ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
ΘΡΟΜΒΩΣΗ ΚΑΙ ΑΝΤΙΘΡΟΜΒΩΤΙΚΗ ΑΓΩΓΗ

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"ΑΝΤΙΜΕΤΩΠΙΣΗ ΑΙΜΟΡΡΑΓΙΚΩΝ ΕΠΙΠΛΟΚΩΝ ΑΠΟ ΤΑ ΑΝΤΙΠΗΚΤΙΚΑ.Ο ΡΟΛΟΣ ΤΩΝ ΑΝΤΙΔΟΤΩΝ"

υπό

ΚΑΡΑΤΑΣΙΤΣΑ Α. ΣΠΥΡΙΔΟΥΛΑ

Ειδικευόμενης Καρδιολογίας

Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διπλώματος Μεταπτυχιακών Σπουδών

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Επιβλέπων:

Τσελέπης Αλέξανδρος , Καθηγητής Κλινικής Βιοχημείας, Τμήμα Χημείας, Πανεπιστήμιο Ιωαννίνων

Τριμελής Εξεταστική Επιτροπή:

1. Τσελέπης Αλέξανδρος, Καθηγητής Κλινικής Βιοχημείας, Τμήμα Χημείας , Πανεπιστήμιο Ιωαννίνων- *(Επιβλέπων)*
2. Αρναούτογλου Ελένη, Καθηγήτρια Αναισθησιολογίας, Πανεπιστήμιο Θεσσαλίας
3. Τσιάρα Σταυρούλα, Καθηγήτρια Παθολογίας, Πανεπιστήμιο Ιωαννίνων

Αναπληρωματικό μέλος:

Ματσάγκας Μιλτιάδης, Καθηγητής Αγγειοχειρουργικής, Τμήμα Ιατρικής Πανεπιστημίου Θεσσαλίας

Τίτλος εργασίας στα αγγλικά:

“Treatment of hemmorhagic complications of anticoagulants. The role of antidotes’’

ΕΥΧΑΡΙΣΤΙΕΣ

Θα ήθελα να ευχαριστήσω τον κ. Τσελέπη Αλέξανδρο Καθηγητή Χημείας και επιβλέπων της εργασίας μου. Τον κύριο Μιλτιάδη Ματσάγκα Καθηγητή Αγγειοχειρουργικής για την πραγμάτωση και δημιουργία του μεταπτυχιακού της θρόμβωσης. Τους διδάσκοντες όλων των σεμιναρίων για τις εξαιρετικές παρουσιάσεις, αλλά και τη γραμματεία του μεταπτυχιακού για την οργάνωση και άμεση ανταπόκρισή της. Τέλος, θα ήθελα να ευχαριστήσω την οικογένειά μου για την συνεχή στήριξή τους σε κάθε μου προσπάθεια.

Περίληψη

Τα αντιπηκτικά είναι φάρμακα που εμποδίζουν τη δημιουργία θρόμβων στο αίμα. Φυσιολογικά ο οργανισμός έχει την ικανότητα μέσω του μηχανισμού πήξεως να ρυθμίζει την πηκτικότητα του αίματος ανάλογα με τις περιστάσεις. Τα αντιπηκτικά παρεμβαίνουν στο μηχανισμό πήξεως με σκοπό να δυσκολέψουν τη διαδικασία της πήξεως για την πρόληψη δημιουργίας θρόμβων και εμβόλων, δηλαδή την απόσπαση θρόμβου και μεταφορά του στη κυκλοφορία του αίματος[1]. Ανάγκη για χορήγηση αντιπηκτικών έχουν οι ασθενείς που έχουν υποστεί κάποια θρόμβωση όπως είναι η εν τω βάθη θρόμβωση, η πνευμονική εμβολή, ασθενείς με κολπική μαρμαρυγή που έχουν κίνδυνο για θρομβοεμβολικά επεισόδια όπως το αγγειακό εγκεφαλικό επεισόδιο και επίσης οι ασθενείς με τεχνητές βαλβίδες[59,60]. Ειδικότερα στην κολπική μαρμαρυγή τα αντιπηκτικά έχουν δείξει μια θεαματική μείωση του κινδύνου για θρομβοεβολικά επεισόδια. Τα από του στόματος αντιπηκτικά προσφέρουν μεγαλύτερη αποτελεσματικότητα από τις κλασσικές επιλογές καθώς διαθέτουν απλούστερη παρέμβαση στη θεραπεία και στη πρόληψη ακόμα και ως μονοθεραπεία χωρίς την ανάγκη για συχνό έλεγχο INR του ασθενούς όπως γίνεται με την λήψη κουμαρινικών αντιπηκτικών. Η επιτυχής αντιπηκτική δράση καθορίζεται από την επιστημονική εξισορρόπηση του κινδύνου θρόμβωσης και της επιπλοκής της αιμορραγίας. Μεγάλη σημασία έχει η εξατομίκευση της αντιθρομβωτικής αγωγής μέσω του υπολογισμού θρομβωτικού και αιμορραγικού κινδύνου του κάθε ασθενούς.

Λέξεις-Κλειδιά: θρόμβωση, αιμορραγικές επιπλοκές, άμεσοι αναστολείς θρομβίνης, κολπική μαρμαρυγή, κλασσικά αντιπηκτικά

Abstract

Anticoagulants are medications that prevent blood clots from forming. Normally, the body has the ability through coagulation mechanism to regulate the coagulation of the blood according to the circumstances. Anticoagulants interfere with the coagulation mechanism in order to make the coagulation process more difficult, the clot and emboli prevention, clot detachment and transportation into the bloodstream[1]. Anticoagulants need to be administered to patients who have suffered some thrombosis such as pulmonary embolism, deep venous thrombosis, patients with atrial fibrillation who are at risk of thromboembolic events such as stroke and also patients with artificial heart valves[59,60]. In atrial fibrillation in particular, anticoagulants have shown a dramatic reduction in the risk of thrombotic and embolic events. Oral anticoagulants offer greater effectiveness compared to classic options as they have a simpler intervention in treatment and prevention even as single therapy without the need for frequent monitoring of INR in case of warfarin. Successful anticoagulation is determined by the scientific balancing of the thrombotic risk and bleeding. The individualization of antithrombotic treatment through the calculation of the thrombotic and bleeding profile of each patient is of great importance.

Key words: Thrombosis, hemorrhagic complications, direct thrombin inhibitors, dabigatran, rivaroxan, apixaban, anticoagulants, atrial fibrillation

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GENERAL PART

Anticoagulants

The main therapy for thrombosis prevention as well as treatment are anticoagulants. The use of anticoagulants is linked with adverse effects, common adverse event is hemorrhage which can be life threatening. Many patients, especially in older ages and patients with concomitant diseases taking warfarin, about half of them will require hospitalization[1]. Despite oral direct anticoagulants aim to replace warfarin and heparin products, dabigatran is linked with serious bleeding, while rivaroxaban with thrombotic events[2].

Types of anticoagulants

ORAL

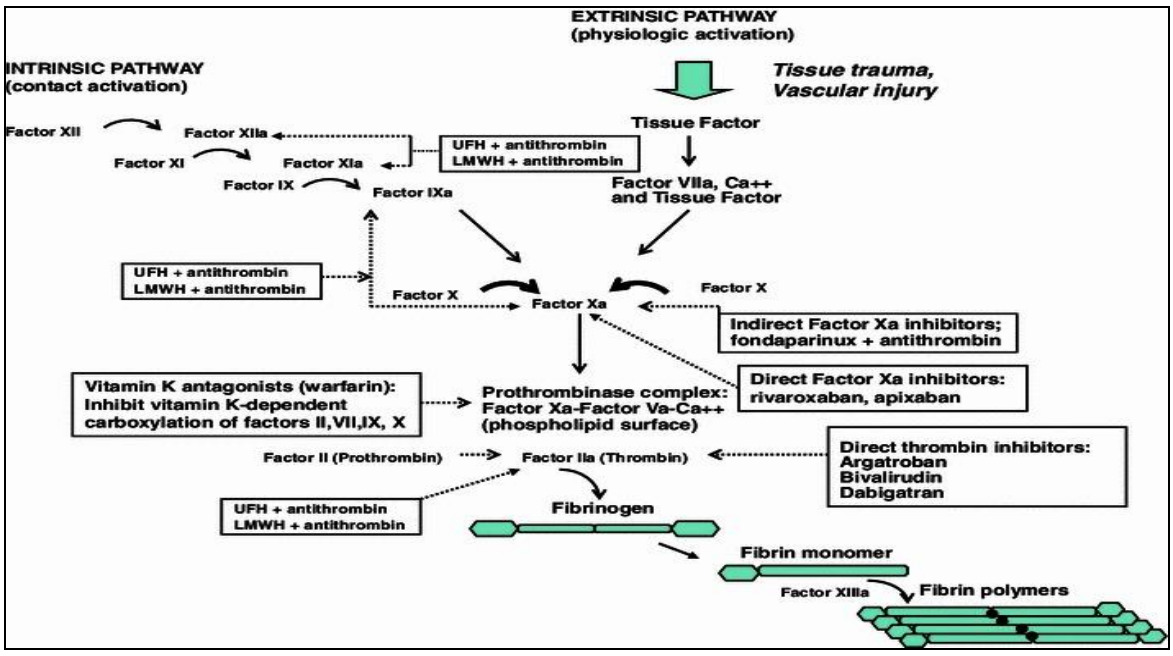
Newer types of anticoagulants are anti-factor Xa inhibitors (rivaroxaban, edoxaban, apixaban) and anti-factor IIa inhibitors (dabigatran).

Vitamin K antagonists require monitoring with INR.

INJECTABLE ANTICOAGULANTS

Heparin and low molecular weight heparins

Fig1.



1.1.1 Pharmacology of Fondaparinux and Heparins

Low molecular weight heparins as well as unfractionated heparin are anticoagulants preferred for acute thrombosis providing rapid onset of anticoagulation activity. The active pentasaccharide that forms heparins, binds to the AT. After binding anticoagulation effect starts to begin, through the inactivation of coagulation factors XIIa, IXa, XIa, Xa and thrombin. The active pentasaccharide is responsible for the catalyzation of AT that is found in 1/3 and 1/5 of the chains of low molecular weight heparin and unfractionated heparin[4,5,6]. A natural synthetic analog deriving from heparin's pentasaccharide is fondaparinux[4,5,6]. Fondaparinux binds to AT. The result is the neutralization of factor Xa, which eventually inhibits the formation of thrombin and the development of thrombus[4,5,6] .

1.1.2 Types of Anticoagulants

1.1.3 Unfractionated Heparin

Administration routes are subcutaneous and intravenous infusion [4,5,6]. When the route is subcutaneous injection aiming therapeutic anticoagulation, needing large doses meaning more than 30.000 units per day in order to overcome unfractionated heparins low bioavailability. After parenteral administration, unfractionated heparin with plasma proteins binding rapid, which contributes in a variable anticoagulant response. Intravenous infusion of unfractionated heparin achieves fast enough the therapeutic plasma concentrations that could be effectively monitored and adjusted according to infusion rates[5]. In order to monitor the anticoagulation effect of the unfractionated heparin is achieved by the activated partial thromboplastin time. To reach therapeutic levels, aPTT is measured every 6 h with intravenous administration, and doses adjusted accordingly, until therapeutic levels are achieved[6,7]. When steady state is achieved then the frequency of monitoring can be extended[6,7]. Dosing depends on weight for the treatment of thromboembolic diseases. Dosing is associated with significantly higher initial UFH doses, shorter time to therapeutic activated aPTT, and no increase in bleeding events[7]. UFH dosing are different in hospitals due to differences of laboratory standardizations of aPTT measurements and agents of thromboplastin[7].

Clinical Indications

Unfractionated heparin used for preventing as well as treating venous thromboembolism, acute coronary syndromes, cardioversion and bridging when needed[4,8,9]. Pharmacokinetic profiles of low molecular weight heparins and fondaparinux are superior compared to unfractionated heparin, because of that, the usage of unfractionated heparin is diminished[4,8,9]. Despite the superiority of pharmacokinetic profiles, in some patients the need of unfractionated heparin is obligatory, examples are patients with underlying bleeding risk, low creatinine clearance meaning less than 30mL/min[10]. Also, unfractionated heparin has short half life and the capability of reversal of effect. Low molecular weight heparin and fondaparinux are not used in patients with less than 30mL/min creatinine clearance because of the accumulation and the increased bleeding risk[11].

Complications and Reversal of Effect

Hemorhage is on of the main complications of unfractionated heparin, including major bleeding with percentage 0–7, also fatal bleeding with percentage 0–3 and heparin induced thrombocytopenia with percentage 1–5[12]. Minor bleeding events are, epistaxis, menorrhagia, metrorrhagia, hematomas etc. Patients who receive unfractionated heparin more than 30 days are at increased risk for vertebral fractures resulting from osteoporosis with percentage around 2[12]. Bleeding events considered major can occur within the range of therapeutic levels. Bleeding risk is increased according to patients profiles, some common risk factors are patients age, gender, creatinine clearance, very low body weight and increased alcohol consumption[12,13,14]. Patients profile is important to calculate bleeding versus thrombotic risk must be evaluated and considered before every surgical procedure. Also except from patients bleeding and thrombotic risk must always been considered the thrombotic and bleeding risk of the surgery or procedure[15,16,17]. Patients who require anticoagulation in elective procedures or surgery, intravenous infusion of unfractionated heparin must be discontinued 4 hours before the surgery and measuring the aPTT. When the aPTT remains elevated, every 1 hour aPTT measurments should occur until reaching the baseline[15,16,17]. After major surgeries the therapy with unfractionated heparin can be continued after 12 hours, in the presence of bleeding signs the therapy must be delayed. Patients in low doses of subcutaneous unfractionated heparin and neuroaxial

techniques are in minimal risk of developing spinal hematomas. But in the need of intraoperative anticoagulation with unfractionated heparin the infusion must begin after one hour of needle placement. In case of indwelling catheters should be taken off 2–4 hours after discontinuation of the UFH infusion and only after coagulation status of patients has been assessed[18].

Reversal of effect

In most hemorrhagic events occuring from unfractionated heparin there is no need of reversal because of the benefit of short half-life. In case of serious and major hemorrhagic events occurring from unfractionated heparin the antidote is protamine sulfate. For immediate reversal, less than 30 min from the last dosing of unfractionated heparin, for every 100 units of unfractionated heparin is given 1mg of protamine sulfate and the reversal response is evaluated by aPTT. Dosing of protamine sulfate is dependent by the timing of the last dose of unfractionated heparin. In cases with unknown dose of unfractionated heparin, dose of protamine sulfate is 50mg given slowly over 10 minutes followed by serial aPTT measurements[19,20]. Common adverse reactions that can be severe after administration of protamine sulfate are slow heart rate, low blood pressure and allergy[19,20]. In case of severity, management achieved by reducing the administration rate to 1-3mg/min while the maximum dose rate is 5mg/min. Patients who have been previously exposed to protamine containing insulin ,have fish allergies ,undergone vasectomy is more common to have allergic reaction to protamine. In such cases or patients in increased risk can be treated with corticosteroids before exposure to protamine[19,20].

1.1.4 Low Molecular Weight Heparins

Compared to unfractionated heparin, low molecular weight heparin have longer half-life around 17 to 21 hours, subcutaneous route and the dose is dependent by the renal function and body weight. It’s common to be used for thromboprophylaxis in hospitalized patients[3,21].

Clinical Indications

For hospitalized patients and patients undergone surgery requiring parenteral thrombo prophylaxis, low molecular weight heparins have become suitable replacement for unfractionated heparin[22,23]. In hospitalized patients who receive thromboprophylaxis, LMWH have been linked with a decreased risk of deep venous thrombosis, lesser hematomas at the injection sites, and no altering the bleeding risk when compared with UFH[24]. Comparing unfractionated heparin with low molecular weight heparin in ST segment elevation the first one have higher incidence of death or non-fatal recurrent myocardial infarction while the low molecular weight heparin have higher rate in bleeding when is used together with fibrinolysis[25]. In cases of non ST segment elevation MI low molecular weight heparin when compared to unfractionated heparin reduced the rates of recurrent MI, death and urgent revascularization[26].

Complications and Reversal Effects

Bleeding events are the most common complication of low molecular weight heparins. Major bleeding reported in percentage of 0-3 and bleeding causing death have been reported in rates of 0-0,8[12]. Before every surgery crucial role plays the thrombotic and bleeding risk of each patient in order to decide the discontinuation or continuation of low molecular weight heparin prophylactic dose. In case of discontinuation of therapeutic doses must be done before 12-24 hours before surgery or even longer in case of low creatinine clearance, and restart after 24 hours of surgery or neuraxial anesthesia[15,25].

Reversal effects

Despite the non-existence of specific antidote that fully reverse the effect of low molecular weight heparin, in cases of major bleeding or over dosing protamine sulfate is used intravenously which neutralize the antithrombotic effect[27,28]. In case of immediate reversal meaning within 8 hours, 1mg of protamine sulfate neutralizes 100 units of low molecular weight heparin[27]. More specific protamine reverses completely the activity of anti-factor IIa, while reverse only the 60 percent anti factor Xa activity. If hemorrhage continues then additional dose of 0,5mg of protamine sulfate for 100 units of low molecular weight heparin is administrated[27,28]. Lower doses of protamine are used when the interval of low molecular weight heparin is more than 8 hours[27,28].

A non hemmorhagic complication to low molecular weight heparin and unfractionated heparin is HIT and HITT[29]. When patients are exposed before to unfractionated heparin and low molecular weight heparin and more than five to seven days a possible immune mediated response called heparin induced thrombocytopenia and heparin induced thrombosis can occur, resulting from antibodies that are against the heparin platelet factor IV complex[29]. The rate of HITT ranges from 1-5 % have been associated with thrombocytopenia and life-threatening thrombosis in approximately 30–50 % of HIT positive patients[29]. After 4 to 10 days of unfractionated heparin or low molecular weight heparin exposure the platelet count can be decreased by 50%. Before every therapy with low molecular weight heparin and unfractionated heparin the platelet count must be measured before the initiation and monitored at least every 5 to 10 days[29].

1.1.5 Fondaparinux

Pharmacodynamics and Monitoring

Fondaparinux is administrated subcutaneous , is rapidly absorbed with 17 to 21 h half life in patients with normal creatinine clearance[4]. Fondaparinux excretion is by the kidneys.

Clinical Indications

It's proven that fondaparinux is safe to be used for treating patients with pulmonary embolism and DVT[33,34]. Fondaparinux, studied extensively for thromboprophylaxis in hospitalized and surgical patients[35,36]. Fondaparinux in several trials have showed better results in reducing the incidence of venous thromboembolism in patients after surgeries like hip and knee arthroplasty and hip fracture surgery[37,38,39]. But the incidence of hemorrhages that can be deadly its not different in comparison with the other agents[37,38,39]. The timing of administration and the dose of fondaparinux is associated with higher rates of major bleeding events[41]. Administration less than 6 hours after procedures is linked with increased rates of major bleeding events[41]. After 6 hours of surgery is recommended for patients with high bleeding risk. Fondaparinux may be an option for thromboprophylaxis in case of HIT allergy but no conclusive data is available[42].

Clinical uses of fondaparinux

Fondaparinux used for treating venous thromboembolism, NSTEMI, STEMI, prophylaxis of VTE in hospitalized patients or patients after surgery. The dosing based on kilograms and creatinine clearance . For patients under 50kg the dose is 5mg sc daily, 50-100kg dose is 7,5mg sc daily and for more than 100kg the dose is 10mg sc daily. For patients with clearance of creatinine lower than 30mL/m fondaparinux is contraindicated[43].

Reversal effects

No specific antidote for fondaparinux existed, but administration of factor VII can normalize thrombin generation and coagulation time[44].

1.1.6 Direct Thrombin Inhibitors (DTIs)

Antithrombotic effect of direct thrombin inhibitors is reversible, selectibe and direct to thrombin's active site[45]. By this leading to the inhibition of thrombin reactions, including activation of factors V, VIII, XIII and protein C factors, also includes formation of fibrin and aggregation of platelets[45]. Desirudin, bivalirudin and argatroban are hirudin analogs and the approved direct thrombin inhibitors[45].

Pharmacology, Pharmacokinetics, and Monitoring

Hirudin analogs bivalirudin and desirudin have anticoagulant activity by binding reversible to the enzymatic site and the anion site of thrombin. In the other hand a small synthetic thrombin inhibitor is argatroban derived from the amino acid arginine that bind to the active site of thrombin[45]. Direct thrombin inhibitors have different pharmacokinetic parameters[45]. Bivalirudin is one of the most useful agent in cases of usage before and after surgery because it has the shortest half-life[45,46]. In order to select the right bivalirudin must always been considered the patients specific characteristics such as age, gender and hepatic and renal dysfunction[45,46]. Patients who have comorbidities or organ dysfunction require low rates of infusion than the recommended[45,46]. Like heparin, monitoring for direct thrombin inhibitors achieved by serial measurements of aPTT. The levels of aPTT must be measured every 6 hours until the reach of sustainable therapeutic levels, then monitoring frequency can be extended[47].

Clinical Indications

In case of heparin induced thrombocytopenia , direct thrombin inhibitors can be used as an alternative anticoagulant to unfractionated heparin[48]. Administration of argatroban lowers the rates of thrombotic and embolic complications in patients with HIT[49]. Also, bivalirudin could be used safely in cases of heparin indused thrombocytopenia[50]. For patients undergoing percutaneous coronary intervention, bivalirudin and argatroban are indicated as an anticoagulant for prevention of thrombosis[50]. Bivalirudin is used as an anticoagulant treating patients with high risk of acute coronary syndrome, non ST segment elevation, unstable angina, and undergoing percutaneous coronary interventions[50].

Clinical Indications

Like all the other anticoagulants hemorrhage is the commonest complication of direct thrombin inhibitors. For direct thrombi inhibitors there is no specific agent although except from the cessation of treatment and preventive measures like blood transfusions, in the case of life threatening hemorrhage, the factor rFVIIa can be effectively be useful[51]. DTIs can elevate the international normalized ratio (INR), complicating the transition to warfarin in HIT. Bridging strategy is achieved by determining the international normalized ratio while the patient is on direct thrombin inhibitors, target INR level is 1,5 to 2. INR is elevated by DTI , when the target INR is achieved then withholding the DTI exposure for 4 to 8 hours and rechecking the INR and aPTT . When the INR is between 2–3 with an aPTT close to baseline the DTI can be discontinued[42].

1.1.7 Oral Anticoagulants –Vit.K Antagonists

The anticoagulant effect of vitamin K antagonists is through the infibition of vit.K epoxy reductase. Environmental and genetic factors can influence the absorption of warfarin their pharmacodynamics and pharmacokinetics[52,53-54-56]. Some of the genetic factors are the age and bleeding profile of the patients while the environmental factors are the dietary intake, drug interactions and comorbidities[52,53,54,55,56]. According to patient age and underlying critical illnesses the therapeutic range of INR can be widened, for example the elderly patients with underlying comorbidities need decreased warfarin doses in order to achieve the desired therapeutic range[57].

Clinical Indications

Warfarin is used for the primary as well as secondary prevention in cases like VTE, systemic embolism in patients with prosthetic heart valves or atrial fibrillation, in primary prevention of acute myocardial infarction, prevention of stroke, recurrent infarction, or death in patients with acute myocardial infarction[52,58-61] .Warfarin is used for treatment of VTE, AF, post myocardial infarction ,mechanical valve in atrial and mitral positions. Warfarin is monitored via INR and should not exceed specific ranges, for example target INR for VTE, AF, post MI and mechanic valve in atrial position should be between 2-3 while mechanic valve in mitral position the target INR is 3.

Complications and Reversal Effects

Hemorrhage, the main and major complication after therapy with warfarin due to the interaction of environmental factors and drug interactions in the very narrow therapeutic ranges[52,53]. Major bleeding is increased 0,3 to 0,5 percentage per year by the use of warfarin and increases the risk of intracranial hemorrhage by 0,2 percentage per year[52,53]. The more higher the goal of therapeutic INR (INR >3), the higher the rates of bleeding risk[52,53]. Patients with lower target goals they have benefit against the hemorrhage[52,53].

Reversal effects

In order to reverse the effect of warfarin the primary strategy is the immediate cessation of the anticoagulant agent. The effect lasts up to few days in the absence of specific reversal agent. Cases of severe hemorrhage the immediate administration of vitamin K is crucial in order to reversal of the effect of vitamin K anticoagulants[53]. When the INR is between 4,5 and 10 with no signs of significant hemorrhage then the appropriate strategy is the discontinuation of the vitamin K antagonist and reevaluation of INR[53]. Guidelines recommend administration of oral vitamin K when the INR exceeds 10, with no signs of significant bleeding. In the other hand, with every life threatening hemorrhage at any range of INR the management is done by holding therapy and administration of 10mg of vitamin K with intravenous infusion, requiring 6 to 12 hours reversal effect. Routes of administration of vitamin K are orally and parenteral, the intravenous administration has more rapid effect. In cases of severe bleeding and need of immediate response the usage of prothrombin comlex

concentrate and fresh frozen plasma are more effective than vitamin K. Adavantages of prothrombin complex concentrates are their smaller volume, faster onset and that there is no need for ABO matching. In cases of increased INR and life threatening bleeding the additional use of factor VIIa may benefit the patients[54,54-62]. Uncommon adverse effects observed in the 8th day of therapy with warfarin, that are not hemorrhagic are limb gangrene, acute skin necrosis. Extensive thrombosis of capillaries and venules within the subcutaneous fat, usually associated with deficiencies of protein C can cause skin necrosis. Before surgery must withhold the therapy with vitamin k antagonists at least 5 days, in case of increased risk of venous or arterial thromboembolism, bridging with unfractionated heparin or low molecular weight heparin may be necessary[15-17]. Restarting of vitamin k antagonists can occur after 12 to 24 hours after surgery, depending on hemorrhagic risk and hemostasis[15-17,63]. Prior to neuroaxial anesthesia assessment of INR is needed. Patients with indwelling catheter who take warfarin the INR must be evaluated and be less than 1,5. However, patients with low hemorrhagic risk may undergo surgery with INR 1,3 to 1,5[15-17,63].

1.1.8 Direct Oral Anticoagulants

Oral direct anticoagulants are dabigatran, rivaroxaban and apixaban and have major advantages compared to other agents. Their prediction of anticoagulant effect and fast onset of action makes them suitable for administration without the need for monitoring. According to several clinical trials direct oral anticoagulants demonstrated lower or similar rates of thrombotic events, adverse effects and major events of bleeding episodes regarding the prevention as well as treatment of the 3 leading causes of cardiovascular death, compared to other agents like low molecular weight heparin or warfarin.

Pharmacology, Pharmacodynamics, and Monitoring

Excretion of dabigatran is by the kidneys, in patients with severe kidney dysfunction dabigatran’s half- life is extended. Rivaroxaban is an oral inhibitor of Xa, Xa inhibition leading to interruption of intrinsic coagulation pathway and extrinsic, preventing generation of thrombin and ensuing thrombus formation. Patients with CrCl 15-30 ml/min , must receive a decreased dose of 75mg two times per day[65]. In patients with CrCl less than 15, rivaroxaban is not recommended[66].

Clinical Indications

Dabigatran indicated in systemic embolism, cerebral infarction and thrombosis prevention of non valvular AF. The dosing of dabigatran depending in creatinine clearance for example above 30ml/min: 150mg two times per day, CrCl 15–30 ml/min: 75 mg two times per day. Rivaroxaban indicated in prevention of cerebral infarction, atrial fibrillation without mechanical valve, treatment of DVT and pulmonary embolism and DVT prevention after surgery of knee or hip replacement. Also, dose depending on creatinine clearance for example CrCl >50 ml/min: 20 mg once per day, CrCl 15–50 ml/min: 15 mg once per day. When treating pulmonary embolism or DVT dose is 15 mg two times per day with meal for 21 days, then 20 mg one time per day with meal until the end of treatment. Apixaban used for ischemic stroke and systemic embolism prophylaxis in non-valvular AF and the dose is 5 mg two times per day or 2.5 mg two times per day in patients having two of those characteristics, age more than 80 years old, weighting less than 60 kg and having serum creatinine less than 1,5mg/dl.

Complications and Reversal Effects

Direct oral anticoagulants achieve a plasma peak concentration about 2- 4 hours after administration. Dabigatran's elimination is mainly achieved by renal excretion thereafter is strongly dependent on renal function. Compared to the other direct iral anticoagulants dabigatran followed by rivaroxaban and then apixaban predisposes to a higher risk of drug accumulation and emergence of adverse effect when is administrated in patients with impaired renal function. Such adverse effects include shortness of breath, dyspepsia, headache, dizziness[77]. Gastrointestinal like symptoms may be due to capsule formulation[77]. Bleeding events are the main adverse effect of all anticoagulants.

Reversal effects

Oral direct anticoagulants, including dabigatran, which ensues anticoagulation by inhibition of thrombin, and rivaroxaban, apixaban, edoxaban and betrixaban, with inhibition of Xa, predispose to a similar or reduced bleeding events in comparison with warfarin[76]. The necessity for immediate cessation of anticoagulation effect may occur in patients who need emergent surgery or patients with life-threatening hemorrhage[76]. Idarucizumab, is the only specific reversal agent for dabigatran available, with a reversal effect starting within few minutes after administration. In addition adnexanet alpha having a reverse effect on factor Xa inhibitors, was approved in United States in 2018[76]. In case of not having reversal agents of the factor Xa inhibitors withholding the direct oral inhibitors dabigatran, rivaroxaban and apixaban may be sufficient because of their short half-life. Blood transfusions and administration of anthrax if the ingestion of the direct anticoagulant is within 2 hours is recommended in case of bleeding. Prothrombin complex concentrate given in patients having life-threatening hemorrhage[76].

1.1 Similar Studies

Choosing the appropriate treatment for thromboembolic disease involves multiple physician specialties. Many studies have been conducted including DOACS compared with vitamin K antagonists, low molecular weight heparins and DOACS compared in different doses.

SPECIFIC PART

2.1 Purpose of review

The purpose of the literature review was to analyze the different types of anticoagulants (injectable and oral administered), their complications and the role of antidotes. Also, to compare anticoagulants in different thrombotic event via randomized clinical trials.

2.2 Inclusion and exclusion criteria

Criteria of inclusion for this literature review are referring in legal age for consent and randomized clinical trials. Before randomization patients were checked if they had consumed doses within the therapeutic ranges of unfractionated heparin, low molecular weight heparin, fondaparinux or more than 1 dose of vitamin K antagonist before 48 hours. Also, checked for history of thombectomy , vena cava filters or any fibrinolytic agents for the current episode of thrombosis as well as contraindications to take enoxaparin, acenocoumarol or warfarin. Therefore patients were eligible if they had symptomatic deep venous thrombosis, pulmonary embolism and have been treated with warfarin or accenocumarol for 6 to 12 months. Criteria of exclusion are referring to patients are randomly assigned, not included in specific groups for example having resistance to anticoagulants, over sensitivity, creatinine clearance below 30mL per minute, liver diseases (acute hepatitis, liver cirrhosis or chronic active hepatitis etc.), bacterial endocarditis , active bleeding or a high risk of bleeding contraindicated anticoagulant treatment, pregnancy or breast feeding, life expectancy less than 3 months, participation in another clinical trial etc.[67-75]

2.3 Strategy of research

The research of data was mainly from Pubmed and the terms that were used are complications of oral anticoagulants, warfarin, venous thromboembolism, non valvular AF, antidotes for DOACS, pulmonary embolism, types of anticoagulants. The initial research pointed out 200 articles, were selected and studied for the final result of the literature review.

2.4 Data export

Data were exctracted for each study based on type, when it was published, the type of anticoagulants and their main characteristics. Comparing direct oral anticoagulants with warfarin in different cases of thrombosis. The complications of oral and injectable anticoagulants, their pharmacokinetic and pharmacodynamics profiles, the treatment of them and the role of antidotes.

2.5 Definitions

Common feature of all studies that were found was the efficacy of oral anticoagulants comparing with warfarin in non valvular AF in pulmonary embolism. Safety is defined based on the occurrence of major hemorrhage. Major bleeding is defined blood loss that cause a hemoglobin drop of 20g/l or bleeding that will followed by 2 units of blood transfusion or a pericardial bleed or a retroperitoneal bleed or a intracranial bleed or bleeding that will be fatal for the patient.

3.1 Selection of studies

RELY TRIAL

Dabigatran is approved in prophylaxis as well as treatment in cases of non valvular atrial fibrillation and venous thromboembolism. It is evaluated in two different doses of 110 mg and 150mg.At a dose of 150mg its approved two time a day with a clearance of creatinine more than 30mg/dl and at a dose of of 75mg two time per day with clearance of creatinine 15 to 30mg/dl[67]. The randomized evaluation of long term anticoagulation therapy (RE-LY) trial, it's a clinical trial that is randomized comparing two doses of dabigatran with warfarin in patients with atrial fibrillation without mechanical valves[67]. At a dose of 150mg of dabigatran two times per day was linked with lower incidence of intracranial hemorrhage, stroke and systemic embolism[67]. Major hemorrhage was the primary safety outcome. Systemic embolism, stroke and death were the secondary outcomes. Pulmonary embolism, transient ischemic attack, myocardial infarction and hospitalization were other outcomes[67]. In conclusion, the comparison between two doses of dabigatran and warfarin the risk for stroke was increased in patients with atrial fibrillation[67]. The two doses of dabigatran were non inferior to warfarin according the primary outcomes of systemic embolism and stroke. Comparing warfarin with dabigatran dose of 110mg was linked with lower rates of major hemorrhage, but similar rates of systemic embolism and stroke. Dabigatran at a dose of 150mg was linkes with similar rates of major hemorrhage but lower rates of systemic embolism and stroke[67].

ROCKET-AF

In patients with atrial fibrillation the administration of warfarin showed a decreased frequency of ischemic stroke events, however, it requires frequent monitoring and dose adjustment in order to achieve the wanted therapeutic effect and diminish the emergence of side effects[72]. Oral factor Xa inhibitors like rivaroxaban provides a more consistent and predictable anticoagulant effect compared to warfarin eliminating the need for monitoring and frequent dose adjustment[72]. In the ROCKET-AF TRIAL rivaroxaban has been evaluated in comparison to warfarin regarding stroke prevention in patients with non valvular atrial fibrillation as well as the frequency of major bleeding. According to ROCKET-AF TRIAL warfarin was non superior to rivaroxaban at a dose of 20mg once per day in decreasing systemic embolism and all cause of stroke events with a similar frequency of major hemorrhagic events[72]. However, rivaroxaban demonstrated a decreased rate of intracranial fatal hemorrhage and on the other hand and an increased rate of bleeding from gastrointestinal sites including upper, lower and rectal sites[72].Rivaroxaban has been evaluated for the acute deep venous thrombosis and pulmonary embolism treatment and for the long-term secondary prevention of recurrent venous thromboembolism[73,74].

EINSTEIN TRIALS

Rivaroxaban provides treatment with a fixed dose in cases of venous thrombosis without the need for monitoring. Rivaroxaban is approved for treatment of deep venous thrombosis and pulmonary embolism as well as the prophylaxis of venous thromboembolism through the EINDTEIN DVT and EINSTEIN PE clinical trials. The EINSTEIN-DVT and EINSTEIN-PE clinical studies found that rivaroxaban at a dose of 15mg two times per day for 21 days followed by a dose of 20mg once daily showed effectiveness of anticoagulation in patients with deep venous thrombosis and pulmonary embolism[67]. In the EINSTEIN-Extension trial, rivaroxaban 20 mg two times per day for an additional treatment in cases of prevention of recurrent venous thromboembolism, for 6–12 months significantly lowered the incidence of VTE without increasing the rates of major hemorrhage or non-major bleeding when compared with placebo[67]. In conclusion, rivaroxaban oral regimen, at a dose of 15mg two time per day for the first 21 days, followed by 20mg once per day, with no need of laboratory monitoring, could provide an effective, safe, single-drug approach to the

initial and continued treatment of venous thrombosis[67]. In EINSTEIN-PE randomized clinical trial involved patients with acute symptomatic pulmonary embolism with or without the presence of deep venous thrombosis, compared rivaroxaban at a dose of 15mg two times per day for 21 days, followed by a dose of rivaroxaban at 20mg once daily with standard therapy with enoxaparin followed by adjusted dose vitamin K antagonist for 3,6 and 12 months. Rivaroxaban is not inferior to enoxaparin when combined with warfarin in preventing recurrent VTE and provides a significant decrease in major bleeding[74].

ARISTOTLE TRIAL

According to ARISTOTLE TRIAL, the use of warfarin to a goal INR 2-3 was inferior in preventing systemic embolism and stroke events compared to administration of apixaban 5 mg twice per day[75]. In addition, apixaban demonstrated a decreased frequency of bleeding events and resulted in lower mortality rates[75].

3.3 Synthesis of results

The main goal of usage of anticoagulants is to choose the appropriate dose and type of anticoagulant according to patients bleeding and thrombotic profiles. DOACS will be safe for patients in terms of bleeding, but it will not adversely affect their quality of life, they are easy to use no need of monitoring and have better outcomes according to bleeding. Vitamin K antagonists need monitoring with INR while low molecular weight heparins are in injectable form at the expense of daily injections for patients. In terms of efficacy, the superiority of DOACS was shown compared to vitamin K antagonists. When compared to placebo, rivaroxaban showed a superiority for treating deep venous thrombosis characterized as acute and also preventing subsequent like events with a decreased risk of bleeding.

Discussion

In the last decades, new oral anticoagulants have been developed. Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and thrombin inhibitors (dabigatran) comprared to vitamin K antagonists have the superiority of shorter half-life , the no need of close monitoring and lower incidence of interaction with environmental,food and drug interactions[79]. Anticoagulants aiming in lowering the incidence of thrombosis by changing the normal coagulation. The main adverse reaction of all anticoagulants is hemorrhage that in some cases can be even life threatening, except from this unlikely reaction other reasons contributing in reversal of effect are in cases of emergent

surgeries or even overdosing. Vitamin K antagonists and heparins have universal available reversal agents but in the case of the direct oral anticoagulants the reversal agents are not in widespread clinical use. Therefore, oral anticoagulants with the no need of close monitoring and dose adjustment enhancing the quality of life, having more predictable outcomes and clinical trials approved that they are more effective and safer than their comparator agents[78]. When reversal is required, for the majority of cases the patient can be stabilized via supportive measures because of their short half-lives[78]. When hemorrhage is life threatening then additional to supportive measures may be considered, like PCC, aPCC, and rFVIIa. Rversal by PCC is faster than aPCC or rFVIIa. aPCC is more thrombogenic increasing the incidence of thrombosis compared to PCC , although containing activated clotting factors[78]. In order to protect patients from deadly outcomes, health care professionals must be educated, having accessible guidelines and reversal agents to ensure proper management and treatment[78].

Limitations

Direct oral anticoagulants include limitations according to the patients renal function, for example patients with severe renal dysfunction cannot consume these oral agents, also limitations according to drug administration (e.g. rivaroxaban of 20mg or 15mg must be consumed with a large meal or must be consumed two times per day), Gastrointestinal bleeding is the most common site of bleeding from direct oral anticoagulants[78]. Vitamin K antagonists and heparins, in the other hand require close monitoring, even daily, in the beginning of the therapy until the dose adjustment according to patients profiles[78]. Also, other important disadvantages of vitamin K antagonists are the food, drug to drug and environmental interactions. Less common is the interactions of direct oral anticoagulants with other drugs. The risk of hemorrhage is increased when there is administration of direct oral anticoagulants with antiplatelet agents, NSAIDS, SSRI, SNRI, and other types of anticoagulants[78]. Most of the patients in every day practice suffer from comorbidities, because of the high risk of renal dysfunction in older patients, the evaluation of renal function must be evaluated before the administration of direct oral anticoagulants to decrease the risk of hemorrhage. Furthermore, no other antidotes are available for DOACs except idarucizumab, which is effective againts dabigatran and this is a problem in case of overdose. Also, specific antidotes of DOACs are not worldwide available in everyday setting.

Conclusions

The cornerstone therapy for the treatment as well as prevention of thrombosis are anticoagulants. For more than a half century vitamin K antagonists have been the anticoagulation therapy. Over the past few years, direct oral anticoagulants came to alter the ordinary practice and the treatment as well as prophylaxis of thrombosis, including the direct thrombin inhibitors (dabigatran) and the factor Xa inhibitors (apixaban, rivaroxaban and edoxaban). Like most drugs, anticoagulants come with adverse events, the most common is the increased risk of hemorrhage. Time is always crucial, faster handling of these situations leading to safer outcomes for the patients. Make use of current clinical treatment guidelines and following the new approved reversal agents will lower the risk that is associated with these medications.

Summary

In conclusion, with the increased rates of venous thromboembolism, atrial fibrillation cases and other thrombotic and embolic diseases, anticoagulants will continue be an important part of treatment plans. Vitamin K antagonists and heparins have many limitations, some of them are the unpredictable pharmacologic and pharmacokinetic responses to many adverse effects including serious bleeding complications. Strict laboratory control is also required for the use of traditional anticoagulants in terms of both insufficient and excessive dosage. The direct oral anticoagulants expected to replace the older agents with their ease of use and more favorable pharmacodynamics profiles. The main adverse effect of all anticoagulants is hemorrhage. Furthermore, is important for the clinicians to have a better understanding of anticoagulant pharmacology, toxicity, dosing and their specific antidotes. Unfortunately, not all specific antidotes of direct oral anticoagulants are available in different hospitals. For example, Andexanet Alpha rivaroxaban's and apixaban's specific antidote is not available in all countries including Greece. The management of mild bleeding from apixaban, rivaroxaban and dabigatran often can be controlled with withholding treatment because of their short half-lives. More severe bleeding episodes require hemodynamic supportive measures, such as blood transfusions, monitoring, usage of anthrax and administration of PCC. When specific antidotes are available in case of life threatening bleeding events or emergent surgeries are always preferable.

References

[1] Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med. 2011;365:2002–2012. doi: 10.1056/NEJMsa1103053.

[2] Institute for Safe Medication Practices. QuarterWatch; monitoring FDA MedWatch reports.

[3] Adams CD, Anger KA, Greenwood BC, Fanikos J. Antithrombotic pharmacotherapy. Chapter 110. In: Irwin and Rippe's intensive care medicine. 7th ed. Philadelphia, PA: Lippincott, Williams, and Wilkins; 2012. p. 1224–42.

[4] 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; 141:24S–43S. This article summarizes the pharmacology and pharmacodynamic properties of parenteral anticoagulants including; unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), fondaparinux, and the direct thrombin inhibitors. There is additional information provided on the dosing, therapeutic monitoring, reversal, and non-hemorrhagic complications.

[5] Weitz DS, Weitz JI. Update on heparin: What do we need to know? J Thromb Thrombolysis. 2010;29:199–207. doi: 10.1007/s11239-009-0411-6. [PubMed]

[6] Bussey H, Francis J, Heparin Consensus Group Heparin overview and issues. Pharmacotherapy. 2004;24:103S–107S. doi: 10.1592/phco.24.12.103S.36109. [PubMed]

[7] Raschke RA, Reilly BM, Guidry JR, et al. The weight-based heparin dosing nomogram compared with a "standard care" nomogram: a randomized controlled trial. Ann Intern Med. 1993;119:874–881. doi: 10.7326/0003-4819-119-9-199311010-00002. [PubMed]

[8] O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. doi:10.1016/CIR.0b013e3182742cf6. [PubMed]

[9] Turpie AGG, Robinson JG, Doyle DJ, et al. Comparison of high-dose with low-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute transmural anterior myocardial infarction. N Engl J Med. 1989;320:352–357. doi: 10.1056/NEJM198902093200604. [PubMed]

[10] Lim W, Dentali F, Eikelboom JW, Crowther MA. Meta analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. Ann Intern Med. 2006;144:673–684. doi: 10.7326/0003-4819-144-9-200605020-00011. [PubMed]

[11] King CS, Holley AB, Jackson JL, et al. Twice vs three times daily heparin dosing for thromboprophylaxis in the general medical population. A metaanalysis. Chest. 2007;131:507–516. doi: 10.1378/chest.06-1861. [PubMed]

[12] Schulman S, Beth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) Chest. 2008;133:257S–298S. doi: 10.1378/chest.08-0674. [PubMed]

[13] Saour JN, Sieck JO, Mamo LAR, Gallus AS. Trial of different intensities of anticoagulation in patients with prosthetic heart valves. N Engl J Med. 1990;322:428–432. doi: 10.1056/NEJM199002153220703. [PubMed]

[14] The Stroke Prevention in Atrial Fibrillation Investigators Bleeding during antithrombotic therapy in patients with atrial fibrillation. Arch Intern Med. 1996;156:409–416. doi: 10.1001/archinte.1996.00440040081009. [PubMed]

[15] Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical

Practice Guidelines (8th Edition) Chest. 2008;133:299S–339S. doi: 10.1378/chest.08-0675. [PubMed]

[16] Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med. 1997;336:1506–1511. doi: 10.1056/NEJM199705223362107. [PubMed]

[17] Smith MS, Muir H, Hall R. Perioperative management of drug therapy, clinical considerations. Drugs. 1996;51:238–259. doi: 10.2165/00003495-199651020-00005. [PubMed]

[18] Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition) Reg Anesth Pain Med. 2010;35:64–101. doi: 10.1097/AAP.0b013e3181c15c70.

[19] Carr JA, Silverman N. The heparin-protamine interaction. A review. J Cardiovasc Surg (Torino) 1999;40:659–666.

[20] McEvoy GK, editor. Protamine sulfate. In: AHFS drug information 2008. Bethesda: American Society of Health-System Pharmacists; 2008. p. 1595–7.

[21] Barrowcliffe TW. Low molecular weight heparins. Br J Haematol. 1995;90:1–7. doi: 10.1111/j.1365-2141.1995.tb03373.x.

[22] Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:195S–226S. doi: 10.1378/chest.11-2296.

[23] Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:227S–277S. doi: 10.1378/chest.11-2297.

[24] Wein L, Wein S, Haas SJ, et al. Pharmacologic venous thromboembolism prophylaxis in hospitalized medical patients. A metaanalysis of randomized controlled trials. Arch Intern Med. 2007;167:1476–1486. doi: 10.1001/archinte.167.14.1476.

[25] ntman EM, Morrow DA, McCabe CH, et al. for the ExTRACT-TIMI-25 Investigators. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-Elevation myocardial infarction. N Engl J Med. 2006;354:1477–1488. doi: 10.1056/NEJMoa060898.

[26] Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-Wave myocardial infarction: results of the Thrombolysis In Myocardial Infarction (TIMI) 11B Trial. Circulation. 1999;100:1593–1601. doi: 10.1161/01.CIR.100.15.1593.

[27] Host J, Lindblad B, Bergqvist D, et al. Protamine neutralization of intravenous and subcutaneous low-molecular-weight heparin (tinzaparin, logiparin). An experimental investigation in healthy volunteers. Blood Coagul Fibrinolysis. 1994;5:795–803. doi: 10.1097/00001721-199410000-00018.

[28] Van Ryn-McKenna J, Cai L, Ofosu FA, et al. Neutralization of enoxaparin-induced bleeding by protamine sulfate. Thromb Haemost. 1990;63:271–274.

[29] Selleng K, Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia in intensive care patients. Crit Care Med. 2007;35:1165–1176. doi: 10.1097/01.CCM.0000259538.02375.A5.

[30] Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood. 2005;106:2710–2715. doi: 10.1182/blood-2005-04-1546.

[31] Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. N Engl J Med. 2001;344:1286–1292. doi: 10.1056/NEJM200104263441704.

[32] Warkentin TE, Greinacher A, Koster A, Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-

Based Clinical Practice Guidelines (8th Edition) Chest. 2008;133:340S–380S. doi: 10.1378/chest.08-0677.

[33] 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;140:867–873. doi: 10.7326/0003-4819-140-11-200406010-00007.

[34] The Matisse Investigators Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med. 2003;349:1695–1702. doi: 10.1056/NEJMoa035451.

[35] Cohen AT, Davidson BL, Gallus AS, et al., for the ARTEMIS Investigators. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomized placebo controlled trial. BMJ. 2006;332:325–9.

[36] Agnelli G, Bergqvist D, Cohen AT, et al. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. Br J Surg. 2005;92:1212–1220. doi: 10.1002/bjs.5154.

[37] Bauer KA, Eriksson BI, Lassen MR, et al., for the Steering Committee of the Pentasaccharide in Major Knee Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med. 2001;345:1305–10.

[38] Lassen MR, Bauer KA, Eriksson BI, et al., for the European Pentasaccharide Elective Surgery Study Steering Committee. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. Lancet. 2002;359:1715–20.

[39] Eriksson BI, Bauer KA, Lassen MR, et al., for the Steering Committee of the Pentasaccharide in Hip-Fracture Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med. 2001;345:1298–1304.

[40] Turpie AGG, Bauer KA, Eriksson BI, et al. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery. A meta-analysis of 4 randomized double-blind studies. Arch Intern Med. 2001;162:1833–1840. doi: 10.1001/archinte.162.16.1833.

[41] Eriksson BI, Lassen MR, for the PENTasaccharide in Hip-FRActure Surgery Plus Investigators. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double blind study. Arch Intern Med. 2003;163:1337–42.

[42] Dager WE, Dougherty JA, Nguyen PH, et al. Heparin-induced thrombocytopenia: treatment options and special considerations. Pharmacotherapy. 2007;27:564–587. doi: 10.1592/phco.27.4.564.

[43] Smythe MA, Dager WE, Patel NM. Managing complications of anticoagulant therapy. J Pharm Pract. 2004;17:327–346. doi: 10.1177/0897190004271776.

[44] Bijsterveld NR, Moons AH, Boekholdt M, et al. Ability of Recombinant Factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. Circulation. 2002;106:2550–2554. doi: 10.1161/01.CIR.0000038501.87442.02.

[45] Di Nisio M, Middeldorp A, Buller HR. Direct thrombin inhibitors. N Engl J Med. 2005;353:1028–1040. doi: 10.1056/NEJMra044440.

[46] Hursting MJ, Soffer J. Reducing harm associated with argatroban; practical considerations of argatroban therapy in heparin-induced thrombocytopenia. Drug Saf. 2009;32:203–218. doi: 10.2165/00002018-200932030-00003.

[47] Love JE, Ferrell C, Chandler W. Monitoring direct thrombin inhibitors with a plasma diluted thrombin time. Thromb Haemost. 2007;98:234–242.

[48] Warkentin TE. Current agents for the treatment of patients with heparin-induced thrombocytopenia. Curr Opin Pulm Med. 2002;8:405–412. doi: 10.1097/00063198-200209000-00011.

[49] Lewis BE, Wallis DE, Hursting MJ, et al. Effects of argatroban therapy, demographic variables, and platelet count on thrombotic risks in heparin-induced thrombocytopenia. Chest. 2006;129:1407–1416. doi: 10.1378/chest.129.6.1407.

[50] Kiser TH, Fish DN. Evaluation of bivalirudin treatment for heparin-induced thrombocytopenia in critically ill patients with hepatic and/or renal dysfunction. Pharmacotherapy. 2006;26:452–460. doi: 10.1592/phco.26.4.452.

[51] Elg M, Carlsson S, Gustafsson D. Effect of activated prothrombin complex concentrate or recombinant factor VIIa on the bleeding time and thrombus formation during anticoagulation with a direct thrombin inhibitor. Thromb Res. 2001;101:145–157. doi: 10.1016/S0049-3848(00)00397-2.

[52] Ageno W, Gallus AS, Wittkowsky A, et al. Oral Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:44S–88S. This article summarizes the unique pharmacology and pharmacodynamic properties of vitamin K antagonists as well as the novel agents dabigatran and rivaroxaban. There is additional provided on the dosing, therapeutic monitoring, and managing reversal.

[53] Holbrook A, Schulman, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012:141;152S–184S. This article provides guidelines on the best practices with anticoagulant use. The focus is on vitamin K antagonists and covers the controversial topics of therapy initiation, pharmacogenetic testing, monitoring frequency, bridging during sub-optimal anticoagulation, and drug interactions. The authors also discuss management of anticoagulant complications including management of patients that are over anticoagulated with and without bleeding.

[54] Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med. 2005;352:2285–2293. doi: 10.1056/NEJMoa044503.

[55] Higashi M, Veenstra DL, Wittkowsky AK, et al. Influence of CYP2C9 genetic variants on the risk of overanticoagulation and of bleeding events during warfarin therapy. JAMA. 2002;287:1690–1698. doi: 10.1001/jama.287.13.1690.

[56] The International Warfarin Pharmacogenetics Consortium Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med. 2009;360:753–764. doi: 10.1056/NEJMoa0809329.

[57] Crowther MA, Ginsberg JB, Kearon C, et al. A randomized trial comparing 5-mg and 10-mg warfarin loading doses. Arch Intern Med. 1999;159:46–48. doi: 10.1001/archinte.159.1.46.

[58] Kearon C, Ginsberg J, Kovacs MJ, et al., for the Extended Low Intensity Anticoagulation for Thrombo-embolism Investigators. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent thromboembolism. N Engl J Med. 2003;349:631–9.

[59] Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. N Engl J Med. 1996;335:540–546. doi: 10.1056/NEJM199608223350802.

[60] Hering D, Piper C, Bergemann R, et al. Thromboembolic and bleeding complications following St. Jude medical valve replacement: results of the German Experience With Low-Intensity Anticoagulation Study. Chest. 2005;127:53–59. doi: 10.1378/chest.127.1.53.

[61] Hurlen M, Abdelnoor M, Smith P, et al. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med. 2002;347:969–974. doi: 10.1056/NEJMoa020496.

[62] Makris M, van Veen JJ, McLean R. Warfarin anticoagulation reversal: management of the asymptomatic and bleeding patient. J Thromb Thrombolysis. 2010;29:171–181. doi: 10.1007/s11239-009-0412-5.

[63] O'Donnell M, Kearon C. Perioperative management of oral anticoagulation. Cardiol Clin. 2008;26:200–309.

[64] Spinler BE, Baetz SA. Dabigatran etexilate: an oral direct thrombin inhibitor for prophylaxis and treatment of thromboembolic diseases. Pharmacotherapy. 2008;28:1354–1373. doi: 10.1592/phco.28.11.1354.

[65] Boehringer Ingelheim. Pradaxa (dabigatran etexilate) Package Insert

[66] Bayer Healthcare. Xarelto (rivaroxaban) Package Insert.

[67] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–1151. doi: 10.1056/NEJMoa0905561.

[68] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–891. doi: 10.1056/NEJMoa1009638.

[69] EINSTEIN Investigators Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363:2499–2510. doi: 10.1056/NEJMoa1007903.

[70] EINSTEIN-PE Investigators Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. New Engl J Med. 2012;366:1287–1297. doi: 10.1056/NEJMoa1113572.

[71] Granger C, Alexander J, McMurray L, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–992. doi: 10.1056/NEJMoa1107039.

[72] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–891. doi: 10.1056/NEJMoa1009638.

[73] EINSTEIN Investigators Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363:2499–2510. doi: 10.1056/NEJMoa1007903.

[74] EINSTEIN-PE Investigators Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. New Engl J Med. 2012;366:1287–1297. doi: 10.1056/NEJMoa1113572.

[75] Granger C, Alexander J, McMurray L, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–992. doi: 10.1056/NEJMoa1107039.

[76] [Management of bleeding associated with direct oral anticoagulants: update on reversal strategies] Andrés Enríquez 1, Adrian Baranchuk 2, Ramón Corbalán 3

[77] Rybak I, Ehle M, Buckley L, Fanikos J. Efficacy and safety ofnovel anticoagulants compared with established agents. Ther AdvHematol. 2011;2:175–95. This article reviews dabigatran,riva-roxaban,and apixaban,focusing on the results from majorclinical trials for venous thromboembolism (VTE)prophylaxis inorthopedic surgery patients,VTE treatment,secondary preven-tion of cardiovascular events after myocardial infarction,andstroke prophylaxis in nonvalvular atrial fibrillation. It alsohighlights agents currently under development that will likelyimpact future practice

[78] Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM.Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials.Lancet. 2014; 383:955–962. doi: 10.1016/S0140-6736(13)62343-0.

[79] Deep vein thrombosis and novel oral anticoagulants: a clinical review. Burgazli KM, Atmaca N, Mericliler M, Parahuleva M, Erdogan A, Daebritz SH.