Standardized secondary prevention in patients with ST-elevation myocardial infarction

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Low-density lipoprotein cholesterol (LDL-C) is one of the most important modifiable cardiovascular risk factors. In 2019, European guidelines lowered the recommended target LDL-C from <1.8 mmol/L (70 mg/dL) to <1.4 mmol/L (55 mg/dL) for secondary prevention in coronary artery disease. Despite well-intentioned recommendations and strong evidence, the previous LDL-C target of <1.8 mmol/L (70 mg/dL) had only been achieved in 21% in registries. In Germany, the reported proportion was even lower with ≤15% of patients achieving the target following an acute coronary syndrome.

This was potentially influenced by the fact that only simvastatin and pravastatin were recommended for out-patient use until 2017. Prescription of more potent statins such as atorvastatin and rosuvastatin or of ezetimibe implied the risk of financial repercussions for the prescribing physician. Upon availability of generic atorvastatin, we initiated a local secondary prevention network together with the regional Association of Statutory Health Insurance Physicians and regional representatives for general practitioners (i) to rapidly diagnose important comorbidities and risk factors, (ii) to initiate evidence-based pharmacological treatment during the index hospital admission, and (iii) to enable general practitioners to continue prescribing the initiated treatment without risking financial repercussions.

In our analysis, we aimed to assess the achievement of LDL-C guideline targets in real-world everyday clinical practice when prescribing restrictions are lifted in a system historically only achieving important modifiable cardiovascular risk factors. In 2019, European guidelines lowered the recommended target LDL-C from <1.8 mmol/L (70 mg/dL) to <1.4 mmol/L (55 mg/dL) for secondary prevention in coronary artery disease. Despite well-intentioned recommendations and strong evidence, the previous LDL-C target of <1.8 mmol/L (70 mg/dL) had only been achieved in 21% in registries. In Germany, the reported proportion was even lower with ≤15% of patients achieving the target following an acute coronary syndrome.

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In our analysis, we aimed to assess the achievement of LDL-C guideline targets in real-world everyday clinical practice when prescribing restrictions are lifted in a system historically only achieving these goals in approximately 10% of patients. We assumed that the percentage of patients reaching guideline-recommended LDL-C levels would increase relatively above the historic rate.

From 1 April 2018 until 29 February 2020, 283 consecutive patients with acute ST-elevation myocardial infarction (STEMI) were admitted to the Department of Cardiology and Angiology at Hannover Medical School (Table 1). Data analysis conforms to the Declaration of Helsinki. Collection of anonymized data was generally approved by the institutional review board. Lipid-lowering therapy was initiated at the day of admission following coronary revascularization. Following a standard-operating procedure of a local secondary prevention network, we initiated lipid-lowering therapy with atorvastatin 40 mg balancing the expected increase in adverse effects on 80 mg to the rather mild increment in lipid-lowering. Lower doses of atorvastatin or other statins were only prescribed when patients were on such prescriptions prior to admission and had reported intolerance to higher doses or atorvastatin at all. Initially, atorvastatin (40 mg) monotherapy was used in patients with LDL-C ≤3.1 mmol/L (120 mg/dL) based on its potential to achieve the target of ≤1.8 mmol/L (70 mg/dL) in ~50% of patients; in patients with LDL-C ≥3.1 mmol/L (120 mg/dL) ezetimibe (10 mg) was added. After lowering the target [≤1.4 mmol/L (55 mg/dL)] ezetimibe was added during the initial prescription in patients with LDL-C ≥100 mg/dL.

Blood samples for lipid profiles were determined upon admission and, therefore, available within 1 h of diagnosing STEMI. Data on efficacy of lipid-lowering therapy were obtained when patients had a second admission for further treatment or from the discharge report of a cardiac rehabilitation centre, which for both occasions was usually 4–6 weeks after discharge from the initial hospitalization. Patients were 62 ± 13 years old, 77% male (Table 1). For history of hyperlipidaemia, we used a conservative definition of either LDL-C >4.9 mmol/L (190 mg/dL) or pre-existing lipid-lowering therapy (Supplementary material online, Table S1). Mean LDL-C was 3.5 ± 1.1 mmol/L (135 ± 41 mg/dL, Figure 1A). In 97 patients, a second lipid assessment was available following per-protocol initiation of lipid-lowering therapy, which resulted in a significant reduction of LDL-C to 1.6 ± 0.6 mmol/L (62 ± 25 mg/dL, Figure 1B). Patients without pre-admission lipid-lowering therapy (n = 190, 75%) had higher baseline LDL-C of 3.7 ± 0.9 mmol/L (146 ± 36 mg/dL, Figure 1C). Of those, a second lipid assessment was available following per-protocol initiation of lipid-lowering therapy in 77 patients and showed a significant reduction of LDL-C to 1.6 ± 0.7 mmol/L (61 ± 26 mg/dL).
| Table 1 Patient characteristics (n = 283) |
|------------------------------------------|
| **Age (years)** | 62 ± 13 |
| **Sex, male** | 219 (77%) |
| **Body mass index (kg/m²)** | 28.5 ± 5.4 |
| **Cardiovascular risk factors (CVRF)** | |
| **Diabetes** | 89/271 (33%) |
| **Hyperlipidaemia** | 80/253 (32%) |
| **Smoker** | 155/271 (57%) |
| **Family history for coronary artery disease** | 55/271 (20%) |
| **Hypertension** | 156/271 (58%) |
| **Number of CVRFs** | 2 (IQR 1–3) |
| **Systolic blood pressure (mmHg)** | 125 ± 27 |
| **LV-EF (%)** | 45 ± 11 |
| **Vasopressor demand** | 63 (22%) |
| **Mechanical circulatory support** | 30 (11%) |
| **Out-of-hospital cardiac arrest** | 56 (20%) |
| **Laboratory results (admission)** | |
| **Arterial lactate (mmol/L)** | 3.5 ± 3.5 |
| **Creatinine kinase maximum (U/L)** | 3408 ± 9349 |
| **Estimated glomerular filtration rate** | 75 ± 23 |
| **Total cholesterol [mmol/L (mg/dL)]** | 4.8 ± 1.1 (186 ± 43) |
| **LDL cholesterol [mmol/L (mg/dL)]** | 3.5 ± 1.1 (135 ± 41) |
| **HDL cholesterol [mmol/L (mg/dL)]** | 1.2 ± 0.3 (46 ± 13) |
| **triglycerides [mmol/L (mg/dL)]** | 2.5 ± 1.8 (98 ± 69) |
| **Percutaneous coronary intervention** | |
| **Culprit vessel** | |
| **LMCA** | 13 (5%) |
| **LAD** | 108 (38%) |
| **LCX** | 43 (15%) |
| **RCA** | 119 (42%) |
| **Conservative treatment** | 5 (2%) |
| **CABG** | 10 (4%) |
| **PCI** | 268 (95%) |
| **Stents (n)** | 1.9 ± 1.1 |
| **Stent length (mm)** | 40 ± 25 |
| **Socioeconomic health insurance** | |
| **Public health insurance** | 270 (95%) |
| **Private health insurance** | 13 (5%) |
| **Additive treatment with ezetimibe** | 167/253 (66%) |
| **In males** | 129/193 (67%) |
| **In females** | 38/60 (63%) |

LDL-C achieved on-treatment

- **In males** 1.6 ± 0.7 (61 ± 26)
- **In females** 1.6 ± 0.6 (63 ± 22)

Values as number (%) of observation or means ± standard deviation.

CABG, coronary artery bypass graft; HDL, high-density lipoprotein; LMCA, left main coronary artery; LV-EF, left-ventricular ejection fraction; PCI, percutaneous coronary intervention; RCA, right coronary artery.

**Figure 1D**, whereby 76/77 patients had been treated with atorvastatin plus ezetimibe.

When focusing on lipid-lowering therapy-naïve patients with acute STEMI, the by protocol initiation of secondary prevention as described above resulted in 53% achieving the new LDL-C target <1.4 mmol/L (55 mg/dL) and 69% achieving LDL-C ≤1.8 mmol/L (70 mg/dL). Average LDL-C reduction was 44 ± 22%.

Implementing a standardized approach resulted in more than two out of three patients achieving an LDL-C ≤1.8 mmol/L (70 mg/dL) under the described prescription restrictions and every second patient reaching an LDL-C ≤1.4 mmol/L (55 mg/dL). This is far more than reported in recent German surveys achieving the previous target only in 10–12% of patients after an acute coronary syndrome.9,10 Therefore, our standardized approach including the prevention of financial repercussions led to a relevant increase in patients achieving guideline-recommended cholesterol targets.

Lipid-lowering is an important intervention to reduce cardiovascular morbidity and mortality in secondary prevention. In a 50-year follow-up of heart disease mortality in different European countries those with declining lipid levels over time showed a change in coronary heart mortality in the same direction, whereas mortality accelerated when lipid levels increased.9 Lipid control should ideally be part of a multifactorial approach on risk modification. Recently, a national initiative on multidisciplinary outpatient cardiac rehabilitation in Austria showed parallel improvements in exercise capacity, blood pressure control, glucose metabolism, and lipid profiles in patients with a chronic rehabilitation programme.10 We implemented our protocol in a regional network, where patients are referred to a structured rehabilitation programme following acute hospitalization. In this network, all regional acute hospitals and subsequent rehabilitation facilities participated in defining the standard-operating procedures for secondary prevention following STEMI in the Hannover area. Then, we ensured the availability of recommended medications for all prescribing general practitioners by incorporating the regional Association of Statutory Health Insurance Physicians considering that 95% of our STEMI patients had public insurance. While this improved drug prescriptions on a regional level, it might differ in other regions. Nevertheless, the example demonstrates that by using structured recommendations and networking, ambitious guideline targets can be achieved in many patients in everyday clinical practice.

In summary, using standardized per-protocol induction of potent lipid-lowering therapy and preventing financial repercussions for prescribers resulted in almost every second STEMI patient achieving an LDL-C ≤ 1.4 mmol/L (55 mg/dL). Local networking strategies bringing...
together acute care providers, general practitioners and regional regulatory bodies which implement protocols allowing to prescribe guideline-recommended treatments can contribute to higher rates of treatment success and will hopefully lower morbidity and mortality.

**Supplementary material**
Supplementary material is available at European Journal of Preventive Cardiology online.

**Conflict of interest:** A.S. received lecture fees and honoraria form Amgen, Astra Zeneca, Daiichi Sankyo, MSD. J.B. received lecture fees and honoraria form Amgen, Astra Zeneca, MSD. H.L. received lecture fees and honoraria form Amgen, Astra Zeneca, MSD, Sanofi-aventis, Berlin-Chemie Menarini, Ipsen. All other authors have no conflict of interest to declare.

**Data availability**
Substantiated requests can be addressed to the corresponding author.

**References**
1. Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;302:1993–2000.
2. Mach F, Baigent C, Catapano AL, Koшкина KC, Casula M, Badmon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen M-R, Tokgozoglu L, Wittlund O; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111–188.
3. De Backer G, Jankowski P, Kotasek V, Mirakhrimov, E. Reiner, Z. Ryden, L. Tokgozoglu, L., Wood, D. De Bacquer, D. Euroaspire V. collaborators. Management of dyslipidaemia in patients with coronary heart disease: results from the ESC-EORP EUROASPIRE V survey in 27 countries. *Atherosclerosis* 2019;285:135–146.
4. Gitt AK, Lautsch D, Ferrière J, De Ferrari GM, Vyas A, Baxter CA, Bash LD, Ashton V, Horack M, Almahmeed W, Chiang F-T, Poh KK, Brudi P, Ambegaonkar B. Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: results from the Dyslipidemia International Study II. *Atherosclerosis* 2017;266:158–166.
5. Marz W, Dippel FW, Thorbald K, García C, Iorga SR, Ansell D. Utilization of lipid-modifying therapy and low-density lipoprotein cholesterol goal attainment in patients at high and very-high cardiovascular risk: real-world evidence from Germany. *Atherosclerosis* 2018;286:99–107.
6. Laufs U, Karmann B, Pitter D. Atravastatin treatment and LDL cholesterol target attainment in patients at very high cardiovascular risk. *Clin Res Cardiol* 2016;105:783–790.
7. Leiter LA, Bays H, Conard S, Bird S, Rubino J, Hanson ME, Tomasini J, Tershakovec AM. Efficacy and safety of ezetimibe added on to atorvastatin (40 mg) compared with uptitration of atorvastatin (to 80 mg) in hypercholesterolemic patients at high risk of coronary heart disease. *Am J Cardiol* 2008;102:1495–1501.
8. Ballantyne CP, Houri J, Notarbartolo A, Melani L, Lipica L, Suresh R, Sun S, LeBeaut AP, Sager PT, Melani L. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. *Circulation* 2003;107:2409–2415.
9. Menotti A, Puddu PE, Kronhout D, Kafatos A, Tolonen H. Coronary heart disease mortality trends during 50 years as explained by risk factor changes: the European cohorts of the Seven Countries Study. *Eur J Prev Cardiol* 2020; 27:988–998.

10. Reich B, Benzer W, Harpf H, Hofmann P, Mayr K, Ocenasek H, Podolsky A, Pokan R, Porodko M, Puelacher C, Sareban M, Traninger H, Ziegelmeyer W, Niebauer J. Efficacy of extended, comprehensive outpatient cardiac rehabilitation on cardiovascular risk factors: a nationwide registry. *Eur J Prev Cardiol* 2020; 27:1026–1033.