

Original Research

Patient characteristics, treatment patterns, and adherence to lipid-lowering therapies following an acute coronary syndrome

Eric Bruckert¹, Gaëlle Desamericq², Artak Khachatryan³, Patrick Ngo⁴, Gaëlle Gusto⁵ and Francesc Sorio-Vilela^{6,*}¹Endocrinologie, Hospital Pitié-Salpêtrière, 75013, Paris, France²Health Economics, Amgen SAS, 92100, Boulogne-Billancourt, France³Pharmacoepidemiology, Certara, Evidence & Access (previously - Analytica Laser), EC1N 6SN, London, United Kingdom⁴Medical Affairs, Amgen SAS, 92100, Boulogne-Billancourt, France⁵Real World Evidence, Certara, Evidence & Access (previously - Analytica Laser), 75009, Paris, France⁶Health Economics and Outcomes Research, Amgen GmbH, 6343, Rotkreuz, Switzerland*Correspondence: fsorio@amgen.com (Francesc Sorio-Vilela)DOI: [10.31083/j.rcm.2020.04.189](https://doi.org/10.31083/j.rcm.2020.04.189)This is an open access article under the CC BY 4.0 license (<https://creativecommons.org/licenses/by/4.0/>).

Despite dyslipidaemia management guidelines, many patients do not reach low-density lipoprotein cholesterol targets due to insufficiently intensive regimens or lack of adherence to their medication. This was a retrospective cohort study on the Pharmacoepidemiologic General Research eXtension (PGRx)-acute coronary syndrome (ACS) registry. Patients included were ≥ 18 years old who suffered an ACS between 2013 and 2016, and treated with lipid-lowering therapy (LLT) at hospital discharge or within 92 days. Patients were followed up to 12 months' post index ACS, a new cardiovascular event, loss to follow-up or death. Treatment intensity (high, moderate and low intensity statins \pm ezetimibe) and adherence (proportion of days covered $> 80\%$) are described. A total of 2,695 patients were included; mean age [SD] was 63.1 [12.8] years, and 77% were men. High, moderate and low intensity statins were started in 56% (1,520), 36% (971), and 3% (86) of patients, respectively. A further 2% (46) were on statin/ezetimibe combination, 2% (42) on other LLT and 1% (30) on ezetimibe alone. At follow-up, around 70% of patients were adherent to LLT, with those on moderate intensity treatments showing better adherence (76%) than those on low (63%) or high (67%) intensity treatments. Despite guideline recommendations, many patients following an ACS are not treated with high intensity statins, and adherence remains far from optimal. Effort should be made to increase the proportion of patients treated with high intensity statins following an ACS and to further improve treatment adherence.

Keywords

Acute coronary syndrome; dyslipidaemias; treatment intensity; adherence; lipid lowering therapy

1. Introduction

Cardiovascular disease (CVD) is a major cause of global morbidity and mortality, with age-standardized CVD mortality rates in France of 275.2 and 174.1 per 100,000 people, for men and women, respectively (Townsend et al., 2016). Acute coronary syndrome (ACS), which includes unstable angina (UA) and both non-ST-elevation myocardial infarction (MI) and ST-elevation MI, accounts for half of all deaths due to cardiovascular disease (Kolan-sky, 2009), with observed 1-year case-fatality rates following ACS of 11.1% (Gabet et al., 2019). Treating ACS is costly: in France, the estimated yearly cost burden (including drug, procedures and hospitalizations), in 2018 Euro, is over € 1.5 billion, resulting in a yearly cost per patient of over € 10,000 (Taylor et al., 2007). Further, lost productivity costs of patients with ACS and their caregivers has been estimated to be € 13,953 per case (Kotseva et al., 2019).

Given the established relationship between reduction in low-density lipoprotein cholesterol (LDL-C) and decrease in the risk of suffering major vascular events (Cholesterol Treatment Trialists' , CTT), lipid-lowering therapies (LLT) are recommended in patients following an ACS by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) (Catapano et al., 2016; Mach et al., 2020; Piepoli et al., 2016). Moreover, ACS patients are recommended to start treatment with high-intensity statins as soon as possible (Class I, Level A recommendation), regardless of LDL-C levels (Ibanez et al., 2018; Roffi et al., 2016).

Despite the availability of effective therapies and clinical practice guidelines for the management of dyslipidaemias, many patients, including those with ACS, do not reach LDL-C targets (Kotseva et al., 2016; Reiner et al., 2016; Schiele et al., 2018). This may be due to either a lack of awareness or compliance to guidelines around the use of more intense therapies or sub-optimal patient adherence (Deshpande et al., 2017; Kotseva et al., 2016; Laufs et al., 2016). This study describes the baseline demographics, clinical characteristics and treatment patterns (intensity and adherence) of patients treated with LLT following an ACS event in France.

2. Methods

2.1 Design and study population

We conducted a retrospective observational cohort study using the Pharmacoeconomic General Research eXtension program (PGRx)-ACS registry. Patients were recruited in the PGRx-ACS registry in a prospective and consecutive manner by participating cardiology centres between 2013 and 2016 (Grimaldi-Bensouda et al., 2010). The registry includes data collected both prospectively (via physicians and patient interviews) and retrospectively (via prescription records). 60 cardiology centres participated in the PGRx-ACS registry. These centres are widely distributed across France and represent a balanced range of health care settings where ACS and cardiac death patients are seen. This methodology has been used for several other studies across numerous therapeutic areas, such as oncology, psychiatry, neurology, rheumatology, internal medicine, endocrinology, and has been validated through extensive studies (Grimaldi-Bensouda et al., 2011, 2012a,b, 2010, 2013, 2017).

Patients were finally included in our study if they were ≥ 18 years old at time of index ACS (unstable angina with myocardial revascularization or MI), and if they were treated with LLT at index ACS upon hospital discharge or within following 92 days (Fig. S1). LLTs included any of the following: nicotinic acid derivatives, fibrates, bile acid sequestrants, lipid regulating drugs (ezetimibe), statins and their combinations. Patients included in the PGRx-ACS registry were followed from index ACS for approximately 12 months until the scheduled follow-up interview, new CV event, death or lost to follow-up. If death occurred within 30 days of a new CV event or a hospitalisation for CVD event, follow-up was censored at date of death. If a same CV event occurred in a patient within 30 days of the index ACS, this was not considered a new CV event and follow-up was not censored.

LDL-C data was not registered during follow-up, so it was not possible to assess treatment effectiveness. However, there were patients in the study who had previous CVD documented before suffering the index ACS. These patients should have already been on LLT before suffering the index ACS to lower their LDL-C below the recommended levels. Therefore, and in the absence of follow-up LDL-C for the overall sample, baseline LDL-C values from this subgroup of patients (248) were used as a proxy to provide information on LDL-C goal achievement among patients diagnosed with CVD (1.8 mmol/L according to ESC/EAS guidelines in force at that time) (Reiner et al., 2011).

It was not an objective of the study to look at cardiovascular outcomes due to the limitations of the dataset and limited follow-up time frame.

2.2 Data collection

Data collection in the PGRx-ACS registry was done prospectively via a physician-completed ACS/MI electronic case report form (eCRF) and patient interviews, and retrospectively via prescription data. The ACS/MI eCRF was completed for drug use with data obtained from hospital reports (e.g. discharge letters including hospital prescriptions); treating cardiologist reports and prescriptions; and treating physician or pharmacist reports (prescriptions or lists of drugs dispensed since the index ACS). The eCRF included details on the index ACS diagnosis, ACS treatment and interventions, baseline LDL-C, and history of the following medical conditions: diabetes (type 1 and 2), hypertension, ischaemic stroke (IS), transient ischemic attack, MI, UA, chronic ischaemic heart disease, heart failure, atrial fibrillation, peripheral arterial disease (PAD), carotid artery disease, abdominal aortic aneurism, chronic obstructive pulmonary disease, and chronic kidney disease. Prescription and patient interview data provided information on drug utilization, including specific name, dose and duration, as well as BMI, alcohol consumption, smoking status and physical exercise.

2.3 Outcomes

Outcomes of interest included treatment intensity and adherence to LLT. Treatment intensity was classified as low, moderate, and high based on the American College of Cardiology and American Heart Association (ACC/AHA) guidelines (Table S1) (Stone et al., 2014). If intensity changed during the observation period, the intensity assigned was the one with the longest duration. Adherence was measured using the proportion of days covered (PDC) based on physicians' prescriptions (Andrade et al., 2006; Anghel et al., 2019; Raebel et al., 2013). Patients with a PDC $\geq 80\%$ were considered as adherent and patients with a PDC $< 80\%$ were defined as non-adherent (Deshpande et al., 2017; Nau, 2011; Stone et al., 2014).

2.4 Statistical methods

Categorical variables were summarized by calculating the number of patients and percentages, and continuous variables were summarized by mean plus standard deviation. Demographic data, baseline clinical characteristics, treatment intensity and adherence are presented using descriptive statistics. In order to represent baseline LDL-C, the value closest to index ACS was selected for those patients with more than one measure available. LLT treatment patterns were described for the overall population.

3. Results

3.1 Baseline characteristics

The PGRx-ACS registry included 3,122 patients with an ACS that may or may not have been their first ACS event. Of these patients, 2,695 met the study inclusion criteria. Patients were predominantly male (77%) with a mean age of 63.1 (SD: 12.8) years (Table 1). The most common diagnosis for the index ACS event was MI (72.7%), and most patients underwent a percutaneous transluminal coronary angioplasty (81.3%) as an ACS intervention (Table 1). Patients had a mean BMI of 27.0 (SD: 4.4); among those reporting data on physical activity, nearly 60% ($n = 954/1,696$) reported doing more than 30 minutes of physical activity per day. Patients had a mean Charlson Comorbidity Index (CCI) of 2.7 (SD: 2.3) (Table 1).

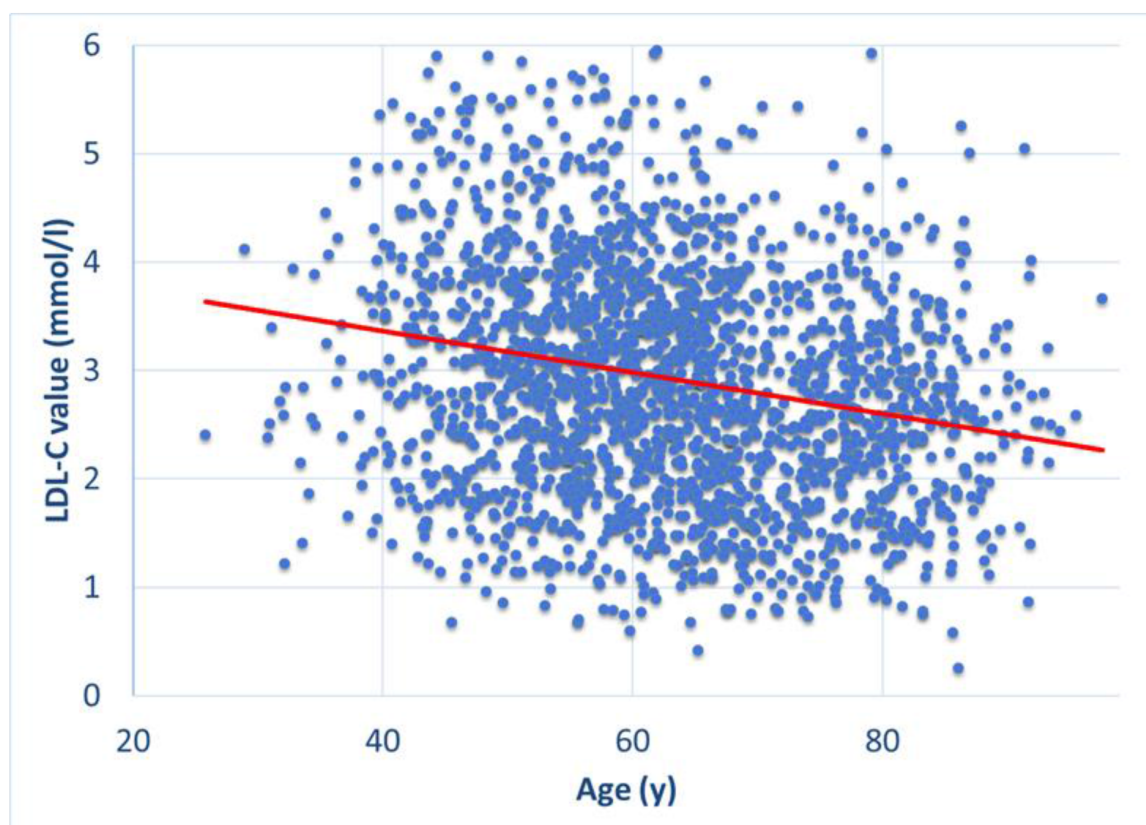


Fig. 1. Representation of LDL-C values (mmol/L) at the time of presenting with an Acute Coronary Syndrome (baseline LDL-C) by age. The red line represents the trend based on a linear model.

3.2 Baseline LDL-C

LDL-C values at baseline were available for 77% of patients (2,076/2,695), with a mean LDL-C of 2.9 mmol/L (SD: 1.2) (Supplementary material Table S2). Among the study population, there was a trend of lower baseline LDL-C in patients with older age at time of index ACS (Fig. 1). A Pearson correlation method was used to evaluate the relationship between age and baseline LDL-C. The correlation coefficient (95% CI) between age and LDL-C was equal to -0.20 (-0.24; -0.16) suggesting that there was a small negative linear relationship between age and LDL-C (i.e. the older the age of the patient, the lower was the baseline LDL-C).

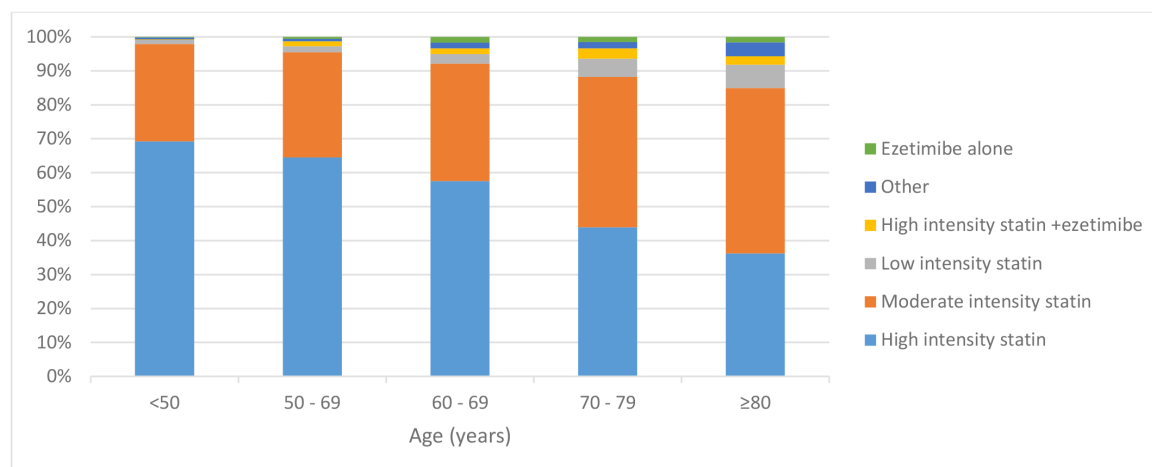
There was a sizeable amount of patients presenting with very high LDL-C values, with 4.6% of patients with LDL-C ≥ 5 mmol/L, 7.6% of patients with LDL-C ≥ 4.5 mmol/L and 15.5% of patients with LDL ≥ 4.0 . The proportion of patients with high LDL-C was higher among younger patients (Table S2). This proportion of patients with high LDL-C values may indicate a relatively high proportion of patients with familial hypercholesterolemia (FH) within those presenting with an ACS. We used the Dutch Lipid Clinic Network Score (DLCNS) to identify patients with "possible" familial hypercholesterolemia. According to the DLCNS, patients with a baseline LDL-C ≥ 5 mmol/L are qualified as "possible" familial hypercholesterolemia (FH) irrespective of presence of other risk factors (WHO Human Genetics Programme, 1999). Additionally, patients presenting with premature coronary artery disease (premature is defined as younger than 55 in men and younger than 60 in women) and with a baseline LDL-C ≥ 4.0

are also classified as possible FH case. In our study, around 61% (61.5%, 139/226) of patients with an LDL-C between 4.0 and 5.0 were younger than 60 years old (Table S2). With this, we estimated that in our study around 11% of patients presenting with an ACS were possible FH patients. This is probably an underestimate since most of the criteria included in the DLCNS to identify FH could not be verified with an information available in the dataset and some of the patients were already treated with LLTs. The majority of patients with a baseline LDL-C ≥ 5 mmol/L (71.6%) were not receiving any previous LLT treatment at the time of suffering the ACS (Table S3).

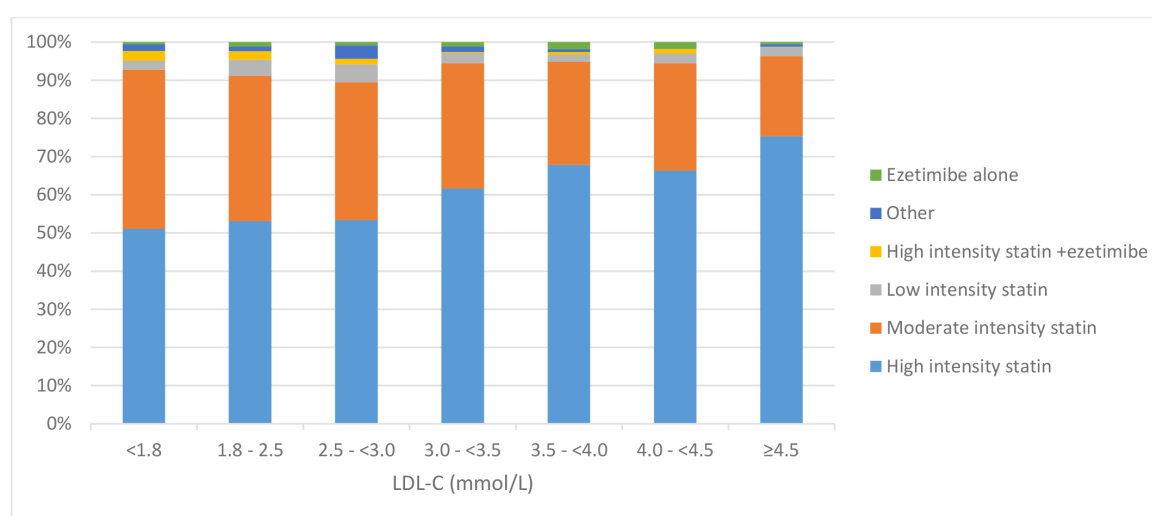
3.3 Treatment intensity and adherence

The majority of patients were started on a high (56.4%, 1,520/2,695) or moderate (36.0%, 971/2,695) intensity statin, whereas only 3.2% of patients (86/2,695) were on low intensity statins. A further 1.7% (46/2,695) were on statin/ezetimibe combination, 1.6% (42/2,695) on other LLT and 1.1% (30/2,695) on ezetimibe monotherapy alone. Age and baseline LDL-C were drivers of treatment intensity (Fig. 2). The use of high intensity statins decreased with age: 69.2% of patients aged < 50 and 36.2% of patients ≥ 80 were on a high-intensity statin. Conversely, the use of high intensity statins increased with baseline LDL-C: 51.1% among those with an LDL-C of < 1.8 mmol/L, and 75.3% among those with an LDL-C of ≥ 4.5 mmol/L were on a high intensity statin. Few patients were on a statin plus ezetimibe or ezetimibe alone (Fig. 2). The relationship between age and baseline LDL-C with the use of high intensity statins was assessed with the Pear-

(A)



(B)



LLT: lipid-lowering therapy; LDL-C: low-density lipoprotein cholesterol.

Fig. 2. Representation of the proportion of patients treated with each LLT category following an ACS, according to age (A) and according to baseline LDL-C (mmol/L) (B).

son Correlation method. The correlation coefficient (95% CI) between age and treatment intensity was equal to -0.19 (-0.23, -0.16) suggesting that there was a very weak negative linear relationship between age and treatment intensity (lower use of high intensity therapies in older patients). The correlation coefficient (95% CI) between baseline LDL-C and treatment intensity was equal to 0.10 (0.05; 0.14) suggesting that there was a very weak positive linear relationship between baseline LDL-C and treatment intensity (higher use of high intensity therapies in patients presenting with higher baseline LDL-C).

Around 70% of patients were considered adherent (defined as PDC \geq 80%) to LLT within one year of follow-up. A higher proportion of adherent patients was observed within those treated with moderate intensity statins (75.6%) as compared to those on low (62.5%) or high intensity statins (66.5%); the Pearson correlation coefficient was -0.052 (-0.090; -0.015) showing a negligible correlation between treatment intensity and adherence. A relationship

between age and treatment adherence was not that clear, although patients older than 80 years old show the lowest proportion of adherent patients (55.6%); the Pearson correlation coefficient was -0.052 (-0.034; 0.042) showing that correlation was not significant (Table S4).

3.4 Subgroup of patients with a previous CVD event

Prior to index ACS, a total of 310 patients had a documented CVD event (237 with previous MI, 49 with a previous IS, 15 with a previous MI and IS and 9 with documented PAD); of these, 248 had baseline LDL-C values available. At time of index ACS, 67.3% (167/248) of patients were already being treated with LLT (prevalent LLT users); and the remaining 32.7% (81/248) initiated LLT treatment for the first time following the index ACS event (incident LLT users). Just over 31% of patients (79/248) had reached a LDL-C level $<$ 1.8 mmol/L (Table 2).

Among these 310 patients with previous CVD, 69.7% (216) were adherent (PDC \geq 0.80) and 30.3% (94) were not adherent

Table 1. Demographic and clinical characteristics of included patients at baseline.

	N = 2,695
Age at index ACS, mean (SD), years	63.1 (12.8)
Sex, n (%), male	2076 (77.0)
Diagnosis of index ACS, n (%)	
Unstable angina	333 (12.4)
Myocardial infarction	1958 (72.7)
Not specified	404 (15.0)
ACS intervention, n (%)	
Coronary artery bypass graft	107 (4.0)
Percutaneous transluminal coronary angioplasty	2191 (81.3)
Not specified	397 (14.7)
Body mass index, mean (SD)	27.0 (4.4)
Alcohol consumption, n (%)	
Every day or several times per week	1123 (41.7)
Occasionally/never	665 (24.7)
Missing	907 (33.7)
Smoking status, n (%)	
Current smoker	560 (20.8)
Past smoker	936 (34.7)
Never smoker	778 (28.9)
Missing	421 (15.6)
Physical activity, n (%)	
30 minutes a day or less	742 (27.5)
More than 30 minutes daily	954 (35.4)
Missing	999 (37.1)
Place of residence, n (%)	
Rural zone	390 (14.5)
Urban zone	2296 (85.2)
Missing	9 (0.3)
Chronic kidney disease, n (%)	83 (3.1)
Hypertension or antihypertensive use, n (%)	2255 (83.7)
History of diabetes or antidiabetics use, n (%)	494 (18.3)
Charlson comorbidity index, mean (SD)	2.7 (2.3)

ACS, acute coronary syndrome; SD, standard deviation.

(PDC < 0.80). These proportions were very similar to those already reported in the overall population: 69.9% (1,871) adherent and 30.1% (807) not adherent (17 patients with missing information on adherence value were not included in the computation).

4. Discussion

In this study, we found that a substantial proportion of patients in France were not treated with high intensity statins after suffering an ACS (even fewer patients were on ezetimibe/statin combination) and only 70% of patients were defined as adherent within the follow-up period. Conversely, very few patients (around 3%) were on low intensity statins following an ACS. It's also noteworthy that in patients who had been previously diagnosed with CVD, almost one third of them were not receiving statin therapy at the time of suffering the index ACS.

ESC/EAS guidelines recommend first-line therapy with statin LLTs to reduce the risk of CVD outcomes and to start high-intensity statins as soon as possible for patients hospitalized with

Table 2. Treatment intensity and baseline LDL-C among patients with previous CVD history*.

LDL-C (mmol/L) at baseline, N (%)	LLT Treatment Users		
	All	Incident users	Prevalent users
All	248 (100.0%)	81 (32.7%)	167 (67.3%)
< 1.8 mmol/L	79 (31.9%)	22 (27.2%*)	57 (34.1%*)
< 2.5 mmol/L	163 (65.7%)	45 (55.6%*)	118 (70.7%*)

*Defined as previous MI, ischaemic stroke or peripheral arterial disease.

LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; CVD, cardiovascular disease.

ACS, irrespective of their LDL-C level (Catapano et al., 2016; Mach et al., 2020; Piepoli et al., 2016; Schiele et al., 2018). At the time of this study, recommendations stated target levels of LDL-C of less than 1.8 mmol/L (Reiner et al., 2011), and 32% of patients met this target. More recent guidelines have lowered the LDL-C target to 1.4 mmol/L; based on this updated recommendation, only 15% (38/248) would have met the target levels (Mach et al., 2020). This low utilization of high intensity statins leaves patients with an ACS at considerable risk of subsequent cardiovascular events (Boklage et al., 2018). In France, a previous real-world effectiveness study done with the PGRx registry demonstrated that statin use was associated with decreased risk of first non-fatal ACS (adjusted odds ratio, 0.67) (Grimaldi-Bensouda et al., 2013).

Patient adherence in our study was sub-optimal, with 70% of patients defined as adherent within one year of follow-up. Previous studies have found that treatment adherence has as much of an impact on reducing the risk of CVD as treatment intensity (Khunti et al., 2018). Strategies to increase treatment adherence among patients should be explored to increase the effectiveness of LLT.

In the present study, we identified a large proportion of patients potentially representing patients with FH. Despite the increased risk of suffering from CVD in this group of patients, most of these patients remained untreated. These findings are consistent with results from another study that found that over one-quarter of FH patients in France may not be receiving LLT and only 13% of those treated with LLTs received high intensity statins (Berard et al., 2019). FH is associated with a 2-fold increased risk of coronary event recurrence at one year following an ACS event (Nanchen et al., 2016). Efforts should be undertaken to identify and adequately control young patients with potentially high LDL-C, as they are at higher risk of excess morbidity and mortality related to dyslipidaemias (Schiele et al., 2018).

Several studies have examined treatment patterns of LLT in a French population. Results from a multicentre European survey, including centres in France, found that there are patients with very-high risk who remain untreated: 1 out of every 10 patients discharged from the hospital after a coronary event did not receive any statin treatment (Reiner et al., 2016). Ferrières et al. examined LLT utilization and lipid goal attainment in a 2015 population of French patients with atherosclerotic CVD disease with or without diabetes, including patients recently diagnosed with an ACS (Ferrières et al., 2018). Similar to our study, they found that LLT usage and LDL-C goal achievement were suboptimal in recent ACS

patients with only 75% prescribed an LLT therapy and 29% of patients achieving LDL-C levels < 1.8 mmol/L (Ferrières et al., 2018). Though the prescribing environment described in Ferrières et al. was a general practice setting, differing from our database informed by cardiologists, the results are consistent in highlighting that patients with ACS remain undertreated.

Several hypotheses have been proposed to explain the discordance between guideline recommendations and what is observed in practice. It may be possible that clinicians are either not aware of guideline recommendations or are avoiding higher-intensity regimens due to concerns about possible side effects (Laufs et al., 2016). Patients' attitude towards statin therapy, as influenced by the media, and thus the decision to discontinue or continue statin therapy, may result in observed lower prevalence of LLT therapy (Nielsen and Nordestgaard, 2016). Despite the unfavourable context in France for statins for cardiovascular prevention during the study period (Bezin et al., 2014), we found overall adherence to be 70% of patients, similar to what was observed in other studies (Danese et al., 2017; Naderi et al., 2012).

This study's key strength is that it uses a real-world dataset, the PGRx-ACS registry, which reflects cardiologist practice conditions in France. Previous studies using these networks have shown that cases and referents are very representative of the population observed in clinical practice (Grimaldi-Bensouda et al., 2010). Further, demographic and clinical characteristics from the current study are also similar to those reported in the EURHOBOP study, a benchmarking study of ACS management in Europe, including France (André et al., 2014). Despite using patient-reported data, the PGRx database has also shown good concordance between physician and patient report of CVD drug utilization (Grimaldi-Bensouda et al., 2010).

Our study also has limitations. The study may not be generalizable to all French patients with ACS since patients in PGRx are recruited by cardiologists and not from a general practice setting; however, in clinical practice, the majority of ACS patients are treated by cardiologists in the first months following the event (?). Missing data are a reality in real-world secondary databases; in this study nearly a quarter of patients had missing LDL-C values at baseline. The proportion of missing data, however, did not appear to differ according to age. Finally, we only had access in our study to limited information (mainly baseline LDL-C) as compared to all the clinical data available to the physician when confronted to the prescription decision. Hence, clinicians may be guided in clinical practice by other sources of data such as imaging at the time of the ACS (multivessel disease vs single lesions) or other forms such as OCT (optical coherence tomography) of other non-culprit lesions. The information provided by these techniques may lead to the clinician to place a patient at an even higher level of risk and to strive to an even lower LDL-C goal with the use of additional and more intensive lipid lowering therapies.

Managing ACS correctly is critical as adherence to guidelines is associated with better patient prognosis in both the acute phase of the syndrome and in longer term secondary prevention (Sabouret et al., 2010). Based on the data observed in this study, there is potential to improve management of patients with ACS, thereby reducing mortality and higher case-fatality rates. Strategies to better identify at-risk patients along with improving com-

pliance with dyslipidemia guidelines, treatment adherence and optimization of therapy, may lead to better LDL-C goal attainment and improved CVD outcomes among patients hospitalized for ACS in France, particularly for those with possible FH and those with a prior history of CVD.

Authors' contributions

AK, FSV and GD contributed to the conception and design of the study. GG conducted the statistical analysis. All authors contributed to the analysis and/or interpretation of the data for this study. AK and FSV drafted the manuscript. All authors critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the study, ensuring integrity and accuracy.

Ethics approval and consent to participate

This research has been performed on the PGRx dataset which has been approved by the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés). All patients included in the PGRx database provided informed consent. As the study was a retrospective analysis using secondary anonymized patient data only, no additional ethical approval was needed.

Acknowledgements

Lianne Barnieh, a Certara employee, provided assistance on editing the final manuscript. PGRx-ACS data is a proprietary asset of Centre for Risk Research Inc, Montreal, Canada. Data for this study was provided by Centre for Risk Research Inc, Montreal, Canada by permission.

Funding

This study was funded by Amgen (Europe) GmbH.

Conflict of Interest

EB declares having received honoraria from Amgen, MSD, Sanofi and Regeneron, Unilever, Danone, Aegerion, Chiesi, Rottapharm-MEDA, Servier, Ionis-pharmaceuticals, AKCEA, Mylan and GENFIT. FS-V, GD and PN are full-time employees at Amgen and own Amgen stock options. AK and GG are full-time employees of Certara, Evidence & Access (previously - Analytica Laser), that received consulting fees from Amgen to conduct the study. EB received consulting fees from Amgen.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at <https://rcm.imrpress.com/EN/10.31083/j.rcm.2020.04.189>.

Submitted: September 16, 2020

Revised: November 09, 2020

Accepted: November 10, 2020

Published: December 30, 2020

References

Andrade, S. E., Kahler, K. H., Frech, F. and Chan, K. A. (2006) Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiology and Drug Safety* **15**, 565-574.

- André, R., Bongard, V., Elosua, R., Kirchberger, I., Farmakis, D., Häkkinen, U., Fusco, D., Torre, M., Garel, P., Araújo, C., Meisinger, C., Lekakis, J., Malmivaara, A., Dovali, M., Pereira, M., Marrugat, J. and Ferrières, J. (2014) International differences in acute coronary syndrome patients' baseline characteristics, clinical management and outcomes in Western Europe: the EURHOBOP study. *Heart* **100**, 1201-1207.
- Anghel, L. A., Farcas, A. M. and Oprean, R. N. (2019) An overview of the common methods used to measure treatment adherence. *Medicine and Pharmacy Reports* **92**, 117-122.
- Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent, C., Blackwell, L., Emberson, J. R., Holland, L. E., Reith, C., Bhalra, N., Peto, R., Barnes, E. H., Keech, A., Simes, J. and Collins, R. (2010) Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *The Lancet* **376**, 1670-1681.
- Berard, E., Bongard, V., Haas, B., Dallongeville, J., Moitry, M., Cottel, D., Ruidavets, J. B. and Ferrières, J. (2019) Prevalence and treatment of familial hypercholesterolemia in France. *Canadian Journal of Cardiology* **35**, 744-752.
- Bezin, J., Pariente, A., Lassalle, R., Dureau-Pournin, C., Abouelfath, A., Robinson, P., Moore, N., Droz-Perroteau, C. and Fourrier-Reglat, A. (2014) Use of the recommended drug combination for secondary prevention after a first occurrence of acute coronary syndrome in France. *European Journal of Clinical Pharmacology* **70**, 429-436.
- Boklage, S. H., Malangone-Monaco, E., Lopez-Gonzalez, L., Ding, Y., Henriques, C. and Ellassal, J. (2018) Statin utilization patterns and outcomes for patients with acute coronary syndrome during and following inpatient admissions. *Cardiovascular Drugs and Therapy* **32**, 273-280.
- Catapano, A. L., Graham, I., De Backer, G., Wiklund, O., Chapman, M. J., Drexel, H., Hoes, A. W., Jennings, C. S., Landmesser, U., Pedersen, T. R., Reiner, Z., Riccardi, G., Taskinen, M., Tokgozoglu, L., Verschuren, W. M. M., Vlachopoulos, C., Wood, D. A. and Zamorano, J. L. (2016) 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *European Heart Journal* **7**, 2999-3058.
- Danese, M. D., Gleeson, M., Kutikova, L., Griffiths, R. I., Khunti, K., Seshasai, S. R. K. and Ray, K. K. (2017) Management of lipid-lowering therapy in patients with cardiovascular events in the UK: a retrospective cohort study. *BMJ Open* **7**, e013851.
- Deshpande, S., Quek, R. G. W., Forbes, C. A., de Kock, S., Kleijnen, J., Gandra, S. R. and Simpson, R. J. (2017) A systematic review to assess adherence and persistence with statins. *Current Medical Research and Opinion* **33**, 769-778.
- Ferrières, J., Gorcyca, K., Iorga, R., Ansell, D. and Steen, D. L. (2018) Lipid-lowering therapy and goal achievement in high-risk patients from French general practice. *Clinical Therapeutics* **40**, 1484-1495.e22.
- Gabet, A., Danchin, N., Puymirat, E., Tuppin, P. and Olié, V. (2019) Early and late case fatality after hospitalization for acute coronary syndrome in France, 2010-2015. *Archives of Cardiovascular Diseases* **112**, 754-764.
- Grimaldi-Bensouda, L., Alperovitch, A., Besson, G., Vial, C., Cuisset, J. M., Papeix, C., Lyon-Caen, O., Benichou, J., Rossignol, M. and Lucien Abenham for the GBS-PGRx Study Group (2011) Guillain-Barre Syndrome, influenzalike illnesses, and influenza vaccination during seasons with and without circulating A/H1N1 viruses. *American Journal of Epidemiology* **174**, 326-335.
- Grimaldi-Bensouda, L., Michel, M., Aubrun, E., Leighton, P., Viallard, J., Adoue, D., Magy-Bertrand, N., Tisserand, G., Khellaf, M., Durand, J., Quittet, P., Fain, O., Bonnotte, B., Morin, A. S., Limal, N., Costedoat-Chalumeau, N., Morel, N., Pan-Petes, B., Decaux, O., Mahevas, M., Ruel, M., Sacre, K., Lefrere, F., Abenham, L. and Godeau, B. (2012a) A case-control study to assess the risk of immune thrombocytopenia associated with vaccines. *Blood* **120**, 4938-4944.
- Grimaldi-Bensouda, L., Rossignol, M., Aubrun, E., Benichou, J., Abenham, L. and the PGRx Study Group (2012b) Agreement between patients' self-report and physicians' prescriptions on nonsteroidal anti-inflammatory drugs and other drugs used in musculoskeletal disorders: the international Pharmacoepidemiologic General Research eXtension database. *Pharmacoepidemiology and Drug Safety* **21**, 753-759.
- Grimaldi-Bensouda, L., Rossignol, M., Aubrun, E., El Kerri, N., Benichou, J. and Abenham, L. (2010) Agreement between patients' self-report and physicians' prescriptions on cardiovascular drug exposure: the PGRx database experience. *Pharmacoepidemiology and Drug Safety* **19**, 591-595.
- Grimaldi-Bensouda, L., Rossignol, M., Danchin, N., Dallongeville, J., Bruckert, E., Banayan, J., Cottin, Y., Aubrun, E., Khachatryan, A., Bénichou, J. and Abenham, L. (2013) Real-life effectiveness of statins in the prevention of first acute coronary syndrome in France: a prospective observational study. *International Journal of Cardiology* **169**, 271-275.
- Grimaldi-Bensouda, L., Rossignol, M., Koné-Paut, I., Krivitzky, A., Lebrun-Frenay, C., Clet, J., Brassat, D., Papeix, C., Nicolino, M., Benhamou, P., Fain, O., Costedoat-Chalumeau, N., Courcoux, M., Viallard, J., Godeau, B., Papo, T., Vermersch, P., Bourgault-Villada, I., Breart, G. and Abenham, L. (2017) Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: six years of case-referent surveillance. *Journal of Autoimmunity* **79**, 84-90.
- Ibanez, B., James, S., Agewall, S., Antunes, M. J., Bucciarelli-Ducci, C., Bueno, H., Caforio, A. L. P., Crea, F., Goudevenos, J. A., Halvorsen, S., Hindricks, G., Kastrati, A., Lenzen, M. J., Prescott, E., Roffi, M., Valgimigli, M., Varenhorst, C., Vranckx, P. and Widimský, P. (2018) 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Kardiologia Polska* **76**, 229-313.
- Khunti, K., Danese, M. D., Kutikova, L., Catterick, D., Sorio-Vilela, F., Gleeson, M., Kondapally Seshasai, S. R., Brownrigg, J., currently with Rare Diseases, Pfizer, London, United Kingdom, Ray, K. K. (2018) Association of a combined measure of adherence and treatment intensity with cardiovascular outcomes in patients with atherosclerosis or other cardiovascular risk factors treated with statins and/or ezetimibe. *JAMA Network Open* **1**, e185554.
- Kolansky, D. M. (2009) Acute coronary syndromes: morbidity, mortality, and pharmacoeconomic burden. *the American Journal of Managed Care* **15**, S36-S41.
- Kotseva, K., Gerlier, L., Sidelnikov, E., Kutikova, L., Lamotte, M., Amarencu, P. and Annemans, L. (2019) Patient and caregiver productivity loss and indirect costs associated with cardiovascular events in Europe. *European Journal of Preventive Cardiology* **26**, 1150-1157.
- Kotseva, K., Wood, D., De Bacquer, D., De Backer, G., Ryden, L., Jennings, C., Gyberg, V., Amouyel, P., Bruthans, J., Castro Conde, A., Cifkova, R., Deckers, J. W., De Sutter, J., Dilic, M., Dolzhenko, M., Erglis, A., Fras, Z., Gaita, D., Gotcheva, N., Goudevenos, J., Heuschmann, P., Laucevicius, A., Lehto, S., Lovic, D., Milicic, D., Moore, D., Nicolaides, E., Oganov, R., Pajak, A., Pogossova, N., Reiner, Z., Stagmo, M., Stork, S., Tokgozoglu, L. and Vulic, D. (2016) EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *European Journal of Preventive Cardiology* **23**, 636-648.
- Laufs, U., Karmann, B. and Pittrow, D. (2016) Atorvastatin treatment and LDL cholesterol target attainment in patients at very high cardiovascular risk. *Clinical Research in Cardiology* **105**, 783-790.
- Mach, F., Baigent, C., Catapano, A. L., Koskinas, K. C., Casula, M., Badimon, L., Chapman, M. J., De Backer, G. G., Delgado, V., Ference, B. A., Graham, I. M., Halliday, A., Landmesser, U., Mihaylova, B., Pedersen, T. R., Riccardi, G., Richter, D. J., Sabatine, M. S., Taskinen, M., Tokgozoglu, L. and Wiklund, O. (2020) 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Russian Journal of Cardiology* **25**, 3826.
- Massoulié, G., Wintzer-Wehekind, J., Chenaf, C., Mulliez, A., Pereira, B., Authier, N., Eschalier, A., Clerfond, G., Souteyrand, G., Tabassome, S., Danchin, N., Citron, B., Lussan, J., Puymirat, E., Motreff, P. and Eschalier, R. (2016) Prognosis and management of myocardial infarction: Comparisons between the French FAST-MI 2010 registry and the French public health database. *Archives of Cardiovascular Diseases* **109**, 303-310.
- Naderi, S. H., Bestwick, J. P. and Wald, D. S. (2012) Adherence to drugs

- that prevent cardiovascular disease: meta-analysis on 376,162 patients. *The American Journal of Medicine* **125**, 882-887.e1.
- Nanchen, D., Gencer, B., Muller, O., Auer, R., Aghlmandi, S., Heg, D., Klingenberg, R., Räber, L., Carballo, D., Carballo, S., Matter, C. M., Lüscher, T. F., Windecker, S., Mach, F. and Rodondi, N. (2016) Prognosis of patients with familial hypercholesterolemia after acute coronary syndromes. *Circulation* **134**, 698-709.
- Nau, D. P. (2011) Proportion of days covered (PDC) as a preferred method of measuring medication adherence. Available at: <http://www.pqaalliance.org/images/uploads/files/PQA>
- Nielsen, S. F. and Nordestgaard, B. G. (2016) Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. *European Heart Journal* **37**, 908-916.
- Piepoli, M. F., Hoes, A. W., Agewall, S., Albus, C., Brotons, C., Catapano, A. L., Cooney, M. T., Corra, U., Cosyns, B., Deaton, C., Graham, I., Hall, M. S., Hobbs, F. D. R., Lochen, M. L., Lollgen, H., Marques-Vidal, P., Perk, J., Prescott, E., Redon, J., Richter, D. J., Sattar, N., Smulders, Y., Tiberi, M., van der Worp, H. B., van Dis, I., Verschuren, W. M. M., Binno, S. and ESC Scientific Document Group. (2016) 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The sixth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts)/developed with the special contribution of the European association for cardiovascular prevention & rehabilitation (EACPR). *European Heart Journal* **37**, 2315-2381.
- Raebel, M. A., Schmittiel, J., Karter, A. J., Konieczny, J. L. and Steiner, J. F. (2013) Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Medical Care* **51**, S11-S21.
- Reiner, Z., Catapano, A. L., De Backer, G., Graham, I., Taskinen, M. R., Wiklund, O., Agewall, S., Alegria, E., Chapman, M. J., Durrington, P., Erdine, S., Halcox, J., Hobbs, R., Kjekshus, J., Filardi, P. P., Riccardi, G., Storey, R. F. and Wood, D. (2011) ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *European Heart Journal* **32**, 1769-1818.
- Reiner, Z., De Backer, G., Fras, Z., Kotseva, K., Tokgözoğlu, L., Wood, D. and De Bacquer, D. (2016) Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries--Findings from the EUROASPIRE IV survey. *Atherosclerosis* **246**, 243-250.
- Roffi, M., Patrono, C., Collet, J., Mueller, C., Valgimigli, M., Andreotti, F., Bax, J. J., Borger, M. A., Brotons, C., Chew, D. P., Gencer, B., Hasenfuss, G., Kjeldsen, K., Lancellotti, P., Landmesser, U., Mehilli, J., Mukherjee, D., Storey, R. F. and Windecker, S. (2016) 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *European Heart Journal* **37**, 267-315.
- Sabouret, P., Asseman, P., Dallongeville, J., Dujardin, J., Philippe, F., Herrmann, M. and Montalescot, G. (2010) Observational study of adherence to European clinical practice guidelines for the management of acute coronary syndrome in revascularized versus non-revascularized patients - the CONNECT Study. *Archives of Cardiovascular Diseases* **103**, 437-446.
- Schiele, F., Farnier, M., Krempf, M., Bruckert, E., Ferrières, J. and French Group. (2018) A consensus statement on lipid management after acute coronary syndrome. *European Heart Journal* **7**, 532-543.
- Stone, N. J., Robinson, J. G., Lichtenstein, A. H., Bairey Merz, C. N., Blum, C. B., Eckel, R. H., Goldberg, A. C., Gordon, D., Levy, D., Lloyd-Jones, D. M., McBride, P., Schwartz, J. S., Shero, S. T., Smith, S. C. Jr., Watson, K., Wilson, P. W. and American College of Cardiology/American Heart Association Task Force on Practice Guidelines.. (2014) 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* **129**, S1-45.
- Taylor, M. J., Scuffham, P. A., McCollam, P. L. and Newby, D. E. (2007) Acute coronary syndromes in Europe: 1-year costs and outcomes. *Current Medical Research and Opinion* **23**, 495-503.
- Townsend, N., Wilson, L., Bhatnagar, P., Wickramasinghe, K., Rayner, M. and Nichols, M. (2016) Cardiovascular disease in Europe: epidemiological update 2016. *European Heart Journal* **37**, 3232-3245.
- WHO Human Genetics Programme. (1999) Familial hypercholesterolaemia (FH): report of a second WHO consultation, Geneva, 4 September 1998. World Health Organization. Available at: <https://apps.who.int/iris/handle/10665/66346>.