Real-life use of anticoagulants in venous thromboembolism with focus on patients with exclusion criteria for direct oral anticoagulants.

DOACS in VTE patients excluded for trials

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Abstract

We assessed the real-life use of direct oral anticoagulants (DOACs) in patients with venous thromboembolism (VTE) and exclusion criteria for randomized trials. From 2013 to 2016, 3578 of 18853 patients (19%) had exclusion criteria. Irrespective of which anticoagulant was chosen, they had more VTE recurrences (hazard ratio [HR]: 3.10; 95%CI: 2.47-3.88), major bleeds (HR: 4.10; 95%CI: 3.38-4.96) and deaths (HR: 9.47; 95%CI: 8.46-10.6) than those without exclusion criteria. During initial therapy, no patient with exclusion criteria on DOACs (n=115) recurred, but those on rivaroxaban bled less often (adjusted HR: 0.18; 95%CI: 0.04-0.79) than those on unfractionated heparin (n=224) and similar to those (n=3,172) on low-molecular-weight heparin (LMWH). For long-term therapy, patients on rivaroxaban (n=151) had non-significantly fewer VTE recurrences (adjusted HR: 0.74; 95%CI: 0.08-1.32) and major bleeds (adjusted HR: 0.41; 95%CI: 0.15-1.15) than those on LMWH (n=2,071). The efficacy and safety of DOACs were similar to standard therapy.

Introduction

Current guidelines of antithrombotic therapy, based on the evidence from randomized trials, recommend the use of dabigatran, rivaroxaban, apixaban or edoxaban as long-term therapy in patients with venous thromboembolism (VTE).[1] The risk reduction of recurrent VTE with the direct oral anticoagulants (DOACs) is similar to the risk reduction with low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKA) while the risk of bleeding (and particularly intracranial bleeding) is less with the DOACs than with VKA therapy.[2–7] However, the pivotal trials where their indication was based applied strict exclusion criteria, aimed to exclude patients with a presumed high risk of bleeding. In real-life, one in every 4 patients receiving long-term anticoagulant therapy would not have been eligible for these trials, and these patients have a higher rate of major bleeding.[8-16]

RIETE (Registro Informatizado Enfermedad TromboEmbólica) is a multicenter, ongoing, international (Spain, Belgium, Brazil, Canada, Czech Republic, Ecuador, France, Israel, Italy, Latvia, Republic of Macedonia, Switzerland, enroll patients) observational registry of consecutive patients with symptomatic, objectively confirmed, acute VTE (ClinicalTrials.gov identifier: NCT02832245). Since its inception in 2001, data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes.[17–22] In the current study, we aimed to determine, within patients with VTE, the proportion of patient with at least one exclusion criterion for the trials where their indication was based and

compare the benefit/risk ratio (VTE recurrences and major bleeding) with DOACs vs. conventional therapy in these patients.

Results

From January 2013 to November 2016, 18,853 VTE patients were recruited. Their mean age was 65±18 years; 9232 (49%) were male and 10,490 (56%) initially presented with PE (with or without associated DVT). Overall, 3,578 patients (19%) had at least one of the predefined exclusion criteria to be recruited in randomized trials: metastatic cancer 1,732 patients (48%); CrCl levels <30 mL/min 1,020 (29%); thrombocytopenia 453 (13%); recent major bleeding 380(11%); chronic liver failure 268 (7.5%) and pregnancy 126 (3.5%). Of these, 3,177 patients (89%) had one exclusion criterion, 369 (10%) had two and 32 patients (0.89%) had three or more exclusion criteria. Mean age of patients with at least one exclusion criterion was 69.7±16.5, while in those without exclusion criteria was 63.4±17.2 years, respectively (p <0.001). During the course of anticoagulant therapy (mean, 176±151 days), patients with exclusion criteria had a higher rate of VTE recurrences (hazard ratio [HR]: 3.10; 95%CI: 2.47-3.88), major bleeding (HR: 4.10; 95%CI: 3.38-4.96), all-cause death (HR: 9.47; 95%CI: 8.46-10.6), fatal PE (HR: 4.84; 95%CI: 3.15-7.42) or fatal bleeding (HR: 6.07; 95%CI: 3.56-10.4) than those without exclusion criteria (Table I).

Patients with exclusion criteria

Among 3,578 patients with exclusion criteria, LMWH was the most often used drug for initial therapy of VTE (89%), and UFH the second (6.3%). The use of

rivaroxaban (2.9%) or apixaban (0.3%) was much lower (Table II). Among 3,208 patients receiving long-term therapy, LMWH was again the most often used drug (65%), followed by VKA (29%), rivaroxaban (4.7%) and apixaban (1.3%). Interestingly however, VKA were the most often used drugs in patients with CrCl levels <30 mL/min (493 of 898 patients, 55%) or chronic liver failure (118 of 241 patients, 49%). Unexpectedly, 6 pregnant women were prescribed long-term therapy with rivaroxaban. For initial therapy, patients without exclusion criteria receiving LMWH were slightly older than those on DOACs: 69±16 vs. 68±18 years ($p < 0.05$). Among patients with at least one exclusion criterion, mean ages were: 65±18 vs. 58±18 years, respectively ($p < 0.01$). For long-term therapy, patients with no exclusion criteria receiving LMWH were slightly older than those on DOACs: 67±16 vs. 66±18 years ($p < 0.05$). Among patients with at least one exclusion criterion, mean ages were: 66±17 vs. 58±18 years, respectively ($p < 0.001$).

Of 31 patients with CrCl levels <30 mL/min receiving rivaroxaban for initial therapy, 19 (61%) received the recommended doses (30 mg daily) and 12 were prescribed lower doses. There also was one patient on apixaban, who received 10 mg daily. Of 39 patients with CrCl levels <30 mL/min receiving rivaroxaban for long-term therapy, 26 (67%) received the recommended doses (20 mg daily), 12 were prescribed lower than recommended doses and one patient received 30 mg daily. There were 17 patients on apixaban, and 12 (71%) received lower than recommended doses (5 mg daily).

During initial therapy, no patients receiving rivaroxaban (n=104) or apixaban (n=11) developed VTE recurrences (Table III). Patients on rivaroxaban had a significantly lower rate of major bleeding than those on UFH (hazard ratio [HR]: 0.18; 95%CI: 0.03-0.64) and a non-significantly lower rate than those on LMWH (HR: 0.39; 95%CI: 0.06-1.30). Multivariable analysis confirmed the lower rate of major bleeding in patients on rivaroxaban than in those on UFH (adjusted HR: 0.18; 95%CI: 0.04-0.79). There were too few patients on apixaban to establish comparisons. During long-term therapy, patients on rivaroxaban had a lower rate of VTE recurrences (HR: 0.25; 95%CI: 0.04-0.84) or major bleeding (HR: 0.44; 95%CI: 0.27-0.71) than those on LMWH (Table IV). On multivariable analysis however, these differences disappeared: adjusted HR: 0.74 (95%CI: 0.08-1.32) for VTE recurrences and 0.41 (95%CI: 0.15-1.15) for major bleeding. They also had a non-significantly lower rate of VTE recurrences (HR: 0.39; 95%CI: 0.06-1.40) and a similar rate of major bleeding (HR: 0.78; 95%CI: 0.49-1.21) than those on VKA. Interestingly, no patients with metastatic cancer (n=45) or with CrCl levels <30 mL/min (n=56) receiving DOACs for long-term therapy bled.

Patients without exclusion criteria

Among 15,275 patients without exclusion criteria, LMWH was the most often used drug for initial therapy of VTE (79%), then rivaroxaban (14%), UFH (3.8%), Fondaparinux (2.7%) and apixaban (0.73%). For long term therapy, VKA drugs were the most often used drugs (57%), then LMWH (24%), rivaroxaban ((17%), apixaban (2.5%) and dabigatran (0.5%).

During initial therapy, patients receiving rivaroxaban (n=2,125) had a lower rate of major bleeding than those on LMWH (HR: 0.57; 95%CI: 0.34-0.92) or UFH (HR: 0.33; 95%CI: 0.16-0.65). During long-term therapy, patients receiving rivaroxaban (n=2,348) had half the rate of VTE recurrences (HR: 0.44; 95%CI: 0.27-0.71) or major bleeding (HR: 0.57; 95%CI: 0.34-0.92) than those on LMWH, and similar rates than those on VKA.

Discussion

Our data, obtained from a large series of consecutive patients with acute VTE, reveal that in real life one in every five such patients had at least one of the exclusion criteria to be recruited in the pivotal randomized trials with DOACs. [8–14] Not unexpectedly, patients with exclusion criteria had a 4-fold higher rate of major bleeding (and a 6-fold higher rate of fatal bleeding) than those without exclusion criteria, as previously reported.[23–25] In our series, this increased rate of major bleeding was found in patients with metastatic cancer, CrCl levels <30 mL/min, thrombocytopenia, recent major bleeding and in those with liver failure, but not in pregnant women. Moreover, patients with exclusion criteria also had a 3-fold higher rate of VTE recurrences (and a 4-fold higher rate of fatal PE) than those without exclusion criteria. This increased rate of VTE recurrences was only found in patients with metastatic cancer or thrombocytopenia (and marginally too in those with recent bleeding), and may likely be due to the use of lower than recommended doses of therapy because of the concern about bleeding.

Data from the PREFER in VTE registry also found that the use of DOACs was less likely in patients with renal insufficiency or at increased risk for bleeding.[26,27] Our findings confirm that the DOACs were used in few patients with exclusion criteria (3.2% for initial therapy and 6.2% for long-term therapy), and this seems paradoxical since its use has been associated with less bleeding in randomized trials.[2–5,7,28] It would seem to be more cost-effective to prescribe safer drugs in patients at increased risk for bleeding.[29] In our cohort, patients with exclusion criteria initially receiving rivaroxaban had fewer bleeds than those on UFH, and patients on long-term rivaroxaban had fewer VTE recurrences and fewer bleeds than those on long-term LMWH. However, given the small number of patients with exclusion criteria receiving rivaroxaban (104 for initial therapy, 151 for long-term), we can only hypothesize that rivaroxaban may be a good alternative to standard therapy in patients with these conditions. There were few patients with exclusion criteria receiving apixaban or dabigatran to make any comparison.

There is no evidence in the literature on the use of DOACs in VTE patients with metastatic cancer, but our preliminary data suggest that they may be effective and safe. Since there were only 45 patients with disseminated cancer receiving DOACs, we may only speculate about a similar safety compared with LMWH. As for renal insufficiency, one in every 18 patients (57 of 1,020, 5.6%) with CrCl levels <30 mL/min in our series was prescribed DOACs, and this is against the recommendations in the product label.[30–33] However, none of these patients bled, thus suggesting that the DOACs might be at least as safe as VKA or LMWH in these patients. Unfortunately, randomized clinical trials to compare

the DOACs vs. standard therapy are not allowed in patients with severe renal insufficiency. Moreover, 6 pregnant women (4.8%) were prescribed rivaroxaban for long-term therapy, and the use of DOACs is formally contraindicated during pregnancy.[1] The ISTH issued a guidance document that recommended the immediate discontinuation of DOACs after confirmation of pregnancy.[34] We are unaware if any of these women had hypersensitivity to LMWH, if it was a medical mistake or choice, but there were no consequences on the new-born. Finally, a number of VTE patients in our cohort had recent major bleeding, liver insufficiency or thrombocytopenia. These patients were also excluded in most randomized trials of antithrombotic therapy. [2–7] In our experience, LMWH was the most often used drug, both initially and for long-term therapy. In our experience, the use of DOACS in these patients was not associated with an increased rate of major bleeding.

RIETE provides data on the treatment of VTE in a real-world situation with an unselected patient population. Hence, it may provide insights into the natural history of VTE in patients that are not often included in randomized clinical trials, and help to identify factors associated with better or worse patient outcomes. However, as an observational study, RIETE is not designed to answer questions regarding the relative efficacy and safety of different drugs. In our series, since the sample of patients with exclusion criteria on DOACs was really small, the results are subject to uncertainty (as shown by the large confidence intervals). Moreover, patients were not treated with a standardized anticoagulant regimen; the duration of therapy varied with local practice, and is likely to have been influenced by a physician's assessment of a patient's risk of

bleeding. Data from registries are hypothesis-generating and provide feedback from real-world clinical situations which is invaluable when designing new randomized clinical studies. Strengths of the current analysis include that a large number of consecutive unselected patients were enrolled.

In summary, VTE patients with exclusion criteria are not uncommon in real life (19% in our cohort), and their outcome during the course of anticoagulation is worse than in those without exclusion criteria. The use of DOACs is rare in these patients, but our data suggest that they may be at least as safe as standard therapy (as it occurs in patients without exclusion criteria).

Methods

Inclusion criteria

Consecutive patients with acute deep vein thrombosis (DVT) or pulmonary embolism (PE) confirmed by objective tests (compression ultrasonography or contrast venography for DVT; helical CT-scan, ventilation-perfusion lung scintigraphy or angiography for PE) were enrolled in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their legal power of attorney) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

Physicians participating in the RIETE registry made all efforts to enroll consecutive patients. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating

center through a secure website. To ensure the validity of the information entered into the database, one of the specially trained monitors visited each participating hospital and compared information in 25 to 50 randomly chosen patient records with the information entered into the RIETE database. For data quality assessment, monitors assessed 4,100 random records from all participating hospitals that included 1,230,000 measurements. These data showed a 95% overall agreement between the registered information and patient records. RIETE also used electronic data monitoring to detect inconsistencies or errors and attempted to resolve discrepancies by contacting the local coordinators.

Study design

We conducted a retrospective study of prospectively collected data from consecutive patients with acute VTE enrolled in the RIETE registry. Data were collected from January 2013 to September 2016, corresponding to the time when the prescription of DOACs was allowed. Our major outcome was the rate of VTE recurrences or major bleeding appearing during therapy with DOACs vs. conventional therapy (LMWH, unfractionated heparin [UFH] or Fondaparinux for initial therapy; LMWH or VKA for long-term therapy) in patients with at least one of the exclusion criteria in the trials where the DOACs demonstrated their efficacy and safety. Comparisons were made separately for initial and long-term therapy and for every DOAC.

We sought the pivotal trials where the indication for the use of DOACs in patients with VTE was based.[2–5] The exclusion criteria slightly varied from each

other, but in general patients were excluded if they had: 1) cancer requiring over 6 months of LMWH therapy or with a life expectancy of 3-6 months; 2) creatinine clearance (CrCl) levels <30 mL/min (<25 mL/min in one trial): 3) a high risk of bleeding; 4) clinically significant liver disease or 5) pregnancy. For the current study, we considered as exclusion criteria any of the following: 1) metastatic cancer; 2) CrCl levels <30 mL/min; 3) platelet count at baseline <100,000/μL; 4) recent (<30 days before) major bleeding; 5) chronic liver failure (defined as biopsy proven liver cirrhosis or AST or ALT levels >3 times the upper normal range), and 6) pregnancy.

Baseline variables

The following parameters are routinely recorded in RIETE: patient's baseline characteristics; clinical status including any coexisting or underlying conditions; risk factors for VTE; diagnostics tools used for diagnosis; laboratory data at baseline; the treatment received upon VTE diagnosis (drugs, doses, regimen and duration) and the outcome during the course of anticoagulation. Active cancer was defined as newly diagnosed cancer, metastatic cancer, or cancer that was being treated (i.e. surgery, chemotherapy, radiotherapy, support therapy). Recent bleeding was defined as a major bleeding episode <30 days prior to VTE.

Treatment

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). The decision on the type and duration of therapy was left to the attending physicians. Patients were

followed-up during the course of therapy in the outpatient clinic or physician's office. During each visit, any signs or symptoms suggesting VTE recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent VTE was investigated by repeat compression ultrasonography, lung scanning, helical-CT scan or pulmonary angiography, as appropriate.

Statistical Analysis

Categorical variables were compared using the chi-square test (two-sided) and Fisher´s Exact Test (two-sided). Continuous variables were compared using Student t test. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were calculated. Incidence rates were calculated as cumulative incidence (events/100 patient-years) and compared using the hazard ratios. Cox proportional hazard models were used to compare the rates of VTE recurrences and major bleeding events occurring during initial and long-term therapy, separately. Crude and adjusted (HR) as well as their 95% CI were estimated. Covariates included in the adjusted model were those for which a statistically significant difference (a threshold p-value of 0.1 was set to assess significance of differences) was found between the different drugs, and a backward selection was used for the covariate selection in the multivariable model. Statistical analyses were conducted with SPSS for Windows Release 17.0 (SPSS, Inc).

Role of the funding source

The sponsors of the study (Sanofi and Bayer) had no role in study design, data collection, data analysis, data interpretation or writing of the report. The

corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Study Highlights

o What is the current knowledge on the topic?

Based on randomized trials, current guidelines recommend to treat venous thromboembolism (VTE) with direct oral anticoagulants (DOACs). However, randomized trials usually exclude patients at increased risk for bleeding.

o What question did this study address?

How common are patients with VTE and exclusion criteria for randomized trials, what was their outcome during anticoagulation and how often were prescribed DOACs?

o What this study adds to our knowledge ?

In real-life, 19% of VTE patients had exclusion criteria, and they had a higher rate of VTE recurrences or major bleeding than those without exclusion criteria. The use of DOACs was rare in these patients (3.2% initially and 6.2% for long-term therapy), and their efficacy and safety were not better than standard therapy.

o How this might change clinical pharmacology or translational science

Patient

Randomized trials are needed on appropriate anticoagulant therapy for VTE in patients excluded from previous studies on NOACs.

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Disclosure

Dr. Moustafa has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals and Sanofi; has served as a speaker for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Daiichi-Sankyo and Sanofi; and has received grants from Sanofi, Bayer HealthCare and LFB.

Dr. Monreal has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Leo Pharma, Pfizer, and Sanofi; has served as a speaker or a member of a speaker's bureau for Bayer Healthcare Pharmaceuticals, Daiichi-Sankyo, Leo Pharma, and Sanofi; and has received grants for clinical research from Sanofi and Bayer.

All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Author Contributions

F.M. and M.M. wrote the manuscript; F.M. and M.M. designed the research; F.M., R.P., P.D.M., J.G-M., R.Q., M-L.P., J.A.P., N.F., P.B., and M.M. performed the research; F.M., R.P., P.D.M., J.G-M., R.Q., M-L.P., J.A.P., N.F., P.B., and M.M. analyzed the data.

References:

1. Kearon, C. *et al.* Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* **149**, 315–352 (2016).
2. Schulman, S. *et al.* Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N. Engl. J. Med.* **361**, 2342–52 (2009).
3. Agnelli, G. *et al.* Oral apixaban for the treatment of acute venous thromboembolism. *N. Engl. J. Med.* **369**, 799–808 (2013).
4. EINSTEIN Investigators *et al.* Oral rivaroxaban for symptomatic venous thromboembolism. *N. Engl. J. Med.* **363**, 2499–510 (2010).
5. EINSTEIN–PE Investigators *et al.* Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N. Engl. J. Med.* **366**, 1287–97 (2012).
6. Hokusai-VTE Investigators *et al.* Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N. Engl. J. Med.* **369**, 1406–15 (2013).
7. Prins, M. H. *et al.* Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb. J.* **11**, 21 (2013).
8. Hägg, L., Johansson, C., Jansson, J. H. & Johansson, L. External validity of the ARISTOTLE trial in real-life atrial fibrillation patients. *Cardiovasc. Ther.* **32**, 214–218 (2014).
9. Apisarnthanarax, S. *et al.* Applicability of randomized trials in radiation oncology to standard clinical practice. *Cancer* **119**, 3092–9 (2013).
10. Saunders, C. *et al.* External validity of randomized controlled trials of

glycaemic control and vascular disease: how representative are participants? *Diabet. Med.* **30**, 300–8 (2013).

11. Moustafa, F. *et al.* Retrospective study about 73 consecutive patients treated by direct oral anticoagulant and admitted to an emergency room. *J. Mal. Vasc.* **40**, 1–9 (2015).
12. Cohen, A. T., Goto, S., Schreiber, K. & Torp-Pedersen, C. Why do we need observational studies of everyday patients in the real-life setting? *Eur. Hear. J. Suppl.* **17**, D2–D8 (2015).
13. Assmann, S. F., Pocock, S. J., Enos, L. E. & Kasten, L. E. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet* **355**, 1064–1069 (2000).
14. Wang, R., Lagakos, S. W., Ware, J. H., Hunter, D. J. & Drazen, J. M. Statistics in Medicine — Reporting of Subgroup Analyses in Clinical Trials. *N. Engl. J. Med.* **357**, 2189–2194 (2007).
15. Levi, M. *et al.* Bleeding in patients receiving vitamin K antagonists who would have been excluded from trials on which the indication for anticoagulation was based. *Blood* **111**, 4471–4476 (2008).
16. Monreal, M. *et al.* Management of patients with acute venous thromboembolism: findings from the RIETE registry. *Pathophysiol. Haemost. Thromb.* **33**, 330–4 (2004).
17. Muriel, A. *et al.* Survival effects of inferior vena cava filter in patients with acute symptomatic venous thromboembolism and a significant bleeding risk. *J. Am. Coll. Cardiol.* **63**, 1675–83 (2014).
18. Farge, D. *et al.* Fatal Events in Cancer Patients Receiving Anticoagulant Therapy for Venous Thromboembolism. *Medicine (Baltimore).* **94**, e1235

(2015).

19. Jiménez, D. *et al.* Trends in the Management and Outcomes of Acute Pulmonary Embolism Analysis from the RIETE Registry. *J. Am. Coll. Cardiol.* **67**, 162–170 (2016).
20. Muñoz-Torrero, J. F. S. *et al.* Effects of age on the risk of dying from pulmonary embolism or bleeding during treatment of deep vein thrombosis. *J. Vasc. Surg.* **54**, 26S–32S (2011).
21. Tzoran, I., Brenner, B., Papadakis, M., Micco, P. Di & Monreal, M. VTE Registry: What Can Be Learned from RIETE? *Rambam Maimonides Med. J.* **5**, e0037 (2014).
22. Jiménez, D. *et al.* Trends in the Management and Outcomes of Acute Pulmonary Embolism Analysis from the RIETE Registry. *J. Am. Coll. Cardiol.* **67**, 162–170 (2016).
23. Carrier, M. *et al.* Efficacy and Safety of Anticoagulant Therapy for the Treatment of Acute Cancer-Associated Thrombosis: A Systematic Review and Meta-Analysis. *Thromb. Res.* **134**, 1214–1219 (2014).
24. Hulle, T. van der *et al.* Meta-analysis of the efficacy and safety of new oral anticoagulants in patients with cancer-associated acute venous thromboembolism. *J. Thromb. Haemost.* **12**, 1116–1120 (2014).
25. Beyer-Westendorf, J. *et al.* Choosing wisely: The impact of patient selection on efficacy and safety outcomes in the EINSTEIN-DVT/PE and AMPLIFY trials. *Thromb. Res.* **149**, 29–37 (2017).
26. Becattini, C. & Agnelli, G. Treatment of Venous Thromboembolism with New Anticoagulant Agents. *J. Am. Coll. Cardiol.* **67**, 1941–1955 (2016).
27. Agnelli, G. *et al.* P5559: the current use of direct oral anticoagulants

(DOACs) for the treatment of VTE in Europe- PREFER in VTE (abstr). *Eur Hear. J* **35**, 1002 (2014).

28. The Hokusai-VTE Investigators Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism. *N. Engl. J. Med.* **369**, 1406–1415 (2013).
29. Gómez-Outes, A., Terleira-Fernández, A. I., Lecumberri, R., Luisa Suárez-Gea, M. & Vargas-Castrillón, E. Direct oral anticoagulants in the treatment of acute venous thromboembolism: A systematic review and meta-analysis. *Thromb. Res.* **134**, 774–782 (2014).
30. Boehringher Ingelheim International GmbH. London (United Kingdom): European Medicines Agency (EMA); 2008 Pradaxa Summary of Product Characteristics. Available at: http://www.ema.europa.eu/docs/es_ES/ (2013).at <https://www.medicines.org.uk/emc/medicine/24839>
31. Bayer Pharma AG Xarelto®: summary of product characteristics. *last Updat. 2013 Sept 23* at <https://www.medicines.org.uk/emc/medicine/21265>
32. European Medicines Agency Eliquis Summary of Product Characteristics. 1–29 (2011).at <https://www.medicines.org.uk/emc/medicine/24988/SPC/Eliquis+2.5+mg+film-coated+tablets/>
33. European Medicines Agency - Find medicine - Lixiana. at <http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002629/human_med_001874.jsp&mid=WC0b01ac058001d124>
34. Cohen, H., Jayakody Arachchillage, D., Middeldorp, S., Beyer-

Westendorf, J. & Kadir, R. A. Management of direct oral anticoagulants in women of childbearing potential: guidance from the SSC of the ISTH. *J. Thromb. Haemost.* 1673–1676 (2016).

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RIETE Registry Coordinating Center: S & H Medical Science Service.

APPENDIX

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Table I. Incidence rates of VTE recurrences and major bleeding during the course of anticoagulant therapy, according to the presence or absence of exclusion criteria.

	Any exclusion criteria		No exclusion criteria		Hazard ratio (95%CI)
	N	Events per 100 patient-years	N	Events per 100 patient-years	
Patients, N		***3,578***		***15,275***	
Mean days of therapy (±SD)		143±159		184±185	<0.001
Median days (IQR)		99 (32-190)		125 (86-228)	<0.001
VTE recurrences	118	8.51 (7.08-10.2)	210	2.75 (2.40-3.14)	3.10 (2.47-3.88)
Major bleeding	181	12.9 (11.2-14.9)	243	3.16 (2.78-3.58)	4.10 (3.38-4.96)
Death	828	58.1 (54.3-62.2)	476	6.14 (5.61-6.71)	9.47 (8.46-10.6)
Fatal PE	40	2.81 (2.03-3.78)	45	0.58 (0.43-0.77)	4.84 (3.15-7.42)
Fatal initial PE	31	2.18 (1.50-3.05)	41	0.53 (0.38-0.71)	4.11 (2.56-6.56)
Fatal recurrent PE	9	0.63 (0.31-1.16)	4	0.05 (0.02-0.12)	12.2 (3.83-45.7)
Fatal bleeding	29	2.04 (1.39-2.88)	26	0.34 (0.22-0.48)	6.07 (3.56-10.4)
Metastatic cancer, N		***1,732***		***17,121***	
VTE recurrences	82	13.9 (11.1-17.2)	246	2.92 (2.57-3.30)	4.77 (3.70-6.10)
Major bleeding	90	14.8 (12.0-18.1)	334	3.94 (3.53-4.38)	3.76 (2.96-4.72)
CrCl levels <30 mL/min, N		***1,020***		***17,833***	
VTE recurrences	12	2.88 (1.56-4.89)	316	3.67 (3.28-4.09)	0.78 (0.42-1.35)
Major bleeding	51	12.3 (9.24-16.0)	373	4.30 (3.88-4.75)	2.85 (2.11-3.80)
PlC <100,000/µL, N		***453***		***18,400***	
VTE recurrences	23	13.0 (8.43-19.2)	304	3.44 (3.07-3.84)	3.77 (2.42-5.67)
Major bleeding	25	14.1 (9.31-20.5)	399	4.48 (4.06-4.94)	3.14 (2.05-4.63)
Recent major bleeding, N		***380***		***18,473***	
VTE recurrences	10	7.02 (3.56-12.5)	318	3.58 (3.20-3.99)	1.96 (0.99-3.54)
Major bleeding	28	19.6 (13.2-27.9)	396	4.43 (4.01-4.88)	4.42 (2.96-6.39)
Chronic liver failure, N		***268***		***18,585***	
VTE recurrences	6	5.41 (2.19-11.2)	322	3.61 (3.23-4.02)	1.50 (0.60-3.14)
Major bleeding	14	12.9 (7.36-21.2)	410	4.56 (4.14-5.02)	2.83 (1.60-4.69)
Pregnancy, N		***126***		***18,727***	
VTE recurrences	0	-	328	3.65 (3.27-4.07)	-
Major bleeding	1	2.03 (0.10-10.0)	423	4.68 (4.25-5.14)	0.43 (0.02-2.15)

Abbreviations: SD, standard deviation; IQR, interquartile range; VTE, venous thromboembolism; PE, pulmonary embolism; CrCl, creatinine clearance; PlC, platelet count; CI, confidence intervals.

Table II. Use of drugs for initial- and for long-term therapy, according to the presence of exclusion criteria.

Initial therapy					
	LMWH	**UFH**	**Rivaroxaban**	**Apixaban**	**Fondaparinux**
Patients, N	***15,208***	***812***	***2,229***	***123***	***481***
Metastatic cancer	1,625 (11%)	54 (6.7%)‡	25 (1.1%)‡	1 (0.81%)‡	27 (5.6%)‡
CrCl levels <30 mL/min	864 (5.7%)	112 (14%)‡	31 (1.4%)‡	1 (0.81%)*	12 (2.5%)†
PlC <100,000/µL	373 (2.5%)	30 (3.7%)*	23 (1.0%)‡	3 (2.4%)	24 (5.0%)†
Recent major bleeding	300 (2.0%)	43 (5.3%)‡	21 (0.94%)‡	6 (4.9%)*	10 (2.1%)
Chronic liver failure	239 (1.6%)	13 (1.6%)	7 (0.31%)‡	2 (1.6%)	7 (1.5%)
Pregnancy	120 (0.79%)	4 (0.49%)	1 (0.04%)‡	0	1 (0.21%)
Any exclusion criteria	**3,172 (21%)**	**224 (28%)‡**	**104 (4.7%)‡**	**11 (8.9%)†**	**67 (14%)‡**
2 exclusion criteria	324 (2.1%)	28 (3.4%)*	3 (0.13%)‡	1 (0.81%)	13 (2.7%)
≥3 exclusion criteria	25 (0.16%)	4 (0.49%)	1 (0.04%)	1 (0.81%)	1 (0.21%)
No exclusion criteria	**12,036 (79%)**	**588 (3.8%)**	**2,125 (14%)**	**112 (0.73%)**	**414 (2.7%)**
Long-term therapy					
	LMWH	**VKA**	**Rivaroxaban**	**Apixaban**	**Dabigatran**
Patients, N	***5,455***	***8,998***	***2,499***	***401***	***81***
Metastatic cancer	1,362 (25%)	124 (1.4%)‡	42 (1.7%)‡	3 (0.75%)‡	0
CrCl levels <30 mL/min	348 (6.4%)	493 (5.5%)*	39 (1.6%)‡	17 (4.2%)	1 (1.2%)
PlC <100,000/µL	201 (3.7%)	158 (1.8%)‡	23 (0.92%)‡	8 (2.0%)	1 (1.2%)
Recent major bleeding	205 (3.8%)	94 (1.0%)‡	36 (1.4%)‡	15 (3.7%)	2 (2.5%)
Chronic liver failure	107 (2.0%)	118 (1.3%)†	13 (0.52%)‡	3 (0.75%)	0
Pregnancy	102 (1.9%)	9 (0.10%)‡	6 (0.24%)‡	0	0
Any exclusion criteria	**2,071 (38%)**	**939 (10%)‡**	**151 (6.0%)‡**	**43 (11%)‡**	**4 (4.9%)‡**
2 exclusion criteria	236 (4.3%)	52 (0.58%)‡	7 (0.28%)‡	3 (0.75%)‡	0
≥3 exclusion criteria	18 (0.33%)	5 (0.06%)‡	1 (0.04%)*	0	0
No exclusion criteria	**3,384 (24%)**	**8,059 (57%)**	**2,348 (17%)**	**358 (2.5%)**	**77 (0.54%)**

Comparisons between patients on LMWH therapy vs. other drugs: *p <0.05; †p <0.01; ‡p <0.001.

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonists; CrCl, creatinine clearance; PlC; platelet count.

Table III. VTE recurrences and major bleeding during initial therapy, according to prescribed drugs. Results expressed as events per 100 patient-years and 95% confidence intervals.

	LMWH	UFH	Rivaroxaban	Apixaban
VTE recurrences,				
Metastatic cancer	14.2 (11.3-17.6)	22.3 (5.68-60.8)	-	-
CrCl levels <30 mL/min	3.09 (1.63-5.38)	2.29 (0.11-11.3)	-	-
PlC <100,000/μL	12.7 (7.87-19.5)	42.4 (13.5-102.3)	-	-
Recent major bleeding	7.18 (3.33-13.6)	6.55 (0.33-32.3)	-	-
Chronic liver failure	4.95 (1.81-11.0)	22.0 (1.10-108.6)	-	-
Pregnancy	-	-	-	-
Any exclusion criteria	**8.73 (7.19-10.5)**	**10.8 (5.28-19.9)**	**-**	**-**
2 exclusion criteria	16.3 (9.29-26.7)	24.5 (1.23-120.9)	**-**	**-**
≥3 exclusion criteria	-	-	**-**	**-**
No exclusion criteria	**2.69 (2.31-3.12)**	**5.37 (3.18-8.53)***	**1.96 (1.20-3.04)**	**-**
Major bleeding,				
Metastatic cancer	13.3 (10.6-16.6)	68.0 (33.2-124.7)†	7.19 (0.36-35.5)	-
CrCl levels <30 mL/min	12.1 (8.83-16.1)	14.5 (5.89-30.3)	-	-
PlC <100,000/μL	10.6 (6.24-16.8)	58.9 (21.6-130.7)†	13.4 (0.67-66.0)	-
Recent major bleeding	19.9 (12.8-29.6)	25.8 (8.19-62.2)	-	-
Chronic liver failure	11.2 (5.90-19.5)	-	-	-
Pregnancy	2.11 (0.11-10.4)	-	-	-
Any exclusion criteria	**11.8 (10.0-13.9)**	**26.2 (16.6-39.3)†**	**4.60 (0.77-15.2)**	**-**
2 exclusion criteria	23.7 (15.1-35.6)	50.1 (8.40-165.5)	**-**	**-**
≥3 exclusion criteria	21.3 (1.06-104.8)	347.9 (17.4-1,715.6)	**-**	**-**
No exclusion criteria	**3.23 (2.81-3.70)**	**5.66 (3.41-8.88)***	**1.85 (1.11-2.90)***	**2.89 (0.14-14.2)**

Comparisons between patients on LMWH therapy vs. other drugs: *p <0.05; †p <0.01.

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; CrCl, creatinine clearance; PlC; platelet count.

Table IV. VTE recurrences and major bleeding during long-term therapy, according to prescribed drugs. Results expressed as events per 100 patient-years and 95% confidence intervals.

	LMWH	VKA	Rivaroxaban	Apixaban
VTE recurrences,				
Metastatic cancer	12.1 (9.34-15.5)	26.3 (15.0-43.1)*	4.12 (0.21-20.3)	93.4 (4.67-460.7)
CrCl levels <30 mL/min	4.07 (1.49-9.03)	2.40 (0.97-5.00)	-	-
PlC <100,000/µL	15.5 (8.39-26.3)	7.24 (2.94-15.1)	9.39 (0.47-46.3)	41.1 (2.06-202.9)
Recent major bleeding	9.26 (4.05-18.3)	4.96 (0.83-16.4)	-	15.3 (0.76-75.4)
Chronic liver failure	8.80 (2.24-23.9)	4.69 (1.19-12.8)	-	-
Pregnancy	-	-	-	-
Any exclusion criteria	**9.78 (7.76-12.2)**	**6.14 (4.19-8.71)***	**2.41 (0.40-7.96)**	**10.4 (1.75-34.4)**
2 exclusion criteria	16.8 (8.85-29.2)	10.1 (1.70-33.5)	-	31.3 (1.57-154.6)
≥3 exclusion criteria	-	-	-	-
No exclusion criteria	**4.21 (3.28-5.33)**	**2.40 (1.98-2.88)‡**	**1.87 (1.22-2.76)**	**0.65 (0.03-3.21)**
Major bleeding,				
Metastatic cancer	12.2 (9.45-15.6)	15.5 (7.57-28.5)	-	-
CrCl levels <30 mL/min	14.8 (9.08-23.0)	7.18 (4.39-11.1)*	-	-
PlC <100,000/µL	15.7 (8.52-26.7)	4.79 (1.52-11.6)*	17.7 (2.96-58.4)	-
Recent major bleeding	24.1 (14.7-37.3)	4.83 (0.81-16.0)*	6.29 (0.31-31.0)	14.2 (0.71-69.8)
Chronic liver failure	23.5 (10.9-44.7)	3.16 (0.53-10.4)†	14.1 (0.71-69.8)	-
Pregnancy	2.42 (0.12-11.9)	-	-	-
Any exclusion criteria	**12.9 (10.5-15.6)**	**7.11 (5.00-9.82)†**	**4.85 (1.54-11.7)**	**4.98 (0.25-24.6)**
2 exclusion criteria	25.4 (15.3-39.8)	4.87 (0.24-24.03)	-	-
≥3 exclusion criteria	24.8 (1.24-122.4)	-	-	-
No exclusion criteria	**4.51 (3.55-5.65)**	**2.38 (1.96-2.86)‡**	**1.61 (1.01-2.45)**	**3.30 (1.21-7.31)**

Comparisons between patients on LMWH therapy vs. other drugs: *p <0.05; †p <0.01; ‡p <0.001.

Abbreviations: LMWH, low-molecular-weight heparin; VKA, vitamin K antagonists; CrCl, creatinine clearance; PlC; platelet count.