immunofluorescence test, which has been mastered only by a few\textsuperscript{[10]} . However, new tests have been developed for the diagnosis of acute infections and their applicability to chronic infections is an open question. It has been suggested that IgA and precipitated or trapped immunocomplexes possess a better predictive value than IgG antibodies\textsuperscript{[11,12]} . Other than IgA, Tavendale et al. also measured immune complexes in sera with the conglutinin method. Both tests were unable to predict events in years to come\textsuperscript{[9]}.

So far, we have not found a specific serological marker which would predict the future activity of \textit{C. pneumoniae} found in plaques. We know that it is very often ‘sitting there’ but what it is doing remains a question. A commercial, reproducible test using PCR from, e.g., circulating white blood cells, is lacking and in-house tests are variable in their results\textsuperscript{[13]} . In the future it is to be hoped that we will find diagnostic markers circulating in the blood which will indicate the amount of \textit{C. pneumoniae} activity in the body and, perhaps in future intervention studies, how well we have succeeded in eradicating the agent from vascular lesions. So far we only have non-specific markers of inflammation or autoimmunity, which, in combination with \textit{C. pneumoniae} markers, may be better predictors of future outcome\textsuperscript{[14,15]}.

P. SAIKKU
Department of Medical Microbiology,
University of Oulu,
Oulu, Finland

References


Moving beyond unfractionated heparin for acute coronary syndromes: Xeno’s Paradox revisited

See page 308, doi:10.1053/euhj.2001.2779 for the article to which this Editorial refers

If we’ve learned anything at all from the numerous clinical trials performed in recent years in patients with acute coronary syndromes, it is that there are a lot of things that can improve clinical outcomes in these patients. Low molecular weight heparins, direct thrombin inhibitors, thienopyridines, GP IIb/IIIa inhibitors, invasive management strategies; all of these have been shown to improve outcomes over ‘standard’ medical management.

In this issue, a report by Antman \textit{et al.}\textsuperscript{[1]} presents 1-year follow-up data from the patients in TIMI 11B...
and ESSENCE, two large-scale trials comparing the low molecular weight heparin enoxaparin to unfractionated heparin in patients with unstable angina. As we examine this report in more detail, three major questions arise: (1) ‘What is important in this paper?’; (2) ‘What are the clinical implications of these findings?’; and (3) ‘What additional questions remain?’

**What is important in this paper?**

The authors report 1 year follow-up in 6646 out of 7081 patients (94%) in ESSENCE[2] and TIMI 11B[3]. Enrollment in these trials was originally from 1994–1996 and 1996–1998, respectively, and both compared enoxaparin (1 mg . kg$^{-1}$ sc q 12 h x 2-8 days median 4-6 days) vs unfractionated heparin (titrated to activated partial thromboplastin times) in patients with unstable angina. While both trials involved similar patients, similar end-points, and generally similar dosing regimens, there are also some important differences between the studies, as summarized in Table 1. Short-term follow-up data on the pooled analysis of the two trials have already been published[4]. For the present analysis, long-term follow-up data were centrally adjudicated, and, as shown by the authors in Fig. 1 and Table 1 of their article, there were significantly fewer composite adverse events with enoxaparin (23-3% in enoxaparin vs 25-8% with unfractionated heparin; hazard ratio 0·88, $P=0·008$). All individual end-points showed a trend favouring enoxaparin, but only urgent revascularization as an individual end-point was significantly lower (13·2% with enoxaparin vs 15·2% with unfractionated

---

**Table 1 Comparison of TIMI 11B and ESSENCE**

<table>
<thead>
<tr>
<th></th>
<th>TIMI 11B (n=3910)</th>
<th>ESSENCE (n=3171)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enoxaparin dose acute</strong></td>
<td>30 mg iv bolus</td>
<td>[no bolus]</td>
</tr>
<tr>
<td></td>
<td>1 mg . kg$^{-1}$ sc q 12 h x 2-8 days median 4-6 days</td>
<td>1 mg . kg$^{-1}$ sc q 12 h x 2-8 days median 2-6 days</td>
</tr>
<tr>
<td><strong>Enoxaparin dose chronic</strong></td>
<td>40 mg q 12 h (&lt;65 kg) x 8-43 days</td>
<td>[no chronic Rx]</td>
</tr>
<tr>
<td></td>
<td>60 mg q 12 h (&gt;65 kg)</td>
<td></td>
</tr>
<tr>
<td><strong>UFH dose</strong></td>
<td>70 U . kg$^{-1}$ bolus</td>
<td>5000 U bolus</td>
</tr>
<tr>
<td></td>
<td>15 U . kg$^{-1}$ infusion (adjusted to aPTT 1-5-2-5 x control)</td>
<td>1000 U . h$^{-1}$ infusion (adjusted to aPTT 55-85 s)</td>
</tr>
<tr>
<td></td>
<td>median 3-0 days</td>
<td>median 2-6 days Rx</td>
</tr>
<tr>
<td><strong>Prior UFH</strong></td>
<td>Approximately 1/3</td>
<td>??</td>
</tr>
<tr>
<td><strong>Trough Anti-Xa</strong></td>
<td>0·5 U . ml$^{-1}$</td>
<td>0·6 U . ml$^{-1}$</td>
</tr>
<tr>
<td><strong>aPTT at 48 h</strong></td>
<td>Low — 7%</td>
<td>Low — 18%</td>
</tr>
<tr>
<td></td>
<td>In-range — 47%</td>
<td>In-range — 51%</td>
</tr>
<tr>
<td></td>
<td>High — 46%</td>
<td>High — 34%</td>
</tr>
<tr>
<td><strong>Median age (years)</strong></td>
<td>66</td>
<td>64</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Smoker</strong></td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>30%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Prior MI</strong></td>
<td>32%</td>
<td>45%</td>
</tr>
<tr>
<td><strong>Prior revasc</strong></td>
<td>25%</td>
<td>41%</td>
</tr>
<tr>
<td><strong>Hx CAD</strong></td>
<td>Allowed initially, dropped later</td>
<td>Allowed</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Within 24 h</td>
<td>Within 24 h</td>
</tr>
<tr>
<td><strong>ST depression</strong></td>
<td>72% (≥0-5 mm)</td>
<td>22% (≥1-0 mm)</td>
</tr>
<tr>
<td><strong>Normal ECG</strong></td>
<td>17%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Unstable angina</strong></td>
<td>59%</td>
<td>69%</td>
</tr>
<tr>
<td><strong>Non-Q MI</strong></td>
<td>35%</td>
<td>21%</td>
</tr>
</tbody>
</table>

UFH=unfractionated heparin; aPTT=activated partial thromboplastin time; MI=myocardial infarction; CAD=coronary artery disease.

**Figure 1** Xeno’s Paradox, in which the Greek hero Achilles and a tortoise are racing; the tortoise has a head start. Whenever Achilles gets to where the tortoise originally started out (1), the tortoise has moved forward (1a) to a new position. When Achilles gets to this new position (2), the tortoise has again moved forward (2a); this cycle continues for subsequent intervals (3, 3a, 4, 4a).
benefit (hazard ratio 0.80, \( P=0.016 \)). The event curves diverged early (in the first 3–4 days), and the absolute benefit present early on was still present at 1 year. The authors also noted the high number of subsequent clinical events that transpired over time in both groups. The superiority of enoxaparin over unfractionated heparin was largely a function of risk; in low-risk patients (0–2 risk factors, assessed by the TIMI risk scale\(^5\)) there was virtually no difference between unfractionated heparin and enoxaparin (hazard ratio 0.96, \( P=0.69 \); \( n=2101 \)); in medium risk patients (3–4 risk factors) there was moderate benefit (hazard ratio 0.87, \( P=0.04 \); \( n=3696 \)); in high-risk patients (5–7 risk factors) there was substantial benefit (hazard ratio 0.80, \( P=0.03 \); \( n=849 \)). More than two-thirds of the patients in the pooled analysis fell into the medium- or high-risk categories.

Interestingly, despite the perception that ESSENCE and TIMI 11B are ‘American’ trials, almost one-half of the patients in TIMI 11B (and approximately 35% in the two trials combined) were European patients; only about 15% of the patients in TIMI 11B (and approximately 21% in the two trials combined) were from the United States.

**What are the clinical implications of these findings?**

Simply stated, the primary finding of the study is that enoxaparin is significantly superior to unfractionated heparin in acute coronary syndrome patients. Does this mean that enoxaparin should broadly replace unfractionated heparin in all patients? Before we can make that leap of faith, two other key ‘what about . . . ’ questions arise. What about the cath lab and an invasive management strategy? What about IIb/IIIa antagonists? As is painfully obvious, despite the robust clinical results of the TIMI 11B/ESSENCE meta-analysis, the question of what to do with these findings and how to apply them to modern-day practice are much more complex and convoluted than simply ‘A is better than B’. Showing the superiority of enoxaparin over unfractionated heparin in this pooled analysis is not necessarily sufficient to change the ‘standard of care’ that we proudly maintain is so evidence-based. The problem with actually trying to practice ‘evidence-based’ medicine is that as we look for evidence relating to a new therapy vs ‘standard’ therapy, the current ‘standard’ is continuously moving forward, and in trials done just a few years ago can lag significantly behind currently available options.

This is exactly the dilemma of Xeno’s Paradox (Fig. 1), in which the classic Greek hero Achilles is racing a tortoise who has a head start. Achilles is much faster than the tortoise, but at time \( t \), when he gets to where the tortoise started out, it has moved forward. When he then arrives at the spot the tortoise was at time \( t \), it has again moved forward. So, according to the so-called paradox, how does Achilles ever actually pass the tortoise (which we all know he must) if it always moves forward? The resolution of this seeming conundrum is that the time interval for each incremental move by the tortoise is progressively shorter and shorter, reaching an asymptote at the time when the two are actually even. In the interval of time limited by this asymptote, he never does pass the tortoise, but as we shift our perspective to real-time, Achilles goes hurtling past the slow-moving tortoise.

Similarly, if we are unwilling to consider a change in the ‘standard’ of care because the standard against which a new form of therapy (such as low molecular weight heparin) was tested did not account for all of our modern-day therapeutic options, we handcuff ourselves because the ‘standard’ never really moves forward, and any new trials that include more up-to-date advances will themselves once again be out of date 2–3 years from now. We will never be able to catch the tortoise unless we can shift our perspective outside the ‘A-to-B’ comparison and take into account the real-time shifts in the so-called ‘control’ arm.

In my opinion, the major clinical implication of this study is that we need to be looking beyond unfractionated heparin and aspirin as a ‘standard’. We have a better form of therapy in low molecular weight heparin (particularly so in higher risk patients); we also have a lot of uncertainty about how to use low molecular weight heparins in those high risk circumstances that would also prompt us to use the newer modalities of GP IIb/IIIa blockers and an invasive management strategy not accounted for in ESSENCE and TIMI 11B.

**What questions remain?**

Three major issues remain as barriers to the more widespread uptake of low molecular weight heparins in acute coronary syndrome patients: (1) Are they safe to combine with GP IIb/IIIa antagonists?; (2) How do we use low molecular weight heparins in conjunction with an invasive management strategy?; and (3) what about the incremental cost?

In answer to the first question, data are beginning to emerge from preliminary studies such as ACUTE I\(^6\), ACUTE II\(^7\), NICE 3\(^8\) and NICE 4\(^9\) that suggest that low molecular weight heparins are at least as safe and effective as unfractionated heparin when combined with GP IIb/IIIa antagonists. Further data will be available when A-to-Z is completed, and this...
issue will be explored prospectively in the larger scale, randomized, efficacy-powered SYNERGY study of enoxaparin vs unfractionated heparin in high-risk acute coronary syndrome patients. SYNERGY will also help to directly confront the second question, adding to existing data on in-cath-lab procedural use of low molecular weight heparins from NICE 1\[^{[9]}\], NICE 4\[^{[9]}\], and a recent dalteparin pilot study\[^{[10]}\]. Additional data from Collet et al\[^{[11]}\] and NICE 3\[^{[8]}\] have provided observational experience in bringing patients forward to the catheterization laboratory, and on interventional procedures on low molecular weight heparin, without the use of unfractionated heparin. Despite these observational data, the ‘optimal’ initial antithrombotic therapy in invasively managed acute coronary syndrome patients has yet to be defined. Low molecular weight heparins are safe and effective, but despite the results of ESSENCE and TIMI 11B, we do not yet know whether they are truly better in the context of an invasive management strategy because, as yet, we have no direct, randomized, active control, efficacy-powered data. Hence the need for a trial such as SYNERGY.

Cost is another issue that assumes ever-increasing importance in modern-day health care. And yes, low molecular weight heparins cost more than unfractionated heparin. In low risk patients they provide no outcome benefit, so why use them? In these patients, the major impetus favouring low molecular weight heparins is one of convenience. They are easily administered, do not require monitoring, and do not require the level of nursing and medical attention seen with intravenous unfractionated heparin. The incremental drug cost of low molecular weight heparin is more than offset by avoiding intravenous infusions and activated partial thromboplastin time monitoring\[^{[12]}\]. At the high risk end of the spectrum, the cost-benefit of reducing clinical events tips the balance even further in favour of low molecular weight heparin.

Another thorny issue is whether there are meaningful clinical differences between the individual low molecular weight heparins, which are structurally unique compounds\[^{[13–16]}\].

That issue was not specifically addressed in ESSENCE or TIMI 11B, but these are in fact the only two large scale active-control trials that have shown a low molecular weight heparin (in this case enoxaparin) to be superior to unfractionated heparin, in contrast to FRIC\[^{[17]}\] and FRAXIS\[^{[18]}\] and other placebo-controlled studies\[^{[19,20]}\]. The inferiority or non-inferiority of one compound in relation to another can really only be objectively assessed with direct head-to-head studies. Until those are available, we have only the evidence from clinical trials, and our own individual experience to guide us.

So how are we supposed to move forward? How do we avoid the pitfalls of Xeno’s Paradox and adopt a more real-time view of our evolving standard of care? We are all looking for evidence, but the evidence we want is not always there for the circumstances we now confront. The long-term TIMI 11b/ESSENCE data are not terribly surprising; enoxaparin provides early clinical benefit over unfractionated heparin; this benefit is most manifest in high-risk patients, and is sustained over time. The challenge is not in the data, or even interpreting the data. The challenge is how we take the data and apply it to our ever-evolving practice.

Ultimately, we have to pass the slow-moving tortoise . . .

J. J. FERGUSON
St Luke’s Episcopal Hospital, Texas Heart Institute, Houston, Texas, U.S.A.

References


Electrocardiographic findings and global coronary risk assessment

See page 315, doi:10.1053/euhj.2001.2774 for the article to which this Editorial refers

In patients with overt clinical heart disease, the prevalence as well as the prognostic value of several kinds of electrocardiographical (ECG) changes are well documented and accounted for. Furthermore, in daily clinical practice or during routine examinations and health check-ups, physicians often deal with ‘non-specific’ ECG changes in asymptomatic individuals without any suggestion or symptoms of disease. These ‘minor’ abnormalities are often discarded as clinically meaningless receiving no further attention. Despite the cumulating evidence from numerous epidemiological studies that subclinical forms of heart disease are highly predictive regarding further development or complications, ECG changes that may be markers of an asymptomatic stage of the disease, rarely yield attention with respect to preventive measures.

One of the major problems in combining evidence from large-scale population based studies, is the comparability of study methods. This is particularly true for epidemiological studies with the resting electrocardiogram as the screening method. Differences in registration (e.g. number of leads), inaccurate readings and observer bias, inconsistencies in interpretation and classification of findings, and the nature of the underlying population and exclusion criteria, all compromise the comparability of large-scale ECG studies to a major extent. Despite these differentiating characteristics inherent to ECG studies, nearly all have in common that abnormalities observed on the resting electrocardiogram, either isolated or concomitantly, emerge as very powerful predictors for future cardiac events, independent of conventional cardiovascular risk factors[1–4].

In the current issue, Larsen and colleagues publish their findings obtained from their follow-up of the original cohort of the Copenhagen City Heart Study[5]. Based on Minnesota Coding criteria, they report on the association between ST depression, negative T waves, and left ventricular hypertrophy defined using voltage criteria only (ECG-left ventricular hypertrophy), and subsequent cardiac events in a large population-based cohort of Danish adults. They provide compelling evidence that these ECG items are associated with elevated risk and particularly that the joint occurrence of ECG-left ventricular hypertrophy in combination with ST-T changes carries the highest prognostic importance in both men and women.