



Original article

Atherogenic dyslipidemia increases the risk of incident diabetes in statin-treated patients with impaired fasting glucose or obesity

Fotios Barkas (MD)^a, Moses Elisaf (MD, PhD)^a, Evangelos Liberopoulos (MD, PhD)^a, George Liamis (MD, PhD)^a, Evangelia E Ntzani (MD, PhD)^b, Evangelos C Rizos (MD, PhD)^{c,d,*}

^aDepartment of Internal Medicine, Faculty of Medicine, University of Ioannina, Ioannina, Greece

^bDepartment of Hygiene and Epidemiology, Faculty of Medicine, University of Ioannina, Ioannina, Greece

^cDepartment of Internal Medicine, University Hospital of Ioannina, Ioannina, Greece

^dDepartment of School of Medicine, European University of Cyprus, Nikosia, Cyprus



ARTICLE INFO

Article history:

Received 16 December 2018

Received in revised form 28 January 2019

Accepted 17 February 2019

Available online 23 March 2019

Keywords:

Diabetes

Mixed dyslipidemia

Prediabetes

Statin

Obesity

ABSTRACT

Aim: To investigate which metabolic factors increase the risk of incident diabetes (T2D) in statin-treated patients.

Methods: A retrospective study conducted in Greece including 1241 consecutive individuals with dyslipidemia attending a lipid clinic for ≥ 3 years. After defining associations with incident T2D, we assessed the risk of new-onset T2D based on the presence of impaired fasting glucose (IFG), atherogenic dyslipidemia, and overweight/obesity.

Results: After excluding 166 patients with baseline T2D and 193 subjects taking lipid-lowering therapy at the baseline visit, 882 participants were included in the study. Eleven percent ($n = 94$) developed T2D during their follow-up (median 6 years; IQR: 4–10). Baseline patients' age (OR: 1.05; 95% CI: 1.02–1.08, $p < 0.01$), family history of diabetes (OR: 3.58; 95% CI: 1.86–6.91, $p < 0.01$), IFG (OR: 6.56; 95% CI: 3.53–12.12, $p < 0.01$), overweight/obesity (OR: 2.65; 95% CI: 1.39–5.05, $p < 0.01$), atherogenic dyslipidemia (OR: 3.27; 95% CI: 1.50–7.15, $p < 0.01$), and treatment with high-intensity statins (OR: 3.51; 95% CI: 1.89–6.51, $p < 0.01$) were independently associated with increased risk of T2D in statin-treated patients. Among the IFG subjects, atherogenic dyslipidemia (OR: 3.44; 95% CI: 1.31–9.04, $p = 0.01$) and overweight/obesity (OR: 2.54; 95% CI: 1.14–5.66, $p < 0.05$) independently increased the risk of T2D. Among the overweight/obese ones, atherogenic dyslipidemia independently increased the risk of T2D (adjusted OR: 5.60; 95% CI: 2.19–14.30, $p < 0.01$).

Conclusion: Atherogenic dyslipidemia appears to be an independent risk factor for new-onset T2D in statin-treated patients, while IFG, overweight/obesity and family history of diabetes remain risk factors for new-onset T2D in this group.

© 2019 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.

Introduction

It is well established that statins are the cornerstone of cardiovascular prevention, but they may increase the incidence of type 2 diabetes mellitus (T2D) [1,2]. As “statinization” of the population is extremely common, it would be of great benefit to identify those individuals at greatest risk for T2D under statin

treatment. An analysis of TNT (Treating to New Targets), IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering), and SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trials was the first to demonstrate that elevations of baseline fasting plasma glucose (FPG), body mass index (BMI), fasting triglycerides (TG), and hypertension increased the risk of new-onset T2D [3]. This phenotype, present in the metabolic syndrome, is closely related with insulin resistance (IR) and the development of T2D [4]. Having a simple method for identifying those insulin-resistant patients before the initiation of statin therapy might be useful in clinical practice. Although hyperinsulinemia is the most accurate estimate for the

* Corresponding author at: Department of Internal Medicine, University Hospital of Ioannina, Stavrou Niarchou Avenue, 45500 Ioannina, Greece.
E-mail address: vagrizos@gmail.com (E.C. Rizos).

direct measurement of IR [5], the absence of a standardized insulin assay along with the lack of insulin measurement in everyday clinical practice, limit its clinical utility [6]. Prediabetes is associated with IR and predicts statin-associated T2D [7,8]. Although the FPG cut point for the definition of prediabetes provides a useful tool identifying enhanced risk of statin-induced T2D, prediabetes remains a heterogeneous entity and not all subjects with IFG are insulin resistant [7]. Likewise, a proportion of obese individuals might not be at increased risk for metabolic complications and has been referred to as ‘metabolically healthy obesity phenotype’ [9]. On the other hand, IR or T2D are closely related to ‘atherogenic’ or ‘mixed’ dyslipidemia (MixDys), characterized by elevated plasma fasting and postprandial triglyceride-rich lipoproteins, small dense low-density lipoprotein, and low high-density lipoprotein cholesterol (HDL-C) [10]. Recently, intriguing evidence supports a causal role of atherogenic dyslipidemia in IR and the development of T2D [11].

We aimed to investigate which metabolic markers and most importantly which combinations of those are associated with incident T2D in statin-treated individuals.

Materials and methods

This was a retrospective observational study as previously described [12]. Briefly, we included 1241 consecutive adults with dyslipidemia who attended the Outpatient Lipid Clinic of the University Hospital of Ioannina in Greece and were followed-up for at least 3 years. Informed consent was obtained from each patient and the study protocol was approved by the institutional Ethics Committee.

All subjects were of Hellenic origin (European ancestry). All participants had a complete assessment of concomitant diseases and their treatment and demographic characteristics along with clinical data were recorded at baseline and at the most recent (final) visit. These included: age, follow-up duration and gender, BMI, blood pressure (BP) readings, family history of diabetes, hypertension, and atherosclerotic cardiovascular disease (ASCVD). ASCVD comprised coronary heart disease, stroke, peripheral arterial disease, and carotid stenosis. Of note, none of the study participants was diagnosed with a recent episode of ASCVD. Laboratory data were also available, such as FPG levels and lipid profile, including total cholesterol (TCHOL), TG, HDL-C, and low-density lipoprotein cholesterol (LDL-C). Considering the lack of a standardized insulin method along with the fact that insulin levels were measured in a minority of the subjects, IR was not used in the analyses of the present study. In addition, glycated hemoglobin (HbA1c) was rarely measured before the diagnosis of diabetes, since national guidelines for diabetes do not recommend HbA1c measurement for the diagnosis of diabetes.

Concomitant medications were also recorded with particular emphasis on the lipid-lowering therapy, including the name and dose of each statin and other lipid-lowering drugs (i.e. ezetimibe, colesvelam, fibrates, and omega-3 fatty acids). In addition, the intensity of statin therapy was classified as ‘high,’ ‘moderate,’ and ‘low’ on the basis of the average expected LDL-C lowering of $\geq 50\%$, 30–50%, and $< 30\%$, respectively. Hence, high-intensity statin therapy comprised rosuvastatin 20–40 mg and atorvastatin 40–80 mg.

The diagnosis of T2D was made in case of fasting glucose levels ≥ 126 mg/dL (6.9 mmol/L) in 2 separate measurements in different visits within 1 month or when glucose levels were ≥ 200 mg/dL (11.1 mmol/L) 2 h following 75 g of oral glucose [13]. The diagnosis of impaired fasting glucose (IFG) was defined by a baseline fasting plasma glucose concentration 100–125 mg/dL (5.5–6.9 mmol/L)

[13]. Based on the results of a previous study of ours showing that the amount of TG-rich lipoproteins and small dense low-density lipoproteins was greater in case of TG ≥ 200 mg/dL (2.3 mmol/L) in our study participants [14], the diagnosis of MixDys was made in case of baseline TG ≥ 200 mg/dL (2.3 mmol/L) and HDL-C < 50 mg/dL (1.3 mmol/L) or < 40 mg/dL (1 mmol/L) for the female and male subjects, respectively. Overweight/obesity was defined in case of BMI ≥ 25 kg/m².

Patients with established T2D or those taking lipid-lowering therapy at the baseline visit were excluded from the present analysis.

After identifying the factors predicting incident T2D in our statin-treated subjects, we evaluated the impact of IFG, MixDys, overweight/obesity, and their combinations on the risk of new-onset T2D.

Statistical analysis

Continuous variables were tested for normality by the Kolmogorov–Smirnov test and logarithmic transformations were performed if necessary. Data are presented as mean \pm standard deviation (SD) and median [interquartile range (IQR)] for parametric and non-parametric data, respectively. The chi-square test and the independent sample *t*-test were performed for categorical and continuous data respectively, as appropriate. Univariate binary logistic regression analyses were performed to define which factors were associated with incident T2D. Multivariate logistic regression analyses were then conducted using variables that were statistically significant in the univariate analysis. Associations with incident T2D were expressed as odds ratios (OR) with accompanying 95% confidence intervals (95% CI). In the final multivariate analyses, *p*-values < 0.05 were considered significant. Finally, multivariate analysis of covariance (MANCOVA) was performed to compare the rates of incident T2D among 2 or more groups, after controlling for predefined factors. Our study had 81% power to detect an increase in diabetes risk corresponding to an odds ratio of 0.8 and assuming a 10% baseline T2D risk.

Analyses were performed with the Statistical Package for Social Sciences (SPSS) v21.0 software (SPSS IBM Corporation, Armonk, NY, USA).

Results

After excluding 166 patients diagnosed with T2D and 193 subjects taking lipid-lowering therapy at the baseline visit, a total of 882 individuals were included in the present study. At baseline, 31% had IFG, 52% had BMI ≥ 25 kg/m², 10% were diagnosed with MixDys, 57% with hypertension, and 9% with ASCVD. Ninety-four (11%) of the study participants developed T2D and 58 (7%) suffered from a new cardiovascular event during their follow-up (median 6 years; IQR: 4–10). Detailed study participants' characteristics are presented in Table 1. The individuals who developed T2D had higher levels of FPG, BMI, TG, BP, and lower HDL-C levels compared with the non-T2D group (Table 1). In addition, T2D patients had higher prevalence of metabolic syndrome, IFG, MixDys, and hypertension and they were more likely to have received high-intensity statins and TG-lowering therapy (i.e. fibrates and omega-3 fatty acids) (Table 1).

Univariate analysis showed that age, family history of diabetes, metabolic syndrome, IFG, increased TG levels, low HDL-C levels, MixDys, and overweight/obesity, along with treatment with high-intensity statins, antihypertensive drugs, or fibrates were statistically significantly associated with incident T2D in our study population (Table 2). In the multivariate regression analysis, participants' age, positive family history of diabetes, IFG, MixDys,

Table 1
Baseline study participants' characteristics.

	Patients without T2D	Patients developing T2D
N	788	94
Gender, male (%)	57	61 [*]
Age (years)	54 (46–62)	59 (54–64)
Family history of diabetes (%)	14	28 [*]
Atherosclerotic cardiovascular disease (%)	9	12
Metabolic syndrome (%)	34	77 [*]
Impaired fasting glucose (%)	26	75 [*]
Body mass index ≥ 25 kg/m ² (%)	50	76 [*]
Hypertension (%)	56	72 [*]
Triglycerides ≥ 200 mg/dL (%)	19	36 [*]
Low high-density lipoprotein cholesterol levels (%)	25	42 [*]
Mixed dyslipidemia (%)	8	24
Systolic blood pressure (mmHg)	140 (125–150)	150 (138–160)
Diastolic blood pressure (mmHg)	87 (80–95)	90 (80–100)
Body mass index (kg/m ²)	27.1 (24.6–29.7)	29.2 (27.3–32.2) [*]
Fasting plasma glucose (mg/dL)	93 (86–100)	108 (99–117)
Total cholesterol (mg/dL)	261 (232–297)	257 (214–293)
Triglycerides (mg/dL)	127 (92–181)	148 (102–233) [*]
High-density lipoprotein cholesterol (mg/dL)	53 (45–64)	48 (41–62) [*]
Low-density lipoprotein cholesterol (mg/dL)	176 (152–209)	175 (134–202)
Assigned treatment		
High-intensity statin (%)	29	42 [*]
Ezetimibe (%)	21	22
Fibrates (%)	4	11 [*]
Omega-3 fatty acids (%)	3	8 [*]
Colesevelam (%)	1	0
Antihypertensive drugs (%)	66	82 [*]

Values are expressed as median (interquartile range), unless percentages are shown.

Conversion factors for units: fasting plasma glucose in mg/dL to mmol/L, $\times 0.05551$; cholesterol, in mg/dL to mmol/L, $\times 0.02586$; triglycerides in mg/dL to mmol/L $\times 0.01129$.

T2D, type 2 diabetes mellitus.

^{*} $p < 0.05$, for the comparison with the patients not developing T2D.

Table 2
Univariate and multivariate analysis of factors associated with incident type 2 diabetes.

Variables	Univariate analysis	Multivariate analysis
Baseline parameters		
Age, per 1-year increase	1.04 (1.02–1.06), $p < 0.01$	1.05 (1.02–1.08), $p < 0.01$
Family history of diabetes	2.40 (1.42–4.06), $p = 0.01$	3.58 (1.86–6.91), $p < 0.01$
Hypertension	2.05 (1.28–3.30), $p < 0.05$	–
Metabolic syndrome	6.59 (3.96–10.97), $p < 0.01$	–
Impaired fasting glucose	8.35 (5.07–13.76), $p < 0.01$	6.56 (3.53–12.18), $p < 0.01$
Body mass index ≥ 25 kg/m ²	3.23 (1.86–5.62), $p < 0.01$	2.65 (1.39–5.05), $p < 0.01$
Triglycerides ≥ 200 mg/dL	2.39 (1.49–3.81), $p < 0.01$	–
Low high-density lipoprotein cholesterol levels	2.14 (1.36–3.36), $p = 0.01$	–
Mixed dyslipidemia	3.58 (2.08–6.17), $p < 0.01$	3.27 (1.50–7.15), $p < 0.01$
Assigned treatment		
High-intensity statin	1.94 (1.24–3.02), $p < 0.01$	3.51 (1.89–6.51), $p < 0.01$
Antihypertensive drugs	2.38 (1.54–3.68), $p < 0.01$	–
Fibrates	2.99 (1.41–6.33), $p < 0.01$	–

The results are expressed as odds ratios (95% confidence intervals).

overweight/obesity, and high-intensity statin therapy remained statistically significantly associated with increased risk of incident T2D (Table 2).

Within the IFG subjects' subgroup, MixDys consistently increased the risk of T2D (adjusted OR: 3.44; 95% CI: 1.31–9.04, $p < 0.05$, after adjusting for participants' age, positive family history of diabetes, overweight/obesity, and high-intensity statin therapy). As shown in Fig. 1A, the IFG patients with

MixDys exhibited the highest rate of incident T2D compared with non-IFG, non-MixDys participants (adjusted OR: 21.01; 95% CI: 7.64–57.78, $p < 0.01$). Moreover, in this group of patients, overweight/obesity consistently increased the risk of T2D despite the smaller sample size (adjusted OR: 2.54; 95% CI: 1.14–5.66, $p < 0.05$, after adjusting for participants' age, positive family history of diabetes, MixDys, and high-intensity statin therapy). As shown in Fig. 1B, the obese patients with IFG exhibited the

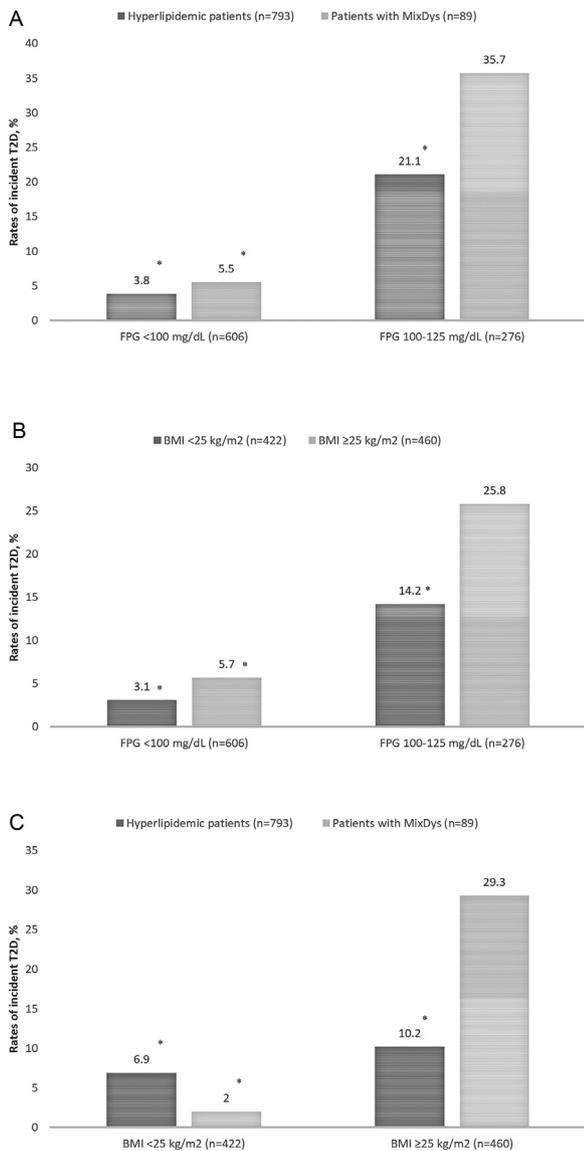


Fig. 1. (A) Risk of incident T2D according to baseline presence of impaired fasting glucose and mixed dyslipidemia. * $p < 0.05$, for the comparison with the subjects with impaired fasting glucose and mixed dyslipidemia. (B) Risk of incident T2D according to baseline presence of impaired fasting glucose and overweight/obesity. * $p < 0.05$, for the comparison with the subjects with impaired fasting glucose and overweight/obesity. (C) Risk of incident T2D according to baseline presence of overweight/obesity and mixed dyslipidemia. * $p < 0.05$, for the comparison with the subjects with overweight/obesity and mixed dyslipidemia. BMI, body mass index; FPG, fasting plasma glucose; MixDys, mixed dyslipidemia; T2D, type 2 diabetes mellitus.

highest rate of incident T2D compared with the non-IFG, non-overweight/obese participants (adjusted OR: 20.10; 95% CI: 6.72–60.15, $p < 0.05$).

Within the subgroup of participants being overweight or obese, MixDys consistently increased the risk of T2D (adjusted OR: 5.60; 95% CI: 2.19–14.30, $p < 0.01$, after adjusting for participants' age, positive family history of diabetes, IFG, and high-intensity statin therapy). As shown in Fig. 1C, the overweight/obese patients with MixDys exhibited the highest rate of incident T2D compared with the other groups (adjusted OR: 10.61; 95% CI: 3.92–28.70, $p < 0.01$, for the comparison with those having BMI $< 25 \text{ kg/m}^2$ and without MixDys).

Discussion

The present study shows that the normoglycemic non-overweight individuals without MixDys exhibited the lowest risk of new-onset T2D among statin-treated individuals. T2D event rates increased in patients with normal FPG and either MixDys or overweight/obesity and became highest for those with IFG and overweight/obesity or MixDys.

Waters et al. were the first to demonstrate that prediabetes, obesity, hypertension, and high levels of TG increased the risk of incident T2D in statin-treated patients [3]. After taking into account that this constellation of abnormalities is tightly related with IR [4], they proposed that IR candidates for statin treatment are prone to T2D development. Although the measurement of insulin levels has been used for the estimation of IR [5], the absence of a standardized insulin assay limits its clinical utility [6]. Prediabetes indicates IR and undoubtedly increases the risk of T2D development in statin-treated patients [8,12,15]. Nevertheless, prediabetes encompasses different entities not always related with IR [7]. For instance, patients with IFG might have similar IR to either normoglycemic individuals or patients with impaired glucose tolerance [7]. Thus, using only the cut-off FPG values of IFG to identify high T2D risk patients could under- or over-estimate the potential diabetogenic impact of statin therapy. Likewise, although overweight/obesity has been considered to be related with IR, a considerable proportion of overweight/obese individuals, the so called 'metabolically healthy obese' patients who have normal FPG and TG levels, exhibit lower rates of metabolic complications than expected, such as new-onset T2D and cardiovascular disease [9,16,17]. On the other hand, overwhelming evidence suggests the association of MixDys with IR [4,18]. Compensatory hyperinsulinemia due to IR has been considered to induce increased flux of free fatty acids, raise TG production, and decrease HDL-C [4,18,19], whereas recent evidence from epidemiological, genetic and intervention studies supports the 'hypertriglyceridemia-IR-hyperinsulinemia' vicious cycle suggesting that atherogenic dyslipidemia itself induces IR [11]. Studies evaluating the association between lipid parameters and IR or T2D risk have demonstrated that markers that take into account FPG, TG, and HDL-C levels for their calculation have a strong predictive value for T2D incidence in the general population [20–23]. For 469 statin-treated patients classified as being at high risk for T2D, Armato et al. showed that those with elevated TG levels displayed markers of IR and compensatory hyperinsulinemia, despite their similar baseline FPG and HbA1c levels to those with isolated hypercholesterolemia [22].

Our study evaluated whether IR, identified by the presence of IFG, MixDys, or overweight/obesity, predicts incident T2D in statin-treated individuals. Our results demonstrating that their combinations increase dramatically the diabetogenic impact of statin therapy are similar to the findings of a recent analysis of TNT and SPARCL trials ($n = 11,354$) [24]. The majority of our study participants who were normoglycemic, non-obese, and had normal TG and HDL-C levels ($\sim 30\%$) exhibited the lowest rates of T2D ($\sim 3\text{--}4\%$). On the other hand, the prediabetic patients with either MixDys ($\sim 5\%$) or obesity ($\sim 16\%$) exhibited the highest rates of incident diabetes after taking statin therapy (36% and 26%, respectively). When presented alone, IFG, MixDys, and obesity were associated with diabetic event rates intermediate between the high- and low-risk groups described above.

Our results provide a simplified tool for the physician to identify patients at high risk of developing T2D after taking statin treatment. In contrast to previously published randomized clinical trials, the rate of new-onset T2D was greater than incident ASVCD

in our study (11% vs. 6% during a median of 6 years) [3,25,26]. Thus, although several trials and meta-analyses have indicated that the cardiovascular and mortality benefits of statin therapy exceed the diabetes hazard [15,25–27], our study underlines the need to identify and minimize this risk in everyday clinical practice. Obtaining simple measurements, such as FPG, BMI, and TG, would help the physician to tailor different pharmacological and non-pharmacological treatment plans before or after initiating statins. Thus, a more frequent monitor of patients' glycemic status would be reasonable for obese patients with IFG and MixDys. Considering the fact that weight gain is associated with increased risk of new-onset T2D according to the results of the TNT trial [28], obese patients with IFG should be encouraged to lose weight with dietary intervention and increased physical activity in order to minimize the risk of statin-induced T2D. In the therapeutic plan, we might consider statins with a more neutral effect on glucose homeostasis or the combinations of a statin therapy, especially in patients at low cardiovascular risk [11].

Study limitations are the retrospective design of our study. The lack of potential confounding factors, such as dietary composition, physical activity, and duration of statin therapy, could have influenced our results. Nevertheless, we managed an extensive follow-up of 6 years conducted in a real-world outpatient lipid clinic setting. As such, this study represents a “pragmatic study” from everyday clinical practice and not a selected sample of patients with a close monitoring like those in a randomized control trial. In contrast to TNT, IDEAL, and SPARCL trials [3,24], our study participants were all statin-treated and followed-up for a longer period, whereas the rate of incident T2D was greater in our study. We showed that both increased TG and low HDL-C (and not only TG as shown by TNT, IDEAL, and SPARCL) were associated with increased risk of statin-induced T2D and highlighted the prognostic value of MixDys for statin-associated T2D.

Conclusion

The present retrospective study with a large number of participants shows that atherogenic dyslipidemia increases the risk of new-onset T2D in statin-treated patients, while IFG and overweight/obesity remain risk factors for incident T2D in this group. These results could help physicians tailor therapeutic strategies minimizing diabetes risk before initiating statin treatment.

Funding sources

The authors have received no payment/grants in preparation of this manuscript.

Conflict of interests

The authors declare conflicts of interest outside the submitted work. Dr F. Barkas reports personal fees from Amgen, Boehringer Ingelheim, Pfizer, and Sanofi; Dr E. Liberopoulos reports personal fees from AstraZeneca, Amgen, MSD, and Sanofi; Dr G. Liamis reports personal fees from Angelini, Bayer, Menarini, and Sanofi. Prof. M. Elisaf reports personal fees from Astra Zeneca, grants and personal fees from MSD, personal fees from Pfizer, personal fees and non-financial support from Abbott, personal fees and non-financial support from Sanofi, non-financial support from Boehringer Ingelheim, personal fees and non-financial support from Eli Lilly, non-financial support and other from GSL, outside the

submitted work. Dr E. Ntzani reports no conflicts of interest and Dr E. Rizos reports personal fees from Pfizer, Boehringer Ingelheim, Novartis, MSD, and Novo Nordisk.

References

- [1] Swerdlow DI, Preiss D, Kuchenbaecker KB, Holmes MV, Engmann JE, Shah T, et al. HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. *Lancet* 2015;385:351–61.
- [2] Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* 2011;305:2556–64.
- [3] Waters DD, Ho JE, DeMicco DA, Breazna A, Arsenault BJ, Wun CC, et al. Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials. *J Am Coll Cardiol* 2011;57:1535–45.
- [4] Reaven GM. Banting lecture 1988 Role of insulin resistance in human disease. *Diabetes* 1988;37:1595–607.
- [5] Yeni-Komshian H, Carantoni M, Abbasi F, Reaven GM. Relationship between several surrogate estimates of insulin resistance and quantification of insulin-mediated glucose disposal in 490 healthy nondiabetic volunteers. *Diabetes Care* 2000;23:171–5.
- [6] Reaven G. Wanted!: a standardized measurement of plasma insulin concentration. *Arterioscler Thromb Vasc Biol* 2011;31:954–5.
- [7] Novoa EJ, Boronat M, Saavedra P, Diaz-Cremades JM, Varillas VF, La Roche F, et al. Differences in cardiovascular risk factors, insulin resistance, and insulin secretion in individuals with normal glucose tolerance and in subjects with impaired glucose regulation: the Telde Study. *Diabetes Care* 2005;28:2388–93.
- [8] Kohli P, Waters DD, Nemr R, Arsenault BJ, Messig M, DeMicco DA, et al. Risk of new-onset diabetes and cardiovascular risk reduction from high-dose statin therapy in pre-diabetics and non-pre-diabetics: an analysis from TNT and IDEAL. *J Am Coll Cardiol* 2015;65:402–4.
- [9] Stefan N, Haring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. *Lancet Diabetes Endocrinol* 2013;1:152–62.
- [10] Taskinen MR, Boren J. New insights into the pathophysiology of dyslipidemia in type 2 diabetes. *Atherosclerosis* 2015;239:483–95.
- [11] Li N, Fu J, Koonen DP, Kuivenhoven JA, Snieder H, Hofker MH. Are hypertriglyceridemia and low HDL causal factors in the development of insulin resistance? *Atherosclerosis* 2014;233:130–8.
- [12] Barkas F, Elisaf M, Liberopoulos E, Klouras E, Liamis G, Rizos EC. Statin therapy with or without ezetimibe and the progression to diabetes. *J Clin Lipidol* 2016;10:306–13.
- [13] American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes – 2018. *Diabetes Care* 2018;41: S13–27.
- [14] Barkas F, Elisaf M, Liberopoulos E, Lontos A, Rizos EC. High triglyceride levels alter the correlation of apolipoprotein B with low- and non-high-density lipoprotein cholesterol mostly in individuals with diabetes or metabolic syndrome. *Atherosclerosis* 2016;247:58–63.
- [15] Waters DD, Ho JE, Boekholdt SM, DeMicco DA, Kastelein JJ, Messig M, et al. Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: effect of baseline risk factors for diabetes. *J Am Coll Cardiol* 2013;61:148–52.
- [16] Bell JA, Kivimaki M, Hamer M. Metabolically healthy obesity and risk of incident type 2 diabetes: a meta-analysis of prospective cohort studies. *Obes Rev* 2014;15:504–15.
- [17] Caleyachetty R, Thomas GN, Toulis KA, Mohammed N, Gokhale KM, Balachandran K, et al. Metabolically healthy obese and incident cardiovascular disease events among 3.5 million men and women. *J Am Coll Cardiol* 2017;70:1429–37.
- [18] Reaven G. Insulin resistance and coronary heart disease in nondiabetic individuals. *Arterioscler Thromb Vasc Biol* 2012;32:1754–9.
- [19] Reaven GM, Lerner RL, Stern MP, Farquhar JW. Role of insulin in endogenous hypertriglyceridemia. *J Clin Invest* 1967;46:1756–67.
- [20] Zhu XW, Deng FY, Lei SF. Meta-analysis of atherogenic index of plasma and other lipid parameters in relation to risk of type 2 diabetes mellitus. *Prim Care Diabetes* 2015;9:60–7.
- [21] Guerrero-Romero F, Villalobos-Molina R, Jimenez-Flores JR, Simental-Mendia LE, Mendez-Cruz R, Murguía-Romero M, et al. Fasting triglycerides and glucose index as a diagnostic test for insulin resistance in young adults. *Arch Med Res* 2016;47:382–7.
- [22] Armato J, Ruby R, Reaven G. Plasma triglyceride determination can identify increased risk of statin-induced type 2 diabetes: a hypothesis. *Atherosclerosis* 2015;239:401–4.
- [23] Abbasi F, Reaven GM. Statin-induced diabetes: how important is insulin resistance? *J Intern Med* 2015;277:498–500.
- [24] Kohli P, Knowles JW, Sarraju A, Waters DD, Reaven G. Metabolic markers to predict incident diabetes mellitus in statin-treated patients (from the Treating

- to New Targets and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels Trials). *Am J Cardiol* 2016;118:1275–81.
- [25] Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet* 2012;380:565–71.
- [26] Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010;375:735–42.
- [27] Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2016;316:2008–24.
- [28] Ong KL, Waters DD, Messig M, DeMicco DA, Rye KA, Barter PJ. Effect of change in body weight on incident diabetes mellitus in patients with stable coronary artery disease treated with atorvastatin (from the treating to new targets study). *Am J Cardiol* 2014;113:1593–8.