ACVC
Association for
Acute CardioVascular Care

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CLINICAL DECISION MAKING TOOLKIT

Instant guidance for diagnosis, risk stratification and management

ESC
European Society
of Cardiology

DRUGS IN ACUTE CARDIOVASCULAR CARE

The Clinical Decision Making Toolkit

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The Association for Acute CardioVascular Care
Clinical Decision-Making TOOLKIT

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CHAPTER 10.1
DRUGS

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Oral antiplatelets

Drug	Indications	Dose	Dose adjustments	Comments
Aspirin	Primary and secondary cardiovascular disease prevention	LD (if ACS): 150-300 mg oral MD: 75-100 mg oral QD	-	Major contraindications: GI bleeding-active peptic ulcer
Ticagrelor	ACS (all patients at moderate-to-high risk of ischaemic events, e.g. elevated cardiac troponins)	LD: 180 mg oral MD: 90 mg oral BID	-	Major contraindications: previous intracerebral hemorrhage, severe hepatic impairment, strong CYP3A4 inhibitors
	Secondary prevention 1-3 years post-MI	MD: 60 mg oral BID	-	
Prasugrel	ACS with planned PCI	LD: 60 mg oral MD: 10 mg oral QD	MD: 5 mg QD weight <60kg	Contraindication: previous stroke/TIA Prasugrel is generally not recommended in elderly, and if positive benefit/risk 5 mg is recommended

Oral antiplatelets (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Clopidogrel	ACS + PCI or medical management (patients who cannot receive ticagrelor or prasugrel) and in ACS patients at high bleeding risk (e.g. patients who require oral anticoagulation)	LD: 300-600 mg oral MD: 75 mg oral QD	-	Prasugrel and ticagrelor have not been studied as adjuncts to fibrinolysis and oral anticoagulants
	STEMI + fibrinolysis <75 years	LD: 300 mg oral MD: 75 mg oral QD	-	
	STEMI + fibrinolysis ≥75 years	LD: 75 mg oral MD: 75 mg oral QD	-	
	Secondary prevention >12 months post coronary stenting	MD: 75 mg oral QD	-	

Intravenous antiplatelets

Drug	Indications	Dose	Dose adjustments	Comments
Eptifibatide	ACS treated medically or with PCI	LD: 180 µg/Kg i.v. (at a 10 min interval) If STEMI and PCI: add a second 180 mcg/kg i.v. bolus at 10 min MD: 2 µg/Kg/min i.v. infusion	Reduce infusion dose to 1 µg/kg/min if CrCl 30-50 ml/min	Contraindications: Bleeding diathesis or bleeding within the previous 30 days - Severe uncontrolled hypertension - Major surgery within the preceding 6 weeks - Stroke within 30 days or any history of hemorrhagic stroke - Coadministration of another parenteral GP IIb/IIIa inhibitor - Severe renal impairment or dependency on renal dialysis - History of intracranial disease - Clinically significant hepatic impairment - Thrombocytopenia - Prothrombine time >1.2 times control or INR ≥2
Tirofiban	ACS treated medically or with PCI	LD: 25 µg/Kg i.v. over 5 min MD: 0.15 µg/Kg/min i.v. Infusion to 18 hours	CrCl <30 ml/min: decrease 50% bolus and infusion dose	Contraindications: A history of thrombocytopenia following prior exposure Active internal bleeding or a history of bleeding diathesis, major surgical procedure or severe physical trauma within the previous month

Intravenous antiplatelets (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Cangrelor	All patients undergoing PCI (elective + ACS) immediate onset + rapid offset (platelet recovery in 60min)	i.v. Bolus of 30 µg/Kg + i.v. infusion of 4 µg/kg/min for at least 2 hours from start of PCI	-	Major contraindications: Significant active bleeding or stroke Transition to oral $P2Y_{12}$ inhibitors variable according to type of agent

Oral anticoagulants and antagonists

Drug	Indications	Dose	Dose adjustments	Comments
Warfarin Acenocoumarol	Treatment and prophylaxis of thrombosis	INR goal of 2-3 (INR: 2.5-3.5 for mechanical mitral valve prostheses or double valve replacement)	Assessing individual risks for thromboembolism and bleeding	-
Apixaban	Prevention of stroke and systemic embolism in NVAF	5 mg oral BID	2.5 mg oral BID 1) when at least 2 of the following characteristics: age ≥80, Cr ≥1.5 mg/dl or weight ≤60Kg 2) when CrCl 15-29 ml/min	Contraindicated if CrCl <15 ml/min or severe hepatic impairment
	Treatment of DVT and PE	10 mg oral BID for the first 7 days followed by 5 mg oral BID	-	
	Prevention of recurrent DVT and PE	2.5 mg oral BID	-	

Oral anticoagulants and antagonists (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Dabigatran	Prevention of stroke and systemic embolism in NVAF	150 mg oral BID	110 mg BID (if age ≥80, increased bleeding risk or concomitant use of verapamil)	Contraindicated if CrCl <30 ml/min or severe hepatic impairment Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and dronedarone
	Treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5-10 days and prevention of recurrent DVT and PE in patients who have been previously treated			
Edoxaban	Prevention of stroke and systemic embolism in NVAF	60 mg oral QD	30 mg oral QD 1) when CrCl 15-50 ml/min 2) weight <60Kg 3) concomitant use of the following P-glycoprotein inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole. 4) Avoid use if BMI > 40 Kg/m2 or weight > 120 Kg	Edoxaban can be initiated in patients who may require cardioversion. Treatment should be started at least 2 hours before cardioversion
	Treatment of DVT and PE and prevention of recurrent DVT and PE	60 mg oral QD		

Oral anticoagulants and antagonists (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Rivaroxaban	Prevention of stroke and systemic embolism in NVAF	20 mg oral QD	CrCl <50 ml/min: 15 mg QD	Contraindicated if CrCl <15 ml/min or hepatic disease associated with coagulopathy and clinically relevant bleeding risk Rivaroxaban can be initiated in patients who may require cardioversion Treatment should be started at least 4 hours before cardioversion
	Treatment of DVT and PE and prevention of recurrent DVT and PE	15 mg oral BID for the first 3 weeks followed by 20 mg QD	Reduce the maintenance dose to 15 mg QD if bleeding risk outweighs the risk for recurrent DVT and PE (not formally approved)	
	Prevention of atherothrombotic events	2.5 mg oral BID	-	
Anticoagulant antagonists				
Idarucizumab	Specific reversal agent for dabigatran	5g i.v. over 5 to 10 min Another 5g dose if prolonged clotting times and: - recurrence of clinically relevant bleeding - if potential re-bleeding would be life-threatening - emergency surgery/urgent procedure	-	Dabigatran treatment can be re-initiated 24h after administration of idarucizumab, other antithrombotic therapy at any time Relevant coagulation parameters are aPTT, dTT or ECT

Oral anticoagulants and antagonists (Cont.)

Anticoagulant antagonists

Phytomenadione (Vitamin K)

Indications: Reversal for vitamin K antagonists

Dose:

Patients with asymptomatic high INR with or without mild haemorrhage

Anticoagulant	INR	Oral Vitamin K	i.v. Vitamin K
Warfarin	5-9	1-2.5 mg or 2-5 mg for a rapid reversal (additional dose of 1-2 mg if INR remains high after 24h)	0.5-1 mg
	>9	2.5-5 mg (up to 10 mg)	1 mg
Acenocoumarol	5-8	1-2 mg	1-2 mg
	>8	3-5 mg	1-2 mg

Severe or life-threatening haemorrhage

Anticoagulant	Situation	i.v. Vitamin K	Concomitant treatment
Warfarin	Severe haemorrhage	5-10 mg	CCP or FFP
	Life-threatening	10 mg	CCP, FFP or rFVIIa
Acenocoumarol	Severe haemorrhage	5 mg	CCP, FFP or rFVIIa

Parenteral anticoagulants

Drug	Indications	Dose	Dose adjustments	Comments
UFH	NSTE-ACS	LD: 4,000 IU i.v. MD: 1,000 IU/h i.v.	Target aPTT: 50-70s or 1.5 to 2.0 times that of control to be monitored at 3, 6, 12 and 24h	Monitoring for heparin-induced thrombocytopenia (HIT) Dose-independent reaction
	STEMI	Primary PCI: 70-100 IU/Kg i.v. when no GP-IIb/IIIa inhibitor is planned. 50-60 IU/Kg i.v. bolus with GP-IIb/IIIa inhibitors - Fibrinolysis/ No reperfusion: 60 IU/kg i.v. bolus (max: 4,000 IU) followed by an i.v. infusion of 12 IU/kg (max: 1,000 IU/h) for 24-48h	Target aPTT: 50-70s or 1.5 to 2.0 times that of control to be monitored at 3, 6, 12 and 24h	
	Treatment of DVT and PE	80 IU/Kg i.v. bolus followed by 18 IU/Kg/h	According to aPTT, thromboembolic and bleeding risk	
Fondaparinux	NSTE-ACS	2.5 mg QD s.c. up to 8 days or hospital discharge	-	Acute bacterial endocarditis Severe hepatic impairment: caution advised Contraindicated if CrCl <20 ml/min Contraindicated for DVT/PE treatment if CrCl <30 ml/min
	STEMI	Fibrinolysis/No reperfusion: 2.5 mg i.v. bolus followed by 2.5 mg QD s.c. up to 8 days or hospital discharge	-	
	Treatment of DVT and PE	5 mg QD s.c. (<50kg); 7.5 mg QD s.c. (50-100kg); 10 mg QD s.c. (>100kg)	If >100Kg and CrCl 30-50 ml/min: 10 mg followed by 7.5 mg/24h s.c.	
	Prevention of VTE	2.5 mg QD s.c.	CrCl 20-50 ml/min: 1.5 mg QD s.c.	

Parenteral anticoagulants (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Bivalirudin	PCI for NSTE-ACS	0.75 mg/kg i.v. bolus followed immediatelly by 1.75 mg/kg/h infusion which may be continued for up to 4h post PCI as clinically warranted and further continued at a reduced infusion dose of 0.25 mg/kg/h for 4-12h as clinically necessary	Patients undergoing PCI with CrCl 30-50 ml/min should receive a lower infusion rate of 1.4 mg/kg/h No change for the bolus dose	Contraindicated if CrCl <30 ml/min or in dialysis-dependent patients Active bleeding or increased risk of bleeding, severe uncontrolled hypertension, subacute bacterial endocarditis
	PCI for STEMI	0.75 mg/kg i.v. bolus followed immediatelly by 1.75 mg/kg/h infusion which should be continued for up to 4h after the procedure After cessation of the 1.75 mg/kg/h infusion, a reduced infusion dose of 0.25 mg/kg/h may be continued for 4-12h		
	PCI for elective cases	0.75 mg/kg i.v. bolus followed immediatelly by 1.75 mg/kg/h infusion which may be continued for up to 4h post PCI as clinically waranted		

Parenteral anticoagulants (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Enoxaparin	NSTE-ACS	1 mg/kg s.c. BID	If >75 years: no LD and MD 0.75 mg/Kg BID s.c. CrCl <30 ml/min: no LD and MD 1 mg/Kg QD s.c. If >75 years and CrCl <30 ml/min: no LD and 0.75 mg/Kg QD s.c.	Monitoring for HIT Anti Xa monitoring during treatment with LMWH might be helpful in pregnancy, extreme body weights and renal impairment
	STE-ACS	a) Age <75 years: 30 mg i.v. bolus followed by 1 mg/Kg BID s.c. until hospital discharge for a max of 8 days The first two doses should not exceed 100 mg b) Age ≥75 years: no bolus; 0.75 mg/Kg BID s.c. - The first two doses should not exceed 75 mg Patients managed with PCI: if last dose of enoxaparin <8h before balloon inflation, no additional dosing is needed. If given >8h, an IV bolus of 0.3 mg/kg should be administered.	In patients with CrCl <30 ml/min: regardless of age, the s.c. doses are given once daily	
	Treatment of DVT and PE	1 mg/Kg s.c. BID or 1.5 mg/Kg s.c. QD	CrCl <30 ml/min: 1 mg/Kg/24h s.c.	
	Prevention of VTE	40 mg s.c. QD	CrCl <30 ml/min: 20 mg s.c. QD	

Parenteral anticoagulants (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Tinzaparin	Prevention of VTE	3,500 IU s.c. QD (moderate risk) 4,500 IU s.c. QD (high risk)	-	Monitoring for HIT Anti Xa monitoring during treatment with LMWH might be helpful in pregnancy, extreme body weights and renal impairment Dalteparin: In cancer patients, dose of 200 IU/kg (max: 18,000 IU)/24h for 1 month, followed by 150 IU/kg/24h for 5 months After this period, vitamin K antag or a LMWH should be continued indefinitely or until the cancer is considered cured
	Treatment of DVT and PE	175 IU/Kg s.c. QD	-	
Dalteparin	Prevention of VTE	2,500 IU s.c. QD (moderate risk) 5,000 IU s.c. QD (high risk)	-	
	Treatment of DVT and PE	200 IU/Kg QD or 100 IU/Kg BID s.c.	Anti Xa monitoring if renal impairment	
Argatroban	Anticoagulant in patients with HIT	Initial i.v. infusion dose: 2 µg/kg/min (not to exceed 10 µg/kg/min) Patients undergoing PCI: 350 µg/kg IV followed by 25 µg/kg/min IV	Renal and hepatic impairment: caution advised	Monitored using aPTT goal: 1.5 to 3.0 times the initial baseline value PCI: ACT goal: 300-450s

Fibrinolytics

Drug	Indications	Dose	Dose adjustments	Comments
Streptokinase (SK)	STEMI <12 hours	1.5 million units over 30-60 min i.v.	-	**Absolute contraindications to fibrinolytics:** Previous intracranial haemorrhage or stroke of unknown origin at any time Ischaemic stroke in the preceding 6 months Central nervous system damage or neoplasms or atrioventricular malformation Recent major trauma/surgery/head injury (within the preceding 3 weeks) Gastrointestinal bleeding within the past month Known bleeding disorder (excluding menses) Aortic dissection Non-compressible punctures in the past 24h (e.g. liver biopsy, lumbar puncture)
	Treatment of PE	250,000 IU as a LD over 30min, followed by 100,000 IU/h over 12-24h	-	
Alteplase (tPA)	STEMI <12 hours	15 mg i.v. bolus: 0.75 mg/kg over 30 min (up to 50 mg) then 0.5 mg/kg over 60 min IV (up to 35 mg)	-	
	Treatment of PE	Total dose of 100 mg: 10 mg i.v. bolus followed by 90 mg IV for 2h	If weight <65 Kg: max dose <1.5 mg/kg	

Fibrinolytics (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Reteplase (rt-PA)	STEMI <12 hours	10 units + 10 units i.v. bolus given 30 min apart	Renal and hepatic impairment: caution advised	**Absolute contraindications to fibrinolytics:** Previous intracranial haemorrhage or stroke of unknown origin at any time Ischaemic stroke in the preceding 6 months Central nervous system damage or neoplasms or atrioventricular malformation Recent major trauma/surgery/head injury (within the preceding 3 weeks) Gastrointestinal bleeding within the past month Known bleeding disorder (excluding menses) Aortic dissection Non-compressible punctures in the past 24h (e.g. liver biopsy, lumbar puncture)
Tenecteplase (TNK-tPA)	STEMI <12 hours	Single i.v. bolus over 10 seconds: 30 mg if <60kg 35 mg if 60 to <70kg 40 mg if 70 to <80kg 45 mg if 80 to <90kg 50 mg if ≥90kg	-	

Antiischemic drugs

Drug	Indications	Dose	Dose adjustments	Comments
Beta-blockers: Preferred over calcium channel blockers - Contraindicated if coronary spasm, severe bradycardia, AV block, severe bronchospasm				
Atenolol (cardio-selective beta-1)	ACS and stable coronary artery disease	MD: 100 mg QD	Elderly: start at a lower dose CrCl 15-35 ml/min: max dose 50 mg/day; CrCl <15 ml/min: max dose 25 mg/day Hemodyalisis: max dose 50 mg after each HD	Only if normal LVEF
Carvedilol (non-cardioselective (beta-1 and beta-2) + alpha-1 antagonist)	ACS and stable coronary artery disease	MD: 25 mg BID	Caution in elderly and hepatic impairment	Preferred if LVSD/HF Avoid in conditions with left ventricular outflow tract obstruction
Bisoprolol (cardio-selective beta-1)	ACS and stable coronary artery disease	Recommended dose: 5 - 10 mg QD MD: 20mg QD	Caution in renal or hepatic impairment	Preferred if LVSD/HF

Antiischemic drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Beta-blockers: Preferred over calcium channel blockers - Contraindicated if coronary spasm, severe bradycardia, AV block, severe bronchospasm				
Metoprolol (cardio-selective beta-1)	ACS and stable coronary artery disease	Oral: MD up to 100mg BID Intravenous: 5mg over at least 1 minute, repeated every 2 minutes up to a maximum of 15 mg	Caution in hepatic impairment	Preferred if LVSD/HF
Calcium antagonists: Consider if beta-blockers are contraindicated. First option in vasospastic angina				
Verapamil	ACS and stable coronary artery disease	Oral: MD up to 480 mg per day, divided into 3 or 4 doses. Intravenous: 10 mg over at least 2 minutes (adults), repeatable after 30 minutes if needed	Caution in elderly, renal or hepatic impairment	Contraindicated if bradycardia, HF, LVSD
Diltiazem	ACS and stable coronary artery disease	Oral: MD up to 360 mg per day, divided into 3 or 4 doses Intravenous: Initial bolus of 0.25 mg/kg over 2 minutes; if needed, a second bolus of 0.35 mg/kg after 15 minutes.	Caution in elderly and hepatic impairment	Contraindicated if bradycardia, HF, LVSD
Calcium antagonists: Consider if beta-blockers are contraindicated. First option in vasospastic angina				

Antiischemic drugs (Cont.)

Drug		Indications	Dose	Dose adjustments	Comments
Amlodipine		ACS and stable coronary artery disease	MD: 5-10 mg QD	Caution in hepatic impairment	Contraindicated if severe hypotension, haemodynamically unstable heart failure after acute myocardial infarction or in left ventricular outflow tract obstruction
Nitrates					
Nitroglycerin	i.v.	ACS	If intolerant or unresponsive to nitroglycerin s.l. 5 µg/min - Increase by 5 mcg/min q3-5 min Max dose: 400 µg/min	-	Contraindicated if severe hypotension and co-administration with phosphodiesterase inhibitors The most common adverse effects are headache and dizziness i.v. nitroglycerin requires NON-PVC containers
	spray	Angina	1-2 puff s.l. every 5 min as needed, up to 3 puffs in 15 min	-	
	sublingual tablet	Angina	0.3 to 0.6 mg s.l. or in the buccal pouch every 5 min as needed, up to 3 doses in 15 min	-	

Antiischemic drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Isosorbide mononitrate	Angina	5-10 mg BID with the two doses given 7h apart (8am and 3pm) to decrease tolerance development - then titrate to 10 mg BID in first 2-3 days **Extended release tablet:** Initial: 30-60 mg given in the morning as a single dose Titrate upward as needed, giving at least 3 days between increases Max daily single dose: 240 mg	-	Contraindicated if severe hypotension and co-administration with phosphodiesterase inhibitors The most common adverse effects are headache and dizziness
Isosorbide dinitrate	Angina	MD: 40 mg orally 2 or 3 times a day. Extended realease: 40 to 160 mg/ day orally	-	
Nitroglycerin transdermal patch	Angina	5 - 15 mg patch applied topically once a day for 12 to 14h per day.	-	
Other antiishemic drugs				

Antiischemic drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Ivabradine	Stable angina	5-7.5 mg oral BID	Caution in elderly and CrCl <15 ml/min	Contraindicated if severe hepatic impairment
Ranolazine	Stable angina	Initial dose: 375 mg oral BID After 2-4 weeks, according to patient's response, titrated to a max dose of 750 mg BID	Use with caution in renal and hepatic impairment, CHF, elderly, low weight (< 60 kg)	Contraindicated if CrCl <30 ml/min, concomitant administration of potent CYP3A4 inhibitors, moderate or severe hepatic impairment
Trimetazidine	Stable angina	**Modified-release:** 20 mg oral TID	Caution in elderly and 30<CrCl <60 ml/min	Contraindicated in parkinson disease, parkinsonian symptoms, tremors, restlessleg syndrome, movement disorders, severe renal impairment CrCl < 30ml/min)

Lipid lowering drugs

Drug	Indications	Dose	Dose adjustments	Comments
Statins: Primary or secondary prevention of cardiovascular disease For secondary prevention, start with high doses initiated early after admission and downtitrate if side effects. Target LDL-C levels <70 mg/dl				
Atorvastatin	LDL reduction 30-40% LDL reduction 40-50% LDL reduction > 50%	10mg 20-40 mg 40-80 mg	no adjustment recommended	Contraindicated in patients with active liver disease or with unexplained elevation of liver function enzyme levels
Rosuvastatin - Concomitant therapy with cyclosporine and darolutamide: max: 5 mg orally once a day - Concomitant therapy with gemfibrozil: Avoid concomitant use, if use cannot be avoided: start 5 mg orally once a day, max: 10 mg orally once a day	LDL reduction 30-40% LDL reduction 40-50% LDL reduction > 50%	10mg 20-40 mg 40-80 mg	CrCl<30 mL/min and not on haemodialysis	

Lipid lowering drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Statins: Primary or secondary prevention of cardiovascular disease For secondary prevention, start with high doses initiated early after admission and downtitrate if side effects. Target LDL-C levels <70 mg/dl				
Pitavastatin - Concomitant use with cyclosporine: Contraindicated - Concomitant use with gemfibrozil: Not recommended - Concomitant use with erythromycin: max: 1 mg orally once a day - Concomitant use with rifampin: max: 2 mg orally once a day	LDL reduction <30% LDL reduction 30-40% LDL reduction 40-50%	1 mg 2 mg 4 mg	CrCl 30-59 ml/min: start 1 mg eGFR 15-59 mL/min/1.73 m2. start: 1 mg orally once a day max: 2 mg orally once a day ESRD receiving haemodialysis: start: 1 mg orally once a day max: 2 mg orally once a day	Contraindicated in patients with active liver disease or with unexplained elevation of liver function enzyme levels

Lipid lowering drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Statins: Primary or secondary prevention of cardiovascular disease For secondary prevention, start with high doses initiated early after admission and downtitrate if side effects. Target LDL-C levels <70 mg/dl				
Simvastatin Contraindications: Concomitant use of gemfibrozil, cyclosporine or danazol	LDL reduction <30% LDL reduction 30-40% LDL reduction 40-50% LDL reduction > 50%	10 mg 20-40mg 20 mg + ezetimibe 10 mg 40 mg + ezetimibe 10 mg	Dialysis: Data not available	Contraindicated in patients with active liver disease or with unexplained elevation of liver function enzyme levels
Fluvastatin Concomitant use with cyclosporine or fluconazole: max: 20 mg orally twice a day	LDL reduction <30% LDL reduction 30-40%	20-40 mg 80 mg	Severe renal dysfunction: doses greater than 40 mg should be use with caution. Dialysis: Data not available	
Pravastatin	LDL reduction < 30%	10-40 mg	Dialysis: Data not available	

Lipid lowering drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Statins: Primary or secondary prevention of cardiovascular disease For secondary prevention, start with high doses initiated early after admission and downtitrate if side effects. Target LDL-C levels <70 mg/dl				
Lovastatin	LDL reduction < 30%	20 mg	Dialysis: Data not available	Contraindications: concomitant use with strong CYP450 3A4 inhibitors, erythromycin, pregnancy and lactation Contraindicated in patients with active liver disease or with unexplained elevation of liver function enzyme levels

Lipid lowering drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Others				
Ezetimibe	Hypercholesterolaemia	10 mg oral QD	Avoid use if moderate-severe hepatic impairment	-
Fenofibrate	Hyperlipidemia	48-160 mg oral QD May adjust dose q4-8 weeks	Mild to moderate renal dysfunction: Initiate at lower doses and increase only after evaluating the effects of therapy on renal function and lipid levels	Contraindicated if severe renal impairment or active liver disease if CrCl <50 ml/min or hepatic impairment
Gemfibrozil	Hyperlipidemia	900-1,200 mg/day oral	-	Contraindications: plus preexisting gallbladder disease, concomitant use with simvastatin, replaglinide, dasabuvir or selexipag
Bempedoic acid	Hypercholesterolaemia and mixed dyslipidaemia	180 mg oral QD	Limited experience if CrCl < 30 ml/min and dialysis	Contraindication if pregnancy, breast-feeding, concomitant use with simvastatin > 40 mg daily

Lipid lowering drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Anti PCSK9				
Evolocumab	Hypercholesterolaemia and mixed dyslipidaemia Homozygous familial hypercholesterolaemia	140 mg s.c. every 2 weeks or 420 mg every month Homozygous familial hypercholesterolaemia: 420 mg s.c every month Up-titrate to 420 mg every 2 weeks if a response is not achieved	Renal dose: No adjustment recommended Mild to moderate liver dysfunction (Child Pugh A or B): No adjustment recommended Severe liver dysfunction: Data not available	Most common side effects: Nasopharingitis, upper respiratory tract infection, headache and back pain
Alirocumab	Hypercholesterolaemia and mixed dyslipidaemia	Start dose: 75 mg s.c. every 2 weeks	If a larger LDL-C reduction (>60%) is required, the start dose could be 150 mg every 2 weeks, or 300 mg every 4 weeks The dose can be individualised based on LDL-C level, goal of therapy, and response. Max dose: 150 mg once every 2 weeks	Most common side effects: Upper respiratory tract signs and symptoms, pruritus and injection site reactions Mild to moderate renal dysfunction: No adjustment recommended Severe renal dysfunction: Data not available Mild to moderate hepatic dysfunction: No adjustment recommended Severe hepatic dysfunction: Data not available

Lipid lowering drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Anti PCSK9				
Inclisiran	Primary hypercholesterolaemia and mixed dyslipidaemia	284 mg s.c. initially, again at 3 months, followed by every 6 months	None	Most common side effects: injection site reactions

Heart failure & hypertension

Drug	Indications	Dose	Dose adjustments	Comments
ACEI				
Captopril	HF max dose: 450 mg/day	Target dose: 50 mg TID	CrCl >50 ml/min: 75-100% of the normal dose CrCl 10-50 ml/min: 25-50% CrCl <10 ml/min: 12.5%	Check renal function, electrolytes, drug interactions Major contraindications: History of angioedema, known bilateral renal artery stenosis, pregnancy (risk)
	HTN	Target dose: 50 mg orally three times a day Max 450 mg/day		
Enalapril	HF start:2.5 mg orally once a day target dose: 2.5 mg to 20 mg in 2 divided doses max dose: 40 mg orally in 2 divided doses HN Max dose: 40 mg orally daily as a single dose or in 2 divided doses	5 - 40 mg per day single QD or BID	CrCl 30-80 ml/min: start 5 mg/day CrCl 10-30 ml/min: start 2.5 mg/day	

Heart failure & hypertension (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
ACEI				
Lisinopril	HF max dose: 40 mg orally once a day	Target dose: 20-35 mg QD	CrCl 31-80 ml/min: start 5-10 mg/day CrCl 10-30 ml/min: start 2.5-5 mg/day CrCl <10 ml/min: start 2.5 mg/day	Check renal function, electrolytes, drug interactions Major contraindications: History of angioedema, known bilateral renal artery stenosis, pregnancy (risk)
	HTN	5-40 mg orally once a day Max: 80 mg QD		

Heart failure & hypertension (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
ACEI				
Perindopril severe renal dysfunction: CrCl less 30 ml/min - not recommended	HF, HTN	2-16 mg QD	CrCl >60 ml/min: start 4 mg/day CrCl 31-60 ml/min: start 2 mg/day CrCl 15-30 ml/min: start 2 mg every other day CrCl <15ml/min: 2 mg on the day of dialysis	Check renal function, electrolytes, drug interactions Major contraindications: History of angioedema, known bilateral renal artery stenosis, pregnancy (risk)
Ramipril	HF, HTN	2.5 to 20 mg/day in 1 or 2 doses	reduce usual dose by 25 %: start 1.25 mg QD, max 5 mg/day Caution in elderly and hepatic impairment	
Trandolapril	HF, HTN	2-4 mg oral QD	CrCl <30 ml/min or severe hepatic impairment: start 0.5 mg	

Heart failure & hypertension (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
ARB				
Candesartan	HF, HTN	4-32mg QD	If renal or hepatic impairment: start 4 mg/day	If ACEI is not tolerated Check renal function, electrolytes, drug interactions Major contraindications: History of angioedema, known bilateral renal artery stenosis, pregnancy (risk)
Losartan	HF, HTN	50 - 150mg QD	no adjustment recommended mild to moderate liver dysfunction: start dose: 25 mg orally once a day CrCl <20 ml/min: 25 mg QD Caution if hepatic impairment	

Heart failure & hypertension (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
ARB				
Valsartan	HF, HTN	40 - 320mg BID	CrCl less than 30 ml/min not recommended mild to moderate liver dysfunction: no adjustment recommended max dose 80 mg/day If mild-moderate hepatic impairment: max dose 80 mg/day	If ACEI is not tolerated Check renal function, electrolytes, drug interactions Major contraindications: History of angioedema, known bilateral renal artery stenosis, pregnancy (risk)

Heart failure & hypertension (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Neprilysin inhibitor/ARB				
Sacubitril/Valsartan	Symptomatic chronic HF with reduced ejection fraction	Start: 24/26 mg BID Target dose: 97 mg/103 mg BID	Do not initiate if K>5.4 mmol/l or SBP<100 mmHg Severe renal dysfunction: eGFR less 30 ml/min/1.73m2 start half of the recommendend initial dose moderate liver dysfunction: start half of the recommendend initial dose severe liver dysfunction: not recommended	Do not co-administer with an ACEI or ARB. It must not be started for at least 36 hours after discontinuing an ACEI Contraindicated if history of angioedema related to ACEI or ARB or hereditary or idiopathic angioedema Avoid concomitant use with aliskiren if diabetes mellitus or renal impairment Contraindicated if severe hepatic impairment, biliary cirrhosis and cholestasis If previously taking a moderate to high dose of an ACEI or ARB: 49/51 mg BID

Heart failure & hypertension (Cont.)

Drug		Indications	Dose	Dose adjustments	Comments
Beta-blockers: Check 12 - lead ECG					
Cardioselective (1)	Atenolol	HTN	50-100 mg QD	CrCl 15-35 ml/min - max dose is 50 mg/day CrCl less than 15ml/min - max dose is 25 mg/day decrease dose 50% CrCl <10 ml/min: decrease dose 75%	Major contraindications: asthma, 2nd or 3rd degree AV block
	Bisoprolol	HF, HTN	1.25mg - 20mg QD	CrCl less than 40ml/min - start dose: 2.5 mg orally once a day - caution with dose titration max dose 10 mg QD start dose: 2.5 mg orally once a day- caution with dose titration	
	Metoprolol	HF, HTN	Start: 12.5-25 mg oral QD Target dose: 200 mg QD Max dose: 450 mg/day	Hepatic impairment: start with low doses and titrate gradually	

Heart failure & hypertension (Cont.)

Drug		Indications	Dose	Dose adjustments	Comments
Beta-blockers: Check 12- lead ECG					
Cardioselective (2)	Nebivolol	HF, HTN	1.25 - 40 mg QD Usual dose: 5mg QD	CrCl less than 30ml/min - 2.5 mg once a day, titrate slowly as needed or elderly: start dose 2.5 mg QD, titrate to 5 mg QD Severe hepatic impairment: not recommended	Major contraindications: asthma, 2nd or 3rd degree AV block
Non-cardioselective	Carvedilol	HF, HTN	3.125 - 50 mg BID	Caution in elderly Severe hepatic impairment: contraindicated if hepatic impairment	

Heart failure & hypertension (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Other vasodilators				
Amlodipine	HTN	Max: 10 mg/day	Elderly or secondary agent: start 2.5 mg QD Hepatic impairment: start 2.5 mg QD	Contraindicated if cardiogenic shock, 2nd or 3rd degree AV block, severe hypotension
Nifedipine	HTN	Extended-release form: Start 20 mg oral BID or TID Max: 60 mg BID	Renal and hepatic impairment: caution advised	
Verapamil	HTN	Immediate-release form: Dose: 80-120 mg oral TID; Start: 80 mg TID; Max: 480 mg/day	Oral administration: severe liver impairment: decrease to 30 % of the recommended dos	Contraindicated if bradycardia, HF, LVSD

Heart failure & hypertension (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Loop diuretics				
Furosemide	HF	20-40 mg i.v. bolus, continuous 100 mg/6h (adjust based on kidney function and clinical findings; monitor creatinine) Oral: Up to 600 mg per day, divided into multiple doses. Intravenous: bolus or perfusion max dose 1g/day	Cirrhosis/ascites: caution advised	-
Torsemide	HF	10-20 mg oral or i.v. QD	Hepatic impairment: use with caution	-

Heart failure & hypertension (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Thiazides				
Chlorthalidone	HF	50-100 mg oral QD MD: 25-50 mg QD	Elderly: max dose 25 mg/day CrCl <25 ml/min: avoid use	-
	HTN	Start 12.5-25 mg oral QD; Max: 50 mg/day	Elderly: max dose 25 mg/day CrCl <25 ml/min: avoid use	-
Hydrochlorothiazide	HF	25-200 mg oral/day	CrCl <25 ml/min: avoid use Hepatic impairment: caution advised	-
	HTN	Start 12.5-25 mg oral QD MD: may increase to 50 mg oral as a single or 2 divided doses	CrCl <25 ml/min: avoid use Hepatic impairment: caution advised	-
Indapamide	HTN	Start 1.25 mg PO QAM x4weeks, then increase dose if no response Max: 5 mg/day	CrCl <25 ml/min: avoid use Hepatic impairment: caution advised	-

Heart failure & hypertension (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Aldosterone-antagonists				
Spironolactone	HF	25-50 mg QD	CrCl <10 ml/min, anuria or acute renal impairment: contraindicated Severe hepatic impairment and elderly: caution advised	Check renal function, electrolytes, drug interactions Produces gynecomastia
	HTN	50-100 mg/day oral		
Eplerenone	HF	25-50 mg QD	Elderly: caution advised HF post IM: CrCl<30 ml/min: contraindicated HTN: CrCl<50ml/min: contraindicated	Check renal function, electrolytes, drug interactions + potassium >5.5 mEq/L at initiation, CrCl<30 ml/min strong CYP3A4 inhibitors
	HTN	50 mg oral QD-BID Max: 100 mg/day		
Others				
Ivabradine	HF	5-7.5 mg oral BID	Caution in elderly and CrCl <15ml/min	Contraindicated if severe hepatic impairment

Inotropics & vasopressors

β effect

Drug	Indications	Dose	Dose adjustments	Comments
Levosimendan	HF/cardiogenic shock	0.05 to 0.2 mcg/kg/min, for a total of 6.25 to 12.5 mg	contraindications: severe hepatic and renal impairment, CrCl<30ml/min	Calcium sensitizer and ATP-dependent potassium channel opener
Milrinone	HF/cardiogenic shock	0.375-0.75 µg/kg/min	Caution in renal impairment	Selective phosphodiseterase III inhibitor Caution if atrial flutter Hypotensive drug
Isoprenaline/ Isoproterenol	Bradyarrhythmias	Bolus: 0.02 to 0.06 mg IV bolus Infusion: 5 mcg/min of 2 mg/100 ml normal saline	-	β1, β2 agonist Contraindicated in patients with tachyarrhythmia, tachycardia or heart block caused by digitalis intoxication, ventricular arrhythmias which require inotropic therapy, angina pectoris, recent ACS, hyperthyroidism

Inotropics & vasopressors (Cont.)

α effect

Drug	Indications	Dose	Dose adjustments	Comments
Dobutamine	Cardiogenic shock	2-20 µg/kg/min i.v. Max dose: 40mcg/kg/min	-	β1, α1/β2 agonist Increases contractility with little effect on heart rate and blood pressure. Reduces pulmonary and systemic VR, PCP
Dopamine	Cardiogenic shock	Dopaminergic effect: 1 to 5 mcg/kg/min β effect : 5-15 µg/Kg/min i.v. α effect : 15-40 µg/Kg/min i.v. Max dose: 50mcg/kg/min	-	β, α, dopaminergic agonist Increases BP, PAP, heart rate, cardiac output and pulmonary and systemic VR More arrhythmogenic than dobutamine and noradrenaline
Noradrenaline	Cardiogenic shock	0.05-0.2 µg/kg/min i.v. titrate to effect	-	α 1, β1 agonist Increases BP and PAP Little arrhythmogenic

Antiarrhythmics

Drug	Indications	Dose	Dose adjustments	Comment
Group I				
Procainamide i.v.	AF (termination); stable VT (with a pulse)	15-18 mg/kg over 25-30 minutes, followed by infusion of 1-4 mg/min	Reduce LD to 12 mg/kg in severe renal impairment Reduce MD by one-third in moderate renal impairment and by two-thirds in severe renal impairment Caution in elderly and asthma Procainamide: liver dose adjustment: 50 % reduction in the dose is recommended	Hypotension (negative inotropic agent) Lupus-like syndrome Contraindicated if myasthenia gravis, AV block, severe renal impairment Procainamide blood dyscrasis: agranulocytosis, neutropenia, hypoplastic anemia and thrombocytopenia
Lidocaine i.v. patients with reduced hepatic function or hepatic blood flow should receive half the usual loading dose : 25-50 mg IV bolus once	Pulseless VT/VF	50 to 100 mg IV bolus once over 2 to 3 minutes, may repeat after 5 minutes not to exceed up to 300 mg in a 1-hour period, followed by infusion of 1-4 mg/min	1-2 mg/min infusion if liver disease or HF	Contraindicated if advanced AV block, bradycardia, hypersensitivity to local anesthetics Caution in HF, renal impairment and elderly May cause seizures, psychosis Stop if QRS widens >50%
	Stable VT (with a pulse)	50 to 100 mg IV bolus once over 2 to 3 minutes, may repeat after 5 minutes not to exceed up to 300 mg in a 1-hour period, followed by infusion of 1-4 mg/min		

Antiarrhythmics (Cont.)

Drug	Indications	Dose	Dose adjustments	Comment
Group I				
Flecainide i.v.	SVT, ventricular arrhythmias	2 mg/kg (max 150 mg) IV over 30 min This may be followed by an infusion at a rate of 1.5 mg/kg/h for 1 h, reduced to 0.1-0.25 mg/kg/h for up to 24h, max cumulative dose = 600 mg	severe renal and hepatic impairment: use with caution	Contraindicated if cardiogenic shock, recent MI, 2nd or 3rd degree AV block
Propafenone i.v.	PSVT, ventricular arrhythmias	LD: 0.5-2 mg/kg i.v. direct over aminimum of 3-5min MD: 0.5-2.5 mg/kg i.v. direct q8h (max 560 mg/day) or continuous infusion up to 23 mg/h	May need to reduce dose in renal or hepatic failure	Contraindicated if unstable HF, cardiogenic shock, AV block, bradycardia, myasthenia gravis severe hypotension, bronchospastic disorders, Brugada syndrome

Antiarrhythmics (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Group II				
Atenolol i.v.	Arrhythmias	2.5 mg i.v. over 2.5 min every 5 min (max 10 mg)	Caution in elderly and/or severe renal impairment	Contraindicated if cardiogenic shock, bradycardia and greater than first-degree block, unstable HF
Metoprolol i.v.	Arrhythmias	2.5-5 mg i.v. over 2-5 min, may repeat every 5 min (max 15 mg)	Caution if severe hepatic impairment	Contraindicated if cardiogenic shock, bradycardia and greater than first-degree block, unstable HF
Propranolol i.v.	Arrhythmias	Initially given 1 to 3 mg at a rate not exceeding 1 mg/min, second dose may be given after 2 minu, repeated at 2 min intervals (max: 10 mg in conscious patients and 5 mg if under anesthesia)	-	Contraindicated if cardiogenic shock, bradycardia and greater than first-degree block, asthma, unstable HF

Antiarrhythmics (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Group III				
Amiodarone i.v.	AF termination, stable VT	300 mg bolus i.v. (can give additional 150 mg i.v. bolus if VF/VT persists) followed by infusion of 900 mg over 24h	-	Reduce infusion rate if bradycardia, AV block, hypotension Bolus should be avoided if hypotension or severe LV dysfunction Highly vesicant agent
Dronedarone	Paroxysmal or persistent AF prevention	400 mg oral BID	-	Contraindicated if severe renal or liver dysfunction, LVSD, or NYHA class IV, AF who cannot be cardioverted into normal sinus rhythm, bradycardia... (multiple contraindications)

Antiarrhythmics (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Group IV				
Diltiazem IV	PSVT; AF (rate control)	0.25 mg/kg i.v. over 2 min (may repeat with 0.35 mg/kg i.v. over 2 min), followed by infusion of 5-15 mg/h	Hepatic impairment: caution advised	-
Verapamil IV	PSVT; AF (rate control)	initial dose: 5-10 mg IV over 2 min repeat dose: 10 mg IV (over 2 minutes) 30 minutes after the initial dose	Hepatic and renal impairment: caution advised	Contraindicated if AF+WPW, tachycardias QRS (except RVOT-VT), fascicular VT, bronchospasm, age >70 years Antidote: - LVD: Calcium gluconate, dobutamine - Bradycardia/AV block: Atropine, Isoproterenol
Adenosine IV	Rapid conversion to a normal sinus rhythm of PSVT including those associated with accessory by-pass tracts (WPW syndrome)	Rapid i.v. boluses separated by 2 min: 6 mg - 12 mg - 18 mg Overdose: Theophyline 50 to 125 mg IV can be used to treat delayed or persistent adverse reactions	-	Contraindicated if sick sinus syndrome, second or third degree Atrio-Ventricular (AV) block (except in patients with a functioning artificial pacemaker), chronic obstructive lung disease with evidence of bronchospasm (e.g. asthma bronchiale), long QT syndrome, severe hypotension; decompensated states of heart failure - Adenosine can cause AF

Antiarrhythmics (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Others				
Magnesium sulfate	VT-Torsades de Pointes	Bolus: 1-2g i.v./i.o. over 5 min Perfusion: 5-20 mg/min i.v.	Caution if severe renal failure	Contraindicated if myasthenia gravis
Vernakalant	Conversion of recent onset AF	3 mg/kg i.v. over 10 min (maximum initial dose of 339 mg) If AF persists, a second 10min-infusion of 2 mg/kg, 15 min later may be administered (maximum second infusion of 226 mg) If conversion to sinus rhythm occurs during either the initial or second infusion, that infusion should be continued to completion	-	Contraindicated if ACS within the last 30 days, severe aortic stenosis, SBP <100 mmHg, HF class NYHA III/i.v., severe bradycardia, sinus node dysfunction or 2nd or 3rd degree heart block, prolonged QT at baseline, use of i.v. antiarrhythmics (class I and class III) within 4h prior to, as well as in the first 4h after, vernakalant administration

Sedatives and neuropsychiatric drugs

Drug	Indications	Dose	Dose adjustments	Comments
Benzodiazepines: Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products. The risk of dependence increases with dose and duration of treatment. Benzodiazepines may induce anterograde amnesia. Discontinuation: dosage should be reduced slowly				
Short-acting benzodiazepines				
Lorazepam oral	Severe anxiety Premedication before suragery	Anxiety: 1-4 mg oral in divided doses Insomnia: 1-2 mg oral before retiring Premedication before surgery: 1 mg oral the night before operation 1 mg oral 1-2h before the procedure	Elderly: may respond to lower doses Renal or hepatic impairment: lower doses may be sufficient	Contraindicated if acute pulmonary insufficiency, respiratory depression, sleep apnoea, obsessional states, severe hepatic insufficiency, myasthenia gravis
Lorazepam injection	Pre-operative medication, acute anxiety states, acute excitement or acute mania, status epilepticus	Premedication: 0.05 mg/Kg By the i.v. route the injection should be given 30-45 min before surgery By the i.m. route the injection should be given 1-1.5h before surgery Acute anxiety: 0.025-0.03 mg/kg i.v./i.m. Repeat 6 hourly Status epilepticus: 4 mg i.v.		

Sedatives and neuropsychiatric drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Short-acting benzodiazepines				
Lormetazepam oral	Short-term treatment of insomnia	0.5-1.5 mg oral before retiring. The initial dosage may be increased to 2 mg in individual cases if this proves necessary	Eldery, debilitated patients, or those with cerebrovascular disorders (arteriosclerosis), mild to moderate respiratory insufficiency, and/or renal and/or hepatic insufficiency: recommended dose 0.5mg	Contraindicated if myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome, acute intoxication with alcohol, hypnotics, analgesics or psychotropic drugs, severe liver insufficiency

Sedatives and neuropsychiatric drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Short-acting benzodiazepines				
Midazolam injection (1)	Short-acting sleep-inducing drug	**DOSE / DOSE ADJUSTMENTS:**		

Indications	Adults <60 y	Adults ≥60 y/debilitated or chronically ill
Conscious sedation	i.v. Initial dose: 2-2.5 mg Titration doses: 1 mg Total dose: 3.5-7.5 mg	i.v. Initial dose: 0.5-1 mg Titration doses: 0.5-1 mg Total dose: <3.5 mg
Anaesthesia premedication	i.v. 1-2 mg repeated i.m. 0.07-0.1 mg/kg	i.v. Initial dose: 0.5 mg Slow uptitration as needed i.m. 0.025-0.05 mg/kg

COMMENTS: Caution in adults >60years, chronically ill or debilitated patients, patients with chronic respiratory insufficiency, patients with chronic renal failure, impaired hepatic function or with impaired cardiac function - Contraindicated if conscious sedation in patients with severe respiratory failure or acute respiratory depression - Severe cardiorespiratory adverse events have been reported (respiratory depression, apnoea, respiratory arrest and/or cardiac arrest). Such life-threatening incidents are more likely to occur when the injection is given too rapidly or when a high dosage is administered

Sedatives and neuropsychiatric drugs (Cont.)

<table>
<tr><th>Drug</th><th>Indications</th><th>Dose</th><th>Dose adjustments</th><th>Comments</th></tr>
<tr><td>Midazolam injection (2)</td><td>Short-acting sleep-inducing drug</td><td colspan="3">
DOSE / DOSE ADJUSTMENTS:
<table>
<tr><th>Indications</th><th>Adults <60 y</th><th>Adults ≥60 y/debilitated or chronically ill</th></tr>
<tr><td>Anaesthesia induction</td><td>i.v. 0.15-0.2 mg/kg
(0.3-0.35 without premedication)</td><td>i.v. 0.05-0.15 mg/kg
(0.15-0.3 without premedication)</td></tr>
<tr><td>Sedative component in combined anaesthesia</td><td>i.v. Intermittent doses of 0.03-0.1 mg/kg or continuous infusion of 0.03-0.1 mg/kg/h</td><td>i.v. Lower doses than recommended for adults <60 years</td></tr>
<tr><td>Sedation in ICU</td><td colspan="2">i.v. LD: 0.03-0.3 mg/kg in increments of 1-2.5 mg
MD: 0.03-0.2 mg/kg/h</td></tr>
</table>
COMMENTS: Caution in adults >60years, chronically ill or debilitated patients, patients with chronic respiratory insufficiency, patients with chronic renal failure, impaired hepatic function or with impaired cardiac function - Contraindicated if conscious sedation in patients with severe respiratory failure or acute respiratory depression - Severe cardiorespiratory adverse events have been reported (respiratory depression, apnoea, respiratory arrest and/or cardiac arrest). Such life-threatening incidents are more likely to occur when the injection is given too rapidly or when a high dosage is administered
</td></tr>
</table>

Sedatives and neuropsychiatric drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Long-acting benzodiazepines				
Bromazepam	Insomnia, short-term treatment of anxiety or panic attacks	1.5-3 mg oral up to TID If a severe condition: 6-12 mg oral BID or TID	Elderly or hepatic impairment: lower doses are recommended	Contraindicated if myasthenia gravis, severe hepatic impairment, severe respiratory insufficiency, sleep apnoea syndrome
Clonazepam	Epileptic disease and seizures	Oral: Initial dose not to exceed 1.5 mg/day; MD: 3-6 mg i.v.: 1 mg by slow injection or slow infusion. Repeat dose if needed (1-4 mg are usually sufficient)	Elderly: Caution Chronic pulmonary insufficiency, renal or mild-moderate hepatic impairment: may require lower doses	Contraindicated if acute pulmonary insufficiency, severe respiratory insufficiency, sleep apnoea syndrome, myasthenia gravis, severe hepatic insufficiency, coma or in patients known to be abusing pharmaceuticals, drugs or alcohol

Sedatives and neuropsychiatric drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Long-acting benzodiazepines				
Clorazepate oral	Anxiety, insomnia	5-30 mg oral at bedtime or in divided doses	Elderly, renal and hepatic impairment: lower doses may be required	Contraindicated if myasthenia gravis, severe decompensated respiratory insufficiency, sleep apnoea syndrome, severe hepatic impairment Caution if alcohol deprivation, give thiamine before administering glucose containing i.v. fluids
Clorazepate injection	Agitation, confusion, aggressiveness, premedication, tetanus, alcoholism	Agitation, confusion, aggressiveness: 20-200 mg/day, i.m./i.v. followed by oral therapy Premedication: 20-50 mg/day i.m./ i.v. Alcoholism: 50-100 mg every 3-4h Benign tetanus (without tracheostomy) 120-500 mg/day i.v. Malignant tetanus (with tracheostomy and assisted ventilation): 500-2,000 mg/day i.v.	Elderly, renal and hepatic impairment: lower doses may be required	Contraindicated if myasthenia gravis, severe decompensated respiratory insufficiency, sleep apnoea syndrome, severe hepatic impairment Caution if alcohol deprivation, give thiamine before administering glucose containing i.v. fluids

Sedatives and neuropsychiatric drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Long-acting benzodiazepines				
Diazepam (1)	Anxiety	2 to 10 mg, 2 to 4 times a day or 10 mg i.v. or i.m. and repeated after an interval of not less than 4h 0.5 mg/kg rectal Dose can be repeated every 4-12h. Max 30 mg	Elderly and debilitated patients: half of the recommended dose Hepatic impairment and severe renal impairment: a lower dose is recommended	Contraindicated if phobic or obsessional states; chronic psychosis, hyperkinesis, acute pulmonary insufficiency; respiratory depression, acute or chronic severe respiratory insufficiency, myasthenia gravis, sleep apnoea, severe hepatic impairment, acute porphyria
	Insomnia associated with anxiety	5-15 mg oral before retiring		
Diazepam (2)	Muscle spasm	5-15 mg oral daily in divided doses or 10 mg i.v. or i.m. and repeated after after an interval of not less than 4h 0.5 mg/Kg rectal. Dose can be repeated every 4-12h. Max 30 mg	Elderly and debilitated patients: half of the recommended dose Hepatic impairment and severe renal impairment: a lower dose is recommended	Contraindicated if phobic or obsessional states; chronic psychosis, hyperkinesis, acute pulmonary insufficiency; respiratory depression, acute or chronic severe respiratory insufficiency, myasthenia gravis, sleep apnoea, severe hepatic impairment, acute porphyria

Sedatives and neuropsychiatric drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Long-acting benzodiazepines				
Diazepam (3)	Alcohol withdrawal	5-20 mg oral, repeated if necessary in 2-4h 0.5 mg/kg rectal Dose can be repeated every 4-12h. Max 30 mg Delirium tremens: 10-20 mg i.v. or i.m.	Elderly and debilitated patients: half of the recommended dose Hepatic impairment and severe renal impairment: a lower dose is recommended	Contraindicated if phobic or obsessional states; chronic psychosis, hyperkinesis, acute pulmonary insufficiency; respiratory depression, acute or chronic severe respiratory insufficiency, myasthenia gravis, sleep apnoea, severe hepatic impairment, acute porphyria
	Premedication before surgery	5-20 mg oral		

Sedatives and neuropsychiatric drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Other sedatives				
Dexmedetomidine	Sedation of adult ICU patients (with the goal of RASS 0 to -3)	Switch to dexmedetomidine: initial i.v. infusion rate of 0.7 mcg/kg/h Titrate upwards to achieve desired level of sedation, range 0.2-1.4 mcg/kg/h Max dose: 1.4 mcg/kg/h Max duration: 14 days Loading doses are not recommended in the ICU	Caution if hepatic impairment, impaired peripheral autonomic activity, pre-existing bradycardia Frail patients: a lower starting infusion rate should be considered	The drug provides analgesia and does not cause respiratory depression. Associated with a lower prevalence of ICU delirium compared to benzodiazepines. Primary adverse effects are dose-related bradycardia and hypotension. Contraindicated in AV block without pacemaker, severe hypotension or acute cerebrovascular disease.
Melatonin	Insomnia	2 mg oral at bedtime Max duration: 13 weeks	Renal impairment: caution Hepatic impairment: not recommended	Do not use in patients with autoimmune diseases Do not crush or chew tablets

Sedatives and neuropsychiatric drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Other sedatives				
Propofol	Sedation during intensive care	Initiate at 5 mcg/Kg/min i.v. (0.3 mcg/Kg/h) and titrate to achieve sedation goals by 5 mcg/Kg/min every 5 min Maintenace rates of 5-50 mcg/Kg/min may be required Avoid prolonged infusions >50 mcg/Kg/min	Elderly: rate of infusion should be reduced. Rapid bolus administration is not indicated in this group of patients	Rapid onset (1-2 min) and short duration (3-5 min or longer if prolonged infusion) Avoid loading doses because of the risk of hypotension Monitor blood lipid levels, blood pressure Propofol has no analgesic properties Contraindicated in patients with hypersensitivity to peanuts or soy.
Zolpidem	Insomnia	10 mg oral at bedtime Max duration: 4 weeks	Elderly, debilitated patients, hepatic impairment: initial dose 5 mg	Contraindicated if obstructive sleep apnoea, myasthenia gravis, severe hepatic insufficiency, acute and/or severe respiratory depression

Sedatives and neuropsychiatric drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Other sedatives				
Ketamine	Sedation during intensive care	Induction: 1 - 4.5 mg/kg. Maintenance rate: 0,1-0,5 mg/kg/min Avoid long periods.	Cirrhosis or hepatic failure: reduced dose	Increases blood pressure; avoid in conditions such as elevated intracranial or intraocular pressure.+ Upon awakening, may cause psychological disturbances (delirium, hallucinations). Avoid in patients with psychiatric disorders. Avoid in patients with coronary artery disease because it increases myocardial oxygen consumption.
Etomidate	Anesthetic induction	0.2-0.3 mh/kg. Not recommmended for maintenance	Eldery: reduced dose (max 0.15-0,2/kg). Hepatic impairment: reduced dose	Hypersensitivity to soy or peanuts

Sedatives and neuropsychiatric drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Typical neuroleptics				
Haloperidol oral (1)	Psychomotor anti-agitation	Moderate symptomology: 0.5 to 2 mg orally 2 to 3 times a day Severe symptomology: 3 to 5 mg orally 2 to 3 times a day Initial doses of up to 100 mg/day have been necessary in some severely resistant cases.	**DOSE ADJUSTMENTS:** Elderly: start with half the dosage stated for adults and adjusted according to the results if necessary	**COMMENTS:** Contraindicated if comatose states, CNS depression, Parkinson, lesions of the basal ganglia, clinical significant cardiac disorders, QT interval prolongation, history of ventricular arrhythmia or Torsades de pointes, clinically significant bradycardia, 2nd or 3rd degree heart block, uncorrected hypokalaemia and use of other QT prolonging drugs Caution if renal failure, liver disease, epilepsy, hyperthyroidism, phaeochromocytoma Bioavailability from the oral route is about 60% of that from the i.m. route and readjustment of dose may be required i.v. haloperidol can be associated with QT prolongation and torsades de pointes

Sedatives and neuropsychiatric drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Haloperidol injection	Rapid control of the symptoms of hostility, aggression, hyperactivity, disruptive and violent behaviour, confusion, emotional withdrawal, hallucinations and delusions associated with acute and chronic schizophrenia, mania, and hypomania, and organic brain syndrome Nausea and vomiting	Haloperidol Lactate for Injection: Prompt control acute agitation: 2 to 5 mg IM every 4 to 8 hours The frequency of IM administration should be determined by patient response and may be given as often as every hour. Maximum dose: 20 mg/day	**DOSE ADJUSTMENTS:** Elderly: start with half the dosage stated for adults and adjusted according to the results if necessary	**COMMENTS:** Contraindicated if comatose states, CNS depression, Parkinson, lesions of the basal ganglia, clinical significant cardiac disorders, QT interval prolongation, history of ventricular arrhythmia or Torsades de pointes, clinically significant bradycardia, 2nd or 3rd degree heart block, uncorrected hypokalaemia and use of other QT prolonging drugs Caution if renal failure, liver disease, epilepsy, hyperthyroidism, phaeochromocytoma Bioavailability from the oral route is about 60% of that from the i.m. route and readjustment of dose may be required i.v. haloperidol can be associated with QT prolongation and torsades de pointes

Sedatives and neuropsychiatric drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Atypical neuroleptics				
Aripiprazole	Schizophrenia, manic episodes in bipolar type I disorder	Oral: 10-15 mg QD with a MD of 10-30 mg QD i.m.: Recommended initial dose: 9.75 mg Dose range: 5.25-15 mg A second injection may be administered 2h after the first injection, on the basis of individual clinical status and no more than three injections should be given in any 24h period Max daily dose: 30 mg/day	Caution if elderly, severe hepatic impairment	Orodispersible tablet should be placed in the mouth, it will rapidly disperse in saliva Caution if known CV disease, history of QT prolongation, epilepsy, concomitant administration of potent CYP3A4 or CYP2D6 inhibitors
Olanzapine	Psichiatric conditions	Schizophrenia: recommended starting dose 10 mg/day orally Manic episode: Starting dose 15 mg QD oral in monotherapy or 10 mg QD in combination therapy. Then, adjust dose according to response: 5-20 mg/day	Elderly, renal or hepatic impairment: consider a lower starting dose (5 mg/day)	Contraindicated if risk of narrow-angle glaucoma, behavioral disorders associated with dementia Caution if Parkinson, CV disease, low leukocyte and/or neutrophil counts for any reason, risk of QT interval prolongation Transient elevations in LFTs can be observed.

Sedatives and neuropsychiatric drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Atypical neuroleptics				
Quetiapine	Schizophrenia	IRF: Total daily dose for the first 4 days is: 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4), then 150-750 mg/day Administered in 2 divided doses PRF: Starting dose 300 mg oral on Day 1 and 600 mg on Day 2 MD: 400-800 mg/day	**DOSE ADJUSTMENTS:** Elderly, hepatic impairment: caution, a lower dose may be necessary	**COMMENTS:** Contraindicated if concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone Caution if low leukocyte and/or neutrophil counts for any reason, history of seizures, cerebrovascular disease, cardiovascular disease, risk of QT interval prolongation It could be used if Parkinson disease PRF: tablets should not be split, chewed or crushed
	Moderate-severe manic episodes in bipolar disorder	IRF: Total daily dose for the first 4 days is: 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4) Further dosage adjustments up to 800 mg/day Administered in 2 divided doses PRF: Starting dose 300 mg oral on Day 1 and 600 mg on Day 2 MD: 400-800 mg/day		
	Depression in bipolar disorders	IRF: Total daily dose for the first 4days is: 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4) The recommended daily dose is 300 mg Administered at bedtime PRF: Total daily dose for the first 4 days is: 50 mg oral (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4) Recommended daily dose: 300 mg		
	Major depressive episodes	PRF: 50 mg on Day 1 and 2, and 150 mg on Day 3 and 4 at bedtime Max dose 300 mg/day		

Sedatives and neuropsychiatric drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Atypical neuroleptics				
Risperidone (1)	Schizophrenia	Start 2 mg/day oral (QD or in 2 divided doses) The dosage may be increased on the 2nd day to 4 mg MD: 4-6 mg	Elderly: 0.5 mg BID Caution if renal or hepatic impairment	Caution if known cardiovascular disease, low leukocyte and/or neutrophil counts for any reason, Parkinson, risk of QT interval prolongation Orodispersable tablet: place the tablet on the tongue
	Manic episodes in bipolar disorder	Start with 2 mg oral QD Dosage adjustments, if needed, should occur at intervals of not less than 24h and in dosage increments of 1 mg/day. Max daily dose 6 mg	Elderly: start with 0.5 mg BID This dosage can be individually adjusted with 0.5 mg BID increments to 1-2 mg BID Caution if renal or hepatic impairment	
	Persistent aggression in patients with moderate to severe Alzheimer's dementia	Start with 0.25 mg oral BID This dosage can be individually adjusted by increments of 0.25 mg BID, not more frequently than every other day, if needed. Optimum dose is 0.5 mg BID for most patients	Caution if renal or hepatic impairment	

Sedatives and neuropsychiatric drugs (Cont.)

Drug	Indications	Dose	Dose adjustments	Comments
Atypical neuroleptics				
Risperidone (2)	Conduct disorder	≥50kg: starting dose 0.5 mg oral QD This dosage can be individually adjusted by increments of 0.5 mg QD not more frequently than every other day, if needed. Optimum dose is 1 mg QD for most patients <50kg: starting dose 0.25 mg oral QD This dosage can be individually adjusted by increments of 0.25 mg QD not more frequently than every other day, if needed. Optimum dose is 0.5 mg QD	Caution if renal or hepatic impairment	Caution if known cardiovascular disease, low leukocyte and/or neutrophil counts for any reason, Parkinson, risk of QT interval prolongation Orodispersable tablet: place the tablet on the tongue

CHAPTER 10.2

MANAGING ANTICOAGULATION IN CRITICALLY ILL IN SPECIFIC SITUATIONS

C. Vandenbriele & A. Oleksiak

THROMBOPROPHYLAXIS

Recommended prevention	High bleeding risk	
High thrombotic risk	**No**	**Yes***
No	**LMWH 50 IU/kg o.d. SC**	**Stop/reduce LMWH-dose, stockings**
Yes**	**LMWH 50 IU/kg o.d. SC** **or UFH 5.000 IU b.d.** i.v.	**Stop/reduce LMWH-dose** **Stockings +/- pneumatic compression therapy**

* Assess individual non-modifiable and modifiable risk factors and renal function, reduce dose of LMWH if CrCl <30 ml/min;
** Assess increased thrombotic risk factors e.g. major trauma, previous VTE, fracture of lower limb, hip or knee replacement, cancer, thrombophilia, post-partum period, intravenous catheters, etc.

MANAGING BLEEDING COMPLICATIONS
Management of antiplatelet therapy after acute GI bleeding

- ✓ Source control (local gauze application, manual pressure, drainage, endoscopic or surgical haemostasis)
- ✓ Tranexamic acid (local gauze application or systemic)
- ✓ Optimization of coagulation (delay or discontinue the next dose, use reversal agents if indicated: see chapter 10.1)
- ✓ Biochemical check-up and control (INR, fibrinogen, DOAC levels when available in specific cases, RBC and platelets count to assess the indications for transfusion)
- ✓ Fluid replacement, RBC and/or platelet substitution if indicated
- ✓ Treatment of factors or comorbidities contibuting to the bleeding

MANAGING BLEEDING COMPLICATIONS

VKA REVERSAL

INR	ACTIVE BLEEDING	PLANNED SURGERY	THERAPY
<3	no	yes	Vitamin K 10 mg i.v.*
<3	yes	no/yes	Vitamin K 10 mg i.v., possibly PCC** 20 U/kg over 20 min
<3	life-threatening	no/yes	Vitamin K 10mg i.v. + PCC 25 U/kg over 20 min
3-6	no	no	Therapy break
6-10	no	no	Vitamin K 2 mg po
>10	no	no	Vitamin K 5 mg po

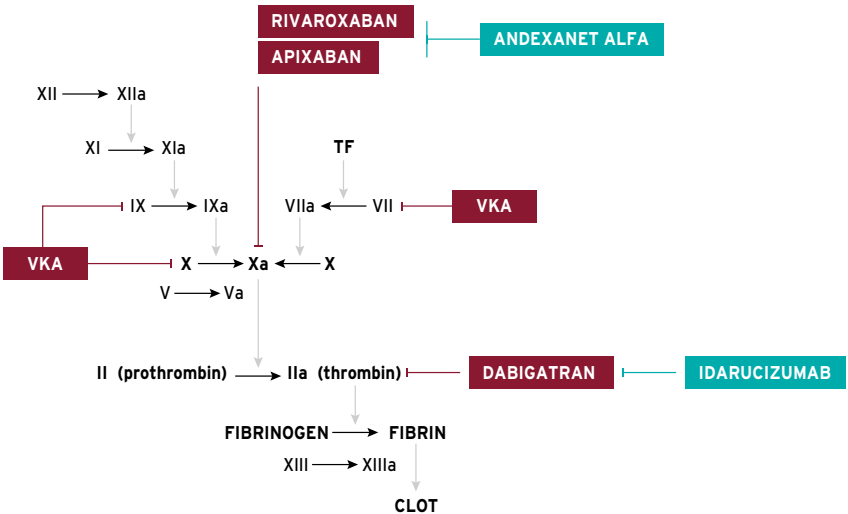
NOAC REVERSAL

LIFE-THREATENING : PCC, 4-FACTOR CONCENTRATE 35-50 U/KG
ANDEXANET ALFA (if available): **LOW DOSE***:** 400 mg i.v. bolus followed by 4 mg/min infusion within 2h **HIGH DOSE***:** 800 mg i.v. bolus followed by 8 mg/min infusion within 2h
IDARUCIZUMAB: 5g i.v. in two consecutive 2.5 g infusions 5-10 minutes each, or consider haemodialysis if idarucizumab is not available

*risk of anaphylaxis; ** PCC: prothrombin complex concentrate (vitamin K dependent factors II, VII, IX and X, plus protein C and S),
*** depending on the dose of anticoagulants taken: HIGH DOSE (apixaban >5mg or rivaroxaban >10mg if last dose <8h or unknown

MANAGING BLEEDING COMPLICATIONS (Cont.)

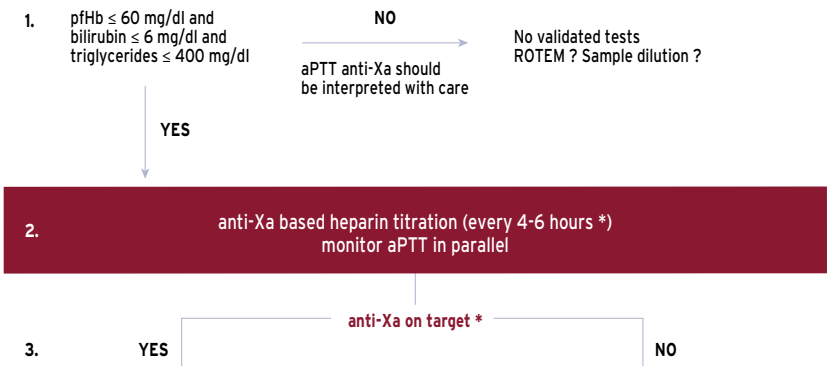
P.72



MANAGING ANTICOAGULATION AND HAEMOLYSIS ON MCS

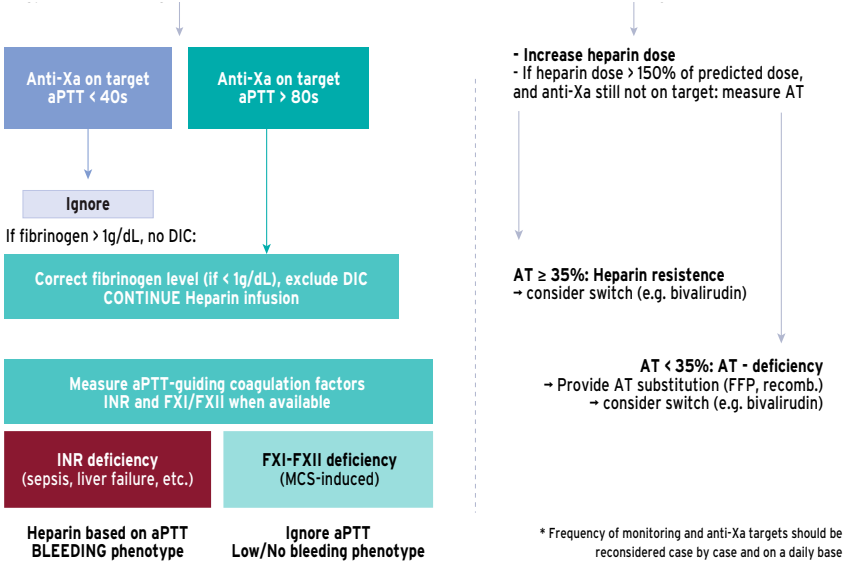
Standard anticoagulation therapy:
Heparin (aiming anti-Xa 0.3 – 0.5 IU/ml); starting dose 11-12 IU/kg/h after a bolus

HIT positive patients (HIT diagnosis always requires a functional test on MCS):
Bivalirudin (aiming APTT 1.5–2.5x baseline); no bolus and 0.15 mg/ kg/h
Argatroban (aiming APTT 1.5–3.0x baseline); no bolus and 0.15 mg/ kg/h
Dosis needs to be revised when kidney or/and liver failure



MANAGING ANTICOAGULATION AND HAEMOLYSIS ON MCS (Cont.)

P.74



* Frequency of monitoring and anti-Xa targets should be reconsidered case by case and on a daily base

Adapted from Vandenbriele et al., JACC, 2022

MANAGING ANTICOAGULATION AND HAEMOLYSIS ON MCS

BLEEDING ON MCS	HAEMOLYSIS ON MCS
✓ SOURCE control	✓ Measured by (at least daily) pfHb
✓ Tranexamic i.v. or local	✓ Check the device position
✓ Diluted adrenalin local	✓ Check for RV-failure in LV supporting MCS
✓ Consider early weaning	✓ Optimize the device preload
✓ Reduce heparin target	✓ Check for pump related clots / failure
x Do not stop immediately heparin (only in life-threatening bleeds)	✓ Treatment: • Consider early weaning / MCS-reduction • add inhaled nitric oxide (20ppm) to avoid vasoconstriction • remove pfHb by plasmapheresis
✓ decide to reduce or stop heparin taking into account the localization and severity of bleeding	

MANAGING ANTICOAGULATION AND HAEMOLYSIS ON MCS

P.76

	CONTRAINDICATIONS
ABSOLUTE	• History of haemorrhagic stroke or stroke of unknown origin • Ischaemic stroke in previous 6 months • Major trauma, surgery, or head injury in previous 3 weeks • Central nervous system neoplasm • Bleeding diathesis • Active bleeding
RELATIVE	• Transient ischaemic attack in previous 6 months • Oral anticoagulation • Pregnancy or first post-partum week • Non-compressible puncture sites or traumatic resuscitation • Refractory hypertension (systolic BP >180 mmHg) • Advanced liver disease or active peptic ulcer • Infective endocarditis

PE - THROMBOLYTIC REGIMENS AND DOSES
rtPA 100 mg over 2 h (10 mg bolus in 1-2 minutes followed by 90 mg i.v. infusion over 2 h) consider 0.6 mg/kg over 15 min (maximum dose 50 mg)*
Streptokinase 250 000 IU as a loading dose over 30 min, followed by 100 000 IU/h over 12-24 h Accelerated regimen: 1.5 million IU over 2 h
Urokinase 4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h over 12-24 h Accelerated regimen: 3 million IU over 2 h

* This is the accelerated regimen for rtPA in pulmonary embolism; it is not officially approved (PEITHO-3 trial), but it is sometimes used in extreme haemodynamic instability such as cardiac arrest.

THROMBOLYSIS
Left-sided obstructive mechanical valve thrombosis

1. Stop VKA.

2. If haemodynamically critical or with absolute contraindication for thrombolysis:
- consult with cardiac surgery for urgent valve replacement (ESC guidelines prefer surgery over thrombolysis, unless contra-indicated)

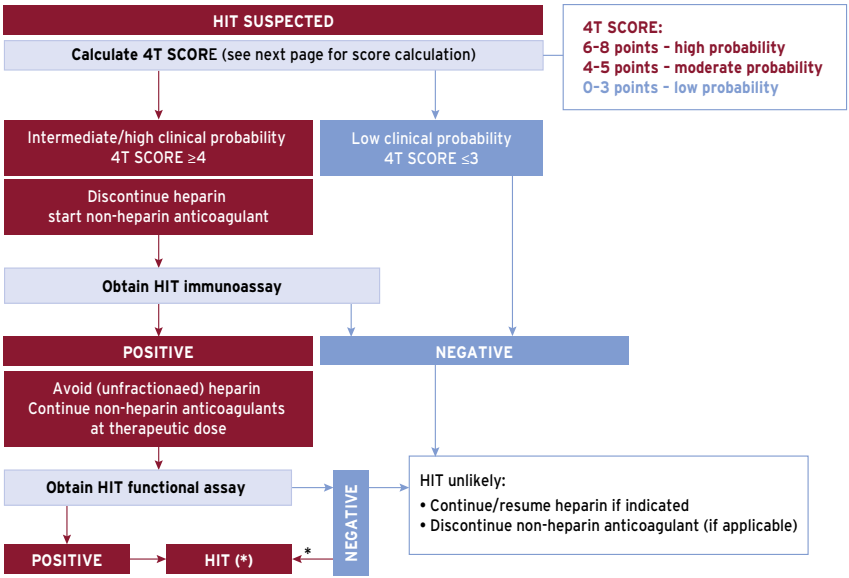
3. If haemodynamically unstable:
- if the patient received inadequate anticoagulantion recently, start i.v. UFH ± ASA, if treatment is ineffective consider surgery or thrombolysis depending on the patient's surgical risk
- notify the cardiac surgeon on call (if surgery unavailable or contraindicated, start thrombolysis)
- if low bleeding risk and INR < 2.5: FULL DOSE FAST protocol: rtPA 10 mg bolus, followed by 90 mg over 2 hours
- if low bleeding risk and INR > 2.5: wait until INR decreases if HD possible, otherwise prefer surgery

4. If haemodynamically stable and no significantly increased bleeding risk:
- wait until INR < 2.5
- 25 mg rtPA over 6 hours
- after 6 hours: heparin bolus 80 IU/kg, start UFH infusion and monitoring
- plan to restart VKA

5. If haemodynamically stable and high bleeding risk:
- wait until INR < 2.5
- 25 mg rtPA over 24 hours; consider reevaluation after 6 to 12 hours with TTE; stop if fully effective, continue if partially effective

6. (Re)evaluate valve gradient and mobility.

Management of heparin-induced thrombocytopenia (HIT)



* False-negative results are possible for some patients with a negative functional assay; consider them as HIT (+), especially if there is a high-probability 4Ts score and a strongly positive immunoassay

4T SCORE	SCORE=2	SCORE=1	SCORE=0
THROMBOCYTOPENIA * Compare the highest platelet count within the sequence of declining platelet counts with the lowest count to determine the % of platelet fall.	• >50% Platelet fall AND a nadir of ≥20 AND no surgery within preceding 3 days	• >50% Platelet fall BUT surgery within preceding 3 days OR • Any combination of platelet fall and nadir that does not fit criteria for Score 2 or Score 0 (e.g., 30–50% platelet fall or nadir 10–19)	• <30% platelet fall • Any platelet fall with nadir <10
TIMING * (of platelet count fall or thrombosis) Day 0 = first day of most recent heparin exposure	• Platelet fall day 5–10 after start of heparin • Platelet fall within 1 day of start of heparin AND exposure to heparin within past 5–30 days	• Consistent with platelet fall day 5–10 but not clear (e.g., missing counts) • Platelet fall within 1 day of start of heparin AND exposure to heparin in past 31–100 days • Platelet fall after day 10	• Platelet fall ≤ day 4 without exposure to heparinin past 100 days
THROMBOSIS * or other clinical sequelae)	• Confirmed new thrombosis (venous or arterial) • Skin necrosis at injection site • Anaphylactoid reaction to i.v. heparin bolus • Adrenal hemorrhage	• Recurrent venous thrombosis in a patient receiving therapeutic anticoagulants • Suspecteda thrombosis (awaiting confirmation with imaging) • Erythematous skin lesions at heparin injection sites	• Thrombosis not suspected
Other cause(s) for thrombocytopenia *	• No alternative explanation for platelet fall is evident	• Possible other cause is evident**	• Probable other cause present***

* Select only 1 option. ** Sepsis without proven microbial source OR thrombocytopenia associated with initiation of ventilator OR other. *** Within 72 h of surgery OR confirmed bacteremia/fungemia OR chemotherapy or radiation within past 20 days OR DIC due to non-HIT cause OR posttransfusion purpura OR thrombotic thrombocytopenic purpura OR platelet count < 20 AND given a drug implicated in causing D-ITP OR non-necrotizing skin lesions at LMWH injection sites (presumed delayed-type hypersensitivity) OR other.

ANTICOAGULATION IN PATIENTS WITH HIT

HIT WITHOUT THROMBOSIS:

✓ fondaparinux 2.5 mg sc once a day (normal kidney function)

✓ fondaparinux 5-10 (*) mg sc once a day in patients requiring therapeutic anticoagulation

HIT WITH THROMBOSIS:

✓ fondaparinux 5-10 (*) mg sc once a day (normal kidney function)

✓ bivalirudin continuous infusion 2-10 days (control aPTT after 4 hours and then daily)

? there is no 'safe' cut-off for NOAC therapy in patients with thrombocytopenia, proceed with caution; avoid NOAC when platelet count is <20 000 /µl

X VKAs are contraindicated in the acute phase of HIT until the platelet count exceeds 150 000/µl

(*) 5 mg (< 50 kg), 7,5 mg (50-100 kg), 10 mg (> 100 kg)

Abbreviations

APTT = Activated partial thromboplastin time
AB = Airway and breathing
ABG = Arterial blood gas
AADs = Antiarrhythmic drugs
AAS = Acute aortic syndrome
ACEI = Angiotensin converting enzyme inhibitor
ACLS = Advanced cardiovascular life support
ACS = Acute coronary syndrome
ACT = Activated clotting time
AD = Aortic Dissection
AED = Automated external defibrillator
AF = Atrial fibrillation
ANA = Antinuclear antibodies
Ao = Aortic
aPTT = Activated partial thromboplastin time
ARB = Angiotensin receptor blockers
AS = Aortic stenosis
AV = Atrioventricular
AVB = Atrioventricular conduction block
AVN = Atrioventricular node
AVNRT = Atrioventricular nodal re-entrant tachycardia
AVNT = Atrioventricular nodal tachycardia
BID = Twice a day
BBB = Bundle branch block
BLS = Basic life support
BNP = Brain natriuretic peptide
BP = Blood pressure
CABG = Coronary artery bypass grafting
CAD = Coronary artery disease
Cath Lab = Catheterisation laboratory
CCB = Calcium channel blockers
CCU = Coronary care unit
CHF = Congestive heart failure
CMR = Cardiovascular magnetic resonance
COPD = Chronic obstructive pulmonary disease
CPAP = Continuous positive airway pressure
CPR = Cardiopulmonary resuscitation
Cr = Creatinine blood level (mg/dL)
CrCl = Creatinine clearance
CRP = C-reactive protein
CS = Cardiogenic shock
CSM = Carotid sinus massage
CSNRT = Corrected sinus node recovery time

Abbreviations (Cont.)

CSS = Carotid sinus syndrome
CT = Computed tomography
CT-angio = Computed tomography angiography
cTn = Cardiac troponin
CUS = Compression venous ultrasound
CV = Cardiovascular
CVA = Cerebrovascular accident
CXR = Chest X-ray
DAPT = Dual antiplatelet therapy
DD = Dyastolic dysfunction
DM = Diabetes mellitus
dTT = Diluted thrombin time
DVT = Deep vein thrombosis
ECG = Electrocardiogram
Echo = Echocardiogram
ECMO = Extracorporeal membrane oxygenation
ECT = Ecarin clotting time
ED = Emergency department
EF = Ejection fraction
EG = Electrograms
eGFR = Estimated glomerular filtration rate (ml/min/1.73 m^2)
EMB = Endomyocardial biopsy
EMS = Emergency medical services
EPS = Electrophysiological study
ERC = European Resuscitation Council
ESR = Erythrocyte sedimentation rate
ETT = Exercice treadmill testing
FFP = Fresh frozen plasma
FMC = First medical contact
GER = Gastroesophageal reflux
GFR = Glomerular flow rate
GI = Gastrointestinal
GP = Glycoprotein
Hb = Haemoglobin
HF = Heart failure
HIT = Heparin-induced thrombocytopenia
HOCM = Hypertrophic obstructive cardiomyopathy
HTN = Hypertension
HR = Heart rate
hsTn = High-sensitive troponin
IABP = Intra-aortic balloon pump
ICC = Intensive cardiac care
ICCU = Intensive cardiac care unit

Abbreviations (Cont.)

ICD = Implantable cardioverter defibrillator
ICI = Immune checkpoint inhibitors
IHD = Ischemic heart disease
IMH = Intramural hematoma
IRF = Immediate-release formulation
ISFC = International Society and Federation of Cardiology
i.o. = Intraosseous
IV = Invasive ventilation
i.v. = Intravenous
KD = Kidney disease
LBBB = Left bundle branch block
LD = Loading dose
LGE = Late gadolinium enhancement
LMWH = Low-molecular weight heparin
LOC = Loss of consciousness
LV = Left ventricular
LVAD/Bi-AD = left ventricular, bi-ventricular assist device
LVD = Left ventricular dysfunction
LVEF = Left ventricular ejection fraction
LVH = Left ventricular hypertrophy
LVSD = Left ventricular systolic dysfunction
MCS = Mechanical circulatory support
MD = Maintenance dose
MDCT = Computed tomography with >4 elements
MI = Myocardial infarction
MRA = Mineralocorticoid receptor antagonist
MRI = Magnetic resonance imaging
Mvo = Microvascular obstruction
NIV = Non-invasive ventilation
NOAC = New oral anticoagulants
NSAID = Non-steroidal anti-inflammatory drugs
NSVT = Non-sustained ventricular tachycardia or recurrent
NSTE-ACS = Non ST-segment elevation acute coronary syndrome
NSTEMI = Non ST-segment elevation myocardial infarction
NTG = Nitroglycerin
NT-proBNP = N-terminal pro brain natriuretic peptide
NVAF = Non-valvular atrial fibrillation
NYHA = New York Heart Association

Abbreviations (Cont.)

OH = Orthostatic hypotension
PAP = Pulmonary arterial pressure
PAU = Penetrating aortic ulcer
PCI = Percutaneous coronary intervention
PCM = Physical counter-measures
PCP = Pulmonary capillary pressure
PE = Pulmonary embolism
PEA = Pulmonary endarterectomy
PEEP = Positive end expiratory pressure
PPC = Prothrombin complex concentrate
PR = Pulmonary regurgitation
PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy
PRF = Prolonged-release formulation
ProCT = Procalcitonin
PRN = Pro re nata
PS-PEEP = Pressure support-positive end-expiratory pressure
PSVT = Paroxysmal supraventricular tachycardia
QD = Once a day
QPM = Every evening
rFVIIa = Recombinant factor VIIa
rtPA = Recombinant tissue plasminogen activator
RV = Right ventricular
RVOT-VT = Right ventricular outflow tract ventricular tachycardia
SBP = Systemic blood pressure
s.c = Subcutaneous
SIRS = Systemic inflammatory response syndrome
SLE = Systemic lupus erythematosus
SMU = Syncope management units
STE-ACS = ST-segment elevation acute coronary syndrome
STEMI = ST-segment elevation myocardial infarction
SVT = Supraventricular tachycardia
Spo_2 = Oxygen saturation
TEE = Transesophageal echocardiography
TEVAR = Thoracic endovascular aortic repair
TIA = Transient ischemic attack
TID = Three times a day
TLOC = Transient loss of consciousness
TOE = Transoesopageal echocardiography

Abbreviations (Cont.)

TSH = Thyroid-stimulating hormone
TTE = Transthoracic echocardiography
UA = Unstable angina
UFH = Unfractionated heparin
ULN = Upper limit of normal
VBGA = Venous blood gas analysis
VF = Ventricular fibrillation
VR = Vascular resistance
VT = Ventricular tachycardia
VTE = Venous thromboembolism
VVS = Vasovagal syncope
WBC = White blood cell count
WHO = World health organization
WPW = Wolff-Parkinson-White

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