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# Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome

Short title: Rivaroxaban in Antiphospholipid Syndrome (TRAPS)

Vittorio Pengo, M.D.[1], Gentian Denas, M.D.[1], Giacomo Zoppellaro, M.D., Ph.D.[1], Seena Padayattil Jose, M.D.[1], Ariela Hoxha M.D., Ph.D.[2], Amelia Ruffatti, M.D., Ph.D.[2], Laura Andreoli, M.D., Ph.D.[3], Angela Tincani, M.D.[3], Caterina Cenci, M.D.[4], Domenico Prisco, M.D.[4], Tiziana Fierro M.D.[5], Paolo Gresele, M.D., Ph.D[5]., Arturo Cafolla, M.D.[6], Valeria De Micheli, M.D.[7], Angelo Ghirarduzzi, M.D.[8], Alberto Tosetto, M.D.[9], Anna Falanga, M.D.[10], Ida Martinelli, M.D.[11], Sophie Testa, M.D.[12], Doris Barcellona, M.D.[13], Maria Gerosa M.D. [14], Alessandra Banzato, Ph.D.[1]

[1]Cardiology Clinic, Thrombosis Centre, Department of Cardiac Thoracic and Vascular Sciences, University of Padua, [2]Rheumatology Unit, Department of Medicine, University of Padua, [3]Rheumatology and Clinical Immunology Unit, Department of Clinical and Experimental Sciences, University of Brescia, [4]Department of Experimental and Clinical Medicine, University of Florence, [5]Section of Internal and Cardiovascular Medicine, Department of Medicine, University of Perugia, [6]Department of Cellular Biotechnologies and Hematology Thrombosis Centre Sapienza University of Rome, [7]Transfusion Medicine, District Hospital, Merate, [8]Angiology Unit, Department of Internal Medicine, Santa Maria Nuova Hospital, Reggio Emilia, [9]Hematology Department, San Bortolo Hospital, Vicenza, [10]Department of Immunohematology and Transfusion Medicine & the Hemostasis and Thrombosis Center, Hospital Papa Giovanni XXIII, Bergamo, [11]A. Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, [12]Hemostasis and Thrombosis Center, Laboratory Medicine Department, ASST, Cremona, [13]Department of Medical Sciences and Public Health, University of Cagliari, [14] Division of Rheumatology, Department of Clinical Sciences and Community Health, Ospedale Gaetano Pini , University of Milan , Milan, all in Italy.

*Correspondence*:

Prof. Vittorio Pengo M.D.

Clinical Cardiology, Thrombosis Center, Department of Cardiac Thoracic and Vascular Sciences, Via Giustiniani 2, 35128 Padova, Italy.

Tel. and Fax +39 (0)49 8215658

Email vittorio.pengo@unipd.it

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**Key points**

- Direct anticoagulants are currently used in patients with thromboembolism irrespective of the presence of antiphospholipid antibodies
- This trial shows an increased rate of events with rivaroxaban as compared with warfarin in patients with antiphospholipid syndrome

**ABSTRACT**

Rivaroxaban is an effective and safe alternative to warfarin in patients with atrial fibrillation and venous thromboembolism. We tested the efficacy and safety of rivaroxaban as compared to warfarin in high-risk patients with thrombotic Antiphospholipid Syndrome.

This is a randomized, open-label, multicenter, non-inferiority study with blinded end-point adjudication. Rivaroxaban 20 mg once daily (15 mg once daily based on kidney function) was compared to warfarin (INR target 2.5), for the prevention of thromboembolic events, major bleeding and vascular death in patients with Antiphospholipid Syndrome. Only high-risk patients triple positive for Lupus Anticoagulant, anti-cardiolipin and anti-β2-glycoprotein I antibodies of the same isotype (triple-positivity) were included in the study. The trial was terminated prematurely after the enrollment of 120 patients (59 randomized to rivaroxaban and 61 to warfarin) because of an excess of events among patients in the rivaroxaban arm. Mean follow up was 569 days. There were 11 (19%) events in the rivaroxaban group and 2 (3%) in the warfarin group. Thromboembolic events occurred in 7 (12%) patients randomized to rivaroxaban (4 ischemic stroke and 3 myocardial infarction) while no event was recorded in those randomized to warfarin. Major bleeding occurred in 6 patients, 4 (7%) in the rivaroxaban and 2 (3%) in the warfarin group. No death was reported.

The use of rivaroxaban in high-risk patients with Antiphospholipid Syndrome was associated with an increased rate of events as compared with warfarin, thus showing no benefit and excess risk. (ClinicalTrials.gov Identifier: NCT02157272).

## INTRDUCTION

Antiphospholipid syndrome (APS) is an acquired autoimmune disease characterized by the association of thromboembolic events or pregnancy morbidity and the presence of antiphospholipid (aPL) antibodies[1]. The laboratory tests exploring the presence of aPL antibodies include Lupus anticoagulant (LA), anti-cardiolipin (aCL) antibodies, and anti-ß2-Glycoprotein I (aß2GPI) antibodies. Laboratory tests may be positive in different combinations. However, a particular group of individuals, those presenting with positivity for all three laboratory tests (triple-positive), are at highest risk of both a first thrombotic event and of a higher rate of recurrence despite antithrombotic treatment[2-7]. Triple-positive individuals are less than 50% of those positive in one or two tests exploring the presence of aPL antibodies[4]. Secondary prevention of thromboembolic events is the primary therapeutic goal in these patients and the mainstay treatment is warfarin, as it significantly reduces thromboembolic recurrences[8-10]. However, the management of warfarin therapy is challenging, and thromboembolic events are frequent when the intensity of anticoagulation is not adequate (i.e., INR<2)[11]. Major bleeding is also a concern among APS patients when INR is kept at target values of more than 3[11,12]. An anticoagulant with a predictable effect and no need for monitoring would be of interest to the young population of patients with thrombotic APS. Rivaroxaban, a direct inhibitor of factor Xa, is at least as effective as warfarin in preventing venous[13] and arterial thromboembolism[14,15]. Moreover, it exhibits a safer profile due to a significantly lower incidence of cerebral bleeding[14]. Under these premises, we designed and conducted a randomized controlled trial aiming to compare the efficacy and safety of rivaroxaban versus warfarin in APS patients (TRAPS) at high-risk of thromboembolic recurrence.

## METHODS

*Study Design*

TRAPS is a prospective, randomized, phase III, open-label, non-inferiority study with blinded end-point adjudication conducted in 14 centers in Italy. The study design has been described previously[16]. The protocol was approved by the Institutional Review Board at each participating site. An independent data and safety monitoring board whose members were unaware of treatment allocation closely monitored the trial.

*Patients and Randomization*

Adult patients were eligible for inclusion if they were between the ages of 18 and 75 years, were positive in all the three aPL tests in the last blood sampling (triple-positivity) and had a history of thrombosis (objectively proven arterial, venous, and/or biopsy-proven micro-thrombosis). Triple-positivity was defined as positivity for IgG and/or IgM aCL (> 40 GPL or MPL or greater than the 99th percentile), IgG and/or IgM aβ2GPI (> 40 U or greater than the 99th percentile) and LA test based on the recommendations of the International Society of Thrombosis and Hemostasis[17,18]. Anticardiolipin and aβ2GPI ELISA tests had to be positive for the same isotype. At the screening visit, as well as at follow up visits, recent laboratory tests (complete blood count, renal and liver function and standard coagulation tests) were examined. After signing an informed consent form, patients underwent web-based randomization using random block sizes of two, four and six and stratified based on gender and the presence or absence of an associated autoimmune disease. In this way, four strata were constructed: females with or without associated autoimmune disease, males with or without associated autoimmune disease. Exclusion criteria are detailed elsewhere[16]. Randomization and study data were managed using REDCap (Research Electronic Data Capture)[19] tools hosted at the Department of Cardiac Thoracic and Vascular Sciences, Padua University Hospital.

*Study drug regimen*

Patients randomized to rivaroxaban received 20 mg once daily if they had a creatinine clearance (CrCl) of more than 50 ml/min as determined by Cockroft–Gault method. In case of CrCl between 30 and 50 ml/min, rivaroxaban 15 mg once daily was administered. Patient compliance was checked by counting residual pills

at each follow-up visit. Patients exiting the study were not considered in compliance calculation. When in warfarin, patients randomized to rivaroxaban started treatment when the International Normalized Ratio (INR) was below 3. If the patient was naïve to anticoagulation and randomized to warfarin, patient maintenance dose was determined using the protocol endorsed by the Italian Federation of Anticoagulation Clinics[20]. INR was maintained between 2.0 and 3.0 and checked at least every four weeks, or more frequently if needed, at the investigator's discretion.

*Follow up and outcomes*

Enrolled patients underwent regularly scheduled visits after one and three months from randomization and every six months thereafter. At each visit, compliance to rivaroxaban was checked by residual pill count, and compliance to warfarin calculating the Time in Therapeutic Range (TTR). Temporary drug discontinuation for surgery or invasive procedures was carried out according to established protocols[21,22]. The reasons for final premature drug discontinuation were recorded. The use of aspirin on top of anticoagulant drugs was allowed at the investigator's discretion.

The primary outcome was the cumulative incidence of thromboembolic events, major bleeding and vascular death. Diagnosis of venous and arterial thromboembolism was based on objective imaging techniques, that of major bleeding on published guidelines[23], and diagnosis of vascular death ascertained from clinical or autopsy reports and/or death certificates[16].

*Statistical analysis*

The primary analysis was designed to test whether the experimental drug (rivaroxaban) is non-inferior to the active control (warfarin). The non-inferiority margin was set to correspond to the preservation of 50% of the warfarin effect, as adopted in the other rivaroxaban registration trials. The non-inferiority margin is derived from the only observational study comparing VKAs versus control in triple positive APS patients[4]. This study showed a rate of composite events (thrombosis, major bleeding, and death) among APS patients receiving warfarin of approximating 6% per year. On the other hand, the incidence of events in untreated patients is 13% per year. The hazard ratio margin corresponding to preservation of 50% of the warfarin

effect is 1.7. To satisfy the non-inferiority hypothesis, the upper bound of the one-sided 95% confidence interval for the hazard ratio of an outcome with rivaroxaban as compared to warfarin must fall below 1.7. A non-inferiority log-rank test with an overall 88 events and sample size of 536 subjects (268 in the reference group and 268 in the treatment group) achieves 80% power at a 0.05 one-tail significance level to detect an equivalence hazard ratio of 1.7.

The primary outcome was analyzed according to both *as treated* and *intention to treat* (ITT) principle; *as treated* analysis included patients who completed the study on the assigned treatment on randomization, while *ITT* all patients who underwent randomization. Final analysis included events that occurred from randomization date to January 25, 2018 (the day on which investigators were instructed to switch patients to a non-study vitamin K antagonist). Baseline continuous and categorical data are reported as appropriate: means and standard deviations for continuous data and as numbers and percentages for categorical data. Cox proportional-hazards modeling was used for the endpoint analyses. Statistical significance was set at a P value of 0.05 or less.

## RESULTS

Trial enrollment began on November 2, 2014 and was stopped ahead of the planned date on January 25, 2018 by the advisory board according to recommendation of the adjudication and safety committee. All participating patients discontinued the assigned study drug and switched to a non-study vitamin K antagonist. At the time of trial termination, 120 patients had been randomized, 59 in the rivaroxaban and 61 in the warfarin group. Patient characteristics are described in Table 1. Randomization produced a satisfactory balance between groups for the considered variables. Risk factors for thrombosis were also comparable between the two study groups. Two patients met the dose reduction criteria based on calculated CrCl and received Rivaroxaban 15 mg.

There were 9 (12%) patients in the rivaroxaban group and 3 (5%) in the warfarin group who permanently stopped their assigned therapy before an end-point event and before the termination date. Reasons for

discontinuation are shown in Table 2. The mean follow-up period was 569 days considering the *as treated* cohort and 611 days considering the *ITT* cohort. No patient was lost to follow up. Adherence to treatment in the rivaroxaban group was 96% and the time in therapeutic range (TTR) in the warfarin group was 67%.

*Clinical outcomes*

Overall, 13 events were reported during follow up in the *as treated* population (Table 3). A post hoc ITT analysis included 2 additional events. In the *as treated* analysis (Table 4, Fig. 1), the composite primary outcome of thromboembolic events, major bleeding and vascular death occurred in 11 patients in the rivaroxaban group and in 2 patients in the warfarin group (HR 6.7, 95% CI 1.5-30.5, p=0.01). In the rivaroxaban arm, ischemic stroke occurred in 4 (7%) patients and myocardial infarction in 3 (5%) patients while there were no cases of ischemic stroke and myocardial infarction in the warfarin group. Of the 7 patients experiencing arterial events in the rivaroxaban arm, 1 patient was on aspirin; conversely, among the 52 patients without arterial events, 10 patients were on aspirin (p=ns). No episode of venous thromboembolism was recorded in both arms. There were 4 and 2 cases of major bleeding in the rivaroxaban and warfarin groups, respectively (HR 2.5, 95% CI 0.5-13.6, p=0.3). Overall, bleeding events were associated to predisposing factors in 5 out of 6 cases (uterine fibroma, anal fissure, Crohn's disease and thrombocytopenia in 2 patients). None of the patients treated with the lower dose rivaroxaban had an event. No patient died during the follow up.

In the ITT analysis (Table 4) that includes the 12 patients who exited the study prematurely, the composite primary outcome of thromboembolic events, major bleeding and vascular death occurred in 13 patients in the rivaroxaban group and in 2 patients in the warfarin group (HR 7.4, 95% CI 1.7-32.9, p=0.008). There were 2 additional events in the rivaroxaban arm with respect to the *as treated* analysis. One bilateral deep vein thrombosis of the lower limbs was recorded 21 days from stopping the study drug (rivaroxaban) for gingival bleeding while the patient was treated with therapeutic doses of low molecular weight heparin.

One cardiovascular death occurred 433 days form study drug (rivaroxaban) suspension in a patient with history of congestive heart failure and while the patient was on warfarin.

**DISCUSSION**

The aim of the present trial was to evaluate whether a direct oral anticoagulant, rivaroxaban, was non-inferior to warfarin in terms of efficacy and safety in high-risk patients with thrombotic APS. However, the trial was stopped prematurely for an excess of events in the rivaroxaban arm. Thromboembolic events, all in the arterial circulation, mainly drove the unbalance in the cumulative primary end-point. Four ischemic strokes and 3 myocardial infarctions occurred in patients treated with rivaroxaban and none in patients taking warfarin. Thus, rivaroxaban apparently does not protect high-risk patients from arterial events. Because there is no strict concordance between the district of the qualifying event at diagnosis and that of recurrent thrombotic event[4], it does not mean that rivaroxaban can be safely used in APS patients with venous thromboembolism at diagnosis. Three out of 7 cases with an arterial outcome were originally patients with venous thromboembolism. Reasons of rivaroxaban failure remain elusive. Possible explanations may be related to poor adherence[24], insufficient drug concentration or a different mechanism of action respect to warfarin. In our study, the excellent adherence based on pill count, does not explain treatment failure in the rivaroxaban arm. A suboptimal drug concentration may account for thromboembolic complications during treatment[25]. The requirement of higher anti-Xa activity and plasma rivaroxaban levels for the prevention of arterial versus venous events has been demonstrated in animal models. Preclinical data showed an $ED_{50}$ of 0.1 mg/kg versus 5.0 mg/kg for the prevention of venous (venous stasis model) versus arterial (AV-shunt model) thrombosis in rats[26]. Although pharmacological studies have demonstrated a predictable rivaroxaban anticoagulant effect, high inter-individual variability may expose some patients to inadequate plasma levels of the drug[27]. Differences in the mechanisms of action of rivaroxaban and warfarin may also in part explain our findings. Thrombin generation in APS patients treated with rivaroxaban is different compared to warfarin, as vitamin K antagonists reduce functional coagulation factors both in the extrinsic and intrinsic pathways of coagulation[28]. The importance

of intrinsic pathway on thrombin generation is highlighted by the ability of warfarin to better attenuate thrombin generation with prosthetic material[29].

Platelets may play a major role in thrombus formation in the arterial circulation as shown in an animal model of aPL-induced arterial thrombosis[30]. Whether additional therapy with aspirin is efficacious in APS patients is not currently known. To this end, conclusions cannot be drawn from this trial, as only a small proportion of patients were taking aspirin and, in any case, they were well balanced in the two groups. Moreover, there was no statistical difference between patients who had arterial events on rivaroxaban and treated with aspirin, as compared to patients on rivaroxaban not receiving aspirin who did not experience arterial events. Hydroxychloroquine (HCQ) was suggested to play a role in lowering antiphospholipid antibody titers and preventing thrombotic recurrences in antiphospholipid syndrome[31,32]. In our study, the small proportion of HCQ treated patients was balanced in both arms and a clear correlation of its use with events cannot be established.

Previous reports and systematic reviews were inconclusive regarding the benefit or harm of direct oral anticoagulants in APS [33,34]. Major bias in the reported studies were the heterogeneous aPL profiles and the lack of reports on drug compliance[33]. A previous randomized trial of rivaroxaban versus warfarin (RAPS) with a biological end-point was conducted in APS patients with venous thromboembolism[28]. However, there are differences between TRAPS and RAPS trial: the uniform high-risk patient population (triple-positivity) enrolled in TRAPS, the inclusion of APS patients with both arterial and venous qualifying events, and the clinical end-point. A strength of the TRAPS trial is that it was designed to confirm clinical efficacy and long-term safety of rivaroxaban in thrombotic APS and, although the trial was not completed, results strongly suggest the lack of benefit of its use in APS patients.

The results of our trial should raise the awareness among healthcare personnel on the lack of efficacy of rivaroxaban in high-risk triple-positive APS patients and may be relevant for the other trials testing direct anticoagulants in this setting[35,36]. In fact, the ASTRO-APS investigators had to modify their protocol due to an increased incidence of arterial events[37]. Results from this study cannot be translated to APS patients

without a "full positive" laboratory profile. At present, the therapeutic strategy in patients with a laboratory profile different from that of this study should be considered on a case-by-case basis, taking into account the presence of additional risk factors for venous and arterial thrombosis[38], the nature of VTE (provoked or unprovoked) and the risk of bleeding.

In conclusion, rivaroxaban in high-risk patients with Antiphospholipid Syndrome was associated with an excess of events as compared to warfarin.

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*Investigators contributing to patient enrollment not listed as authors:* M. Taraborelli (University of Brescia), E. Silvestri (University of Florence), T. Del Ross (University of Padua), A. Doria (University of Padua)

*Author contributions*

V.P. conceived and planned the study and took the lead in writing the manuscript. G. Z., S. P.J. A.H, A.R, L.A., A.T., C.C., D.P., T.F., P.G., A.C., V. DeM., A.G., A.F., I.M., S.T., D.B., M.G. gave substantial contributions to acquisition and interpretation of data; G.D. and A.T. computed data and performed data analysis. A.B. was the monitor of database. All authors critically revised the manuscript and gave their approval to the final version.

*Disclosure of conflict of interest*

None to declare

*Appendix*

*Study coordinator:* V. Pengo (University of Padua); *Steering Committee:* V. Pengo (University of Padua), A. Ruffatti (University of Padua), A. Tincani (University of Brescia), P. L. Meroni (University of Milan);

*Independent blinded Safety and Event-Adjudication Committee:* G. Palareti (University of Bologna); P. Prandoni (University of Padua).

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**Table 1.** Baseline characteristics of the patients*

| Characteristic | Rivaroxaban (N = 59) | Warfarin (N = 61) |
|---|---|---|
| Female sex — no. (%) | 39 (66) | 38 (62) |
| Age — years | 46.5 ±10.2 | 46.1 ±13.2 |
| BMI | 26.1 ±6.1 | 25.5 ±5.9 |
| Creatinine clearance — ml/min | 117.0 ±38.6 | 109.3 ±36.7 |
| Hemoglobin (g/L) | 131.7 ±17.6 | 135.9 ±17.1 |
| Platelet count no. ($x10^9$/L) | 214.9 ±73.8 | 209.3 ±63.5 |
| APS laboratory tests positivity — no. | | |
| LA – dRVVT/aPTT/both | 16/5/38 | 14/7/40 |
| aCL – IgG or both IgG and IgM/ IgM only | 57/2 | 52/9 |
| aβ2GPI – IgG or both IgG and IgM/ IgM only | 57/2 | 52/9 |
| Autoimmune disease — no. (%) | 24 (41) | 25 (41) |
| Distribution — no. | | |
| SLE | 10 | 15 |
| Other autoimmune disease | 14 | 10 |
| Previous thrombotic events — no. (%) | | |
| Arterial events | 11 (19) | 14 (23) |
| Distribution — no. | | |
| Stroke | 8 | 8 |
| AMI | 0 | 2 |
| Other sites | 3 | 4 |
| Venous events | 38 (64) | 39 (64) |
| Distribution — no. | | |
| DVT and/or PE | 36 | 32 |
| Other sites | 2 | 7 |
| Venous and arterial events — no. (%) | 10 (17) | 8 (13) |
| Pregnancy morbidity — no. (%)† | 16 (41) | 12 (32) |
| Risk factors — no. (%) | | |
| Smoking‡ | 31 (53) | 29 (48) |
| Hypertension | 15 (25) | 22 (36) |
| Diabetes | 4 (7) | 0 (0) |
| Dyslipidemia | 12 (20) | 15 (25) |
| Other hypercoagulable condition | 9 (15) | 9 (15) |
| Medications at time of randomization — no. (%) | | |

| | | |
|---|---|---|
| Hydroxychloroquine | 15 (25) | 23 (38) |
| Corticosteroids | 11 (19) | 13 (21) |
| Other immunosuppressive drugs | 17 (29) | 21 (34) |
| Aspirin | 11 (19) | 10 (16) |
| Statins | 7 (12) | 10 (16) |

*Plus-minus denotes means ±SD; percentages rounded to the nearest whole number. †Percentages calculated in women. ‡ Including history of smoking.

BMI denotes body mass index; SLE – systemic lupus erythematosus; APS – Antiphospholipid Syndrome; LA – lupus anticoagulant; aCL – anticardiolipin; aβ2GPI – anti-β2-glycoprotein I; AMI – acute myocardial infarction; DVT – deep vein thrombosis; PE – pulmonary embolism;

**Table 2.** Reasons for rivaroxaban or warfarin discontinuation during the study period

| | Rivaroxaban | Warfarin |
|---|---|---|
| Discontinuation n—(%) | 9 (15) | 3 (5) |
| Withdrawal of informed consent | 2 | 1 |
| Clinically relevant non-major bleeding | 2 | 0 |
| Planned pregnancy | 3 | 1 |
| Other | 2 | 1 |

**Table 3.** Characteristics of patients and endpoints according to *as treated* and *intention to treat* analysis

| # | Gender | age | BMI | Arm | History of events | Event | Description* | DAYS from randomization |
|---|---|---|---|---|---|---|---|---|
| 1 | F | 44 | 49,6 | R | A+V+O | Bleeding | Metrorrhagia causing acute Hb fall | 21 |
| 2 | M | 39 | 25,2 | R | V | Thrombosis | Acute myocardial infarction | 709 |
| 3 | F | 47 | 35,6 | R | A+O | Bleeding | Rectorrhagia requiring transfusion | 429 |
| 4 | M | 59 | 24,5 | R | A+O | Thrombosis | Ischemic Stroke | 322 |
| 5 | F | 35 | 32,8 | R | A | Thrombosis | Ischemic Stroke | 36 |
| 6 | F | 57 | 26,1 | R | V | Thrombosis | Ischemic Stroke | 299 |
| 7 | F | 55 | 24,7 | R | A | Thrombosis | Acute myocardial infarction | 253 |
| 8 | M | 52 | 19,8 | R | A | Bleeding | Gastrointestinal bleeding causing acute Hb fall | 681 |
| 9 | F | 58 | 24,2 | R | A+V | Thrombosis | Ischemic Stroke | 110 |
| 10 | M | 47 | 29,6 | R | V | Thrombosis | Acute myocardial infarction | 20 |
| 11 | F | 43 | 19,1 | R | V | Bleeding | Hb fall | 28 |
| 12 | F | 51 | 20,5 | W | A+V | Bleeding | Provoked Hb fall | 365 |
| 13 | F | 36 | 21,3 | W | A+V | Bleeding | Metrorrhagia requiring intervention | 280 |
| Additional endpoints considered in ITT analysis | | | | | | | | |
| 14 | M | 47 | 22,5 | R | V | Thrombosis | Bilateral DVT in the lower limbs | 175 |
| 15 | M | 55 | 27,4 | R | A | Death | Cardiovascular death | 475 |

* Hb fall denotes a fall in hemoglobin of more than 2 g/L; all thrombotic events were documented by imaging.

F = female; M = male; BMI = body mass index; R = rivaroxaban; W = warfarin; A = arterial event; V = venous event; O = Obstetric event; DVT = deep vein thrombosis; ITT = intention to treat

**Table 4.** Adjudicated efficacy and safety outcomes*

| Outcome | Rivaroxaban N=59 | Warfarin N=61 | HR (95% CI) | P Value | Rivaroxaban N=59 | Warfarin N=61 | HR (95% CI) | P Value |
|---|---|---|---|---|---|---|---|---|
| | As treated analysis | | | | ITT analysis | | | |
| Thromboembolic events, major bleeding and vascular death | 11 (19) | 2 (3) | 6.7 (1.5-30.5) | 0.01 | 13 (22) | 2 (3) | 7.4 (1.7-32.9) | 0.008 |
| Arterial thrombosis | 7 (12) | 0 | | | 7 (12) | 0 | | |
| Ischemic stroke | 4 (7) | 0 | - | - | 4 (7) | 0 | - | - |
| Myocardial Infarction | 3 (5) | 0 | | | 3 (5) | 0 | | |
| Venous thromboembolism | 0 | 0 | | | 1 (2) | 0 | | |
| Major bleeding | 4 (7) | 2 (3) | 2.5 (0.5-13.6) | 0.3 | 4 (7) | 2 (3) | 2.3 (0.4-12.5) | 0.3 |
| Death | 0 | 0 | - | - | 1 (2) | 0 | - | - |

*number in parenthesis denotes percent with respect to total

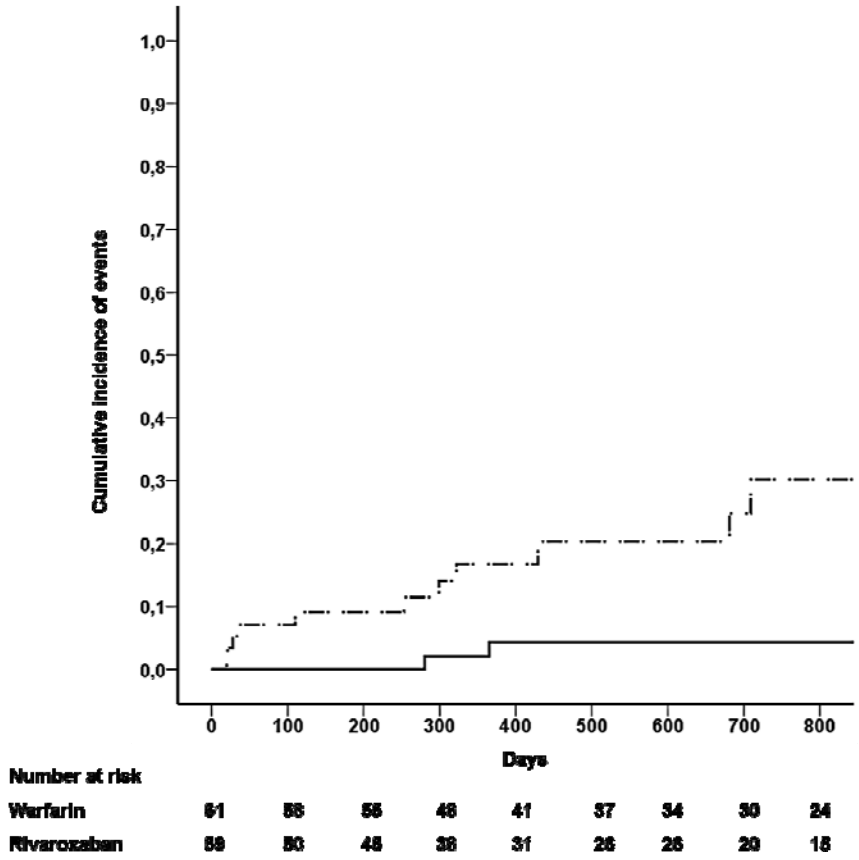


**Figure 1.** Cumulative incidence of events (death, thromboembolic events and major bleeding) in the rivaroxaban group (dashed line) and in the warfarin group (continuous line).

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# Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome

Vittorio Pengo, Gentian Denas, Giacomo Zoppellaro, Seena Padayattil Jose, Ariela Hoxha, Amelia Ruffatti, Laura Andreoli, Angela Tincani, Caterina Cenci, Domenico Prisco, Tiziana Fierro, Paolo Gresele, Arturo Cafolla, Valeria De Micheli, Angelo Ghirarduzzi, Alberto Tosetto, Anna Falanga, Ida Martinelli, Sophie Testa, Doris Barcellona, Maria Gerosa and Alessandra Banzato



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