Six almost unknown reasons why LMWH is better than unfractionated heparin in therapy of patients with present or threatening heart failure

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Abstract: The general advantages of low molecular weight heparin (LMWH) over unfractionated heparin (UFH) are well-known. However, in patients with present or threatening heart failure (HF), other characteristics of LMWH become additionally advantageous. These characteristics are almost unknown and it can be useful to recognize them, because heparins are extraordinarily potent drugs (they might cause even fatal bleeding) and such patients are very prevalent. The first of the advantages of LMWH, especially important in HF patients, is subcutaneous (s.c.) administration – without infusion. On the contrary, UFH is given in therapeutic doses by means of infusion, so-called “heparin pump”. It produces volume load, which can be very bad for patients with present or threatening HF, who are (or will become soon) overloaded. Furthermore, “heparin pump” requires immobilization, which is a thrombogenic situation per se. Besides, prolonged immobilization required for “heparin pump” undoubtedly produces stress, which is arrhythmogenic, enhances platelet aggregation, rises blood pressure (and thus afterload), may lead to vasospasm, etc. UFH damages veins, especially if “heparin pump” is administered more than 24 hours. In addition, UFH causes local bleeding at the infusion site. The damage of veins and local bleedings are more common in older patients with many comorbidities and HF patients are prototype for this. Moreover, the concentrations of the acute phase reactants are increased in HF, possibly leading to the UFH resistance. Furthermore, UFH can cause hyperkalemia, which complicates already delicate potassium regulation in HF.

Key-Words: Unfractionated heparin; low molecular weight heparin (LMWH); heart failure; immobilization; stress; heparin resistance; hyperkalemia.

1 Introduction
Relevance of the problem
The actuality of the problem is obvious from the numerous indications for rapid-acting (mostly parenteral) anticoagulants (AC) as well as from the high absolute numbers of such patients (millions in Europe or USA). Compromised heart function has been found in three following main large groups of hospitalized patients with indication for AC.

A. HF patients
Patients with both acute HF and decompensated chronic HF have been numerous. For example, in USA there were 1 106 000 hospital discharges for HF in 2006 [1]. HF is the cause of 5% of acute hospital admissions and it is present in 10% of patients in hospital beds [2]. In the PRIME-II trial of 1825 CHF patients [New York Heart Association (NYHA) functional classes III and IV], 43% of patients were taking anticoagulants [3]. HF patients need therapeutic dose of rapid-acting AC due to thrombus in heart chamber, atrial fibrillation and/or dilated left ventricle and/or very low ejection fraction with the marked activation of coagulation (e.g. very high D dimer), etc. In less risky situations, prophylactic AC dose will suffice. Then, we may continue with vitamin K antagonist [3]. Even prophylactic anticoagulation with unfractionated heparin can be applied intravenously, as suggested by guidelines [4].

B. Acute coronary syndrome (ACS) patients
Guidelines for both ST elevation myocardial infarction (STEMI) and non ST elevation acute coronary syndrome (NSTEMI) suggest AC use, indeed [5], [6], [7]. Many ACS patients have HF or incline to it. For example, in one series out of 2089 STEMI
patients, 17% presented HF on admission and 1% developed HF after hospitalization [8]. Another group founded high HF prevalence: 56.2% among 3548 non-STEMI (NSTEMI) and 27.4% out of 1989 unstable angina (UA) patients [9]. Incidence of ACS is also high: annual incidence of hospital admissions for NSTE-ACS is in the range of 3 per 1000 inhabitants [7]. In 2004, the National Center for Health Statistics (in USA) reported 1 565 000 hospitalizations for primary or secondary diagnosis of an ACS, 669 000 for UA and 896 000 for myocardial infarction (MI) [10].

C. Venous thromboembolism (VTE) patients
HF is one of the crucial medical risk factors for VTE [11]. Vice versa, pulmonary embolism (PE) is one of the important reasons for HF worsening [11]. Accordingly, many hospitalized HF patients are and should be evaluated for PE, receiving therapeutic doses of AC therapy at least until results of imaging tests become available [11]. Thus, HF is present or threatening in many hospitalized patients (mostly at Cardiology departments), some of whom with the above-mentioned indication for therapeutic doses of AC. Moreover, in many patients without HF, heart function can deteriorate rapidly due to acute arrhythmia (e.g. new-onset atrial fibrillation), or (hospital-acquired) infection, or anaemia, or drugs with negative inotropic effect, nonsteroidal anti-inflammatory drugs, excessive alcohol or illicit drug use, etc. (or their combination) [4]. Such patients have life-threatening diseases and often important comorbidities, which can interfere with AC metabolism (e.g. renal dysfunction) and can increase risk of bleeding. The choice of AC is therefore, very frequent and very important issue in clinical practice.

2 Problem Formulation
For patients with present or threatening HF, the choice of parenteral anticoagulant (in therapeutic doses) is frequent and important in clinical practice and there are no specific suggestions to guide the choice for this situation.

3 Problem Solution

3.1 Choice of AC in patients with present or threatening HF
Indeed, ACS patients who require coronary angiography represent a special group- as far as AC therapy is concerned. For other patients with HF, if there is an indication for therapeutic doses of rapid acting AC, one should carefully evaluate between UFH and LMWH.

There are 3 main advantages of UFH over LMWH:
1. Patients with renal dysfunction (because LMWHs are excreted via kidneys, when risk of accumulation and over dosage of LMWH rises, with possible consequent haemorrhage);
2. Patients with relatively high bleeding risk (old age, previous gastrointestinal bleeding, previous non-cardioembolic stroke, chronic renal or hepatic disease, concomitant antiplatelet therapy), because LMWH can be less effectively neutralized by protamine;
3. Patients with massive PE (in this situation LMWHs have not been tested). Moreover, UFH may be better choice in rare situations when subcutaneous route is compromised and when embolectomy / vena cava filter is planed in PE [11], [12] [13].

On the other hand, LMWHs have numerous well-known general advantages over UFH [3] [14] [15] [16] [17] [18] [19]:

1. Predictable effect due to higher bioavailability (the result of almost complete absorption after s.c. application and less binding to plasma proteins, macrophages, endothelial cells, and so on) and thus both smaller variation of concentration and a longer half-life);
2. Application of LMWH is more comfortable for the patient (it is less stressful to receive drug subcutaneously than via 24-hour infusion, especially having in mind that in the PE heparin should be given for at least 5 days. In addition, blood is taken for analysis more rarely with LMWH than with UFH. For UFH, two analyses should be commonly performed: aPTT and the number of platelets [2-3 times a week - as the incidence of heparin induced thrombocytopenia (HIT) is the highest among all anticoagulants].
3. Application of LMWH is more comfortable for the medical staff (saves time, because aPTT should not be performed when LMWH is applied and platelet count should be checked more rarely);
4. There is less frequent HIT (0.25 to 1% for LMWH, compared with 0.5 to 5% when UFH is administered) -due to decreased binding to platelet factor 4 (PF4);
5. There is less activation of platelets with LMWHs.
6. There is less frequent resistance to heparin and less frequent heparin rebound (due to longer LMWH administration)
7. There is less frequent osteoporosis (due to decreased binding to osteoblasts) during prolonged use of LMWH.
Thus, it is not surprising that LMWHs are gradually replacing UFH for most indications [3].

Fondaparinux shares all the pharmacological and biological advantages of LMWHs over UFH [3]. Subcutaneous administration of UFH is not suggested for therapy [3]. UFH causes less bleeding when given as continuous i.v. infusion in comparison with intermittent i.v. injections [20]. Although high-dose subcutaneous heparin can be used in place of LMWH, the volume of injection tends to be large [21]. Thus, the important problem of UFH in therapeutic doses is that it should be administered in 24-hour infusion (“heparin pump”) [22] [23].

Altogether, there are at least six almost unknown reasons why LMWH is better than UFH for therapy of patients with concomitantly present or threatening HF. Basically, when administered in therapeutic doses, some “UFH specific shortcomings for HF patients” are due to:

- problems with the mode of administration [how is UFH applied]: local side effects, time-related harms (continuity of infusion);
- problems with the drug and/or solution [what is administered] (chemical characteristics of UFH and solution given, etc).

Thus, “UFH specific shortcomings” are more common / more pronounced in HF patients (as compared to patients who do not have HF).

3.2 Almost unknown reasons why LMWH is better than UFH in therapy of patients with present or threatening HF

1) LMWH does not produce volume load (as “heparin pump” does), which can be very bad for patients with present or threatening HF. Namely, hospitalized patients are often both elderly [and left ventricle (LV) diastolic function decreases with age] and have multiple comorbidities [which may further diminish LV function (e.g. diabetes mellitus)] [27]. This side effect of “heparin pump” was not considered in the recent excellent HF guidelines, stating: “If AF is of ≥48 h duration or of unknown duration, heparin by intravenous (i.v.) bolus should be administered followed by a continuous infusion” [2]. Patients with HF or prone to it may concomitantly receive volume load by means of another infusion (e.g. nitroglycerin in ACS patients), increasing the probability for worsening haodynamics with “heparin pump”. Additionally, solution used for “heparin pump” may contribute to hemodilution, which may lead to potentially dangerous electrolyte abnormalities [28].

Moreover, the choice of solution for “heparin pump” could be wrong for an individual patient.

2) LMWHs do not require immobilization, but “heparin pump” does, which is thrombogenic situation per se [7], [11]. (This has been known for over 150 years -since R. Virchow had published his triad).

3) Prolonged immobilization required for “heparin pump” undoubtedly produces stress, which is arrhythmogenic, enhances platelet aggregation, rises blood pressure (and thus afterload), may lead to vasospasm, etc [29].

4) LMWH is not administered via I.V. infusion, sparing veins, which are often already damaged and prone to bleeding with advancing age. The incidence rate of phlebitis rose sharply after 24 hours of infusion [24]. In many cardiologic patients heparin is given more than one day. For example, in NSTE ACS if conservative strategy is applied, Fondaparinux, Enoxaparin, or other LMWH may be maintained up to hospital discharge [7]. Moreover, heparin is the strongest natural acid in the body [25]. The acidity of the drug is not favorable for peripheral veins, as two controlled studies clearly demonstrated a significant decrease in the incidence of thrombophlebitis when buffered glucose solutions (buffered to pH 6.8 and 7.4, respectively) were used [26]. Moreover, „heparin pump“ frequently causes local bleeding. The damage of veins and local bleedings are more common in older patients with many comorbidities and HF patients represent a prototype for this situation.

5) The concentrations of the acute phase reactants are increased in HF, leading possibly to the UFH resistance, the situation when patients require unusually high doses of UFH to achieve a therapeutic APTT [3] [14] [30].

6) UFH can cause hyperkalemia, which complicates delicate potassium regulation in HF [31]. [Approximately one quarter of HF patients has renal dysfunction (which is typically characterized by hyperkalemia); some medications indicated in HF - ACE inhibitors and spironolactone- raise serum K+ level, while loop diuretics decrease it].

4 Conclusion

1. Millions of patients hospitalized annually all over the world may require therapeutic doses of rapidly acting anticoagulants. As many of them have heart failure (or are very prone to it), the choice of anticoagulant is very important.

2. General advantages of LMWHs over UFH (and vice versa) are repeatedly elaborated in details. To the best of our knowledge, there is no paper with the main topic to compare LMWHs with UFH in this very
References:


