ORANGE Study

ORal **AN**ticoagulant a**GE**nt associated bleeding events reporting system study

Dr Peter MacCallum and Dr Laura Green

Barts and the London School of Medicine and Dentistry, Queen Mary University of London
Barts Health NHS Trust, London
NHS Blood and Transplant, London

Description

The ORANGE study is a three year prospective observational study collecting data on the management and clinical outcome of patients who develop major bleeding whilst on oral anticoagulants (OACs) across the UK (*IRAS Ref: 105050, UKCRN Study ID:15322*).

The most detrimental complication of all OACs is the potential development of major bleeding, particularly intracranial haemorrhage (ICH), leading to significant mortality and morbidity. Whilst there is an antidote for warfarin, none exists for the three new NICE-approved OACs and hence it is imperative for studies like ORANGE to monitor outcomes and evaluate the efficacy of reversal methods, with a view to developing better bleeding management strategies for the future.

Sponsorship

The ORANGE study is sponsored by Queen Mary University of London and funded by the British Society for Haematology.

Aim and objectives

The ORANGE study is three-year study whose aim is to pave the way for the establishment of a national reporting system for oral anticoagulant agent associated bleeding events.

Its primary objective is to ascertain the proportion of patients who develop major bleeding while on oral anticoagulants (OACs) and who: (a) present with intracranial haemorrhage (ICH); and/or (b) die within 30 days of the event.

In addition the effectiveness of products such as prothrombin complex concentrate (PCC) will be assessed - in terms of clinical outcome - in treating major bleeding associated with OACs; the coagulation abnormalities at presentation of major bleeding will be characterised and any associations between clinical outcomes and the management of major bleeding will be assessed.

Context

The most detrimental complication of all OACs is the potential development of major bleeding, particularly intracranial haemorrhage (ICH), leading to significant mortality and morbidity which, in turn, lowers the benefit-risk ratio of anticoagulation therapy (Linkins et al, 2003).

The reported annual rate of major bleeding with oral anticoagulant therapy in recent clinical trials of warfarin versus the new OACs in atrial fibrillation varied from 1.2% to 3.6%, while that of ICH was less than 1% (Connolly et al, 2009; Granger et al, 2011; Patel et al, 2011).

Unlike warfarin, whose anticoagulant effect can be wholly reversed by prothrombin complex concentrate (PCC), there is currently no antidote for the new OACs. Since there have been no studies to inform the management of bleeding associated with these new OACs, attempts to reverse their activity will understandably rely on existing strategies. It is anticipated that reversal for the new OACs will be at best partial and associated bleeding outcomes may therefore be worse than those associated with warfarin.

Further, one of the major side effects of administering products like PCC, Recombinant Activated Factor VII (rVIIa) or Factor Eight Inhibitor Bypassing Activity (FEIBA) is the potential elevation of thrombotic risk in patients who are already predisposed to such outcomes. Therefore, it is imperative that we conduct studies to monitor outcomes and evaluate the efficacy of reversal methods, so as to develop better bleeding management strategies for the future. It should also be recognised that the clinical outcome of major bleeds for NHS patients on warfarin are uncertain despite the existence of national guidelines that recommend interventions known to reverse the effects of warfarin on the coagulation system. Based on extrapolation of data from clinical trials and the estimated 1million UK patients on OACs, there are likely to be around 20,000 major bleeds per year related to OAC use within the NHS.

The Orange study began recruitment on 1 October 2013 and will continue until 31 December 2016, with a recruitment target of at least 2250 cases. There are currently 11 hospitals across the UK participating in the study and we are open to new sites.

Methods

The ORANGE study is a prospective observational study collecting information across the UK, over three years, on the management and clinical outcome of patients who develop major bleeding whilst on OACs (*IRAS Ref: 105050, UKCRN Study ID:15322*). It has been funded by the British Society for Haematology and has received significant buy-in from haematologists throughout the UK who advise on local management of oral anticoagulant-related major bleeds.

Results and evaluation

The Orange study began recruitment on 1 October 2013 and will continue until 31 December 2016. There are currently 11 hospitals across the UK participating in the study and we are open to new sites.

If you would like to find out more about the study, or are interested in joining, please contact the study coordinator at **BHNT.Orangestudy@nhs.net** for more information.

Discussion points

Oral anticoagulants are being increasingly used for stroke prevention in atrial fibrillation and long-term management of venous thromboembolism because of their proven efficacy. However, they carry a small but significant risk of major bleeding, including intracranial haemorrhage and fatal bleeding.

The NICE-approved new oral anticoagulants have significant advantages over warfarin, particularly in terms of patient convenience, and are being increasingly introduced. However, they lack an antidote at present in the event of major bleeding and therefore evaluation of the outcomes of major bleeding in routine clinical practice and of current management strategies are important.

Even for warfarin, where long-established reversal strategies are available, outcome data following major bleeding are lacking and further study is required to optimise emergency care.

The possible thrombotic effect of reversal strategies in individuals on oral anticoagulants (and who are therefore predisposed to thrombosis) requires evaluation, as does the effect of co-morbidities on the outcomes of major bleeding in real-world practice.