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ANTICOAGULATION WITH LOW-MOLECULAR-WEIGHT HEPARIN IN PATIENTS WITH HEART DISEASES

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Abstract: Low-molecular-weight heparins (LMWH) were investigated in different cardiac diseases requiring anticoagulation. In case of short term usage advantages over intravenous unfractionated heparin (UFH) are of relevance, such as simple subcutaneous application, possibility for outpatient treatment and predictable effect on anticoagulation enabling abstention of laboratory monitoring in most cases. Thromboprophylaxis in acute medically ill patients and therapy of non-ST-elevation acute coronary syndromes (NSTE-ACS) are important indications, in which significant advantages for special LMWH as compared to Placebo or UFH were shown. A significant effect versus Placebo was demonstrated for the LMWH Dalteparin in prolonged anticoagulation until revascularisation procedure in NSTE-ACS. Promising results from trials were also published concerning use of LMWH Dalteparin and Enoxaparin in TEE-guided cardioversion. Findings from cohort trials are available for temporary or long term switch from oral anticoagulation to LMWH. Due to limited data, determination of individual benefit-to-risk ratio is of special importance to select suitable anticoagulation regimen in this case. Further investigations as a basis of general recommendations on standard dosing regimen are outstanding for use of each LMWH in percutaneous coronary interventions, as combination with Glycoprotein IIb/IIIa-inhibitors, in acute myocardial infarction and in artificial heart valves. In cardiology, most studies were performed with Dalteparin and Enoxaparin, suggesting these to be used in established cardiac indications as well as in further investigations.

Key words: thromboembolism; anticoagulation; heparin; dalteparin; enoxaparin; coronary syndrom; heart insufficiency; heart valves; cardioversion; atrial fibrillation

Abbreviations: AF = atrial fibrillation, ASA = aspirin, acetylsalicylic acid; aSTEMI = acute ST-elevation myocardial infarction; CV = cardioversion; db = double-blind study; DVT = deep vein thrombosis; HIT = heparin induced thrombocytopenia; Iv = intravenous; LA = left atrium; LAA = left atrial appendage; LMWH = low-molecular-weight heparin(s); MI = myocardial infarction; nvAF = nonvalvular atrial fibrillation; NSTE-ACS = non-ST-elevation acute coronary syndrome; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; pt./pts. = patient/patients; rd = randomized study; RR = relative risk reduction; sc = subcutaneous; SR = sinus rhythm; Sub = subgroup; TEC = thromboembolic complication; TEE = transesophageal echocardiography; TP = thromboprophylaxis; UFH = unfractionated heparin; VTE = venous thromboembolic events

INTRODUCTION

Anticoagulants, platelet-active drugs and thrombolytic agents are available to prevent or treat thromboembolism in heart diseases. Choosing the optimal drug or combination of drugs and answering questions on timing, dosing and duration of antithrombotic therapy is fundamental for therapeutic success. Since first market authorization in 1985 low-molecular-weight-heparins (LMWH) have replaced unfractionated heparin (UFH) in many indications. Use of LMWH in cardiology has increased after Enoxaparin and Dalteparin were approved for treatment of unstable angina and non-ST-elevation myocardial infarction, summarized in this article as non-ST-elevation acute coronary syndromes (NSTE-ACS), in many countries at the end of the last decade. For clinicians it is important to be updated on studies performed and conclusions, which can be drawn for the use of LMWH. Table 1 summarizes indications, which were investigated with LMWH and are of relevance for clinical practice. A more detailed information is then given within the text by listing relevant studies performed.

HEART FAILURE AND DEEP VEIN THROMBOSIS (DVT)

A hypercoagulable state was discovered in patients with heart failure by laboratory assessments [67]. Treatment with a LMWH (Bemiparin, 3500 IU anti-Xa) improved these abnormalities [19].

Table 1. Indications for anticoagulation in pts. with heart diseases, in which efficacy and/or safety was documented with LMWH.

Indication	LMWH [reference]	Dosing-regimen investigated	Study-design (pts. treated with LMWH)	Efficacy results	Safety results: major bleedings
TP in heart failure NYHA III or IV	Dalteparin [oral presentation ISTH Birmingham 2003]	5000 IU; 14d	db (sub of n = 1518)	Superior to placebo	no increase vs. placebo
	Enoxaparin [84] Enoxaparin [56]	4000 IU; 6-14d 4000 IU, 8-12 d	db (sub of n = 291) db (sub of n = 93)	superior to placebo, non-inferior to UFH	no increase vs. placebo and UFH
TP in chronic heart failure / cardiomyopathy or in chronic AF	Dalteparin [42]	1x100 IU/kg long term	cohort (n = 25)	justified in case of contraindication to OAC	1 major bleeding in 40 treatment years
TP in TEE-guided CV	Dalteparin [6, 81] Dalteparin [109]	2x100 IU/kg 2x5000 IU	2 cohorts (n = 145 + 34) rd (n = 88) vs. UFH	no TEC no TEC	no major bleeding no major bleeding
	Enoxaparin [20] Enoxaparin [91]	2x1 mg/kg 2x1 mg/kg	cohort (n = 57) rd (n = 212) vs. UFH	no TEC death, TEC, major bleeding 3,3% vs. 5,6%, p<0,02	no major bleeding
TP in artifical heart valves, long term	Dalteparin [42]	120-150 up to 200 IU/kg[1)]	cohort (n = 16)	no TEC, justified only in case of contraindication to OAC	no major bleeding
	Nadroparin [63]	2x0,01 ml/kg[1)]	case reports (n = 2)		
Therapy in NSTE-ACS, acute phase[5)]	Dalteparin [29] Dalteparin [30, 31] Dalteparin [58]	2x120 IU/kg, 5-7d	db (n = 741) vs. Placebo rd (n = 751) vs. UFH non-rd (n = 3489)	63% RR vs. Placebo no difference vs. UFH	no increase vs. Placebo or UFH
	Enoxaparin [12, 4]	2x1 mg/kg, 2-8d (median 2.6d)	db (n = 1607+1953)	superior to UFH 47% RR vs. Placebo	no increase vs. UFH
	Nadroparin [95]	2x 87 IU/kg, 6/14d	rd (n = 1166+1151)	no difference. vs. UFH	no increase vs. UFH
Therapy in NSTE-ACS, prolonged	Dalteparin [30, 61]	2x5000-7500 IU[2)] 30d (45d)[3)]	db (n = 1049) vs. Placebo	47% RR vs. Placebo after 30d, disappeared at day 90	after 90d: 3.3% Dalteparin vs. 1.5% Placebo (p = 0,01)
aSTEMI, without revascularisation[6)]	Dalteparin [50]	2x120 IU/kg, 3d	non-rd (n = 1128)	mortality 1,4%	no major bleeding
	Enoxaparin [15]	bolus 30mg iv, 2x 1mg/kg; 2-8d	db (n = 604)	no difference vs. UFH	no difference vs. UFH
TP related to intervention in pts. receiving OAC	Dalteparin [86] Dalteparin [97, 99]	2x5000 IU[4)] 2x100 IU/kg[4)]	cohort (>200) 2 cohorts (n = 244+24)	not reported 1 TEC	not reported 1 major bleeding
	Enoxaparin [26, 90]	2x1 mg/kg[4)]	2 cohorts (n = 82 +20)	no TEC	2 major bleedings

Abbreviations: AF = atrial fibrillation; aSTEMI = acute ST-elevation myocardial infarction; CV = Cardioversion; db = double-blind study; NSTE-ACS = Non-ST-Elevation Acute Coronary Syndrome; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; pts. = patients; rd = randomized study; RR = relative risk reduction; Sub = subgroup; TEC = thromboembolic complication; TEE = transesphageal echocardiography; TP = thromboprophylaxis

1) dosage should be adapted to anti-Xa-measurements
2) Women < 80 kg, men < 70 kg: 2x5000 IU; women ≥ 80 kg, men ≥ 70 kg: 2x7500 IU
3) effect shown if revascularization procedure is performed within 45d. No significant effect after 90d
4) special instructions on day of procedure; on principle, determination of individual risk-to-benefit-ratio; special care in artificial heart valves
5) for combination with PCI and/or GP IIb/IIIa inhibitors see further information in text
6) for pts. eligible for lysis see detailed information in text

Thrombembolic risk depends on severity of heart failure. Prevention of DVT as well as thrombi in the left heart are the main objectives for anticoagulation.

Prevention of DVT in acute medically ill patients (pts.) was effective with 4000 IU anti-Xa (IU) Enoxaparin and 5000 IU anti-Xa (IU) Dalteparin. After 6-14 days of prophylaxis with Enoxaparin DVT-rate identified by phlebography was reduced from 14.9% in the placebo-group (n = 288) to 5.5% in 4000 IU Enoxaparin-group (n = 291) (p = 0.0002) [84]. About 1/3 of pts. investigated had diagnosis of congestive heart failure NYHA class III or IV. The PRINCE-trial revealed that in the "heart failure-subgroup" 4000 IU Enoxaparin (n = 113) was non-inferior in phlebographically identified thromboembolic complications (TEC) as compared to 3 x 5000 IU UFH (n = 93) (16.1% UFH vs. 9.7% Enoxaparin), whereas non-inferiority could not be shown in pts. with respiratory diseases (5.9% UFH vs. 7.1% Enoxaparin) [56]. In the PREVENT-study a significant (p = 0.0015) reduction of clinical relevant venous thromboembolic events (VTE) from 4.96% to 2.77% was seen with 5000 IU Dalteparin administered for 14 days (n = 1518) as compared to Placebo (n = 1473) in hospitalized medical pts., such as congestive heart failure [oral presentation ISTH 2003, Birmingham]. Safety, especially bleeding, was not significantly different as compared to placebo for Enoxaparin and Dalteparin.

In conclusion 4000 IU Enoxaparin and 5000 IU Dalteparin are effective and safe in the prevention of DVT in pts. with congestive heart failure NYHA class III or IV and can therefore be recommended for use in this indication. Prophylaxis should at least be continued until patient is discharged from hospital as this usually reflects sufficient treatment of underlying disease and that the patient is mobilized. However, the studies mentioned above did not focus on duration of prophylaxis and prevention of cardiac thrombi. Especially in case of atrial fibrillation thromboembolic risk continues.

Chronic Heart Failure due to Cardiomyopathy

In dilated hypokinetic cardiac chambers low flow and stasis of blood can cause an intracardiac thrombus with subsequent arterial embolism [93]. Rates for TEC of 1-3%/year were reported in pts. with stable chronic heart failure [11]. The prospective, non-randomized EPICAL-study identified a significant effect of long term antithrombotic therapy with oral anticoagulants (OAC) in pts. with severe heart failure and left ventricular systolic dysfunction (e.g. ejection fraction ≤ 30%) with an increase of survival after 5 years from 31% to 40% as compared to no OAC [23]. As randomized trials are lacking in pts. with chronic heart failure evidence for anticoagulation is limited. Anticoagulation may be beneficial especially in pts. with severe depressed left ventricular function. More conclusive recommendations will likely follow results of ongoing clinical trials, notably the "Warfarin and Antiplatelet Therapy in Chronic Heart Failure" (WATCH) trial with 4500 pts. randomized to clopidogrel 75 mg/d, aspirin 160 mg/d or warfarin (INR 2.5-3.0) [67].

Published experiences on the use of LMWH in pts. with cardiomyopathy are limited to 15 pts. with contraindications to OAC treated with an average LMWH-dose of 100 IU/kg/d [42]. 10 other pts. were treated with the same dose for AF and 79 for secondary prevention of DVT. 16 additional pts. received a more intensive anticoagulation because of artificial heart valves. Predominantly, Dalteparin was used, but 19 pts. also received Certoparin or Nadroparin. Long term treatment with LMWH up to 10.8 years was well tolerated. In pts. with cardiomyopathy or AF no TEC was seen and only one major but not life threatening bleeding occurred during a cumulative treatment period of 40 years. Based on this experiences long term use of LMWH Dalteparin can be justified in pts. with contraindications to OAC in case of severe left ventricular dysfunction.

Nonvalvular Atrial Fibrillation (nvAF)

Chronic nvAF is the most dominant rhythm disorder in the elderly population and is associated with an increased risk for embolism and stroke (relative risk 2.4 for men and 3.0 for women) [32]. Stasis of blood predominantly in the left atrium (LA) and left atrial appendage (LAA) and activation of haemostasis are the main reasons for intracardial thrombus formation. Pts. with atrial fibrillation (AF) in association with rheumatic valvular heart disease or with mechanical heart valves have a much higher risk for TEC (about 15-18 times) [85, 107]. The risk for stroke in pts. with nvAF increases with age from 1.3%/year in those aged 50 to 59 years to 5.1%/year in elderly pts. aged 80 to 89 years. The incidence of TEC could be reduced by 47-86% in case of OAC as derived from the pooled data of five primary prevention trials in nvAF [1]. Based on ACCP- and ACC/ AHA/ESC-recommendations [1, 34] coumarins or aspirin (ASA) are indicated in most cases of chronic AF the choice of which depending on additional risk factors like higher age (> 75 y), hypertension, previous TEC, left ventricular dysfunction and diabetes [1, 34]. Nevertheless, ischemic stroke in pts. on ASA-treatment seems to have a higher probability to result in death with a hazard ratio of 2.5 (p = 0.09) as compared to pts. on sufficient OAC (INR ≥ 2.0) [46]. So, pts. with contraindications to coumarins might profit from LMWH instead of ASA as an alternative for long term anticoagulation in chronic AF. Limited experiences have been published so far [42].

Cardioversion (CV) to Sinus Rhythm (SR) in Atrial Fibrillation or Flutter

In pts. with AF or flutter lasting more than 48 hours there is a high risk for TEC and stroke of approximately 5% if no sufficient antithrombotic treatment is performed peri-CV and after restoration of SR [1, 88]. There are also reports about thrombus formation before 3rd day of onset of AF [24]. OAC (INR ≥ 2.0) initiated 3-4 weeks before CV and continued up to 4-6 weeks after CV reduces the risk for TEC to about 1% [1, 88]. The so called "conventional" anticoagulation approach is recommended by most authorities but leads to marked timely delay of CV in practice for a mean of 5 weeks [87]. By ruling out LA and especially LAA thrombi with transoesophageal echocardiography (TEE; so-called TEE-guided CV) pretreatment period with OAC can be omitted. There are two potential advantages for the TEE-guided approach as compared to the conventional strategy: (1) shortened period until CV raising hope to preserve SR longer and in a greater percentage of pts. by avoiding time-dependent unfavourable atrial remodeling processes [105]. (2) reduced CV-associated embolic risk by ruling out thromboembolic risk markers before CV like thrombi in LA or LAA, very dense spontaneous echocontrast, low outflow rates in the LAA (< 20cm/s) and complex plaques (thickness ≥ 4 mm) in the thoracic aorta [110].

A further important finding derived from TEE-studies was, that there is a transient post-CV mechanical dysfunction of the LA and LAA described as atrial "stunning" [49], which lasted for several days up to three or four weeks and further elevates risk for TEC. This is in accordance with the observation that nearly all TEC were seen on days 1 to 18 after successful CV (mean after 2 days). 98% of such events occurred within 10 days after CV [7]. Therefore, in these first 10 days after CV and sustained SR a sufficient anticoagulation must be provided to reduce embolic risk. After this period anticoagulant intensity might be somewhat reduced. For TEE-guided CV a quick and effective antithrombotic treatment at time of TEE and peri-CV is needed. At present, intravenous (iv) UFH with aPTT-dose adjustments and overlapping start of a coumarin are recommended [34]. The recently published multicentre ACUTE-trial supports the use of UFH for TEE-guided CV with subsequent Warfarin for 4 weeks [57]. Five of 619 pts. (0.8%) with exclusion of thrombi by TEE had a subsequent TEC with no significant difference as compared to conventional treatment (0.5%; pre-treatment before CV lasted for about 5 weeks). There was a significant reduction of major haemorrhagic events favouring TEE-approach (5.5% vs. 2.9%, p = 0.03) but no difference in 8-week maintenance of SR between the two arms.

However, iv UFH is associated with a reduced mobility of the pts. and need for inpatient treatment. Use of LMWH would offer a considerable simplification of therapy by its subcutaneous (sc) administration enabling full mobility, usually without need for monitoring the anticoagulant response [44]. Based on results from a trial performed with Dalteparin TEE-guided CV with LMWH offers the potential of significant cost reduction by outpatient treatment as compared to a inpatient-regimen with UFH [55]. Furthermore, ease of use of LMWH permits an extended overlap therapy when coumarins are initiated. This is useful as, due to the long half-life of clotting factor II (about 2.5-3 days), coumarins need about 6-8 days to reach their full anticoagulatory activity. As recommended now, that overlap-time should be at least 4 days [43]. It might be criticized in the ACUTE-study that overlap between iv UFH and coumarin lasted only for 2.5 days and therefore insufficient anticoagulation after CV might have happened.

In a study with 413 pts. early TEE-guided CV was associated with a low rate for TEC of 0.24% by using UFH with consecutive Warfarin. Additionally, rate for recurrence of AF was significantly reduced, if duration of AF was below 3 weeks [103]. Studies performed with LMWH so far confirm low event rates in TEE-guided CV: a trial investigating Dalteparin at a daily dose of 200 IU/kg in 145 pts. with successful TEE-guided CV revealed no TEC [81]. In our cohort study, which enrolled 125 pts. with newly diagnosed atrial fibrillation or flutter, Dalteparin was initiated on day of admission to the hospital with a dose of 2 x 100 IU/kg (maximum dose 2 x 10.000 IU) [6]. TEE was done in 39 (31%) pts. at day 2 (median, range 0-14 days) after onset of Dalteparin. CV was successful in 26 of 34 pts. (76%), who had no thrombus in TEE. No TEC or serious bleeding occurred during Dalteparin-treatment and an overlap-time of median 9 days between start of coumarin and stop of LMWH could be provided easily. Another non-randomized prospective trial included 57 pts.[20]. TEE was performed within 24 h after initiation of treatment with Enoxaparin 1 mg/kg every 12 h. Again, no TEC and no major bleeding was reported after CV to SR as well as in a study performed with 26 pts. treated with the same dose and simultaneous start of OAC in an outpatient setting [62]. In the randomized ACE study (Anticoagulation for Cardioversion with Enoxaparin) [91] a TEE-guided arm using iv UFH followed by phenprocoumon (n = 216; overlap time ≥ 3 days) was compared with a pure sc LMWH-arm (n = 212), in which Enoxaparin was given 4 weeks throughout with a reduced dose after first 3 to 8 days. The incidence of death from any cause, systemic thromboembolism, cerebral ischemic events or major bleedings was 3.3% with LMWH as compared to 5.6% in the UFH-group showing non-inferiority for LMWH ($p < 0.02$). In another prospective randomized trial investigating TEE-guided CV (n = 172) 2 x 5000 IU Dalteparin was compared with aPTT-adjusted iv UFH. Immediately after TEE warfarin was initiat-

ed and continued for 4 weeks after CV. No TEC was detected in either group [109, for review of studies see 106].

Based on study results mentioned above, sc treatment of Enoxaparin (2 x 1 mg/kg bw) or Dalteparin (2 x 100 IU/kg bw) can be regarded as safe and effective alternative to iv UFH in TEE-guided CV, even though official registrations are lacking.

Mechanical Prosthetic Heart Valves

Depending on type of heart valve implanted and intensity of OAC pts. with mechanical heart valves have a risk for TEC of up to 6.5%/y [45]. With modern bileaflet valves the risk decreases to about 0.5%/y [92]. As major haemorrhagic events in pts. with prosthetic heart valves treated with OAC ranged from 0.7%/y to 6.6%/y as well [92], the antithrombotic regimen should be well defined in each patient [9, 38, 40, 92, 98, 100]. With biological heart valves a duration for anticoagulation of 3 months after valve insertion is usually sufficient with some exceptions such as AF. Permanent antithrombotic treatment is indicated in pts. with mechanical heart valves. In a non-randomized trial (n = 208) Enoxaparin (2 x 1 mg/kg) or Nadroparin (2 x 87 IE/kg) were given postoperatively for a mean of 14 days and compared with UFH. Therapeutic anticoagulation on day 2 was documented in 87% of pts. treated with LMWH and only 9% of pts. treated with UFH [74]. In case of contraindications for coumarin derivatives (Table 2) UFH and LMWH were used as alternative in pregnancy and in non-pregnant pts. in absence of controlled trials [42, 65, 83].

In pregnancy low dose sc UFH was associated with a significant risk of valve thrombosis [10, 36, 83] as well as bone loss and heparin induced thrombocytopenia (HIT II). Subsequent osteoporotic fractures were observed in 2.2% of pregnant women on long term treatment with UFH [18]. LMWH is an alternative as it does not cross the placenta and less effect on bone metabolism was documented [78].

Concerns were raised after reports of valve thrombosis with LMWH in 6 cases which were published not only in pregnant women. As quite low daily doses of 2850 or 5700 IU Nadroparin [47], 5000 IU Dalteparin [2], 2000-8000 IU Enoxaparin [8, 64] were used in 5 of 6 cases a more intensive anticoagulation should be the consequence. In a series of 16 pts. with mechanical heart valves no TEC occurred with a daily LMWH-dose of 120-150 IU/kg bw [42] as well as with a Nadroparin-dose of 2 x 0.01 ml/kg/day (n = 2) [63] and a Dalteparin-dose of 16000 IU/day (n = 1) [68]. The reports about prosthetic valve thrombosis under treatment with LMWH show the importance of careful antithrombotic management with close monitoring to ensure four to six-hour postinjection anti-factor Xa levels of ≥ 0.5 U/mL [69]. Especially during pregnancy one must expect altered haemostatic conditions and variable pharmacodynamic and pharmacokinetic effects of LMWH [22]. In the guidelines of the sixth ACCP Consensus Conference adjusted-dose LMWH in pregnant women with mechanical heart valves were listed as grade 2C recommendation [37]. On the other hand, a consensus statement of the European Society of Cardiology [25] on the management of cardiovascular diseases stated that LMWH should not be recommended in pts. with heart valve prostheses during pregnancy. An evidence-based review of strategies for anticoagulation of pregnant women with prosthetic heart valves is discussed in detail in a clinical cardiology consensus report of the American Health Consultants [3]. More controlled studies are urgently needed [40, 72]. Newer data on LMWH in a dose up to 200 IU Dalteparin/kg/d may be available after termination of the German "EThIG"-trial ("Effektivität von Thromboseprophylaxe als Intervention in der Gravidität"). Among others the inclusion criteria of this trial with the LMWH Dalteparin accept pregnant women with artificial heart valves [35].

Table 2. Reasons for replacing Coumarin derivatives with LMWH.

Temporary switch	Permanent replacement
Periprocedural risk for bleeding	Pts. at bleeding risks Intolerance of Coumarin
Pregnancy	Coumarin-induced severe bleeding complication
Prolonged postoperative treatment after heart valve replacement surgery	Malignancy TEC while on Coumarin

Non-ST-Elevation Acute Coronary Syndrome (NSTE-ACS)

Non-occlusive thrombus due to plaques rupture or fissuring is the pathophysiologic correlate in pts. presenting with unstable angina or non-ST-elevation myocardial infarction (NSTE-ACS). Six randomized trials performed to compare combination of UFH and ASA with ASA alone failed to show a significant benefit. Even by pooling data of all 1353 pts. no significance was reached (p = 0.06) as risk reduction of 33% was too low [76]. For the first time the FRISC-study (Fragmin during Instability in Coronary Artery Disease) with 1506 pts. could demonstrate a significant risk reduction of 63% vs. placebo in composite endpoint death or myocardial infarction (MI) after sc treatment with 2 x 120 IU Dalteparin/kg, maximum dose 2 x 10000 IU, for 6 days [29]. The rate for major bleedings was low and not significantly elevated in Dalteparin-group as compared to placebo (0.8% vs. 0.5%). No direct comparison between the LMWH

Enoxaparin and Placebo has been performed. By using a special statistical technique to combine studies with Enoxaparin/UFH-comparisons and Placebo/UFH-comparisons a risk reduction of 47% (p = 0.023) for death and MI was calculated [71].

The ESSENCE trial compared Enoxaparin (1 mg/kg every 12 h) with iv aPTT-adjusted UFH [12]. 3171 pts. with unstable angina or non-q-wave myocardial infarction received the study drug for 48 hours to a maximum of 8 days (median 2.6 days). At day 30 a significant reduction with Enoxaparin in the incidence of death, MI and recurrent angina (combined endpoint) was seen (19.8% Enoxaparin vs. 23.3% UFH, p = 0.016). After one year, the difference was maintained with event rate of 32% vs. 36%. Safety was comparable with incidences for major bleedings at day 30 of 6.5% with Enoxaparin vs. 7.0% with UFH. In the TIMI 11B trial LMWH treatment was started by a iv bolus of 30 mg Enoxaparin and therapy continued sc with the same dose as in ESSENCE for 3 to a maximum of 8 days. After termination of the in-hospital acute phase pts. in the Enoxaparin-group received 2 x 40 mg or 2 x 60 mg up to day 43. The comparator group received iv aPTT-adjusted UFH in the acute phase followed by placebo during outpatient phase. Efficacy with Enoxaparin was significant better with regard to combined endpoint at day 8 (12.5% vs. 14.5%, p = 0.048). No significant difference in major bleedings until end of initial hospitalisation was detected (1.5% Enoxaparin vs. 1.0% UFH, p = 0.143) [4].

Other randomized trials investigating acute treatment phase in NSTE-ACS with the LMWH Dalteparin 2 x 120 IU/kg [58] and Nadroparin 2 x 87 IU/kg [95] gave evidence for similar efficacy and safety of LMWH as compared to aPTT-adjusted UFH. Superior efficacy of Enoxaparin twice daily as compared to LMWH Tinzaparin was reported in an open, randomized trial with 438 pts. [73]. Tinzaparin was given once daily at the same dose used for DVT-treatment. It is likely that once daily injections of LMWH are insufficient in acute phase of NSTE-ACS. Direct comparisons between LMWH given twice daily in NSTE-ACS are lacking. Treatment regimen in the UFH comparator groups differed between studies. For example, in the FRIC-study performed with Dalteparin 44.0% of the UFH-pts. reached therapeutic level (1.5 to 2.0 fold prolongation) within 6 h [59] as compared to only 30.3% of UFH-pts. reaching aPTT of 55-85 sec within 6 to 12 h in ESSENCE-trial [12].

In conclusion, the FRISC-trial has shown a safety profile for Dalteparin, that compares well with placebo and a risk reduction for death and MI that is nearly twice as high as shown with UFH. Superior efficacy for Enoxaparin in the ESSENCE trial and TIMI 11B trial is another reason to replace UFH by LMWH. Dalteparin (120 IU/kg every 12 h) and Enoxaparin (1 mg/kg every 12 h) have been registered in the United states and several European countries for treatment of NSTE-ACS.

Combination of LMWH with Glycoprotein (GP) IIb/IIIa-Inhibitors in NSTE-ACS

GP IIb/IIIa inhibitors have shown to be beneficial in pts. with NSTE-ACS, especially if early percutaneous coronary interventions (PCI) are performed. Therefore, efficacy and safety of combining LMWH with GP IIb/IIIa inhibitors was investigated.

The ACUTE I pilot study compared 26 pts. treated with Enoxaparin 1 mg/kg every 12 h and Tirofiban (0.1 μg/kg/min iv for 48-108 h) with 27 pts. treated with UFH and the same Tirofiban regimen [13]. PCI was planned to be performed between 48 h and 96 h after onset of study medication. There was no major nor moderate bleeding. The INTERACT trial randomized 746 pts. with acute coronary syndrome treated with the GP IIb/IIIa inhibitor Eptifibatide to UFH or Enoxaparin 1 mg/kg twice daily. Incidence of major bleeding within first 96 h was significantly reduced by the LMWH (1.8% vs. 4.6% UFH) [41]. A significant reduction of ischemic events within first 48 h from 25% with UFH to 14% with LMWH could also be shown. Further trials have been performed with Enoxaparin 1 mg/kg twice daily or Dalteparin 2 x 120 IU/kg/d:

- ACUTE II (Enoxaparin and Tirofiban vs. UFH and Tirofiban) [14]
- NICE 3 (Enoxaparin and 3 different GPIIb/IIIa-inhibitors) [27]
- NICE 4 (Enoxaparin and Abciximab before PCI) [52]
- PARAGON-B (type of LMWH not specified in protocol) [75]
- GUSTO IV Dalteparin-substudy (no early intervention, Dalteparin for 5 – 7 days combined with Abciximab 24h- or 48h- infusion after bolus injection or placebo) [48]

At least similar efficacy and safety of GP IIb/IIIa-inhibitors in combination with therapeutic dose of LMWH as compared to combination with UFH could be demonstrated [for detailed review see 108].

Percutaneous Coronary Intervention (PCI)

The FRISC II-study indicates that an early invasive strategy is superior to a conservative approach in NSTE-ACS [31]. In this study, PCI in combination with periprocedural Dalteparin was performed in 742 pts.. Last injection of 2 x 120 IU Dalteparin/kg (maximum 2 x 10000 IU) was administered latest 12 h before PCI. The first sc injection of 120 IU Dalteparin/kg post PCI was given 2 to 6 h after sheath removal. In case of concomitant therapy with the GP IIb/IIIa inhibitor Abciximab Dalteparin was not given within 24 h after infusion. The same sc Dalteparin dose before

PCI and Abciximab was used by Kereiakes et al. (2001) [54], but before PCI additional iv injections were given:

- 40 IU Dalteparin/kg in case of PCI performed 8–12 h after sc injection
- 40 IU (n = 27) or 60 IU (n = 28) Dalteparin/kg in case of PCI performed > 12 h after sc injection or no prior sc injection given.

Incidence of procedural thrombosis was significantly reduced by higher iv dose (11.1% vs. 0%, $p < 0.01$) without increasing risk for major bleedings (3.7% in 40 IU/kg group vs. 2.6% in 60 IU/kg group).

Subanalysis of pts. with PCI after 24 h initial treatment in ESSENCE- or TIMI 11B-study have shown a non-significant (p = 0.06) reduction in death and MI after 43 days for 431 pts. treated with 2 x 1 mg/kg Enoxaparin as compared to 493 pts. treated in UFH-groups (3.3% vs. 5.9%). No difference was seen in major bleedings (5.4% vs. 6.2%) [28]. Further trials with different dosing regimen for Enoxaparin in PCI were published by

- Rabah et al. (1999) [79]: One single dose of 1 mg/kg iv immediately at PCI (n = 30) as compared to UFH (n = 30)
- NICE 1 [53]: One single dose of 1.0 mg/kg iv immediately at time of PCI (n = 828)
- Choussat et al. (2002) [17]: One single dose of 0.5 mg/kg iv immediately at time of PCI (n = 242)
- Martin et al. (2001) [70]: 1 mg/kg sc twice daily, last dose 8-12 h before PCI with additional iv dose of 0.3 mg/kg at time of PCI (n = 40).
- Collet et al. (2001) [16]: 1 mg/kg sc twice daily, last dose 4-8 h before PCI (n = 132).

In the small trial performed by Rabah et al. no ischemic complication was seen in the Enoxaparin-group within 30 days, whereas 3 events occurred in the UFH-group [79]. Incidence for death, MI and revascularisation after 30 days ranged between 2.5% and 7.7% in the four non-comparative Enoxaparin-trials mentioned above with major bleedings occurring in 0% to 1.1% of pts. treated. With the LMWH Reviparin (7000 IU iv followed by 10500 IU within 24 h period and 3500 IU sc for 28 days) no difference in efficacy and major bleedings was seen in 306 pts. undergoing PCI as compared to 306 pts. treated with UFH (death, MI or revascularisation within 30 weeks: 33% vs. 32%) [51].

In conclusion LMWH seem to be as effective and safe as UFH in anticoagulation during PCI. It should be considered that some trials allowed additional UFH-injections during PCI. No clear recommendation can be drawn from study results as different dosing regimen were examined with sc as well as iv injections of LMWH. Package labelling of Enoxaparin states that sc injections for therapy of NSTE-ACS should be stopped before PCI and changed to standard antithrombotic treatment (e.g. UFH).

Long Term Treatment in NSTE-ACS

After cessation of initial treatment with UFH reactivation of coagulation activity and increased event rates were observed [80]. 7500 IU Dalteparin/day for 35-45 days reduced incidence of death or MI at day 40 from 14.2% to 7.4% ($p < 0.01$) in pts. with serum troponin T levels 0.1 μg/l in the FRISC-trial [66]. No additional benefit was seen in the TIMI 11B trial for extended Enoxaparin as compared to placebo at day 43, whereas significant more major bleedings were reported with Enoxaparin in the outpatient phase (2.9% vs. 1.5% for Placebo, p = 0.021) [4]. The FRIC-trial did not show a benefit of prolonged treatment with 7500 IU Dalteparin/day at day 45. Incidences of major bleedings were similar (0.4% Placebo vs. 0.5% Dalteparin) [58]. In the FRAXIS-trial no advantage for 14-days treatment with Nadroparin as compared to 6-days treatment was seen, but major haemorrhage occurred in 3.5% of pts. with 14-days Nadroparin 87 IU/kg twice daily as compared to 1.6 % for 6-days UFH (p = 0.0035) [95].

In the FRISC II-trial pts. were randomized to 90 days treatment with 5000 IU or 7500 IU Dalteparin every 12 h or placebo. There was a significant 47%-reduction of death and MI with prolonged Dalteparin-treatment at day 30 after termination of initial phase (3.1% vs. 5.9% Placebo, p = 0.002). This benefit disappeared at day 90 (6.7% Dalteparin vs. 8.0% Placebo, p = 0.17) and rates for major bleedings were than increased from 1.5% with Placebo to 3.3% with Dalteparin (p = 0.01) [30]. Subanalysis have shown that pts. treated with Dalteparin, who underwent revascularization within 45 days, had a significant benefit with a relative risk reduction of 35% for death and MI after one year (p = 0.02) [61]. No additional effect was seen for treatment with LMWH after successful revascularisation procedure [30]. Nevertheless, after coronary artery bypass surgery (CABG-surgery) prophylaxis for TEC was done in FRISC II-study using twice daily sc-injections of 5000 IU Dalteparin until mobilization.

The market authorizations granted from some European authorities for prolonged treatment with 2 x 5000 – 2 x 7500 Dalteparin in NSTE-ACS support the recommendation for use of Dalteparin as "bridging therapy" for up to 45 days in pts. awaiting revascularization-procedure.

Acute ST-elevation Myocardial Infarction (aSTEMI)

LMWH in the treatment of aSTEMI were investigated in combination with several thrombolytic agents as well as in pts., who are ineligible for thrombolysis.

Addition of LMWH to Streptokinase in aSTEMI

Iv UFH did not seem to be beneficial in pts. treated with streptokinase [96]. In the placebo-con-

trolled double blind FRAMI-study (n = 776) 150 IU/kg Dalteparin every 12h (first dose 8 h after lysis with streptokinase) reduced incidence for formation of left ventricular thrombus to 14.2% as compared 21.9% with placebo (p = 0.02), but major haemorrhage increased (2.9% vs. 0.3%, p = 0.006), which can be explained by high dose of 300 IU/kg/d. The placebo controlled AMI-SK study (n = 496) could demonstrate a significant reduction of death, reinfarction or recurrent angina after 30 days (13% vs. 21%) in favour of Enoxaparin, but major bleedings increased with LMWH (4.8% vs. 2.8% Placebo) [89]. In a placebo-controlled study (BIOMAX II) with 101 pts. 100 IU Dalteparin/kg was administered just before lysis with streptokinase followed by a second injection of 120 IU Dalteparin/kg after 12 h. There were significant fewer ischemic episodes 6-24 h after onset of treatment (16% Dalteparin vs. 38% placebo, p = 0.04), whereas no significance was reached in the rate of TIMI grade 3 flow (68% vs. 51%, p = 0.10) [33].

Combination of LMWH with Alteplase, rt-PA or Tenecteplase

In the HART-2 study addition of UFH or Enoxaparin (30 mg iv followed by 1 mg/kg every 12 h for at least 72h) to Alteplase and ASA was compared in 400 pts. with aSTEMI [82]. Incidence of TIMI grade 2 or 3 flow after 90 minutes was more frequent with Enoxaparin (80% vs. 75%). Subsequent reocclusion to TIMI grade 0 or 1 after 5 to 7 days was 5.9% with Enoxaparin and 9.8% with UFH without reaching significance. In the ASSENT-3 trial full dose of Tenecteplase combined with Enoxaparin (same dose as in HART-2 study up to maximum of 7 days) was as effective as half-dose Tenecteplase plus aPTT-adjusted UFH and Abciximab: Rates for combined endpoint (death after 30 days, in-hospital reinfarction, or in-hospital refractory ischemia) in these 2 groups were 11.4% vs. 11.1% and significantly lower than in the third group treated with Tenecteplase and aPTT-adjusted UFH (15.4%). A non-significant increase of major bleedings was observed with Enoxaparin as compared to UFH (4.0% vs. 2.8%) [94]. The ENTIRE-TIMI 23 trial with 456 pts. treated with Tenecteplase or half dose of Tenecteplase with Abciximab resulted in a comparable rate of TIMI 3 flow with UFH (51%) vs. Enoxaparin (50%, same dose as in HART-2 study up to 8 days) with slightly elevated risk for major bleedings with Enoxaparin (5.2% vs. 3.8%) [5]. Incidence of death or recurrent infarction at 30 days was lower in Enoxaparin-group (4.4% vs. 15.9% UFH-group). A prehospital setting was investigated in the ASSENT-3 PLUS trial [102]. In 1639 pts. receiving Tenecteplase treatment with Enoxaparin (same dose as in HART-2 trial to a maximum of 7 days) showed a non-significant reduction in 30-day mortality, in-hospital reinfarction or refractory ischemia (14.2% vs. 17.4%, p = 0.08) as compared to UFH, but rates for stroke (2.9% vs. 1.3%) and intracranial haemorrhage (2.2% vs. 1.0%) were significantly higher with Enoxaparin, predominantly in older pts. (>75 years).

In the ASSENT PLUS-trial 439 pts. treated with rt-PA were randomly assigned to LMWH Dalteparin (30 IU iv bolus followed by 90 IU/kg and then 120 IU/kg, maximum 2x12000 IU every 12 h for 4-7 days) or aPTT-adjusted UFH for 48 h [101]. After 4-7 days there was a significant difference in favour of Dalteparin in frequency of TIMI 2-3 flow (72% vs. 58% UFH, p = 0.004) and in rate for reinfarction after 7 days (1.4% vs. 5.4% UFH, p = 0.02). There was a trend towards lower risk for major bleedings with Dalteparin (3.6% vs. 5.2% UFH).

Patients with aSTEMI Ineligible for Reperfusion

In the TETAMI-trial 1224 pts. ineligible for reperfusion were randomly assigned in four groups: LMWH Enoxaparin (same dose as in HART-2 trial, to a maximum of 8 days) with or without addition of Tirofiban and aPTT-adjusted UFH with or without addition of Tirofiban. No differences were seen in combined endpoint death, reinfarction or recurrent angina (15.7% Enoxaparin vs. 17.3% UFH) and major haemorrhage (1.5% vs. 1.3%). Adding Tirofiban did not show any effect (16.6% vs. 16.4% Placebo) [15].

Dalteparin was investigated in pts. ineligible for lysis as well, but the FAMI-study aimed at effect of 30-days treatment with 7500 IU Dalteparin as compared to placebo. During the first 3 days 2 x 120 IU Dalteparin/kg was administered in all 1128 pts. and showed a low mortality rate of 1.4% without any major bleeding. The prolonged treatment resulted in no difference concerning mortality (1.9% in each group) but a non-significant reduction in left ventricular thrombi (1.5% Dalteparin vs. 2.7% placebo). One major bleeding (0.2%) was reported with Dalteparin in the prolonged phase [50].

In conclusion treatment of pts. with aSTEMI has been investigated with the LMWH Dalteparin and Enoxaparin. The combination with thrombolytics or GP IIb/IIIa-inhibitors seem to be as safe as UFH with some advantages shown concerning efficacy parameters. So, replacement of UFH by LMWH can be discussed keeping in mind, that no official recommendation or market authorization is available so far and an increased risk for intracerebral haemorrhage in elderly pts. treated with combination of tenecteplase and enoxaparin was detected. In pts. ineligible for reperfusion LMWH seem to be at least as effective and safe as UFH. Therefore replacement of UFH by the LMWH Dalteparin or Enoxaparin should be considered after treatment regimen have been well defined.

Peri-interventional Anticoagulation in Patients Receiving Coumarins

31 publications have been identified by a systematic review about perioperative management in

pts. under long term OAC, but there was no randomized controlled trial [21]. In some cases, e.g. dental procedures or cataract surgery, OAC might be continued without changes as low rates for major bleedings of 0.2% or less were calculated. Other invasive interventions require the temporary replacement of Coumarins by UFH or LMWH. Low TEC-rates in case of well defined treatment protocols between 0 and 0.6% as compared to not specified or unclear strategies (8.0%) would require a large trial to compare LMWH with UFH. Bridging-treatment protocols using LMWH were developed on clinical experiences, e.g. for Dalteparin (2 x 5000 IU/d) [86] and Enoxaparin (2 x 1 mg/kg/d) [77]. A large case series included 244 pts. treated with sc injections of 2 x 100 IU Dalteparin/kg with intervals of 12 h prior to surgery and 8-12 h after haemostasis was secured postoperatively [99]. No TEC and one major haemorrhage at injection site were seen in pts. predominantly on OAC because of mechanical heart valves (n = 118), other artificial heart valves (n = 29), AF (n = 35), stroke (n = 40) and VTE (n = 22).

Spandorfer et al. (1999) [90] published data on 20 pts. treated with Enoxaparin 1 mg/kg every 12 h. There was 1 major bleeding and no VTE. Sc injections were stopped 12-18 h prior to surgery and started again once haemostasis was achieved. In another small prospective trial with 24 pts. Dalteparin was administered [97]. Because of once daily injection of 200 IU/kg the preoperative interval for the last injection was one day. Dalteparin was reinitiated in the morning after surgery using twice daily injections (2 x 100 IU/kg) during hospital stay followed by 1 x 200 IU Dalteparin/kg after discharge. One TEC and no major bleeding was reported.

In conclusion pre- and postinterventional LMWH (e.g. Dalteparin 100 IU/kg every 12 h as well as Enoxaparin 1 mg/kg every 12 h) with reduced dose on day of surgery seem to be safe and effective in cardiac pts. requiring temporary cessation of OAC. But as general consensus is lacking, in each individual patient the risk-to-benefit ratio for bleeding and TEC must be thoroughly defined to determine a suitable anticoagulation regimen (Note added in proof: A detailed and updated review about periprocedural thromboprophylaxis has just appeared [Jafri SM (2004) Periprocedural thromboprophylaxis in patients receiving chronic anticoagulation therapy. Am Heart J 147: 3-15]).

Overall Conclusions

Over the last years numerous studies have been published with LMWH administered in heart diseases. LMWH seems to be advantageous over UFH as in case of sc prophylaxis pts. need less injections and there is no need for venous access and aPTT-Monitoring. Its ease of use allows outpatient treatment. Findings in pts. with heart diseases were predominantly generated with Dalteparin and Enoxaparin showing some benefits as compared to UFH in thromboprophylaxis (pts. with acute heart failure, AF or CV) and in therapy of NSTE-ACS. Dalteparin and Enoxaparin are therefore the two LMWH of choice in cardiology. As long as direct valid comparisons of these two LMWH are lacking no statement should be made concerning superiority of one LMWH over the other [104]. LMWH are easier to handle. Therefore, comparisons with UFH performed under well defined study conditions might underestimate the benefit of switching the anticoagulation to LMWH in clinical practice. Even though no market authorization for LMWH is available in situations with contraindications to Coumarin derivatives, LMWH offer important options in management of pts. on long term anticoagulation. It is expected that evidence for use of LMWH in other cardiac indications will grow. As long as conclusive data with a well defined dosing regimen for the respective LMWH are lacking special precautions should be taken in case of combination with GP IIb/IIIa inhibitors, in case of PCI (with and without additional UFH), in pts. with artificial heart valves, during pregnancy and in pts. with renal insufficiency.

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