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Research Article

Analysis of the frequency of detection of hypercholesterolemia, carotid atherosclerosis and lipid-lowering therapy prescription in young adults under 45 years old according to the Duplex registry database

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Abstract

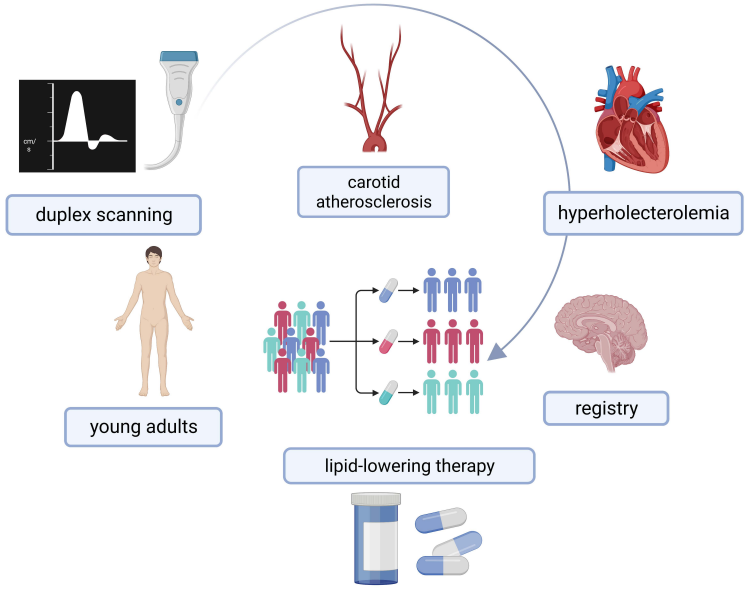
Aim of the study to analyze the detection of hypercholesterolemia (HCHL) and carotid atherosclerosis (CAS), verified by duplex scanning of the carotid arteries (DSCA) in young adults (YA), and to evaluate the lipid-lowering therapy (LLT) prescription among them according to the local registry database.

Materials and methods: The Duplex registry database was used for this study (n=2548). YA up to 45 years old were selected for the final analysis (n=351).

Results: HCHL (> 5 mmol/L) was detected in 68.9% of patients (n=241), and only 9.5% of them received LLT (n=23). CAS was detected in 12.8% (n=45), only 17.8% of them had received LLT (n=8). Men and women differed 1.5 times by the incidence of CAS in this age range: 15.7% (30 out of 191) vs 9.4% (15 out of 160), p=0.05. Men also generally have a higher prevalence of other risk factors/diseases: HCHL (78.0% (n=149) vs 58.1% (n=93) in women, p=0.00004), hypertension (AH) (15.7% (n=30) vs 9.4% (n=15) in women, p=0,05), history of myocardial infarction (MI) (1,6% (n=3) vs 0% (n=0) in women, ns). Signs that had a significant impact on LLT intake were the following: CAS (OR 2.8 [1.09;6.6] p=0.036); AH (OR 3.1 [1.32; 7.16] p=0.009); HCHL (> 5 mmol/L) (OR 4.2 [1.12; 26.83] p=0.06); HCHL (ICD-10 code E78) (OR 5.4 [2.04; 13.7] p=0.0003); MI history (OR 22.3 [1.65;675.5] p=0.009).

Conclusion: The insufficient LLT prescription in young adults with HCHL and CAS was ascertained in the present study. The use of imaging methods to clarify the degree of cardiovascular risk is advisable for low and intermediate risk patients, which include young adults. DSCA is the main method for subclinical atherosclerosis verification. LLT should be prescribed to all YA patients with CAS (in the absence of contraindications).

Graphical Abstract



Keywords

lipid-lowering therapy, young adults, hypercholesterolemia, carotid atherosclerosis, duplex scanning, registry.

Introduction

The underprescribing of statins is a well-known practical medicine problem, which still remains relevant, despite the large evidence base obtained over the past decades for this group of drugs (Sever et al. 2003; Crouse et al. 2007; Ray et al. 2010; Chou et al. 2016). Yusuf et al. (2011) confirmed the lowest percentage of statin prescription compared to other classes of cardiac drugs in patients at high cardiovascular risk (HCR) in a large population-based PURE study (Prospective Urban Rural Epidemiological study, n=153,996): antiplatelet drugs (25.3%), β-blockers (17.4%), ACE inhibitors/ARBs (19.5%), and statins (14.6%). An analysis of statin prescribing in primary prevention (for participants without CVD at baseline) showed that prescribing for lipid-lowering therapy (LLT) was generally very low, with higher prescribing rates in high-income countries, intermediate – in middle-income countries and lowest – in low-income countries (10.3%, 1.6% and 0.3%, respectively) (Yusuf et al. 2014). Similar trends were noted for individuals with cardiovascular disease: 25% of HCR patients did not receive drugs proven to affect the prognosis in this category of patients (antihypertensive drugs, antiplatelet agents, statins) (Chow et al. 2020). In addition to insufficient prescribing, there is also a lack of effectiveness of LLT in patients with HCHL, including patients with more severe hereditary forms of HCHL (D'Erasmo et al. 2020). Elis et al. (2020) stated in their large cohort study (n=12494) that the majority of patients with probable familial hypercholesterolemia did not initially control their LDL-C levels and only a quarter of them received medical treatment.

At the same time, CAD patients are more adherent to LLT. Zyryanov et al. (2020) noted a significant increase in the use of lipid-lowering drugs over a 7-year follow-up period in outpatients with CAD (mean age 68.9 + 9.9 years) from 48.5% to 86.4%. The most LLT adherent were patients who had undergone MI and coronary intervention, which was previously confirmed in a study performed according to the Profile registry (age 64.0 (57.0–72.0)). Factors that increased LLT adherence in this study were CAD (OR 4.3, 95% CI [2.18;8.67], p=0.0001), MI history (OR 4.8, 95% CI [1.76;13.25], p=0.002), previous coronary intervention (OR 5.16, 95% CI [2.05;12.9], p=0.0001) (Gaisenok et al. 2015).

CAD patients represent an older age group who have already begun to move along the cardiovascular continuum. The greatest effect should be expected from the statins appointment at the earliest stage of this process, even before the atherosclerotic plaque formation (Tabas et al. 2007).

There are practically no studies that have analyzed the problem of LLT prescribing in young patients in aspect of HCHL and CAS detection, and those studies of LLT in young adults (YA) that have been performed have often concerned very narrow specific patient categories (Joyce et al. 2015; Arora et al. 2019).

Aim of the study: to analyze the detection of hypercholesterolemia (HCHL) and carotid atherosclerosis (CAS), verified by duplex scanning of

the carotid arteries (DSCA) in young adults (YA), and to evaluate the lipid-lowering therapy (LLT) prescription among them according to the local registry database.

Material and Methods

Group description

The Duplex registry database was used for this study. The detailed methodology for conducting this registry was described earlier in previous publications (Gaisenok et al. 2018; Gaisenok and Drapkina 2022). The registry protocol conforms to the ethical guidelines of the Helsinki Declaration. There were no exclusion criteria: all patients who had undergone DSCA in the United Hospital with Outpatient Clinic in 2013 were included in this registry. The final database included 2548 primary patients (excluding recurrences within a year), the percentage of men was 51% (n=1301).

Study design

The study was performed by two experienced specialists who applied a single unified protocol using 9-12MHz multi-frequency linear sensors on GE devices according to the standard technique. Common carotid arteries and their bifurcations, internal and external carotid arteries and subclavian arteries were examined. The percentage of stenosis was determined in the area of maximum narrowing of the lumen of the artery in accordance with the ECST criteria (European Carotid Surgery Trial 1998). All patients initially signed informed consent for the study and the processing of personal data. Additional written consent was not required given the retrospective nature of this study. The study was approved by the Ethics Committee of the United Hospital with Outpatient Clinic (№7 of 02/09/2021). All patient data were anonymized prior to final analysis. CAS verification during DSCA was based on the detection of atherosclerotic plaque (AP), stenosing the carotid lumen by 20% or more. Verification of registry patients by ICD-10 diagnoses was carried out according to the diagnosis code that preceded the referral for DSCA during the previous medical examination and was registered in the electronic database.

Statistical analysis

Statistical data processing was performed using the Statistica 10.0 software package (Statsoft Inc.). Data of groups were presented as median, 25% and 75% percentile (or if applicable as absolute numbers and percentages). The Yates-corrected $\chi 2$ test was used to compare groups on a qualitative sign (if necessary, Fisher's exact test was applied depending on the size of the subgroups). Odds ratios (OR) and 95% confidence interval (95% CI) were calculated to determine the effect of various diseases/risk factors on the likelihood of prescribing lipid-lowering therapy. Differences were considered statistically significant at $p<0.05$.

Results

YA up to 45 years old (based on WHO criteria) were selected for the final analysis (n=351). The average age of the patients was 37.1±6.3 years; male – 54.4% (n=191). The study design and patient selection scheme are shown in Figure 1.

The analysis of ongoing LLT was carried out in YA among the representatives of the Duplex registry database sample. HCHL > 5 mmol/L was detected in 68.9% of patients (n=241), and only 9.5% of them had received LLT (n=23). LLT was mainly represented by statins (rosuvastatin – 11, atorvastatin – 8, and simvastatin – 2). Fenofibrate was taken by 2 patients. Another 2 patients had received plasmapheresis procedures. LDL-C > 3 mmol/L was detected in 59.5% of patients (n=209). LLT received only 8.6% of them (n=18): rosuvastatin – 9, atorvastatin – 8, simvastatin – 1, fenofibrate – 1, and plasmapheresis – 1.

Patients characteristics by baseline diagnoses (prior to inclusion in the registry database) are presented in Table 1, which also contains the clinical characteristics of patients in each nosological group: their distribution by gender, age, total cholesterol and LDL-C data, the number of patients who received LLT in each subgroup.

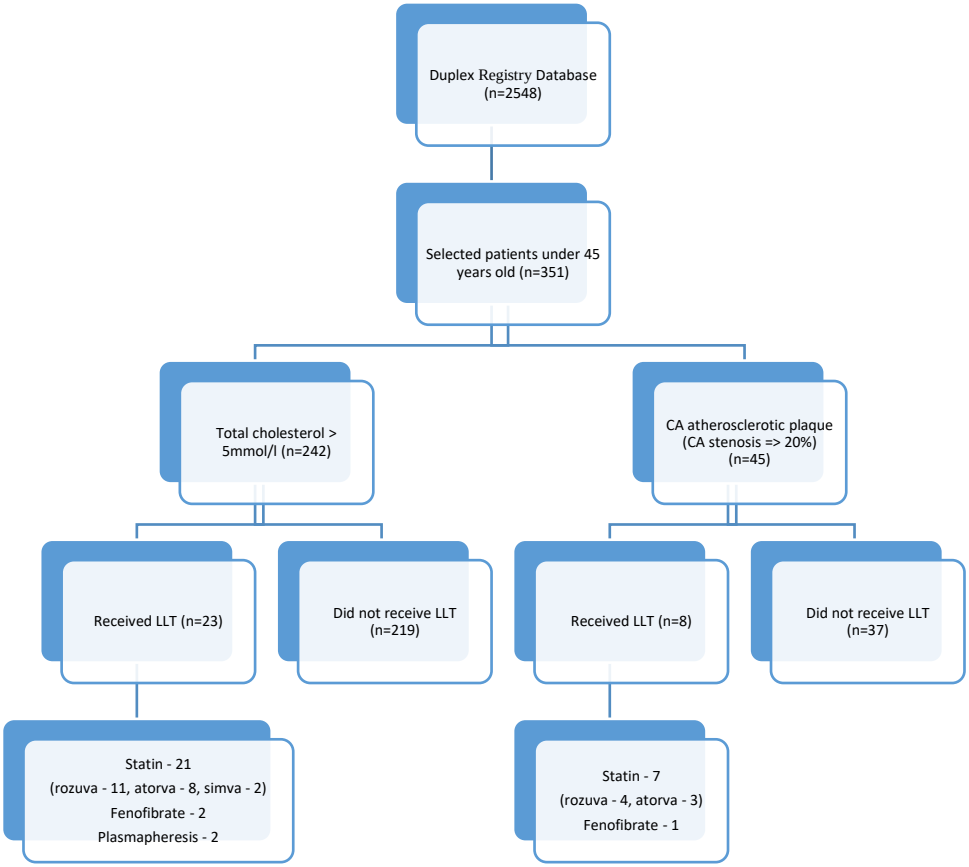


Figure 1. Study design and patient selection scheme. **Note:** CA – carotid artery, LLT – lipid-lowering therapy, rozuva – rosuvastatin, atorva – atorvastatin, simva – simvastatin.

Table 1. Clinical characteristics of young adults and the number of persons receiving LLT in each nosological group

Diagnosis	Diagnosis Verification	No. of patients	Gender	Age	Total cholesterol	LDL-C	Received LLT
HCHL	ICD-10 code E78	29	M/20 F/9	41.0 [37.0;43.0]	6.51 [5.64;7.6]	4.06 [3.55;5.27]	8*
HCHL	Total cholesterol > 5mmol/L	242	M/149 F/93	40.0 [36.0;42.0]	5.96 [5.47;6.61]	3.77 [3.38;4.34]	25**
Hypertension	ICD-10 code I10-I11	56	M/45 F/11	40.0 [34.0;41.0]	5.54 [5.22;6.21]	3.47 [3.06;3.94]	10*
History of MI	ICD-10 code I25.2	3	M/3	37.0 [36.0;44.0]	5.86 [3.79;6.64]	4.32 [2.15;4.93]	2
TIA	ICD-10 code G45	1	F/1	40.0	6.08	4.43	–
Stroke	ICD-10 code I63.4	1	M/1	43.0	6.12	3.9	–
CAS	DSCA: stenosis > 20%	46	M/30 F/15	41.0 [38.0;43.0]	5.82 [5.41;6.38]	3.84 [3.31;4.26]	8
Diabetes mellitus	ICD-10 code E11.8	4	M/2 F/2	37.0 [34.0;40.5]	5.33 [4.29;6.17]	3.18 [2.61;3.61]	–
Atrial fibrillation	ICD-10 code I48	2	M/2	40.0 [39.0;41.0]	5.33 [5.01;5.66]	3.52 [3.39;3.83]	–

Note: (including patients who had received plasmapheresis procedures (* – 1 patient, ** – 2 patients)): HCHL – hypercholesterolemia, LDL-C – low density lipoprotein cholesterol, LLT – lipid-lowering therapy, M – male, F – female, ICD-10 – international classification of diseases 10th revision, MI – myocardial infarction, TIA – transient ischemic attack, CAS – carotid atherosclerosis, DSCA – duplex scanning of the carotid arteries.

As for patients with carotid atherosclerosis, their percentage was 12.8% (n=45). LLT had been received by 17.8% of them (n=8): rosuvastatin – by 4 patients, atorvastatin – by 3 patients, fenofibrate – by 1 patient (Fig. 1).

In total, in the general study group (n=351) 8.5% of patients (n=30) had received LLT: statins – 24 patients (atorvastatin – 11 patients, rosuvastatin – 11, and simvastatin – 2), fenofibrate – 4 patients, and plasmapheresis – 2 patients.

An analysis of the influence of the main clinical conditions on the fact of prescribing LLT according to the data of this study is presented in Table 2.

Table 2. Analysis of the influence of main clinical conditions on the fact of prescribing lipid-lowering therapy

Sign	OR	95% CI	χ^2	p-level (2-t)
CAS (stenosis > 20%)	2.8	[1.09;6.6]	4.35	0.036
Hypertension	3.1	[1.32;7.16]	6.65	0.009
HCHL (TC > 5mmol/L)	4.2	[1.12;26.83]	3.38	0.06
HCHL (ICD-10 code E78)	5.4	[2.04;13.7]	12.92	0.0003
History of MI	22.3	[1.65;675.5]	6.65	0.009

Note: OR – odds ratio, CI – confidence interval, CAS – carotid atherosclerosis, HCHL – hypercholesterolemia, TC – total cholesterol, ICD-10 – international classification of diseases 10th revision, MI – myocardial infarction.

Disscussion

The problem of insufficient prescription of statin therapy for both primary and secondary prevention is extremely relevant for Russia. Thus, an analysis of LLT prescribing in secondary prevention in the ARGO study showed that statins were not prescribed to 49% of outpatients in the Central Federal District with hypercholesterolemia who needed them (mean level of total cholesterol (TC) 6.10 ± 0.015 mmol/L; TC >5 mmol/L – 81.44%). It should be noted that, in accordance with the protocol of this cross-sectional study, it included patients aged over 30 years who consulted a doctor about the following diseases: stable CAD, any type of revascularization, arterial hypertension (AH), history of ischemic stroke, atherosclerotic lesions of peripheral arteries (carotid, femoral arteries), and aortic aneurysm (Akhmedzhanov et al. 2015). Analysis of adherence to statin therapy in patients with AH of high and very high cardiovascular risk in real clinical practice in Irkutsk revealed that 64% of high-risk patients were non-compliant to LLT (Ivanova et al. 2021). At the same time, Berdalin et al (2021) showed in their study that in AH patients compared with patients without AH history there was a more frequent detection of atherosclerotic plaques in the carotid artery (right CCA/ICA 37.2% vs 14.4%, p=0.027; left CCA/ICA 41.9% vs 13.5%, p=0.001) and a greater degree of stenotic narrowing of the carotid arteries.

Högberg et al. (2014), using a multivariate logistic regression model in their study, found that AH (OR 1.5, 95% CI 1.3-1.7) and CAD (OR 1.5, 95% CI 1.3–1.8) were associated with the prevalence of CAS. The use of statins in participants of that study with verified CAS was only 29%. But that Swedish study was performed on a 65-year-old male population cohort. In our study, the average age of the study participants was 37.1 ± 6.3 years, and the LLT prescription in people under 45 years old with CAS was registered at 17.7% level (Fig. 2).

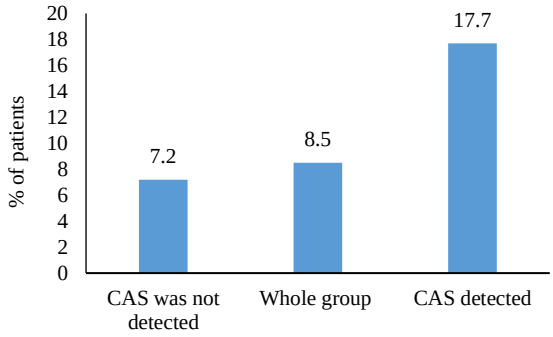


Figure 2. Prescribing lipid-lowering therapy in persons under 45 years old (in %). **Note:** CAS – carotid atherosclerosis.

At the same time, there is evidence that the beginning of an active increase in the severity of CAS is observed at the age of 40-44 years in men and 45-49 years in women (Kaveshnikov et al. 2019). Kaveshnikov et al. (2029), according to the results of their study, stated that among individuals with the presence of AP in the carotid artery, all quantitative indicators were statistically significantly higher in men than in women. Similar data were also obtained in our study. Men and women differed by 1.5 times by the incidence of CAS in this age range: 15.7% (30 out of 191) vs 9.4% (15 out of 160), p=0.05. Men also generally have a higher prevalence of other risk factors/diseases, such as HCHL (78.0% (n=149) vs 58.1% (n=93) in women, p=0.00004), AH (15.7% (n=30) vs 9.4% (n=15) in women, p=0,05), and history of myocardial infarction (1,6% (n=3) vs 0% (n=0) in women, ns). Similar data on the greater prevalence of severe HCHL in young men under 40 years compared with women were previously obtained in another Russian study (Korneva et al. 2015).

Aggressive statin therapy (alone or in combination with another lipid-lowering drug) has been proven to promote regression of carotid atherosclerosis. So Sibley et al. (2013) observed in their study a significant decrease in the main indicator of the ICA wall volume assessment, which regressed by 0.5%/month (SEM 0.2, p=0.004) in the group of patients receiving statin monotherapy, and by 0.7 % per month in the group of patients receiving combination therapy with statin and niacin (SEM 0.2, p<0.001) (Sibley et al. 2013).

Similar results were obtained in the SANDS study (Stop Atherosclerosis in Native Diabetics Study) (Fleg et al. 2008). Mean IMT in the group of patients receiving aggressive lipid-lowering therapy (maximum doses of statins) after 36 months decreased compared with the baseline in the statin plus ezetimibe combination subgroup (-0.025 [-0.05 to 0.003] mm) and in the statin monotherapy subgroup (-0.012 [-0.03 to 0.008] mm). At the same time, an increase in IMT was noted in the standard treatment group (low and medium doses of statins) (0.039 [0.02–0.06] mm, p<0.0001) (Fleg et al. 2008).

Unfortunately, it is worth noting the predominant use of low- and/or medium-dose statins in our study, as well as the almost complete absence of combination therapy: none of the patients received a combination of a statin with ezetimibe or niacin; and only 2 patients received a combination of a statin with fenofibrate. In general, we can state the insufficient LLT prescription in young patients in the present study (8.5%, n=30 (Fig. 2)) and a greater likelihood of CAS progression in these patients with this choice of drug strategy. The estimated percentage of statin prescription in this cohort (based on the data in Table 1), depending on the objectives of secondary or primary prevention could be from 13.7 to 68.9%.

It is probably worth considering the young age of patients (37.1 + 6.3 years) as the main factor that discouraged physicians from prescribing and patients from adhering to lipid-lowering therapy in the present study. In conclusion it is worth noting the limitations of this study, which are typical for all observational studies based on local registries and analysis of electronic databases (Martsevich et al. 2021).

Conclusion

The insufficient LLT prescription in young adults with HCHL and CAS was ascertained in the present study. Clinical guidelines suggest that the use of imaging methods to clarify the degree of cardiovascular risk is advisable for low and intermediate risk patients, which include young adults (Mach et al. 2020). This implies that the main method for verifying subclinical atherosclerosis in clinical practice is duplex scanning of the carotid arteries. The logical conclusion of this study is the decision that statin therapy should be prescribed when carotid atherosclerosis detected in 100% of patients including young adults (in the absence of contraindications). Active promotion among physicians and patients of the ideas of early prescription of statin therapy is necessary to achieve this goal. Statin therapy slows down the progression of carotid atherosclerosis, which indicates the expediency of its initiation at an early subclinical stage of the disease (Bedi et al. 2010).

Conflict of interest

The authors declare no conflict of interests.

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