

Backgrounder

Current anticoagulant therapies

Anticoagulant drugs have significantly reduced the risk of thromboembolic events and associated death across a range of medical conditions, with notable decreases in:

- ◆ The risk of death after a heart attack/myocardial infarction
- ◆ The number of strokes with subsequent disability or death in atrial fibrillation (AF)¹
- ◆ The incidence of venous thromboembolism (VTE) after orthopaedic surgery¹

The first anticoagulant, heparin, was discovered in 1914, and was commercialized as unfractionated heparin (UFH) nearly 30 years later. Vitamin K antagonists (VKAs) – primarily warfarin – were first approved for use as anticoagulants in humans in 1954, having been well established as effective rat poison. The low molecular weight heparins (LMWHs) were introduced in the 1980s and, together with UFH and VKAs, are the mainstay of anticoagulation therapy worldwide.

Despite the benefits of current therapies, there is a clear clinical need for new anticoagulants, due to:

- ◆ The trend for shorter hospital stays and early discharge for many procedures, such as hip or knee replacement surgery
- ◆ Changing population demographics, giving an increasing number of people presenting with risk factors for thromboembolic disorders²

Intravenous/subcutaneous anticoagulants: UFHs, LMWHs, and the parenteral, indirect Factor Xa inhibitor fondaparinux. These drugs are effective and generally well tolerated and indicated for short-term use up to ~30 days

- ◆ Their use is limited by parenteral administration,³ which is impractical for many patients, especially if they are unable to self-administer the drug, as they will need to visit, or be visited by, nursing staff frequently

Oral anticoagulants: VKAs (warfarin) are the only oral agents approved for long-term use. Warfarin requires close monitoring to ensure that the level of anticoagulation – measured using the international normalized ratio (INR) – is within

the target range. Studies show that less than 50% of patients on warfarin are within the therapeutic range in the community setting.⁴

- ◆ If the INR is >3, anticoagulation is too high, and patients are at increased risk of serious and fatal bleeding
- ◆ If the INR is <2, anticoagulation is inadequate, and patients are at increased risk of a thromboembolic event

This need for regular monitoring, together with its many food and drug interactions, make warfarin a difficult drug to manage well,⁵ one of the main reasons why so many patients are not being treated according to guidelines.

The oral anticoagulant ximelagatran is approved only for short-term use.⁶ This drug failed to gain approval in the US because of safety concerns.

Who requires anticoagulation therapy?

Patients at risk of a thromboembolic event fall into several broad categories, usually characterized by the underlying medical conditions:

Major orthopaedic surgery

- ◆ Without preventive treatment with an anticoagulant, approximately 50% of patients undergoing elective total hip or knee replacement develop VTE⁷
- ◆ The number of patients undergoing major orthopaedic surgery is set to rise [Figure 1]. With prophylaxis, the risk of deep vein thrombosis (DVT) after major orthopaedic surgery falls to between 15% and 20%¹

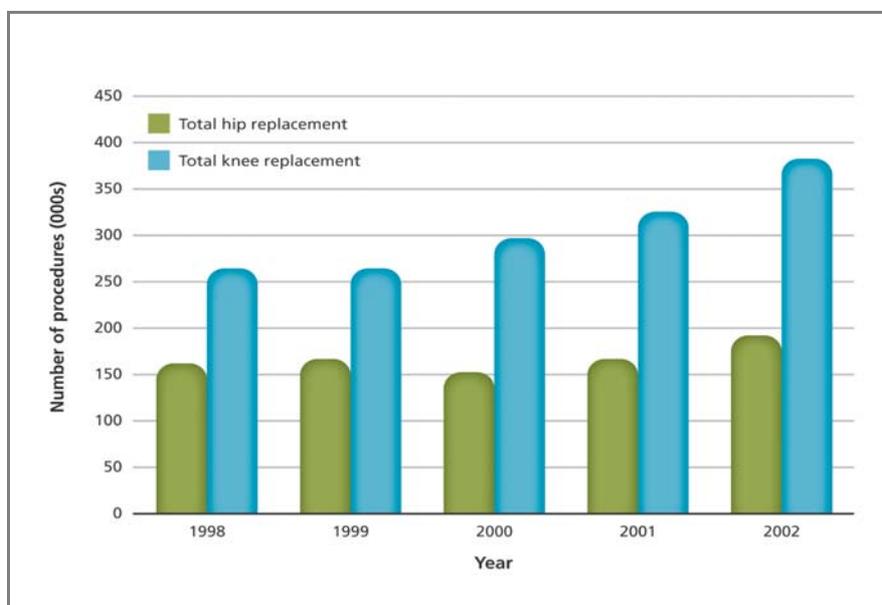


Figure 1. Number of joint replacement procedures in the US, 1998–2002.⁸

- ◆ Recent guidelines recommend extended anticoagulation in high-risk patients for up to 35 days¹

- ◆ Due to the decreasing length of hospital stay after orthopaedic surgery, much of this anticoagulant therapy will be administered out of the hospital setting, highlighting the need for a predictable oral anticoagulant with no requirement for monitoring

Atrial fibrillation (AF)

Primarily a disease of the elderly, AF places patients at a high risk of stroke⁹

- ◆ Oral anticoagulation with VKAs (warfarin) is recommended for medium- to high-risk patients to prevent stroke and other thromboembolic events¹⁰
- ◆ The risk of DVT in acute stroke is also reduced by anticoagulant therapy¹¹

In clinical practice, many patients, especially the elderly, do not receive any, or adequate, anticoagulation.¹²

- ◆ Studies have shown that warfarin is under-prescribed and poorly managed; only 27–53% of eligible patients receive the drug, and 50–60% of patients on warfarin do not receive the correct dose^{13,14} [Figure 2]. This puts patients at increased risk of either fatal bleeding or VTE/stroke

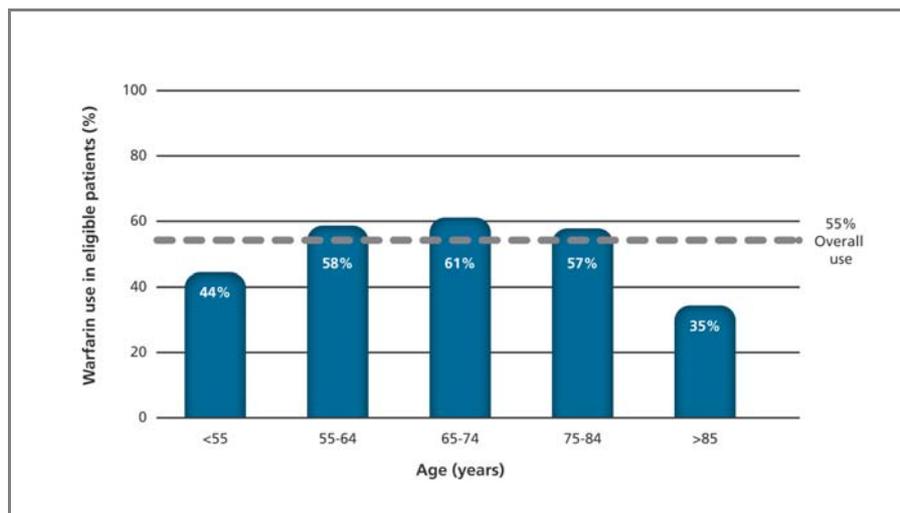


Figure 2. Warfarin use in 11,082 ambulatory patients with atrial fibrillation. Reproduced from Hart RG *et al. Ann Intern Med.* 1999;131:492–501, with permission from the American College of Physicians, Philadelphia, PA, USA.

- ◆ The monitoring costs of warfarin are high and increasing: estimates suggest that up to 63% of the cost is attributable to monitoring.¹⁵ Patients must attend regular coagulation clinics to ensure that their INR is within the target range, and so that dose adjustments can be made if required

In the absence of an alternative, current ACCP guidelines recommend the use of warfarin for patients with sustained AF, who are elderly or have certain risk factors, with a target INR of 2.5 (range 2.0–3.0).¹⁰

Acute coronary syndromes

These are numerous heart conditions that carry a high risk of morbidity and mortality.

- ◆ Short- to medium-term anticoagulation therapy with LMWHs or UFHs, in addition to antiplatelet therapy, is recommended for patients with unstable angina and after certain types of myocardial infarctions (heart attacks)¹⁶

In addition...

Chronic medical illnesses, such as congestive heart failure, chronic obstructive pulmonary disease and cancer, place patients at an increased risk of VTE compared with the general population.⁷

- ◆ Long-term anticoagulation using VKAs is associated with higher rates of recurrent VTE and bleeding in patients with cancer than in non-cancer patients¹⁷
- ◆ Results from the CLOT study showed that patients who received LMWHs had a significant decrease in recurrent VTE compared with patients who received heparin or VKAs¹⁸

Many other risk factors place people at risk of a VTE, including: obesity; immobility due to prolonged bed-rest or long-haul flights; circulation or heart problems; the contraceptive pill; and hormone replacement therapy.⁷

Treatment of VTE

Despite the use of preventive strategies, 15–20% of patients undergoing major orthopaedic surgery develop a DVT or pulmonary embolism, and require treatment.

- ◆ As the only approved oral drug in this indication, warfarin must be used with a LMWH/UFH until the appropriate INR is reached (generally at least 5 days), due to its slow onset of action; moreover, extended treatment strategies are poorly defined, and the optimum duration of therapy remains unclear.

Again, due to the need for dose adjustment and regular monitoring, warfarin – though effective – is a less than ideal therapy in this setting.

What is needed to improve care?

An innovative approach would combine the effectiveness of current treatments with:

- ◆ Fixed dosing ⇒ no dose adjustment in different populations to simplify prescribing
- ◆ Oral dosing ⇒ no need for injections; convenient to take, especially in an outpatient setting and long term
- ◆ Predictable pharmacology ⇒ reduced risk of drug–drug and food–drug interactions, providing more-predictable anticoagulation without the need for monitoring
- ◆ Fast, predictable anticoagulation without the need for regular monitoring ⇒ a lower risk of under- or over-coagulation, which is reassuring for the physician, patient, and care group
- ◆ A wide therapeutic window to increase the safety margin
- ◆ Effective, with a good safety profile and a low risk of bleeding ⇒ the benefits of treatment outweigh the associated risks

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