Dissertation

Treatment for venous thromboembolism with direct oral anticoagulants in patients with overweight and obesity – Does size matter?

submitted by

Dr. med. univ. Katharina KURZMANN-GÜTL

for the Academic Degree

Doctor of Medical Science

(Dr. scient. med.)

at the

Medical University of Graz

Department of Internal Medicine, Division of Angiology

Supervised by

Assoz. Prof. Priv. Doz. Dr. Thomas Gary

2026

Declaration of Academic Integrity

I hereby confirm that the present dissertation thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism. Furthermore, I hereby declare that if artificial intelligence tools were used for the generation and/or correction of certain text passages in the creation of this work, such employment was conducted in compliance with ethical principles, academic integrity, and the regulations of my university. Additionally, it was ensured that this usage was transparently disclosed and appropriately attributed.

Graz, 30. April 2026 Katharina Kurzmann-Gütl, m.p.

Disclosures

Parts of this doctoral thesis have been published in:

Kurzmann-Guetl K,[1] Leitner DR,[2] Gary T,[1] Avian A,[3] Beck A,[2] Rabensteiner J,[4] Prueller F,[4] Raggam RB,[1] Brodmann M,[1] Toplak H.[2] The impact of body composition variability on coagulation monitoring in patients on direct oral factor Xa inhibitors for treatment of venous thromboembolism. Front. Cardiovasc. Med. 13:1773664.
Published on March 13 2026 (open access).

Authors' affiliations:
[1] Division of Angiology, Department of Internal Medicine, Medical University of Graz, Austria
[2] Lipid Clinic, Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, Austria
[3] Medical Institute of Medical Informatics, Statistics and Documentation, Medical University of Graz, Austria
[4] Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Austria

All contributing authors have explicitly provided their written consent for the use of these data in this thesis.

To improve clarity and readability, several figures and tables in the Introduction section of this thesis were developed based on existing publications. All such materials were created by the author of this dissertation. Where necessary, permission to reproduce content was obtained from the respective copyright holders.

For partial linguistic refinement of text passages, an AI based tool was used (ChatGPT-5.4 Thinking, OpenAI, chatgpt.com).

Acknowledgements

I would like to express my sincere gratitude to Prof. Dr. Marianne Brodmann and to my primary supervisor, Assoz. Prof. Priv. Doz. Dr. Thomas Gary, for their outstanding professional and personal support throughout the entire project. Their continuous guidance, motivation and valuable supervision have been essential to the successful completion of this work. I also thank my co-supervisors, Priv. Doz. Priv. Doz. Dr. Reinhard B. Raggam, Prof. Dr. Hermann Toplak, and Priv. Doz. DDr. Jasmin Rabensteiner, for their valuable contributions.

I would also like to express my special thanks to my family and friends for their steady support during the implementation of this project and the writing of this dissertation. Their encouragement during both difficult and successful times has been a constant source of motivation and has helped me stay committed to my goals. I am especially grateful to my husband Christof, as well as Anna and Mathilda, for their patience, understanding, and continuous support.

The doctoral student Katharina Kurzmann-Gütl received funding from the Medical University of Graz through the Doctoral School “Lifestyle-Related Diseases”.

Table of Contents

Abbreviations

ACC ..... American College of Cardiology
ACR ..... American College of Rheumatology
AF ..... Atrial fibrillation
AHA ..... American Heart Association
APC ..... Activated protein C
APS ..... Antiphospholipid syndrome
aPTT ..... Activated partial thromboplastin time
AT ..... Antithrombin
AUC ..... Area under the curve
AWMF ..... Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
β2GPI ..... Beta2-glycoprotein I
BIA ..... Bioimpedance analysis
BMI ..... Body mass index
BP ..... Blood pressure
BNP ..... B-type natriuretic peptide
CAT ..... Cancer-associated thrombosis
CCDS ..... Colour-coded duplex sonography
CI ..... Confidence interval
CL ..... Cardiolipin
CRNMB ..... Clinically relevant non-major bleeding
CT ..... Computed tomography
CTED ..... Chronic thromboembolic disease
CTEPH ..... Chronic thromboembolic pulmonary hypertension
CTPA ..... Computed tomography pulmonary angiography
CVT ..... Cerebral venous thrombosis
DOAC ..... Direct oral anticoagulant
dTT ..... Diluted thrombin time
ds-CS ..... Duplex-supported compression sonography
DVT ..... Deep vein thrombosis
DXA ..... Dual-energy X-ray absorptiometry
ECG ..... Electrocardiogram
ECT ..... Ecarin clotting time
ESC ..... European Society of Cardiology
ESVM ..... European Society of Vascular Medicine
EULAR ..... European Alliance of Associations for Rheumatology
F ..... Factor
FM ..... Fast mass
FFM ..... Fat-free mass
FVL ..... Factor V Leiden
GFR ..... Glomerular filtration rate
GSV ..... Grand saphenous vein
HAM ..... High-affinity material
HIT ..... Heparin-induced thrombocytopenia
HIV ..... Human immunodeficiency virus
ICU ..... Intensive care unit
INR ..... International normalized ratio

ICSH ..... International Council for Standardization in Haematology
ICD ..... International Statistical Classification of Diseases and Related Health Problems
IQR ..... Interquartile range
ISTH ..... International Society on Thrombosis and Hemostasis
ITAC ..... International Initiative on Thrombosis and Cancer
IVC ..... Inferior vena cava
LMWH ..... Low-molecular weight heparin
LA ..... Lupus anticoagulant
LV ..... Left ventricular
MRA ..... Magnetic resonance angiography
MRT ..... Magnetic resonance tomography
MTHFR ..... Methylenetetrahydrofolate reductase
NNT ..... Number needed to treat
NSAID ..... Nonsteroidal anti-inflammatory drug
NT-pro(BNP) ..... N-terminal-pro(BNP)
od ..... Once daily
OR ..... Odds ratio
PAD ..... Peripheral arterial disease
PAP ..... Pulmonary artery pressure
PCC ..... Prothrombin complex concentrate
PD ..... Pharmacodynamic
PE ..... Pulmonary embolism
PERC ..... Pulmonary Embolism Rule-Out Criteria
PERT ..... Pulmonary Embolism Response Team
P-gp ..... P-glycoprotein
PK ..... Pharmacokinetic
PNH ..... Paroxysmal nocturnal haemoglobinuria
POCUS ..... Point-of-care ultrasound
PT ..... Prothrombin time
PTS ..... Post-thrombotic syndrome
PVR ..... Pulmonary vascular resistance
RCT ..... Randomised controlled trial
RNA ..... Ribonucleic acid
RR ..... Relative risk
rt-PA ..... Recombinant tissue factor plasminogen activator
RV ..... Right ventricular
SPECT ..... Single-photon emission computed-tomography
SSC ..... Scientific and Standardization Committee
TAPSE ..... Tricuspid annular plane systolic excursion
td ..... Twice daily
TTE ..... Transthoracic echocardiography
UFH ..... Unfractionated heparin
VKA ..... Vitamin K antagonist
VTE ..... Venous thromboembolism
V/Q ..... Ventilation/perfusion
WHO ..... World Health Organization
WHR ..... Waist to hip ratio

Tables

Figures

Abstract

Background: Venous thromboembolism (VTE) is a frequent condition, particularly in patients with obesity, as excess body weight itself represents a significant risk factor. Direct oral anticoagulants (DOACs) are the preferred treatment, but existing data for their use in obese populations primarily relied on body weight or body mass index (BMI), without accounting for body composition.

Objectives: The BIARIVA prospective, single-center, cross-sectional pilot study investigated whether body composition affects coagulation monitoring parameters in VTE patients receiving oral factor (F.) Xa inhibitors rivaroxaban or edoxaban across a wide range of BMI categories.

Methods: Patients were assigned to various weight categories based on their BMI: group I = BMI 18–25 kg/m^2, group II = BMI 30–35 kg/m^2, group III = BMI >35 kg/m^2. Body composition comprising fat mass (FM) and fat-free mass (FFM) was determined by two different bioimpedance analysis (BIA) systems. Coagulation monitoring parameters evaluated were anti-F.Xa activity levels and plasma concentration levels at trough, at peak and the absolute anticoagulant increase. The primary endpoint was the association between body composition and coagulation measurements, assessed by correlation analysis.

Results: Thirty-six patients on rivaroxaban treatment and 35 patients on edoxaban treatment were finally analysed. The main finding in the BIARIVA study was a significant negative correlation observed in the edoxaban group for the absolute FFM with peak plasma concentration levels (BIA method 1: r_s = -0.439, p = 0.008; BIA method 2: r_s = -0.431, p = 0.010) and with the absolute increase in plasma concentration levels from trough to peak (BIA method 1 and 2: r_s = -0.446, p = 0.007). No significant correlations of body composition measures with coagulation parameters were found in the rivaroxaban group.

Conclusion: The BIARIVA study indicates that body composition may affect specific coagulation measurements in patients on anticoagulant treatment with edoxaban. However, further research is needed to clarify the role of body composition in this context and to assess potential clinical implications.

Kurzfassung

Hintergrund: Venöse Thromboembolien (VTE) sind eine häufige Erkrankung, insbesondere bei Patient*innen mit Adipositas, da Übergewicht selbst einen bedeutsamen Risikofaktor darstellt. Direkte orale Antikoagulanzien (DOACs) sind die bevorzugte Therapie, jedoch basieren verfügbare Daten zur Anwendung bei adipösen Patient*innen auf Körpergewicht oder Body-Mass-Index (BMI), ohne die Körperzusammensetzung zu berücksichtigen.

Ziele: Die prospektive, monozentrische, Pilot-Querschnittsstudie BIARIVA untersuchte, inwiefern die Körperzusammensetzung die Gerinnungsparameter bei VTE-Patient*innen mit einem breiten BMI-Spektrum unter einer Antikoagulationstherapie mit den oralen Faktor-Xa-Inhibitoren Rivaroxaban oder Edoxaban beeinflusst.

Methoden: Geeignete Patient*innen wurden anhand des BMI in verschiedene Kategorien eingeteilt: Gruppe I = BMI 18–25 kg/m², Gruppe II = BMI 30–35 kg/m², Gruppe III = BMI >35 kg/m². Die Körperzusammensetzung, bestehend aus Fettmasse (FM) und fettfreier Masse (FFM), wurde mit zwei verschiedenen Bioimpedanzanalyse (BIA)-Systemen bestimmt. Die erhobenen Gerinnungsparameter umfassten die Anti-Faktor-Xa-Aktivität und die Plasmakonzentrationen, jeweils zum Tal- und Spitzenspiegel sowie die absolute Zunahme der Antikoagulationsaktivität. Als primärer Endpunkt wurde der Zusammenhang zwischen Körperzusammensetzung und Gerinnungsparametern definiert und mittels Korrelationsanalyse analysiert.

Ergebnisse: Für die finale Analyse wurden 36 Patient*innen in der Rivaroxaban-Gruppe und 35 Patient*innen in der Edoxaban-Gruppe berücksichtigt. Die zentrale Erkenntnis in der BIARIVA-Studie war eine signifikante negative Korrelation in der Edoxaban-Gruppe zwischen der absoluten FFM und den Spitzen-Plasmakonzentrationen (BIA-Methode 1: r_s = -0,439, p = 0,008; BIA-Methode 2: r_s = -0,431, p = 0,010) und der absoluten Zunahme der Plasmakonzentration vom Tal- zum Spitzenspiegel (BIA-Methode 1 und 2: r_s = -0,446, p = 0,007). In der Rivaroxaban-Gruppe wurden keine signifikanten Korrelationen zwischen Körperzusammensetzung und Gerinnungsparametern gefunden.

Schlussfolgerung: Die BIARIVA-Studie legt nahe, dass die Körperzusammensetzung spezifische Gerinnungsparameter bei Patient*innen unter Antikoagulation mit Edoxaban beeinflussen könnte. Zur definitiven Klärung der Rolle der Körperzusammensetzung in diesem Kontext und potenzieller klinischer Konsequenzen sind weitere Studien erforderlich.

1 Introduction

1.1 Venous thromboembolism (VTE)

Venous thromboembolism (VTE) comprises the clinical manifestations of deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] PE frequently results from venous blood clots originating from the deep venous vascular bed and migrating to the lungs as emboli.[2] In clinical routine, DVT appears twice as common as PE, whether or not DVT is present in conjunction with PE.[3] In general, VTE constitutes the third most prevalent cardiovascular entity.[2,4] The entire spectrum of thromboembolic conditions – including myocardial infarction, ischaemic stroke and VTE – is the leading cause of death worldwide and is estimated to account for one in four deaths.[2] Time trend analyses from European, Australian, Asian and North American populations report an increase in annual incidence rates over the past decades, but a decrease in case fatality rates due to the establishment of more effective therapies and interventions as well as improved adherence to clinical guidelines.[1,5-15]

1.1.1 Epidemiology

The incidence of VTE is up to 269/100,000 as found in a Danish population.[16] Annual incidence estimates for VTE are reported highest in European populations and are substantially lower in Asian populations.[16,17] For PE, incidence estimates are reported lowest in Asian populations by 39/100,000 and higher in the United States by 115/100,000.[18,19] For DVT, incidence estimations range from 53/100,000 in an Asian population to 162/100,000 in a Swedish population.[20,21] Lifetime prevalence in an adult German population for DVT is 3–5%.[22]

1.1.2 Risk factors

The pathogenesis of VTE is multifactorial and results from the interaction between patient-specific risk factors and setting-related risk factors. Furthermore, predisposing risk factors may be either permanent or transient, with the majority of VTE events being associated with transient risk factors.[23] Of note, almost one third of patients experience VTE of unknown cause without any identifiable risk factors.[22] Patient-related risk factors encompasses a range of conditions, comprising previous VTE events, a family history of VTE, thrombophilia, increased age, overweight and obesity, active cancer, pregnancy, hormonal contraception or hormone replacement therapies, and autoimmune disease, among others. In contrast, the major setting-related risk factors include surgery and/or trauma with immobilisation, hospitalisation for an

acute medical illness, systemic infection, central venous lines, and long-distance travels. A distinction into strong risk factors (Odds Ratio [OR] >10), moderate risk factors (OR 2–9) and weak risk factors (OR <2) is recommended.[1] After an initial VTE event, the risk of recurrence remains elevated throughout life compared with individuals without prior VTE.[24]

A triad describing three categories of factors contributing to thrombogenesis was first published in the late 19th century by Rudolf Virchow, comprising abnormalities of the blood vessel wall (endothelial dysfunction and/or injury), abnormalities of blood constituents (hypercoagulability), and abnormalities of blood flow (haemodynamic changes).[25] Typical risk factors for VTE are attributable to those Virchow's categories.

1.1.2.1 Age

VTE is known to increase with age, with the highest incidence observed in patient populations older than 80 years (1,134/100,000).[19] The median age at the first event of VTE is 60 years, and nearly 60% of all VTE events occur in patients older than 60 years.[26]

1.1.2.2 Gender

Regarding sex, women develop VTE more frequently in premenopausal ages, but men have higher incidence between 60 and 80 years. In populations over 80 years of age, women exhibit a higher incidence of VTE than men, largely due to their longer life expectancy.[27]

1.1.2.3 Obesity

Obesity is a well-established and independent risk factor for VTE, with obese individuals having a significantly higher risk of developing VTE compared with those of normal weight.[28] The body mass index (BMI) is a widely used method for the classification of overweight and obesity.[29]

1.1.2.4 Hormone use

Intake of oestrogen-containing oral contraception, hormone replacement therapy and in-vitro fertilisation are typical risk factors for VTE. In women of reproductive age, the use of oestrogen-based oral contraceptives represents the most frequent risk factor for VTE. Combined oral contraceptives containing oestrogen and progestogen are associated with up to a six-fold increase in VTE risk compared with baseline. Notably, third-generation combined formulations confer a higher risk than second-generation contraceptives.[30-34]

1.1.2.5 Pregnancy

Acute PE still remains one of the leading causes of maternal death in high-income countries around the world.[35,36] During pregnancy, the risk for VTE rises continuously and reaches its peak in the post-partum period.[37] Additional risk factors comprising in-vitro fertilisation, prior VTE, obesity, medical illness as well as obstetric specifications and complications (multiple pregnancy, hyperemesis gravidarum, maternal age >35 years, prolonged uterine contractions, stillbirth, pre-eclampsia, post-partum bleeding, caesarian section) further increase the VTE risk in pregnant women.[38-40]

1.1.2.6 Cancer-associated thrombosis (CAT)

CAT presents one of the most frequent complications in patients with active cancer disease. Approximately 20% of all VTE events are associated with cancer, and cancer patients are associated with a lifetime risk for VTE up to 30% depending on type of cancer and type of cancer therapies. [41-43] In patients with an event of VTE, the incidence of newly diagnosed cancer is up to six-fold higher as compared to sex- and age-matched controls.[44] The highest risk of being diagnosed with cancer occurs within the first few months following acute unprovoked VTE in patients older than 50 years.[45,46] The one-year incidence of cancer is approximately 1% in association with a provoked VTE, but 5% with unprovoked VTE. Patients with pancreatic, lung, brain, or gastric cancer, as well as those with haematological malignancies – particularly in the presence of metastatic disease – are at highest risk of CAT.[47,48] Of note, extensive cancer screening allows cancer to be diagnosed earlier, but evidence for screening to reduce cancer-related morbidity and mortality is missing.[49]

1.1.2.7 Thrombophilia

Thrombophilia is either inherited – including Factor V Leiden (FVL) mutation, prothrombin G20210A mutation, and deficiencies of antithrombin (AT), protein C or protein S – or acquired, such as antiphospholipid syndrome (APS). Inherited thrombophilia is found in almost one third of VTE patients.[50] The prevalence is highest in the general population for heterozygous FVL and prothrombin G20210A mutations, but the associated thrombotic risk is relatively mild. Some forms of thrombophilia – such as deficiencies in protein C, protein S, or AT – are classified as severe due to their higher associated risk of VTE, but they are relatively rare in the general population. Clinical characteristics suggestive of inherited thrombophilia comprise VTE at younger age (<50 years) and associated with weak risk factors, pronounced family history for VTE (affection of first-degrees family members at young age), recurrent VTE

(mostly at young age), and VTE at unusual sites (e.g. splanchnic vein thrombosis, cerebral vein thrombosis).[51]

1.1.3 Clinical aspects and presentation of deep vein thrombosis (DVT)

DVT is predominantly located in lower extremity veins including pelvic, femoral, popliteal or distal veins in the calf. Typical symptoms comprise pain, swelling, tension, prominent superficial veins and cyanosis. DVT in the lower extremity veins can either originate in distal veins and extend proximally, referred to as ascending thrombosis, or arise in the proximal veins and extend distally, referred to as descending thrombosis. Events of descending thrombosis are rare as compared with ascending thrombosis and are usually associated with vein compression of extravascular cause or anatomic variations (e.g. May-Thurner-syndrome or constitutional inferior vena cava [IVC] aberration). Due to an extensive limitation in venous return flow in the proximal deep venous bed, patients suffering from descending thrombosis often present with severe clinical symptoms from venous congestion.

In later stages of the disease, recanalisation of affected veins may be either partial or complete. In case of persisting impairment of the venous return, patients may experience post-thrombotic syndrome (PTS).[22] PE is the most serious complication in the acute phase of DVT, but can also occur in association with thrombosis of superficial or muscle veins. Of note, the risk of PE is more pronounced in patients with clot formation in the proximal deep venous bed as compared with affection of distal deep veins in the calf only.[22]

Clots can also develop in the veins of the upper extremities, representing the second most common manifestation of DVT, but accounting only for 5–7% of cases. [52-54] Anatomic variants including neurovascular compression syndromes and muscle overstrain may contribute to the formation of DVT at this site. Furthermore, upper extremity DVT typically occurs in the presence of significant risk factors, such as central venous catheters, active cancer, trauma, or surgery, and most commonly affects the subclavian vein.[22] The risk for PE in association with upper extremity DVT is reported up to 14%.[52,54,55]

Further manifestations include thrombosis in cerebral, sinus, and visceral veins. Cerebral and sinus vein thrombosis are rare, with a reported incidence of 1.3/100,000. Of note, 75% of thrombotic events in cerebral and sinus veins are found in females. Clinical symptoms caused by either the increase in intracranial pressure and oedema or infarction are often unspecific, but may comprise headache, seizure, emesis, papilloedema, impaired consciousness, dysarthria and

aphasia.[56-58] Visceral vein thrombosis encompasses thrombosis in portal, mesenteric or splenic veins, but also Budd-Chiari-Syndrome. With an incidence of up to 3/100,000, portal vein thrombosis is the most frequent manifestation of visceral vein thrombosis.[59] The risk for portal vein thrombosis is highest in advanced liver disease, with a cumulative incidence of nearly 40%. The clinical presentation mainly depends on the extent and location of the thrombotic event, ranging from symptoms associated with intestinal infarction to those of acute liver failure. Of note, up to 25% of thrombotic events in visceral veins are even asymptomatic and detected incidentally.[60]

1.1.4 Clinical aspects and presentation of pulmonary embolism (PE)

Symptoms of acute PE are often non-specific and comprise dyspnoea, chest pain, syncope, or haemoptysis.[61-63] Chest pain is usually caused by pleural irritation due to pulmonary infarction with distal emboli, but may sometimes have a character of angina in central PE due to right ventricular (RV) ischaemic condition.[1,64] Nevertheless, also asymptomatic PE discovered by incidence during diagnostic workup for another disease might appear. Haemodynamic instability from PE alone is relatively rare, but if present, the central pulmonary arteries are typically involved. The European Society of Cardiology (ESC) defines haemodynamic instability in the context of PE by cardiac arrest, or obstructive shock, or persistent hypotension (**Figure 1)**. The failure of RV function due to pressure overload is assumed the primary cause leading to death in association with severe PE. Occlusion of at least 30% of the entire pulmonary artery bed by emboli is required to increase pulmonary artery pressure (PAP).[1] Mechanical obstruction of pulmonary arteries in combination with vasoconstriction in the affected lung area as mediated by release of thromboxane A2 and serotonine cause a rise in pulmonary vascular resistance (PVR).[65,66] This sudden increase in PVR induces RV dilatation and, thus, alters the contractility of the RV myocardium. Compensatory mechanisms – including systemic vasoconstriction, inotropic and chronotropic stimulation by neurohumoral activation, and prolonged RV contraction time – result in an increasing PAP, but also improved pulmonary vascular bed perfusion and a temporary stabilisation of systemic blood pressure (BP).[1] An electrocardiogram (ECG) showing a right bundle branch block is a common finding in severe PE, which mirrors exacerbated ventricular desynchronisation due to prolonged RV contraction, and, thus, leftward bowing of the intraventricular septum. As a consequence, left ventricular (LV) filling is narrowed and leads to a reduction in cardiac output, systemic hypotension and haemodynamic instability.[67,68]

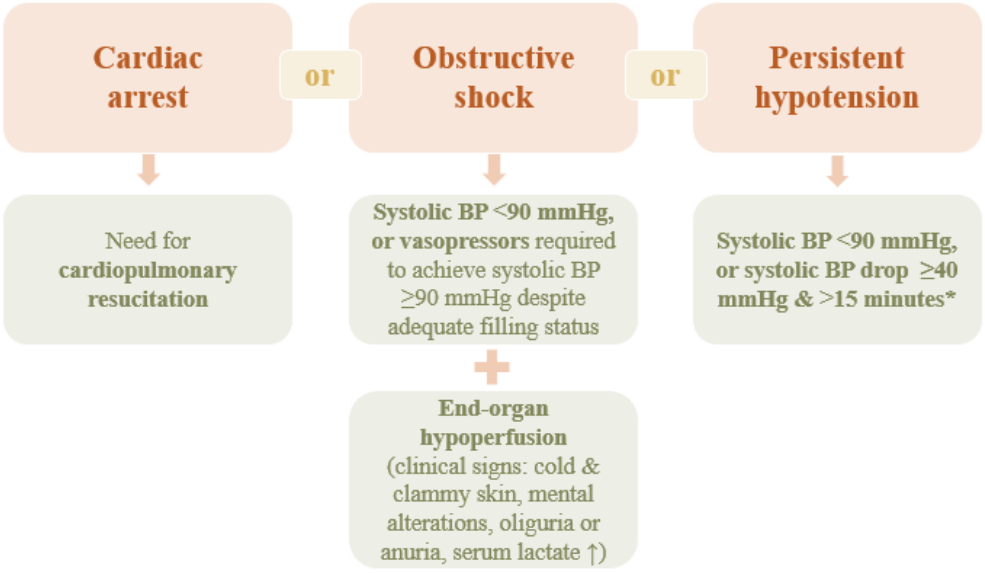

Figure 1. Haemodynamic criteria for patients with suspected PE
(Figure created by Katharina Kurzmann-Gütl, based on recommendations from the ESC guideline for the diagnosis and management of acute pulmonary embolism, published by Konstantinides et al.[1], reproduced with permission from the publisher)
BP = blood pressure; ESC = European Society of Cardiology; PE = pulmonary embolism
*persistent hypotension is not caused by new-onset arrhythmia, hypovolaemia, or sepsis

Beyond the acute effects of PE, chronic thromboembolic pulmonary hypertension (CTEPH) represents a serious long-term complication. CTEPH is defined a dual-pathway vasculopathy, with persistent pulmonary artery obstruction following PE, but also showing changes including intimal hyperplasia and vessel wall remodeling in smallest pulmonary vessels.[69] CTEPH affects approximately 3% of patients following PE and typically evokes within the first two years after the acute event. CTEPH has a strong impact on the long-term outcome, with five-year survival rates in patients with a median PAP >40 mmHg of 30%.[70-72]

1.1.5 Diagnosis of deep vein thrombosis (DVT)

1.1.5.1 Clinical probability

When lower extremity vein thrombosis is suspected, clinical probability is usually assessed based on patients' history and physical examination. Validated scores such as the Wells-Score may help to determine clinical probability. The Wells-Score is available with two levels or three levels. By using the two-level-score, DVT confirmation is predicted for high-probability patients in 28% and for low-probability patients in only 6%.[73] By using the three-level-score, DVT confirmation is predicted for high-probability patients in 53%, for intermediate-

probability patients in 27%, and for low-probability patients in only 5%.[74-76] Current guidelines recommend to evaluate clinical probability as the first step within a diagnostic work-up by validated scores or, alternatively, for very experienced investigators, also empirically.[22] The assessment of the clinical probability presents a key step, as subsequent diagnostics are guided by its results.

1.1.5.2 D-Dimer

D-Dimer levels rise in plasma during acute thrombosis due to concurrent activation of coagulation and fibrinolysis, but they can also be elevated in a variety of other conditions, including cancer, infection, inflammatory diseases, pregnancy, and several others. D-Dimer testing is associated with a high negative-predictive value allowing to rule out VTE with negative test results. In contrast, confirmation of VTE should not be based solely on positive D-Dimer levels, as their positive predictive value is low. In general, D-Dimer measurement is recommended as the next diagnostic step in patients with a not-high clinical probability for DVT. Notably, recent guidelines recommend for vascular specialists to primarily perform imaging by use of sonography to confirm or exclude DVT suspicion, regardless of clinical probability, but D-Dimer measurement may help if sonography does not safely rule out DVT.[22]

1.1.5.3 Imaging

Patients with a high clinical probability for DVT are recommended for further diagnostic work-up by imaging. The imaging method of first choice is duplex-supported compression sonography (ds-CS) of the entire deep venous system of the respective leg. Alternatively, a point-of-care sonography (POC) approach, with examination of femoropopliteal veins, or an even more limited strategy of two-point sonography, with examination of common femoral and popliteal veins only, provide options in case of limited expertise with sonography. Both of these limited strategies require repeated investigation within four to seven days. The rationale behind this limited sonography approach is to image proximal DVT even during the first examination, but also ascending DVT originating from distal clots within a repeated sonography. [22] Evidence supporting the safety of these limited sonography strategies is available.[77-80] However, DVT will be confirmed only in 14–32% in an unselected patient population, with the majority of patients without DVT confirmation during the first examination remaining for a second one to be done.[81]

Some specific cases may require further diagnostic imaging, especially when thrombotic involvement of pelvic veins or the IVC is suspected and information from sonography is insufficient. Magnetic resonance tomography (MRT) venography or computed tomography (CT) venography present appropriate imaging options, but bring some disadvantages such as intravenous application of contrast media, radiation exposure with CT examinations and limited feasibility with MR examinations in context with implants. Of note, conventional phlebography is outdated in recent times.[22] **Figure 2** summarises a diagnostic algorithm for patients with suspected DVT based on recommendations from the current guideline published by *Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften* (AWMF).[22]

1.1.5.4 Diagnosis of thrombosis at unusual sites

When upper extremity DVT is suspected, compression sonography alone is not sufficient for most cases, but colour-coded duplex sonography (CCDS) may add substantive information in order to exclude or confirm thrombosis. Of note, a combined examination with compression sonography and CCDS demonstrated sensitivity of 91% and specifity of 93%.[22] Sonography is the tool of first choice recommended within the diagnostic work up, but clinical probability determination – e.g. by use of the Constans clinical probability score – together with D-Dimer measurement may help if sonography is not available.[22,82] In the rare cases where additional imaging is required, MRT or CT venography is preferred over conventional phlebography.[22]

In patients with suspected visceral vein thrombosis, imaging is of utmost importance, either by sonography and/or by CT or MRT modalities.[22] Of note, sonography of mesenteric veins is often insufficient and may require further imaging to reliably confirm or exclude thrombosis. Sensitivity and specifity for CT and MRT venography for the evaluation of for mesenteric veins have proven superiority over sonography.[83,84]

1.1.6 Diagnosis of pulmonary embolism (PE) in haemodynamically stable patients

As PE is a potentially life-threatening condition, the initial decision is whether the patient presents as haemodynamically stable or unstable, based on clearly defined criteria (**Figure 1**). Further diagnostic steps are determined based on the patient's haemodynamic status.

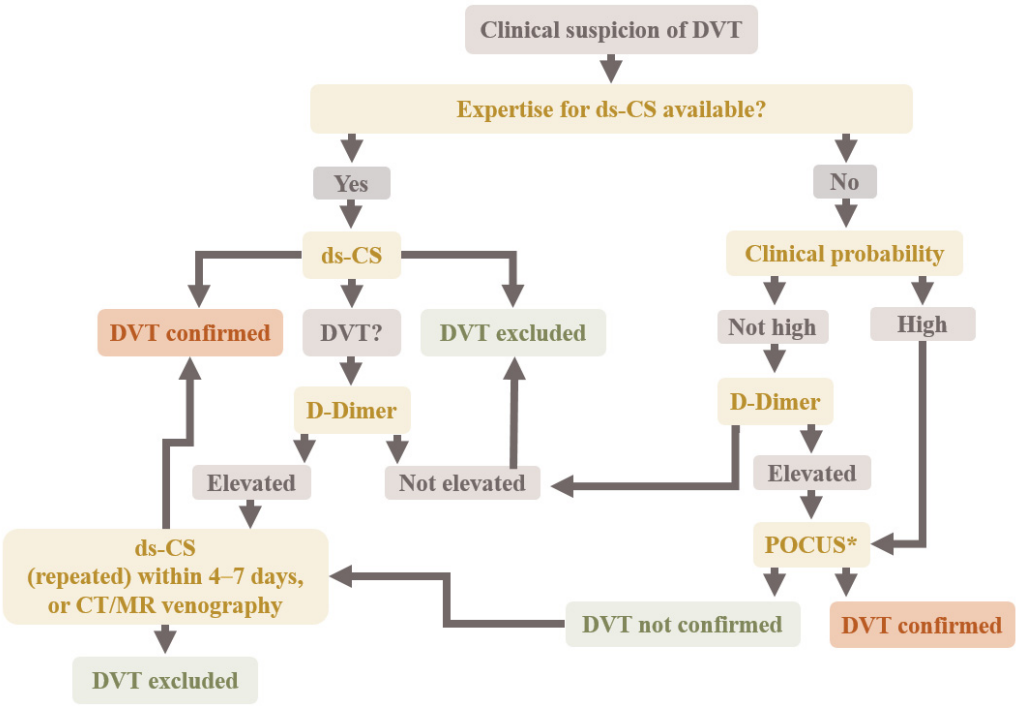

Figure 2. Diagnostic algorithm for DVT
(Figure created by Katharina Kurzmann-Gütl, based on recommendations from the AWMF guideline, published by Linnemann et al.[22])
* If POCUS is not available, establishment of anticoagulant treatment is recommended until confirmation or exclusion of DVT suspicion
AWMF = *Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*; CT = computed tomography; DVT = deep vein thrombosis; ds-CS = duplex-supported compression sonography; MRT = magnetic resonance tomography; POCUS = point-of-care ultrasound

1.1.6.1 Clinical probability

For patients presenting in a haemodynamically stable condition, the first diagnostic step is to classify patients into distinct categories of clinical probability, either by use of empirical clinical expert judgement or by use of prediction rules.[1,22] Clinical expert judgement – even if including commonplace diagnostic tools such as chest X-rays and ECG to rule out differential diagnoses – has proven a certain value, but does not allow for standardisation.[1,22] Accordingly, clinical prediction rules have become central for the determination of clinical probability. The most frequently used prediction rules are the revised Geneva score and the Wells score for PE. Both of these rules are available as an original version, but also as externally validated simplified versions.[85-90] For the original Wells criteria, PE is expected to be confirmed in approximately 10% of patients with low probability, 30% of those with intermediate probability, and 65% of those with high probability. In case of using simplified scores, which do distinct into two instead

of three categories only, PE is expected to be confirmed in approximately 12% in the not-high probability group and 30% in the high-probability group.[91]

Furthermore, the Pulmonary Embolism Rule-Out Criteria (PERC) have been created with an intention for use in an emergency department setting. The underlying idea was that applying a diagnostic algorithm for PE to all patients that present at an emergency department with dyspnoea and chest pain is resource consuming, but also very costly. With using the PERC rule, safe-exclusion of PE without any further diagnostic procedures is suggested for VTE-naïve patients with an age <50 years, a heart rate <100 bpm (beats per minute), oxygen saturation >94%, and in the absence of unilateral leg swelling, haemoptysis, recent trauma/surgery and hormone use. Notably, the low overall prevalence of PE in studies evaluating the PERC limits the generalisability of safely excluding suspected PE using this rule.[92,93]

1.1.6.2 D-Dimer

D-Dimer tests are recommended in patients assigned to a not-high probability group. D-Dimer tests in combination with clinical probability applied accurately allow for exclusion in approximately 30% of all patients with a suspicion of PE.[94-96] In case of elevated D-Dimer levels, further diagnostic imaging is necessary. To reduce the need for imaging, cut-off adjustment for D-Dimer levels either by age (age x 10/µg/L for patients aged >50 years) or by clinical probability are recommended. Adjustment of the D-Dimer cut-off according to clinical probability is implemented in the YEARS rule, consisting of three clinical Wells items (signs of DVT, haemoptysis, and PE is more likely than any other diagnosis) in combination with D-Dimer measurement. When applying the YEARS rule, PE can be safely ruled out either in patients without presence of any of the three Wells criteria and D-Dimer levels below 1000 ng/mL, or in patients with at least one of the three Wells criteria but D-Dimer levels <500 ng/mL.[97,98] Notably, POC D-Dimer assays in outpatients have lower sensitivity and negative predictive value than standard laboratory tests, and are appropriate only for patients with a low clinical probability.[99,100]

1.1.6.3 Imaging

Appropriate imaging techniques in patients with either high clinical probability or not-high clinical probability but elevated D-Dimer levels comprise computed tomographic pulmonary angiography (CTPA), scintigraphy and pulmonary angiography.[1,22] Magnetic resonance angiography (MRA) provides a promising future technique in this field, but available data do

not allow to recommend MRA in this setting for clinical routine due to low sensitivity, a high proportion of inconclusive scans, but also low availability in an emergency setting.[101,102]

Pulmonary angiography presents the historical gold standard, but is rarely used in recent times due to its invasive character, lack of availability, highest radiation exposure (effective dose 10–20 mSv) and particularly for the reason of less-invasive strategies as CTPA providing similar diagnostic accuracy.[103]

Multi-detector CTPA is widely available in most centers and offers excellent accuracy, low rates of inconclusive results, and short acquisition times. Therefore, CTPA presents the imaging modality of first choice for the evaluation of pulmonary arteries down to the subsegmental level.[1,22] Notably, CTPA may provide substantial information regarding alternative diagnoses in case of PE exclusion. Nevertheless, limitations comprise exposure to radiation (effective dose 3–10 mSv) and iodine contrast. Major concern with the use of CTPA exists in young females and especially in those being pregnant or breastfeeding, but also in patients with severe renal insufficiency, hyperthyroidism or iodine allergy.[104-106]

Scintigraphy, which presents an alternative to CTPA, may be conducted either as a planar ventilation/perfusion (V/Q) scan or as a V/Q single-photon emission computed tomography (SPECT) scan. Performing only a perfusion scan might be acceptable in patients with a normal chest x-ray. Adding a ventilation scan increases specificity by allowing the detection of ventilation–perfusion mismatch, as ventilation is expected to be preserved in hypoperfused segments in acute PE. Even if V/Q scans require a lower radiation dose compared with CTPA (approximately 2 mSv), availability is limited and results are inconclusive in up to 50% of cases. Further disadvantages of V/Q scans comprise the inter-observer variability in interpretations and the lack of possibility to provide an alternative diagnosis.[1] V/Q SPECT allows to significantly decrease the proportion of non-diagnostic tests, with only a maximum of 5% tests remaining inconclusive. However, limitations include variability in techniques and diagnostic criteria, a lack of validation in prospective studies, and limited data on diagnostic accuracy.[107-110]

Notably, a sonographic approach combining transthoracic echocardiography (TTE), ds-CS and lung sonography should be taken into consideration if neither CTPA nor scintigraphy is available or feasible.[22]

In general, TTE is not mandatory in the diagnostic work-up of haemodynamically stable patients, but is a useful tool for risk stratification by demonstrating signs of RV pressure overload and dysfunction, as seen in acute severe PE.[111] Typical signs in the assessment of RV pressure overload and dysfunction comprise RV enlargement, RV dilatation with basal RV/LV ratio >1.0, Mc Connell sign, flattening of the intraventricular septum, IVC distension with diminished inspiratory collapsibility, thrombus detection in right heart cavities, decrease in tricuspid annular plane systolic excursion (TAPSE), decrease of peak systolic velocity of the tricuspid annulus, and a 60/60 sign, which describes the co-existence of acceleration time of pulmonary ejection <60 ms and mid-systolic notch with mildly elevated <60 mmHg peak systolic gradient at the tricuspid valve.[1] Of note, these findings are not specific for PE, but may also occur in association with a variety of cardiac and respiratory diseases. Therefore, TTE might offer misleading incidental findings (e.g. LV dysfunction or valvular heart disease) in up to 10% of PE patients.[112]

Ds-CS of the limbs presents a useful test especially in patients where CTPA is contraindicated. The finding of proximal DVT in this setting warrants treatment initiation without further diagnostic testing.[113] Patients with suspected PE and an indirect confirmation by detection of DVT should be assessed for their PE severity the same way as patients with direct PE confirmation.[1]

1.1.7 Diagnosis of pulmonary embolism (PE) in haemodynamically unstable patients

In contrast to haemodynamically stable patients, TTE is recommended as the first diagnostic step if patients with suspected PE present in haemodynamically compromised condition. The absence of RV overload or dysfunction excludes PE as the cause of instability, while its presence supports immediate reperfusion therapy when CTPA is not feasible.[114] If echocardiographic signs of RV overload and/or dysfunction are verified, immediate CTPA is recommended, if available. **Figure 3** summarises a diagnostic algorithm for stable and unstable patients with suspected PE based on recommendations from current guidelines.[1,22]

1.1.8 Diagnosis of venous thromboembolism (VTE) during pregnancy

VTE clinically presents with comparable symptoms in pregnant and non-pregnant women, but during pregnancy, these symptoms are more difficult to distinguish from pregnancy-related physiological complaints.[1] Therefore, VTE is confirmed only in 2–7% of suspected cases in

pregnant women.[115-118] In pregnant women with suspected DVT, sonography is recommended as the diagnostic modality of first choice.[119]

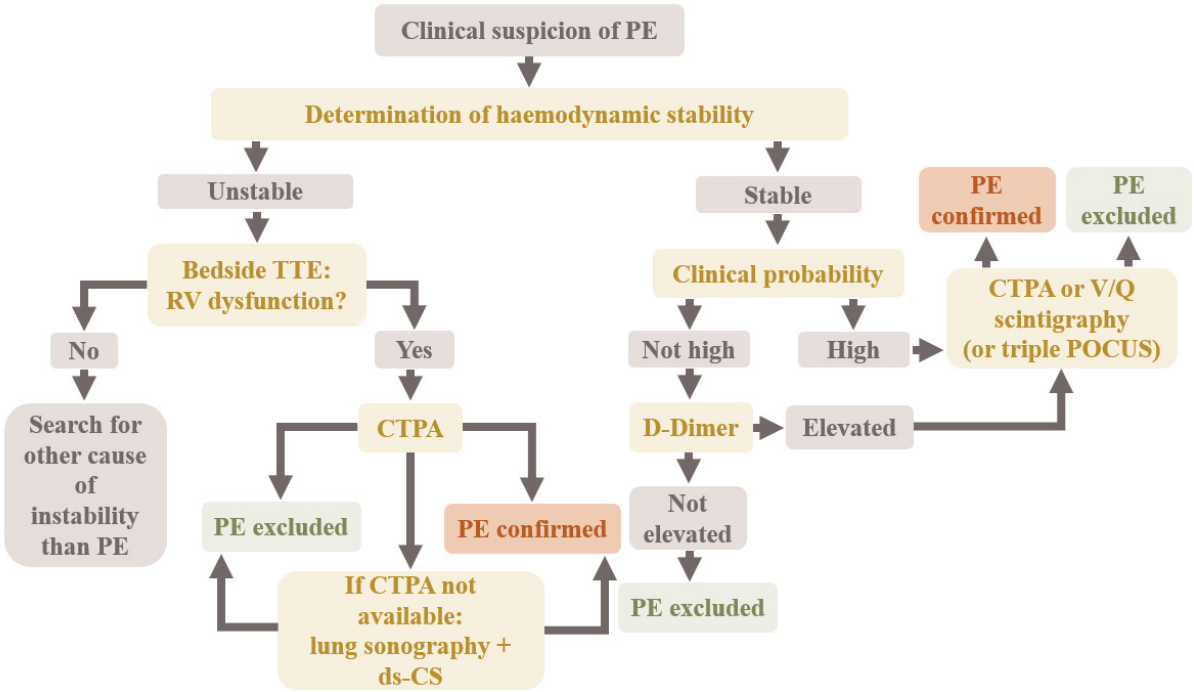

Figure 3. Diagnostic algorithm for PE
(Figure created by Katharina Kurzmann-Gütl, based on recommendations from the AWMF guideline, published by Linnemann et al.[22], and the ESC guideline, published by Konstantinides et al.[1])
AWMF = *Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*; CTPA = computed-tomography pulmonary angiography; ds-CS = duplex-supported compression sonography; ESC = European Society of Cardiology; PE = pulmonary embolism; POCUS = point-of-care ultrasound; RV = right ventricular; TTE = transthoracic echocardiography; V/Q = ventilation/perfusion

As pregnancy is associated with an increased risk for isolated pelvic vein thrombosis, ds-CS and CCDS comprising bilateral flow determination in femoral veins is required. If sonography does not allow to rule out or to confirm DVT, options for further diagnostic work-up include D-Dimer measurement, follow-up sonography within four to seven days, and/or conduction of native MR phlebography. As D-Dimer levels are associated with a physiological increase during pregnancy, their specifity is even more reduced as compared to non-pregnant patients and, thus, they are not routinely recommended within the diagnostic algorithm for DVT in pregnancy.[22] While up to 85% of pregnant women have normal D-Dimer levels in the first trimester, this proportion decreases to about one-third in the second trimester and to as few as 4% in the third trimester.[119] Native MR-phlebography allows for imaging of the IVC and the

pelvic veins and is considered harmless in the second and third trimester of pregnancy.[120] Application of gadolinium contrast media during pregnancy does not present an absolute contraindication, but requires for thorough evaluation of potential benefits and risks.[121-123]

In pregnant women with suspected PE and haemodynamically stable condition, D-Dimer testing plays a relevant role, as recently incorporated into current clinical guidelines.[124] The pregnancy-adapted YEARS algorithm has been developed as a safe tool to rule out PE during pregnancy. It allows D-dimer levels up to 1,000 ng/mL (instead of the standard 500 ng/mL threshold) in women who meet none of the three high-probability criteria. These criteria include clinical signs of DVT, haemoptysis, and PE being the most likely diagnosis. If at least one of these three criteria is present, only a D-Dimer level below 500 ng/mL is accepted for PE-rule out and, thus, all others require further imaging.[125] Even if foetal radiation doses with modern-technology protocols for both CTPA and V/Q scans are far below the threshold for complications as associated with exposure to radiation, and also the effect on maternal risk for cancer has been reported to be negligible, there is still a strong effort to avoid radiation exposure during pregnancy.[115,126-130] Therefore, sonographic evaluation of DVT is recommended in pregnant women in whom rule-out of PE suspicion failed with D-Dimer measurement.[124] For those with an established diagnosis of DVT with sonography, PE is considered confirmed and, in general, there is no need for further imaging. For pregnant women in whom imaging is still required, CTPA using pregnancy-adapted protocols is recommended, but V/Q scans may be conducted as an alternative.[1,22,124]

Haemodynamically unstable women with suspected pregnancy-related PE should be evaluated in the same manner as non-pregnant patients. In the presence of RV dysfunction reported from TTE, further evaluation with CTPA is also indicated during pregnancy. In both haemodynamically stable and unstable women with suspected PE, a multidisciplinary Pregnancy Heart Team should be involved in management decisions.[124]

1.1.9 Risk stratification in patients with confirmed pulmonary embolism (PE)

Risk stratification is mandatory for all patients with a confirmed diagnosis of acute PE. Risk stratification indicates the individual risk of early death in association with PE and has a relevant impact on treatment decisions. All PE patients in a haemodynamic unstable condition are categorised high-risk. For the remaining haemodynamically stable patients, further

assessment is required, including evaluation of RV dysfunction (by laboratory and/or imaging tests) as well as comorbidities and other factors that may adversely affect prognosis.[1,22]

Laboratory biomarkers to assess myocardial injury in the context of PE include cardiac troponins I and T, while B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) serve as markers of RV dysfunction. In haemodynamically stable patients, these laboratory parameters may help to detect patients with an elevated PE-related risk. Cardiac troponins, BNP and NT-proBNP within a normal range have a high negative predictive value and allow for safe exclusion of unfavourable early clinical outcomes.[131,132]

Among echocardiographic parameters, an RV/LV diameter ratio ≥1.0 and a TAPSE <16 mm are reported most commonly for their association with a poor prognosis.[133] Beyond TTE, CTPA can also detect RV dysfunction by demonstrating RV enlargement, including RV end-diastolic diameter and RV/LV ratio. Reviewing the available evidence, a meta-analysis reported an increased RV/LV ratio of ≥1.0 to be associated with a two-and-a-half-fold increase of risk for all-cause mortality, and with an even five-fold increase of risk for PE-related mortality.[134]

In addition to imaging and laboratory findings, baseline parameters reflecting comorbidities and aggravating conditions should be assessed to provide a comprehensive evaluation of a patient's individual mortality risk and early outcome. The original Pulmonary Embolism Severity Index (PESI) incorporates 11 variables (age, sex, cancer, chronic heart failure, chronic pulmonary disease, heart rate ≥110 bpm, systolic blood pressure <100 mmHg, respiratory rate >30 breaths per minute, temperature <36 °C, altered mental status, arterial oxyhaemoglobin saturation <90%) with various weighting to estimate 30-day mortality following acute PE. The PESI stratifies patients into five risk classes, from risk class I, associated with very a low 30-day mortality up to 1.6%, to risk class V, associated with a very high 30-day mortality up to 24.5%.[135] The simplified PESI (sPESI) requires only five variables derived from the original PESI which are equally weighted (one point score each) to stratify patients into low 30-day mortality risk (1.0% with zero score points) and high 30-day mortality risk (10.9% with ≥one score point).[136] Notably, PESI and also sPESI have undergone extensive validation.[135-141]

Integrating these risk indicators enables stratification of patients with pulmonary embolism into high, intermediate-high, intermediate-low, or low risk of early mortality.The high risk group is made up of patients with haemodynamic instability, PESI class of at least III or sPESI ≥ one point, imaging signs of RV dysfunction and elevated laboratory markers (troponins or also

BNP/NT-proBNP). Patients classified as high-risk – representing approximately 12% of all acute PE cases – have a 30-day mortality exceeding 20%. For the low-risk category, patients are haemodynamically stable, fall into PESI class I or II or have a sPESI score of zero points, and show no signs of RV dysfunction on laboratory testing or imaging. Low-risk patients account for approximately 22% of acute PE cases and have a predicted 30-day mortality <1%. **Table 1** presents risk stratification in patients with acute PE, distinguishing four risk categories.[1,22]

1.1.10 Management of acute venous thromboembolism (VTE)

Decisions regarding the acute treatment of VTE should be based on the extent and severity of the disease. In patients with acute DVT, treatment consists primarily of anticoagulation, with compression therapy also playing an important role. Patients with PE likewise require anticoagulation, but those with severe disease additionally need reperfusion strategies as well as haemodynamic and respiratory support.[1,22] Interventional treatment options for both PE and DVT increasingly gain importance in clinical practice, but remain reserved for selected cases.[142]

In recent times, hospitalisation is not mandatory for all patients with an acute diagnosis of VTE. For patients with isolated DVT, hospitalisation is recommended particularly for those with severe symptoms, those with high risk of bleeding, those with advanced liver and/or kidney disease, those who are pregnant and also those with extended and proximal thrombosis affecting pelvic veins or even more proximal veins. For patients with PE, treatment decisions are strongly guided by the risk category assigned during risk stratification (**Table 1**). Patients with low-risk PE are potentially suitable for ambulatory management, but the final decision regarding home treatment or also early discharge is to be made individually. In this context, assessment of alternative indications for hospitalisation, available family and social support, and access to immediate medical care is essential.[1,22] The Hestia criteria present a checklist of clinical parameters and questions which are useful to fully understand PE-severity, comorbidities and also feasibility of home treatment. If at least one criterion is fulfilled or at least one question is answered with “yes”, hospitalisation is recommended.[143] All patients with intermediate-risk PE are recommended for hospitalisation, and those showing pronounced signs of RV dysfunction are even recommended for close monitoring, as haemodynamic deterioration may occur. Patients with high-risk PE as defined by haemodynamic instability should receive treatment and monitoring in an intensive care unit (ICU) setting.[1,22]

For high-risk patients, clinical decision making should arise from an Pulmonary Embolism Response Team (PERT), bringing together specialists from different disciplines including cardiology, vascular medicine, emergency medicine, pulmonology, anaesthesiology and intensive care, cardiac surgery, vascular surgery and radiology (including interventional radiology).[1,142] Notable, there is no exact definition on how to composite PERT, as this may vary with resources and expertise present in each hospital treating patients with acute PE.[144]

Early mortality risk (30-day mortality)	Risk indicators			
	Haemodynamic instability	PESI III–V or sPESI ≥1	RV dysfunction (TTE or CTPA)	↑ Troponins/ NT-proBNP
High	+	+	+	+
Intermediate high	-	+	+	+
Intermediate low	-	+	One or none +	
Low	-	-	-	- (if assessed)

Table 1. Risk stratification in patients with acute PE
(Reproduced with modification from the ESC guideline for the diagnosis and management of acute pulmonary embolism, published by Konstantinides et al.[1], reproduced with permission from the publisher)
CTPA = computed tomography pulmonary angiography; ESC = European Society of Cardiology; NT-proBNP = N-terminal pro B-type natriuretic peptide; PE = pulmonary embolism; RV = right ventricular; (s)PESI = (simplified) pulmonary embolism severity index; TTE = transthoracic echocardiography

1.1.11 Anticoagulation

Anticoagulation represents the central pillar of acute VTE treatment and should be initiated at the latest immediately upon confirmation of VTE, or even during the diagnostic work-up. This approach is in line with current guideline recommendations across different societies and continents.[1,22,142,145] The rationale behind anticoagulant therapy is not to resolute the thrombus, but to avoid thrombus progression and appositional growth. Anticoagulant treatment affects the coagulation cascade by shifting the balance towards anticoagulant factors and allowing for thrombus resolution by endogenous fibrinolysis.[22] In patients with DVT, prevention of embolism to the pulmonary circulation and thus, prevention of PE, is of utmost importance.[22] Following an acute phase, maintenance of anticoagulant treatment is required for at least three to six months.[1,22,145] In the long term, extended anticoagulation aims to reduce VTE recurrence as well as complications, including CTEPH and PTS.[22]

1.1.11.1 Parenteral anticoagulants

Parenteral anticoagulants are most frequently used in clinical practice for the initial treatment phase. The most relevant therapeutic agents comprise low-molecular weight heparin (LMWH), unfractionated heparin (UFH), the synthetic pentasaccharid fondaparinux, and the direct thrombin inhibitor argatroban.

Both UFH and LMWH require binding to AT as an initial step, inducing a conformational change that accelerates the inhibition of factor (F).Xa and thrombin. The anticoagulant effect of heparins can be reversed with protamine, which acts by displacing heparins from its binding to AT. Only a certain proportion of heparin molecules contains the AT-binding site required for the binding of heparin to AT. For UFH preparations, the average amount of molecules with an AT-binding site – so-called high-affinity material (HAM) – typically ranges from 30% to 50%. UFH unfolds its anticoagulant effect by inhibition of both F.Xa and thrombin, but the inhibition of thrombin requires a simultaneous docking of heparin to AT and thrombin. In contrast, binding of UFH to AT is sufficient to unfold F.Xa inhibition. LMWH is produced from UFH by depolimerisation and, therefore, has a significantly lower relative molecular mass (ranging from 1,000 to 10,000 for LMWH compared with 5,000 to 30,000 for UFH), but also lower proportions of HAM. Consequently, higher doses are required for LMWH compared with UFH. While UFH inhibits F.Xa and thrombin to a similar extent, LMWH shows a predominant inhibition of F.Xa.[146] Compared with UFH, LMWH offers several advantages, including simple subcutaneous administration once daily (od) or twice daily (td), minimal need for laboratory monitoring and dose adjustment, and a lower risk of heparin-induced thrombocytopenia (HIT). In general, UFH is administered intravenously as a continuous, weight-adjusted infusion and requires close monitoring of activated partial thromboplastin time (aPTT).[147,148] In case of any need for monitoring of anticoagulant treatment with LMWH, anti-F.Xa activity measurements is recommended.[148,149]

UFH is most commonly used in haemodynamically unstable PE patients and in those with advanced renal impairment. Additionally, UFH may be preferred temporarily in pregnant women requiring peripartum anticoagulation.[1,22,119,150] In haemodynamically stable patients, LMWH and fondaparinux are preferred over UFH due to their more favourable safety and efficacy profiles.[1,147,151-154] For fondaparinux, which contains a heparin-like AT-binding site and selectively inhibits F.Xa, advantages are comparable to those of LMWH, including a fixed-dose od subcutaneous administration and a low risk of HIT.[22,146] Direct thrombin inhibitors –

most commonly argatroban in clinical practice – exert their anticoagulant effect independently of AT. Due to its reversible binding to thrombin, argatroban has a favourable safety profile. However, its use in clinical practice remains largely restricted to patients with HIT, owing to the need for continuous intravenous administration, close aPTT monitoring, and dose adjustment.[146,155]

1.1.11.2 Vitamin K antagonists (VKAs)

For several decades, VKAs – including phenprocoumon, acenocoumarol, and warfarin – have constituted the standard treatment for VTE. The mechanism of anticoagulant activity is based on the inhibition of the synthesis of vitamin K dependent coagulation factors II, VII, IX and X in the liver. Because initiation of VKA treatment is associated with a transient hypercoagulable state – due to a more rapid decline of natural anticoagulants such as protein C compared with procoagulant factors – concomitant heparin administration is recommended until VKAs has achieved a therapeutic anticoagulant effect, as confirmed by coagulation monitoring.[146] On the one hand, VKAs are highly effective in preventing recurrent VTE, with a relative risk reduction of approximately 85% compared with placebo. On the other hand, they are associated with major bleeding rates of approximately 2.1% within the first six months of treatment and a case fatality rate of 11%.[156,157] Intracranial bleeding accounts for 8.7% of all major bleeding events in VTE patients receiving VKAs, with a risk of mortality of approximately 46%.[158] Apart from bleeding issues, VKAs necessitate strict coagulation monitoring by measurement of the international normalized ratio (INR) and adequate dose adaptions. In recent times, oral anticoagulant treatment for VTE with VKAs is rare.[1,22,145,159]

1.1.11.3 Direct oral anticoagulants (DOACs)

Following general recommendations from recent guidelines, most patients should preferably be treated with DOACs, comprising the direct thrombin inhibitor dabigatran and F.Xa inhibitors apixaban, edoxaban and rivaroxaban.[1,22,145] This guidance is based on results from huge international, randomised-controlled trials (RCTs) reporting comparable effectiveness and a favourable safety profile for DOACs compared with VKAs, LMWH and fondaparinux.[160-165] In addition, DOACs also provide practical advantages such as stable pharmacodynamics and pharmacokinetics, no need for routine monitoring, and less interactions with food and drugs. Pharmacokinetic key characteristics of the DOACs including bioavailability, renal clearance, time to peak and elimination half-life are presented in **Table 2**. DOACs may be either started directly after confirming the diagnosis of VTE or at any later time point. For the initial treatment

phase, only the F.Xa inhibitors apixaban and rivaroxaban are approved as monotherapy, requiring a higher initial dosing regimen. In contrast, dabigatran and edoxaban require a lead-in phase of a minimum of five days with parenteral anticoagulants. However, DOACs are not recommended in patients suffering from severe renal impairment (defined by a glomerular filtration rate [GFR] below 15 mL/min for apixaban, rivaroxaban and edoxaban, and below 30 mL/min for dabigatran), during pregnancy and lactation, and in patients with severe APS.[1,22]

	Dabigatran[166,167]	**Apixaban**[168]	**Edoxaban**[169]	**Rivaroxaban**[170,171]
Bioavailability	3–7%	50%	62%	100%*
Renal clearance	80%	27%	50%	35%
Time to peak	3 h	3 h	2–4 h	2–4 h
Elimination half-life	12–17 h	12 h	10–14 h	5–13 h

Table 2. Pharmacokinetic key characteristics of the DOACs
DOACs = direct oral anticoagulants
* Only in case of intake together with food

1.1.11.3.1 Phase III trials

The AMPLIFY trial compared the safety and efficacy of apixaban with conventional treatment by use of enoxaparin and warfarin within a randomised-controlled double-blind setting. A total of 5,395 patients with an acute event of DVT and/or PAE was enroled. Patients assigned to the apixaban study group received apixaban 10 mg td for the first seven days, followed by apixaban 5 mg td for six months. The primary efficacy outcome, which was a composite of VTE recurrence and VTE-related death, occurred in 2.2% of patients in the apixaban group and in 2.7% in the conventional treatment group. Regarding safety, major bleeding was reported in 0.6% of patients in the apixaban group and in 1.8% of patients in the conventional treatment group. Based on these results, the AMPLIFY authors concluded that fixed-dose apixaban as a stand-alone strategy was non-inferior to conventional therapy in terms of efficacy, while significantly reducing major bleeding events.[172]

For rivaroxaban, the EINSTEIN program evaluated the concept of using rivaroxaban alone for the acute treatment of VTE and, thus, replacing both heparin and VKAs. Both EINSTEIN-DVT and the EINSTEIN-PE were conducted randomised-controlled, open-label trials with a non-inferiority design for the primary efficacy endpoint of recurrent VTE. In total, 8,282 patients

were randomised. Patients in the experimental group received rivaroxaban 15 mg td for an initial phase of 21 days and thereafter rivaroxaban 20 mg od for at least three months and up to 12 months. Non-inferiority of rivaroxaban compared to standard treatment using enoxaparin and VKAs was demonstrated in patients with DVT (rate of recurrence: 2.1% in the rivaroxaban group versus 3.0% in the conventional treatment group) and in those with PE (rate of recurrence: 2.1% in the rivaroxaban group versus 1.8% in the conventional treatment group). In the EINSTEIN-PE study, major bleeding occurred in 1.1% of patients treated with rivaroxaban compared with 2.2% in those receiving conventional therapy. For the EINSTEIN-DVT trial, the primary safety was defined as a composite of major bleeding and clinically-relevant non major bleeding (CRNMB), which was reported in 8.1% of patients in each treatment group.[162,165] Moreover, the EINSTEIN-DVT study also conducted a double-blind, randomised, event-driven superiority trial in parallel, comparing extended treatment with rivaroxaban 20 mg od to placebo for an additional six or 12 months. Patient were eligible for this EINSTEIN-Extension trial if they had already completed treatment of acute VTE for at least six months and up to 12 months (either rivaroxaban or VKAs) and if there was equipoise with regard to the need for continued anticoagulant treatment. The EINSTEIN-Extension study, which included approximately 1,200 patients, demonstrated superior efficacy of rivaroxaban, with recurrent VTE occurring in 1.3% of patients compared with 7.1% in the placebo group. In terms of safety, major bleeding or CRNMB occurred more frequently with rivaroxaban than with placebo, with a statistically significant difference for overall bleeding. Notably, major bleeding events were also more common in the rivaroxaban group, but this difference was not statistically significant.[162]

The HOKUSAI-VTE trial, which was randomised, double-blind and designed a non-inferiority study, investigated the early use of the oral F.Xa inhibitor edoxaban after initial treatment with enoxaparin or UFH for at least five days in patients with acute DVT and/or PE. Patients were randomised either to receive edoxaban 60 mg od, edoxaban 30 mg od (in case of impaired renal function with a GFR between 30 mL and 50 mL/min or body weight below 60 kg) or VKAs. Study treatment was prescribed for at least three months and up to 12 months. Notably, 8,292 patients underwent randomisation. Within the HOKUSAI trial, edoxaban has proven non-inferiority in terms of efficacy, with rates of symptomatic recurrent VTE of 3.2% in the edoxaban group and 3.5% in the VKA group. In terms of safety, major bleeding and CRNMB

occurred in 8.5% of edoxaban patients and in 10.3% of warfarin patients, which was statistically significant for superiority.[164]

Evidence for the use of the direct oral thrombin inhibitor dabigatran in patients with acute VTE derives from RE-COVER and RE-COVER II trials. In the RE-COVER randomised, double-blind, non-inferiority trial, patients with acute VTE received initial parenteral anticoagulation for a median of nine days before randomisation to dabigatran 150 mg td or warfarin. A total of 2,539 patients underwent randomisation. The primary outcome of recurrent symptomatic VTE through six months occurred in 2.4% of dabigatran patients and in 2.1% of warfarin patients, which was statistically significant for non-inferiority. For safety, major bleeding through six months was reported in 1.6% of dabigatran patients and in 1.9% of warfarin patients.[161] The RE-COVER II trial, which was initiated to extent findings of the original RE-COVER study, was essentially identical in design. The authors of the RE-COVER II trial concluded that dabigatran provides comparable efficacy, but a lower risk of bleeding than warfarin, thereby confirming the findings of the original RE-COVER study.[160,161]

A meta-analysis of phase III trials demonstrates an up to 4% reduction in major bleedings for DOACs compared with VKAs, with particularly pronounced reductions in intracranial and fatal bleeding (relative reductions of 63% and 64%, respectively). Notably, DOACs were also associated with fewer CRNMB events.[173] However, the number needed to treat (NNT) when using DOACs instead of VKAs to prevent a single major bleeding event is relatively high (n = 149). When examining bleeding outcomes in greater detail, the risk of all assessed bleeding complications was significantly lower with DOACs than with VKAs, with the exception of major gastrointestinal bleeding.[174]

1.1.11.3.2 Coagulation monitoring

Coagulation monitoring is not routinely required in patients receiving DOACs, but may help in specific situations (e.g. acute bleeding or need for urgent surgery, suspected drug-drug interactions) to assess drug exposure and anticoagulant activity. Specific coagulation assays have been developed to measure DOAC plasma concentration levels and, thus, to assess anticoagulant activity.[175-177] Anti-F.Xa chromogenic assays used in combination with validated calibrators for the F.Xa inhibitors apixaban, rivaroxaban and edoxaban, and the diluted thrombin time (dTT) for dabigatran, are available as an alternative to the measurement of plasma concentration levels.[178] Expected trough and peak levels for patients receiving DOACs

for a diagnosis of VTE were published in 2021 by the International Council for Standardization in Haematology (ICSH) and are presented in **Table 3**.[179] Routine coagulation monitoring tests such as prothrombin time (PT) and aPTT may be affected by the intake of DOACs, but do not provide an accurate measurement of the anticoagulant activity and are, thus, not reliable.[178]

1.1.11.3.3 Reversal strategies

Although bleeding complications are reduced with DOACs compared with VKAs, the lack of specific antidotes initially raised major concerns when DOACs were introduced into clinical practice. To date, antidotes are available, comprising idarucizumab, which is a humanised antibody fragment specifically binding dabigatran, and andexanet-alpha, which is a recombinant inactive human F.Xa non-specifically binding F.Xa. Idarucizumab may be used in patients on anticoagulant treatment with dabigatran when presenting with major or life threatening bleeding or requiring for emergency surgery. Administration of idarucizumab 5 g has shown to completely reverse the anticoagulant activity within minutes in most patients. As low levels of dabigatran might also reappear after 12 to 24 hours, close and continued monitoring is required.[180]

	Dabigatran (150 mg td)	**Apixaban (5 mg td)**	**Edoxaban (60 mg od)**	**Rivaroxaban (20 mg od)**
Trough levels (ng/mL)	**60 (39–95)**	**63 (22–177)**	**19 (10–39)** * 16 (8–32)	**32 (6–239)**
Peak levels (ng/mL)	**175 (117–275)**	**132 (59–302)**	**234 (149–317)** *164 (99–225)	**215 (22–535)**

Table 3. Expected trough and peak plasma levels with full-dose anticoagulant treatment for VTE
Expected reference levels as published by Douxfils et al.[179] are expressed as median (interquartile range) for dabigatran and edoxaban, median (5^{th}–95^{th} percentile) for apixaban, and mean (10^{th}–90^{th} percentile) for rivaroxaban
* levels to be applied for patients receiving edoxaban 30 mg
od = once daily; td = twice daily; VTE = venous thromboembolism

Andexanet-alpha can, in principle, be used for the reversal all oral F.Xa inhibiting anticoagulants. However, in the European Union, it is approved only for patients treated with apixaban or rivaroxaban who present with life-threatening or uncontrolled bleeding.

Andexanet-alpha is administered according to two dosing regimens, determined by the interval since the last intake of the anticoagulant agent (< eight hours or ≥ eight hours) and its dose. For both the high-dose and the low-dose regimen, an initial bolus over 15 to 30 minutes is followed by an infusion over two hours.[181] However, even if specific antidotes are available, observational data in patients suffering from major bleedings indicate that (activated) prothrombin complex concentrate (PCC) may substantially contribute to restore intact haemostasis.[182-186] Thus, application of (activated) PCCs is to be considered in patients with life-threatening bleeding, but without access to specific reversal agents.[178]

1.1.11.4 Factor (F.) XI inhibitors

Although DOACs dominate routine practice due to the favourable pharmacological profile and ease of use, the risk of bleeding remains clinically relevant. Fear of bleeding contributes to under-use und under-dosing of anticoagulant treatment, and a high-risk bleeding profile remains the most important contraindication to long-term anticoagulation.[187-189] As a consequence, ongoing research is focused on developing next-generation anticoagulant agents that prevent thrombosis without impairing haemostasis, for example by selectively targeting the intrinsic coagulation pathway.[187] Based on available evidence for F.XI, reporting that elevated levels are associated with an increased risk of VTE and stroke[190-192], while reduced levels correlate with a lower risk of VTE and cardiovascular events[193-196], and considering that congenital deficiency rarely causes spontaneous bleeding[197], F.XI inhibition is proposed as a very promising target for future anticoagulant therapies. F.XI inhibitors that are currently under investigation comprise the antisense oligonucleotides inhibiting F.XI messenger ribonucleid acid (RNA) F.XI IONIS-FXI_{RX} and Fersomeren, the monoclonal antibodies to F.XIa osocimab und abelacimab, the monoclonal antibody to F.XI xisomab 3G3, and the small molecule inhibitors of F.XIa milvexian and asundexian. Among these agents, the small molecule inhibitors of F.XIa milvexian and asundexian are administered orally, whereas all others require subcutaneous or intravenous administration at varying intervals. Several phase II dose-finding trials evaluating VTE prophylaxis in patients undergoing elective knee arthroplasty have already been published, all assessing a primary safety endpoint of major bleeding and CRNMB.[198-201] A meta-analysis of these completed studies reports a 41% reduction in VTE events and a 59% reduction of clinically relevant bleeding events with F.XI inhibitors compared with standard prophylaxis using enoxaparin.[187] Moreover, a few phase II studies in patients with end-stage renal disease on haemodialysis and atrial fibrillation (AF) have been completed,

indicating safety and opening doors to phase III trials, but not allowing to determine efficacy.[202-204] Further trials investigating F.XI inhibitors in patients with end-stage kidney disease, AF, CAT but also acute myocardial infarction and stroke are still ongoing. To date, no evidence is available for anticoagulant treatment by use of F.XI inhibitors in patients with acute VTE. An overview of anticoagulant agents and their specific targets within the coagulation cascade is presented in **Figure 4.**

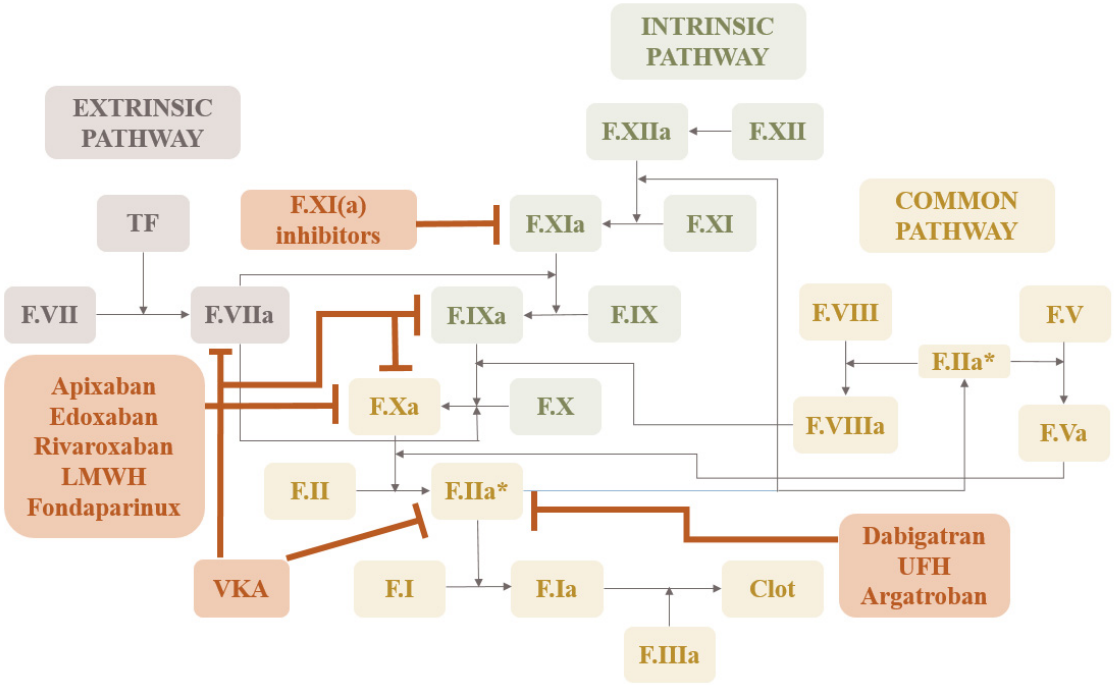

Figure 4. Anticoagulants and their specific targets within the coagulation cascade
(Figure created by Katharina Kurzmann-Gütl, based on the current understanding of the coagulation cascade, e.g. reported by Lang et al.[205])
F. = factor; LMWH = low-molecular weight heparin; TF = tissue factor; UFH = unfractionated heparin; VKA = vitamin K antagonist

1.1.11.5 Anticoagulant treatment in specific patient populations and conditions

1.1.11.5.1 Treatment of minor events

Minor events of VTE include isolated distal DVT, isolated subsegmental PE, asymptomatic and incidental PE, muscle vein thrombosis, and superficial vein thrombosis.

Isolated distal DVT, defined as involvement of below-the-knee calf veins only, is associated with a more favourable prognosis than proximal DVT.[22] Even if symptomatic PE originating from isolated distal DVT is rare, asymptomatic PE was found in 13% of patients in screening

studies.[206,207] Guideline recommendations regarding treatment of isolated distal DVT are inconsistent. While the German AWMF guideline recommends a three-month course of full-dose anticoagulation for isolated distal DVT, the CHEST 2021 guideline from the United States takes a more individualised approach, suggesting either withholding anticoagulation with close serial imaging for up to two weeks, or initiating full-dose anticoagulation, particularly in patients with high-risk features such as extensive thrombus burden, proximity to the deep venous system, active cancer, marked symptoms, or a history of VTE.[22,208]

Regarding anticoagulant treatment for isolated subsegmental PE, the most recent guideline published by the American Heart Association (AHA) and the American College of Cardiology (ACC) in 2026 recommends a risk-adapted approach. In symptomatic cases, anticoagulation is generally recommended, similar to other forms of PE, depending on the overall clinical and bleeding risk. In incidentally detected or very low-risk cases, management may be individualised, with either anticoagulation or close clinical surveillance in selected patients with low recurrence risk and reliable follow-up.[145] The AWMF clearly postulates that for patients with a single subsegmental filling defect, false-positivity with imaging techniques have to be taken into consideration and, thus, anticoagulation is to be avoided if symptoms are lacking. In cases of uncertainty, further diagnostic steps (sonographic evaluation of a potential vein thrombosis as an origin for the embolus, D-Dimer measurement) are optional.[22]

Incidental PE is most commonly detected in association with cancer-staging examinations. Notably, patients with cancer are at increased risk of both VTE recurrence and bleeding, which complicates the management of anticoagulant treatment. The 2023 AWMF and 2019 ESC guidelines recommend anticoagulant treatment for cancer patients with incidental VTE, with the exception of isolated subsegmental PE, and advise adherence to standard recommendations regarding dose and treatment duration for CAT.[1,22,209-211]

Muscle vein thrombosis is typically located in gastrocnemius and/or soleus muscles in the calf. Progression to deep distal veins is reported in up to 25% of cases, with thrombus formation in gastrocnemius veins being at higher risk for progression to deep veins, as they are anatomically connected to popliteal veins.[22] Data on the optimal treatment strategy for isolated muscle vein thrombosis is scarce, but with regard to available literature, the AWMF recommends to provide full-dose anticoagulant treatment for at least one week and up to four weeks, depending on the patient's individual risk profile. For some rare cases with a decision against anticoagulant

treatment, follow-up sonography is required to allow for timely detection of thrombus progression.[22,212-214]

Superficial vein thrombosis most commonly affects lower extremity varicose veins, with the grand saphenous vein (GSV) being affected in up to 70% of cases. The AWMF guideline recommends sonographic confirmation of suspected superficial vein thrombosis and, once confirmed, consideration of anticoagulant treatment. The therapeutic recommendations for superficial vein thrombosis are very clear and detailed, making a distinction into three groups. Patients with superficial vein thrombosis >5 cm in length and a distance of >3 cm from the point of drainage into the deep venous system are recommended for first-line therapy with fondaparinux 2.5 mg od or, as an alternative, rivaroxaban 10 mg od, or also LMWH in half-therapeutic dose. If superficial vein thrombosis is located within 3 cm of the junction with the deep venous system, treatment according to DVT regimens is recommended. For patients with short superficial vein thrombosis (<5 cm in length) and located >3 cm from the deep venous system, symptomatic treatment including compression, cooling, and nonsteroidal anti-inflammatory drugs (NSAIDs) is primarily recommended.[22] The 2021 CHEST guideline recommends anticoagulant treatment in patients with an increased risk of progression to DVT and/or PE for 45 days by use of fondaparinux 2.5 mg od or, as an alternative, by use of rivaroxaban 10 mg od for patients who are unable or refuse to use parenteral therapy.[208]

1.1.11.5.2 Treatment of thrombosis at unusual sites

In general, acute upper extremity thrombosis affecting deep veins is managed in accordance with established recommendations for DVT. RCTs investigating safety and efficacy of anticoagulants in upper extremity thrombosis are lacking, but available evidence from observational studies and case series supports the use of DOACs.[55,215-217] The optimal duration of anticoagulant therapy in upper extremity vein thrombosis remains unclear, but a minimum of three months is recommended. For patients experiencing catheter-related upper extremity vein thrombosis, extended anticoagulant treatment is required, at least for the duration of the catheter being in situ. Catheter removal is essential as soon as possible in case of infection or dislocation, but not in all patients experiencing catheter-related thrombosis.[22] Even occlusion of the catheter do not require instant removal, but functionality may be restored by use of local fibrinolytic agents such as alteplase, which is a recombinant tissue plasminogen activator (rt-PA).[218,219] For patients developing upper extremity vein thrombosis and venous thoracic outlet syndrome, surgical decompression has to be evaluated.[22]

In patients with visceral vein thrombosis, anticoagulation presents the primary therapeutic approach. Especially in patients with severe affection by an acute event of visceral vein thrombosis and in whom surgery or interventional treatment might be required, initial treatment by use of UFH is preferred due to its short elimination time. Notably, up to 5% of all patients with visceral vein thrombosis discover deterioration despite anticoagulant treatment within the first days.[84] In patients with visceral vein thrombosis and concomitant hepatic impairment, an increased risk of both thromboembolic recurrence and bleeding must be considered, particularly in those with underlying cirrhosis. The most relevant bleeding complications in these patients are gastrointestinal bleedings.[59,83] Nevertheless, even patients with acute portal vein thrombosis in underlying cirrhosis have shown to benefit from anticoagulant treatment.[220,221] Results from a recently published meta-analysis propagate the use of anticoagulants by reporting reduced thrombus progression and recurrence, lower mortality, improved recanalisation rates, and even a long-term reduction in severe bleeding.[220] The strongest evidence for anticoagulant treatment in patients with visceral vein thrombosis is available for LMWH and VKAs.[220-223] Anticoagulant treatment using DOACs may provide an option for many patients with visceral vein thrombosis, but the optimal therapeutic strategy should be determined on an individual basis.[224] Regarding the optimal duration of anticoagulant treatment, guidelines recommend a minimum of three to six months. [59,83,84] Notably, also patients with asymptomatic portal vein thrombosis and with a suspected new-onset within the past three months are recommended for anticoagulant treatment for at least three months. In contrast, patients with chronic portal vein occlusion have not shown to profit from anticoagulant treatment.[59]

The management of patients suffering from cerebral venous thrombosis (CVT) typically follows specific guidelines issued by neurological societies. This is particularly relevant since the management of complications associated with CVT, especially intracranial haemorrhage, requires specialised neurological expertise. Therefore, therapeutic recommendations for anticoagulant treatment are not discussed in detail here. In summary, patients with a diagnosis of CVT are recommended for acute-phase, therapeutic-dose anticoagulation with heparins. Following this acute-phase, a switch preferably to a DOAC and continuation for at least three to 12 months is recommended.[225]

1.1.11.5.3 Cancer-associated thrombosis (CAT)

Treatment of established VTE in patients with cancer is complex for various reasons, including drug-drug-interactions between anticoagulants and systemic cancer therapy, challenges for

oral-route anticoagulants, thrombocytopenia as frequently induced by cancer therapy, and increased risk of bleeding. The definition of active cancer as proposed by the Haemostasis and Malignancy Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) comprises 1.) cancer diagnosed within the previous six months, or 2.) recurrent, regionally advanced or metastatic cancer, or 3.) cancer with specific ongoing treatment, or 4.) haematological malignancy not being in complete remission.[226] Based on data from RCTs and metaanalyses, monotherapy with LMWH for at least three to six months had been the standard of care for anticoagulant treatment in cancer populations as for its superior safety and efficacy profile compared to VKAs. The landmark CLOT study attracted attention by evaluating full-dose LMWH treatment for only four weeks followed by reduced dose LMWH, demonstrating a reduction in VTE recurrence and similar bleeding rates compared with VKAs.[227] With the establishment of DOACs for treatment of VTE in clinical practice, RCTs have been conducted in cancer populations comparing apixaban, rivaroxaban and edoxaban to standard treatment with LMWH. All of these studies – ADAM-VTE, CARAVAGGIO, SELECT-D and HOKUSAI-VTE-Cancer – reported comparable safety and efficacy of these agents.[228-231] In 2022, the International Initiative on Thrombosis and Cancer (ITAC) released an updated clinical practice guideline on the treatment and prophylaxis of VTE in patients with cancer, recommending initial therapy with LMWH or oral F.Xa inhibitors in patients without a high risk for gastrointestinal or genitourinary bleeding. Regarding maintenance anticoagulant treatment – both early maintenance up to six months and long-term maintenance beyond six months – the ITAC recommends to use LMWH or oral F.Xa inhibitors. Notably, these recommendations apply only to individuals with a glomerular filtration rate >30 mL/min. In addition, eligibility for treatment with oral F.Xa inhibitors is given only in absence of strong drug-drug interactions or gastrointestinal absorption impairment, and cautious use is required for patients with (upper) gastrointestinal tract malignancies. After six months, the decision whether to terminate or continue anticoagulant treatment should be based on an individual evaluation of risks and benefits, cancer activity, anticoagulant's tolerability and also patients' preference.[232] Especially in patients with a palliative cancer setting and in the absence of contraindication, an indefinite anticoagulant treatment is to be preferred.[22]

1.1.11.5.4 Renal insufficiency

DOAC clearance is reduced in patients with renal insufficiency, leading to drug accumulation and an increased risk of bleeding. However, renal insufficiency itself also presents a risk factor

for thromboembolic events. For apixaban and rivaroxaban, standard-dose treatment for acute VTE is permitted in patients with moderate renal impairment (GFR ≥30 mL/min), while cautious use may be considered in underlying severe renal impairment (GFR 15–29 mL/min). For rivaroxaban, a dose reduction to 15 mg od should be considered when the bleeding risk is estimated to outweigh the risk of recurrent VTE. Edoxaban requires dose reduction in all patients with a GFR between 15 and 50 mL/min. Given its predominant renal clearance, dabigatran is contraindicated already in patients with a GFR <30 mL/min.[22] Data on the use of DOACs in end-stage renal disease, defined by a GFR <15 mL/min and requiring haemodialysis, are scarce and are mainly derived from retrospective analyses. For apixaban, retrospective data suggest comparable safety and efficacy of reduced-dose regimens (2.5 mg td) compared with VKAs in patients with AF and severe renal impairment. Therefore, apixaban may present a reasonable but still off-label alternative to long-term treatment with VKAs in patients on haemodialysis and requiring for anticoagulant treatment following VTE. [233-237]

1.1.11.5.5 Liver disease

Anticoagulant treatment in patients with liver disease is challenging due to impaired drug clearance, reduced plasma protein binding, and the resulting increase in circulating anticoagulant levels. In addition, routine coagulation parameters – such as INR for VKAs, aPTT for UFH, and anti-F.Xa activity for LMWH – are often altered in advanced liver disease even in the absence of anticoagulation, limiting their usefulness for assessing anticoagulant effects. Even if bleeding complications appear frequently in patients with advanced liver disease and coagulopathy, there is also an increased risk to develop thromboembolic complications.[238-240] A few cohort studies are available on the use of DOACs in patients with cirrhosis, reporting comparable efficacy but reduced risk for major bleeding compared with VKAs.[241-243] Based on available evidence, current guidelines recommend the use of all DOACs in patients with cirrhosis Child-Pugh A, and all DOACs except for rivaroxaban in Child-Pugh B, albeit with caution. In advanced cirrhosis (Child-Pugh C), DOACs are not recommended. Notably, this clear guidance refers specifically to the use of DOACs in patients with AF.[178]

1.1.11.5.6 Advanced age

The risk of VTE increases steadily with advanced age, making decisions regarding anticoagulant therapy a frequent clinical challenge in an ageing patient population. Due to age-related changes in body composition and organ function, the pharmacokinetics and pharmacodynamics of DOACs may differ in older compared with younger individuals.

Nevertheless, DOACs have demonstrated comparable efficacy to VKAs even in patients aged ≥75 years.[244] Regarding safety, concern remains as the risk of bleeding is increased in older patients and especially in those with an impairment of renal function.[245,246] Close monitoring of renal function is required in older patients in order to allow for appropriate dose reduction arrangements. Decisions on the frequency of renal function monitoring should be guided by the severity of renal impairment.[22] Taking a look on subgroup analysis from phase III DOAC VTE trials, the risk of major bleeding was reduced as compared with VKAs for apixaban and rivaroxaban, but was increased with dabigatran and edoxaban in patients aged ≥75 years.[160,163,247,248] Notably, geriatric patients were underrepresented in the phase III trials. In older patient populations on anticoagulant treatment for AF, frailty and cognitive impairment were shown to be associated with greater mortality and underuse of oral anticoagulants, while the net clinical benefit is maintained when oral anticoagulant treatment is used.[249] Frailty, which is associated with weight loss and risk for deterioration of renal function, commonly raises specific considerations regarding risk and benefit of anticoagulants in those patients. In patients at risk of falls, oral anticoagulant therapy has historically been considered a contraindication due to concerns about intracranial bleeding. However, subgroup analyses from phase III AF trials have shown that edoxaban was associated with a reduced risk of major bleeding, including intracranial haemorrhage, compared with VKAs in patients prospectively classified as being at high risk of falls.[250] For AF patients on anticoagulant treatment with apixaban, patients with a history of falls had an increased risk of major bleeding, intracranial bleeding and death, but the benefit in terms of safety and efficacy by use of apixaban over VKAs was not affected by the falling status.[251] Given the reduced risk for intracranial bleeding with DOACs as compared with VKAs, an increased risk of falls or even previous falls is not a contraindication to receive DOAC anticoagulant treatment in general, but cautious use and reduction of modifiable bleeding risk factor are essential.[178,252]

1.1.11.5.7 Antiphospholipid syndrome (APS)

APS is a systemic autoimmune disease characterised by arterial, venous or microvascular thrombosis, obstetric complications, or non-thrombotic manifestations. The diagnosis of APS requires the fulfilment of both clinical and laboratory criteria. As antiphospholipid antibodies may appear transiently, persistence must be confirmed. Updated classification criteria for APS – endorsed by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) – have been published recently.[253] In general,

patients experiencing thrombotic complications in the context of APS are recommended for life-long anticoagulant treatment, yet they remain at higher risk for recurrent events compared with patient without APS.[1,22] The TRAPS trial was the first and remains the only RCT comparing a DOAC (rivaroxaban) with VKAs in high-risk patients with triple-positive APS, defined by the presence of lupus anticoagulant (LA), anti-cardiolipin (CL) antibodies and anti-β2-glycoprotein I (β2GPI) antibodies. Rivaroxaban was associated with a significantly higher occurrence of the composite primary endpoint – comprising thromboembolic events, major bleeding, and vascular death – leading to the premature termination of the study. Notably, thromboembolic events consisted of myocardial infarction and stroke, but no cases of recurrent VTE.[254] Based on available evidence, current guidelines recommend to use VKAs (and/or heparin) in patients with thrombotic APS and with triple-positive profile, as well as in those with arterial events.[1,22]

1.1.11.5.8 Pregnancy

Heparins are the anticoagulants of first choice for the treatment of VTE during pregnancy.[22] In contrast to DOACs or VKAs, they do not cross the placenta and therefore do not cause foetal haemorrhage or teratogenic effects. Owing to the more predictable pharmacokinetics and favourable risk profile, LMWH is preferred over UFH. LMWH dosing is recommended to be based on early-pregnancy body weight and administered od or td. [150,255,256] Fondaparinux may be considered as an alternative in selected cases where LMWH is not feasible. However, caution is warranted, as limited placental transfer has been reported.[257]

UFH plays an important role particularly in women diagnosed with VTE in late pregnancy (≥37 weeks of gestation). Given the increased peripartum bleeding risk associated with anticoagulation, a planned switch from LMWH to UFH 24 to 36 hours before delivery should be considered, with discontinuation of UFH approximately four to six hours prior to the planned delivery (including caesarean section). Re-initiation of UFH may be considered no earlier than four to six hours postpartum.[119,150]

For VTE occurring during pregnancy with the diagnosis established before 37 weeks of gestation, LMWH should be discontinued at least 24 hours prior to delivery. In most women, planned delivery is not required.[22,258]

Regarding regional anaesthesia, epidural or spinal puncture requires an interval of at least 24 hours after the last therapeutic dose of LMWH. Re-initiation of LMWH should be considered no earlier than four hours after removal of an epidural catheter.[259,260]

For pregnant women presenting with high-risk PE, UFH is first choice for initial anticoagulant treatment.[1,22] If reperfusion therapy is required, systemic thrombolysis or mechanical thrombectomy may be considered.[261]

In general, anticoagulant treatment for pregnancy-associated VTE should be continued for at least six weeks postpartum and for a minimum total duration of three months. During the postpartum period, treatment options in breastfeeding women include heparins and VKAs, whereas DOACs are not recommended.[22,119,262]

1.1.11.5.9 Recurrence of venous thromboembolism (VTE)

VTE recurrence with adequate anticoagulant therapy is rare, but occurs in approximately 2% of patients.[173] In patients with suspected VTE recurrence, the initial step is to verify adherence to the prescribed anticoagulant regimen. In selected cases, measurement of coagulation parameters may help to assess compliance. Furthermore, potential drug-drug interactions should be evaluated. To confirm recurrence and to distinguish acute events from residual thrombotic changes, imaging and documentation regarding the location and extent of previous events should be carefully reviewed. Therefore, thorough documentation at all stages of the disease – from initial diagnosis to the most recent follow-up examination – is essential to enable reliable confirmation or exclusion of recurrence. If adherence to anticoagulant therapy is assured, the next step is to assess whether the prescribed dose is adequate. In patients receiving a DOAC, potential risk factors for VTE recurrence include low-dose maintenance therapy with apixaban or rivaroxaban, intake of rivaroxaban without food, drug-drug interactions, extreme obesity, and malabsorption. In patients receiving VKAs, coagulation monitoring records should be reviewed with particular attention to values below the therapeutic range. Furthermore, dietary factors as well as potential drug-drug interactions should be carefully evaluated. In patients receiving LMWH or UFH, AT-deficiency, HIT, and correct drug administration should be assessed. If there is no evidence of inadequate anticoagulation, further evaluation for alternative causes of VTE recurrence is essential, including screening for malignancy, myeloproliferative disorders, thrombophilia, paroxysmal nocturnal haemoglobinuria (PNH), venous compression, Behçet's disease, and vasculitis.[22,263] Beyond these diagnostic

considerations, determining further anticoagulant management is of utmost importance. If there is pre-existing but not fully therapeutic anticoagulant treatment (e.g. rivaroxaban 10 mg od, or apixaban 2.5 mg td, or VKAs with an INR below 1.5), dose escalation on the one hand or switching to an alternative anticoagulant strategy on the other hand are available options. If full-dose anticoagulant treatment is already established, management options include dose escalation (e.g. 120–125% for LMWH, or targeting a higher INR range with a lower limit of 2.5 or even 3.0 for VKAs), or switching to an alternative anticoagulant regimen (e.g. from LMWH to a DOAC, from a VKA to LMWH or a DOAC, or from a DOAC to LMWH or to a different DOAC regimen).[22]

1.1.12 Adjunctive treatment in venous thromboembolism (VTE)

1.1.12.1 Compression

The aim of compression therapy is to reduce pain and swelling in the acute phase and to decrease the risk of PTS in the long term. Both compression stockings and compression bandages can be used in this context and are considered comparable in terms of efficacy when applied correctly. However, in cases of pronounced swelling during the acute phase, initial treatment with compression bandages is preferred, followed by fitting of compression stockings once the swelling has subsided. For acute DVT, class II compression stockings are generally recommended, corresponding to an ankle pressure of 23 to 32 mmHg. As orthostatic pressure is significantly reduced in the supine position, compression therapy is primarily beneficial during daytime and in ambulatory patients. The choice between knee-high and thigh-high stockings should be guided by the degree of clinical swelling rather than the extent of thrombosis on imaging.[22] Data from a RCT in patients with proximal DVT showed that thigh-high compression was not superior to knee-high compression in preventing PTS, but was less well tolerated and therefore associated with higher rates of premature discontinuation.[264] After an initial treatment period of three to six months, the decision to discontinue or continue compression therapy should be guided by the patient's residual symptoms of venous congestion. Available evidence does not demonstrate any benefit of a prolonged compression up to two years compared with an individualised treatment approach in the prevention of PTS.[265,266] Regarding PTS, data from a Cochrane systematic review has shown a reduction in the overall incidence of PTS, but no reduction of severe PTS.[267] Taking a close look at data from a RCT, immediate initiation of adequate compression therapy was associated with a 20% absolute reduction in residual venous obstruction, which in turn corresponded to an 8% absolute

reduction in PTS at 24 months.[268] However, compression therapy should be used with reduced pressure (e.g. 18–21 mmHg) in patients with peripheral arterial disease (PAD), as well as in those with polyneuropathy or paresis. In patients with critical limb ischaemia as an advanced stage of PAD, compression therapy is contraindicated.[269,270]

1.1.12.2 Inferior vena cava (IVC) filter implantation

The rationale for IVC filter implantation is to prevent thrombi originating in the pelvic and lower extremity veins from migrating to the pulmonary arteries, thereby reducing the risk of PE. An endovascular approach is typically used for both filter implantation and retrieval, with removal usually performed after a few weeks to months.[1] Filters are available for either temporary or permanent use, but temporary filters are generally preferred.[271] Given that complications associated with IVC filters occur frequently and may cause serious harm, the indication for placement should be critically evaluated before implantation.[1] Frequent complications following IVC filter placement include iatrogenic vascular injury at the access site, filter fracture, filter migration, and IVC thrombosis.[272] Indeed, only a minority of patients with acute VTE require IVC filter implantation. According to the 2019 ESC guidelines for the diagnosis and management of acute PE, the main indications for IVC filter placement are acute DVT or PE in the presence of an absolute contraindication to anticoagulation, as well as recurrent PE despite adequately dosed anticoagulant therapy.[1] These recommendations are largely consistent with the recently published 2026 AHA/ACC guideline, which also emphasises that in patients requiring an IVC filter, a retrievable filter should be preferred.[145]

1.1.12.3 Interventional treatment for acute deep vein thrombosis (DVT)

Therapeutic-dose anticoagulation prevents thrombosis progression and recurrence, but does not actively dissolve thrombotic material. The rationale for revascularisation of occluded veins in the acute phase is to accelerate thrombus resolution compared with anticoagulation as a stand-alone strategy, thereby achieving faster symptom relief, preserving venous valve function, and ultimately reducing the risk of PTS. A range of endovascular revascularisation techniques is currently available, including catheter-directed thrombolysis, mechanical thrombectomy, and pharmaco-mechanical approaches combining both strategies.[22]

So far, there are four RCTs comparing endovascular recanalisation versus anticoagulation alone in patients with acute DVT. The CaVenT study investigated catheter-directed thrombolysis in combination with anticoagulation versus anticoagulation alone in patients with iliac and/or

femoral DVT. In the interventional arm, additional procedures such as balloon angioplasty, stenting, or mechanical thrombectomy were permitted. At the six months' follow-up, patients in the interventional group showed significantly higher venous patency rates, with a sustained reduction in overall PTS observed up to five years. Notably, no differences were found between the groups regarding severe PTS or quality of life.[273,274] The ATTRACT trial evaluated pharmaco-mechanical catheter-directed thrombolysis and showed no significant benefit of endovascular therapy compared with standard anticoagulation regarding the overall incidence of PTS up to 24 months. However, a significant reduction in moderate to severe PTS was observed. Although only 57% of participants had iliac and/or femoral vein thrombosis, the reduction in moderate and severe PTS was also evident in this subgroup. Overall quality of life was comparable between the two study arms, but a significant increase in quality of life related to venous symptoms was recorded in the interventional treatment arm.[275] The CAVA study evaluated ultrasound-accelerated catheter-directed thrombolysis in patients with acute iliac and/or femoral vein thrombosis, showing no significant differences in rates of major bleeding or development of PTS up to three years.[276,277] A pooled analysis of the CaVenT, ATTRACT, and CAVA trials did not demonstrate a significant benefit of interventional treatment for acute proximal DVT compared with anticoagulation alone.[278] Lastly, the TORPEDO trial randomised patients with popliteal or more proximal DVT to catheter-based therapy, which was pharmaco-mechanical thrombolysis in addition to anticoagulation for most cases, or anticoagulation alone. The interventional approach was associated with significantly lower incidence of PTS and VTE recurrence at six months, with these effects persisting during follow-up. However, interpretation of the results is limited by the lack of a standardised method used for assessing PTS.[279]

Modern catheter-based mechanical thrombectomy systems allow treatment of acute DVT without the need for thrombolytic agents, thereby potentially reducing the bleeding risk associated with interventional procedures. To date, RCT data are lacking, and results from ongoing studies are expected to provide further evidence on the efficacy and safety of mechanical catheter-based thrombectomy in acute DVT. The recent 2025 European Society of Vascular Medicine (ESVM) guideline on the interventional management of VTE continues to emphasize anticoagulation as the cornerstone of DVT treatment, but patients with iliofemoral or iliocaval thrombosis are recommended for an individualised assessment of whether catheter-based therapy is reasonable. In any case, management of DVT requiring interventional

treatment should be performed in a specialised treatment center.[142] In conclusion, endovascular recanalisation presents an option for some patients with a diagnosis of acute proximal DVT and suffering from severe congestion symptoms.[22]

1.1.12.4 Reperfusion strategies for acute pulmonary embolism (PE)

Patients with PE and haemodynamic instability are recommended for reperfusion therapy. The choice of reperfusion strategy should be individualised and may include systemic thrombolysis, surgical embolectomy, or an endovascular approach. The 2023 AWMF guideline and the 2019 ESC guideline recommend systemic thrombolysis as the first-line reperfusion strategy, with surgical embolectomy and percutaneous catheter-directed interventions reserved as alternative options. These alternative approaches should be considered in patients with contraindications to systemic thrombolysis or in case of failed thrombolysis, defined by persistent haemodynamic instability and ongoing RV dysfunction on echocardiography within 36 hours after thrombolytic therapy.[1,22] Contraindications to fibrinolysis are listed in **Table 4**.

Contraindications to fibrinolysis	
Absolute	**Relative**
History of haemorrhagic stroke	TIA ≤6 months
History of stroke of unknown cause	Oral anticoagulation
Ischaemic stroke in ≤6 months	Pregnancy/first week post-partum
CNS neoplasm	Non-compressible puncture site
Major trauma ≤3 months	Traumatic resuscitation
Major surgery ≤3 months	Uncontrolled hypertension*
Head injury ≤3 months	Advanced liver disease
Bleeding diathesis	Infective endocarditis
Active bleeding	Active peptic ulcer

Table 4. Absolute and relative contraindications to systemic fibrinolysis
(Reproduced with modification from the ESC guideline for the diagnosis and management of acute pulmonary embolism, published by Konstantinides et al.[1], reproduced with permission from the publisher)
* Defined as a systolic BP >180 mmHg
BP = blood pressure; CNS = central nervous system; ESC = European Society of Cardiology; TIA = transient ischaemic attack

The 2026 AHA/ACC guideline provides Class IIa recommendation for reperfusion strategies in patients with PE complicated by cardiopulmonary failure. In more detail, systemic thrombolysis, mechanical thrombectomy, catheter-directed thrombolysis and surgical embolectomy are each considered reasonable therapeutic options when used in combination with anticoagulation. In this high-risk setting, these reperfusion modalities are favoured over anticoagulation alone to prevent further clinical deterioration and reduce early mortality. Notably, this guideline does not favour one reperfusion strategy over another in patients with cardiopulmonary failure, but the choice of modality should depend on clinical context, contraindications, and local expertise. Similarly, in patients with early cardiorespiratory failure, the aforementioned reperfusion strategies may be considered, but only as a Class IIb recommendation. When interpreting the recommendations of this new guideline, it should be noted in particular that a new PE severity classification system ranging from A to E has been introduced, which somewhat limits comparability with other guidelines.[145] The 2025 ESVM guideline recommends establishing a PERT team including a vascular specialist for all intermediate- and high-risk PE patients. In high-risk PE, the next step is to assess contraindications to systemic thrombolysis, and catheter-based therapies should be considered for patients in whom thrombolysis is contraindicated. In patients with intermediate-risk PE, catheter-based therapy should be considered within 24 hours in cases of severe clinical presentation. In summary, systemic thrombolysis remains the first-line therapy for patients with high-risk PE according to this ESVM guideline.[142] However, the field of interventional treatment of PE is highly dynamic, and various studies and devices are currently under investigation in both high-risk and intermediate-risk patients.

In patients selected for systemic thrombolysis, the rt-PA alteplase is most commonly used, although first-generation agents such as urokinase and streptokinase are also approved. Alteplase is typically administered at a dose of 100 mg over two hours, but an accelerated rescue-regimen using a weight-adjusted dose (0.6 mg/kg, maximum 50 mg) over 15 minutes may be considered in cases of extreme haemodynamic instability or in initially non-high-risk patients who subsequently deteriorate haemodynamically. Notably, formal approval for this accelerated alteplase regimen is lacking.[1] However, there is still a number of 8% of high-risk PE patients in whom thrombolytic therapy is unsuccessful.[280-282] Systemic thrombolysis has been shown to provide the greatest benefit when initiated early, ideally within 48 hours of

symptom onset in acute PE, although it may still be considered in selected patients presenting within up to 14 days after symptom onset.[283]

1.1.13 Long-term treatment and follow-up

After a first episode of PE associated with transient risk factors, the recurrence rate after discontinuation of anticoagulation is approximately 2.5% per year, compared with almost 4.5% per year for unprovoked PE.[284] The risk of recurrence is comparable between patients with PE and those with proximal DVT. However, patients with previous PE are more likely to experience PE again, whereas those with prior DVT typically present with recurrent DVT.[285] Oral anticoagulants are highly effective in preventing VTE recurrence during treatment, but this protective effect does not persist after discontinuation.[284,286] For secondary prevention, patients can be stratified into distinct groups according to their individual risk of VTE recurrence, which supports decision-making regarding ongoing anticoagulant therapy. Patients at highest risk are those with active cancer, APS, severe inherited thrombophilia, or a history of recurrent VTE in the absence of major transient or reversible risk factors. As these patients have an estimated recurrence risk of at least 8% per year after treatment discontinuation, indefinite therapeutic-dose anticoagulation is generally recommended. For patients in whom a major transient or reversible risk factor such as general anaesthesia, major trauma with fracture, or hospitalisation with immobilisation for at least three days is identified as the trigger of the index event, the long-term risk of recurrence is considered low. As the estimated annual recurrence risk in this population is below 3%, discontinuation of anticoagulant therapy is generally recommended after completion of the initial treatment phase of three to six months. An intermediate long-term recurrence risk is assigned to patients whose index event is associated with minor risk factors only, as well as to those without any identifiable provoking factors. If risk factors are classified as minor but persistent (e.g. mild thrombophilia, chronic inflammatory bowel disease, or active autoimmune disease), extended long-term anticoagulation is recommended, with consideration of dose reduction after at least six months of full-dose therapy. In cases with minor but transient risk factors, anticoagulant treatment should be continued for at least the duration of the provoking factor. If such risk factors persist beyond six months after VTE diagnosis, dose reduction may be considered. Common transient risk factors include minor surgery, oestrogen therapy, pregnancy and the puerperium, as well as prolonged travel exceeding six to eight hours. For patients in whom VTE occurs in the absence of identifiable risk factors, further evaluation is required, and the decision to continue

or discontinue anticoagulation after the mandatory initial treatment phase should be individualised based on patient characteristics. In the presence of factors such as male sex, positive family history of VTE, mild thrombophilia, high residual thrombotic burden on imaging follow-up, and/or elevated D-dimer levels, continuation of anticoagulation at a reduced (prophylactic) dose is generally preferred.[1,22] The categorisation of risk factors for venous thromboembolism based on the risk of recurrence over the long-term as recommended by the ESC is illustrated in **Table 5**.

Recurrence risk	Risk factor category	Risk factors/situations
Low <3% per year	**Major transient or reversible risk factors (associated with >10-fold increased risk for the index VTE event compared to patients without the risk factor)**	**Surgery with general anaesthesia >30 min** **Confined to bed in hospital ≥3 days due to an acute illness or acute exacerbation of a chronic illness** **Trauma with fractures**
Intermediate 3–8% per year	**Transient or reversible risk factors (associated with ≤10-fold increased risk for the index VTE event compared to patients without the risk factor)**	**Minor surgery (general anaesthesia <30 min)** **Admission to hospital <3 days** **Oestrogen therapy/contraception** **Pregnancy/puerperium** **Confined to bed out of hospital ≥3 days due to an acute illness** **Leg injury without fracture associated with reduced mobility for ≥3 days** **Long-haul flight**
	Non-malignant persistent risk factors	**Inflammatory bowel disease** **Active autoimmune disease**
	No identifiable risk factor	**-**
High >8% per year		**Active cancer** **One or more previous episodes of VTE in the absence of a major transient or reversible risk factor** **APS**

Table 5. Categorisation of VTE risk factors and the risk of VTE recurrence
(Reproduced with modification from the ESC guideline for the diagnosis and management of acute pulmonary embolism, published by Konstantinides et al.[1], reproduced with permission from the publisher)
APS = antiphospholipid syndrome; ESC = European Society of Cardiology; VTE = venous thromboembolism

Beyond the risk of VTE recurrence, the individual risk of bleeding must be considered when deciding on the duration and dose of anticoagulant therapy. Although major and life-threatening bleeding events occur less frequently with DOACs compared with VKAs, the bleeding risk remains clinically relevant and should not be neglected. The risk of bleeding in patients receiving long-term anticoagulant therapy is influenced by individual patient factors, including renal impairment, age, anaemia, concomitant use of antiplatelet agents, and history of bleeding events.[287] The VTE-BLEED score provides a well-established and validated option to identify patients on long-term anticoagulant treatment with a high risk of bleeding.[288,289] In patients receiving long-term anticoagulant therapy, the individual risks of VTE recurrence and bleeding should be regularly reassessed and should also incorporate patient preferences.[22] **Table 6** provides an overview of general treatment regimens with DOACs for patients with VTE, with specifications for treatment phases and providing dose reduction criteria as reflected in current guidelines.[1,22]

	5–21 days	3–6 months	>6 months
F.Xa inhibition	**Apixaban 10 mg td for 7 days**	**Apixaban 5 mg td**	**Apixaban 2.5 mg td**
	Rivaroxaban 15 mg td for 21 days	**Rivaroxaban 20 mg od**	**Rivaroxaban 20 mg od, or 10 mg od**
		Rivaroxaban 15 mg od if GFR 15–50 mL/min*	**Rivaroxaban 15 mg* od, or 10 mg od**
	Parenteral ≥5 days	**Edoxaban 60 mg**	
		Edoxaban 30 mg od if GFR 15–50 mL/min, or <60 kg, or intake of P-gp inhibitor	
F.IIa inhibition	**Parenteral ≥5 days**	**Dabigatran 150 mg td**	
		Dabigatran 110 mg td if high-bleeding risk, or age ≥80 years, or intake of verapamil	

Table 6. Treatment regimens and dose reduction criteria for DOACs
* Dose reduction in patients with renal insufficiency and GFR 15–50 mL/min is recommended only if the risk of bleeding is estimated to exceed the risk of recurrent or progressing VTE
GFR = glomerular filtration rate; od = once daily; td = twice daily; P-gp = P-glycoprotein

1.1.14 Screening for thrombophilia

Decisions on how, in whom, and when to perform thrombophilia screening remain frequently unclear in daily clinical practice. In general, thrombophilia testing after VTE should only be performed if the results are likely to influence subsequent anticoagulant management.[290,291] In the acute phase of VTE, knowledge of most thrombophilic conditions is unlikely to influence the anticoagulant management, making thrombophilia testing during this period generally unnecessary. After completion of the initial treatment phase of three to six months, thrombophilia screening may provide useful information, particularly when the decision to continue, reduce, or discontinue anticoagulation has not yet been clearly established.[292] The timing of thrombophilia testing should be carefully considered, as most assays – except for measurements of anti-CL antibodies, anti-β2GPI antibodies and genetic analyses – may yield unreliable results during the acute phase of the thromboembolic events or in the presence of anticoagulant treatment. [22] VTE in the context of hereditary thrombophilia typically occurs at a younger age. Therefore, thrombophilia testing should be conducted particularly in younger patients with an additional positive family history of VTE. For hereditary thrombophilia, recommended testing includes genetic analysis for FVL mutation (possibly preceded by screening for activated protein C [APC] resistance as a non-genetic screening method), genetic analysis for the prothrombin G10210A mutation, and measurement of AT, protein C and protein S activity levels. Genetic analyses are regarded reliable, but suspected hereditary deficiencies of AT, protein C or protein S always require confirmatory testing and should never to be diagnosed based on a single functional assay alone.[22] Notably, secondary deficiencies appear much more frequently compared with hereditary deficiencies.[293] APS should be considered in patients aged <50 years presenting with VTE in the absence of identifiable risk factors, in those with thrombosis at unusual sites, or in cases of thrombus progression despite adequate anticoagulant therapy. The presence of arterial thrombosis, pregnancy complications (e.g. miscarriage, preeclampsia, or placental insufficiency), or autoimmune disease (e.g. systemic lupus erythematosus) should further raise the suspicion of APS. In cases of suspected APS, diagnostic testing should include measurement of LA, anti-CL antibodies and anti-β2GPI antibodies. Laboratory criteria require confirmatory testing with repeat measurements at least 12 weeks apart.[294]

1.1.15 Screening for cancer

Patients presenting with VTE in the absence of identifiable risk factors have a higher risk of underlying malignancy compared with those in whom provoking factors are present. Within 24 months after a VTE event, cancer was found in 8.5% of patients with unprovoked VTE and in 4.8% of patients with VTE associated with risk factors.[295] In general, the risk of occult cancer in patients with acute VTE has been shown to be higher in those aged >50 years compared with younger patients.[44] However, the extent of recommended cancer screening remains unclear. Data from a prospective RCT did not demonstrate any benefit of an extensive screening strategy compared with a limited screening approach with regard to cancer-related mortality.[296] According to current guideline recommendations, cancer screening should be considered particularly in patients with unprovoked VTE, with the extent of screening guided by age- and sex-specific risk factors.[22]

1.1.16 Suspicion of post-thrombotic syndrome (PTS)

Following the acute phase of DVT, processes of thrombus organisation, resolution, and vascular remodelling occur to varying degrees. Recanalisation of the affected veins may be either partial or complete. In cases of incomplete recanalisation and/or venous valve damage, impaired venous return may persist, contributing to the development of PTS.[22] Residual symptoms for more than three to six months after the acute event are supposed to be predictive for the development of PTS.[297] Typical symptoms of PTS are similar to those of acute DVT, but patients may additionally present with pruritus, muscle cramps, paraesthaesia, skin induration, hyperpigmentation, venous ectasia, erythema, or even venous ulceration.[22] The diagnosis of PTS is established clinically. The Villalta score is commonly used to assess and grade the severity of PTS following lower-extremity DVT. After proximal DVT, clinically relevant PTS occurs in approximately 20–50% of patients, with severe PTS reported in 5–10%.[298,299] Data from a prospective German registry with a three-year follow-up reported a prevalence of 33% for any PTS, but only 1.4% for severe PTS.[300]

For patients with PTS, key components of management include compression therapy and regular physical activity. Physical activity activates the calf muscle pump and thereby enhances venous return. Compression therapy is generally recommended using at least class II compression stockings, corresponding to an ankle pressure of 23 to 32 mmHg. In cases of severe PTS and good tolerance, class III compression stockings with an ankle pressure of 34 to 46 mmHg may be considered, provided there are no contraindications. Although evidence for

the long-term benefit is limited and partly conflicting, compression therapy remains recommended, particularly given the lack of effective alternative treatments and its potential to improve clinical symptoms.[22,301]

In patients with severe PTS following proximal DVT, endovascular recanalisation may be considered. Such intervention should be reserved for patients with insufficient symptomatic improvement despite optimal conservative management.[22] Technical success rates for recanalisation of obstructed veins are reported to range from 91% to 98% in available meta-analyses and systematic reviews, while patency rates range between 70% and 80% at a median follow-up of approximately two years.[302-305] In patients with iliac vein occlusion, primary patency after stenting has been reported at 68% at three years.[303] In patients with ulceration due to veno-occlusive post-thrombotic disease, healing of ulceration was accomplished in up to 80% of cases, but recurrence of ulcers was reported in up to 17%.[303,306] However, the quality of available evidence should be critically appraised, particularly in view of the lack of RCTs comparing endovascular with conservative treatment and the absence of standardised approaches to venous interventions.

1.1.17 Suspicion of chronic thromboembolic pulmonary hypertension (CTEPH)

For most patients, complete recanalisation of pulmonary arteries is achieved within a few months after acute PE. Therefore, routine follow-up imaging is not required.[307] A minority of patients present with persistent organised thrombotic material, which may lead to CTEPH.[1] CTEPH is a rare but potentially life-threatening complication, with a cumulative incidence of 0.79% at two years following acute PE, as reported from a Swiss prospective observational screening study.[308] The hallmark of CTEPH is the organisation of thrombus into fibrotic tissue, resulting in mechanical obstruction of the affected pulmonary arteries. Subsequent processes include redistribution of blood flow, with overflow of unobstructed pulmonary arteries, as well as microvascular remodelling.[309] In patients with suspected CTEPH due to persistent dyspnoea and/or functional limitation, diagnostic work-up should be initiated no earlier than after completion of at least three to six months of anticoagulant therapy, in order to differentiate from symptoms related to the acute event. The first recommended diagnostic step is TTE. However the diagnosis of CTEPH finally requires a V/Q scan showing mismatched perfusion filling defects, followed by a right heart catheterisation examination measuring an elevated PAP of >25 mmHg and a pulmonary arterial wedge pressure of ≤15 mmHg. In patients without pulmonary haemodynamic abnormalities required for a diagnosis of CTEPH, chronic

thromboembolic disease (CTED) may be considered, if other causes of exercise limitation have been excluded.[310] All patients with suspected CTEPH in whom mismatched perfusion defects have been confirmed should be referred to an expert center for further diagnostic work-up and evaluation of specific treatment options, including pharmacological, surgical, or endovascular therapies. Notably, all patients with CTEPH require basic medical management by use of lifelong anticoagulation with VKAs.[1]

1.2 Venous thromboembolism (VTE) in overweight and obesity

1.2.1 2016 guidance from the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH)

In 2016, the SSC of the ISTH published a guidance document on the use of DOACs in obese patients, reviewing available evidence from clinical outcome studies as well as pharmacokinetic (PK) and pharmacodynamic (PD) data regarding safety and efficacy. This guidance considered not only data from VTE studies, but also evidence from studies evaluating DOAC therapy for stroke prevention in patients with AF. BMI-based stratification is available only in a minority of the included phase III trials, and outcomes for patients with a BMI ≥40 kg/m² have not been analysed separately. Furthermore, cross-study comparisons are limited by the heterogeneity in the applied weight and BMI cut-offs.[311] **Table 7** provides an overview of phase III trials evaluating DOACs in patients with VTE, and additionally reports the proportion of patients with overweight and obesity included in these studies. Notably, no large RCTs have specifically evaluated safety and efficacy outcomes of DOACs in obese patients, and the proportion of patients with overweight and obesity included in phase III trials was relatively low.

Phase III trial data including available weight-based analyses demonstrate comparable efficacy for DOACs and VKAs in preventing either VTE recurrence or stroke in AF patients.[311] Taking a closer look, pooled analyses in obese patients with VTE demonstrate comparable efficacy of VKAs and DOACs, both when defined by body weight (including data from RECOVER II[160], EINSTEIN-DVT[162], EINSTEIN-PE[165], AMPLIFY[172], and HOKUSAI-VTE[164]) and when defined by BMI (including data from RECOVER II[160], EINSTEIN-PE[165], and AMPLIFY[172]), with no relevant differences in relative risk observed between the treatment groups. When comparing primary efficacy in obese versus normal-weight patients defined by body weight in

VTE trials (including data from RECOVER II[160], EINSTEIN-DVT[162], EINSTEIN-PE[165], AMPLIFY[172], and Hokusai-VTE[164]), the relative risk ratio was in favour of normal-weight patients, suggesting a modest advantage for this group. However, this difference was not statistically significant (RR 1.28, 95% confidence interval [CI] 0.98–1.67), and the overall trend was largely driven by the results of RECOVER II (RR 2.04, 95% CI 1.20–3.51), in which patients weighing >100 kg were at higher risk for primary efficacy outcomes compared with those weighing 50–100 kg.[311]

Drug	Trial	Weight category	Obese patients
Dabigatran	RE-COVER I[161]	≥100 kg BMI ≥35 kg/m²	502/2,539 (20%) 306/2,539 (12%)
	RE-COVER II[160]	≥100 kg BMI ≥35 kg/m²	438/1,280 (34.2%) 302/1,280 (23.6%)
Rivaroxaban	EINSTEIN DVT[162]	>100 kg	245/1,731 (14.2%)
	EINSTEIN PE[165]	>100 kg	345/2,419 (14.3%)
Apixaban	AMPLIFY[172]	≥100 kg BMI >35 kg/m²	522/2,691 (19.4%) 349/2,691 (13.0%)
Edoxaban	HOKUSAI VTE[164]	>100 kg	611/4,118 (14.8%)

Table 7: Representation of patients with overweight and obesity in major DOAC phase III trials
BMI = body-mass index; DOACs = direct oral anticoagulants; VTE = venous thromboembolism

Regarding safety, subgroup analyses by body weight are available for most phase III VTE trials (AMPLIFY[172], EINSTEIN-DVT[162], EINSTEIN-PE[165], HOKUSAI-VTE[164]). All of the aforementioned trials reported a composite safety outcome of major bleeding and CRNMB, except for the AMPLIFY trial, which reported only major bleeding. Regarding primary safety, the overall relative risk in obese VTE patients (including data from EINSTEIN-PE[165], EINSTEIN-DVT[162], and HOKUSAI-VTE[164]) indicated comparable safety of DOACs and VKAs when stratified by body weight. Notably, the AMPLIFY trial demonstrated significantly reduced rates of major bleeding in patients with a BMI >35 kg/m² when treated with DOACs compared with VKAs.[172]

Taking a closer look on data from EINSTEIN DVT and EINSTEIN PE trials, a subgroup analysis revealed no association between body weight or BMI and VTE-recurrence or bleeding (major bleeding as well as clinically relevant bleeding).[312]

Regarding PK/PD, a subgroup analysis of the RE-LY study, which evaluated dabigatran versus VKAs in patients with AF, demonstrated lower dabigatran trough concentrations in patients with a body weight >100 kg compared with those weighing 50–100 kg. Furthermore, an inverse relationship was observed between trough concentration levels and ischaemic events, but logistic regression did not determine weight as a significant covariate for stroke.[313] For apixaban, PK data from a study in healthy volunteers demonstrated a 31% reduction in mean peak concentrations and a 23% decrease in drug exposure, alongside a 24% increase in volume of distribution in participants weighing >120 kg and with a BMI ≥30 kg/m² compared with a reference weight group.[314] In contrast to the PK data reported for apixaban, comparable peak plasma concentrations were observed for rivaroxaban in healthy volunteers with a body weight >120 kg and those weighing 70–80 kg.[315] A second study, based on pooled data from patients with acute DVT, likewise found no significant effect of body weight on the maximum plasma concentrations of rivaroxaban.[316]

1.2.1.1 Summary of guidance recommendations

Taken together, the available evidence led the SSC/ISTH to recommend against the use of DOACs in patients with a BMI >40 kg/m² or a body weight >120 kg. Alternatively, if DOACs are used in patients at extremes of body weight, measurement of drug-specific trough and peak levels may be considered. Recommended laboratory assessments include anti-F.Xa activity for the F.Xa inhibitors apixaban, rivaroxaban, and edoxaban, and either ecarin clotting time (ECT) or diluted thrombin time (dTT) for the direct thrombin inhibitor dabigatran. Alternatively, direct quantification of DOAC plasma levels can be used for any DOAC. If measured levels are below the expected therapeutic range, the SSC/ISTH recommends switching from a DOAC to a VKA rather than adjusting dose.[311]

1.2.2 2021 guidance from the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH)

An updated communication from the ISTH Subcommittee on Control of Anticoagulation was published in 2021, providing guidance on the use of DOACs in patients with VTE and obesity,

based on available evidence from phase III and phase IV trials, meta-analyses, as well as PK/PD studies.[317]

For apixaban, although no post hoc analyses from the phase III AMPLIFY trial are available, data from a small, single-center retrospective study indicate comparable rates of VTE recurrence and major bleeding with apixaban and VKAs in patients with a BMI ≥40 kg/m² and even in more extreme obesity (BMI ≥50 kg/m²). Notably, the sample size in the subgroup of patients with a BMI ≥50 kg/m²was very limited (10 patients on apixaban and 52 patients on VKAs). Rivaroxaban was also evaluated in this retrospective analysis and showed comparable safety and efficacy to VKAs in patients with a BMI ≥40 kg/m². For patients with a BMI ≥50 kg/m², data from 30 individuals treated with rivaroxaban similarly demonstrated no significant difference in VTE recurrence compared with those receiving VKAs.[318] A second analysis providing data for this 2021 SSC/ISTH guidance reports lower rates of VTE recurrence and major bleedings for apixaban than achieved with VKAs in patients with a BMI ≥40 kg/m². Of note, this observational data derived from medical healthcare databases in the United States, and all outcome events as well as the categorisation for obesity were based on the presence of International Statistical Classification of Diseases and Related Health Problems (ICD) codes for inpatients only.[319]

For rivaroxaban, evidence considered in this guidance derives from a phase III post hoc analysis and from several observational and retrospective studies. The post hoc analysis of the EINSTEIN-DVT and EINSTEIN-PE trials included a substantial cohort of 861 patients with a BMI ≥35 kg/m² and showed no significant differences in rates of recurrent VTE or major bleeding over a follow-up period of up to 12 months compared with VKAs. Stratified analyses by body weight similarly demonstrated comparable VTE recurrence rates between the two treatment groups in patients weighing ≥120 to <140 kg and ≥140 kg. Notably, these post hoc data from the EINSTEIN program had already been considered in the 2016 SSC/ISTH guidance.[312] Some more data derive from observational and retrospective studies and, in summary, demonstrate at least comparable efficacy and safety with rivaroxaban as with VKAs in obese patients.[320,321]

Additional evidence from pooled analyses demonstrates comparable rates of safety and efficacy outcomes with DOACs in comparison with VKAs across different weight and BMI

categories.[322-327] However, neither phase III nor phase IV studies provide data on the use of edoxaban or dabigatran in VTE patients with a BMI >35 kg/m² or a body weight >120 kg.

Regarding PK/PD studies, a trial comparing two weight-based groups (body weight ≤120 kg with a mean BMI of 31 kg/m², versus body weight >120 kg with a mean BMI of 49 kg/m²) in patients predominantly receiving apixaban for AF showed significantly lower anti-F.Xa levels in the >120 kg group at two hours after anticoagulant intake, but anti-F.Xa levels did not differ significantly between groups at four hours post-dose.[328] Furthermore, a cohort study by Martin et al. including patients with a body weight ≥120 kg evaluated anticoagulant therapy with both apixaban and rivaroxaban in individuals treated for either VTE or AF. In this analysis, apixaban concentrations were within the expected therapeutic range in all patients for peak measurements and in 16 of 18 patients (89%) for trough measurements. For rivaroxaban, only 26 of 58 peak level measurements (45%) fell within the expected therapeutic range, but all trough level measurements were within the anticipated therapeutic window.[329] Further studies on rivaroxaban in patients weighing >120 kg demonstrated peak plasma concentrations comparable to those observed in reference weight groups.[315,330] Additional evidence indicates that both body weight and BMI have only a minor influence on the pharmacokinetics of rivaroxaban.[316,331-333] PK/PD data on the use of dabigatran in overweight and obese patients are very limited, comprising only peak level measurements from 10 patients with a body weight >120 kg, of whom one-fifth had peak concentrations below the expected on-therapy range.[334]

1.2.2.1 Summary of guidance recommendations

The updated practical guidance statements are consistent with the 2016 recommendation regarding the use of DOACs in patients with a BMI up to 40 kg/m² or a body weight up to 120 kg. For patients exceeding these thresholds, the SSC/ISTH suggests the use of standard doses of apixaban and rivaroxaban irrespective of weight and BMI, while acknowledging the limited evidence for extremes of body weight (BMI ≥50 kg/m² and bodyweight >150 kg). Given the lack of convincing evidence for dabigatran and insufficient data for edoxaban, the use of these agents is not recommended in patients with a BMI >40 kg/m² or a body weight >120 kg. Furthermore, the SSC/ISTH advises against routine measurement of peak and trough DOAC plasma levels even in patients with severe obesity, due to insufficient evidence regarding the impact of these findings on treatment decisions, as well as the lack of established correlations between on-treatment plasma levels and clinical outcomes.[317]

1.2.3 2023 Expert Consensus Panel recommendations

The 2021 ISTH SSC guidance indicates that both apixaban and rivaroxaban are appropriate for the treatment of VTE irrespective of BMI or body weight. Since then, however, additional evidence has become available. In light of these data, an expert panel published updated recommendations and concluded that apixaban and rivaroxaban are both suitable first-line options for treatment of VTE in severely obese patients. The panel further agreed that no preference can be stated for one agent over the other. Of particular relevance to these recommendations are several published systematic reviews and meta-analyses evaluating the safety and efficacy of DOACs compared with other anticoagulants in severely obese patients with VTE.[335]

A systematic review and meta-analysis by Mai et al.[336] included 21 studies with a total of 50,360 patients, of whom 16,150 had a BMI ≥30 kg/m² and 6,443 had a BM I≥40 kg/m². VTE recurrence rates were similar with DOACs compared with non-DOAC anticoagulants (VKAs, LMWH) in obesity (RR 1.03; 95% CI 0.93–1.15; p = 0.55) and even in morbid obesity (RR 1.06; 95% CI 0.94–1.19; p = 0.35). Moreover, DOACs were associated with a reduced risk of major bleeding in patients with obesity (RR 0.57; 95% CI 0.34–0.94; p = 0.03) and in those with morbid obesity (RR 0.71; 95% CI 0.50–1.00; p = 0.05). Notably, the majority of patients received rivaroxaban, followed by apixaban, with smaller proportions treated with dabigatran and edoxaban.[336] A smaller comparative analysis including five studies with a total of 3,207 patients demonstrated similar efficacy in terms of VTE recurrence between DOACs and VKAs/LMWH (2.96% versus 2.54%; OR 1.17, 95% CI 0.87–1.59; p = 0.30). Major bleeding events were less frequent with DOACs than with VKAs or LMWH, but this difference did not reach statistical significance (1.89% versus 2.54%; OR 0.74, 95 %CI 0.53–1.03; p = 0.08).[337] Lastly, an analysis by Elshafei et al.[323] including five retrospective studies in morbidly obese patients (BMI ≥40 kg/m² or body weight >120 kg), which – except for one – overlapped with the studies included in the analysis by Katel et al.[337], similarly demonstrated non-inferiority of DOACs. This was shown for the primary efficacy outcome of recurrent VTE (OR 1.07; 95% CI 0.93–1.23) as well as for the primary safety outcome of major bleeding (OR 0.80; 95% CI 0.54–1.17).[323]

2 Methods

2.1 Aim of the study

According to the World Health Organization (WHO), the definitions for overweight and obesity are based on the BMI, with thresholds of ≥25 kg/m² for overweight and ≥30 kg/m² for obesity, respectively.[29] Although the BMI is intended to classify body fat accumulation, it does not assess body composition and therefore cannot distinguish between FM and FFM. The determination of body composition presents an alternative approach to the traditional BMI classification to unmask patients with overweight and obesity, but is not broadly used. While substantial variability in the distribution of FM and FFM exists even among patients with normal BMI, this variability is anticipated to be markedly greater in the context of obesity. The Lancet Diabetes and Endocrinology Commission recently published a novel concept for the definition and diagnosis of obesity, recommending to confirm obesity by direct measurement of body fat or by collecting anthropometric parameters such as the waist circumference or the waist-to-hip ratio (WHR) in addition to BMI.[338] Despite robust evidence supporting the safety and efficacy of DOACs in VTE, existing data in obese populations are largely limited to stratification by BMI or total body weight, while body composition has not been assessed in the available studies. The prevalence of overweight and obesity continues to rise, and concerns persist regarding anticoagulant management with fixed-dose DOACs due to potential alterations in pharmacokinetics and pharmacodynamics, particularly in patients with severe obesity.[29,339-341]

The aim of the BIARIVA study presented in this thesis was to investigate the potential association between body composition parameters and coagulation monitoring parameters in VTE patients who receive anticoagulant treatment with oral F.Xa inhibitors rivaroxaban or edoxaban.

2.2 Study design

The BIARIVA prospective, single-center, cross-sectional pilot study was conducted at the Medical University of Graz (Division of Angiology and Lipid Clinic, Department of Internal Medicine). Patient recruitment was performed between November 2018 and January 2020. All patients were under pre-existing medical care for their anticoagulant therapy at the Division of

Angiology. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and all applicable amendments laid down by the World Medical Assemblies and the International Conference of Harmonization Guidelines for good clinical practice. The study protocol was approved by the Ethics Committee of the Medical University of Graz (29-440 ex 16/17). All study participants provided written informed consent prior to participation.

2.2.1 Study inclusion criteria

The BIARIVA study enroled adult patients (≥18 years) who were suitable for bioimpedance measurements. Patients were treated with rivaroxaban or edoxaban based on a clinical decision that was made prior to the study visit and independent of the participation in the BIARIVA study. All patients were required to meet the criteria for full-dose anticoagulant treatment, which is corresponding to edoxaban 60 mg od or rivaroxaban 20 mg od. Inclusion of patients on a reduced dose was permitted only in case of a dose reduction to edoxaban 30 mg due to body weight <60 kg. Patients eligible for participation in the BIARIVA study were selected based on the outpatient clinic's documentary system. For study inclusion, patients were required to fit into one of three predefined BMI groups: normal weight - group I: BMI = 18–25 kg/m², moderate obesity - group II: BMI = 30–35 kg/m², and severe obesity - group III: BMI = >35 kg/m². Designed as a pilot study, each BMI group was planned to require 10 patients for each substance, totaling a minimum of 60 patients.

2.2.2 Endpoints

The primary endpoint in the BIARIVA study was the association between body composition parameters and coagulation monitoring parameters in patients on therapeutic-dose anticoagulant treatment with rivaroxaban or edoxaban, assessed by correlation analysis. To account for potential confounders including age, sex, and renal function, an exploratory sensitivity analysis was performed employing multivariable linear regression.

2.2.3 Study visits

All enroled patients completed one study visit at the outpatient clinic comprising 1.) two blood draws, 2.) measurement of anthropometric parameters and 3.) measurement of body composition. The observational period for each participant was approximately four hours. The first blood draw was taken in fasting condition and included routine laboratory parameters and specific coagulation monitoring parameters for determining trough levels of the respective

anticoagulant, rivaroxaban or edoxaban. Patients were instructed to have their last anticoagulant dose approximately 24 hours prior to the study visit to provide valid measurement of trough levels. The second blood draw was conducted at least two and at a maximum of three hours after intake of the respective substance to determine specific peak coagulation parameters. All rivaroxaban patients were instructed for intake of their medication with food as recommended for proper use following the official drug information.[342] **Figure 5** provides a graphical summary of the design of the BIARIVA study.

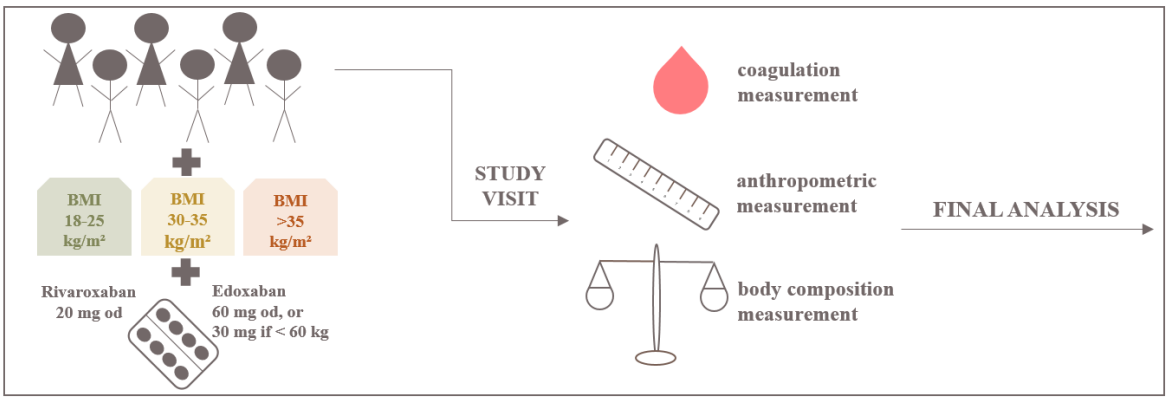

Figure 5. Design of the BIARIVA study

2.3 Coagulation measurements

Specific coagulation measurements included anti-F.Xa levels and direct plasma concentration levels for rivaroxaban, and anti-F.Xa levels for edoxaban. Venous blood samples for coagulation measurement were collected in Vacuette tubes of 3.5 mL volume (Greiner Bio-One, Kremsmünster, Austria) containing 3.8 %-trisodium citrate. Samples were centrifuged at room temperature for 10 minutes and then stored at -20 °C until analysis. Anti-F.Xa levels calibrated for LMWH were obtained from all patients by use of the BIOPHEN Heparin LRT reagent (HYPHEN BioMed, Neuilly-sur Oise, France) on the automated Atellica COAG 360 coagulation analyser system (Siemens Healthineers, Marburg, Germany). For rivaroxaban, plasma concentration levels were directly measured on the automated Atellica COAG 360 analyser (Siemens Healthineers, Marburg, Germany). For edoxaban, plasma concentration levels were calculated based on LMWH-calibrated anti-F.Xa levels following calibration with

the BIOPHEN edoxaban calibrator (HYPHEN Biomed, Neuilly-sur Oise, France). The formula for the calculation of edoxaban plasma concentration levels was as follows:

anti-F.Xa level $_{edoxaban}$ (U/mL) x 148 = plasma concentration level $_{edoxaban}$ (ng/mL)

In addition, the increase in anticoagulant activity, which was defined as the absolute difference between trough and peak levels, was assessed for both anti-F.Xa levels and plasma concentration levels and expressed as Δ.

2.3.1 Plasma concentration levels

Plasma concentration trough and peak levels obtained in the BIARIVA study were compared with expected therapeutic ranges for patients on anticoagulant treatment for VTE as available from a 2021 Update of the International Council for Standardization in Haematology by Douxfils et al.[179] The expected range for trough plasma levels was 32 (6–239) ng/mL for rivaroxaban 20 mg od, 19 (10–39) ng/mL for full-dose edoxaban (60 mg od), and 16 (8–32) ng/mL for reduced-dose edoxaban (30 mg od in patients with <60 kg body weight). For peak levels, the expected ranges were 215 (22–535) ng/mL for rivaroxaban 20 mg od, 234 (149–317) ng/mL for full-dose edoxaban (60 mg od), and 164 (99–225) ng/mL for reduced edoxaban (30 mg od in patients with <60 kg body weight). These expected concentrations correspond to the mean (10^{th}–90^{th} percentile) for rivaroxaban and the median (interquartile range [IQR]) for edoxaban.[179]

2.4 Anthropometric measurements

All participants were weighted in light clothing, without shoes and with an empty bladder on an electronic scale (Seca mBCA 515, Seca GmbH, Hamburg, Germany). The height was measured barefoot using the Seca 360° length measuring device (Seca 274, Seca GmbH, Hamburg, Germany). Weight and height were recorded to the nearest 0.05 kg and 0.1 cm, respectively.

Hip and waist measurements were performed according to the WHO guidelines.[343] Both measurements were taken to the nearest 0.5 cm by use of a flexible tape (Seca GmbH, Hamburg, Germany). To analyse the risk of obesity-related illness due to abdominal fat accumulation, the current waist circumference cut-off points for Caucasians were used (cut-off values for increased risk: ≥80 cm in females, ≥94 cm in males; cut-off values for substantially increased

risk for obesity-related illness: ≥88 cm in females, ≥102 cm in males). The WHR was calculated to further differentiate fat distribution. Established cut-offs that are associated with an increased risk were applied (ratios of ≥0.85 for females and ≥0.90 for males).[343]

2.4.1 Body mass index (BMI)

The BMI of each participant was calculated as the ratio between the measured body weight (kg) and the square of the body height (m). Based on the calculated BMI, the participants were assigned to three BMI categories: normal weight - group I: BMI 18–25 kg/m^2, moderate obesity - group II: BMI 30–35 kg/m^2, severe obesity - group III: BMI >35 kg/m^2.

2.5 Body composition measurement

Two different bioimpedance analysis (BIA) methods, the medical body composition analyser Seca mBCA 515 (method 1; Seca GmbH, Hamburg, Germany) and the BIACorpus RX4000 (method 2; MEDI CAL HealthCare GmbH, Karlsruhe, Germany), were used to provide an accurate and reliable estimation of body composition. The Seca mBCA 515 device enables a tetrapolar measurement in an upright position, whereas the BIACorpus RX4000 device is used for bipolar measurements in a supine position. Both devices were used according to the manufactures' manual.[344,345] FFM and FM were automatically calculated using the Seca analytics 115 PC software and the bodycomposition V9 software. Body composition measures of FM and FFM are expressed as a percentage (%) and as an absolute measure in kg.

2.6 Statistical analysis

Data are given as median and IQR for continuous data, and as a frequency for categorical data. With regard to the primary endpoint, associations between body composition and coagulation parameters were investigated by correlation analyses. Pearson's correlation coefficient (r) or Spearman's rank correlation coefficient (r_s) were used as appropriate. Correlation coefficients are presented with a 95% CI. The magnitude of correlation coefficients is defined as poor <|0.3|, fair |0.3| to |0.5|, moderately strong |0.6| to |0.8| and very strong >|0.8|.[346] An additional multivariable linear regression analysis was performed as an exploratory sensitivity analysis. Potential confounders included in this sensitivity analysis were age, sex and creatinine. Regression coefficients (β) are presented with a 95% CI. Differences in bioimpedance measures evolving from the two different BIA methods were analysed using t-Test or Mann Whitney U-

Test within BMI groups. Differences in measures between BMI categories for each substance were analysed by Kruskal-Wallis test or ANOVA as appropriate (for post hoc pairwise comparison Bonferroni adjustment was used). The decision for parametric or non-parametric analysis was based on visual inspections of Q-Q plots and statistical tests (Shapiro-Wilk test). A p-value less than 5% was considered as statistically significant. Data analysis was performed with IBM SPSS Statistics (IBM Corporation, Armonk, NY, USA).

3 Results

Eighty patients were enrolled in the BIARIVA study, among them 41 with rivaroxaban treatment and 39 with edoxaban treatment. Seven patients did not meet the predefined BMI categories and were not included for the final statistical analysis (four patients of the rivaroxaban group and three patients of the edoxaban group). Two patients were excluded because of errors with body composition measurements (one patient in each study group). Finally, 71 patients were considered for the analysis, with 36 patients in the rivaroxaban group and 35 patients in the edoxaban group. All patients in the rivaroxaban group received full-dose treatment (20 mg od). In the edoxaban group, 31 patients received full-dose treatment (60 mg od), and four patients received a reduced-dose (30 mg od) because of a body weight below 60 kg.

The median age was 49.5 (33.7–61.9) in the rivaroxaban group and 58.0 (43.5–67.0) in the edoxaban group. Female patients accounted for 50.0% and 45.7% of the rivaroxaban and edoxaban groups, respectively.The median BMI was 33.0 (23.5–37.8) kg/m² in rivaroxaban patients and 33.7 (22.9–36.5) kg/m² in edoxaban patients. Isolated DVT was the most common indication for anticoagulant treatment in the rivaroxaban group (n = 14/36, 38.9%), whereas patients in the edoxaban group most frequently had a history of combined DVT and PE (n = 18/35, 51.4%). Patient characteristics are presented in **Table 8.**

3.1 Rivaroxaban

3.1.1 Characteristics of the rivaroxaban study population

From the 36 patients on full-dose anticoagulant treatment with rivaroxaban 20 mg od that were finally analysed, 10 (27.8%) were assigned to BMI group I, 12 (33.3%) to BMI group II, and

14 (38.9%) to BMI group III. The median BMI was 21.0 (18.6–22.7) kg/m² in BMI group I, 31.9 (31.1–33.6) kg/m² in BMI group II and 39.2 (36.9–40.9) kg/m² in BMI group III. The distribution of BMI across the three groups is shown in **Figure 6.**

3.1.1.1 Age

Within BMI categories, the median age was 31.5 (22.8–50.2), 50.5 (42.8–73.9) and 56.0 (43.3–65.5) in BMI groups I, II and III. Age distribution across BMI categories is shown in **Figure 7.**

	Rivaroxaban (n = 36)	**Edoxaban (n = 35)**
BMI group I (18–25 kg/m²)	n = 10/36 (27.8%)	n = 11/35 (31.4%)
BMI group II (30–35 kg/m²)	n = 12/36 (33.3%)	n = 10/35 (28.6%)
BMI group III (>35 kg/m²)	n = 14/36 (38.9%)	n = 14/35 (40.0%)
BMI (kg/m^2)	33.0 (23.5–37.8)	33.7 (22.9–36.5)
Age (years)	49.5 (33.7–61.9)	58.0 (43.5–67.0)
Female sex	n = 18/36 (50.0%)	n = 16/35 (45.7%)
Laboratory parameters		
Haemoglobin (g/dL)	14.1 (13.3–15.7)	13.8 (13.3–15.0)
Platelet count (10^9/L)	227.5 (188.0–260.8)	243.0 (196.0–278.0)
WBC (10^9/L)	6.16 (4.89–7.16)	5.99 (5.29–7.53)
Renal function		
Creatinine (mg/dL)	0.83 (0.73–0.97)	0.92 (0.80–0.99)
GFR (mL/min)	92.4 (82.3–111.0)	82.3 (72.0–94.7)
Event		
PE	n = 12/36 (33.3%)	n = 10/35 (28.6%)
DVT	n = 14/36 (38.9%)	n = 7/35 (20.0%)
DVT + PE	n = 10/36 (27.8%)	n = 18/35 (51.4%)
Recurrent VTE$^+$	n = 8/36 (22.2%)	n = 6/35 (17.1%)
Family history for VTE	n = 12/36 (33.3%)	n = 11/35 (31.4%)
VTE without any risk factor	n = 5/36 (13.9%)	n = 5/35 (14.3%)

Table 8: Patient characteristics
(Reproduced from Kurzmann-Guetl et al.[347])
Data are presented as frequency (%) or median (IQR)
BMI = body mass index; DVT = deep vein thrombosis; GFR = glomerular filtration rate; IQR = interquartile range; PE = pulmonary embolism; VTE = venous thromboembolism; WBC = white blood cell count

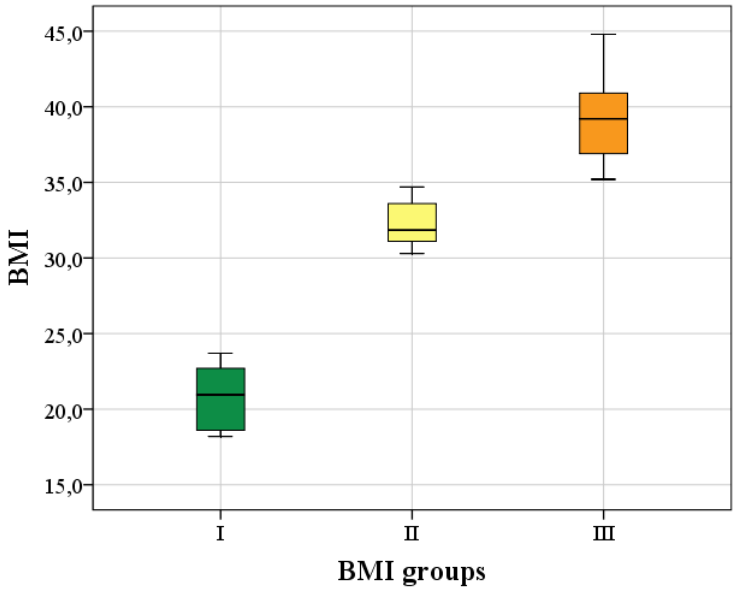

Figure 6: The distribution of BMI in the rivaroxaban group
BMI = body-mass index

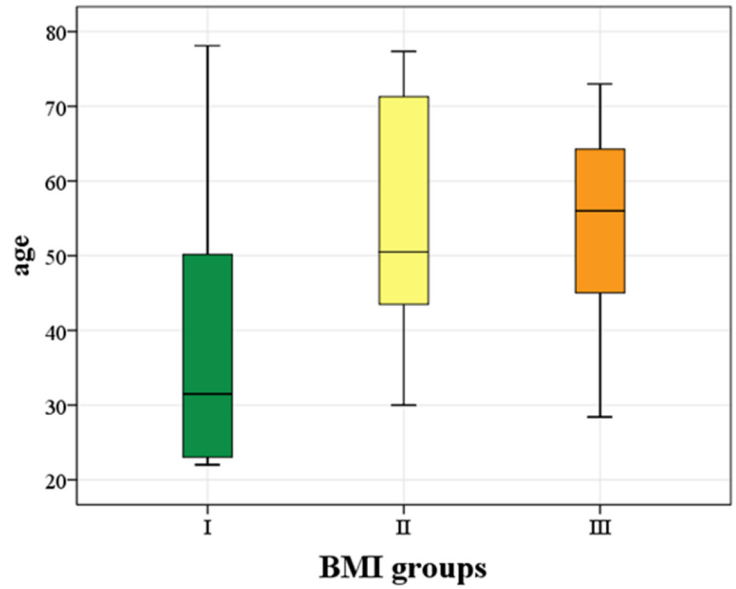

Figure 7: The distribution of age in the rivaroxaban group
BMI = body-mass index

3.1.1.2 Gender

Female patients numbered eight of 10 (80.0%) in BMI group I, four of 12 (33.3%) in BMI group II, and six of 14 (42.9%) in BMI group III.

3.1.1.3 Renal function

The median serum creatinine levels were 0.73 (0.70–0.90) mg/dL in BMI group I, 0.86 (0.64–0.98) mg/dL in BMI group II and 0.92 (0.80–0.97) mg/dL in BMI group III. The median GFR was 110.5 (83.0–118.1) mL/min in BMI group I, 94.1 (79.9–114.9) mL/min in BMI group II and 89.9 (78.6–99.4) mL/min in BMI group III. Neither serum creatinine ($p = 0.16$) nor GFR ($p = 0.30$) differed significantly across BMI categories. Notably, renal function parameters were unavailable for one patient in BMI group II due to difficulties with laboratory measurements. The distribution of renal function parameters among BMI categories is shown in **Figure 8**.

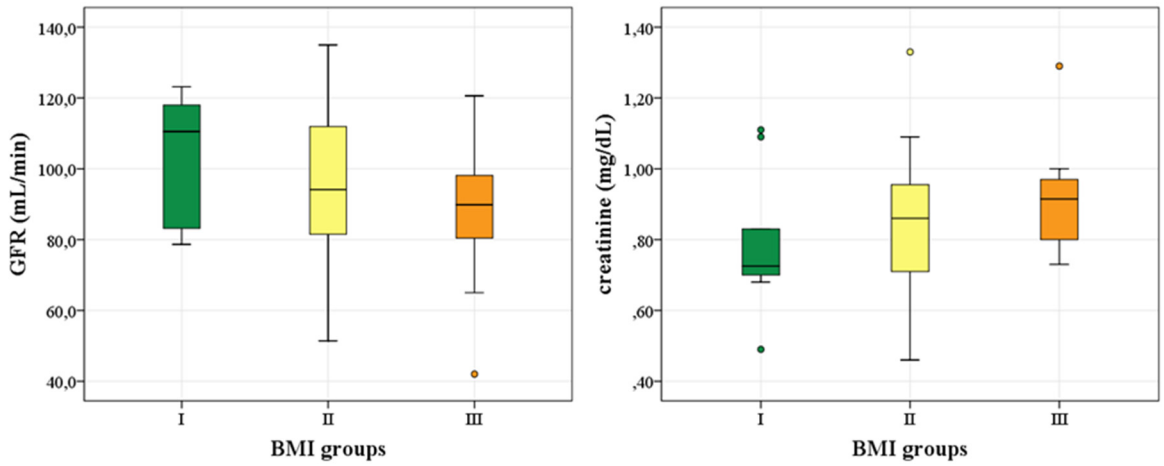

Figure 8: The distribution of renal function parameters among BMI groups in rivaroxaban patients
BMI = body-mass index; GFR = glomerular infiltration rate

3.1.1.4 Events

Among rivaroxaban patients, 14 of 36 (38.9%) discovered isolated DVT, 12 of 36 (33.3%) isolated PE, and 10 of 36 (27.8%) a combined event of DVT and PE. Recurrent VTE – defined as more than one documented VTE event in the medical history at the time of study inclusion – was documented in eight of 36 patients (22.2%).

In BMI group I (n = 10), five patients were diagnosed with DVT, two with PE, and three with combined DVT and PE. Seven patients from BMI group I discovered a single event of VTE. Two patients were classified as having recurrent VTE. Among them, one patient had multiple

DVT events documented in the medical history and also superficial vein thrombosis. The recurrence status was unclear for one patient.

For BMI group II (n = 12), two patients had DVT, five had PE, and five had combined DVT and PE. Seven patients discovered a single event of VTE, and three patients were classified as having recurrent VTE. Furthermore, two patients experienced additional thrombotic events involving superficial or muscle veins.

In BMI group III (n = 14), seven patients had DVT, five had PE, and two had a combined event of DVT and PE. Notably, one patient assigned to the group with isolated PE also had an event of prior CVT in the medical history, and another patient with isolated DVT was additionally diagnosed with AF. Eleven of the 14 patients had a single event of VTE, with one of these patients having an additional event of superficial vein thrombosis, and the three remaining patients discovered more than one event of VTE.

3.1.1.5 Risk factors

Regarding VTE risk factors, intake of oral hormonal contraception was reported in six of the 18 female patients in the rivaroxaban group, including four in BMI group I, and one each in BMI groups II and III. Notably, VTE was directly associated with hormonal contraceptive use only in two females, both belonging to BMI group I.

The most common risk factor identified in the rivaroxaban group was thrombophilia, which was reported in 10 of 36 patients (27.8%). Thrombophilia was reported in seven patients from BMI group I, in one patient from BMI group II, and in two patients from BMI group III. In BMI group I, two patients had a combined thrombophilic disorder, one with methylenetetrahydrofolate reductase (MTHFR) mutation plus APS, and the other one with heterozygous FVL mutation in combination with protein S deficiency. Heterozygous FVL mutation was the most common thrombophilia across all BMI categories, observed in five of ten patients with documented thrombophilic disorders. Other thrombophilic disorders detected within the rivaroxaban group were MTHFR mutation (n = 4, three patients from BMI group I, and one patient from BMI group III), APS (n = 2, both patients from BMI group I), and protein S deficiency (n = 1, from BMI group I). Notably, diagnostics for thrombophilia were available from 28 of 36 patients (77.8%) in the rivaroxaban group, but were missing from four patients from BMI groups II and III, each.

Furthermore, eight patients described immobility as a risk factor with relevant contribution to the development of VTE, which is corresponding to 22.2% of patients in the rivaroxaban group. Immobility due to long-distance travel was found in three patients (one from each BMI category), and immobility due to acute illness was found in five patients (two from BMI group I, one from BMI group II, and two from BMI group III). VTE in a postoperative context was found in three patients (8.3%), all of them belonging to BMI group II.

A single case of CAT was observed, occurring in a patient from BMI group II.

Family history for VTE was positive in 12 of 36 patients (33.3%) of the rivaroxaban group, with six patients belonging to BMI group I, three to BMI group II, and three to BMI group III.

VTE without any identifiable risk factor or risk situation was found in six of 36 patients (16.7%), with all of them belonging to BMI group III.

3.1.1.6 Bleeding complications

Bleeding complications were reported in 10 of 36 patients (27.8%) among the rivaroxaban group. Taking a closer look at the BMI categories, bleeding was reported from two patients in BMI group I, five patients from BMI group II, and three patients from BMI group III. Notably, all bleeding complications were classified minor (prolonged/increased menstrual bleeding: n = 3, gingival bleeding: n = 3, skin bleeding/haematoma: n = 4, nosebleeds: n = 1). In detail, eight patients had bleeding at only one site, and two patients had two manifestations of bleeding (one each from BMI groups II and III).

3.1.2 Coagulation measurements

Coagulation measures comprising anti-F.Xa activity levels and plasma concentration levels at trough, at peak and also the calculated absolute anticoagulant increase from trough to peak for each BMI category are summarised in **Table 9** and are graphically presented in **Figure 9.** No significant differences were found for coagulation measures between BMI groups (Bonferroni adjustment).

	Rivaroxaban
BMI group I (18–25 kg/m^2)	**n = 10**
Anti-F.Xa	
Trough (U/mL)	0.39 (0.27–0.50)
Peak (U/mL)	2.75 (2.41–2.92)
Δ (U/mL)	2.35 (1.91–2.67)
Plasma concentration	
Trough (ng/mL)	23.4 (12.0–26.6)
Peak (ng/mL)	232.9 (207.0–291.7)
Δ (ng/mL)	212.0 (176.7–282.1)
BMI group II (30–35 kg/m^2)	**n = 12**
Anti-F.Xa	
Trough (U/mL)	0.27 (0.13–0.36)
Peak (U/mL)	2.33 (1.80–2.70)
Δ (U/mL)	1.97 (1.58–2.45)
Plasma concentration	
Trough (ng/mL)	16.9 (6.5–30.5)
Peak (ng/mL)	176.3 (156.7–258.2)
Δ (ng/mL)	171.4 (132.4–229.2)
BMI group III (>35 kg/m^2)	**n = 14**
Anti-F.Xa	
Trough (U/mL)	0.30 (0.17–0.73)
Peak (U/mL)	2.68 (2.30–2.92)
Δ (U/mL)	2.10 (1.61–2.63)
Plasma concentration	
Trough (ng/mL)	9.3 (5.0–50.4)
Peak (ng/mL)	244.9 (177.8–271.9)
Δ (ng/mL)	203.8 (150.3–239.8)

Table 9: Coagulation measures for study participants assigned to BMI groups I–III on anticoagulant treatment with rivaroxaban
(Reproduced from Kurzmann-Guetl et al.[347])
Data are given as median (IQR)
BMI = body mass index; anti-F.Xa = anti-factor Xa; IQR = interquartile range; Δ = calculated difference between trough and peak coagulation parameters (= increase in anticoagulant activity/plasma drug levels)

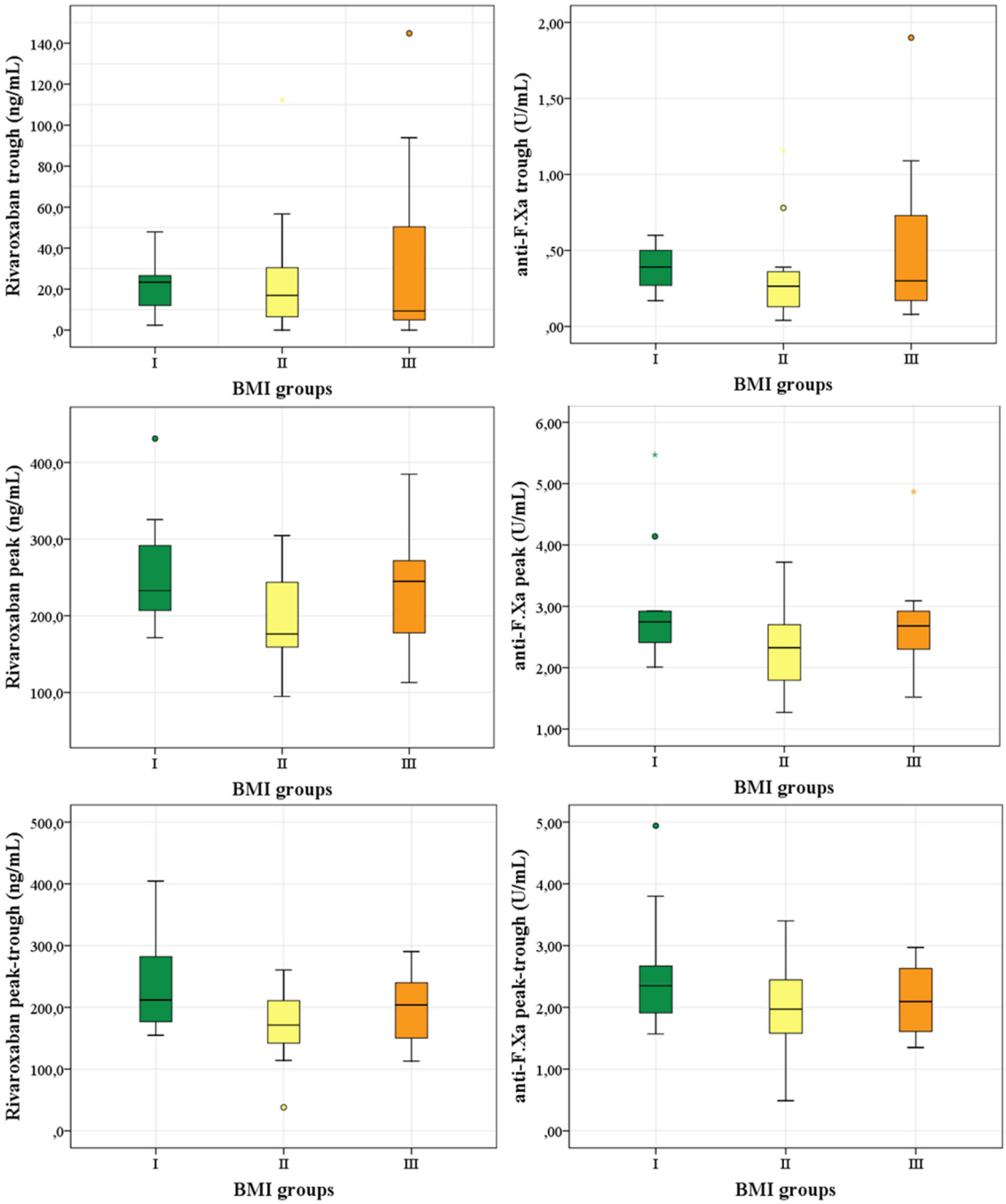

Figure 9: The distribution of plasma concentration and anti-F.Xa activity among BMI categories in the rivaroxaban group
BMI = body-mass index; F. = factor

3.1.2.1 Plasma drug concentration in relation to expected on-therapy ranges

When expected on-therapy ranges were applied to the plasma drug concentration levels that were obtained within the BIARIVA study, trough levels from 10 of 36 patients (27.8%) were below the lower limit. Among these patients, one patient was assigned to BMI group I, three

patients to BMI group II and six to BMI group III. No single patient exceeded the expected range for trough levels. For plasma peak levels, all patients (100.0%) met the expected therapeutic range. Plasma concentration levels at trough and at peak in relation to the expected on-therapy ranges are shown in **Figure 10**.

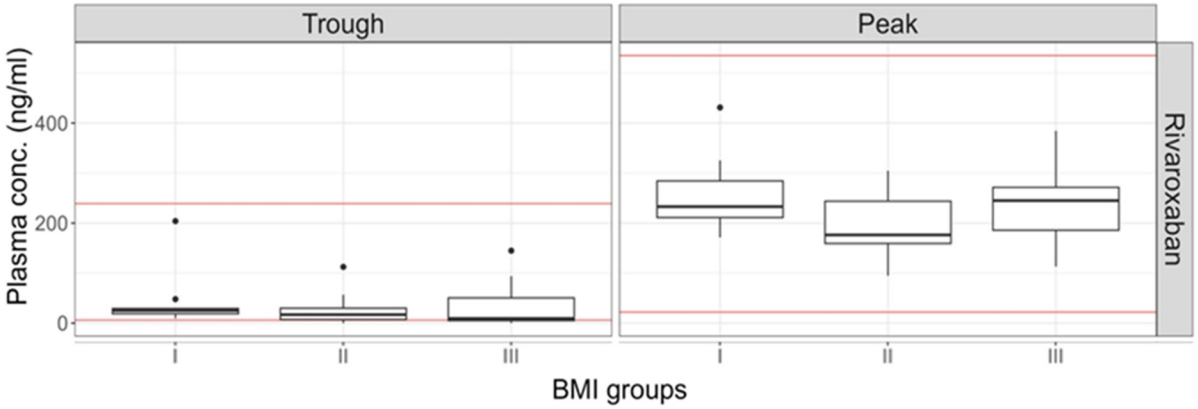

Figure 10: The distribution of plasma drug concentration levels at trough and at peak in patients receiving full-dose rivaroxaban (20 mg od) in relation to expected on-therapy ranges for the treatment of VTE
(Reproduced from Kurzmann-Guetl et al.[347])
BMI = body-mass index; od = once daily; VTE = venous thromboembolism

3.1.3 Anthropometric measurements

The measures for waist circumference and WHR are presented in **Table 10**. The distribution of the WHR among BMI categories for males and females is shown in **Figure 11**.

3.1.4 Body composition measurements

Measures of FM and FFM obtained by Seca mBCA 515 (BIA method 1) and BIACorpus RX 4000 (BIA method 2) for BMI categories are shown in **Table 11.** The distribution of FM and FFM among BMI categories is shown in **Figure 12** for the Seca mBCA 515 device and in **Figure 13** for the BIACorpus RX4000 device. Interestingly, FM was significantly different within each BMI category when comparing Seca mBCA 515 versus BIACorpus RX4000 measures, with a significantly higher FM when using the Seca mBCA 515 system ($p = 0.013$ for BMI group I, $p = 0.002$ for BMI group II, $p = 0.002$ for BMI group III). In general, a higher BMI correlated with a higher body fatness with either measurement.

	Males	Females
BMI group I (18–25 kg/m^2)		
Waist circumference (cm)	84.5 (82.0–87.0)	72.0 (65.8–76.8)
Hip circumference (cm)	92.8 (88.0–97.5)	87.0 (76.5–89.5)
WHR	0.91 (0.89–0.93)	0.87 (0.78–0.92)
BMI group II (30– 35 kg/m^2)		
Waist circumference (cm)	117.3 (107.5–120.5)	101.5 (95.5–108.5)
Hip circumference (cm)	111.0 (107.0–112.5)	110.8 (108.0–113.8)
WHR	1.05 (0.93–1.09)	0.91 (0.86–0.98)
BMI group III (>35 kg/m^2)		
Waist circumference (cm)	130.3 (129.5–132.0)	119.0 (106.5–128.0)
Hip circumference (cm)	124.5 (117.5–134.5)	130.5 (125.0–133.5)
WHR	1.05 (0.9–1.08)	0.90 (0.85–0.93)

Table 10: Waist and hip circumference and the WHR for male and female study participants assigned to BMI groups I–III on anticoagulant treatment with rivaroxaban
Data are given as median (IQR)
BMI = body mass index; IQR = interquartile range; WHR = waist to hip ratio

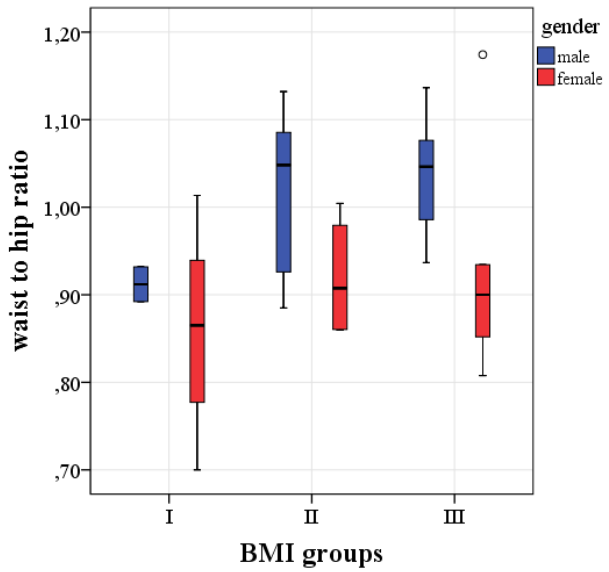

Figure 11: The distribution of the WHR for males and females among BMI categories in the rivaroxaban group
BMI = body-mass index; WHR = waist-to-hip ratio

	Rivaroxaban (n = 36)
BMI group I (18–25 kg/m^2)	**n = 10**
BMI (kg/m^2)	21.0 (18.6–22.7)
BIA method 1 (Seca mBCA 515)	
FM (kg)	15.8 (13.6–17.4)
FFM (kg)	39.3 (37.8–43.9)
BIA method 2 (BIACorpus RX4000)	
FM	12.3 (9.7–15.0)
FFM	41.9 (40.3–45.3)
ΔFM_method 1 versus method 2 (kg)	2.4 (1.7–2.9)
ΔFM_method 1 versus method 2 (%)	4.3 (3.4–5.0)
BMI group II (30–35 kg/m^2)	**n = 12**
BMI (kg/m^2)	31.9 (31.1–33.6)
BIA method 1 (Seca mBCA 515)	
FM (kg)	38.5 (32.9–43.4)
FFM (kg)	63.1 (52.7–71.8)
BIA method 2 (BIACorpus RX4000)	
FM (kg)	33.6 (30.2–39.2)
FFM (kg)	65.8 (55.9–78.6)
ΔFM_method 1 versus method 2 (kg)	4.2 (2.4–6.0)
ΔFM_method 1 versus method 2 (%)	4.4 (2.6–5.2)
BMI group III (>35 kg/m^2)	**n = 14**
BMI (kg/m^2)	39.2 (36.9–40.9)
BIA method 1 (Seca mBCA 515)	
FM (kg)	53.6 (48.5–58.9)
FFM (kg)	73.7 (53.1–77.2)
BIA method 2 (BIACorpus RX4000)	
FM (kg)	46.8 (44.2–57.8)
FFM (kg)	80.8 (54.4–85.6)
ΔFM_method 1 versus method 2 (kg)	5.0 (1.4–7.6)
ΔFM_method 1 versus method 2 (%)	4.1 (1.2–6.0)

Table 11: Bioimpedance measures for rivaroxaban patients assigned to BMI groups I–III
(Reproduced from Kurzmann-Guetl et al.[347])
Data are given as median (IQR).
BIA = bioimpedance analysis; BMI = body mass index; FM = fat mass; FFM = fat-free mass; IQR = interquartile range

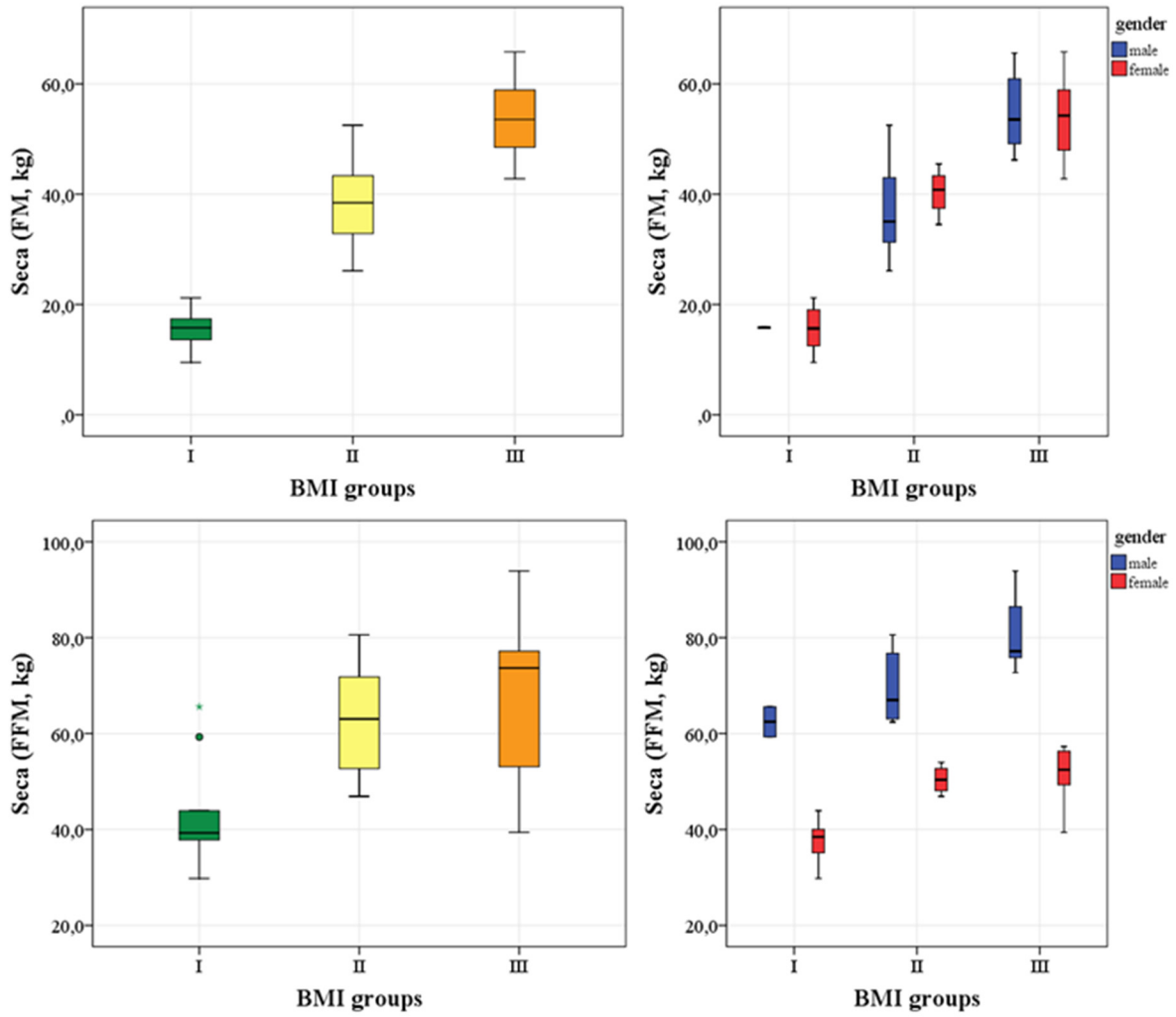

Figure 12: The distribution of FM and FFM among BMI categories obtained with BIA method 1 in the rivaroxaban group
BIA = bioimpedance analysis; BMI = body mass-index; FFM = fat-free mass, FM = fat mass

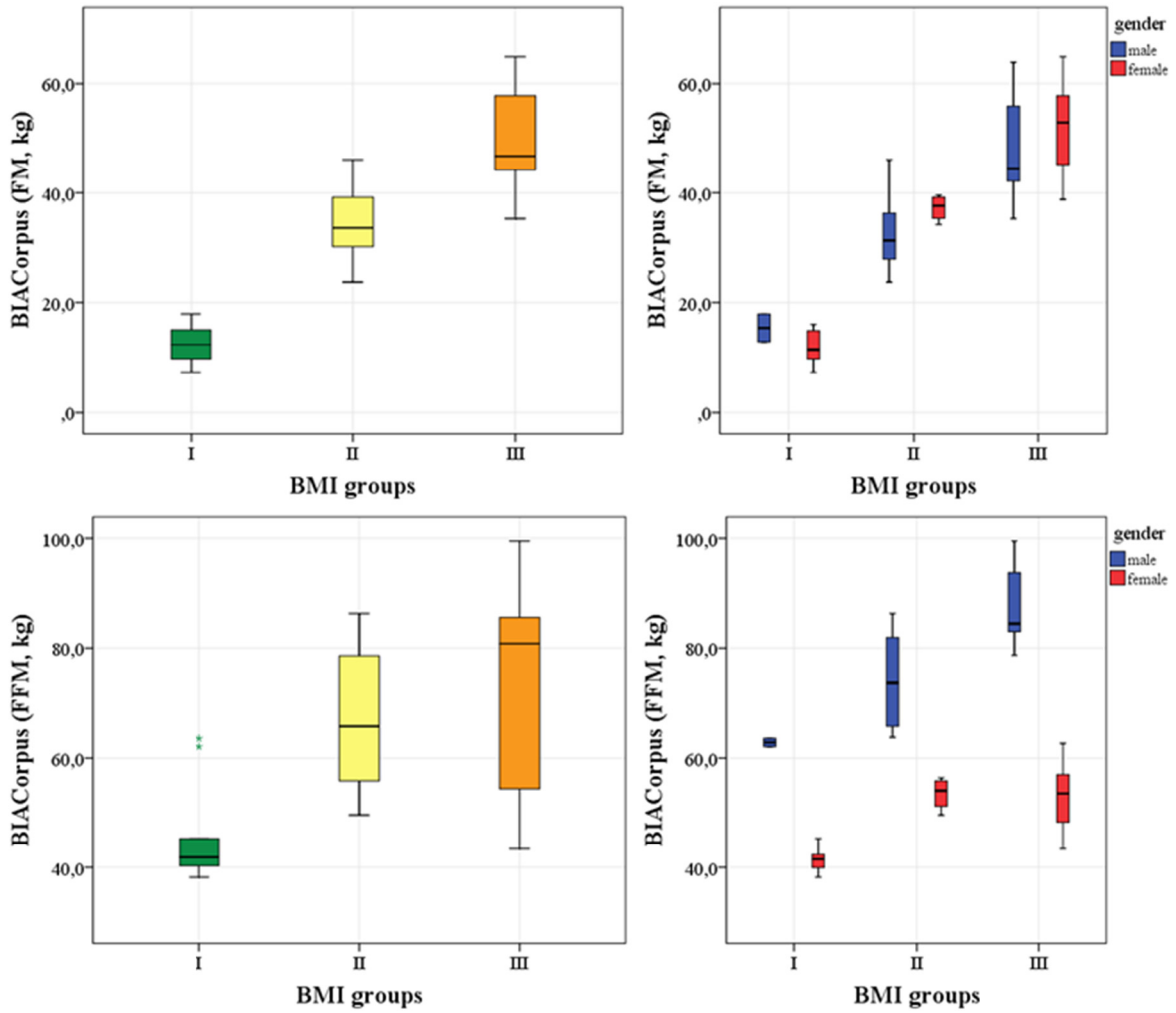

Figure 13: The distribution of FM and FFM among BMI categories obtained with BIA method 2 in the rivaroxaban group
BIA = bioimpedance analysis; BMI = body mass-index; FFM = fat-free mass, FM = fat mass

3.1.5 Primary endpoint analysis: correlation and regression analysis

Body composition measures obtained by Seca mBCA 515 (BIA method 1) and BIACorpus RX 4000 (BIA method 2) did not reveal any significant correlation with specific coagulation measures among patients receiving anticoagulant treatment with rivaroxaban. Correlation coefficients and their 95% CI are shown in **Table 12** (seca mBCA 515 was used for body composition measurements) and **Table 13** (BIACorpus RX4000 was used for body composition measurements). In addition to the primary correlation analysis, an exploratory multivariable linear regression analysis confounding for age, sex and renal function was conducted (**Table 14)**.

Rivaroxaban		BIA method 1 (seca mBCA 515)			
		FM (kg)	**FM (%)**	**FFM (kg)**	**FFM (%)**
Anti-F.Xa (trough; U/mL)	r_s (95% CI)	-0.17 (-0.48–0.17)	-0.09 (-0.42–0.25)	-0.19 (-0.49–0.16)	0.09 (-0.25–0.42)
	p-value	0.31	0.59	0.28	0.59
Anti-F.Xa (peak; U/mL)	r_s (95% CI)	-0.07 (-0.40–0.28)	-0.01 (-0.35–0.33)	-0.10 (-0.43–0.24)	0.01 (-0.33–0.35)
	p-value	0.70	0.94	0.56	0.94
Anti-F.Xa (Δ; U/mL)	r_s (95% CI)	-0.09 (-0.42–0.25)	-0.03 (-0.36–0.31)	-0.13 (-0.45–0.22)	0.03 (-0.31–0.36)
	p-value	0.59	0.88	0.45	0.88
$Plasma_{conc.}$ (trough; ng/mL)	r_s (95% CI)	-0.12 (-0.44–0.23)	-0.04 (-0.38–0.30)	-0.10 (-0.42–0.25)	0.04 (-0.30–0.38)
	p-value	0.49	0.80	0.58	0.80
$Plasma_{conc.}$ (peak; ng/mL)	r_s (95% CI)	-0.05 (-0.39–0.30)	-0.01 (-0.35–0.33)	-0.12 (-0.45–0.23)	0.01 (-0.33–0.35)
	p-value	0.76	0.95	0.49	0.95
$Plasma_{conc.}$ (Δ.; ng/mL)	r_s (95% CI)	-0.10 (-0.43–0.25)	-0.08 (-0.41–0.27)	-0.17 (-0.48–0.19)	0.08 (-0.27–0.41)
	p-value	0.56	0.67	0.34	0.67

Table 12: Correlations between coagulation measures and body composition parameters obtained with BIA method 1 in patients on anticoagulant treatment with rivaroxaban
(Reproduced from Kurzmann-Guetl et al.[347])
Data are presented as correlation coefficients with a 95% CI and p-values for their significance levels
BIA = bioimpedance analysis; CI = confidence interval; FM = fat mass; FFM = fat-free mass; Δ = calculated difference between trough and peak coagulation parameters (= increase in anticoagulant activity/plasma drug levels)

Rivaroxaban		BIA method 2 (BIACorpus RX4000)			
		FM (kg)	**FM (%)**	**FFM (kg)**	**FFM (%)**
Anti-F.Xa (trough; U/mL)	r_s (95% CI)	-0.25 (-0.54–0.10)	-0.20 (-0.50–0.1)	-0.14 (-0.45–0.21)	0.20 (-0.15–0.50)
	p-value	0.15	0.25	0.43	0.25
Anti-F.Xa (peak; U/mL)	r_s (95% CI)	-0.13 (-0.45–0.22)	-0.16 (-0.47–0.19)	-0.10 (-0.43–0.24)	0.16 (-0.19–0.47)
	p-value	0.44	0.37	0.55	0.37
Anti-F.Xa (Δ; U/mL)	r_s (95% CI)	-0.14 (-0.46–0.21)	-0.15 (-0.46–0.20)	-0.16 (-0.47–0.19)	0.15 (-0.20–0.46)
	p-value	0.42	0.40	0.35	0.40
$Plasma_{conc.}$ (trough; ng/mL)	r_s (95% CI)	-0.19 (-0.49–0.16)	-0.12 (-0.44–0.23)	-0.05 (-0.38–0.30)	0.12 (-0.23–0.44)
	p-value	0.28	0.50	0.78	0.50
$Plasma_{conc.}$ (peak; ng/mL)	r_s (95% CI)	-0.12 (-0.44–0.23)	-0.14 (-0.46–0.21)	-0.11 (-0.43–0.25)	0.14 (-0.21–0.46)
	p-value	0.50	0.42	0.55	0.42
$Plasma_{conc.}$ (Δ.; ng/mL)	r_s (95% CI)	-0.15 (-0.47–0.20)	-0.18 (-0.49–0.17)	-0.18 (-0.49–0.18)	0.18 (-0.17–0.49)
	p-value	0.39	0.30	0.31	0.30

Table 13: Correlations between blood coagulation measures and body composition parameters obtained with BIA method 2 in patients on anticoagulant treatment with rivaroxaban
(Reproduced from Kurzmann-Guetl et al.[347])
Data are presented as correlation coefficients with a 95% CI and p-values for their significance levels
BIA = bioimpedance analysis; FM = fat mass; FFM = fat-free mass; Δ = calculated difference between trough and peak coagulation parameters (= increase in anticoagulant activity/plasma drug levels)

Rivaroxaban	Predictor		BIA method 1 (Seca mBCA 515)	BIA method 2 (BIACorpus RX4000)
Anti-F.Xa (trough; U/mL)	FM, kg	p-value β (95% CI)	0.76 -0.001 (-0.009–0.007)	0.64 -0.002 (-0.009–0.006)
	FM, %	p-value β (95% CI)	0.87 0.001 (-0.013–0.016)	0.87 -0.001 (-0.013–0.012)
	FFM, kg	p-value β (95% CI)	0.35 -0.006 (-0.02–0.007)	0.55 -0.004 (-0.017–0.009)
	FFM, %	p-value β (95% CI)	0.87 -0.001 (-0.016–0.013)	0.87 0.001 (-0.012–0.013)
Anti-F.Xa (peak; U/mL)	FM, kg	p-value β (95% CI)	0.30 -0.01 (-0.028–0.009)	0.20 -0.012 (-0.03–0.006)
	FM, %	p-value β (95% CI)	0.88 -0.003 (-0.038–0.033)	0.24 -0.017 (-0.047–0.012)
	FFM, kg	p-value β (95% CI)	**0.03*** -0.034 (-0.065–-0.003)	0.13 -0.023 (-0.054–0.007)
	FFM, %	p-value β (95% CI)	0.80 0.003 (-0.033–0.038)	0.24 0.017 (-0.012–0.047)
Anti-F.Xa (Δ; U/mL)	FM, kg	p-value β (95% CI)	0.31 -0.008 (-0.025–0.008)	0.22 -0.01 (-0.026–0.006)
	FM, %	p-value β (95% CI)	0.80 -0.004 (-0.035–0.027)	0.22 -0.016 (-0.042–0.01)
	FFM, kg	p-value β (95% CI)	0.05 -0.028 (-0.056–0.0)	0.15 -0.019 (-0.047–0.008)
	FFM, %	p-value β (95% CI)	0.80 0.004 (-0.027–0.035)	0.22 0.016 (-0.01–0.042)
$Plasma_{conc.}$ (trough; ng/mL)	FM, kg	p-value β (95% CI)	0.74 -0.11 (-0.82–0.59)	0.66 -0.15 (-0.85–0.54)
	FM, %	p-value β (95% CI)	0.84 0.14 (-1.18–1.45)	0.99 -0.009 (-1.14–1.12)
	FFM, kg	p-value β (95% CI)	0.33 -0.60 (-1.84–0.65)	0.48 -0.41 (-1.58–0.76)
	FFM, %	p-value β (95% CI)	0.84 -0.14 (-1.45–1.18)	0.99 0.009 (-1.12–1.14)

Rivaroxaban	Predictor		BIA method 1 (Seca mBCA 515)	BIA method 2 (BIACorpus RX4000)
$Plasma_{conc.}$ (peak; ng/mL)	FM, kg	p-value β (95% CI)	0.27 -0.90 (-2.53–0.73)	0.19 -1.05 (-2.65–0.55)
	FM, %	p-value β (95% CI)	0.67 -0.65 (-3.75–2.45)	0.24 -1.53 (-4.13–1.07)
	FFM, kg	p-value β (95% CI)	0.07 -2.61 (-5.43–0.21)	0.18 -1.82 (-4.54–0.90)
	FFM, %	p-value β (95% CI)	0.67 0.65 (-2.45–3.75)	0.24 1.53 (-1.07–4.13)
$Plasma_{conc.}$ (Δ.; ng/mL)	FM, kg	p-value β (95% CI)	0.29 -0.79 (-2.27–0.70)	0.22 -0.90 (-2.36–0.56)
	FM, %	p-value β (95% CI)	0.57 -0.78 (-3.6–2.03)	0.20 -1.52 (-3.88–0.83)
	FFM, kg	p-value β (95% CI)	0.13 -2.01 (-4.62–0.60)	0.26 -1.41 (-3.90–1.08)
	FFM, %	p-value β (95% CI)	0.57 0.78 (-2.031–3.60)	0.20 1.52 (-0.83–3.88)

Table 14: Multivariable linear regression analysis confounding for age, sex and renal function in patients on anticoagulant treatment with rivaroxaban
(Reproduced from Kurzmann-Guetl et al.[347])
P-values for predictors and regression coefficients (β) with a 95% CI are shown
BIA = bioimpedance analysis; conc. = concentration; F. = factor; FFM = fat-free mass; FM = fat mass; Δ = calculated difference between trough and peak coagulation parameters (= increase in anticoagulant activity/plasma drug levels)

3.2 Edoxaban

3.2.1 Characteristics of the edoxaban study population

From the 35 patients that were analysed, 31 patients received edoxaban in a full-dose of 60 mg od and four patients were on a reduced-dose of edoxaban 30 mg od because of a body weight below 60 kg. When stratifying the edoxaban study group by BMI, 11 patients (31.4%) were assigned to BMI group I, 10 (28.6%) to BMI group II, and 14 (40.0%) to BMI group III. The median BMI was 22.3 (19.6–22.9) kg/m² in BMI group I, 33.5 (32.2–34.0) kg/m² in BMI group II and 37.6 (36.1–41.4) kg/m² in BMI group III. The distribution of BMI across the three groups is shown in **Figure 14.**

3.2.1.1 Age

Within the BMI categories, the median age was 43.0 (24.0–67.0) in BMI group I, 63.0 (51.5–71.5) in BMI group II, and 58.0 (53.9–63.0) in BMI group III. The distribution of age among BMI categories is shown in **Figure 15**.

3.2.1.2 Gender

Female patients numbered eight of 11(72.7%) in BMI group I, four of 10 (40.0%) in BMI group II, and four of 14 (28.6%) in BMI group III.

3.2.1.3 Renal function

The median serum creatinine levels were 0.89 (0.78–0.92) mg/dL in BMI group I, 0.96 (0.88–1.02) mg/dL in BMI group II and 0.97 (0.80–1.02) mg/dL in BMI group III. The median GFR was 88.0 (73.1–103.8) mL/min in BMI group I, 79.5 (64.7–82.6) mL/min in BMI group II and 86.4 (70.0–98.4) mL/min in BMI group III. Neither serum creatinine ($p = 0.14$) nor GFR ($p = 0.25$) differed significantly across BMI categories. The distribution of renal function parameters among BMI categories is shown in **Figure 16**.

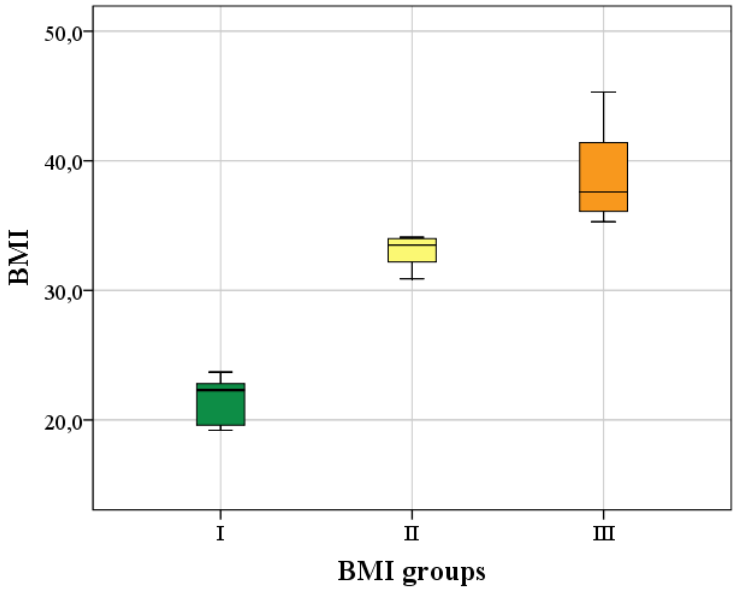

Figure 14: The distribution of BMI in the edoxaban group
BMI = body-mass index

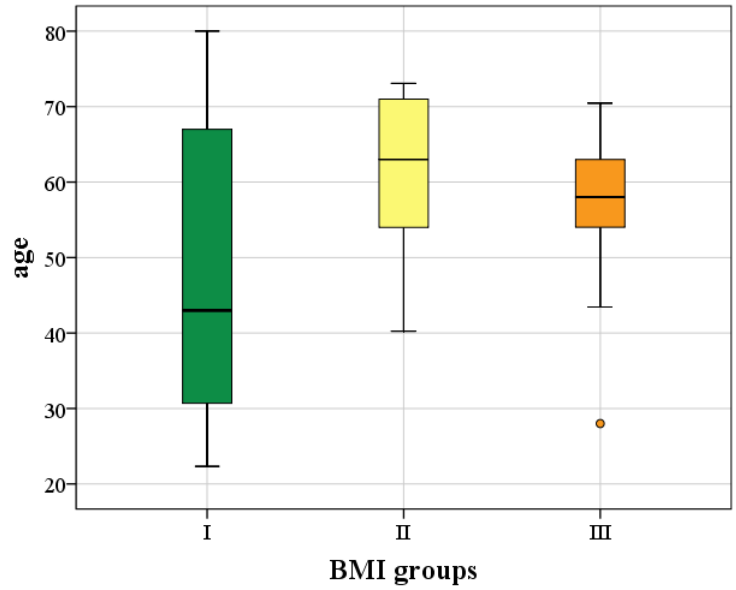

Figure 15. The distribution of age in the edoxaban group
BMI = body-mass index

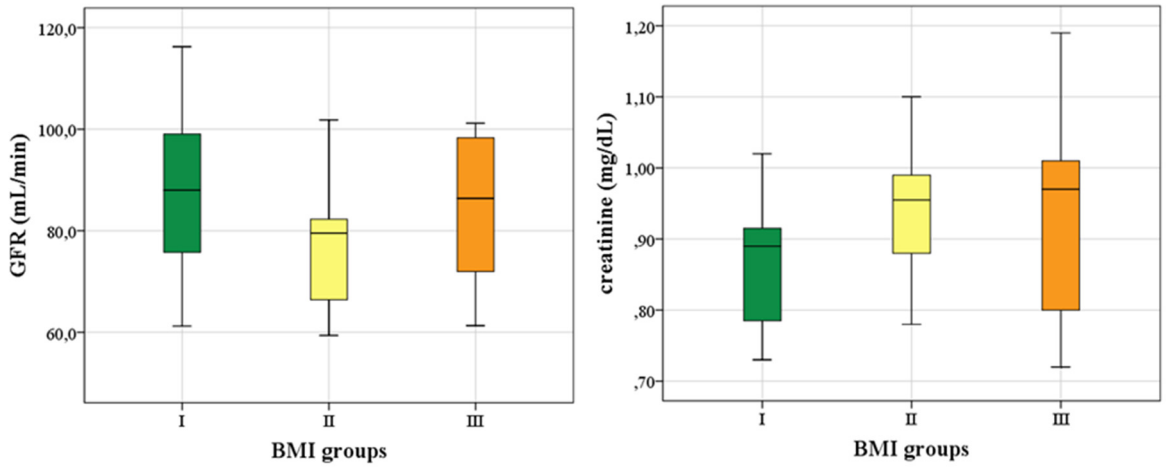

Figure 16. The distribution of renal function parameters among BMI categories in edoxaban patients
BMI = body-mass index; GFR = glomerular filtration rate

3.2.1.4 Events

Among edoxaban patients, seven of 35 (20.0%) discovered isolated DVT, 10 of 35 (28.6%) isolated PE, and 18 of 35 (51.4%) a combined event of DVT and PE. Recurrent VTE was reported in six of 35 patients (17.1%).

In BMI group I (n = 11), four patients were diagnosed with DVT, three with PE, and four with combined DVT and PE. Eight patients from BMI group I discovered a single event, and the remaining three patients in this BMI group had recurrent VTE. Notably, three patients assigned to the category of DVT experienced events at unusual sites (one with thrombosis on the upper extremity deep veins, one with recurrent DVT of the internal jugular veins, and another one with liver vein thrombosis).

For BMI group II (n = 10), one patients had DVT, three had PE, and six had combined DVT and PE. Nine patients of 10 assigned to BMI group II discovered a single event of VTE. For one patient, it remained unclear whether there was a single event or recurrent VTE.

In BMI group III (n = 14), two patients had DVT, four had PE, and eight had combined DVT and PE. Eleven patients had a single event, while the remaining three patients in this group had recurrent VTE. One patient assigned to the group with a single event of combined DVT and PE also had an event of prior superficial vein thrombosis. Additionally, one patient experienced a single PE event, which occurred concurrently with superficial vein thrombosis.

3.2.1.5 Risk factors

Regarding VTE risk factors, hormonal contraceptive use was reported in four of the 16 female patients in the edoxaban group, each belonging to BMI group I. Notably, three females used oral contraceptives, while one used a transdermal method. In three of these four female patients, an additional risk factor or risk situation was also present at the time of VTE occurrence.

Only three patients (8.6%) in the edoxaban group had thrombophilia, all with a heterozygous FVL mutation. Thrombophilia diagnostics – at least to some extent – were only available in 19 patients, which is corresponding to 54.3% of the entire edoxaban group.

Furthermore, seven patients described immobility as a risk factor with relevant contribution to the development of VTE, which is corresponding to 20.0% of the edoxaban study group. Immobility due to long-distance travel was found in one patient who was assigned to BMI group III, and immobility due to acute illness was found in six patients (two from BMI group I, two from BMI group II, two from BMI group III). Four patients experienced a VTE event in a postoperative context, including two from BMI group I and one each from BMI groups II and III. Notably, two of these four patients underwent surgery for an underlying malignancy.

Furthermore, VTE was classified as paraneoplastic, and thus as CAT, in seven patients (20.0%), three from BMI groups I and four from BMI group II.

Family history for VTE was positive in 11 of 35 patients (31.4%) of the edoxaban study group, with three patients belonging to BMI group I, three to BMI group II, and five to BMI group III.

VTE without any identifiable risk factor or risk situation was found in five of 35 patients (14.3%), with one belonging to BMI group I, two to BMI group II, and two to BMI group III.

3.2.1.6 Bleeding complications

Bleeding complications with full-dose anticoagulant treatment were reported in seven of 34 patients (20.6%) among the edoxaban group. Notably, data regarding bleeding complications were not available from one patient from BMI group I. Taking a closer look on the distribution of bleeding complications, bleeding was reported for three patients in BMI group I, two patients from BMI group II, and two patients from BMI group III. Notably, all bleeding complications were classified minor (prolonged/increased menstrual bleeding: n = 1, gingival bleeding: n = 2, skin bleeding/haematoma: n = 2, nosebleeds: n = 4). In detail, five patients had bleeding at only one site, and two patients had at least two manifestations of bleeding (one each from BMI

groups II and III). In addition to the seven patients with bleeding complications mentioned, one further patient showed reduced hemoglobin levels suggestive of gastrointestinal bleeding; however, extensive surgery had been performed, making it impossible to attribute the bleeding only to anticoagulant treatment.

3.2.2 Coagulation measurements

Coagulation measures comprising anti-F.Xa activity levels and plasma concentration levels at trough, at peak and also the calculated absolute anticoagulant increase from trough to peak for each BMI category are summarised in **Table 15** and are graphically presented in **Figure 17**. No significant differences were found for coagulation measures between BMI groups (Bonferroni adjustment).

3.2.2.1 Plasma drug concentration in relation to expected on-therapy ranges

Nine of 35 patients (25.7%) did not meet the lower limit of the expected therapeutic range for edoxaban plasma trough levels. Among these patients, four were assigned to BMI group I and five to BMI group III. In four patients, trough levels were above the upper limit, three of them belonging to BMI group I and only one patient belonging to BMI group II. The predefined therapeutic range for edoxaban peak levels was not met for 19 of 35 patients (54.3%). While 17 of these exceeded the upper limit (seven from BMI group I, six from BMI group II, and four from BMI group III), two of them underwent the lower limit of the expected therapeutic range. Plasma drug concentration levels at trough and at peak in relation to the expected on-therapy ranges are shown in **Figure 18**.

	Edoxaban
BMI group I (18–25 kg/m^2)	**n = 11**
Anti-F.Xa	
Trough (U/mL)	0.08 (0.05–0.32)
Peak (U/mL)	2.11 (1.51–2.44)
Δ (U/mL)	2.00 (1.43–2.40)
Plasma concentration	
Trough (ng/mL)	11.8 (7.4–47.4)
Peak (ng/mL)	312.3 (223.5–361.1)
Δ (ng/mL)	296.0 (211.6–355.2)
BMI group II (30–35 kg/m^2)	**n = 10**
Anti-F.Xa	
Trough (U/mL)	0.15 (0.09–0.16)
Peak (U/mL)	2.21 (1.57–2.46)
Δ (U/mL)	2.10 (1.50–2.29)
Plasma concentration	
Trough (ng/mL)	21.5 (13.3–23.7)
Peak (ng/mL)	327.1 (232.4–364.1)
Δ (ng/mL)	310.8 (222.0–338.9)
BMI group III (>35 kg/m^2)	**n = 14**
Anti-F.Xa	
Trough (U/mL)	0.08 (0.05–0.13)
Peak (U/mL)	1.96 (1.55–2.22)
Δ (U/mL)	1.82 (1.47–2.17)
Plasma concentration	
Trough (ng/mL)	11.8 (7.4–19.2)
Peak (ng/mL)	289.3 (229.4–328.6)
Δ (ng/mL)	268.6 (217.6–321.2)

Table 15: Coagulation measures for study participants assigned to BMI groups I–III on anticoagulant treatment with edoxaban
(Reproduced from Kurzmann-Guetl et al.[347])
Data are given as median (IQR).
BMI = body mass index; anti-F.Xa = anti-factor Xa; IQR = interquartile range; Δ = calculated difference between trough and peak coagulation parameters (= increase in anticoagulant activity/plasma drug levels)

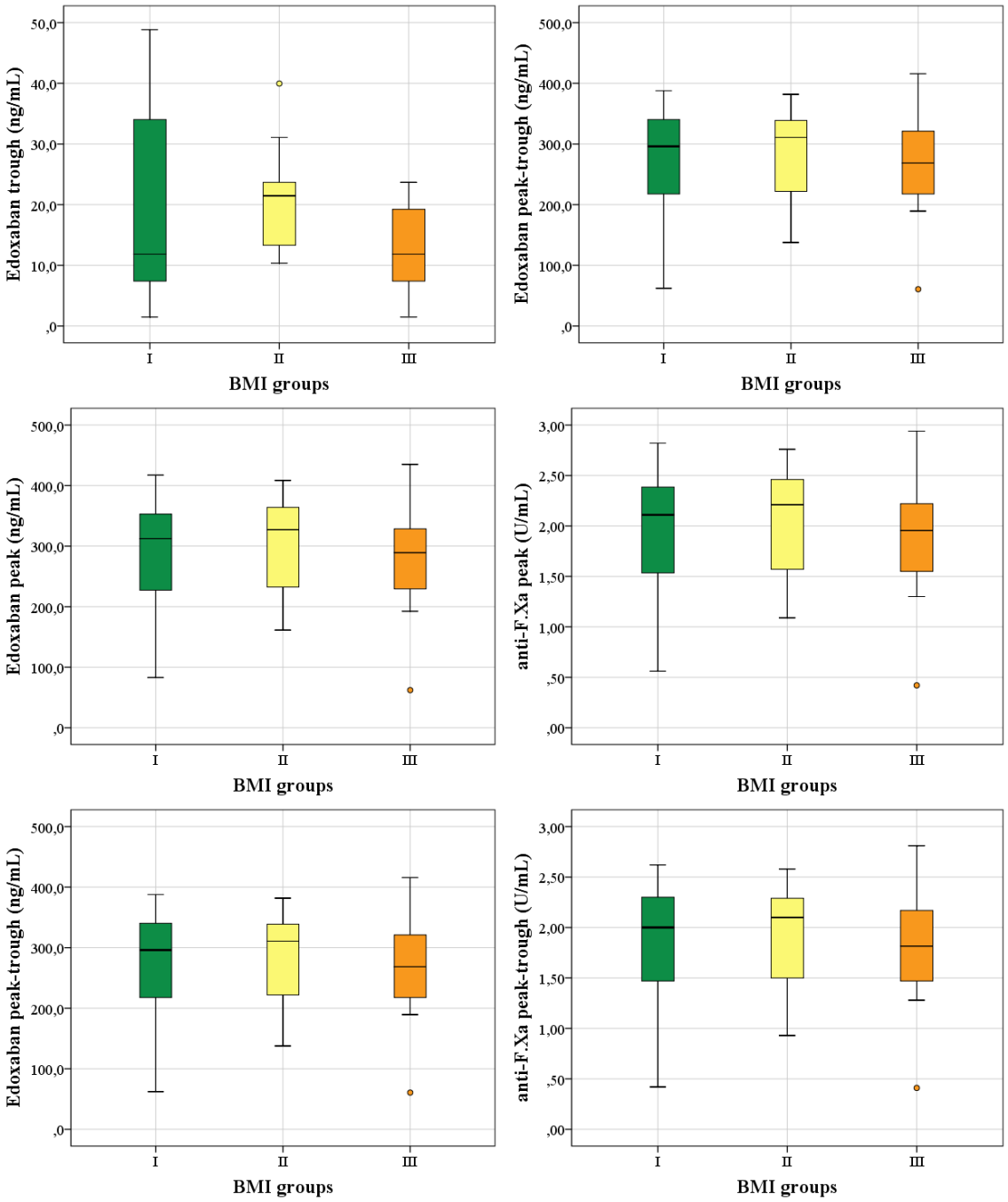

Figure 17. The distribution of plasma concentration and anti-F.Xa activity among BMI categories in the edoxaban group
BMI = body-mass index; F. = factor

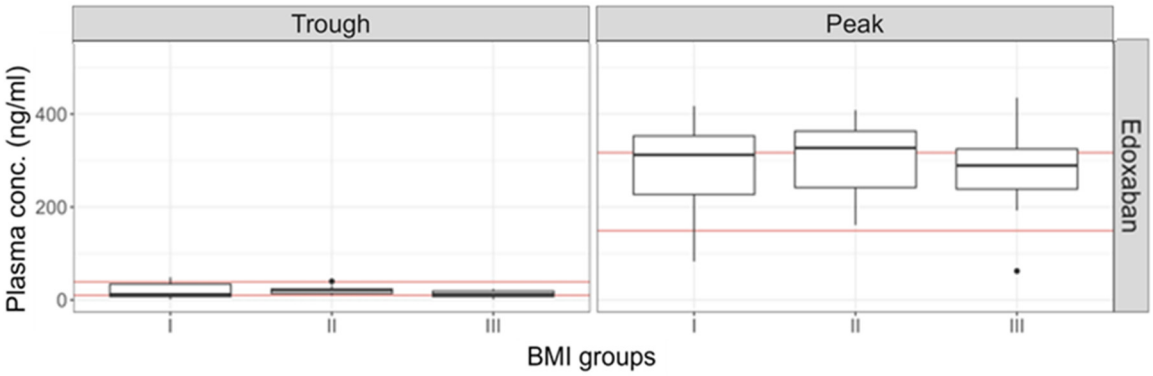

Figure 18: The distribution of plasma drug concentration levels at trough and at peak in patients receiving full-dose edoxaban (60 mg od) in relation to expected on-therapy ranges for the treatment of VTE
(Reproduced from Kurzmann-Guetl et al.[347])
BMI = body-mass index; od = once daily; VTE = venous thromboembolism

3.2.3 Anthropometric measurements

The measures for waist circumference and WHR are presented in **Table 16.** The distribution of the WHR among BMI categories for men and women is shown in **Figure 19**.

	Males	Females
BMI group I (18–25 kg/m^2)		
Waist circumference (cm)	86.5 (85.0–87.5)	72.0 (64.5–78.0)
Hip circumference (cm)	94.0 (90.0–95.0)	86.5 (80.3–88.0)
WHR	0.92 (0.89–0.97)	0.87 (0.81–0.89)
BMI group II (30–35 kg/m^2)		
Waist circumference (cm)	121.0 (119.5–122.0)	104.5 (100.3–111.5)
Hip circumference (cm)	112.8 (108.0–116.0)	122.5 (118.0–125.5)
WHR	1.07 (1.02–1.10)	0.87 (0.84–0.90)
BMI group III (>35 kg/m^2)		
Waist circumference (cm)	130.3 (126.0–133.0)	108.5 (101.5–114.0)
Hip circumference (cm)	122.5 (115.0–131.0)	127.5 (118.0–131.5)
WHR	1.06 (1.04–1.09)	0.88 (0.81–0.92)

Table 16: Waist and hip circumference and the WHR for male and female study participants assigned to BMI groups I–III on anticoagulant treatment with edoxaban
Data are given as median (IQR)
BMI = body mass index; IQR = interquartile range; WHR = waist to hip ratio

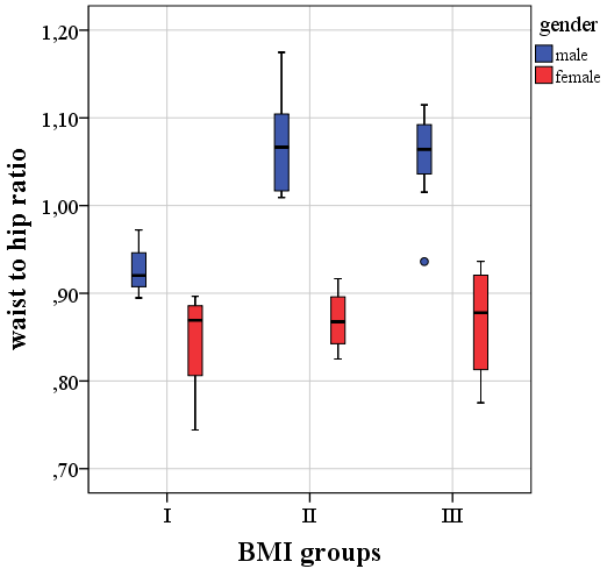

Figure 19. The distribution of the WHR for males and females among BMI categories in the edoxaban group
BMI = body-mass index; WHR = waist-to-hip ratio

3.2.4 Body composition measurements

Measures of FM and FFM obtained by Seca mBCA 515 (BIA method 1) and BIACorpus RX 4000 (BIA method 2) for BMI categories are shown in **Table 17.** The distribution of FM and FFM among BMI categories is graphically shown in **Figure 20** for measures obtained with Seca mBCA 515 (BIA method 1) and in **Figure 21** for measures obtained with BIACorpus RX4000 (BIA method 2). FM was significantly different within each BMI category when comparing measures obtained from the two BIA methods, with a significantly higher FM when using BIA method 1 ($p = 0.008$ for BMI group I, $p = 0.005$ for BMI group II, $p = 0.003$ for BMI group III).

	Edoxaban (n = 35)
BMI group I (18–25 kg/m^2)	**n = 11**
BMI (kg/m^2)	22.3 (19.6–22.9)
BIA method 1 (Seca mBCA 515)	
FM (kg)	15.5 (13.4–19.3)
FFM (kg)	45.3 (38.7–57.7)
BIA method 2 (BIACorpus RX4000)	
FM	12.8 (11.1–16.6)
FFM	45.9 (40.1–62.0)
ΔFM_method 1 versus method 2 (kg)	2.6 (0.9–7.4)
ΔFM_method 1 versus method 2 (%)	3.9 (1.2–10.0)
BMI group II (30–35 kg/m^2)	**n = 10**
BMI (kg/m^2)	33.5 (32.2–34.0)
BIA method 1 (Seca mBCA 515)	
FM (kg)	42.2 (36.0–45.8)
FFM (kg)	65.0 (47.6–72.4)
BIA method 2 (BIACorpus RX4000)	
FM (kg)	33.1 (26.2–38.4)
FFM (kg)	70.3 (56.4–78.3)
ΔFM_method 1 versus method 2 (kg)	6.2 (5.3–7.7)
ΔFM_method 1 versus method 2 (%)	6.2 (5.3–8.0)
BMI group III (>35 kg/m^2)	**n = 14**
BMI (kg/m^2)	37.6 (36.1–41.4)
BIA method 1 (Seca mBCA 515)	
FM (kg)	48.0 (45.4–59.5)
FFM (kg)	73.2 (59.5–80.1)
BIA method 2 (BIACorpus RX4000)	
FM (kg)	43.7 (41.3–55.7)
FFM (kg)	76.3 (58.2–86.6)
ΔFM_method 1 versus method 2 (kg)	4.0 (2.2–6.4)
ΔFM_method 1 versus method 2 (%)	3.4 (1.5–5.1)

Table 17: Bioimpedance measures for edoxaban patients assigned to BMI groups I–III
(Reproduced from Kurzmann-Guetl et al.[347])
Data are given as median (IQR)
BMI = body mass index; FFM = fat-free mass; FM = fat mass; IQR = interquartile range

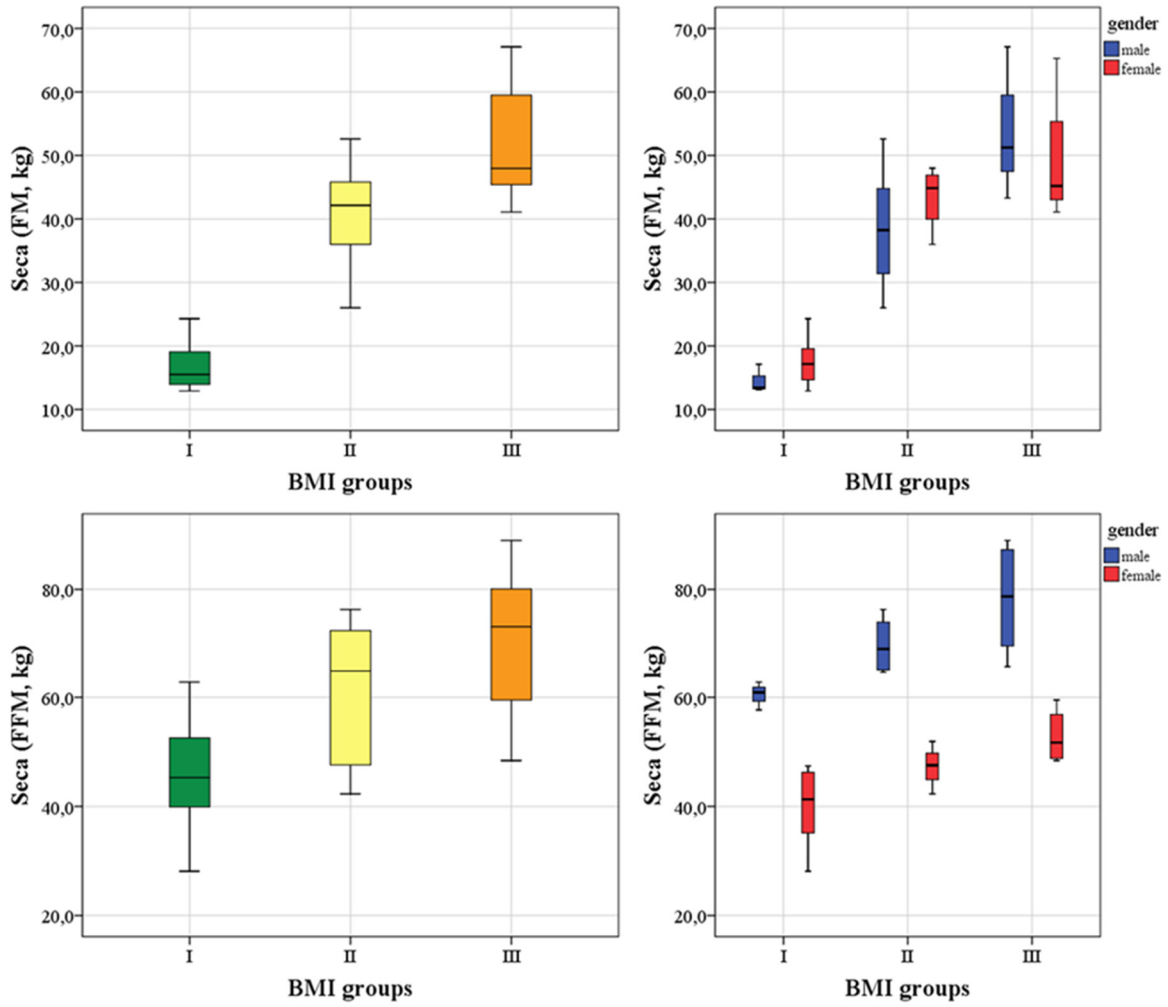

Figure 20. The distribution of FM and FFM among BMI categories obtained with BIA method 1 in the edoxaban group

BIA = bioimpedance analysis; BMI = body-mass index; FFM = fat-free mass; FM = fat mass

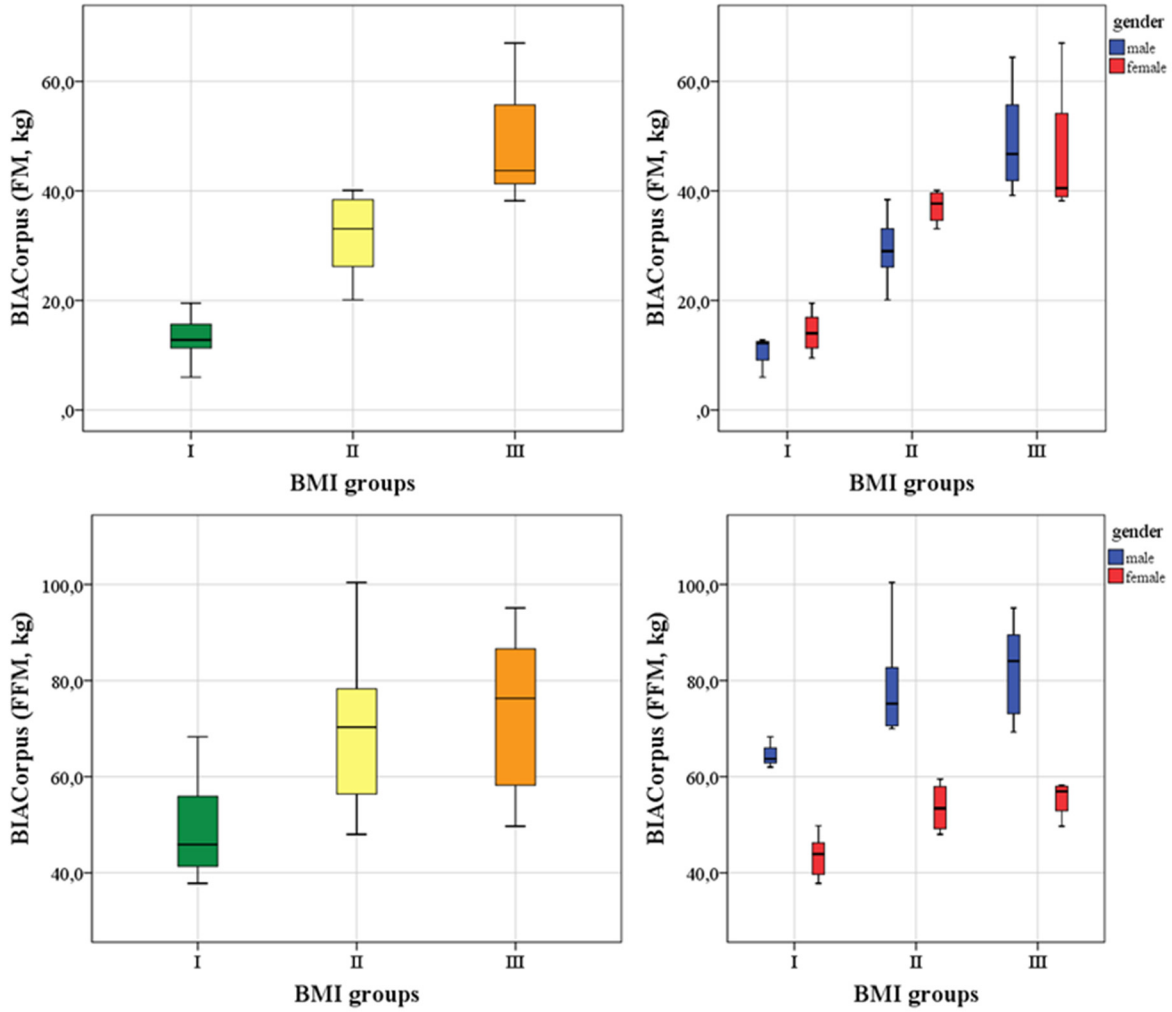

Figure 21. The distribution of FM and FFM among BMI categories obtained with BIA method 2 in the edoxaban group
BIA = bioimpedance analysis; BMI = body-mass index; FFM = fat-free mass; FM = fat mass

3.2.5 Primary endpoint analysis: correlation and regression analysis

For body composition measures obtained by use of method 1, a significant negative correlation was found for absolute FFM with peak anti-F.Xa activity (r_s = -0.44, p = 0.008), the anti-F.Xa absolute increase (r_s = 0.45, p = 0.007), peak plasma concentration levels (r_s = 0-.44, p = 0.008) and with the absolute increase of plasma concentration (r_s = -0.45, p = 0.007). In concordance, significant negative correlations for the absolute FFM obtained with BIA method 2 were found with peak anti-F.Xa activity (r_s = -0.43, p = 0.010), the anti-F.Xa absolute increase (r_s = -0.44, p = 0.008), peak plasma concentration levels (r_s = -0.43, p = 0.010) and with the absolute increase in plasma concentration levels (r_s = -0.45, p = 0.007). Measurements for absolute FM, percentage FM and percentage FFM obtained with both BIA methods did not unveil statistically

significant correlations with coagulation parameters. Correlation coefficients and their 95% CI are shown in **Table 18** for body compositions measurements performed with BIA method 1 and in **Table 19** for body composition measurements performed with BIA method 2. To complement the primary analysis method, which is the correlation analysis, an exploratory multivariable regression analysis was conducted to account for potential confounders including sex, age, and renal function. (**Table 20**). This sensitivity analysis did not confirm the statistically significant findings observed in the correlation analysis, and, in particular, indicated an influence by age and sex.

Edoxaban		**BIA method 1 (Seca mBCA 515)**			
		FM (kg)	**FM (%)**	**FFM (kg)**	**FFM (%)**
Anti-F.Xa (trough; U/mL)	r_s (95% CI)	0.007 (-0.34–0.35)	0.12 (-0.23–0.45)	-0.07 (-0.40–0,28)	-0.12 (-0.45–0.23)
	p-value	0.97	0.48	0.69	0.48
Anti-F.Xa (peak; U/mL)	r_s (95% CI)	-0.12 (-0.44–0.24)	0.28 (-0.07–0.57)	-0.44 (-0.68–-0,11)	-0.28 (-0.57–0.07)
	p-value	0.51	0.10	**0.008***	0.10
Anti-F.Xa (Δ; U/mL)	r_s (95% CI)	-0.11 (-0.44–0.24)	0.29 (-0.06–0.57)	-0.45 (-0.68–-0.12)	-0.29 (-0.57–0.06)
	p-value	0.53	0.09	**0.007***	0.09
$Plasma_{conc.}$ (trough; ng/mL)	r_s (95% CI)	0.007 (-0.34–0.35)	0.12 (-0.23–0.45)	-0.07 (-0.40–0.28)	-0.12 (-0.45–0.23)
	p-value	0.97	0.48	0.69	0.48
$Plasma_{conc.}$ (peak; ng/mL)	r_s (95% CI)	-0.12 (-0.44–0.24)	0.28 (-0.07–0.57)	-0.44 (-0.68–-0.11)	-0-28 (-0.57–0.07)
	p-value	0.51	0.10	**0.008***	0.10
$Plasma_{conc.}$ (Δ.; ng/mL)	r_s (95% CI)	-0.11 (-0.44–0.24)	0.29 (-0.06–0.57)	-0.45 (-0.68–-0.12)	-0.29 (-0.57–0.06)
	p-value	0.52	0.093	**0.007***	0.093

Table 18: Correlations between coagulation measures and body composition parameters obtained with BIA method 1 in patients on anticoagulant treatment with edoxaban
(Reproduced from Kurzmann-Guetl et al.[347])
Data are presented as correlation coefficients with a 95% CI and p-values for their significance levels
BIA = bioimpedance analysis; CI = confidence interval; FFM = fat-free mass; FM = fat mass; Δ = calculated difference between trough and peak coagulation parameters (= increase in anticoagulant activity/plasma drug levels)

Edoxaban		BIA method 2 (BIACorpus RX4000)			
		FM (kg)	**FM (%)**	**FFM (kg)**	**FFM (%)**
Anti-F.Xa (trough; U/mL)	r_s (95% CI)	-0.15 (-0.47–0.21)	-0.08 (-0.41–0.27)	0.009 (-0.33–0.35)	0.08 (-0.27–0.41)
	p-value	0.40	0.65	0.96	0.65
Anti-F.Xa (peak; U/mL)	r_s (95% CI)	-0.09 (-0.42–0.27)	0.29 (-0.06–0.57)	-0.43 (-0.67–-0.10)	-0.29 (-0.57–0.06)
	p-value	0.63	0.096	**0.010***	0.096
Anti-F.Xa (Δ; U/mL)	r_s (95% CI)	-0.064 (-0.40–0.28)	0.31 (-0.04–0.59)	-0.44 (-0.68–-0.12)	-0.31 (-0.59–0.041)
	p-value	0.71	0.074	**0.008***	0.074
$Plasma_{conc.}$ (trough; ng/mL)	r_s (95% CI)	-0.15 (-0.47–0.21)	-0.08 (-0.41–0.27)	0.009 (-0.33–0.35)	0.08 (-0.27–0.41)
	p-value	0.40	0.65	0.96	0.65
$Plasma_{conc.}$ (peak; ng/mL)	r_s (95% CI)	-0.085 (-0.42–0.27)	0.29 (-0.063–0.57)	-0.43 (-0.67–-0.10)	-0.29 (-0.57–0.063)
	p-value	0.63	0.096	**0.010***	0.096
$Plasma_{conc.}$ (Δ.; ng/mL)	r_s (95% CI)	-0.065 (-0.40–0.28)	0.31 (-0.04–0.59)	-0.45 (-0.68–-0.12)	-0.31 (-0.59–0.04)
	p-value	0.71	0.073	**0.007***	0.073

Table 19: Correlations between blood coagulation measures and body composition parameters obtained with BIA method 2 in patients on anticoagulant treatment with edoxaban
(Reproduced from Kurzmann-Guetl et al.[347])
Data are presented as correlation coefficients with a 95% CI and p-values for their significance levels
FFM = fat-free mass, FM = fat mass; Δ = calculated difference between trough and peak coagulation parameters (= increase in anticoagulant activity/plasma drug levels)

Edoxaban	Predictor		BIA method 1 (Seca mBCA 515)	BIA method 2 (BIACorpus RX4000)
Anti-F.Xa (trough; U/mL)	FM, kg	p-value β (95% CI)	**0.02*** -0.002 (-0.003–0.0)	**0.009*** -0.002 (-0.003–-0.001)
	FM, %	p-value β (95% CI)	**0.029*** -0.003 (-0.006–0.0)	**0.003*** -0.003 (-0.006–-0.001)
	FFM, kg	p-value β (95% CI)	**0.034*** -0.003 (-0.006–0.0)	0.17 -0.002 (-0.004–0.001)
	FFM, %	p-value β (95% CI)	**0.029*** 0.003 (0.0–0.006)	**0.003*** 0.003 (0.001–0.006)
Anti-F.Xa (peak; U/mL)	FM, kg	p-value β (95% CI)	0.74 0.002 (-0.01–0.015)	0.59 0.003 (-0.009–0.015)
	FM, %	p-value β (95% CI)	0.80 0.003 (-0.02–0.026)	0.49 0.007 (-0.013–0.027)
	FFM, kg	p-value β (95% CI)	0.79 0.003 (-0.02–0.027)	0.90 -0.001 (-0.022–0.02)
	FFM, %	p-value β (95% CI)	0.80 -0.003 (-0.026–0.02)	0.49 -0.007 (-0.027–0.013)
Anti-F.Xa (Δ; U/mL)	FM, kg	p-value β (95% CI)	0.53 0.004 (-0.008–0.016)	0.38 0.005 (-0.007–0.017)
	FM, %	p-value β (95% CI)	0.59 0.006 (-0.017–0.029)	0.29 0.01(-0.009 – 0.03)
	FFM, kg	p-value β (95% CI)	0.59 0.006 (-0.017–0.029)	0.96 0.001 (-0.02–0.021)
	FFM, %	p-value β (95% CI)	0.59 -0.006 (-0.029–0.017)	0.29 -0.01 (-0.03–0.009)
$Plasma_{conc.}$ (trough; ng/mL)	FM, kg	p-value β (95% CI)	**0.02*** -0.26 (-0.48–-0,045)	**0.009*** -0.28 (-0,49–-0.075)
	FM, %	p-value β (95% CI)	**0.029*** -0.46 (-0.86–-0.051)	**0.003*** -0.51 (-0.83–-0.18)
	FFM, kg	p-value β (95% CI)	**0.034*** -0.446 (-0.86–-0.036)	**0.17*** -0.26 (-0.65–0.12)
	FFM, %	p-value β (95% CI)	**0.029*** 0.46 (0.051–0.86)	**0.003*** 0.51 (0.18–0.83)

Edoxaban	Predictor		BIA method 1 (Seca mBCA 515)	BIA method 2 (BIACorpus RX4000)
$Plasma_{conc.}$ (peak; ng/mL)	FM, kg	p-value β (95% CI)	0.74 0.31 (-1.55–2.17)	0.59 0.48 (-1.32–2.29)
	FM, %	p-value β (95% CI)	0.80 0.44 (-3.01–3.89)	0.49 1.01 (-1.92–3.94)
	FFM, kg	p-value β (95% CI)	0.79 0.46 (-3.01–3.94)	0.90 -0.19 (-3.32–2.94)
	FFM, %	p-value β (95% CI)	0.80 -0.44 (-3.89–3.01)	0.49 -1.01 (-3.94–1.92)
$Plasma_{conc.}$ (Δ.; ng/mL)	FM, kg	p-value β (95% CI)	0.53 0.57 (-1.25–2.38)	0.38 0.76 (-1.0–2.52)
	FM, %	p-value β (95% CI)	0.59 0.90 (-2.48–4.28)	0.29 1.52 (-1.33–4.37)
	FFM, kg	p-value β (95% CI)	0.59 0.91 (-2.49–4.31)	0.96 0,074 (-3.0–3.15)
	FFM, %	p-value β (95% CI)	0.59 -0.90 (-4.28–2.48)	0,29 -1.52 (-4.37–1.33)

Table 20: Multivariable linear regression analysis confounding for age, sex and renal function in patients on anticoagulant treatment with edoxaban
(Reproduced from Kurzmann-Guetl et al.[347])
P-values for predictors and regression coefficients (β) with 95% CI are shown
BIA = bio impedance analysis; conc. = concentration; CI = confidence interval; F. = factor; FFM = fat-free mass; FM = fat mass; Δ = increase from trough to peak levels (= increase in anticoagulant activity/plasma drug levels)

4 Discussion

4.1 Study rationale and results overview

The BIARIVA study was designed as a prospective, single-center, cross-sectional pilot study in patients with VTE, spanning a wide range of BMI categories and focusing particularly on obesity. The primary endpoint was the association between body composition and coagulation measurements in patients treated with rivaroxaban or edoxaban, assessed by correlation analysis.

This study was the first to investigate the relationship between a detailed body composition profile and both peak and trough DOAC coagulation monitoring parameters. By moving beyond conventional metrics such as body weight or BMI, this approach provides a more nuanced characterisation of the interindividual variability in body composition. This concept aligns with recent recommendations from the Lancet Diabetes & Endocrinology Commission, which advocates for a revised and more comprehensive framework for the definition and diagnosis of obesity. These recommendations emphasize the direct assessment of FM or, at a minimum, the use of anthropometric measures such as waist circumference and the WHR to better capture adiposity beyond BMI.[338] The relevance of this research question is further underscored by the continuously rising global prevalence of obesity, with a substantial increase expected over the coming decades.[339,348] Variability in body composition – particularly in the relative distribution of FM and FFM – exists among individuals with normal BMI, but is likely to be more pronounced in patients with obesity.

The main finding in the BIARIVA study was a significant negative correlation of the absolute FFM with coagulation peak parameters and with the absolute increase in anticoagulant activity from trough to peak in patients on anticoagulant treatment with edoxaban. This finding indicates that lower absolute FFM was associated with increased anticoagulant activity and, vice versa, that increased absolute FFM was associated with lower anticoagulant activity. In the rivaroxaban study group, the correlation analysis revealed no significant associations between body composition measures and coagulation parameters. An additional multivariable linear regression analysis was conducted as a sensitivity analysis to evaluate potential confounders comprising age, sex, and renal function. In the edoxaban study group, the observed negative correlations between the absolute FFM and coagulation parameters were not confirmed in the

exploratory multivariable linear regression analysis, suggesting that age and sex could be relevant confounders.

4.2 Interpretation of primary endpoint results

The observed inverse correlations of the absolute FFM with peak coagulation parameters and with the increase in anticoagulant activity from trough to peak in the edoxaban group warrant further investigation in larger, adequately powered studies. In particular, the potential influence of age and sex should be explored in greater detail. The results of the regression analysis should be interpreted with caution, as the limited sample size restricts the robustness and generalisability of these findings. However, both correlation and regression analyses revealed some associations between body composition and coagulation monitoring parameters in the edoxaban group. Therefore, further investigation is justified, particularly in patients receiving edoxaban therapy.

The primary correlation analysis between body composition parameters and coagulation monitoring parameters consistently revealed statistically significant findings across measurements using both BIA methods, the Seca mBCA 515 and the BIACORPUS RX4000. These findings suggest that both approaches may be similarly suitable for addressing the research question. This has potential implications not only for the design of future, larger-scale studies, but also for possible integration into clinical routine.

However, given the pilot nature of the present study, the relatively small sample size, and the absence of clinical outcome data, no direct implications for the use of body composition assessment in guiding DOAC therapy can be drawn at this stage.

4.3 Interpretation of patient characteristics and risk factors

In the BIARIVA study, gender distribution across BMI categories was similar in both treatment groups, with the highest proportion of females observed in BMI group I (eight of 10 in the rivaroxaban group and eight of 11 in the edoxaban group) and the lowest proportion of females in BMI group III (four of 14 in both groups).

The median age of the study population was relatively young, with 49.5 (33.7–61.9) in the rivaroxaban group and 58.0 (43.5–67.0) in the edoxaban group. Patients in both treatment

groups were youngest in BMI group I. The variability of age distribution across the BMI categories and particularly the relatively young median age in study both groups may limit the generalisability of the study findings, especially to older patient populations, who constitute a substantial proportion of individuals that receive anticoagulant treatment with DOACs. Even if patients in BMI group I were significantly younger than in BMI groups II and III, they did not represent a uniformly healthy population with VTE as an isolated medical condition. For example, three patients of 11 from BMI group I experienced VTE in the context of malignancy in the edoxaban group. However, the relatively young median age in BMI group I may be explained by the fact that most patients who experienced VTE in the context of oral hormonal contraception were assigned to this group. VTE events that occurred in patients with an intake of oral hormonal contraception were found in six of 18 females in the rivaroxaban study group and in four of 16 females in the edoxaban group. Except for two females on rivaroxaban treatment, all of these mentioned were belonging to BMI group I. At this point, it should be noted that a causal relationship of VTE with hormonal contraception was assumed only in two cases in the rivaroxaban group and in a single case in the edoxaban group in a female subject that was on transdermal hormonal contraception.

Closer analysis of risk factor distribution revealed a higher prevalence of thrombophilia in the rivaroxaban group compared with the edoxaban group. Overall, thrombophilia was identified in 10 of 36 patients (27.8%) treated with rivaroxaban versus three of 35 patients (8.6%) receiving edoxaban. Notably, the frequencies of thrombophilia in both treatment groups should be interpreted with caution, as thrombophilia screening was not performed as a part of the study, but was based solely on pre-existing records. Consequently, thrombophilia testing was available in nearly 80% of patients in the rivaroxaban group, but only in approximately half of the patients in the edoxaban group. Moreover, in some patients of the edoxaban group, only limited thrombophilia testing had been conducted. Severe thrombophilia was only reported in the rivaroxaban group, with two patients with APS and a single patient with protein S deficiency. All patients in the edoxaban group with thrombophilia had isolated heterozygous FVL mutation, which represents a mild form of thrombophilia.

A positive family history of VTE was observed in approximately one-third of patients in both treatment groups. A history of VTE in the family is associated with an increased risk of VTE recurrence compared with patients without a family history of VTE events. [349] It may therefore

represent a clinically identifiable predisposition in the absence of laboratory confirmation of thrombophilia.

VTE without any identifiable risk factor or risk situation was found more frequently in obese patients than in patients with normal weight. Overall, unprovoked VTE was documented in six of 36 patients (16.7%) in the rivaroxaban group and in five of 35 patients (14.3%) in the edoxaban group. All affected patients in the rivaroxaban group belonged to BMI group III, while among the affected edoxaban patients, two were in BMI group II, two in BMI group III, and only one in BMI group I. Notably, the frequency of VTE without identifiable risk factors in the BIARIVA study was lower than that reported in the literature, in which nearly one third of patients present with VTE of unknown origin.[22]

4.4 Interpretation of body composition and anthropometric measurements

The study results for FM were significantly different within each BMI category when comparing measures obtained with the two methods, with a significantly higher FM when using the Seca mBCA 515. This difference was approximately 5% and has been described previously.[350]

When considering sex-specific differences, absolute FM was more comparable for males and females within BMI categories than FFM, which was much higher for males than for females. This was a general observation in the BIARIVA study, for both study groups and also for measurements performed with both BIA methods. This increased FFM might result from an increased muscle mass in males as compared to females. In existing literature, males are reported to have higher FFM resulting from an increased muscle mass than females, whereas females are known to typically exhibit a higher FM related to their weight, independent of age and BMI.[351-353] However, males are often associated with higher visceral adipose tissue compared with females. Therefore, males were shown to have a more detrimental cardiometabolic risk profile at similar age and BMI. Interestingly, in case of an increased visceral adipose tissue in females, the associated risk was more pronounced than those of males.[353] In the BIARIVA study, for both groups, rivaroxaban and edoxaban, the WHR was lower for females compared to males in BMI groups I to III. While the waist circumference was higher in males for each BMI category, hip circumference was more comparable between males and females among the rivaroxaban study group. Thus, the increased waist circumference

among rivaroxaban patients was the main factor for the higher WHR in males than in females. Among the edoxaban study group, waist circumference was higher for males than for females among BMI groups I to III. Interestingly, hip circumference among edoxaban patients was higher in males in BMI group I than in females, but was higher in females than in males in BMI groups II and III. The finding of an increased waist circumference in males mirrors again the known male pattern of visceral fat distribution. Fat distribution has a major impact on cardiovascular risk and may be more predictive than total body fat mass.[353] In contrast to males, females often present with an increase in lower extremity fat, which has proven kind of protective force against cardiometabolic disease.[354]

4.5 Body composition measurement methods

Body composition measurements in the BIARIVA study were conducted using two different BIA methods; the Seca mBCA 515, which is a tetrapolar measurement method on patients in an upright position, and the BIACorpus RX4000, which is a bipolar measurement method to be performed on patients in a supine position. The decision to use two different BIA systems was made to strengthen the study's robustness and minimise method-specific biases. In general, BIA is readily applicable and is commonly used to assess body composition in clinical practice, but also in research studies. However, BIA is not classified as a reference method.[355] Key limitations of BIA include its reliance on empirical equations and assumptions of constant tissue hydration, rendering it sensitive to hydration status, body geometry, and population characteristics, which may lead to systematic bias in estimated FM and FFM.[356] Traditional reference methods to assess body composition comprise dual-energy X ray absorptiometry (DXA), CT or MRI.[357]

DXA was originally developed to measure bone mineral density for osteoporosis screening.[357] Body composition estimates comprising FM and FFM are derived by differentiating bone mineral, lean soft tissue, and FM, with FFM calculated as the sum of bone mineral and lean soft tissue.[358,359] Unlike CT or MRI, which require patients to lie within an enclosed or semi-enclosed imaging device, DXA scans are performed on an open padded table over which a scanning arm passes across the body. DXA offers several advantages. For example, scans are rapid and take only a few minutes, and radiation exposure is minimal, and even low enough to be safely used in children or in pregnant women. Limitations include the need for a licensed technologist to operate the device and the associated operational costs, which confine most

DXA availabilities to hospitals or research centers that frequently perform body composition assessments.[357] Regarding accuracy, DXA is also sensitive to changes in the body fluid status. Therefore, recent water intake, strenuous exercise or oedema may alter estimates of FFM.[360] Despite these limitations, DXA's low participant burden and the reasonable cost profile makes this method the most commonly used to assess FM and FFM in large-scale body composition studies.[357] Whole-body MRI is regarded as one of the most accurate techniques for assessing body adipose tissue, with an error margin of less than 3%, validated through comparisons between MRI measurements and direct cadaver analyses.[361] Key advantages of MRI include the absence of ionising radiation and its superior ability to differentiate muscle from adipose tissue.[362] Importantly, contrast agents are not required for whole-body composition scans, and MRI is less sensitive to fluctuations in hydration compared with DXA.[355,363] However, the high cost of MRI equipment, ongoing maintenance, operational requirements, and the need for a licensed technician limit its application to smaller sample sizes in specialized research centers or hospitals. Considering the aging population and the associated higher incidence of metallic implants, the use of MRI in this patient group is inherently limited. Like MRI, CT can differentiate between subcutaneous and visceral adipose tissue. Advantages compared to MRI are that CT scans can be performed more rapidly, are more widely available in hospitals, are less costly per scan and can be used in patients with metallic implants. CT scans provide excellent accuracy, but due to radiation exposure, repeated or research-focused measurements are often not feasible.[357] DXA offers a lower-cost and safer alternative for estimating visceral adipose tissue; however, its predictive accuracy is limited, with percentage errors around 16%.[364-366]

The BIARIVA study was designed with a pragmatic and clinically oriented approach, and therefore, body composition was exclusively assessed using BIA as a non-invasive, cost-effective and easily applicable method. The absence of body composition measurements using reference methods can be considered a limitation.

Several studies have evaluated the accuracy of BIA in comparison with reference methods, reporting inconsistent results. A comparative study of three methods to assess body composition including DXA, CT and BIA reported an excellent correlation between DXA and CT measurements. A similarly strong correlation was observed between DXA and BIA measurements; correlations between measurements from CT and BIA were lower but remained statistically significant. The BIA method that was used in this study is the Bodystat

QuadScan4000 (Bodystat Ltd., Isle of Man), which is a multiple-frequency device that performs whole-body impedance measurements using a tetrapolar configuration on patients in the supine position.[367] Some more evidence is available from a large retrospective analysis comparing body composition assessment by DXA and BIA also using the Bodystat QuadScan4000. In this analysis, a higher concordance was reported for FM than for FFM.[356] With its characteristics, the Bodystat Quad Scan 4000 is methodologically comparable to other multiple-frequency BIA devices, such as the Seca mBCA and the BIACorpus RX4000 that were used in the BIARIVA study.

For the Seca mBCA 515 device, some validation against reference techniques is available. In a clinical evaluation, BIA measurements obtained with the Seca mBCA515 were compared against DXA measurements in adults across a broad BMI spectrum.[368] For the BIACorpus RX 4000, there is a relative paucity of device specific validation studies in peer-reviewed literature. However, the system is based on established methodological principles. These technical characteristics are shared with a range of clinically validated BIA platforms that have been evaluated against DXA.[356] A key finding across the two aforementioned validation studies is that BIA tends to overestimate FFM and to underestimate FM compared with DXA measurements.[356,368]

4.6 Interpretation of plasma concentration levels

In the present BIARIVA study, both anti-F.Xa activity and plasma DOAC concentrations were measured at trough and peak. While plasma concentration measurements reflect the absolute amount of circulating drug, anti-F.Xa activity directly reflects coagulation inhibition. In general, anti-F.Xa measurements are easier to implement and more widely available in routine clinical practice. Both anti-F.Xa measurements and plasma concentration levels were considered for the primary endpoint correlation analysis. Since edoxaban plasma levels were calculated from anti-F.Xa activity, no differences between correlations based on anti-F. Xa and those based on plasma concentrations were anticipated.

When expected “on therapy” plasma drug concentration ranges were applied to trough levels as obtained for BIARIVA study participants, 27.8% of rivaroxaban patients and 25.7% of edoxaban patients had levels below the anticipated range. For peak levels, all rivaroxaban patients fell within the expected range, whereas two edoxaban patients (5.7%) were below their

range. Notably, most rivaroxaban patients with trough levels below the expected "on-therapy" range belonged to BMI groups II or III (nine of 10 patients), with the highest proportion observed in patients with a BMI >35 kg/m² (six of 10 patients).

Previous studies assessing rivaroxaban plasma concentration levels reported that 25–50% of patients with obesity did not meet the expected "on-therapy" ranges.[317,334] This is consistent with the BIARIVA results for rivaroxaban trough levels, but not for peak levels. Notably, the expected on-therapy peak ranges published for patients receiving full-dose rivaroxaban for the diagnosis of VTE are extremely wide (215 [22–535] ng/mL, given as mean [10th–90th] percentile) as compared to peak ranges published for other indications such as AF (249 [164–343 ng/mL], given as mean [IQR]).[178,179] This very broad therapeutic window might explain our observation that 100% of rivaroxaban patients were within the expected therapeutic range for peak level measurements. For edoxaban, almost half of the study participants (48.6%) exceeded the expected therapeutic peak range. Of these, seven were from BMI group I, six from BMI group II, and four from BMI group III. In total, four participants in the BIARIVA study from BMI group I were receiving reduced-dose edoxaban because their body weight was below 60 kg. Due to the established reduction in drug exposure associated with reduced-dose edoxaban, specific "on-therapy" plasma drug concentration ranges have been defined.[179,369] When these specific ranges published for VTE were applied to the four patients in the BIARIVA study on reduced-dose edoxaban, most trough and peak levels measured were outside these predefined target ranges, above or also below. As for the very small sample size, further analysis was not feasible. However, definite therapeutic targets are still unknown for DOACs. Currently available reference levels vary in literature and only represent "expected" or "on-therapy" ranges rather than explicit therapeutic targets.[317]

The recommendation to consider plasma level measurements of DOACs in obese patients originated primarily from early pharmacokinetic concerns and limited clinical evidence in this population. Initial guidance from the SSC/ISTH in 2016 advised against the use of DOACs in patients with a total body weight >120 kg or a BMI >40 kg/m², and suggested measuring drug-specific trough and peak levels if DOACs were used, due to the paucity of data and the potential for reduced drug exposure in extreme body weights.[311] This cautious approach was largely based on pharmacokinetic studies showing modest reductions in drug exposure at higher body weights, as observed with apixaban and rivaroxaban, although the clinical relevance of these changes remained uncertain.[314,315] Additionally, small observational studies reported that a

substantial proportion of patients with a body weight >120 kg exhibited peak DOAC concentrations below the expected on-therapy ranges, further supporting concerns about potential underexposure.[334] Subsequent evidence from post-hoc analyses of large RCTs, particularly in VTE populations, challenged this initial concerns. For example, analyses from the AMPLIFY VTE trial demonstrated consistent efficacy and safety of apixaban in patients with high body weight or obesity, supporting the use of standard dosing strategies in this population.[319] In post-hoc analyses of EINSTEIN-DVT and EINSTEIN-PE trials, patients with a high BMI or body weight showed similar outcomes with rivaroxaban and VKAs.[312] As a result, the updated SSC/ISTH guidance published in 2021 no longer recommended routine monitoring of DOAC plasma levels in obese patients with VTE and instead supports the use of standard doses of apixaban and rivaroxaban regardless of body weight.[317]

Data on the relationship between measured trough and peak levels of DOACs and clinical outcomes are scarce, and most available evidence is derived from cohorts with AF rather than VTE. The relationship between trough and peak DOAC plasma concentrations and bleeding complications – including major bleeding, CRNMB, and minor bleeding – was evaluated in a cohort of 565 patients with AF. Of these, 172 received rivaroxaban, 185 dabigatran, and 280 apixaban; patients on edoxaban were not included in this analysis. At the one-year follow-up, event rates were low, with 3.36% experiencing major bleeding, 1.06% CRNMB, and 8.31% minor bleeding. Patients who experienced bleeding events had higher peak DOAC plasma concentrations, whereas trough levels showed no association with bleeding occurrence. Notably, all bleeding events – including minor ones – were analysed regardless of their clinical relevance.[370] Another analysis conducted in the same cohort showed that thromboembolic events occurred only in patients who had very low trough levels.[371]

For rivaroxaban, the relationship between drug exposure and clinical outcomes in patients treated for VTE was evaluated using data from the phase III EINSTEIN-DVT and EINSTEIN-PE trials. As direct plasma concentration measurements were not available, exposure was estimated based on individual changes in prothrombin time (PT) and its established correlation with rivaroxaban plasma levels. Both efficacy (recurrent DVT and PE) and safety outcomes (major and non-major bleeding) were assessed, and exposure-response relationships were analysed using regression models. Exposure estimates were evaluated for 4,130 patients during the td dosing phase and for 3,953 patients during the od phase. Notably, body weight and BMI were not considered in this analysis. Overall, exposure-response relationships were shallow or

absent for both efficacy and safety outcomes. Accordingly, no clear therapeutic exposure window associated with an improved benefit-risk profile could be identified, suggesting that routine monitoring of rivaroxaban levels is unlikely to provide clinical benefit in patients with VTE.[372]

For edoxaban, evidence on the association between BMI and clinical outcomes is available from the phase III ENGAGE AF-TIMI 48 trial conducted in patients with AF. The study population included a substantial proportion of patients with elevated BMI, with 40.3% classified as obese (BMI >30 kg/m²). Within this group, 24.8% were moderately obese (BMI 30 to <35), 10.0% were severely obese (BMI 35 to <40), and 5.5% very severely obese (BMI ≥40). This distribution indicates that the trial captured a broad spectrum of obesity, supporting the applicability of its findings to overweight and obese populations, although extrapolation to VTE patients should be made with caution given the AF setting. In the ENGAGE AF-TIMI 48 trial, trough plasma concentrations were assessed one month after randomisation in the high-dose arm of the trial. Patients received edoxaban 60 mg once daily, with dose reduction to 30 mg in the presence of predefined criteria (estimated creatinine clearance ≤50 mL/min, body weight ≤60 kg, or concomitant use of P-glycoprotein inhibitors). Trough concentrations as well as anti-F.Xa activity were comparable across BMI categories, irrespective of the dose reduction status. Despite the absence of BMI-related differences in PK/PD, a higher BMI was independently associated with a lower risk of stroke or systemic embolism and reduced mortality. At the same time, increasing BMI was linked to a higher risk of major and CRNMB. Notably, no detailed body composition profile was obtained in the ENGAGE AF-TIMI 48 trial, and there were only trough but not peak coagulation measurements performed.[373,374]

The pattern observed in the ENGAGE AF-TIMI 48 study – where a higher BMI was associated with lower risks of stroke, systemic embolism, and mortality, but increased bleeding risk – is consistent with the so-called “obesity paradox,” suggesting a dissociation between drug exposure and clinical outcomes. The obesity paradox refers to the observation that, despite its well-known detrimental effects on disease development, obesity appears to confer a protective effect against recurrent vascular events and mortality.[375] Although both obesity and AF are diseases associated with negative outcomes, studies have shown that patients with a high BMI and AF have a better prognosis than patients with a normal BMI.[376,377] Several explanations have been proposed for the “obesity paradox” phenomenon. First, residual confounding may play an important role, as patients with normal BMI are often older, frailer, or have a higher

burden of comorbidities, all of which are strong predictors of adverse outcomes. Second, obese patients may benefit from greater metabolic and nutritional reserves, potentially conferring resilience in the setting of chronic disease. Third, differences in treatment patterns, including more intensive medical therapy and closer follow-up, may contribute to improved outcomes in higher BMI groups.[378] Importantly, a meta-analysis of DOAC-AF trials indicates that this paradox is more consistently observed in randomised datasets than in observational studies, further supporting the role of study design and residual confounding.[379]

Evidence for an "obesity paradox" has also been described in patients with VTE, with some studies reporting an inverse association between BMI and adverse outcomes such as mortality or recurrent events.[380,381] Similarly, analyses from clinical trial populations have suggested that a lower BMI may be associated with a higher risk of VTE or worse outcomes, further supporting a paradoxical relationship between body composition and prognosis.[382] However, these findings remain inconsistent across studies and are less robust than in other cardiovascular conditions.[383] Since the BIARIVA study did not assess clinical safety and efficacy outcomes, no conclusions regarding the obesity paradox can be drawn.

4.7 Pharmacodynamic and pharmacokinetic aspects

From a pharmacokinetic perspective, both rivaroxaban and edoxaban exhibit only moderate lipophilicity, with limited accumulation in adipose tissue.[170,384] This provides a biological rationale for a stronger association with FFM than with FM. Based on these considerations, FFM was assumed to be the more relevant determinant for the presented research question.

When comparing the pharmacodynamics and pharmacokinetics of the two DOACs, rivaroxaban and edoxaban, significant differences in their profiles are evident, despite both being highly selective, competitive and concentration-dependent inhibitors of F.Xa. Differences include various plasma protein binding (98% for rivaroxaban and 55% for edoxaban) and volume of distribution (50 L for rivaroxaban and 107 L for edoxaban).[385,386] Notably, the lowest plasma-protein binding among DOACs is reported for dabigatran (3%).[387] Lipophilicity of drugs influences their distribution within the body and is quantified as log P, with higher values indicating greater lipophilicity. In this context, edoxaban not only has a lower lipophilicity compared to rivaroxaban (log $P_{edoxaban}$ 0.90–1.61 versus log $P_{rivaroxaban}$ 1.74–1.90), but it also has the lowest lipophilicity among all approved DOACs (log $P_{apixaban}$ 1.83–

2.22, and log $P_{dabigatran}$ 4.59–5.17).[384] On the basis of log P as a measure of DOAC lipophilicity, both agents evaluated in the BIARIVA study were hypothesised to be more strongly associated with FFM than with FM, which is consistent with the reported results. A reduction in FFM may result in a smaller distribution volume and higher systemic exposure at a given dose, potentially contributing to increased plasma concentrations and anticoagulant activity. This may partially explain the findings of the present BIARIVA study, as there was a tendency of an association of the absolute FFM with coagulation peak parameters in the edoxaban study group. Overall, the substantial dependence of absolute measures of FM and FFM on total body size should be considered. Furthermore, decreased absolute FFM is commonly observed in elderly individuals, patients with chronic diseases (e.g., cancer), and those affected by malnutrition, sarcopenia, or prolonged physical inactivity. Conversely, increased FFM is typically found in physically trained individuals and, particularly, in males, reflecting established physiological differences in muscle mass distribution.[388] In the BIARIVA study, absolute FFM was lowest in BMI group I and highest in BMI group III. Furthermore, absolute FM was lowest in BMI group I and was highest in BMI group III. An increase in both absolute FM and absolute FFM was found with a rise in BMI, but the increase of FM was much more pronounced.

4.8 Limitations of the study

The BIARIVA study was designed as a prospective, single-center, cross-sectional pilot study. Given its exploratory character, no formal sample size calculation was performed. Instead, a pragmatic sample size of 10 patients per BMI group was chosen to assess feasibility and to investigate preliminary associations between body composition parameters and specific coagulation measures. As a result, the analyses are based on a relatively small overall number of patients, which should be taken into account when interpreting the findings. In particular, representation of individuals with extreme obesity was limited, as only 14.1% of the overall BIARIVA study population had a BMI >40 kg/m², and only a single patient exceeded a BMI of 45 kg/m². The small sample size is associated with limited statistical power, thereby reducing the ability to detect small effects. Subgroup findings are reported primarily in a descriptive manner. In particular, the available data do not allow for a meaningful assessment of sex-specific differences within the individual subgroups beyond descriptive statistics. In addition, the exploratory nature of the analyses increased the likelihood of false-positive findings due to

multiple testing. In line with the pilot character of the study, no formal adjustment for multiple comparisons was performed.

Several further methodological limitations should be acknowledged. The single-center, cross-sectional study design with the restriction to a single study visit limit the interpretability of the findings. In particular, this design precludes any conclusions regarding causality and is susceptible to selection bias. Moreover, intraindividual variability over time cannot be captured, which may be especially relevant for anticoagulation parameters.

Another important limitation is the absence of clinical endpoint evaluation. As a result, the study does not allow for an assessment of the clinical relevance of the observed associations between body composition and coagulation. Consequently, the findings must be interpreted as hypothesis-generating rather than outcome-driven.

Finally, body composition assessment was performed exclusively using BIA methods. The lack of confirmatory or reference methods, such as DXA or CT-based measurements, may introduce methodological limitations regarding the accuracy and precision of body composition estimates.

4.9 Conclusion

In this prospective, single-center, cross-sectional pilot study, no association was observed between body composition and coagulation monitoring parameters in VTE patients on anticoagulant treatment with rivaroxaban, whereas a potential association between FFM with coagulation peak parameters and the absolute anticoagulant increase from trough to peak emerged in patients treated with edoxaban. This key finding of the BIARIVA study should be considered hypothesis-generating and may serve as a basis for future research. Given the absence of sufficient safety and efficacy outcome data, no direct clinical implications can be drawn from the current results. Larger, adequately powered studies are warranted to further explore the role of body composition in anticoagulant therapy and to assess potential associations with clinical endpoints.

5 References

1. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2019;41:543-603.

2. Wendelboe AM, Raskob GE. Global Burden of Thrombosis: Epidemiologic Aspects. Circ Res 2016;118:1340-7.

3. Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. Circulation 2003;107:I9-16.

4. Raskob GE, Angchaisuksiri P, Blanco AN, et al. Thrombosis: a major contributor to global disease burden. Semin Thromb Hemost 2014;40:724-35.

5. Keller K, Hobohm L, Ebner M, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. Eur Heart J 2020;41:522-9.

6. de Miguel-Diez J, Jimenez-Garcia R, Jimenez D, et al. Trends in hospital admissions for pulmonary embolism in Spain from 2002 to 2011. Eur Respir J 2014;44:942-50.

7. Dentali F, Ageno W, Pomero F, Fenoglio L, Squizzato A, Bonzini M. Time trends and case fatality rate of in-hospital treated pulmonary embolism during 11 years of observation in Northwestern Italy. Thromb Haemost 2016;115:399-405.

8. Lehnert P, Lange T, Moller CH, Olsen PS, Carlsen J. Acute Pulmonary Embolism in a National Danish Cohort: Increasing Incidence and Decreasing Mortality. Thromb Haemost 2018;118:539-46.

9. Jimenez D, de Miguel-Diez J, Guijarro R, et al. Trends in the Management and Outcomes of Acute Pulmonary Embolism: Analysis From the RIETE Registry. J Am Coll Cardiol 2016;67:162-70.

10. Agarwal S, Clark D, 3rd, Sud K, Jaber WA, Cho L, Menon V. Gender Disparities in Outcomes and Resource Utilization for Acute Pulmonary Embolism Hospitalizations in the United States. Am J Cardiol 2015;116:1270-6.

11. Roy PM, Meyer G, Vielle B, et al. Appropriateness of diagnostic management and outcomes of suspected pulmonary embolism. Ann Intern Med 2006;144:157-64.

12. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Arch Intern Med 2011;171:831-7.

13. Shiraev TP, Omari A, Rushworth RL. Trends in pulmonary embolism morbidity and mortality in Australia. Thromb Res 2013;132:19-25.

14. Tsai J, Grosse SD, Grant AM, Hooper WC, Atrash HK. Trends in in-hospital deaths among hospitalizations with pulmonary embolism. Arch Intern Med 2012;172:960-1.

15. Yang Y, Liang L, Zhai Z, et al. Pulmonary embolism incidence and fatality trends in chinese hospitals from 1997 to 2008: a multicenter registration study. PLoS One 2011;6:e26861.

16. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. Circulation 2010;121:1896-903.

17. Woo KS, Tse LK, Tse CY, Metreweli C, Vallance-Owen J. The prevalence and pattern of pulmonary thromboembolism in the Chinese in Hong Kong. Int J Cardiol 1988;20:373-80.

18. Cheuk BL, Cheung GC, Cheng SW. Epidemiology of venous thromboembolism in a Chinese population. Br J Surg 2004;91:424-8.

19. Centers for Disease Control and Prevention (CDC). Venous thromboembolism in adult hospitalizations - United States, 2007-2009. MMWR Morb Mortal Wkly Rep 2012;61:401-4.

20. Jang MJ, Bang SM, Oh D. Incidence of venous thromboembolism in Korea: from the Health Insurance Review and Assessment Service database. J Thromb Haemost 2011;9:85-91.

21. Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A Prospective-Study of the Incidence of Deep-Vein Thrombosis within a Defined Urban-Population. Journal of Internal Medicine 1992;232:155-60.

22. Diagnostik und Therapie der tiefen Venenthrombose und Lungenembolie – AWMF-S2k-Leitlinie (German). 2023. (Accessed April 30, 2026, at https:/register.awmf.org/de/leitlinien/detail/065-002.)

23. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol 2015;12:464-74.

24. Martinez C, Cohen AT, Bamber L, Rietbrock S. Epidemiology of first and recurrent venous thromboembolism: a population-based cohort study in patients without active cancer. Thromb Haemost 2014;112:255-63.

25. Chung I, Lip GY. Virchow's triad revisited: blood constituents. Pathophysiol Haemost Thromb 2003;33:449-54.

26. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost 2007;5:692-9.

27. Engbers MJ, van Hylckama Vlieg A, Rosendaal FR. Venous thrombosis in the elderly: incidence, risk factors and risk groups. J Thromb Haemost 2010;8:2105-12.

28. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation 2008;117:93-102.

29. World Health Organization (WHO). Obesity and Overweight (Accessed April 19, 2026, at https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.)

30. Blanco-Molina A, Trujillo-Santos J, Tirado R, et al. Venous thromboembolism in women using hormonal contraceptives. Findings from the RIETE Registry. Thromb Haemost 2009;101:478-82.

31. van Hylckama Vlieg A, Middeldorp S. Hormone therapies and venous thromboembolism: where are we now? J Thromb Haemost 2011;9:257-66.

32. Lidegaard O, Nielsen LH, Skovlund CW, Skjeldestad FE, Lokkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ 2011;343:d6423.

33. Tricotel A, Collin C, Zureik M. Impact of the sharp changes in the use of contraception in 2013 on the risk of pulmonary embolism in France. J Thromb Haemost 2015;13:1576-80.

34. Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. BMJ 2001;323:131-4.

35. Berg CJ, Callaghan WM, Syverson C, Henderson Z. Pregnancy-related mortality in the United States, 1998 to 2005. Obstet Gynecol 2010;116:1302-9.

36. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ, 3rd. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med 2005;143:697-706.

37. Sultan AA, West J, Tata LJ, Fleming KM, Nelson-Piercy C, Grainge MJ. Risk of first venous thromboembolism in and around pregnancy: a population-based cohort study. Br J Haematol 2012;156:366-73.

38. Henriksson P, Westerlund E, Wallen H, Brandt L, Hovatta O, Ekbom A. Incidence of pulmonary and venous thromboembolism in pregnancies after in vitro fertilisation: cross sectional study. BMJ 2013;346:e8632.

39. Sultan AA, West J, Grainge MJ, et al. Development and validation of risk prediction model for venous thromboembolism in postpartum women: multinational cohort study. BMJ 2016;355:i6253.

40. Abbasi N, Balayla J, Laporta DP, Kezouh A, Abenhaim HA. Trends, risk factors and mortality among women with venous thromboembolism during labour and delivery: a population-based study of 8 million births. Arch Gynecol Obstet 2014;289:275-84.

41. Ay C, Pabinger I, Cohen AT. Cancer-associated venous thromboembolism: Burden, mechanisms, and management. Thromb Haemost 2017;117:219-30.

42. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med 2006;166:458-64.

43. Ku GH, White RH, Chew HK, Harvey DJ, Zhou H, Wun T. Venous thromboembolism in patients with acute leukemia: incidence, risk factors, and effect on survival. Blood 2009;113:3911-7.

44. van Es N, Le Gal G, Otten HM, et al. Screening for cancer in patients with unprovoked venous thromboembolism: protocol for a systematic review and individual patient data meta-analysis. BMJ Open 2017;7:e015562.

45. Marks MA, Engels EA. Venous thromboembolism and cancer risk among elderly adults in the United States. Cancer Epidemiol Biomarkers Prev 2014;23:774-83.

46. Sorensen HT, Mellemkjaer L, Steffensen FH, Olsen JH, Nielsen GL. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. N Engl J Med 1998;338:1169-73.

47. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood 2013;122:1712-23.

48. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 2005;293:715-22.

49. Robertson L, Yeoh SE, Broderick C, Stansby G, Agarwal R. Effect of testing for cancer on cancer- or venous thromboembolism (VTE)-related mortality and morbidity in people with unprovoked VTE. Cochrane Database Syst Rev 2018;11:CD010837.

50. Klok FA, Ageno W, Ay C, et al. Optimal follow-up after acute pulmonary embolism: a position paper of the European Society of Cardiology Working Group on Pulmonary Circulation and Right Ventricular Function, in collaboration with the European Society of Cardiology Working Group on Atherosclerosis and Vascular Biology, endorsed by the European Respiratory Society. Eur Heart J 2022;43:183-9.

51. Connors JM. Thrombophilia Testing and Venous Thrombosis. N Engl J Med 2017;377:2298.

52. Ageno W, Haas S, Weitz JI, et al. Upper Extremity DVT versus Lower Extremity DVT: Perspectives from the GARFIELD-VTE Registry. Thromb Haemost 2019;119:1365-72.

53. Isma N, Svensson PJ, Gottsater A, Lindblad B. Upper extremity deep venous thrombosis in the population-based Malmo thrombophilia study (MATS). Epidemiology, risk factors, recurrence risk, and mortality. Thromb Res 2010;125:e335-8.

54. Cote LP, Greenberg S, Caprini JA, et al. Comparisons Between Upper and Lower Extremity Deep Vein Thrombosis: A Review of the RIETE Registry. Clin Appl Thromb Hemost 2017;23:748-54.

55. Houghton DE, Casanegra AI, Peterson LG, et al. Treatment of upper extremity deep vein thrombosis with apixaban and rivaroxaban. Am J Hematol 2020;95:817-23.

56. Riva N, Ageno W. Approach to thrombosis at unusual sites: Splanchnic and cerebral vein thrombosis. Vasc Med 2017;22:529-40.

57. Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med 2005;352:1791-8.

58. Ropper AH, Klein JP. Cerebral Venous Thrombosis. N Engl J Med 2021;385:59-64.

59. Northup PG, Garcia-Pagan JC, Garcia-Tsao G, et al. Vascular Liver Disorders, Portal Vein Thrombosis, and Procedural Bleeding in Patients With Liver Disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2021;73:366-413.

60. Ageno W, Squizzato A, Togna A, et al. Incidental diagnosis of a deep vein thrombosis in consecutive patients undergoing a computed tomography scan of the abdomen: a retrospective cohort study. J Thromb Haemost 2012;10:158-60.

61. Pollack CV, Schreiber D, Goldhaber SZ, et al. Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: initial report of EMPEROR (Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry). J Am Coll Cardiol 2011;57:700-6.

62. Miniati M, Prediletto R, Formichi B, et al. Accuracy of clinical assessment in the diagnosis of pulmonary embolism. Am J Respir Crit Care Med 1999;159:864-71.

63. Wells PS, Ginsberg JS, Anderson DR, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Ann Intern Med 1998;129:997-1005.

64. Stein PD, Henry JW. Clinical characteristics of patients with acute pulmonary embolism stratified according to their presenting syndromes. Chest 1997;112:974-9.

65. Smulders YM. Pathophysiology and treatment of haemodynamic instability in acute pulmonary embolism: the pivotal role of pulmonary vasoconstriction. Cardiovasc Res 2000;48:23-33.

66. Lankhaar JW, Westerhof N, Faes TJ, et al. Quantification of right ventricular afterload in patients with and without pulmonary hypertension. Am J Physiol Heart Circ Physiol 2006;291:H1731-7.

67. Marcus JT, Gan CT, Zwanenburg JJ, et al. Interventricular mechanical asynchrony in pulmonary arterial hypertension: left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling. J Am Coll Cardiol 2008;51:750-7.

68. Mauritz GJ, Marcus JT, Westerhof N, Postmus PE, Vonk-Noordegraaf A. Prolonged right ventricular post-systolic isovolumic period in pulmonary arterial hypertension is not a reflection of diastolic dysfunction. Heart 2011;97:473-8.

69. Lang IM, Dorfmuller P, Vonk Noordegraaf A. The Pathobiology of Chronic Thromboembolic Pulmonary Hypertension. Ann Am Thorac Soc 2016;13 Suppl 3:S215-21.

70. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. Eur Respir J 2017;49:1601792.

71. Radegran G, Kjellstrom B, Ekmehag B, et al. Characteristics and survival of adult Swedish PAH and CTEPH patients 2000-2014. Scand Cardiovasc J 2016;50:243-50.

72. Quadery SR, Swift AJ, Billings CG, et al. The impact of patient choice on survival in chronic thromboembolic pulmonary hypertension. Eur Respir J 2018;52:1800589.

73. Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med 2003;349:1227-35.

74. Wells PS, Hirsh J, Anderson DR, et al. Accuracy of clinical assessment of deep-vein thrombosis. Lancet 1995;345:1326-30.

75. Wells PS, Owen C, Doucette S, Fergusson D, Tran H. Does this patient have deep vein thrombosis? JAMA 2006;295:199-207.

76. Geersing GJ, Zuithoff NP, Kearon C, et al. Exclusion of deep vein thrombosis using the Wells rule in clinically important subgroups: individual patient data meta-analysis. BMJ 2014;348:g1340.

77. Bhatt M, Braun C, Patel P, et al. Diagnosis of deep vein thrombosis of the lower extremity: a systematic review and meta-analysis of test accuracy. Blood Adv 2020;4:1250-64.

78. Kraaijpoel N, Carrier M, Le Gal G, et al. Diagnostic accuracy of three ultrasonography strategies for deep vein thrombosis of the lower extremity: A systematic review and meta-analysis. PLoS One 2020;15:e0228788.

79. Lim W, Le Gal G, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. Blood Adv 2018;2:3226-56.

80. Bernardi E, Camporese G, Buller HR, et al. Serial 2-point ultrasonography plus D-dimer vs whole-leg color-coded Doppler ultrasonography for diagnosing suspected symptomatic deep vein thrombosis: a randomized controlled trial. JAMA 2008;300:1653-9.

81. Johnson SA, Stevens SM, Woller SC, et al. Risk of deep vein thrombosis following a single negative whole-leg compression ultrasound: a systematic review and meta-analysis. JAMA 2010;303:438-45.

82. Constans J, Salmi LR, Sevestre-Pietri MA, et al. A clinical prediction score for upper extremity deep venous thrombosis. Thromb Haemost 2008;99:202-7.

83. European Association for the Study of the Liver (EASL).EASL Clinical Practice Guidelines: Vascular diseases of the liver. J Hepatol 2016;64:179-202.

84. Bjorck M, Koelemay M, Acosta S, et al. Editor's Choice - Management of the Diseases of Mesenteric Arteries and Veins: Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2017;53:460-510.

85. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost 2000;83:416-20.

86. Klok FA, Mos IC, Nijkeuter M, et al. Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism. Arch Intern Med 2008;168:2131-6.

87. Gibson NS, Sohne M, Kruip MJ, et al. Further validation and simplification of the Wells clinical decision rule in pulmonary embolism. Thromb Haemost 2008;99:229-34.

88. Douma RA, Gibson NS, Gerdes VE, et al. Validity and clinical utility of the simplified Wells rule for assessing clinical probability for the exclusion of pulmonary embolism. Thromb Haemost 2009;101:197-200.

89. Douma RA, Mos IC, Erkens PM, et al. Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study. Ann Intern Med 2011;154:709-18.

90. Le Gal G, Righini M, Roy PM, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med 2006;144:165-71.

91. Ceriani E, Combescure C, Le Gal G, et al. Clinical prediction rules for pulmonary embolism: a systematic review and meta-analysis. J Thromb Haemost 2010;8:957-70.

92. Penaloza A, Soulie C, Moumneh T, et al. Pulmonary embolism rule-out criteria (PERC) rule in European patients with low implicit clinical probability (PERCEPIC): a multicentre, prospective, observational study. Lancet Haematol 2017;4:e615-e21.

93. Freund Y, Cachanado M, Aubry A, et al. Effect of the Pulmonary Embolism Rule-Out Criteria on Subsequent Thromboembolic Events Among Low-Risk Emergency Department Patients: The PROPER Randomized Clinical Trial. JAMA 2018;319:559-66.

94. Perrier A, Roy PM, Aujesky D, et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. Am J Med 2004;116:291-9.

95. Perrier A, Roy PM, Sanchez O, et al. Multidetector-row computed tomography in suspected pulmonary embolism. N Engl J Med 2005;352:1760-8.

96. Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. Ann Intern Med 2001;135:98-107.

97. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA 2014;311:1117-24.

98. van der Hulle T, Cheung WY, Kooij S, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. Lancet 2017;390:289-97.

99. Geersing GJ, Erkens PM, Lucassen WA, et al. Safe exclusion of pulmonary embolism using the Wells rule and qualitative D-dimer testing in primary care: prospective cohort study. BMJ 2012;345:e6564.

100. Geersing GJ, Janssen KJ, Oudega R, et al. Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis. BMJ 2009;339:b2990.

101. Revel MP, Sanchez O, Couchon S, et al. Diagnostic accuracy of magnetic resonance imaging for an acute pulmonary embolism: results of the 'IRM-EP' study. J Thromb Haemost 2012;10:743-50.

102. Stein PD, Chenevert TL, Fowler SE, et al. Gadolinium-enhanced magnetic resonance angiography for pulmonary embolism: a multicenter prospective study (PIOPED III). Ann Intern Med 2010;152:434-43, W142-3.

103. Qanadli SD, Hajjam ME, Mesurolle B, et al. Pulmonary embolism detection: prospective evaluation of dual-section helical CT versus selective pulmonary arteriography in 157 patients. Radiology 2000;217:447-55.

104. Patel S, Kazerooni EA, Cascade PN. Pulmonary embolism: optimization of small pulmonary artery visualization at multi-detector row CT. Radiology 2003;227:455-60.

105. Ghaye B, Szapiro D, Mastora I, et al. Peripheral pulmonary arteries: how far in the lung does multi-detector row spiral CT allow analysis? Radiology 2001;219:629-36.

106. Carrier M, Righini M, Wells PS, et al. Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications. A systematic review and meta-analysis of the management outcome studies. J Thromb Haemost 2010;8:1716-22.

107. Bajc M, Olsson B, Palmer J, Jonson B. Ventilation/Perfusion SPECT for diagnostics of pulmonary embolism in clinical practice. J Intern Med 2008;264:379-87.

108. Gutte H, Mortensen J, Jensen CV, et al. Detection of pulmonary embolism with combined ventilation-perfusion SPECT and low-dose CT: head-to-head comparison with multidetector CT angiography. J Nucl Med 2009;50:1987-92.

109. Reinartz P, Wildberger JE, Schaefer W, Nowak B, Mahnken AH, Buell U. Tomographic imaging in the diagnosis of pulmonary embolism: a comparison between V/Q lung scintigraphy in SPECT technique and multislice spiral CT. J Nucl Med 2004;45:1501-8.

110. Collart JP, Roelants V, Vanpee D, et al. Is a lung perfusion scan obtained by using single photon emission computed tomography able to improve the radionuclide diagnosis of pulmonary embolism? Nucl Med Commun 2002;23:1107-13.

111. Kurnicka K, Lichodziejewska B, Goliszek S, et al. Echocardiographic Pattern of Acute Pulmonary Embolism: Analysis of 511 Consecutive Patients. J Am Soc Echocardiogr 2016;29:907-13.

112. Bova C, Greco F, Misuraca G, et al. Diagnostic utility of echocardiography in patients with suspected pulmonary embolism. Am J Emerg Med 2003;21:180-3.

113. Le Gal G, Righini M, Sanchez O, et al. A positive compression ultrasonography of the lower limb veins is highly predictive of pulmonary embolism on computed tomography in suspected patients. Thromb Haemost 2006;95:963-6.

114. Dresden S, Mitchell P, Rahimi L, et al. Right ventricular dilatation on bedside echocardiography performed by emergency physicians aids in the diagnosis of pulmonary embolism. Ann Emerg Med 2014;63:16-24.

115. Sheen JJ, Haramati LB, Natenzon A, et al. Performance of Low-Dose Perfusion Scintigraphy and CT Pulmonary Angiography for Pulmonary Embolism in Pregnancy. Chest 2018;153:152-60.

116. van Mens TE, Scheres LJ, de Jong PG, Leeflang MM, Nijkeuter M, Middeldorp S. Imaging for the exclusion of pulmonary embolism in pregnancy. Cochrane Database Syst Rev 2017;1:CD011053.

117. Hamilton EJ, Green AQ, Cook JA, Nash H. Investigating for pulmonary embolism in pregnancy: Five year retrospective review of referrals to the acute medical unit of a large teaching hospital. Acute Med 2016;15:58-62.

118. Righini M, Robert-Ebadi H, Elias A, et al. Diagnosis of Pulmonary Embolism During Pregnancy: A Multicenter Prospective Management Outcome Study. Ann Intern Med 2018;169:766-73.

119. Linnemann B, Bauersachs R, Rott H, et al. Diagnosis of pregnancy-associated venous thromboembolism - position paper of the Working Group in Women's Health of the Society of Thrombosis and Haemostasis (GTH). Vasa 2016;45:87-101.

120. Ray JG, Vermeulen MJ, Bharatha A, Montanera WJ, Park AL. Association Between MRI Exposure During Pregnancy and Fetal and Childhood Outcomes. JAMA 2016;316:952-61.

121. Wang PI, Chong ST, Kielar AZ, et al. Imaging of pregnant and lactating patients: part 1, evidence-based review and recommendations. AJR Am J Roentgenol 2012;198:778-84.

122. Masselli G, Brunelli R, Casciani E, et al. Acute abdominal and pelvic pain in pregnancy: MR imaging as a valuable adjunct to ultrasound? Abdom Imaging 2011;36:596-603.

123. Sundgren PC, Leander P. Is administration of gadolinium-based contrast media to pregnant women and small children justified? J Magn Reson Imaging 2011;34:750-7.

124. De Backer J, Haugaa KH, Hasselberg NE, et al. 2025 ESC Guidelines for the management of cardiovascular disease and pregnancy. Eur Heart J 2025;46:4462-568.

125. van der Pol LM, Tromeur C, Bistervels IM, et al. Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism. N Engl J Med 2019;380:1139-49.

126. Mitchell DP, Rowan M, Loughman E, Ridge CA, MacMahon PJ. Contrast monitoring techniques in CT pulmonary angiography: An important and underappreciated contributor to breast dose. Eur J Radiol 2017;86:184-9.

127. Shahir K, McCrea JM, Lozano LA, Goodman LR. Reduced z-axis technique for CT Pulmonary angiography in pregnancy--validation for practical use and dose reduction. Emerg Radiol 2015;22:651-6.

128. Perisinakis K, Seimenis I, Tzedakis A, Damilakis J. Perfusion scintigraphy versus 256-slice CT angiography in pregnant patients suspected of pulmonary embolism: comparison of radiation risks. J Nucl Med 2014;55:1273-80.

129. Astani SA, Davis LC, Harkness BA, Supanich MP, Dalal I. Detection of pulmonary embolism during pregnancy: comparing radiation doses of CTPA and pulmonary scintigraphy. Nucl Med Commun 2014;35:704-11.

130. Nijkeuter M, Geleijns J, De Roos A, Meinders AE, Huisman MV. Diagnosing pulmonary embolism in pregnancy: rationalizing fetal radiation exposure in radiological procedures. J Thromb Haemost 2004;2:1857-8.

131. Coutance G, Cauderlier E, Ehtisham J, Hamon M, Hamon M. The prognostic value of markers of right ventricular dysfunction in pulmonary embolism: a meta-analysis. Crit Care 2011;15:R103.

132. Lankeit M, Friesen D, Aschoff J, et al. Highly sensitive troponin T assay in normotensive patients with acute pulmonary embolism. Eur Heart J 2010;31:1836-44.

133. Pruszczyk P, Goliszek S, Lichodziejewska B, et al. Prognostic value of echocardiography in normotensive patients with acute pulmonary embolism. JACC Cardiovasc Imaging 2014;7:553-60.

134. Meinel FG, Nance JW, Jr., Schoepf UJ, et al. Predictive Value of Computed Tomography in Acute Pulmonary Embolism: Systematic Review and Meta-analysis. Am J Med 2015;128:747-59.e2.

135. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005;172:1041-6.

136. Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010;170:1383-9.

137. Donze J, Le Gal G, Fine MJ, et al. Prospective validation of the Pulmonary Embolism Severity Index. A clinical prognostic model for pulmonary embolism. Thromb Haemost 2008;100:943-8.

138. Elias A, Mallett S, Daoud-Elias M, Poggi JN, Clarke M. Prognostic models in acute pulmonary embolism: a systematic review and meta-analysis. BMJ Open 2016;6:e010324.

139. Kohn CG, Mearns ES, Parker MW, Hernandez AV, Coleman CI. Prognostic accuracy of clinical prediction rules for early post-pulmonary embolism all-cause mortality: a bivariate meta-analysis. Chest 2015;147:1043-62.

140. Righini M, Roy PM, Meyer G, Verschuren F, Aujesky D, Le Gal G. The Simplified Pulmonary Embolism Severity Index (PESI): validation of a clinical prognostic model for pulmonary embolism. J Thromb Haemost 2011;9:2115-7.

141. Sam A, Sanchez D, Gomez V, et al. The shock index and the simplified PESI for identification of low-risk patients with acute pulmonary embolism. Eur Respir J 2011;37:762-6.

142. Schlager O, Campello E, Madaric J, et al. 2025 ESVM Guidelines on interventional treatment of venous thromboembolism. Vasa 2025;54:365-81.

143. Zondag W, Mos IC, Creemers-Schild D, et al. Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study. J Thromb Haemost 2011;9:1500-7.

144. Dudzinski DM, Piazza G. Multidisciplinary Pulmonary Embolism Response Teams. Circulation 2016;133:98-103.

145. Creager MA, Barnes GD, Giri J, et al. 2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN Guideline for the Evaluation and Management of Acute Pulmonary Embolism in Adults: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2026;87:1626-710.

146. Barthels M, Alban S, Bergmann F, et al. Das Gerinnungskompendium: Schnellorientierung, Befundinterpretation, klinische Konsequenzen (in German). 2., vollständig überarbeitete und erweiterte Auflage ed. Stuttgart: Georg Thieme Verlag KG; 2013.

147. Erkens PM, Prins MH. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev 2010:CD001100.

148. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e24S-e43S.

149. Bhutia S, Wong PF. Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism. Cochrane Database Syst Rev 2013;2013:CD003074.

150. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J 2018;39:3165-241.

151. Cossette B, Pelletier ME, Carrier N, et al. Evaluation of bleeding risk in patients exposed to therapeutic unfractionated or low-molecular-weight heparin: a cohort study in the context of a quality improvement initiative. Ann Pharmacother 2010;44:994-1002.

152. Buller HR, Davidson BL, Decousus H, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. Ann Intern Med 2004;140:867-73.

153. Buller HR, Davidson BL, Decousus H, et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med 2003;349:1695-702.

154. Robertson L, Jones LE. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for the initial treatment of venous thromboembolism. Cochrane Database Syst Rev 2017;2:CD001100.

155. Di Nisio M, Middeldorp S, Buller HR. Direct thrombin inhibitors. N Engl J Med 2005;353:1028-40.

156. Hutten BA, Prins MH. Duration of treatment with vitamin K antagonists in symptomatic venous thromboembolism. Cochrane Database Syst Rev 2006:CD001367.

157. Carrier M, Le Gal G, Wells PS, Rodger MA. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. Ann Intern Med 2010;152:578-89.

158. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. Ann Intern Med 2003;139:893-900.

159. Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica 2007;92:199-205.

160. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 2014;129:764-72.

161. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361:2342-52.

162. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-510.

163. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699-708.

164. Buller HR, Decousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013;369:1406-15.

165. Buller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-97.

166. Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. Drug Metab Dispos 2008;36:386-99.

167. Stangier J, Stahle H, Rathgen K, Roth W, Shakeri-Nejad K. Pharmacokinetics and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor, are not affected by moderate hepatic impairment. J Clin Pharmacol 2008;48:1411-9.

168. Raghavan N, Frost CE, Yu Z, et al. Apixaban metabolism and pharmacokinetics after oral administration to humans. Drug Metab Dispos 2009;37:74-81.

169. Ogata K, Mendell-Harary J, Tachibana M, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. J Clin Pharmacol 2010;50:743-53.

170. Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet 2014;53:1-16.

171. Kubitza D, Becka M, Voith B, Zuehlsdorf M, Wensing G. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. Clin Pharmacol Ther 2005;78:412-21.

172. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369:799-808.

173. van Es N, Coppens M, Schulman S, Middeldorp S, Buller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood 2014;124:1968-75.

174. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost 2014;12:320-8.

175. Douxfils J, Ageno W, Samama CM, et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. J Thromb Haemost 2018;16:209-19.

176. Douxfils J, Mullier F, Loosen C, Chatelain C, Chatelain B, Dogne JM. Assessment of the impact of rivaroxaban on coagulation assays: laboratory recommendations for the monitoring of rivaroxaban and review of the literature. Thromb Res 2012;130:956-66.

177. Douxfils J, Mullier F, Robert S, Chatelain C, Chatelain B, Dogne JM. Impact of dabigatran on a large panel of routine or specific coagulation assays. Laboratory recommendations for monitoring of dabigatran etexilate. Thromb Haemost 2012;107:985-97.

178. Steffel J, Collins R, Antz M, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace 2021;23:1612-76.

179. Douxfils J, Adcock DM, Bates SM, et al. 2021 Update of the International Council for Standardization in Haematology Recommendations for Laboratory Measurement of Direct Oral Anticoagulants. Thromb Haemost 2021;121:1008-20.

180. Pollack CV, Jr., Reilly PA, van Ryn J, et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med 2017;377:431-41.

181. Connolly SJ, Crowther M, Eikelboom JW, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med 2019;380:1326-35.

182. Albaladejo P, Samama CM, Sie P, et al. Management of Severe Bleeding in Patients Treated with Direct Oral Anticoagulants: An Observational Registry Analysis. Anesthesiology 2017;127:111-20.

183. Majeed A, Agren A, Holmstrom M, et al. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. Blood 2017;130:1706-12.

184. Schulman S, Gross PL, Ritchie B, et al. Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study. Thromb Haemost 2018;118:842-51.

185. Xu Y, Schulman S, Dowlatshahi D, et al. Direct Oral Anticoagulant- or Warfarin-Related Major Bleeding: Characteristics, Reversal Strategies, and Outcomes From a Multicenter Observational Study. Chest 2017;152:81-91.

186. Zada I, Wang S, Akerman M, Hanna A. Four-Factor Prothrombin Complex Concentrate for the Reversal of Direct Oral Anticoagulants. J Intensive Care Med 2021;36:58-62.

187. Nopp S, Kraemmer D, Ay C. Factor XI Inhibitors for Prevention and Treatment of Venous Thromboembolism: A Review on the Rationale and Update on Current Evidence. Front Cardiovasc Med 2022;9:903029.

188. Steinberg BA, Gao H, Shrader P, et al. International trends in clinical characteristics and oral anticoagulation treatment for patients with atrial fibrillation: Results from the GARFIELD-AF, ORBIT-AF I, and ORBIT-AF II registries. Am Heart J 2017;194:132-40.

189. Sanghai S, Wong C, Wang Z, et al. Rates of Potentially Inappropriate Dosing of Direct-Acting Oral Anticoagulants and Associations With Geriatric Conditions Among Older Patients With Atrial Fibrillation: The SAGE-AF Study. J Am Heart Assoc 2020;9:e014108.

190. Key NS. Epidemiologic and clinical data linking factors XI and XII to thrombosis. Hematology Am Soc Hematol Educ Program 2014;2014:66-70.

191. Yuan S, Burgess S, Laffan M, et al. Genetically Proxied Inhibition of Coagulation Factors and Risk of Cardiovascular Disease: A Mendelian Randomization Study. J Am Heart Assoc 2021;10:e019644.

192. Gill D, Georgakis MK, Laffan M, et al. Genetically Determined FXI (Factor XI) Levels and Risk of Stroke. Stroke 2018;49:2761-3.

193. Salomon O, Steinberg DM, Koren-Morag N, Tanne D, Seligsohn U. Reduced incidence of ischemic stroke in patients with severe factor XI deficiency. Blood 2008;111:4113-7.

194. Salomon O, Steinberg DM, Zucker M, Varon D, Zivelin A, Seligsohn U. Patients with severe factor XI deficiency have a reduced incidence of deep-vein thrombosis. Thromb Haemost 2011;105:269-73.

195. Preis M, Hirsch J, Kotler A, et al. Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events. Blood 2017;129:1210-5.

196. Duga S, Salomon O. Congenital factor XI deficiency: an update. Semin Thromb Hemost 2013;39:621-31.

197. Lowenberg EC, Meijers JC, Monia BP, Levi M. Coagulation factor XI as a novel target for antithrombotic treatment. J Thromb Haemost 2010;8:2349-57.

198. Buller HR, Bethune C, Bhanot S, et al. Factor XI antisense oligonucleotide for prevention of venous thrombosis. N Engl J Med 2015;372:232-40.

199. Weitz JI, Bauersachs R, Becker B, et al. Effect of Osocimab in Preventing Venous Thromboembolism Among Patients Undergoing Knee Arthroplasty: The FOXTROT Randomized Clinical Trial. JAMA 2020;323:130-9.

200. Weitz JI, Strony J, Ageno W, et al. Milvexian for the Prevention of Venous Thromboembolism. N Engl J Med 2021;385:2161-72.

201. Verhamme P, Yi BA, Segers A, et al. Abelacimab for Prevention of Venous Thromboembolism. N Engl J Med 2021;385:609-17.

202. Walsh M, Bethune C, Smyth A, et al. Phase 2 Study of the Factor XI Antisense Inhibitor IONIS-FXI(Rx) in Patients With ESRD. Kidney Int Rep 2022;7:200-9.

203. Lorentz CU, Tucker EI, Verbout NG, et al. The contact activation inhibitor AB023 in heparin-free hemodialysis: results of a randomized phase 2 clinical trial. Blood 2021;138:2173-84.

204. Piccini JP, Caso V, Connolly SJ, et al. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet 2022;399:1383-90.

205. Lang T, Prüller, F., Bauer, F., Gary, T., Gattringer, T., Weihs, W., Kölblinger, C.J., Seidel, G., Acham, S., Schöllnast, H., Wurzer, H., Bachler, M., Muhr, T., Pfanner, G., Gebhart, J., Hass, T., Ziegler, B., Neumeister, P. Gerinnung im klinischen Alltag (in German)2024.

206. Horner D, Hogg K, Body R, Nash MJ, Mackway-Jones K. The Anticoagulation of Calf Thrombosis (ACT) project: study protocol for a randomized controlled trial. Trials 2012;13:31.

207. Righini M, Galanaud JP, Guenneguez H, et al. Anticoagulant therapy for symptomatic calf deep vein thrombosis (CACTUS): a randomised, double-blind, placebo-controlled trial. Lancet Haematol 2016;3:e556-e62.

208. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. Chest 2021;160:e545-e608.

209. Khorana AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost 2018;16:1891-4.

210. Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv 2021;5:927-74.

211. Key NS, Khorana AA, Kuderer NM, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 2020;38:496-520.

212. Henry JC, Satiani B. Calf muscle venous thrombosis: a review of the clinical implications and therapy. Vasc Endovascular Surg 2014;48:396-401.

213. Schwarz T, Buschmann L, Beyer J, Halbritter K, Rastan A, Schellong S. Therapy of isolated calf muscle vein thrombosis: a randomized, controlled study. J Vasc Surg 2010;52:1246-50.

214. Gillet JL, Perrin MR, Allaert FA. Short-term and mid-term outcome of isolated symptomatic muscular calf vein thrombosis. J Vasc Surg 2007;46:513-9.

215. Montiel FS, Ghazvinian R, Gottsater A, Elf J. Treatment with direct oral anticoagulants in patients with upper extremity deep vein thrombosis. Thromb J 2017;15:26.

216. Schastlivtsev I, Lobastov K, Tsaplin S, et al. Rivaroxaban in the treatment of upper extremity deep vein thrombosis: A single-center experience and review of the literature. Thromb Res 2019;181:24-8.

217. Porfidia A, Agostini F, Giarretta I, et al. Upper extremity deep vein thrombosis treated with direct oral anticoagulants: a multi-center real world experience. J Thromb Thrombolysis 2020;50:355-60.

218. Deitcher SR, Fesen MR, Kiproff PM, et al. Safety and efficacy of alteplase for restoring function in occluded central venous catheters: results of the cardiovascular thrombolytic to open occluded lines trial. J Clin Oncol 2002;20:317-24.

219. Ponec D, Irwin D, Haire WD, et al. Recombinant tissue plasminogen activator (alteplase) for restoration of flow in occluded central venous access devices: a double-blind placebo-controlled trial--the Cardiovascular Thrombolytic to Open Occluded Lines (COOL) efficacy trial. J Vasc Interv Radiol 2001;12:951-5.

220. Candeloro M, Valeriani E, Monreal M, et al. Anticoagulant therapy for splanchnic vein thrombosis: an individual patient data meta-analysis. Blood Adv 2022;6:4516-23.

221. Valeriani E, Di Nisio M, Riva N, et al. Anticoagulant Treatment for Splanchnic Vein Thrombosis in Liver Cirrhosis: A Systematic Review and Meta-Analysis. Thromb Haemost 2021;121:867-76.

222. Ghazaleh S, Beran A, Aburayyan K, et al. Efficacy and safety of anticoagulation in non-malignant portal vein thrombosis in patients with liver cirrhosis: a systematic review and meta-analysis. Ann Gastroenterol 2021;34:104-10.

223. Loffredo L, Pastori D, Farcomeni A, Violi F. Effects of Anticoagulants in Patients With Cirrhosis and Portal Vein Thrombosis: A Systematic Review and Meta-analysis. Gastroenterology 2017;153:480-7.e1.

224. Di Nisio M, Valeriani E, Riva N, Schulman S, Beyer-Westendorf J, Ageno W. Anticoagulant therapy for splanchnic vein thrombosis: ISTH SSC Subcommittee Control of Anticoagulation. J Thromb Haemost 2020;18:1562-8.

225. Weimar C, Beyer-Westendorf J, Bohmann FO, et al. New recommendations on cerebral venous and dural sinus thrombosis from the German consensus-based (S2k) guideline. Neurol Res Pract 2024;6:23.

226. Samuelson Bannow BT, Lee A, Khorana AA, et al. Management of cancer-associated thrombosis in patients with thrombocytopenia: guidance from the SSC of the ISTH. J Thromb Haemost 2018;16:1246-9.

227. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349:146-53.

228. Young AM, Marshall A, Thirlwall J, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). J Clin Oncol 2018;36:2017-23.

229. McBane RD, 2nd, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. J Thromb Haemost 2020;18:411-21.

230. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. N Engl J Med 2020;382:1599-607.

231. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. N Engl J Med 2018;378:615-24.

232. Farge D, Frere C, Connors JM, et al. 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19. Lancet Oncol 2022;23:e334-e47.

233. Mavrakanas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML. Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients. J Am Soc Nephrol 2017;28:2241-8.

234. Siontis KC, Zhang X, Eckard A, et al. Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States. Circulation 2018;138:1519-29.

235. Reinecke H, Engelbertz C, Bauersachs R, et al. A Randomized Controlled Trial Comparing Apixaban With the Vitamin K Antagonist Phenprocoumon in Patients on Chronic Hemodialysis: The AXADIA-AFNET 8 Study. Circulation 2023;147:296-309.

236. Cheung CYS, Parikh J, Farrell A, Lefebvre M, Summa-Sorgini C, Battistella M. Direct Oral Anticoagulant Use in Chronic Kidney Disease and Dialysis Patients With Venous Thromboembolism: A Systematic Review of Thrombosis and Bleeding Outcomes. Ann Pharmacother 2021;55:711-22.

237. Sy J, Hsiung JT, Edgett D, Kalantar-Zadeh K, Streja E, Lau WL. Cardiovascular and Bleeding Outcomes with Anticoagulants across Kidney Disease Stages: Analysis of a National US Cohort. Am J Nephrol 2021;52:199-208.

238. Sogaard KK, Horvath-Puho E, Gronbaek H, Jepsen P, Vilstrup H, Sorensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. Am J Gastroenterol 2009;104:96-101.

239. Ambrosino P, Tarantino L, Di Minno G, et al. The risk of venous thromboembolism in patients with cirrhosis. A systematic review and meta-analysis. Thromb Haemost 2017;117:139-48.

240. Stine JG, Niccum BA, Zimmet AN, et al. Increased risk of venous thromboembolism in hospitalized patients with cirrhosis due to non-alcoholic steatohepatitis. Clin Transl Gastroenterol 2018;9:140.

241. Intagliata NM, Henry ZH, Maitland H, et al. Direct Oral Anticoagulants in Cirrhosis Patients Pose Similar Risks of Bleeding When Compared to Traditional Anticoagulation. Dig Dis Sci 2016;61:1721-7.

242. Hum J, Shatzel JJ, Jou JH, Deloughery TG. The efficacy and safety of direct oral anticoagulants vs traditional anticoagulants in cirrhosis. Eur J Haematol 2017;98:393-7.

243. Davis KA, Puleo CR, Kovalic AJ, Nisly SA. Efficacy and safety of direct oral anticoagulant therapy for the treatment of venous thromboembolism in patients with chronic liver disease. Thromb Res 2019;176:27-9.

244. Geldhof V, Vandenbriele C, Verhamme P, Vanassche T. Venous thromboembolism in the elderly: efficacy and safety of non-VKA oral anticoagulants. Thromb J 2014;12:21.

245. Goldhaber SZ, Schulman S, Eriksson H, et al. Dabigatran versus Warfarin for Acute Venous Thromboembolism in Elderly or Impaired Renal Function Patients: Pooled Analysis of RE-COVER and RE-COVER II. Thromb Haemost 2017;117:2045-52.

246. Poli D, Antonucci E, Bertu L, et al. Very elderly patients with venous thromboembolism on oral anticoagulation with VKAs or DOACs: Results from the prospective multicenter START2-Register Study. Thromb Res 2019;183:28-32.

247. Prins MH, Lensing AW, Bauersachs R, 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 2013;11:21.

248. Vanassche T, Verhamme P, Wells PS, et al. Impact of age, comorbidity, and polypharmacy on the efficacy and safety of edoxaban for the treatment of venous thromboembolism: An analysis of the randomized, double-blind Hokusai-VTE trial. Thromb Res 2018;162:7-14.

249. Madhavan M, Holmes DN, Piccini JP, et al. Association of frailty and cognitive impairment with benefits of oral anticoagulation in patients with atrial fibrillation. Am Heart J 2019;211:77-89.

250. Steffel J, Giugliano RP, Braunwald E, et al. Edoxaban Versus Warfarin in Atrial Fibrillation Patients at Risk of Falling: ENGAGE AF-TIMI 48 Analysis. J Am Coll Cardiol 2016;68:1169-78.

251. Rao MP, Vinereanu D, Wojdyla DM, et al. Clinical Outcomes and History of Fall in Patients with Atrial Fibrillation Treated with Oral Anticoagulation: Insights From the ARISTOTLE Trial. Am J Med 2018;131:269-75.e2.

252. Tinetti ME, Baker DI, McAvay G, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. N Engl J Med 1994;331:821-7.

253. Barbhaiya M, Zuily S, Naden R, et al. The 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthritis Rheumatol 2023;75:1687-702.

254. Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood 2018;132:1365-71.

255. Romualdi E, Dentali F, Rancan E, et al. Anticoagulant therapy for venous thromboembolism during pregnancy: a systematic review and a meta-analysis of the literature. J Thromb Haemost 2013;11:270-81.

256. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood 2005;106:401-7.

257. Dempfle CE. Minor transplacental passage of fondaparinux in vivo. N Engl J Med 2004;350:1914-5.

258. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e691S-e736S.

259. Leffert L, Butwick A, Carvalho B, et al. The Society for Obstetric Anesthesia and Perinatology Consensus Statement on the Anesthetic Management of Pregnant and Postpartum Women Receiving Thromboprophylaxis or Higher Dose Anticoagulants. Anesth Analg 2018;126:928-44.

260. Gogarten W, Vandermeulen E, Van Aken H, et al. Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. Eur J Anaesthesiol 2010;27:999-1015.

261. Martillotti G, Boehlen F, Robert-Ebadi H, Jastrow N, Righini M, Blondon M. Treatment options for severe pulmonary embolism during pregnancy and the postpartum period: a systematic review. J Thromb Haemost 2017;15:1942-50.

262. Cohen H, Arachchillage DR, Middeldorp S, Beyer-Westendorf J, Abdul-Kadir R. Management of direct oral anticoagulants in women of childbearing potential: guidance from the SSC of the ISTH. J Thromb Haemost 2016;14:1673-6.

263. Schulman S. How I treat recurrent venous thromboembolism in patients receiving anticoagulant therapy. Blood 2017;129:3285-93.

264. Prandoni P, Noventa F, Quintavalla R, et al. Thigh-length versus below-knee compression elastic stockings for prevention of the postthrombotic syndrome in patients with proximal-venous thrombosis: a randomized trial. Blood 2012;119:1561-5.

265. Ten Cate-Hoek AJ, Amin EE, Bouman AC, et al. Individualised versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome (IDEAL DVT): a multicentre, randomised, single-blind, allocation-concealed, non-inferiority trial. Lancet Haematol 2018;5:e25-e33.

266. Mol GC, van de Ree MA, Klok FA, et al. One versus two years of elastic compression stockings for prevention of post-thrombotic syndrome (OCTAVIA study): randomised controlled trial. BMJ 2016;353:i2691.

267. Appelen D, van Loo E, Prins MH, Neumann MH, Kolbach DN. Compression therapy for prevention of post-thrombotic syndrome. Cochrane Database Syst Rev 2017;9:CD004174.

268. Amin EE, Bistervels IM, Meijer K, et al. Reduced incidence of vein occlusion and postthrombotic syndrome after immediate compression for deep vein thrombosis. Blood 2018;132:2298-304.

269. Rother U, Grussler A, Griesbach C, Almasi-Sperling V, Lang W, Meyer A. Safety of medical compression stockings in patients with diabetes mellitus or peripheral arterial disease. BMJ Open Diabetes Res Care 2020;8:e001316.

270. Andriessen A, Apelqvist J, Mosti G, Partsch H, Gonska C, Abel M. Compression therapy for venous leg ulcers: risk factors for adverse events and complications, contraindications - a review of present guidelines. J Eur Acad Dermatol Venereol 2017;31:1562-8.

271. De Gregorio MA, Guirola JA, Sierre S, et al. Ibero-American Society of Interventionism (SIDI) and the Spanish Society of Vascular and Interventional Radiology (SERVEI) Standard of Practice (SOP) for the Management of Inferior Vena Cava Filters in the Treatment of Acute Venous Thromboembolism. J Clin Med 2021;11:77.

272. Rezaei-Kalantari K, Rotzinger DC, Qanadli SD. Vena Cava Filters: Toward Optimal Strategies for Filter Retrieval and Patients' Follow-Up. Front Cardiovasc Med 2022;9:746748.

273. Enden T, Haig Y, Klow NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. Lancet 2012;379:31-8.

274. Haig Y, Enden T, Grotta O, et al. Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. Lancet Haematol 2016;3:e64-71.

275. Comerota AJ, Kearon C, Gu CS, et al. Endovascular Thrombus Removal for Acute Iliofemoral Deep Vein Thrombosis. Circulation 2019;139:1162-73.

276. Notten P, de Smet A, Tick LW, et al. CAVA (Ultrasound-Accelerated Catheter-Directed Thrombolysis on Preventing Post-Thrombotic Syndrome) Trial: Long-Term Follow-Up Results. J Am Heart Assoc 2021;10:e018973.

277. Notten P, Ten Cate-Hoek AJ, Arnoldussen C, et al. Ultrasound-accelerated catheter-directed thrombolysis versus anticoagulation for the prevention of post-thrombotic syndrome (CAVA): a single-blind, multicentre, randomised trial. Lancet Haematol 2020;7:e40-e9.

278. Broderick C, Watson L, Armon MP. Thrombolytic strategies versus standard anticoagulation for acute deep vein thrombosis of the lower limb. Cochrane Database Syst Rev 2021;1:CD002783.

279. Sharifi M, Mehdipour M, Bay C, Smith G, Sharifi J. Endovenous therapy for deep venous thrombosis: the TORPEDO trial. Catheter Cardiovasc Interv 2010;76:316-25.

280. Meneveau N, Seronde MF, Blonde MC, et al. Management of unsuccessful thrombolysis in acute massive pulmonary embolism. Chest 2006;129:1043-50.

281. Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet 1993;341:507-11.

282. Dalla-Volta S, Palla A, Santolicandro A, et al. PAIMS 2: alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism. Plasminogen activator Italian multicenter study 2. J Am Coll Cardiol 1992;20:520-6.

283. Daniels LB, Parker JA, Patel SR, Grodstein F, Goldhaber SZ. Relation of duration of symptoms with response to thrombolytic therapy in pulmonary embolism. Am J Cardiol 1997;80:184-8.

284. Agnelli G, Prandoni P, Becattini C, et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med 2003;139:19-25.

285. Murin S, Romano PS, White RH. Comparison of outcomes after hospitalization for deep venous thrombosis or pulmonary embolism. Thromb Haemost 2002;88:407-14.

286. Couturaud F, Sanchez O, Pernod G, et al. Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial. JAMA 2015;314:31-40.

287. Khan F, Tritschler T, Kimpton M, et al. Long-Term Risk for Major Bleeding During Extended Oral Anticoagulant Therapy for First Unprovoked Venous Thromboembolism : A Systematic Review and Meta-analysis. Ann Intern Med 2021;174:1420-9.

288. Klok FA, Huisman MV. How I assess and manage the risk of bleeding in patients treated for venous thromboembolism. Blood 2020;135:724-34.

289. Badescu MC, Ciocoiu M, Badulescu OV, et al. Prediction of bleeding events using the VTE-BLEED risk score in patients with venous thromboembolism receiving anticoagulant therapy (Review). Exp Ther Med 2021;22:1344.

290. Stevens SM, Woller SC, Bauer KA, et al. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. J Thromb Thrombolysis 2016;41:154-64.

291. Moll S. Thrombophilia: clinical-practical aspects. J Thromb Thrombolysis 2015;39:367-78.

292. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e419S-e96S.

293. Linnemann B, Hart C. Laboratory Diagnostics in Thrombophilia. Hamostaseologie 2019;39:49-61.

294. Devreese KMJ, Ortel TL, Pengo V, de Laat B, Subcommittee on Lupus Anticoagulant/Antiphospholipid A. Laboratory criteria for antiphospholipid syndrome: communication from the SSC of the ISTH. J Thromb Haemost 2018;16:809-13.

295. Rosell A, Lundstrom S, Mackman N, Wallen H, Thalin C. A clinical practice-based evaluation of the RIETE score in predicting occult cancer in patients with venous thromboembolism. J Thromb Thrombolysis 2019;48:111-8.

296. Carrier M, Lazo-Langner A, Shivakumar S, et al. Screening for Occult Cancer in Unprovoked Venous Thromboembolism. N Engl J Med 2015;373:697-704.

297. Roumen-Klappe EM, den Heijer M, Janssen MC, van der Vleuten C, Thien T, Wollersheim H. The post-thrombotic syndrome: incidence and prognostic value of non-invasive venous examinations in a six-year follow-up study. Thromb Haemost 2005;94:825-30.

298. Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996;125:1-7.

299. Prandoni P, Kahn SR. Post-thrombotic syndrome: prevalence, prognostication and need for progress. Br J Haematol 2009;145:286-95.

300. Hach-Wunderle V, Bauersachs R, Gerlach HE, et al. Post-thrombotic syndrome 3 years after deep venous thrombosis in the Thrombosis and Pulmonary Embolism in Out-Patients (TULIPA) PLUS Registry. J Vasc Surg Venous Lymphat Disord 2013;1:5-12.

301. Azirar S, Appelen D, Prins MH, Neumann MH, de Feiter AN, Kolbach DN. Compression therapy for treating post-thrombotic syndrome. Cochrane Database Syst Rev 2019;9:CD004177.

302. Razavi MK, Jaff MR, Miller LE. Safety and Effectiveness of Stent Placement for Iliofemoral Venous Outflow Obstruction: Systematic Review and Meta-Analysis. Circ Cardiovasc Interv 2015;8:e002772.

303. Qiu P, Zha B, Xu A, et al. Systematic Review and Meta-Analysis of Iliofemoral Stenting for Post-thrombotic Syndrome. Eur J Vasc Endovasc Surg 2019;57:407-16.

304. Majeed GM, Lodhia K, Carter J, et al. A Systematic Review and Meta-Analysis of 12-Month Patency After Intervention for Iliofemoral Obstruction Using Dedicated or Non-Dedicated Venous Stents. J Endovasc Ther 2022;29:478-92.

305. Rossi FH, Kambara AM, Izukawa NM, et al. Randomized double-blinded study comparing medical treatment versus iliac vein stenting in chronic venous disease. J Vasc Surg Venous Lymphat Disord 2018;6:183-91.

306. Seager MJ, Busuttil A, Dharmarajah B, Davies AH. Editor's Choice-- A Systematic Review of Endovenous Stenting in Chronic Venous Disease Secondary to Iliac Vein Obstruction. Eur J Vasc Endovasc Surg 2016;51:100-20.

307. den Exter PL, van Es J, Kroft LJ, et al. Thromboembolic resolution assessed by CT pulmonary angiography after treatment for acute pulmonary embolism. Thromb Haemost 2015;114:26-34.

308. Coquoz N, Weilenmann D, Stolz D, et al. Multicentre observational screening survey for the detection of CTEPH following pulmonary embolism. Eur Respir J 2018;51:1702505.

309. Dorfmuller P, Gunther S, Ghigna MR, et al. Microvascular disease in chronic thromboembolic pulmonary hypertension: a role for pulmonary veins and systemic vasculature. Eur Respir J 2014;44:1275-88.

310. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67-119.

311. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J Thromb Haemost 2016;14:1308-13.

312. Di Nisio M, Vedovati MC, Riera-Mestre A, et al. Treatment of venous thromboembolism with rivaroxaban in relation to body weight. A sub-analysis of the EINSTEIN DVT/PE studies. Thromb Haemost 2016;116:739-46.

313. Reilly PA, Lehr T, Haertter S, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol 2014;63:321-8.

314. Upreti VV, Wang J, Barrett YC, et al. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. Br J Clin Pharmacol 2013;76:908-16.

315. Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. J Clin Pharmacol 2007;47:218-26.

316. Mueck W, Lensing AW, Agnelli G, Decousus H, Prandoni P, Misselwitz F. Rivaroxaban: population pharmacokinetic analyses in patients treated for acute deep-vein thrombosis and exposure simulations in patients with atrial fibrillation treated for stroke prevention. Clin Pharmacokinet 2011;50:675-86.

317. Martin KA, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. J Thromb Haemost 2021;19:1874-82.

318. Kushnir M, Choi Y, Eisenberg R, et al. Efficacy and safety of direct oral factor Xa inhibitors compared with warfarin in patients with morbid obesity: a single-centre, retrospective analysis of chart data. Lancet Haematol 2019;6:e359-e65.

319. Cohen A, Sah J, Lee T, et al. Effectiveness and Safety of Apixaban vs. Warfarin in Venous Thromboembolism Patients with Obesity and Morbid Obesity. J Clin Med 2021;10:200.

320. Costa OS, Beyer-Westendorf J, Ashton V, et al. Effectiveness and safety of rivaroxaban versus warfarin in obese patients with acute venous thromboembolism: analysis of electronic health record data. J Thromb Thrombolysis 2021;51:349-58.

321. Spyropoulos AC, Ashton V, Chen YW, Wu B, Peterson ED. Rivaroxaban versus warfarin treatment among morbidly obese patients with venous thromboembolism: Comparative effectiveness, safety, and costs. Thromb Res 2019;182:159-66.

322. Di Minno MN, Lupoli R, Di Minno A, Ambrosino P, Scalera A, Dentali F. Effect of body weight on efficacy and safety of direct oral anticoagulants in the treatment of patients with acute venous thromboembolism: a meta-analysis of randomized controlled trials. Ann Med 2015;47:61-8.

323. Elshafei MN, Mohamed MFH, El-Bardissy A, et al. Comparative effectiveness and safety of direct oral anticoagulants compared to warfarin in morbidly obese patients with acute venous thromboembolism: systematic review and a meta-analysis. J Thromb Thrombolysis 2021;51:388-96.

324. Tittl L, Endig S, Marten S, Reitter A, Beyer-Westendorf I, Beyer-Westendorf J. Impact of BMI on clinical outcomes of NOAC therapy in daily care - Results of the prospective Dresden NOAC Registry (NCT01588119). Int J Cardiol 2018;262:85-91.

325. Wysokinski WE, Froehling DA, Houghton DE, et al. Effectiveness and safety of apixaban and rivaroxaban for acute venous thromboembolism therapy in patients with extremes in bodyweight. Eur J Haematol 2020;105:484-94.

326. Coons JC, Albert L, Bejjani A, Iasella CJ. Effectiveness and Safety of Direct Oral Anticoagulants versus Warfarin in Obese Patients with Acute Venous Thromboembolism. Pharmacotherapy 2020;40:204-10.

327. Aloi KG, Fierro JJ, Stein BJ, Lynch SM, Shapiro RJ. Investigation of Direct-Acting Oral Anticoagulants and the Incidence of Venous Thromboembolism in Patients Weighing >/=120 kg Compared to Patients Weighing <120 kg. J Pharm Pract 2021;34:64-9.

328. Wasan SM, Feland N, Grant R, Aston CE. Validation of apixaban anti-factor Xa assay and impact of body weight. Thromb Res 2019;182:51-5.

329. Martin AC, Thomas W, Mahir Z, et al. Direct Oral Anticoagulant Concentrations in Obese and High Body Weight Patients: A Cohort Study. Thromb Haemost 2021;121:224-33.

330. Arachchillage D, Reynolds R, Devey T, Maclean R, Kitchen S, van Veen JJ. Effect of extremes of body weight on drug level in patient treated with standard dose of rivaroxaban for venous thromboembolism; real life experience. Thromb Res 2016;147:32-5.

331. Barsam SJ, Patel JP, Roberts LN, et al. The impact of body weight on rivaroxaban pharmacokinetics. Res Pract Thromb Haemost 2017;1:180-7.

332. Speed V, Green B, Roberts LN, et al. Fixed dose rivaroxaban can be used in extremes of bodyweight: A population pharmacokinetic analysis. J Thromb Haemost 2020;18:2296-307.

333. Willmann S, Zhang L, Frede M, et al. Integrated Population Pharmacokinetic Analysis of Rivaroxaban Across Multiple Patient Populations. CPT Pharmacometrics Syst Pharmacol 2018;7:309-20.

334. Piran S, Traquair H, Chan N, Bhagirath V, Schulman S. Peak plasma concentration of direct oral anticoagulants in obese patients weighing over 120 kilograms: A retrospective study. Res Pract Thromb Haemost 2018;2:684-8.

335. Rosovsky RP, Kline-Rogers E, Lake L, et al. Direct Oral Anticoagulants in Obese Patients with Venous Thromboembolism: Results of an Expert Consensus Panel. Am J Med 2023;136:523-33.

336. Mai V, Marceau-Ferron E, Bertoletti L, et al. Direct oral anticoagulants in the treatment of acute venous thromboembolism in patients with obesity: A systematic review with meta-analysis. Pharmacol Res 2021;163:105317.

337. Katel A, Aryal M, Neupane A, et al. Efficacy and Safety of Direct Oral Anticoagulants in Venous Thromboembolism Compared to Traditional Anticoagulants in Morbidly Obese Patients: A Systematic Review and Meta-Analysis. Cureus 2021;13:e14572.

338. Rubino F, Cummings DE, Eckel RH, et al. Definition and diagnostic criteria of clinical obesity. Lancet Diabetes Endocrinol 2025;13:221-62.

339. N. C. D. Risk Factor Collaboration. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet 2017;390:2627-42.

340. Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. State-Level Prevalence of Adult Obesity and Severe Obesity. N Engl J Med 2019;381:2440-50.

341. Wang TF, Carrier M. How I treat obese patients with oral anticoagulants. Blood 2020;135:904-11.

342. European Medicines Agency (EMA): Xarelto European Public Assessment Report. (Accessed April 21, 2026, at https://www.ema.europa.eu/en/medicines/human/EPAR/xarelto#product-info.)

343. World Health Organization (WHO). Waist circumference and waist-hip ratio: report of a WHO expert consultation. 2008. (Accessed April 19, 2026, at https://www.who.int/publications/i/item/9789241501491.)

344. seca GmbH & Co. KG.seca mBCA 515 manufacturer's manual. (Accessed April 19, 2026, at https://www.seca.com/fileadmin/documents/CEP_documents/515_DE/BA_seca_515.pdf.)

345. MEDI CAL HealthCare GmbH. BIACORPUS RX 4000 manufacturer's manual. (Accessed April 19, 2026, at https://medi-cal.de/wp-content/uploads/2025/03/2023-06-05-Korrekte-Durchfuehrung-Biacorpus-Messung.pdf.)

346. Chan YH. Biostatistics 104: correlational analysis. Singapore Med J 2003;44:614-9.

347. Kurzmann-Guetl K, Leitner DR, Gary T, et al. The impact of body composition variability on coagulation monitoring in patients on direct oral factor Xa inhibitors for treatment of venous thromboembolism. Front Cardiovasc Med 2026;13:1773664.

348. Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. Int J Obes (Lond) 2008;32:1431-7.

349. Noboa S, Le Gal G, Lacut K, et al. Family history as a risk factor for venous thromboembolism. Thromb Res 2008;122:624-9.

350. Sekli E LM, Kruschitz R, Kral M, Langer F, Krebs M, Prager G, Ludvik B, Schindler K. Vergleich zweier BIA Geräte zur Ermittlung der Körperzusammensetzung (in German). Aktuelle Ernährungsmedizin 2015;40.

351. Abe T, Kearns CF, Fukunaga T. Sex differences in whole body skeletal muscle mass measured by magnetic resonance imaging and its distribution in young Japanese adults. Br J Sports Med 2003;37:436-40.

352. Karastergiou K, Smith SR, Greenberg AS, Fried SK. Sex differences in human adipose tissues - the biology of pear shape. Biol Sex Differ 2012;3:13.

353. Schorr M, Dichtel LE, Gerweck AV, et al. Sex differences in body composition and association with cardiometabolic risk. Biol Sex Differ 2018;9:28.

354. Snijder MB, Visser M, Dekker JM, et al. Low subcutaneous thigh fat is a risk factor for unfavourable glucose and lipid levels, independently of high abdominal fat. The Health ABC Study. Diabetologia 2005;48:301-8.

355. Lemos T, Gallagher D. Current body composition measurement techniques. Curr Opin Endocrinol Diabetes Obes 2017;24:310-4.

356. Achamrah N, Colange G, Delay J, et al. Comparison of body composition assessment by DXA and BIA according to the body mass index: A retrospective study on 3655 measures. PLoS One 2018;13:e0200465.

357. Thomas DM, Crofford I, Scudder J, Oletti B, Deb A, Heymsfield SB. Updates on Methods for Body Composition Analysis: Implications for Clinical Practice. Curr Obes Rep 2025;14:8.

358. Shepherd JA, Ng BK, Sommer MJ, Heymsfield SB. Body composition by DXA. Bone 2017;104:101-5.

359. Brownbill RA, Ilich JZ. Measuring body composition in overweight individuals by dual energy x-ray absorptiometry. BMC Med Imaging 2005;5:1.

360. Barreira TV, Tseh W. The effects of acute water ingestion on body composition analyses via Dual-Energy X-Ray Absorptiometry. Clin Nutr 2020;39:3836-8.

361. Abate N, Burns D, Peshock RM, Garg A, Grundy SM. Estimation of adipose tissue mass by magnetic resonance imaging: validation against dissection in human cadavers. J Lipid Res 1994;35:1490-6.

362. Borga M. MRI adipose tissue and muscle composition analysis-a review of automation techniques. Br J Radiol 2018;91:20180252.

363. Xiao YD, Paudel R, Liu J, Ma C, Zhang ZS, Zhou SK. MRI contrast agents: Classification and application (Review). Int J Mol Med 2016;38:1319-26.

364. Murata H, Yagi T, Midorikawa T, Torii S, Takai E, Taguchi M. Comparison between DXA and MRI for the Visceral Fat Assessment in Athletes. Int J Sports Med 2022;43:625-31.

365. Micklesfield LK, Goedecke JH, Punyanitya M, Wilson KE, Kelly TL. Dual-energy X-ray performs as well as clinical computed tomography for the measurement of visceral fat. Obesity (Silver Spring) 2012;20:1109-14.

366. Gradmark AM, Rydh A, Renstrom F, et al. Computed tomography-based validation of abdominal adiposity measurements from ultrasonography, dual-energy X-ray absorptiometry and anthropometry. Br J Nutr 2010;104:582-8.

367. Tewari N, Awad S, Macdonald IA, Lobo DN. A comparison of three methods to assess body composition. Nutrition 2018;47:1-5.

368. Day K, Kwok A, Evans A, et al. Comparison of a Bioelectrical Impedance Device against the Reference Method Dual Energy X-Ray Absorptiometry and Anthropometry for the Evaluation of Body Composition in Adults. Nutrients 2018;10:1469.

369. Niebecker R, Jonsson S, Karlsson MO, et al. Population pharmacokinetics of edoxaban in patients with symptomatic deep-vein thrombosis and/or pulmonary embolism--the Hokusai-VTE phase 3 study. Br J Clin Pharmacol 2015;80:1374-87.

370. Testa S, Legnani C, Antonucci E, et al. Drug levels and bleeding complications in atrial fibrillation patients treated with direct oral anticoagulants. J Thromb Haemost 2019;17:1064-72.

371. Testa S, Paoletti O, Legnani C, et al. Low drug levels and thrombotic complications in high-risk atrial fibrillation patients treated with direct oral anticoagulants. J Thromb Haemost 2018;16:842-8.

372. Solms A, Willmann S, Reinecke I, et al. Associations between model-predicted rivaroxaban exposure and patient characteristics and efficacy and safety outcomes in the treatment of venous thromboembolism. J Thromb Thrombolysis 2020;50:1-11.

373. Boriani G, Ruff CT, Kuder JF, et al. Edoxaban versus Warfarin in Patients with Atrial Fibrillation at the Extremes of Body Weight: An Analysis from the ENGAGE AF-TIMI 48 Trial. Thromb Haemost 2021;121:140-9.

374. Boriani G, Ruff CT, Kuder JF, et al. Relationship between body mass index and outcomes in patients with atrial fibrillation treated with edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. Eur Heart J 2019;40:1541-50.

375. Ten Cate V, Koeck T, Prochaska J, et al. A targeted proteomics investigation of the obesity paradox in venous thromboembolism. Blood Adv 2021;5:2909-18.

376. Badheka AO, Rathod A, Kizilbash MA, et al. Influence of obesity on outcomes in atrial fibrillation: yet another obesity paradox. Am J Med 2010;123:646-51.

377. Pandey A, Gersh BJ, McGuire DK, et al. Association of Body Mass Index With Care and Outcomes in Patients With Atrial Fibrillation: Results From the ORBIT-AF Registry. JACC Clin Electrophysiol 2016;2:355-63.

378. Lima Filho AIN, do Rego Barros MC, de Barros Guimaraes AA, Celestino Sobral Filho D. Obesity Paradox in Atrial Fibrillation and its Relation with the New Oral Anticoagulants. Curr Cardiol Rev 2022;18:8-10.

379. Proietti M, Guiducci E, Cheli P, Lip GY. Is There an Obesity Paradox for Outcomes in Atrial Fibrillation? A Systematic Review and Meta-Analysis of Non-Vitamin K Antagonist Oral Anticoagulant Trials. Stroke 2017;48:857-66.

380. Barba R, Zapatero A, Losa JE, et al. Body mass index and mortality in patients with acute venous thromboembolism: findings from the RIETE registry. J Thromb Haemost 2008;6:595-600.

381. Keller K, Hobohm L, Munzel T, et al. Survival Benefit of Obese Patients With Pulmonary Embolism. Mayo Clin Proc 2019;94:1960-73.

382. Kalayci A, Gibson CM, Hernandez AF, et al. Inverse relationship between body mass index and risk of venous thromboembolism among medically ill hospitalized patients: Observations from the APEX trial. Thromb Res 2022;211:63-9.

383. Zawadzka PS, Imiela AM, Pruszczyk P. The Interplay Between Obesity and Venous Thromboembolism: From Molecular Aspects to Clinical Issue. Int J Mol Sci 2025;26:10292.

384. Borst JM, van Rein N, Bakker E, et al. Body weight is negatively associated with direct oral anticoagulant trough concentrations in dabigatran and apixaban users. Br J Haematol 2020;191:941-4.

385. Piccini JP, Patel MR, Mahaffey KW, Fox KA, Califf RM. Rivaroxaban, an oral direct factor Xa inhibitor. Expert Opin Investig Drugs 2008;17:925-37.

386. Camm AJ, Bounameaux H. Edoxaban: a new oral direct factor xa inhibitor. Drugs 2011;71:1503-26.

387. Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor xa inhibitors in development. Clin Pharmacokinet 2009;48:1-22.

388. Muller MJ, Geisler C, Hubers M, Pourhassan M, Bosy-Westphal A. Body composition-related functions: a problem-oriented approach to phenotyping. Eur J Clin Nutr 2019;73:179-86.