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Lipid-lowering treatment and low-density lipoprotein cholesterol target achievement in patients with type 2 diabetes and acute coronary syndrome

Abbreviated title: Lipid-lowering treatment in patients with type 2 diabetes and ACS

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Summary

Background. – Patients with type 2 diabetes mellitus characteristically display an atherogenic lipid profile, with high triglyceride concentrations, low high-density lipoprotein cholesterol (HDL-C) concentrations and low-density lipoprotein cholesterol (LDL-C) concentrations not always elevated. It is unclear if patients with diabetes who present with an acute coronary syndrome (ACS) receive different or more-potent lipid-lowering therapy (LLT).

Aims. – To investigate lipid abnormalities in patients with and without type 2 diabetes hospitalized for an ACS, and use of LLT before admission and 4 months after the event.

Methods. – Patients were included in the observational DYSIS II study if they were hospitalized for an ACS and had a full lipid profile.

Results. – Of 3803 patients, diabetes was documented in 1344 (54.7%). Compared to patients without diabetes, those with diabetes had a lower mean LDL-C (101.2 vs 112.0 mg/dL; 2.6 vs 2.9 mmol/L; $P < 0.0001$), with a greater proportion attaining concentrations < 70 mg/dL (1.8 mmol/L) (23.9% vs 16.0%; $P < 0.0001$) and < 55 mg/dL (1.4 mmol/L) (11.3% vs 7.3%; $P < 0.0001$), a higher mean triglyceride concentration (139.0 vs 121.0 mg/dL; 1.6 vs 1.4 mmol/L; $P < 0.0001$) and a lower HDL-C concentration. LLT was more commonly given to patients with diabetes (77.5% vs 58.8%; $P < 0.0001$); there were no differences in types of therapy prescribed. Four months after hospitalization, most patients from both groups were being treated with LLT (predominantly statin monotherapy).

Conclusions. – Despite the different lipid profiles, the type of LLT prescribed did not vary depending on the presence or absence of type 2 diabetes. There was no difference in LLT in patients with and without diabetes at 4-month follow-up, except for fibrates, which were used in 2% of patients with and 1% of patients without diabetes. Statin monotherapy of intermediate potency was the predominant treatment in both groups.

Résumé

Contexte. – Les patients avec un diabète de type 2 sont à très haut risque d'événements cardiovasculaires. Ces patients présentent typiquement un profil lipidique athérogène avec des niveaux élevés de triglycérides, de bas niveaux de cholestérol des lipoprotéines de haute densité et un cholestérol des lipoprotéines de basse densité qui n'est pas toujours élevé. Il n'est pas clair si les

patients diabétiques se présentant avec un syndrome coronaire aigu reçoivent ou non des traitements hypolipidémiant différents ou plus puissants.

Objectifs. – Nous avons cherché à étudier les différences d'anomalies lipidiques chez les patients atteints et sans diabète de type 2 hospitalisés pour un syndrome coronarien aigu, et dans l'utilisation d'un traitement hypolipidémiant avant l'admission et 4 mois après l'événement de syndrome coronarien aigu.

Méthodes. – DYSIS II était une étude observationnelle et multinationale dans 17 pays. Les sujets étaient inclus s'ils étaient hospitalisés pour un syndrome coronarien aigu et avaient un profil lipidique complet disponible.

Résultats. – Sur les 3803 patients inclus, le diabète de type 2 a été documenté pour 1344 (54,7 %) patients. Les patients avec un diabète avaient des niveaux inférieurs de cholestérol des lipoprotéines de basse densité (101,2 vs 112,0 mg/L ; 2,6 vs 2,9 mmol/L ; $P < 0,0001$) – une proportion plus élevée atteignait un niveau < 70 mg/dL (1,8 mmol/L) (23,9 % vs 16,0 % ; $P < 0,0001$) et < 55 mg/dL (1,4 mmol/L) (11,3 % vs 7,3 % ; $P < 0,0001$) – le niveau moyen de triglycérides était plus élevé (139 vs 121 mg/dL ; 1,6 vs 1,4 mmol/L ; $P < 0,0001$) et les niveaux de cholestérol des lipoprotéines de haute densité étaient inférieurs à ceux sans diabète. Le traitement hypolipidémiant était plus fréquemment utilisé par les patients avec du diabète que par ceux sans (77,5 % vs 58,8 % ; $P < 0,0001$), mais il n'y avait pas aucune différence dans les thérapeutiques prescrites. Quatre mois après l'hospitalisation, la majorité des patients des deux groupes étaient traités par un traitement hypolipidémiant: une statine en monothérapie a été utilisée principalement.

Conclusions. – Malgré les différents profils lipidiques, le type de traitement hypolipidémiant prescrit ne varie pas en présence ou en l'absence d'un diabète de type 2. Il n'y avait pas de différence de traitement hypolipidémiant chez les patients diabétiques ou non au 4e mois du suivi à l'exception des fibrates qui étaient prescrits chez 2 % des patients diabétiques contre 1 % chez les patients non diabétiques. La monothérapie par statine d'intensité intermédiaire est la thérapeutique prédominante dans les deux groupes.

KEYWORDS

Low-density lipoprotein cholesterol;

Hyperlipidaemia;

Diabetes;

Statins;

Acute coronary syndrome

MOTS CLÉS

Cholestérol des lipoprotéines de basse densité ;

Hyperlipidémie ;

Diabète ;

Statines ;

Syndrome coronarien aigu

Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; DYSIS, Dyslipidemia International Study; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; NSTEMI, non-ST-segment elevation myocardial infarction; OR, odds ratio; STEMI, ST-segment elevation myocardial infarction.

Background

Type 2 diabetes mellitus is associated with an increased risk of cardiovascular events, including acute coronary syndrome (ACS) and stroke. This risk is amplified in the presence of dyslipidaemia, which is common in patients with diabetes [1]. With the prevalence of both of these conditions rising steadily, cardiovascular morbidity and mortality are likely to reach alarming levels.

Patients with diabetes display an atherogenic lipid profile that is distinct from that seen in patients without diabetes. This is characterized by high concentrations of triglyceride-rich lipoproteins and small, dense lipoprotein particles, in addition to low concentrations of high-density lipoprotein cholesterol (HDL-C), with low-density lipoprotein cholesterol (LDL-C) concentrations being elevated to a lesser extent [1-3]. However, reducing the LDL-C concentration remains the main focus of current guidelines [4-7]. Whereas the current European Society of Cardiology/European Atherosclerosis Society guidelines now recommend an LDL-C goal of < 55 mg/dL (1.4 mmol/L) for patients with an ACS, this goal was < 70 mg/dL (1.8 mmol/L) at the time of our study [5, 6, 8]. There is significant evidence that lowering LDL-C has beneficial effects for individuals with diabetes. Li et al. showed that LDL-C reduction was associated with a significantly reduced risk of adverse cardiovascular events in a cohort of patients with diabetes [9]. Similarly, the Cholesterol Treatment Trialists reported a 21% proportional reduction in major coronary events per mmol/L decrease in LDL-C in patients with diabetes [10].

Despite the benefits of LDL-C lowering, there remains a level of cardiovascular risk for patients with diabetes that is not addressed sufficiently by this alone. Additional consideration of alternative lipid abnormalities may therefore be valuable [11]. Studies have demonstrated reductions in triglyceride concentrations and increases in HDL-C concentrations on treatment with statins, which are the mainstay of lipid-lowering therapy (LLT) [12, 13]. Other drugs have beneficial effects on these particular lipids, including ezetimibe [14, 15], fibrates [16, 17], niacin [12, 16] and omega-3 fatty acids [18, 19], yet no clinical benefit of raising HDL-C has ever been elucidated – therefore, this is not a recommended treatment strategy.

In the Dyslipidemia International Study (DYSIS), statin-treated patients with diabetes were more likely to achieve the guideline-recommended LDL-C target of < 70 mg/dL (1.8 mmol/L) than those without diabetes [20]. We sought to put these historical data into recent context; we therefore investigated if these results could be repeated in DYSIS II_{ACS}, and aimed to determine if there were

differences in treatment, such as use of higher statin doses. In the present analysis of DYSIS II_{ACS} we focus on the differences in lipid abnormalities between patients with and without diabetes, and investigate the use of LLT before admission and 4 months after the ACS event.

Methods

Study design and patients (Fig. 1)

DYSIS II_{ACS} was a multinational, observational, longitudinal study evaluating the characteristics and treatment of patients admitted to a hospital with an ACS [21-23]. From November 2012 to November 2014, 3867 patients were enrolled at centres in 17 countries across the world (Belgium, France, Greece, India, Indonesia, Ireland, Italy, Jordan, Lebanon, Philippines, Russia, Saudi Arabia, Singapore, South Korea, Taiwan, United Arab Emirates and Vietnam). These centres were selected to best represent the acute and ambulatory treatment provided in each country.

Subjects were included in the present analysis if they were being hospitalized for an ACS, were at least 18 years of age and had a full lipid profile available. These were consecutive patients who were included by treating physicians without additional selection or discrimination.

ACS was defined as an ST-segment elevation myocardial infarction (STEMI)/left bundle branch block myocardial infarction, a non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina. We documented whether patients were being treated with LLT for at least 3 months before hospitalization. Data were collected on admission to hospital and 4 months (\pm 15 days) after admission.

The study received ethical approval from the relevant committees at each participating centre, and was carried out in accordance with the Declaration of Helsinki and its amendments.

Documentation

Data were recorded on a standardized case report form at admission and at discharge from the hospital, as well as after 120 ± 15 days during a telephone interview; they were subsequently entered into a central online database. Type 2 diabetes mellitus was defined as current treatment for diabetes, a previous diagnosis of type 2 diabetes or a fasting plasma glucose concentration ≥ 126 mg/dL. Hypertension was defined as current blood pressure-lowering treatment, a previous diagnosis of hypertension or having blood pressure $> 140/90$ mm Hg. A sedentary lifestyle was defined as $< 20-30$

minutes of walking on < 3–4 days per week. A blood test was carried out within 24 hours of admission to hospital, and a full lipid profile was documented.

Statistics

Patients were divided into groups depending on whether or not they had type 2 diabetes. Data are presented as means \pm standard deviations, medians (interquartile ranges) or percentages with absolute values. Statistical significance was determined using the χ^2 test or the Mann-Whitney-Wilcoxon test. Kaplan-Meier analysis was used to provide estimates of mortality and non-fatal events after ACS, with log-rank tests used to determine statistically significant differences between the groups of patients with versus without diabetes. All data analysis was carried out using SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patients

A total of 3803 patients were included in DYSIS II_{ACS} after being admitted to hospital for an ACS. The mean age of the population was 62.4 years and 76.3% were male (Table 1). Diabetes was documented in 1344 patients (54.7%), who were significantly older than those without diabetes (63.9 vs 61.5 years; $P < 0.0001$). Patients with diabetes had a higher mean body mass index than those without diabetes, and significantly more often were classified as obese (29.2% vs 19.5%; $P < 0.0001$). Comorbidities were more common in the group with diabetes than in the group without diabetes, including hypertension, chronic kidney disease, previous stroke and history of peripheral artery disease. A significantly higher proportion of patients with versus without diabetes were hospitalized as a result of an NSTEMI (38.4% vs 34.0%; $P < 0.01$).

LLT at hospital admission

A total of 65.4% of patients were treated with some kind of LLT before their admission (Table 2): 77.5% of the patients with diabetes and 58.8% of those without diabetes ($P < 0.0001$). The majority of patients who were receiving LLT had a statin as part of their treatment (97.8%), with no difference between the groups with and without diabetes ($P = 0.31$). The atorvastatin equivalent statin dosage was slightly higher for patients with diabetes (23 ± 16 vs 22 ± 18 mg/day; $P < 0.05$). Non-statin LLT

was used by 9.5% of the total population: 8.5% of the group with diabetes and 10.3% of the group without diabetes ($P = 0.15$). Ezetimibe was less commonly used by the patients with diabetes (3.6% vs 5.4%; $P < 0.05$), while there were no differences in terms of the other non-statin therapies prescribed.

Lipid profile at hospital admission

The mean LDL-C concentration at hospital admission was significantly lower for the patients with versus without diabetes (101.2 vs 112.0 mg/dL; 2.6 vs 2.9 mmol/L; $P < 0.0001$), and a higher proportion had a value < 70 mg/dL (1.8 mmol/L) (23.9% vs 16.0%; $P < 0.0001$) (Table 3). For patients who were not at target, the median distance to goal was 38.0 mg/dL (1.0 mmol/L) for the group with diabetes and 47.0 mg/dL (1.2 mmol/L) for the group without diabetes ($P < 0.0001$). Likewise, a higher proportion of patients with diabetes had reached a value < 55 mg/dL (1.4 mmol/L) (11.3% vs 7.3%; $P < 0.0001$), although both rates were at an extremely low level. Similarly, non-HDL-C was lower in patients with diabetes, and more patients with diabetes had reached the threshold of < 100 mg/dL (2.6 mmol/L) (28.4% vs 20.6%; $P < 0.0001$). The median total cholesterol was also lower for the group with diabetes. Triglyceride concentrations, on the other hand, were higher in patients with diabetes (median 139.0 vs 121.0 mg/dL; 1.6 vs 1.4 mmol/L; $P < 0.0001$). For both men and women, HDL-C concentrations were lower in patients with diabetes.

The patients were further divided into subgroups depending on whether or not they were treated with LLT before hospital admission. For patients with diabetes, the mean LDL-C concentration for the LLT group was found to be significantly lower than that for the no LLT group (94.2 vs 125.2 mg/dL; 2.4 vs 3.2 mmol/L; $P < 0.0001$) (Table 4). Non-HDL-C, total cholesterol and triglyceride concentrations were also lower in the LLT group. For patients without diabetes, those receiving LLT also had a significantly lower mean LDL-C concentration compared with their non-treated counterparts (99.7 vs 129.6 mg/dL; 2.6 vs 3.4 mmol/L; $P < 0.0001$). Total cholesterol concentrations followed the same trend as for patients with diabetes; however, triglyceride concentrations did not vary between the LLT and no LLT subgroups in the absence of diabetes (median 122.0 vs 119.0 mg/dL; 1.4 vs 1.3 mmol/L; $P = 0.35$). Furthermore, triglyceride concentrations appeared to be lower for patients without diabetes, for both the LLT and no LLT groups. Unlike for patients with diabetes, HDL-C concentrations varied slightly for those without diabetes, with lower values for those being treated compared with those not

being treated (men: 40.0 vs 41.0 mg/dL; 1.0 vs 1.1 mmol/L; $P < 0.05$; women: 47.0 vs 51.0 mg/dL; 1.2 vs 1.3 mg/dL; $P < 0.01$).

In the group of patients with diabetes, certain variables were predictive of achieving an LDL-C concentration < 70 mg/dL (1.8 mmol/L). The presence of hypertension (odds ratio [OR] 1.44, 95% confidence interval [CI] 1.04–2.00; $P < 0.05$) or chronic kidney disease (OR 1.62, 95% CI 1.12–2.35; $P < 0.01$) increased the likelihood of reaching this concentration. On the other hand, female patients (OR 0.70, 95% CI 0.53–0.94; $P < 0.05$) and those who were current smokers (OR 0.57, 95% CI 0.40–0.80; $P < 0.01$) were less likely to reach LDL-C < 70 mg/dL (1.8 mmol/L). Use of LLT before hospital admission (OR 4.19, 95% CI 2.74–6.41; $P < 0.0001$) was strongly associated with achieving LDL-C < 70 mg/dL (1.8 mmol/L), as was statin treatment in particular (OR 4.60, 95% CI 3.01–7.02; $P < 0.0001$). The use of non-statins did not affect the likelihood of reaching this value, even when combined with a statin.

LLT, lipid values and adverse events at 4-month follow-up

At 4-month follow-up, the majority of patients with and without diabetes were being treated with LLT (95.3% and 95.9%, respectively; $P = 0.45$) (Table 2). This difference from baseline was mainly attributable to the initiation of statin therapy, with few patients not receiving a statin as part of their treatment 4 months after admission for the index ACS. The atorvastatin equivalent statin dosages were higher for patients with versus without diabetes compared with at hospital admission (both $P < 0.0001$), and were similar between patients with and without diabetes (33 ± 20 vs 32 ± 22 mg/day; $P = 0.10$). In terms of non-statins, in contrast with hospital admission, there was no significant difference in the proportions of patients with versus without diabetes being treated with ezetimibe at 4-month follow-up. Fibrates, on the other hand, were used significantly more often in patients with diabetes (2.3% vs 1.2%; $P < 0.05$). The use of combination therapy appeared to increase slightly from baseline to 4 months, although, again, no difference was seen between those with and without diabetes.

The situation was improved at follow-up, where 41.4% and 34.4% of patients with or without diabetes, respectively, had an LDL-C value < 70 mg/dL (1.8 mmol/L), and 22.5% and 15.4%, respectively, had an LDL-C value < 55 mg/dL (1.4 mmol/L) (Table 3). Furthermore, more patients had normal total cholesterol, triglyceride and HDL-C concentrations, and more had a non-HDL-C concentration < 100 mg/dL (2.6 mmol/L).

Sixty patients (1.7%) died between hospital admission for the index event and the 4-month follow-up (Table 5). A slightly higher proportion of these deaths were in the group with versus without diabetes (2.4% vs 1.4%). Cardiovascular deaths were more common than non-cardiovascular deaths in both groups; however, it should be noted that there were more deaths from unknown causes in the group without diabetes. Furthermore, the groups were not compared statistically because of the high number of unknown causes of death. Kaplan-Meier estimates of 60- and 120-day mortality rates were higher for patients with versus without diabetes: 1.5% vs 0.7% ($P < 0.05$) and 2.1% vs 1.3% ($P = 0.05$), respectively. No differences were found in the Kaplan-Meier estimates of non-fatal events, including myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass graft and rehospitalization.

Discussion

The patients with type 2 diabetes included in DYSIS II_{ACS} had lipid profiles with lower concentrations of LDL-C and HDL-C, but higher triglyceride concentrations compared to patients without diabetes.

When we compared patients with and without diabetes, there were no significant differences in the drugs being prescribed. Four months after hospital admission for an ACS, the majority of patients who had not been treated for hyperlipidaemia before hospitalization were predominantly treated with statin monotherapy. There were no apparent differences in the treatment strategy after the ACS depending on the presence or absence of diabetes, indicating that the distinct lipid profile of the patients with diabetes was not taken into account by adding alternative treatment options, such as ezetimibe or omega-3 fatty acids.

The interplay between diabetes and other cardiovascular risk factors, including hyperlipidaemia and hypertension, is well established. It is therefore not surprising that significantly higher proportions of the group with diabetes displayed these characteristics. The risk of having an ACS is greatly increased in these multimorbid patients, and while many were treated with LLT, there remained over 20% who were not. International guidelines for patients with diabetes recommend statin therapy for those with established cardiovascular disease or any other risk factor, such as hypertension, hyperlipidaemia or chronic kidney disease, and for those aged > 40 years [24, 25]. However, almost a quarter of the group with diabetes in the present analysis was not being treated with a statin before their ACS, despite the high prevalence of cardiovascular risk factors and the mean age of 63.9 years.

The mean LDL-C concentration was found to be lower in patients with diabetes compared with those without the condition. This is likely, at least in part, because of the greater use of LLT by the patients with diabetes, with the LDL-C concentration for those not treated with LLT being significantly higher than for those who were treated. However, LDL-C values appeared slightly lower for the patients with diabetes on LLT compared with those without diabetes on LLT, indicating that the presence of diabetes had an effect on the concentration of this lipid. Such a phenomenon has been demonstrated in other studies [10, 26]. In the statin-treated global population included in DYSIS, patients with diabetes were more likely to have attained their LDL-C target [20], as defined by European guidelines [5, 6]. However, there were regional differences, with the Middle East and China reporting a lower likelihood of target achievement [27, 28], and Europe and Canada following the global trend [29, 30]. Independent of the presence of diabetes, attainment of an LDL-C concentration < 70 mg/dL (1.8 mmol/L) was extremely low in the present study. This is particularly worrying for patients with diabetes, who are classed as being at very high cardiovascular risk, even before an ACS [5, 6].

The increased likelihood of patients with diabetes achieving an LDL-C concentration of < 70 mg/dL (1.8 mmol/L) if they had hypertension or chronic kidney disease suggests that the additional comorbidity led to superior treatment. This may have been the result of more regular contact with a physician, improving medication adherence – a phenomenon that has been termed “white-coat adherence” [31, 32]. Alternatively, the higher risk at which these multimorbid patients were at may have encouraged physicians to prescribe more intensive treatment compared with a patient with diabetes alone; however, comorbidities have been previously associated with poor medication adherence [33]. The use of LLT, and statins specifically, increased the likelihood of the patients with diabetes reaching LDL-C concentrations < 55 mg/dL (1.4 mmol/L) and < 70 mg/dL (1.8 mmol/L), providing further evidence of the benefits of such therapy. While 23.9% of patients with diabetes and 16.0% of patients without diabetes reached an LDL-C < 70 mg/dL (1.8 mmol/L), rates of treatment target attainment roughly halved (11.3% and 7.3%, respectively) when the new treatment target of < 55 mg/dL (1.4 mmol/L) [8] was considered. These recommendations were made on the background of recent studies, such as IMPROVE-IT [14], but the clinical practice situation documented in DYSIS II challenges whether this even more stringent treatment target can be reached in a broader patient population.

The mean triglyceride concentration was much higher in patients with versus without diabetes, which is in agreement with other studies [10, 34]. This phenomenon has been attributed both to the visceral obesity often found in patients with diabetes, with the lipolytic activity of abdominal fat being greater than that of subcutaneous, and to reduced tissue response to insulin [1]. Insulin resistance is thought to disrupt hepatic lipid metabolism, resulting in overproduction of triglyceride-containing very-low-density lipoprotein particles [2]. Although the use of LLT appeared to reduce triglyceride concentrations in patients with diabetes, the difference between treated and non-treated patients was not substantial. Statins have previously been shown to reduce triglyceride concentrations [12, 34, 35]. Even so, it is clear that in these very-high-risk patients, further intervention is necessary. In the IMPROVE-IT randomized trial, the addition of ezetimibe to simvastatin therapy reduced the triglyceride concentration by 17.2 mg/dL over 1 year, while statin treatment alone gave a negligible decrease of 0.4 mg/dL [14]. A fibrate added to statin therapy has also been shown to reduce triglyceride concentrations to a greater extent than statin monotherapy [36, 37]. Omega-3 fatty acids have demonstrated beneficial effects [18, 19]. However, in the present study, only 8.5% of the group with diabetes and 10.2% of the group without diabetes were being treated with a non-statin.

Mean HDL-C concentrations were lower for both male and female patients with diabetes compared with their counterparts in the group without diabetes. Unlike for LDL-C, however, there was no effect of LLT on HDL-C concentrations for the patients with diabetes. Statins have previously shown only a modest ability to raise HDL-C concentrations [34, 35], while the additional use of a fibrate has resulted in slightly greater increases [36, 37]. Currently available evidence suggests that no clinical benefit is derived from raising HDL-C concentrations [38-41], and it is not advocated as a treatment strategy [5].

Guidelines recommend that all patients who have had an ACS should be prescribed intensive LLT within the first 4 days after the event [5]. Accordingly, the majority of patients in the present analysis were treated with a statin at 4-month follow-up; however, the rate of use of combination LLT was comparably low. There were no differences in the types of LLT that the two groups of patients were prescribed, indicating that the presence of diabetes did not affect treatment patterns to any extent.

At baseline (hospitalization for an ACS), there was a significant difference in type of ACS between patients with versus those without diabetes. We observed a significant inequality of recurrent

events in patients with or without diabetes. Patients without diabetes had a higher rate of STEMI and left bundle branch block myocardial infarction (41% vs 33%), whereas NSTEMI and angina pectoris were more pronounced in patients with diabetes (38% vs 34% and 29% vs 25%, respectively). This is in line with previous reports. The Euro Heart Survey reported diabetes in 27% of patients with NSTEMI and 22% of those with STEMI [42]. Likewise, in 63,450 patients in China, a higher proportion of patients with diabetes was found in patients with STEMI versus NSTEMI (39% vs 36%, respectively) [43].

While the 4-month follow-up period might have been too short to comprehensively appreciate the risk of patients with type 2 diabetes and ACS, the rate of recurrent myocardial infarction was numerically higher (1.2% vs 0.7%; $P = 0.14$). With regard to 120-day mortality, 1.6% of all patients died, and the proportion was greater among those with versus without diabetes (2.1% vs 1.3%; $P = 0.05$). Furthermore, both 60- and 120-day mortality estimates were higher for the patients with diabetes. The very distinct difference in type of myocardial infarction between patients with versus without diabetes might explain the longitudinal outcomes. This is in agreement with other studies, in which diabetes has been associated with higher mortality [44, 45]. Evidence of an association between diabetes and a higher risk of cardiovascular events after an ACS has previously been reported [46]. It is possible that the 4-month follow-up in the present analysis may have been too short to identify the full differences between the groups.

Overall, we knew from previous studies that LDL-C target concentration attainment is low, and we now know that the prevalence of diabetes – which puts the individual patients at much higher risk following an ACS – did not have any impact on LLT [20, 21, 47].

Study limitations

Although 17 countries were included in our analysis, the absence of certain areas of the world (e.g. Japan, Africa and the Americas) prevents us from gaining a more complete picture of hyperlipidaemia in patients with ACS on a global scale. However, the countries that were included were spread across a number of continents, containing wide-ranging differences in terms of ethnicities, lifestyles and healthcare systems. Apolipoprotein concentrations were not collected; therefore, we cannot firmly assess the relationships between hyperlipidaemia, LLT, glycaemia, and insulin resistance. Finally, the

relatively short follow-up time resulted in insufficient cardiovascular events occurring for analysis of the effects of lipid concentrations and LLT.

Conclusions

The patients with diabetes included in DYSIS II_{ACS} had a distinct lipid profile compared with that of patients without diabetes, with lower concentrations of LDL-C and HDL-C, but higher triglyceride concentrations. LDL-C is the primary target for therapy, although physicians rarely venture beyond the use of statins. The extremely high cardiovascular risk that these multimorbid patients display may indicate a need to consider additional treatment options.

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Figure legend

Figure 1. Flow chart indicating the number of patients at each stage of the study. ACS: acute coronary syndrome; EC: ethics committee; IRB: institutional review board; NSTEMI: non–ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina.

Table 1 Patient characteristics.

	Total (n = 3803)	Type 2 diabetes (+) (n = 1344)	Type 2 diabetes (-) (n = 2459)	P ^a
Age (years)	62.4 ± 12.1	63.9 ± 10.9	61.5 ± 12.7	< 0.0001
Male sex	2902/3803 (76.3)	955/1344 (71.1)	1947/2459 (79.2)	< 0.0001
BMI (kg/m ²)	26.8 ± 4.8	27.6 ± 5.0	26.4 ± 4.6	< 0.0001
Systolic blood pressure (mmHg)	135 ± 25	137 ± 26	134 ± 24	< 0.0001
Diastolic blood pressure (mmHg)	79 ± 14	79 ± 15	79 ± 14	0.56
HbA _{1c} (%)	6.8 ± 1.8	8.0 ± 1.9	5.9 ± 1.0	< 0.0001
Random glucose (mg/dL)	145.8 ± 167.7	200.1 ± 267.9	117.9 ± 58.9	< 0.0001
Cardiovascular risk factors				
Family history of CHD	914/3542 (25.8)	294/1241 (23.7)	620/2301 (26.9)	< 0.05
Obesity (BMI > 30 kg/m ²)	865/3779 (22.9)	389/1334 (29.2)	476/2445 (19.5)	< 0.0001
Current smoker	1034/3803 (27.2)	273/1344 (20.3)	761/2459 (30.9)	< 0.0001
Sedentary lifestyle	1533/3439 (44.6)	621/1250 (49.7)	912/2189 (41.7)	< 0.0001
Comorbidities (%)				
Hypertension	2498/3803 (65.7)	1064/1344 (79.2)	1434/2459 (58.3)	< 0.0001
Chronic kidney disease	260/3802 (6.8)	148/1344 (11.0)	112/2458 (4.6)	< 0.0001
Previous stroke ^b	196/3749 (5.2)	93/1321 (7.0)	103/2428 (4.2)	< 0.001

History of PAD	186/3771 (4.9)	96/1330 (7.2)	90/2441 (3.7)	< 0.0001
Type of ACS				
STEMI/LBBB MI	1461/3803 (38.4)	442/1344 (32.9)	1019/2459 (41.4)	< 0.0001
NSTEMI	1352/3803 (35.6)	516/1344 (38.4)	836/2459 (34.0)	< 0.01
UA	990/3803 (26.0)	386/1344 (28.7)	604/2459 (24.6)	< 0.01

Data are expressed as mean \pm standard deviation or number/number (%). ACS: acute coronary syndrome; BMI: body mass index; CHD: coronary heart disease; HbA1c: glycated haemoglobin; LBBB: left bundle branch block; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PAD: peripheral artery disease; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina.

^a *P* values calculated using the χ^2 test or the Mann-Whitney-Wilcoxon test.

^b Includes ischaemic and haemorrhagic stroke.

Table 2 Lipid-lowering therapy within 24 hours of admission to hospital and at follow-up.

	Within 24 hours of admission to hospital			At follow-up		
	Type 2 diabetes (+) (<i>n</i> = 1344)	Type 2 diabetes (-) (<i>n</i> = 2459)	<i>P</i> ^a	Type 2 diabetes (+) (<i>n</i> = 1189)	Type 2 diabetes (-) (<i>n</i> = 2146)	<i>P</i> ^a
Any LLT	1042/1344 (77.5)	1445/2459 (58.8)	< 0.0001	1133/1189 (95.3)	2057/2146 (95.9)	0.45
Statin	1023/1042 (98.2)	1410/1445 (97.6)	0.31	1127/1133 (99.5)	2048/2057 (99.6)	0.72
Statin dosage (mg/day) ^b	23 ± 16 (<i>n</i> = 971)	22 ± 18 (<i>n</i> = 1319)	< 0.05	33 ± 20 (<i>n</i> = 1115)	32 ± 22 (<i>n</i> = 2039)	0.10
Non-statin LLT	89/1041 (8.5)	148/1443 (10.3)	0.15	115/1120 (10.3)	183/2038 (9.0)	0.24
Ezetimibe	38/1041 (3.6)	78/1443 (5.4)	< 0.05	62/1120 (5.5)	109/2038 (5.3)	0.82
Fibrate	37/1041 (3.6)	36/1443 (2.5)	0.12	26/1120 (2.3)	24/2038 (1.2)	< 0.05
Niacin	0/1041 (0.0)	0/1443 (0.0)	-	3/1120 (0.3)	5/2038 (0.2)	0.90
Omega-3 fatty acid	10/1041 (1.0)	19/1443 (1.3)	0.41	29/1120 (2.6)	54/2038 (2.6)	0.92
Statin monotherapy	952/1041 (91.4)	1295/1443 (89.7)	0.15	1005/1120 (89.7)	1855/2038 (91.0)	0.24
Non-statin monotherapy	19/1041 (1.8)	35/1443 (2.4)	0.31	6/1120 (0.5)	9/2038 (0.4)	0.71
Statin plus non-statin	70/1041 (6.7)	113/1443 (7.8)	0.30	109/1120 (9.7)	174/2038 (8.5)	0.26

Data are expressed as number/number (%). LLT: lipid-lowering therapy.

^a *P* values calculated using the χ^2 test or the Mann-Whitney-Wilcoxon test.

^b Normalized to atorvastatin potency [48].

Table 3 Lipid profile within 24 hours of admission to hospital and at follow-up.

	Within 24 hours of admission to hospital			At follow-up		
	Type 2 diabetes (+) (<i>n</i> = 1344)	Type 2 diabetes (-) (<i>n</i> = 2459)	<i>P</i>	Type 2 diabetes (+) (<i>n</i> = 1253)	Type 2 diabetes (-) (<i>n</i> = 2247)	<i>P</i>
LDL-C (mg/dL; mmol/L)	101.2 ± 43.4;	112.0 ± 43.1;	< 0.0001	80.3 ± 34.3;	82.9 ± 27.7;	< 0.05
	2.6 ± 1.1	2.9 ± 1.1		2.1 ± 0.9	2.1 ± 0.7	
< 70 mg/dL (1.8 mmol/L) ^a	321/1344 (23.9)	394/2458 (16.0)	< 0.0001	147/355 (41.4)	243/707 (34.4)	< 0.05
Distance to < 70 mg/dL; < 1.8 mmol/L ^a	38.0 (16.0, 66.0);	47.0 (23.0, 76.0);	< 0.0001	23.0 (11.0, 44.0);	23.0 (10.0, 40.0);	0.46
	1.0 (0.4, 1.7)	1.2 (0.6, 2.0)		0.6 (0.3, 1.1)	0.6 (0.3, 1.0)	
< 55 mg/dL (1.4 mmol/L) ^b	152/1344 (11.3)	179/2459 (7.3)	< 0.0001	80/355 (22.5)	109/707 (15.4)	< 0.01
Distance to < 55 mg/dL; < 1.4 mmol/L ^b	46.0 (23.0, 75.0);	57.0 (31.0, 88.5);	< 0.0001	30.0 (15.0, 50.0);	30.0 (16.0, 49.0);	0.84
	1.2 (0.6, 1.9)	1.5 (0.8, 2.3)		0.8 (0.4, 1.3)	0.8 (0.4, 1.3)	
Total cholesterol (mg/dL; mmol/L)	173.8 ± 55.1;	183.7 ± 50.5;	< 0.0001	149.5 ± 42.5;	150.2 ± 33.2;	0.32
	4.5 ± 1.4	4.8 ± 1.3		3.9 ± 1.1	3.9 ± 0.9	
< normal ^c	1188/1323 (89.8)	2129/2433 (86.6)	< 0.01	354/363 (97.5)	712/718 (99.2)	< 0.05
Distance to normal (mg/dL; mmol/L)	28.0 (10.0, 65.0);	24.0 (8.0, 45.0);	< 0.05	46.2 ± 45.7;	18.0 ± 10.0;	0.35
	0.7 (0.3, 1.7)	0.6 (0.2, 1.2)		1.2 ± 1.2	0.5 ± 0.3	
Non-HDL-C (mg/dL; mmol/L)	125.0 (95.0, 164.0);	135.0 (105.0, 171.0);	< 0.0001	108.1 ± 41.0;	105.8 ± 31.7;	0.98

	3.2 (2.5, 4.2)	3.5 (2.7, 4.4)		2.8 ± 1.1	2.7 ± 0.8	
< 100 mg/dL ^a	381/1342 (28.4)	506/2455 (20.6)	< 0.0001	161/348 (46.3)	315/678 (46.5)	0.95
Distance to < 100 mg/dL; < 2.6 mmol/L	46.0 (21.0, 78.0);	48.0 (23.0, 81.0);	0.09	37.0 ± 33.1;	28.7 ± 23.2;	< 0.01
	1.2 (0.5, 2.0)	1.2 (2.6, 2.1)		1.0 ± 0.9	0.7 ± 0.6	
Triglycerides (mg/dL; mmol/L)	139.0 (102.0, 192.0);	121.0 (86.0, 171.0);	< 0.0001	147.5 ± 94.5;	130.6 ± 80.1;	< 0.01
	1.6 (1.2, 2.2)	1.4 (1.2, 1.9)		1.7 ± 1.1	1.5 ± 0.9	
≤ normal (200 mg/dL)	1040/1344 (77.4)	2050/2459 (83.4)	< 0.0001	1310/1344 (97.5)	2406/2459 (97.8)	0.46
Distance to normal (mg/dL; mmol/L)	72.0 (27.0, 151.5);	57.0 (21.0, 126.0);	< 0.05	32.5 ± 40.6;	18.7 ± 16.8;	0.33
	0.8 (0.3, 1.7)	0.6 (0.2, 1.4)		0.4 ± 0.5	0.2 ± 0.2	
HDL-C in men (mg/dL; mmol/L)	37.0 (31.0, 44.0);	40.0 (34.0, 48.0);	< 0.0001	40.6 ± 14.9;	43.7 ± 12.4;	< 0.0001
	1.0 (0.8, 1.1)	1.0 (0.9, 1.2)		1.1 ± 1.1	1.1 ± 0.3	
≥ normal (35 mg/dL)	592/954 (62.1)	1406/1947 (72.2)	< 0.0001	168/250 (67.2)	445/568 (78.3)	< 0.001
Distance to normal (mg/dL; mmol/L)	7.0 (3.0, 13.0);	9.0 (4.0, 16.0);	< 0.0001	11.4 ± 14.6;	12.6 ± 10.9;	< 0.01
	0.2 (0.1, 0.3)	0.2 (0.1, 0.4)		0.3 ± 0.4	0.3 ± 0.3	
HDL-C in women (mg/dL; mmol/L)	40.0 (34.0, 48.0);	48.5 (40.0, 58.0);	< 0.0001	43.4 ± 9.2;	51.2 ± 14.9;	< 0.0001
	1.0 (0.9, 1.2)	1.3 (1.0, 1.5)		1.1 ± 0.2	1.3 ± 0.4	
≥ normal (45 mg/dL)	137/389 (35.2)	315/512 (61.5)	< 0.0001	45/104 (43.3)	89/135 (65.9)	< 0.001
Distance to normal (mg/dL; mmol/L)	7.0 (3.0, 15.0);	10.0 (5.0, 19.0);	< 0.01	6.6 ± 5.9;	13.8 ± 12.0;	< 0.001
	0.2 (0.1, 0.4)	0.3 (0.1, 0.5)		0.2 ± 0.1	0.4 ± 0.3	

Data are expressed as mean \pm standard deviation, number/number (%) or median (interquartile range). Distances to target/normal are based on patients that were not at target/normal concentration. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

^a European Society of Cardiology/European Atherosclerosis Society 2011 guidelines [5, 6].

^b European Society of Cardiology/European Atherosclerosis Society 2019 guidelines [8].

^c Age < 19 years: < 170 mg/dL (4.4 mmol/L); age 20–29 years: < 200 mg/dL (5.2 mmol/L); age 30–40 years: < 220 mg/dL (5.7 mmol/L); age > 40 years < 240 mg/dL (6.2 mmol/L).

Table 4 Lipid profile by lipid-lowering therapy use in patients with type 2 diabetes at hospital admission.

	Type 2 diabetes (+)			Type 2 diabetes (-)		
	LLT (+) (n = 1042)	LLT (-) (n = 302)	<i>P</i>	LLT (+) (n = 1445)	LLT (-) (n = 1014)	<i>P</i>
LDL-C (mg/dL; mmol/L)	94.2 ± 40.2; 2.4 ± 1.0	125.2 ± 45.3; 3.2 ± 1.2	< 0.0001	99.7 ± 39.2; 2.6 ± 1.0	129.6 ± 42.3; 3.4 ± 1.1	< 0.0001
< 70 mg/dL (1.8 mmol/L) ^a	295/1042 (28.3)	26/302 (8.6)	< 0.0001	338/1445 (23.4)	56/1013 (5.5)	< 0.0001
Distance to < 70 mg/dL; < 1.8 mmol/L ^a	32.0 (14.0, 57.0); 0.8 (0.4, 1.5)	58.0 (32.5, 86.0); 1.5 (0.8, 2.2)	< 0.0001	37.0 (18.0, 62.2); 1.0 (0.5, 1.6)	61.0 (35.0, 89.0); 1.6 (0.9, 2.3)	< 0.0001
< 55 mg/dL (1.4 mmol/L) ^b	139/1042 (13.3)	13/302 (4.3)	< 0.0001	146/1445 (10.1)	33/1014 (3.3)	< 0.0001
Distance to < 55 mg/dL; < 1.4 mmol/L ^b	38.0 (20.0, 65.0); 1 (0.5, 1.7)	70.0 (43.0, 99.0); 1.8 (1.1, 2.6)	< 0.0001	44.0 (24.0, 71.0); 1.1 (0.6, 1.8)	73.0 (49.0, 103.0); 1.9 (1.3, 2.7)	< 0.0001
Total cholesterol (mg/dL; mmol/L)	166.5 ± 52.1; 4.3 ± 1.3	199.2 ± 57.4; 5.2 ± 1.5	< 0.0001	171.9 ± 49.0; 4.4 ± 1.3	200.6 ± 47.6; 5.2 ± 1.2	< 0.0001
< normal ^c	953/1028 (92.7)	235/295 (79.7)	< 0.0001	1312/1429 (91.8)	795/1004 (79.2)	< 0.0001
Distance to normal (mg/dL; mmol/L)	24.0 (7.0, 61.0); 0.6 (0.2, 1.6)	32.0 (14.0, 68.5); 0.8 (0.4, 1.8)	0.20	23.0 (9.0, 47.0); 0.6 (0.2, 1.2)	24.0 (8.0, 43.0); 0.6 (0.2, 1.1)	0.52
Non-HDL-C (mg/dL; mmol/L)	117.5 (91.0, 155.0);	153.0 (123.0, 188.0);	< 0.0001	122.0 (94.0, 156.0);	155.0 (122.5, 186.5);	< 0.0001

	3.0 (2.4, 4.0)	4.0 (3.2, 4.9)		3.2 (2.4, 4.0)	4.0 (3.2, 4.8)	
< 100 mg/dL ^a	338/1040 (32.5)	43/302 (14.2)	< 0.0001	419/1443 (29.0)	87/1012 (8.6)	< 0.0001
Distance to < 100 mg/dL; < 2.6 mmol/L	38.0 (16.0, 74.0);	61.0 (37.0, 99.0);	< 0.0001	40.5 (18.0, 71.0);	59.0 (30.0, 90.0);	< 0.0001
	1.0 (0.4, 1.9)	1.6 (1.0, 2.6)		1.0 (0.5, 1.8)	1.5 (0.8, 2.3)	
Triglycerides (mg/dL; mmol/L)	138.0 (101.0, 188.0);	145.5 (105.0, 217.0);	< 0.05	122.0 (89.0, 171.0);	119.0 (84.0, 172.0);	0.35
	1.6 (1.1, 2.2)	1.6 (1.2, 2.5)		1.4 (1.0, 1.9)	1.3 (0.9, 1.9)	
≤ normal (200 mg/dL)	823/1042 (79.0)	217/302 (71.9)	< 0.01	1213/1445 (83.9)	837/1014 (82.5)	0.36
Distance to normal (mg/dL; mmol/L)	62.0 (23.0, 145.0);	80.0 (39.0, 170.0);	< 0.05	57.0 (17.0, 128.0);	57.0 (22.0, 126.0);	0.55
	0.7 (0.3, 1.6)	0.9 (0.4, 1.9)		0.6 (0.2, 1.4)	0.6 (0.2, 1.4)	
HDL-C in men (mg/dL; mmol/L)	37.0 (31.0, 43.0);	38.0 (32.0, 45.0);	0.20	40.0 (33.0, 47.0);	41.0 (34.0, 49.0);	< 0.05
	1.0 (0.8, 1.1)	1.0 (0.8, 1.2)		1.0 (0.9, 1.2)	1.1 (0.9, 1.3)	
≥ normal (35 mg/dL)	445/722 (61.6)	147/232 (63.4)	0.64	800/1126 (71.0)	606/821 (73.8)	0.18
Distance to normal (mg/dL; mmol/L)	7.0 (3.0, 12.0);	8.0 (4.0, 15.0);	0.11	8.0 (4.0, 15.0);	10.0 (4.0, 18.0);	< 0.05
	0.2 (0.1, 0.3)	0.2 (0.1, 0.4)		0.2 (0.1, 0.4)	0.3 (0.1, 0.5)	
HDL-C in women (mg/dL; mmol/L)	41.3 (34.0, 48.0);	41.5 (36.0, 49.0);	0.19	47.0 (38.0, 56.0);	51.0 (43.0, 59.0);	< 0.01
	1.1 (0.9, 1.2)	1.1 (0.9, 1.3)		1.2 (1.0, 1.4)	1.3 (1.1, 1.5)	
≥ normal (45 mg/dL)	110/319 (34.5)	27/70 (38.6)	0.52	182/319 (57.1)	133/193 (68.9)	< 0.01
Distance to normal (mg/dL; mmol/L)	7.0 (2.0, 15.0);	7.0 (3.0, 21.0);	0.75	9.0 (5.0, 19.0);	10.0 (5.0, 18.0);	0.88
	0.2 (0.1, 0.4)	0.2 (0.1, 0.5)		0.2 (0.1, 0.5)	0.3 (0.1, 0.5)	

Data are expressed as mean \pm standard deviation, number/number (%) or median (interquartile range). Distances to target/normal are based on patients that were not at target/normal concentration. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LLT: lipid-lowering therapy.

^a European Society of Cardiology/European Atherosclerosis Society 2011 guidelines [5, 6].

^b European Society of Cardiology/European Atherosclerosis Society 2019 guidelines [8].

^c Age < 19 years: < 170 mg/dL (4.4 mmol/L); age 20–29 years: < 200 mg/dL (5.2 mmol/L); age 30–40 years: < 220 mg/dL (5.7 mmol/L); age > 40 years < 240 mg/dL (6.2 mmol/L).

Table 5 Mortality and non-fatal cardiovascular events during the 4 months following hospital admission for index acute coronary syndrome event.

	Total (<i>n</i> = 3434)	Type 2 diabetes (+) (<i>n</i> = 1223)	Type 2 diabetes (–) (<i>n</i> = 2211)	<i>P</i>
Deaths	60/3434 (1.7)	29/1223 (2.4)	31/2211 (1.4)	ND
Cardiovascular	35/60 (58.3)	18/29 (62.1)	17/31 (54.8)	ND
Non-cardiovascular	13/60 (21.7)	7/29 (24.1)	6/31 (19.4)	ND
Unknown	12/60 (20.0)	4/29 (13.8)	8/31 (25.8)	ND
Kaplan-Meier estimates (%) ^a				
Death				
60-day mortality	1.0	1.5	0.7	< 0.05
120-day mortality	1.6	2.1	1.3	0.05
Non-fatal events				
MI	0.9	1.2	0.7	0.14
Stroke	0.3	0.2	0.3	0.70
PCI	5.8	5.9	5.8	0.99
CABG	1.8	1.2	2.1	0.08
Rehospitalization	15.8	16.7	15.2	0.31

Data are expressed as number/number (%) unless otherwise indicated. CABG: coronary artery bypass graft; MI: myocardial infarction; ND: not determined

(because of high proportion of unknown causes of death); PCI: percutaneous coronary intervention.

^a *P* values calculated using log-rank test.

DYSIS II_{ACS}

- Patients aged ≥ 18 years and presenting an ACS
- Written informed consent
- Institutional IRB / EC approval

Hospitalized for ACS
(STEMI, NSTEMI, UA)

n = 3,867

Full lipid panel available within
24 hours from hospital admission

n = 3,803

120 days
telephone follow-up

n = 3,434

