The importance of VTE prevention after orthopaedic surgery

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In *The Lancet* today, Alexander Turpie and colleagues[1] present the findings from RECORD4 (Regulation of Coagulation in Orthopaedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism)—a component of four large phase III clinical trials in orthopaedic surgery that compared the oral, direct, and selective factor Xa inhibitor, rivaroxaban, with enoxaparin, a subcutaneously administered, indirect, and non-selective anticoagulant. The investigators detected a 3·19% absolute risk reduction (95% CI 0·71–5·67, p=0·0118; relative risk reduction 31·36%, 95% CI 7·50–49·06) in the primary efficacy outcome favouring rivaroxaban, with concomitant reductions in proximal deep-vein thrombosis (DVT), distal DVT, and non-fatal pulmonary embolism. Bleeding with rivaroxaban was higher than with enoxaparin, although this finding was not significant. Mortality rates, as expected, did not differ between treatment groups.

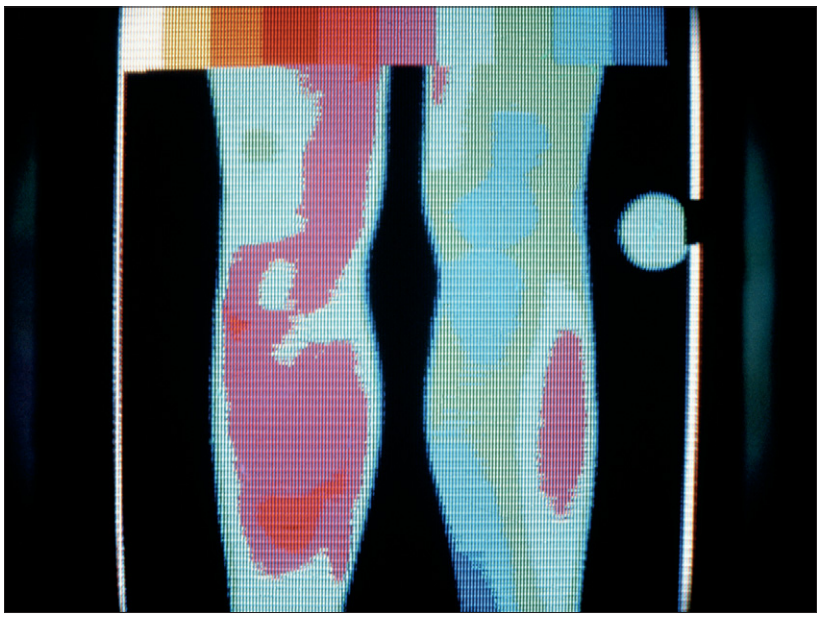
Although practising clinicians and surgeons recognise that venous thromboembolism (VTE) is potentially life-threatening and best avoided, a more globally relevant question from a patient's and health-care perspective is: "What is the overall effect of VTE after orthopaedic surgery?"

Compared with patients without postoperative VTE, those with VTE either remain in hospital for an extended period or are promptly readmitted. They need systemic anticoagulation for 6–12 weeks, exposed to its inherent risks, and can face substantial physical limitations during rehabilitation and recovery. In addition, people with VTE are more likely to remain out of work longer than anticipated, present to outpatient clinics or emergency departments, and endure substantial cost burden.[2,3]

In the intermediate to long term, the effect of VTE is equally as burdensome as the acute phase ramifications. Post-thrombotic syndrome and its attendant clinical and socioeconomic consequences,[4–6] the uncommon but highly physically and emotionally debilitating complex regional pain syndrome,[7] and recurring VTE[8] represent three disorders or events of great relevance to patients, health-care providers, and people who pay for health care.

The long-term consequences of VTE are being increasingly recognised and defined with clarity. An area of particular interest, and concomitant clinical relevance, considers the association between VTE, acute arterial cardiovascular events, and future malignant disease. In a large Danish cohort study,[9] patients with VTE had a two-fold increased risk of myocardial infarction or stroke during the first year, and the relative risks for arterial events remained raised during the subsequent 20 years of follow-up. The association between occult malignancy and VTE is well known. However, VTE as a potential precipitant of malignant disease represents a new paradigm, which Douketis and colleagues[10] recently introduced.

We must conclude, on the basis of the available evidence, that the overall effect of VTE after orthopaedic surgery is substantial. Accordingly, reducing the occurrence of VTE must continue to be a high priority in drug development, national health quality, best practice initiatives, and clinician-based care of patients. Clear progress has been achieved over the past decade, and oral drug-delivery platforms could represent a vital step forward. However, the pinnacle of care remains a goal worthy of ongoing investigation towards understanding the pathobiology of disease and defining widely translatable management strategies for patients at risk for VTE and related disorders.



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Thermogram of DVT

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I declare that I have no conflicts of interest.

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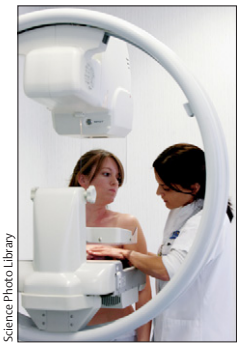
Unravelling the mystery of the TACT trial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In *The Lancet* today, Paul Ellis and colleagues[1] report the TACT randomised trial, the largest first-generation taxane study, in which they compared a standard adjuvant treatment (either eight cycles of fluorouracil, epirubicin 60 mg/m², and cyclophosphamide [FEC] or four cycles of epirubicin 100 mg/m² followed by four cycles of cyclophosphamide, methotrexate, and fluorouracil [E-CMF]) with an experimental treatment of four cycles of FEC followed by four cycles of docetaxel (FEC-D) as adjuvant chemotherapy for early breast cancer. Contrary to other adjuvant trials in which docetaxel was administered sequentially,[2–4] and the data from taxane meta-analyses,[5–7] TACT did not show any advantage with the sequential administration of docetaxel in the primary endpoint of disease-free survival.

What might be the reason for this discrepancy? A false-negative result (FEC-D actually being superior to the control treatment) is always possible in a phase III trial. But TACT was more than adequately powered, so this explanation is unlikely. Further, I agree with Ellis and colleagues that the very minor imbalance between treatment groups in subsequent adjuvant therapies (particularly aromatase inhibitors) probably did not affect the results. The inclusion in the trial of a population predominantly of patients with breast cancer whose tumours could have a low sensitivity to taxanes (ie, hormone-receptor-positive, HER2-negative) is also unlikely to be a reason for the results, because this population is similarly represented in other positive-outcome first-generation taxane trials. The effect of the diversity of regimens in the standard group on the final results of TACT is difficult to determine, although the authors did not find any statistically significant differences in treatment effects compared with control regimens.

TACT's results are particularly surprising because the experimental group included the sequential administration of full-dose docetaxel (100 mg/m² every 3 weeks), a schedule that has consistently shown efficacy in other breast cancer adjuvant trials.[2–4,8,9] Sequential administration of two cytotoxic drugs has several potential advantages compared with the same drugs administered concurrently, particularly the ability to deliver full doses. On the other hand, there is an important and often neglected disadvantage of sequential therapies: the drugs could be delivered in the wrong order. Thus the administration of the less effective drug (or regimen) first can jeopardise the efficacy of a more effective drug or regimen administered later. Compliance with adjuvant treatment decreases over time, especially in protracted regimens. As clearly shown in TACT, nearly 20% of the patients did not complete the scheduled four cycles of docetaxel in the experimental group. Nevertheless, the trial's sensitivity analysis did not reveal any relation between non-adherence and outcome and, therefore, non-compliance does not explain the unexpected results.

Studies in preclinical models (including myeloma, breast cancer, and other cancer cell lines) show that the exposure of tumour cells to anthracyclines, especially at suboptimum doses or schedules, can trigger a secondary resistance to multiple drugs, including the taxanes,