



Efficacy and Cost-Effectiveness of Low-Dose vs Standard Dose Prophylaxis for Hemophilia in Indonesia: A Systematic Review

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Abstract: Studies on high-dose prophylaxis therapy using Factor VIII show promising decrease in the Annual Bleeding Rates (ABR) in hemophilia patients. However, the greater dose and frequency raise concerns on cost considerations and adherence of the patients, especially in several countries where resources are limited. Other data has proven that the low dose prophylaxis is also promising regarding the decrease of ABR. The purpose of this systematic review is to conduct a comprehensive analysis of the lower dosage formulation used for prophylaxis in hemophilia. A PubMed and Embase database search was performed based on articles that met the following criteria: written in English language and published within the last 10 years. Consequently, the following key terms were used in combination: ‘high dose’, ‘low dose’, ‘recombinant’, ‘prophylaxis’, and ‘hemophilia’ in different combinations. 19 articles were included for this review. 10 of the investigated papers demonstrated decrease in ABR, functional improvement of affected joints, alleviation of pain, and a better quality of life in hemophilia patients. Low dose prophylaxis has proven to significantly improve symptoms, lower ABR and preserve joint and bone health compared to episodic or on-demand treatment. Furthermore, low dose prophylaxis (LDP) was also observed to be cost-effective and more convenient in certain countries, especially in south-east Asia where resources are limited. Overall, low dose prophylaxis appears to be non-inferior in improving the overall Quality of Life in people with hemophilia, and therefore could be a beneficial alternative in countries of the south east Asian region.

Keywords: hemophilia, prophylaxis, South-East Asia, factor VIII

Introduction

Hemophilia is an X-linked inherited hematologic disorder characterized by the deficiency of Factor VIII (Hemophilia A) or Factor IX (Hemophilia B), the crucial proteins involved in the blood coagulation cascade. This deficiency leads to prolonged bleeding episodes, particularly in joints and muscles. Globally, hemophilia affects approximately 1 in 5000 male births for hemophilia A and 1 in 30,000 for hemophilia B, making it a rare disorder.^{1,2} By the end of 2018, there were 2098 haemophilia patients recorded based on data from the Indonesian Hemophilia Society, which is estimated to be only 10% of the total estimated number of patients (20,000–25,000 cases in total) suspected due to the inadequate screening. The management of haemophilia in Indonesia has been improving since the 1970-1980s era, both in diagnosis and in treatment.^{1,2}

In high-resource countries, early diagnosis and treatment options, including prophylaxis with clotting factor concentrates, have dramatically improved patient outcomes. Prophylactic therapy with FVIII is considered to be the optimal treatment for patients and is aimed at reducing the number of spontaneous hemorrhages as for improving overall quality of life in People with Hemophilia (PWH). In adults, prophylaxis is aimed at slowing the progression of joint deterioration and improving

mobility, namely secondary prophylaxis. Previous studies have confirmed the efficacy of prophylaxis in children in preventing or delaying arthropathy, and early initiation of prophylaxis may have a protective effect against inhibitor development.^{3,4}

The World Federation of Hemophilia (WFH) recommends that high- or intermediate-dose prophylaxis be started early for all severe haemophilia patients as the primary option, substantially reducing bleeds compared with on-demand treatment. On the other hand, low-dose prophylaxis was recommended for countries with limited resources. Recent studies investigated low-dose factor prevention as an alternative economically feasible approach.^{2,5} In Indonesia prophylaxis with standard dose is beyond affordability due to the high cost, availability of concentrate across all provinces and limited financial support from the government.^{2,5}

The first low-dose prophylaxis (LDP) study in Indonesia by Chozie et al proved that low-dose prophylaxis significantly reduced bleeding episodes compared to on-demand therapy.¹ In another study, long-term low-dose prophylaxis of children with severe haemophilia A reduced their joint damage and improved their quality of life (QOL) compared with on-demand treatment.^{1,6} A study about haemophilia patients in the Netherlands and Sweden found a more intensive and higher-dosed regimen may provide slightly improved outcomes at a significant cost increase.⁷

The aim of this literature study is to compare the effectiveness of FVIII prophylaxis for hemophilia A, based on the Annual Bleeding Rate (ABR), Annual Joint Bleeding Rate (AJBR), Functional Independence Score in Hemophilia (FISH) and other parameters defining overall quality of life in PWH. The purpose of this study is to give recommendations for deciding the best prophylaxis dose and method, based on availability and cost-effectiveness, that could be applied in South-East Asia, especially Indonesia.

Materials and Methods

Database Search and Article Selection

We conducted comprehensive literature study from PUBMED and Embase database, for the past 15 years, starting from 1 January 2009 to 1 October 2024. The following keywords are used with boolean operators; (Hemophilia) AND ((“Prophylaxis” AND “High Dose”) OR (“Prophylaxis” AND “Low Dose”) OR (“Prophylaxis” AND “Recombinant”). All original articles are included in this study. All publications were examined against pre-set inclusion and exclusion criteria. For the selection process, Rayyan software was used to assist in the screening and selection of the studies.

Inclusion and Exclusion Criteria

Inclusion and Exclusion criteria were labeled in the application. The inclusion criteria are as follows: systematic review, meta-analysis, literature review, interventional and non-interventional studies, studies comparing two or more of the following; high-dose, low-dose, and recombinant therapy, multi-centered or single-centered studies. Exclusion criteria are as follows: conference abstracts, reviews, commentary, immune tolerance induction protocols using LDP, studies not mentioning specific dose of FVIII usage, on going studies, studies published in other languages.

Study Selection and Data Extraction

The study selection, method planning, and instruction provided by author 1 in the first step. Data extraction of all publications, screening, inclusion and exclusion processes were performed by author 2, 3 and 4, and being reviewed by author 5. Duplicates of publications were further screened. Any conflicts during the selection process were resolved by consensus or through arbitration by author 5. Study group and treatment are sorted using the following protocols: 1) Low dose efficacy compared to on-demand or episodic treatment, 2) Low dose efficacy compared to intermediate or higher dose prophylaxis. At the final step, the review and editing of the manuscript was directed by authors 1, 3 and 5. The following [Figure 1](#) describes the flowchart of the process.

Results

We identified 1409 studies from the search output. After screening the titles, abstracts, removal of duplicates and non-English publications, 779 articles were assessed in full ([Figure 1](#)). Of these, 19 studies were included in the final review. Of these, ten compared LDP with episodic or on-demand treatment, seven examined the efficacy of recombinant Factor

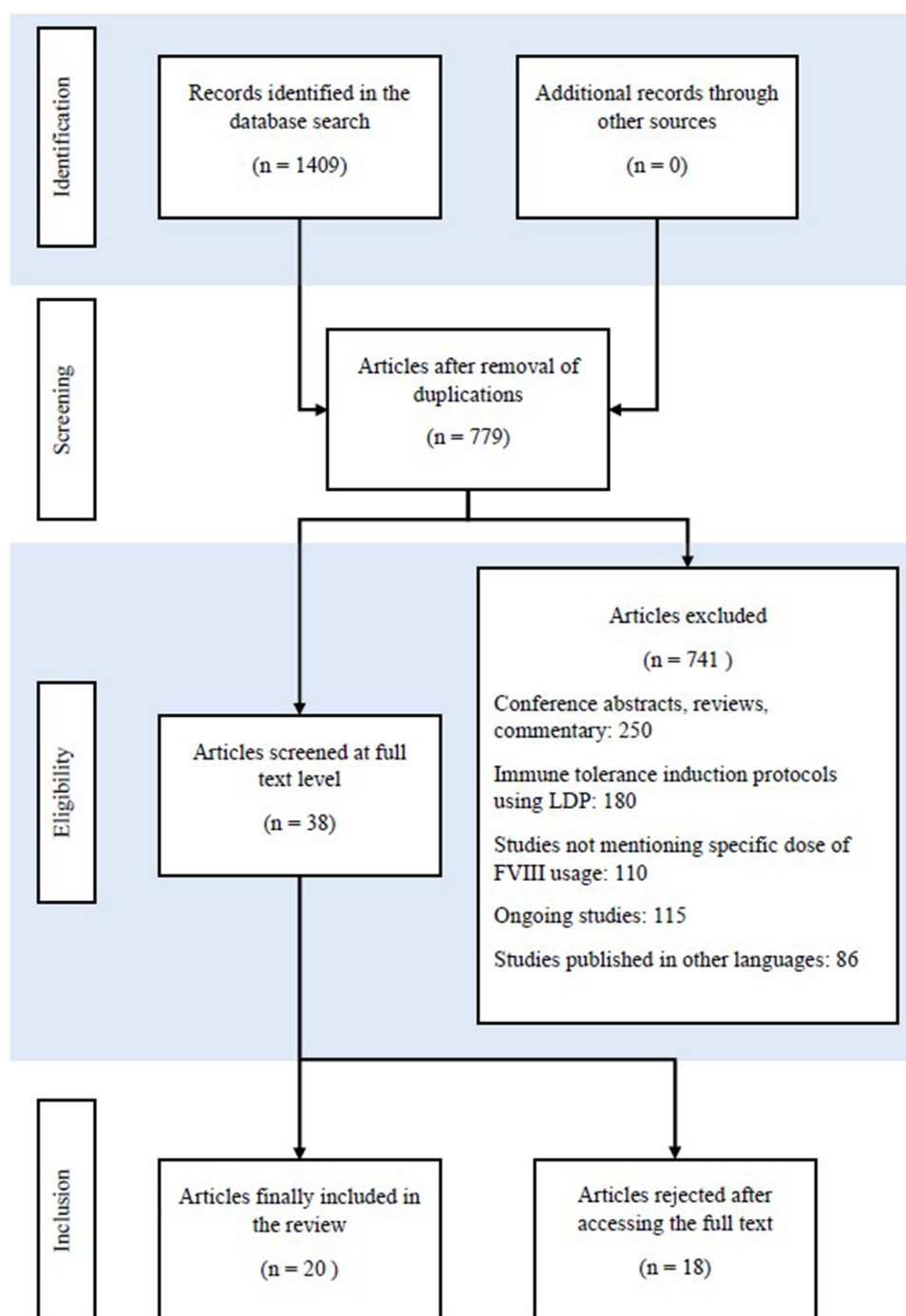


Figure 1 Flowchart of the process.

VIII (rFVIII) administered in low doses, while three studies directly compared LDP with intermediate- and high-dose regimens in reducing the annualized bleeding rate.

Of the selected articles, 10 studies were prospective cohorts of patients on LDP in [Table 1](#). Studies of Low dose prophylaxis effectivity compared with on-demand or episodic treatment in hemophilia. Five of these studies were long-term studies extending beyond two years, while five had implemented dose/frequency escalation protocols based on clinical outcomes and PK parameters. Of these, four were randomized controlled trials. The most frequent LDP regimen used among the various studies was administration at 10–15 IU/kg body weight twice a week.

Table 1 Studies of Low Dose Prophylaxis Effectivity Compared with On-Demand or Episodic Treatment in Hemophilia

	Study & Reference	Country	Participants	Age Range & Condition	Care Level	Treatment	Observation Period	Results
1	Lambert et al, 2021 ⁸	Ivory Coast	25 (HA 21, HB 4; severe 24, moderate 1)	Age <10 years; treated on demand with SHL FVIII or IX, limited functional joint impairment; (AJBR) ≥5	Primary 5 and secondary 20	HA 20 IU/kg once a week; HB 20 IU/kg every 10 days	12 months LDP + 12 months follow-up	Reduction in AJBR by 87.6%; marginal decrease in HJHS scores and remained unchanged in 12 patients; 12.5% positive for inhibitors
2	Gulshan et al, 2020 ⁹	India	30 hA	Age ≤12 years	Secondary and tertiary	FVIII 10 IU/kg twice weekly	1 year	AJBR reduced by 85.76% and school absenteeism by 86%; 93% improvement in HJHS score; reduction in mean hospitalization rate from 8.7 to 1.1. Improvement in SAPS was mild in 57% of patients and moderate in 38%. No further change was seen in 5% of patients
3	Singh et al, 2019 ¹⁰	India	70 (HA 58, HB 12; severe 21, moderate 49)	Patients on ET; having clinical joint disease with ≥3 joint bleeds into a single joint	Tertiary	FVIII 10 IU/kg twice weekly; FIX 20 IU/kg once a week	12 weeks	ABR reduced by 69% and 65% in moderate and severe haemophilia, respectively, during LDP; 60% reduction in hospitalization rate and 54% reduction in absenteeism from school/work
4	Chozi, et al, 2019 ¹	Indonesia	50 (25 in prophylaxis group, 25 in on-demand group)	Children aged 4–18 years with severe hemophilia A	undescribed	Prophylaxis group: Low-dose FVIII (10 IU/kg, twice per week) On-demand group: Standard on-demand treatment	12 months	<ul style="list-style-type: none"> - Prophylaxis group had significantly fewer total and joint bleeding episodes ($P < 0.001$). - Improvement in joint function (HJHS) in the prophylaxis group ($P = 0.004$), deterioration in on-demand group ($P = 0.001$). - HEAD-US scores improved at 6 months in prophylaxis group, no significant difference at 12 months. - No significant complications were noted.
5	Chuansumrit et al, 2018 ¹¹	Thailand	Multi-centered study of 50 Thai patients with severe HA	Age range 20.4 + 6.9, 39 severe HA, 11 moderate HA	Secondary and tertiary	8–10 IU/kg, twice a week	3 months	Patients with prophylaxis had significantly less target joints bleeding than those on episodic treatment (6/15 = 40% vs 26/35 = 74.3%, $P = 0.021$)
6	Sidharthan et al, 2017 ¹²	India	11 (severe HA and HB)	>20 ED; having clinical joint disease	Secondary	FVIII 10–20 IU/kg twice weekly; FIX 25–40 IU/kg weekly	6 months	Significant reduction in ABR; differences in HJHS and FISH scores were not statistically significant; mean hospitalization rate decreased from 12.45 to 2.36

7	Hua et al, 2016 ¹³	China	33 (severe HA)	Adult severe haemophilia; age ≥ 18 years	Tertiary	5–10 IU/kg twice or thrice weekly	20.8 \pm 9.9 months	ABR reduced by 71% during LDP; no change in the Pettersson score; significant improvement in FISH score; scores for self-care and mobility both improved significantly
8	Verma, et al, 2016 ¹⁴	India	21 (11 in prophylaxis group, 10 in episodic group)	Children aged 1–10 years with severe hemophilia	unknown	Prophylaxis group: Very low-dose FVIII (10 units/kg, 2 days/week) Episodic group: Standard recommended doses	11.5 months	<ul style="list-style-type: none"> - Prophylaxis group: 11 joint bleeds, 0.08 haemarthrosis per patient per month, 1 hospital emergency visit, 3 days absenteeism. - Episodic group: 57 joint bleeds, 0.48 haemarthrosis per patient per month, 9 hospital emergency visits, 25 days absenteeism. - FVIII consumption: 87.51 units/kg/month in prophylaxis, 56.32 units/kg/month in episodic. - No significant complications in prophylaxis group, compliance 98%.
9	Wu et al, 2011 ¹⁵	China	34 (HA 28, HB 6)	2–18 years; presence of clinical joint disease	Secondary and tertiary	FVIII 10 IU/kg twice weekly; FIX 20 IU/kg twice weekly	12 weeks; ≥ 3 bleeds during observation period	AJBR reduced by 83% compared with ET; moderate improvement in joint function, daily activity, sports participation, and school attendance

Abbreviations: SHL, Standard Half-life; EHL, Extended Half-life; ET, Episodic Treatment; ABR, Annualized Bleeding Rate; AJBR, Annualized Joint Bleeding Rate; FISH, Functional Independence Score in Hemophilia Score; HEAD-US, Hemophilia Early Arthropathy Detection with Ultrasound; LDP, Low Dose Prophylaxis.

Studies on efficacy of prophylaxis using recombinant Factor VIII regimens are summarized in [Table 2](#) (Effectivity of Low Dose Prophylaxis using Recombinant Factor VIII). Patients treated with recombinant FVIII at various dosing and frequency schedules have demonstrated significant reductions in bleeding episodes. The studies also suggest a good safety profile, with no development of FVIII inhibitors and only a few adverse events reported. [Table 3](#) (Low dose prophylaxis compared to intermediate or higher dose prophylaxis) presents data comparing low-dose and high-dose prophylaxis. They achieved an ABR of 5.0 for low-dose and 2.0 for high-dose prophylaxis, though the latter did not attain statistical significance.

We assessed the medical costs of hemophilia across several countries, including nations in South Asia, parts of Greater Asia, and some Western countries in [Table 4](#): Cost comparison of hemophilia prophylaxis treatment across countries, to estimate the costs associated with low-dose compared to higher-dose treatment and to review government policies regarding hemophilia care, as detailed in [Tables 4](#) and [5](#). Cost data were gathered from published studies specific to each country. Where data on certain costs were not available, we estimated them using data from the Report on the Annual Global Survey of Hemophilia in 2021, in which data on FVIII consumption by country are made available.²⁵ In [Table 5](#) (Government Health Policy supporting hemophilia prophylaxis therapy), different government policies across the countries listed in [Table 4](#) are represented for the comparison and analysis of policies from different regions feasible.

Discussion

Low-Dose Prophylaxis Effectivity in Lowering ABR and AJBR in Hemophilia

Based on the literature review of 19 articles including systematic review, meta-analysis and multicentered observational studies, most of the study results describe that low-dose prophylaxis is non-inferior in improving ABR (Annualized Bleeding Rate), AJBR (Annualized Joint Bleeding Rate), FISH (Functional Independence Score in Hemophilia Score), and HEAD-US (Hemophilia Early Arthropathy Detection with Ultrasound) in PWH. As presented in [Table 1](#), low-dose prophylaxis compared to on-demand/episodic prophylaxis has shown significant results. All studies in [Table 1](#) conclude that low-dose prophylaxis has shown to significantly reduce ABR, 4 studies specifically describe improvement in AJBR.^{8,9,15,16} Three studies specifically presented improvement of the Hemophilia Joint Health Score (HJHS).^{1,8,9} One study conducted by Chozie et al presented an improvement in HEAD-US, and 2 studies showed improvement in FISH score in PWH receiving prophylaxis treatment.¹³

Low-dose prophylaxis in hemophilia has been shown to significantly reduce the frequency of bleeding episodes and improve joint outcomes compared with on-demand treatment. A study by Lambert et al (2021), including patients from the Ivory Coast, determined LDP associated with an AJBR reduction by 87.6% over a continuous period of 12 months.⁸ This study further reiterated that there were minor changes in HJHS; 12 patients did not deteriorate in joint health, and inhibitors developed in only 12.5% of the participants. A study by Gulshan et al (2020), conducted in India with hemophilia A patients discovered that infusions of 10 IU/kg twice a week cause a reduction of 85.76% in AJBR, whereas school absenteeism was reduced by 86%.⁹ The study also noted that the improvement in joint health was remarkable and increased the HJHS scores by 93%, drastically reducing hospitalization rates from 8.7 to 1.1 admissions per year.

A study conducted by Singh et al further concluded that the effectiveness of LDP in twice-weekly prophylaxis with 10 IU/kg of FVIII for patients with moderate-to-severe hemophilia led to a 69% reduction in ABR and a 65% reduction in AJBR, among other advantages over reductions in hospitalization rates and absence from school or work.¹⁰ In the much smaller study by Verma et al (2016) in India, children on very low-dose FVIII regimen of 10 IU/kg twice per week had significantly fewer joint bleeds, 0.08 haemarthrosis per patient per month, and less hospitalization compared to those on episodic therapy, 0.48 haemarthrosis per patient per month.¹⁴ The study also reported better compliance, 98%, in the LDP group, with no significant complications. Concisely, these data support the fact that the clinical benefit of LDP depends on an improvement in bleeding control and joint health in patients with hemophilia, while LDP may also be a viable option for on-demand treatments in reducing morbidity and improving the quality of life.^{8–10,14}

A systematic review and meta-analysis study, conducted by Delgado-Flores et al, in [Table 3](#), calculated the pooled statistic of 9 RCT studies of prophylaxis effectivities in lowering ABR and AJBR. It compared prophylaxis in all kinds of doses (low, intermediate, high) to on-demand and episodic treatment.²⁴ There is a significant difference of ABR and AJBR rates in the two

Table 2 Effectivity of Low Dose Prophylaxis Using Recombinant Factor VIII

	Study & Reference	Country	Participants	Duration	Age Range & Condition	Treatment	Observation Period	Results
1	Tang et al, 2013 ¹⁶	China	66 (severe HA 34, moderate HA 32)	2–18 years; clinical joint disease	Tertiary	FVIII 10 IU/kg twice weekly	6–12 weeks	Reduction in ABR by 68.9% and AJBR by 78.8% between ET and LDP period; improved daily activities; no increase in factor consumption in LDP period compared with optimal regimen ET. Daily activities as measured by BCH scale upgraded in 31% and 60% improvement in FISH score
2	Mathias et al, 2023 ¹⁷	Multi-centered	108 previously untreated patients (PUPs) with severe hemophilia A	Not mentioned	Previously untreated patients (PUPs) with severe hemophilia A	Simoctocog alfa for prophylaxis, treatment of bleeding episodes (BEs), and surgical prophylaxis	24 months	<ul style="list-style-type: none"> - 92.9% of BEs were rated as excellent or good in treatment. - 92.3% of BEs treated with 1 or 2 infusions. - 94.7% of surgical prophylaxis rated as excellent or good. - No safety concerns or thromboembolic events reported.
3	Choraria et al, 2022 ¹⁸	India	50 hemophilia patients	Up to 8 weeks (with up to 4-week screening and 28-day post-treatment observation)	Moderate or severe congenital hemophilia A	Intravenous moroctocog alfa (30±5 IU/kg, 3 times weekly for bleeding prophylaxis)	8 weeks treatment + 28-day safety observation	Evaluated safety and efficacy of moroctocog alfa; specific results not detailed in the provided text.
4	Wu et al, 2020 ¹⁹	China	42 pediatric, 26 adolescent/ adult	6 months (main phase), up to 24 months (full trial)	Severe hemophilia A patients of all ages	Turoctocog alfa (ELH rFVIII) for prophylaxis or on-demand treatment	6 months (main phase), 24 months (full trial)	<ul style="list-style-type: none"> - Hemostatic success: 95.1% (main phase), 95.4% (full trial). - Median annualized bleeding rate: 1.18 bleeds/patient/year for prophylaxis. - 51% of patients with target joints had all resolved. - No FVIII inhibitors reported.

(Continued)

Table 2 (Continued).

	Study & Reference	Country	Participants	Duration	Age Range & Condition	Treatment	Observation Period	Results
5	Gringeri et al, 2011 ²⁰	Multi-\-centered	45 (21 prophylaxis, 19 episodic)	10 years	Children with severe hemophilia A (factor VIII <1%), aged 1–7 years	Prophylaxis with recombinant factor VIII (25 IU/kg, 3 times a week) vs Episodic therapy (≥25 IU/kg every 12–24 hours)	10 years	<ul style="list-style-type: none"> - Fewer hemarthroses in prophylaxis group (0.20 vs 0.52 per patient per month, $P < 0.02$). - Fewer radiologic signs of arthropathy in prophylaxis group (29% vs 74%, $P < 0.05$). - Prophylaxis was more effective when started early (<36 months), with fewer joint bleeds (0.12 per patient per month) and no radiologic signs of arthropathy.
6	Valentino et al, 2012 ³	Multi-centered	66 adult and pediatric on-demand treatment hemophilia patients	18 months	Previously on-demand -treated patients, aged 7–59 years, with FVIII levels ≤ 2%	On-demand treatment followed by 12 months of either: <ul style="list-style-type: none"> - Standard prophylaxis (20–40 IU/kg every other day) - PK-tailored prophylaxis (20–80 IU/kg every third day) 	6 months (on-demand) + 12 months (prophylaxis)	<ul style="list-style-type: none"> - 33.3% of prophylaxis subjects had no bleeding episodes, compared to none in the on-demand group. - Comparable ABRs for standard and PK-tailored prophylaxis. - Significant reduction in ABRs with prophylaxis compared to on-demand ($P < 0.0001$). - No differences in FVIII consumption or adverse event rates between prophylaxis regimens. - No FVIII inhibitors developed.
7	Powell et al, 2012 ²¹	Multi-centered	270 (139 for safety, 131 for efficacy)	52 weeks	Previously treated, severe hemophilia A patients	BAY 79–4980 (35 IU/kg, once a week) vs rFVIII-FS (25 IU/kg, three times per week)	52 weeks	<ul style="list-style-type: none"> - 38.1% of BAY 79–4980-treated subjects had <9 bleeds/year vs 72.1% in rFVIII-FS group. - 38.1% of BAY 79–4980 subjects had <5 joint bleeds/year vs 63.2% in rFVIII-FS group. - 61% of bleeds with BAY 79–4980 occurred after day 4 post-dosing. - No safety concerns, but BAY 79–4980 was discontinued due to failure to achieve the primary endpoint.
8	Manco-Johnson et al, 2013 ²²	Multinational	84 (42 per group)	1 year (of 3 years)	Males aged 12–50 years with severe hemophilia A, 6–24 bleeding episodes in the past 6 months	rFVIII-FS prophylaxis (25 IU/kg, three times weekly) vs on-demand treatment	1 year	Prophylaxis significantly reduced total bleeding episodes (median 0 vs 54.5) and annualized bleeding rates (0 vs 27.9). No treatment-related adverse events, no FVIII inhibitors developed.

Abbreviations: SHL, Standard Half-life; EHL, Extended Half-life; ET, Episodic Treatment; ABR, Annualized Bleeding Rate; AJBR, Annualized Joint Bleeding Rate; FISH, Functional Independence Score in Hemophilia Score; HEAD-US, Hemophilia Early Arthropathy Detection with Ultrasound; LDP, Low Dose Prophylaxis.

Table 3 Low Dose Prophylaxis Compared to Intermediate or Higher Dose Prophylaxis

	Study & Reference	Country	Sample	Duration	Age Range & Condition	Treatment	Observation Period	Results
1	Yang, et al, 2019 ²³	China	Males with severe hemophilia A	1 year	12–65 years	- Low-dose prophylaxis (20–30 IU/kg twice-weekly) - High-dose prophylaxis (30–40 IU/kg 3 times weekly) - On-demand treatment	6 months to 1 year	ABR in patients receiving on demand treatment vs prophylaxis were statistically significant, but median ABR for patients receiving low-dose or high-dose prophylaxis were 5.0 (2.0; 11.0) and 2.0 (0; 2.0), respectively, and the difference was not statistically significant.
2	Delgado-Flores et al, 2022 ²⁴	Multicenter	Hemophilia A patients	All studies meet the inclusion criteria up to 2020	Hemophilia A patients with Inhibitor level $\leq 2\%$	Comparing pooled result of ABR and AJBR between Hemophilia A with prophylaxis in all doses (Low, intermediate and high dose) vs on demand and episodic treatment Comparing pooled result of ABR and AJBR in all dose treatment	No observation	All three methods of prophylactic dose significantly lower ABR & AJBR compared to on demand / episodic treatment. ($p = 0.003$, $I^2 = 82.9\%$) No significant difference among the three groups of prophylactic dose.

Abbreviations: SHL, Standard Half-life; EHL, Extended Half-life; ET, Episodic Treatment; ABR, Annualized Bleeding Rate; AJBR, Annualized Joint Bleeding Rate; FISH, Functional Independence Score in Hemophilia Score; HEAD-US, Hemophilia Early Arthropathy Detection with Ultrasound; LDP, Low Dose Prophylaxis.

Table 4 Cost Comparison of Hemophilia Prophylaxis Treatment Across Countries

Countries	Dosing and Product Available	Cost*
Indonesia	5–10 IU/kg, 2x/ week, concentrate FVIII (250, 500 IU Injection), CFC and SHL recombinant product available. High dose prophylaxis for severe case only.	Estimated cost: USD 8320 annually (USD 49.20–82 per 250 IU injection) ²
Thailand	5–10 IU/kg, 2x / week, concentrate FVIII (250, 500 IU Injection), CFC, and recombinant products available, SHL and EHL (efanesoctocog alfa). High dose prophylaxis for severe case only.	Estimated cost: USD 9830 annually (for >10-year-old and adult) ²⁶
Vietnam	5–10 IU/kg, 2x/ week 8Y, Hemofil – M, Octanat (Octapharma), Haemoctin (Biotest), Green 8 (Green Cross) High dose prophylaxis for severe case only.	No specific data available
Malaysia	Utrecht protocol (15 IU/kg–30 IU/kg) for low dose prophylaxis is more preferred, high dose prophylaxis for severe cases only, CFC and recombinant product available.	USD 175 (102;246) IU/kg/year or approximately USD 10,500 for people weighted 60 kg ²⁷

(Continued)

Table 4 (Continued).

Countries	Dosing and Product Available	Cost*
Singapore	10 IU/kg, 2x/ week of FVIII concentrate (low dose), 25–40 IU/kg 3–4x a week for high dose (severe case only), SHL and EHL recombinant product available, Octocog alfa (Advate), Rurioctocog alfa pegol (Adynovate), Nonacog alfa (BeneFIX).	USD 595/month or USD 7140 annually (Based on maximum claim for patient aged 13 years and above)
China	Low dose FVIII regiment (10–15 IU/kg), once or twice per week. High dose prophylaxis for severe case only.	Average cost for tertiary prophylaxis: USD 12,334 Short-term low-dose tertiary prophylaxis: USD 46,848 ^{28,42}
Taiwan	Recombinant product: Eloctate's health insurance benefit specifications for preventive treatment are as follows: 25–35 iu/kg once every three days, 36–50 iu/kg once every four days, 51–65 iu/kg once every five days	25–35 IU/kg every three days: \$794,220 USD, 36–50 IU/kg every four days: \$849,121 USD, 51–65 IU/kg every five days: \$918,778 USD
India	Low dose prophylaxis quantity of 10 IU/kg once or twice a week. High dose prophylaxis for severe case only.	Adults (Prophylaxis) - Annual Factor VIII Cost USD 8294.74 ^{29,30}
USA	20–40 IU/kg 2 to 3 times per week (low dose), 50–65 IU/kg 3 times per week (high dose), CFC and recombinants product available.	Tota Annual Cost per patient Ranged: USD 213,874 to USD 869,940 ³¹ Annual prophylaxis treatment cost per patient, mean: EHL products: USD 933,828 ³¹
Brazil	25 IU/kg to 40 IU/kg / 2–4 times a week. 50–65 IU/kg 3 times per week or every other day (high dose).	The price of 1000 IU of recombinant factor VIII concentrate is approximately USD 406.63. The cost per dose ranges from USD 7080.66 to USD 20,309.40 ⁴³
Canada	20–25 IU/kg 2 to 3 times per week (low dose), 50–65 IU/kg 3 times per week or every other day (high dose).	Total annual cost for low dose ranged from: USD 3923.30 to USD 7356.18 per year ⁴⁴
Colombia	500 IU once weekly, or 500 IU 2–3x/week in higher bleeding frequency	The lower cost USD 358 450
Europe	Based on CHESS study ³² Pharmacokinetic guided prophylaxis dose and regiment, specifically in patient with severe inherited haemophilia A or B (FVIII/FIX level <1 IU dL ⁻¹)	Total per patient cost in severe hemophilia (converted to USD): USD 210,597.36
French		Approximately USD 206,766
Germany		Approximately USD 336,399
Italy		Approximately USD 232,344
Spain		Approximately USD 183,235
UK		Approximately USD 136,389

Note: *Unspecified data estimated based on information from the Report on the Annual Global Survey 2021 by the World Federation of Hemophilia²⁵.

Abbreviations: SHL, Standard Half-life; EHL, Extended Half-life;

groups ($p = 0.003$, $I^2 = 82.9\%$). While there is no significant difference between the three sub-groups (Low vs Intermediate vs High dose) in lowering ABR and AJBR. These findings further enhanced the evidence that low dose is indeed non-inferior compared to high-dose prophylactic, especially when the goal is to lower ABR and AJBR.²⁴

When using a recombinant factor (Table 2), it is more convenience to administer Low Dose prophylaxis, especially for Extended Half Life (EHL) products. It is suggested that low-dose prophylaxis with various recombinant factor VIII (rFVIII) products can provide significant clinical benefits in hemophilia A patients, showing the non-inferiority of lower dose prophylaxis compared to standard higher dose treatment. Mathias et al showed that 92.9% of bleeding episodes were markedly reduced in the population treated with simoctocog alfa treatment, and 92.3% were controlled with just 1

Table 5 Government Health Policy Supporting Hemophilia Prophylaxis Therapy

Countries	Government Health Policy and Subsidy
Indonesia	Low dose prophylaxis: Product available and listed in national insurance for episodic and on demand treatment. Recombinant FVIII Concentrate is available, but not subsidized by the government health insurance. High Dose prophylaxis: Does not covered by the government health care policy. ²
Thailand	Low dose prophylaxis: provided by the Thai National Health Security Office, on-demand/inpatient only. Recombinant FVIII provided by the Thai National Health Security Office. High Dose prophylaxis: Covered only for certain cases. ³³
Vietnam	Low dose prophylaxis: Insurance cover 100% of patients below 6 years old, and 70% poor people and handicap for on demand/ episodic treatment. Continuous prophylaxi only for some severe cases High Dose prophylaxis: Covered only for certain cases. ³⁴
Philippines	Low dose prophylaxis: The government does not cover hemophilia care, FVIII products are available from humanitarian aid, supported by social organization. ²⁵
Malaysia	Low dose prophylaxis: All prophylaxis therapy is covered by Government Health Policy. Recombinant Product covered by the government are as follows; Adynovate, Advate and Xyntha. Recombinant products available but not covered by the government includes; Afstyla, Novoeight and Nuwiq. High Dose prophylaxis: For certain severe cases, partially subsidized by the government with private insurance collaboration. ³⁵
Singapore	Low dose prophylaxis: All covered by Singapore Health Care System. Recombinant products are available and more preferred. Recombinant product covered by Singapore's healthcare system, which includes MediShield Life and additional subsidies (unless Novoeigh and Nuwiq) High Dose Prophylaxis: Partially covered, Available only for people using MediShield Life, MediSave, or private insurance plan. ³⁶
China	Low dose prophylaxy: Costs covered by insurance vary widely (40–94%) among cities with differing economies, and the out-of-pocket expense is a continual challenge for many patients. As a result, full-dose prophylaxis in use in the west is unattainable for most patients in China. Hemophilia is covered by health insurance in Shanxi Province (SP) China. ²⁸
India	Low dose prophylaxys: 74% of the country is covered under complete, partial or free factor support. ³⁰
South Korea	Recombinant and High dose prophylaxys: covered by the National Health Insurance in Korea. The Korea Hemophilia Foundation (KHF) supports hemophilia patients by sharing health care cost. ²⁵
Taiwan	Prophylactic coagulation replacement therapy is covered by national health insurance program. ²⁵
European Countries	Based on CHES II Study, countries with national health systems (eg, the UK, Italy, and Spain) typically provide comprehensive coverage for hemophilia treatment, including prophylaxis. In Germany and France, where there is a mix of public and private insurance, the mandatory insurance covers the costs of prophylaxis treatments. In many countries, such as Sweden and the Netherlands, high-dose prophylaxis is the standard approach for severe hemophilia, and the public health systems cover the costs completely. In some regions, particularly where private insurers play a larger role (like Germany), there may be some negotiation or co-payment involved for high-dose regimens, but overall, the public coverage remains strong for these treatments. ³²
USA	In the United States, hemophilia treatment-both standard and high-dose prophylaxis-is covered under a complex mix of private and public insurance programs. Co-payments vary widely, depending on the type of insurance and coverage details. For lower-income individuals, Medicaid offers coverage for hemophilia treatments, many times with very minimal out-of-pocket expenses. Both standard and high dose prophylaxis are covered, at the discretion of each state's policy. Medicare covers the treatments for hemophilia for individuals above 65 years of age and those with disabilities. High-dose regimens are usually covered, but state Medicaid programs may have more strict criteria for prescribing high doses, especially for newer products. Medicare may cover high doses under Part B, which is outpatient care, or Part D, which is prescription drug plans, but patients may be out of pocket more if they are above spending limits or in the coverage gap. ²⁶
Brazil	In Brazil, the public healthcare system, known as the Sistema Único de Saúde (SUS) provides full coverage for prophylaxis for PWH including regular doses of FVIII or FIX, and high-dose prophylaxis regimens (availability can vary by region due to funding limitations and supply). ²⁵
Columbia	Colombia has a universal health coverage system with both public and private insurers (the Sistema General de Seguridad Social en Salud). In the public system, high-dose prophylaxis is provided, particularly for children and severe cases. ⁴

or 2 dose per week, showing effective bleeding control even at lower doses.¹⁷ Similarly, Choraria et al demonstrated the safety and efficacy of moroctocog alfa, while Wu et al reported a high hemostatic success rate of over 95% with turoctocog alfa, showing its effectiveness in both pediatric and adult patients.¹⁸

Valentino et al (2012) showed that prophylaxis cut annual bleeding rates (ABRs) by 60% compared to on-demand treatment ($P < 0.0001$) where a third of clients on treatment did not have bleeding episodes.³ In comparison to Powell et al (2012), Manco-Johnson et al (2013) confirmed that rFVIII-FS prophylaxis virtually eliminated his patients' bleeding episodes that required in-patient admission and also lowered his patients' ABRs from 27.9 to zero when compared with on-demand treatment.^{21,22} These results are reinforcing that prophylaxis during treatment does not increase adverse events or FVIII inhibitors but rather improves the patient's health by reducing bleeding episodes.

Low-Dose Prophylaxis in Comparison with Standard or Higher Dose Prophylaxis

Low-dose prophylaxis has demonstrated efficacy in reducing the annualized bleeding rate (ABR) in patients with severe hemophilia A, even when compared to higher-dose regimens. Multiple studies support the notion that LDP provides sufficient control of bleeding episodes, contributing to a reduction in joint damage and improvement in overall patient outcomes. For instance, Yang et al²³ found that while high-dose prophylaxis (30–40 IU/kg, three times weekly) produced a numerically lower ABR (median: 2.0; range: 0–2.0) than low-dose prophylaxis (20–30 IU/kg, twice weekly), ABR (median: 5.0; range: 2.0–11.0), the difference was not statistically significant, suggesting that LDP can achieve comparable bleeding control. This result is consistent with evidence from the studies in Table 1, where patients on LDP experienced a clinically acceptable reduction in bleeding episodes, particularly in resource-limited settings where high-dose regimens may be impractical.^{9,10,14}

Further evidence by Gringeri et al and Mathias et al also supports the effectiveness of prophylaxis, including lower-dose regimens, in reducing hemarthroses and preventing joint damage over time.^{17,20} Gringeri et al reported fewer joint bleeds in children receiving 25 IU/kg thrice a week, with no radiologic signs of arthropathy when early prophylaxis has been initiated, while Mathias et al demonstrated that simoctocog alfa prophylaxis achieved a success rate of 92.9% in treating bleeding episodes.²⁰ Although higher-dose prophylaxis may show prominent advantage in ABR, the clinical impact of the LDP is quite significant and hence clinically effective as a viable non-inferior strategy for the patients. The same result of significant outcome comparing low-dose prophylaxis and on-demand prophylaxis also found in the study conducted by Chuansumrit et al (2019) shows that low-dose prophylaxis could significantly lower overall bleeding rate compared to on-demand treatment.¹¹ This concluded that low-dose treatment, however, has a robust advantage in improving bleeding rate, musculoskeletal health, and overall quality of life in PWH.

Musculoskeletal Health Improvement in Low Dose Prophylaxis

Joint and bone health are important aspects of hemophilia management, aiming for the prevention of hemarthroses and long-term arthropathy. Choji et al conducted a study comparing low dose and on-demand prophylaxis in children PWH.¹ The result showed a significantly fewer total and joint bleeding rate episode ($p < 0.001$), and improvement in all functions including, HJHS score ($p = 0.001$) in the prophylactic group by 6 months of treatment compared to the on-demand group, and no significant complications were found. HEAD-US Score, however, showed no significant difference between the two groups.¹ Sidhartan et al (2017) conducted the prophylaxis study in resource limited setting in India with the result of significant reduction in ABR; though differences in HJHS and FISH were not statistically significant. However, mean hospitalization rate decreased from 12.45 to 2.36.¹²

In a study by Gringeri et al, prophylactic treatment with recombinant factor VIII significantly reduced joint bleeds and the progression of joint damage compared to episodic therapy.²⁰ Patients in the prophylaxis group exhibited fewer hemarthrosis (0.20 vs 0.52 per patient per month) and a lower percentage of radiological signs of arthropathy (29% vs 74%), demonstrating the efficacy of early intervention in preserving joint function. Moreover, in Valentino et al, a comparison between standard prophylaxis and PK-tailored prophylaxis revealed that both regimens resulted in a notable reduction in annual bleeding rates (ABRs), particularly in joint bleeds, further highlighting the importance of consistent factor replacement therapy for maintaining joint health.³

Newer imaging techniques include HEAD-US for early diagnosis of joint changes in hemophilia patients. HEAD-US, combined with clinical assessment, such as HJHS, thus enables clinicians to monitor subtle damage arising from progressive

joint disease. Yang et al demonstrated that while prophylaxis with a low dose was effective, high-dose prophylaxis slightly fared better in terms of the outcome of preventing bleeding.³⁷ Such studies using HEAD-US and HJHS applications underpin the need for early detection and individualized prophylaxis regimens to reduce joint damage in patients with hemophilia, especially given that low-dose prophylaxis has been considered adequate to prevent deterioration of the joints.

Annual Cost for Hemophilia Treatment in Different Countries

Cost of treatment for hemophilia using FVIII prophylaxis is quite different in different countries, which depends upon health policy, local production, importation, and various subsidies available in each country. In the low-income category of countries, the prices of FVIII concentrates like Octanate, Beriate, and Haemoctin might be high since their medicines are highly dependent on imports. A single 250 IU FVIII injection costs ranging USD 49.20–82 in Indonesia.² In Thailand, Standard Half Life (SHL) FVIII concentrate of 34,500–55,500 IU (approximately 750–1000 IU/week) and SHL FIX concentrate of 23,000–24,000 IU (approximately 500 IU/week), intended for prophylaxis, are reimbursable annually.^{33,34} With lower product costs, however, many patients in these countries still cannot access higher dose prophylaxis; the main reasons include high prices and generally limited insurance coverage, especially in the cases of severe conditions.

On the other hand, countries like Malaysia and Singapore provide better government support for the treatment of hemophilia and hence have given better access to the patients. The annual treatment cost of FVIII in Malaysia reportedly could go as high as RM 4.5 million (approximately USD 1 million). Low dose prophylaxis is more preferred in practice with Utrecht protocol of 15–30 IU/kg, two to three times a week. The price per patient is approximately USD 175 (102;246) IU/kg/year or approximately USD 10,500 for people weighted 60 kg.²⁷ The cost of the low dose prophylaxis is higher compared to on-demand treatment, however prophylactic therapy results in significantly less ABR and better joint health. In Singapore, there are subsidies from the Hemophilia Society of Singapore. A member is able to claim with the maximum of approximately USD 595 per month or approximately USD 7140 annually for those aged 13 years and above.³⁶

Large-population countries indeed face special challenges in gaining appropriate access to FVIII prophylaxis. Tertiary prophylaxis in China can amount to as much as USD 12,334 per patient annually, amidst large disparities in coverage across various cities.^{28,38} India does report that 74% of people with hemophilia receive some kind of support either free or at low cost, but access to prophylaxis, especially low-dose, is challenging in this setting, particularly in rural areas.^{29,30} Most high-income countries such as the USA, Canada, and European countries have government programs that cover the majority of the costs for FVIII prophylaxis. In the USA, Medicaid pays the majority cost of this treatment for those of low incomes, while in Canada provincial health plans fund a significant proportion of treatment costs.³¹ In fact, Belgium currently offers high-dose options through its government-funded health insurance, with options up to 69 IU/kg/week available for the most severe cases.³⁹

The huge cost and the availability contrast among countries bring into focus the difficulties that low- and middle-income countries face in offering sustainable care for hemophilia. While high-income countries have more access to treatment due to better government subsidies for treatment and insurance coverage, individuals in poorer countries often rely on humanitarian aid, charity, or cost-sharing mechanisms to afford the treatment they so desperately need. This wide disparity in treatment availability between countries, therefore, calls for more holistic policies and international cooperation to meet the needs of the disadvantaged regions regarding persons with hemophilia.

Cost-Effective Prophylaxis Treatment in Developing Countries

The management of hemophilia includes integrated care and primary care strategies to develop cost-effective treatment approaches, not only in developed countries but also in resource-limited settings. Key aspects of this care include treatment types, prevention of bleeding episodes, joint health maintenance, and quality of life improvement. Access to effective treatment remains a challenge in many nations, especially in countries where government policies do not adequately support hemophilia care. Socioeconomic factors, age, and the severity of hemophilia significantly impact treatment availability and accessibility. Although several countries have made significant advances in hemophilia management and insurance coverage, considerable disparities persist globally.^{1,2}

Table 4 and 5 show studies comparing low-dose prophylaxis (LDP) and high-dose prophylaxis (HDP), highlighting outcome parameters from various countries, including available products and government coverage. Primary prophylaxis doses range

from low-dose options (10–15 IU/kg) to high-dose regimens (25–40 IU/kg), with administration typically 2–3 times weekly. Secondary prophylaxis has been shown to effectively reduce bleeding episodes and improve quality of life compared to on-demand treatment. A study by the Hemophilia Society reported that LDP led to reductions in annualized bleeding rate (ABR), improvements in joint function, pain, and health-related quality of life (HRQoL) when compared to episodic treatment (ET). Developing countries may consider LDP as a first step before transitioning to a recombinant regimen.

A randomized study from Indonesia, using LDP (5–10 IU/kg twice weekly) with FVIII concentrates (eg, Octanate, Beriate, Haemoctin), showed a marked reduction in ABR and improved joint function, although insurance coverage was limited.¹ The Hemophilia Society's ASEAN consensus journal analysis recommended fixed doses (5–10 IU/kg twice weekly) supported by government health insurance, with IDP reporting zero bleeds at the end of treatment. In Singapore and under the Malmo protocol, HDP (25–40 IU/kg three times/week) and 50 IU/kg twice/week for hemophilia B showed efficacy in severe cases, with partial government coverage.^{25,36}

Robust health systems and financial support mean that, in most European countries, as represented by the CHES study, full coverage of prophylaxis treatment for hemophilia is possible.³² The high cost of treatment, especially EHL products, does not represent a barrier in these regions, with the annual prophylaxis cost ranging from 210,597 to 933,828 USD per patient. Such coverage is critical for ensuring that patients can receive consistent and effective prophylactic treatment for reducing bleeding episodes and long-term complications from hemophilia. This comprehensive prophylaxis coverage in high-income countries further illustrates how well the delivery of preventive care works and underlines the important role of government healthcare programs in supporting the financial accessibility of essential treatments.

On the contrary, middle to low-income countries like Indonesia, Thailand, and Malaysia have increasingly considered low-dose prophylaxis regimens as reasonable cost-effective alternatives. Low-dose prophylaxis remains quite within the budgets of governments, costing from USD 8320 to USD 28,988 annually.^{2,33,35} This means that even highly resource-constrained countries can still afford to make sure the health of their hemophilia patients is brought to the forefront of their agendas. With the institution of low-dose prophylaxis, governments can still attain a good level of reduction in bleeding episodes and enjoy an improved quality of life by the hemophilia patients.

Conclusion

The recognized standard dose of hemophilia prophylaxis ranges from 30 to 60 IU/kg of FVIII, administered 3 to 4 times a week, which makes it inconvenient for certain regions with limited resource. Cost and accessibility remain barriers in developing countries, especially in low- to middle-income countries where access to treatment is limited by high costs and inadequate support. Several researches have been conducted to study the efficacy of lower prophylaxis dose as the alternative to lower bleeding rates and improving quality of life of PWH. This review highlights that low-dose prophylaxis (LDP) is effective in reducing annualized bleeding rates (ABR) and annual joint bleeding rates (AJBR), making it a viable alternative to the standard dose, especially in resource limited countries. LDP is associated with notable reductions in bleeding episodes, without increased risks of thrombosis or FVIII Inhibitor formation. Early prophylaxis, using low dose FVIII, has been shown to significantly improve outcomes. However, continued advocacy for equitable healthcare policies and resources to support hemophilia management will be essential in addressing the global disparities in treatment access and outcomes. As the hemophilia community moves forward, strategies centered on LDP can provide a meaningful balance between clinical efficacy, cost-effectiveness, and improved quality of life for patients navigating the complexities of hemophilia. Overall, LDP is non-inferior to higher doses of prophylaxis in managing hemophilia and improving patient quality of life, particularly in settings where cost and accessibility are concerns.

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Disclosure

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