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disease—VTE. Forty per cent (40%) of patients with DVT without clinical evidence of PE have

section 16 Cardiovascular disorders 3730 evidence of emboli on lung scanning. The principles of therapeutic anticoagulation are the same for both. In proximal DVT and PE this has historically involved immediate anticoagulation with heparin, followed by a period of anticoagulation with warfarin (or other oral vitamin K antagonists). Distal DVT can be managed in the same way, but an alternative strategy is to use serial noninvasive testing (e.g. ultrasonography), which only reliably detects proximal throm- bosis, to ensure that suspected distal thrombosis does not extend above the knee, withholding treatment if it does not. There is clear evidence that an immediately acting anticoagu- lant is needed in the initial phase and that anticoagulation with oral vitamin K antagonists alone is inadequate. Warfarin can be commenced on the first day and heparin is continued for 5 days or until the international normalized ratio (INR) is greater than 2.0 for two consecutive days, whichever is the longer. Extending the period of heparinization from 5 to 10 days is not more effective and increases the risk of heparin-induced thrombocytopenia. The DOACs act immediately and rivaroxaban and apixaban have been used to treat acute VTE without initial heparin. Dabigatran and edoxaban have also been used for acute VTE, but with initial heparin. Heparin Heparin, a glycosaminoglycan, is composed of alternating uronic acid and glucosamine saccharides that are sulphated to a varying degree. Its mode of action is to potentiate the activity of the serine protease inhibitor (serpin) antithrombin, whose main mode of ac- tion is to inhibit thrombin, but which also inhibits several other coagulant proteases such as factor Xa. A specific pentasaccharide sequence (see ‘Fondaparinux’) determined by the sulphation pat- tern along the heparin chain binds to antithrombin and causes a conformational change, giving it full activation against factor Xa but only partial activation against thrombin. Heparins of 18 sac- charides (molecular weight (MW) 5400) or more can extend across the intermolecular gap and also bind to thrombin giving full antithrombin activity, which is lost if the chains are shorter. Unfractionated or standard heparins are a mixture of chains of dif- ferent lengths (MW 5000–35 000, mean 13 000) and low-molecular- weight heparins (LMWH, MW 2000–8000, mean 5000) are derived from them by enzymatic or physicochemical cleavage. LMWH have, with good reason, largely replaced unfractionated heparin for the treatment of venous thromboembolism, but the use of the latter is discussed first. Anticoagulation with unfractionated heparin Unfractionated heparin has most often been given by continuous intravenous infusion, the rate of which has to be adjusted, usually by measuring the activated partial thromboplastin time (APTT). An inadequate APTT response in the first 24 h may increase the risk of recurrence of thromboembolism, although this does not seem to be critical if the starting infusion rate is at least 1250 IU/h. A validated regimen is to give a bolus dose of 80 IU/kg and to start the infusion at 18 IU/kg/h, performing the first APTT estimate after 6 h. The dose is then usually adjusted to maintain the APTT between 1.5 to 2.5 times the average laboratory control value. With older APTT reagents, this corresponded to a therapeutic heparin level of 0.3–0.7 IU/ml by anti-Xa assay. However, many current APTT reagents show an increased sensitivity to unfractionated heparin and, with these, higher ratios should be aimed for. The local laboratory should advise on the appropriate therapeutic range with its reagent. When the dose is therapeutic, the APTT should be checked daily. An alternative is to give unfractionated heparin subcutaneously once every 12 h, and a meta-analysis suggested that this might be more effective and at least as safe as continuous intravenous infu- sion. A reasonable starting dose is 250 IU/kg, adjusting the dose ac- cording to the mid-interval APTT. Anticoagulation with LMWH The key clinical property of LMWHs is that they produce a much more predictable anticoagulant response than unfractionated hep- arin. This, combined with the fact that they have very high bio- availability

after subcutaneous injection, means that the dose can be calculated by body weight and be given subcutaneously without any monitoring or dose adjustment. The actual dosage used dif- fers slightly with the different LMWH and the manufacturers' re- commendations should be followed, but a typical dose is 200 IU/ kg once a day. They are at least as effective and at least as safe as unfractionated heparin. Their widespread use resulted in most pa- tients with DVT being managed as outpatients, and this is increas- ingly the case for low-risk PE. LMWH is renally excreted and so the dose needs to be reduced in patients with renal failure, with monitoring and (if necessary) adjustment of the dose based on anti-Xa levels. In patients with cancer, giving LMWH for the first 6 months of long-term anticoagulant therapy has been shown to be superior to switching to a vitamin K antagonist. Complications of heparin treatment If a patient on intravenous unfractionated heparin is excessively anticoagulated, it is usually sufficient simply to stop the infusion, the half-life being 1 to 2 h. If bleeding is severe, the heparin can be neutralized with protamine sulphate, giving 1 mg for every 100 IU that has been infused over the previous hour. The reversal of LMWH is more problematic. Although protamine sulphate may not neutralize the smaller chains, it is often clinically effective, though estimating an appropriate dose is more difficult (the max- imum dose is 50 mg, so this is often given if the subcutaneous in- jection was recent). Heparin-induced thrombocytopenia is a feared complication, but much less common now that short courses of LMWH are used. It is due to the development of an antibody to the heparin–platelet factor 4 complex and can be associated with serious venous and arterial thrombosis. Heparin must be stopped if heparin-induced thrombo- cytopenia is likely and an alternative immediately acting nonheparin anticoagulant substituted. Fondaparinux The specific pentasaccharide sequence of heparin which binds to antithrombin has been chemically synthesized and is marketed as the drug fondaparinux. Like LMWH it is given by subcutaneous injection with no monitoring. It is equivalent to heparin in the treatment of venous thromboembolism, and is superior to heparin in the treatment of unstable angina and non-ST elevation myo- cardial infarction. It carries virtually no risk of heparin-induced thrombocytopenia.

16.16.2 Therapeutic anticoagulation 3731 Warfarin The oral vitamin K antagonists have historically been the mainstay of long-term anticoagulant therapy. Warfarin is the commonest vitamin K antagonist given; acenocoumarol (which has a shorter half-life) and phenindione (which has a higher incidence of skin rashes) are seldom used in the United Kingdom. The procoagulant factors II, VII, IX, and X (and the anticoagulants protein C and pro- tein S) need vitamin K for the γ-carboxylation of the glutamic acid residues that form their gla domains. Without this post-translational modification they cannot bind calcium, and as a consequence cannot bind to anionic phospholipid surfaces such that assembly of the key coagulation complexes is disrupted. Warfarin takes several days to become effective, so heparin is given initially if immediate anticoagulation is needed. When war- farin is started, the vitamin K-dependent factors fall according to their half-lives. Factor VII and protein C have the shortest half-lives, so that despite a prolongation of the INR due to factor VII deficiency, warfarin may initially be procoagulant. This is the mechanism for the rare problem of warfarin-induced skin necrosis, most often de- scribed in those with protein C deficiency. Initiation and monitoring of anticoagulation with warfarin Monitoring of warfarin treatment is by the INR. This is a manipu- lation of the prothrombin time (PT) to allow for the different sen- sitivities of various laboratory reagents to the warfarin-induced coagulopathy. The INR equals (PT/MNPT)ISI where MNPT is the (mean normal) control PT and ISI is the international sensitivity index of the thromboplastin used in the assay. For the treatment of DVT and PE, the target INR should be 2.5 (target range 2.0–3.0). If the initial coagulation tests are not prolonged, it

has been cus- tomary to give 10 mg of warfarin on the first evening and check the INR the following morning, adjusting the dose according to the daily INR results until the patient is stable. With such regimens, most patients received 10 mg of warfarin on the first 2 days. There is, however, no evidence to suggest a 10 mg loading dose is superior to 5 mg, and regi- mens that start with 5 mg doses, or a single 10 mg dose followed by 5 mg doses, may be preferable to regimens that start with repeated 10 mg doses. This is the case in patients with an increased risk of bleeding (e.g. people >60 years old, and those with liver disease or cardiac failure). The dosing algorithm used in Oxford is shown in Table 16.16.2.1. When patients are stable, they may go for up to 8 weeks between INR checks. If the INR is unstable, patients are seen more frequently, but it should be noted that with warfarin it takes approximately 1 week (5 times the half-life of 36 h) to reach a new steady state after dose ad- justment, hence more frequent dosage alteration is inadvisable. Complications of warfarin treatment The only major complication of warfarin treatment is bleeding. Risk factors for bleeding are increasing age, a history of stroke, a history of gastrointestinal bleeding, anaemia, renal impairment, diabetes, and recent myocardial infarction. A significant problem in control is the starting and stopping of other medication. Many drugs interact with warfarin (see Table 16.16.2.2 for those with the most evidence) such that patient (and doctor) education and constant vigilance are essential. Close monitoring of the INR is advised when concomitant medication is altered. The approach taken to reverse over-anticoagulation with warfarin depends on the circumstances (see Box 16.16.2.1). Prothrombin complex concentrates, unlike fresh frozen plasma, reliably and rap- idly correct the defect and should be used in life-threatening situ- ations such as intracranial bleeding. Small doses of phytomenadione (vitamin K1) can lower a high INR without making subsequent anticoagulation difficult, as is the case if high doses are given. Direct acting oral anticoagulants (DOACs) The ideal anticoagulant would be orally active and have a wide thera- peutic index, predictable pharmacokinetics and dynamics (negating the need for monitoring), minimal interactions with other drugs and food, a rapid onset of action, an antidote, and minimal non- anticoagulant side effects. Heparin needs to be given parenterally. Warfarin has a slow onset of action, a narrow therapeutic index, unpredictable pharmacokinetics and dynamics, and significant Table 16.16.2.1 A warfarin induction regimen Days 1 and 2 Day 3 Day 4 INR Dose (mg) INR Dose (mg) Give 5 mg
each evening
if baseline
INR <1.4 <1.5 10 <1.6 10 1.5–2.0 5 1.6–1.7 7 2.1–2.5 3 1.8–1.9 6 2.6–3.0 1 2.0–2.3 5

> 3.0a 0 2.4–2.7 4 2.8–3.0 3 3.1–3.5 2 3.6–4.0 1 4.0a 0 a and seek advice on further management Table 16.16.2.2 Many drugs interact with warfarin; the evidence is strongest for those listed Potentiation Inhibition Amiodarone Barbiturates Cimetidine Carbamazepine Clofibrate Chlordiazepoxide Cotrimoxazole Cholestyramine Erythromycin Griseofulvin Fluconazole Rifampicin Isoniazid Sucralfate Metronidazole Miconazole Omeprazole Paracetamol Phenylbutazone Piroxicam Propafenone Propranolol Statins Sulfinpyrazone

section 16 Cardiovascular disorders 3732 drug and dietary interactions that make regular monitoring essen- tial. New anticoagulants were therefore much sought, and the most promising targets were Xa and thrombin (Fig. 16.16.2.1). An oral direct thrombin inhibitor (dabigatran) and

three oral direct Xa in- hibitors (rivaroxaban, apixaban, and edoxaban) have now emerged into clinical practice. These DOACs directly inhibit their target co- agulation factors and so do not require antithrombin for their action. Oral direct thrombin (IIa) inhibitors Dabigatran etexilate is orally absorbed and rapidly converted to dabigatran, which inhibits both free and clot-bound thrombin. Peak levels occur 2 h after a dose and the half-life is 12–17 h, the drug being 80% renally excreted. A fixed dose of 150 mg twice a day has been shown to be as effective as warfarin in the treatment of acute venous thromboembolism, though heparin was still given for the first 5 days. It has also been compared with warfarin for the prevention of stroke and systemic embolization in atrial fibrillation, with 110 mg twice a day showing similar efficacy with reduced major bleeding, and 150 mg twice a day showing improved efficacy with similar major bleeding. A specific antidote for dabigatran, the monoclonal antibody idarucizumab, is available, which rapidly and completely reverses anticoagulation in patients taking dabigatran. Oral direct Xa inhibitors Three oral direct Xa inhibitors are currently available (rivaroxaban, apixaban, and edoxaban). All have a rapid onset of action and inhibit free Xa and Xa bound in the prothrombinase complex. • Rivaroxaban has a half-life of 7–13 h and renal clearance is 33%. 15 mg twice a day for 3 weeks followed by 20 mg once a day is as ef- fective as warfarin in the treatment of venous thromboembolism, with reduced major bleeding; 20 mg once a day is equivalent to warfarin for the prevention of stoke and systemic embolization in atrial fibrillation, • Apixaban has a half-life of 10–14 h and renal clearance is 25%. 10 mg twice a day for 1 week followed by 5 mg twice a day is as ef- fective as warfarin in the treatment of venous thromboembolism with reduced major bleeding; 5 mg twice a day is more effective than warfarin for the prevention of stoke and systemic emboliza- tion in atrial fibrillation with less major bleeding. • Edoxaban has a half-life of 8–10 h and renal clearance is 50%; 60 mg once a day is as effective as warfarin in the treatment of venous thromboembolism, but heparin was still used for the first 5 days. 60 mg once a day is as effective as warfarin for the prevention of stoke and systemic embolization in atrial fibrillation with less major bleeding; 30 mg once a day is used in those with renal im- pairment or low body weight. At present there are no factor Xa inhibitor antidotes that are widely available. Andexanet alfa is a decoy receptor for apixaban and rivaroxaban that as of 2019 had been approved or conditionally approved by some regulatory authorities, but is available only in few locations at considerable expense. Low (<20 units/kg) or moderate (20–30 units/kg) doses of FEIBA (factor eight inhibitor bypassing activity) may be effective in DOAC-related major bleeding. Clinical decision making in venous thromboembolism Selecting an anticoagulant The DOACs offer an alternative to vitamin K antagonists for the treatment and secondary prevention of VTE and for stroke preven- tion in atrial fibrillation. They cannot be used in patients with mech- anical heart valves. Logistically they are much simpler to use as they do not require dose adjustment or monitoring. They result in less major bleeding and carry half the risk of intracranial haemorrhage. The lack of a specific antidote to reverse the effects of oral direct Xa inhibitors is a disadvantage compared to vitamin K antagonists and dabigatran, but all the current Xa inhibitors have short half-lives, hence this has not been a major problem in clinical practice and a specific antidote should become more widely available. The DOACs are not a good choice for the poorly compliant, and renal function should be assessed before they are prescribed. Duration of anticoagulation After an acute VTE event, 6 months of anticoagulation has been shown to be more effective than 6 weeks of anticoagulation, and 3 months has been shown to be equivalent to 6 months. After three months of anticoagulation the important clinical decision is to de- cide who can stop anticoagulation and who should take some form of Box 16.16.2.1 Management of over-anticoagulation with warfarin Major bleeding • Stop warfarin • Give prothrombin complex concentrate (PCC) 25–50 IU/kg (only use fresh frozen plasma (FFP) 15 ml/kg if

PCC is not available) • Give phytomenadione 5 mg intravenously Minor bleeding • Stop warfarin • Give phytomenadione 1–3 mg intravenously High INR without bleeding • Stop warfarin until INR <5 • If INR >8 give phytomenadione 1–5 mg orally TF/VIIa IX IXa VIIIa X II IIa Va AT Fondaparinux Fibrinogen Fibrin Bivalirudin Argatroban Dabigatran Rivaroxaban Apixaban Edoxaban Xa
Fig. 16.16.2.1 Anticoagulants targeting Xa and thrombin. Roman numerals represent the coagulation factors (a—indicates the activated forms), TF, tissue factor; AT, antithrombin.

16.16.2 Therapeutic anticoagulation 3733 long-term anticoagulation for secondary prevention. This is a matter of balancing the risk of recurrence against the risk of bleeding on anticoagulation: 2–3% of people on warfarin have a major bleed each year and the case fatality is 10%, giving a fatality rate of 0.25% per year (mostly from intracranial haemorrhage). However, warfarin is highly (approximately 90%) effective at preventing recurrence. The risk of a recurrent venous thromboembolism (VTE) after a first VTE is approximately 5% per year, which with a case fatality rate of 5% also gives a fatality rate of 0.25% per year. Factors that may either increase the risk of bleeding or increase the risk of recurrence need to be taken into account. The risk of recurrence is higher for proximal DVT and PE than for distal DVT, and it is lower if a transient risk factor was present (e.g. recent surgery, use of the contraceptive pill). For patients with a first episode of distal DVT (whether provoked or unprovoked), or a first episode of proximal DVT or PE secondary to a transient (reversible) risk factor, treatment is recommended for 3 months. For patients with a first episode of unprovoked proximal DVT or PE, treatment is recommended for at least 3 months and con- sideration should be given to long-term treatment where there are no risk factors for bleeding and where anticoagulant control is good. An important consideration is that recurrences are more common in men than women. It has also been shown that a raised D-dimer level after discontinuing anticoagulation predicts an increased risk of re- currence. Factor V Leiden and the prothrombin mutation do not in- crease the risk of recurrence of a clinically significant event. Whether deficiencies of antithrombin, protein C, or protein S increase the risk of recurrence is less clear, but testing for these is less helpful than paying attention to the history (unprovoked versus provoked, male versus female) and considering, in selected cases, a D-dimer test. Antiphospholipid antibodies are thought to increase the risk of re- currence, but the evidence is from poor quality studies. If the first event was a symptomatic PE, subsequent events are more likely to be PE, as compared to if the first event was a DVT. For patients with two or more episodes of objectively documented venous thrombo- embolism, or those with a first event and an ongoing risk factor (such as cancer), indefinite treatment should be considered. Taking all this into account, a reasonable approach is indicated in Table 16.16.2.3. Fibrinolysis Thrombolytic agents dissolve thrombi by directly or indirectly activating the zymogen plasminogen to plasmin. Plasmin then de- grades fibrin to soluble peptides, but cannot distinguish fibrin in pathological thrombi from fibrin in haemostatic plugs. The use of thrombolytic agents for venous thromboembolism re- quires careful individual assessment. It is not often given in DVT, though its use should be considered in iliofemoral thrombosis. Thrombolysis in massive PE may be life-saving but for submassive PE, although thrombolysis achieves more rapid resolution than heparin alone, there is no clear evidence of lasting benefit (see Chapter 16.16.1). Streptokinase (which forms a complex with plasminogen that then activates free plasminogen), urokinase, and tissue plasminogen activator (tPA) have all been used. For PE, streptokinase is recom- mended as a 250 000-IU loading dose followed by an infusion for 24 h at 100 000 IU/h. Urokinase is given as a 4400 IU/kg loading dose followed by 2200 IU/kg for 12 h. Following the success of rapid fibrinolytic regimens in myocardial infarction, tPA given as 100 mg over 2 h has been used for PE, and the use of more rapid regimens

with the other two agents has also been suggested (see Chapter 16.16.1 for further discussion). Treatment in pregnancy Heparin and LMWH do not cross the placenta and can be used in pregnancy. LMWH is more convenient, and the osteopenia some- times seen with prolonged use of unfractionated heparin seems not to be a problem with LMWH. Warfarin, which crosses the placenta, can cause an embryopathy if given between 6 and 12 weeks of gesta- tion. At any time, it can cause fetal bleeding and has been associated with central nervous system abnormalities. The DOACs cannot be used in pregnancy. The usual treatment recommended for venous thromboembolism in pregnancy is to continue with full-dose subcutaneous LMWH until term. Warfarin can be used for the 6 weeks of the puer- perium: women taking warfarin can breastfeed. See Chapter 14.7 for further discussion. Treatment for atrial fibrillation Atrial fibrillation affects 2–5% of people over the age of 60 and is associated with a stroke rate of 5% a year. In patients with atrial fib- rillation, warfarin given to a target INR of 2.5 (target range 2.0–3.0) prevents two-thirds of fatal or disabling strokes, though it becomes less effective when the INR is less than 2.0. Aspirin reduces stroke in atrial fibrillation by only approximately 20% and should not be used for this purpose. Compared to warfarin the DOACs are as or more effective, with the same or reduced major bleeding. In patients with atrial fibrillation, the following increase the risk of stroke: congestive heart failure, hypertension, increasing age, dia- betes, previous ischaemic stroke or transient ischaemic attack, vas- cular disease, and female sex. One scheme used to assess patients (CHA2DS2-VASc) gives points for these risk factors. Patient with a score of zero do not usually receive anticoagulation, whereas those with a score of 2 or more are usually anticoagulated. Women with a score of 1 are not anticoagulated, but for men there has been a trend to recommend anticoagulation. If warfarin is used rapid anticoagulation is not usually required and a slow-loading regimen (such as starting patients on 3 mg of war- farin daily for 1 week and determining subsequent doses by weekly INR measurement) is safe and achieves therapeutic anticoagulation in most patients within 3 to 4 weeks. Treatment for mechanical heart valves Vitamin K antagonists are recommended for all patients with mech- anical prosthetic heart valves, the overall risk of embolic stroke if not anticoagulated being 8% per year. Emboli are more common from mi- tral mechanical valves than from aortic mechanical valves, and caged- ball valves are more thrombogenic than bileaflet or tilting-disc valves. Table 16.16.2.3 Duration of warfarin treatment Event Duration of treatment 1st distal DVT 1st proximal DVT or PE with TRFa 3 months 1st unprovoked proximal DVT or PE 3 months or long term 1st proximal DVT or PE with ongoing risk factor Recurrent VTE Long term a TRF, transient risk factor (e.g. surgery, combined pill, pregnancy, plaster cast).

 Various national and international recommendations are made regarding the target INR in patients with mechanical heart valves, with 3.5 traditionally being advised. This is reasonable for caged-ball valves, but for tilting-discs and bileaflet valves the target INR can pos- sibly be lower, for example, 2.5 (range 2.0–3.0) for aortic valves and 3.0 (range 2.5–3.5) for mitral valves. When a new valve is inserted, it is recommended that unfractionated heparin or LMWH be given until the INR is stable and at a therapeutic level for two consecutive days. Perioperative management of therapeutic anticoagulation Warfarin does not need to be stopped for dentistry, nor for some minor surgery. For many operations, however, warfarin will need to be temporarily discontinued. It can generally be stopped 5 days be- fore surgery and the INR be checked on the day of surgery (checking the day before obviates the risk of cancellation as a small dose of oral vitamin K can be given if necessary). The main clinical deci- sion is whether to give bridging therapy with treatment-dose hep- arin perioperatively when the INR is less than 2.0. This depends on balancing the risk of bleeding with the risk of

thromboembolism. Treatment-dose heparin is usually given for those at high risk of thromboembolism, such as patients with a mechanical mitral valve, but must not be (re-)started for at least 48 h after high bleeding risk surgery (Table 16.16.2.4). The DOACs have short half-lives and so bridging is not required. They can normally be stopped 1 or 2 days preoperatively, although renal function needs to be taken into consideration, particularly for dabigatran. They must not be given for at least 48 h after surgery with a high bleeding risk. FURTHER READING Burnett AE, et al. (2016). Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. J Thromb Thrombolysis, 41, 206–32. Connolly SJ, et al. (2009). Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med, 361, 1139–51. Dager WE, Roberts AJ, Nishijima DK (2019). Effect of low and mod- erate dose FEIBA to reverse major bleeding in patients on direct oral anticoagulants. Thromb Res, 173, 71–6. Giugliano RP, et al. (2013). Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med, 369, 2093–104. Granger CB, et al. (2011). Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med, 365, 981–92. Kearon C, et al. (2016). Antithrombotic therapy for VTE dis- ease: CHEST guideline and expert panel report. Chest, 149, 315–52. Keeling D, et al. (2011). Guidelines on oral anticoagulation with warfarin—fourth edition. Br J Haematol, 154, 311–24. Keeling D, et al. (2016). Peri-operative management of anticoagulation and antiplatelet therapy. Br J Haematol, 175, 602–13. Patel MR, et al. (2011). Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med, 365, 883–91. Table 16.16.2.4 Management of warfarin anticoagulation perioperatively, recommendations for bridging when warfarin is stopped 5 days before surgery Risk Preoperatively Postoperatively until INR> 2 High risk e.g. VTE within 1 month; mechanical mitral valve; AF and history of stroke in last three months Treatment-dose heparina (either IV UFH or SC LMWH) Treatment-dose heparinb (either IV UFH or SC LMWH) Low risk e.g. VTE >3 months ago, bi-leaflet aortic valve with no other risk factors, AF without recent stroke Nil or prophylactic LMWH Prophylactic LMWH AF, atrial fibrillation; IV, intravenous; LMWH, low-molecular-weight heparin; SC, subcutaneous; UFH, unfractionated heparin; VTE, venous thromboembolism. a Stop full-dose IV UFH 6 h before surgery and check APTT before operation begins, omit full-dose SC LMWH on day of surgery. b Therapeutic dose heparin must not be given for at least 48 h after high bleeding risk surgery.

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