NICE National Institute for Health and Care Excellence

2023 exceptional surveillance of venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism (NICE guideline NG89)

Surveillance report

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Surveillance decision

We will not update NICE's guideline on venous thromboembolism in over 16s.

Reasons for the decision

A new trial [GAPS trial (Shalhoub et al. 2020)] compared a combination of low molecular weight heparin (LMWH) plus anti-embolism stockings (AES) versus LMWH alone and found LMWH alone to be non-inferior in venous thromboembolism (VTE) reduction at 90 days post-surgery. This trial recruited non-orthopaedic, elective surgery patients. Patients with some of the highest risk factors for VTE (such as a history of VTE or thrombophilia); or with certain features in the procedure or history requiring them to have extended prophylaxis were excluded. This trial did not stratify or conduct subgroup analyses based on different types of surgical procedures.

The trial's findings do not affect the current recommendations. The guideline recommends considering either a pharmacological prophylaxis or a mechanical prophylaxis as an alternative if there are bleeding risks for the surgical procedure. The option of using both a mechanical and pharmacological prophylaxis, rather than only 1 type of prophylaxis is limited to certain circumstances.

For patients undergoing bariatric or other procedures in the abdominal area, the recommendation was to start a mechanical prophylaxis on admission. If an individual patient has VTE risks which outweigh the risk of bleeding, a pharmacological option such as LMWH should be offered as an additional prophylaxis method. A similar approach is recommended for procedures where the risk of bleeding is important (cranial, spinal, thoracic, or cardiac surgery), except that the recommendation is to consider rather than offer these options. The choice of wording used reflected the strength of the evidence base supporting the recommendations and emphasised balancing the risks of VTE and bleeding in individual patients.

As the NICE guideline limits the use of combination prophylaxis to specific circumstances, it will not be necessary to update it. The new evidence does not provide evidence to support the replacement of mechanical prophylaxis with pharmacological prophylaxis as single therapy.

Overview of 2023 surveillance methods

NICE's surveillance team checked whether recommendations in NICE's guideline on venous thromboembolism in over 16s remain up to date.

The surveillance process consisted of:

- Feedback from topic experts via a questionnaire.
- Examining related NICE guidance and quality standards and NIHR signals.
- A search for ongoing research.
- Examining the NICE event tracker for relevant ongoing and published events.
- Literature searches to identify relevant evidence.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.
- Consulting on the proposal with stakeholders.
- Considering comments received during consultation and making any necessary changes to the proposal.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Evidence considered in surveillance

The GAPS trial

The GAPS trial (Shalhoub et al. 2020) was identified through NIHR. This study was first published in the BMJ in May 2020, and a full report was available in December 2020. The trial was a multicentre, non-blinded non-inferiority trial conducted in 7 centres across the UK between May 2016 and January 2019. The non-inferiority margin was defined as a 3.5% VTE event reduction in the LMWH only arm.

In this trial, patients aged 18 and over, due for elective surgery and eligible for

thromboprophylaxis (at least 1 thrombosis risk on the Department of Health risk assessment tool) were recruited. Patients with 1 risk factor were considered as moderate risk, and those with more than 1 risk factor were considered as high risk. A minimisation algorithm that incorporated centre, sex and risk of VTE (moderate versus high risk) was used. Patients were not stratified by the types of surgical procedures at randomisation.

The trial excluded patients who required extended prophylaxis according to the NICE guideline (such as major abdominal cancer surgery patients, or orthopaedic surgery patients), or had certain clinical factors which put them at a higher risk of VTE (such as pregnancy, requiring braces or casts, known thrombophilia or thrombogenicity, previous VTE, fitted with an inferior vena cava filter) or required IPCD (intermittent pneumatic compression device) beyond the post anaesthesia recovery area. Therefore, most patients who had orthopaedic surgery, or were at a higher risk of VTE, were excluded.

The primary outcome measured was VTE occurring within 90 days of surgery, defined as either a deep vein thrombosis (DVT) detected by whole leg ultrasound at 14 to 21 days post-surgery, or symptomatic pulmonary embolism (PE) or DVT confirmed by imaging and verified by blinded experts up to 90 days post-surgery. The other outcomes included all-cause mortality, major bleeding, and adverse effects from AES.

The type and brand of LMWH and AES used in this trial varied according to local practice. LMWH were given for the period of admission according to manufacturers' recommended doses. Patients who were randomised to the combination prophylaxis group also received AES providing 18 mmHg compression at the ankle level and were asked to wear AES for the duration of hospital admission. The trial report stated that the AES could be fitted at the time of admission or immediately post-operatively in accordance to local practice and to facilitate pragmatism. However, there is no information provided about the percentage of patients fitted with AES on admission (as recommended by the NICE guideline) versus those who only received it post-surgery.

GAPS trial study results

Of 11,679 patients screened, 1,905 (16.3%) were randomised into the trial, and 1,858 were included in the intention-to-treat (ITT) analysis, 1,780 declined and 1,304 were missed from being approached about participation in the study, while 6,690 (57%) patients were ineligible. The most common reason was day surgery (20.8%). Slightly over one-quarter of all screened participants were ineligible due to characteristics related to increased VTE risks. See table 1.

Table 1 Reasons for exclusions from trial

-	Number of participants	Percentage
Total number of participants screened	1,1679	100%
Total number of participants ineligible	6,690	57.3%
Reasons for ineligibility (some participants had more than 1 reason for exclusions):	-	0.0%
Day case	2,427	20.8%
Patients requiring thromboprophylaxis to be extended beyond discharge	1,270	10.9%
Patients having IPCD beyond theatre and recovery	682	5.8%
Contraindications to low LMWH or high risk of bleeding	690	5.9%
Individuals requiring therapeutic anticoagulation	643	5.5%
Contraindications to AES	345	3.0%
Previous VTE	331	2.8%
Lack of capacity	290	2.5%
Not 65 years of age and not at high risk of VTE	244	2.1%
Clinical team did not give agreement	168	1.4%
Surgery cancelled	134	1.1%
Documented or known thrombophilia or thrombogenic disorder	110	0.9%
Contraindications to LMWH: high risk of bleeding	21	0.2%
Aged under 18 years	14	0.1%
Pregnant	7	0.1%
Application of a cast or brace in theatre	7	0.1%
Patients requiring inferior vena cava filter	6	0.1%
Unknown	23	0.2%

-	**Number of participants**	**Percentage**
Total number of patients declined	1,780	15.2%
Did not want to wear stockings	18	0.2%
Did not want to use LMWH	5	0.0%
Others (not related to intervention option)	1,757	15.0%

Of the patients included in the ITT analysis, 70% (n=1,292) received surgery in the abdominal area. See table 2.

Table 2 Types of surgical procedures received

Types of surgical procedure	**LMWH plus AES**	**LMWH**
Total participants randomised	940	948
Number of participants receiving surgery (ITT population)	921	937
General: upper GI	289 (31.4%)	293 (31.3%)
O&G	163 (17.7%)	160 (17.1%)
General: Lower GI	116 (12.6%)	106 (11.3%)
Urology	79 (8.6%)	86 (9.2%)
Total abdominal area	647 (70.2%)	645 (68.8%)
General (no details provided in paper)	54 (5.9%)	50 (5.3%)
General surgery: breast	50 (5.4%)	54 (5.8%)
ENT	43 (4.7%)	44 (4.7%)
Neurosurgery	26 (2.8%)	36 (3.8%)
Plastics	21 (2.3%)	18 (1.9%)
Orthopaedics	17 (1.8%)	11 (1.2%)

Types of surgical procedure	LMWH plus AES	LMWH
Cardiothoracic	1 (0.1%)	3 (0.3%)
Vascular	1 (0.1%)	2 (0.2%)
Other	61 (6.6%)	74 (7.9%)
Total other procedures	274 (29.8%)	292 (31.2%)

More than 80% of participants received the interventions allocated (80.0% in the LMWH alone group and 79.8% in the LMWH plus AES group). More than 95% AES used were below-knee stockings. Patients were considered fully compliant for LMWH if they received all prescribed LMWH doses. Compliance with AES was defined as good if participants wore stockings for at least 75% of their hospital admission. About 80% of participants were rated as having full compliance with LMWH, or good compliance with GCS.

VTE within 90 days occurred in 1.4% (13 out of 921) of patients in the LMWH plus AES arm compared to 1.7% (16 out of 937) of patients in the LMWH arm: risk difference of -0.30% (95% confidence interval -0.65% to 1.26%). The risks of bleeding complications were 9/1,566 (0.57%) among participants who had received LMWH, and 1/160 (0.6%) among participants who did not receive any LMWH, 6.4% (50/787) of participants who received LMWH, and AES had related complications; 82% (41 participants) of these were discomfort.

Implications and limitations of GAPS trial study findings

The trial is the first major randomised controlled trial (RCT) involving AES in surgical patients in recent years and conducted within the NHS. The study's findings suggest that there is little advantage in offering combination prophylaxis, compared to only LMWH to patients undergoing elective surgery. While some commentators had observed that the number of VTE events (29/1,958 or 1.5%) in this study is relatively low, this has to be interpreted with caution; only 16.3% of screened participants were recruited into this trial, and more than a quarter of screened participants were not eligible due to reasons related to a higher risk of VTE. Participants with additional risks of VTE (such as known thrombophilia or previous VTE) who may benefit from combination prophylaxis were excluded. Furthermore, both intervention arms received an effective pharmacological prophylaxis.

The current NICE guideline was published while the GAPS trial was underway and recommendations about the choice of prophylaxis have changed. Combination prophylaxis is no longer recommended for most types of non-orthopaedic elective surgery procedures, and only remains an option for certain types of procedures if the risk of VTE is high and outweigh the risk of bleeding in an individual patient. Therefore, a significant portion of participants in this trial would no longer be considered for combination prophylaxis according to the current NICE guideline. Without a stratification according to the types of surgery and relatively low event rates, it is difficult to extrapolate the study's findings according to surgical procedure types where combination prophylaxis remains an option for higher risk patients.

Although compliance was considered as full for LMWH and good for AES for more than 80% of participants, it is not possible to eliminate this as a factor affecting the observed effectiveness. The AES compliance report is self-reported. Furthermore, participants who received AES in this trial could have it fitted either on admission or after surgery (the current NICE guideline recommended on admission) and there was no information on how many only initiated AES after surgery.

Focused literature search

Search and selection strategy

We searched for new evidence related to the combination of LMWH plus AES versus AES alone in patients with elective surgery in the abdominal area.

We found 154 studies in a search for RCTs and systematic reviews published between 1 June 2017 and 9 June 2022. However, none of the studies retrieved met the inclusion criteria considered by the NICE guideline, published in 2018.

Ongoing research

We checked for relevant ongoing research. Of the ongoing studies identified, we found 1 RCT on AES versus no AES in surgical patients with low thrombosis risk, and 1 protocol for a systematic review of the baseline risk of VTE and major bleeding in patients with general and gynaecologic surgery. These have the potential to affect recommendations. The publication of the results of these studies will be monitored. Once results are available, the impact on current recommendations will be evaluated as quickly as possible. These

studies are:

- Examining the benefit of graduated compression stockings in the prevention of venous thromboembolism in low-risk surgical patients: a multicentre cluster randomised controlled trial
- Systematic reviews of observational studies of risk of thrombosis and bleeding in general and gynaecologic surgery: introduction and methodology.

In addition to the studies on the prophylaxis strategy, we also followed up on the status of the recommendation for research in the NICE guideline on what is the accuracy of individual risk assessment tools in predicting the risk of VTE and risk of bleeding in people admitted to hospital. There is a major study funded by NIHR, and the initial results were published in the BMJ in 2021 (Horner et al. 2021). The review concluded that it is uncertain which risk assessment model (RAM) is optimal for assessing the risk of VTE and variation exists in their composition of risk factors and thresholds for high and low risk. The full NIHR report is yet to be published.

Intelligence gathered during surveillance

Views of topic experts

In this exceptional review, we contacted 11 topic experts who were members of the guideline committee for the NICE guidelines or recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their speciality and had an interest in VTE. The topic experts completed a questionnaire about the impact of the GAPS trial on the guideline and current clinical practice. Seven topic experts responded: 2 vascular surgeons, 1 haematologist, 1 vascular consultant nurse, 1 thrombosis and haemostasis consultant nurse, 1 colorectal surgeon and 1 bariatric surgeon. Two of the respondents were also investigators in the GAPS trial.

All topic experts responded that, based on the new evidence reported in the GAPS trial, the recommendations in the NICE guideline should be updated. One of the main considerations is the costs of AES to the NHS if it is not effective.

However, as there is a mix of patients with different surgical procedures included in the GAPS trial, the experts seemed to differ in their interpretation of the trial and how it should be implemented. Some seemed to have misinterpreted the GAPS trial widely across all

elective surgery patients and the effectiveness of AES when used without LMWH. The GAPS trial did not suggest that LMWH is superior to AES as monotherapy. Nevertheless, there were suggestions of stopping the use of stockings (in all patients) or only limiting AES to patients with LMWH contraindication or other clinical factors which would have excluded them from the GAPS trial. Two of the respondents (who were involved in the GAPS trial) were aware that some trusts have changed policies and stopped stockings in surgical patients inappropriately whereas the others noted that there is no change in policies in their local areas. The rationale the topic experts provided includes concerns about the costs of AES to the NHS, the lower baseline risk of VTE shown in recent reviews (of orthopaedic patients only). The experts also pointed out that a survey also suggested varied interpretations and implementation of the GAPS trial by individual trusts (Lawton et al. 2022). In addition, there seem to be some variations in practice, as some of the responses implied that AES is often used in combination with LMWH in most elective surgery patients, and AES is regularly offered to most elective surgery patients, regardless of risk factors.

Information considered when developing the guideline

The evidence review on risk assessment was unable to identify a risk assessment tool or model that can accurately predict the risks of VTE and bleeding. Therefore, the guideline did not specify which tool should be used or the choice of prophylaxis on the risk scores. Instead, the risk assessment approach emphasised balancing VTE risks against adverse effects of prophylaxis. Clinicians have a choice of using the Department of Health VTE risk assessment tool (2010), or other validated risk assessment tools.

Recognising that the type of surgery received is an important factor affecting the risk of VTE, clinical health economics data were analysed and interpreted based on the type of surgery received by study participants. Unlike earlier versions of VTE prophylaxis guidelines, extrapolation of evidence from one surgical population to another was minimal. This change in evidence interpretation approach led to a change in recommendations; the current guideline recommends considering using either a pharmacological prophylaxis (or a mechanical prophylaxis if there are bleeding risks) for most types of non-cancer and non-orthopaedic elective surgical procedures. The choice of recommendation wording (offer versus consider) reflects the certainty of the evidence base supporting the recommendation and whether it applies to every patient or only to patients with certain risk profiles.

For the non-orthopaedic, elective surgery population, the largest body of evidence was in abdominal surgery. There was data from 67 RCTs, and 11 of these RCTs were published after the year 2000. A network meta-analysis (NMA) was conducted for the outcomes DVT, PE and major bleeding to identify the most effective VTE prophylaxis strategy. 48 RCTs were included in the NMA for the outcomes of DVT, 26 for PE and 24 for major bleeding. The NMA showed that combination prophylaxis strategies using both pharmacological and mechanical interventions were more clinically beneficial for reducing DVT compared to pharmacological or mechanical interventions as standalone interventions. LMWH initiated post-operatively in combination with IPCD was ranked as the most clinically effective prophylaxis in the NMA for DVT.

Therefore, the recommendations are to offer a mechanical prophylaxis option, and if the VTE risks outweigh the bleeding risks in an individual patient, another pharmacological prophylaxis should be offered in addition to the mechanical prophylaxis. The same recommendations were made for bariatric surgery, based on the extrapolation of evidence from the abdominal surgery group (due to the site of the surgery), and the concerns that this group of patients are often at an increased risk of VTE due to obesity.

As there was less data for surgery, thoracic surgery and cardiac surgery and there are some similarities, data from abdominal surgery was considered as indirect evidence. For these surgical procedures, the recommendations were to consider a mechanical prophylaxis if the patient has an increased risk of VTE and if the VTE risks outweigh the risk of bleeding in an individual patient, consider adding a LMWH (or fondaparinux if LMWH is contradicted). Similar recommendations were also made for certain surgical procedures where bleeding is an important risk (such as intra-cranial and spinal surgery), and an addition of LMWH to AES may provide additional VTE prevention.

Equalities

No equalities issues were identified during the surveillance process.

Stakeholder consultation

We received consultation responses from 8 stakeholders, which included 4 professional organisations, 1 patient organisation, 1 hospital trust and 2 commercial companies.

See appendix A for stakeholder consultation comments and our responses.

Of the stakeholders, 2 agreed with our proposal to not update the guideline based on the GAPS trial. Of the 6 stakeholders who thought the guideline should be updated, 3 provided suggestions that are out of scope of this surveillance review. These suggestions included considering a new trial on aspirin in orthopaedic surgery patients (this study is being assessed by NICE), and concerns about clarity or the wording of the recommendations, implementation challenges, and other areas of the guideline such as risk assessment and prophylaxis in gynaecology.

Of the stakeholders who thought that the guideline should be updated based on the trial, 1 suggested that the study is hard evidence showing that AES have no clinical benefit, and strongly urged the committee to reconsider their evidence on mechanical thromboprophylaxis, to reflect that the benefits of IPC are clear but that there is no evidence to support AES. The other stakeholder who disagreed with the proposal not to update the guideline suggested that clarity is needed around the use of AES, as clinicians find the recommendations around AES unhelpful as the advice differs for different specialities. This stakeholder was also concerned that since the publication of the trial, many centres have stopped stockings usage in medical and obstetrics specialities and some have also stopped in surgery as the evidence for stockings is mostly very old, and the trial did support the use of stockings in surgical specialities included in the study. One stakeholder suggested that there is very little evidence to support their use generally and stronger statements would facilitate withdrawal of use (with consequent cost savings). However, these concerns are more suggestive of misinterpretation and implementation issues of the current NICE guidelines and misinterpretation of the impact of the GAPS trial.

All three stakeholders also referred to the implementation issues, such as those found in the NHS GIRFT-Thrombosis report from 2021, which suggested that inadequate funding for a VTE prevention team (only 22% of surveyed trusts have 1), and variations in prophylaxis methods used.

There were no equality issues specific to the prophylactic choices in non-orthopaedic elective surgery patients. One stakeholder noted the concern of inadequate funding for a VTE prevention team found in the GRIFT report, while another suggested that the alternatives to people who refuse heparins (due to porcine origin) should be stated in the guideline.

See ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual for more details on our consultation processes.

Overall decision

After considering the evidence, stakeholder feedback, intelligence and the impact on current recommendations, we decided that it would not be appropriate to recommend updating the guideline based on this study alone. Instead, we will be monitoring this area for more studies especially those related to surgical procedures in the abdominal area, the risk of VTE in current NHS practice, and VTE risk assessment/stratification.

In the absence of accurate risk stratification tools, extrapolating the overall findings of this study to the specific groups of elective surgery patients is difficult as risks may differ based on the type of procedure. Furthermore, the suggestions that the risk of VTE in surgical patients is now low in the NHS (and therefore, combination prophylaxis is not needed) were based mainly on non-UK based, orthopaedic surgery data only. The variation of interpretations and actions taken to implement the findings of this trial by topic experts and trusts probably reflects the challenges of interpreting this study and this is confirmed by the feedback received from some of the stakeholders during the consultation.

It is concerning that several stakeholders and topic experts had expressed the opinion that the GAPS trial showed that AES is not effective and should be withdrawn. It is important to emphasise this trial should not be taken as evidence that AES is ineffective, and the 1.5% incidence of VTE events observed as evidence that the risk of VTE is low in current NHS practice. The 1.5% incidence of VTE events was observed in a population that had excluded people who are most at risk of VTE and had more than 80% full compliance (for example, received all prescribed LMWH doses) of a pharmacological agent known to be effective. As the trial evaluated the effects of adding AES to LMWH; it should not be interpreted as evidence that AES is not effective when used on its own. The trial results suggested that adding AES to patients who are on LMWH probably offer no additional benefit for most elective surgery patients (without specific risk factors which put them at high risk of VTE).

In conclusion, despite the topic experts and the general impression from some stakeholders that the GAPS trial findings would necessitate the update of the NICE guideline, we do not think it does. The current guideline does not recommend combination prophylaxis for most of non-orthopaedic, elective surgery procedures; it recommends considering 1 type of prophylaxis (either a pharmacological option such as LMWH, or a mechanical option, such as AES) and the choice depends on the bleeding risks associated with the type of procedure, and individual risk factor. Combination prophylaxis is

recommended or considered only in situations where the individual's increased risk of VTE still outweigh the risk of bleeding from the use of pharmacological prophylaxis despite the use of a mechanical prophylaxis. Therefore, a guideline update is not proposed at this point.

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