ESC European Society of Cardiology

European Heart Journal (2022) **43**, 985–992
https://doi.org/10.1093/eurheartj/ehab637

CLINICAL RESEARCH
Thrombosis and antithrombotic treatment

Ciraparantag reverses the anticoagulant activity of apixaban and rivaroxaban in healthy elderly subjects

Jack Ansell [1]*, Sasha Bakhru [2], Bryan E. Laulicht[3], Gregory Tracey[4], Stephen Villano[5], and Daniel Freedman[5]

Background

- Ciraparantag is a small synthetic water-soluble molecule with broad activity, reversing both the oral direct FXa inhibitors and the parenteral indirect Fxa and FIIa inhibitor enoxaparin.
- Ciraparantag directly binds to DOACs and to enoxaparin through non-covalent hydrogen bonds and charge–charge interactions, removing these drugs from their intended target site and reversing their anticoagulant effects.

AIM of the study

- To evaluate the safety and tolerability of escalating intravenous (IV) doses of ciraparantag.
- To evaluate the pharmacodynamic effects of these ciraparantag doses administered 3 h after the Day 3 dose of steady-state apixaban (Study 1) or rivaroxaban (Study 2) as measured by serial manual whole blood clotting time (WBCT).

Methods (I)

- Randomized, single-blind, placebo-controlled, Phase 2 clinical trials.
- Healthy non-smoking subjects, aged 50–75 years (inclusive) were eligible to participate in the studies.
- Enrolled subjects were treated with apixaban (10 mg orally, twice daily for 3.5 days or rivaroxaban (20 mg orally, once daily for 3 days) to steady-state anticoagulation.
- In Study 1, steady-state anticoagulation was defined as WBCT ≥20% above baseline 2.75 h after last apixaban dose. In Study 2, steady-state anticoagulation was defined as WBCT ≥ 25% above baseline 3.75 h after last rivaroxaban dose.
- Subjects who reached steady-state anticoagulation were randomized, in blinded fashion, to receive either ciraparantag or placebo in a 3:1 ratio.
- In Study 1 (apixaban), three dosing cohorts of ciraparantag were studied (30, 60, and 120mg); in Study 2 (rivaroxaban), four dosing cohorts of ciraparantag were studied (30, 60, 120, and 180 mg).

Methods (II)

- Study drug (ciraparantag or placebo) was administered as a single IV infusion over 10 min at either 3 h (Study 1, apixaban) or 4 h (Study 2, rivaroxaban) after the last dose of the anticoagulant.
- ‘Complete reversal’ of anticoagulation was defined as a return of WBCT to ≤10% above baseline at any time point within 1 h of study drug administration.
- Complete and sustained reversal’ was defined as a return of mean manual WBCT to ≤ 10% above baseline during all time points between 1 and 5 h (Study 1) or 6 h (Study 2) after administration of study drug. (Table 1)
- Safety evaluations included a continuous assessment of adverse events (AEs), and intermittent assessments of vital signs, electrocardiograms, and standard laboratory testing (chemistry, haematology, and urinalysis).
- Follow-up contact (phone call) was made between Days 7 and 10 to assess any AEs.

Table I **Summary of key design elements**

	Study 1 Apixaban	Study 2 Rivaroxaban
Anticoagulant regimen	Apixaban 10 mg orally, twice daily for 3.5 days	Rivaroxaban 20 mg orally, once daily for 3 days
Criteria for sufficient anticoagulation for randomization	2.75 h after last apixaban dose, WBCT ≥20% above baseline	3.75 h after last rivaroxaban dose, WBCT ≥25% above baseline
Timing of ciraparantag/placebo after last anticoagulant dose	3 h	4 h
Ciraparantag doses (mg)[a]	30, 60, 120	30, 60, 120, 180
WBCT timepoints after ciraparantag/placebo (h)	0.25, 0.5, 0.75, 1, 3, 5, 24	0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 24
'Responder' defined as WBCT ≤10% above baseline within 1 h and sustained after 1 h through X h	X = at least 5 h	X = at least 6 h

WBCT, whole blood clotting time.
[a]Active study drug (ciraparantag) doses are expressed as active drug moiety.

Results (I)

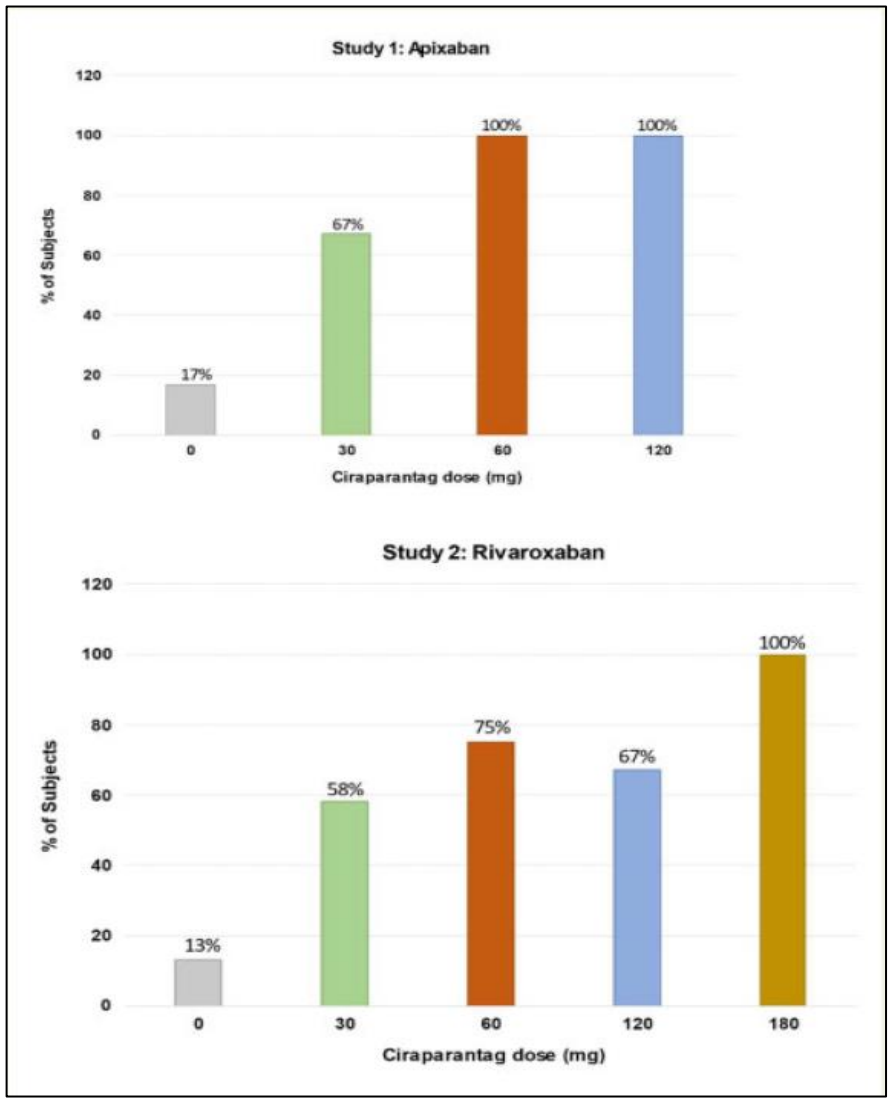
- In Study 1, 49 subjects were randomized (36 ciraparantag, 13 placebo).
- In study 2 64 subjects were randomized (48 ciraparantag, 16 placebo); all but one subject (who had an unrelated AE) completed the trial as planned.
- There were no important differences in demographic or clinical characteristics between any of the study groups.
- Ciraparantag produced a rapid and dose-related reversal of anticoagulation induced by apixaban and rivaroxaban compared with placebo as measured by WBCT.

Results (II)

- The effect was dose related and observed with apixaban (Study 1) in 67%, 100%, 100%, and 17% of subjects receiving ciraparantag 30 mg, 60 mg, 120 mg, or placebo, respectively, and with rivaroxaban (Study 2) in 58%, 75%, 67%, 100%, and 13% of subjects receiving ciraparantag 30 mg, 60 mg, 120 mg, 180 mg, or placebo, respectively. (Table 2 A and Table 4)
- At the highest doses of ciraparantag studied (120 mg for apixaban, 180 mg for rivaroxaban), complete reversal of anticoagulation within the first hour to ≤10% above baseline occurred:
  - in 83%, 92%, and 100% of apixaban subjects at 15, 30, and 60 min, respectively.
  - in 83%, 100%, and 100% of rivaroxaban subjects at 15, 30, and 60 min, respectively. (Table 2 B)
- The most common AEs were mild, transient sensations of warmth (reported as hot flashes, feeling hot, or flushing), which were dose related and resolved spontaneously. (Table 3)

Table 2

A. Proportion of subjects with complete and sustained reversal of steady-state anticoagulation induced by apixaban (Study 1) or rivaroxaban(Study 2)



B. Proportion of subjects with complete reversal of steady-state anticoagulation induced by apixaban (Study 1) or rivaroxaban (Study 2)

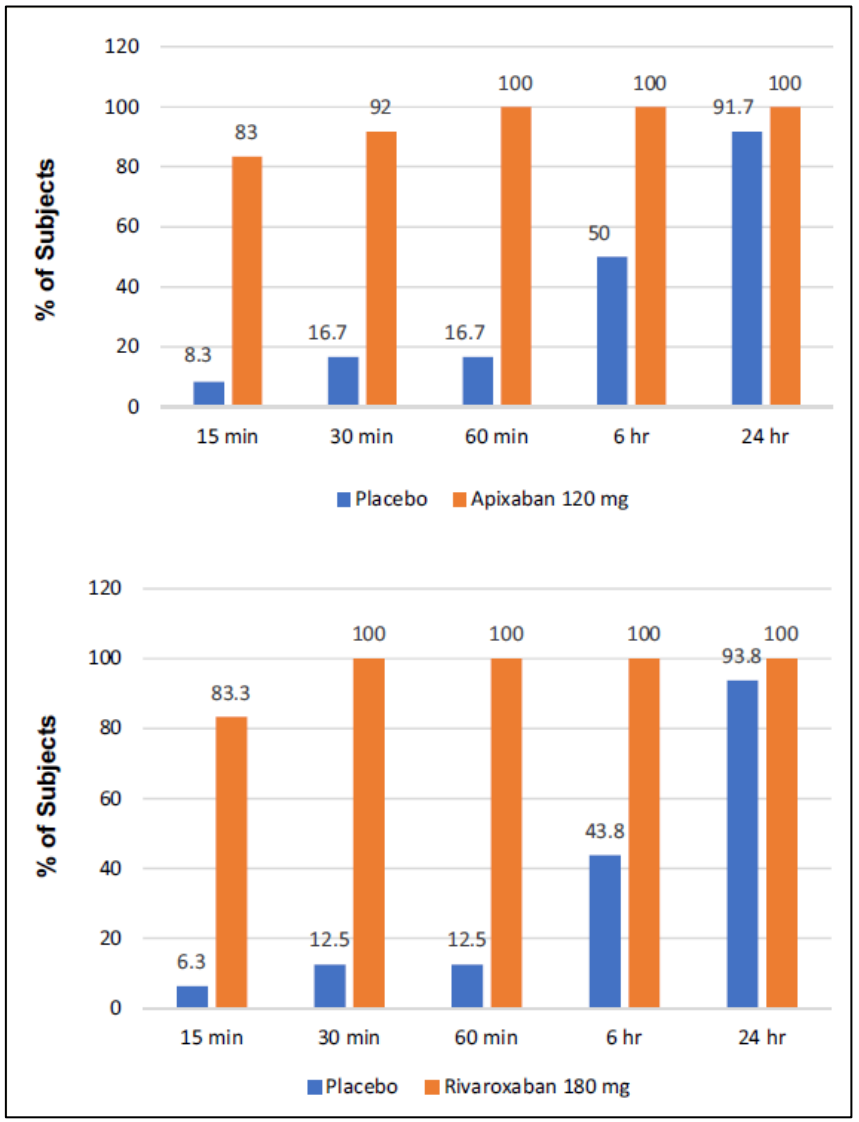


Table 3 Treatment-emergent adverse events

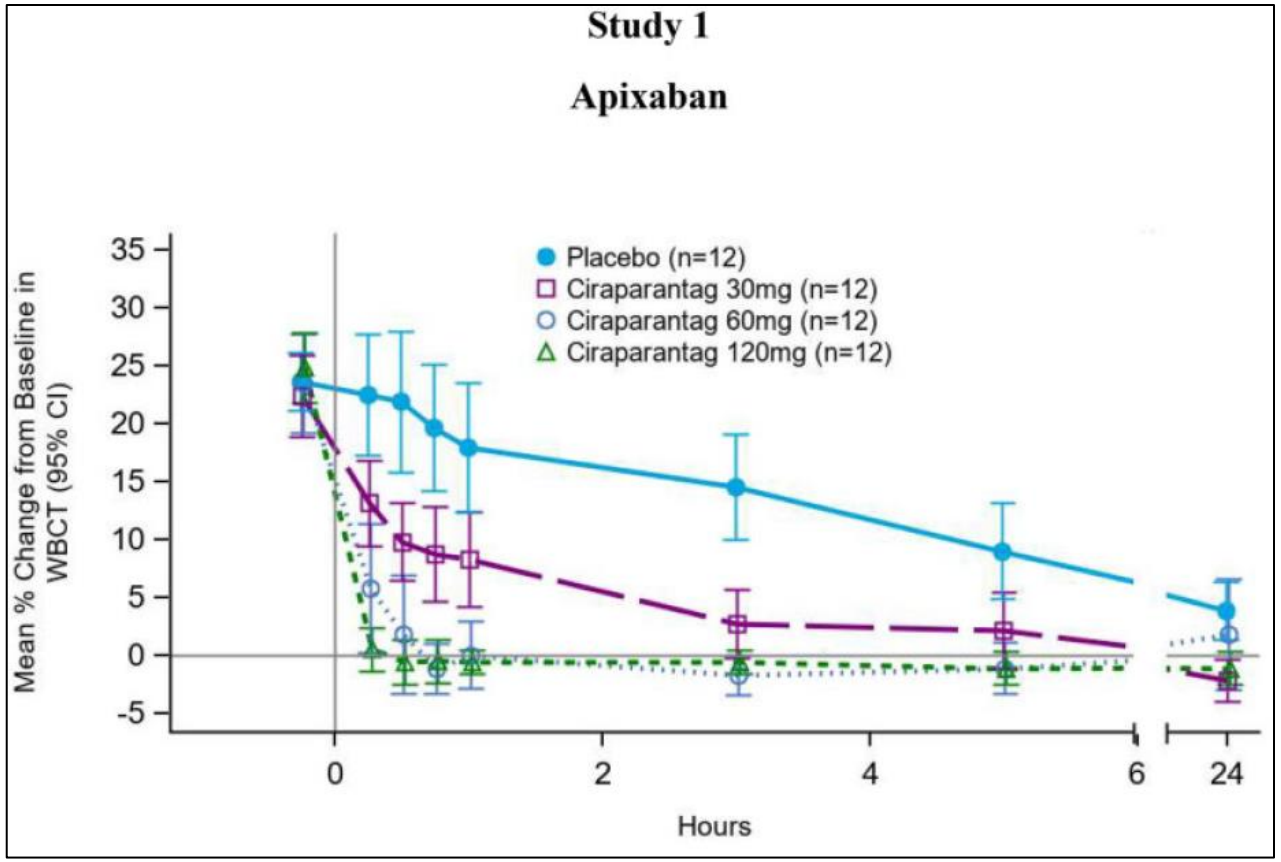
	Study 1		Study 2	
	Apixaban		Rivaroxaban	
Subjects with	Ciraparantag ($n = 36$)	Placebo ($n = 13$)	Ciraparantag ($n = 48$)	Placebo ($n = 16$)
TEAEs	13 (36.1%)	0	20 (41.7%)	2 (12.5%)
TEAEs in >1 subject				
Hot flush	8 (22.2%)	0	9 (18.8%)	0
Feeling hot	3 (8.3%)	0	2 (4.2%)	0
Feeling cold	1 (2.8%)	0	4 (8.3%)	0
Paraesthesia	0	0	3 (6.3%)	0
Flushing	0	0	2 (4.2%)	0
Dizziness	0	0	2 (4.2%)	0
Dysgeusia	0	0	2 (4.2%)	0

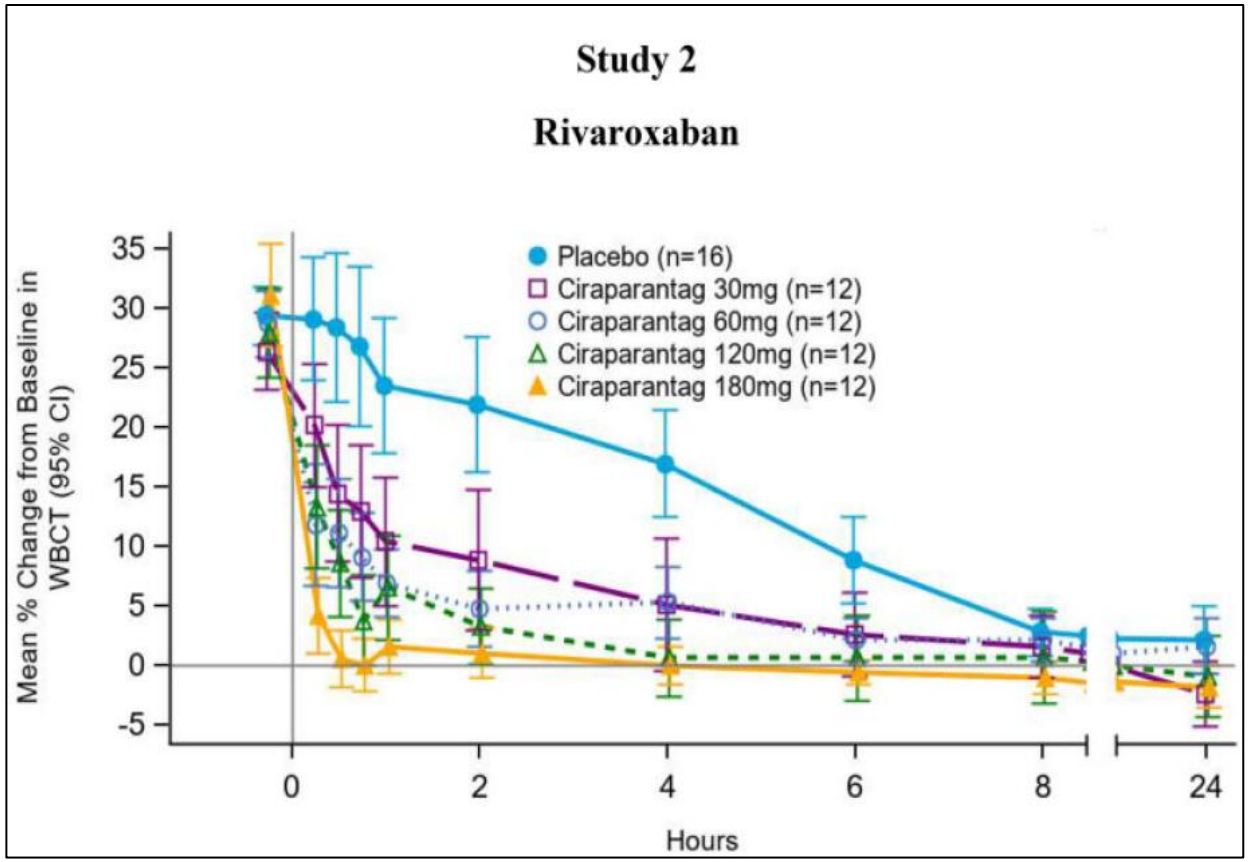
TEAE, treatment-emergent adverse event.

Table 4

Percent change from baseline in whole blood clotting time over time.

The first displayed timepoint represents the time of peak anticoagulant effect, measured 15 min prior to study drug infusion. Time 0 represents the end of study drug infusion. CI, confidence interval; WBCT, whole blood clotting time.





Conclusions

- In these two randomized, single-blind, placebo-controlled Phase 2 clinical trials, ciraparantag was shown to be safe and well tolerated at all doses.
- Ciraparantag was shown to reverse the anticoagulant effect induced by steady-state dosing of apixaban and rivaroxaban in healthy subjects and maintain reversal over a minimum of 5 and 6 h, respectively.
- The reversal effect was dose dependent, with higher doses required for full reversal of rivaroxaban than for apixaban.
- Further studies to confirm these results are needed.