Press Release
February 28th, 2025

The RENOVE trial will be published on Saturday, March 1, 2025, at 11:30 PM (UTC) on *The Lancet* website (open access). The study is coordinated by Professor Francis Couturaud, pulmonologist at Brest University Hospital, a university professor at UBO, Director of INSERM Unit U1304, and Coordinator of the F-CRIN "INNOVTE" network (National Investigation Network for Venous Thromboembolic Disease).

Brest, February 28th, 2025
In patients with venous thromboembolic disease, which can manifest as deep vein thrombosis or pulmonary embolism, prolonged anticoagulation is indicated in more than half of cases. However, this treatment carries a significant risk of bleeding.
Until now, no study had demonstrated the possibility of reducing the dose of direct oral anticoagulants (DOACs), particularly rivaroxaban and apixaban, after the initial months of treatment. Current European (European Society of Cardiology/European Respiratory Society) and American (American Society of Hematology) guidelines suggest dose reduction. However, no solid evidence regarding clinical benefits, specifically in terms of thrombotic recurrence and bleeding risks, supports the systematic prescription of a half-dose in patients requiring prolonged anticoagulation.

In this context, the RENOVE study was designed with academic funding from the **National Hospital Clinical Research Program (***Programme Hospitalier de Recherche Clinique National*), under the Ministry of Labor, Health, Solidarity, and Families.
The study's primary objective was to demonstrate that a reduced dose of direct oral anticoagulants (DOACs) was not less effective than a full dose in preventing thromboembolic recurrence. Additionally, it aimed to assess whether the reduced dose could lower the risk of major bleeding and clinically relevant non-major bleeding.

Coordination of the RENOVE Study:
CHU de Brest (sponsor); UMR INSERM 1304-GETBO (*Groupe d'Étude de la Thrombose de Bretagne Occidentale*); UBO (*Université de Bretagne Occidentale*).
The F-CRIN INNOVTE (*Investigation Network on Venous Thrombo-Embolism*) network coordinated the 47 CHUs and CHGs that enabled the inclusion of 2,768 patients in France within the planned timeframe.
This study was also supported by the global INVENT network (*International Network of Venous Thromboembolism Clinical Research Networks*).

About the RENOVE study:

The RENOVE academic non-inferiority trial was designed as a multicenter, open-label, randomized study with blinded adjudication of all events.

All included patients (>18 years old) had received full-dose anticoagulation for an initial period of 6 to 24 months without interruption. Only those for whom continued anticoagulation was deemed necessary were randomized to either: Standard-dose anticoagulation (full-dose apixaban: 5 mg twice daily; rivaroxaban: 20 mg once daily), or reduced-dose anticoagulation (half-dose), for an unlimited duration.

A total of 2,768 patients with symptomatic acute venous thromboembolism (pulmonary embolism or proximal deep vein thrombosis) were followed for a median duration of 37.1 months. The study was conducted from November 2017 to July 2022.
In 85% of cases, the included patients had pulmonary embolism.
60% were included after a first unprovoked episode (occurring without a triggering factor), while 34% were included following a second or third unprovoked venous thromboembolic event. 30% of patients were at high bleeding risk. Thus, the study population was at high risk of thromboembolic recurrence, with severe episodes, while also being at high risk of bleeding.

The key results of RENOVE

Non-inferiority for the primary endpoint of venous thromboembolic recurrence was not demonstrated. The cumulative recurrence rate at 5 years was 2.2% in the reduced-dose DOAC group, compared to 1.8% in the full-dose DOAC group (a non-significant difference).
"In other words," explains **Professor Francis Couturaud,** *"we cannot formally exclude a slight loss of efficacy with a reduced DOAC dose. However, the recurrence rates observed in both groups are very similar and more than three times lower than initially anticipated, confirming that the anticoagulant treatments used are highly effective."* The second key finding is the reduction in major bleeding risk and clinically relevant non-major bleeding: the reduced-dose group showed a 39% decrease in these bleeding events.

Pr Francis Couturaud: *“ In summary, the cumulative incidence of venous thromboembolic recurrences at 5 years is approximately 2% in both groups.*
However, for bleeding events, the incidence at 5 years is 15% in the full-dose group, compared to 9.9% in the reduced-dose group (including both major and clinically relevant non-major bleeding events).
The combined endpoint (venous thromboembolic recurrences and bleeding events) shows an overall reduction of 33%, representing a major clinical benefit, demonstrated for the first time in this population.”

** See detailed figures (see box)*

Practical Implications of the RENOVE Study?

Given the results, for most patients who have received curative anticoagulant treatment for at least six months and require long-term treatment, the preferred option is to reduce the dose of DOACs by half. However, this may not apply to certain subgroups, such as patients with a high-risk pulmonary embolism and those with obesity.

"*The study opens up an interesting perspective," highlights the pulmonologist. "It is now possible to explain to the patient that both options: half-dose or full-dose DOACs are highly effective. Although we have not been able to prove that they are strictly identical, the incidence of events remains extremely low. The benefit in terms of bleeding risk is significant, with a relative risk reduction of 39%, and the combined risk of recurrences and bleeding is reduced by 33%.*"

In this regard, the results of the RENOVE study support a shared medical decision-making process, where the therapeutic choice is guided by the patient's preferences and priorities while integrating scientific data.
"*Some patients, particularly those who prioritize minimizing the risk of recurrence at all costs, may be willing to accept the slight bleeding risk associated with taking a full-dose DOAC to protect themselves from another pulmonary embolism*," explains Professor Couturaud. "*On the other hand, other patients, understanding that this is a preventive strategy, may consider the risk of recurrence to be extremely low (0.4% per year, regardless of the DOAC dose). For them, the incidence of recurrences is negligible, and their priority may instead be to minimize the side effects of treatment, namely the bleeding risk inherent to anticoagulants. This can be achieved through a reduced-dose DOAC »*

Note: No signal has emerged indicating an increased risk of arterial thromboembolic events (myocardial infarction, stroke, etc.) in the group that received the half-dose compared to the full-dose group. Thus, no loss of opportunity in cardiovascular risk prevention has been observed, nor any increased risk of death. Furthermore, this is the first study to compare these two commonly used medications: rivaroxaban and apixaban. No significant difference in terms of efficacy and safety has been reported.

RENOVE will influence recommendations and clinical practices.
"These results will lead to a revision of guidelines at both national and international levels, confirms Professor Francis Couturaud. "*In France, together with all the scientific societies involved in venous thromboembolism, we will refine our recommendations to integrate these new findings. According to our information, European and American guidelines are also expected to evolve. Our RENOVE study will serve as a basis to justify that a 50% reduction in DOAC dosage is highly beneficial for most patients, particularly those at high risk of bleeding, such as the elderly. At the same time, it clarifies that this approach may not be suitable for patients with obesity or those with severe unprovoked pulmonary embolisms at high risk of death.*
Given the simplicity of the RENOVE study's patient inclusion criteria, the study population was highly representative of patients encountered in routine practice. This makes the results widely applicable to the majority of our patient population in everyday clinical practice."

*** Going Further: A detailed look at the RENOVE study results .**
The median follow-up was 37.1 months. Recurrent venous thromboembolism occurred in 19 of the 1,383 patients in the reduced-dose group (5-year cumulative incidence of 2.2% [95% CI 1.1–3.3]) compared with 15 of the 1,385 patients in the full-dose group (5-year cumulative incidence of 1.8% [95% CI 0.8–2.7]; adjusted HR 1.32 [95% CI 0.67–2.60]; absolute difference of 0.40% [95% CI –1.05 to 1.85]; p=0.23 for non-inferiority).

Major or clinically relevant bleeding occurred in 96 patients in the reduced-dose group (5-year cumulative incidence of 9.9% [95% CI 7.7–12.1]) and in 154 patients in the full-dose group (5-year cumulative incidence of 15.2% [95% CI 12.8–17.6]; adjusted HR 0.61 [95% CI 0.48–0.79]).
The composite outcome (recurrent thromboembolism and major or clinically relevant bleeding) occurred in 113 patients in the reduced-dose group (5-year cumulative incidence of 11.8% [95% CI 9.4–14.3]) and in 166 patients in the full-dose group (5-year cumulative incidence of 16.6% [95% CI 14.0–19.0]; adjusted HR 0.67 [95% CI 0.53–0.86]).

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