Low-molecular-weight heparins for the treatment of acute coronary syndrome and venous thromboembolism in patients with chronic renal insufficiency

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Abstract The clinical management of patients with renal insufficiency who develop an acute coronary syndrome or venous thromboembolism is a common clinical scenario that is problematic because of the lack of well-designed randomized trials assessing management strategies in such patients. Impaired renal function is common in patients who develop thromboembolic disorders, particularly in elderly patients in whom renal insufficiency is under-recognized. Low-molecular-weight heparins (LMWHs), which are the most widely used anticoagulant for the treatment of patients with an acute coronary syndrome or venous thromboembolism, are eliminated primarily by the kidney and, therefore, pose treatment challenges in patients with impaired renal function. However, there is emerging evidence regarding the use of LMWHs in patients with impaired renal function suggesting that some preparations may be safe in such patients. The objective of this review is to discuss the clinical management of patients with renal insufficiency who develop an acute coronary syndrome or venous thromboembolism, and to explore similarities and differences of LMWHs when used in this clinical setting.

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Introduction

The anticoagulant management of patients with an acute coronary syndrome (ACS) or venous thromboembolism (VTE) who also have chronic renal insufficiency is a challenging scenario because of the lack of evidence-based guidelines that inform clinical practice. At the end of the
day; clinicians are left with two anticoagulant management options: 1) avoid low-molecular-weight heparins (LMWHs) and instead use unfractionated heparin, or 2) use LMWHs cautiously, with anticoagulant monitoring using anti-(factor) Xa levels. Both options have drawbacks: unfractionated heparin requires intravenous administration and frequent blood testing for anticoagulant monitoring, and anti-Xa levels are difficult to obtain and interpret for LMWH therapy dose adjustments. Against this background, the objective of this review is to discuss the clinical management of patients with impaired renal function who develop an ACS or VTE, and explore the use of LMWHs in this clinical setting.

What is the scope of this clinical problem?
Renal insufficiency is common in patients with ACS or VTE.
In a study of 163 consecutive outpatients with chronic renal insufficiency at St. Joseph’s Healthcare, Hamilton, 44% had ischemic heart disease, 33% had peripheral vascular disease, and 10% had chronic atrial fibrillation [1]. These findings are supported by a larger Canadian population-based study of patients with chronic renal insufficiency, in whom 46% had cardiovascular disease at baseline and 20% developed a new cardiovascular event after 20 months of follow-up [2]. Conversely, about 50% of patients with an ACS have renal insufficiency or will develop it during the course of their illness [3–5], and in a study of 2200 patients with VTE, 52% had mild or moderate renal insufficiency [6]. Although these prevalence estimates appear high, this is likely because chronic renal insufficiency is under-recognized, particularly in the elderly in whom an ACS and VTE are most common [7,8].

Chronic renal insufficiency is under-recognized.
Elderly patients with a serum creatinine in the normal laboratory range (usually up to 110 or 120 μmol/L) are often misrepresented as having ‘normal’ renal function [9]. However, because creatinine production decreases as muscle mass declines with age, the same creatinine value represents a lower glomerular filtration rate (GFR) in an elderly than younger person [10]. Thus, a 75-year-old, 65-kg woman with a ‘normal’ creatinine of 115 μmol/L has, in fact, moderate renal insufficiency (GFR: 55 mL/min). In the NHANES III database, a population-based survey of clinical and laboratory characteristics, the prevalence of renal insufficiency increased with age: in subjects aged 70–79 years, a GFR of 60–79 mL/min was found in 16% of subjects, and a GFR of 30–59 mL/min was found in 44% of subjects [11]. In a community-based study of 2543 subjects with a ‘normal’ creatinine, a GFR of 60–79 mL/min was found in 47% of people aged >70 years [12]. Overall, the high prevalence of renal insufficiency in the elderly underscores the need for judicious use of LMWHs in such patients who are most likely to develop an ACS or VTE.

Use of LMWHs in patients with renal insufficiency.
In contrast to unfractionated heparin, which is eliminated through hepatic (reticuloendothelial system) and renal mechanisms, LMWHs are predominantly cleared by the kidney. Accumulation of the anticoagulant effect of LMWHs (as measured using anti-Xa levels), and more importantly, excessive bleeding complications, are concerns which currently limit LMWH use in patients with renal insufficiency.

Current management recommendations.
Management guidelines for use of LMWHs in patients with renal insufficiency are inconsistent regarding the severity of renal disease that would preclude LMWH use [13]. Thus, some experts recommend avoiding LMWHs in patients with moderate-to-severe renal insufficiency, with a GFR <40 mL/min [14,15], and others recommend avoiding LMWHs only in patients with severe renal insufficiency, with a GFR <30 mL/min [16,17]. Finally, some guidelines do not specify the GFR level that warrants avoidance of LMWH [18,19]. A recent critical review of the literature assessed if current guidelines for LMWH use in patients with renal insufficiency are justified [20]. In this review, few studies met inclusion criteria, and most studies used prophylactic dose LMWH to prevent hemodialysis access thrombosis in patients with end-stage renal disease (GFR <15 mL/min) [21–25]. The method of assessing renal insufficiency was frequently not specified, and varied among the studies. The authors concluded that management guidelines are not based on good quality evidence, and the potential for an excessive anticoagulant effect due to accumulation of LMWH could not be excluded if LMWHs
were given to patients with mild-to-moderate renal insufficiency (GFR: 30—89 mL/min).

Advantages of LMWHs in patients with ACS or VTE

LMWHs are first-line anticoagulants for the initial treatment of patients with an ACS or VTE [26—29], and have several advantages over unfractionated heparin. First, because of predictable pharmacokinetics, LMWHs are easier to administer with once-daily, weight-based, subcutaneous dose regimens that do not require laboratory monitoring [30]. In comparison, unfractionated heparin, which is often used in patients with renal insufficiency, has unpredictable pharmacokinetics and requires frequent blood testing for dose adjustments [18]. Second, unfractionated heparin requires in-hospital intravenous administration, whereas LMWH therapy can be given out of hospital [31,32] and is, consequently, more cost-effective than unfractionated heparin for the treatment of VTE [33,34]. LMWHs have also been found to be more cost effective for the treatment of ACS [35,36]. Third, compared to unfractionated heparin, LMWH therapy is associated with a lower risk of heparin-induced thrombocytopenia, an infrequent but devastating thromboembolic complication [37]. Finally, and perhaps most important, one LMWH (enoxaparin) has superior antithrombotic efficacy compared to unfractionated heparin in patients with an ACS [15,38], and its use is endorsed by cardiology consensus groups [26—28]. Should LMWHs prove safe in patients with renal insufficiency, they offer a number of therapeutic and practical advantages over unfractionated heparin.

Practical management considerations

In patients with renal insufficiency in whom treatment with LMWHs provides therapeutic advantages, an approach to clinical management would incorporate several considerations that are illustrated in the Case Presentation. First, anticoagulant monitoring can be done with anti-Xa levels measured 4 h after a subcutaneous dose of LMWH. Although there is no validated anti-Xa therapeutic range in patients who receive LMWHs, consensus groups have endorsed the following parameters: in patients receiving twice-daily LMWH (e.g., enoxaparin 1 mg/kg BID), the target therapeutic anti-Xa level is 0.6—1.0 IU/mL; and in patients receiving once-daily LMWH (e.g., tinzaparin 175 IU/kg), the target therapeutic anti-Xa level is 1.0—2.0 IU/mL [18]. Measuring the anti-Xa level after the second or third day of treatment can be done to ensure there is no excessive anticoagulation, especially in patients with severe renal insufficiency (GFR <30 mL/min). Second, other measures can be undertaken to minimize the risk for anticoagulant-related bleeding complications. These measures may include: standing orders on admission of medical patients to record body weight and calculated GFR, so as to avoid LMWH dose errors; documentation of risk factors for bleeding (e.g., recent gastrointestinal bleeding, active peptic ulcer disease, thrombocytopenia), so as to identify patients in whom closer clinical surveillance may be warranted; and avoidance of drugs that affect hemostasis (e.g., anti-platelet agents, non-steroidal anti-inflammatory drugs). Third, consideration may be given to administering a LMWH preparation that may be less likely to accumulate when administered in patients with renal insufficiency, as outlined below.

Differentiation of LMWHs in patients with renal insufficiency

The potential for accumulation and an excessive anticoagulant effect is considered to apply to all LMWHs [18,19]. However, there is emerging evidence that some LMWHs may be safer than others. The biological basis for this premise relates to the polysaccharide chain length of LMWHs: larger molecules are more negatively charged, which favors non-renal clearance, and have greater anti-IIa vs. anti-Xa activity, which favors hepatic clearance [39,40]. It is, therefore, plausible that as the size of a LMWH decreases (tinzaparin, 6.8 kD; dalteparin, 5.6 kD; enoxaparin, 4.5 kD; fondaparinux, 1.7 kD), there is less clearance, and more accumulation, in patients with renal insufficiency. With this reasoning, tinzaparin, which is the largest LMWH with the most anti-IIa activity, would have the most favorable pharmacokinetic profile, whereas fondaparinux, the smallest LMWH without any anti-IIa activity, would have the least favorable pharmacokinetic profile in the setting of renal impairment. The evidence, outlined below, examines the influence of LMWH molecular size and the potential for renal clearance and accumulation in patients with renal insufficiency.

Tinzaparin

Tinzaparin is the largest LMWH (6.5 kD) with the following properties [41,42]: anti-Xa-to-anti-IIa, 1.6-to-1; peak activity, 3—4 h; half-life, 3.4—4.1 h; and undetectable at approximately 24 h. There is emerging evidence from 3 studies suggesting that tinzaparin has a favorable safety profile in patients
with renal insufficiency. In a study in which therapeutic-dose tinzaparin was given to 30 elderly patients (87 ± 6 years) with VTE and a GFR of 41 ± 15 mL/min, there was no correlation between anti-Xa levels and GFR, thereby suggesting that tinzaparin does not accumulate and cause an excessive anticoagulant effect in patients with a low GFR [50]. Another study involved 200 elderly patients (85 ± 7 years) with less severe renal disease (GFR: 51 ± 23 mL/min) who received therapeutic-dose tinzaparin for VTE or arterial thromboembolism [43]. In this study, there was no correlation between anti-Xa levels and GFR. However, the strength of this finding is limited because the dose of tinzaparin was decreased in patients with 4-h post-injection anti-Xa levels >1.3 IU/mL. Consequently, one could not exclude the possibility of tinzaparin accumulation if the dose had not been decreased. In a sub-study of a clinical trial involving 187 patients with VTE who received tinzaparin and underwent 4-h post-injection anti-Xa measurements after 3 days of treatment [44], an excessive anticoagulant effect appeared to occur only in patients with severe renal insufficiency (GFR<30 mL/min) in whom tinzaparin clearance decreased by 24% [45]. Taken together, these findings suggest that the larger molecular size of tinzaparin makes it less likely to accumulate than other LMWHs in patients with mild-to-moderate renal insufficiency (GFR>30 mL/min).

Dalteparin

Dalteparin is a smaller LMWH (5.8 kD) than tinzaparin, and has the following properties [46]: anti-Xa-to-anti-IIa, 2.1-to-1; peak activity, 2.8—4.0 h; half-life, 2.8—3.8 h; and undetectable at approximately 24 h. Dalteparin is widely used in patients with VTE [47], particularly in those with cancer [48], and for peri-operative anticoagulation in patients receiving warfarin [49]. The only studies examining dalteparin in patients with renal disease are in hemodialysis-dependent patients [50—53], with no studies in patients with chronic renal insufficiency. Based on the size of dalteparin, it would be expected to have pharmacokinetic properties intermediate between those of enoxaparin and tinzaparin.

Enoxaparin

Enoxaparin is a smaller LMWH (4.5 kD) than dalteparin, and has the following properties [46]: anti-Xa-to-anti-IIa, 2.8-to-1; peak activity, 2.7—3.5 h; half-life, 3.5—4.1 h; and undetectable at approximately 30 h. Enoxaparin is as effective or more effective than unfractionated heparin for the treatment of an ACS or VTE [15,38,54], and it is the most widely prescribed LMWH in Canada [55]. In a single-dose pharmacokinetic study involving 12 healthy subjects and 12 patients with a GFR of 5—21 mL/min who received enoxaparin 0.5 mg/kg twice daily (50% of therapeutic dose), the half-life of enoxaparin was significantly longer in patients with chronic renal insufficiency (5.1 vs. 2.9 h; P<0.01) [22]. A sub-study of the TIMI-11A trial involved 445 patients with an ACS who received enoxaparin in whom trough anti-Xa levels were measured after 3 days of treatment [5]. In this study, there was a strong, inverse correlation between decreasing GFR and trough anti-Xa levels (R=0.80; P<0.01). In a cohort study of 106 patients with an ACS who received enoxaparin, patients with renal disease had a higher risk of major bleeding (30% vs. 2%; P<0.01) than those without renal disease [3]. These findings are supported by a study involving 224 patients with an ACS who received enoxaparin [4], in which a 20 μmol/L creatinine increase conferred a 40% increase in the risk of major bleeding (OR=1.4; 95% CI: 1.0—2.2). Finally, there are case reports of enoxaparin-associated bleeding in patients with renal insufficiency [56—58], and in a sub-study of the ESSENCE and TIMI-11B trials involving patients with an ACS who received enoxaparin, the risk of major bleeding was higher in patients with renal insufficiency (7% vs. 1%; P<0.01) [59]. Although it is difficult to exclude confounding by a possible increased risk of bleeding attributable to renal insufficiency itself, these findings support the premise that because of its small size, enoxaparin is more likely to accumulate and cause bleeding complications than other LMWHs.

Fondaparinux

This novel drug is a 1.7 kD synthetic pentasaccharide heparin analogue, with the following properties [60]: 100% anti-Xa activity; peak activity, 3 h; half-life, 17—21 h; and undetectable at approximately 36 h. Fondaparinux was recently approved in Canada for VTE prophylaxis after orthopedic surgery. It is more effective than enoxaparin in preventing postoperative VTE [61], and as effective as unfractionated heparin or enoxaparin for the treatment of VTE [6,62].Clinical trials are ongoing in patients with an ACS. Based on its molecular size, fondaparinux might be expected to accumulate in patients with renal insufficiency. However, there are two pieces of evidence suggesting the opposite is true. First, because fondaparinux is tightly bound to antithrombin, animal studies have
found that it is cleared along with antithrombin by the liver, thereby bypassing renal clearance [63,64]. Second, in an analysis of the Matisse Pulmonary Embolism Study (fondaparinux vs. unfractionated heparin) database, the risk of clinically important bleeding was similar in fondaparinux-treated compared to heparin-treated patients (4.5% vs. 6.3%; P=NS), despite the fact that 52% of all patients had a GFR of 30—80 mL/min [6]. This finding implies that fondaparinux may not accumulate in patients with renal insufficiency, since accumulation of fondaparinux would have been expected to result in an increased frequency of bleeding. Regrettably, anti-Xa levels were not measured in this study to assess the potential for accumulation in such patients.

**Case presentation**

You are called to see a 67-year-old man with type 2 diabetes mellitus and end-stage renal failure secondary to diabetic nephropathy who presents with retrosternal chest pain and hypotension (blood pressure 85/60 mmHg) one h into his usual hemodialysis session. Despite receiving 2 doses of nitroglycerin 0.3 mg sublingually, the patient continues to complain of chest pain, now ongoing for 20 min. Review of the patient’s medical chart reveals a longstanding history of hypertension, dyslipidemia and a prior transient ischemic attack, with no prior history of cardiac disease or serious bleeding. You note that his dry weight is 85 kg. His current medications include aspirin, atorvastatin, diltiazem and ramipril. On examination, he appears pale, with cool, clammy extremities. His blood pressure has increased to 95/70 mmHg after stopping hemodialysis, heart rate is 90 per min and regular respiratory rate is 25 per min and shallow, and he is afebrile. A 12-lead electrocardiogram demonstrates 1—2 mm ST-segment depression in the anterolateral leads. Cardiac troponin I levels are drawn, but are pending. You make a provisional diagnosis of an ACS.

**Q: What are the options for antithrombotic management in this patient?**

Antithrombotic therapies for non-ST elevation ACS include both antiplatelet and anticoagulant agents. Antiplatelet therapies, including aspirin, thienopyridines (ticlopidine, clopidogrel), glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) will not be discussed in this review. The anticoagulant management options include unfractionated heparin or LMWH. Most randomized trials have examined combination therapy (unfractionated heparin and aspirin) and demonstrated decreased death and recurrent myocardial infarction (combined end points) with combination, as opposed to aspirin monotherapy. The optimal level of anticoagulation with an ACS has not been established, but available evidence supports a weight-adjusted dosing regimen when using unfractionated heparin. An initial bolus of 60—70 U/kg (maximum 5000 U) and initial infusion of 12—15 U/kg/h (maximum 1000 IU/h) titrated to a target activated partial thromboplastin time (aPTT) of 50—75 s is recommended [27]. In patients with normal renal function, clinical trials using LMWHs (mainly enoxaparin, but also dalteparin and to a lesser degree, nadroparin and tinzaparin) have generally shown decreased risk of death, recurrent angina and MI compared to unfractionated heparin, with equivalent or slightly decreased risk of bleeding.

Most of these trials, however, did not adjust LMWH doses according to anti-Xa levels. Consequently, the level of LMWH anticoagulation that is safe and effective is uncertain. In the TIMI IIA study, a relationship between enoxaparin dose and hemorrhagic complications was noted, particularly among those patients undergoing interventions (angiography, surgery, percutaneous coronary intervention). In those patients with major hemorrhage, the anti-Xa levels ranged from 1.8 to 2.0 IU/mL. While this may provide estimates of the anti-Xa range for safety, the optimal level for efficacy is less certain. Based on animal studies, and non-randomized clinical studies of percutaneous coronary interventions, anti-Xa levels $>$0.5 IU/mL result in decreased rates of recurrent thrombosis. Consequently, anti-Xa levels ranging from 0.5 to 1.0 IU/mL measured 3—4 h following a subcutaneous injection, likely provides adequate anticoagulation for the management of an ACS and VTE, although it is acknowledged that this is based on little evidence.

In this Case Presentation, use of LMWHs in this patient is limited by the presence of end-stage renal disease. While an initial therapeutic dose of LMWH may be utilized, the subsequent doses and frequency of dosing resulting in a safe level of anticoagulation is unknown. Trough anti-Xa levels, drawn immediately prior to the next scheduled dose, could be utilized but interpretation of these results is not guided by evidence-based practice and hence no recommendations can be made. Last, an important consideration in the anticoagulant management is whether an interventional or non-interventional approach to the ACS management is
taken. In general, since the possibility of an interventional strategy for ACS management cannot frequently be definitively determined at presentation of an ACS, and because consistent therapeutic anticoagulation has been demonstrated to reduce mortality in ACS, our recommendation in the setting of end-stage renal disease failure would consist of unfractionated heparin, as outlined above.

In comparison to unfractionated heparin, reversal of the LMWH anticoagulant effect is unpredictable using protamine sulfate. Animal and in vitro studies have demonstrated that protamine neutralizes the antithrombin (anti-IIa) activity, but only 60% of the anti-factor Xa activity of LMWHs [65]. There are no available studies in humans which have supported or refuted a beneficial effect of protamine II on LMWH-induced bleeding.

Case presentation continued...

The patient’s symptoms resolve following the third administration of nitroglycerine, and blood pressure increases to 120/75 mmHg. The electrocardiogram returns to baseline, and troponin-I level peaks at 12.1 ng/dL. The patient is started on unfractionated heparin (bolus 5000 IU, and infusion 1000 IU/h), and receives aspirin 160 mg orally, followed by 81 mg daily, and clopidogrel 300 mg orally, followed by 75 mg daily. Following assessment by the cardiologist, cardiac catheterization is scheduled within the next week.

Q: When should antithrombotic therapy be interrupted prior to interventional procedures in patients with renal insufficiency?

The presence of renal insufficiency does not influence the timing of discontinuation of antithrombotic therapies. Unfractionated heparin is usually discontinued 6 h prior to interventional procedures, with an aPTT level drawn prior to the procedure to ensure no anticoagulant activity is present. For LMWHs, the dose immediately prior to the procedure is usually held; hence, when administered on a twice-daily, or once-daily basis, a minimum of 12 or 24 h occurs between the last dose and procedure, respectively. Anti-Xa levels are not routinely measured prior to the procedure. Thienopyridines such as clopidogrel should be discontinued 5–7 days prior to cardiac surgery, and should not be administered at presentation in patients in whom diagnostic catheterization or bypass surgery is anticipated within 5 days. There is currently no antidote to reverse the antplatelet effects of thienopyridines, and platelet transfusions may be indicated in patients who have received these agents and experience bleeding symptoms.

References

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