Institution: University of Glasgow

Unit of Assessment: Unit 1; Clinical Medicine

Title of case study: Changing clinical guidelines and government policy on VTE prevention among women

1. Summary of the impact

Approximately 25,000 people in the UK die each year from venous thromboembolism (VTE); furthermore, VTE affects 1 in 100,000 women of childbearing age and causes one-third of all maternal deaths. Thrombophilia, pregnancy and the use of oral oestrogens can all place women at increased risk of VTE when compared with other individuals. University of Glasgow researchers quantified the probability of VTE among at-risk women and analysed the benefits and cost-effectiveness of thrombophilia screening. Their research is cited in the recommendations and evidence bases of leading national and international clinical guidelines. This work also galvanised an overhaul of VTE prevention policy within NHS Scotland by emphasising the need for regional health boards to implement and audit standardised in-house protocols and provide accessible patient information on VTE.

2. Underpinning research

University of Glasgow researchers have acknowledged expertise in blood-clotting research, women's health, systematic review (evidence synthesis), risk assessment and health economics. This knowledge was applied to quantify risk of venous thromboembolism (VTE) and determine whether identifying thrombophilia in at-risk groups would be clinically beneficial and cost-effective.

Thrombophilia increases the risk of VTE

Thrombophilia is a broad term used to describe an increased tendency of blood to clot; this condition may be heritable or else result from another medical issue. Within the UK population, heritable thrombophilias ('factor V Leiden' and 'prothrombin 20210') affect 1 in 20 and 1 in 50 individuals of European background, respectively. The prevalence of antiphospholipid syndrome (an acquired form of thrombophilia) is around 2–4%. Individuals with thrombophilia are at greater risk of developing a clot within a deep vein than people without this condition. If this clot becomes dislodged and travels elsewhere in the body, a potentially life-threatening event (pulmonary embolism) can occur. The combination of deep-vein thrombosis and pulmonary embolism is referred to as VTE. In addition, pregnancy or the intake of oral oestrogen preparations, such as combined oral contraceptives (COCs) or menopausal hormone replacement therapy (HRT), can also place women at a higher risk of VTE. In 2001, University of Glasgow researcher Prof Gordon Lowe demonstrated that the levels of three thrombotic factors associated with VTE were more likely to be increased among menopausal women who received HRT orally rather than through the skin.[1] Women not taking HRT were included as the comparator group.

Who should be screened for thrombophilia?

VTE is an avoidable condition. Clinicians have, therefore, come under increasing pressure to identify at-risk women and offer them preventative treatment (thromboprophylaxis). Two thrombophilia screening strategies have been considered. Universal screening involves testing all individuals within a particular population to identify unrecognised disorders (that is, before the onset of any symptoms). By contrast, targeted screening is conducted among only those individuals who are thought to be at increased risk based on their medical or family history. In 1997, a study led by Prof Ian Greer of the University of Glasgow showed that universal screening for thrombophilia during pregnancy was unlikely to be useful for preventing VTE.[2] His team evaluated 72,000 pregnancies and found only 62 confirmed VTE events. Of the 62 affected women, 50 underwent screening for factor V Leiden, which was detected in only 4 cases. These data suggested that the level of risk was too low to support the screening of all pregnant women.

TREATS study group defines VTE risk and the need for targeted screening among women

The National Institute for Health Research recognised the importance of quantifying the value of targeted screening of high-risk women for clinical practice and policy decision-making; this organisation therefore issued a call for research proposals. The Thrombosis: Risk and Economic

Assessment of Thrombophilia Screening (TREATS) team – a group of experts in thrombosis, haemostasis and health technology assessment led by Greer – won the commissioning bid. Between 2002 and 2006, the TREATS team used hypothetical modelling methods to evaluate populations of women known to be at risk of VTE. Their key findings are summarised below:

- Significant risk factors for pregnancy-associated VTE, as well as for adverse pregnancy outcomes (including miscarriage and restricted growth of the foetus), correlate with different types of heritable or acquired thrombophilia.[3,4]
- There is a substantial risk of VTE among women taking COCs compared with other at-risk populations, although taking into account the potential number of women who may be affected, the absolute number of women at risk is low.[3,5] Thus, screening at-risk women before prescribing COCs is unlikely to be cost-effective, as this strategy potentially prevents only three VTE events for every 10,000 women screened.[3,5]
- Women with thrombophilia who also take COCs are 5-15 times more likely to develop VTE than those without thrombophilia; a similar effect was found among women taking HRT.[3,6]

Key University of Glasgow TREATS researchers: Olivia Wu (Research Associate, 2001–2008; Reader in Health Economics and Health Technology Assessment, 2008–present); Ian Greer (Professor of Obstetrics and Gynaecology, 1991–2007); Gordon Lowe (Professor of Vascular Medicine, 1978–2009; Honorary Senior Research Fellow, 2009–present); Isobel Walker (Honorary Professor, 2005–present); Peter Langhorne (Professor of Stroke Care, 1994–present); Lindsay Robertson (Research Assistant, 2006–2007). **External members of the TREATS steering committee:** Peter Clark (Ninewells Hospital, Dundee, UK; deceased); Mike Greaves (University of Aberdeen, UK); Sara Twaddle (Health Improvement Scotland, UK).

3. References to the research

1. Lowe GD *et al*. Different effects of oral and transdermal hormone replacement therapies on factor IX, APC resistance, t-PA, PAI and C-reactive protein—a cross-sectional population survey. *Thromb Haemost*, 2001; **86:** 550–556.
2. McColl MD *et al*. Risk factors for pregnancy associated venous thromboembolism. *Thromb Haemost*, 1997; **78:** 1183–1188. PDF available on request.
3. Wu O *et al*. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. *Health Technol Assess* 2006; **10:** 1–110. doi:10.3310/hta10110.
4. Robertson L *et al*. Thrombophilia in pregnancy: a systematic review. *Br J Haematol* 2005; **132:** 171–196. doi:10.1111/j.1365-2141.2005.05847.x.
5. Wu O *et al*. Screening for thrombophilia in high-risk situations: a meta-analysis and cost-effectiveness analysis. *Br J Haematol* 2005a; **131:** 80–90. doi:10.1111/j.1365-2141.2005.05715.x.
6. Wu O *et al*. Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. *Thromb Haemost* 2005b; **94:** 17–25. doi:10.1160/TH04-11-0759.

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National Institute for Health Research. *Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study* (July 2002-April 2006, £119,211); awarded to Ian Greer.

4. Details of the impact

It has been suggested that thrombophilia screening may help to identify women at risk of VTE and provide an opportunity to intervene with thromboprophylaxis. Nevertheless, as with any testing strategy, the potential benefits must be weighed against the potential harm of screening-related anxiety and the adverse effects of thromboprophylaxis among women who are either genuinely at risk or who may be misdiagnosed as being at risk. Furthermore, substantial investment in healthcare, such as large-scale screening, must demonstrate value for money to ensure that limited resources are appropriately deployed. The need to provide direct, evidence-based guidance

to clinicians about risk stratification and screening is therefore paramount. University of Glasgow research into VTE risk among women has provided substantial insight into this issue – TREATS data influenced the development of clinical guidelines and recommendations both in the UK and internationally and shaped the VTE prevention strategy of NHS Scotland.

TREATS informs recommendations on patient stratification for VTE risk

Medical societies

The UK Royal College of Obstetricians and Gynaecologists (RCOG) have produced three clinical guidelines on VTE risk citing TREATS research:

- Green-top guideline 37a on pregnancy (November 2009) cites Robertson *et al.*[4] as level 2++ evidence for the recommendation that pregnant women with asymptomatic heritable thrombophilia (i.e. those showing no symptoms) should be stratified by degree of risk, taking family history and other clinical risk factors, such as age and weight, into account.[a]
- Green-top guideline 40 on COCs (July 2010) cites Wu *et al.* 2005b[6] as level 1- evidence against routine screening for thrombophilia before starting COCs.[b]
- Green-top guideline 19 on HRT (May 2011) cites Wu *et al.* 2005a[5] as level 2+ evidence against universal screening for heritable thrombophilias before starting HRT.[c] University of Glasgow investigator Prof Isobel Walker was a member of this guideline committee.

Walker was also a member of the writing group tasked by the British Committee for Standards in Haematology (BCSH) with developing a guideline on testing for heritable thrombophilia (April 2010).[d] These guidelines cite two TREATS papers:

- Wu *et al.* 2005b[6] is cited as evidence for the recommendation against screening before prescribing HRT or COCs unless a high-risk thrombophilia has been confirmed in a relative showing symptoms.
- Robertson *et al.*[4] is cited in the section on preventing VTE during pregnancy, with the recommendation for targeted screening of asymptomatic women with a family history of VTE triggered by pregnancy or use of COCs.

The American College of Chest Physicians (ACCP) guidelines on VTE during pregnancy were published in February 2012.[e] Data from Robertson *et al.*[4] is cited as follows:

- Tables 3 and S10 list factors the ACCP recommends clinicians use to identify women at elevated risk of VTE after caesarean delivery (Robertson *et al*. was one of seven studies cited). Recommendation 6.2.2 states that women with at least one major risk factor or two minor risk factors qualify for thromboprophylaxis (Grade 2B).
- Table 7 outlines the risk of VTE among pregnant women with heritable thrombophilias (Robertson *et al*. was one of 11 studies cited). Recommendations 9.2.1-9.2.3 state that thromboprophylaxis should be considered only for pregnant women with both copies of the gene affected for factor V Leiden or prothrombin 20210 regardless of their family history and for women with other heritable thrombophilias and a family history of VTE (Grade 2B and 2C).
- Table 9 summarises the risk of pregnancy complications among women with heritable and acquired thrombophilias (Robertson *et al*. was the only study cited). For women with a history of recurrent early miscarriage, screening for antiphospholipid syndrome is advised (recommendation 10.2.1, Grade 1B) whereas screening for heritable thrombophilias is not advised (recommendation 10.2.2, Grade 2C).

The ACCP recommendations are endorsed by several other US medical societies, including the American Society of Hematology and the American College of Obstetricians and Gynecologists.

Government bodies

The Scottish Intercollegiate Guidelines Network (SIGN) has responsibility for developing evidence-based clinical guidelines for NHS Scotland. In addition, SIGN takes a proactive approach to dissemination and implementation of its guidelines, campaigning for inclusion in national strategies and action plans. Named individuals within each regional Scottish health board are recruited to promote new and updated SIGN guidelines and to draw up plans for their subsequent implementation. SIGN guideline 122 on prevention and management of VTE was published in

December 2010.[f] Walker was a member of the guideline development group, with Lowe participating in the literature review. This guideline cites Wu *et al.* 2006[3] and Robertson *et al.*[4] as evidence for the evaluation of VTE risk associated with pregnancy, HRT or COCs. These papers are also cited in recommendations advising against routine screening for thrombophilias because it is neither cost-effective nor indicated. In the 3 months following publication, 77,263 copies of SIGN 122 were downloaded; in addition, 1,803 copies of the junior doctor audit activity based on this guideline were downloaded between April 2011 and April 2013.[g]

TREATS highlights the need for a Scotland-wide policy on VTE prevention

In light of their expertise on VTE risk, the TREATS researchers were commissioned by NHS Quality Improvement Scotland (now Healthcare Improvement Scotland) to assess the national VTE prevention strategy. This inspection (undertaken in 2007) identified unacceptable deficiencies and substantial variation in guideline implementation, audit and clinical practice. The key findings of this audit were later summarised in the *British Journal of Haematology* (2010); this paper also included an analysis of audit activity in England.[h]

As a result of the 2007 TREATS audit, the Chief Medical Officer for Scotland and NHS Quality Improvement Scotland contacted all 14 Scottish health boards to request a report on their efforts to write up-to-date standard operating procedures for VTE prevention that were based on SIGN recommendations. A summary report of this exercise, published in May 2008 and citing the TREATS audit, suggested that implementation of these national guidelines was still a work in progress for many health boards.[i] However, a follow-up report in December 2008 found that all health boards "*provided reasonable reassurance that the actions originally outlined in the May 2008 report have continued to be implemented and, in some Board areas, completed*."[i] In March 2010, the thrombosis charity Lifeblood presented a report to the Scottish Parliament on VTE prevention in NHS Scotland that included an audit it had conducted as a follow-up to the original TREATS inspection.[j] The Lifeblood audit showed that 11 of the Scottish health boards had a written policy in place for VTE; 13 had policies for mandatory risk assessment of all inpatients, with 6 boards undertaking routine reassessments; and 5 conducting regular audit of their risk assessment policies. These findings confirmed that marked improvements had occurred in Scottish VTE prevention policy since deficiencies were first highlighted by TREATS in 2007.

The TREATS audit also stressed the need for consistent and accessible patient information on VTE as part of the Scotland-wide policy for preventing this condition.[h,i] The Scottish Government therefore provided Lifeblood with funds to develop a leaflet for dissemination via general practitioners to promote awareness of VTE among their patients.[k] The Lifeblood leaflet covered risk factors for VTE, including pregnancy, use of oral oestrogens and family history of thrombophilia. In March 2008, 50 copies of this leaflet were mailed to every GP practice in Scotland (approximately 1,000 practices in total), a campaign that featured in the Scottish press.[l] The leaflet was also made freely available to download from the Lifeblood website.

5. Sources to corroborate the impact

a. RCOG Green-top guideline 37a, 2009 (see ref 47, subsection 4.2 and Table 2a, pg 11-13)
b. RCOG Green-top guideline 40, 2010 (see ref 58, section 6, pg 9)
c. RCOG Green-top guideline 19, 2011 (see ref 74, section 6, pg 7)
d. BCSH guideline [doi:10.1111/j.1365-2141.2009.08022.x], 2010 (see pg 215-216)
e. ACCP guideline [doi:10.1378/chest.11-2300], 2012 (see ref 151, e708S and e715S-e721S)
f. SIGN guideline 122, 2010 (see refs 64 and 69, section 3.2, recommendations 3.3 and 7.2)
g. SIGN guideline No. 122 download metrics – available on request
h. TREATS audit summary, 2010 [doi: 10.1111/j.1365-2141.2010.08080.x]
i. NHS Quality Improvement Scotland implementation and follow-up reports (May 2008, pg 2; December 2008, pg 3)
j. Lifeblood Scottish VTE audit, 2010 (see pg 2-3 and Tables 5, 8, 10 and 13)
k. Lifeblood patient information leaflet, 2008
l. Media coverage of the Lifeblood patient information leaflet mail drop, 2008