Next Generation Antithrombotic Agents: What's On The Horizon For Anticoagulant And Antithrombotic Drugs

Elliot L. Chaikof, MD, PhD
Department of Surgery
Beth Israel Deaconess Medical Center
Harvard Medical School

Beth Israel Lahey Health

Beth Israel Deaconess Medical Center | HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Beth Israel Deaconess Medical Center

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Promise of FXI inhibitors:
Differential roles of FXI in hemostasis and thrombosis

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Vol. 325 No. 3 FACTOR XI DEFICIENCY IN ASHKENAZI JEWS — ASAKAI ET AL.

FACTOR XI DEFICIENCY IN ASHKENAZI JEWS IN ISRAEL

Rei Asakai, M.D., Ph.D., Dominic W. Chung, Ph.D., Earl W. Davie, Ph.D., and Uri Seligsohn, M.D.

Abstract *Background and Methods.* Severe factor XI deficiency, which is relatively common among Ashkenazi Jews, is associated with injury-related bleeding of considerable severity. Three point mutations — a splice-junction abnormality (Type I), Glu^{117}→Stop (Type II), and Phe^{283}→Leu (Type III) — have been described in six patients with factor XI deficiency. Clinical correlations with these mutations have not been carried out. We determined the relative frequency of the mutations and their association with plasma levels of factor XI clotting activity and bleeding, analyzing the mutations with the polymerase chain reaction and restriction-enzyme digestion.

Results. The Type II and Type III mutations had similar frequencies among 43 Ashkenazi Jewish probands with severe factor XI deficiency; these two mutations accounted for 49 percent and 47 percent, respectively, of a total of 86 analyzed alleles. Among 40 of the probands and 12 of their relatives with severe factor XI deficiency, patients homozygous for Type III mutation had a significantly higher level of factor XI clotting activity (mean [±SD] percentage of normal values, 9.7±3.8 percent; n = 13) than those homozygous for Type II mutation (1.2±0.5 percent, n = 16) or compound heterozygotes with Type II/III mutation (3.3±1.6 percent, n = 23), as well as significantly fewer episodes of injury-related bleeding. Each of these three groups had a similarly increased proportion of episodes of bleeding complications after surgery at sites with enhanced local fibrinolysis, such as the urinary tract, or during tooth extraction.

Conclusions. Type II and Type III mutations are the predominant causes of factor XI deficiency among Ashkenazi Jews. Genotypic analysis, assay for factor XI, and consideration of the type and location of surgery can be helpful in planning operations in patients with this disorder. (N Engl J Med 1991; 325:153-8.)

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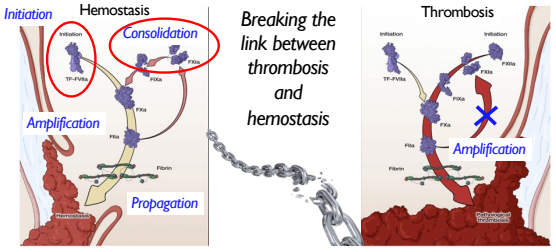

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Promise of FXI inhibitors:
Drug development and clinical trials

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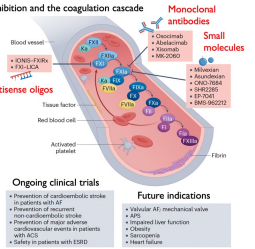
- FXI-ASO TKA phase 2 trial (2015)
  - ISIS-FXIRx (weekly) vs. enoxaparin in total knee arthroplasty (n = 300)
- ANT-005 TKA phase 2 trial (2021)
  - Abelacimab (monthly) vs. enoxaparin for prevention of VTE in total knee arthroplasty (n = 412)
- AZALEA-TIMI 71 (November 2023)
  - Abelacimab vs. rivaroxaban (Xarelto) in patients with Afib (n = 1,200)

FXI inhibition and the coagulation cascade



Ongoing clinical trials

- Prevention of cardioembolic stroke in patients with AF
- Prevention of recurrent non-cardioembolic stroke
- Prevention of major adverse cardiovascular events in patients with ACS
- Safety in patients with ESRD

Future indications

- Valvular AF; mechanical valve
- APS
- Impaired liver function
- Obesity
- Sarcopenia
- Heart failure

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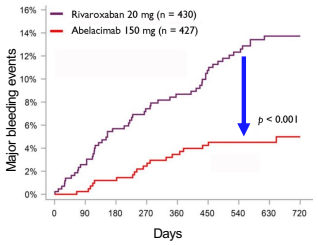
67% reduction in bleeding risk compared with Xarelto

93% reduction in GI bleeding



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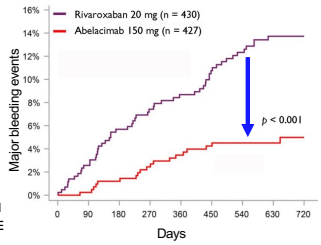
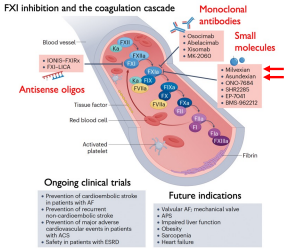
- AZALEA-TIMI 71 (November 2023)
  - Abelacimab vs. rivaroxaban (Xarelto) in patients with Afib (n = 1,200)
- LILAC-TIMI 76 phase 3 study in Afib
- Magnolia phase 3 study in cancer-associated VTE in whom a DOAC is not recommended
- Aster phase 3 study in cancer-associated VTE in whom a DOAC is recommended



Promise of FXI inhibitors:
Drug development and clinical trials

- Pacific-Stroke phase 2 trial (September 2022)
  - Asundexian vs placebo in patients with non-cardioembolic acute CVA (n = 1,880)
  - All patients received SAPT or DAPT
- Pacific-AMI phase 2 trial (November 2022)
  - Asundexian vs placebo in patients after acute MI (n = 1,601)
  - All patients received DAPT
- Axiomatic-SSP phase 2 trial (November 2022)
  - Milvexian vs placebo in patients with non-cardioembolic acute CVA/TIA (n = 2,300)
  - All patients received DAPT
- Oceanic-AF phase 3 trial (November 2023)
  - Asundexian vs apixaban (Eliquis) in patients with Afib (n = 18,000)



Promise of FXI inhibitors:
Drug development and clinical trials: **Current Phase 3 Trials**

- Asundexian (Bayer)
  - Phase 3: Asundexian vs placebo for prevention of recurrent non-cardioembolic stroke (n = 12,300) 2025
- Milvexian (BMS, J&J)
  - Phase 3: Milvexian vs Eliquis (Apixaban) for prevention of cardioembolic stroke in patients with AF (n =15,500) 2027
- Abelacimab (Anthos)
  - LILAC-TIMI 76 Phase 3: Abelacimab vs placebo for prevention of cardioembolic stroke in patients with AF (n =1,900)
  - Magnolia and Aster Phase 3 trials (Ca-VTE)