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Letter to the Editors-in-Chief

Effect of statin intake on FVIII levels and bleeding outcomes in hypercholesterolemic patients with hemophilia A

Introduction

Patients with hemophilia A are not protected from atherosclerosis, despite their condition of hypocoagulablity, and nowadays that life expectancy of hemophiliacs approaches that of non-hemophilic peers, cardiovascular (CV) disease represents a significant cause of morbidity and mortality also in this patient population [1]. However, since the use of either antiplatelet or anticoagulant agents associates with a relevant bleeding risk in these patients, the control of CV-risk factors, and in particular of hypercholesterolemia, becomes pivotal for primary and secondary CV prophylaxis. Low density lipoprotein (LDL) cholesterol is cleared from plasma by LDL receptors (LDLR) mainly present on liver cells. Statins, the most widely used lipid-lowering agents, act by inhibiting the enzyme hydroxymethylglutarylCoA (HMG-CoA) reductase but they also increase hepatocyte LDLR expression. FVIII is cleared from blood through the binding to several receptors including LRP1, that belongs to the LDLR family, which cooperate with LDLR in regulating its plasma levels [2]. Atorvastatin was shown to increase the hepatic expression of LRP1 [3]. Interestingly, factor VIII levels were reported to be lower in healthy subjects treated with statins compared with untreated controls [4], and a recent trial in patients with venous thrombosis showed that a brief course of high-dose rosuvastatin (20 mg/d) significantly reduced FVIII levels [5]. It can thus be hypothesized that statins may reduce FVIII levels by increasing LDLR and LRP1 [6]. Indeed, in a mouse model of increased circulating FVIII levels we recently showed that a 5-day treatment with alirocumab and atorvastatin produced a significant reduction of FVIII levels in concomitance with enhanced hepatocyte and monocyte LRP1 expression [7]. According to these premises, the use of statins in subjects with hemophilia A might increase FVIII clearance reducing FVIII levels thus possibly increasing bleeding or FVIII-concentrate consumption. To the best of our knowledge, no data are available on the influence of statins on FVIII levels and the bleeding phenotype in patients with hemophilia A. Aims of our study were to evaluate the use of statins in hemophiliacs in a real life setting and their effect on bleeding outcomes and FVIII concentrate consumption.

We performed a multicenter, retrospective study among 9 hemophilia centers in Italy. The study was approved by the Bioethical committee of the coordinating Center (University of Perugia appr. n. 79061) and each participant center adhered to local IRB rules.

Patients were included if they were >40 years-old, had hypercholesterolemia [8] and had been put on lipid-lowering therapy for at least 4 weeks. A similar number of untreated hyperlipemic, severity-matched hemophiliac controls were recruited. Medical history, hemophilia severity, inhibitor status, lipid profile, concomitant treatments, FVIII-concentrate consumption, ABR and median FVIII levels in the year preceding enrollment, and for the statin-treated subjects also in the year before statin initiation, were recorded. In patients on regular prophylaxis FVIII levels refer to through levels.

Variables not normally distributed are reported as medians and interquartile ranges (IQR), and differences between variables were tested using the Mann–Whitney *U* test or the Kruskal-Wallis analysis of variance (ANOVA) test. Categorical variables were analysed using the $\chi 2$ test. All analyses were performed using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA).

A total of 1193 hemophilia A patients were screened for possible enrollment, 494 of whom (41.4 %) were >40 years-old, the conventional age threshold for starting pharmacologic lipid-lowering therapy. Prevalence of hypercholesterolemia, defined according with the European Guidelines on dyslipidemia management [8], was 4.5 % (54 patients) in the total hemophilic population and 10.9 % (54 patients) in those > 40 years-old. Statins were used in 23 hyperlipemic patients (42.6 %) and one patient was treated with ezetimibe alone (1.8 %). No patient was on other lipid-lowering therapies. In 20 of the treated patients (86.9 %) statins were used with a moderate intensity regimen (rosuvastatin 5 mg or more, atorvastatin 10 mg or more) and in three (13.1 %) with a low-intensity regimen (simvastatin 10 mg). Median duration of statin treatment at the moment of data-analysis was 4 (IQR: 3–5) years. Among the 54 dyslipidemic patients, 20 (37 %) had severe, 14 (26 %) moderate and 20 (37 %) mild hemophilia A; of these 4 (20 %), 8 (57 %), and 11 (55 %) were treated with statins, respectively. Statin users were significantly older and more frequently affected with non-severe hemophilia than statin non-users (Table 1). Twenty-seven patients (50 %; 12 with mild hemophilia) were treated on demand and 27 were on regular prophylaxis (8 with mild hemophilia) with either FVIII concentrates (20, 74 %; 8 on tertiary and 12 on secondary prophylaxis) or emicizumab (7, 26 %). Four patients (3 with severe and 1 with moderate hemophilia) had anti-FVIII neutralizing antibodies. Median total cholesterol levels in the whole dyslipidemic patient population (n = 54) were 5.2 mmol/L (IQR 4.4–5.8), tryglicerides 1.2 mmol/L (IQR 0.8–1.9), HDL cholesterol 1.4 mmol/L (IQR 1.2–1.6) and LDL-cholesterol 3.3 mmol/L (IQR 2.2–3.6). Twelve patients were classified as at high or very high cardiovascular risk according to EAS/ESC 2019 Guidelines for the management of dyslipidemias and three (5.6 % of the overall dyslipidemic-population; 1 severe, 1 moderate and 1 mild) were on antiplatelet therapy for a previous cardiovascular event (myocardial infarction). In patients on treatment with a statin median total cholesterol levels were 4.9 mmol/L (IQR 3.6–5.8), tryglicerides

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Table 1
Dyslipidemic hemophilia A patient characteristics.

	Statin users (23)	Statin non-users (31)	*P* value
Age [years, median (IQR)]	60 (54–72)	53 (44–63)	0.02
Severe hemophilia (%)	4 (17.4)	16 (51.6)	0.05
Total cholesterol [mmol/L, median (IQR)]	4.9 (3.6–5.8)	5.3 (4.9–5.8)	NS
Triglycerides [mmol/L, median(IQR)]	1.2 (0.9–1.9)	1.2 (0.8–2)	NS
LDL-c [mmol/L, median(IQR)]	2.7 (1.7–4.1)	3.5 (2.8–3.6)	NS
HDL-c [mmol/L, median(IQR)]	1.4 (1.2–1.6)	1.3 (1.1–1.6)	NS

IQR: interquartile range; LDL-c: low density lipoprotein cholesterol; HDL-c high density lipoprotein cholesterol; NS: not significant.

1.2 mmol/L (IQR 0.9–1.8), HDL cholesterol 1.4 mmol/L (IQR 1.2–1.6) and LDL cholesterol 2.7 mmol/L (1.7–4.1) (Table 1). Among patients treated with a statin, 2 of whom were at high or very high CV risk (8.7 %), only 30 % attained LDL levels at guideline-recommended targets [8]. No significant difference in FVIII levels, annual FVIII concentrate consumption and annual bleeding rates (ABR) were found between statin users and non-users, neither before vs after statin initiation in those treated with statins (Table 2), nor in any hemophilia severity subgroup (data not shown). The small increase in FVIII levels after statin introduction in our population was not statistically significant and can be attributed to the small sample size and/or to the slight intrinsic variability of FVIII levels in mild/moderate hemophiliacs.

Our study in a real life setting in Italy shows that the prevalence of dyslipidemia among adult patients with hemophilia A is significant and that there is a global underuse of statins in dyslipidemic hemophiliacs and an unsatisfactory level of dyslipidemia control in those treated, but it also suggests that statins may not negatively impact on FVIII levels and concentrates consumption.

In a previous large cohort study including 2506 hemophilia A patients and 7518 controls, prevalence of hyperlipidemia was significantly higher in hemophiliacs (15.9 % vs. 11.9 %, $P < 0.001$) [9]. In our study, statins seem to be less used among >40 age-year old hemophiliacs than in an age-matched general population (4.1 % vs 16 %). The low statin use in hemophiliacs may reflect either the groundless belief that they are protected from atherosclerosis and thus do not require CV risk-factor control or the infrequent use of CV-risk screening in these patients. Our results suggest that statins do not associate with a reduction of FVIII levels, an increase of bleeding events or an enhanced FVIII concentrate consumption in hemophiliacs. Given previous results showing that statins reduce plasma FVIII in patients with increased baseline levels [5] and in mice infused with FVIII [7], the present observation suggests that their FVIII-reducing action may not take place when baseline FVIII levels are low. Advanced age of our dyslipidemic hemophilic population and possibly other PK determinants (such as plasma von Willebrand factor levels or AB-0 group), which were not measured in the present study, might also have attenuated the effect of statins on FVIII clearance, given that age negatively correlates with FVIII clearance [10].

Our study has several limitations: first, its retrospective design lowers the accuracy of our findings allowing only a descriptive analysis. However, this is the first study exploring this aspect and our results should be considered hypothesis-generating for future investigations; secondly, pharmacokinetic data on FVIII plasma levels after concentrate infusion, which would be relevant to understand the potential impact of statins on FVIII clearance in a condition with high circulating FVIII levels, were not available. However, the lack of effect of statin use on the ABR in our study suggests that a significant effect on FVIII PK is unlikely.

Table 2
FVIII levels, FVIII consumption and ABR before and after statin introduction in statin users ($n = 23$ patients).

	Before Statin	After Statin
FVIII levels, U/dL, median (IQR)	4.25 (0.5–40)	9.8 (1–40)
ABR median (IQR)	0 (0–6)	0 (0–4)
FVIII consumption, U/kg per year, median (IQR)	0 (0–537)	0 (0–425)

ABR: annual bleeding rate; IQR: interquartile range.

In conclusion, statins seem to be a safe and underused treatment in patients with hemophilia A at high cardiovascular risk. Ad hoc designed, prospective studies to confirm the safety of statins, and possibly of other lipid-lowering agents, on FVIII levels and on the risk of bleeding in patients with hemophilia A and PK studies exploring whether in conditions of enhanced FVIII levels, such as those found immediately after FVIII-concentrate infusion, FVIII half-life is shortened by statins, are highly warranted.

CRediT authorship contribution statement

Francesco Paciullo: Writing – original draft. **Stefania Momi:** Formal analysis. **Maria Elisa Mancuso:** Investigation. **Cristina Santoro:** Investigation. **Mariasanta Napolitano:** Investigation. **Giancarlo Castaman:** Investigation. **Ezio Zanon:** Investigation. **Laura Contino:** Investigation. **Raimondo De Cristofaro:** Investigation. **Rita Carlotta Santoro:** Investigation. **Paolo Gresele:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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