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ORIGINAL RESEARCH

Efficacy and Safety of Rivaroxaban for Extremely Aged Patients with Venous Thromboembolism: A Retrospective, Cross-Sectional Real-World Study

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Background: Rivaroxaban, a non-vitamin K antagonist oral anticoagulant, has become widely used for the management of venous thromboembolism (VTE) in adult patients. However, few trials have explored the efficacy and safety of rivaroxaban in VTE patients over 80 years of age. This necessitates further real-world studies of rivaroxaban across elderly populations.

Methods: We performed a retrospective single center study involving extremely aged VTE sufferers treated with rivaroxaban. The sample comprised 121 patients newly initiated on rivaroxaban diagnosed between January 2018 and January 2020. Patients were followed up for no less than 2 years. The effectiveness outcome was the disappearance of thromboembolism. The safety outcome was the incidence of major bleeding events. Comorbidities and complications were recorded throughout the entire study.

Results: The efficacy outcome occurred in 114 of 121 patients (94.21%) and the safety outcome occurred in 12 of 121 patients (9.91%). Increased hemorrhages were observed in patients with infection (15.15% vs 7.80%), but no significant difference was observed due to limited sample size (P=0.3053). Patients with an age-adjusted Charlson comorbidity index score higher than 6 points exhibited higher bleeding rates (14.08% vs 4.00%; P=0.0676) and lower thrombus cure rates (88.73% vs 100%; P=0.0203).

Key conclusions: Patients with infection should be more careful of bleeding events during rivaroxaban therapy. An age-adjusted Charlson comorbidity index score higher than 6, which predicted poor survival, indicated inferior safety and efficacy of rivaroxaban.

Aim: To investigate the efficacy and safety of Rivaroxaban in an aged venous thromboembolism patient population under real-world conditions.

Keywords: rivaroxaban, anticoagulation, venous thromboembolism, retrospective trial, extremely old

Introduction

The overall incidence of venous thromboembolism (VTE), comprising deep-vein thrombosis (DVT) and pulmonary embolism, is approximately 1% per year in the elderly.[1] It is foreseeable that the risk of VTE will increase with age. Efficacious treatment of VTE relies on a balance between anticoagulation and prevention of bleeding.[2] Clinical guidelines suggest novel oral anticoagulants (NOACs) over vitamin K antagonist (VKA) and low-molecular-weight heparin (LMWH) therapy as long-term anticoagulant therapy for VTE patients without cancer.[3,4] A dominant antithrombotic guideline suggests LMWH over VKA and NOACs for VTE in patients with cancer.[4–6] Although LMWH has demonstrated effectiveness and safety in several cardiovascular diseases associated with thrombosis as treatment and prophylaxis in different groups of patients, it is inconvenient to perform subcutaneous injection every 12 hours, which can negatively affect quality of life. Incidentally, the popularity of NOACs and their ease of use have raised interest in their utility for treating patients with VTE and cancer.[7,8] Rivaroxaban, an orally active direct factor Xa

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inhibitor, is a safe and effective anticoagulant that may have the potential to provide a simple and fixed-dose regimen for managing thromboembolic disorders.[9,10] It is believed to improve medication adherence, minimize errors, and improve efficacy and safety. Zhang et al comprehensively reviewed the use of rivaroxaban in elderly VTE patients. They sum up perspectives including drug interactions, monitoring, reversal agents of rivaroxaban, and the use of small dosages of rivaroxaban in elderly patients.[11] Elderly patients are characterized by increased blood levels of FVIII, increases in other coagulation factors such as plasma fibrinogen and von Willebrand factor, vascular endothelium injury in pathogenesis, and pathophysiology.[12] Old age is regarded as a risk factor for increased bleeding when evaluating patients receiving anticoagulation treatment.[13] However, the product labels for rivaroxaban recommend no dose adjustment in the elderly population. Unfortunately, increased bleeding risk and mortality in elderly patients were observed after using rivaroxaban.[14] The risk of bleeding during anticoagulation is generally higher in the elderly for several reasons.[15,16] First, they have reduced metabolic clearance due to a high incidence of renal or hepatic impairment. Second, they have an increased prevalence of comorbidity and polypharmacy. Third, they are more likely to develop vascular or endothelial fragility compared with younger patients.[17–19] In view of these challenges, most anticoagulant clinical trials have excluded extremely aged patients. Clinical strategies for anticoagulation in extremely aged patients with VTE are unclear.[20] The well-known Einstein study, which compared the efficacy and safety of rivaroxaban with standard therapy, enrolled limited numbers of extremely aged patients.[21–24] This lack of clinical data often leads physicians to not prescribe the fixed dose of rivaroxaban as the product labels recommend. Dose adjustment of rivaroxaban for VTE patients aged over 80 is common in real-world practice. Prudent physicians expect dose adjustment in the extremely old to be associated with lower rates of major bleeding and a passable cure rate of thrombus.[25] Nevertheless, it remains to be verified whether dose reduction will obtain net clinical benefit in super elderly VTE patients. Accordingly, the purpose of this retrospective study was to evaluate the efficacy and safety of rivaroxaban for patients with VTE who are over 80 years of age.

Methods

Study Design and Population

This was a retrospective study using data from Nanjing Drum Tower Hospital. The study cohort constituted patients treated from January 2019 to January 2020. The inclusion and exclusion criteria are as follows. Patients with documented VTE on vascular color Doppler ultrasound or computed tomography angiography of the pulmonary artery, originating from Nanjing Drum Tower Hospital were included. Being younger than 80 years of age using rivaroxaban for less than 7 days or using other anticoagulants were the exclusion criteria.

Patients were followed up every 3 months for no less than 12 months. The study was conducted under real-life conditions of daily clinical practice and was in accordance with the Declaration of Helsinki. The ethics committee of Nanjing Drum Tower Hospital approved the protocol. As this study concerns retrospective research, no patient consent was needed according to Chinese law. Protection of patients' identity was guaranteed by assigning study-specific unique patient numbers as identifiers.

Data Collection

Patient information and treatment characteristics were collected from the electronic medical record system of Nanjing Drum Tower Hospital at baseline. These included clinical characteristics, medications taken and most recent laboratory data (haemoglobin, serum creatinine), eGFR (glomerular filtration rate estimated with the Cockcroft–Gault formula), and age-adjusted Charlson comorbidity index (ACCI). At each 3-month follow-up, all bleeding events, anticoagulant discontinuation, VTE disappearance, recurrent VTE, and deaths were prospectively registered.

Outcome Measures

Due to the peculiar study population and limited sample size, we set disappearance of venous thromboembolism as the principal efficacy outcome. Other efficacy outcomes were ischemic stroke, myocardial infarction, systemic embolism, thrombus in other parts, and death from any cause. The primary safety outcome was major bleeding. Other safety

outcomes were as follows. Clinically relevant non-major bleeding. Major bleeding was defined as overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more, led to transfusion of 2 or more units of red cells, occurred in a critical site, or contributed to death. Clinically relevant non-major bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with the need for medical intervention, unscheduled contact with a physician, interruption or discontinuation of the study drug, or discomfort or impairment of activities of daily living.[26]

Statistical Analysis

Baseline characteristics were analyzed in terms of means and standard deviations (SDs) for continuous variables, and in terms of counts and percentages for categorical variables. Missing data were not imputed, and patients were censored from analysis at the point of loss to follow-up. We performed contingency table analyses using chi-square and Fisher's exact tests. A two-sided p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics 24.0 and GraphPad prism 6.

Results

Patient Characteristics

Of the 1843 patients who were diagnosed with venous thromboembolism between January 1, 2018, and January 1, 2020, at Nanjing Drum Tower Hospital, 854 were treated with rivaroxaban. Of these patients, 122 were 80 years or older. After the exclusion of 1 patient (0.82%) because they had received rivaroxaban therapy less than 7 days previously, 121 patients were enrolled in the study cohort (Figure 1). The characteristics of patients are shown in Table 1. Of the enrolled patients, 107 (88.43%) received mono-dose rivaroxaban therapy, including 1.65% (2) prescribed 5mg daily, 0.83% (1) prescribed 7.5mg daily, 50.41% (61) prescribed 10mg daily, 20.66% (25) prescribed 15mg daily, and 14.88% (18) prescribed 20mg daily. In addition, 14 (11.57%) received an overloading-dose of rivaroxaban, including 1.65% (2) prescribed 15/10mg daily, 7.43% (9) prescribed 20/10mg daily, 1.65% (2) prescribed 30/20mg daily, and 0.83% (1) prescribed 30/20/10mg daily. Six patients died before the final follow up: 5 patients died of septic multiple-organ failure resulting from lung or urinary tract infection and one patient died of acute cerebral infarction. No deaths reported during the study were considered drug-related.

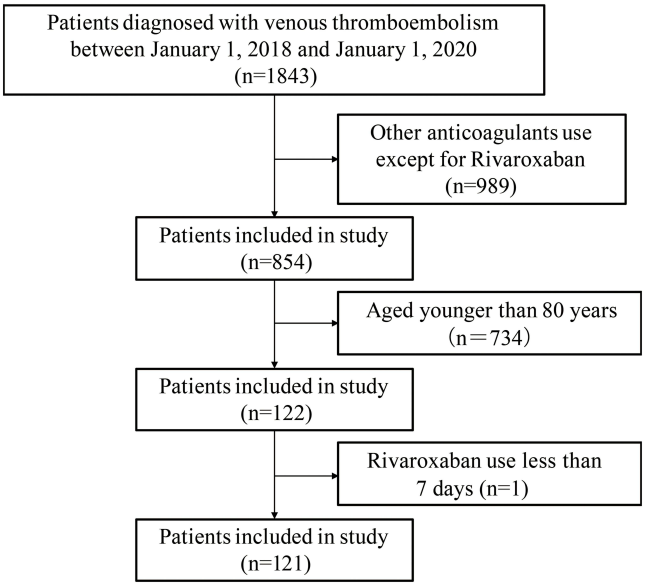

Figure 1 Flow chart.

Table 1 Baseline Characteristics

General Characteristics, M (SD)	Rivaroxaban (n=121)
Age (years)	85.0 + 3.9
Woman, % (n)	52.89 (64)
Weight (kg)	61.3 + 10.5
Body mass index (kg/m^2)	22.9 + 3.6
Charlson comorbidity index (score)	7.1 + 2.8
Serum creatinine	81.4 + 51.1
eGFR (mL/min)	56.7 + 23.6
Haemoglobin (g/dL)	118 + 21.6
Daily dose (without loading dose), % (n)	88.43 (107)
5mg, % (n)	1.65 (2)
7.5mg, % (n)	0.83 (1)
10mg, % (n)	50.41 (61)
15mg, % (n)	20.66 (25)
20mg, % (n)	14.88 (18)
Daily dose (with loading dose), % (n)	11.57 (14)
15/10mg, % (n)	1.65 (2)
20/10mg, % (n)	7.43 (9)
30/20mg, % (n)	1.65 (2)
30/20/10mg, % (n)	0.83 (1)

Notes: M (SD), mean (standard deviation); % (n), percentage (count).
Abbreviation: eGFR, glomerular filtration rate estimated using the Cockcroft–Gault formula.

Bleeding Events

We observed bleeding events in 9.68%, 12.50% and 11.76% of patients receiving rivaroxaban 10mg, 15mg or 20mg once daily, respectively (Table 2). No bleeding event was observed in patients prescribed a mono-dose regimen of 5mg daily and 7.5mg daily rivaroxaban. But no statistical difference was observed in the dose gradient groups. One bleeding event occurred in a patient prescribed a loading-dose regimen of 30/20/10mg daily. No major bleeding event was observed in the study cohort. No deaths reported during the study were considered to be caused by drug-related bleeding. The incidence of bleeding events in different dose gradients without loading is described in Figures 2A and B). The incidence

Table 2 Efficacy and Safety of Rivaroxaban Classified by Multiplex Dosage Regimen

Daily Dose	Hemorrhages, % (n)	Thrombus Disappeared, % (n)
Without loading dose (mg)	10.28 (11)	93.45 (100)
5	0 (0)	66.67 (2)
7.5	0 (0)	100 (1)
10	9.68 (6)	91.94 (57)
15	12.50 (3)	95.83 (23)
20	11.76 (2)	100 (17)
With loading dose (mg)	7.14 (1)	100 (14)
15/10	0 (0)	100 (2)
20/10	0 (0)	100 (9)
30/20/10	0 (0)	100 (1)
30/20	50 (1)	100 (2)

Note: % (n), percentage (count).

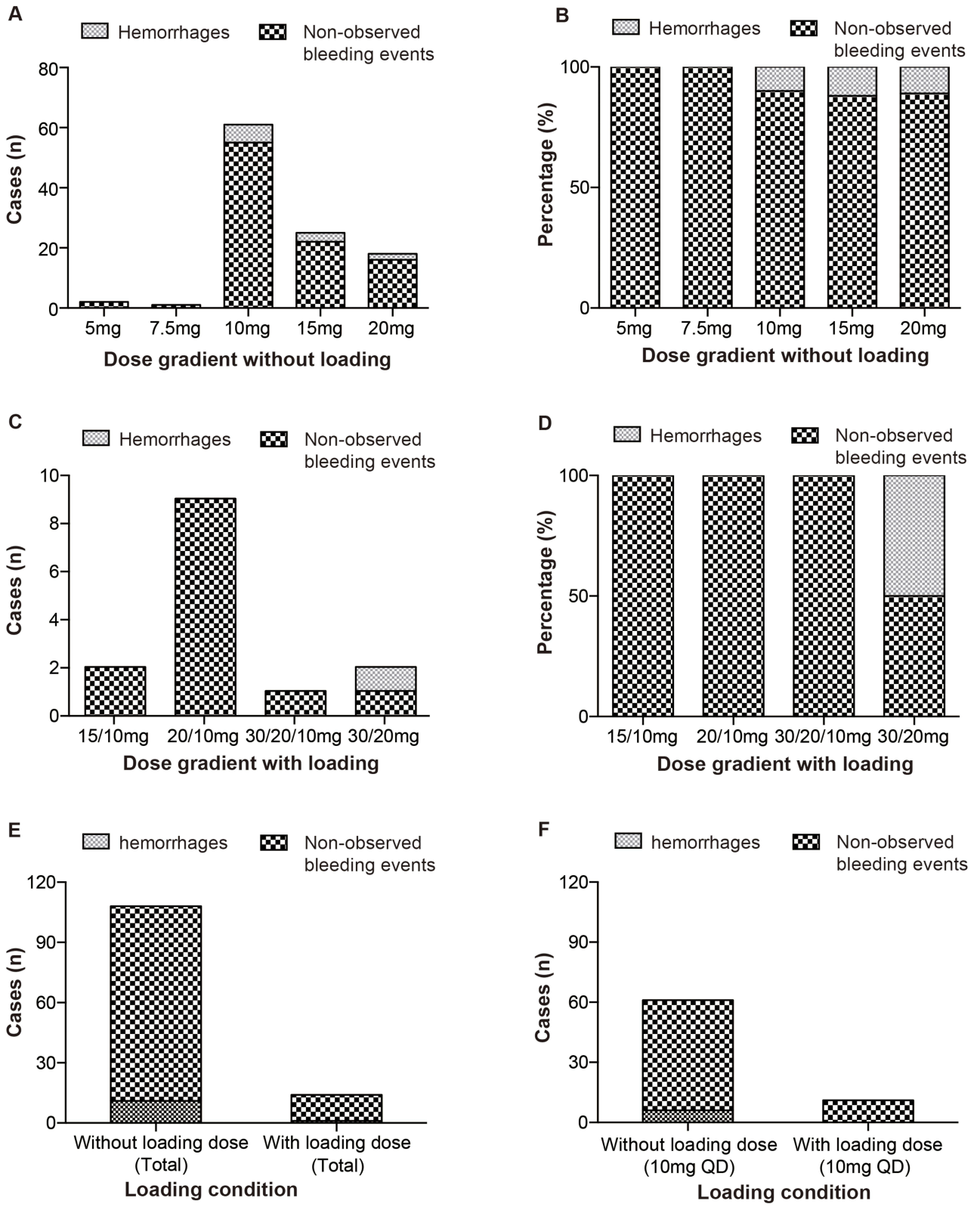

Figure 2 Pattern of rivaroxaban dose associated safety observation. (**A**) Cases of hemorrhages in different dose gradients without loading. (**B**) Percentage of hemorrhages in different dose gradients without loading. (**C**) Cases of hemorrhages in different dose gradients with loading. (**D**) Percentage of hemorrhages in different dose gradients without loading. (**E**) Cases of hemorrhages in different loading conditions. (**F**) Percentage of hemorrhages in different loading conditions.

of bleeding events in different dose gradients with loading is described in Figures 2C and D. We did not observe an increase in the risk of major bleeding in patients who received a loading dose of rivaroxaban (Figures 2E and F).

Thrombus Disappearance Rate

We observed thrombus disappearance in 66.67%, 100%, 91.94%, 95.83%, and 100% of patients receiving rivaroxaban 5mg, 7.5mg, 10mg, 15mg, 20mg once daily, respectively (Table 2). But due to the limitations of this real-world study, there were fewer people in the 5mg daily and 10mg daily groups ithan in 10mg daily, 15mg daily, 20mg daily groups; however, no statistical difference in thrombus cure rate was observed in the dose gradient groups. The minimum maintenance dose of the patients prescribed a loading dose of rivaroxaban was 10mg daily. No deaths reported during the study were considered to be caused by VTE. The incidence of thrombus disappearance without loading is described in Figures 3A and B. The incidence of thrombus disappearance with a loading dose is described in Figures 3C and D. We did not observe a significant difference in the incidence of thrombus disappearance between patients prescribed rivaroxaban with and without a loading dose (Figure 3E and F.

Influence of Complications or Comorbidities on Bleeding Events

We observed 2 bleeding events (11.76%) in patients with malignancy and 10 bleeding events (9.62%) in patients without malignancy (Figure 4A). In patients prescribed the most common dose regimen (10mg daily), 2 bleeding events (16.67%) occurred in malignant disease sufferers and 4 bleeding events (8.00%) occurred in patients without malignancy (Figure 4B). Malignant disease sufferers exhibited a higher bleeding risk but there was no significant statistical difference (P=0.7834 and P=0.3279, respectively). We observed 5 bleeding events (15.15%) in patients with infection; 7 bleeding events (7.95%) were observed in patients without infection (Figure 4C). In patients prescribed the most common dose regimen (10mg daily), 2 bleeding events (10.52%) occurred in patients with infection and 4 bleeding events (9.30%) occurred in patients without infection (Figure 4D). Patients with infection showed increased incidence of bleeding compared to patients without infection, but no significant difference was observed due to limited sample size (P=0.3053). As to patients with severe renal insufficiency (eGFR<30mL/min/1.73m^2), no bleeding event was observed (0/10). We observed 12 bleeding events (10.81%) in patients with an eGFR value higher than or equal to 30mL/min/1.73m^2, but the incidence of bleeding is valueless as a result of the inevitable enrollment bias of the two groups (Figures 4E and F).

Influence of Complications or Comorbidities on Thrombus Disappearance Rate

We observed disappearance of thrombus in 16 patients with malignancy (94.12%) and 97 patients without malignancy (93.26%). (Figure 5A). In patients prescribed the most common dose regimen (10mg daily), we observed 100% thrombus disappearance in those with malignancy (n=12) and 92.00% thrombus disappearance in those without malignancy (n=46) (Figure 5B). No decreased disappearance rate of thrombus was observed in malignant disease sufferers. We observed disappearance of thrombus in 30 patients with infection (90.91%) and 84 patients without infection (94.32%) (Figure 5C). In patients prescribed 10mg daily rivaroxaban, we observed 89.47% thrombus disappearance in those with infection (n=17) and 93.02% thrombus disappearance in those without infection (n=40) (Figure 5D). There was no statistical difference between the two groups (Figure 5D). As to patients with severe renal insufficiency (eGFR<30mL/min/1.73m^2), no thrombus persisting was observed (0/10). We observed a 93.69% disappearance of thrombus in patients with an eGFR value higher than or equal to 30mL/min/1.73m^2 (n=104), but the incidence of thrombus persisting is valueless as a result of the inevitable enrollment bias of the two groups (Figure 5E and F).

Influence of Predicted Survival

It has been reported that an ACCI score higher than or equal to 6 predicts poor survival. We observed 10 bleeding events (14.08%) in patients with an ACCI score higher than or equal to 6, and 2 bleeding events (4.00%) in patients with an ACCI score lower than 6 (Figure 6A). In patients prescribed the most common dose regimen (10mg daily), 5 bleeding events (17.24%) occurred in those with an ACCI score higher than or equal to 6, and 1 bleeding event (3.03%) occurred in patients with an ACCI score lower than 6 (Figure 6B). Patients with an ACCI score higher than or equal to 6 exhibited a higher bleeding risk, but there was no significant statistical difference because of the limited sample size (chi-square

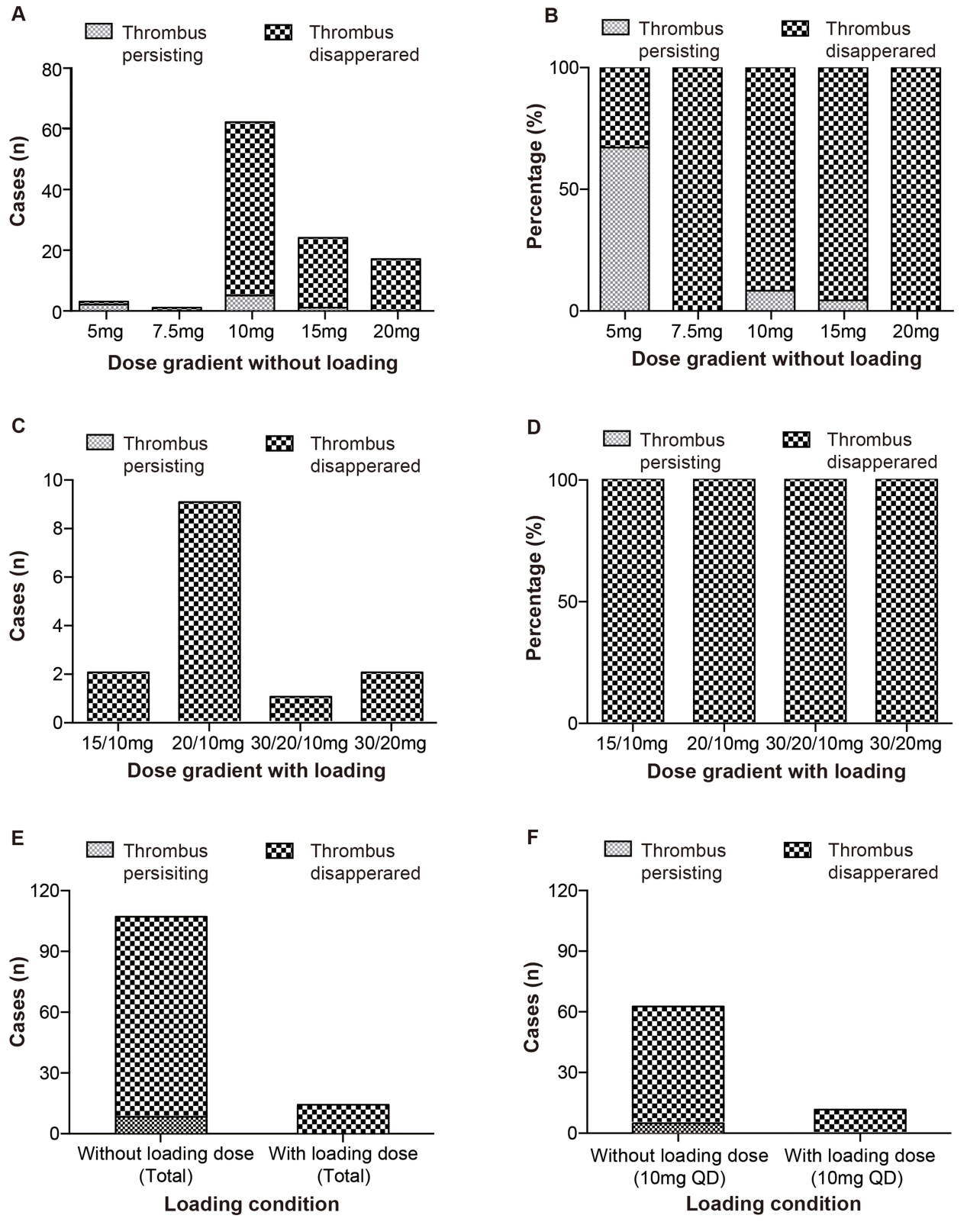

Figure 3 Pattern of rivaroxaban dose associated efficacy observation. (**A**) Cases of thrombus persisting in different dose gradients without loading. (**B**) Percentage of thrombus persisting in different dose gradients without loading. (**C**) Cases of thrombus persisting in different dose gradients with loading. (**D**) Percentage of thrombus persisting in different dose gradients with loading. (**E**) Cases of thrombus persisting in different loading conditions. (**F**) Percentage of thrombus persisting in different loading conditions.

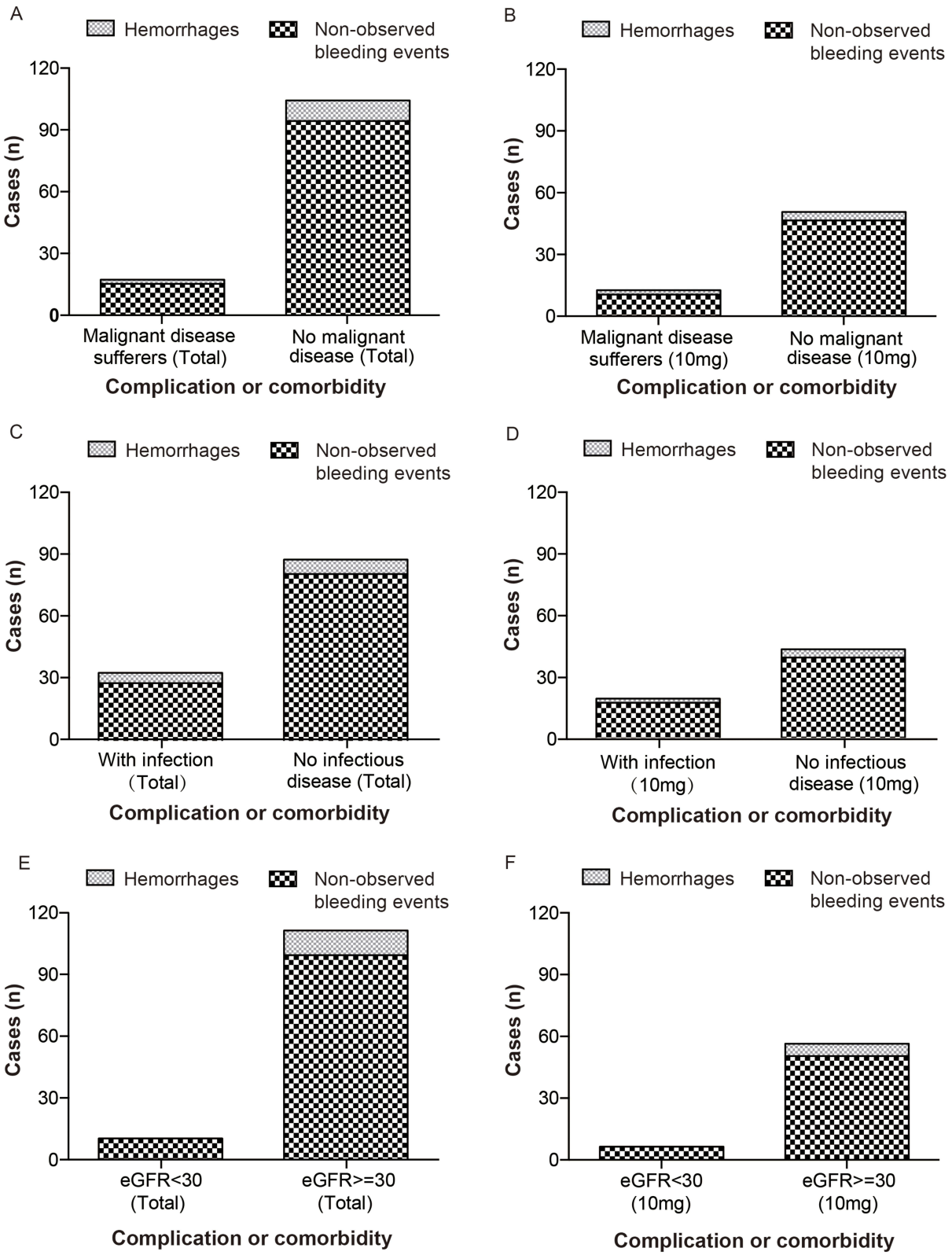

Figure 4 Pattern of complication or comorbidity associated safety observation. (**A**) Cases of hemorrhages in patients with and without malignancy. (**B**) Cases of hemorrhages in 10mg rivaroxaban recipients with and without malignancy. (**C**) Cases of hemorrhages in patients with and without infection. (**D**) Cases of hemorrhages in 10mg rivaroxaban recipients with and without infection. (**E**) Cases of hemorrhages in patients with different eGFR levels. (**F**) Cases of hemorrhages in 10mg rivaroxaban recipients with different eGFR levels. Note: eGFR = glomerular filtration rate estimated using the Cockcroft–Gault formula.

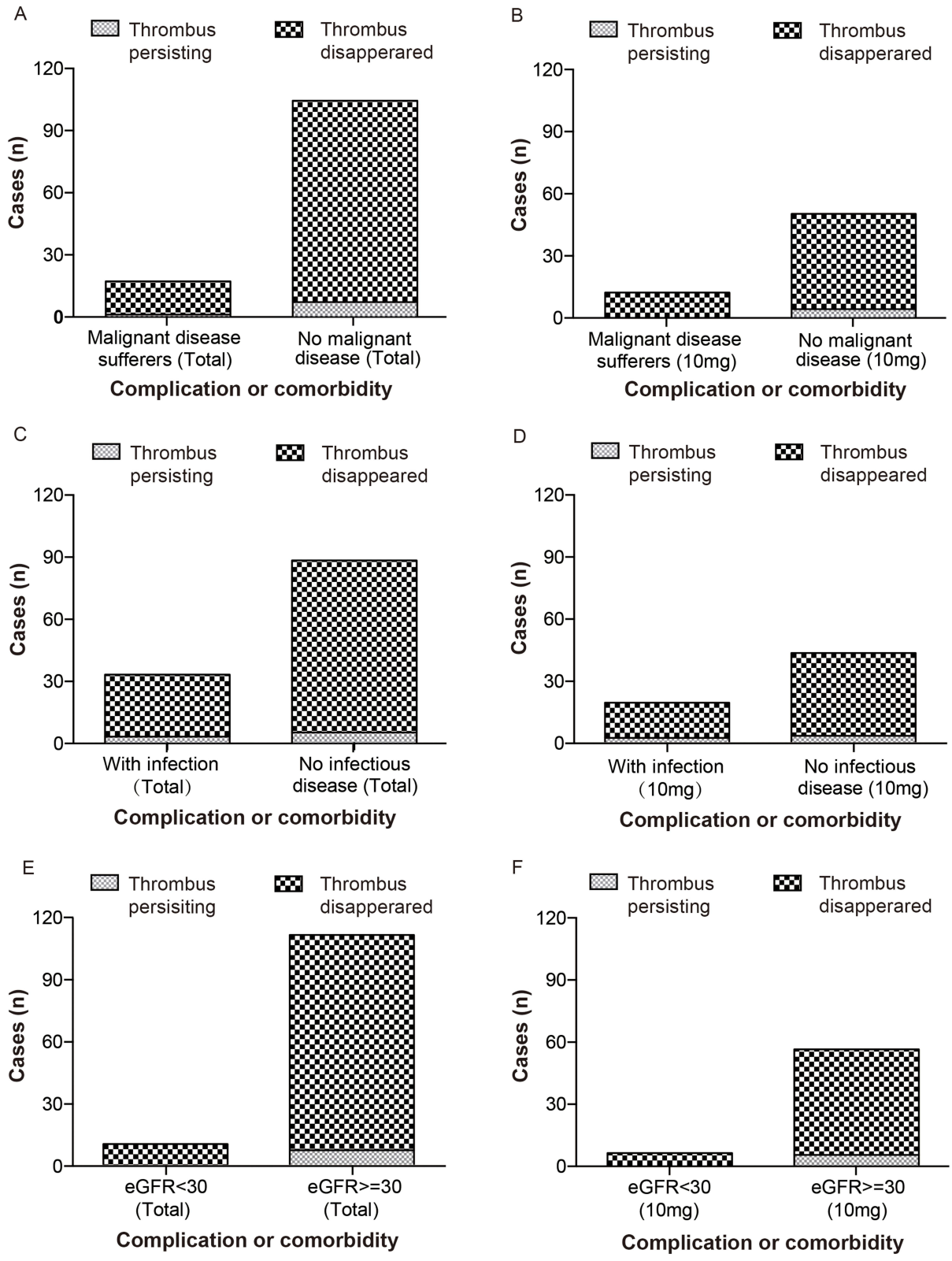

Figure 5 Pattern of complication or comorbidity associated efficacy observation. (**A**) Cases of thrombus persisting in patients with and without malignancy. (**B**) Cases of thrombus persisting in 10mg rivaroxaban recipients with and without malignancy. (**C**) Cases of thrombus persisting in patients with and without infection. (**D**) Cases of thrombus persisting in 10mg rivaroxaban recipients with and without infection. (**E**) Cases of thrombus persisting in patients with different eGFR levels. (**F**) Cases of thrombus persisting in 10mg rivaroxaban recipients with different eGFR levels. Note: eGFR = glomerular filtration rate estimated using the Cockcroft–Gault formula.

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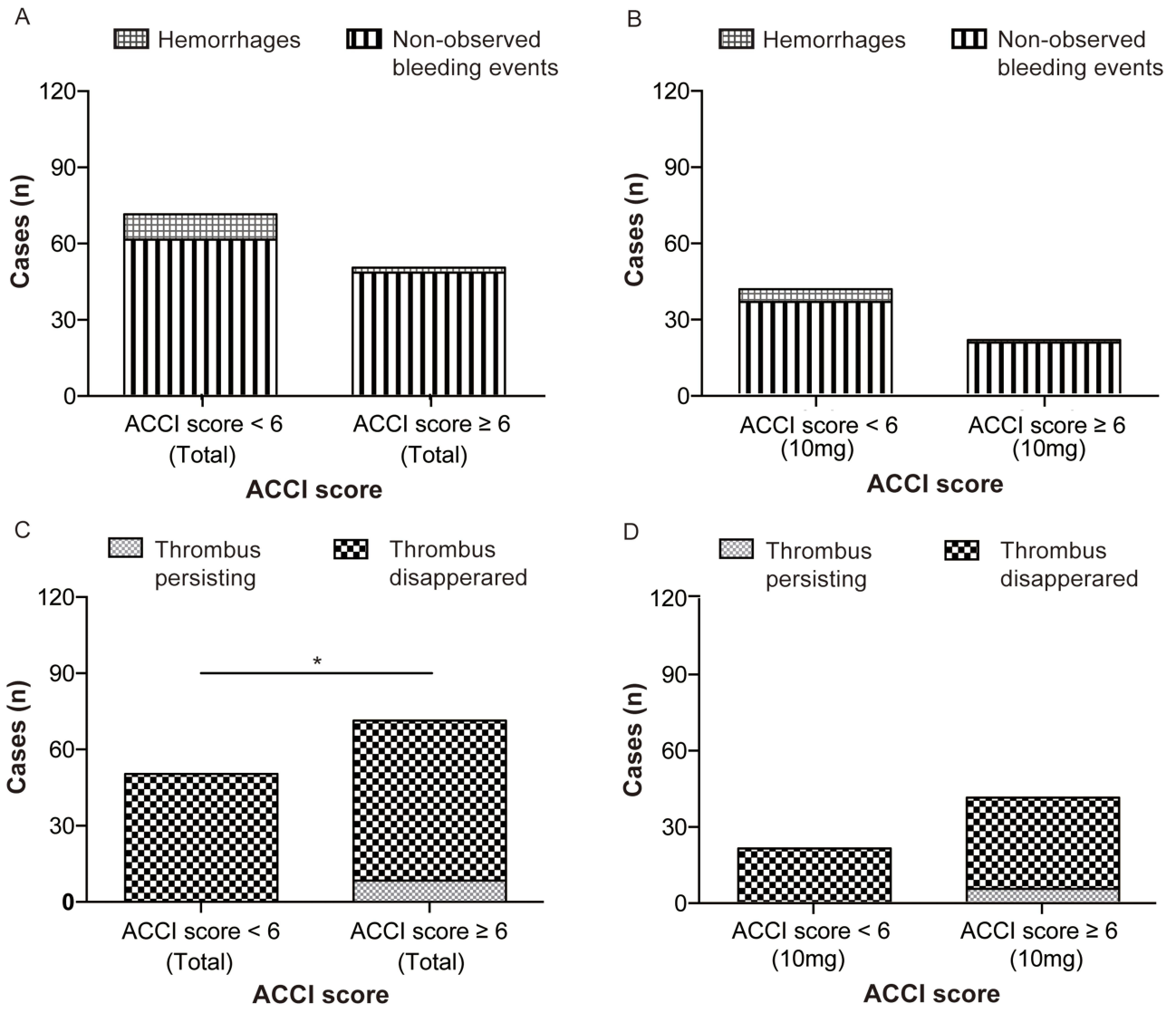

Figure 6 Efficacy and safety outcomes of patients with different ACCI scores. (**A**) Cases of hemorrhages in patients with different ACCI scores. (**B**) Cases of hemorrhages in 10mg rivaroxaban recipients with different ACCI scores. (**C**) Cases of thrombus persisting in patients with different ACCI scores. (**D**) Cases of hemorrhages in 10mg rivaroxaban recipients with different ACCI scores. Note: ACCI= age-adjusted Charlson comorbidity index. *P<0.05.

test: ^{Total}P=0.0676, ^{10mg}P=0.3488; Fisher's exact test ^{Total}P=0.1196, ^{10mg}P=0.6541). We observed 88.73% thrombus disappearance in patients with an ACCI score higher than or equal to 6 (n=63) and 100% thrombus disappearance in patients with an ACCI score lower than 6 (n=50) (Figure 6C). Patients with an ACCI score higher than or equal to 6 exhibited a higher incidence of persisting thrombus (P=0.0203). In patients prescribed 10mg daily rivaroxaban, we observed 36 thrombus disappearance events in patients with an ACCI score higher than or equal to 6 (87.80%) and 21 thrombus disappearance events in patients with an ACCI score lower than 6 (100%), but there was no significant statistical difference because of the limited sample size (chi-square test: P=0.0951; Fisher's exact test: P=0.1569) (Figure 6D).

Discussion

It is an ongoing concern that humans from the age of 70 years onwards are most likely to get VTE while those under 70 are most often enrolled in clinical trials.[20,27] The mismatch is more prominent in individuals aged 80 years or older. Few clinical trials are designed to address this imbalance. Sporadic data are available to help guide geriatricians in choosing

the appropriate anticoagulation regimens for individuals aged 80 years or older. Recent studies reported that the risk of bleeding was significantly higher in elderly patients requiring oral anticoagulant treatment.[19] The initial and maintenance doses of rivaroxaban are usually lower in elderly VTE patients, and the recommended standard rivaroxaban starting dose of 15mg twice daily for 3 weeks, followed by 20mg once daily may be too high for patients aged over 80 years.[18,28] Because of the age-related physiological changes, comorbidities, and concomitant medications, the anticoagulation in elderly patients is challenging and associated with an increased risk of adverse events.[15,17] Many clinical trials of anticoagulant therapy have excluded older patients, and it is controversial whether older patients are at higher risk for bleeding during anticoagulant therapy than are younger patients. Some researchers think that age alone is not a contraindication for full dose anti-coagulation, but few prescribers made no dose adjustment in rivaroxaban in real-world practice.[16] Theoretically, reducing the anticoagulation drug dose in elderly VTE patients will reduce bleeding risk and meanwhile reduce the thrombus cure rate, but how the dose adjustment of rivaroxaban can actually be performed remains to be explored.

This retrospective study showed that 10mg daily rivaroxaban was the most common dose regimen for treating VTE sufferers aged over 80. The incidence of bleeding events mildly increased in patients prescribed 20mg, 15mg or 10mg rivaroxaban compared with patients prescribed 7.5mg or 5mg rivaroxaban, but no statistical difference was observed. As the result of poor compliance with long-lasting drug use, as guidelines suggest, and high incidence of thrombosis in patients aged over 80, thrombus recurrence rates rise sharply in the extremely old. In this study, we did not choose symptomatic, recurrent venous thromboembolism as an effectiveness outcome assessment pattern. We set disappearance of venous thromboembolism as the principal efficacy outcome instead. We observed a decline in disappearance rate of venous thromboembolism in patients prescribed 5mg rivaroxaban. But due to the limitations of this real-world study, the number of people in the 5mg daily and 10mg daily groups was lower than that in the 10mg daily, 15mg daily, 20mg daily group; however, no statistical difference in thrombus cure rate was observed in the dose gradient groups. Larger trials are needed to explore the impact of dose reduction. A loading dose of rivaroxaban is recommended in the antithrombotic guidelines, but only about one-tenth of patients were prescribed a loading-dose of rivaroxaban in this study. We did not observe an increase in the risk of major bleeding or in the incidence of thrombus disappearance in patients who received a loading dose of rivaroxaban. But the modified recommended standard rivaroxaban regimen, which started with a loading dose of 30mg daily for one week followed by 20mg daily, exhibited numerically higher bleeding rates (50%). But due to the rare prescribing frequency of full-dose anticoagulation, only one patient was prescribed 30/20mg rivaroxaban; no statistical difference was observed between the different dose groups in our study.

As to cancer sufferers, they typically possess increased incidence of thromboembolic events and bleeding complications.[8] Lee AY et al performed a randomized trial comparing LMWH with warfarin for the treatment of VTE patients with cancer. The trial provided evidence that LMWH is more effective than VKA for long-term treatment of VTE, but no difference was observed in major bleeding or death. Nonetheless, NOACs for treatment of VTE patients with cancer have limited evidence in the corresponding period. The 10th edition of the antithrombotic guideline suggests LMWH over VKA and NOACs for VTE in patients with cancer.[4] To our knowledge, subcutaneous injection of LMWH is recommended every 12 hours, which requires professional nursing operations and causes pain. The above disadvantages of LMWH can interfere with quality of life. Incidentally, the popularity of NOACs and their ease of use have raised interest in their utility for treating patients with VTE and cancer. Recently, clinical trials have provided valuable evidence that NOACs may play a role in treating VTE in cancer sufferers. NOACs appear to be similar to LMWH in efficacy for treating VTE in patients with cancer. But in specified malignant diseases such as gastrointestinal or genitourinary malignancies, patients treated with NOACs have a greater bleeding risk than those treated with LMWH.[29] In our study, we found that malignant disease sufferers prescribed rivaroxaban exhibit higher bleeding risk, but no statistically significant difference was observed owing to the bias of enrollment. No decreased disappearance rate of thrombus was observed in malignant disease sufferers. The application of rivaroxaban in cancer sufferers deserves larger studies.

Older people are at higher risk of infection than younger people.[19] Infection as a pathological state refers to an invasion of the body by viruses, bacteria, or other microbes. It is accompanied by complex pathophysiological changes, which interfere with the coagulation mechanism.[30–32] In addition, the application of antibiotics is known to have adverse side effects on the hematopoietic system, which may be manifested as hemolysis or platelet dysfunction.[33,34] We

observed 5 bleeding events (15.15%) in patients with infection and 7 bleeding events (7.59%) in patients without infection (Figure 4C). Patients with infection showed increased incidence of bleeding compared with patients without infection, but no significant difference was observed due to the limited sample size (P=0.3053). We made a calculation of sample size for further investigation using Epitools (http://epitools.ausvet.com.au/content.php?page=home). To detect significant differences, 654 patients (α [one-side]=0.05; β=1–0.80=0.20) for both groups are required, which is far more than the sample size of this study. No significant decreased disappearance rate of thrombus was observed in VTE patients complicated with infection (90.91% vs 94.32%).

The excretion of rivaroxaban is partly performed by the kidneys. It is plausible to prescribe a discount dose of rivaroxaban in patients with renal impairment in order to reduce the risk of bleeding. Previous studies showed that renal impairment did not increase the risk of bleeding in rivaroxaban-treated patients.[28,35] However, clinicians are desirous of knowing the influence of renal insufficiency on the efficacy and safety of rivaroxaban in extremely old VTE patients in order to minimize the risk of hemorrhage while ensuring the optimal anticoagulation effect. In this study, we observed 12 bleeding events (10.81%) in patients with an eGFR value higher than or equal to 30mL/min/1.73m^2, while no bleeding event was observed in patients with severe renal insufficiency (eGFR<30mL/min/1.73m^2). No persistent thrombus was observed (0/10) in patients with severe renal insufficiency (eGFR<30mL/min/1.73m^2). We observed 93.69% disappearance of thrombus in patients with an eGFR value higher than or equal to 30mL/min/1.73m^2 (n=111). The findings in our study are unsatisfactory as a result of the inevitable enrollment bias of the two groups.

In this retrospective study, VTE patients with malignant disease and patients with severe renal insufficiency (eGFR<30mL/min/1.73m^2) both occupied a small proportion of the total enrollment. The proportion of patients with infection disease is barely than one-third. The enrollment bias made statistical analysis difficult. To further explore the influence of complications or comorbidities in extremely old VTE patients, we adopted the ACCI score to reveal their intricacies. In 1994, Charlson et al established the ACCI scoring system to predict the incidence of complications during the perioperative period.[36] In the last few years, investigators have determined the predictive value of the ACCI on the long-term prognosis of patients with malignant tumors (such as ovarian cancer, prostate cancer, pancreatic cancer, gastric cancer, colorectal cancer, hilar cholangiocarcinoma and so on).[37–43] Recently, ACCI has also been regarded as a haemorrhagic and thrombotic scoring system.[26] However, the predictive value of the ACCI score on the efficacy and safety of rivaroxaban in patients with VTE has not been reported. Patients with an ACCI score higher than or equal to 6 exhibited a higher bleeding risk (P=0.1196) and lower thrombus cure rate (P=0.0203); however, the P-value was greater than 0.05 (0.0583) for bleeding risk. Larger trials are needed to verify the above conclusions.

What makes our study unique is that it summarizes real-world practice experience in the oldest old. The novelty of our study is that we use ACCI score, which predicts survival to some extent, to describe comorbid conditions in a very old population. The study shows for the first time that an ACCI score higher than 6, which predicted poor survival, indicated inferior safety and efficacy of rivaroxaban. Our study has some limitations. First, we chose disappearance of venous thromboembolism instead of symptomatic, recurrent venous thromboembolism as the effectiveness endpoint, which overstated the anticoagulation efficacy of rivaroxaban. Second, the follow-up time was not long enough, and only a small amount of data on survival was available, which reduces the strength of the study. Lastly, this study was conducted in a single center with an insufficient sample size, which limits the convincingness of the results. This retrospective study showed that 10mg daily rivaroxaban was the most common dose regimen in treating VTE sufferers aged over 80. Daily dosage of rivaroxaban less than or equal to 20mg exhibits tolerable safety. Daily dosage of rivaroxaban more than or equal to 7.5mg exhibits decent efficacy. In conclusion, patients with infection should be more careful about bleeding events during rivaroxaban therapy. An age-adjusted Charlson comorbidity index score higher than 6, which predicted poor survival, indicated the inferior safety and efficacy of rivaroxaban. To adjust rivaroxaban dosage individually, it is recommended to take into account ACCI score and infection status in clinical practice.

Conclusion

Our study summarized real-world practice experience in the oldest old. The novelty of our study is that we used the ACCI score, which predicts survival to some extent, to describe comorbid conditions in a very old population. Patients

with infection showed increased incidence of bleeding compared with patients without infection, but no significant difference was observed as a result of the limited sample size. Prescribers should take ACCI score and infection status into consideration when choosing individual dosage of rivaroxaban for elderly patients with VTE.

Data Sharing Statement

The raw data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study. Data are, however, available from the authors upon reasonable request and with permission of the corresponding author (Wangshu Dai).

Ethics Approval

All methods of this study were carried out in accordance with the guidelines of the Declaration of Helsinki and were approved by the Ethics Committee of Nanjing Drum Tower Hospital (2021-195-02).

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Disclosure

The authors declare that they have no competing interests in this work.

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