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Compliance with Early Long-Term Prophylaxis Guidelines for Severe Hemophilia A

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Authors contribution: Paul Saultier and Yves Guillaume analyzed data and wrote the manuscript; Virginie Demiguel and Mohamed Boucekine performed the statistical analysis; Claire Berger, Annie Borel-Derlon, Ségolène Claeysens, Annie Harroche, Caroline Oudot, Anne Rafowicz, Marc Trossaert, Bénédicte Wibaut, Christine Vinciguerra and Sandrine Meunier collected data and revised the manuscript; Karine Baumstarck and Thierry Calvez analyzed data and participated in the study design, Hervé Chambost designed and supervised the research, and wrote the manuscript; All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT

Objectives: To evaluate applicability and compliance with guidelines for early initiation of long-term prophylaxis (LTP) in infants with severe hemophilia A and to identify factors associated with guideline compliance.

Study design: This real-world, prospective, multicenter, population-based FranceCoag study included almost all French boys with severe hemophilia A, born between 2000 and 2009 (*i.e.* after guideline implementation).

Results: We included 333 boys in the study cohort. The cumulative incidence of LTP use was 61.2% at three years of age *vs.* 9.5% in a historical cohort of 39 boys born in 1996 (*i.e.* before guideline implementation). The guidelines were not applicable in 23.1% of patients and 27% of patients complied with the guidelines (4.5% timely LTP initiation and 22.5% absence of LTP indication). Non-compliance was due to delayed (10.8%) or premature (39.0%) LTP initiation. In the multivariate analysis, treatment in centers located in southern regions of France (OR 23.6, 95%CI 1.9-286.7, $p=0.013$ *vs.* Paris Area) and older age at LTP indication (OR 7.2 for each additional year, 95%CI 1.2-43.2, $p=0.031$) were significantly associated with “timely LTP” *vs.* “delayed LTP”. Earlier birth year (OR 0.5, 95%CI 0.3-0.8, $p=0.010$ for birth years 2005-2009 *vs.* 2000-2004) and age at first factor replacement (OR 1.9 for each additional year, 95%CI 1.2-3.0, $p=0.005$) were significantly associated with “LTP guideline compliance” *vs.* “premature LTP”.

Conclusions: LTP guidelines improve care for hemophilia patients. However, early initiation of LTP remains a challenge.

Abbreviations: CI: confidence interval; HA: hemophilia A; HTC: hemophilia treatment centers; ICH: intracranial hemorrhage; IQR: interquartile range; LTP: Long-term prophylaxis; PUP: previously untreated patients.

INTRODUCTION

Long-term prophylaxis (LTP) represents a paradigm shift in severe hemophilia A (HA) treatment. LTP efficiently prevents hemophilic arthropathy, which is one of the most disabling and costly complications of HA, provided that treatment is started at a young age.[1–3] Accordingly, national and international guidelines that promote early initiation of LTP in infants with severe HA have been published. Early LTP guidelines published by the French society of hemophilia healthcare workers (CoMETH) have been available since 2000.[4]

Despite clear advantages, LTP is associated with several issues in infants and young children with HA. During LTP therapy, clotting factor must be regularly administered and a significant time commitment is required of the children and their parents. When venous access is difficult, the patient may require a central venous access device, which is also associated with complications. Although LTP is considered the gold standard treatment for infants and young children with HA, LTP use must be closely monitored. Importantly, longer-acting clotting factors, which have become increasingly available, only partly resolve these issues especially for HA, for which the drug half-life has been extended by only a factor of 1.5-1.6.[5] Other promising approaches (non-FVIII therapeutic approaches, gene therapy) have also been evaluated for HA. However, as none of these are currently approved for use in previously untreated patients (PUPs), LTP remains the gold standard treatment for HA during infancy.

Studies evaluating the implementation of national or international primary LTP guidelines and the consequences for patients are scarce. Carcao *et al.* and Chambost *et al.* have reported data from international surveys regarding prophylaxis use.[6,7] Manco-Johnson *et al.* have described prophylaxis use data from the US Hemophilia Treatment Center Network and the Centers for Disease Control and Prevention surveillance registry.[8]

However, these studies did not specifically monitor prophylaxis initiation in PUP populations, nor did they perform a comprehensive evaluation of compliance with national or international guidelines.

FranceCoag includes a French prospective national cohort of patients with hemophilia or a severe form of other inherited coagulation disorders. Preliminary data concerning the impact of the French primary LTP guidelines have been reported[9]; however, the retrospective study design did not include data on the oldest patients. The present study focused on boys in the FranceCoag PUPs Cohort born after the guidelines were published. This study aimed to (1) evaluate applicability and compliance with primary LTP guidelines and (2) identify determinants of compliance.

METHODS

French long-term prophylaxis guidelines

The French long-term prophylaxis guidelines, which promote early and escalating LTP, have been described in detail elsewhere.[4,9] The guidelines were adopted by the French society of hemophilia healthcare workers (CoMETH) in 2000. We focused on the primary LTP guidelines dedicated to children with severe HA, aged <3 years. The guidelines included early initiation of LTP based on the occurrence of bleeding in the major joints, with a four-step increase in LTP treatment in case of any additional recurrent joint bleeding. Primary LTP initiation was recommended after two joint bleeding events in the same major joint within six months or after three bleeding events in any major joint. The guidelines were not applicable to patients with an early intracranial hemorrhage (ICH) or inhibitor development.

FranceCoag and the PUPs cohort

FranceCoag included almost all French children born after 1999 and suffering from severe hemophilia.[10] Hemophilia healthcare workers prospectively recorded data during dedicated medical visits at hemophilia treatment centers (HTCs). The FranceCoag PUPs cohort prospectively includes French hemophilia patients with FVIII/FIX levels below 2%.[11] Informed written consent was obtained in accordance with protocols approved by local and national (French National Clinical Research Program) institutional review boards as well as the Declaration of Helsinki principles.

Study cohort and historical cohort

The study cohort consisted of boys with severe HA (FVIII <1%), born consecutively between January 2000 and December 2009, who were included in the PUPs cohort in one of 33 metropolitan HTCs of FranceCoag. As the study cohort included patients born after 2000, these patients were treated after the guidelines were implemented in all French HTCs. Patients from French overseas territories and girls were excluded from the study to optimize cohort homogeneity. Patients ≥ 3 years of age at the time of hemophilia diagnosis were excluded, as the study aimed to evaluate early LTP guidelines dedicated to children <3 years of age.

The historical cohort consisted of boys with severe HA (FVIII <1%), born consecutively in 1996. These patients were thus treated before the guideline elaboration process. At this time, no national LTP guidelines were available in France.

Applicability and compliance of long-term prophylaxis guidelines

For each patient, the nature and time of major events (ICH, inhibitor development, joint bleeding events, LTP initiation) determined LTP guideline applicability and compliance status (Figure 1 and Table 1).

Patients from the study cohort were divided into five groups: (1) patients for whom the guidelines were not applicable (due to early ICH or early inhibitors development), (2) patients with “premature LTP initiation” (*i.e.*, before LTP indication according to the guidelines), (3) patients with “no LTP indication and no LTP initiation” (due to few joint bleeding events until the age of three years), (4) patients with “timely LTP initiation” and (5) patients with “delayed LTP initiation”. “Timely LTP initiation” and “no LTP indication and no LTP initiation” were both situations in compliance with the guidelines (“LTP guideline compliance” group).

Statistical analyses

Quantitative variables were expressed using median and interquartile range (IQR) and compared using the Mann-Whitney test. Qualitative variables were compared using χ^2 or Fischer’s exact test. The cumulative incidence of LTP use according to age was estimated for the entire study cohort and the historical cohort using the Kaplan-Meier method and compared using the log-rank test. Prevalence rates are displayed with a 95% confidence interval (CI).

To identify factors independently associated with LTP guideline compliance, two analyses were performed on the study cohort data: (1) factors associated with delayed LTP initiation: “timely LTP” vs. “delayed LTP” (delayed LTP initiation may only occur in patients with LTP indication) and (2) factors associated with premature LTP initiation: “LTP guideline compliance” (*i.e.*, “timely LTP” + “no LTP indication and no LTP initiation”) vs. “premature LTP” (premature LTP initiation may occur in patients with or without LTP indication). For each analysis, multivariate logistic regression analysis was performed including variables selected on a threshold p-value ≤ 0.2 during the univariate analysis. The final models express the odds ratios and 95% CIs. Statistical analysis was performed using Stata software, release 10.0 (Stata Corporation, College Station, Texas).

RESULTS

Availability, applicability and compliance of LTP guidelines

Patients from the study cohort were categorized into five groups according to applicability and compliance with the French LTP guidelines (Figure 1 and Table 1) as stated in the methods section. The LTP guidelines were not applicable for 77 (23.1%) patients due to early occurrence of a major complication (ICH or inhibitor development). A total of 90 patients (27.0%) complied with the LTP guidelines, due to timely LTP initiation (n=15; 4.5%) or absence of LTP initiation consistent with no indication of early LTP (n=75; 22.5%). A total of 166 patients (49.8%) did not comply with the LTP guidelines, due to delayed LTP initiation (n=36; 10.8%) or premature LTP initiation (n=130; 39.0%). The historical cohort included 39 patients treated when the French LTP guidelines were not available.

Patient characteristics

The study flow chart is shown in Figure 1. A total of 10,107 patients were included in FranceCoag at the time of the study, of which 333 boys with severe HA from the PUP cohort, born between 2000 and 2009, were ultimately included in the study cohort. The median age at diagnosis of the study cohort patients was 0.4 years (IQR 0-0.8 years). Thirty-nine boys with severe HA born consecutively in 1996 were included in the historical cohort (median age at diagnosis was 0.7 years; IQR 0-1.0 years). The patient characteristics are presented in Table 1. Patients for whom the primary LTP guidelines were not applicable (patients with early ICH or early inhibitor development) were primarily diagnosed during the neonatal period at a median age of five days after birth (IQR 0-0.6 years). For the entire study cohort, the cumulative incidence of ICH and inhibitor was 8.1% and 34.8%, respectively. Children with delayed LTP initiation were younger at the time of LTP indication compared with those with timely LTP initiation (1.6, IQR 1.1-2.2 years of age vs. 1.9, IQR 1.6-2.5 years of age). The

cumulative incidence of target joints was higher for the delayed LTP initiation patients than the premature and timely LTP initiation patients (55.6% vs. 10.0% and 26.7%, respectively).

Prophylaxis use

The cumulative incidence of LTP use according to age was significantly higher in the study group compared with the historical group ($p < 0.001$; Figure 2). Cumulative incidence at three years of age was 61.2% and 9.5%, respectively.

Factors associated with LTP guideline compliance

“Timely LTP” versus “delayed LTP”

In the univariate analysis, age at diagnosis, factor leading to diagnosis, *F8* gene defect class according to inhibitor risk, number of treated non-joint bleeding events prior to LTP indication and year of birth were not significantly associated with “timely LTP” compared with “delayed LTP” (Supplemental Table).

In the multivariate analysis, two variables were significantly associated with “timely LTP” as compared with “delayed LTP”: HTC location in the southern regions of France (OR 23.6, 95% CI 1.9-286.7, $p = 0.013$ vs. Paris Area) and older age at LTP indication (OR 7.2 for each additional year, 95% CI 1.2-43.2, $p = 0.031$) (Figure 3).

“LTP guideline compliance” versus “premature LTP”

In the univariate analysis, age at diagnosis, family history of hemophilia, factor leading to diagnosis, *F8* gene defect class according to inhibitor risk, number of treated non-joint bleeding events prior to LTP indication and HTC location were not significantly associated with “LTP guidelines compliance” as compared with “premature LTP” (Supplemental Table).

In the multivariate analysis, two variables were significantly associated with “LTP guideline compliance” as compared with “premature LTP”: earlier year of birth (OR 0.5, 95% CI 0.3-0.8, $p=0.010$ for years of birth 2005-2009 vs. years of birth 2000-2004) and older age at first factor replacement (OR 1.9 for each additional year, 95% CI 1.2-3.0, $p=0.005$) (Figure 3).

DISCUSSION

Early LTP is considered the gold standard treatment for boys with severe HA and has been reinforced by clinical studies.[3,12] As a result, guidelines from several medical societies have been published to promote the early use of LTP.[13,14] However, no study has prospectively evaluated the impact on LTP use of such guidelines. Using the prospective data of almost all French boys with severe HA born during a 10-year period, we describe the characteristics of one of the largest cohorts ever published. We describe the LTP prophylaxis use and initiation timing during the first years of life and evaluated the proportion of patients for whom LTP guidelines were applicable. We determined whether the timing of LTP initiation complied with the guidelines. We showed that year of birth, HTC location, age at first factor replacement and age at LTP indication were independently associated with compliance with the recommended time for LTP initiation.

In the study cohort, LTP was initiated significantly earlier in life compared with the historical cohort. LTP guideline implementation may thus have played a pivotal role in the increased use of LTP in young boys with HA in France. The structured implementation of these guidelines using the French HTC network and the global trend towards the promotion of LTP may partly explain the effectiveness of the guidelines.[15] However, the guidelines were not applicable in almost one in four patients. Excluded patients were those with early ICH, which requires immediate intensive LTP initiation instead of an increasing regimen, and those

with early inhibitor development, which precludes the standard Factor VIII replacement therapy.

One in ten patients had delayed LTP initiation according to the guidelines. Manco-Johnson *et al.* have reported that prophylaxis is effective in reducing joint bleeding rates and total bleeding rates, regardless of age at LTP initiation.[8] However, they found that LTP initiation after the age of four is associated with loss of joint motion.[8] Furthermore, in patients with delayed LTP initiation, joint structure lesions did not improve based on magnetic resonance imaging assessment.[16] In our cohort, the cumulative incidence of target joints was much higher in delayed LTP initiation patients compared with premature and timely LTP initiation patients. Efforts must be pursued to increase the rates of early LTP initiation in boys with severe HA. Further long-term orthopedic follow-up of this cohort is required, and the effect of LTP guideline compliance and LTP postponement should be evaluated and compared with previously reported studies.[17]

Several factors were independently associated with delayed LTP initiation according to the guidelines. HTC location appeared to be an important driver of LTP timing. While such disparities have already been shown between centers from different countries,[7] we found that disparities may also exist within a country despite the existence of national recommendations. The trauma associated with administration of virally-contaminated blood products during the 1980s might have influenced LTP implementation in French centers over subsequent decades. The fear of replacement products and the overall loss of confidence in the healthcare system may have likely influenced medical decisions in a heterogeneous manner during this period, thereby hindering prophylaxis in some cases.[18]

Younger age at LTP indication was significantly associated with delayed LTP initiation compared with timely LTP initiation. This parameter could not be assessed among patients with premature LTP, as prophylaxis was started before the initiation criteria were

met. Children with delayed LTP initiation were almost four months younger at the time of LTP indication compared with those with timely LTP. LTP initiation at a young age is associated with several challenges. Safe venous access, a prerequisite for LTP initiation, is difficult in young children with hemophilia.[19] Frequent peripheral venous access in infants has been associated with complications such as failure of venous access, pain or fear of bleeding complications. As a result, a central venous access device may be required, which is also associated with specific complications (*e.g.*, device malfunction, infections and thrombosis).[20] The difficulty concerning venous access in infants may be even more significant in HTCs with relatively less pediatric-specific capacity or experience. However, this could not be evaluated in the present study. Proposing LTP initiation for infants is also more likely to be refused by the family due to psychological reasons, including fear of venipuncture and acute trauma following recent diagnosis. Providing regular intravenous prophylaxis to infants with hemophilia remains very challenging. To improve such care for young children, pediatric training may be useful for hemophilia teams that often provide care to both children and adults. The role that specific pediatric training and multidisciplinary approaches, including psychological care, may play in guideline compliance should be evaluated.

We found that a significant percentage of patients started LTP earlier than recommended (*i.e.*, in most cases before any joint bleeding or after the first joint bleeding event). Using LTP before the second joint bleeding event is recommended by recent guidelines, such as the World Federation of Hemophilia Guidelines for the Management of Hemophilia published in 2013.[13] Some clinicians may have anticipated this evolution in LTP use. Indeed, our multivariate analysis results show that an earlier year of birth was significantly associated with premature LTP initiation. The decision to initiate LTP in patients with no joint bleeding remains unclear and was not addressed in this study. This may be partly

due to a marked family history of hemophilic arthropathy or motivation on the behalf of the physician or parents to initiate LTP. While evidence of a potential benefits of prophylaxis to prevent intracranial hemorrhaging has recently been shown, the fear of such serious bleeding events may also play a role in the decision to initiate LTP.[21] Younger age at first factor replacement was significantly associated with premature LTP initiation. Consistently, we showed a non-significant tendency between older age at first factor replacement and delayed LTP initiation. Older age at first factor replacement may be associated with a less severe bleeding phenotype, thus leading to decreased use of LTP. In a European survey of compliance to hemophilia therapy, one of the main reasons to not adhere to the prescribed intensity of clotting factor treatment was reduction, fluctuation or disappearance of symptoms.[22] A delayed use of factor concentrate may also hamper acceptance of LTP by the parents.

This study shows that implementation of the French guidelines was associated with significantly earlier initiation of LTP. Analysis of the PUPs FranceCoag cohort provided pivotal data to evaluate guideline compliance and the consequences for patients, stressing the strong interest of such regulations. The large number of consecutive PUPs that were included and prospectively followed up represents a major strength of this study. Furthermore, the highly exhaustive study population included French boys with severe HA from one age group,[10] which renders the results very representative at a national level. Concerning the study limitations, markers of bleeding phenotype severity before initiating LTP could not be included in the multivariate model, as LTP initiation is an early event in a significant proportion of patients. Furthermore, the educational level of the parents, the parents' knowledge and preconceived notions regarding hemophilia and LTP, the type of childcare, the parents' perception of venous access during the first injections of factor concentrate and

transport time to the HTC should be investigated in further studies in terms of decision to initiate LTP.

Innovative therapies have emerged for HA patients in recent years, although they have not been approved or commonly used in PUPs. Early LTP thus remains the gold standard treatment to prevent hemophilic arthropathy in these patients. The current study highlights the importance of treatment guidelines and the remaining issues concerning early LTP initiation. The availability of clotting factors with an extended half-life and other innovative therapies are likely to significantly change the strategies of pediatric hemophilia healthcare in the near future. Evidenced-based guidelines are critical to avoid disparities in the use of these new drugs. As shown in the present study, further prospective evaluations of guideline compliance are required to continue improving the quality of care for hemophilia patients.

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FIGURE LEGENDS

Figure 1: Cohort flow diagram and study design

Abbreviations: ICH: intracranial hemorrhage; LTP: long-term prophylaxis interquartile range; LTP: long-term prophylaxis.

Figure 2: Cumulative incidence of prophylaxis use according to age

Figure 3: Determinants of long-term prophylaxis initiation compliance

Multivariate analysis. “timely LTP initiation” and “no LTP indication and no LTP initiation” were the situations in compliance with the guidelines (“LTP guideline compliance”). For each variable, the odds ratio is shown with 95% confidence interval. The dotted lines represent the absence of statically significant effects (odds ratio of 1). Odds ratio for “age at first factor replacement” and “age at LTP indication” are shown for each additional year. Abbreviations: HTC: hemophilia treatment center; LTP: long-term prophylaxis; ref: reference.

Table 1: Patient characteristics and prophylaxis profile

	Study cohort (born between 2000 and 2009)						Historical cohort (born in 1996) ^o
	Guidelines not applicable	Premature LTP	Delayed LTP	Timely LTP	No LTP indication and no LTP initiation		
Patient characteristics	n=333 (100%)	n=77 (23.1%)	n=130 (39.0%)	n=36 (10.8%)	n=15 (4.5%)	n=75 (22.5%)	n=39 (100%)
<u>LTP Guidelines</u>							
Availability	+	+	+	+	+	-	-
Applicability	-	+	+	+	+	+	NA
Compliance	NA	-	-	+	+	+	NA
Age at diagnosis (years)	0.4 (0.0-0.8)	0.0 (0.0-0.6)	0.6 (0.0-0.8)	0.5 (0.0-0.8)	0.3 (0.0-0.8)	0.5 (0.0-1.0)	0.7 (0.0-1.0)
Age at last evaluation (years)	10.1 (7.7-13.5)	10.4 (7.6-12.8)	9.1 (7.2-11.7)	12.4 (7.8-14.4)	11.8 (8.6-15.4)	10.2 (8.4-14.1)	18.9 (16.9-19.8)
Family history of hemophilia							
No	203 (61.0%)	40 (51.9%)	86 (66.2%)	22 (61.1%)	12 (80.0%)	43 (57.3%)	10 (25.6%)
Yes	115 (34.5%)	32 (41.6%)	43 (33.1%)	11 (30.6%)	2 (13.3%)	27 (36.0%)	8 (20.5%)
Unknown	15 (4.5%)	5 (6.5%)	1 (0.8%)	3 (8.3%)	1 (6.7%)	5 (6.7%)	21 (53.9%)
Factor leading to diagnosis							
Family history	106 (31.8%)	30 (39.0%)	39 (30.0%)	10 (27.8%)	3 (20.0%)	24 (32.0%)	10 (25.6%)
Bleeding	217 (65.2%)	45 (58.4%)	87 (66.9%)	25 (69.4%)	12 (80.0%)	48 (64.0%)	28 (71.8%)
Incidental	10 (3.0%)	2 (2.6%)	4 (3.1%)	1 (2.8%)	0 (0.0%)	3 (4.0%)	1 (2.6%)
HTC location							
Paris area	104 (31.2%)	32 (41.6%)	30 (23.1%)	18 (50.0%)	1 (6.7%)	23 (30.7%)	NA
North	121 (36.3%)	33 (42.9%)	46 (35.4%)	8 (22.2%)	6 (40.0%)	28 (37.3%)	
South	108 (32.4%)	12 (15.6%)	54 (41.5%)	10 (27.8%)	8 (53.3%)	24 (32.0%)	

F8 gene defect							
inhibitor risk							
High	245 (73.6%)	68 (88.3%)	90 (69.2%)	24 (66.7%)	11 (73.3%)	52 (69.3%)	NA
Low	83 (24.9%)	9 (11.7%)	37 (28.5%)	12 (33.3%)	3 (20.0%)	22 (29.3%)	
Unknown	5 (1.5%)	0 (0.0%)	3 (2.3%)	0 (0.0%)	1 (6.7%)	1 (1.3%)	
Age at initial factor replacement (years)	0.8 (0.5-1.2)	0.6 (0.1-0.9)	0.8 (0.5-1.1)	0.8 (0.6-1.3)	0.6 (0.2-0.9)	1.1 (0.8-1.7)	1.0 (0.7-1.2)
Annualized joint bleeding rate	0.5 (0.2-0.9)	0.5 (0.1-0.9)	0.4 (0.2-0.7)	1.1 (0.6-1.9)	0.5 (0.4-1.0)	0.4 (0.2-0.6)	NA
Target joint							
Yes	52 (15.6%)	0 (0.0%)	13 (10.0%)	20 (55.6%)	4 (26.7%)	15 (20.0%)	NA
No	281 (84.4%)	77 (100%)	117 (90.0%)	16 (44.4%)	11 (73.3%)	60 (80.0%)	
Age at LTP initiation (years)	2.4 (1.5-3.5)	2.7 (1.7-3.6)	1.5 (1.1-2.1)	3.0 (2.5-3.5)	1.9 (1.6-2.5)	3.9 (3.5-5.3)	6.5 (4.0-7.5)
Intracranial bleeding							
Yes	27 (8.1%)	26 (33.8%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
No	306 (91.9%)	51 (66.2%)	130 (100%)	35 (97.2%)	15 (100%)	75 (100%)	39 (100%)
Inhibitor development							
Yes	116 (34.8%)	64 (83.1%)	30 (23.1%)	6 (16.7%)	5 (33.3%)	11 (14.7%)	11 (28.2%)
No	217 (65.2%)	13 (16.9%)	100 (76.9%)	30 (83.3%)	10 (66.7%)	64 (85.3%)	28 (71.8%)
Number of treated non-joint bleeding events prior to LTP indication	NA	NA	NA*	3.0 (0.0-6.0)	6.0 (2.0-7.0)	12.0 (5.0-26.0)	NA

Age at LTP								
indication	NA	NA	NA*	1.6 (1.1-2.2)	1.9 (1.6-2.5)	3.9 (3.5-5.3)		NA
(years)								

The data are expressed as the median (interquartile range) or number and percentage. Target joints were defined according to the World Federation of Hemophilia 2012 guidelines as a joint in which three or more spontaneous bleeding events occurred within a consecutive six-month period. Abbreviations: HTC: hemophilia treatment center; IQR: interquartile range; LTP: long-term prophylaxis; NA: not available / applicable; *not applicable as LTP was initiated before criteria were met, thus rendering the theoretical time of initiation unknown.

FIGURE 1

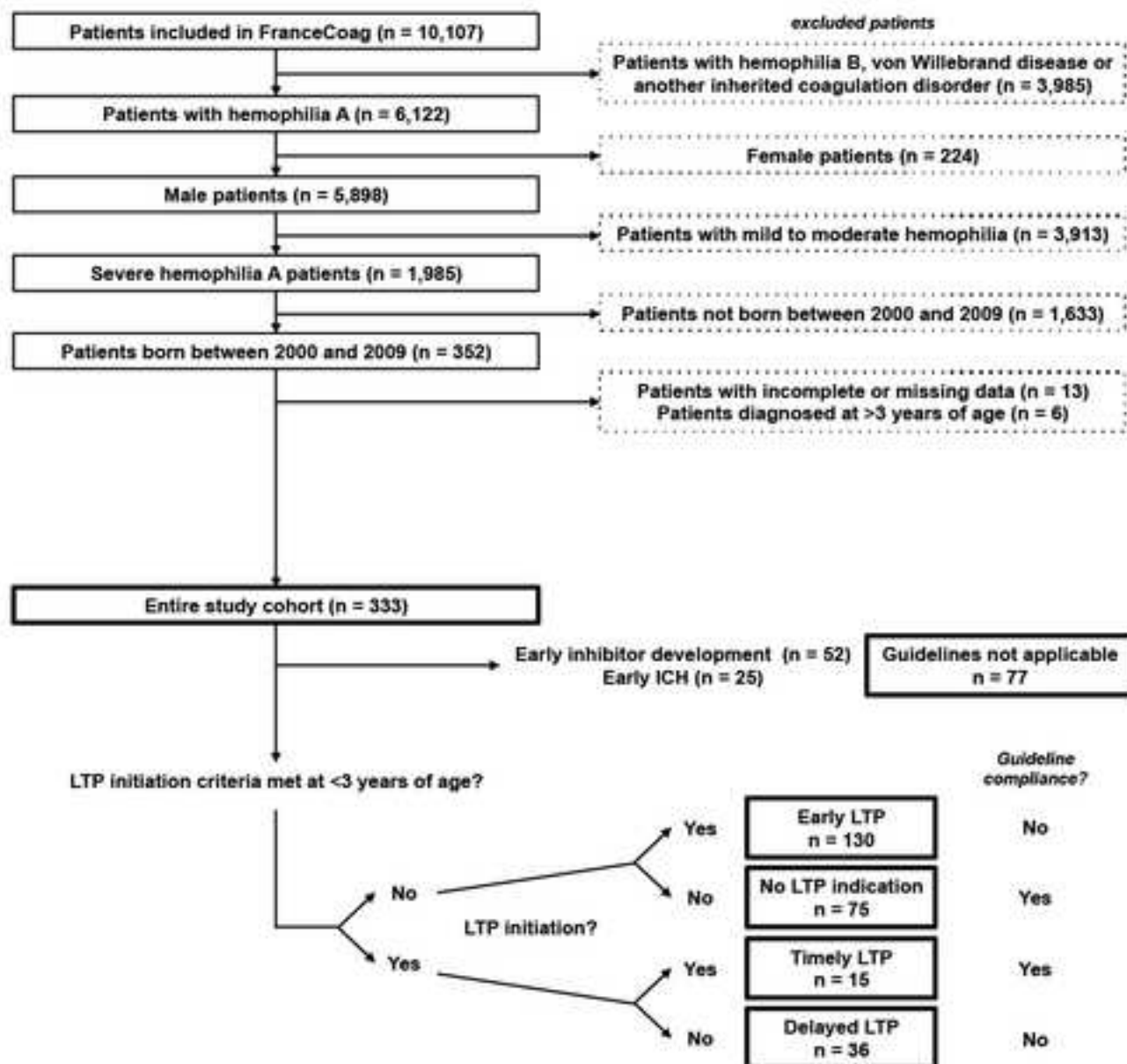
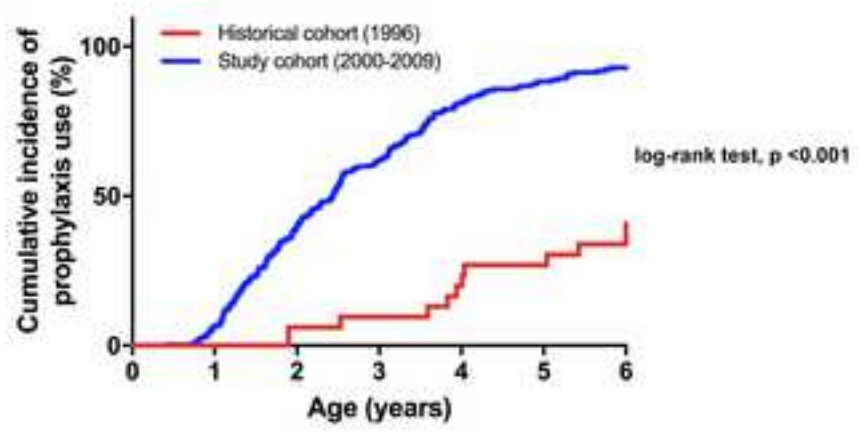


Figure 2

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FIGURE 2



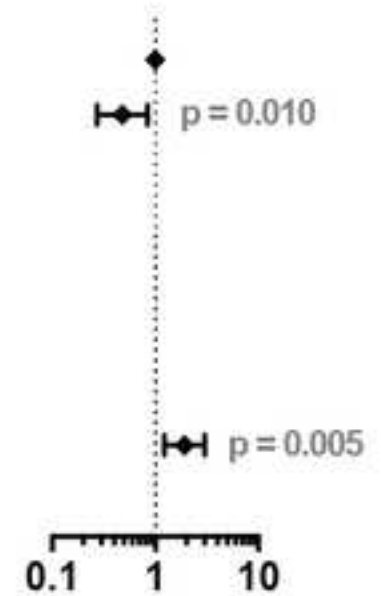
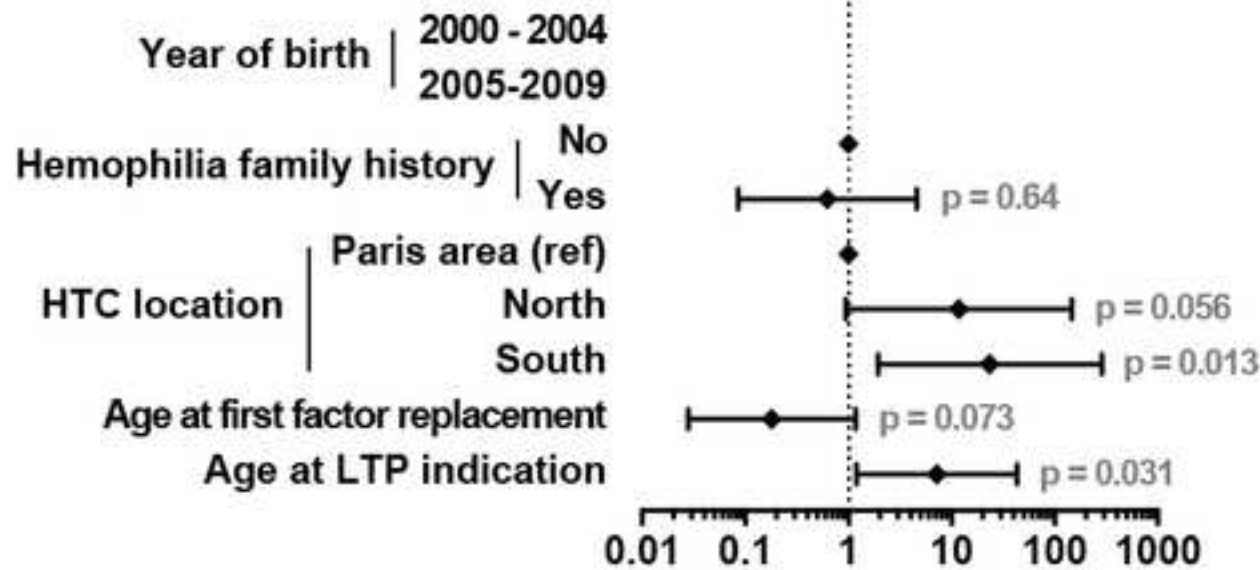
Patients at risk:

Historical Cohort (born in 1996)	39	36	31	27	24	22	20
Study Cohort (born 2000-2009)	333	279	154	92	41	24	15

FIGURE 3

Timely LTP vs. Delayed LTP

LTP guideline compliance vs. Premature LTP



APPENDIX

Collaborators

The following members of the FranceCoag PUPs / CoMETH Prophylaxis Study Group are non-author contributors.

HTC of Paris-Necker: Achille Aouba*, Annie Harroche, Faezeh Legrand*, Chantal Rothschild and Marie-Françoise Torchet*; HTC of Kremlin Bicêtre: Roseline d'Oiron, Thierry Lambert, Yves Laurian* and Anne Rafowicz; HTC of Lille: Jennifer Biernat, Jenny Goudemand, Armelle Parquet*, Véronique Tintillier and Bénédicte Wibaut; HTC of Lyon: Anne Durin-Assollant*, Sandrine Meunier and Claude Négrier; HTC of Bordeaux: Sabine Castet, Viviane Guérin*, Yohann Huguenin; Marguerite Micheau* and Anne Ryman*; HTC of Marseille: Hervé Chambost and Céline Falaise; HTC of Toulouse: Ségolène Claeysens and Marie-Françoise Thiercelin-Legrand; HTC of Nantes: Marianne Fiks-Sigaud, Marc Fouassier, Edith Fressinaud*, Marc Trossaert and Sophie Voisin; HTC of Strasbourg: Albert Faradji* and Patrick Lutz; HTC of Nancy: Marie-Elisabeth Briquel* and Birgit Frotscher; HTC of Tours: Béatrice Fimbel*, Yves Gruel, Claude Guerois*, Sandra Regina* and Jean Baptiste Valentin; HTC of Montpellier: Christine Biron-Andreani, Philippe Codine, Daniel Donadio, Robert Navarro, Paola Rospide and Jean-François Schved; HTC of Saint-Etienne: Claire Berger and Bénédicte Collet; HTC of Caen: Annie Borel Derlon and Philippe Gautier; HTC of Rennes-Pontchaillou: Sophie Bayart and Benoît Guillet; HTC of Rouen: Jeanne-Yvonne Borg, Cécile Dumesnil, Charline Normand*, Pascale Schneider, Philippe Tron* and Jean-Pierre Vannier; HTC of Dijon: Fabienne Dutrillaux and Fabienne Volot; HTC of Clermont Ferrand: Piotr Gembara and Alain Marques-Verdier; HTC of Grenoble: Dalila Adjaoud, Claire Barro, Gilles Pernod*, Benoît Polack and Patricia Pouzol; HTC of Paris-Cochin: Nadra Ounnoughene, Patricia Paugy*, Valérie Robert and Natalie Stieltjes; HTC of Le Chesnay: Brigitte Bastenaire, Emmanuelle de Raucourt; Jocelyne Peynet and Anne Rafowicz; HTC of Amiens: Valérie Li-Thiao-Te and Brigitte Pautard*; HTC of Reims: Catherine Behar*, Stéphanie Gorde and Martine Munzer; HTC of Chambéry: Valérie Gay; HTC of Poitiers: Elisabeth Benz Lemoine and Laurent Macchi; HTC of Limoges: Lionel De Lumley*, Solange Gaillard* and Caroline Oudot; HTC of Nice: Anne Deville and Fabrice Monpoux; HTC of Besançon: Marie Anne Bertrand; HTC of Brest: Brigitte Pan-Petesck;

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* Centers and investigators no longer involved in the FranceCoag Network.

Haemophilia treatment centers (HTCs) listed in decreasing order based on the number of PUPs enrolled in the study. The investigators who followed these patients in the FranceCoag PUP cohort are also included.

A list of the Steering Committee and Coordinating Centre members of the FranceCoag Network is available at <http://www.francecoag.org/>.