Management of dyslipidemia in elderly diabetic patients

C Verny

SUMMARY

The prevalence of diabetes increases with age, potentially affecting 20% of the 75 years and older elderly population. Overmortality and increased cardiovascular morbidity-mortality are common in diabetic populations, including elderly diabetes. This increased cardiovascular risk must therefore be taken into consideration when discussing management of dyslipidemia in elderly diabetics. Should dyslipidemia be treated in elderly diabetics? What are the objectives and with what means? Whether the significance of dyslipidemia is different in this growing population compared with younger subjects remains unknown due to the lack of specific studies. The only results available come from a few primary or secondary cardiovascular prevention trials using statins or fibrates with subgroups of elderly diabetic patients, or subgroups of diabetic patients and also subgroups of patients aged over 65. Three recent studies detailed the potential benefit of such treatment: PROSPER in elderly subjects aged 70-82 years, HPS in diabetics before and after the age of 70 years and CARDS in diabetics aged up to 75 years. The results of these studies provide a few indirect elements of interest, keeping in mind the generally higher iatrogenic risk of treatment in elderly populations.

Key-words: Diabetes mellitus · Elderly · Dyslipidemia · Statin · Vascular risk.


RéSUMÉ

Prise en charge des dyslipidémies chez les diabétiques âgés

La prévalence du diabète augmente avec l’âge, pouvant atteindre 20 % des sujets âgés de 75 ans et plus. Même chez les sujets âgés, le diabète est responsable d’une surmortalité et d’une augmentation de la morbi-mortalité cardio-vasculaire. C’est dans ce contexte de haut risque cardio-vasculaire que se discute la prise en charge des dyslipidémies du diabétique âgé. Faut-il traiter les dyslipidémies des diabétiques de plus de 75 ans ? Avec quels objectifs et quels moyens ? Aucune étude n’a été menée spécifiquement dans cette population pourtant de plus en plus nombreuse, chez laquelle les dyslipidémies n’ont peut-être pas la même signification que chez les plus jeunes. Pour certains essais conduits avec des statines ou des fibrates en prévention cardio-vasculaire primaire ou secondaire, des résultats sont disponibles pour les sous-groupes de diabétiques âgés, ou à défaut, pour les sous-groupes de diabétiques d’une part, et de sujets de plus de 65 ans, d’autre part. Toutefois, trois études récentes précisent le bénéfice potentiel d’un tel traitement chez les sujets âgés, de 70 à 82 ans pour l’étude PROSPER, et chez des diabétiques dans les études HPS (avant et après 70 ans) et CARDS (jusqu’à 75 ans). Les résultats de ces études permettent d’apporter quelques éléments de réponse indirects, à convaincre avec le risque iatrogène habituellement plus important chez les sujets âgés.

Mots-clés : Diabète · Sujet âgé · Dyslipidémie · Statine · Risque vasculaire.

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The prevalence of diabetes increases with age, potentially affecting 20% of the 75 years and older population [1]. Vascular complications are the main causes of morbidity and mortality in patients with type 2 diabetes [2], known to be a source of overmortality, even in the elderly population [3], and higher cardiovascular morbidity and mortality [4-6]. Besides the deleterious effect of hyperglycaemia itself, other vascular risk factors very often associated with diabetes play an essential role, particularly qualitative and quantitative anomalies of lipid metabolism [7, 8] leading to increased triglyceride (TG) levels (increased qualitative and quantitative anomalies of lipid metabolism [7, 8] leading to increased triglyceride (TG) levels). These variations are related to aging lipid metabolism, but especially to weight changes observed in elderly subjects, declining activity level, co-morbid conditions, and the overall health status [10, 11]. The management of dyslipidemia in the elderly diabetic must therefore be discussed in this context of high cardiovascular risk. Should dyslipidemia be treated in diabetics aged over 75 years? With what objective and what means?

Over the last decade, several large-scale trials have demonstrated the usefulness of statin treatment for the middle-aged general population. Three recent studies have detailed the potential benefit in elderly subjects, up to the age of 82 years for PROSPER [12], and in diabetics [HPS [13] and CARDS [14]]. An analysis of these studies provides a few indirect elements of interest but leaves open several questions which could be usefully answered by studies specifically devoted to elderly diabetics aged 75 years or older.

**Benefit of treating dyslipidemia in elderly subjects**

**Dyslipidemia and aging**

The link between the different lipoproteins and cardiovascular disease, mainly coronary artery disease, is clearly established for middle-aged subjects but for older subjects the available evidence remains discordant. In the Framingham population aged 65 years and free of cardiovascular disease at inclusion, hypercholesterolemia remains a factor of vascular risk. After adjustment for other risk factors, following this population for 30 years demonstrated a positive correlation between cardiovascular mortality and total cholesterol for all age groups, but less and less so with increasing age [15]. This age-related decline in risk has been confirmed in other studies [16]. In the *Cardiovascular Health Study*, nearly 6,000 subjects aged over 65 were followed for slightly over 7 years. Mortality was not associated with HDL-C nor with LDL-C [17]. In this study, total cholesterol and LDL-C were not major variables predictive of risk for myocardial infarction or ischemic cerebral events [18]. In a prospective study involving more than 1,000 non-demented subjects aged 75 years on average and followed for 7 years, LDL-C > 1.4 g/l increased the risk of vascular dementia 3-fold compared with < 1 g/l at inclusion. This study also found that diabetes was clearly a risk factor for vascular dementia and cerebral vascular events [19]. In subjects over 70, and even in subjects over 80, HDL-C < 0.35 g/l remained a risk factor for cardiovascular mortality and coronary events in both men and women [20], while high levels of HDL-C were associated with lower risk for ischemic cerebral events [21]. Conversely, epidemiological data in very old populations show an increased risk of mortality in subjects with lower total cholesterol, death mainly being caused by cancer and infection, while the risk of cardiovascular mortality is not different in subjects with the highest and lowest cholesterol levels [10, 22, 23]. These studies investigated spontaneous serum cholesterol levels. Is there a cause and effect relationship or is hypocholesterolemia simply a biological marker of an underlying disease or unfavorable nutritional status? The question remains open but is quite illustrative of the specific situation of very old subjects for whom the objectives set for younger patients might actually be dangerous.

In all of the studies cited above, diabetes was mentioned in the population description but the diabetic population was not analyzed separately. Would the presence of diabetes alter the relationship between total cholesterol, LDL-C or HDL-C and cardiovascular events in the elderly? The question remains open.

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**Acronyms of cardiovascular prevention studies**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ALLHAT-LIT</td>
<td>Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm</td>
</tr>
<tr>
<td>CARDS</td>
<td>Collaborative Atorvastatin Diabetes Study</td>
</tr>
<tr>
<td>CARE</td>
<td>Cholesterol And Recurrent Events</td>
</tr>
<tr>
<td>DAIS</td>
<td>Diabetes Atherosclerosis Intervention Study</td>
</tr>
<tr>
<td>DALI</td>
<td>Diabetes Atorvastatin Lipid Intervention</td>
</tr>
<tr>
<td>HPS</td>
<td>Heart Protection Study</td>
</tr>
<tr>
<td>LIPID</td>
<td>Long-term Intervention with Pravastatin in Ischemic Disease</td>
</tr>
<tr>
<td>LIPS</td>
<td>Lescol Intervention Prevention Study</td>
</tr>
<tr>
<td>PROSPER</td>
<td>PROspective Study of Pravastatin in the Elderly at Risk</td>
</tr>
<tr>
<td>PROVE-IT</td>
<td>Pravastatin or Atorvastatin Evaluation and Infection Therapy</td>
</tr>
<tr>
<td>SENCAP</td>
<td>St. Mary’s, Eating, Northwick Park Diabetes Cardiovascular Disease Prevention</td>
</tr>
<tr>
<td>VA-HIT</td>
<td>Veterans Affairs High-density lipoprotein cholesterol Intervention Trial</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>West Of Scotland Coronary Prevention Study</td>
</tr>
<tr>
<td>4S</td>
<td>Scandinavian Simvastatin Survival Study</td>
</tr>
</tbody>
</table>

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Benefit of lipid lowering treatment in the elderly

Large-scale trials

Over the last fifteen years, prospective interventional studies have demonstrated the benefit of treating dyslipidemia in terms of cardiovascular morbidity and mortality. Most of the studies used statins for primary or secondary prevention. A secondary prevention study in coronary patients with and without a history of myocardial infarction (VA-HIT) was conducted with gemfibrozil. Patient age at inclusion and presence of diabetes were variable (Table I). The recent meta-analysis published by Cheung et al. [32] collected data from the main trials using statins and gave summary of their efficacy in the tested populations [32]:

- Treatment with statin significantly reduces the risk of major coronary events (non-fatal myocardial infarction and coronary heart disease-related death) by 27% (95% CI: 23-30%). For two studies, ALLHAT-LLT and LIPS, the difference did not reach the level of significance. For the first, the comparator arm was defined by standard care and not by placebo so that a certain number of patients also received statins [29]. In LIPS, the number of events was very low [28].
- Despite discordant results between studies, treatment with statins significantly reduced the risk of all-cause mortality by 15% (95% CI: 8-21%) but did not have any impact on non-cardiovascular mortality.
- Treatment with statins significantly reduces the risk of stroke by 18% (95% CI: 10-25%) with less efficacy for pravastatin, perhaps in relation with its hydrophilic properties compared with other lipophilic statins.

In the VA-HIT study [31], gemfibrozil reduced the risk of death from coronary causes and myocardial infarction by 22% among coronary patients with HDL-C < 0.4 g/l, LDL-C < 1.4 g/l and TG < 3 g/l. The result was not significant in the absence of prior myocardial infarction nor for LDL-C < 1.04 g/l.

Most of the statin trials involved subjects aged up to 75 years. HPS and PROSPER however included subjects aged up to 80 and 82 years respectively. Analysis by age group was not performed in some trials (4S and LIPS). LIPID demonstrated less favorable efficacy for pravastatin in reducing the relative risk of nonfatal myocardial infarction and coronary death with age (–32% before 55 years, –15% in 70 years and more, NS), but in terms of absolute risk, efficacy increased with age: in subjects aged 65 years or older, 22 patients must be treated to avoid one death, 35 to avoid one coronary death and 21 to avoid one nonfatal myocardial infarction or coronary death. In this study, hepatic and muscular adverse effects were not affected by age. Conversely, there were more cancers in subjects aged over 65, independently of treatment [33]. This study did not show any impact on stroke after the age of 65 years [34]. The other studies demonstrated that the efficacy of statins on lipid parameters and prevention of cardiovascular morbidity and mortality is not modified by age (before and after 65), which has been confirmed by the two large meta-analyses [32, 35], and even in HPS, before and after 70 years [13]. Unlike LIPID conducted with pravastatin, ASCOT-LLA conducted with atorvastatin showed a better efficacy for the prevention of stroke in subjects aged over 70 years, with a 31% reduction in risk (versus 24% before 70 years) [30]. In VA-HIT, gemfibrozil exhibited the same efficacy before and after 66 years [31]. But none of these studies specifically addressed the question of old diabetic patients.

PROSPER

PROSPER is the only study specifically including elderly subjects aged 70-82 years, either for secondary prevention or for primary prevention in high risk subjects with vascular disease other than coronary heart disease or with at least one other risk factor (smoking, high blood pressure, diabetes). The subjects were free of cognitive impairment (Mini-Mental Score > 24/30) and had total cholesterol levels ranging from 1.6 to 3.6 g/l (mean LDL-C = 1.5 g/l). The study lasted 3.2 years [12]. Compared with placebo, pravastatin reduced the risk by 15% for one of the following events: nonfatal myocardial infarction or coronary death or fatal or nonfatal cerebrovascular events (P = 0.014). Detailing each of these events, pravastatin significantly reduced the risk of myocardial infarction and coronary mortality, especially in the low HDL-C group (< 0.40 g/l) or in the secondary prevention group. Conversely, there was no significant effect on stroke, probably because of a too short study duration and perhaps because of hydrophilic property of pravastatin. No effect was observed on overall mortality. Similarly, pravastatin did not affect the decline in cognitive function. Unfortunately the number of diabetics (11% of the cohort) was too small to allow separate analysis. In terms of tolerance, adverse effects were not more frequent on pravastatin and there were no cases of rhabdomyolysis or increased creatine kinase levels above 10 times normal. One subject in each group presented transaminase levels 3 times normal. The major problem was a 25% increase in cancer risk in the pravastatin group (P = 0.02), a link which had been previously reported in the CARE study.

Benefit of treating dyslipidemia in elderly diabetics

Analysis of diabetes subgroups in large-scale studies

Some of the large-scale studies (4S, CARE, ASCOT-LLA, VA-HIT) included a separate analysis of diabetic patients. In the 4S study, simvastatin reduced the risk of vascular events by 37 to 55% (significant except for stroke) in 202 subjects known to have diabetes [37]. Another analysis by subgroups defined by blood glucose level compared subjects with a normal fasting level (< 1.10 g/l, n = 3,237 subjects), with a moderately impaired fasting level (1.10-1.26 g/l, n = 678), and with a fasting glucose > 1.26 g/l (n = 281) or with known diabetes mellitus (n = 202), i.e. a total of 483 subjects with dia-
Dyslipidemia in elderly diabetics

Table I

Large-scale therapeutic trials on the impact of lipid lowering therapy for the prevention of cardiovascular disease.

<table>
<thead>
<tr>
<th>Study [ref.] (n subjects)</th>
<th>Type of subjects</th>
<th>Age at inclusion (yr) (mean)</th>
<th>Duration (yr)</th>
<th>Treatment Pl = (vs placebo)</th>
<th>Baseline LDL-C (mmol/l)</th>
<th>Baseline TG (mmol/l)</th>
<th>Diabetics (%)</th>
<th>Elderly subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S [24] (4,444)</td>
<td>Secondary prevention</td>
<td>35-70 (59)</td>
<td>5.4</td>
<td>Simvastatin/Pl</td>
<td>4.9</td>
<td>1.5</td>
<td>11</td>
<td>?</td>
</tr>
<tr>
<td>WOSCOPS [25] (6,595 men)</td>
<td>Primary prevention</td>
<td>45-64 (55)</td>
<td>5</td>
<td>Pravastatin/Pl</td>
<td>5</td>
<td>1.8</td>
<td>1</td>
<td>?</td>
</tr>
<tr>
<td>CARE [26] (4,159)</td>
<td>Secondary prevention</td>
<td>21-75 (59)</td>
<td>5</td>
<td>Pravastatin/Pl</td>
<td>3.6</td>
<td>1.8</td>
<td>14</td>
<td>≥ 60: 50%</td>
</tr>
<tr>
<td>LIPID [27] (9,014)</td>
<td>Secondary prevention</td>
<td>31-75 (62)</td>
<td>6</td>
<td>Pravastatin/Pl</td>
<td>3.9</td>
<td>1.6</td>
<td>9</td>
<td>65-6: 24%</td>
</tr>
<tr>
<td>HPS [13] (20,536)</td>
<td>Primary prevention (high risk)</td>
<td>40-80 (59)</td>
<td>5</td>
<td>Simvastatin/Pl</td>
<td>3.4</td>
<td>2.1</td>
<td>29</td>
<td>≥ 70: 28%</td>
</tr>
<tr>
<td>LIps [28] (1,677)</td>
<td>Secondary prevention</td>
<td>18-80 (60)</td>
<td>4</td>
<td>Fluvastatin (F)/Pl</td>
<td>3.4</td>
<td>1.7</td>
<td>14.2 gr F</td>
<td>9.8 gr P</td>
</tr>
<tr>
<td>PROSPER [12] (5,804)</td>
<td>Secondary prevention (high risk)</td>
<td>70-82 (75)</td>
<td>3.2</td>
<td>Pravastatin/Pl</td>
<td>3.8</td>
<td>1.5</td>
<td>11</td>
<td>?</td>
</tr>
<tr>
<td>ALLHAT [29] (10,355)</td>
<td>Primary prevention hypertension + 1 other risk factor</td>
<td>≥ 55 (66)</td>
<td>8</td>
<td>Pravastatin/Standard care</td>
<td>3.8</td>
<td>1.7</td>
<td>35</td>
<td>≥ 65: 55%</td>
</tr>
<tr>
<td>ASCOT-LLA [30] (10,305)</td>
<td>Primary prevention in high-risk hypertensive patients</td>
<td>40-79 (63)</td>
<td>3.3</td>
<td>Atorvastatin</td>
<td>3.4</td>
<td>1.7</td>
<td>25</td>
<td>&gt; 60: 63%</td>
</tr>
<tr>
<td>VA HIT [31] (2,531 men)</td>
<td>Coronary artery disease LDL-C ≤ 1 mmol/l HDL-C ≥ 3.6 mmol/l TG ≤ 3.4 mmol/l</td>
<td>40-74 (59)</td>
<td>5</td>
<td>Gemfibrozil/Pl</td>
<td>2.8</td>
<td>1.8</td>
<td>25</td>
<td>&gt; 60: 77%</td>
</tr>
<tr>
<td>CARDS [14] (2,838)</td>
<td>Primary prevention in diabetics</td>
<td>40-75 (64)</td>
<td>4</td>
<td>Atorvastatin/Pl</td>
<td>3.02</td>
<td>1.70</td>
<td>100</td>
<td>&gt; 70: 12%</td>
</tr>
</tbody>
</table>

betes [38]. The efficacy of simvastatin was confirmed in the three groups, except for overall and coronary disease-related mortality in diabetics (non-significant reduction). But in terms of absolute risk, the benefit was related to glucose status: to avoid one event, it was necessary to treat 12 patients with normal glucose, 8 with impaired fasting glucose, and 7 with diabetes. These findings were irrespective of the LDL-C level.

In CARE study, the analysis confirmed the great vascular risk in diabetics, independently of age. At five years the incidence of myocardial infarction was 20% and that of stroke 8% among diabetics (versus 12% and 3% in non-diabetics, P = 0.001) in the placebo group [39]. Curiously, despite the fact that all included patients had a myocardial infarction, fewer diabetics had received aspirin (78.2%) than non-diabetics (84.4%, P = 0.001), which may have participated in their higher risk. The diabetics had the usual lipid profile (lower LDL-C and HDL-C and higher TG than non-diabetics). Pravastatin had the same effect on lipid parameters in diabetics and non-diabetics. It enabled a 25% decrease in the risk of coronary events (fatal or nonfatal myocardial infarction, revascularizations) (P < 0.001) in both diabetes and non-diabetics, with a greater decline in the absolute risk in diabetics (−8.1%) than non-diabetics (−5.2%).

In the Prospective Pravastatin Pooling project (PPP) of three earlier trials (WOSCOPS, CARE, LIPID), the reduction in the risk of nonfatal myocardial infarction and coro-
nary disease-related mortality was 19% in diabetics taking pravastatin. This was not significant [40], probably because of the heterogeneous nature of the study population in terms of age and risk level (primary or secondary prevention). Furthermore, the reduction in coronary risk was also lower in subjects with TG ≥ 2.20 g/l at inclusion (diabetics and non-diabetics not distinguished).

In the ASCOT-LLA primary prevention study in hypertensive patients aged 40-79 years, the reduction in the risk of nonfatal myocardial infarction and coronary mortality in subjects taking 10 mg atorvastatin was not significant in diabetics [30]. Despite the association of several vascular risk factors in this population, the number of coronary events was surprisingly low: 3.6% incidence in the placebo group over 3.3 years. Two subgroups in the study, diabetics and subjects aged 65 years or older, had a higher risk (incidence of coronary events on placebo 3.6 and 3.4% over 3.3 years). The authors did not report an analysis of diabetic subjects aged over 60 years.

**HPS**

The Heart Protection Study (HPS) concerned patients aged 40 to 80 years given 40 mg simvastatin or placebo for secondary (coronary heart disease with or without history of myocardial infarction) or primary (history of cerebrovascular disease, arteritis of the lower limbs, or diabetes) prevention therapy for five years. This was a high risk population: the rate of cardiovascular events reached 25% for the five years in the placebo group. The efficacy of simvastatin was found to be the same in the age groups < 65 y, 65-70 yr, and > 70 yr. Simvastatin also significantly reduced the risk of a first stroke by 25% in both diabetics and non-diabetics, even after 70 years of age. But when given after a first stroke, simvastatin decreased the risk of all vascular events, except recurrent stroke [36]. Tolerance was not analyzed by age group.

A specific analysis was conducted for 3,982 diabetics free of coronary artery disease and for 1,981 diabetics in secondary prevention [41]. Simvastatin significantly reduced the risk of all vascular events by 22% in the diabetic group, by 33% in the diabetics free of vascular disease at inclusion, and by 27% in diabetics with LDL-C < 1.16 g/l at inclusion. The preventive efficacy of a 0.4 g/l reduction in LDL-C was the same, irrespective of the baseline level of LDL-C. There was no impact of diabetes duration nor quality of glucose control. In diabetics aged 65-80 years, simvastatin enabled a 31% reduction in the risk of major cardiovascular events (nonfatal myocardial infarction, coronary mortality, fatal or nonfatal stroke, revascularization) (P = 0.03) [41]. In this study, serum creatinine increased less on simvastatin, with a lesser decrease in calculated clearance. Simvastatin did not have any deleterious effect on glucose control. Elevated serum transaminase levels more than 4 times normal were observed in 0.47% of subjects on simvastatin (versus 0.37% on placebo) and elevated serum creatinine kinase (assayed in patients with muscular symptoms) of more than 10 times normal in 0.13% of the subjects on simvastatin (versus 0.05% on placebo).

**CARDs**

The Collaborative Atorvastatin Diabetes Study (CARDs) tested atorvastatin 10 mg/d versus placebo in a cohort of diabetic subjects aged 40-75 years free of pre-existing vascular disease whose LDL-C level was ≤ 1.6 g/l and who had at least one of the following complications: diabetic retinopathy, microalbuminuria > 20 µg/l or proteinuria, smoking, or high blood pressure [14]. Twelve percent of the participants were aged 70 years or older and 84% had high blood pressure. Unlike the ASCOT-LLA study, this was a high-risk population: 10% of the subjects in the placebo arm had a vascular event during the four years of the study. Atorvastatin enabled a 0.48 g/l reduction in LDL-C with no significant effect on HDL-C and a 37% reduction in the risk of a first cardiovascular event (P = 0.001) (coronary event -36%; stroke –48%), with a non-significant effect on overall mortality (~27%; P = 0.059). The results appeared at the end of the first year of treatment. Age at inclusion or baseline LDL-C level did not appear to have any effect. Adverse effects were not more frequent in the atorvastatin arm and no cases of rhabdomyolysis were observed.

**Statins or fibrates?**

Fibrates should be considered for diabetics whose lipid profile is similar to a metabolic syndrome with hypertriglyceridermia and reduced HDL-C level. In the Helsinki Heart Study, lipid parameters were measured in 96 type 2 diabetics taking simvastatin (10-40 mg/d) or gemfibrozil (1,200 mg/d) after 24 months of treatment. The fibrate was found to be more active on TG level and on HDL-C, and the statin on LDL-C [42]. Thus theoretically, gemfibrozil could be used in diabetics presenting hypertriglyceridermia and normal or low LDL-C. In the VA-HIT study, the efficacy of gemfibrozil was the same in diabetics and non-diabetics for prevention of coronary events, but the reduction in the stroke risk was not significant in diabetics [43].

Two studies were specifically conducted in subjects with type 2 diabetes: DAIS with fenofibrate [44] and SENDCAP with bezafibrate [45]. The progression of coronary atherosclerosis was slower in subjects on fenofibrate on the basis of non-clinical angiographic data and the incidence of cardiovascular events over three years was lower with bezafibrate than with placebo. But these studies only included a small number of patients aged 65 or less. Considering the body of evidence on the efficacy of statins for the prevention of cardiovascular morbidity and mortality in the setting of secondary prevention or for high-risk diabetic populations, the ideal treatment could be combined therapy. However, the role of this therapeutic strategy remains to be clearly demonstrated [46, 47].

**Which statin and at what dose?**

The DALI study compared the effect of atorvastatin (10 and 80 mg) versus placebo on lipid parameters in type 2 diabetics aged 45-75 years. Lipid values were measured after...
30 weeks of treatment. The reduction in LDL-C was greater with 80 mg atorvastatin (–52% versus –40% with 10 mg atorvastatin) while the difference between the two doses (10 and 80 mg) was not significant for the reduction of TG and increase of HDL-C (–25 and –35% and +6 and +5.2% respectively). It is noteworthy that there were no more adverse effects with 80 mg atorvastatin [48].

In the PROVE-IT study conducted in patients with an acute coronary syndrome within the 10 preceding days, the preventive efficacy of atorvastatin given at the dose of 80 mg/d was significantly greater than pravastatin given at the dose of 40 mg/d, except in subjects aged 65 years or older (30% of the study population). In this subpopulation, the difference between the two statins was not significant. Separate analyses of diabetic subpopulations was not conducted [49].

Potential problems of lipid lowering in elderly subjects

The large-scale prevention studies included a significant proportion of subjects aged 65-75 years. The efficacy of the agents studied was equivalent in this population to that observed in the younger subjects, or even greater because of the higher cardiovascular risk in the older subjects. However, in Canada for example, there is some resistance against prescribing statins for subjects over 65 despite the fact that this population has a very high risk or needs secondary prevention [50].

This could be related to a problem of observance in older populations or because of worries about adverse effects. It could also simply result from insufficient knowledge of recent evidence providing a certain level of proof up to the age of 80 or even 82 years. The problem of observance of old patients is well-known, even for statins: excepted in large-scale trials, at six months 43% of subjects aged over 65 take their treatment correctly and 29% do not take prescribed statins. The problem of observance is even more acute with subjects aged over 75 years, and subjects with dementia or depression. An other risk factor of bad observance is the high number of prescribed drugs. Conversely, compliance with treatment is improved in patients with diabetes, high blood pressure or a prior cardiovascular event [51]. Physicians should give their patients clear and precise explanations (and be convinced themselves) concerning the indications and the objectives of the prescribed drugs. Worries about adverse effects are always legitimate in subjects taking multiple medications. The benefit of statins is significant within one year, without any self-perceptible deleterious effect on quality-of-life or health status [52]. Data available from the large-scale trials do not show any difference in tolerance of statins by age. Muscular involvement, defined by an elevated serum creatine kinase level (> 10 times normal) is observed in 0.1 to 0.5% of patients in controlled studies. Rhabdomyolysis requiring hospitalization was studied in one retrospective analysis of cohorts of subjects taking different lipid lowering regimens (statins, fibrates, or combined). With atorvastatin, pravastatin or simvastatin, the incidence of rhabdomyolysis was 0.44/10,000 patient-years. With fibrates (gemfibrozil and fenofibrate) it was 2.82/10,000 patient years. On combination statin-fibrate therapy, the rate varied from 17 to 22.5/10,000 patient-years (except for gemfibrozil+cerivastatin where it was 789 to 1,035/10,000 patient-years). The risk factors are age ≥ 65 years (relative risk 5.4) and diabetes (relative risk 2.9). The authors emphasized the importance of drug interactions with statins (all statins except pravastatin are metabolized in the liver by cytochrome P450), especially with erythromycin and ketoconazole [53].

Conclusion

The objectives and the therapeutic modalities for the treatment of dyslipidemia in middle-aged diabetics have become clearer with new evidence provided by recent trials using statins. There remain some questions however, in particular concerning the indications for the use of statins for primary prevention in diabetics [54] and on the respective indications for statins and fibrates in this specific population. The American Diabetes Association recommends the use of statins for primary prevention in diabetics whose LDL-C is > 1.3 g/l, with an objective of < 1 g/l, irrespective of age [55]. In France, diabetics requiring secondary prevention and diabetics with renal problems (calculated creatinie clearance < 60 ml/min or proteinuria > 300 mg/24 h) or with at least two other risk factors should reach these objectives [56]. No special mention is made concerning older diabetics, who therefore should be included in this category, because of their age and the frequency of associated high blood pressure. The most recent guidelines from the American Geriatrics Society for the management of older diabetics sets the same theoretical objectives but advises physicians to take into consideration the patient’s general status [57]. There is currently no information concerning the usefulness of statins in diabetics aged over 80 years. Up to this age, the results of the large-scale trials favor the prescription of statins, using the same general rules as for younger subjects, except for demented or very frail patients who have been excluded from this scales. In these patients, prescriptions depend on the overall objectives of medical care and the necessary priorities. For secondary prevention after a vascular event, irrespective of the nature and probably irrespective of the LDL-C level, there is no reason not to prescribe statins (excepting life-threatening events or co-morbid conditions). For primary prevention in the elderly diabetic aged less than 80 years, prescription of a statin with the objective of reaching an LDL-C level < 1 g/l should be discussed if there is another risk factor, recalling that diabetes and age are already two factors favoring serious muscle complications with these treatments. While one must be prudent after the age of 80 years, especially for particularly frail patients, those who are not frail should be allowed to benefit from this effective treatment.
Evidence concernant les fibates n’est pas au moment présent suffisant pour arrêter nos conclusions pour cette population. L’importance de la gestion de la nutrition doit être rappelée, principalement pour éviter l’alimentation déficiente chez les patients âgés diabétiques, mais aussi avec une dépense énergétique non fréquent chez les patients âgés. Dans n’importe quel cas, une évaluation globale de la gestion de la nutrition permet d’évaluer l’impact de l’alimentation déficiente dans cette population pour l’efficacité, la sécurité et l’impact économique de la gestion de la nutrition déficiente.

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