EDITORIAL

Is There a Role for Hypolipidaemic Drug Therapy in the Prevention or Treatment of Microvascular Complications of Diabetes?

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A plethora of statin survival trials and meta-analyses have demonstrated a substantial reduction in cardiovascular disease (CVD) morbidity and mortality, mainly related to a low-density lipoprotein cholesterol (LDL-C) reduction [1]. One of them, the prospective, randomised, double-blind, secondary prevention Treating to New Targets (TNT, n = 10,001) trial, randomised patients to either 10 or 80 mg/day of atorvastatin. During a 5-year period the 10 mg/day patients had a rate of major CVD events of 10.9%, while those randomised to 80 mg/day had an 8.7% event rate. This was despite the concurrent and successful treatment of other CVD risk factors, the 22% ($p<0.001$) CVD risk reduction compared with atorvastatin 10 mg/day, and the achievement of LDL-C levels of 77 mg/dl (well below those suggested by guidelines at that time) [2]. Similar were the data from the prespecified *post hoc* subgroup analysis of TNT that included patients (n = 1,401) with type 2 diabetes mellitus (T2DM) that had mild to moderate chronic kidney disease (CKD, a microvascular complication of DM) or normal renal function [3]. Compared with 10 mg of atorvastatin, 80 mg of atorvastatin reduced the relative risk (RR) of major CVD events by 35% (absolute event rate 21 *vs* 14%; hazard ratio (HR) = 0.65; 95% confidence interval (CI) = 0.43-0.98; p = 0.04) in those with CKD and by 10% in patients with T2DM and normal renal function (14.8 *vs* 14%; HR = 0.90; p = 0.56) [3]. In any case (with or without diabetic nephropathy) a residual CVD risk was present, as in all statin survival trials [1]. In the Steno-2 study, intensive multifactorial intervention in patients with T2DM during a 5-year follow-up, significantly reduced CVD events (HR = 0.47, 95% CI = 0.24-0.73, p = 0.008) and CVD mortality (HR = 0.43, 95% CI = 0.19-0.94, p = 0.04), but failed to prevent the development or the progression of microvascular complications of T2DM in up to 50% of patients [4, 5]. This contributed to a lesser reduction of CVD mortality or morbidity rates, and was recorded despite the effort to control glycaemia, blood pressure, body weight, smoking, physical activity, and LDL-C levels [4,5]. Thus, residual risk is related both to macrovascular complications connected to atherogenic dyslipidaemia [high triglycerides (TGs) and low high density lipoprotein cholesterol (HDL-C) levels, prevalent in DM] and to microvascular complications of T2DM, which contribute to the excess CVD and all cause morbidity and mortality [6-8].

The gains in CVD prevention and treatment are being challenged by the impact of global epidemics of obesity, metabolic syndrome (MetS) and T2DM [9]. Recent data suggest a possible reversal in CVD mortality rates, especially in younger men and women [10, 11]. These trends have a negative impact on life expectancy (each year 4.3 million CVD deaths are reported in Europe [12]) and quality of life as well as on the cost of managing CVD, estimated in 2008 at about $450 billion per annum in the United States (US) [13] and $300 billion in Europe [12]. DM-related complications, including CVD, CKD, neuropathy, blindness, and lower-extremity amputation, are significant causes of increased morbidity and mortality, and further increase the economic burden on health care systems. In 2050, the number of people in the US with diagnosed DM is estimated to grow to 48.3 million, from 20 million in 2005 [14].

It was thought until recently that current standards of care, such as effective glycaemic control, reduce CVD events (on a very long term basis), and improve micro-vascular complications of DM [diabetic retinopathy (DR), nephropathy (DNeph) or neuropathy (DNeur) [6]. A recent meta-analysis of 14 clinical trials that randomised 28,614 participants with T2DM (15,269 to intensive and 13,345 to conventional glycaemic control) showed that intensive control did not significantly affect the relative risks of all

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cause or macrovascular and microvascular disease (as a composite outcome or retinopathy or nephropathy or amputations alone) [15], while compared with conventional glycaemic control it increased the risk of severe hypoglycaemia by 30%. The latter might lead to increased mortality rates [15]. If intensive glycaemic control is dangerous and does not prevent microvascular complications of DM, as we believed until recently, then what can? Is it possible that arterial hypertension or atherogenic dyslipidaemia (both closely related to DM) may contribute to the pathogenesis of microvascular complications of DM [16]? The Action to Control Cardiovascular Risk in Diabetes - Eye (ACCORD-EYE) study showed that there was no significant effect of intensive *vs* standard blood-pressure control on the progression of macrovascular and at least the 1 microvascular complication (DR) of DM during a 4 year follow-up [17]. On the other hand it seems that there is a link between atherogenic dyslipidaemia and micro-vascular complications of DM [18, 19]; this is further confirmed by data suggesting that combinations or mono-therapies of hypolipidaemic drugs (through hypolipidaemic [20] or off-target effects) improve existing or prevent new microvascular complications of DM [21, 22] thus providing a fresh approach for the treatment of this feature of DM that still has unmet needs [21, 22]. There are some data suggesting that this might be one way to solve this problem [7,16,23].

A. DIABETIC RETINOPATHY

The number of Americans 40 years or older with DR and vision-threatening DR (VTDR), the leading cause of blindness in the Western world, will triple in 2050, from 5.5 million in 2005 to 16.0 million for DR and from 1.2 million in 2005 to 3.4 million for VTDR [24]. Increases among those 65 years or older will be more pronounced (2.5 million to 9.9 million for DR and 0.5 million to 1.9 million for VTDR) [24]. Thus, DR and VTDR will grow to be even more significant public health problems. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, among others, the severity of DR and macular oedema were positively associated with high TGs and negatively associated with HDL-C levels [25]. This is the reason that the beneficial effect of fenofibrate on DR did not come as a total surprise. Data from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (n = 9,795 patients, aged 50-75 years with T2DM) [26] showed that fenofibrate had significant preventive effect on the development of DR, reducing first laser treatment (a predefined tertiary endpoint of FIELD) by 31% (p = 0.0002) and proliferative retinopathy by 30%, (p = 0.015) [27]. The benefit of treatment was enhanced in patients without prior retinopathy [relative risk reduction (RRR) for all laser events by 49%, p = 0.002 in DR free patients, compared with 24%, p = 0.01, in patients with a history of DR]. These effects were achieved within 8 months of treatment, and increased during the study [27].

The ACCORD study [28] randomized 5,518 high risk T2DM patients at target for LDL-C (100 mg/dl) on simvastatin to fenofibrate or placebo. Fenofibrate treatment lowered TGs by 22% from baseline *vs* 8.7% with simvastatin alone, and raised HDL-C by 8.4 *vs* 6.0% with simvastatin alone ($p<0.05$). The study failed to demonstrate a benefit for a composite of CVD death, nonfatal myocardial infarction (MI) or nonfatal stroke [28]. A subgroup of patients with atherogenic dyslipidaemia had a 31% ($p < 0.05$) reduction in primary endpoint (death and major CVD events) with combination treatment compared with simvastatin treatment alone [29]. Similar results were reported from all fibrate trials [29].

The ACCORD-EYE study [17] showed that intensive glycaemia therapy significantly reduced the risk of progression of DR. However, tight glycaemic control [< 7% glycosylated haemoglobin (HbA_{1c})] was also associated with an increased rate of death from any cause after a mean of 3.5 years of follow-up compared with the standard strategy [17]. The ACCORD EYE study also reported a beneficial effect of fenofibrate on the progression of DR (6.5 *vs* 10.2% with placebo; p = 0.006; both groups were on simvastatin) [17], while there was no significant effect of intensive *vs* standard blood-pressure control on the progression of DR at 4 years (10.4 *vs* 8.8%, p = 0.29) [17].

In the Collaborative Atorvastatin Diabetes Study (CARDS), a primary prevention study in T2DM patients, there was no evidence of a significant benefit on the progression of DR among patients treated with atorvastatin [30]. It should also be noted that in the Steno-2 study [4,5] DR developed or progressed in 48% of patients treated with intensive multifactorial therapy (including optimal statin treatment) over a 7.8-year period [4,5].

This evidence supports a beneficial role for fenofibrate treatment in preventing the development or progression of DR in T2DM, especially among patients at the early stages of DR [7]. The use of fenofibrate in T2DM patients with atherogenic dyslipidaemia appears useful, because besides its effect on macrovascular (residual) CVD risk [28,29], it may also reduce microvascular complications of DM [29].

B. DIABETIC NEPHROPATHY

DNeph expressed as a loss of kidney function (reduced glomerular filtration rate-GFR) or as albuminuria/proteinuria is a major CVD risk factor. CKD (with a GFR < 60 ml/min/ 1.73 m^2) was characterised in guidelines as a coronary heart disease (CHD) equivalent [31]. The GREACE (Greek Atorvastatin and Coronary Heart Disease Evaluation) study showed an improvement in kidney function (mean GFR increase by 12%) over a period of 3 years in 800 patients treated with atorvastatin, compared with a decrease in kidney function by 4% in placebo patients [32]. The TNT (n = 10,001) study showed that statin-related improvement in estimated GFR (eGFR) was significantly greater in patients with CKD treated with atorvastatin 80 mg (9.9%, $p<0.0001$) compared with those with CKD on 10 mg daily (6.6%) [33, 34], while those with normal renal function had lower increases in GFR at both the 10 and the 80 mg/day atorvastatin doses [33]. This was related with a greater RRR (32%, p = 0.0003) in primary endpoint (death and all major CVD events) in patients with stage 3 CKD (n = 3,107, GFR 30-59 ml/min/1.73m^2) than in patients with normal renal function (n = 6,549, 15%, p = 0.049) [33].

In a meta-analysis (1,384 patients during 24 weeks of follow-up) investigating the effect of statins on albuminuria/ proteinuria regardless of aetiology statins reduced albuminuria (11 studies) and proteinuria (4 studies) in 13 of 15 studies [35]; the reduction in excretion being greater among studies with higher baseline albuminuria/proteinuria. The change in excretion was 2% (95% CI = -32 to 35%) for those with excretion < 30 mg/day, -48% (95% CI = -71 to -25%) for those with excretion of 30-300 mg/day and -47% (95% CI = -67 to -26%) for those with excretion > 300 mg/day [35]. Statins may have a beneficial effect on albuminuria/proteinuria, however, the validity of this finding, and whether this effect translates into reduction of CVD or end-stage renal disease (ESRD) requires larger studies [35].

In patients with T2DM the effect of statins on urinary albumin excretion (UAE) may be different. In CARDS [36], a randomized, placebo-controlled trial that included 2,838 patients with T2DM and free of CVD at baseline, 34% (n = 970) of the patients had an eGFR of 30-59 ml/min/1.73m^2. In these patients atorvastatin 10 mg/day was associated with a modest improvement in the annual change in eGFR (p = 0.01), and with substantial reduction in major CVD events (42%) and stroke (61%) [36]. At baseline, 21.5% of patients had albuminuria and an additional 6.8% developed albuminuria during follow-up. Atorvastatin did not influence the incidence of albuminuria or regression to normo-albuminuria [36]. In the Use of Rosuvastatin versus Atorvastatin iN type 2 diabetes mellitUS patients (URANUS) trial [37] the effect of rosuvastatin or atorvastatin on UAE was determined in T2DM. This was a randomized, double-blind, parallel-group, response-based design study that compared rosuvastatin 10 mg (titrated to 40 mg) with atorvastatin 10 mg (titrated to 80 mg) in T2DM patients with dyslipidaemia. Results suggest that no significant change from baseline in UAE was observed for either treatment group or between-treatment groups at 16 weeks, and UAE for both treatment groups remained within normal limits [37].

In a recent *post hoc* analysis of FIELD [38], fenofibrate reduced albuminuria and slowed eGFR loss over 5 years, despite initially and reversibly increasing plasma creatinine. In the fenofibrate group there was a 5.0 ml/min/1.73 m^2 (95% CI = 2.3-7.7, p < 0.001) smaller loss of renal function compared with placebo [38]. Fenofibrate reduced urine albumin concentrations and hence albumin/creatinine ratio by 24% (p < 0.001), with 14% less progression and 18% more albuminuria regression (p < 0.001) than placebo. Thus, fenofibrate reduced UAE and delayed GFR impairment in T2DM [38], 2 independent predictors of CVD events and total mortality in T2DM patients [39].

C. DIABETIC PERIPHERAL NEUROPATHY AND LOWER-EXTREMITY AMPUTATION

The age-adjusted rate of lower-extremity amputation (LEA) in DM patients is approximately 15 times that of the non-diabetic population. Over 50,000 LEAs were performed on individuals with DM in the United States in 1985 [40]. Among individuals with DM, diabetic peripheral neuropathy (DPN), peripheral arterial disease (PAD), and impaired microvascular circulation are the major predisposing factors for LEA. Lack of adequate foot care and infection are additional risk factors [40]. A study from US demonstrated that the prevalence of patients with DPN symptoms was high, and that DPN was alarmingly underdiagnosed in study participants [41]. These could influence the development of severe foot complications like diabetic foot ulcer, and even possibly increase the risk of lower extremity amputation. This study is a stimulus to help educators develop targeted education and intervention programs for DPN and diabetic foot [41].

The FIELD study showed that fenofibrate reduced the number of lower-extremity non-traumatic amputations (a prespecified tertiary outcome) compared with placebo (38%, p = 0.011) [42]. The cumulative hazard curves showed a reduction in amputation rates that seemed to diverge from the placebo rates after just 1.5 years of fenofibrate use. The reduction in the risk of first amputation (36%, p = 0.02) and minor amputation (there was no known large-vessel disease, 47%, p = 0.027) were striking, by contrast with a non-significant reduction (7%, p = 0.79) for major (large-vessel-related) amputations [42]. Of note, atorvastatin reduces amputation in T2DM mice with PAD through p53 degradation [43]. Although it has been hypothesised that statins have a favourable effect on DPN, independent of its lipid-lowering effect by demonstrating restoration or preservation of microcirculation of the sciatic nerve [44], there are no actual data on humans.

D. DIABETIC AUTONOMIC NEUROPATHY

(DAN): is a major microvascular complication because it is associated with high morbidity and mortality (sudden cardiac death and malignant ventricular arrhythmias) [45-47]. The evolution of DAN is related to a gradual increase of sympathetic tone that overrides the reduced parasympathetic tone until the patients reach a full (autonomic nervous system) cardiac denervation, resulting in a permanent and significant decrease in heart rate variability (HRV) in an increase in resting heart rate [45]. The aetiology of DAN has not been fully elucidated, but increased oxidative stress may be involved [48,49]. Hyperglycaemia causes oxidative stress through the increased activity of the polyol route, and is associated with increased production of advanced glycation end-products (AGEs), another possible cause of DAN [49]. We have shown that atorvastatin improves DAN, increasing parasympathetic tone and decreasing sympathetic tone, in dyslipidaemic patients with or without CVD, but free of DM at baseline [50]. Fluvastatin seems to have a beneficial effect on DAN and reduces sympathetic tone in patients with DM [51], while the beneficial effect of atorvastatin on diabetic foot was attributed partly to favourable action on the DAN and DPN [52]. Other lipid-lowering drugs (fibrates or omega-3 fat) have not been tested in that field.

Any potential explanations for the observed discrepancies in results of various studies mentioned above could be explained by differences in study populations, study protocols, study duration and drug specific properties. Another issue was that all studies used assessed eGFR using the MDRD equation. However, eGFR has limitations in comparison with the measurement of GFR with Cr-EDTA, [53], but Cr-EDTA can not be used in routine practice.

The beneficial effects of drug treatment for dyslipidaemia on microvascular complications of DM are probably related both to the hypolipidaemic and the "pleiotropic" effects of these drugs [54]. A plethora of additional effects has been ascribed as "pleiotropic" effects, and these may be essential for manifestation of the clinical benefit by these drugs. This interpretation is supported by the fact that improvement of renal function became evident from week 6 of the treatment [32].

Therefore, it seems that some lipid-lowering drugs have a favourable effect on microvascular complications of DM when administered in combination or as monotherapy. Much remains to be clarified in this field. It is of outmost interest to find out whether or not microvascular complications share a common pathogenesis and whether or not a hypolipidaemic drug can be effective against microvascular complications. This has not been investigated yet, probably because microvascular complications of DM are related to several specialties (e.g. internal medicine, diabetology, nephrology, ophthalmology, neurology, cardiology and vascular surgery), making it difficult to coordinate the efforts to elucidate their pathogenesis and treatment. It is therefore useful to explore the effects of lipid-lowering in the pathogenesis, prevention or treatment of microvascular complications of DM, because these are significant public health problems and there is still no standard therapy for them.

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CONFLICT OF INTEREST

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