Treatment of Diabetic Dyslipidemia and Prevention of Cardiovascular Disease

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Research Interests:

1. diabetic dyslipidemia
2. implantable insulin pumps
3. PPAR gamma agonists

Advances in the treatment of lipid disorders during the last decade have resulted in the ability to successfully carry out clinical trials which have demonstrated the benefits of LDL-lowering for the prevention of cardiovascular disease (CVD). Patients with Type 2 diabetes mellitus (T2DM) are at high risk of developing CVD, and recent clinical trials have also shown the benefit of LDL-C lowering with HMG-CoA reductase inhibitors (statins) in T2DM. Although it is generally agreed that high-risk patients with T2DM should be aggressively treated for elevated LDL-C, a number of questions remain:

- In diabetic patients, what are the most appropriate LDL-C goal?
- Should all patients with T2DM be on statins, independent of their baseline LDL-C level?
- What is the role of TG lowering / HDL raising, after LDL-C is at goal?
- What is the role of glycemic control in prevention of CVD?
- Do these recommendations also apply to younger patients with Type 1 diabetes mellitus

Diabetes and Atherosclerotic Cardiovascular Disease (ASCVD)

ASCVD risk is increased 2- to 4-fold in T2DM, and accounts for approximately 80% of all mortality in patients with diabetes (Stamler, 1993). About 75% is due to coronary atherosclerosis, and 25% is due to cerebral or peripheral vascular disease. It is estimated that 50% of newly diagnosed patients with T2DM already have CHD. Several, but not all, studies suggest that patients with T2DM and no history of CHD have rates of new CV events similar to non-diabetics with previous myocardial infarction (Haffner, 1998; Howard, 2006). In addition, clinical outcomes are worse for patients with T2DM after myocardial outcome or stroke (Sprafka, 1991; Miettinen, 1998). For these reasons, NCEP considers diabetes a CHD risk equivalent (Grundy, 2006).

Diabetic Dyslipidemia in T2DM

Diabetic dyslipidemia is characterized by high triglycerides, low HDL-C and small dense LDL. This atherogenic lipid profile contributes to the excess risk of CVD in patients with T2DM. The dyslipidemia is partially corrected by control of the hyperglycemia (Abrams, 1982), but abnormalities persist due to the effect of insulin resistance on lipoprotein metabolism (Goldberg, 2001; Garvey, 2003; Krauss, 2004; Boden, 2004; Ginsberg, 2005, Resnick, 2006).

- Effects on VLDL metabolism

Increased hepatic production of VLDL, apoB and TG results from insulin resistance. Poor insulinization increases mobilization of fatty acids from adipose tissue resulting in increased lipid availability in the liver for triglyceride synthesis and assembly with apoB into VLDL. Reduced ability of insulin to degrade newly

synthesized apoB may also be important. Impaired lipolysis of circulating VLDL-TG results from decreased activity of the enzyme lipoprotein lipase (reduced by insulin deficiency). Hypertriglyceridemia in turn contributes to lower HDL-C levels and smaller cholesterol depleted LDL.

- Effects on LDL metabolism

LDL-C levels in T2DM are usually the same or modestly elevated compared to non-diabetic individuals of similar age and sex. However, these LDL particles have abnormal composition (small, dense LDL particles) resulting in increased number of LDL particles that are cholesterol depleted. CETP (cholesterol ester transfer protein) mediates the exchange of VLDL-TG for LDL-cholesterol. Increased levels of VLDL-TG in the presence of CETP promote the transfer of TG to LDL in exchange for LDL-cholesterol. The TG-rich LDL undergoes hydrolysis by hepatic lipase (increased in insulin resistance), which produces small, dense cholesterol-depleted LDL. These small dense LDL particles are more atherogenic and more susceptible to oxidation of glycated LDL-cholesterol.

- Effects on HDL metabolism

Low levels of HDL-C and apoA-I are also characteristic of T2DM. This is derived largely from the interaction between HDL, TG-rich lipoproteins and the enzyme CETP, which transfers cholesterol esters from HDL to TG-rich lipoproteins. HDL-TG in turn is hydrolyzed by hepatic lipase which leads to smaller dense particles. ApoA-1 is then rapidly cleared from the circulation due to these compositional changes, leading to fewer HDL particles.

Effect of Glycemic Control on CVD Risk in T2DM: the United Kingdom Prospective Diabetes Study (UKPDS)

The effect of glycemia on microvascular and macrovascular complications in T2DM was best demonstrated by the UKPDS (UKPDS, 1998). This study enrolled 5102 newly diagnosed patients with T2DM, with fasting plasma glucose between 110 and 270 mg/dl after 3 months diet treatment. Subjects were randomly assigned:

- intensive therapy with sulfonylurea, metformin (if obese) or insulin with goal FPG < 110 mg/dl
- conventional therapy with diet alone (drugs added if hyperglycemic symptoms or FPG > 270 mg/dl)

Over 10 years of follow-up, HbA1c averaged 7.0% in the intensive therapy group compared to 7.9% in conventional group. This improvement in glycemic control resulted in a 25% reduction in risk for microvascular endpoints (p=0.0099). There was a 16% risk reduction for MI (p=0.054), which was not statistically significant.

The investigators also examined the relationship between the incidence of diabetic complications and glycemic control (Stratton, 2000). They found a

curvilinear relationship between complications and HbA1c levels. Overall, each 1% reduction in HbA1c was associated with 21% risk reduction for any diabetes related endpoint. However, the rate of increase of risk for microvascular disease with hyperglycemia was greater than that for macrovascular disease (each 1% reduction in HbA1c was associated with a risk reduction of 37% for microvascular complications and 14% for myocardial infarction). No threshold of risk was observed for any endpoint.

UKPDS also examined the importance of baseline risk factors for predicting the development of coronary artery disease in a sub-set of patients with T2DM without evidence of CHD at entry to the study (Turner, 1998). Using a Cox proportional hazards model, they found that the development of CHD was significantly associated with, in order, increased LDL-C, decreased HDL-C, HbA1c, systolic BP and smoking, after adjustment for age and sex. While HbA1c was highly statistically significant, the conventional risk factors, LDL-C and HDL-C, seemed to be most important. Triglycerides were not a independent predictor of CV risk in their multivariate model.

Effect of Statins on CVD in T2DM

- Mechanism of action of statins in T2DM (Ginsberg, 2006)

Statins lower LDL-C primarily via inhibition of hepatic cholesterol synthesis and up-regulation of LDL receptors. This increases the liver's receptor-mediated clearance of LDL and VLDL remnants. In mixed dyslipidemia (as often associated with insulin resistance and T2DM), high dose statins also decrease production of apo B lipoproteins from the liver, which further lowers both VLDL and LDL levels (Myerson, 2005). Statins therefore are excellent agents for removal of atherogenic lipoproteins.

- Diabetes Subgroup Analysis

A number of the original cholesterol lowering trials with statins enrolled small numbers of subjects with diabetes (CIT collaborators, 2005). In post-hoc analysis, these trials showed that the benefit in patients with T2DM was similar to non-diabetics, but the numbers were often too small for statistical significance. In the Scandinavian Simvastatin Survival Study (4S), 483 of 4444 subjects had a previous history of T2DM or elevated fasting glucose levels (Haffner, 1999). There was a 42% reduction in major coronary events in the simvastatin treated diabetics ($p=0.01$), and a 48% reduction in coronary revascularization ($p=0.005$). Total and coronary mortality were reduced, but not significantly.

- Heart Protection Study (HPS)

The largest study to date of cholesterol lowering in patients with diabetes is the Heart Protection Study (HPS Collaborative Group, 2002). 20536 high-risk subjects aged 40-80 years with coronary heart disease, peripheral vascular disease, diabetes or hypertension were randomized to simvastatin 40 mg or

placebo, resulting in an average difference in LDL-C of 39 mg/dl between the two groups. After 5 years of treatment, there was a 13% decrease in all cause mortality primarily due to a reduction in coronary death rate. They also observed a 27% decrease in major coronary events, 25% decrease in stroke and 25% decrease in revascularizations.

5963 of the 20536 subjects entered into HPS had known diabetes (HPS Collaborative Group, 2003). 2912 (49%) of the diabetic participants did not have prior history of coronary or other vascular disease (primary prevention), and the rest (51%) had a prior history of MI, other CHD or other vascular disease (secondary prevention). The reduction in LDL-C with simvastatin treatment compared to placebo in the diabetic subjects (-35 mg/dl) was similar to the non-diabetic subjects. This resulted in a reduction in CV event rates with simvastatin treatment that was similar in the diabetic subjects as in the other high-risk groups. There was a 22% decrease in major coronary events, strokes or revascularizations in the diabetic group compared to 24% for the overall population. The greatest risk reduction (33%) was in those without previous vascular disease. The risk reduction was independent of the baseline LDL-C, glycemic control, duration or type of diabetes, age or presence of hypertension. The authors' concluded that statin therapy was beneficial in patients with diabetes, and should be considered routinely for all diabetic patients at high risk of major vascular events, independent of their initial cholesterol concentrations.

- Collaborative Atorvastatin Diabetes Study (CARDS)

CARDS was a primary prevention trial that examined the effectiveness of LDL-C lowering on major CV events in patients with T2DM and without elevated LDL-C (Colhoun, 2004). 2838 subjects with T2DM ages 40-75 years without history of CVD were randomized to atorvastatin 10 mg/day or placebo. Baseline LDL-C was required to be < 160 mg/dl, and TG < 600 mg/dl. Subjects were also required to have at least one of the following: retinopathy, albuminuria, current smoking, hypertension. The primary endpoint was time to first occurrence of acute CHD events, coronary revascularization or stroke

The trial was terminated 2 years early because the pre-specified early stopping rule for efficacy was met. Median duration of follow-up was 3.9 years. Average treatment effect across the study: LDL-C -40%, total cholesterol -26%, HDL-C +1%, TG -19%. These changes resulted in a 37% reduction in major cardiovascular events with atorvastatin (p=0.001). When the components of the primary endpoint were assessed separately, acute CHD events were reduced by 36%, coronary revascularizations by 31% and stroke by 48%. There was also a 27% reduction in death rate in the atorvastatin group (p=0.059). There was no evidence of a threshold level of baseline LDL-C for determining the benefit of statin therapy, and the authors suggested that all patients with diabetes would benefit from statin therapy, independent of baseline LDL-C.

- Treating to New Targets Study (TNT)

The TNT study showed that in patients with stable CHD intensive lipid-lowering with high dose statin (atorvastatin 80 mg/day) provided significant clinical benefit compared to starting dose statin (atorvastatin 10 mg/dl). A post hoc subset analysis of the diabetic patients in the TNT study included 1501 of 10,001 patients with diabetes and CHD (Shepherd, 2006). In order to qualify for the study, LDL-C levels were required to be < 130 mg/dl on atorvastatin 10 mg/dl. Subjects were randomized to either atorvastatin 10 mg or 80 mg qd, and followed for a median 4.9 years. Primary end-point was time to first major CV event (death from CHD, nonfatal MI, resuscitate cardiac arrest, or fatal/nonfatal stroke).

End of study lipids were similar in the diabetic sub-group as the group overall (atorvastatin 10 vs 80 mg): LDL-C 99 vs 77 mg/dl; total cholesterol 178 vs 151 mg/dl; triglycerides 178 vs 145 mg/dl; HDL-C 44.0 vs 44.9 mg/dl. This difference in lipids resulted in a 25% reduction in risk of major CV events (p=0.026). There were also trends toward benefit with atorvastatin 80 mg for several primary endpoint components (non-procedure-related MI, fatal/nonfatal stroke and CHD death). Secondary outcomes showed significant benefit with atorvastatin 80 mg for cerebrovascular events and CV events. As in other studies, there was a higher incidence of events in patients with diabetes than in the overall group. The authors concluded that the benefits of intensive cholesterol lowering with high dose statin were similar in patients with and without diabetes and clinically evident CHD. They suggested that their results supported recent NECP ATP III and ADA recommendations that the use of high-dose statins to achieve an LDL-C < 70 mg/dl was an appropriate therapeutic option in diabetic patients with CVD.

- Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN)

This study was published last month, and is important because its results do not support aggressive treatment recommendations with statins. ASPEN studied 2410 patients with T2DM with and without CHD randomized to atorvastatin 10mg or placebo in a 4-year study (Knoop, 2006). Entry LDL-C was required to be ≤140 mg/dl if the patient had CHD, and ≤160 mg/dl if there was no known CHD. A composite primary endpoint was used: CV death, nonfatal MI, nonfatal stroke, recanalization, CABG surgery, resuscitated cardiac arrest, and worsening or unstable angina requiring hospitalization.

Mean reduction in LDL-C levels with atorvastatin 10 mg was 29%. This resulted in a non-significant reduction in the composite primary endpoint of 10%. This small reduction in CV risk was primarily due to the subjects with prior CHD (in the subset of 505 subjects with prior CHD, there was an 18% reduction in composite primary endpoint, whereas in the subset of 1910 subjects without prior CHD, there was a 3% reduction in the composite primary endpoint). However, the relative reduction in risk for fatal and nonfatal MI was 27% overall (p=0.10) and 36% for subjects with prior CHD (p=0.11).

Part of the reason for the unexpected results in ASPEN was due to changes in the study design after the start of enrollment. This study was originally designed as a secondary CV prevention study in patients with T2DM and prior MI or interventional procedure. However, changes in treatment guidelines for individuals with CHD impaired recruitment, and the protocol was amended within 2 years of the start of the study to also include subjects without CHD. In addition, with the publication of NCEP ATP III in 2001 recommending an LDL-C goal of <100 mg/dl in all patients with CHD, the study's DSMB required that all secondary prevention subjects and primary prevention subjects with a primary CVD endpoint to discontinue study medication and begin active therapy per local guidelines. Thus only 67% of atorvastatin- and 58% placebo-treated patients completed the double-blind treatment phase on study medication. Concomitant lipid-lowering treatment in the placebo group was 26.9% vs 15.4% in the atorvastatin group

The authors' concluded that the negative result in ASPEN was probably related to the required changes in the protocol during the study because of changes in treatment guidelines. In addition, overall study design, types of subjects recruited, and nature of primary endpoint may have contributed to the negative results. Nevertheless, the point estimate for CVD benefit observed in the secondary prevention cohort for fatal and nonfatal MI was similar to other trials. The authors concluded that the negative results in this study should not change current treatment guideline recommendations for aggressive LDL-lowering in high-risk patients with T2DM.

Fibrate Studies

- Mechanisms of Action of Fibrates

Fibrates activate the peroxisome proliferator-activated receptor-alpha (PPARalpha), which is a member of the steroid hormone receptor superfamily and modulates several aspects of lipid metabolism. Fibrates decrease triglycerides and VLDL levels by increasing VLDL catabolism and triglyceride clearance. This is achieved through an increase in lipoprotein lipase (LPL) activity, and a decrease in ApoC-III production (an inhibitor of LPL). Fibrates also initiate a shift from small, dense, atherogenic LDL particles to large, less atherogenic LDL particles. Fibrates increase HDL production by increasing ApoAI and ApoAII synthesis, and stimulate reverse cholesterol transport by increasing synthesis of the ATP binding cassette A1 (ABCA1) transporter.

- Helsinki Heart Study (HHS)

The HHS was a primary prevention trial with gemfibrozil in middle-aged men with high non-HDL-C. 135 of 4081 subjects enrolled in the HHS had known T2DM (Kosokinen, 1992). The incidence of MI and cardiac death was higher in the subjects with T2DM than non-diabetic subjects (7.4% vs 3.3%, $p<0.02$). Gemfibrozil treatment reduced the incidence of CHD in the diabetic men to 3.4%

compared to 10.5% in the diabetic placebo group (NS). Changes in lipid and lipoprotein levels in the gemfibrozil treated diabetic subjects were similar to those in non-diabetic subjects

- Veterans Affairs HDL Intervention Trial (VA-HIT)

The VA-HIT trial was also a secondary prevention trial with gemfibrozil in 2531 men with known CHD (Rubins, 1999). This population was different from HHS in that the VA-HIT subjects were selected for low HDL-C (< 40 mg/dl) and "normal" LDL-C (< 140 mg/dl). Primary outcome was nonfatal MI or coronary death. During the trial, the effect on lipids at one year was: HDL-C 6% higher, TG 31% lower, total cholesterol 4% lower and LDL-C was not different in the gemfibrozil compared to the placebo group. The trial reported a 22% reduction in nonfatal MI or CHD death, and a 24% reduction in the combined endpoint of CHD death, nonfatal MI and stroke. Of the lipid changes reported in the study, only the increase in HDL-C significantly predicted a lower risk of CHD (neither changes in TG or LDL-C predicted CHD events) (Robins, 2003).

30% of subjects in VA-HIT had known (n=627) or undiagnosed (n=142) diabetes (Rubins, 2002). As expected, the event rates for major CV events in the placebo group with known (36.5%) and undiagnosed (34.3%) diabetes was higher than in non-diabetic group with normal fasting glucose (21%) ($p<0.01$). Gemfibrozil treatment was associated with a risk reduction for the combined end point of 32% for persons with diabetes compared to 18% for those without diabetes ($p=0.26$). Both groups had comparable 22% to 21% reduction in nonfatal MI. The group with diabetes had 41% reduction in CHD death ($p=0.02$) and 40% reduction in stroke ($p=0.046$) compared to a non-significant reduction in the non-diabetic group of 3% and 10%, respectively. The rate of new CV events and reduction of events with gemfibrozil was greatest in subjects with insulin resistance (as estimated by HOMA-IR) than without (Robins, 2003). The benefit of fibrate therapy was less dependent on levels of HDL-C or TG than on presence or absence of insulin resistance.

- Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study

The FIELD study was a CV outcome study with another fibrate (fenofibrate) in patients with Type 2 DM aged 50-75 years not taking statin at study entry. 2131 (21%) of the subjects had known CVD and 7664 were without CVD at study entry. Lipids to qualify for the study were: cholesterol 116-251 mg/dl, and chol/HDL > 4.0 or TG 89-444 mg/dl. Subjects were randomized to fenofibrate 200 mg/day or placebo and followed for an average of 5 years. Primary study outcome was coronary events (CHD death or non-fatal MI). Outcome for pre-specified subgroup analyses was: total CV events (composite of CV death, MI, stroke, coronary and carotid revascularization)

The effect of fenofibrate on lipids after 4 months treatment was: total cholesterol reduced 11%, LDL-C reduced 12%, TG reduced 29%, and HDL-C increased 5%. However, the magnitude of the changes in lipids was less at the end of study

(fenofibrate vs placebo): total cholesterol reduced 7.2%, LDL-C reduced 6.5%, TG reduced 21%, HDL-C increased < 1%. Part of the reason for this change in efficacy with fenofibrate was a difference in concomitant statin therapy between the placebo and fenofibrate groups (17% vs 8%, p<0.01).

There was no difference in coronary events between the two groups (5.9% placebo vs 5.2% fenofibrate). The relative reduction of 11% (p=0.16) consisted of a 24% reduction in non-fatal MI (p=0.01) but a nonsignificant increase in CHD mortality. Total CV events were reduced significantly by 11% (p=0.035), primarily due to a 21% reduction in coronary revascularization (p=0.003). A post-hoc subgroup analysis revealed a 19% reduction in CHD events in subjects without previous CV disease (p=0.03) but no change in those with previous CV disease. After adjustment for starting new lipid lowering therapy (primarily statins) during the trial, fenofibrate reduced CHD events by 19% (p=0.01) and total CVD events by 15% (p=0.004). There was no significant change in total mortality (placebo 6.6% vs fenofibrate 7.3%, p=0.18). There was a slight increase in pancreatitis (0.5% vs 0.8%, p=0.03) and pulmonary embolism (0.7% vs 1.1%, p=0.02) with fenofibrate therapy, and slight increase in plasma creatinine and homocyteine in the fenofibrate group.

The authors' concluded that fenofibrate did not significantly reduce risk of coronary events (primary outcome). Fenofibrate did reduce total CV events, mainly due to fewer non-fatal MI and revascularizations. However, the higher rate of starting statin therapy in the placebo group compared to the fenofibrate group made it difficult to determine the benefit of fenofibrate treatment. The authors speculated that the use of fenofibrate should be considered in the context of the well-established benefits of statin therapy, and that its main use will probably be in combination with a statin. Although the addition of fenofibrate to a statin is effective for the treatment of mixed dyslipidemia (Grundy, 2005), the additional benefit in terms of CV outcomes is unknown.

- ACCORD (www.accordtrial.org)

This on-going NHLBI trial is addressing the question of the benefit of adding fenofibrate to statin therapy for prevention of CVD. 10,000 subjects with T2DM at risk for CVD events (with and without existing CVD) were randomized in a double 2 x 2 factorial design:

  - intensive glycemic control (HbA1c < 6.0% vs 7.0-7.9%)
  - intensive BP control (SBP < 120 vs < 140 mmHg)
  - fenofibrate (to raise HDL-C/lower TG) + statin (for treatment of LDL-C) vs statin alone

The primary outcome is major CVD event (nonfatal MI, nonfatal stroke or CV death). The study is scheduled to end in June 2009, with results available early 2010.

Type I Diabetes

Individuals with type 1 diabetes mellitus are also at high risk of premature CAD (Krolewski, 1987). This was demonstrated by long-term follow-up of the Joslin cohort of juvenile-onset T1DM (292 patients with T1DM diagnosed before age 21 years followed for 20-40 years). Mortality rate due to CAD increased rapidly after age 30 years, equally in men and women. By age 55 years, cumulative mortality rate due to CAD was 35% in the T1DM cohort compared to 8% men and 4% women in the Framingham Heart Study.

Patients with T1DM do not generally have insulin resistance, and their lipid levels are usually normal (compared to non-diabetics of same age and sex) if their diabetes is well controlled. However, compositional abnormalities of VLDL, LDL and HDL are improved but not corrected by intensive insulin therapy (Dunn, 1992; Purnell, 1995). The Heart Protection Study suggested that statin therapy was also beneficial in T1DM to reduce CV risk, but the effect was not statistically significant due to the small number of subjects (N=615).

Recently, the Diabetes Control and Complications Trial (DCCT) reported the benefits of intensive diabetes therapy on reducing the increased risk of CVD in T1DM (DCCT/EDIC Study Research Group, 2005). During the DCCT, fewer CV events occurred in the intensive treatment group than with conventional therapy, but the effect was not statistically significant (though there were a small number of events and a relatively young cohort). Last year, the DCCT reported long-term follow-up (mean 17 years) of the original cohort (10 years after completion of randomized study). They reported a 42% reduction in risk of any CVD event ($p=0.02$), and a 57% reduction in risk of nonfatal MI, stroke or death from CVD ($p=0.02$). This effect was observed despite the fact that the separation in HbA1c between the groups was not maintained during the last 10 years of observation.

Guidelines

- National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III) Update (Grundy, 2004)

In 2004, NCEP-ATP III issued an update of their cholesterol management recommendations based on the results of 5 major clinical trials of statin therapy published since their previous guidelines in 2001. The update specifically addressed the implication of the HPS results for patients with diabetes. They confirmed their classification of diabetes as a high risk condition (CHD risk equivalent) for the following reasons: (1) the majority of patients with diabetes have a relatively high 10-year risk for developing CVD (10-year risk > 20%); (2) the onset of CVD in patients with diabetes carries a poor prognosis, both at time of acute CVD event and post-event period.

In patients with diabetes plus CVD, they felt that HPS supported initiation of statin therapy regardless of baseline LDL-C level. When starting LDL-C lowering therapy, the intensity of therapy should be sufficient to achieve at least a 30-40% reduction in LDL-C levels. In addition, it is reasonable to attempt to achieve a very low LDL-C < 70 mg/dl as a therapeutic option.

In patients with diabetes but without CVD, HPS supported an LDL-C goal < 100 mg/dl if high risk (older age and/or other CV risk factors). If baseline LDL-C was already < 100 mg/dl, the absolute benefit of LDL-C to prevent a first coronary event was less, and it was left to clinical judgment whether to start LDL-lowering drug therapy. In addition, if a patient with diabetes was at lower risk because of young age or lack of other CV risk factors (not studied in HPS), they might be considered to be at only moderately high risk (10-year risk 10-20%). For these patients, ATP III recommended LDL-C lowering drugs along with dietary therapy if LDL-C ≥ 130 mg/dl. If LDL < 130 mg/dl but > 100 mg/dl, maximal TLC is indicated, and clinical judgment should be used when to start LDL-C lowering drugs.

For high-risk persons with high triglycerides or low HDL-C, ATP III recommended considering combining a fibrate or nicotinic acid with an LDL-C lowering drug. When triglycerides are ≥ 200 mg/dl, ATP III recommended using non-HDL-C as a secondary target of therapy, with a goal 30 mg/dl higher than the identified LDL-C goal. The usefulness of non-HDL-C as a secondary target for therapy was recently supported by a post hoc analysis of data from several publicly available data sets (Framingham, LRC, MRFIT) to evaluate the role of non-HDL-C and LDL-C as predictors of CHD in individuals with and without diabetes (Liu, 2005). . Among those without diabetes, the relative risk increased with higher levels of both non-HDL-C and LDL-C. Among those with diabetes, the130 mg/dl cutoff for non-HDL-C appeared to be a better predictor of risk for CHD death than the 100 mg/dl cutoff for LDL-C.

- American Diabetes Association (ADA) Standards of Medical Care in Diabetes

The ADA's most recent position statement on management of dyslipidemia in diabetes (ADA, 2003) was recently modified by their 2006 Standards of Medical Care in Diabetes (ADA, 2006). They recommended that in individuals without overt CVD, the primary goal should be an LDL-C < 100 mg/dl. If the patient is over age 40 years of age, the ADA recommends statin therapy *for all diabetic patients* to achieve an LDL-C reduction of 30-40% regardless of baseline LDL-C level. If the patient is under age 40 years but at increased risk due to other CV risk factors and does not achieve lipid goals with lifestyle modifications, addition of pharmacologic therapy is appropriate. In individuals with overt CVD, all patients should be treated with a statin to achieve an LDL-C reduction of at least 30-40%. A lower LDL-C goal of < 70 mg/dl, using high dose statin, is an option. In addition (and significantly different from NCEP ATP III), the ADA recommended secondary lipid goals to lower TG to < 150 mg/dl and raise HDL-C

to > 40 mg/dl (in women, an HDL-C goal > 50 mg/dl should be considered) using a fibrate or niacin.

- AHA/ACC Joint Guidelines for Secondary Prevention (Smith, 2006)

Earlier this spring, the AHA and ACC issued an updated joint guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease. These guidelines addressed goals for various CV risk factors. In terms of lipid management, they recommended a primary goal of LDL-C < 100 mg/dl, but that a reduction to LDL-C < 70 mg/dl was reasonable (or > 50% reduction in LDL-C if it is difficult to attain an LDL-C < 70 because of a high baseline LDL-C). However, they did not modify the ATP III LDL-C goal < 100 mg/dl in patients without ASCVD who have diabetes (or other multiple risk factors) and a 10-year risk of CHD > 20%. If triglycerides > 200 mg/dl, they recommended a non-HDL-C goal < 130 mg/dl (further reduction of non-HDL-C to < 100 mg/dl reasonable). In terms of diabetes management, they recommended a goal HbA1c < 7%.

Recommendations

- Diabetes is a high CV risk condition

The majority of individuals with diabetes are at high risk of CV events (10-year risk > 20%), and all of their cardiovascular risk factors should be aggressively treated. A long-term intensified multifactorial intervention program aimed at multiple risk factors can result in a 50% reduction in cardiovascular events (Gaede, 2003).

- Therapeutic Lifestyle Changes (TLC)

TLC (diet, exercise and weight loss) is important as adjunct to glycemic control and lipid therapies. It is generally not effective at reaching therapeutic goals when used alone.

- Glycemic control

Glycemic control is important for improvement of diabetic dyslipidemia. This is most beneficial for lowering elevated triglycerides and/or non-HDL-C. The effect is small for raising low HDL-C, and it may modestly reduce the proportion of small dense LDL. Glycemic control appears to have an independent effect on CV risk reduction, but the magnitude is less than lipid lowering therapy or treatment of hypertension.

- LDL-C

The primary goal of therapy should be an LDL-C < 100 mg/dl. If CVD is present, then there is a very high risk of new CV events, and it is reasonable to achieve an LDL-C goal < 70 mg/dl (or a 50% reduction in LDL-C if baseline LDL-C is very high). If CVD is not present, but the patient has multiple other CV risk factors, then a 30-40% reduction in LDL-C regardless of baseline LDL-C is appropriate.

However, if the patient < 40 years or age and has no other CV risk factors, then it is not necessary to be quite as aggressive with starting drug treatment, and it is reasonable to initiate lifestyle changes to achieve an LDL-C < 100 mg/dl, and not treat with LDL-C lowering therapy unless LDL-C remains > 130 mg/dl.

- Triglycerides / non-HDL-C

If TG > 200 mg/dl after the LDL-C goal is achieved, non-HDL-C should be used as a target of therapy (< 130 or for patients with CVD optional goal < 100 mg/dl). Consider using a higher dose of statin, fibrate or niacin. Unfortunately, the CV outcome data with fenofibrate is not conclusive. The best data is with gemfibrozil, but it interferes with metabolism of several statins which increases the risk of myopathy (Bottorff, 2006).

- Low HDL-C

Low HDL-C is difficult to treat. Glycemic control, statins and fibrates have small effects. Niacin is most effective, but may impair glycemic control (Grundy, 2002). TZD's (rosiglitazone and pioglitazone) appear to increase HDL-C by about 10% (Goldberg, 2005), and can be chosen for glycemic control, but the long-term benefit of this approach is unknown. CETP inhibitors may be available in the future (Schaefer, 2006).

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