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Purpose of review

Despite that statin treatment substantially reduces cardiovascular morbidity and mortality, many treated patients still experience a high residual risk. Statins lower LDL-cholesterol (LDL-C), with limited effects on other lipid parameters. Fibrates improve atherogenic dyslipidemia characterized by high triglyceride and/or low HDL-C levels and elevated concentrations of small dense LDL particles, with or without high LDL-C levels. Fibrates decrease cardiovascular morbidity especially in patients with the metabolic syndrome. The purpose of this review is to provide a rationale for the combined use of statins and fibrates in the management of patients with high residual cardiovascular risk related to atherogenic dyslipidemia and persisting after single therapy.

Recent findings

A meta-analysis from 14 randomised trials conducted in high-risk patients reported that statin therapy is effective in reducing the proportional risk for major vascular events by 21% for each mmol/L lowering of LDL-C. However, on average 14% of patients still experienced an event despite being allocated to statin. Beyond LDL-C, other factors, including triglycerides, non-HDL-C, HDL-C and apolipoprotein B, have been identified as factors determining residual risk, and normalization of these parameters may further decrease cardiovascular disease in patients treated with statins. Data from fibrate trials indicate that these drugs are particularly effective in reducing cardiovascular morbidity in patients with atherogenic dyslipidemia.

Summary

Reducing the residual cardiovascular risk in patients treated with statins requires addressing multiple lipid goals. In this context, future therapeutic interventions based on combination therapy, such as statins and fibrates, appears particularly promising.

Keywords

Cardiovascular risk factors, residual risk, statins, fibrates, dyslipoproteinemia

Introduction

An elevated low-density lipoprotein cholesterol (LDL-C) level is a major risk factor for cardiovascular disease (CVD), and several randomised clinical trials have shown that lowering LDL-C levels with statins results in a substantial reduced CVD morbidity and mortality [1,2•,3]. However, a significant number of treated patients continue to experience events, despite targeting LDL-C levels according to current guidelines [3,4]. Moreover, even upon high doses of statins, a substantial residual risk remains [5,6].

Data from the INTERHEART study indicated that dyslipidemia is responsible for more than 50% of population-attributable vascular risk [7]. Within this context, more and more attention is now being paid to atherogenic dyslipidemia which is characterized by elevated triglyceride (TG) and low HDL-C levels, a preponderance of small, dense LDL particles, and an accumulation of cholesterol-rich remnant particles with high levels of apolipoprotein (apo) B. These lipoprotein abnormalities are frequently found in patients with high vascular risk, including patients with the metabolic syndrome (MS) or type 2 diabetes mellitus (T2DM) [8,9]. Although the primary goal to reduce the cardiovascular risk in these patients is LDL-C lowering [10], current treatment guidelines emphasize the relevance of considering the other lipoprotein abnormalities, but also non-lipid risk factors (such as tobacco consumption, blood pressure, physical activity, weight management….) that contribute to global risk [11,12,13].

Statins and fibrates are both lipid-lowering drugs. Statins are hydroxymethylglutaryl-coenzyme A reductase inhibitors, inhibiting the synthesis of cholesterol, and are primarily LDL-C-lowering agents. Fibrates activate the peroxisome proliferator-activated receptor α (PPARα), a transcription factor that regulates the expression of a number of genes involved in multiple metabolic pathways including lipid metabolism, ultimately reducing plasma TG concentrations and enhancing HDL levels [14••]. Fibrates have a beneficial action on the atherogenic dyslipidemia**.** The differences in action mechanisms of statins and fibrates,

resulting in distinct pharmacological effects and an improvement of different components of the lipid profile, provide a rationale for their use in combination in patients with high residual cardiovascular risk related to atherogenic dyslipidemia and persisting after single therapy, such as patients with the MS or T2DM.

Besides their effects on lipid metabolism, fibrates and statins display other pleiotropic effects, such as an improvement of endothelial function, a reduced inflammation at both vascular and systemic levels, an increased stability of atherosclerotic plaques, and a decreased thrombogenic response. Evidence suggests that, at least for statins, these pleiotropic effects may play a role in the reduction of cardiovascular morbidity and mortality [15,16••]. Pleiotropic effects of fenofibrate might explain the positive effects of fenofibrate on microvascular complications of T2DM, and a potential benefit on the CVD risk [17]. However, whether combination statin-fibrate therapy is more effective on inflammatory markers than either form of monotherapy requires further investigation [18,19].

Patients treated with statins still experience a residual cardiovascular risk

A meta-analysis from 14 randomized secondary and/or primary prevention trials studied the efficacity of cholesterol-lowering therapy by statin therapy in patients with pre-existing coronary heart disease (CHD), history of diabetes or hypertension, i.e in a wide range of high-risk patients, having variable baseline lipid profile [1]. This analysis reported that statin therapy efficaciously reduces the risk for vascular events (defined as the composite outcome of myocardial infarction (MI) or coronary death, stroke, or coronary revascularisation) by 21% for each mmol/L lowering of LDL-C (relative risk (RR), 0.79 ; 95% confidence interval (CI), 0.77-0.81 ; $p<0.0001$) [1]. Despite this, treated patients are left with a substantial relative residual risk, and 1 in 7 patients experienced events over a 5-year period. More recently, analyses of the diabetic patients in these studies showed that statin therapy results in a

proportionally similar reduction in vascular events irrespective of whether diabetes was present (0.79 ; 0.72-0.86 ; p<0.0001 with diabetes versus 0.79 ; 0.76-0.82 ; p<0.001 without diabetes) [3]. However, among the diabetic patients, the presence of low HDL-C and/or elevated TG limits the reduction in vascular events, even if patients achieve LDL-C levels below current targets [3].

Intensive statin therapy with high-dose statins, resulting in LDL-C levels that are maximally reduced below currently optimal thresholds for treatment of very high-risk patients (i.e <70 mg/dL), provides an additional and significant cardiovascular benefit in patients with recent acute coronary syndromes (ACS) and stable CHD over standard-dose therapy [5,6]. However, despite this, patients were still at very high residual risk, and although the combined analysis from 4 large trials yielded a 16% relative reduction of coronary death or any cardiovascular event (defined as MI, stroke, hospitalization for unstable angina, or revascularization) (p<0.0001), 28.8% of patients still experienced events [5]. More recently, pooled data from 6 trials, analysing separately recent ACS and stable CHD, showed that intensive statin therapy is associated with a reduction of 14 and 18% in cardiovascular death, ACS, or stroke, but is still leaving respectively 1 in 4 and 10 patients at risk, depending on their clinical subcategory [6]. Whether further increasing statin doses in monotherapy to further enhance LDL-C lowering is an appropriate strategy is a matter of debate for different reasons. First, because of the flattening of the dose-response curve at higher doses, the therapeutic benefit of dose increases likely becomes smaller, and recent data indicated that ACS patients with the lowest LDL-C levels have only modest clinical benefits after intensive statin therapy [20]. Second, increasing the statin dose occurs at the expense of increased risk for adverse events such as myalgia and/or elevations in liver or muscle enzymes. Third, the optimal target for LDL-C remains unknown and a large randomized trial is underway to examine whether the addition of ezetimibe to simvastatin, resulting in further decreased LDL-C as compared to changes

obtained after simvastatin alone, translates into clinical benefit on cardiovascular events in patients with ACS [21•]. Finally, beyond LDL-C other additional lipid, especially those associated with atherogenic dyslipidemia, and non-lipid factors determine the cardiovascular risk. Therefore it cannot be determined whether benefits of intensive statin therapy are due to high-dose statins resulting in effects on other factors than solely LDL-C, or solely due to LDL-C level lowering. Interestingly, it has been recently demonstrated that statin-treatment decreases cardiovascular event rates even in asymptomatic subjects with normal LDL-C concentrations but with evidence of inflammation as assessed by increased levels of the inflammatory biomarker high-sensitive C-reactive protein (hsCRP) [16••], and that clinical benefits are maximised when both LDL-C and hsCRP are reduced [22••]. These studies demonstrate the need for considering markers of inflammation beyond LDL-C in the management of CVD.

Other lipoprotein parameters beyond LDL-C determine the CVD risk

Post-hoc analysis of 4S trial showed that patients with combined dyslipidemia at baseline, i.e elevated LDL-C, low HDL-C, and elevated TGs, had increased morbidity and an increased major coronary event (death, MI) rate on placebo [23]. Moreover, patients with T2DM experience higher rates of cardiovascular events with decreasing HDL-C and increasing TG concentrations, and an increasing LDL/HDL ratio [3]. Finally, retrospective analyses demonstrate that the achievement of combined lipid values, rather than solely reducing LDL-C, is associated with a reduced risk of cardiovascular events [24].

The residual cardiovascular risk that remains after statin treatment is of multifactorial origin, and recent post-hoc analyses from clinical trials suggests an important contribution of lipid parameters other than LDL-C. It has long been established that HDL-C levels are a strong, independent inverse predictor of CVD [25]. Accordingly, post-hoc analyses showed that the

risk of CVD events was inversely related to HDL-C levels in individuals with CVD who achieved LDL-C levels <70mg/dL upon statin treatment [26,27]. A pooled analysis of 4 statin trials showed that a moderate increase in HDL-C (7.5%) correlated with atheroma regression [28]. Finally, from the BIP study, post-hoc extended analysis showed that HDL-C increments during bezafibrate therapy are inversely correlated with cardiovascular risk [29•], and long-term follow-up reported long-term reduction in mortality [30].

Extensive evidence supports elevated TG levels, predominantly in the post-prandial state, as a predictor for CVD [31,32], and a recently published meta-analysis of 29 prospective studies (262,525 participants, 10,158 with CHD confirmed this association, showing independence from other risk factors, including HDL-C [33]. Post-hoc analysis of the PROVE-IT TIMI-22 trial showed that among patients with ACS treated with statins, on-treatment TG>150mg/d was associated with a higher risk of recurrent CVD events independently of the level of LDL-C [34••]. Finally, a post-hoc analysis of the FIELD study showed that the largest effects of fenofibrate to reduce CVD risk is obtained in individuals with the MS and hypertriglyceridemia or combined dyslipidemia (defined as TG levels >2.3 mmol/L alone or with a low HDL-C level, respectively) [35••]. The absolute risk reduction in the presence of marked dyslipidemia was 4.3% compared with 0.8% in its absence, corresponding to a number needed to treat of 23 compared with 143, respectively.

An accurate management of cardiovascular risk requires assessment of all atherogenic lipoprotein particles, not only LDL. Non-HDL-C levels correspond to the mass of cholesterol within all atherogenic lipoprotein particles, and apoB and/or LDL particle number provides an estimate of atherogenic particle concentrations. Although it has been shown that non-HDL-C is an important target of therapy for non-fatal MI and coronary death [36]**,** whether it may further reduce excessive residual CVD risk along with LDL-C still remains open [37,38]. Studies reporting both measurement of LDL particles by nuclear magnetic resonance and/or

apoB, and LDL-C have consistently found that total LDL particle number is a better predictor of CVD risk than LDL-C with the objective to reduce this risk [39,40,41•], particularly in patients with the MS [42•].

Mechanistic rationale for statin and fibrate combination therapy

Statins primarily lower LDL-C and have only limited effects on TGs and HDL-C at commonly used doses and in patients without marked hypertriglyceridemia. Moreover they do not normalize the LDL size-distribution pattern. Fibrate treatment results in reduced plasma TG, non-HDL-C, and apoB. Fibrates also positively influence HDL metabolism, through an increase in the PPARα-mediated transcription of apoAI and apoAII, the two major apolipoproteins of HDL, and stimulate reverse cholesterol transport by modulating macrophage cholesterol efflux and cholesterol transport, resulting in raised levels of HDL with absolute changes that depend on the fibrate. The effect of fibrates on LDL-C is variable, ranging from a small decrease to essentially no changes or even a slight increase in highly hypertriglyceridemic patients. Moreover, fibrates increase LDL particle size and modify LDL subclass distribution from small, dense particles to large buoyant LDL particles, and reduce the number of small LDL particles in patients with hypertriglyceridemia and the MS [43,44,45]. In vivo kinetic experiments showed that atorvastatin or fenofibrate treatment of patients with T2DM or the MS and hypertriglyceridemia, results in a similar decrease of plasma TG levels probably due to comparable effects on VLDL-apoCIII kinetics [46], and distinct but favourable effects on apoB-containing lipoproteins with apoB100 and apoB48 metabolism [47]. By contrast to atorvastatin, fenofibrate displayed significant effects on apoAI metabolism in HDL [48]. All these observations provide the rationale for the use of fibrate-statin combination therapy to optimally control dyslipoproteinemia in patients with T2DM or the MS.

Fibrates reduce CVD in patients with atherogenic dyslipidemia

A number of angiographic and intervention trials have shown that fibrates can slow the progression of atherosclerotic disease and decrease CVD morbidity [14••]. However, most of the large prospective trials have been disappointing with respect to the primary endpoints, and meta-analysis suggest that fibrates do not influence overall mortality [49]. It is likely that these fibrate trials produced mixed results due to the large differences in study populations. Indeed, post-hoc or follow-up analyses have consistently demonstrated that fibrates are more effective at reducing macrovascular events among patients with the MS. The HHS was a primary prevention trial testing gemfibrozil as active agent in men with primary dyslipidemia (non-HDL-C > 200mg/dL). An 18-year mortality follow-up analysis showed that patients with a body mass index and TG concentrations in the highest tertile had significantly lower rates of CHD mortality (71% lower relative risk) and all-cause mortality (33% lower relative risk) compared with those in the original placebo group [50]. The VA-HIT trial randomized men with low HDL-C, and LDL-C concentrations nearly at goal (<100 mg/dL) at baseline, to treatment with gemfibrozil or placebo. Participants with T2DM or those without T2DM but with insulinemia in the highest fasting plasma insulin quartile benefited from a higher reduction in the RR for major cardiovascular events (a composite of CHD death, stroke, and non-fatal MI) than in the entire study population (RR of 32, 35 and 24% respectively) [51] after fibrate therapy. In the BIP study, bezafibrate treatment failed to achieve significance of the primary end point (a composite of fatal or non-fatal MI or sudden death) in patients with elevated LDL-C, low HDL-C and TG<150mg/dL. However, a post-hoc analysis showed significantly reduced event rates in patients with elevated TG levels [52]. More recently, a further post-hoc analysis confirmed that bezafibrate is more effective at reducing cardiovascular events among patients with the MS, with a more pronounced reduction in cardiac mortality depending on the number of MS features [53]. Finally, the FIELD study

investigated the effects of fenofibrate on CVD morbidity and mortality in patients with early-stage, well-controlled T2DM. Although after 5 years of treatment there was not a significant risk reduction in the primary end point (CVD death or nonfatal MI), there was a significant reduction of total CVD events, particularly nonfatal MI and coronary revascularization. One potential problem in the study was the higher rate of statin therapy drop-in in the placebo group, which might have masked treatment benefit. Nevertheless, further subgroup analyses demonstrated that in the cohort with the most dyslipidemic profile, i.e low HDL-C and/or elevated TG levels, fenofibrate was significantly more efficacious (27% RR reduction) [35••].

Statin and fibrate combination therapy may be an appropriate therapeutic approach to reduce the global cardiovascular risk in patients with atherogenic or combined dyslipidemia

The distinct mechanisms of action, resulting in different clinical effects, of statins and fibrates provide a rationale for combined use in the treatment of patients with dyslipidemia and high residual cardiovascular risk persisting after single therapy.

A recent post-hoc analysis of the BIP study using bezafibrate showed that in patients with low HDL-C and moderately elevated LDL-C, the clinical benefit of HDL-C and TG modification in terms of cardiac events (nonfatal MI or death) is inversely related with baseline levels of LDL-C, demonstrating enhanced benefit in patients with low LDL-C, whereas the benefit of LDL-C modification is more prominent in patients with increased LDL-C [54•]. Hence, combined assessment of LDL-C, HDL-C and TGs as therapeutic targets for lipid modification using lipid-lowering drugs may provide an incremental benefit on top of approaches based solely on LDL-C modification. Hence, a statin combination therapy with fibrates or other drugs that would enhance HDL-C and decrease TGs is recommended in such patients [10].

Short-term clinical studies have shown that combined therapy with statin and fenofibrate is more effective in controlling atherogenic dyslipidemia in patients with T2DM, the MS or combined dyslipidemia than the administration of either drug alone [18,55,56,57,58•]. Accordingly, it has been calculated that atorvastatin-fenofibrate combination therapy for 24 weeks to patients with T2DM, free of CVD at entry, would reduce the estimated risk for MI within the next 10 years from 21.6 to 4.2% [55]. Fenofibrate is an ester of fenofibric acid and requires first pass metabolism to form the active metabolite, fenofibric acid. ABT-335, the choline salt of fenofibric acid, is more hydrophilic than fenofibrate. This compound dissociates to form the free acid in the gastrointestinal tract, and fenofibric acid is rapidly absorbed without requiring first-pass metabolism. Recently, a large phase III clinical trial evaluating ABT-335 in combination with simvastatin, atorvastatin or rosuvastatin in patients with mixed dyslipidemia (TG>150mg/dL, HDL-C<40mg/dL for men and <50mg/dL for women, LDL-C>130mg/dL) demonstrated that combination results in a more effective control of lipid parameters than either monotherapy alone [59•,60•,61•].

Thus, from these data, it is evident that the combination of statin and fibrates results in an improved control of the atherogenic lipid profile often found in high-cardiovascular risk patients. However, whether this beneficial effect translates into risk reduction is not yet known. This will be answered by the lipid-lowering arm of the ongoing ACCORD study [62••]. The ACCORD trial is a randomized clinical trial aimed at determining the effects on CVD of intensive glycemic control in combination with strategies for lipid and/or blood pressure management in patients with T2DM. In February 2008, the glycemic control study was halted due to the finding of an increased rate of mortality in the intensive arm compared with the standard arm. The blood pressure and lipid studies are still ongoing. The lipid arm tests the hypothesis whether, in the context of good glycemic control, adding fenofibrate to simvastatin will reduce the rate of CVD events compared to statin plus placebo.

Despite the potential benefit of fibrate statin combination therapy on the lipid profile, case reports of severe myopathy and rhabdomyolysis have raised concerns regarding safety of this coadministration. However, the absolute risk is low. Moreover, differences exist due to differences in pharmacokinetics and drug-drug interactions [63]. Pharmacokinetic data on the interactions between statins and fibrates suggest that gemfibrozil inhibits statin glucuronidation and its hepatic metabolism, inducing therefore higher statin concentrations, whereas other fibrates, such as fenofibrate, have a relatively low potential for interaction with statin metabolism [64]. Indeed, the combination of ABT-335 and rosuvastatin did not alter fenofibric acid pharmacokinetics, nor the rosuvastatin AUC, indicating that ABT-335 does not have a clinically significant pharmacokinetic interaction with rosuvastatin in humans [65]. Hence, current guidelines recommend fenofibrate as the fibrate of choice for high-risk statin-treated patients with atherogenic dyslipidemia [66].

Conclusion and future perspectives

Although statins reduce cardiovascular morbidity and mortality owing, in part, to reduced LDL-C, a number of treated patients still face a very high cardiovascular risk. In fact, significant proportions of such patients are not reaching lipid goals. Generally they suffer from an atherogenic dyslipidemia associated to T2DM or the MS, which is not adequately corrected by statin therapy. Therefore, beyond a further decrease in LDL-C which could be achieved through the addition of other cholesterol-lowering agents, such as intestinal cholesterol absorption inhibitors (ezetimibe), other therapeutical approaches have to be developed for these dyslipidemic patients. Indeed, current guidelines recommend the addition of other drugs to achieve multiple lipid goals after LDL-C targets have been reached by statin therapy. Among these drugs, fibrates present a great interest because of its effects to reduce TG levels, improve LDL particle size and number, and increase HDL-C concentrations. Other

drugs, such as niacin, merit also further investigation since these compounds increase HDL-C even more pronouncedly.

References

1. Baigent C, Keech A, Kearney PM et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005; 366:1267-1278.

2. Mills EJ, Rachlis B, Wu P et al. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. J Am Coll Cardiol 2008; 52:1769-1781.

• A meta-analysis demonstrating a clear role of statin therapy in primary prevention of CVD mortality and major events.

3. Kearney PM, Blackwell L, Collins R et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008; 371:117-125.

4. Delahoy PJ, Magliano DJ, Webb K et al. The relationship between reduction in low-density lipoprotein cholesterol by statins and reduction in risk of cardiovascular outcomes: an updated meta-analysis. Clin Ther 2009; 31:236-244.

5. Cannon CP, Steinberg BA, Murphy SA et al. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol 2006; 48:438-445.

6. Afilalo J, Majdan AA, Eisenberg MJ. Intensive statin therapy in acute coronary syndromes and stable coronary heart disease: a comparative meta-analysis of randomised controlled trials. Heart 2007; 93:914-921.

7. Yusuf S, Hawken S, Ounpuu S et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004; 364:937-952.

8. Carr MC, Brunzell JD. Abdominal obesity and dyslipidemia in the metabolic syndrome: importance of type 2 diabetes and familial combined hyperlipidemia in coronary artery disease risk. J Clin Endocrinol Metab 2004; 89:2601-2607.

9. Tenenbaum A, Fisman EZ. Which is the best lipid-modifying strategy in metabolic syndrome and diabetes: fibrates, statins or both? Cardiovasc Diabetol 2004; 3:10.

10. Grundy SM, Cleeman JI, Merz CN et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110:227-239.

11. Smith SC, Jr., Allen J, Blair SN et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006; 113:2363-2372.

12. Buse JB, Ginsberg HN, Bakris GL et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation 2007; 115:114-126.

13. Graham I, Atar D, Borch-Johnsen K et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Eur Heart J 2007; 28:2375-2414.

14. Staels B, Maes M, Zambon A. Fibrates and future PPARalpha agonists in the treatment of cardiovascular disease. Nat Clin Pract Cardiovasc Med 2008; 5:542-553.

•• A review on the contribution of the atherogenic lipid profile to residual CVD after statin treatment, exploring to what extent PPARα agonists can decrease this risk.

15. Athyros VG, Kakafika AI, Tziomalos K et al. Pleiotropic effects of statins--clinical evidence. Curr Pharm Des 2009; 15:479-489.

16. Ridker PM, Danielson E, Fonseca FA et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359:2195-2207.

•• An intervention study (JUPITER trial) showing the efficacy of rosuvastatin in decreasing hsCRP and CVD event rates in asymptomatic subjects without hyperlipidemia.

17. Ansquer JC, Foucher C, Aubonnet P et al. Fibrates and microvascular complications in diabetes--insight from the FIELD study. Curr Pharm Des 2009; 15:537-552.

18. Koh KK, Quon MJ, Han SH et al. Additive beneficial effects of fenofibrate combined with atorvastatin in the treatment of combined hyperlipidemia. J Am Coll Cardiol 2005; 45:1649-1653.

19. Muhlestein JB, May HT, Jensen JR et al. The reduction of inflammatory biomarkers by statin, fibrate, and combination therapy among diabetic patients with mixed dyslipidemia: the DIACOR (Diabetes and Combined Lipid Therapy Regimen) study. J Am Coll Cardiol 2006; 48:396-401.

20. Giraldez RR, Giugliano RP, Mohanavelu S et al. Baseline low-density lipoprotein cholesterol is an important predictor of the benefit of intensive lipid-lowering therapy: a PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) analysis. J Am Coll Cardiol 2008; 52:914-920.

21. Cannon CP, Giugliano RP, Blazing MA et al. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. Am Heart J 2008; 156:826-832.

• A trial (still ongoing) examining whether the addition of ezetimibe to simvastatin translates into a clinical benefit on CVD.

22. Ridker PM, Danielson E, Fonseca FA et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet 2009; 373:1175-1182.

•• Follow-up analysis of the JUPITER trial demonstrating that achievement of low LDL-C and hsCRP levels together results in improved event-free survival compared with achievement of neither parameter or reduced LDL-C alone.

23. Ballantyne CM, Olsson AG, Cook TJ et al. Influence of low high-density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvastatin therapy in 4S. Circulation 2001; 104:3046-3051.

24. Cziraky MJ. The impact of residual CVD risk in the managed care setting. Am J Manag Care 2009; 15:S74-S80.

25. Gordon T, Castelli WP, Hjortland MC et al. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. Am J Med 1977; 62:707-714.

26. Barter P, Gotto AM, LaRosa JC et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med 2007; 357:1301-1310.

27. deGoma EM, Leeper NJ, Heidenreich PA. Clinical significance of high-density lipoprotein cholesterol in patients with low low-density lipoprotein cholesterol. J Am Coll Cardiol 2008; 51:49-55.

28. Nicholls SJ, Tuzcu EM, Sipahi I et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. JAMA 2007; 297:499-508.

29. Goldenberg I, Benderly M, Goldbourt U. Secondary prevention with bezafibrate therapy for the treatment of dyslipidemia: an extended follow-up of the BIP trial. J Am Coll Cardiol 2008; 51:459-465.

• An extended follow-up of the BIP trial demonstrating that, after appropriate adjustment for the use of nonstudy lipid-lowering drugs during follow-up, bezafibrate therapy is associated with significant long-term CVD protection.

30. Goldenberg I, Boyko V, Tennenbaum A et al. Long-term benefit of high-density lipoprotein cholesterol-raising therapy with bezafibrate: 16-year mortality follow-up of the bezafibrate infarction prevention trial. Arch Intern Med 2009; 169:508-514.

31. Bansal S, Buring JE, Rifai N et al. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. JAMA 2007; 298:309-316.

32. McBride PE. Triglycerides and risk for coronary heart disease. JAMA 2007; 298:336-338.

33. Sarwar N, Danesh J, Eiriksdottir G et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation 2007; 115:450-458.

34. Miller M, Cannon CP, Murphy SA et al. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2008; 51:724-730.

•• A post-hoc analysis of the PROVE-IT TIMI-22 trial reporting that the reduced risk of CHD with low on-treatment TG (<150mg/dL) is independent of the level of LDL-C.

35. Scott R, O'Brien R, Fulcher G et al. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetes Care 2009; 32:493-498.

•• A post-hoc analysis of the FIELD study showing that the highest CVD risk and greatest benefits of fenofibrate are seen among patients with T2DM and atherogenic dyslipidemia.

36. Robinson JG, Wang S, Smith BJ et al. Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. J Am Coll Cardiol 2009; 53:316-322.

37. Ray KK, Cannon CP, Cairns R et al. Prognostic utility of apoB/AI, total cholesterol/HDL, non-HDL cholesterol, or hs-CRP as predictors of clinical risk in

patients receiving statin therapy after acute coronary syndromes: results from PROVE IT-TIMI 22. Arterioscler Thromb Vasc Biol 2009; 29:424-430.

38. Kastelein JJ, van der Steeg WA, Holme I et al. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. Circulation 2008; 117:3002-3009.

39. Cromwell WC, Otvos JD, Keyes MJ et al. LDL particle number and risk of future cardiovascular disease in the Framingham Offspring Study - Implications for LDL management. J Clin Lipidol 2009; 1:583-592.

40. Sniderman AD. Differential response of cholesterol and particle measures of atherogenic lipoproteins to LDL-lowering therapy: implications for clinical practice. J Clin Lipidol 2008; 2:36-42.

41. Contois JH, McConnell JP, Sethi AA et al. Apolipoprotein B and cardiovascular disease risk: position statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. Clin Chem 2009; 55:407-419.

• A position statement from the AACC “Lipoproteins and vascular diseases division working group on best practices” on apoB and cardiovascular risk.

42. Rosenson RS, Otvos JD, Hsia J. Effects of rosuvastatin and atorvastatin on LDL and HDL particle concentrations in patients with metabolic syndrome: a randomized, double-blind, controlled study. Diabetes Care 2009; 32:1087-1091.

• A study documenting the differential effects of statin therapy on the lowering of LDL-C and increasing of HDL-C to LDL and HDL particle concentration in patients with the MS.

43. Farnier M, Roth E, Gil-Extremera B et al. Efficacy and safety of the coadministration of ezetimibe/simvastatin with fenofibrate in patients with mixed hyperlipidemia. Am Heart J 2007; 153:335-338.

44. Filippatos T, Milionis HJ. Treatment of hyperlipidaemia with fenofibrate and related fibrates. Expert Opin Investig Drugs 2008; 17:1599-1614.

45. Rosenson RS, Wolff DA, Huskin AL et al. Fenofibrate therapy ameliorates fasting and postprandial lipoproteinemia, oxidative stress, and the inflammatory response in subjects with hypertriglyceridemia and the metabolic syndrome. Diabetes Care 2007; 30:1945-1951.

46. Chan DC, Watts GF, Ooi EM et al. Atorvastatin and fenofibrate have comparable effects on VLDL-apolipoprotein C-III kinetics in men with the metabolic syndrome. Arterioscler Thromb Vasc Biol 2008; 28:1831-1837.

47. Hogue JC, Lamarche B, Deshaies Y et al. Differential effect of fenofibrate and atorvastatin on in vivo kinetics of apolipoproteins B-100 and B-48 in subjects with type 2 diabetes mellitus with marked hypertriglyceridemia. Metabolism 2008; 57:246-254.

48. Watts GF, Barrett PH, Ji J et al. Differential regulation of lipoprotein kinetics by atorvastatin and fenofibrate in subjects with the metabolic syndrome. Diabetes 2003; 52:803-811.

49. Saha SA, Arora RR. Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus - A pooled meta-analysis of randomized placebo-controlled clinical trials. Int J Cardiol 2009.

50. Tenkanen L, Manttari M, Kovanen PT et al. Gemfibrozil in the treatment of dyslipidemia: an 18-year mortality follow-up of the Helsinki Heart Study. Arch Intern Med 2006; 166:743-748.

51. Rubins HB, Robins SJ, Collins D et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). Arch Intern Med 2002; 162:2597-2604.

52. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) study. Circulation 2000; 102:21-27.

53. Tenenbaum A, Motro M, Fisman EZ et al. Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. Arch Intern Med 2005; 165:1154-1160.

54. Goldenberg I, Benderly M, Sidi R et al. Relation of clinical benefit of raising high-density lipoprotein cholesterol to serum levels of low-density lipoprotein cholesterol in patients with coronary heart disease (from the Bezafibrate Infarction Prevention Trial). Am J Cardiol 2009; 103:41-45.

• A post-hoc analysis of the BIP study showing that the clinical response to HDL-C and TG changes upon bezafibrate therapy are most pronounced in patients with low baseline LDL-C levels.

55. Athyros VG, Papageorgiou AA, Athyrou VV et al. Atorvastatin and micronized fenofibrate alone and in combination in type 2 diabetes with combined hyperlipidemia. Diabetes Care 2002; 25:1198-1202.

56. Vega GL, Ma PT, Cater NB et al. Effects of adding fenofibrate (200 mg/day) to simvastatin (10 mg/day) in patients with combined hyperlipidemia and metabolic syndrome. Am J Cardiol 2003; 91:956-960.

57. Grundy SM, Vega GL, Yuan Z et al. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). Am J Cardiol 2005; 95:462-468.

58. May HT, Anderson JL, Pearson RR et al. Comparison of effects of simvastatin alone versus fenofibrate alone versus simvastatin plus fenofibrate on lipoprotein subparticle profiles in diabetic patients with mixed dyslipidemia (from the Diabetes and Combined Lipid Therapy Regimen study). Am J Cardiol 2008; 101:486-489.

• DIACOR study reporting that combination therapy with simvastatin and fenofibrate has a greater positive effect on the LDL particle size profile, with a shift from the more atherogenic small, dense LDL to larger subparticles compared to either fenofibrate or simvastatin monotherapy. Reductions of dense VLDL and IDL and increases in HDL_3 are also most pronounced in patients receiving combination therapy.

59. Mohiuddin SM, Pepine CJ, Kelly MT et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with simvastatin in patients with mixed dyslipidemia: a phase 3, randomized, controlled study. Am Heart J 2009; 157:195-203.

60. Goldberg AC, Bays HE, Ballantyne CM et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with atorvastatin in patients with mixed dyslipidemia. Am J Cardiol 2009; 103:515-522.

61. Jones PH, Davidson MH, Kashyap ML et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with rosuvastatin in patients with mixed dyslipidemia: a phase 3 study. Atherosclerosis 2009; 204:208-215.

• A large phase III clinical trial demonstrating a better efficacy of ABT-335 with simvastatin [59], atorvastatin [60] or rosuvastatin [61] in patients with elevated TG and lowered HDL-C levels than statin monotherapy alone.

62. Buse JB, Bigger JT, Byington RP et al. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. Am J Cardiol 2007; 99:21i-33i.

•• A trial (ongoing for the lipid and blood pressure arms) documenting for the first time the benefits and risks of intensive glucose control, intensive blood pressure control, and the combination of fenofibrate and simvastatin in managing blood lipids in patients with T2DM.

63. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. Am J Cardiol 2005; 95:120-122.

64. Prueksaritanont T, Tang C, Qiu Y et al. Effects of fibrates on metabolism of statins in human hepatocytes. Drug Metab Dispos 2002; 30:1280-1287.

65. Zhu T, Awni WM, Hosmane B et al. ABT-335, the choline salt of fenofibric acid, does not have a clinically significant pharmacokinetic interaction with rosuvastatin in humans. J Clin Pharmacol 2009; 49:63-71.

66. Grundy SM, Hansen B, Smith SC, Jr. et al. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. Circulation 2004; 109:551-556.

Acronyms

4S : Scandinavian Simvastatin Survival Study

BIP : Bezafibrate Infarction Prevention

PROVE-IT TIMI-22 : Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22

FIELD : Fenofibrate Intervention and Event Lowering in Diabetes

HHS : Helsinki Heart Study

VA-HIT : Veterans Affairs High Density Lipoprotein Intervention Trial

ACCORD : Action to Control Cardiovascular Risk in Diabetes

JUPITER : Justification for the Use of Statins in Prevention: an Intervention trial Evaluating Rosuvastatin

DIACOR : Diabetes and Combined Lipid Therapy Regimen