of percutaneous coronary intervention\[11\], and as an adjunct to fibrinolysis (with streptokinase only)\[12\] validate continued interest in pursuing better thrombin inhibitors. Low molecular weight, active site thrombin inhibitors, (argatroban and melogatran) are currently approved (for HIT) or are in late stage clinical trials. In addition, new parenteral agents which block the coagulation cascade upstream of thrombin, by targeting Factor VII/tissue factor (tissue factor pathway inhibitor), Factor X (pentasaccharide and DX-9065a), or enhancing the Protein C pathway, all offer potential improvements in the therapeutic options for thrombin inhibition for patients with acute coronary disease. If clinical trials evaluate these novel compounds in conjunction with conventional treatments such as percutaneous coronary intervention, GP IIb/IIIa inhibitors and fibrinolytics, clinicians will be able to integrate these agents into current clinical practice. It is important to note that while clinical trials of the available antithrombins have thus far demonstrated important effects during the period of drug infusion, these effects are not consistently maintained following cessation of drug administration. The availability of an oral direct antithrombin permitting long-term antithrombin treatment would be of great benefit to the clinical cardiovascular community. Hence, the results of ongoing late-stage clinical trials studying the safety and efficacy of several oral antithrombins in a variety of clinical indications are awaited. Oral formulations may yield realistic opportunities for safe, chronic anticoagulation without the need for regular laboratory monitoring in patients at highest risk. Optimally, observations such as those in the study by Kottke-Marchant et al. will guide the clinical development of better thrombin inhibitors that will finally consign unfractionated heparin to the retirement it so richly deserves.

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References


Low molecular weight heparin: a bridge over troubled water

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Coronary artery thrombosis plays a major role in the development and complications of coronary atheroma aggravated by plaque rupture. Patients presenting with ST-segment elevation have a markedly improved coronary artery patency, reduced infarct size and, thereby, early and long-term mortality[11]. In patients without ST-segment elevation, antithrombotic therapy
invasive strategy\[9\]. Dalteparin or placebo was given
disease–2) trial in patients randomized to a non-
from a substudy of the FRISC-2 (Fast Revascular-
conservative approach\[6–7\].

Mechanical therapy for coronary artery thrombo-
sis, developed since the 1980s, has been a matter of
debate until recently. Primary angioplasty of the
infarct-related artery in patients presenting with
ST-segment elevation has proven to be superior to
in-hospital fibrinolytic therapy\[5\]. Also, in patients
presenting without ST-segment elevation an early
invasive strategy is beneficial compared to a more
conservative approach\[6–7\].

Early coronary revascularization requires a com-
plex infrastructure, which is only available in the
more affluent Western countries. In ST-segment
elevation myocardial infarction, time-to-treatment is
crucial, whereas in patients without ST elevation this
is not convincingly established. However, American
and non-American practices differ considerably. In
the United States, revascularization is usually per-
formed within 48 h after presentation of acute cor-
ony syndromes without ST-segment elevation, whereas outside the United States invasive treatment
is done later but usually within the first week. The
waiting time for coronary artery bypass surgery is in
general much longer than for percutaneous coronary
intervention. The reasons for this are logistical, but
also surgeons are reluctant to operate on patients with
evolving myocardial infarction without ST-segment
elevation, since mortality is unacceptably high in such
patients\[8\]. It is generally thought that patients await-
ing coronary revascularization in unstable coronary
disease face a risk of recurrent ischaemic events: a period of troubled water. Therefore, many
feel that prolonged antithrombotic therapy is war-
ranted in these patients. Once the procedure has
taken place, it is unlikely that patients benefit from
continued antithrombotic therapy thereafter\[6\].

In the current issue, Husted and colleagues report
from a substudy of the FRISC-2 (Fast Revascular-
ization during InStability in Coronary artery
disease–2) trial in patients randomized to a non-
invasive strategy\[9\]. Dalteparin or placebo was given
after hospital discharge, in which dalteparin showed a
significant benefit over placebo in the first 45 days,
which seemed to dissipate over the weeks thereafter.
In the current study, patients who underwent
 coronary revascularization were evaluated. Con-

dalteparin treatment reduced death and myocard-
dial infarction by 45 days very significantly by 57%,
and by 90 days this difference was still significant at
29%. These results are more favourable than in the
main analysis of dalteparin in a conservative strategy
per se. The authors conclude that low molecular
weight heparin can be used as a bridge to revascular-
ization in patients surviving acute coronary syndrome
without ST segment elevation.

Can these results be translated to the general prac-
tice of cardiologists taking care of patients with acute
coronary syndromes? The FRISC-2 study was a well-
designed and well-performed clinical trial with both
invasive and pharmacological hypotheses. Yet, the
data presented by Husted were not pre-specified and
were part of a post-hoc analysis. Therefore, the results
should be read with caution. It may be that patients
who needed revascularization were selected not only
on their clinical condition, but also on other less
well-known features. However, the randomization
procedure was successful and the treatment was
double-blind. Ideally, a subsequent randomized
placebo-controlled study should be performed with
low-molecular weight heparin in patients undergoing
late revascularization for acute coronary syndromes
without ST-segment elevation. However, since the pub-
lication of the FRISC-2 study such a trial is no longer
ethical\[6\]. Also the TACTICS TIMI-18 (Treat Angina
with aggrastat and determine Cost of Therapy with an
Invasive or Conservative Strategy) trial supports the
strategy of early rather than late invasive therapy\[7\].
Therefore, it is unlikely that the results of Husted will
be the subject of a prospective randomized trial.

Are there antithrombotic treatments other than
low molecular weight heparin which could support
patients awaiting revascularization for unstable
coronary artery disease? A clear alternative to low
molecular weight heparin is the use of oral anticoagu-
ants. Several recent trials have shown that oral
anticoagulants on top of aspirin may protect patients
after myocardial infarction or unstable angina\[10\].

Recently, the WARIS-2 (WArfarin ReInfarction
Study) trial in 3600 patients compared aspirin alone,
warfarin alone and their combination in patients
surviving acute myocardial infarction and clearly
showed a 30% reduction of the primary end-point
(death, stroke or myocardial infarction) by warfarin
over a 4 year period\[11\]. Yet, oral anticoagulation is a
cumbersome treatment which may become simpler
when self-adjustment of the international normalized
ratio has become routine\[12\]. A clear alternative to
oral anticoagulation on top of aspirin is dual anti-
platelet therapy in the form of aspirin plus clopi-
dogrel. A substudy of the CURE trial was the
PCI-CURE study. In this study, patients with acute
coronary syndromes without ST elevation were revas-
cularized while on clopidogrel or placebo, and it was
found that pre-treatment with clopidogrel significantly reduced the periprocedural event rate and also the long-term outcome. Interestingly, the patients benefited from clopidogrel before the revascularization, in the same way as in the CURE main trial.

Husted and colleagues have introduced a new way to better protect patients awaiting revascularization for unstable coronary artery disease: a bridge over troubled water. However, the therapeutic strategy is still not fully clear: is it low molecular weight heparin, oral anticoagulation, clopidogrel or a combination?

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Late is perhaps not . . . too late for primary PCI in acute myocardial infarction

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The short and long-term prognosis after myocardial infarction depends on infarct size, which itself depends on the quality and rapidity of reperfusion. Thus, quality and rapidity are the master words in terms of coronary recanalization.

Myocardial reperfusion can be achieved with either pharmacological means (fibrinolytic drugs) or mechanical means (percutaneous coronary intervention (PCI). In terms of quality, it is now well established that PCI is superior to thrombolysis. Normal anterograde flow (TIMI 3) can be obtained in around 90% of patients with balloon angioplasty alone and this has been further improved with the use of coronary stenting as demonstrated by several recent studies (PAMI-stent, PASTA, ESCOBAR[1–3]). Even the most effective fibrinolytic agents achieve TIMI 3 flow in only 55–60% of patients. The combination of a fibrinolytic agent with adjunctive therapy such as a GpIIb/IIIa receptor blocker may improve the early TIMI 3 flow rate (up to 72–75%). Nevertheless, the rate of TIMI 3 flow obtained with medical reperfusion is, by far, inferior to that routinely obtained with mechanical reperfusion i.e. by PCI.