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Disclosure of interest

The authors declare that they have no competing interest.

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Can the ESC/EAS LDL-cholesterol target in patients with diabetes and high cardiovascular risk be achieved in clinical practice? Results from an ambulatory multidisciplinary diabetes center cohort

Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
BMI	body mass index
CAD	coronary artery disease
CD	cerebrovascular disease
CUDC	Centre universitaire du diabète et de ses complications
CVD	cardiovascular disease
DN	diabetic nephropathy
ESC	European Society of Cardiology
EAS	European Atherosclerosis Society
GFR	glomerular filtration rate
HDL-c	high-density lipoprotein cholesterol
IQR	interquartile range
LDL-c	low-density lipoprotein cholesterol
LLT	lipid-lowering treatment
PAD	peripheral arterial disease
PCSK9	proprotein convertase subtilisin/kexin type 9
TC	total cholesterol
TG	triglycerides

Dyslipidaemia is a major risk factor of cardiovascular disease (CVD), and lowering low-density lipoprotein cholesterol (LDL-c) can prevent cardiovascular (CV) morbidity and mortality in patients with diabetes in both primary and secondary prevention [1]. According to the 2005 French guidelines, LDL-c should be < 2.58 mmol/L in patients at very high CV risk, whereas the 2011 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines for management of dyslipidaemia recommended an LDL-c level target of < 1.8 mmol/L in patients with established CVD or nephropathy at its early stage of microalbuminuria [2]. However, several studies have shown that this goal is not reached in a large proportion of outpatients (around 70%) in a number of European countries [3–5]. For this reason, in 2013, an outpatients university multidisciplinary centre dedicated to diabetes care – the centre universitaire du diabete et de ses complications (CUDC) – was set up at Lariboisière hospital in Paris, France, to allow global outpatient care of diabetes and its complications at the same site where diabetological, cardiological, nephrological and ophthalmological evaluations are also performed. Each patient's record is computerized in a structured manner and available to all these different specialists.

In the present study, the aim was to investigate whether ESC/EAS LDL-c targets can be implemented in clinical practice in patients attending such a center, with a focus on very high-risk CV patients – in other words, patients with diabetes in secondary or primary prevention and with diabetic nephropathy (DN). This retrospective observational study included patients with diabetes attending the CUDC between September 2014 and August 2015. Patients were included if they had attended the CUDC at least twice and had at least one fasting lipid profile available in their electronic medical records. Exclusion criteria included those

with non-available LDL-c data because of hypertriglyceridaemia (> 4.51 mmol/L) or other missing data.

The 2011 ESC/EAS guidelines recommended that patients with diabetes and CVD or DN should have LDL-c levels < 1.8 mmol/L. Thus, the primary endpoint of our present study was the proportion of patients meeting this LDL-c target. Secondary endpoints were use of lipid-lowering treatment (LLT), particularly the proportion of patients treated with statins (daily dose and/or intensity), and the use of other lipid-modifying therapies. Statins were classified as "high", "moderate" or "low" in intensity according to American College of Cardiology (ACC)/American Heart Association (AHA) guidelines [6]. For patients not receiving LLT, each of their records was investigated for the reasons, if any, for this lack of prescription.

Each patient's most recent electronic medical records were painstakingly assessed and the following clinical variables recorded: demographic data (age, gender); diabetes history (type of diabetes, diabetes duration, HbA1c, insulin treatment); anthropometric data (height, weight, body mass index [BMI], waist circumference); lipid profile (total cholesterol [TC], LDL-c, high-density lipoprotein cholesterol [HDL-c], triglycerides [TG]); and LLT use. The reasons for LLT non-prescription were collected from clinical observations (statin intolerance, goal considered as met, age, renal or hepatic dysfunction, non-compliance). Also collected were CV data: hypertension; blood pressure; smoking history; first-degree family history of premature CVD; history of CVD [coronary artery disease (CAD), cerebrovascular disease (CD), peripheral arterial disease (PAD)]; and nephrological information (microalbuminuria, proteinuria, creatininaemia, glomerular filtration rate [GFR)]).

CAD was defined as previous myocardial infarction, coronary revascularization, or documented coronary stenosis or myocardial ischaemia on invasive or non-invasive testing. CD was defined as ischaemic stroke, carotid plaque on ultrasound or carotid revascularization, and PAD was defined as revascularization or documented arterial stenosis > 50%. Patients with DN were identified by the presence of micro- or macroalbuminuria (> 300 mg/L) or GFR < 60 mL/min/1.73 m^2.

Categorical variables are presented as absolute numbers and percentages, and continuous variables as medians and interquartile range (IQR; 25th–75th percentiles) as appropriate. In addition, for each variable and because of various missing data, the absolute numbers of patients whose data were used are also given (Table 1). Group comparisons for variables with two or more than two categories were performed using Student's *t* or Kruskal–Wallis tests, respectively, and Kendall's correlation test was used to

Table 1
Demographic and clinical characteristics of the entire study population, and in those with cardiovascular disease (CVD) and diabetic nephropathy (DN).

Variables	Study population (*n* = 3670)	CVD patients (*n* = 472)	DN patients (*n* = 792)
Age in years, median (IQR)	60 (18–89)	66 (35–88)	62 (20–88)
Males, *n* (%)	2110/3670 (57.5)	349 (73.9)	479 (60.5)
Diabetes mellitus:			
Type 1, *n* (%)	672/3612 (18.6)	37/468 (7.9)	69/785 (8.8)
Type 2, *n* (%)	2724/3612 (75.4)	412/468 (88.0)	653/785 (83.2)
Other, *n* (%)	216/3612 (6.0)	19/468 (4.1)	63/785 (8.0)
Diabetes duration in years, median (IQR)	13 (0–60) (*n* = 3592)	15 (0–52) (*n* = 466)	14 (0–53) (*n* = 776)
Haemoglobin A1c in mg/dL, %	7.4 (4.6–14) (*n* = 3615)	7.6 (5.4–11.5) (*n* = 462)	7.5 (5–13.4) (*n* = 785)
Haemoglobin A1c in mmol/mol, %	57.4 (26.8–129.5) (*n* = 3615)	59.6 (35.5–102.2) (*n* = 462)	58.5 (31.1–123) (*n* = 785)
Insulin regimen, *n* (%)	1408/3263 (43.2)	197/404 (48.8)	289/686 (42.1)
First-degree family history of premature CVD, *n* (%)	353/1770 (19.9)	61/231 (26.4)	63/371 (17.0)
Body mass index, in kg/m^2, median (IQR)	27.5 (16.4–52.0) (*n* = 3562)	27.9 (18.2–45.0) (*n* = 467)	28.7 (17.5–47.5) (*n* = 761)
Waist circumference, in cm, median (IQR)	99 (57–160) (*n* = 1299)	103 (72–137) (*n* = 178)	102 (63–148) (*n* = 271)
Obesity as per body mass index ≥ 30 kg/m^2, *n* (%)	1186/3562 (33.3)	168/467 (36.0)	31/761 (40.9)
Treated hypertension, *n* (%)	1868/2541 (73.5)	378/400 (94.5)	515/608 (84.7)
Current smoker, *n* (%)	516/3176 (16.2)	71/446 (15.9)	96/667 (14.4)
Systolic blood pressure, in mmHg, median (IQR)	128 (81–196) (*n* = 3484)	130 (98–180) (*n* = 448)	131 (92–189) (*n* = 753)
Diastolic blood pressure in mmHg, median (IQR)	72 (36–111) (*n* = 3480)	68 (40–96) (*n* = 447)	72 (43–107) (*n* = 753)
CVD in secondary prevention, *n* (%)	472/2395 (19.7)	472/472 (100)	0/792 (0)
CAD, *n* (%)	341/2774 (12.3)	341/451 (75.6)	
CD, *n* (%)	89/2718 (3.3)	89/421 (21.1)	
PAD, *n* (%)	113/2506 (4.5)	113/388 (29.1)	
DN, *n* (%)	997/2769 (36.0)	205/378 (54.2)	792/792 (100)
DN without CVD, *n* (%)	792/2769 (28.6)	0/472 (0)	792/792 (100)
Microalbuminuria, *n* (%)	568/2793 (20.3)	108/365 (29.6)	460/695 (66.2)
Proteinuria, *n* (%)	257/2916 (8.8)	58/382 (15.2)	199/737 (27.0)
GFR< 60 mL/min, *n* (%)	397/2851 (13.9)	94/376 (25.0)	303/685 (44.2)
Creatininaemia, in µmol/L, median (IQR)	76 (36–727) (*n* = 2850)	85 (76–318) (*n* = 376)	92 (42–681) (*n* = 684)
GFR by MDRD formula in mL/min/1.73 m^2, median (IQR)	97.7 (7.2–240) (*n* = 2849)	82.5 (17.6–173) (*n* = 376)	76.7 (7.5–207.3) (*n* = 684)
Microalbuminuria, in mg/L, median (IQR)	9 (1–3320) (*n* = 2793)	16 (2–1692) (*n* = 365)	61 (2–2964) (*n* = 695)
Macroalbuminuria, in g/L, median (IQR)	0.08 (0–3.89) (*n* = 1522)	0.11 (0–2.59) (*n* = 215)	0.2 (0.07–3.89) (*n* = 387)
Lipid-lowering treatment, *n* (%)	1512 (65.7)	426 (90.25)	503 (63.5)

For each variable of interest, absolute numbers (*n*) with non-missing data are given in parentheses; IQR: interquartile range; CAD: coronary artery disease; CD: cerebrovascular disease; PAD: peripheral arterial disease; GFR: glomerular filtration rate; MDRD: modification of diet in renal disease.

compare continuous variables in ordinal, ordered groups (for example, statin treatment intensity). All statistical comparisons were two-tailed, and $P < 0.05$ was considered statistically significant. All analyses were performed using Stata (version SE 12.0p) software (StataCorp, College Station, TX, USA).

Of the 5758 patients with diabetes mellitus seen at our CUDC over 1 year (2014–2015), 1984 patients (34.4%) were excluded because of missing data and 104 patients (1.8%) due to hypertriglyceridaemia. Ultimately, our cohort included 3670 patients, and their demographic characteristics and comorbidities are summarized in Table 1.

Lipid median (IQR) concentrations for the entire cohort ($n = 3670$), and CVD ($n = 472$) and DN ($n = 792$) patients, were respectively distributed as follows: TC, 4.44 mmol/L (2.17–7.84), 3.82 mmol/L (2.32–6.99) and 4.33 mmol/L (2.32–7.72); HDL-c, 1.21 mmol/L (0.49–3.53), 1.06 mmol/L (0.54–2.19) and 1.14 mmol/L (0.62–2.61); LDL-c, 2.5 mmol/L (0.57–5.73), 2.04 mmol/L (0.8–4.9) and 2.48 mmol/L (0.65–5.39); and TG, 1.17 mmol/L (0.17–4.25), 1.32 mmol/L (0.48–4.06) and 1.39 mmol/L (0.38–3.94).

Of the 472 patients with CVD, only 168 (35.6%) achieved the ESC/EAS LDL-c target (< 1.8 mmol/L): 124/331 (36.4%) patients with CAD; 55/149 (36.9%) patients with CD; and 29/113 (25.7%) patients with PAD. Of the 792 patients in primary prevention with DN, only 144 (18.1%) achieved the LDL-c target: 35/199 (17.6%) patients with proteinuria; 71/460 (15.4%) patients with microalbuminuria; and 43/303 (14.2%) patients with chronic renal insufficiency.

In our cohort overall, 1512 patients (65.7%), including 426/472 (90.25%) patients with CVD and 503/792 (63.5%) patients with DN, were using LLTs consisting of statins in 410/472 (86.9%) and 456/792 (51.3%) patients, respectively. The most frequently used statin was atorvastatin [208/410 (50.7%) cases with CVD and 233/456 (51.1%) cases with DN], followed by rosuvastatin [in 125/410 (30.5%) and 113/456 (24.8%), respectively], simvastatin [in 52/410 (12.7%) and 68/456 (14.9%), respectively], pravastatin [in 23/410 (5.6%) and 30/456 (6.6%), respectively] and fluvastatin [in 2/410 (0.5%) and 12/456 (2.6%), respectively].

The intensity of statin treatment was distributed in patients with CVD as follows: 149 (36.4%) with high-intensity statin; 249 (60.7%) with moderate-intensity statin; and 12 (2.9%) with low-intensity statin; the corresponding median LDL-c levels were 1.81 mmol/L (0.9–4.28), 1.96 mmol/L (0.9–4.28) and 2.35 mmol/L (2.19–2.61), respectively (Kendall's correlation: $P = 0.011$). For patients with DN, statin treatment intensity was as follows: 68 (14.9%) with high intensity; 365 (79.9%) with moderate intensity; and 24 (5.2%) with low intensity; the corresponding median LDL-c levels were 2.19 mmol/L (1.03–4.33), 2.09 mmol/L (0.77–4.49) and 2.53 mmol/L (1.99–3.15), respectively (Kendall's correlation: $P = 0.35$).

Statin in combination with ezetimibe was used by 34/472 (4.3%) patients with CVD and by 26/792 (3.3%) patients with DN. Median LDL-c levels with combined treatment vs. monotherapy were 1.81 mmol/L (1.11–2.71) vs. 1.94 mmol/L (1.11–2.71) in patients with CVD ($P = 0.38$), and 1.92 mmol/L (0.77–4.59) vs. 2.17 mmol/L (0.77–4.59) in patients with DN ($P = 0.13$).

No LLT use was observed in 46/472 (9.7%) patients with CVD and in 289/792 (36.5%) patients with DN. In these CVD and DN patients, LDL-c concentrations were 2.94 mmol/L (1.68–4.67) and 2.89 mmol/L (1.29–5.39), respectively. In patients not using LLTs, the LDL-c target (< 1.8 mmol/L) was achieved in 30/335 (8.9%), and the main reason for no LLT [in 132/335 (39.4%) patients], as stated by their physicians, was because of goals already met. However, statin intolerance was clearly stated in seven cases (2.1%), and poor treatment adherence in two further cases (0.6%). Pathologies such as hepatic dysfunction and renal grafts accounted for 4.7% ($n = 16$) of cases, and ageing for 6.7% ($n = 23$). Finally, unknown causes accounted for 16.1% ($n = 55$).

Our analysis has revealed that most of our very high-risk CV patients with diabetes fail to meet the recommended LDL-c goals of the 2011 European guidelines, despite looking at a period beginning > 3 years after their publication and the use of multidisciplinary care. Similar inadequate results for the management of dyslipidaemia have also been reported. In the Portuguese Dyslipidaemia International Study (DYSIS) population, > 77% of statin-treated patients failed to achieve these same goals [3]. In a retrospective UK cohort [7], only 35–42% of patients with diabetes and CVD events reached the recommended LDL-c target.

The 2005 French guidelines [8] recommended a less stringent LDL-c target (< 2.58 mmol/L), which was achieved by the majority of our very high-risk CV patients with diabetes: 73.1% of CVD patients and 55.2% of patients with DN. In addition, although most of our patients in secondary prevention failed to meet the ESC/EAS guidelines, better results were achieved than in previous studies in France. Indeed, the median LDL-c concentration was higher, and proportion of patients using LLT lower, in the 2007 nationwide ENTRED study [12] compared with our present cohort: 2.73 mmol/L vs. 2.45 mmol/L and 59% vs. 65.7%, respectively. The proportion of diabetes patients treated with LLT was lower at 57.1% in the *Système national d'information inter-régime de l'assurance maladie* (SNIIRAM; the French national healthcare system claims database) registry in 2011 [9]. The ESC/EAS updated the guidelines in 2016 with a more advanced renal dysfunction stage to define patients at high CV risk in cases of DN (GFR < 30 mL/min/1.73 m^2 and/or macroproteinuria). Given these updated criteria, the number of DN patients achieving the LDL-c target in our cohort was roughly similar: 44/213 (20.7%).

Thus, the ESC/EAS LDL-c target is difficult to achieve routinely even by an aware and focused university centre, and mainly due to the lack of statin therapy prescriptions in patients with DN. In contrast, most patients with CVD are given statins. The main explanation for these observations could be an insufficient dosage or intensity of statin therapy and/or underuse of the statin–ezetimibe combination, which may be related not only to a lack of physician awareness, but also to treatment intolerability. In addition, patient compliance problems cannot be excluded, considering the controversial benefits of statins and of decreasing LDL-c [10,11], which have been widely disseminated by the press to the general population in France [12]. However, the recent French consensus statement on the management of dyslipidaemia in adults [13] confirms the ESC/EAS LDL-c targets in patients with diabetes and high CV risk, and should help to get physicians and patients on the same page. Nevertheless, some patients, especially those with diabetes in secondary prevention, will still fail to achieve LDL-c targets even with LLT. In such cases, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may be the solution for such patients in secondary prevention, especially after considering the cost-effectiveness of this new class of drug [14].

In conclusion, our present study data suggest that the 2011 ESC/EAS guidelines are difficult to implement in real-life clinical practice, thereby raising the question of the achievability of such an LDL-c target with the currently available LLTs. Our data also highlight the necessity of disseminating these guidelines and particularly the need to start LLT in primary prevention in patients with DN, most of whom are currently not receiving such treatment.

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Subcutaneous advanced glycation end-products and lung function according to glucose abnormalities: The ILERVAS Project

The lung is not usually included in the list of organs that might be affected by type 2 diabetes (T2D). However, its abundance of collagen and elastin fibers, crucial proteins in the extracellular matrix, together with its vascularization reach, make the lung parenchyma a potential target for chronic hyperglycaemia [1]. Indeed, cross-sectional studies conducted during the past few decades have shown that adults with T2D have lower forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1) than adults without T2D [2]. A few pathophysiological mechanisms have also been well documented, including insulin and leptin resistance, low-grade chronic inflammatory status, microvascular lung damage and autonomic neuropathy [1].

However, little is known of the potential relationship between advanced glycation end-products (AGEs) and lung function, and what scarce information there is has been focused on patients with chronic obstructive pulmonary disease (COPD), in which higher skin AGE deposition and plasma AGE concentrations have been reported [3]. Yet, the relationship between AGEs and pulmonary function, taking into account the presence of glucose abnormalities, has not been previously examined. For this reason, skin AGE accumulation and spirometric maneuvers were assessed in a large population with no known pulmonary disease according to the presence of glucose abnormalities.

Both our control and prediabetes populations were recruited from a total of 1924 Caucasian subjects enrolled between July 2015 and May 2017 into the ILERVAS project (ClinTrials.gov Identifier: NCT03228459). This ongoing randomized interventional study is concerned with early diagnosis of subclinical vascular and "hidden" kidney diseases [4]. Inclusion criteria were: age between 45–70 years; no history of cardiovascular disease or T2D; and at least one cardiovascular risk factor (obesity, hypertension, dyslipidaemia, smoking or first-degree relative with premature cardiovascular disease). Exclusion criteria were: COPD; T2D; chronic kidney disease; active neoplasia; life expectancy < 18 months; pregnancy; and darker skin color (Fitzpatrick scale types > 5).

Smokers who had stopped smoking ≥ 1 year prior to recruitment were considered former smokers. Prediabetes was diagnosed in 34.6% ($n = 660$) of subjects according to American Diabetes Association criteria [glycosylated haemoglobin (HbA_{1c}): 39–47 mmol/mol or 5.7–6.4%]. Also, 79 age-matched T2D patients were recruited from the outpatients diabetic clinic of University Hospital Arnau de Vilanova in July 2017. Informed consent was obtained from all participants, and the protocol was approved by the Arnau de Vilanova University Hospital ethics committee.

Anthropometric data were obtained by standardized protocols. Glycosylated haemoglobin was determined using the cobas b 101®