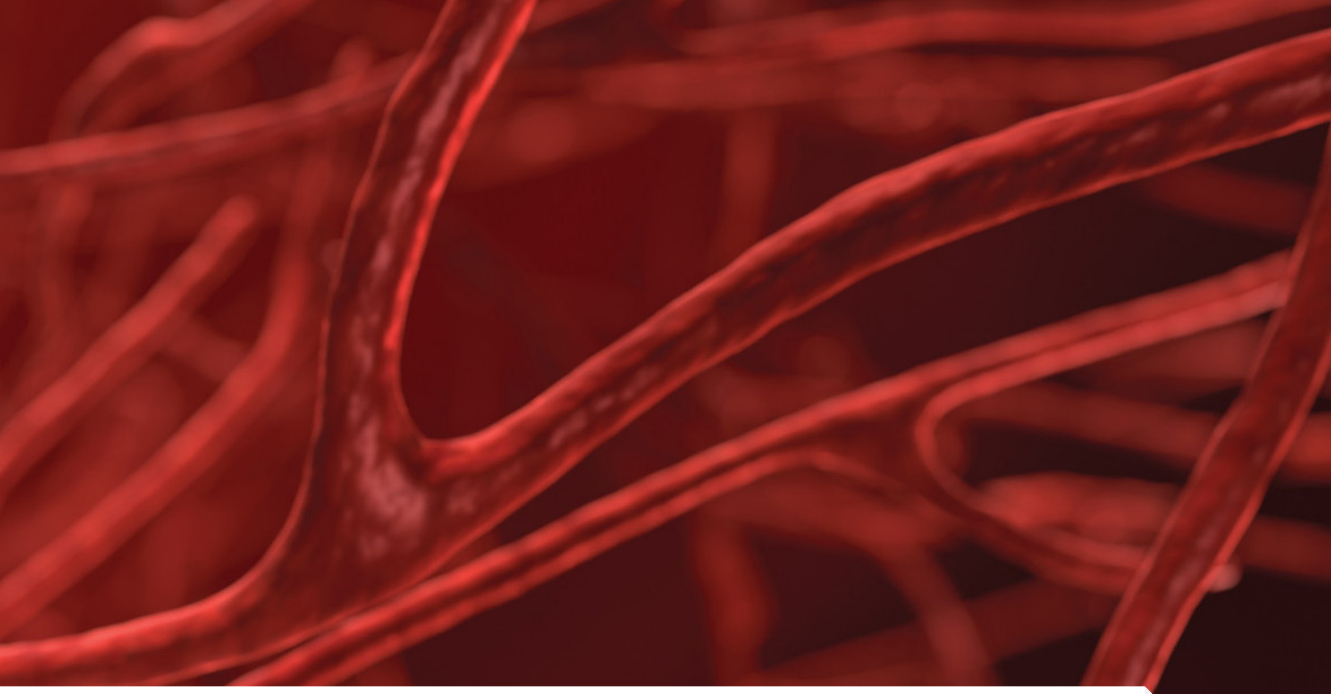

SIPPET STUDY Q&A

The SIPPET trial on inhibitors in haemophilia A

FONDAZIONE ANGELO BIANCHI BONOMI
Per lo studio e la ricerca nel campo dell'emofilia, della trombosi e delle malattie emorragiche

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THE SIPPET TRIAL ON INHIBITORS IN HAEMOPHILIA A

Antibodies to clotting Factor VIII (inhibitors) block the effectiveness of replacement therapy in haemophilia A. Inhibitors develop in 35% or more of patients.

There are several causes of inhibitors, and in the SIPPET trial, published in the New England Journal of Medicine in May 2016, previously untreated young boys given recombinant FVIII were nearly twice as likely to develop inhibitors as young boys receiving plasma-derived FVIII.

Haemophilia is a rare inherited disorder that is caused by a lack of clotting factors. Haemophilia A is caused by a lack of clotting factor VIII (FVIII).

Most haemophilia patients are male because of the way that the disorder is inherited and they are affected from birth. Boys and men with severe haemophilia are at risk of internal bleeding, usually around joints and muscles. This causes pain and stiffness, and can also eventually result in serious, disabling joint damage.

There is no cure for haemophilia, but the risk of bleeding can be controlled by replacement therapy, when the missing clotting factor is replaced through regular intravenous infusions. However, 35% or more of patients develop antibodies to the injected clotting factor, which are also called inhibitors. They make it difficult to stop bleeding, which increases the risk of joint damage.

Inhibitors most often appear within the first 50 infusions of the lacking factor (exposure days or ED). It is possible to

treat inhibitors, but treatment is difficult, costly and can take a long time.

Why was the SIPPET trial needed?

There are several causes for inhibitors, and it has been suggested that they are less likely to occur during treatment with replacement factors made from blood (plasma-derived) than with factors manufactured in the laboratory (recombinant). Since the results of previous studies were unclear and their conclusions were uncertain, the researchers decided to undertake the SIPPET trial (Survey of Inhibitors in Plasma-Product Exposed Toddlers). This large study compared the risk of inhibitors in previously untreated young boys with severe haemophilia A treated with either plasma-derived FVIII or recombinant FVIII.

What kind of study was the SIPPET trial?

The SIPPET trial was a randomised trial. This means that the boys were assigned to their treatment at random. Randomisation is important because it rules out that treatment groups were different because of decisions by the physicians. None of the previous studies comparing plasma-derived with recombinant factor VIII were randomised, which may explain why some reported a difference while others did not.

The researchers' aims were to compare the overall risk of inhibitor development with plasma-derived and recombinant FVIII in the first 50 days of exposure (exposure days) or three

years of treatment, whichever came first. Boys who developed an inhibitor were monitored for a further 6 months. They also wanted to see if the inhibitors were persistent and whether the inhibitors were at high levels (high-titre inhibitors) and so more difficult to eliminate.

SIPPET was initiated by doctors who are specialised in treating people with haemophilia. The non-profit Angelo Bianchi Bonomi Foundation, in Milan, Italy, and the Italian Ministry of Health sponsored the study. Three pharmaceutical companies (Grifols, Kedrion and LFB) provided unrestricted grants to the Angelo Bianchi Bonomi Foundation. The funders were not involved in the design or conduct of the study.

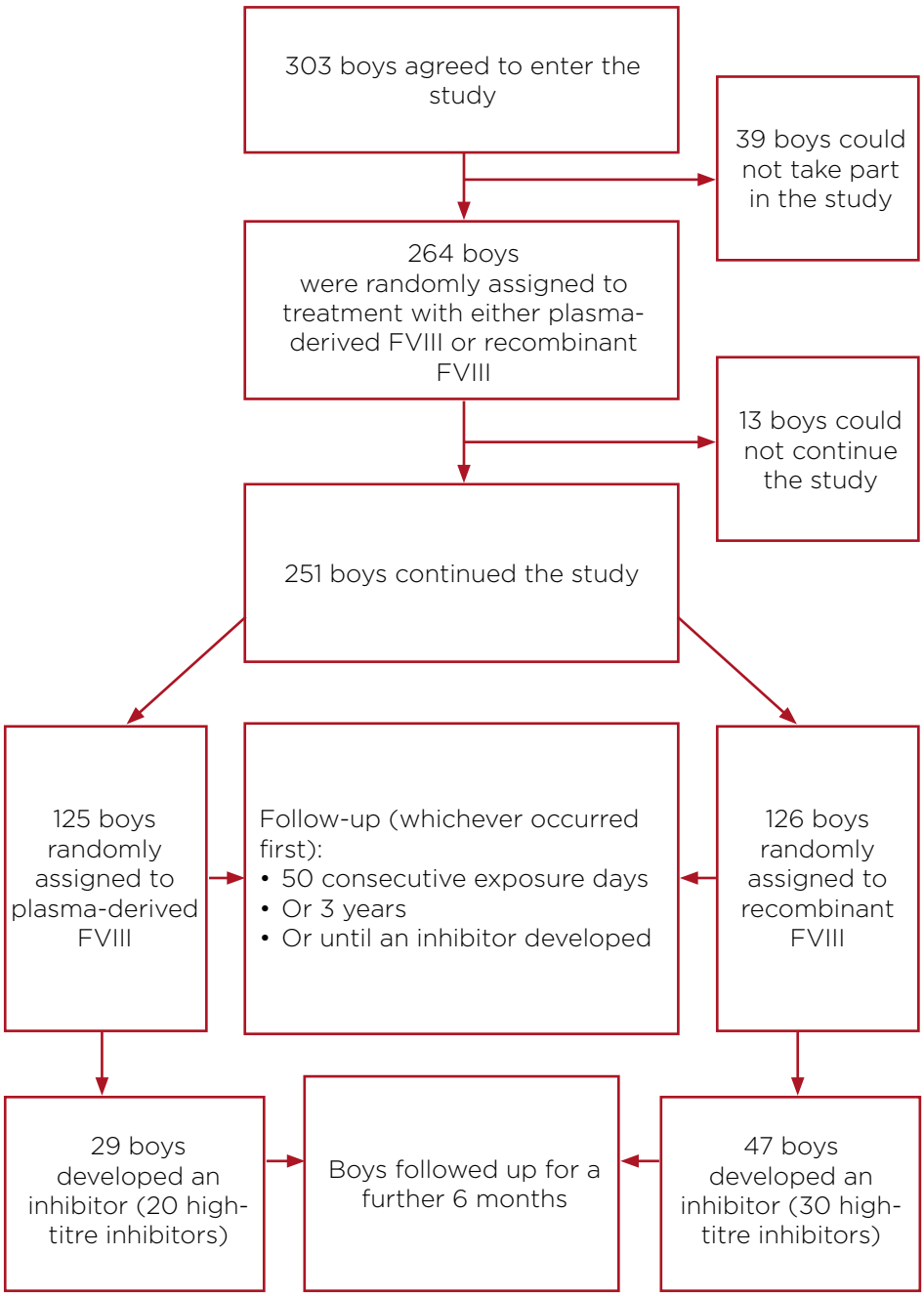
Who was included in the SIPPET trial?

SIPPET included 251 young boys with severe haemophilia A, who were being treated at 42 haemophilia centres. Most boys (218) were recruited in India, Egypt, Iran, the USA and Italy, and the others were treated at centres in Spain, Mexico, Brazil, Chile, Austria, South Africa, Turkey, Argentina and Saudi Arabia.

Only boys aged less than 6 years were included in the study. They had never received treatment with any FVIII product nor been in any new clinical trial, and had no inhibitors at the beginning of treatment.

What happened during the SIPPET trial?

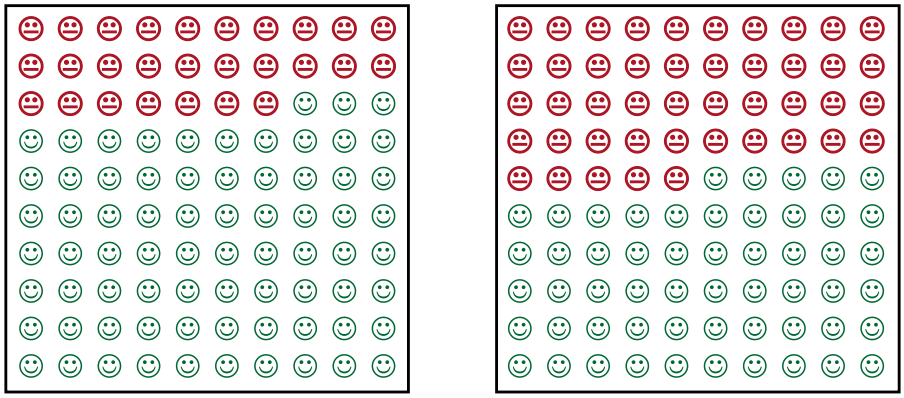
The SIPPET trial began in January 2010 and ended in May 2015. Of the 251 boys who were randomised to receive treatment, 125 were assigned to receive plasma-derived FVIII and 126 were assigned to treatment with recombinant FVIII. Several brands of plasma-derived and recombinant FVIII were used in the SIPPET trial.


303 boys agreed to enter the study
39 boys could not take part in the study
264 boys were randomly assigned to treatment with either plasma-derived FVIII or recombinant FVIII
13 boys could not continue the study
251 boys continued the study
125 boys randomly assigned to plasma-derived FVIII
Follow-up (whichever occurred first):
• 50 consecutive exposure days
• Or 3 years
• Or until an inhibitor developed
126 boys randomly assigned to recombinant FVIII
29 boys developed an inhibitor (20 high-titre inhibitors)
Boys followed up for a further 6 months
47 boys developed an inhibitor (30 high-titre inhibitors)

What were the results of the SIPPET trial?

Inhibitors were nearly twice as likely to occur in boys treated with recombinant FVIII compared to boys treated with plasma-derived FVIII, i.e. 45% vs 27%.

Young boys with haemophilia A who developed inhibitors by end of the SIPPET trial



Plasma-derived FVIII (27%)

Recombinant FVIII (45%)

Boys who developed an inhibitor

Boys without inhibitors

By the end of the study:

- Inhibitors had developed in 27% of the boys treated with plasma-derived FVIII, compared with 44% of the boys treated with recombinant FVIII.
- High-titre inhibitors, i.e. those clinically more demanding, had developed in 19% of boys treated with plasma-derived FVIII, compared with 28% of boys treated with recombinant FVIII.

All the inhibitors appeared before 39 exposure days, with high-titre inhibitors occurring before 34 exposure days. The type of replacement FVIII had no effect on the likelihood

that the inhibitor would be permanent. Of the 76 boys who developed inhibitors, 52 had inhibitors that lasted longer than 6 months.

The type of replacement FVIII had no effect on the boys' risk of serious side effects. In total, there were 11 serious side effects: 9 episodes of bleeding in the brain (intracranial bleeding) and 2 episodes of bleeding from the gastrointestinal tract.

What does the SIPPET trial mean for people with haemophilia?

The results of the SIPPET trial apply only to the type of people with haemophilia included in the study: i.e. young boys aged less than six years with severe haemophilia A, who had not been previously treated with any kind of FVIII replacement therapy.

As the researchers highlight, boys treated with plasma-derived FVIII had a lower incidence of inhibitors than those treated with recombinant FVIII. So this study has important clinical implications.

Anyone concerned about the results of the SIPPET trial should seek advice from their doctor.

The SIPPET trial was published in the *New England Journal of Medicine* on May 26th 2016: http://www.nejm.org/doi/full/10.1056/NEJMoa1516437

To find out more about the trial, visit the study website at http://www.sippetstudy.org/

Other links:

http://eahad.org/
http://www.ehc.eu/
http://www.hemophiliafed.org/
https://www.hemophilia.org/
https://www.wfh.org/

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