

Doctor, I have heart disease. What is the best medication to prevent future heart attacks and strokes: aspirin, a low dose of Xarelto®, or both taken together?

In people with chronic cardiovascular disease, a low dose of Xarelto® plus aspirin was better at preventing heart attacks, strokes, or death due to heart disease than either medication alone. Xarelto® plus aspirin led to a higher risk of bleeding but did not lead to more life-threatening bleeding. We should talk about the best option for you.

What's the evidence?

Understanding the problem

Chronic cardiovascular disease refers to narrowing or blockages of important arteries such as those found within the heart, legs, and brain. These blockages occur over a long period of time and can lead to symptoms such as angina (chest pain) and leg pain. Some people require surgery to remove or bypass the blockage. People with chronic cardiovascular disease also have an increased risk of suddenly forming new blood clots that get stuck within these narrowed arteries and can lead to heart attacks and strokes.

Aspirin is a medication that is commonly used to help prevent new blood clots from forming within arteries. Xarelto® is an anticoagulant that is commonly used to prevent blood clots from forming within veins (e.g., DVT or PE). However, researchers thought Xarelto® might also prevent blood clots from forming within arteries in people with chronic cardiovascular disease.

Both aspirin and Xarelto® increase the risk of bleeding. This bleeding may occur in the stomach, intestines, brain, or in other places in a person's body if there is already a reason for bleeding to occur.

Researchers in this study wanted to find the best medication or combination of medications to prevent new blood clots in people with chronic cardiovascular disease. The best medication is one that prevents new blood clots while keeping the risk of bleeding low. A medication that prevents heart attacks but causes many people to have major bleeding would not be a good choice. Each person's risk for bleeding is different, but most doctors believe that if less than 5 out of 100 people taking an anticoagulant for a year will have major bleeding, the risk is acceptable if it means that blood clots will be prevented.

Researchers in this study compared (1) aspirin alone, (2) a low dose of Xarelto® alone, and (3) Xarelto® plus aspirin for preventing heart attacks or strokes or death due to cardiovascular disease.

The study

Who? The study included 27,395 people from 33 countries who had chronic cardiovascular disease (average age 68 years; 82% men). People were not allowed into the study if their doctor thought their bleeding risk was too high or if they had a medical illness that made it unsafe for them to take aspirin or Xarelto®. People with recent strokes (within one month) were also excluded.

What? The study compared aspirin alone, Xarelto® alone (5 mg twice a day), and Xarelto® plus aspirin (2.5 mg twice a day)

Aspirin	vs.	Xarelto®	vs.	Xarelto® plus Aspirin
Aspirin, 100 mg once a day		Rivaroxaban (Xarelto®), 5 mg twice a day		Rivaroxaban (Xarelto®), 2.5 mg twice a day plus Aspirin, 100 mg once a day

What the researchers found

In people with chronic cardiovascular disease, those who took Xarelto® plus aspirin were less likely to have a heart attack or stroke or die from cardiovascular disease than people taking aspirin or Xarelto® alone.

People who took Xarelto® plus aspirin were more likely to have major bleeding than people taking aspirin alone.

Overall, 1 less person out of 100 taking Xarelto® plus aspirin had a bad medical event (either a new blood clot or a major bleed) than people taking aspirin or Xarelto® alone.

Summary of findings

Aspirin vs Xarelto® vs Xarelto® plus aspirin in people who have cardiovascular disease

Outcomes at 2 years	Rate of events with aspirin	Rate of events with Xarelto®	Rate of events with Xarelto® plus aspirin	Results
Heart attack, stroke, or cardiovascular death*	5 out of 100 people	5 out of 100 people	4 out of 100 people	About 1 less person out of 100 who took Xarelto® plus aspirin had a heart attack, stroke, or cardiovascular death at 2 years compared to aspirin or Xarelto® alone.
Major bleeding†	2 out of 100 people	3 out of 100 people	3 out of 100 people	About 1 more person out of 100 who took Xarelto® either alone or with aspirin had major bleeding at 2 years compared to aspirin alone.
Fatal or life-threatening internal bleeding	1 out of 100 people	1 out of 100 people	1 out of 100 people	No effect‡
Total number of fatal or life-threatening events§	6 out of 100 people	6 out of 100 people	5 out of 100 people	About 1 less person out of 100 who took Xarelto® plus aspirin had a fatal or life-threatening event at 2 years compared with aspirin alone or Xarelto® alone.

*Included deaths after a heart attack or other diseases that damage the heart. All people who did not have a clear alternate cause of death (e.g., cancer or serious infection) were assumed to have had cardiovascular death.

†Major bleeding included any bleeding that was severe enough to require a doctor visit (including fatal or life-threatening bleeding). Life-threatening bleeding included bleeding that occurred within the head or another critical organ (e.g., eyes).

‡Although the rates for the 2 groups look slightly different, the differences were not statistically significant—this means that the difference could simply be due to chance rather than due to the different treatments.

§Total number of fatal or life-threatening events including heart attacks, strokes, cardiovascular death, fatal bleeding, or bleeding into a major organ.

This Evidence Summary is based on the following article:

Eikelboom JW, Connolly SJ, Bosch J, et al. **Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease.** *N Engl J Med.* 2017 Oct 5;377(14):1319-1330. doi: 10.1056/NEJMoa1709118. Epub 2017 Aug 27. PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/28844192?dopt=Abstract>)

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Glossary

angina	chest pain due to reduced blood flow to the heart, if the blockage continues, permanent damage to the heart muscle may occur (aka heart attack, MI)
anticoagulant	medications that prevent blood clots from forming or travelling (aka blood thinner)
arteries	blood vessel with muscular walls that carries oxygen-containing blood from the heart to other parts of the body
cardiovascular disease	narrowing or blockages of important blood vessels in the heart, brain and legs

DVT	formation of a blood clot within a vein deep within the leg
major bleeding	serious bleeding (e.g. requiring a visit to the doctor or hospital, an invasive test to find the source of bleeding or a blood transfusion)
PE	blood clot(s) that cause obstruction of blood vessels within the lungs (pulmonary artery), after travelling from veins, most commonly within the leg or arm or pelvis
rivaroxaban	Xarelto®
stroke	damage to the brain due to lack of blood supply (aka cerebral vascular accident or CVA)
strokes	damage to the brain due to lack of blood supply (aka cerebral vascular accident or CVA)
Xarelto®	rivaroxaban; anticoagulant pill that does not require blood tests to monitor the effect