SDM
WFH SHARED DECISION MAKING TOOL

HEMOSTATIC REBALANCING THERAPY

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What are hemostatic rebalancing therapies?

Hemostatic rebalancing therapies belong to the non-factor therapy class and can be used to treat hemophilia A and hemophilia B, with and without inhibitors.

To understand how these medications work, we need to know more about how a blood clot forms. When we are injured, our body's natural system stops the bleeding through activation of the clotting factors already present in the blood and through thrombin generation. People with hemophilia have no or low levels of clotting factor VIII (hemophilia A), or factor IX (hemophilia B) and low thrombin generation, so their blood cannot clot effectively. In other words, in people with hemophilia, there is an imbalance between the factors that help the blood clot (clotting factors) and the factors that prevent clotting (anticoagulation factors).

Hemostatic Rebalancing Therapy

Rebalancing therapies help to restore this balance by decreasing the anticoagulation factor levels, which helps prevent bleeding events and restore normal blood clotting.

What are the different types of hemostatic rebalancing therapies?

As of April 2023, one hemostatic rebalancing therapy, concizumab, has been approved for use in Canada for people with hemophilia B with inhibitors.[1] Other rebalancing therapies are in phase 3 clinical trials[1], including fitusiran[2] and marstacimab.[3]

Concizumab and marstacimab are monoclonal antibodies that target a natural anticoagulation factor called *tissue factor pathway inhibitor* (TFPI). By inhibiting TFPI (also known as anti-TFPI) these medications increase thrombin generation and blood clotting in people with hemophilia A and B, with and without inhibitors.

Fitusiran works differently. Fitusiran is a *small interfering RNA* (siRNA) that inhibits the production of another coagulant, antithrombin. This increases thrombin generation and results in increased blood clotting in people with hemophilia A and B, with and without inhibitors.

How is the mechanism of action of hemostatic rebalancing therapies different from other treatments for hemophilia?

The main treatment types for hemophilia are clotting factor replacement therapy, bispecific antibodies, re-balancing agents, and gene therapy. All these treatments help the blood clot more efficiently, but they all work in different ways.

Clotting factor replacement therapies temporarily increase factor levels by injecting the needed clotting factor protein directly into the blood of a person with hemophilia.

Bispecific antibodies are Y-shaped proteins that act as a bridge between factor IXa and factor X, which helps the blood to clot more efficiently. This antibody bridge mimics the function of the missing activated factor VIII (i.e., factor VIIIa-mimetic).

(continued)	Rebalancing therapies restore the disrupted balance between the levels of anticoagulation (i.e., anti-clotting) factors and clotting factors in the blood, thereby improving blood clotting. Gene therapy introduces a working copy of the missing clotting factor gene. Once the gene is introduced, the body can produce the missing protein and maintain adequate clotting factor levels, on its own, for an extended time.

TREATMENT WITH HEMOSTATIC REBALANCING THERAPIES

Who is eligible to use rebalancing agents?	Hemostatic rebalancing therapies are being developed for people with hemophilia A and B, including those with inhibitors. Concizumab is currently approved in Canada for use in people aged 12 years and older with hemophilia B, who have inhibitors and require prophylaxis.[2]
How are prophylactic rebalancing therapies administered?	Rebalancing therapies are administered by subcutaneous injection under the skin. The injection takes approximately one minute and can be done at home or at a clinic.
What is the treatment frequency for prophylaxis with hemostatic rebalancing therapies?	Prophylactic treatment with hemostatic rebalancing therapies is administered on a daily to bi-monthly basis and is determined by the medication type. Concizumab is the only approved rebalancing therapy and is administered daily.
Can hemostatic rebalancing therapies be used in combination with other hemophilia treatments?	In some cases, additional treatments (clotting factor replacement therapies or bypassing agents) may be required. It is important to discuss with your healthcare team how to treat breakthrough bleeding as the dosing of other therapies may need to be adjusted.

EFFICACY OF HEMOSTATIC REBALANCING THERAPIES

How will clotting factor levels be affected?	Hemostatic rebalancing therapies will not change the clotting factor levels. Studies show that the effect of hemostatic rebalancing therapies is similar to having mild hemophilia.
How will hemostatic rebalancing therapies affect my annual bleed rate?	Any form of regular prophylactic treatment is likely to reduce your annual bleed rate. In clinical trials for concizumab, people with hemophilia A or B with inhibitors had very few bleeding events and averaged less than 2 bleeds per year during the first year following treatment,[2] and people with hemophilia A without inhibitors had approximately 5 bleeds per year during the first year following treatment.

SAFETY OF HEMOSTATIC REBALANCING THERAPIES

What are the possible side effects of hemostatic rebalancing therapies?	The most common side effects of concizumab are reactions related to the injection.[1] Other reported side effects include joint pain (arthralgia), upper respiratory tract infection, and headache.
Are there any known serious side effects?	Thromboembolic events (blood clots in the veins or arteries), which can be dangerous and life-threatening have been reported in patients taking rebalancing therapies. It is important to discuss with your healthcare team how you will treat bleeding, injury, and/or surgery while taking hemostatic rebalancing therapies.

MONITORING AND FOLLOW-UP AFTER HEMOSTATIC REBALANCING THERAPY TREATMENT

How often will you need follow up and monitoring with hemostatic rebalancing therapies?	As with all hemophilia treatment classes, regular monitoring by your healthcare team is recommended. Clinical review should be conducted every 6 months and as needed.
What will happen in the event of a bleed, injury, or surgery?	In the event of a bleed, injury, or planned surgical procedure, additional therapies may be required and your options should be discussed with your healthcare team.

HEMOSTATIC REBALANCING THERAPY TREATMENT IN CHILDREN AND ADOLESCENTS

Are hemostatic rebalancing agents approved for use in children and adolescents?	Hemostatic rebalancing agents are approved in Canada for use in pediatric patients who are aged 12–18 years.
Are there any special considerations for treating children with hemostatic rebalancing agents?	The safety and efficacy of hemostatic rebalancing therapy are generally the same between adults and pediatric patients older than 12 years. The safety and efficacy have not been established in patients aged less than 12 years.

1 Product Monograph for Alhemo. Health Canada, 2023.
2 ClinicalTrials.gov. Ongoing Phase 3 studies for Fitusiran: NCT03974113, NCT03754790, and NCT05662319.
3 ClinicalTrials.gov. Ongoing Phase 3 studies for Marstacimab: NCT05611801, NCT05145127, and NCT03938792.

Last reviewed: March 2024
This is a living document that will be updated with new evidence twice per calendar year. The cutoff dates are June 30 and December 31, with updates taking place in the following month(s). Any new evidence after these cutoffs will be included in the next update.