) and aspirin-treated healthy volunteers (Feng *et al.*, 2000; Feldman *et al.*, 2001). Currently, meta-analyses indicate that aspirin therapy should only be recommended for the most at-risk patients for the prevention of cardiovascular events in diabetics due to its pro-haemorrhagic effects (Pignone *et al.*, 2010). Mechanistically, in addition to its effects on COX-1 and COX-2, aspirin inhibits the activation of NF-κB, activator protein 1 and MAPK (Amann and Peskar, 2002). In terms of its direct impact on HDL-C metabolism, studies in isolated human macrophages showed that aspirin increased SR-B1 expression and labelled HDL-associated cholesteryl oleate uptake, as well as enhancing SR-B1 expression in mice *in vivo* (Tancevski *et al.*, 2006). Additional studies in M1 macrophages showed reduced inflammatory cytokine secretion upon exposure to aspirin, which was associated with a reduction in chemerin secretion by adipose tissue (Herová *et al.*, 2014). Increased levels of circulating chemerin have been shown to inversely associate with HDL-C levels (Herová *et al.*, 2014). Rodent studies demonstrated that aspirin increases the expression of ATP binding cassette subfamily B member 11 (ABCB11) in the liver leading to increased bile acid excretion and enhanced RCT, indicating an improvement in cholesterol transfer to HDL-C (Demetz *et al.*, 2014). Further studies in diabetic rats showed that long-term aspirin therapy reduces HbA1c and advanced glycated end product formation while improving HDL functionality (Jafarnejad *et al.*, 2008). Additionally, HDL-C may play a role in increasing the oxidative capacity of aspirin via the HDL-associated enzyme PON-1, which actively hydrolyzes aspirin to salicylate, whose free radical scavenging properties may protect against atherosclerosis (Santanam and Parthasarathy, 2007). Interestingly, aspirin-resistant patients were revealed to have reduced HDL-C

levels, indicating that aspirin efficacy may in some way be associated with HDL-C function (Azmin *et al.*, 2013).

Salsalate, which is chemically related to aspirin, has been shown to increase the levels of adiponectin, HDL-C and Apo-A1 (Goldfine *et al.,* 2013a,b; Fakhri *et al.*, 2014; Fullerton *et al.*, 2015) while also suppressing the activation of NF-κB. Salsalate increases the expression of ABCA1 gene and activates AMPK, leading to increased cholesterol efflux to HDL-C and Apo-A1 (Goldfine *et al.*, 2013a,b; Fakhri *et al.*, 2014; Fullerton *et al.,* 2015). Additionally, salsalate decreases the levels of HbA1c, fasting blood sugar and C-peptide.

Metformin. Metformin is an anti-diabetic drug, which also suppresses inflammation, decreases the levels of LDL-C and leptin and reduces body weight (Camps *et al.*, 2016; Yoshifumi, 2016). It activates AMPK, which suppresses pathways associated with NF-κB. It also reduces the levels of other biomarkers of inflammation, including CRP, IL-6, E-selectins, intracellular adhesion molecule 1 (ICAM-1), fibrinogen and tissue plasminogen activator, but with less effect than lifestyle modifications (Goldberg *et al.*, 2016). Furthermore, metformin up-regulates the activity of PON-1 and thus increases the anti-oxidative capacity of HDL-C to prevent LDL oxidation. Goldberg *et al.* (2016) report that metformin increases HDL-C independently of changes in adiponectin. In spite of these effects, recent reports suggest that metformin-sensitive AMPK could be a key player in the development of Alzheimer's disease pathology (Domise *et al.*, 2016). Thus, careful consideration in using metformin, as well as salsalate (Goldfine *et al.*, 2013a,b; Fakhri *et al.*, 2014; Fullerton *et al.*, 2015), may be required. Metformin has been reported to cause metabolic acidosis and renal failure in some patients, which also needs to be taken into consideration.

Statins. Statins have been shown to have anti-inflammatory effects, which are most evident at higher dosages. High-dose atorvastatin (80 mg) suppresses NF-κB-associated inflammation, reduces the levels of MMP9 (Kim *et al.*, 2007; Singh *et al.*, 2008) and markedly decreases the concentration of CRP (van de Ree *et al.*, 2003; Bonnet *et al.*, 2008). Statin therapy is known for its ability to not only decrease LDL-C levels but also concurrently increase HDL-C. Multiple pathways are involved in the elevation of HDL-C levels. Firstly, statins inhibit Rho factor, which results in increased activation of PPAR-α and thus in an increased expression of the Apo-A1 gene (Martin *et al.*, 2001; Schaefer and Asztalos, 2006). Secondly, statins decrease VLDL-TG and TG levels as well as CETP activity. The synergetic effect is an increased concentration of HDL-C (Martin *et al.*, 2001; Schaefer and Asztalos, 2006).

Extended release niacin. Niacin exerts its atheroprotective effects by acting on AT through GPCRs, thereby influencing both pro- and anti-inflammatory markers. *In vivo* studies show that niacin decreases the levels of inflammatory markers TNF-α and IL-6 and suppresses the activation of the NF-κB pathway (Si *et al.*, 2014). The use of extended release niacin increases Apo-A1 and HDL-C levels while decreasing levels of total cholesterol, TG, LDL, monocyte chemoattractant protein (MCP-1) and SAA (Si *et al.*, 2014; Yadav *et al.*, 2015). While some studies showed that niacin administration had no effect on the anti-oxidative capacity of HDL, others demonstrated a decrease in oxidized-LDL-induced cell apoptosis and a reduction in blood vessel wall inflammation (Si *et al.*, 2014; Yadav *et al.*, 2015). Niacin also up-regulates the expression of factors involved in RCT (Si *et al.*, 2014), decreases CETP activity and reduces HDL-C clearance. Additionally, niacin increases adiponectin mRNA expression (Digby *et al.*, 2010).

Methotrexate and etanercept. Methotrexate is a disease modifying anti-rheumatic drug, which is used as a first line treatment for RA. It exerts its anti-inflammatory effect by promoting the accumulation of adenosine, which subsequently binds to the A_{2A} receptor. As a result, the expression of ABCA1 and 27-hydroxylase is promoted and RCT is increased. This action reverses the atherosclerotic effect of other COX-2 inhibitors used to treat RA, as has been demonstrated in RA patients (Reiss *et al.*, 2008; Chan and Cronstein, 2010). Additionally, methotrexate decreases MMP1, LTB_4, inflammatory cytokine (e.g. TNF-α, IL-6 and IL-1β) and INF-γ expression while increasing the expression of anti-inflammatory IL-10 (Coomes *et al.*, 2011; Cutolo *et al.*, 2001). The ongoing cardiovascular inflammation reduction trial will probe the efficacy of methotrexate therapy on patients who have suffered from prior myocardial infarction combined with diabetes or metabolic syndrome (Everett *et al.*, 2013). Although a negative impact on the ratio of total cholesterol to HDL-C has been observed following methotrexate administration, the impact of methotrexate on HDL-C function is unknown (Navarro-Millán *et al.*, 2013). The impact of targeting methotrexate-sensitive pathways on CVD progression will provide useful insights into the inflammation processes at work in atherosclerosis.

Etanercept is a TNF-α inhibitor that is used to treat RA. Several clinical trials have investigated its effect on inflammation and HDL-C parameters in patients with RA (van Eijk *et al.*, 2009; Charles-Schoeman *et al.*, 2016). These and other studies have demonstrated improvements in HDL-C metabolism. Interestingly, the majority, but not all (Rodriguez-Jimenez *et al.*, 2014), reports showed that treatment with etanercept also decreased the concentration of TNF-α (van Eijk *et al.,* 2009; Charles-Schoeman *et al.*, 2016). It is possible that the effect of etanercept on HDL-C metabolism was exerted *via* the SAA mechanism (van Eijk *et al.*, 2009).

Peroxisome proliferator-activated receptors agonists. PPARs are a nuclear receptor subfamily with three members, PPAR-α, PPAR-γ and PPAR-β/δ. PPAR agonists have been shown to have anti-inflammatory properties. PPAR-γ agonists increase the expression of adiponectin and display anti-inflammatory activity by promoting the polarization of monocytes towards alternative M2 macrophages (Colin *et al.*, 2015). Rosiglitazone decreases the levels of inducible NO synthase (iNOS), ICAM-1 and COX-2 (Cuzzocrea *et al.*, 2004). The PPAR-γ agonist 15-deoxy-delta12, 4-PGJ_2 (15d–PGJ2) reverses the INF-γ-related effects on HDL-C metabolism (Zuckerman *et al.*, 2000; Bujold *et al.,* 2009). This agonist enhances CD36 messaging, leading to increased cholesterol efflux to HDL-C, and increases the

expression of SR-B1 and its binding to HDL-C (Zuckerman *et al.*, 2000; Bujold *et al.*, 2009). PPAR-α agonists, for example, fibrates, ameliorate inflammation by decreasing the levels of CRP and IL-6 while inhibiting the activation of the NF-κB pathway (Ogata *et al.*, 2009; Mahdy *et al.,* 2012). PPAR-α agonists additionally decrease VLDL-TG levels by increasing β-oxidation of free FAs in the liver, thus decreasing the availability of FAs for VLDL-TG synthesis (Mahdy *et al.*, 2012). Reduced VLDL-TG levels are also facilitated by PPAR-γ agonists, which increase the expression of ABCA1. However, the reports on the effect of PPAR-γ agonists on the concentration of HDL-C are not consistent. Carreón-Torres *et al*. (2009) demonstrated that in rabbits, rosiglitazone increases the production rate of Apo-A1, resulting in increased concentration of HDL-C and increased activity of PON-1. Mizoguchi *et al*. (2011), who studied insulin tolerant and diabetic patients, reported that treatment with pioglitazone increased HDL-C levels while decreasing CRP and the size of atherosclerotic plaques. In this particular study, patients receiving aspirin, renin angiotensin system inhibitors and statins were included, which may have biased the final results. In contrast, Millar *et al*. (2010) demonstrated that in subjects with metabolic syndrome, rosiglitazone increased the production rate of Apo-A2 with no effect on Apo-A1 metabolism. PPAR-α agonists have been shown to stimulate the synthesis of both Apo-A1 and Apo-A2 and thus increase plasma HDL-C levels (Colin *et al.*, 2015). They have also been shown to stimulate the activity of ABCA1, ABCG1 and SR-B1 in macrophages and thus increase RCT (Mahdy *et al.*, 2012; Colin *et al.*, 2015).

PPAR agonists are already being used in clinical practice; however, they are primarily used to treat dyslipidaemia and insulin resistance. PPAR-γ agonists are primarily used to treat type 2 diabetes and they play a significant role in enhancing FA oxidation in the liver (Colin *et al.*, 2015). PPAR-β/δ agonists are used to improve lipid metabolism, as they by reduce TG and LDL-C and increase HDL-C levels. Moreover, PPAR-β/δ activation increases the expression of genes promoting insulin sensitivity (Colin *et al.*, 2015). Unfortunately, many of the currently available medications are either ineffective or have adverse effects that may outweigh their benefits for treating inflammation-related impairments in HDL-C function. For example, fibrates have a weak impact on PPAR-α activity, although a newer agent, K-877, binds strongly to PPAR-α and is in phase III clinical trials for atherosclerotic dyslipidaemia in Japan (Colin *et al.,* 2015). Wagner *et al*. (2010) demonstrated that in monkeys, the new PPAR-α agonist CP-900691 increases the levels of adiponectin and HDL-C while decreasing the levels of CRP, TG, VLDL and LDL-C. Other selective PPAR agonists, for example, CER-002 (PPAR-δ), DSP-8658 (PPAR-α/ϒ), INT131 (PPAR-α/ϒ) and GFT505 (PPAR-α/δ), are undergoing clinical trials and exhibit promise for treating the cardiovascular risks associated with metabolic syndrome and type 2 diabetes (Colin *et al.*, 2015). To date, there is no information on the effect of these new agonists on inflammation-related abnormalities.

Future therapies

HDL-C reconstituted therapy. The use of artificial components of HDL-C, as a reconstituted therapy (i.e. rHDL), has also been investigated. Apo-A1 Milano and Fukuoka Apo-A1 mimetic peptides have proved effective in animal models (Uehara *et al.*, 2015). This approach enhanced the biological function of HDL-C without elevating its concentration. Both therapeutics act as anti-atherosclerotic agents and remove cholesterol via the ABCA1 transporter. Notably, when these agents were used in patients with symptomatic carotid plaque, no significant differences were noted in expression of genes involved in formation of thrombus (Nasr *et al.,* 2015). However, the use of reconstituted peptides prevented the significant postoperative surge in plasma IL-6, which was seen in the placebo group. Surgical intervention reduced systemic levels of tissue factor, MMP9 and MCP-1 in the rHDL group, although the effects on MMP9 and MCP-1 were abolished in the immediate postoperative period (Nasr *et al.*, 2015). The 4F mimetic peptide was studied and found to have anti-inflammatory properties *in vitro* and in humans (Bloedon *et al.*, 2008; Smythies *et al.*, 2010). The mimetic peptide decreased the levels of pro-inflammatory cytokines and the adhesion of monocytes to human endothelial cells while increasing RCT by enhancing cholesterol efflux in macrophages (Smythies *et al.*, 2010).

Liver X receptors agonists. The results from studies in mice have demonstrated that agonists of liver X receptors -α and -β (LXR-α and LXR-β respectively) increase the total concentration and the size of HDL-C particles by up-regulating the expression of ABCA1 and ABCG1 (Repa *et al.*, 2000b; Jiang *et al.*, 2003; *Miao et al.,* 2004). Furthermore, LXR agonists have been shown to promote RCT resulting in the reduced deposition of cholesterol in atherosclerotic plaques (*Naik et al.,* 2006). Conflictingly, LXR agonists have also been shown to up-regulate the expression of CETP in CETP-expressing transgenic mice, which completely abolished the beneficial effect of LXR on HDL-C metabolism and increased the levels of LDL-C and VLDL-TGs (Jiang *et al.*, 2003; Masson *et al.*, 2004; Beltowski, 2008). LXR agonists also induced the sterol regulatory element binding protein-1c in the liver, which has been shown to associate with the increased concentration of TGs (Repa *et al.,* 2000a; Schultz *et al.,* 2000; Grefhorst *et al.,* 2002). In contrast, it has been hypothesized that LXR-β selective agonists would decrease the levels of TG and LDL-C. Several LXR-β selective pyrazole and imidazole biaryl sulfones have been prepared. In particular, imidazole 18 (EXEL-04286652, BMS-779788) is an LXR-β partial agonist that induces ABCA1, making it a reagent of interest for further study (Kick *et al.*, 2015; Matsuda *et al.*, 2015). Additionally, a novel synthetic, steroidal LXR ligand, ATI-111, has been developed. This molecule exhibits a strong effect on LXR-α with a modest effect on LXR-β. Encouragingly, animal and *in vitro* studies indicate that ATI-111 has beneficial anti-atherosclerotic and anti-inflammatory effects ranging from reduced hypertriglyceridaemia to decreased atherosclerotic lesions. To assess the full potential of ATI-111, clinical trials will be necessary. Presently, a phase I clinical trial with XL-652 (XL-014), a novel LXR ligand, is underway (Colin *et al.*, 2015). Furthermore, the LXR agonists have been shown to have anti-inflammatory properties. Mouse studies with LXR agonists T0901317 and GW3965 demonstrated

decreased levels of inflammatory cytokines TNF-α, IL-6, IL-1β, IFN-γ, MMP-9 and ICAM-1 (Joseph *et al.*, 2003; Wang *et al.*, 2006; Jamroz-Wisniewska *et al.*, 2007), indicating another beneficial side of LXR agonists warranting further investigation.

Phosphodiesterase-5 inhibitors. Sildenafil inhibits cGMP-specific PDE5, an enzyme that promotes degradation of cGMP. Inhibition of PDE5 results in smooth muscle relaxation, which alleviates erectile dysfunction and pulmonary arterial hypertension (Balhara *et al.*, 2015; Igarashi *et al.*, 2016). Sildenafil therapy increased HDL-C and decreased P-selectin and LDL-C levels through mechanisms which are not yet understood (Mandosi *et al.*, 2015). Nunes *et al.* (2015) reported that administration of sildenafil reduces the expression of pro-inflammatory cytokines IL-1β and TNF-α while increasing the levels of anti-inflammatory cytokine IL-10. In addition, sildenafil has been shown to reduce the expression of GFAP, NF-κB, inactive AMPK and iNOS and to increase IKβα levels (Nunes *et al.*, 2015). Thus, sildenafil may potentially be used to treat inflammation and the associated decrease in HDL-C function.

Monoclonal antibodies. A monoclonal antibody, canakinumab, is an IL-1β inhibitor which has been shown to be effective in treating juvenile RA (Gencer *et al.*, 2015). The canakinumab anti-inflammatory thrombosis outcomes study trial is currently underway to determine the effects of canakinumab on stable CVD patients who exhibit high levels of inflammation (hsCRP >2 mg. L^{-1}; Ridker *et al.*, 2011). While existing data on canakinumab would indicate that overall HDL-C levels will not be affected (Ridker *et al.*, 2012), the impact of targeting inflammation via the IL-1β pathway for reducing cardiovascular events will provide insight into the role of inflammation in CVD and the potential benefits of a more thorough investigation of the effect of canakinumab on HDL-C. A similar but more direct approach for treating dyslipidaemia may reside in the use of monoclonal antibody inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9), such as alirocumab and evolocumab, which were approved by the FDA in 2015. PCSK9, which contributes to the development of atherosclerosis, is believed to be expressed in macrophages, smooth muscles and endothelium. Functionally, PCSK9 down-regulates the expression of the stress response genes and reduces inflammation in liver cells, indicating that PCSK9 affects metabolic pathways beyond cholesterol metabolism. Inhibition of PCSK9 improves the removal of LDL-C from blood by the liver (Lan *et al.*, 2010). Furthermore, Walley *et al.* (2014) demonstrated that reducing PCSK9 function increases pathogen lipid clearance via the LDL receptor, thereby decreasing the inflammatory response and improving sepsis outcomes in both mice and humans. This finding is in contrast to that of Sahebkar *et al.* (2016), who conducted a meta-analysis evaluating the effects of several PCSK9 inhibitors on the levels of high-sensitivity CRP (hs-CRP) and demonstrated that PCSK9 inhibitors do not affect the hs-CRP levels. The PCKS9 story is relatively new and will be revisited in coming years. Nevertheless, monoclonal antibodies show promise for ameliorating inflammation and related dyslipidaemia.

Biological agents. According to several recent studies and meta-analyses, biological agents for the treatment of inflammatory arthritis induced changes in several lipid profiles. Specifically, tocilizumab, an IL-6 inhibitor, and tofacitinib, a JAK inhibitor, are recombinant proteins, which have been shown to decrease the levels of inflammatory cytokines and increase HDL-C concentration. The mechanisms whereby these agents exert their beneficial effect involve modulation of the immune response. JAK inhibitors block intracellular signalling of several cytokines. This effect was confounded by the inability of the TNF-α antagonists to show any marked improvement in HDL-C (Dahlqvist *et al.*, 2006; Genovese *et al.*, 2008; Soubrier *et al.*, 2008; Mathieu *et al.*, 2010; Ghoreschi *et al.*, 2011; Kawashiri *et al.*, 2011; van Vollenhoven *et al.*, 2012; McInnes *et al.*, 2013; Souto *et al.*, 2015).

5-LOX inhibitors (theophylline and montelukast). Theophylline and montelukast have been investigated for the treatment of inflammation-related asthma (Allayee *et al.*, 2007). Both of these drugs inhibit the pathway controlled by 5-lipoxygenase (5-LOX), a critical agent in the leukotriene pathway, which is expressed in AT and plays a significant role in obesity-related AT inflammation (Horrillo *et al.*, 2010). Modulation of the leukotriene pathway, using 5-LOX activated protein (i.e. FLAP) inhibitors, has been shown to decrease the levels of systemic pro-inflammatory cytokines, AT macrophage content and systemic insulin resistance (Bäck *et al.*, 2007; Horrillo *et al.*, 2010). Hakonarson *et al.* (2005) demonstrated that interventions using 5-LOX inhibitors decreased the levels of inflammatory markers such as SAA, CRP and MPO. Similarly, Allayee *et al.* (2007) showed that treatment of asthmatics with theophylline and montelukast decreased the levels of CRP, IL-6, VLDL-TG and LDL-C. Unfortunately, in this report, the HDL-C levels were reduced in the treatment group compared with placebo, indicating a potential detrimental effect of montelukast and theophylline therapy on HDL-C metabolism. Nevertheless, because of the reported significance of 5-LOX-associated pathways in obesity-related inflammation, further studies that target this strategy for reducing inflammation are of interest.

Non-pharmaceutical approaches

Diet and dietary components. A hypocaloric, high-fat, low-carb diet has been found to decrease CRP and increase adiponectin. This regime has also been shown to lower hepatic VLDL-TG and TG secretion and decrease their hydrolysis by hepatic lipase, thereby increasing HDL-C (Ruth *et al.*, 2013). Increased intake of tree nuts causes a decrease in total cholesterol, LDL-C, TG and Apo-B, while exerting no effect on HDL-C, Apo-A1, CRP and hypertension (Ros *et al.*, 2004; Demonty *et al.*, 2009; Sabate and Wien, 2013; Del Gobbo *et al.*, 2015). Although numerous isolated reports show the beneficial effect of red wine and resveratrol supplementation on inflammatory markers, the meta-analyses demonstrated no positive impact from resveratrol supplementation on cardiovascular risk factors (Sahebkar *et al.*, 2015). In fact, a slight decrease in HDL-C levels has been reported (Sahebkar *et al.*, 2015). Krill oil consumption, which has an anti-oxidative effect, is associated with increased HDL-C and

Table 2

Side effects of pharmaceutical agents that have anti-inflammatory properties and can contribute to improving the HDL-C function

Pharmaceutical agents	Side effects	References
Aspirin	Drug resistance can occur in some patients.	Azmin *et al.*, 2013; Zhang *et al.*, 2017
	Polyp formation and exacerbation of respiratory disease has been observed.	Eskandarian *et al.*, 2012; Cook and Stevenson, 2016
	Chronic salicylate intoxication can cause SIRS.	Chalasani *et al.*, 1996
	Aspirin can cause gastritis and increased risk of gastrointestinal bleeding.	Gartner, 1976
Salsalates	Poor tolerance in HIV patients.	Hileman *et al.*, 2010
	Activate AMPK and may cause Alzheimer's disease.	Domise *et al.*, 2016
Metformin	Effect may depend on race and ethnicity.	Zhang *et al.*, 2015
	It may cause lactic acidosis especially if given in renal diseases.	Lalau, 2010
	It causes hepatotoxicity in PON-1- deficient mice.	García-Heredia *et al.*, 2016
	Activates AMPK and may cause Alzheimer's disease.	Domise *et al.*, 2016
Statins	Down-regulate ABCA1 and ABCG1 activity in macrophages.	Sone *et al.*, 2004; Wang *et al.*, 2013; Wong *et al.*, 2008
	Cause myopathy in some patients.	Lahaye *et al.*, 2014; Brinton *et al.*, 2016; Jacobson, 2009; Rosenson, 2004
	Rosuvastatin did not reduce inflammation in sepsis associated acute respiratory distress syndrome.	Truwit *et al.*, 2014
	Unsafe in pregnancy.	Hosokawa *et al.*, 2003
	They may cause hepatotoxicity.	Russo *et al.*, 2014
Niacin	There is increased risk of flushing with niacin use.	Maccubbin *et al.*, 2009
	May cause macular oedema.	Domanico *et al.*, 2015
	May lead to the development of hepatitis.	Etchason *et al.*, 1991
PPAR-α agonists	Did not decrease inflammation in rodents with renal crystal formation.	Taguchi *et al.*, 2016
	Fenofibrate did not decrease inflammatory markers in one study.	Hogue *et al.*, 2008
	Fibrates may cause increased risk of renal problems.	Zhao *et al.*, 2012
PPAR-γ agonists	Thiazolidinediones may increase risk of myocardial infarction and heart failure especially rosiglitazone.	Singh *et al.*, 2007 Nissen and Wolski, 2007
	Increased risks of fractures in women.	Loke *et al.*, 2009
	There is increased risk of bladder cancer with pioglitazone.	Ferwana *et al.*, 2013
Biological agents (IL-6 inhibitor, JAK inhibitor and TNF-α inhibitor)	Several toxic side effects.	Pichler, 2006
	Increase chance of fungal infections with anti-TNF-α fusion inhibitors.	Tragiannidis *et al.*, 2016
LXR agonists	May cause increase in TGs, VLDL and LDL by inducing SREBP-1c	Repa *et al.*, 2000a; Schultz *et al.*, 2000; Grefhorst *et al.*, 2002
Sildenafil	May cause hypotension if given with nitrates.	Webb *et al.*, 1999

continues

Table 2 (Continued)

Pharmaceutical agents	Side effects	References
Monoclonal antibodies	Adverse effects including acute anaphylaxis, serum sickness, cardiotoxicity etc.	Hansel *et al.*, 2010; Kizhedath *et al.*, 2016
	Increase chance of fungal infections with anti-TNFα monoclonal antibodies.	Tragiannidis *et al.*, 2016
5-Lipoxygenase inhibitors		
Theophylline	Can cause adverse effects due to theophylline toxicity.	Eason and Markowe, 1989
Montelukast	Increased risk of ecchymosis.	Aypak *et al.*, 2013
Methotrexate	May cause elevation of liver enzymes and hepatotoxicity.	Curtis *et al.*, 2010
	May cause bone marrow suppression.	Sosin and Handa, 2003

Apo-A1 and decreased TG and inflammation levels in healthy young adults (Berge *et al.*, 2015; Cicero *et al.*, 2016). Caffeic acid is a naturally occurring phenolic compound found in many fruits, vegetables and herbs (Moon *et al.*, 2009). It decreases TNF-α-induced induction of adhesion molecules including ICAM-1, vascular adhesion molecule (VCAM-1) and P selectin. It also decreases TNF-α-induced activation of IL-8 and NF-κB (Moon *et al.*, 2009). *Aloe vera* exhibits several beneficial effects. It decreases the activation of inflammasome NLRP3, IL-8, IL-6, IL-1β and TNF-α, as well as the activation of inflammatory NF-κB, p38 and JNK pathways, and thus decreases inflammation and raises HDL-C levels (Budai *et al.*, 2013; Kumar *et al.*, 2013).

Exercise and life style interventions; bariatric surgery; and electro acupuncture therapy. Exercise and life style interventions show promising effects on inflammatory markers and lipid profiles. These strategies increase the levels of adiponectin and HDL-C and decrease inflammatory cytokines such as INF-γ (Nishida *et al.*, 2015; Davidson *et al.*, 2017, Wefers *et al.*, 2016). The improvement in HDL-C metabolism with weight loss can occur via improvements in several of the mechanisms discussed above. For example, increased levels of adiponectin activate ceramidase and the formation of sphingosine-1-phosphate, thus altering HDL-C sphingolipid content, thereby improving HDL-C function (Belalcazar *et al.*, 2012). Goldberg *et al.* (2016) showed that lifestyle intervention increases the levels of adiponectin and HDL-C while decreasing the levels of inflammatory markers CRP, IL-6, E selectin, ICAM-1 and fibrinogen. Moreover, weight loss results in decreased levels of TG, which diminishes the activity of CETP and thus results in higher levels of functional HDL-C. Animal studies demonstrated that weight loss results in increased expression of ABCG1 protein in AT leading to increased cholesterol efflux (Edgel *et al.*, 2012), which is associated with enhanced levels of functional HDL-C particles (Wesnigk *et al.*, 2016). Taken together, these and other reports suggest that weight loss beneficially affects HDL-C metabolism.

Roux en-Y gastric bypass surgery boosts HDL-C levels and endothelial function. This results in decreased apoptosis of endothelial cells and increased production of nitric oxide and enhanced PON-1 activity. Additionally, there is an increase in macrophage-induced cholesterol efflux. Furthermore, anti-inflammatory and anti-oxidative effects are enhanced because of a decrease in TNF-α-mediated VCAM-1 expression and NADPH oxidase activity (Adams *et al.*, 2012; Osto *et al.*, 2015).

Electro-acupuncture shows promise in treating obesity and controlling inflammation. It decreases BMI and the concentrations of IL-6, TNF-α, TG and LDL-C, while increasing the levels of adiponectin and HDL-C (Firouzjaei *et al.*, 2016).

Conclusions

While the association of HDL-C metabolism with the progression of CVD is still being investigated, the evidence supporting a link between tissue and systemic inflammation, lipid kinetics and CVD progression continues to grow. Our current review details the manner in which tissue and systemic inflammation modulates HDL-C metabolism via several pathways, for example, cholesterol efflux, hyperlipidaemia and apolipoprotein modification. The data available suggest that regardless of its correlation with the progression of CVD, HDL-C metabolism may provide a window into systemic or tissue (i.e. adipose) health. Our survey of available anti-inflammatory interventions indicates that increasing Apo-A1, ABCA1, SR-B1 and adiponectin levels may improve the production and functioning of HDL-C particles. The potential health benefits and indirect improvements in HDL-C metabolism resulting from anti-inflammatory interventions must, however, be balanced with their potential side effects (Table 2). Additionally, it should be noted that not all the agents discussed are purely anti-inflammatory and thus may affect HDL-C metabolism via other factors and mechanisms. Although a healthy lifestyle is the best approach to prevent the development of inflammation, the challenges of implementing lifestyle modification in the general population will require consistent social and medical support. Thus, pharmaceutical interventions to ameliorate inflammation and improve the functionality of HDL-C and dyslipidaemia are of significant interest. A summary of the common anti-inflammatory agents of interest for enhancing HDL-C function, with a list of associated side effects, is presented in Table 2. The question of whether the

side effects outweigh the benefits of these agents for ameliorating inflammation and HDL-C metabolism will need to be addressed by future clinical trials. In conclusion, further research is needed to elucidate and target the mechanisms linking HDL-C metabolism to both inflammation and the progression of CVD. Some of the studies should address the key mechanisms underlying the complexity and heterogeneity of HDL-C particles, which should provide a more detailed understanding of the specific functions of these particles.

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Author contributions

F.I., W.S.B. and D.T. did the literature search; F.I., W.S.B. and D.T. wrote the manuscript; and F.I., W.S.B., M.I.K., S.T., K.H. M., N.A. and D.T discussed and edited the manuscript.

Conflict of interest

The authors declare no conflicts of interest.

References

Abd-Elrahman I, Meir K, Kosuge H, Ben-Nun Y, Weiss Sadan T, Rubinstein C *et al.* (2016). Characterizing cathepsin activity and macrophage subtypes in excised human carotid plaques. Stroke 47: 1101–1108.

Adams TD, Davidson LE, Litwin SE, Kolotkin RL, LaMonte MJ, Pendleton RC (2012). Health benefits of gastric bypass surgery after 6 years. JAMA 308: 1122–1131.

Alexander SPH, Kelly E, Marrion N, Peters JA, Benson HE, Faccenda E *et al.* (2015a). The Concise Guide to PHARMACOLOGY 2015/16: Overview. Br J Pharmacol 172: 5729–5743.

Alexander SPH, Cidlowski JA, Kelly E, Marrion N, Peters JA, Benson HE *et al.* (2015b). The Concise Guide to PHARMACOLOGY 2015/16: Nuclear hormone receptors. Br J Pharmacol 172: 5956–5978.

Alexander SPH, Fabbro D, Kelly E, Marrion N, Peters JA, Benson HE *et al.* (2015c). The Concise Guide to PHARMACOLOGY 2015/16: Catalytic receptors. Br J Pharmacol 172: 5979–6023.

Alexander SPH, Kelly E, Marrion N, Peters JA, Benson HE, Faccenda E *et al.* (2015d). The Concise Guide to PHARMACOLOGY 2015/16: Transporters. Br J Pharmacol 172: 6110–6202.

Alexander SPH, Fabbro D, Kelly E, Marrion N, Peters JA, Benson HE *et al.* (2015e). The concise guide to PHARMACOLOGY 2015/16: Enzymes. Br J Pharmacol 172: 6024–6109.

Allayee H, Hartiala J, Lee W, Mehrabian M, Irvin CG, Conti DV *et al.* (2007). The effect of montelukast and low-dose theophylline on cardiovascular disease risk factors in asthmatics. Chest 132: 868–874.

Amann R, Peskar BA (2002). Anti-inflammatory effects of aspirin and sodium salicylate. Eur J Pharmacol 447: 1–9.

Annema W, Nijstad N, Tölle M, De Boer JF, Buijs RV, Heeringa P *et al.* (2010). Myeloperoxidase and serum amyloid A contribute to impaired in vivo reverse cholesterol transport during the acute phase response but not group IIA secretory phospholipase A(2). J Lipid Res 51: 743–754.

Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J *et al.* (1999). Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 257: 79–83.

Asztalos BF, Schaefer EJ, Horvath KV, Yamashita S, Miller M, Franceschini G *et al.* (2007). Role of LCAT in HDL remodeling: investigation of LCAT deficiency states. J Lipid Res 48: 592–599.

Asztalos BF, Tani M, Schaefer EJ (2011). Metabolic and functional relevance of HDL subspecies. Curr Opin Lipidol 22: 176–185.

Aypak C, Türedi Ö, Solmaz N, Yıkılkan H, Görpelioğlu S (2013). A rare adverse effect of montelukast treatment: ecchymosis. Respir Care 58: e104-e106.

Azmin S, Sahathevan R, Rabani R, Nafisah WY, Tan HJ, Raymond AA *et al.* (2013). Biochemical aspirin resistance in stroke patients – a cross-sectional single centre study. EXCLI J 12: 907.

Bäck M, Sultan A, Ovchinnikova O, Hansson GK (2007). 5-Lipoxygenase-activating protein: a potential link between innate and adaptive immunity in atherosclerosis and adipose tissue inflammation. Circ Res 100: 946–949.

Badimon JJ, Badimon L, Fuster V (1990). Regression of atherosclerotic lesions by high density lipoprotein plasma fraction in the cholesterol fed rabbit. J Clin Invest 85: 1234–1241.

Balhara YP, Sarkar S, Gupta R (2015). Phosphodiesterase-5 inhibitors for erectile dysfunction in patients with diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Indian J Endocrinol Metab 19: 451–461.

Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M *et al.* (2007). Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 357: 2109–2122.

Basso F, Freeman L, Knapper CL, Remaley A, Stonik J, Neufeld EB *et al.* (2003). Role of the hepatic ABCA1 transporter in modulating intrahepatic cholesterol and plasma HDL cholesterol concentrations. J Lipid Res 44: 296–302.

Batuca JR, Amaral MC, Favas C, Paula FS, Ames PR, Papoila AL *et al.* (2016). Extended release-niacin increases anti-ApoA-I antibodies that block the anti-oxidant effect of HDL-C: the EXPLORE clinical trial. Br J Clin Pharmacol. doi:10.1111/bcp.13198.

Belalcazar LM, Lang W, Haffner SM, Hoogeveen RC, Pi-Sunyer FX, Schwenke DC (2012). Adiponectin and the mediation of HDL-cholesterol change with improved lifestyle: the Look AHEAD Study. J Lipid Res 53: 2726–2733.

Beltowski J (2008). Liver X receptors (LXR) as therapeutic targets in dyslipidemia. Cardiovasc Ther 26: 297–316.

Berge RK, Ramsvik MS, Bohov P, Svardal A, Nordrehaug JE, Rostrup E *et al.* (2015). Krill oil reduces plasma triacylglycerol level and improves related lipoprotein particle concentration, fatty acid composition and redox status in healthy young adults – a pilot study. Lipids Health Dis 4: 163.

Berg AH, Scherer PE (2005). Adipose tissue, inflammation, and cardiovascular disease. Circ Res 96: 939–949.

Bloedon LT, Dunbar R, Duffy D, Pinell-Salles P, Norris R, DeGroot BJ *et al.* (2008). Safety, pharmacokinetics, and pharmacodynamics of oral apoA-I mimetic peptide D-4F in high-risk cardiovascular patients. J Lipid Res 49: 1344–1352.

Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K *et al.* (2011). Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 365: 2255–2267.

Bonnet J, McPherson R, Tedgui A, Simoneau D, Nozza A, Martineau P (2008). Effects of l0-mg versus 80-mg atorvastatin on high-sensitivity C-reactive protein in patients with stable coronary artery disease: results of the CAP (comparative atorvastatin pleiotropic effects) Study. Clin Ther 30: 2298–2313.

Brehm A, Geraghty P, Campos M, Garcia-Arcos I, Dabo AJ, Gaffney A *et al.* (2014). Cathepsin G degradation of phospholipid transfer protein (PLTP) augments pulmonary inflammation. FASEB J 28: 2318–2331.

Brewer HB (2007). HDL metabolism and the role of HDL in the treatment of high-risk patients with cardiovascular disease. Curr Cardiol Rep 9: 486–492.

Brinton EA, Maki KC, Jacobson TA, Sponseller CA, Cohen JD (2016). Metabolic syndrome is associated with muscle symptoms among statin users. J Clin Lipidol 10: 1022–1029.

Brown WV, Ansell BJ, Mackey RH, Toth PP (2014). JCL roundtable: HDL in the primary care setting. J Clin Lipidol 8: 364–372.

Brousseau ME, Schaefer EJ, Wolfe ML, Bloedon LT, Digenio AG, Clark RW *et al.* (2004). Effects of an inhibitor of cholesteryl ester transfer protein on HDL cholesterol. N Engl J Med 350: 1505–1515.

Bruce C, Chouinard RA Jr, Tall AR (1998). Plasma lipid transfer proteins, high-density lipoproteins, and reverse cholesterol transport. Annu Rev Nutr 18: 297–330.

Budai MM, Varga A, Milesz S, Tőzsér J, Benkő S (2013). *Aloe vera* downregulates LPS-induced inflammatory cytokine production and expression of NLRP3 inflammasome in human macrophages. Mol Immunol 56: 471–479.

Bujold K, Rhainds D, Jossart C, Febbraio M, Marleau S, Ong H (2009). CD36-mediated cholesterol efflux is associated with PPARgamma activation via a MAPK-dependent COX-2 pathway in macrophages. Cardiovasc Res 83: 457–464.

Camps J, Hernández-Aguilera A, García-Heredia A, Cabré N, Luciano-Mateo F, Arenas M *et al.* (2016). Relationships between metformin, paraoxonase-1 and the chemokine (C-C motif) ligand 2. Curr Clin Pharmacol 11. doi:10.2174/1574884711666160915152941.

Carreón-Torres E, Rendón-Sauer K, Monter-Garrido M, Toledo-Ibelles P, Gamboa R, Menjivar M *et al.* (2009). Rosiglitazone modifies HDL structure and increases HDL-Apo AI synthesis and catabolic rates. Clin Chim Acta 401: 37–41.

Chalasani N, Roman J, Jurado RL (1996). Systemic inflammatory response syndrome caused by chronic salicylate intoxication. South Med J 89: 479–482.

Chan ES, Cronstein BN (2010). Methotrexate – how does it really work? Nat Rev Rheumatol 6: 175–178.

Charles-Schoeman C, Lee YY, Shahbazian A, Wang X, Elashoff D, Curtis JR *et al.* (2016). Improvement in HDL function in early rheumatoid arthritis patients treated with methotrexate monotherapy or combination therapy in the TEAR trial. Arthritis Rheumatol . doi:10.1002/art.39833.

Chung S, Sawyer JK, Gebre AK, Maeda N, Parks JS (2011). Adipose tissue ATP binding cassette transporter A1 contributes to high-density lipoprotein biogenesis in vivo. Circulation 124: 1663–1672.

Cicero AF, Rosticci M, Morbini M, Cagnati M, Grandi E, Parini A *et al.* (2016). Lipid-lowering and anti-inflammatory effects of omega 3 ethyl esters and krill oil: a randomized, cross-over, clinical trial. Arch Med Sci 12: 507–512.

Clifton PM, Mackinnon AM, Barter PJ (1985). Effects of serum amyloid A protein (SAA) on composition, size, and density of high density lipoproteins in subjects with myocardial infarction. J Lipid Res 26: 1389–1398.

Colin S, Chinetti-Gbaguidi G, Kuivenhoven JA, Staels B (2015). Emerging small molecule drugs. Handb Exp Pharmacol 224: 617–630.

Cook KA, Stevenson DD (2016). Current complications treatment of aspirin-exacerbated respiratory disease. Expert Rev Respir Med 10: 1305–1316.

Coomes E, Chan ESL, Reiss AB (2011). Methotrexate in atherogenesis and cholesterol metabolism. Cholesterol 2011, Article ID 503028: 8. doi:10.1155/2011/503028.

Curtis JR, Beukelman T, Onofrei A, Cassell S, Greenberg JD, Kavanaugh A *et al.* (2010). Elevated liver enzyme tests among patients with rheumatoid arthritis or psoriatic arthritis treated with methotrexate and/or leflunomide. Ann Rheum Dis 69: 43–47.

Cutolo M, Sulli A, Pizzorni C, Seriolo B (2001). Anti-inflammatory mechanisms of methotrexate in rheumatoid arthritis. Leader Ann Rheum Dis 60: 729–735.

Cuzzocrea S, Pisano B, Dugo L, Ianaro A, Maffia P, Patel NS (2004). Rosiglitazone, a ligand of the peroxisome proliferator-activated receptor-gamma, reduces acute inflammation. Eur J Pharmacol 483: 79–93.

Dahlqvist SR, Engstrand S, Berglin E, Johnson O (2006). Conversion towards an atherogenic lipid profile in rheumatoid arthritis patients during long-term infliximab therapy. Scand J Rheumatol 35: 107–111.

Davidson WS, Inge TH, Sexmith H, Heink A, Elder D, Hui DY *et al.* (2017). Weight loss surgery in adolescents corrects high-density lipoprotein subspecies and their function. Int J Obes (Lond). 41: 83–89.

De Haan W, Bhattacharjee A, Ruddle P, Kang MH, Hayden MR (2014). ABCA1 in adipocytes regulates adipose tissue lipid content, glucose tolerance, and insulin sensitivity. J Lipid Res 55: 516–523.

Del Gobbo LC, Falk MC, Feldman R, Lewis K, Mozaffarian D (2015). Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose–response of 61 controlled intervention trials. Am J Clin Nutr 102: 1347–1356.

Demetz E, Schroll A, Auer K, Heim C, Patsch JR, Eller P *et al.* (2014). The arachidonic acid metabolome serves as a conserved regulator of cholesterol metabolism. Cell Metab 20: 787–798.

Demonty I, Ras RT, van der Knaap HC, Duchateau GS, Meijer L, Zock PL *et al.* (2009). Continuous dose–response relationship of the LDL-cholesterol-lowering effect of phytosterol intake. J Nutr 139: 271–284.

Digby JE, McNeill E, Dyar OJ, Lam V, Greaves DR, Choudhury RP (2010). Anti-inflammatory effects of nicotinic acid in adipocytes demonstrated by suppression of fractalkine, RANTES, and MCP-1 and upregulation of adiponectin. Atherosclerosis 209: 89–95.

Dinnes DL, White MY, Kockx M, Traini M, Hsieh V, Kim MJ *et al.* (2016). Human macrophage cathepsin B-mediated C-terminal cleavage of apolipoprotein A-I at Ser228 severely impairs

antiatherogenic capacity. FASEB J. pii: fj.201600508R. doi:10.1096/fj.201600508R.

Dobiásová M, Frohlich JJ. Clin Chim Acta(1999). Advances in understanding of the role of lecithin cholesterol acyltransferase (LCAT) in cholesterol transport. Clin Chim Acta 286: 257–271.

Domanico D, Verboschi F, Altimari S, Zompatori L, Vingolo EM (2015). Ocular effects of niacin: a review of the literature. Med Hypothesis Discov Innov Ophthalmol 4: 64–71.

Domise M, Didier S, Marinangeli C, Zhao H, Chandakkar P, Buée L *et al.* (2016). AMP-activated protein kinase modulates tau phosphorylation and tau pathology in vivo. Sci Rep 6: 26758.

Dusanov S, Heggen E, Tonstad S (2016). Characteristics of metabolic syndrome in morbidly obese subjects. Metab Syndr Relat Disord. doi:10.1089/met.2016.0062.

Eason J, Markowe HL (1989). Aminophylline toxicity–how many hospital asthma deaths does it cause? Respir Med 83: 219–226.

Edgel KA, McMillen TS, Wei H, Pamir N, Houston BA, Caldwell MT *et al.* (2012). Obesity and weight loss result in increased adipose tissue ABCG1 expression in db/db mice. Biochim Biophys Acta 1821: 425–434.

Eskandarian R, Darabian M, Heshmatnia J, Ghorbani R (2012). Acetyl salicylic acid resistance in patients with chronic stable angina and the correlation with coronary risk factors. Saudi Med J 33: 39–43.

Etchason JA, Miller TD, Squires RW, Allison TG, Gau GT, Marttila JK *et al.* (1991). Niacin-induced hepatitis: a potential side effect with low-dose time-release niacin. Mayo Clin Proc 66: 23.

Everett BM, Pradhan AD, Solomon DH, Paynter N, MacFadyen J, Zaharris E *et al.* (2013). Rationale and design of the cardiovascular inflammation reduction trial: a test of the inflammatory hypothesis of atherothrombosis. Am Heart J 166: 199–207.e15.

Fakhri M, Imani EF, Khalili N (2014). The effect of salsalate on biochemical factors and endothelial dysfunction of prediabetic patients: a randomized clinical trial. J Res Med Sci 19: 287–292.

Feldman M, Jialal I, Devaraj S, Cryer B (2001). Effects of low-dose aspirin on serum C-reactive protein and thromboxane B2 concentrations: a placebo-controlled study using a highly sensitive C-reactive protein assay. J Am Coll Cardiol 37: 2036–2041.

Feng D, Tracy RP, Lipinska I, Murillo J, McKenna C, Tofler GH (2000). Effect of short-term aspirin use on C-reactive protein. J Thromb Thrombolysis 9: 37–41.

Ferwana M, Firwana B, Hasan R, Al-Mallah MH, Kim S, Montori VM *et al.* (2013). Pioglitazone and risk of bladder cancer: a meta-analysis of controlled studies. Diabetes Med 30: 1026–1032.

Firouzjaei A, Li GC, Wang N, Liu WX, Zhu BM (2016). Comparative evaluation of the therapeutic effect of metformin monotherapy with metformin and acupuncture combined therapy on weight loss and insulin sensitivity in diabetic patients. Nutr Diabetes 6: e209.

Fullerton MD, Ford RJ, McGregor CP, LeBlond ND, Snider SA, Stypa S *et al.* (2015). Salicylate improves macrophage cholesterol homeostasis via activation of AMPK. J Lipid Res 56: 1025–1033.

García-Heredia A, Riera-Borrull M, Fort-Gallifa I, Luciano-Mateo F, Cabré N, Hernández-Aguilera A *et al.* (2016). Metformin administration induces hepatotoxic effects in paraoxonase-1-deficient mice. Chem Biol Interact 249: 56–63.

Gartner AH (1976). Aspirin-induced gastritis and gastrointestinal bleeding. J Am Dent Assoc 93: 111–117.

Gencer B, Laaksonen R, Buhayer A, Mach F (2015). Use and role of monoclonal antibodies and other biologics in preventive cardiology. Swiss Med Wkly 145: w14179.

Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E *et al.* (2008). Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease modifying antirheumatic drug therapy study. Arthritis Rheum 58: 2968–2980.

Ghoreschi K, Jesson MI, Li X, Lee JL, Ghosh S, Alsup JW *et al.* (2011). Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). J Immunol 186: 4234–4243.

Gofman JW, Young W, Tandy R (1966). Ischemic heart disease, atherosclerosis, and longevity. Circulation 34: 679–697.

Goldfine AB, Buck JS, Desouza C, Fonseca V, Chen YD, Shoelson SE *et al.* (2013a). Targeting inflammation using salsalate in patients with type 2 diabetes: effects on flow-mediated dilation (TINSAL-FMD). Diabetes Care 36: 4132–4139.

Goldfine AB, Conlin PR, Halperin F, Koska J, Permana P, Schwenke D *et al.* (2013b). A randomised trial of salsalate for insulin resistance and cardiovascular risk factors in persons with abnormal glucose tolerance. Diabetologia 56: 714–723.

Goldberg RB, Temprosa M, Mele L, Orchard T, Mather K, Bray G *et al.* (2016). Change in adiponectin explains most of the change in HDL particles induced by lifestyle intervention but not metformin treatment in the Diabetes Prevention Program. Metabolism 65: 764–775.

Gordon SM, Hofmann S, Askew DS, Davidson WS (2011). High density lipoprotein: it's not just about lipid transport anymore. Trends Endocrinol Metab 22: 9–15.

Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR (1977). The Framingham Study. High density lipoprotein as a protective factor against coronary heart disease. Am J Med 62: 707–714.

Grefhorst A, Elzinga BM, Voshol PJ, Plösch T, Kok T, Bloks VW *et al.* (2002). Stimulation of lipogenesis by pharmacological activation of the liver X receptor leads to production of large, triglyceride-rich very low density lipoprotein particles. J Biol Chem 277: 34182–34190.

Hakonarson H, Thorvaldsson S, Helgadottir A, Gudbjartsson D, Zink F, Andresdottir M (2005). Effects of a 5-lipoxygenase-activating protein inhibitor on biomarkers associated with risk of myocardial infarction a randomized trial. JAMA 293: 2245–2256.

Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJT (2010). The safety and side effects of monoclonal antibodies. Nat Rev Drug Discov 9: 325–338.

Haroon M, Devlin J (2009). Marked hypertriglyceridemia upon treatment with etanercept. Joint Bone Spine 76: 570–571.

Hazzard WR, Applebaum-Bowden D (1990). Why women live longer than men: the biologic mechanism of the sex differential in longevity. Trans Am Clin Climatol Assoc 101: 168–188.

He BM, Zhao SP, Peng ZY (2013). Effects of cigarette smoking on HDL quantity and function: implications for atherosclerosis. J Cell Biochem 114: 2431–2436.

Herová M, Schmid M, Gemperle C, Loretz C, Hersberger M (2014). Low dose aspirin is associated with plasma chemerin levels and may reduce adipose tissue inflammation. Atherosclerosis 235: 256–262.

Hileman CO, Carman TL, Gripshover BM, O'Riordan M, Storer NJ, Harrill DE *et al.* (2010). Salsalate is poorly tolerated and fails to improve endothelial function in virologically suppressed HIV-infected adults. AIDS 24: 1958–1961.

Hogue JC, Lamarche B, Tremblay AJ, Bergeron J, Gagné C, Couture P (2008). Differential effect of atorvastatin and fenofibrate on plasma oxidized low-density lipoprotein, inflammation markers, and cell adhesion molecules in patients with type 2 diabetes mellitus. Metabolism 57: 380–386.

Horrillo R, González-Périz A, Martínez-Clemente M, López-Parra M, Ferré N, Titos E *et al.* (2010). Lipoxygenase activating protein signals adipose tissue inflammation and lipid dysfunction in experimental obesity. J Immunol 184: 3978–3987.

Hosokawa A, Bar-Oz B, Ito S (2003). Use of lipid-lowering agents (statins) during pregnancy. Can Fam Physician 49: 747.

Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y *et al.* (2000). Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 20: 1595–1599.

Hotta K, Funahashi T, Bodkin NL, Ortmeyer HK, Arita Y, Hansen BC *et al.* (2001). Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. Diabetes 50: 1126–1133.

Hotamisligil GS, Shargill NS, Spiegelman BM (1993). Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 259: 87–91.

Hovens MMC, Snoe JD, Groeneveld Y, Frlich M, Tamsma JT, Huisman MV (2008). Effects of aspirin on serum C-reactive protein and interleukin-6 levels in patients with type 2 diabetes without cardiovascular disease: a randomized placebo-controlled crossover trial. Diabetes Obes Metab 10: 668–674.

Igarashi A, Inoue S, Ishii T, Tsutani K, Watanabe H (2016). Comparative effectiveness of oral medications for pulmonary arterial hypertension. Int Heart J 57: 466–472.

Imachi H, Murao K, Cao WM, Ohyama T, Sato M, Sasaguri Y*et al.* (2001). Expression of HDL receptor, CLA-1 in human smooth-muscle cells and effect of interferon-gamma on its regulation. Horm Metab Res 33: 389–393.

Jacobson TA (2009). Myopathy with statin-fibrate combination therapy: clinical considerations. Nat Rev Endocrinol 5: 507–518.

Jafarnejad A, Bathaie SZ, Nakhjavani M, Hassan MZ (2008). Investigation of the mechanisms involved in the high-dose and long-term acetyl salicylic acid therapy of type I diabetic rats. J Pharmacol Exp Ther 324: 850–857.

Jamroz-Wisniewska A, Wojcicka G, Horoszewicz K, Beltowski J (2007). Liver X receptors (LXRs). Part II: non-lipid effects, role in pathology, and therapeutic implications. Postepy Hig Med Dosw (Online) 61: 760–785.

Ji A, Wroblewski JM, Cai L, de Beer MC, Webb NR, van der Westhuyzen DR (2012). Nascent HDL formation in hepatocytes and role of ABCA1, ABCG1, and SR-BI. J Lipid Res 53 (3): 446–455.

Ji A, Wroblewski JM, Webb NR, van der Westhuyzen DR (2014). The impact of phospholipid transfer protein on nascent HDL formation and remodeling. Arterioscler Thromb Vasc Biol 34: 1910–1916.

Jiang XC, Beyer TP, Li Z, Liu J, Quan W, Schmidt RJ *et al.* (2003). Enlargement of high density lipoprotein in mice via liver X receptor activation requires apolipoprotein E and is abolished by cholesteryl ester transfer protein expression. J Biol Chem 278: 49072–49078.

Joseph SB, Castrillo A, Bryan A, Laffitte BA, Mangelsdorf DJ, Tontonoz P (2003). Reciprocal regulation of inflammation and lipid metabolism by liver X receptors. Nat Med : 213–219.

Jung UJ, Seo YR, Ryu R, Choi MS (2016). Differences in metabolic biomarkers in the blood and gene expression profiles of peripheral blood mononuclear cells among normal weight, mildly obese and moderately obese subjects. Br J Nutr 116: 1022–1032.

Kappelle PJ, Bijzet J, Hazenberg BP, Dullaart RP (2011). Lower serum paraoxonase-1 activity is related to higher serum amyloid a levels in metabolic syndrome. Arch Med Res 42: 219–225.

Kawashiri SY, Kawakami A, Yamasaki S, Imazato T, Iwamoto N, Fujikawa K *et al.* (2011). Effects of the anti-interleukin-6 receptor antibody, tocilizumab, on serum lipid levels in patients with rheumatoid arthritis. Rheumatol Int 31: 451–456.

Kennedy MA, Barrera GC, Nakamura K, Baldan A, Tarr P, Fishbein MC *et al.* (2005). ABCG1 has a critical role in mediating cholesterol efflux to HDL and preventing cellular lipid accumulation. Cell Metab 1: 121–131.

Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G (2001). Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab 280: E745–E751.

Khera AV, Cuchel M, De la Llera-Moya M, Rodrigues A, Burke MF, Jafri K *et al.* (2011). Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. N Engl J Med 364: 127–135.

Kick E, Martin R, Xie Y, Flatt B, Schweiger E, Wang TL *et al.* (2015). Liver X receptor (LXR) partial agonists: biaryl pyrazoles and imidazoles displaying a preference for LXRβ. Bioorg Med Chem Lett 25: 372–377.

Kim YS, Ahn Y, Hong MH, Kim KH, Park HW, Hong YJ *et al.* (2007). Rosuvastatin suppresses the inflammatory responses through inhibition of c-Jun N-terminal kinase and nuclear factor-kappaB in endothelial cells. J Cardiovasc Pharmacol 49: 376–383.

Kizhedath A, Wilkinson S, Glassey J (2016). Applicability of predictive toxicology methods for monoclonal antibody therapeutics: status quo and scope. Arch Toxicol. doi:10.1007/s00204-016-1876-7.

Kondo H, Shimomura I, Matsukawa Y, Kumada M, Takahashi M, Matsuda M *et al.* (2002). Association of adiponectin mutation with type 2 diabetes: a candidate gene for the insulin resistance syndrome diabetes. Diabetes 51: 2325–2328.

Kumar M, Rakesh S, Nagpal R, Hemalatha R, Ramakrishna A, Sudarshan V*et al.* (2013). Probiotic lactobacillus rhamnosus GG and *Aloe vera* gel improve lipid profiles in hypercholesterolemic rats. Nutrition 29: 574–579.

Lahaye C, Beaufrére AM, Boyer O, Drouot L, Soubrier M, Tournadre A (2014). Immune-mediated myopathy related to anti 3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies as an emerging cause of necrotizing myopathy induced by statins. Joint Bone Spine 81: 79–82.

Lalau JD (2010). Lactic acidosis induced by metformin: incidence, management and prevention. Drug Saf 33: 727–740.

Lan H, Pang L, Smith MM, Levitan D, Ding W, Liu L *et al.* (2010). Proprotein convertase subtilisin/kexin type 9 (PCSK9) affects gene expression pathways beyond cholesterol metabolism in liver cells. J Cell Physiol 224: 273–281.

Lautermann D, Braun J (2002). Ankylosing spondylitis – cardiac manifestations. Clin Exp Rheumatol 20 (6 Suppl 28): S11–S15.

Le Lay S, Robichon C, Le Liepvre X, Dagher G, Ferre P, Dugail I (2003). Regulation of ABCA1 expression and cholesterol during adipose differentiation of 3 T3-L1 cells. J Lipid Res 44: 1499–1507.

Lee JY, Parks JS (2005). ATP-binding cassette transporter AI and its role in HDL formation. Curr Opin Lipidol 16: 19–25.

Lehtinen K (1993). Mortality and causes of death in 398 patients admitted to hospital with ankylosing spondylitis. Ann Rheum Dis 52: 174–176.

Li WL, Hua LG, Qu P, Yan WH, Ming C, Jun YD *et al.* (2016). NLRP3 inflammasome: a novel link between lipoproteins and atherosclerosis. Arch Med Sci 12: 950–958.

Lindstedt L, Saarinen J, Kalkkinen N, Welgus H, Kovanen PT (1999). Matrix metalloproteinases-3, -7, and -12, but not -9, reduce high density lipoprotein-induced cholesterol efflux from human macrophage foam cells by truncation of the carboxyl terminus of apolipoprotein A-I: PARALLEL losses of pre-{beta} particles and the high affinity component of efflux. J Biol Chem 274: 22627–22634.

Liu AC, Lawn RM, Verstuyft JG, Rubin EM (1994). Human apolipoprotein A-I prevents atherosclerosis associated with apolipoprotein[a] in transgenic mice. J Lipid Res 35: 2263–2267.

Liu Z, Tang Q, Wen J, Tang Y, Huang D, Huang Y *et al.* (2016). Elevated serum complement factors 3 and 4 are strong inflammatory markers of the metabolic syndrome development: a longitudinal cohort study. Sci Rep 6: 18713.

Loke YK, Singh S, Furberg CD (2009). Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. CMAJ 180: 32–39.

Lüscher TF, Taddei S, Kaski JC, Jukema JW, Kallend D, Münzel T*et al.* (2012). Vascular effects and safety of dalcetrapib in patients with or at risk of coronary heart disease: the dal-VESSEL randomized clinical trial. Eur Heart J 33: 857–865.

Maccubbin D, Koren MJ, Davidson M, Gavish D, Pasternak RC, Macdonell G *et al.* (2009). Flushing profile of extended-release niacin/laropiprant versus gradually titrated niacin extended-release in patients with dyslipidemia with and without ischemic cardiovascular disease. Am J Cardiol 104: 74.

Mahdy AK, Wonnerth A, Huber K, Wojta J (2012). Cardiovascular disease risk reduction by raising HDL cholesterol – current therapies and future opportunities. Br J Pharmacol 167: 1177–1194.

Maitra U, Li L (2013). Molecular mechanisms responsible for the reduced expression of cholesterol transporters from macrophages by low-dose endotoxin. Arterioscler Thromb Vasc Biol 33: 24–33.

Malle E, Stienmetz A, Raynes JG (1993). Serum amyloid A (SAA): an acute phase protein and apolipoprotein. Atherosclerosis 102: 131–146.

Mandosi E, Giannetta E, Filardi T, Lococo M, Bertolini C, Fallarino M *et al.* (2015). Endothelial dysfunction markers as a therapeutic target for sildenafil treatment and effects on metabolic control in type 2 diabetes. Expert Opin Ther Targets 19: 1617–1622.

Martin G, Duez H, Blanquart C, Berezowski V, Poulain P, Fruchart JC *et al.* (2001). Statin-induced inhibition of the Rho-signaling pathway activates PPAR-a and induces HDL apoA-I. J Clin Invest 107: 1423–1432.

Masson D, Staels B, Gautier T, Desrumaux C, Athias A, Le Guern N *et al.* (2004). Cholesteryl ester transfer protein modulates the effect of liver X receptor agonists on cholesterol transport and excretion in the mouse. J Lipid Res 45: 543–550.

Mathieu S, Dubost JJ, Tournadre A, Malochet-Guinamand S, Ristori JM, Soubrier M (2010). Effects of 14 weeks of TNF alpha blockade treatment on lipid profile in ankylosing spondylitis. Joint Bone Spine 77: 50–52.

Matsuda T, Okuda A, Watanabe Y, Miura T, Ozawa H, Tosaka A *et al.* (2015). Design and discovery of 2-oxochromene derivatives as liver X receptor β-selective agonists. Bioorg Med Chem Lett 25: 1274–1278.

McInnes IB, Thompson L, Giles JT, Bathon JM, Salmon JE, Beaulieu AD *et al.* (2013). Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study. Ann Rheum Dis 74: 694–702.

McKenney JM, Davidson MH, Shear CL, Revkin JH (2006). Efficacy and safety of torcetrapib, a novel cholesteryl ester transfer protein inhibitor, in individuals with below-average high-density lipoprotein cholesterol levels on a background of atorvastatin. J Am Coll Cardiol 48: 1782–1790.

Miao B, Zondlo S, Gibbs S, Cromley D, Hosagrahara VP, Kirchgessner TG *et al.* (2004). Raising HDL cholesterol without inducing hepatic steatosis and hypertriglyceridemia by a selective LXR modulator. J Lipid Res 45: 1410–1417.

Miller GJ, Miller NE (1975). Plasma-high-density-lipoprotein concentration and development of ischaemic heart-disease. Lancet 1: 16–19.

Millar JS, Ikewaki K, Bloedon LT (2010). The effect of rosiglitazone on HDL metabolism in subjects with metabolic syndrome and low HDL. J Lipid Res 52: 136–142.

Mizoguchi M, Tahara N, Tahara A, Nitta Y, Kodama N, Oba T*et al.* (2011). Pioglitazone attenuates atherosclerotic, plaque inflammation in patients with impaired glucose tolerance or diabetes, a prospective, randomized, comparator-controlled study using serial FDG PET/CT imaging study of carotid artery and ascending aorta. JACC Cardiovasc Imaging 4: 1110–1118.

Moon MK, Lee YJ, Kim JS, Kang DG, Lee HS (2009). Effect of caffeic acid on tumor necrosis factor-alpha-induced vascular inflammation in human umbilical vein endothelial cells. Biol Pharm Bull 32: 1371–1377.

Mortensen R (2001). C-reactive protein, inflammation, and innate immunity. Immunol Res 24: 163–176.

Naik SU, Wang X, Da Silva JS, Jaye M, Macphee CH, Reilly MP *et al.* (2006). Pharmacological activation of liver X receptors promotes reverse cholesterol transport in vivo. Circulation 113: 90–97.

Nakajima T, Origuchi N, Matsunaga T, Kawai S, Hokari S, Nakamura H *et al.* (2000). Localization of oxidized HDL in atheromatous plaques and oxidized HDL binding sites on human aortic endothelial cells. Ann Clin Biochem 37: 179–186.

Nasr H, Torsney E, Poston RN, Hayes L, Gaze DC, Basser R *et al.* (2015). Investigating the effect of a single infusion of reconstituted high-density lipoprotein in patients with symptomatic carotid plaques. Ann Vasc Surg 29: 1380–1391.

Navab M, Imes SS, Hama SY, Hough GP, Ross LA, Bork RW *et al.* (1991). Monocyte transmigration induced by modification of low density lipoprotein in cocultures of human aortic wall cells is due to induction of monocyte chemotactic protein 1 synthesis and is abolished by high density lipoprotein. J Clin Invest 88: 2039–2046.

Navab M, Hama SY, Hough GP, Subbanagounder G, Reddy ST, Fogelman AM (2001). A cell-free assay for detecting HDL that is dysfunctional in preventing the formation of or inactivating oxidized phospholipids. J Lipid Res 42: 1308–1317.

Navarro-Millán I, Charles-Schoeman C, Yang S, Bathon JM, Bridges SL, Chen L *et al.* (2013). Changes in lipoproteins associated with methotrexate or combination therapy in early rheumatoid arthritis: results from the treatment of early rheumatoid arthritis trial. Arthritis Rheum 65: 1430–1438.

Nishida Y, Tanaka K, Hara M, Hirao N, Tanaka H, Tobina T*et al.* (2015). Effects of home-based bench step exercise on inflammatory cytokines and lipid profiles in elderly Japanese females: a randomized controlled trial. Arch Gerontol Geriatr 61: 443–451.

Nissen SE, Wolski K (2007). Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 356: 2457–2471.

Nunes AK, Rapôso C, Rocha SW, Barbosa KP, Luna RL, da Cruz-Höfling MA *et al.* (2015). Involvement of AMPK, IKβα-NFκB, and eNOS in the sildenafil anti-inflammatory mechanism in a demyelination model. Brain Res 1627: 119–133.

Ogata M, Tsujita M, Hossain MA, Akita N, Gonzalez FJ, Staels B *et al.* (2009). On the mechanism for PPAR agonists to enhance ABCA1 gene expression. Atherosclerosis 205: 413–419.

Oku H, Matsuura F, Koseki M, Sandoval JC, Yuasa-Kawase M, Tsubakio-Yamamoto K *et al.* (2007). Adiponectin deficiency suppresses ABCA1 expression and ApoA-I synthesis in the liver. FEBS Lett 581: 5029–5533.

Onat A, Uzunlar B, Hergenç G, Yazici M, Sari I, Uyarel H *et al.* (2005). Cross-sectional study of complement C3 as a coronary risk factor among men and women. Clin Sci (Lond) 108: 129–135.

O'Reilly M, Dillon E, Guo W, Finucane O, McMorrow A, Murphy A *et al.* (2016). High-density lipoprotein proteomic composition, and not efflux capacity, reflects differential modulation of reverse cholesterol transport by saturated and monounsaturated fat diets. Circulation 133: 1838–1850.

Osto E, Doytcheva P, Corteville C, Bueter M, Dörig C, Stivala S *et al.* (2015). Rapid and body weight-independent improvement of endothelial and high-density lipoprotein function after Roux-en-Y gastric bypass: role of glucagon-like peptide-1. Circulation 131: 871–881.

Ottobelli CE, De Souza WM, Da Silva TP, Moresco RN, Moretto MB (2016). Adipocytokines, inflammatory and oxidative stress markers of clinical relevance altered in young overweight/obese subjects. Clin Biochem 49: 548–553.

Pasqui AL, Giovanni B, Luca P, Auteri A (2000). Complement activation in hypercholesterolemia. Nutr Metab Cardiovasc Dis 10: 137–142.

Pasqui AL, Puccetti G, Bova M, Di Renzo F, Bruni M, Pastorelli A *et al.* (2002). Relationship between serum complement and different lipid disorders. Clin Exp Med 2: 33–38.

Peters MJ, van der Horst-Bruinsma IE, Dijkmans BA, Nurmohamed MT (2004). Cardiovascular risk profile of patients with spondylarthropathies, particularly ankylosing spondylitis and psoriatic arthritis. Semin Arthritis Rheum 34: 585–592.

Phillips MC (2014). Molecular mechanisms of cellular cholesterol efflux. J Biol Chem 289: 24020–24029.

Pichler WJ (2006). Adverse side-effects to biological agents. Allergy 61: 912–920.

Pignone M, Alberts MJ, Colwell JA, Cushman M, Inzucchi SE, Mukherjee D *et al.* (2010). Aspirin for primary prevention of cardiovascular events in people with diabetes. J Am Coll Cardiol 55: 2878–2886.

Plump AS, Scott CJ, Breslow JL (1994). Human apolipoprotein A-I gene expression increases high density lipoprotein and suppresses atherosclerosis in the apolipoprotein E-deficient mouse. Proc Natl Acad Sci U S A 91: 9607–9611.

Poitou C, Viguerie N, Cancello R, De Matteis R, Cinti S *et al.* (2005). Serum amyloid A: production by human white adipocyte and regulation by obesity and nutrition. Diabetologia 48: 519–528.

Rader DJ (2009). Lecithin: cholesterol acyltransferase and atherosclerosis, another high-density lipoprotein story that doesn't quite follow the script. Circulation 120: 549–552.

Rader DJ, Daugherty A (2008). Translating molecular discoveries into new therapies for atherosclerosis. Nature 451: 904–913.

Rashid S, Barrett PH, Uffelman KD, Watanabe T, Adeli K, Lewis GF (2002). Lipolytically modified triglyceride-enriched HDLs are rapidly cleared from the circulation. Arterioscler Thromb Vasc Biol 22: 483–487.

Rashid S, Genest J (2007). Effect of obesity on high-density lipoprotein metabolism. Obesity (Silver Spring) 15: 2875–2888.

Reiss AB, Carsons SE, Anwar K, Rao S, Edelman SD, Zhang H *et al.* (2008). Atheroprotective effects of methotrexate on reverse cholesterol transport proteins and foam cell transformation in human THP-1 monocyte/macrophages. Arthritis Rheum 58: 3675–3683.

Repa JJ, Liang G, Ou J, Bashmakov Y, Lobaccaro JM, Shimomura I *et al.* (2000a). Regulation of mouse sterol regulatory element-binding protein-1c gene (SREBP-1c) by oxysterol receptors, LXRalpha and LXRbeta. Genes Dev 14: 2819–2830.

Repa JJ, Turley SD, Lobaccaro JA, Medina J, Li L, Lustig K *et al.* (2000b). Regulation of absorption and ABC1-mediated efflux of cholesterol by RXR heterodimers. Science 289: 1524–1529.

Rhoads GG, Gulbrandsen CL, Kagan A (1976). Serum lipoproteins and coronary heart disease in a population study of Hawaii Japanese men. N Engl J Med 294: 293–298.

Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH (1997). Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 336: 973–979.

Ridker PM, Thuren T, Zalewski A, Libby P (2011). Interleukin-1β inhibition and the prevention of recurrent cardiovascular events: rationale and design of the canakinumab anti-inflammatory thrombosis outcomes study (CANTOS). Am Heart J 162: 597–605.

Ridker PM, Howard CP, Walter V, Everett B, Libby P, Hensen J *et al.* (2012). Effects of interleukin-1β inhibition with canakinumab on hemoglobin A1c, lipids, C-reactive protein, interleukin-6, and fibrinogen: a phase IIb randomized, placebo-controlled trial. Circulation 126: 2739–2748.

Rinninger F, Kaiser T, Mann WA, Meyer N, Greten H, Beisiegel U (1998). Lipoprotein lipase mediates an increase in the selective uptake of high density lipoprotein-associated cholesteryl esters by hepatic cells in culture. J Lipid Res 39: 1335–1348.

Rinninger F, Brundert M, Brosch I, Donarski N, Budzinski RM, Greten H (2001). Lipoprotein lipase mediates an increase in selective uptake of HDL-associated cholesteryl esters by cells in culture independent of scavenger receptor BI. J Lipid Res 42: 1740–1751.

Rodríguez-Hernández H, Simental-Mendía LE, Rodríguez-Ramírez G, Reyes-Romero MA (2013). Obesity and inflammation: epidemiology, risk factors, and markers of inflammation. Int J Endocrinol 2013: 678159. doi:10.1155/2013/678159.

Rodriguez-Jimenez NA, Garcia-Gonzalez CE, Ayala-Lopez KP, Trujillo-Hernandez B, Aguilar-Chavez EA, Rocha-Muñoz AD *et al.* (2014). Modifications in lipid levels are independent of serum TNF-α in rheumatoid arthritis: results of an observational 24-week cohort study comparing patients receiving etanercept plus methotrexate or methotrexate as monotherapy. Biomed Res Int 2014: 510305. doi:10.1155/2014/510305.

Ros E, Nuñez I, Pérez-Heras A, Serra M, Gilabert R, Casals E *et al.* (2004). A walnut diet improves endothelial function in hypercholesterolemic subjects: a randomized crossover trial. Circulation 109: 1609–1614.

Rosenson RS (2004). Current overview of statin-induced myopathy. Am J Med 116: 408.

Rosenson RS (2010). Functional assessment of HDL: moving beyond static measures for risk assessment. Cardiovasc Drug Ther 24: 71–75.

Rubin EM, Krauss RM, Spangler EA, Verstuyft JG, Clift SM (1991). Inhibition of early atherogenesis in transgenic mice by human apolipoprotein AI. Nature 353: 265–267.

Russo MW, Hoofnagle JH, Gu J, Fontana RJ, Barnhart H, Kleiner DE *et al.* (2014). Spectrum of statin hepatotoxicity: experience of the drug-induced liver injury network. Hepatology 60: 679.

Ruth MR, Port AM, Shah M, Bourland AC, Istfan NW, Nelson KP *et al.* (2013). Consuming a hypocaloric high fat low carbohydrate diet for 12 weeks lowers C-reactive protein, and raises serum adiponectin and high density lipoprotein-cholesterol in obese subjects. Metabolism 62: 1779–1787.

Ryden M, Dicker A, van Harmelen V, Hauner H, Brunnberg M, Perbeck L *et al.* (2002). Mapping of early signaling events in tumor necrosis factor-alpha-mediated lipolysis in human fat cells. J Biol Chem 277: 1085–1091.

Rye KA, Duong MN (2000). The influence of phospholipid depletion on the size, structure and remodeling of reconstituted high density lipoproteins. J Lipid Res 41: 1640–1650.

Sabate J, Wien M (2013). Consumption of nuts in the prevention of cardiovascular disease. Curr Nutr Rep 2: 258–266.

Sahebkar A, Serban C, Ursoniu S, Wong ND, Muntner P, Graham IM *et al.* (2015). Lack of efficacy of resveratrol on C-reactive protein and selected cardiovascular risk factors -results from a systematic review and meta-analysis of randomized controlled trials. Int J Cardiol 189: 47–55.

Sahebkar A, Di Giosia P, Stamerra CA, Grassi D, Pedone C, Ferretti G *et al.* (2016). Effect of monoclonal antibodies to PCSK9 on high-sensitivity C-reactive protein levels: a meta-analysis of 16 randomized controlled treatment arms. Br J Clin Pharmacol 81: 1175–1190.

Sahoo D, Trischuk TC, Chan T, Drover VA, Ho S, Chimini G *et al.* (2004). ABCA1-dependent lipid efflux to apolipoprotein A-I mediates HDL particle formation and decreases VLDL secretion from murine hepatocytes. J Lipid Res 45: 1122–1131.

Santanam N, Parthasarathy S (2007). Aspirin is a substrate for paraoxonase-like activity: implications in atherosclerosis. Atherosclerosis 191: 272–275.

Schaefer EJ, Asztalos BF (2006). The effects of statins on high-density lipoproteins. Curr Atheroscler Rep 8: 41–49.

Schultz JR, Tu H, Luk A, Repa JJ, Medina JC, Li L *et al.* (2000). Role of LXRs in control of lipogenesis. Genes Dev 14: 2831–2838.

Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J *et al.* (2012). Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med 367: 2089–2099.

Si Y, Zhang Y, Zhao J, Guo S, Zhai L, Yao S *et al.* (2014). Niacin inhibits vascular inflammation via downregulating nuclear transcription factor-κB signaling pathway. Mediators Inflamm 2014, Article ID 263786, 12 pages. doi:10.1155/2014/263786.

Singaraja RR, Van Eck M, Bissada N, Zimetti F, Collins HL, Hildebrand RB *et al.* (2006). Both hepatic and extrahepatic ABCA1 have discrete and essential functions in the maintenance of plasma high-density lipoprotein cholesterol levels in vivo. Circulation 114: 1301–1309.

Singh S, Loke YK, Furberg CD (2007). Thiazolidinediones and heart failure: a teleo-analysis. Diabetes Care 30: 2148–2153.

Singh U, Devaraj S, Jialal I, Siegel D (2008). Comparison effect of atorvastatin (10 versus 80 mg) on biomarkers of inflammation and oxidative stress in subjects with metabolic syndrome. Cardiol 102: 321–325.

Sjöholm K, Palming J, Olofsson LE, Gummesson A, Svensson PA, Lystig TC *et al.* (2005). A microarray search for genes predominantly expressed in human omental adipocytes: adipose tissue as a major production site of serum amyloid A. J Clin Endocrinol Metab 90: 2233–2239.

Smith JD (2010). Myeloperoxidase, inflammation, and dysfunctional high-density lipoprotein. J Clin Lipidol 4: 382–388.

Smythies LE, White CR, Maheshwari A, Palgunachari MN, Anantharamaiah GM, Chaddha M *et al.* (2010). Apolipoprotein A-I mimetic 4F alters the function of human monocyte-derived macrophages. Am J Physiol Cell Physiol 298: C1538–C1548.

Sone H, Shimano H, Shu M, Nakakuki M, Takahashi A, Sakai M *et al.* (2004). Statins downregulate ATP-binding-cassette transporter A1 gene expression in macrophages. Biochem Biophys Res Commun 316: 790–794.

Sosin M, Handa S (2003). Low dose methotrexate and bone marrow suppression. BMJ 326: 266–267.

Soubrier M, Jouanel P, Mathieu S, Poujol D, Claus D, Dubost JJ *et al.* (2008). Effects of anti-tumor necrosis factor therapy on lipid profile in patients with rheumatoid arthritis. Joint Bone Spine 75: 22–24.

Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SP *et al.* (2016). The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl Acids Res 44: D1054–D1068.

Souto A, Salgado E, Maneiro JR, Mera A, Carmona L, Gómez-Reino JJ (2015). Lipid profile changes in patients with chronic inflammatory arthritis treated with biologic agents and tofacitinib in randomized clinical trials: a systematic review and meta-analysis. Arthritis Rheumatol 67: 117–127.

Spite M, Serhan CN (2010). Novel lipid mediators promote resolution of acute inflammation: impact of aspirin and statins. Circ Res 107: 1170–1184.

Stienstra R, Tack CJ, Kanneganti TD, Joosten LA, Netea MG (2012). The inflammasome puts obesity in the danger zone. Cell Metab 15: 10–18.

Suzuki M, Pritchard DK, Becker L, Hoofnagle AN, Tanimura N, Bammler TK *et al.* (2010). High-density lipoprotein suppresses the type I interferon response, a family of potent antiviral immunoregulators, in macrophages challenged with lipopolysaccharide. Circulation 122: 1919–1927.

Taguchi K, Okada A, Hamamoto S, Unno R, Kobayashi T, Ando R *et al.* (2016). Differential roles of peroxisome proliferator-activated receptor-α and receptor-γ on renal crystal formation in hyperoxaluric rodents. PPAR Res 2016: 9605890. doi:10.1155/2016/9605890.

Tall AR, Krumholz S, Olivecrona T, Deckelbaum RJ (1985). Plasma phospholipid transfer protein enhances transfer and exchange of

phospholipids between very low density lipoproteins and high density lipoproteins during lipolysis. J Lipid Res 26: 842–851.

Tancevski I, Wehubgerm A, Schgoer W, Eller P, Cuzzocrea S, Foeger B *et al.* (2006). Aspirin regulates expression and function of scavenger receptor-BI in macrophages: studies in primary human macrophages and in mice. FASEB J 20: 1328–1335.

Tietge UJF, Maugeais C, Cain W, Grass D, Glick JM, deBeer FC *et al.* (1999). Overexpression of secretory phospholipase A2 causes rapid catabolism and altered tissue uptake of high density lipoprotein cholesteryl esters and apolipoprotein A-I. Arterioscler Thromb Vasc Biol 19: 1284–1290.

Timmins JM, Lee JY, Boudyguina E, Kluckman KD, Brunham LR, Mulya A *et al.* (2005). Targeted inactivation of hepatic Abca1 causes profound hypoalphalipoproteinemia and kidney hypercatabolism of apoA-I. J Clin Invest 115: 1333–1342.

Toth PP, Barter PJ, Rosenson RS, Boden WE, Chapman MJ, Cuchel M *et al.* (2013). High-density lipoproteins: a consensus statement from the National Lipid Association. J Clin Lipidol 7: 484–525.

Toth PP, Barylski M, Nikolic D, Rizzo M, Montalto G, Banach M (2014). Should low high-density lipoprotein cholesterol (HDL-C) be treated? Best Pract Res Clin Endocrinol Metab 28: 353–368.

Tragiannidis A, Kyriakidis I, Zündorf I, Groll AH (2016). Invasive fungal infections in pediatric patients treated with tumor necrosis alpha (TNF-α) inhibitors. Mycoses . doi:10.1111/myc.12576.

Trieb M, Horvath A, Birner-Gruenberger R, Spindelboeck W, Stadlbauer V, Taschler U *et al.* (2016). Liver disease alters high-density lipoprotein composition, metabolism and function. Biochim Biophys Acta 861: 630–638.

Truwit JD, Bernard GR, Steingrub J, Matthay MA, Liu KD, Albertson TE *et al.* (2014). Rosuvastatin for sepsis-associated acute respiratory distress syndrome. N Engl J Med 370: 2191–2200.

Turner SM, Murphy EJ, Neese RA, Antelo F, Thomas T, Agarwal A *et al.* (2003). Measurement of TG synthesis and turnover in vivo by 2H2O incorporation into the glycerol moiety and application of MIDA. Am J Physiol Endocrinol Metab 285: E790–E803.

Tuvdendorj D, Chandalia M, Batbayar T, Saraf M, Beysen C, Murphy EJ *et al.* (2013). Altered subcutaneous abdominal adipose tissue lipid synthesis in obese, insulin-resistant humans. Am J Physiol Endocrinol Metab 305: E999–E1006.

Tuvdendorj D, Munoz AO, Ruiz-Barros V, Schwarz JM, Montalto G, Chandalia M *et al.* (2016). In vivo triglyceride synthesis in subcutaneous adipose tissue of humans correlates with plasma HDL parameters. Atherosclerosis 251: 147–152.

Uehara Y, Chiesa G, Saku K (2015). High-Density Lipoprotein-Targeted Therapy and Apolipoprotein A-I Mimetic Peptides. Circ J 79: 2523–2528.

van de Ree MA, Huisman MV, Princen HM, Meinders AE, Kluft C, DALI-Study Group (2003). Strong decrease of high sensitivity C-reactive protein with high-dose atorvastatin in patients with type 2 diabetes mellitus. Atherosclerosis 166: 129–135.

van Eijk IC, de Vries MK, Levels JH, Peters MJ, Huizer EE, Dijkmans BA *et al.* (2009). Improvement of lipid profile is accompanied by atheroprotective alterations in high-density lipoprotein composition upon tumor necrosis factor blockade: a prospective cohort study in ankylosing spondylitis. Arthritis Rheum 60: 1324–1330.

van Lenten BJ, Hama SY, De Beer FC, Stafforini DM, McIntyre TM, Prescott SM *et al.* (1995). Anti-inflammatory HDL becomes pro-inflammatory during the acute phase response. Loss of protective effect of HDL against LDL oxidation in aortic wall cell cocultures. J Clin Invest 96: 2758–2767.

van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S *et al.* (2012). Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 367: 508–519.

Verghese PB, Arrese EL, Soulages JL (2007). Stimulation of lipolysis enhances the rate of cholesterol efflux to HDL in adipocytes. Mol Cell Biochem 302: 241–248.

Wagner JD, Shadoan MK, Zhang L, Ward GM, Royer LJ, Kavanagh K *et al.* (2010). A selective peroxisome proliferator-activated receptor alpha agonist, CP-900691, improves plasma lipids, lipoproteins, and glycemic control in diabetic monkeys. J Pharmacol Exp Ther 333: 844–853.

Walley KR, Thain KR, Russell JA, Reilly MP, Meyer NJ, Ferguson JF *et al.* (2014). PCSK9 is a critical regulator of the innate immune response and septic shock outcome. Sci Transl Med 6: 258ra143. doi:10.1126/scitranslmed.3008782.

Wang YY, Dahle MK, Agren J, Myhre AE, Reinholt FP, Foster SJ *et al.* (2006). Activation of the liver X receptor protects against hepatic injury in endotoxemia by suppressing Kupffer cell activation. Shock 25: 141–146.

Wang W, Song W, Wang Y, Chen L, Yan X (2013). HMG-CoA reductase inhibitors, simvastatin and atorvastatin, downregulate ABCG1-mediated cholesterol efflux in human macrophages. J Cardiovasc Pharmacol 62: 90–98.

Webb DJ, Freestone S, Allen MJ, Muirhead GJ (1999). Sildenafil citrate and blood-pressure-lowering drugs: results of drug interaction studies with an organic nitrate and a calcium antagonist. Am J Cardiol 83: 21C–28C.

Wefers JF, Woodlief TL, Carnero EA, Helbling NL, Anthony SJ, Dubis GS *et al.* (2016). Relationship among physical activity, sedentary behaviors, and cardiometabolic risk factors during gastric bypass surgery-induced weight loss. Surg Obes Relat Dis S1550-7289(16) 30675-X.

Wesnigk J, Bruyndonckx L, Hoymans VY, De Guchtenaere A, Fischer T, Schuler G *et al.* (2016). Impact of lifestyle intervention on HDL-induced eNOS activation and cholesterol efflux capacity in obese adolescent. Cardiol Res Pract 2016: 2820432.

Williams CM (1997). Cardiovascular risk factors in women. Proc Nutr Soc 56: 383–391.

Wolfe RR, Chinkes DL (2005). Isotope tracers in metabolic research: principles and practice of kinetic analysis, 2nd edn. Wiley-Liss: New York, New York, USA.

Wong J, Quinn CM, Gelissen IC, Jessup W, Brown AJ (2008). The effect of statins on ABCA1 and ABCG1 expression in human macrophages is influenced by cellular cholesterol levels and extent of differentiation. Atherosclerosis 196: 180–189.

Xu H, Burnes GT, Yang Q, Tan G, Yang D, Chou CJ *et al.* (2003). Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 112: 1821–1830.

Yadav R, Liu Y, Kwok S, Hama S, France M, Eatough R *et al.* (2015). Effect of extended-release niacin on high-density lipoprotein (HDL) functionality, lipoprotein metabolism, and mediators of vascular inflammation in statin-treated patients. J Am Heart Assoc 4: e001508. doi:10.1161/JAHA.114.001508.

Yan D, Wang HW, Bowman RL, Joyce JA (2016). STAT3 and STAT6 signaling pathways synergize to promote cathepsin secretion from macrophages via IRE1α activation. Cell Rep 16: 2914–2927.

Yoshifumi S (2016). Metformin and inflammation: its potential beyond glucose-lowering effect. Endocr Metab Immune Disord Drug Targets 15: 196–205.

Zannis VI, Chroni A, Krieger M (2006). Role of apoA-I, ABCA1, LCAT, and SR-BI in the biogenesis of HDL. J Mol Med (Berl) 84: 276–294.

Zhang Y, Zanotti I, Reilly MP, Glick JM, Rothblat GH, Rader DJ (2003). Overexpression of apolipoprotein A-I promotes reverse transport of cholesterol from macrophages to feces in vivo. Circulation 108: 661–663.

Zhang YZ, McGillicuddy FC, Hinkie CC, O'Neill S, Glick JM, Rothblat GH *et al.* (2010). Adipocyte modulation of high-density lipoprotein cholesterol. Circulation 121: 1347–1355.

Zhang C, Gao F, Luo H, Zhang CT, Zhang R (2015). Differential response in levels of high-density lipoprotein cholesterol to one-year metformin treatment in prediabetic patients by race/ethnicity. Cardiovasc Diabetol 14: 79.

Zhang H, Xie H, Zheng X, Chai Y, Tang Z, Chen H *et al.* (2017). Salicylic acid retention impairs aspirin reactivity in type 2 diabetes. Eur J Pharmacol 794: 234–245.

Zhao YY, Weir MA, Manno M, Cordy P, Gomes T, Hackam DG *et al.* (2012). New fibrate use and acute renal outcomes in elderly adults: a population-based study. Ann Intern Med 156: 560.

Zuckerman SH, Panousis C, Mizrahi J, Evans G (2000). The effect of gamma-interferon to inhibit macrophage-high density lipoprotein interactions is reversed by 15-deoxy-delta12,14-prostaglandin J2. Lipids 35: 1239–1247.