NAC STATEMENT ON FACTOR XIII CONCENTRATE USE

Author: Ryan Lett, MD

Authors of Previous Version: Susan Nahirniak, MD
Alan Tinmouth, MD
Dana Devine, PhD

NAC Chair: Andrew Shih, MD

Provincial Ministry Representative: Antje Helmuth (BC)
Pouya Pour (BC)

NAC Coordinator: Kendra Stuart

Publication Date: April 12, 2018

Date of Last Revision: July 17, 2024

Cite As:

Lett R. NAC Statement on Factor XIII Concentrate Use [Internet]. Ottawa: National Advisory Committee on Blood and Blood Products; April 12, 2018 [updated 2024 07 17; cited YYYY MM DD]. Available from: https://nacblood.ca/en/resource/nac-statement-factor-xiii-concentrate-use-0

RECOMMENDATION:

A librarian assisted literature review from 2013-2023 was performed reviewing the use of Factor XIII in clinical practice. There was no high-quality evidence found to support routine replacement without knowledge of existing Factor XIII levels. There is a need to assess outcomes based on testing in Canada.

ACKNOWLEDGMENTS:

The National Advisory Committee on Blood and Blood Products would like to acknowledge and thank the Saskatchewan Health Authority Library and Librarian Mark Mueller for providing the literature search required to update this recommendation.

The following is the evidence search report performed by the Saskatchewan Health Authority Library which informed this recommendation.

Saskatchewan Health Authority Library
https://saskhealthauthority.libguides.com/home
library@saskhealthauthority.ca
306-766-4142

Evidence Search Report

Evidence to support Factor XIII replacement therapy

Lab Assays for Factor XIII Levels in acute hemorrhages

Request ID#: 3130058
Date Submitted: 5 DEC 2023
Date Completed: 22 DEC 2023
Librarian: mark.mueller@saskhealthauthoriy.ca

Notes & Comments:

Our search report format has changed! Please let us know if you have any questions or if you encounter issues viewing/browsing your search results.

Please advise if you prefer to receive electronic references (e.g. .RIS file compatible with citation management software).

Thank you for your patronage!

Contents

Tips & Instructions

How to View Complete References and Abstracts

- Follow the link/URL provided along with the journal and article title to see the complete reference in PubMed or from the journal publisher.

How to Access or Request Full-Text (PDFs)

- Use the **LibKey Nomad** browser extension for Chrome/Edge to acquire or request full-text PDFs.
- **Check our FAQ** for solutions to common problems and questions, or use our **Chat Service** to connect with library staff
- Submit an electronic **Service Request** or **email the library** for additional help and support.

How to Access Remotely

- An SHA library card number is necessary to access resources when working off-site: **Register for remote resources access**.

Reference Management & Citation

- The library encourages use of reference managers (EndNote, Zotero, RefWorks, etc.). Let your librarian know if you prefer to receive search results electronically (.RIS)
- Be advised that articles listed below **do not adhere to any standard publication format or writing style**; they are formatted for quick review of search findings.
- See the SHA Library **Citing & Reference Guide** for information on proper referencing and citation styles. SHA documents should have references formatted according to **Vancouver Style.**

Search Results

Journal Articles – Recombinant Factor XIII

1. Albrecht A, Macke C, Wilhelmi M, et al. The potential impact of coagulation factor XIII in trauma-induced coagulopathy - a retrospective case series analysis. European journal of trauma and emergency surgery : official publication of the European Trauma Society. 2023;49(3):1517-23.
ABSTRACT: BACKGROUND: The role of factor XIII (FXIII) in trauma-induced coagulopathy (TIC) is not fully understood. METHOD(S): We evaluated FXIII supplementation in severely injured patients with persistent bleeding. This was a retrospective case series analysis. RESULT(S): Twenty-four patients received FXIII concentrate within 24 h of admission for bleeding that continued after transfusion of>6 U red blood cells (RBCs); control patients (n=27) did not receive FXIII concentrate. Both study groups were similar regarding injury severity score and global coagulation tests, but FXIII activity levels were significantly higher and lactate levels significantly lower in the control group, respectively. The differences in FXIII activity between the groups could be attributed to a more severe trauma-induced coagulopathy in FXIII-deficient patients, as demonstrated by lower fibrinogen and higher lactate levels. The median dose of FXIII concentrate within 24 h of admission was 2500 IU (IQR: 1250-4375). Median 24-h transfusion of RBCs (primary study endpoint) was significantly higher in the FXIII group versus controls (10.0 U, IQR 5-14 U vs. 2, IQR 0-6 U; p<0.01). Subsequently, while patients were in the intensive care unit, there was no statistically significant difference regarding RBC transfusion anymore and the overall clinical outcomes were similar in both patient groups. CONCLUSION(S): The substitution of FXIII in patients who were more seriously compromised due to higher lactate levels and who presented with initially more severe bleedings than patients in the control group, resulted in a comparable transfusion necessity after 24 h. Thus, we guess that the substitution of FXIII in severely injured patients with ongoing bleeding might have an impact on their clinical outcome. Copyright © 2023. The Author(s).
URL: https://pubmed.ncbi.nlm.nih.gov/36670303/
DOI: https://doi.org/10.1007/s00068-023-02221-z

2. Ito Y, Tsuji S, Kasahara M, et al. Successful perinatal management of a woman with congenital factor XIII deficiency using recombinant factor XIII: A case report and literature review. The journal of obstetrics and gynaecology research. 2023. DOI: 10.1111/jog.15819
ABSTRACT: Factor XIII deficiency is an extremely rare autosomal recessive genetic disorder, occurring in 1 of 3-5 million people, and is associated with perinatal complications, such as habitual abortion and prolonged bleeding. Although plasma-derived factor XIII (Fibrogamin(R)) carries a risk of infection and contains very low concentrated forms of factor XIII (FXIII) used for a pregnant woman with congenital coagulation factor XIII deficiency, recombinant factor XIII (rFXIII, Novo Thirteen(R); Tretten(R), Novo Nordisk, Bagsvaerd, Denmark), which has no risk of infection and is highly concentrated, has emerged as a novel formulation. Herein, we report the first case of a Japanese pregnant woman with congenital coagulation factor XIII deficiency successfully managed by rFXIII. She had a good perinatal course without pregnancy-related complications and transfusion through the perinatal period.
URL: https://www.ncbi.nlm.nih.gov/pubmed/37875278
DOI: https://dx.doi.org/10.1111/jog.15819

3. Zanon E, Pasca S, Sottilotta G, et al. A multicenter, real-world experience with recombinant FXIII for the treatment of patients with FXIII deficiency: from pharmacokinetics to clinical practice. The Italian FXIII Study. Blood Transfus. 2023;21(4):350-5. DOI: 10.2450/2022.0121-22
ABSTRACT: BACKGROUND: Congenital factor XIII (FXIII) deficiency is a rare coagulation disorder characterized by muscular or mucocutaneous bleeding with life-threatening intracranial hemorrhages (ICHs), especially in cases with severe disease. The best treatment is the use of prophylactic plasma-derived or recombinant FXIII (rFXIII). Few data on the use of rFXIII in the real-world scenario are available. The main goal of this study was to assess the efficacy and safety of catridecacog (NovoThirteen((R))) in a population of patients with FXIII deficiency. Other objectives were to compare the different pharmacokinetic (PK) profiles of each patient and to use them to create a

tailored prophylaxis regimen. MATERIALS AND METHODS: We collected and analyzed all pharmacokinetic and clinical data in our registry of the patients with congenital FXIII deficiency treated with rFXIII at eleven Italian hemophilia centers. Data were collected from January 2019 to December 2020. RESULTS: Overall, data on 20 patients with FXIII deficiency were collected, 16 of whom presented with severe disease. Pharmacokinetics was assessed in 18 cases before starting prophylaxis. Prophylaxis was subsequently started in these patients using a wide range of dosages (25.0-80.0 IU/kg; mean 33.8 IU/kg) and infusion intervals (3.0-8.0 weeks). During a mean follow up of 47 months, two minor bleeds and one ICH in a severe patient who had remained under on-demand treatment were reported. DISCUSSION: Efficacy and safety of rFXIII were proven in all patients. The dosage and infusion timing for the treated patients sometimes differed to those reported in the MENTOR pivotal studies, thus underlying the importance of tailored management in a real-world scenario.
URL: https://www.ncbi.nlm.nih.gov/pubmed/36580025
DOI: https://dx.doi.org/10.2450/2022.0121-22

4. Cojutti PG, Zanon E, Pasca S, et al. Real-Life Population Pharmacokinetics of Recombinant Factor XIII and Dosing Considerations for Preventing the Risk of Bleeding in Patients with FXIII Congenital Deficiency. Clin Pharmacokinet. 2022;61(4):505-13. DOI: 10.1007/s40262-021-01079-x
ABSTRACT: BACKGROUND AND OBJECTIVE: Recombinant factor XIII (rFXIII) at the recommended dosage of 35 IU/kg every 4 weeks is currently used for prophylaxis of bleeding in patients affected by FXIII deficiency. The aim of this study was to describe the population pharmacokinetics of rFXIII in patients with FXIII deficiency being treated with rFXIII in real-life and to assess, using Monte Carlo simulations, the attainment of defined FXIII concentration thresholds associated with prevention of the risk of bleeding over time. METHODS: A nonlinear mixed-effects model approach was used for population analysis. Monte Carlo simulations were used to generate 10,000 FXIII concentration-time profiles associated with incremental doses of 25, 30, 35, 40, 45 and 50 IU/kg of rFXIII. The probability of target attainment (PTA) of FXIII concentrations at thresholds of > 0.05, > 0.10 and > 0.15 IU/mL were calculated weekly, from days 7 to 49. RESULTS: A total of 18 patients provided 99 FXIII concentrations; most patients (77.8%, 14/18) had severe FXIII deficiency. A two-compartment pharmacokinetic model with linear elimination from the central compartment best described rFXIII data. No covariates were associated with rFXIII disposition. Pharmacokinetic parameter estimates were 0.16 mL/h/kg for clearance, 57.35 mL/kg for volume of distribution at steady-state, and 11.72 days for elimination half-life. The standard 35 IU/kg dose resulted in PTAs of the pharmacodynamic thresholds of FXIII concentrations of > 0.05, > 0.10 and > 0.15 IU/mL at day 28 that were equal to 89.9%, 68.9% and 47.8%, respectively. CONCLUSIONS: Intensive FXIII monitoring from day 14, and/or shortening the dosing interval between rFXIII administrations, should be considered to minimise the risk of bleeding.
URL: https://www.ncbi.nlm.nih.gov/pubmed/34718987
DOI: https://dx.doi.org/10.1007/s40262-021-01079-x

5. Pasca S, PierGiorgio C, Pea F. The pharmacokinetics of recombinant FXIII (catridecacog) from the MENTOR TM trial to a real-world study: a head-to-head comparison. Journal of Thrombosis and Thrombolysis. 2022;54(4):593-6.
ABSTRACT: Background: FXIII deficiency is a very rare coagulation disorder that can affect equally males and females with an estimated incidence of 1 in 2 million persons worldwide. Due to this rarity, there are only few clinical and pharmacokinetic (PK) data deriving from the real-world. Aim(s): The aim of this report is to compare head-to-head the pharmacokinetic data of catridecacog derived from the MENTOR^{TM}2 trial with our real-world (RW) study. Method(s): The PK-profiles of all patients with FXIII deficiency treated with catridecacog at eleven Italian Hemophilia Centers were compared with PK data obtained by Kerlin et al. in the MENTOR^{TM}2. Result(s): Overall 18 real-world PK were compared with 23 PK derived from the pivotal study. In the RW 55.6% of patients were females, 26.2% in the MENTOR^{TM}2 ($p < 0.05$). The mean dosage of drug used for the PK assessment was 35 IU/kg in the MENTOR^{TM}2, and 33.9 IU/kg in the RW study.
URL: https://pubmed.ncbi.nlm.nih.gov/36094687/
DOI: https://doi.org/10.1007/s11239-022-02700-x

6. Poulsen LH, Kerlin BA, Castaman G, et al. Safety and effectiveness of recombinant factor XIII-A in congenital factor XIII deficiency: Real-world evidence. Research and Practice in Thrombosis and Haemostasis. 2022;6(2) (no pagination).
ABSTRACT: Background: Regular factor XIII (FXIII) prophylaxis is standard treatment for congenital FXIII A-subunit deficiency (FXIII-A CD). Recombinant factor XIII-A<inf>2</inf> (rFXIII-A<inf>2</inf>) was extensively evaluated in the mentor trials. Objective(s): To assess real-world safety and treatment effectiveness of rFXIII-A<inf>2</inf> prophylaxis from the mentor 6 trial. Patients/Methods: mentor 6 was a noninterventional, postauthorization safety study investigating rFXIII-A<inf>2</inf> prophylaxis in FXIII-A CD. rFXIII-A<inf>2</inf> treatment was observed for 2 to 6 years per patient. The primary end point was documentation of adverse drug reactions (including anti-FXIII antibody development). Secondary end points were serious adverse events (SAEs), medical events of special interest (MESIs), and annualized bleeding rate (ABR). Result(s): Among 30 patients (mean age, 25.5 years), there were 44 adverse events (AEs) (30 mild, 13 moderate, 1 severe). Eleven AEs were possibly/probably related to rFXIII-A<inf>2</inf>. Of four MESIs, two were unlikely related to rFXIII-A<inf>2</inf> (accidental overdose, deep vein thrombosis), and two were possibly/probably related (nonneutralizing anti-FXIII antibody, decreased therapeutic response). All 10 SAEs were unlikely related to rFXIII-A<inf>2</inf>. Over a follow-up of 75.4 patient-years, there were six treatment-requiring bleeds (all trauma-related with no spontaneous bleeds), giving a treatment-requiring ABR of 0.066; five bleeds were treated successfully with rFXIII-A<inf>2</inf>. Eight of nine minor surgeries performed during rFXIII-A<inf>2</inf> prophylaxis reported successful hemostatic outcomes (one missing evaluation). Conclusion(s): These data confirm that rFXIII-A<inf>2</inf> prophylaxis is well tolerated as long-term care. There were no spontaneous bleeds, ABR was low, and rFXIII-A<inf>2</inf> successfully treated bleeds in patients receiving rFXIII-A<inf>2</inf> prophylaxis. Copyright © 2022 The Authors. Research and Practice in Thrombosis and Haemostasis published by Wiley Periodicals LLC on behalf of International Society on Thrombosis and Haemostasis (ISTH).
URL: https://pubmed.ncbi.nlm.nih.gov/35243202/
DOI: https://doi.org/10.1002/rth2.12628

7. Carcao M, Altisent C, Castaman G, et al. Recombinant FXIII Prophylaxis Prevents Bleeding and Allows for Surgery in Patients with Congenital FXIII A-Subunit Deficiency. Thrombosis and Haemostasis. 2018;118(3):451-60.
ABSTRACT: Recombinant factor XIII-A <inf>2</inf> (rFXIII-A <inf>2</inf>) was developed for prophylaxis and treatment of bleeds in patients with congenital FXIII A-subunit deficiency. mentorTM2 (NCT00978380), a multinational, open-label, single-arm, multiple-dosing extension to the pivotal mentorTM1 trial, assessed long-term safety and efficacy of rFXIII-A <inf>2</inf> prophylaxis in eligible patients (patients with severe [<0.05 IU/mL] congenital FXIII subunit A deficiency) aged >=6 years. Patients received 35 IU/kg rFXIII-A <inf>2</inf> (exact dosing) every 28 +/- 2 days for >=52 weeks. Primary endpoint was safety (adverse events including immunogenicity); secondary endpoints were rate of bleeds requiring FXIII treatment, haemostatic response after one 35 IU/kg rFXIII-A <inf>2</inf> dose for breakthrough bleeds and withdrawals due to lack of rFXIII-A <inf>2</inf> efficacy. Steady-state pharmacokinetic variables were also summarized. Elective surgery was permitted during the treatment period. Sixty patients were exposed to rFXIII-A <inf>2</inf>; their median age was 26.0 years (range: 7.0-77.0). rFXIII-A <inf>2</inf> was well tolerated without any safety concerns. No non-neutralizing or neutralizing antibodies (inhibitors) against FXIII were detected. Mean annualized bleeding rate (ABR) was 0.043/patient-year. Mean spontaneous ABR was 0.011/patient-year. No patients withdrew due to lack of efficacy. Geometric mean FXIII trough level was 0.17 IU/mL. Geometric terminal half-life was 13.7 days. rFXIII-A <inf>2</inf> prophylaxis provided sufficient haemostatic coverage for 12 minor surgeries without the need for additional FXIII therapy; eight procedures were performed within 7 days of the patient's last scheduled rFXIII-A <inf>2</inf> dose, and four were performed 10 to 21 days after the last dose. Copyright © 2018 Schattauer.
URL: https://pubmed.ncbi.nlm.nih.gov/29448295/
DOI: https://doi.org/10.1055/s-0038-1624581

8. Takeda Y, Mise Y, Ishizuka N, et al. Effect of early administration of coagulation factor XIII on fistula after pancreatic surgery: the FIPS randomized controlled trial. Langenbecks Arch Surg. 2018;403(8):933-40. DOI: 10.1007/s00423-018-1736-4

ABSTRACT: PURPOSE: The administration of exogenous factor XIII (FXIII) is reportedly effective for fistula closure in patients with a low plasma FXIII level. This study was performed to analyze the effect of early administration of exogenous FXIII on postoperative pancreatic fistula (POPF). METHODS: A single-center randomized controlled, open-label, parallel group, superiority trial was conducted from October 2015 to August 2016 in Japan. Patients with POPF and a plasma FXIII level of </= 70% on postoperative day 7 were randomly assigned to an early replacement (ER) group or control group in a 1:1 ratio by an independent coordinator using a computer-generated random number table. The ER group received FXIII concentrate the day after randomization, and the control group received no FXIII concentrate within 2 weeks. The primary endpoint was the duration of drain placement from randomization (DDPR). RESULTS: Fifty patients were randomized (ER group, 24; control group, 26), and all were analyzed with an intention-to-treat approach. There was no significant difference in the DDPR between the two groups (18 vs. 16 days; hazard ratio, 1.45; 95% confidence interval, 0.813-2.583). No serious harm was reported in either group. CONCLUSION: Early administration of exogenous FXIII does not facilitate the healing of POPF. TRIAL REGISTRATION: University Hospital Medical Information Network (UMIN) Center (UMIN000019480, http://www.umin.ac.jp).
URL: https://www.ncbi.nlm.nih.gov/pubmed/30506109
DOI: https://dx.doi.org/10.1007/s00423-018-1736-4

9. Ivaskevicius V, Biswas A, Garly ML, et al. Comparison of F13A1 gene mutations in 73 patients treated with recombinant FXIII-A. Haemophilia. 2017;23(3):e194-e203.
ABSTRACT: Introduction: Congenital factor XIII (FXIII) deficiency is a rare, autosomal recessive bleeding disorder usually caused by mutations in the F13A1 gene that produce a severe quantitative (type I) deficiency of the FXIII-A subunit. Aim(s): To determine the genotypes of patients with severe FXIII-A deficiency treated with recombinant FXIII-A subunit (rFXIII-A<inf>2</inf>) participating in three international efficacy and safety trials. Method(s): We determined the genotypes of 73 patients in total; 32 had already undergone genotype analysis and were known to carry F13A1 mutations that have been previously reported in the literature. Mutation screening was performed in 41 patients with unknown genetic status using direct sequencing. Result(s): In total, 51 distinct mutations in 73 patients were identified. Two patients showed a phenotype of severe FXIII-A deficiency, despite having heterozygous missense mutations. Two siblings carried a missense mutation in the F13A1 gene (p.Ser296Arg) in combination with a novel, probably polymorphic variant of the F13B gene (p.Ser654Phe). Molecular modelling of five F13A1 novel missense mutations (p.Leu171Phe, p.Glu204Lys, p.Leu276Phe, p.Asp405His and p.Gly411Cys) predicted a damaging effect of these mutations on protein structure. Although five patients treated with rFXIII-A<inf>2</inf> had transient, low-titre, non-neutralizing anti-rFXIII antibodies, no patients developed FXIII-neutralizing antibodies (inhibitors). Conclusion(s): The identified mutations are causally implicated in severe FXIII deficiency; however, they do not appear to increase the risk of neutralizing antibody development against rFXIII-A<inf>2</inf>. Copyright © 2017 John Wiley & Sons Ltd
URL: https://pubmed.ncbi.nlm.nih.gov/28520207/
DOI: https://doi.org/10.1111/hae.13233

10. Kerlin BA, Inbal A, Will A, et al. Recombinant factor XIII prophylaxis is safe and effective in young children with congenital factor XIII-A deficiency: international phase 3b trial results. Journal of Thrombosis and Haemostasis. 2017;15(8):1601-6.
ABSTRACT: Essentials Prophylaxis is the standard of care for congenital factor XIII-A (FXIII-A) deficiency. Six children with FXIII-A deficiency received once-monthly prophylaxis with recombinant FXIII-A. Prophylaxis was well tolerated and no anti-FXIII antibodies were detected. Prophylaxis was effective with an annualized bleeding rate of zero. Summary: Background Factor XIII deficiency is a rare, severe congenital bleeding disorder. Monthly prophylaxis with recombinant FXIII A-Subunit (rFXIII) has demonstrated favorable safety and efficacy in patients aged >= 6 years, and may similarly benefit younger children. Objective To evaluate the long-term safety and efficacy of rFXIII in children aged < 6 years with congenital FXIII A-subunit deficiency. Patients/methods Six children, who had previously completed a single-dose pharmacokinetic trial of rFXIII, received 35 IU kg⁻¹ rFXIII every 28 days (+/- 2 days) for a minimum of 52 weeks, and were evaluated for bleeding and adverse events. The Berichrom FXIII activity assay was used to monitor FXIII activity. Results The children, three girls and three boys, had an average age of 3.0 years (range: 1-4 years) at enrollment. The total treatment duration was 1.8-3.5 years, giving a total of 16.6 patient-years. No antibody development, thromboembolic events or allergic reactions occurred.

There were 93 mild and seven moderate adverse events. Two adverse events (lymphopenia and gastroenteritis) were reported as probably or possibly related to rFXIII in two children. Two serious adverse events, unrelated to rFXIII, were reported in a single child, each related to head injury, and neither resulting in intracranial hemorrhage. The geometric mean FXIII activity trough was 0.19 IU mL⁻¹. No bleeding episodes requiring treatment with an FXIII-containing hemostatic agent occurred during the trial; thus, the annualized bleeding rate was 0. Conclusions Consistent with data from older age groups, prophylaxis with rFXIII appears to be safe and effective in young children with congenital FXIII A-subunit deficiency. Copyright © 2017 International Society on Thrombosis and Haemostasis
URL: https://pubmed.ncbi.nlm.nih.gov/28581691/
DOI: https://doi.org/10.1111/jth.13748

11. Solomon C, Korte W, Fries D, et al. Safety of Factor XIII Concentrate: Analysis of More than 20 Years of Pharmacovigilance Data. Transfusion Medicine and Hemotherapy. 2016;43(5):365-73.
ABSTRACT: Background: Plasma-derived factor XIII (FXIII) concentrate is an effective treatment for FXIII deficiency. We describe adverse drug reactions (ADRs) reported during pharmacovigilance monitoring of Fibrogammin/Corifact and review published safety data. Method(s): Postmarketing safety reports recorded by CSL Behring from June 1993 to September 2013 were analyzed. Clinical studies published during the same period were also reviewed. Result(s): Commercial data indicated that 1,653,450,333 IU FXIII concentrate were distributed over the review period, equivalent to 1,181,036 doses for a 70 kg patient. 75 cases were reported (one/15,700 standard doses or 22,046,000 IU). Reports of special interest included 12 cases of possible hypersensitivity reactions (one/98,400 doses or 137,787,500 IU), 7 with possible thromboembolic events (one/168,700 doses or 236,207,200 IU), 5 of possible inhibitor development (one/236,200 doses or 330,690,100 IU), and 20 of possible pathogen transmission (one/59,100 doses or 82,672,500 IU). 19 pathogen transmission cases involved viral infection; 4 could not be analyzed due to insufficient data, but for all others a causal relationship to the product was assessed as unlikely. A review of published literature revealed a similar safety profile. Conclusion(s): Assessment of ADRs demonstrated that FXIII concentrate carries a low risk of ADRs across various clinical situations, suggesting a favorable safety profile. Copyright © 2016 S. Karger GmbH, Freiburg.
URL: https://pubmed.ncbi.nlm.nih.gov/27781024/
DOI: https://doi.org/10.1159/000446813

12. Ashley C, Chang E, Davis J, et al. Efficacy and safety of prophylactic treatment with plasma-derived factor XIII concentrate (human) in patients with congenital factor XIII deficiency. Haemophilia. 2015;21(1):102-8. DOI: 10.1111/hae.12524
ABSTRACT: Congenital factor XIII (FXIII) deficiency is an extremely rare, potentially life-threatening bleeding disorder. Routine prophylactic management is recommended for individuals with clinically relevant FXIII deficiency. This prospective, multicentre, open-label study evaluated the long-term efficacy and safety of prophylactic infusions of FXIII concentrate (human) 40 IU kg(-1) in patients with congenital FXIII deficiency. FXIII concentrate (human) was administered every 4 weeks for 12 months. Dosing was adjusted to maintain trough FXIII activity levels of 5-20%. Logistical and ethical constraints precluded use of a placebo control group. Annualized incidence of spontaneous bleeding was compared with historical rates; safety was assessed as a secondary objective. Forty-one patients were enrolled and completed the study. The annualized rate for spontaneous bleeding episodes requiring FXIII treatment was 0.000 episodes per patient-year (95% CI: 0.000; 0.097). The study met its primary endpoint: the upper limit of the 95% CI was substantially below the historical rate of 2.5 bleeding episodes per patient-year. Five spontaneous bleeding episodes (involving three patients; none requiring FXIII treatment) and eight trauma-related bleeding episodes (two requiring FXIII treatment) occurred. Five patients had surgery during the study, only one of whom required FXIII treatment for post-surgical bleeding. Most patients (>/= 85%) had trough FXIII activity levels >/= 10%. No patient discontinued treatment due to an adverse event. No adverse events related to thromboembolism or viral transmission were reported. Prophylactic treatment with FXIII concentrate (human) was well tolerated and prevented spontaneous bleeding episodes that were serious enough to require treatment with FXIII-containing product. CLINICAL TRIAL REGISTRATION: www.clinicaltrials.gov/ct2/show/NCT00885742.
URL: https://www.ncbi.nlm.nih.gov/pubmed/25377187
DOI: https://dx.doi.org/10.1111/hae.12524

13. Brand-Staufer B, Carcao M, Kerlin BA, et al. Pharmacokinetic characterization of recombinant factor XIII (FXIII)-A2 across age groups in patients with FXIII A-subunit congenital deficiency. Haemophilia. 2015;21(3):380-5. DOI: 10.1111/hae.12616
ABSTRACT: Three trials investigated the pharmacokinetics (PK) of recombinant factor XIII (rFXIII) A-subunit. To compare the PK characteristics of rFXIII among trials and different age groups of patients. Dosing with rFXIII 35 IU kg(-1) every 4th week. Blood samples for PK assessments were collected regularly throughout the dosing interval from a total of 68 individual patients with FXIII congenital deficiency. The mean PK parameters were similar across the three age groups, and for the three trials, as well as constant over time based on results from patients participating in both mentor 1 and mentor 2 trials. The geometric mean half-life ranged from 11.6 to 15.0 days, and the trough FXIII activity levels ranged from 0.15 to 0.21 IU mL(-1) . The population PK model identified body weight as a statistically significant covariate influencing clearance (CL) and volume of distribution (Vd), with a similar increase in both parameters with increased body weight. The half-life was not affected by body weight. Gender (females vs. males) and age category (paediatric vs. adult) did not affect CL. The PK profile of rFXIII, after dosing with 35 IU kg(-1) of rFXIII, was independent of age and comparable between trials and FXIII trough activity levels were constant. Despite rather large individual variation in the maximal FXIII activity levels, all individual mean trough activity levels were above 0.1 IU mL(-1) during the entire duration of the trials. The results support that monthly dosing with 35 IU kg(-1) of rFXIII to patients with FXIII A-subunit deficiency, regardless of age, is adequate for prophylaxis.
URL: https://www.ncbi.nlm.nih.gov/pubmed/25643920
DOI: https://dx.doi.org/10.1111/hae.12616

14. Janbain M, Nugent DJ, Powell JS, et al. Use of Factor XIII (FXIII) concentrate in patients with congenital FXIII deficiency undergoing surgical procedures. Transfusion. 2015;55(1):45-50. DOI: 10.1111/trf.12784
ABSTRACT: BACKGROUND: Patients with congenital Factor XIII (FXIII) deficiency have impaired fibrin stabilization and are at high risk for surgical bleeding. Data regarding the use of FXIII concentrates before and during surgery are lacking. The objective of this study was to report the use of plasma-derived FXIII concentrate (Corifact in the United States; Fibrogammin P in other countries) in patients with congenital FXIII deficiency undergoing surgical procedures. STUDY DESIGN AND METHODS: FXIII concentrate at preoperative doses ranging from 25 to 40 U/kg was administered to six patients with congenital FXIII deficiency undergoing major or minor surgeries. RESULTS: FXIII concentrate was administered immediately before surgery for five surgical cases; three of these patients achieved excellent hemostasis during and after surgery, while two had intraoperative bleeding. In one surgical case, a regular prophylactic dose of FXIII concentrate was administered to the patient 1 week before minor surgery. FXIII concentrate provided rapid replacement of FXIII activity. In all but one of the patients given a dose of FXIII designed to increase FXIII levels more than 50%, there was satisfactory intraoperative and postoperative hemostasis. One patient undergoing aortic valve replacement on cardiopulmonary bypass (CPB) was the exception. Intraoperative bleeding in this patient was associated with lower-than-expected blood levels of FXIII. CONCLUSION: Preoperative plasma-derived FXIII concentrate allowed for sufficient hemostasis in most patients with FXIII deficiencies. Additional doses were necessary to achieve hemostasis in one patient who underwent a CPB procedure.
URL: https://www.ncbi.nlm.nih.gov/pubmed/25070582
DOI: https://dx.doi.org/10.1111/trf.12784

15. Nugent DJ, Ashley C, Garcia-Talavera J, et al. Pharmacokinetics and safety of plasma-derived factor XIII concentrate (human) in patients with congenital factor XIII deficiency. Haemophilia. 2015;21(1):95-101. DOI: 10.1111/hae.12505
ABSTRACT: Congenital factor XIII (FXIII) deficiency is a rare condition with substantial risk for life-threatening bleeding. Replacement of deficient FXIII with plasma-derived FXIII concentrate is a treatment option. The current 12-week study evaluated the steady-state pharmacokinetic (PK) and safety profile of prophylactic infusions of FXIII concentrate (human) in patients with congenital FXIII deficiency. Patients received FXIII concentrate (human) 40 IU kg(-1) on Days 0, 28, and 56. FXIII levels were assessed before and after each infusion; steady-state PK parameters were assessed up to 28 days after the infusion on Day 56. Treatment effectiveness in maintaining trough FXIII activity levels >/= 5% over 28 days and safety parameters were also assessed. Fourteen patients received FXIII

concentrate (human) and 13 completed the study. Post-infusion, FXIII activity levels increased to within the range found in patients without congenital FXIII deficiency without reaching supra-therapeutic levels. Non-baseline-adjusted trough FXIII activity levels were maintained at or above 10% at all post-baseline visits in all patients. Steady-state PK parameters were baseline-adjusted; maximum FXIII activity was 87.7% at 1.72 h post-infusion, subsequently declining to a minimum of 5.0%. The half-life was 6.6 days. FXIII concentrate (human) was generally well tolerated. Two patients had possibly treatment-related adverse events. There were no reports of thromboembolism, viral transmission, bleeding events or treatment-related hypersensitivity. These findings support use of FXIII concentrate (human) 40 IU kg(-1) every 28 days as an appropriate regimen for routine, long-term prophylaxis in children and adults with congenital FXIII deficiency. CLINICAL TRIAL REGISTRATION: www.clinicaltrials.gov/ct2/show/NCT00883090.
URL: https://www.ncbi.nlm.nih.gov/pubmed/25458735
DOI: https://dx.doi.org/10.1111/hae.12505

16. Kerlin B, Brand B, Inbal A, et al. Pharmacokinetics of recombinant factor XIII at steady state in patients with congenital factor XIII A-subunit deficiency. Journal of Thrombosis and Haemostasis. 2014;12(12):2038-43.
ABSTRACT: The use of monthly recombinant factor XIII (rFXIII) recently demonstrated favorable safety and efficacy for congenital FXIII A-subunit deficiency patients aged >= 6 years (mentor^{TM}1 trial), although the pharmacokinetics (PK) were not fully evaluated. Objective(s): To comprehensively evaluate the steady-state PK of rFXIII in patients aged >= 6 years with congenital FXIII A-subunit deficiency. Patients/methods: mentor^{TM}2 is an ongoing, multinational safety and efficacy trial in which patients are receiving monthly rFXIII (35 IU kg⁻¹) for >= 52 weeks. For this 28-day PK analysis, blood samples were collected immediately predosing, and 1 h, 2 h, 3, 7, 14, 21, and 28 days postdosing. FXIII activity was measured and PK parameters were calculated using non-compartmental analysis, without prior baseline adjustment. Information regarding adverse events and bleeding was collected at each visit. Antibody assessments were performed predosing and at day 28. Result(s): PK analysis in 23 patients revealed first-order elimination of rFXIII with a geometric mean half-life of 13.6 days. Mean FXIII activity was > 0.1 IU mL⁻¹ throughout the 28-day period, with a geometric mean peak activity of 0.87 IU mL⁻¹ and trough of 0.16 IU mL⁻¹. The geometric mean clearance was 0.15 mL h⁻¹ kg⁻¹. No bleeding episodes occurred during the PK session, and no anti-rFXIII antibodies were detected. Peak and trough FXIII activities were constant over time, compared with previous activities (>= 10 rFXIII doses) in the same patients. Conclusion(s): Clearance of rFXIII is unaffected over time, and monthly prophylaxis with 35 IU kg⁻¹ rFXIII provides FXIII activity > 0.1 IU mL⁻¹ throughout the dosing interval in patients with congenital FXIII A-subunit deficiency.
URL: https://pubmed.ncbi.nlm.nih.gov/25263390/
DOI: https://doi.org/10.1111/jth.12739

17. Williams M, Will A, Stenmo C, et al. Pharmacokinetics of recombinant factor XIII in young children with congenital FXIII deficiency and comparison with older patients. Haemophilia. 2014;20(1):99-105. DOI: 10.1111/hae.12224
ABSTRACT: Congenital factor XIII (FXIII) deficiency is a rare bleeding disorder, which in its severe form is associated with a significant bleeding phenotype, requiring regular prophylactic therapy. A recently developed recombinant FXIII (rFXIII) has demonstrated safety and efficacy in children aged >/=6 years and adults (mentor1 trial). This article describes the mentor4 trial, which has assessed the pharmacokinetics (PK) and safety of rFXIII in younger children (1 to <6 years) with congenital FXIII deficiency, and compares extrapolated PK parameters with the mentor1 trial. Six children with congenital FXIII A-subunit deficiency received a single, 35 IU kg(-1) rFXIII dose. PK properties were similar in all the children, with a mean area under the concentration vs. 30-day time curve of 248.6 IU h(-1) mL(-1) , maximal FXIII activity (30 min) of 0.67 IU mL(-1) , and mean 30-day trough of 0.21 IU mL(-1) . All patients maintained FXIII activity above the lower target level (0.1 IU mL(-1)). rFXIII half-life was 15.1 days (range, 10-25). No safety findings of clinical concern were observed. PK properties of rFXIII were similar in patients from both trials. The study demonstrated that a single dose of 35 IU kg(-1) rFXIII maintained plasma FXIII levels above 0.1 IU mL(-1) over a 30-day period in young children with congenital FXIII deficiency, and is, therefore, likely to provide adequate prophylaxis in this age group. The study extends the previous findings of the mentor1 trial and confirms that no dose adjustment is required for different age groups with congenital FXIII deficiency.

URL: https://www.ncbi.nlm.nih.gov/pubmed/23834599
DOI: https://dx.doi.org/10.1111/hae.12224

18. He S, Johnsson H, Zabczyk M, et al. A fibrinogen concentrate Haemocomplettan or a Factor XIII concentrate Fibrogammin combined with a mini dose of tranexamic acid can reverse the fibrin instability to fibrinolysis induced by thrombin- or FXa-inhibitor. British Journal of Haematology. 2013;160(6):806-16.
ABSTRACT: To assess whether Haemocomplettan (fibrinogen concentrate) or Fibrogammin (Factor XIII concentrate) can be used to manage bleeding complications of antithrombotic treatment, we examined a normal plasma pool spiked with AR-H067637 (thrombin inhibitor) or rivaroxaban (activated factor X-inhibitor), to which one of the concentrates was added. Fibrin network permeability (Ks), images of Scanning Electron Microscopy (SEM) and Clot Lysis Time (CLT) were examined. Both inhibitors increased the Ks levels, which could be fully or partly reversed by Haemocomplettan or Fibrogammin respectively. However, these modified clots with tightened network remained non-resistant to fibrinolysis, shown as unaffected CLT. Tranexamic acid at a very low concentration (0.4 mg/ml) aided the two concentrates to stabilize the clots, where the prolongation of CLT was more pronounced for a lower dose than a higher dose of Haemocomplettan while Fibrogammin brought the greatest delay to CLT out of all additions. These observations were partly supported by SEM images, displaying alterations of fibrin fibre arrangement known to influence fibirinolysis. The in vitro data suggest that Haemocomplettan or Fibrogammin given in combination with a mini dose of tranexamic acid may slow down the natural clearance of fibrin clot by plasmin and thus prevent patients from haemorrhagic complications during antithrombotic therapy. © 2013 Blackwell Publishing Ltd.
URL: https://pubmed.ncbi.nlm.nih.gov/23360261/
DOI: https://doi.org/10.1111/bjh.12189

19. Karkouti K, von Heymann C, Jespersen CM, et al. Efficacy and safety of recombinant factor XIII on reducing blood transfusions in cardiac surgery: a randomized, placebo-controlled, multicenter clinical trial. J Thorac Cardiovasc Surg. 2013;146(4):927-39. DOI: 10.1016/j.jtcvs.2013.04.044
ABSTRACT: OBJECTIVES: Cardiac surgery with cardiopulmonary bypass frequently leads to excessive bleeding, obligating blood product transfusions. Because low factor XIII (FXIII) levels have been associated with bleeding after cardiac surgery, we investigated whether administering recombinant FXIII after cardiopulmonary bypass would reduce transfusions. METHODS: In this double-blinded, placebo-controlled, multicenter trial, 409 cardiac surgical patients at moderate risk for transfusion were randomized to receive an intravenous dose of recombinant FXIII, 17.5 IU/kg (n = 143), 35 IU/kg (n = 138), or placebo (n = 128) after cardiopulmonary bypass. Transfusion guidelines were standardized. The primary efficacy outcome was avoidance of allogeneic blood products for 7 days postsurgery. Secondary outcomes included amount of blood products transfused and reoperation rate. Serious adverse events were measured for 7 weeks. RESULTS: Study groups had comparable baseline characteristics and an approximately 40% decrease in FXIII levels after cardiopulmonary bypass. Thirty minutes postdose, FXIII levels were restored to higher than the lower 2.5th percentile of preoperative activity in 49% of the placebo group, and 85% and 95% of the 17.5- and 35-IU/kg recombinant FXIII groups, respectively (P < .05 for both treatments vs placebo). Transfusion avoidance rates were 64.8%, 64.3%, and 65.9% with placebo, 17.5 IU/kg, and 35 IU/kg recombinant FXIII (respective odds ratios against placebo, 1.05 [95% confidence interval, 0.61-1.80] and 0.99 [95% confidence interval, 0.57-1.72]). Groups had comparable adverse event rates. CONCLUSIONS: Replenishment of FXIII levels after cardiopulmonary bypass had no effect on transfusion avoidance, transfusion requirements, or reoperation in moderate-risk cardiac surgery patients (ClinicalTrials.gov identifier: NCT00914589).
URL: https://www.ncbi.nlm.nih.gov/pubmed/23820174
DOI: https://dx.doi.org/10.1016/j.jtcvs.2013.04.044

Journal Articles – Lab Assays

1. Byrnes JR, Lee T, Sharaby S, et al. Reciprocal stabilization of coagulation factor XIII-A and -B subunits is a determinant of plasma FXIII concentration. Blood. 2023.

ABSTRACT: Transglutaminase factor XIII (FXIII) is essential for hemostasis, wound healing, and pregnancy maintenance. Plasma FXIII is composed of A and B subunit dimers synthesized in cells of hematopoietic origin and hepatocytes, respectively. The subunits associate tightly in circulation as FXIII-A<inf>2</inf>B<inf>2</inf>. FXIII-B<inf>2</inf> stabilizes the (pro)active site-containing FXIII-A subunits. Interestingly, people with genetic FXIII-A deficiency have decreased FXIII-B<inf>2</inf>, and therapeutic infusion of recombinant FXIII-A<inf>2</inf> (rFXIII-A<inf>2</inf>) increases FXIII-B<inf>2</inf>, suggesting FXIII-A regulates FXIII-B secretion, production, and/or clearance. We analyzed humans and mice with genetic FXIII-A deficiency and developed a mouse model of rFXIII-A<inf>2</inf> infusion to define mechanisms mediating plasma FXIII-B levels. Like humans with FXIII-A deficiency, mice with genetic FXIII-A deficiency had reduced circulating FXIII-B<inf>2</inf>, and infusion of FXIII-A<inf>2</inf> increased FXIII-B<inf>2</inf>. FXIII-A-deficient mice had normal hepatic function and did not store FXIII-B in liver, indicating FXIII-A does not mediate FXIII-B secretion. Transcriptional analysis and polysome profiling indicated similar F13b levels and ribosome occupancy in FXIII-A-sufficient and -deficient mice and in FXIII-A-deficient mice infused with rFXIII-A<inf>2</inf>, indicating FXIII-A does not induce de novo FXIII-B synthesis. Unexpectedly, pharmacokinetic/pharmacodynamic modeling of FXIII-B antigen after rFXIII-A<inf>2</inf> infusion in humans and mice suggested FXIII-A<inf>2</inf> slows FXIII-B<inf>2</inf> loss from plasma. Accordingly, comparison of free FXIII-B<inf>2</inf> vs FXIII-A<inf>2</inf>-complexed FXIII-B<inf>2</inf> (FXIII-A<inf>2</inf>B<inf>2</inf>) infused into mice revealed faster clearance of free FXIII-B<inf>2</inf>. These data show FXIII-A<inf>2</inf> prevents FXIII-B<inf>2</inf> loss from circulation and establish the mechanism underlying FXIII-B<inf>2</inf> behavior in FXIII-A deficiency and during rFXIII-A<inf>2</inf> therapy. Our findings reveal a unique, reciprocal relationship between independently synthesized subunits that mediate an essential hemostatic protein in circulation. This trial was registered at www.ClinicalTrials.com as #NCT00978380. Copyright © 2023 The American Society of Hematology

URL: https://pubmed.ncbi.nlm.nih.gov/37883802/

DOI: https://doi.org/10.1182/blood.2023022042

2. Duque P, Korte W. Factor XIII in the Acute Care Setting and Its Relevance in Obstetric Bleeding. Transfus Med Hemother. 2023;50(1):10-7. DOI: 10.1159/000526489

ABSTRACT: BACKGROUND: Major hemorrhage is one of the main causes of preventable mortality in either severe trauma, high-risk surgical patient, or the obstetric population. As underlined by the cell-based coagulation model, a resistant and stable clot is essential to prevent or to stop an ongoing bleeding. Coagulation factor XIII (FXIII) stabilizes the newly formed clot by cross-linking the fibrin monomers into a three-dimensional network and by impeding fibrinolysis. Thus, FXIII is an essential coagulation factor in the acutely bleeding patient. SUMMARY: Acquired FXIII deficiency is much more common than the inherited form. On the basis of acute tissue injury which leads to major bleeding, acquired FXIII deficiency is traditionally considered to be secondary to consumption. However, recent evidence in the field of obstetrics and high-risk surgery suggests that it might be an associated factor rather than a consequence of the bleeding, which would mean that early replacement of FXIII could potentially improve outcomes. However, FXIII measurement is not universally available. Assessing FXIII through viscoelastic assays seems feasible, though likely it is not yet accurate. Moreover, the target population at risk and the aimed FXIII level required to achieve hemostasis in each condition are yet to be defined. KEY MESSAGES: FXIII should be assessed and replaced if necessary in the acutely bleeding patient. We recommend FXIII to be included in an escalating scheme of hemostatic therapies in the acute care setting.

URL: https://www.ncbi.nlm.nih.gov/pubmed/36818773

DOI: https://dx.doi.org/10.1159/000526489

3. Amano S, Oka K, Sato Y, et al. Measuring Factor XIII Inhibitors in Patients with Factor XIII Deficiency: A Case Report and Systematic Review of Current Practices in Japan. J Clin Med. 2022;11(6). DOI: 10.3390/jcm11061699

ABSTRACT: Factor XIII (FXIII) deficiency is a rare but serious coagulopathy. FXIII is critical in blood coagulation, and FXIII deficiencies can lead to uncontrolled or spontaneous bleeding. FXIII deficiencies can be congenital or acquired; acquired FXIII deficiency can be categorized as autoimmune and non-autoimmune. Immunological tests to measure FXIII inhibitors are required to diagnose acquired FXIII deficiency; however, appropriate test facilities are limited, which increases the turnaround time of these tests. In the case of critical bleeding, delayed test results may worsen prognosis due to delayed treatment. Here, we report a case of acquired FXIII deficiency, followed by a

review of FXIII deficiency cases in Japan. We performed a systematic review to investigate the present conditions of the diagnosis and treatment of FXIII deficiency, including the measurement of FXIII inhibitors in Japan. FXIII inhibitor testing was only performed in 29.7 of acquired FXIII deficiency cases. Clinical departments other than internal medicine and pediatrics were often involved in medical treatment at the time of onset. Therefore, it is important for doctors in clinical departments other than internal medicine and pediatrics to consider FXIII deficiency and perform FXIII inhibitor testing when examining patients with prolonged bleeding of unknown cause or persistent bleeding after trauma.
URL: https://www.ncbi.nlm.nih.gov/pubmed/35330024
DOI: https://dx.doi.org/10.3390/jcm11061699

4. Kleber C, Sablotzki A, Casu S, et al. The impact of acquired coagulation factor XIII deficiency in traumatic bleeding and wound healing. Crit Care. 2022;26(1):69. DOI: 10.1186/s13054-022-03940-2
ABSTRACT: Factor XIII (FXIII) is a protein involved in blood clot stabilisation which also plays an important role in processes including trauma, wound healing, tissue repair, pregnancy, and even bone metabolism. Following surgery, low FXIII levels have been observed in patients with peri-operative blood loss and FXIII administration in those patients was associated with reduced blood transfusions. Furthermore, in patients with low FXIII levels, FXIII supplementation reduced the incidence of post-operative complications including disturbed wound healing. Increasing awareness of potentially low FXIII levels in specific patient populations could help identify patients with acquired FXIII deficiency; although opinions and protocols vary, a cut-off for FXIII activity of ~ 60-70% may be appropriate to diagnose acquired FXIII deficiency and guide supplementation. This narrative review discusses altered FXIII levels in trauma, surgery and wound healing, diagnostic approaches to detect FXIII deficiency and clinical guidance for the treatment of acquired FXIII deficiency.
URL: https://www.ncbi.nlm.nih.gov/pubmed/35331308
DOI: https://dx.doi.org/10.1186/s13054-022-03940-2

5. Ozaki S, Mizuguchi M, Okamoto Y, et al. Frequent bleeding symptoms associated with autoimmune acquired factor XIII/13 deficiency due to anti-factor XIII A and B subunit antibodies. American Journal of Hematology. 2022;97(11):1497-500.
URL: https://pubmed.ncbi.nlm.nih.gov/35957554/
DOI: https://doi.org/10.1002/ajh.26685

6. Chuliber FA, Schutz NP, Vinuales ES, et al. Nonimmune-acquired factor XIII deficiency: a cause of high volume and delayed postoperative hemorrhage. Blood Coagul Fibrinolysis. 2020;31(8):511-6. DOI: 10.1097/MBC.0000000000000953
ABSTRACT: : Factor XIII (FXIII) levels may decrease because of surgical consumption. Acquired FXIII deficiency could be a cause of postoperative hemorrhage usually underdiagnosed in clinical practice. To determine the diagnosis confirmation rate of acquired FXIII deficiency in postsurgical patients with clinical suspicion and to compare the characteristics and evolution of patients with or without FXIII deficiency. We performed a retrospective cohort study, which included 49 inpatients who were attended at our university hospital from 2014 to 2018 with suspicion of acquired FXIII deficiency because of disproportionate postoperative hemorrhage. FXIIIA levels less than 50% was considered a deficiency. Persistence of bleeding for more than 48 h, drop in hematocrit points, red blood cells transfused units, hemoglobin levels 12-36 h after bleeding, and time elapsed from the procedure to the bleeding were assessed as outcome variables. Logistic regression was employed for both univariate and multivariate analyses. Of the 49 patients included, 27(55%) had FXIII deficiency, with a median level of 34% [interquartile range (IQR) 19-42]. Abdominal surgery was the most common [n = 21 (43%)]. All patients had routine coagulation tests within the hemostatic range. FXIII deficiency was associated with a drop of more than 4 points in hematocrit [OR 59.69 (95% CI 4.71-755.30)], red blood transfused units >2 [OR 45.38 (95% CI 3.48-590.65)], and delayed bleeding >36 h after surgery [OR 100.90 (95% CI 3.78-2695.40)]. Plasma-derived FXIII concentrate was administered to eight patients with life-threatening bleeding with resolution within 24 h. Only one deficient patient died from bleeding. FXIII levels were measured 15 days after diagnosis or more in 20 out of 27 deficient patients, with normal results. Acquired FXIII deficiency may be a frequent underdiagnosed entity that should be considered when high-volume and delayed postoperative hemorrhage is present in patients with hemostatic routine coagulation test results.
URL: https://www.ncbi.nlm.nih.gov/pubmed/32852328

DOI: https://dx.doi.org/10.1097/MBC.0000000000000953

7. Schroeder V. Laboratory Assessment of Coagulation Factor XIII. Hamostaseologie. 2020;40(4):467-71. DOI: 10.1055/a-1181-0327
ABSTRACT: Laboratory diagnosis of congenital and acquired deficiencies of coagulation factor XIII (FXIII) can be challenging. Determination of FXIII function requires specific and sensitive assays which are not always available. This brief review article summarizes currently used FXIII assay methods, their principles and difficulties, and discusses the recommended diagnostic workup in case of a suspected FXIII deficiency. The article also briefly touches on experimental methods used in FXIII research.
URL: https://www.ncbi.nlm.nih.gov/pubmed/32869231
DOI: https://dx.doi.org/10.1055/a-1181-0327

8. Naderi M, Cohan N, Haghpanah S, et al. Correlation of bleeding score with frequency and severity of bleeding symptoms in FXIII deficiency assessing by the ISTH Bleeding Assessment Tool. Transfus Apher Sci. 2019;58(4):495-7. DOI: 10.1016/j.transci.2019.05.012
ABSTRACT: OBJECTIVES: The ISTH bleeding assessment tool (ISTH-BAT) is developed for standardization of bleeding symptoms in bleeding disorders. The aim of this study is to apply this bleeding score for FXIII deficient patients and its relation to the frequency and severity of symptoms. METHODS: In this cross-sectional study, 63 patients with severe FXIII deficiency were evaluated for the assessment of bleeding score according to the standard ISTH-BAT questionnaire. All patients were registered at two major thrombosis and hemostasis centers in Iran affiliated to Zahedan University of medical sciences (50 patients) and Shiraz University of medical sciences (13 patients). RESULTS: Significant correlations between the bleeding score and number of symptoms ($r = 0.668$, $P < 0.001$) and with a number of severe symptoms ($r = 0.938$, $P < 0.001$) were detected. There was no significant relationship between the mean bleeding score and CNS bleeding ($P = 0.390$). CONCLUSION: The ISTH-BAT score is an acceptable bleeding assessment tool for standardization and evaluation of patients with FXIII deficiency.
URL: https://www.ncbi.nlm.nih.gov/pubmed/31303509
DOI: https://dx.doi.org/10.1016/j.transci.2019.05.012

9. Durda MA, Wolberg AS, Kerlin BA. State of the art in factor XIII laboratory assessment. Transfus Apher Sci. 2018;57(6):700-4. DOI: 10.1016/j.transci.2018.07.006
ABSTRACT: Factor XIII, a heterotetrameric proenzyme, is converted to an activated transglutaminase by thrombin and calcium in the final phases of coagulation. Factor XIII catalyzes the formation of crosslinks between fibrin monomers and between alpha2-antiplasmin and fibrin. These crosslinks mechanically stabilize fibrin against shear stress, enable red cell retention within the clot, and protect the clot from premature degradation. Congenital factor XIII deficiency is caused by autosomal recessive mutations, presenting early in life with a severe bleeding diathesis. Acquired deficiency may be caused by autoimmunity. Currently available assays for laboratory diagnosis of factor XIII deficiency include clot solubility assays, quantitative factor XIII activity assays, factor XIII antigen assays, and genetic testing. The International Society on Thrombosis and Haemostasis Scientific and Standardization Committee has recommended an algorithm for the laboratory diagnosis and differentiation of the different forms of factor XIII deficiency. However, implementation of this algorithm has been limited by technical and budgetary challenges associated with the currently available factor XIII-specific assays. The purpose of this review is to discuss the advantages and limitations of the currently available assays employed for the laboratory diagnosis of factor XIII deficiency.
URL: https://www.ncbi.nlm.nih.gov/pubmed/30087086
DOI: https://dx.doi.org/10.1016/j.transci.2018.07.006

10. Karimi M, Peyvandi F, Naderi M, et al. Factor XIII deficiency diagnosis: Challenges and tools. Int J Lab Hematol. 2018;40(1):3-11. DOI: 10.1111/ijlh.12756
ABSTRACT: Factor XIII deficiency (FXIIID) is a rare hereditary bleeding disorder arising from heterogeneous mutations, which can lead to life-threatening hemorrhage. The diagnosis of FXIIID is challenging due to normal standard coagulation assays requiring specific FXIII assays for diagnosis, which is especially difficult in developing countries. This report presents an overview of FXIIID diagnosis and laboratory methods and suggests an algorithm to improve diagnostic efficiency and prevent missed or delayed FXIIID diagnosis. Assays measuring FXIII activity:

The currently available assays utilized to diagnose FXIIID, including an overview of their complexity, reliability, sensitivity, and specificity, as well as mutational analysis are reviewed. The use of a FXIII inhibitor assay is described. Diagnostic tools in FXIIID: Many laboratories are not equipped with quantitative FXIII activity assays, and if available, limitations in lower activity ranges are important to consider. Clot solubility tests are not standardized, have a low sensitivity, and are therefore not recommended as routine screening test; however, they are the first screening test in almost all coagulation laboratories in developing countries. To minimize the number of patients with undiagnosed FXIIID, test quality should be improved in less well-equipped laboratories. Common country-specific mutations may facilitate diagnosis through targeted genetic analysis in reference laboratories in suspected cases. However, genetic analysis may not be feasible in every country and may miss spontaneous mutations. Centralized FXIII activity measurements should also be considered. An algorithm for diagnosis of FXIIID including different approaches dependent upon laboratory capability is proposed.
URL: https://www.ncbi.nlm.nih.gov/pubmed/29027765
DOI: https://dx.doi.org/10.1111/ijlh.12756

11. Ichinose A. Autoimmune acquired factor XIII deficiency due to anti-factor XIII/13 antibodies: A summary of 93 patients. Blood Reviews. 2017;31(1):37-45.
ABSTRACT: Autoimmune acquired factor XIII (F13) deficiency or autoimmune hemophilia-like disease (hemorrhaphilia) resulted from the generation of anti-F13 antibodies (AH13) is a severe bleeding disorder that occurs mainly in the elderly. Although rare, the number of patients diagnosed with AH13 has recently increased. To improve understanding of this disease, the author summarized 93 ever reported/diagnosed AH13 cases. About 50% of cases were idiopathic. In the remaining half of the patients, autoimmune diseases and malignancies were the most common underlying diseases. Intramuscular and subcutaneous bleeding were the most frequently reported symptoms. Hemorrhage was the cause of death in 13 patients. In 4 patients, the diagnosis was established after hemorrhagic death. Therefore, physicians/hematologists must raise the awareness of AH13 as a life-threatening disease. Most patients were treated with F13 concentrates to arrest bleeding and with prednisolone and cyclophosphamide to eradicate anti-F13 autoantibodies. AH13 cases tend to become chronic and intractable and require close follow-up over an extended period. Copyright © 2016 Elsevier Ltd
URL: https://pubmed.ncbi.nlm.nih.gov/27542511/
DOI: https://doi.org/10.1016/j.blre.2016.08.002

12. Dorgalaleh A, Kazemi A, Zaker F, et al. Laboratory Diagnosis of Factor XIII Deficiency, Routine Coagulation Tests with Quantitative and Qualitative Methods. Clin Lab. 2016;62(4):491-8. DOI: 10.7754/clin.lab.2015.150619
ABSTRACT: BACKGROUND: Factor XIII (FXIII) deficiency is a severe bleeding disorder with normal routine coagulation tests that makes diagnosis of the disorder complicated. After normal results in routine coagulation tests, clot solubility test, and FXIII activity, antigen assays along with molecular methods can be used for precise diagnosis of disorder. In the present study, we described routine coagulation tests along with clot solubility test and FXIII activity and antigen assays. METHODS: Data were collected from all relevant publications until 2015. RESULTS: All routine coagulation tests including prothrombin time (PT), partial thromboplastin time (PTT), thrombin time (TT), and platelet count are normal in FXIII deficiency (FXIIID) but different conditions such as blood collection, transport, and storage can result in abnormal results in these first line screening tests. In addition to these tests, clot solubility tests as the most common screening tests of FXIIID can influenced by different factors including clotting and solubilizing agents. Different commercial kits are available for FXIII activity and antigen assays with different sensitivity and specificity which could affect diagnosis of FXIIID. CONCLUSIONS: Results of routine coagulation tests as well as clot solubility tests along with specific coagulation tests can affect diagnosis of FXIIID; therefore, all steps of these tests should be under control.
URL: https://www.ncbi.nlm.nih.gov/pubmed/27215067
DOI: https://dx.doi.org/10.7754/clin.lab.2015.150619

13. Dorgalaleh A, Tabibian S, Hosseini MS, et al. Diagnosis of factor XIII deficiency. Hematology. 2016;21(7):430-9.
ABSTRACT: Background: Factor XIII (FXIII) deficiency is an extremely rare bleeding disorder with estimated incidence of one per two million. All routine coagulation tests are normal in FXIII deficiency (FXIIID), which complicates the diagnosis of this disorder. Precise diagnosis of FXIIID requires more specific tests, including

qualitative tests as well as quantitative tests such as FXIII activity, antigen assays, and finally molecular studies to confirm FXIIID. Objective(s): This study was conducted to present different quantitative and qualitative methods as well as molecular approaches for screening and diagnosis of FXIIID with advantages and disadvantages of each method. Method(s): All relevant English-language publications were searched in Medline (until 2015). Results and discussion: Clot solubility assay is the most widely used method for detection of FXIIID but it is not standardized. The sensitivity of this method is dependent upon different factors mainly clotting factors and the solubilizing agents; therefore, FXIII activity assay is recommended for screening of FXIIID. Among FXIII activity assays, photometric assay is more common but FXIII activity is overestimated in this assay due to lack of sample blank in commercial assay, which can have fatal consequences in severe FXIIID, for which fluorometric assay is an appropriate alternative preventing the overestimation observed in photometric assay. There are different methods for measurement of FXIII-A<inf>2</inf>, FXIII-B<inf>2</inf>, and FXIII-A<inf>2</inf>B<inf>2</inf>as well as detection and quantification of FXIII inhibitor, which are mentioned in detail in this review. There are no mutational hotspots in FXIII-A and FXIII-B genes with a few recurrent mutations in some populations; therefore, full sequencing of FXIII genes has remained a main molecular approach for confirmation of FXIIID. Conclusion(s): Familiarity with different methods for diagnosis of FXIIID and their advantages and disadvantages can help in appropriate and timely diagnosis of this disorder to prevent misdiagnosis of FXIIID and its fatal consequences. Copyright © 2015, © W. S. Maney & Son Ltd 2015.
URL: https://pubmed.ncbi.nlm.nih.gov/27077776/
DOI: https://doi.org/10.1080/10245332.2015.1101975

14. Dorgalaleh A, Tabibian S, Hosseini S, et al. Guidelines for laboratory diagnosis of factor XIII deficiency. Blood Coagul Fibrinolysis. 2016;27(4):361-4. DOI: 10.1097/MBC.0000000000000459
ABSTRACT: Factor XIII (FXIII) deficiency is an extremely rare hemorrhagic disorder with an approximate worldwide incidence of one per two million. With current tests, diagnosis of this disease can be made more precisely. However, factors such as the number of patients with FXIII deficiency (FXIIID), available diagnostic coagulation tests and the number of molecular studies have affected the diagnosis of FXIIID in different parts of the world. Various laboratory approaches can be used, including screening and diagnosis of the disorder in countries with a relatively high rate of FXIIID and recurrent mutation(s) with a simple polymerase chain reaction-restriction fragment length polymorphism analysis or polymerase chain reaction-sequencing for detection of one or a few specific mutations. In other countries, two different laboratory approaches can be used, depending on available coagulation tests. In less-equipped coagulation laboratories, the clot solubility test remains the only diagnostic test for FXIIID. Even in these countries, at least one referral laboratory should perform FXIII activity and, if possible, confirmation of FXIIID by molecular analysis. In countries with well equipped coagulation laboratories, FXIII activity should be used to screen suspected FXIIID patients; more specific tests such as molecular analysis should be used for confirmation. This study suggests a simple, reliable and flexible algorithm for early diagnosis of FXIIID, and may, with one-time diagnosis of FXIIID, reduce the rate of morbidity and mortality in patients with the disorder.
URL: https://www.ncbi.nlm.nih.gov/pubmed/26588445
DOI: https://dx.doi.org/10.1097/MBC.0000000000000459

15. Tahlan A, Ahluwalia J. Factor XIII: congenital deficiency factor XIII, acquired deficiency, factor XIII A-subunit, and factor XIII B-subunit. Arch Pathol Lab Med. 2014;138(2):278-81. DOI: 10.5858/arpa.2012-0639-RS
ABSTRACT: Factor XIII (FXIII) is a transglutaminase consisting of 2 catalytic A subunits and 2 noncatalytic B subunits in plasma. The noncatalytic B subunits protect the catalytic A subunits from clearance. Congenital FXIII deficiency may manifest as a lifelong bleeding tendency, abnormal wound healing, and recurrent miscarriage. Acquired FXIII deficiency, with significant reductions in FXIII levels, has been reported in several medical conditions. The routine screening tests for coagulopathies-prothrombin time, activated partial thromboplastin time, and thrombin time-do not show abnormalities in cases of FXIII deficiency. A quantitative, functional, FXIII activity assay that detects all forms of FXIII deficiency should be used as a first-line screening test. Treatment consists of recombinant FXIII or FXIII concentrate. If these are unavailable, then fresh-frozen plasma and cryoprecipitates may be used. Factor XIII has a long half-life; therefore, the patients can lead near-normal lives with regular replacements. Patients with acquired FXIII deficiency with inhibitors need immunosuppressive therapy in addition to factor replacements.
URL: https://www.ncbi.nlm.nih.gov/pubmed/24476525
DOI: https://dx.doi.org/10.5858/arpa.2012-0639-RS

16. Grossmann E, Akyol D, Eder L, et al. Thromboelastometric detection of clotting Factor XIII deficiency in cardiac surgery patients. Transfus Med. 2013;23(6):407-15. DOI: 10.1111/tme.12069
ABSTRACT: AIM(S): In this article, we aimed to investigate plasma Factor XIII levels after extracorporeal circulation in cardiac surgery by thromboelastometric detection, as extracorporeal circulation causes various coagulation disorders due to the exposure of blood to artificial surfaces, inflammatory induction and mechanical destruction of platelets and coagulation factors, which may particularly affect factors with long half-lives, such as Factor XIII. BACKGROUND: Since transfusion algorithms are often empirical and laboratory analysis of Factor XIII plasma levels may not be available 24 h a day, bed-side testing using rotational thromboelastometry (ROTEM) could offer a splendid option to define the cause of excessive peri-operative bleeding disorders in general and Factor XIII levels in particular in a timely manner and thus facilitating exact substitution therapy. METHODS: In this trial, we investigated 25 cardiac surgery patients with extracorporeal bypass times over 100 min. Standard laboratory and ROTEM analyses were performed post-operatively at the time of intensive care unit admission and 6 h later. We implemented EXTEM with additional Factor XIII (teenTEM) as additional test by adding 0.625 IU Factor XIII to standard EXTEM reagents. RESULTS: In this observational study, we could not demonstrate a correlation between Factor XIII and MCFEXTEM , CFTEXTEM or MLEXTEM . Neither Factor XIII plasma levels nor MCFEXTEM could predict blood loss. In accordance with previous findings, we were able to demonstrate increased maximum clot firmness (MCF), decreased clot formation time and decreased maximum lysis by adding Factor XIII in vitro (teenTEM vs EXTEM) indicating an improvement in the coagulation process. As shown before, we also found a strong correlation between MCF and platelet and fibrinogen plasma levels. CONCLUSION: In summary, 'teenTEM' test does not seem to detect Factor XIII deficient patients in cardiac surgery. Furthermore, post-operative blood loss could not be predicted neither by ROTEM nor by laboratory analysis of Factor XIII. In vitro administration of Factor XIII appears to improve laboratory measures of haemostasis.
URL: https://www.ncbi.nlm.nih.gov/pubmed/23962029
DOI: https://dx.doi.org/10.1111/tme.12069

17. Kessel R, Hu C, Shore-Lesserson L, et al. A child with acquired factor XIII deficiency: case report and literature review. Haemophilia. 2013;19(6):814-26. DOI: 10.1111/hae.12145
ABSTRACT: Factor XIII (FXIII) deficiency is a rare bleeding disorder, which can result in life threatening hemorrhage. Rarer still is acquired FXIII deficiency, in which the disorder is due to autoantibodies that inhibit the factor. To describe one of the youngest reported patients with this condition. To discuss the challenges we encountered in monitoring response with the available assays. To review the literature and provide a review of all acquired FXIII cases. We present the case of our patient, a 9-year-old girl with acquired FXIII deficiency. We present a comprehensive review of all acquired FXIII deficiency cases reported globally in English, with focus on clinical presentation, diagnostic assays, treatment and prognosis. There is no current standard for therapy and measuring response to therapy can be complicated by limitations of assays in the presence of inhibitors. Clinicians should be aware of acquired FXIII deficiency as a potentially life threatening bleeding disorder even in young children. The case presented illustrates a young patient with acquired FXIII deficiency with a good clinical response to cryoprecipitate and difficulty in hemostasis monitoring utilizing clinically available assays.
URL: https://www.ncbi.nlm.nih.gov/pubmed/23607876
DOI: https://dx.doi.org/10.1111/hae.12145

18. Levy JH, Greenberg C. Biology of Factor XIII and clinical manifestations of Factor XIII deficiency. Transfusion. 2013;53(5):1120-31. DOI: 10.1111/j.1537-2995.2012.03865.x
ABSTRACT: Factor XIII (FXIII) is activated by thrombin to form a transglutaminase (FXIIIa) that stabilizes clot formation by the cross-linking of fibrin monomers and antifibrinolytic proteins. Although rare, FXIII deficiency is characterized by variable bleeding manifestations depending on the magnitude of the deficiency. A congenital FXIII deficiency with levels less than 1% can be detected in children who present with prolonged bleeding from the umbilical stump as well as protracted bleeding after trauma. An acquired FXIII deficiency may occur in a number of diseases or clinical situations where FXIII levels and/or its activity are decreased. Patients may also develop a relative deficiency in FXIII as a result of hemorrhage or dilutional changes from transfusions during surgery or trauma and are at increased risk for postoperative bleeding. Genetic studies have identified a wide range of mutations that affect the activity of the FXIII protein but in lieu of molecular genetic analyses, FXIII deficiency can

be identified by specific diagnostic assays that measure either the transglutaminase activity of the protein or the levels of the protein and its individual subunits. Replacement therapy has also been shown to increase FXIII levels and reduce bleeding symptoms in patients with congenital FXIII deficiency. This review presents recent findings on the biology of FXIII and the clinical manifestations observed among patients with congenital and acquired FXIII deficiencies.
URL: https://www.ncbi.nlm.nih.gov/pubmed/22928875
DOI: https://dx.doi.org/10.1111/j.1537-2995.2012.03865.x

19. Naderi M, Dorgalaleh A, Tabibian S, et al. Current understanding in diagnosis and management of factor XIII deficiency. Iran J Ped Hematol Oncol. 2013;3(4):164-72.
ABSTRACT: Factor XIII or "fibrin-stabilizing factor," is a transglutaminase circulates in the blood circulation as a hetero tetramer with two catalytic A subunits and two carrier B subunits. This important coagulation factor has a crucial role in clotting cascade and produces strong covalent bonds between soluble formed fibrin monomers during coagulation. This stable cross linked fibrin strands are resistanttodegradationby thefibrinolyticsystem that enablesthe bodyto stoppotential bleeding episodes. In the absence or severe decrease of factor XIII, although the clot is formed, but is rapidly degraded by the fibrinolytic system, and delayed bleedingoccurs.Factor XIII deficiency is an extremely rare bleeding disorder with estimated incidence of 1/2-3000, 000 in the general population. Presumptive diagnosis of factor XIII deficiency was by clot solubility test in 5M urea or 1% monochloroacetic acid environments. In patients with abnormal screening clot solubility test, the disease can be confirmedbymore specifictestssuch as quantitative factor XIII activity assay andFXIIIAgassay.After diagnosis of disease all patients with severe factor XIII deficiency(<1 U/dl) shouldreceive prophylactic substitution therapywith fresh frozen plasma (FFP) and cryoprecipitate as traditional choices or purified concentrateof blood coagulation factor XIII (Fibrogammin P) inorder to control severe and life-threatening clinical complications of factor XIII deficiency.
URL: https://www.ncbi.nlm.nih.gov/pubmed/24575291

20. Schroeder V, Kohler HP. Factor XIII deficiency: an update. Semin Thromb Hemost. 2013;39(6):632-41. DOI: 10.1055/s-0033-1353392
ABSTRACT: Confirmation of suspected congenital factor XIII (FXIII) deficiency still represents a diagnostic challenge in the field of rare bleeding disorders. Because of the lack of awareness and difficulties associated with timing of blood sampling, FXIII laboratory assays, and interpretation of laboratory results, diagnoses of FXIII deficiency are still missed all over the world with potentially fatal consequences from severe bleeding complications. Better knowledge of FXIII biochemical properties and function and understanding of the principles and limitations of FXIII laboratory assays can prevent missed diagnoses, and patients will benefit from better care. This review gives a detailed overview and update about congenital FXIII deficiency, its epidemiology, and molecular genetics. It highlights the importance of newer specific FXIII assays and their principles to avoid any missed diagnosis of FXIII deficiency. This review also gives an update on the therapeutic options for patients suffering from this rare but life-threatening disease.
URL: https://www.ncbi.nlm.nih.gov/pubmed/23929307
DOI: https://dx.doi.org/10.1055/s-0033-1353392

Evidence Summaries and Other Literature

DynaMed

- Factor XIII Recombinant. [Last updated 15 November 2022]. https://www.dynamed.com/drug-monograph/factor-xiii-recombinant

- Lab Monograph – Plasma Factor XIII Screening Test. https://www.dynamed.com/lab-monograph/plasma-factor-xiii-screening-test

...

Search Details & History

Date range filter: 2013-2023
Limits: English Language, Research Articles
Sources searched: Embase (OVID), MEDLINE (OVID)

Search history:

Embase, Ovid MEDLINE(R)

#	Searches	Results
1	exp Hemorrhage/ or exp Blood Coagulation Disorders/	2233684
2	exp bleeding/ or exp blood clotting disorder/	2172579
3	Factor XIII Deficiency/	1845
4	blood clotting factor 13 deficiency/	1218
5	((bleeding or blood coagulat* or blood clot? or blood clotting or coagulat* or h?emorrhag* or h?emostatic*) adj2 (abnormal* or anomaly or anomalies or defect? or deficien* or disease? or disfunction* or disorder? or dysfunction* or problem* or symptom* or syndrome? or unusual)).ti,ab.	112428
6	(coagulopath* or h?emorrhag*).ti. or (coagulopath* or h?emorrhag*).ab. /freq=2	376534
7	(((FXIII or factor-13 or factor-xiii or factor-thirteen or fibrin stabili?ing) adj2 (defect* or defici* or deplet* or inhibitor or low or low-level?)) or FXIIID).ti,ab.	2497
8	(factor adj2 ("13" or XIII or thirteen) adj2 (defect* or defici* or deplet* or inhibitor? or low or low-level?)).ti,ab.	1892
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	2346638
10	blood clotting factor 13 concentrate/	421
11	(((FXIII or factor-13 or factor-xiii or factor-thirteen or fibrin stabili?ing) adj2 (concentrate? or concentration? or infusion? or intravenous or replacement or recombinant or supplement* or transfusion?)) or rFXIII).ti. or (((FXIII or factor-13 or factor-xiii or factor-thirteen or fibrin stabili?ing) adj2 (concentrate? or concentration? or infusion? or intravenous or replacement or recombinant or supplement* or transfusion?)) or rFXIII).ab. /freq=2	604
12	(cluvot or corifact or fibrogammin or novothirteen or tretten).ti. or (cluvot or corifact or fibrogammin or novothirteen or tretten).ab. /freq=2	47
13	10 or 11 or 12	957
14	9 and 13	750
15	remove duplicates from 14	599
16	(book? or commentary or conference abstract? or dissertation abstract? or editorial? or letter? or news or note?).pt.	10205443
17	15 not 16	393

18	limit 17 to english language	351
19	limit 18 to yr="2013 -Current"	178
20	exp hematologic tests/ or diagnostic tests, routine/	700002
21	assay/ or diagnostic test/ or exp laboratory test/ or exp blood clotting test/	502297
22	(assay? or assessment? or bioassay? or biometric? or calculat* or diagnos* or indicat* or level? or measur* or metric? or scale? or score? or test? or testing or value?).ti.	6018207
23	((diagnos* or lab or laboratory) adj2 (assay? or assessment? or bioassay? or biometric? or calculat* or indicat* or level? or measur* or metric? or scale? or score? or test? or testing or value?)).ti,ab.	708339
24	20 or 21 or 22 or 23	7251015
25	Factor XIII/	7728
26	blood clotting factor 13/ or blood clotting factor 13a/ or blood clotting factor 13b/	6586
27	(FXIII or factor-13 or factor-xiii or factor-thirteen or fibrin stabili?ing or (factor adj2 ("13" or XIII or thirteen))).ti,ab.	11487
28	25 or 26 or 27	15875
29	24 and 28	2996
30	((FXIII or factor-13 or factor-xiii or factor-thirteen or fibrin stabili?ing) adj2 (assay? or assessment? or bioassay? or biometric? or calculat* or indicat* or level? or measur* or metric? or scale? or score? or test? or testing or value?)).ti,ab.	1412
31	(factor adj2 ("13" or XIII or thirteen) adj2 (assay? or assessment? or bioassay? or biometric? or calculat* or indicat* or level? or measur* or metric? or scale? or score? or test? or testing or value?)).ti,ab.	793
32	29 or 30 or 31	3772
33	exp Hemorrhage/	1519292
34	exp bleeding/	1519292
35	((bleeding or h?emorrhag*) adj2 (consistent* or continu* or disorder? or extensive or major or persist* or problem* or symptom* or unusual)).ti,ab.	107488
36	(h?emorrhag* or bleeding).ti. or (h?emorrhag* or bleeding).ab. /freq=2	646788
37	33 or 34 or 35 or 36	1694632
38	32 and 37	1508
39	remove duplicates from 38	1206
40	(book? or commentary or conference abstract? or dissertation abstract? or editorial? or letter? or news or note?).pt.	10205443
41	39 not 40	700
42	limit 41 to english language	596
43	limit 42 to yr="2013 -Current"	341

44	limit 43 to "reviews (best balance of sensitivity and specificity)"	66
45	Acute Disease/ or Early Diagnosis/	484854
46	(acute* or concomitant? or new onset or new-onset or present* or symptom*).ti. or (acute* or concomitant? or new onset or new-onset or present* or symptom*).ab. /freq=2	7097138
47	45 or 46	7295117
48	43 and 47	87
49	44 or 48	138

Terms of Use, Disclaimer & Copyright

You may only share a copy of this search report with other Saskatchewan Health Authority staff. All requests are kept confidential. The library assumes no liability for information retrieved, its interpretation, applications, or omissions. The selection of materials is not intended as advice or recommendations.

Disclaimer: This material is intended for general information only and is provided on an "as is," "where is" basis. Although reasonable efforts were made to confirm the accuracy of the information, the Saskatchewan Health Authority does not make any representation or warranty, express, implied or statutory, as to the accuracy, reliability, completeness, applicability or fitness for a particular purpose of such information. This material is not a substitute for the advice of a qualified health professional. The Saskatchewan Health Authority expressly disclaims all liability for the use of these materials, and for any claims, actions, demands or suits arising from such use.