Higher responsiveness to rosuvastatin in polygenic versus monogenic hypercholesterolaemia: a propensity score analysis

A. Mickiewicz[1], M. Futema[2], A. Cwiklinska[3], A. Kuchta[3], M. Kaszubowski[4], M. Chmara[5], M. Jankowski[3], B. Wasag[5], M. Fijalkowski[1], M. Jaguszewski[1], S.E. Humphries[6], M. Gruchala[1]

[1]Medical University of Gdansk, 1st Department of Cardiology, Gdansk, Poland; [2]University College London, Centre for Heart Muscle Disease, Institute of Cardiovascular Science, London, United Kingdom; [3]Medical University of Gdansk, Department of Clinical Chemistry, Gdansk, Poland; [4]Gdansk University of Technology, Institute of Statistics, Department of Economic Sciences, Faculty of Management and Economics, Gdansk, Poland; [5]Medical University of Gdansk, Department of Biology & Genetics, Gdansk, Poland; [6]University College London, Centre for Cardiovascular Genetics,Institute of Cardiovascular Science, London, United Kingdom

Funding Acknowledgement: Type of funding source: Public grant(s) – EU funding. Main funding source(s): 1. Polish Ministry of Science and Higher Education European Regional Development Fund under the Programme Innovative Economy 2007–2013 (POIG.01.01.02-22-079/09). 2. British Heart Foundation (PG 08/008). 3. The National Institute for Health Research, University College London Hospitals, Biomedical Research Centre. 4. The Foundation Leducq Transatlantic Networks of Excellence Program grant (no. 14 CVD03)

Background: The underlying monogenic defect in familial hypercholesterolemia (FH) can be detected in ∼40% of cases. The majority of mutation-negative patients have a polygenic cause of high LDL-cholesterol (LDL-C) due to having inherited a greater than average number of common LDL-C raising single nucleotide polymorphisms (SNPs).

Purpose: We sought to investigate, whether the monogenic or polygenic defect in FH is associated with the response to rosuvastatin.

Methods: Individuals with a clinical diagnosis of FH were tested for mutations in LDLR and APOB genes. A previously established LDL-C-specific polygenic risk score (PRS) was used to examine the possibility of polygenic hypercholesterolemia in mutation negative patients. The propensity score analysis was performed to evaluate the variables associated with the response to rosuvastatin. The type of hypercholesterolemia (polygenic or monogenic) and following variables: age, gender, LDL-baseline, statin intolerance, ezetimibe use, rosuvastatin dose, diabetes and cardiovascular disease (CVD), were examined to minimize the bias of this observational study.

Results: LDLR/APOB mutation was found in 47 (42%) patients, whereas polygenic hypercholesterolemia was diagnosed in 65 (58%) of patients. Mean age was comparable in both groups (54±13 vs 51±13, p=0.134). CVD was diagnosed in ≈26% of individuals in both cohorts (p=0.343). There was no difference in the distribution of CV risk factors, such as arterial hypertension, smoking, diabetes, body mass index and in rate of statin intolerance. Monogenic subjects had higher baseline LDL-C compared to polygenic (Table 1). Adjusted model showed a lower percentage of change in LDL-C after rosuvastatin treatment in monogenic vs. polygenic subjects (46% vs 55%, p<0.001) (Figure 1). The probability of achieving LDL-C targets in monogenic FH was lower than in polygenic subjects (0.075 vs. 0.245, p=0.004). Polygenic patients were more likely to achieve LDL-C goals, compared to mutation-positive patients (OR 3.28; 95% CI:1.23–8.72).

Conclusion: Our findings indicate an essentially higher responsiveness to rosuvastatin in patients with a polygenic cause, as compared to those carrying monogenic mutations.

Table 1. LDL-C and rosuvastatin treatment

	Polygenic (n=65)	Monogenic (n=47)	P value
LDL-C baseline, mg/dl	238±47	293±56	<0.001
LDL-C after treatment, mg/dl	110±27	146±44	<0.001
Rosuvastatin 5–10 mg daily	22 (34%)	9 (19%)	0.134
Rosuvastatin 15–20 mg daily	20 (31%)	22 (47%)	
Rosuvastatin 30–40 mg daily	23 (36%)	16 (34%)	
LDL-C goal achieved	20 (31%)	5 (11%)	0.012

Data are presented as mean ± standard deviation and number (percentage).

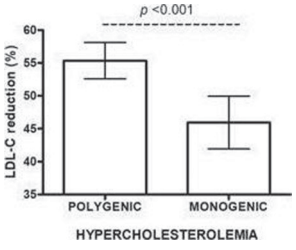

Figure 1