Treating deep vein thrombosis and pulmonary embolism in the elderly – current perspectives

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Introduction

In recent years our understanding of venous thromboembolism (VTE) in the elderly has been increased by the availability of extensive epidemiological information from the RIETE registry (an ongoing, prospective registry of consecutive patients with acute, objectively confirmed, symptomatic deep vein thrombosis [DVT] or pulmonary embolism [PE]) [1–5] and from other studies such as the Worcester VTE study [6]. These studies have confirmed previous observations that elderly people are at a higher risk of VTE than younger ones, and that the risk rises rapidly with age above 60 years [6–8]. Furthermore, the prognosis of VTE worsens with age: after the occurrence of a VTE, elderly patients are more likely to experience major bleeding [6] or to experience fatal PE [1,3] (patients aged >80 and >90 years, respectively).

The frequency of renal impairment increases with age [2,9,10], and reduced renal function leads to the accumulation of some drugs resulting in a greater susceptibility to side effects [11] – an issue which complicates the treatment of elderly patients with anticoagulants. Indeed, there are no definitive guidelines or best practice statements for the anticoagulant treatment of elderly patients with renal impairment. The elderly may also be subject to further specific age-related diseases and risk factors for both thrombosis and bleeding, including a higher likelihood of comorbidities such as peptic ulcer disease, cardiovascular disease or malignancy; a higher likelihood of restricted mobility; a higher risk of falling and fractures; and an increased prevalence of polypharmacy, possibly involving other antithrombotic drugs such as antiplatelet agents. Management of elderly patients with VTE is therefore challenging. However, as randomised studies have not been conducted in this population, there are few publications available to guide physicians as they attempt to practise evidence-based medicine.

This review summarises the presentations and discussions at a meeting held in November 2010, entitled ‘Treating DVT and PE in the elderly – current perspectives’ (with updated information where relevant). The meeting was sponsored by LEO Pharma, manufacturers of the low molecular weight heparin (LMWH) tinzaparin. The meeting’s aims were to increase awareness of how elderly patients with VTE differ from other patient groups, and how best to treat them; to discuss current clinical data and possible implications for clinical practice; and to share experience between continents, countries and hospitals. Input was provided not only by haematologists but also by specialists in internal medicine and nephrology. Points about clinical practice that are not specifically referenced are the authors’ understanding of opinions that were expressed at the meeting.
Polypharmacy in the elderly

The elderly with VTE have progressively more concomitant diseases as they age [6]. It is not unusual for an elderly patient presenting with a need for VTE prophylaxis or treatment to already be receiving 12 or more other drugs, including antithrombotic agents such as antiplatelet drugs (e.g. aspirin, clopidogrel, NSAIDS) or novel anticoagulant drugs such as dabigatran, rivaroxaban, or apixaban. Indeed, antithrombotic treatment is becoming increasingly aggressive, with growing use of combination treatments, and combined antithrombotic treatment is associated with a high incidence of gastrointestinal bleeding [12]. The risk of upper gastrointestinal bleeding can also be increased by drugs given for indications not related to thrombosis, such as selective serotonin-reuptake inhibitors [13].

Whereas it may be relatively simple to describe the possible drug interactions between two or three agents, doing so between multiple drugs becomes almost impossible. For example, the number of drugs which should either not be co-administered with warfarin, or closely monitored, continues to expand [14]. A study of the use of warfarin in patients with atrial fibrillation showed that bleeding rates were much higher in patients aged ≥80 vs. those aged <80 years, and concluded that rates derived from younger cohorts underestimate the bleeding that occurs in practice [15]. It is difficult to know where to start, therefore, if asked by a general practitioner regarding an elderly patient on multiple medications: ‘What are the possible interactions with warfarin?’

The effects of polypharmacy can be particularly severe in ‘frail’ elderly patients, who are characterised by functional decline, loss of independence and increased mortality [16]. These patients are more vulnerable than fitter individuals to acute and chronic stressors, due to a reduced physiological reserve, and frailty is also correlated to inflammation and a pro-thrombotic state. Clearly, bleeding in these patients will have serious consequences.

For any physician prescribing anticoagulant treatment to elderly patients, there are some practical steps to prevent bleeding. It is crucial to use the correct drug and find the correct dose. Renal function, weight, and age must all be considered. Weight is worth mentioning in particular because for elderly patients it is often based on old records and thus over-estimated, resulting in the prescribing of drug doses that are too high. The duration of treatment with combinations of antithrombotic drugs should be
kept as short as possible. If platelet inhibitors are prescribed, concomitant use of a proton pump inhibitor, to minimise potential gastric bleeding, should be considered. When trying to reduce the risk of future events, this should always be weighed against the risk of bleeding. Patients’ full medication lists should be checked to see that they are correct and up to date. Drug interactions should be checked for, inasmuch as this is possible. When using warfarin physicians should be sure of the indication and of the desired international normalised ratio (INR).

In summary, prescribing anticoagulant or antithrombotic medication for elderly patients requires caution and vigilance.

Renal impairment in the elderly

Renal haemodynamics change with aging, due in part to atherosclerotic and glomerulosclerotic changes [17,18]. As a result, glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) decline. The most important point about renal function in elderly patients is that it is frequently over-estimated – in part because estimates are based on serum creatinine values. Serum creatinine values alone do not reflect kidney function in the elderly; an accurate assessment requires estimation of creatinine clearance (CrCl), which in turn provides an estimate of GFR. Several formulae exist to estimate CrCl values on the basis of serum creatinine levels, such as the Cockcroft–Gault formula or the Modification of diet in renal disease (MDRD) formula (Box 1). These two formulae cannot easily be ‘translated’, e.g. between recommendations, as they were calculated based on different populations. The Cockcroft–Gault formula has limitations (e.g. no correction for ethnicity) and many nephrologists prefer the MDRD. To date, however, most trials of anticoagulants have used Cockcroft–Gault to define the threshold of renal function for eligibility, and the MDRD does not allow calculation for very heavy or light patients. Until other classifications are widely used to define patient populations, therefore, it is wise to use the Cockcroft–Gault formula for making decisions on anticoagulant treatment.

Renal impairment, VTE, and the risk of bleeding are closely intertwined. The risk of VTE increases with severity of chronic kidney disease [19]. The RIETE Registry has shown that patients with CrCl <30 ml/min were more likely to experience major and/or fatal bleeding after a VTE [3] and that, in elderly patients, the risk of developing fatal bleeding increases with decreasing CrCl [2].
Due to this complexity, nephrologists are concerned about prescribing drugs to their patients with impaired renal function. Like all clinicians, they want drugs that are effective and well tolerated. Simplicity of administration is also important, because more complex regimens are likely to result in more errors and lower compliance.

**Current guidelines on the treatment of elderly/renally impaired patients with VTE**

LMWHs are the accepted initial treatment of choice for most patients with VTE [20]. For renally impaired patients, however, the picture is not clear. How should we treat these patients?

There are data for a considerable subset of elderly patients in trials on VTE prophylaxis and coronary indications (described in Hirsh *et al.* [11]). However, the population age in VTE treatment trials is considerably lower than the mean age of VTE patients in real-life clinical practice. Furthermore, most trials of the use of LMWH to treat VTE and cardiac indications have excluded patients with severe renal impairment [21]. The current American College of Chest Physicians (ACCP) recommendation is to use unfractionated heparin (UFH) over LMWH for patients with acute DVT and severe renal failure [11]. This is a grade 2C recommendation, i.e. a weak recommendation based on low-quality evidence.

The guidelines also recommend anti-Xa monitoring and/or dose reduction if patients are treated with LMWH, to ensure that there is no accumulation of anticoagulant activity. The recommended dose of enoxaparin in particular is 50% of the usual dose, although there are no data to show efficacy of this lower dose. No recommendations are made for dosing of other LMWHs [11]. Very similar recommendations have been made by other authors, such as Nutescu *et al.* [21].

In reality, monitoring LMWH treatment with anti-Xa levels is not an exact science. There is wide disagreement on the desired target levels, and they are not the same for all LMWHs [22]. This subject was extensively discussed at the meeting and it was concluded that anti-Xa monitoring is generally of little use, with two exceptions. The first is pregnancy; the second is renal impairment, where trough anti-Xa monitoring may be used to evaluate accumulation at the end of the dosing interval, if there is
concern that accumulation may occur. Monitoring of the activated partial prothrombin time (APTT) has no value in guiding treatment with LMWHs.

Evidence on the use of currently available drugs in elderly/renally impaired patients with VTE

LMWHs: The clearance of LMWHs with higher mean molecular weight is less dependent on renal function than it is for LMWHs with lower molecular weight [11]. LMWHs are therefore not interchangeable, and need to be considered individually. Studies have shown that tinzaparin (a LMWH with a relatively high mean molecular weight of 6,500 Da) does not accumulate in renally impaired patients at therapeutic doses, at least down to a CrCl value of 20 ml/min [23,24].

While the topic of this review is mainly treatment of VTE in the elderly, some data are available for prophylaxis. The PREVENT [25], DIRECT [26] and PROTECT [27] studies have indicated that a fixed prophylactic dose of dalteparin (mean molecular weight 5,700 Da) can be used without bioaccumulation or increased bleeding in the following patient groups: elderly patients (PREVENT); patients with renal insufficiency, including patients with end stage renal failure requiring haemodialysis (DIRECT); and critically ill patients (PROTECT). A small study also showed that, in renally impaired patients, tinzaparin did not accumulate at prophylactic doses, whereas enoxaparin did [28].

The trial by Mahé et al. mentioned above, was small [28]; only a few large head-to-head trials comparing different LMWHs have been undertaken [29,30]. These trials did not specifically consider elderly or renally impaired patients. As comparative trials are unlikely ever to be conducted in this population, treatment decisions have to be made based on available evidence. Many experts are firmly of the opinion that some patients currently die unnecessarily from VTE because thromboprophylaxis is under-used.

Warfarin: Bleeding with warfarin increases substantially with age [15,31]. In elderly patients the INR target remains the same as for younger patients, but this can be achieved with a reduced dose. Many hospitals therefore have algorithms for warfarin dosing in elderly patients, e.g. use of a starting dose of 3 mg for 3 days, after which the INR is checked.
**Newer anticoagulant drugs:** Fondaparinux [32] and dabigatran [33] are contraindicated in patients with CrCl <30 ml/min. Rivaroxaban can be used at 10 mg/day ‘with caution’ in elderly patients or those with renal impairment, but is contraindicated if CrCl <15 mL/min [33]. However, data on the safety of these drugs in older/renally impaired patients are scarce, and to date dabigatran and rivaroxaban have been approved only for prophylaxis, not therapy.

In patients who develop heparin-induced thrombocytopenia, the treatment options are fondaparinux, danaparoid, or bivalirubin.

**Available evidence: how does the IRIS study add to our understanding?**

The Innohep® in Renal Insufficiency Study (IRIS) compared the use of full, unadjusted-dose LMWH with APPT-adjusted UFH in an elderly population with renal insufficiency and acute DVT [34]. Patients with an acute DVT who were aged ≥70 years and with CrCl ≤30 ml/min, or aged ≥75 years and with CrCl ≤60 ml/min, were eligible; enrolment was not restricted by life expectancy. Thus, IRIS included ‘real-life patients’ often excluded from other trials.

Patients were randomised to open-label tinzaparin at a fixed weight-adjusted dose or APTT-adjusted UFH for at least 5 days. The randomisation was stratified by severity of renal insufficiency, so that in each treatment group approximately 25% of patients had CrCl ≤30 ml/min. Treatment with a vitamin K antagonist (VKA) was initiated between day 1 and day 3 and was continued for at least 90 days.

The primary endpoint was clinically relevant bleedings (CRBs) up to day 90 ± 5. Secondary endpoints were major and minor bleedings, and symptomatic recurrent VTE, both up to day 90 ± 5. Tertiary endpoints included death from any cause up to day 90 ± 5. CRBs up to day 12 ± 2 were also examined. All critical safety or efficacy events were adjudicated blindly by an independent Critical Event Committee.
A scheduled interim analysis showed a difference in mortality rates between the treatment groups; as a result, the study was closed early and the final analysis was performed on 537 patients who were followed for 90 days. The mean age was 83 years and mean CrCl was 39 ml/min. The treatment groups did not differ significantly with regard to CRBs at day 12 or at day 90, major or minor bleedings at 90 days, CRBs during SC treatment, or recurrent VTE. A prospective substudy in 87 of the tinzaparin-treated patients also showed that anti-Xa activity did not systematically increase, and that mean anti-Xa levels did not differ significantly between patients with severe renal impairment and those without [35]. Unexpectedly, however, there were more deaths with tinzaparin than with UFH (11.5% vs. 6.3%, respectively; p=0.035); this difference could not be explained by an excess of deaths due to bleeding or VTE.

The mortality curves did not diverge until approximately 20 days after tinzaparin/heparin treatment cessation. Furthermore, the 90-day mortality rate in the UFH group in IRIS (6.3%) was exceptionally low, compared with published data for similar patient populations (e.g. [1,3,5,6]), where reported rates have ranged from 11 to 25%.

In an attempt to find an explanation for the difference, a post-hoc multivariate analysis was done. According to this analysis, the excess mortality in the tinzaparin group was not correlated with treatment group. The presence of infectious disease, presence of ongoing malignancy, age ≥90 years, leg paralysis, presence of cardiac insufficiency and renal impairment strata were all statistically significantly correlated to mortality. All of these risk factors except renal impairment were over-represented in the tinzaparin group. Thus a viable explanation for the excess of deaths in the tinzaparin group is an unfortunate imbalance in baseline risk factors, with risk factors for adverse outcomes disproportionally present in tinzaparin treated patients; premature stopping of the study likely exacerbated this imbalance.

This pioneering trial was intended to show whether tinzaparin was as safe as, or safer than, UFH with regards to CRBs in elderly renally impaired patients. Due to its premature termination, the trial did not reach the sample size required to answer this question. What IRIS does tell us is that there are no apparent differences in bleeding complications between tinzaparin and UFH in the elderly, and it
confirms previous studies [23,24] showing no evidence of bioaccumulation of tinzaparin irrespective of renal function. The excess mortality in the tinzaparin group is unexplained and may have resulted from a chance between-group imbalance in baseline risk factors.

Case history workshops

The meeting included four parallel workshops which allowed participants to discuss how they would deal with different clinical scenarios. ‘Take-home messages’ from these workshops are presented in Box 2.

Conclusion

The treatment of elderly renally impaired patients with VTE is complicated by a higher innate risk of bleeding compared with younger patients, together with the frequent presence of concomitant conditions and polypharmacy. The cornerstone of initial treatment after an acute VTE in elderly patients, as in younger patients, remains UFH or LMWH. IRIS was a pioneering trial, performed in the very patients who have been excluded from previous trials, that was intended to shed light on whether tinzaparin is as safe as UFH in elderly renally-impaired patients. Unfortunately, the premature termination of the trial means that this question remains unanswered. IRIS did, however, show no difference in bleeding between patients treated with tinzaparin or UFH, thus adding to earlier pharmacological studies which showed no evidence of accumulation of tinzaparin in patients with renal impairment.

Decisions on anticoagulant treatment of this challenging patient group need to be made on the available evidence for each drug. It is also necessary to bear in mind that the patient’s concomitant medications may increase bleeding risk.
Box 1. Formulae for assessing renal function.

<table>
<thead>
<tr>
<th>Name</th>
<th>Calculation</th>
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<tbody>
<tr>
<td>Cockcroft–Gault</td>
<td>CrCl (ml/min) = ((140\text{-}\text{age [years]} \times \text{weight [kg]}) / (\text{serum creatinine [mg/dl]} \times 72))  Multiply by 0.85 if female</td>
</tr>
<tr>
<td>Modification of diet in renal disease (MDRD)(^a)</td>
<td>CrCl (ml/min/1.73 m(^2)) = 186 x (serum creatinine [mg/dl])(^{-1.154}) x age(^{-0.203}) Multiply by 1.212 if black; by 0.742 if female</td>
</tr>
</tbody>
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\(^a\)Many variations of the MDRD exist. The example quoted is a four-item abbreviated MDRD, found at: [http://www.kidney.org/professionals/KDOQI/guidelines_ckd/p5_lab_g4.htm. Accessed June 2011](http://www.kidney.org/professionals/KDOQI/guidelines_ckd/p5_lab_g4.htm).

Numerous online resources allow rapid calculation of these formulae to guide clinical practice (e.g. [http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm](http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm); [http://www.nkdep.nih.gov/professionals/gfr_calculators/idms_con.htm](http://www.nkdep.nih.gov/professionals/gfr_calculators/idms_con.htm); [http://www.patient.co.uk/showdoc/40001093/](http://www.patient.co.uk/showdoc/40001093/).
Box 2. Take-home messages from the case history workshops.

These messages are clinical opinions representing the discussions that took place.

An elderly patient and renal impairment

- Diagnosis can be difficult in elderly patients, and misdiagnosis is common.
- It is very important to assess bleeding risk before deciding on treatment.
- Thrombolysis carries special risks in the elderly.

An elderly renally impaired patient with cancer

- To allow for renal impairment the LMWH dose can be reduced, as was done in the CLOT study [36]. However, there is little evidence on the efficacy of reduced doses.
- Inferior vena cava filters should not be used unless clinically indicated (i.e. acute leg DVT and absolute contraindication to anticoagulation).
- Some health authorities encourage the use of long-term LMWH in cancer patients whereas others do not, and some specify reduced dose after the first month, whereas others do not.

Patients with renal impairment on haemodialysis

- Management of anticoagulation in haemodialysis-dependent patients is challenging because of a lack of data in this population.
- Patients with confirmed VTE need to be assessed for the benefit:risk ratio of anticoagulation, just as non-haemodialysis patients require this.
- Controversy exists as to whether UFH or LMWH is better to prevent dialysis circuit clotting.
- All anticoagulants should be used with increased care in patients with renal impairment on haemodialysis due to their increased risk of bleeding.

Prophylaxis in a patient with renal impairment

- The most important thing to do in deciding on prophylaxis is a proper risk assessment. Clinical judgement and individual assessment are key.
- There are no ideal tests to ensure that drugs will not accumulate in renal impairment.
- Issues in an individual patient’s medical history may make drug prophylaxis unfeasible; then mechanical prophylaxis has to be used.
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Conflicts of Interest
Alain Leizorovicz declares consultancies for Leo Pharma, GSK, Bayer, Sanofi Aventis and Boehringer Ingelheim. Mark Crowther declares chairing advisory boards for Leo Pharma, CSL Behring, Pfizer, Octapharma and receiving research funding from BI and LEO Pharma. Dr Crowther holds a Research Chair at McMaster University endowed by LEO Pharma and is a Career Investigator of the Heart and Stroke Foundation of Canada.

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