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Anticoagulation UK	Guideline	General	General	Rec 1.9.3/4. Welcome addition to guidelines.	Thank you for your comment and support regarding this matter.
Anticoagulation UK	Guideline	General	General	Critical that the review pathway from diagnosis to three-month period is adequately provided for to encourage patient's understanding and knowledge of ongoing risk, importance of staying on treatment and well – being and lifestyle to reduce recurrence where possible.	Thank you for your comment and support regarding this matter. The committee agreed that it was important to involve the patient in the decision-making process and understood the risks and benefits as fully as possible when reviewing treatment.
Anticoagulation UK	Guideline	18	18 - 21	1.4.8. If an individual is continuing with anticoagulation therapy post 3-month review, a full discussion must be undertaken with the patient to advise on the clinical rationale for a switch from one DOAC to another. A patient who is prescribed one treatment may feel apprehensive in changing to another treatment and this must be taken into consideration as to not cause anxiety and challenges around adherence and compliance. There may also be local directives around the first line treatment options for treatment and prevention of VTE which will then conflict with these recommendations… the priority must be keeping the patient optimally treated from a clinical perspective.	Thank you for your comment. The recommendations (1.4.1) on reviewing anticoagulation treatment mention discussing the benefits and risks of continuing, stopping or changing the anticoagulant with people who have had 3 months of anticoagulation treatment. From recommendation 1.4.8 the first option is continue taking the same treatment. This recommendation also mentions the need to take the person with VTE's preferences and clinical situation into account. There is therefore no reason that an individual will be forced to change treatment if they do not wish to do so and it is not clinically advantageous for them to do so.
Anticoagulation UK	Guideline	19	17 - 19	1.5.2. NHS Standardised alert cards should be available with prescribers not relying on the manufacturers alert cards provided within the medication boxes. ACUK has been part of a working group to review the current Anticoagulation patient	Thank you for your comment and this information.

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				information for all anticoagulation therapies (warfarin and DOACs). Currently with NHS Improvement.	
Bayer plc	Guideline	General	General	The NICE guidelines development manual (last updated 2018) suggests that clinical guidelines should not revisit areas already evaluated under the technology appraisal process, stating that *"a guideline committee cannot usually publish its own recommendations on health technologies covered by published or in development health technologies guidance"*, and also that *"when related technology appraisal guidance is identified, the usual approach is for the guideline to make a recommendation to follow the technology appraisal recommendations with a link to where these appear in the NICE Pathway"*. As acknowledged in the draft guideline, technology appraisals have been published assessing the clinical and cost effectiveness of the DOACs (TA341, TA327, TA354, TA287 and TA261), all of which are recommended as options for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. Re-reviewing the evidence and carrying out further analyses for these anticoagulant therapies is a duplication of effort and represents a significant waste of public resources. We therefore suggest that this guideline should reference the relevant published technology appraisals, and not make further	Thank you for your comment. This update of the VTE guideline acknowledges that technology appraisals (TAs) exist for the DOACs and, as a result, that they are all options for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. As you note, the manual states that 'a guideline committee cannot usually publish its own recommendations on health technologies covered by published or in development health technologies guidance'. However, section 8.1 of the guidelines manual also states that: 'If needed, a brief explanation can be included in the guideline recommendation, for example, if it covers the sequencing of treatments recommended in technology appraisals. Any explanation needs to be agreed with the technology appraisals team at NICE'. As noted within the Guidance Executive Technology Appraisal Review Proposal paper, it was within the scope of this update to decide how to include the TAs and this document also notes that the 'clinical guideline will also be able to place these treatments into the appropriate clinical context'. A core function of NICE's approach and its guideline committees is to examine the cost effectiveness of treatment options to support the NHS to make the best use of its limited resources.

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				recommendations in accordance with NICE's own published process manual.	
Bayer plc	Guideline	18	5 - 12	Recommendation 1.4.8, regarding the continuation of anticoagulation treatment beyond 3 months, includes the suggestion that if the current treatment is a direct-acting oral anticoagulant other than apixaban, consider changing to apixaban. The uncertainties regarding the cost-effectiveness of apixaban vs rivaroxaban for the treatment and secondary prevention of VTE also apply here, and so for consistency within the guideline we suggest that this recommendation should be amended to state "…if the current treatment is a direct-acting oral anticoagulant other than apixaban *or rivaroxaban*, consider changing to apixaban *or rivaroxaban".*	Thank you for your comment. This recommendation has been amended to clarify that for most people, assuming the drug is already well tolerated, the first option should be to continue with the same treatment. If it is not well tolerated or the person has preferences to change and the person is currently taking a DOAC, changing to apixaban should be considered. The committee agreed that there are uncertainties surrounding the trials for the extended treatment of VTE and tried to reflect this uncertainty in the strength of the recommendation ('consider' rather than 'offer') and by limiting the recommendation to a specific group of people. For the base case cost-effectiveness analysis in which no sequencing of treatments was considered, uncertainty about the data informing the relative effectiveness (driven by differences in the initial treatment trials) led to a recommendation prioritising the more cost-effective options (apixaban and rivaroxaban). However, for the extended treatment of VTE, rivaroxaban generated fewer total QALYs than the other DOACs (due primarily to greater uncertainty for major bleeds during this phase of treatment). Based on the cost-effective evidence and evidence from the extended treatment NMA suggesting the potential for fewer bleeds with apixaban, the committee agreed to recommend considering switching to apixaban if on a different DOAC which is not well tolerated.

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Bayer plc	Guideline	18 34	5 - 12 17 - 25	Over and above the suggestion in comment number 4, we are also concerned that the guideline is recommending switching between DOACs once treatment has been initiated and without clinical justification. In general, switching between agents potentially exposes patients to periods of increased thromboembolic and bleeding risks. Indeed, it is acknowledged on page 34 of the guideline that *"The committee agreed that there are risks involved in switching anticoagulant treatment, particularly if there have been no adverse events with the current treatment."* This recommendation is also likely to cause more confusion and error in the treatment paradigm given each agent has different posology at the initial treatment phase and in extending treatment beyond 3 to 6 months, as well as once-daily (edoxaban and rivaroxaban) vs twice daily dosing (dabigatran and apixaban). Apixaban is indicated at the dose of 10 mg twice daily for one week, followed by 5 mg twice daily for six months, then extended prevention with 2.5 mg twice daily). All four DOACs are recommended as options for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism in NICE technology appraisals and therefore switching should only be on the basis of clinical justification.	Thank you for your comment. Following discussion of the stakeholder comments, the committee amended this recommendation to make clear that for most people, the first option would be to continue with the same treatment if it is already well tolerated. If not well tolerated, if clinical circumstances or personal preferences change and the person is currently taking a DOAC, changing to apixaban should be considered. The committee did not specify which dose to use as it is intended that dose-adjustments are made in line with the summary of product characteristics (SPCs) for the drug being used, which provide detailed information on when to adjust the dose. The committee agreed not to duplicate this information within the recommendations themselves to limit complexity. The committee agree that decisions to switch treatment should always consider specific clinical circumstances and be made on a case by case basis.

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				In addition, the recommendation does not appear to clearly reflect the rationale on page 34 of the guideline, which states that *"the first option for most people should be to continue the current treatment."* We suggest that the recommendation is amended to clarify the sequential intention of the options. e.g. 1.4.8 For people who are continuing anticoagulation treatment beyond 3 months and do not have any of the comorbidities listed in recommendation 1.4.9: ***1.*** *the first option for most people should be to* carry on with the current treatment…	
Bayer plc	Guideline (and Evidence review D - Pharmacological treatment)	29 - 30 79	23 - 3 6 - 19	We agree that the narrower inclusion criteria in the apixaban trial in comparison to the rivaroxaban trial and the greater proportion of people with unprovoked VTE might have reduced the number of bleeds compared to the EINSTEIN trial where there was a greater proportion of people with provoked VTE. We therefore agree that both apixaban and rivaroxaban should be recommended.	Thank you for your comment and support regarding this matter.
Bayer plc	Evidence review D – Pharmacological treatment	General	General	We consider that cost-effectiveness modelling shows the results for apixaban and rivaroxaban to be very similar and sensitive to small changes in assumptions. Indeed, had slightly different assumptions been made then the cost-effectiveness result would favour rivaroxaban - a recently published	Thank you for your comment. Where possible, we have undertaken a range of sensitivity analyses to explore the impact of uncertainty in the cost-effectiveness analysis. Inputs for which it was not possible to fully quantify uncertainty within the cost-effectiveness analysis were discussed extensively by the committee alongside the

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	Evidence review G – Economic model report			cost-effectiveness analysis by Folkerts *et al.* 2019[1] concluded that rivaroxaban was associated with a slightly lower total cost and increased QALYs compared with apixaban for VTE management in the UK. This suggests that neither rivaroxaban nor apixaban can be considered to be more or less cost-effective than the other. We therefore agree that both apixaban and rivaroxaban should be recommended. We suggest that this uncertainty should be reflected in the conclusions made regarding the outcome of the cost-effectiveness modelling in the guideline. 1. Folkerts, K. *et al.* Cost-effectiveness of rivaroxaban versus apixaban for the initial treatment of venous thromboembolism and extended prevention of recurrences in the UK. Journal of medical economics. 2019;22(11):1179-91.	rest of the evidence, documented in the review and are reflected in the recommendations. The study by Folkerts (2019) not included in the evidence review because it was published after the cut-off for the search for this question. We will pass this study to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
Boston Scientific	Guideline	General	General	We would suggest stratifying the risk for patients with PE using the recently published European Society of Cardiology (ESC) 2019 Guideline. Risk stratification of patients with acute PE is mandatory for determining the appropriate therapeutic management approach. The ESC 2019 Guideline have 4 defined categories for PE. These are: 1. High risk = hemodynamic unstable - mortality >50%	Thank you for your comment. The section of the guideline that covers diagnosis was out of scope of this update with the exception of the use of age adjusted and point of care D-dimer tests. Risk stratification was only considered within this update in relation to outpatient treatment for low risk PE and the type of risk stratification tool to use was also out of scope. The committee were therefore unable to review the use of specific risk stratification tools. As a result, they were unable to write recommendations on this topic and could not stratify haemodynamic stable or unstable PE further using ESC categories mentioned. However, we will

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				2. Inter mediate High risk= hemodynamic stable but right heart dysfunction and elevated biomarkers- mortality 21%-29% 3. Inter mediate Low risk= Hemodynamic stable with right heart strain but no elevated biomarkers 3%- 10% 4. Low risk= Hemo dynamic stable, no right heart strain or elevated biomarkers <1% At the moment the guideline only mentions haemodynamic stable or unstable PE. The range of difference in presentations in this population (PE) combined with comorbidities are not considered in the updates. Probably due to the lack of stratification there are no recommendations on where to hold these patients. For example, the ESC guideline recommends that intermediate and high-risk patients should be held in a monitoring ward such as HDU/CCU. Please refer to the National Confidential Enquiry into Patient Outcome and Death Report (NCEPOD) 2019, this report reviewed the quality of care provided to patients with a new diagnosis of PE in the UK. <u>Reference</u> 1. European Heart Journal (2019) 00, 1_61: 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism	pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

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				developed in collaboration with the European Respiratory Society (ERS) 2. The National Confidential Enquiry into Patient Outcome and Death Report (NCEPOD) 2019: A review of the quality of care provided to patients aged over 16 years with a new diagnosis of pulmonary embolism	
Boston Scientific	Guideline	General	General	We would like you to consider using a more precise tool such as the Lower extremity thrombosis score (LET) throughout your guideline. The LET score when used complimentary to the 2 level DVT well score offers the benefit of a clearer anatomical division and improved patient selection. The LET classification is designed to identify patients at high risk for developing post-thrombotic syndrome in the acute phase using thrombus location and extent. The guidance should emphasis the need for proper diagnosis and management of the iliofemoral DVT population. Patients with iliofemoral DVT have worse outcomes if treated with an oral anticoagulant alone, and the potential for benefit from interventional treatments such as Pharmacocomechanical thrombectomy is likely to be greater. A more precise complimentary tool such as the LET will support accurate diagnosis of iliofemoral DVT. References	Thank you for your comment. The section of the guideline that covers diagnosis was out of scope of this update with the exception of the use of age adjusted and point of care D-dimer tests. The committee were therefore unable to review the use of the lower extremity thrombosis score (LET) and were unable to write additional recommendations for people with iliofemoral DVT. However, in the diagnosis of DVT section there is a cross reference for people with iliofemoral DVT to the DVT section on thrombolytic therapy, which recommends that catheter-directed thrombolytic therapy can be considered for these people if they meet certain conditions. Therefore, people with iliofemoral DVT who meet these conditions will not be treated with anticoagulants alone. We will pass the information about the role of the LET score during diagnosis to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

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				1. Wittens et al 2019, The future of iliofemoral deep vein thrombosis treatment DOI: https://doi.org/10.1016/j.jvsv.2019.07.002 2. Strijkers et al Phlebology. 2015 Mar;30(1 Suppl):14-9. doi: 10.1177/0268355515569133.	
Boston Scientific	Guideline	8	6	We support the use of the PERC score, as it supports better use of resources, planning and reduces patient's exposure to radiation. However as mentioned in comment 1, currently there is no mention of risk stratification for PE based on mortality in the guideline. This means that whilst low risk PE patients are the biggest category, the group of Intermediate High Risk (IHR) PE is not taken into consideration. The publications from Klok and Barco (see reference below) on stable patients and functional outcome shows that improper risk stratification leads to improper treatment and deterioration of certain groups and brings them into danger of haemodynamic collapse. This reinforces the need to use the recently published ESC which categorise in 4 categories, as mentioned in comment 1. References 1. Klok et al 2019, Thrombosis Research 178 (2019) 59–62 Measuring functional	Thank you for your comment and support for the use of PERC. Risk stratification was only considered within this update in relation to outpatient treatment for low risk PE and the type of risk stratification tool to use was also out of scope. The committee were therefore unable to review the use of specific risk stratification tools and were unable to write recommendations relating to this topic. We encourage you to submit suggestions for areas that NICE guidelines should address or where an update is needed of an existing topic. We pass comments onto surveillance where there is something that could trigger an update. For example, if there is new evidence that is likely to change recommendations, or if there is new evidence about topics that are not covered by the existing guidance, or if issues concerning safety are raised. If there is new evidence this needs to be verifiable by the inclusion of supporting references,

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				limitations after venous thromboembolism: A call to action 2. European Heart Journal (2019) 00, 1_61: 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS)	specifically primary studies or systematic reviews of primary studies.
Boston Scientific	Guideline	25	7	Could the committee be more specific on the definition of lower dose thrombolysis? In addition, what specific type of data collection would the committee recommend? To support this, we would like to bring to the committee's attention relevant trial data that looks at lower dose thrombolysis for people with acute PE and right ventricular dysfunction. The ULTIMA trial (n=60): Randomized, Controlled Trial (RCT) of Ultrasound-Assisted Catheter-Directed Thrombolysis (USAT) vs AC for Acute Intermediate-Risk Pulmonary Embolism. In the USAT group, the mean RV/LV ratio was reduced from 1.28±0.19 at baseline to 0.99±0.17 at 24 hours (P<0.001); in the heparin group, mean RV/LV ratios were 1.20±0.14 and 1.17±0.20, respectively (P=0.31). The mean decrease in RV/LV ratio from baseline to 24 hours was 0.30±0.20 versus 0.03±0.16 (P<0.001), respectively. At 90 days, there was 1 death (in the heparin group), no major bleeding, 4 minor bleeding episodes (3 in the USAT group and 1 in the heparin group; P=0.61), and no recurrent venous	Thank you for your comment. The research recommendation for lower dose thrombolysis was written by a previous committee and as a result the current committee are unable to be more specific about a definition of this term at this point in time. This is also the case for the research recommendation for a trial comparing thrombolytic therapy for DVT to anticoagulant therapy. The committee agree that the research recommendation for low-dose thrombolysis is still relevant to a UK audience as the ULTIMA trial is a very small trial and although the PEITHO-III trial is relevant to this research recommendation, it is still a long way from completion and uncertainties in this area may remain after this trial.

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				thromboembolism. The trial concluded that in patients with pulmonary embolism at intermediate risk, a standardized USAT regimen was superior to anticoagulation with heparin alone in reversing RV dilatation at 24 hours, without an increase in bleeding complications. In addition, the PEITHO-III trial (EU) will start soon: this is a RCT assessing the efficacy of a reduced dose of thrombolytic treatment for patients with intermediate to high-risk acute pulmonary embolism. References 1. Kucher et al 2014, Randomized, Controlled Trial of Ultrasound-Assisted Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism 2. https://www.invent-vte.com/studies/study/~708-peitho-iii	
Boston Scientific	Guideline	29	17	We would like to suggest that the guideline emphasises the importance of considering the future role of interventional treatments before deciding on an AC regimen for patients presenting with VTE. This is important since the use of NOAC/DOAC in patients with PE will limit the future use of in interventional procedure such as Ultrasound enhanced catheter directed thrombolysis.	Thank you for your comment. The use of mechanical interventions was out of scope for this review and therefore the committee could not make recommendations in these areas. However, surveillance will monitor these areas for any developments for future updates. Although mechanical interventions were out of scope, during the update the committee raised a safety issue

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				Please refer to the National Confidential Enquiry into Patient Outcome and Death Report (NCEPOD) 2019. References 1. Kucher et al 2014, Randomized, Controlled Trial of Ultrasound-Assisted Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism. 2. Rationale for catheter directed therapy in pulmonary embolism Cardiovasc Diagn Ther. 2017 Dec; 7(Suppl 3): S320–S328. doi: 10.21037/cdt.2017.08.14 3. The National Confidential Enquiry into Patient Outcome and Death Report (NCEPOD) 2019: A review of the quality of care provided to patients aged over 16 years with a new diagnosis of pulmonary embolism 4. European Heart Journal (2019) 00, 1_61: 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS)	concerning the use of IVC filters and identified new evidence that was likely to change the existing recommendations. As a result, despite being initially out of scope, this section was updated at the end of the current work.
Boston Scientific	Guideline	37	20	We ask the committee to take into account the publication from Morales and consider less restrictive description of the use of IVC filters from that stated in the draft guideline. "For people with VTE at acute risk of thrombosis, clinicians may fit an IVC filter as part of a clinical trial." This publication gives some	Thank you for your comment. The paper by Morales does not meet the inclusion criteria for this review question as it is a benefit/risk analysis and not an intervention study. Therefore, this paper could not be included in our evidence review. However, the recommendations the committee have made still allow

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				clarification around the Benefit/Risk profile of using Retrievable Filters, which we ask the committee to consider. Morales et al found that they agreed with the use of an IVC Filter for patients with a contra indication to AC, however for patients with retrievable IVC filters in whom the transient risk of PE had passed, quantitative decision analysis suggested that the benefit/risk profile begins to favour filter removal between 29 and 54 days after implantation. Reference Morales et al 2013, Decision analysis of retrievable inferior vena cava filters in patients without pulmonary embolism - J Vasc Surg Venous Lymphat Disord. 2013 Oct;1(4):376-84. doi: 10.1016/j.jvsv.2013.04.005. Epub 2013 Jul 4.	for use of IVC filters as part of a prospective clinical study, when anticoagulation is contraindicated or when a PE occurs during anticoagulation treatment.
Bristol-Myers Squibb/ Pfizer Alliance	Guideline	General	General	Support increase patient involvement The increased emphasis on increased patient involvement in their management is welcome and in line with established principles of robust medicines optimisation.	Thank you for your comment and support regarding this matter.

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Bristol-Myers Squibb/ Pfizer Alliance	Guideline	11	6	Support recommendation for outpatient treatment for low-risk PE We support the recommendation to consider outpatient treatment for suspected or confirmed low-risk pulmonary embolism (PE), consistent with the recommendation of the British Thoracic Society (BTS) guideline for the initial outpatient management of pulmonary embolism (2018)[1]. [1] British Thoracic Society (BTS) guideline for the initial outpatient management of pulmonary embolism, 2018. *Available at*: https://www.guidelines.co.uk/respiratory/bts-guideline-initial-outpatient-management-of-pe/454314.article).	Thank you for your comment and support regarding this matter.
Bristol-Myers Squibb/ Pfizer Alliance	Guideline	12	23	Propose DOACs ahead of LWMW as interim anticoagulation We note the recommendation that patients with confirmed proximal DVT or PE should be offered apixaban or rivaroxaban ahead of LMWH. This is not consistent with the (earlier) recommendation for interim anticoagulation and may lead to unnecessary treatment switching, cost to the NHS and burden to patients.	Thank you for your comment. Following discussion of the stakeholder comments, the committee decided to amend the recommendation on which anticoagulants to use for interim treatment. As you note, the previous recommendation was inconsistent with the recommendations for confirmed DVT or PE. The committee now recommend that the clinician choose an anticoagulant that can be continued if DVT or PE is confirmed, if possible. This recommendation should prevent unnecessary switches in treatment following diagnosis and therefore prioritise the use of DOACs, and rivaroxaban and apixaban in particular, over LMWH. However, LMWH may also be used as an interim

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				We suggest that the recommendation for interim anticoagulation should be updated to prefer LMWH only if the DOACs are not suitable:
				
				• It is prudent to maintain continuity of therapy, in order to minimise risk of medication errors and maximise patient concordance, as the current guideline could lead to patients prescribed LMWH as interim anticoagulation, followed by a recommendation to switch to a DOAC once confirmed.
				• Patients generally prefer the convenience of oral anticoagulation.
				• We would highlight the NHS burden presented by the use of LMWH, potentially including:
				  ○ Very high NHS financial cost and nursing resource impact of patients re-presenting to hospital for LMWH injections (where they are unwilling or unable to self-inject, or as required by Trust policy)
				  ○ High NHS cost of LWMH syringes, up to £10 each (NHS Drug Tariff, 2019[2])
				
				[2] NHS Drug Tariff (2019). *Available at:* https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff.
					treatment to lead into dabigatran and edoxaban treatment. This amended recommendation will also take into account people with comorbidities (such as renal impairment and DOACs) for whom apixaban and rivaroxaban are not necessarily the first choice.

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Bristol-Myers Squibb/ Pfizer Alliance	Guideline	12	26 (and elsewhere)	Propose consistent inclusion of MHRA Drug Safety Updates We note the reminder of the MHRA Drug Safety Update (June 2019) on the increased risk of recurrent thrombotic events in patients with antiphospholipid syndrome. We suggest the guideline also references the MHRA Drug Safety Update (July 2019[3]) reminding physicians that patients should take rivaroxaban with food. This is a relevant consideration when making a prescribing decision for patients with acute VTE. [3] MHRA Drug Safety Update volume 12, issue 12: July 2019: 3. Rivaroxaban (Xarelto▼): reminder that 15 mg and 20 mg tablets should be taken with food. *Available at*: *https://www.gov.uk/drug-safety-update/rivaroxaban-xarelto-reminder-that-15-mg-and-20-mg-tablets-should-be-taken-with-food.*	Thank you for your comment. As this direction to take with food is contained within the summary for product characteristics (SPCs) and British national Formulary (BNF) for rivaroxaban and as it is not expected that this requirement will affect the decision to prescribe rivaroxaban, this MHRA alert has not been included as a footnote. Additionally, to be consistent, the footnotes for the MHRA alert for the use of DOACs in people with APS have been removed. It is intended that the relevant SPCs and the BNF should be reviewed when prescribing anticoagulants and that the MHRA alert and the direction to take with food should be something that the dispensing pharmacist should highlight.
Bristol-Myers Squibb/ Pfizer Alliance	Guideline	13	5 - 7	Support recommendations for immediate interim therapeutic anticoagulation We welcome the recommendations to offer interim therapeutic anticoagulation on suspicion of DVT or PE, and that clinicians should not wait for baseline blood tests before starting this interim anticoagulation. This will help protect patients at risk of recurrent VTE by starting anticoagulation as soon as this risk is suspected.	Thank you for your comment and support regarding this matter.

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Bristol-Myers Squibb/ Pfizer Alliance	Guideline	14	4	Propose apixaban as preferred DOAC in confirmed DVT or PE We note that apixaban and rivaroxaban are placed alongside each other options for treating most patients confirmed proximal DVT or PE. However, the evidence suggests that there are significant differences in bleeding rates between the DOACs and favour apixaban: • A 2019 systematic review of network meta-analyses of RCTs (Cohen *et al*[4]) found that apixaban is associated with fewer clinically relevant bleeds (major or clinically relevant non-major bleeds) compared with all other DOACs. • Only apixaban has demonstrated significant reductions in both major and CRNM bleeding compared with enoxaparin in pivotal RCTs AMPLIFY[5] and EINSTEIN[6,7]. • A 2019 systematic review of observation studies (Aryal *et al*[8]) concluded that apixaban and rivaroxaban have equivalent efficacy in prevention of recurrent VTE, but apixaban has a decreased risk of major and minor bleeding events.	Thank you for your comment. The committee noted that for the initial treatment of VTE, apixaban was associated with a reduction in major bleeds and CRNM bleeds compared to LMWH+VKA. Rivaroxaban also demonstrated a reduction in major bleeding compared to LMWH+VKA, but not CRNMBs . The committee noted that apixaban and rivaroxaban were the two most cost-effective options for the initial treatment of VTE based on the economic model (please see the economic model report in document G for more information). The committee were concerned that the inclusion criteria for the AMPLIFY trial may select for participants less prone to bleeds. The committee were less concerned with the heterogeneity of the remaining DOAC trials. As a result, committee agreed that they could not make a recommendation to offer apixaban on its own, but could recommend the use of apixaban and rivaroxaban, as both of these options demonstrated a reduction in major bleeds compared to VKA and as these drugs are the two most cost-effective options. . The rationale for this decision is explained in detail in evidence review D. The committee agreed that continuity of therapy is important to avoid medication errors, as well as patient safety and concordance issues with switching medicines. Following discussion of stakeholder comments, they amended the recommendation for continued treatment to make clear that, if the drug is well

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				The draft guideline already notes (line 23/24, page 29) the evidence that apixaban is the most cost-effective DOAC because it results in the fewest bleeds, so apixaban should be the recommended choice of DOAC in the acute setting. Finally, continuity of therapy is important to avoid medication errors, as well as patient safety and concordance issues with switching medicines. 58% of patients are expected to present with unprovoked VTE (Martinez et al, 2014)[9] and are thereby indicated for lifelong anticoagulation; after 3 months treatment, a change to apixaban is to be considered for most of these patients (page 18, section 1.4.8). Recommending apixaban as the first choice DOAC in the acute setting will therefore minimise unnecessary therapy changes for patients requiring anticoagulation beyond 3 months. We agree that the other DOACs should be available as options as apixaban may not be suitable for everyone. [4] Cohen AC *et al* (2019). Anticoagulant selection for patients with VTE—Evidence from a systematic literature review of network meta-analyses. Pharmacological Research 143:166–177.	tolerated, most people should continue with the same treatment. However, they agreed that if the drug is not well tolerated or if the clinical situation or personal preferences have changed then switching to apixaban could be considered if the person is already taking a DOAC. Therefore, in practice, most people will remain on their initial treatment and the only people changing will be those who fit the criteria listed above. The recommendations for initial treatment include all of the DOACs as options because they all have Technology Appraisals and because, as you note, apixaban (and rivaroxaban) may not be suitable for everyone.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				[5] Agnelli G et al (2013). Oral Apixaban for the Treatment of Acute Venous Thromboembolis (the AMPLIFY trial). NEJM 369;9:799-808. [6] Bauersachs R et a. (2010). Oral Rivaroxaban for Symptomatic Venous Thromboembolism (the EINSTEIN-DVT trial). NEJM 363:2499-510. [7] Bueller HR et al (2012). Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism (the EINSTEIN-PE trial). NEJM 366:1287-97. [8] Aryal MR et al (2019). Systematic review and meta-analysis of the efficacy and safety of apixaban compared to rivaroxaban in acute VTE in the real world. Blood Advances 3(15):2381-2387. [9] Martinez C et al (2014). Epidemiology of first and recurrent venous thromboembolism: a population-based cohort study in patients without active cancer. Thromb Haemost 112(2):255-63.	
Bristol-Myers Squibb/ Pfizer Alliance	Guideline	14	25	Propose clarify dosing adjustments for patients with renal impairment Apixaban is the only DOAC to require no dose adjustment in VTE patients with moderate or severe renal impairment, reducing the chance of prescribing error. It has the lowest renal clearance of all the DOACs.	Thank you for your comment. The committee decided not to amend the recommendation to make it clearer which DOACs need dose adjustment because this would add extra detail to an already long and complicated recommendation. The recommendation already states that people should note the cautions and requirements for dose adjustment and monitoring in the medicine's

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We recommend that the dosing adjustments for the DOACs in patients with renal impairment is more clearly presented: *For apixaban:* Moderate Renal Impairment (30–49 mL/min): No dose adjustment required. Severe Renal Impairment (15–29 mL/min) (<30 mL/min): No dose adjustment. Use with caution. *For edoxaban:* *15–50 mL/min reduc*e to 30 mg OD. *For dabigatran:* Moderate renal impairment (30–49 mL/min): Consider a dose reduction to 110 mg BD based on individual assessment of bleeding and thromboembolic risk if CrCl 30-50 mL/min. Severe Renal Impairment (15–29 mL/min): Contraindicated. *For rivaroxaban:* 15–50 mL/min15 mg BD for 3 weeks; if the recommended dose thereafter is 20 mg OD, consider dose reduction to 15 mg OD if bleeding risk outweighs risk of recurrent DVT and PE. No dose adjustment required if dose is 10 mg OD. If CrCl 15-29 mL/min.- use with caution.	summary of product characteristics and the committee agreed that this was sufficient.

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Bristol-Myers Squibb/ Pfizer Alliance	Guideline	15	18	Propose DOACs may be appropriate for obese patients We are concerned that the recommendation to consider VKA in patients with a BMI of 40kg/m^2 does not reflect the latest evidence, based as it is on the 2016 ISTH guidance[10]. A 2019 post-hoc analysis of the AMPLIFY RCT[11] found that the safety and efficacy of apixaban in patients with extremes of body weight are consistent with results in the broader trial population (ASH 2019[11]). This is supported by observational data gathered by Martin K *et al* (ISTH 2019[12]), which found no correlation between DOAC levels and weight, concluding that obesity alone is not sufficient to preclude the use of DOACs. We therefore suggest the recommendation is updated to reflect this emerging evidence. [10] Martin K et al (2016). Use of Direct Oral Anticoagulants in Obese Patients: Guidance from the SSC of the ISTH. J Thromb Haemost 14:1308-1313. [11] Lee T et al (2019). Safety and Efficacy of Apixaban Versus Enoxaparin/Warfarin in Patients With Extremes of Body Weight: Post Hoc Analysis of the AMPLIFY Trial. Poster presented at the 61st American Society of Hematology (ASH) Annual	Thank you for your comment and this information. This update followed the methods outline in the NICE guideline manual based on the best available evidence and we are unable to comment on how other guidelines conduct their reviews or examine how they reach their recommendations. The recommendation relating to BMI was based primarily on consensus due to limited evidence from randomized controlled trials in this population and as the available sub-group analyses (of the DOAC RCTs) were specifically in people with a BMI >30kg/m2. The committee discussed feedback from stakeholders and agreed that there may be circumstances in which the DOACs could be used in people with BMI >40 kg/m2. They amended the recommendation to allow for this possibility by removing the reference to a specific anticoagulant, and instead stressing the importance of monitoring, using dose adjustments where necessary and following locally agreed protocols or advice from a specialist or multidisciplinary team. Additionally, based on stakeholder responses, the committee decided to make reference to absolute weight rather than BMI and amended the recommendation to cover people at both extremes of weight (<50kg or >120kg).

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				Meeting and Exposition; December 7–10, 2019; Orlando, FL, USA. Available at: https://ash.confex.com/ash/2019/webprogram/Paper121542.html [12] Martin A.C et al (2019). DOAC Plasma Concentrations in High Weight Patients: An Observational Study. Presented at ISTH 2019, Melbourne. Available at: https://academy.isth.org/isth/2019/melbourne/273958/anne.celine.martin.doac.plasma.concentrations.in.high.weight.patients.an.html?f=menu%3D3%2Abrowseby%3D8%2Asortby%3D2%2Amedia%3D1	
Bristol-Myers Squibb/ Pfizer Alliance	Guideline	16	1	Support preference for DOACs over LMWH in people with cancer The recommendation that DOACs should be preferred over LMWH for anticoagulation in people with cancer and confirmed DVT or PE is welcome. Latest evidence for apixaban in people with VTE and cancer includes: • The AMPLIFY RCT sub-group analysis[13] suggested that apixaban is a convenient option for cancer patients with VTE. • The 2019 ADAM VTE trial (McBane RD *et al*[14]) found that apixaban for VTE treatment in cancer was associated with greater reduction	Thank you for your comment supporting the use of DOACs over LMWH in people with cancer. Following discussion of the stakeholder comments, the committee amended this recommendation to state that if a DOAC is unsuitable, LMWH alone or LMWH with a VKA should be considered. This wording allows the use of LMWH in people with cancer where a DOAC is not suitable, but does not specify that basis for this suitability leaving it open for the clinician to decide on the basis of clinical factors and patient preference, while still having a DOAC as the preferred option where possible.

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				in VTE recurrence and similar bleeding rates compared to dalteparin. • A 2019 systematic review and network meta-analysis of trials comparing DOACs to dalteparin in cancer-associated VTE (Fuentes HE *et al*[15]) found that apixaban may be associated with the lowest risk of VTE recurrence compared with the other DOACs. • A study presented at the 2019 American Society of Haematology (ASH) Annual Meeting (Cohen AT *et al*[16]) found that VTE patients with active cancer initiating apixaban had significantly lower risk of major bleeding, CRNM bleeding, and recurrent VTE compared to LMWH patients. Apixaban patients also had a lower risk of recurrent VTE compared to warfarin patients. • A 2019 observational study (Wygant G *et al*[17]) showed the risks of major bleeding and recurrent VTE to be significantly lower with apixaban than LMWH followed by warfarin in patients with or without active cancer. • The CARAVAGGIO RCT (Agnelli G *et al*[18]*)* is investigating the value of apixaban compared to dalteparin, results of which are anticipated in March 2020. We request the removal of the word 'only' in the sentence outlined below, there may be situations	

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				whereby patient preference supports the use of LMWH over no treatment at all. • Consider LMWH on its own only if the person finds oral medicine difficult to tolerate or a VKA is contraindicated. [13] Agnelli G et al (2015). Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. J Thromb Haemost 13:2187–91. [14] McBane D et al (2019). Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. J Thromb Haemost 00:1-11 (in press). Available at: https://doi.org/10.1111/jth.14662 [15] Fuentes HE et al (2019). Direct Oral Factor Xa Inhibitors for the Treatment of Acute Cancer-Associated Venous Thromboembolism: A Systematic Review and Network Meta-analysis. Mayo Clin Proc 00:1-11 (in press). Available at: https://doi.org/10.1016/j.mayocp.2019.05.035 [16] Cohen AT et al (2019). Safety and Effectiveness of Apixaban, LMWH, and Warfarin Among Venous Thromboembolism Patients with Active Cancer: A Retrospective Analysis Using Four US Claims Databases. Oral presentation at the 61st American Society of Hematology (ASH) Annual Meeting and	

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				Exposition; December 7–10, 2019; Orlando, FL, USA. Available at: https://ash.confex.com/ash/2019/webprogram/Paper121769.html. [17] Wygant GD et al (2019). Comparative effectiveness of apixaban versus warfarin for treatment of venous thromboembolism in patients with and without active cancer. JACC 73; issue 9 (suppl. 1). Available at: http://www.onlinejacc.org/content/73/9_Supplement_1/1926. [18] Agnelli G et al (2018). Apixaban versus Dalteparin for the Treatment of Acute Venous Thromboembolism in Patients with Cancer: The Caravaggio Study. Thromb Haemost 118;1668-1678.	
Bristol-Myers Squibb/ Pfizer Alliance	Guideline	17	7 (and elsewhere)	Propose to discontinue the use of the terms 'provoked' and 'unprovoked' The 2019 European Society of Cardiology (ESC) Pulmonary Embolism guidelines[19] no longer support terminology such as 'provoked' vs. 'unprovoked' PE/VTE, as it is potentially misleading and not helpful for decision-making regarding the duration of anticoagulation. The use of these terms causes potential confusion among prescribers because it can lead to a belief	Thank you for your comment. The committee decided not to change the definition of provoked and unprovoked for the purposes of this update as the evidence reviewed over the course of the update, and the discussions surrounding provoked/unprovoked VTE have been in relation to our definitions as detailed in the terms used in the guideline section of the guideline and not the definition used by the ESC. While the use of prognostic tools to predict risk of recurrence was within the scope of this update, the use

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				that VTE events triggered by minor provoking factors do not require extended treatment. However, the latest evidence (Prins MH *et al*[20]) confirms minor transient risk factors or minor persistent risk factors still have a high risk of recurrence, so therefore these patients should be considered for extended treatment. We would therefore recommend following the ESC guidelines for risk-stratifying patients: • Low risk of recurrence (major transient or reversible factors) - discontinue anticoagulation after 3 months. • Intermediate risk of recurrence (minor transient or persistent risk factors; no identifiable risk factors) - consider extension of anticoagulation. • High risk of recurrence (active cancer, previous episodes of VTE in the absence of major transient or reversible factor or antiphospholipid antibody syndrome) - recommend extension of anticoagulation. The majority of patients are expected to present without an identifiable risk factor[9] and latest evidence[20] shows that the risk of recurrent VTE is negligible only in those patients who have experienced a major transient risk factor. As such, we	of other methods to stratify risk were out of scope and the committee were therefore unable to review the evidence from Prins et al (2018) when making their recommendations. However, we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date The existing recommendations make it clear that stopping treatment should be considered in people who have had a provoked VTE (defined as a transient major clinical risk factor for VTE, such as surgery, trauma, significant immobility (bedbound, unable to walk unaided or likely to spend a substantial proportion of the day in bed or in a chair), pregnancy or puerperium – or in a person who is having hormonal therapy (combined oral contraceptive pill or hormone replacement therapy)). Following stakeholder comments, the committee amended the text to make it clearer within the recommendation that the risk factor must not be persistent. The committee agreed that for people with unprovoked VTE it is generally advisable to continue treatment. However, they noted that the decision to continue or stop anticoagulation therapy needed to be made on an individual basis taking into account bleeding risk and risk of recurrence on a case by case basis and the preferences of the individual concerned who may not want to continue treatment.

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				would suggest that, instead of the guideline specifying when to offer extended treatment, it is more appropriate to define when NOT to offer extended treatment (i.e., not to those patients suffering DVT/PE subsequent to a major transient risk factor. [19] Konstantinides SV et al (2019). ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Available at: https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehz405/5556136 [20] Prins MH, Lensing AW, Prandoni P, et al (2018). Risk of recurrent venous thromboembolism according to baseline risk factor profiles. Blood Adv 2018;2:788–96.	
Bristol-Myers Squibb/ Pfizer Alliance	Guideline	17	7 (and elsewhere)	If proceeding with 'provoked/unprovoked' terminology, please consider the following: 1. Propose modifying definitions for provoked DVT or PE We suggest the following changes to the definition of provoked DVT or PE, to reflect latest evidence (Prins MH et al, 2018):	Thank you for your comment. The committee decided not to change the definition of provoked and unprovoked for the purposes of this update as the evidence reviewed over the course of the update, and the discussions surrounding provoked/unprovoked VTE have been in relation to our definitions as detailed in the terms used in

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				• Change from 'surgery' to 'major surgery' • Change from 'trauma' to 'major trauma' • Change 'Significant immobility (bedbound, unable to walk unaided or likely to spend a substantial proportion of the day in bed or in a chair)' to the ESC Pulmonary Embolism guidelines definition: 'Confined to bed in hospital (only bathroom privileges) for >3 days due to an acute illness, or acute exacerbation of a chronic illness'. We suggest this because it avoids confusion of major provoking transient risk factors. • Remove 'Pregnancy or puerperium – or in a person who is having hormonal therapy (oral contraceptive or hormone replacement therapy)'. This is because the ESC, in line with latest evidence, classify these risk factors as minor transient risk factors that have an intermediate risk, and extended anticoagulation should be considered. 2. Propose expanding definition of 'unprovoked' We recommend considering the inclusion of minor transient and minor persistent risk factors within the 'unprovoked' classification, as they carry an intermediate risk of VTE recurrence[20]. This will make it clear that these patients are not in the provoked	the guideline section of the guideline and not the definition used by the ESC. While the use of prognostic tools to predict risk of recurrence was within the scope of this update, the use of other methods to stratify risk were out of scope and the committee were therefore unable to review the evidence from Prins et al (2018) when making their recommendations. However, we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date. This update followed the methods outline in the NICE guideline manual based on the best available evidence and we are unable to comment on or examine how the ESC guideline reach their recommendations.

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				DVT/PE group and therefore should be considered for extended anticoagulation.	
Bristol-Myers Squibb/ Pfizer Alliance	Guideline	18	5	Support preference for apixaban in non-complex patients for anticoagulation >3 months We welcome the preference for apixaban in non-complex patients requiring anticoagulation beyond 3 months' duration, based on evidence that apixaban is the most cost-effective option because it results in the fewest bleeds *(lines 23/24, page 29)*. This recommendation reflects the evidence provided by: • AMPLIFY-EXT RCT[21], showing that extended anticoagulation with apixaban has similar rates of bleeding to placebo, while reducing the risk of recurrent VTE or death, and • The 2019 Cohen *et al*[4] SLR of NMAs which found apixaban to have the lowest bleeding rates of all DOACs. For the long-term prevention of recurrent DVT / PE, apixaban is the only DOAC to demonstrate comparable rates of both major and clinically relevant bleeding vs. placebo.	Thank you for your comment and support regarding this matter.

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				[21] Agnelli G et al (2013). Apixaban for Extended Treatment of Venous Thromboembolism (the AMPLIFY-EXT trial). NEJM 368;8:699-708	
Bristol-Myers Squibb/ Pfizer Alliance	Guideline	32	17 - 21	Costs in the economic model when LMWH remains the anti-coagulation for patients with VTE & cancer The statement "*and the committee agreed that reducing its use would be beneficial in conserving NHS resources"* is not proven in the economic model when consideration is given to the points highlighted below.	We have addressed this comment in our response to ID#200 as we believe these comments are linked. This response is reproduced below. Thank you for your comment. We have noted that the study you cited by Noble et al. is a case series of 62 patients published in 2007 and reported that 74% of patients self-administered LMWH, 24% had it given by a carer and 2% by a district nurse. It was the committee's opinion that in current practice across the country, 15% of all patients would require nurse support for administration. In response to your comment we considered an exploratory sensitivity analysis assuming 2% of patients receiving LMWH required nurse support; while this reduced the treatment cost for LMWH, it did not change the overall conclusions of the cost-effectiveness analysis.
Bristol-Myers Squibb/ Pfizer Alliance	Guideline	32	22	Support link between increasing DOAC use and reduced NHS resource use We are pleased to see the clear evidence-based link made between increasing DOAC use, reduced NHS resources to monitor INR, manage bleeding complications, and administer parenteral anticoagulation.	Thank you for your comment and support in this matter.

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				A 2019 study[22] (ALPHA-PE) investigated the opportunity to reduce length of hospitalisation for patients with objectively confirmed acute PE with the introduction of apixaban. It founds significantly shorter hospital admissions with apixaban compared to standard of care (mean 3.2-day reduction). Shorter hospital stays are expected to benefit the NHS through increasing hospital capacity and reduction of waiting times for hospital procedures. [22] Alikhan R et al (2019). Apixaban Length-Of-Stay Pulmonary Embolism study - Hospital Admissions. Poster presented at the British Society of Haematology Annual Scientific Meeting, Glasgow, 1-3 April 2019.	
Bristol-Myers Squibb/ Pfizer Alliance	Guideline	33	8 - 9	LMWHs are on the whole self-administered in the community.	We have addressed this comment in our response to ID#200 as we believe these comments are linked. This response is reproduced below. Thank you for your comment. We have noted that the study you cited by Noble et al. is a case series of 62 patients published in 2007 and reported that 74% of patients self-administered LMWH, 24% had it given by a carer and 2% by a district nurse. It was the committee's opinion that in current practice across the country, 15% of all patients would require nurse support for administration. In response to your comment we considered an exploratory sensitivity analysis assuming

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					2% of patients receiving LMWH required nurse support; while this reduced the treatment cost for LMWH, it did not change the overall conclusions of the cost-effectiveness analysis.
Bristol-Myers Squibb/ Pfizer Alliance	Economic model report	35	1	The administration costs in Table 30 that are attributed to the drug cost per cycle (Table 31) assumes that 15% of patients requiring LMWH need nurse administration *"Assuming nurse administration in 15% of patients for LMWH, UFH and fondaparinux" reference provided in the text: Committee consensus.*	We have addressed this comment in our response to ID#200 as we believe these comments are linked. This response is reproduced below. Thank you for your comment. We have noted that the study you cited by Noble et al. is a case series of 62 patients published in 2007 and reported that 74% of patients self-administered LMWH, 24% had it given by a carer and 2% by a district nurse. It was the committee's opinion that in current practice across the country, 15% of all patients would require nurse support for administration. In response to your comment we considered an exploratory sensitivity analysis assuming 2% of patients receiving LMWH required nurse support; while this reduced the treatment cost for LMWH, it did not change the overall conclusions of the cost-effectiveness analysis.
Bristol-Myers Squibb/ Pfizer Alliance	Economic Model report	36	1	As previously stated LMWHs are on the whole self-administered in the community by the patient themselves, family member or carer. The model assumes 15% requiring nurse administration for the duration of their treatment. LMWH patients are supported by injection training videos, sharps bins and self-administering leaflets. A more likely scenario	Thank you for your comment. We have noted that the study you cited by Noble et al. is a case series of 62 patients published in 2007 and reported that 74% of patients self-administered LMWH, 24% had it given by a carer and 2% by a district nurse. It was the committee's opinion that in current practice across the country, 15% of all patients would require nurse support for

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				would be that the 15% requiring nurse administration would likely, after their first visit self-administer. We note that Noble et al. "The use of long-term low-molecular weight heparin for the treatment of venous thromboembolism in palliative care patients with advanced cancer: a case series of sixty-two patients"[23] found that only 2% of patients receiving LMWH required nurse administration. In the LMWH/VKA the current model attributes 38% of the drug/administration associated with LMWH to nurse administration. And of equal concern, the LMWH (cancer subgroup only) whereby 40% drug/administration (£539.62 / £361.44) costs are attributed to nurse administration. We therefore request the economic model is adapted to attribute only 2% of patients requiring nurse administration for LMWH. [23] Noble S et al (2007). The use of long-term low-molecular weight heparin for the treatment of venous thromboembolism in palliative care patients with advanced cancer: a case series of sixty-two patients. Palliative medicine 21: 473—476 PMID: 17846086	administration. In response to your comment we considered an exploratory sensitivity analysis assuming 2% of patients receiving LMWH required nurse support; while this reduced the treatment cost for LMWH, it did not change the overall conclusions of the cost-effectiveness analysis.
British Society for Haematology	Guideline	7	18	When offering D-dimer testing for suspected DVT or PE, consider a point-of-care test *'of sufficient*	Thank you for your comment. The committee made a recommendation to consider a point of care test if laboratory facilities are not immediately available and a

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				sensitivity' if laboratory facilities are not immediately available.	second recommendation that if a point of care is used, to specifically choose a quantitative test because the evidence showed that quantitative D-dimer tests have comparable sensitivity to laboratory tests. The committee agreed that it is therefore unnecessary to specify that the test should be of 'sufficient sensitivity' in the first recommendation.
British Society for Haematology	Guideline	11	18 - 20	Providing 24-hour specialist advice and guidance is likely to be costly, unworkable and we are not aware of any evidence that this will improve outcomes. In many cases, the people delivering this advice are unlikely to be able to deliver any subsequent direct care leading to a disconnect in the care pathway. The other 2 comments in section 1.2.4 are more realistic.	Thank you for your comment. It is intended that the person with VTE is provided with direct contact details of a healthcare professional or team to contact **only** during the normal working hours of specialist services. The recommendations clearly state that a separate, out-of-hours service should be contacted at all other times. The rationale for outpatient treatment has been expanded to clarify this.
British Society for Haematology	Guideline	13 (& 22)	3, 12, 13	Clotting profile requires definition. BSH would consider this to be a prothrombin time (PT) and Activated Partial Thromboplastin Time (APTT). This will generally be unhelpful but provides a useful baseline for any future testing whilst on anticoagulation and may point to the occasional lupus anticoagulant if the APTT prolonged.	Thank you for your comment. Following discussion of the stakeholder comments, the committee decided to amend the recommendation to remove mention of clotting profile and instead specifically recommend that tests for prothrombin time (PT) and Activated Partial Thromboplastin Time (APTT) be conducted.
British Society for Haematology	Guideline	14 - 15	29 (& 1)	Exclusion criteria for patients in the AMPLIFY acute management of VTE study was CrCl <25 (PMID: 23808982) and for EINSTEIN study <30 ml/min (PMID: 21128814).	Thank you for your comment. The committee decided not to amend the recommendation because the suggested detail would add text to an already long and complicated recommendation. However, the recommendation already states that people should note the cautions and requirements for dose adjustment and

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				Would be better to state 'CrCl 15-30 use with caution'. There is no trial safety data using the initial treatment doses in patients with such a low CrCl. The spc seems to be a bit of a fudge, perhaps translating the AF data on lower doses with CrCl 15-30 across to the VTE population – but lower doses are not being used for the initial management of VTE.	monitoring in the medicine's summary of product characteristics (SPCs) and the SPCs for apixaban and rivaroxaban state that they should be used with caution if creatinine clearance is 15-30ml/min.
British Society for Haematology	Guideline	15	10	If recommending LMWH with CrCl <15 ml/min, laboratory monitoring (anti-Xa) should be recommended.	Thank you for your comment. The committee decided not to include details of specific tests because this would add extra detail to an already long and complicated recommendation and the committee were concerned that any tests that weren't listed would not be carried out. However, the recommendation already states that monitoring should be carried out as detailed in the summary of product characteristics and this includes anti-Xa monitoring.
British Society for Haematology	Guideline	15	17 - 20	There is no evidence to support this statement and accumulating evidence to completely refute it eg. Boonyawat K et al Thromb Haemost. 2017;15:1322-1333 PMID: 28407368 Kushnir M et al Lancet Haematol. 2019;6:e359-e365 PMID 31133411 Piran S et al Res Pract Thromb Haemost. 2018;2:684-6 PMID:30349887 And the use of BMI rather than actual weight makes no biological sense for a fixed dose drug. It would be far more accurate to have no recommendation or	Thank you for your comment. The recommendations relating to BMI were based primarily on consensus due to limited evidence from randomized controlled trials in this population. The papers you have cited did not meet the criteria for inclusion in this review due to either not being an RCT or because the population was mixed between people with atrial fibrillation and those with VTE. However, the committee did note that there is accumulating evidence that the DOACs are safe to use in people with obesity. The committee discussed feedback from stakeholders concerning the use of absolute weight instead of BMI

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				state that there is no evidence to support a defined upper limit of weight for the use of VKA over DOACS.	and that there are concerns with treating people with low body weight as well as those with high body weight. The committee agreed with stakeholder concerns and decided to specifically make reference to absolute weight rather than BMI and amended the recommendation to cover people at both extremes of weight (<50kg or >120kg). However, they agreed that uncertainty surrounding effective treatment for these groups remains. Taking into account suggestions from stakeholders that there is some evidence that the DOACs could be used in obese patients and that more evidence may be forthcoming, the committee made a more general recommendation to enable the clinician to decide which treatment would be most effective on an individual basis and to allow for the use of DOACs. They noted that whatever the choice of anticoagulant is, it is important to ensure that there is effective monitoring of therapeutic levels and any dose adjustments and monitoring requirements stated in the SPCs are followed, along with locally agreed protocols or advice from a specialist or multidisciplinary team.
British Society for Haematology	Guideline	16	7 - 8	Does this account for the reduced bleeding and potential greater efficacy of LMWH over VKAs in historical trials? The difficulties/practicalities of monitoring warfarin in patients with cancer/on chemotherapy are significant in the real world and this recommendation does not reflect this. The patient burden is substantial, and the cost of the drugs is not the only consideration. There are many chemotherapy regimes causing thrombocytopenia	Thank you for your comment. This update followed the methods outline in the NICE guideline manual based on the best available evidence and we are unable to comment on how other guidelines conduct their reviews or examine how they reach their recommendations. Following discussion of stakeholder comments, the committee agreed to amend the recommendations to make it clear that if a DOAC is unsuitable, to consider

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				and we are familiar with dose adjustments of LMWH but not with the use of warfarin. (Samuelson et al. Management of cancer-associated thrombosis in patients with thrombocytopenia: guidance from the SSC of the ISTH. J Thromb Haemost. 2018 Jun;16(6):1246-1249). We recommend modifying the statement to 'Consider LMWH on its own if the person finds oral medicine difficult to tolerate or a VKA is contraindicated or if LMWH is considered a safer option by the treating cancer specialist'.	LMWH alone or LMWH with a VKA. The committee agreed that for most people, VKA will be unsuitable due to the potential for drug interactions and is less favourable efficacy profile compared to alternatives. However, the committee agreed that in a small number of people, such as those unable to take DOACs who request an oral treatment, VKA may be an option. It was included in the draft recommendations as an alternative to a DOAC because it was more cost effective than LMWH. LMWH was not cost effective due to its high cost compared to DOACs and LMWH with VKA. The committee agreed not to make more specific recommendations for when a specific drug is unsuitable due to a lack of evidence, to prevent the recommendations from becoming overly complex and because the suitability of each drug for an individual needs to be assessed on a case by case basis. However, to ensure that the treatment of people with VTE and cancer is individualised, the committee made a separate recommendation to ensure that tumour site, drug interactions and the person's bleeding risk are taken into account when choosing an anticoagulant. These updated recommendations should ensure that an individual can receive LMWH if it is the most appropriate treatment option while supporting the NHS to make the best use of its limited resources.
British Society for Haematology	Guideline	17	12 - 14	Very difficult to deliver this second recommendation for similar reasons to comment 1. We understand that from a patient's perspective, this would seem	Thank you for your comment. The committee agreed that this direct contact relates specifically to the working hours of specialist services and that a separate, out-of-

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				favourable but effective delivery would require a redesign of current services. We agree with the other two recommendations in 1.4.2.	hours service should be contacted at all other times. The rationale for outpatient treatment has been expanded to clarify this point. The committee envisaged that this recommendation would direct people to use existing out of hours services. Please also see our response to your other comment regarding this and the discussion section of the outpatient review for further details.
British Society for Haematology	Guideline	17	27 - 30	In practice, many find this score unhelpful as most men are usually sufficiently high risk anyway to continue anticoagulation and it's not as useful for women where a risk assessment tool is more important in view of the lower overall recurrence risk. Some find HERDOO2 far more useful. We would therefore suggest that only recommending DASH is not clinically useful. There may be more scientific merit to suggest using the D dimer as a biomarker without associating it with any single risk tool (e.g. Palareti G, et al. *Blood* 2014;124:196–203).	Thank you for your comment. The recommendation for DASH was specifically for people aged under 65 who were wanting to stop using anticoagulation. The intention was for DASH to be used as supporting evidence to help inform these people of their risk of recurrence. However, after re-reviewing the evidence and the feedback from stakeholders, the committee decided not to recommend the use of DASH or any other tool to predict VTE-recurrence. This review question only included studies in which participants received at least 3 months of anticoagulation treatment, stopped treatment, were tested using prognostic tool(s) and followed up off-treatment. As the HERDOO2 study was a management study, only the data pertaining to those participants who stopped treatment were extracted for this review. The committee agreed that they could not recommend the use of HERDOO2 based on this data.

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					The committee recognised that a clinical risk tools would only be useful in practice if it had better prognostic accuracy than clinician judgement. This judgement may include the use of D-dimer results as you suggest.
British Society for Haematology	Guideline	18	1 - 4	The utility of the HAS-BLED score in VTE patients was low in the initial published studies but more recent studies are more supportive. However, is there evidence to support DASH over VTE-BLEED which was developed with the inclusion of patients on DOACS?	Thank you for your comment. The committee reviewed evidence for multiple different tools to predict major bleeding alongside HAS-BLED, including VTE-BLEED. Many of these tools had poor to adequate prognostic accuracy and the committee agreed that they could not recommend them. The committee noted that VTE-BLEED had adequate accuracy and that this tool had been developed in participants receiving a DOAC but agreed that the HAS-BLED was preferable due to evidence suggesting it is more accurate. For example, when looking at evidence from C-statistics, HAS-BLED had a C-statistic of 0.71 (95%CIs 0.70-0.72) (see Brown, 2018 and Kooiman 2015) whereas the studies assessing VTE-BLEED found it to have a C-statistic of 0.67 (0.62, 0.71) (see Klok 2017 and 2018). In addition, HAS-BLED has been validated in a population of people with VTE who were taking LMWH, VKA or a DOAC (Brown 2018). The evidence is presented fully in evidence review F, which also contains details of the committee discussions concerning this topic. Brown J D, Goodin A J, Lip G Y. H, and Adams V R (2018) Risk Stratification for Bleeding Complications in Patients With Venous Thromboembolism: Application of the HAS-BLED Bleeding Score During the First 6

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					Months of Anticoagulant Treatment. Journal of the American Heart Association 7(6), 07 Klok F A, Barco S, and Konstantinides S V (2017) External validation of the VTE-BLEED score for predicting major bleeding in stable anticoagulated patients with venous thromboembolism. Thrombosis & Haemostasis 117(6), 1164-1170 Klok F A, Barco S, Turpie A G. G, Haas S, Kreutz R, Mantovani L G, Gebel M, Herpers M, Bugge J P, Kostantinides S V, and Ageno W (2018) Predictive value of venous thromboembolism (VTE)-BLEED to predict major bleeding and other adverse events in a practice-based cohort of patients with VTE: results of the XALIA study. British Journal of Haematology 19, 19 Kooiman J, van Hagen , N , Iglesias Del Sol, A , Planken E V, Lip G Y, van der Meer , F J, Cannegieter S C, Klok F A, and Huisman M V (2015) The HAS-BLED Score Identifies Patients with Acute Venous Thromboembolism at High Risk of Major Bleeding Complications during the First Six Months of Anticoagulant Treatment. PLoS ONE [Electronic Resource] 10(4), e0122520
British Society for Haematology	Guideline	18	10	In the absence of head to head trials, this is a very controversial recommendation.	Thank you for your comment. In the absence of head to head trials, a series of network meta-analyses (NMAs) were conducted to address the relative effectiveness of different

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					anticoagulation therapies. This an established approach that is widely used in international health research, including Cochrane review and WHO guidelines [see http://www.who.int/bulletin/volumes/94/10/16-174326/en/] and NICE guidelines, for some years now (for example, see the following NICE mental health guidelines: Schizophrenia CG 178, Generalised anxiety disorder CG 113, Social anxiety disorder CG159, Bipolar disorder CG 185, Eating disorders NG69). In addition, the NICE guidelines manual states "When multiple options are being appraised, a network meta-analysis should be considered" (p104). The committee agreed that in the absence of head to head trials, there are remaining uncertainties concerning the most effect option for secondary prevention of VTE. In particular, the committee were concerned that the inclusion criteria for the AMPLIFY-EXT trial may select for participants less prone to bleeds. This was also relevant to the AMPLIFY trial for initial treatment. When the results from the NMAs were combined with the economic model and multiple scenarios (including those for switching treatment and staying on the same treatment for secondary prevention) were analysed, switching to apixaban if on a different DOAC, was the most cost-effective option due to primarily to evidence from the NMA suggesting fewer major bleeds associated with apixaban during this phase of treatment (please see the economic model report in document G and evidence review D for more information). Based on this, the

					committee agreed to recommend considering switching to apixaban if on a different DOAC which is not well tolerated. However, due to the acknowledged uncertainty remaining in this area and the difficulties associated with changing an established therapy, the committee originally made a recommendation to specify that people who are continuing treatment, should carry on with the same treatment they are currently taking, as a first option, and to consider changing to apixaban (if on another DOAC) as a second option. Following discussion of the stakeholder comments the committee agreed that the intention of the recommendation as outlined above wasn't clear and they amended it to try to improve this. The recommendation now states that for most people, the first option would be to continue with the same treatment if it is already well tolerated. If not well tolerated or the clinical situation or personal preferences change, changing to apixaban should be considered if the person is currently taking a DOAC. In practice, these recommendations will likely mean that most people continue with the same treatment initially given. In a small number of cases, in which the initial treatment is no longer suitable, people on a DOAC (that is not apixaban) may switch to apixaban. This is therefore unlikely to prove controversial in practice.
British Society for Haematology	Guideline	18	13 - 18	We would argue that there is insufficient evidence to make any of these recommendations (especially in	Thank you for your comment. In the absence of evidence to the contrary and taking into account the

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				relation to renal function) and suggest removing section 1.4.9.	inherent difficulties surrounding changing treatment unnecessarily, the committee used their clinical expertise to recommend considering continuing the same treatment for these groups of people. The committee agreed that it was important to provide guidance in these areas and that the decision should take into account the person's preferences and their clinical situation to cover situations in which changing treatment may be appropriate.
British Society for Haematology	Guideline	19	1 - 3	Is this cost effective/evidence based? It would require redesign of services in either primary or secondary care (perhaps specify which). It would be difficult for a non-specialist primary care physician to deliver this.	Thank you for your comment. This recommendation was based on committee consensus rather than a formal search for effectiveness and cost-effectiveness evidence comparing different frequencies of review. The committee agreed that reviewing general health, risk of recurrence, bleeding risk and treatment preferences for people having long-term anticoagulation treatment is in line with good clinical practice. They noted that the review could take place in either primary or secondary care and did not wish to specify which setting because this would depend on local configuration of services. The committee noted that annual reviews for people having long-term anticoagulation treatment are already common in current practice, including for people who are discharged to primary care. The cost-effectiveness analysis of pharmacological treatments also took into account the cost of primary care appointments for monitoring and reviewing treatment for people on long-term (extended) therapy. It was assumed that the

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					frequency of review would depend on the type of treatment and the individual's clinical circumstances.
British Society for Haematology	Guideline	20	13 - 19	Since these recommendations were made, 2 further RCTs are not supportive (PMID: 29211671; PMID: 31786086) We suggest a rewording. It would be better to state that this should not routinely be offered outside of registry or research context.	Thank you for your comment. The use of catheter-directed thrombolysis was not within the scope of this update. Therefore, the committee did not review any evidence and were unable to make recommendations on this topic. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
British Society for Haematology	Guideline	21	5 - 24	This section on IVC filters needs to be clearer in each recommendation and about whether it is referring to temporary or permanent filters. How long should you wait after establishment of anticoagulation before you take out the filter?	Thank you for your comment. The committee agreed that the current wording was confusing because some recommendations referred to temporary filters and other did not. The committee advised that the same device is used for both temporary and permanent filters and the difference is use depends on whether removal is planned or not. Taking this into account with stakeholder comments, the committee decided to remove any mention of temporary or permanent from the recommendations. This allows for the clinician to decide

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					whether the filter should be permanent or temporary based on the needs of the individual patient. The recommendation for using a filter when anticoagulants are contraindicated specifies that the filter should be removed at anticoagulation treatment is no longer contraindicated and has been established. The committee discussed your comment and decided that they could not give further guidance on how long to wait after establishment of anticoagulation before a filter removed as this may vary between patients and needs to be decided on an individual basis.
British Society for Haematology	Guideline	22	12	Recommend rewording: The use of the term 'imaging results' risks misinterpretation and those who still practice routine CT imaging to look for cancer (despite evidence from studies) may consider this as justification to continue that practice as recommended in CG144. It should be made clearer that CT imaging is recommended against in the absence of symptoms or signs or laboratory features suggestive of cancer.	Thank you for your comment. The committee agreed that inclusion of the term 'imaging results' risks confusion and does not make clear that the committee are recommending against CT imaging. The committee removed the reference to imaging results from the recommendation as they expect that any existing imaging results will be consulted during a history review. This point is explained in the rationale.
British Society for Haematology	Guideline	23	6 - 8	We recommend having a new recommendation 1.9.3b (for patients who are continuing anticoagulation as 1.9.3 is only for those stopping anticoagulation) Consider testing for antiphospholipid antibodies in people who have had unprovoked DVT or PE.	Thank you for your comment. In light of the MHRA alert, the committee amended the recommendations for thrombophilia testing to allow for the possibility of testing for acquired thrombophilia in people continuing anticoagulation and amended subsequent recommendations to clarify that these tests may be

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				Patients with high risk APS (triple positive) should be offered a VKA rather than DOAC. Be aware that these tests are affected by anticoagulants and specialist advice may be needed.	affected by anticoagulants. This section was out of the scope for this update. Therefore, the committee did not review the evidence and were unable to make new recommendations in this section. However, they were able to make a recommendation for the use of VKA in people with triple positive APS and VTE in the anticoagulation treatment section of the guideline which was in scope. We encourage you to submit suggestions for areas that NICE guidelines should address or where an update is needed of an existing topic. We pass comments onto surveillance where there is something that could trigger an update. For example, if there is new evidence that is likely to change recommendations, or if there is new evidence about topics that are not covered by the existing guidance, or if issues concerning safety are raised. If there is new evidence this needs to be verifiable by the inclusion of supporting references, specifically primary studies or systematic reviews of primary studies.
British Society for Haematology	Guideline	23	23	In the section "Terms used" the definition of hormonal therapy requires clarification. For example, use of progesterone only contraceptives and transdermal HRT are of unclear risk.	Thank you for your comment. Following discussion of stakeholder comments, the committee amended these definitions to refer to the combined oral contraceptive pill. They did not specify the type of HRT because they did not review the evidence for the risks associate with different types of HRT.

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British Thoracic Society	Guideline	General	General	The ESC 2019 guidelines have been published during the period of preparation of this NICE update. We would suggest that the recommendations of the ESC group are taken into consideration throughout to ensure that (a.) recent relevant data have been incorporated in the NICE guidance and that (b.) the NICE guidance do not, where possible, contradict that of the ESC guidance.	Thank you for your comment. This update followed the methods outline in the NICE guideline manual based on the best available evidence . We endeavour to create guidance that works for the system as a whole and rely on the committee members to bring their knowledge of the wider system to help draft recommendations.
British Thoracic Society	Guideline	General	General	As per other NICE guidelines we find that NICE CG 144 is much less easy to navigate than international guidelines (e.g. ACCP and ESC) which are much more clinically useful.	Thank you for your comment. We are sorry to hear that you think this is the case. NICE has developed visual summaries of the recommendations on diagnosis, initial management and anticoagulation treatment for DVT and PE, and this should aid in comprehension of the guideline. In addition, the NICE connect project is aimed at improving the accessibility of our guidance.
British Thoracic Society	Guideline	8	7	The PERC score is currently not widely used and the NICE guidelines would likely increase its use in the UK. The ESC 2019 guidelines comment that as the prevalence of PE in the studies of PERC was low then generalisability of their results is not possible.	Thank you for your comment. The conclusion made by the ESC was based on a different evidence base to the one assessed by the committee. The ESC evaluated two studies (a validation study and a management study) which, as you note, had a low prevalence of PE, however our review also assessed diagnostic accuracy studies, several of which had a high prevalence of PE. Based on the reviewed evidence, the committee came to a different conclusion to the ESC and agreed that the results were generalisable. Please see the chapter on PERC for more information on these studies and the committee's discussion of the evidence.

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British Thoracic Society	Guideline	16	4 - 8	The guideline states that LMWH alone is only second line therapy for patients with malignancy, with VKA and DOACs being preferable. Up until recently, LMWH was the treatment of choice in patients with malignancy, and we do not think that the data supports the use of VKA over LMWH. Two recent studies of edoxaban and rivaroxaban demonstrated adequate efficacy compared with LMWH in patients with malignancy except in GI related malignancy where the incidence of bleeding was high. The guidelines should highlight that the DOACS edoxaban and rivaroxaban may be first line therapy in patients with malignancy except in cancer of the GI tract.	Thank you for your comment. Although there have only been direct trials between edoxaban and rivaroxaban compared to LMWH alone, the NMA also used subgroup data for people with active cancer from the main DOAC trials for apixaban and dabigatran compared to warfarin. The committee noted that the effects reported in these trials were roughly consistent with those for the population without cancer, and the NMA allowed for indirect comparisons to be made using this data to compare the treatments to the other DOACs and LMWH alone. Additionally, the committee noted that the ADAM-VTE trial (McBane 2019), a small (~300 participants) trial comparing apixaban to LMWH alone recently published and that the results were consistent with that of the other DOACs without evidence of increased bleeds. Based on the above points the committee agreed to not specify particular DOACs in this recommendation. The committee noted that many of the bleeds associated with the DOACs were specifically gastrointestinal (GI) and genitourinary (GU) bleeds and that the safety profile of the DOACs compared to LMWH alone improved when only looking at other bleeds (see the benefits and harms section of the evidence review D for more information on this discussion). However, the committee agreed not to specifically prohibit the use of DOACs in people with GI and/or GU malignancy or give specific guidance on who is/is not suitable for a DOAC as there are potentially other types of malignancies

					which make a DOAC unsuitable. They were concerned that if they provided a list of tumours with which to avoid DOAC use this would not be exhaustive and could mislead clinicians. Instead, the committee made a separate recommendation to take into account the tumour site and bleeding risk when prescribing anticoagulation for people with cancer (which will include considerations of whether the person has a GI/GU malignancy or another tumour type that may be associated with a higher bleeding risk. In addition, following discussion of stakeholder comments, the committee agreed to amend the recommendations to make it clearer that if a DOAC is unsuitable, to consider LMWH alone or LMWH with a VKA, placing LMWH with VKA last because they recognised it was unlikely to be a suitable treatment option for most people with cancer and VTE. These recommendations were intended to ensure that the individual with cancer received the most appropriate treatment for their VTE whilst supporting the NHS to make the best use of its limited resources. Reference: McBane, RD, Wysokinski W , Le-Rademacher J G…., &. Loprinzi CL. (2019) Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. J. Thromb Haemost, [epub ahead of print]

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British Thoracic Society	Guideline	17	7	The ESC guidelines have moved away from using terminology of provoked or unprovoked since several provoking factors are associated with only a small increase in risk.	Thank you for your comment. The committee decided not to change the definition of provoked and unprovoked for the purposes of this update as the evidence reviewed over the course of the update, and the discussions surrounding provoked/unprovoked VTE have been in relation to our definitions as detailed in the terms used in the guideline section of the guideline and not the definition used by the ESC. However, following stakeholder comments, the committee amended the text to make it clearer within the recommendation for stopping treatment if the person had a provoked VTE that the risk factor must not be persistent. This update followed the methods outline in the NICE guideline manual based on the best available evidence and we are unable to comment on how other guidelines conduct their reviews or examine how they reach their recommendations.
British Thoracic Society	Guideline	26	28	The comment that there are only limited prospective evidence for DVT and retrospective evidence for PE is incorrect. The adjust-PE, YEARS and ARTEMIS studies are large prospective studies.	Thank you for your comment. The YEARS and ARTEMIS trials are both large prospective studies however these assess the use of a diagnostic algorithm (which includes a D-dimer measurement) however this was not within the scope of this update. This update only included diagnostic accuracy studies in which all participants received a D-dimer tests and a reference standard (such as CTPA), in order to assess the accuracy of laboratory, point-of-care and age-adjusted D-dimer tests. The ADJUST-PE study did not meet inclusion criteria for this review as not all participants went on to receive the reference standard. However, the

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					committee were aware of this study and included it in their discussions which can be found within evidence review A.
Cambridge University Hospitals NHS Foundation Trust	Guideline	General	General	Distal DVT – the guideline lacks any clarity on this controversial area. Please provide some guidance.	Thank you for your comment. The scope of this update of the VTE guideline did not include diagnosis (apart from the use of age adjusted and point of care D-dimer). Therefore, the committee did not review the evidence and were unable to make any recommendations concerning the diagnosis of distal/below the knee DVT. For the areas of the management part of the guideline that were updated the reviews did not identify any evidence specific to distal DVT and the committee were therefore unable to make any recommendations for this type of DVT. We encourage you to submit suggestions for areas that NICE guidelines should address or where an update is needed of an existing topic. We pass comments onto surveillance where there is something that could trigger an update. For example, if there is new evidence that is likely to change recommendations, or if there is new evidence about topics that are not covered by the existing guidance, or if issues concerning safety are raised. If there is new evidence this needs to be verifiable by the inclusion of supporting references, specifically primary studies or systematic reviews of primary studies.

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Cambridge University Hospitals NHS Foundation Trust	Guideline	General	General	There is no mention of pregnant patients. Is this presumed to be covered in the RCOG guidance? Please be explicit if this is outside the guideline scope and reference the RCOG guidance.	Thank you for your comment. Pregnant women are excluded from this guideline as stated in the published scope document and EIA. However, the committee have added text to the context section of the guideline to specify that this is the case. As you note, there is separate guidance on managing DVT and PE in this population group, published by the Royal College of Gynaecologists (RCOG), (RCOG, 2015).
Cambridge University Hospitals NHS Foundation Trust	Guideline	General	General	There were some local points raised by my colleagues at CUH about things that were not fully addressed in the guidance: • Early thrombus removal for iliofem DVT • Role of residual thrombus / D-Dimer to help decide whether to extend anticoagulation (DACUS trial) • Defining what type of ultrasound (3-point compression vs whole leg) • Upper extremity DVT • Anticoagulation treatment 'failures' –role of Xa monitoring, increasing therapeutic dose etc. • Use of compression therapy – there is some fairly compelling evidence (accepting SOX-2)	Thank you for your comment. This scope of this update of the VTE guideline did not include thrombolytic therapy, mechanical interventions or diagnosis (apart from the use of age adjusted and point of care D-dimer). Therefore, the committee did not review the evidence relating to the early removal of iliofemoral DVT, investigations for optimal type of ultrasound and the use of compression therapy and were unable to make recommendations on these topics. Although mechanical interventions were out of scope, during the update the committee raised a safety issue concerning the use of IVC filters and identified new evidence that was likely to change the existing recommendations. As a result, despite being initially out of scope, this section was updated at the end of the current work. The optimal duration of anticoagulation treatment section was updated, however, the evidence review

					dealt specifically with the use of risk tools to predict the occurrence of major bleeding or VTE-recurrence and therefore the DACUS trial did not meet the inclusion criteria for this review. The management of upper extremity DVT was not within the scope of this update and was listed in the areas not covered by the guideline as DVT in the arms. Therefore, the committee could not make any recommendations on this topic. In response to your comment about anticoagulation treatment failures, the committee have added a recommendation that in the event of treatment failure, adherence to the anticoagulation treatment should be checked, other sources of hypercoagulability addressed and the dose increased or treatment changed to an anticoagulant with a different mode of action. We encourage you to submit suggestions for areas that NICE guidelines should address or where an update is needed of an existing topic. We pass comments onto surveillance where there is something that could trigger an update. For example, if there is new evidence that is likely to change recommendations, or if there is new evidence about topics that are not covered by the existing guidance, or if issues concerning safety are raised. If there is new evidence this needs to be verifiable by the inclusion of supporting references,

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					specifically primary studies or systematic reviews of primary studies.
Cambridge University Hospitals NHS Foundation Trust	Guideline	7	21	1.1.13. This NICE guideline stipulates not prescribing the only drug licenced for cancer VTE on the market (LMWH) and this needs revision. The NICE recommendation is advising off label/licence prescribing and this is going to put many doctors in a difficult position. This recommendation by this guidance is likely to be widely derogated from.	Thank you for your comment. The recommendation in the consultation version of the guideline does not prevent prescription of LMWH for people with active cancer, but rather places some conditions on its use based on the lack of cost-effectiveness of this treatment. The committee recognised that LMWH is the established treatment, is licensed for this indication and may be the only suitable treatment for certain people. However, if a DOAC is suitable, then they agreed that this should be used in preference to LMWH as this is a better use of NHS resources. Following discussion of stakeholder comments, the committee rewrote the recommendations to make it clearer that the choice of anticoagulant treatment should take into account the tumour site, interactions with other drugs and bleeding risk. DOACs remain the first treatment option, but if they are unsuitable then LMWH alone or LMWH+VKA can be considered. They agreed that these recommendations should enable the clinician, in discussion with their patient, to choose the appropriate treatment on a case by case basis while trying to support the NHS to make the best use of its limited resources. Although DOACs are not currently licensed for use in

					people with active cancer, there is evidence regarding their efficacy in comparison to LMWH from clinical trials. For example, the trials for rivaroxaban (Young, 2018) and edoxaban (Raskob, 2018). Based on this evidence, evidence from subgroup analyses for the other two DOACs and the economic modelling, the committee agreed that it was appropriate to recommend the DOACs as first line treatment if they are suitable. In addition, the new ADAM-VTE trial looking at apixaban also supports the use of apixaban in people with active cancer (McBane, 2019). It found that apixaban for VTE treatment in cancer was associated with greater reduction in VTE recurrence and similar bleeding rates compared to dalteparin. References McBane R.D et al. (2020). Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial.J Thromb Haemost. (Epub 2019 Nov 28. doi: 10.1111/jth.14662.) Raskob, G. E., et al. (2018). Edoxaban for the treatment of cancer-associated venous thromboembolism. New England Journal of Medicine, 378(7), 615-624 Young, A. M., et al. (2018). Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). Journal of Clinical Oncology, 36(20), 2017-2023.

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Cambridge University Hospitals NHS Foundation Trust	Guideline	7	23, 24	Rec 1.1.14. Why can a 'main lab' D-dimer also not be age adjusted? I think if using age adjustment each Trust should validate this given the heterogenous nature of D-dimer testing and be aware that for each assay there needs to be a separate validation done.	Thank you for your comment. A laboratory D-dimer test can be age-adjusted and the committee have recommended that age-adjustment be considered when using a point of care or laboratory test.
Cambridge University Hospitals NHS Foundation Trust	Guideline	13	11 - 12	Rec 1.3.4. You advise a clotting profile is performed. Is this evidence based? I could not find any evidence to support this in evidence summary D or E when the document is searched for 'clotting profile. The British Committee for Standards in Haematology does not recommend clotting tests routinely before surgery. In the case of anticoagulation in the absence of a known or suspected clotting disorder then I suspect there is little evidence to support the recommendation in this NICE guidance. This is a large burden of tests for laboratories and therefore can this recommendation be justified?	Thank you for your comment. The recommendation to perform a clotting profile was based on committee consensus. However, following discussion of the stakeholder comments, the committee decided to amend the recommendation to remove mention of clotting profile and instead specifically recommend that tests for prothrombin time (PT) and Activated Partial Thromboplastin Time (APTT) be conducted. This should reduce the burden of tests.
Cambridge University Hospitals NHS Foundation Trust	Guideline	17	27 - 30	Rec 1.4.5. The DASH score gives an insufficient estimation of risk when we have audited it at our centre (MacDonald et al, 2019, BJH,185, 631-633) and I am concerned that you have overlooked this and also that other validated tools are available (I can see in the evidence summary you have looked at these). In the external validation of DASH by Tosetto et al (2017, JTH) the VTE recurrence rate per year was 3.9 (95 % CI 3.6–4.2) and at 2 years was 5.9 (95 % 0.3–11.3) for a score of 0 (i.e. female >50). This is	Thank you for your comment. The recommendation for DASH was specifically for people aged under 65 who were wanting to stop using anticoagulation. The intention was for DASH to be used as supporting evidence to help inform these people of their risk of recurrence. However, after re-reviewing the evidence and the feedback from stakeholders, the committee decided not to recommend the use of DASH or any other tool to predict VTE-recurrence.

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				above the 15% recurrence at 5 years rate threshold at which the ISTH recommend long-term anticoagulation (Kearon C, Iorio A, Palareti G.; Subcommittee on Control of Anticoagulation of the SSC of the ISTH. Risk of recurrent venous thromboembolism after stopping treatment in cohort studies: recommendation for acceptable rates and standardized reporting. J Thromb Haemost. 2010;8:2313-2315). Widespread use of the DASH may lead to unacceptable rates of recurrence. The guideline needs to make clear that a low risk DASH actually has a VTE recurrence rate higher than the original model (please see the paper by MacDonald et al and also table 3 in Tosetto et al 2017). In addition, the HERDOO2 score is prospectively validated. This guidance puts an over reliance on the DASH tool. In addition, in our audit when patients 50-65 were looked at with a low DASH score recurrence rate was >5/100 patient years (MacDonald et al, 2019, BJH,185, 631-633).	This review question only included studies in which participants received at least 3 months of anticoagulation treatment, stopped treatment, were tested using prognostic tool(s) and followed up off-treatment. As the HERDOO2 study was a management study, only the data pertaining to those participants who stopped treatment were extracted for this review. The committee agreed that they could not recommend the use of HERDOO2 based on this data.
Cambridge University Hospitals NHS Foundation Trust	Guideline	18	5 - 12	Rec 1.4.8. Please make clear that low dose rivaroxaban 10mg daily is also a licenced treatment for long-term prophylaxis per the EINSTEIN-CHOICE study and has been audited by us (Thomas W et al, 2019, BJH, 186(3): e39-e41.). Our current practice would be to de-escalate if there is no compelling reason (detailed in Thomas et al – see above) to rivaroxaban 10mg after 6 months and I am concerned that you are suggesting apixaban is the	Thank you for your comment. The committee did not intend apixaban to be the mandated long-term treatment. In response to stakeholder comments they have amended the recommendation to make it clearer that the first option for long term treatment of VTE is continuing with the same treatment if it is well tolerated, the clinical situation or personal preferences have not changed. Based on the recommendations in the section on initial treatment of VTE the majority of people, who do

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				mandated long-term agent of choice when there are no head to head trials of low dose rivaroxaban v apixaban. In addition, the use of low dose DOAC long-term is not universally accepted and is the subject of on-going RCT's: the RENOVE (NCT 032854380) and COVET (NCT03196349) trials. In addition, there are other long-term VTE treatment trials using other agents. The way this reads currently is far too biased in favour of apixaban, which is only licenced at low dose 2.5mg BD for the long-term.	not have one of the conditions that require a different treatment regimen, will be prescribed a DOAC with apixaban or rivaroxaban. The people who are taking rivaroxaban will therefore be able to stay on this anticoagulant with the above caveats. They will only switch to apixaban if there is specific reason for this change. You note that there are no head to head trials of low dose rivaroxaban v apixaban, the network meta-analyses were carried out to compare these treatments and included the results in an economic model. Based on the cost-effective evidence and evidence from the extended treatment NMA suggesting the potential for fewer bleeds with apixaban, the committee agreed to recommend considering switching to apixaban if on a different DOAC which is not well tolerated. This recommendation does not prevent the clinician from de-escalating treatment with rivaroxaban to 10mg. The committee agreed not to specify which dose to use as it is intended that dose-adjustments are made in line with the summary of product characteristics (SPCs) for the drug being used, which provide detailed information on when to adjust the dose and recommend that rivaroxaban is adjusted to 10mg once daily after 6 months of treatment. The committee agreed not to

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					duplicate this information within the recommendations themselves to limit complexity. We will pass the information about the ongoing trials to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
Cambridge University Hospitals NHS Foundation Trust	Guideline	18	21 - 22	Rec 1.4.10. You may wish to consider the data from the EINSTEIN-CHOICE trial in regard to the fact that aspirin provides less protection from VTE whilst having the same bleeding risk as low dose rivaroxaban. I did find this recommendation extremely helpful however as there are some patients whose occupations allow low dose aspirin as long-term thromboprophylaxis but not DOAC and thus this is a helpful statement.	Thank you for your comment. The committee agreed that aspirin was less effective than the DOACs and that aspirin use is associated with a risk of bleeding. The recommendation to consider aspirin relates specifically to those people who are suitable for but decline continued treatment with anticoagulation. The committee agreed that in the absence of alternative anticoagulation aspirin would be suitable due to evidence suggesting a reduction in VTE-recurrence at 2 years compared to placebo. However, it is intended that any decision to continue treatment will include an informed discussion with the person with VTE and that this would include information on the efficacy and bleeding risk associated with aspirin.
Cambridge University Hospitals NHS Foundation Trust	Guideline	19	1 - 3	Rec 1.4.11. Have you factored in the cost on primary care as many services discharge long-term anticoagulation patients to the GP and therefore this recommendation is a potential burden on the primary care services?	Thank you for your comment. This recommendation was based on committee consensus rather than a formal search for effectiveness and cost-effectiveness evidence comparing different frequencies of review. The committee agreed that reviewing general health, risk of recurrence, bleeding risk and treatment preferences for people having long-term anticoagulation treatment is in line with good clinical practice. They noted that the review could take place in either primary or secondary

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Cambridge University Hospitals NHS Foundation Trust	Guideline	19	6 - 9	Rec 1.9.3. In light of the recent EMA warning on DOAC and APS a clearer statement from NICE is required here. Presumably any patient where long-term anticoagulation is planned would also need APL screening because of the EMA warning and also the recent data from the TRAPS study which showed the treatment of choice for APS patients was warfarin. The current draft provides insufficient advice for doctors. Patients planning to continue long-term anticoagulation need APL screening to be able to counsel them, if they have APS, on DOAC v warfarin. In addition, the guideline does not contain details on DOAC v warfarin which it should do.	Thank you for your comment. Thrombophilia testing was not within the scope of this guideline and therefore the committee did not review the relevant evidence and were unable to make new recommendations in this area. However, in response to the EMA and MHRA alerts, the committee have amended the recommendations in this section. Specifically, they now recommend against tests for hereditary thrombophilia (instead of just saying thrombophilia). This recommendation therefore now allows for the testing for acquired thrombophilia. The committee were able to include a specific recommendation for the treatment of people with triple positive APS with warfarin in the anticoagulation treatment section because this section was within the scope of this update.

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Cambridge University Hospitals NHS Foundation Trust	Guideline	19	10 - 14	Rec 1.9.4. It is not clear whether testing for thrombophilia in patients with unprovoked VTE is helpful because even if they have a normal screen they are at high recurrence risk and thus this recommendation does not seem logical.	Thank you for your comment. In response to the EMA and MHRA alerts suggesting safety issues with the use of DOACs, the committee were able to make slight amendments to the recommendations in the section on thrombophilia. However, as this section was not within the scope of this update they were unable to make new recommendations or substantially alter the existing ones apart from addressing these safety concerns.
Cambridge University Hospitals NHS Foundation Trust	Guideline	19	10 - 15	Rec 1.8.1. Please clarify whether urinalysis means a simple/common urine dip or whether you also mean cytology. Many clinicians complain this is too vague.	Thank you for your comment. The committee agreed that the recommendation was referring to a simple urine dip. Following discussion of stakeholder comments, they decided to amend this recommendation to remove mention of urinalysis due to the potential for confusion and because the committee did not consider that a full urinalysis was needed.
Cambridge University Hospitals NHS Foundation Trust	Guideline	21	8	Re: IVC filters. The guidance is helpful but still a little unclear. For example, is an IVC filter required for a recent popliteal DVT where a 24-hour break in anticoagulation required?	Thank you for your comment. The committee agreed that they could not give further guidance on how long to wait after anticoagulation is contraindicated before a filter is considered as this may vary between patients and needs to be decided on an individual basis.
Cambridge University Hospitals NHS Foundation Trust	Guideline	23	17	The term contraceptive pill is inaccurate. This should be the combined oral contraceptive pill (COCP) and tablet HRT. The mini-pill for example is safe in terms of VTE risk. In addition, you should consider guidance stating that patients on the COCP that have VTE can remain on the COCP so long as they are taking therapeutic anticoagulation – there is literature on this.	Thank you for your comment. Following discussion of the stakeholder comments, the committee have amended the wording of the definitions of provoked and unprovoked VTE to refer specifically to the combined oral contraceptive pill (COCP). However, the use of COCP by people with VTE was not within the scope of this update and the committee did not review the evidence concerning its safety for people taking

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					anticoagulants. They were therefore unable to make recommendations on this topic. We encourage you to submit suggestions for areas that NICE guidelines should address or where an update is needed of an existing topic. We pass comments onto surveillance where there is something that could trigger an update. For example, if there is new evidence that is likely to change recommendations, or if there is new evidence about topics that are not covered by the existing guidance, or if issues concerning safety are raised. If there is new evidence this needs to be verifiable by the inclusion of supporting references, specifically primary studies or systematic reviews of primary studies.
Chelsea and Westminster Hospital NHS Foundation Trust	Guideline	General	General	Chelsea and Westminster Hospital NHS Foundation Trust' endorses the response submitted by the UK Clinical Pharmacy Association (UKCPA).	Thank you for your comment, please see the responses to the UKCPA comments.
Chesterfield Royal Hospital NHS Foundation Trust	Guideline	15	10	We are concerned that offering LMWH for people with established renal failure (CrCl < 15 ml/min) may lead to increased risk of bleeding due to accumulation of the LMWH.	Thank you for your comment. The committee agreed that there is a risk of accumulation associated with the use of LMWH alone in people with established renal failure. They agreed that LMWH alone should only be used on a case by case basis but decided not to remove it as LMWH alone is still a viable option for some people. They also noted that LMWH accumulation can be

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					avoided with effective anti-Xa monitoring and by consulting the information in the summary of product characteristics and locally agreed protocols. However, following stakeholder comments the committee have also included LMW+VKA as an option.
Chesterfield Royal Hospital NHS Foundation Trust	Guideline	15	17	Monitor trial evidence closely as preliminary data suggest that using DOACs in people with BMI >40 kg/m2 is actually safe and effective.	Thank you for your comment and this information. The committee discussed feedback from stakeholders and agreed that there may be circumstances in which the DOACs could be used in people with BMI >40 kg/m2. They amended the recommendation to allow for this possibility by removing the reference to a specific anticoagulant, and instead stressing the importance of monitoring, using dose adjustments where necessary and following locally agreed protocols or advice from a specialist or multidisciplinary team. Additionally, based on stakeholder responses, the committee decided to make reference to absolute weight rather than BMI and amended the recommendation to cover people at both extremes of weight (<50kg or >120kg).
Chesterfield Royal Hospital NHS Foundation Trust	Guideline	17	27	There is evidence using the Vienna and HERDOO2 validated scores (not only the DASH score) to inform discussions regarding the risk of VTE recurrence.	Thank you for your comment. This review question only included studies in which participants received at least 3 months of anticoagulation treatment, stopped treatment, were tested using prognostic tool(s) and followed up off-treatment. As the HERDOO2 study was a management study, only the data pertaining to those participants who stopped treatment were extracted for this review. The

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					committee agreed that they could not recommend the use of HERDOO2 based on this data. Additionally, the committee agreed that the evidence suggested that the diagnostic accuracy of VIENNA was too low to support its use. Following feedback from stakeholders, the committee agreed to remove the recommendation for the use of DASH also. Please see the chapter on prognosis for further discussion of the evidence for each of these tools.
Chesterfield Royal Hospital NHS Foundation Trust	Guideline	18	1	There is evidence using the VTE-BLEED score (not only the HAS-BLED score) to assess the risk of major bleeding in people having anticoagulation for unprovoked VTE.	Thank you for your comment. The committee reviewed evidence for multiple different tools to predict major bleeding alongside HAS-BLED, including VTE-BLEED. Many of these tools had poor to adequate prognostic accuracy and the committee agreed that they could not recommend them. The committee noted that VTE-BLEED had adequate accuracy and that this tool had also been evaluated in participants receiving a DOAC but agreed that the HAS-BLED was preferable due to evidence suggesting it is more accurate. In addition, HAS-BLED has been validated in a population of people with VTE who were taking LMWH, VKA or a DOAC (Brown 2018). The evidence is presented fully in evidence review F, which also contains details of the committee discussions concerning this topic. Brown J D, Goodin A J, Lip G Y. H, and Adams V R (2018) Risk Stratification for Bleeding Complications in Patients With Venous Thromboembolism: Application of the HAS-BLED Bleeding Score During the First 6

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					Months of Anticoagulant Treatment. Journal of the American Heart Association 7(6), 07
Clinical Leaders of Thrombosis	Guideline	8	7	The "PERC" rule out criteria is only validated for use in ED.	Thank you for your comment. Although the studies using PERC were all performed in the emergency department the committee agreed that the results could be extrapolated to other settings.
Clinical Leaders of Thrombosis	Guideline	15	18	The drug SPC and other national and international guidelines use weight not BMI when deciding what anticoagulant to use.	Thank you for your comment. The recommendation relating to BMI was based primarily on consensus due to limited evidence from randomized controlled trials in this population. The committee discussed feedback from stakeholders concerning the use of absolute weight instead of BMI and that there are concerns with treating people with low body weight as well as those with high body weight. The committee agreed with stakeholder concerns and decided to specifically make reference to absolute weight rather than BMI and amended the recommendation to cover people at both extremes of weight (<50kg or >120kg). The committee selected these cut-off points based on clinical experience and due to these cut-offs being most commonly highlighted in the summary of product characteristics (SPCs)for the DOACs.
Clinical Leaders of Thrombosis	Guideline	17	27	The DASH score cannot be used whilst the patient is taking anticoagulation as it requires a d dimer to be measured off treatment the HERDOO2 Score which can be used whilst on treatment may be a better score to use.	Thank you for your comment. The recommendation for DASH was specifically for people aged under 65 who were wanting to stop using anticoagulation. The intention was for DASH to be used as supporting evidence to help inform these people of their risk of recurrence. However, after re-reviewing the evidence and the feedback from stakeholders, the committee

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					decided not to recommend the use of DASH or any other tool to predict VTE-recurrence. This review question only included studies in which participants received at least 3 months of anticoagulation treatment, stopped treatment, were tested using prognostic tool(s) and followed up off-treatment. As the HERDOO2 study was a management study, only the data pertaining to those participants who stopped treatment were extracted for this review. The committee agreed that they could not recommend the use of HERDOO2 based on this data.
Clinical Leaders of Thrombosis	Guideline	18	9	Not clear why you would switch to Apixaban if they are on another DOAC with no problems.	Thank you for your comment. This recommended has been amended to clarify that for most people, assuming the drug is well tolerated, the first option should be to continue with the same treatment. However, if the drug is a DOAC, and it is not well tolerated or the clinical circumstances or preferences of the person with VTE change then they could consider changing to apixaban. For the initial treatment of VTE, the committee recommended the more cost-effective options (apixaban and rivaroxaban). However, for the extended treatment of VTE, rivaroxaban was not the second most cost-effective strategy (due primarily to greater uncertainty for major bleeds during this phase of treatment). Based on cost-effective evidence and evidence from the NMA suggesting the potential for fewer bleeds with apixaban, the committee agreed to recommend considering

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					switching to apixaban if on a different DOAC which is not well tolerated.
Clinical Leaders of Thrombosis	Guideline	18	21	Trials have shown aspirin inferior to DOAC to prevent VTE recurrence and this would need to be explained to the patient if following this action.	Thank you for your comment. The committee agreed that aspirin was less effective than the DOACs. The recommendation contains a footnote specifying that informed consent should be obtained and documented, previous recommendations (such as 1.4.3) should involve a discussion of the benefits and harms of any potential treatment strategy before this is commenced. This should involve discussion of the efficacy and bleeding risk of aspirin.
Daiichi Sankyo Ltd	Guideline	General	General	Daiichi Sankyo would like to thank NICE for the opportunity to comment on the draft Venous thromboembolic diseases: diagnosis, management and thrombophilia testing consultation document. In general, Daiichi Sankyo considers that the document is well written and contains important information on the diagnosis, management and thrombophilia testing in venous thromboembolic diseases. That said, Daiichi Sankyo is concerned that the current draft recommendations on anticoagulation treatment for suspected or confirmed deep vein thrombosis or pulmonary embolism (section 1.3.6) do not reflect adequately the acknowledged uncertainty in the relative clinical and economic effects between NICE recommended Direct Acting Oral Anticoagulant	Thank you for your comment. The guideline recommendations acknowledge that all DOACs in TA327, TA341, TA354, TA261, TA287 remain treatment options. The Guidance Executive Technology Appraisal Review Proposal paper stated that the guideline will cross-refer to and contextualise to relevant NICE technology appraisal guidance on pharmacological treatment for confirmed deep vein thrombosis (DVT) and pulmonary embolism (PE) and that the guideline will also be able to place these treatments into the appropriate clinical context, which is what has been done. The cost-effectiveness analysis was developed in line with our methods as described in Developing NICE guidelines: the manual. The manual states that public list prices for medicines should be used in the reference-case analysis. Analyses based on price reductions for the NHS will be considered only when the reduced

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				(DOAC) treatment options in this indication based on the available evidence. The current sequencing draft recommendations set out in section 1.3.6 would limit clinician and patient choice rather than offering the full range of DOAC options in accordance with NICE Single Technology Appraisals 261, 287, 327, 341 and 354. We believe that the draft recommendations fail to appropriately reflect the uncertainty in the indirect evidence when comparing between DOAC treatments based on the significant heterogeneity in patient populations across trials in this indication. The decision to restrict Lixiana® (Edoxaban▼) as an option after apixaban and rivaroxaban▼ is based on marginal differences in treatment effects when comparing across heterogenous patient populations. Additionally, the cost effectiveness analyses are based on NHS list price and do not consider the primary care rebate scheme for edoxaban which significantly improves the cost-effectiveness of the product and provides an opportunity for significant savings for the NHS. Daiichi Sankyo also notes that the draft recommendations made in section 1.3.6 appear inconsistent with the recent NICE Technology Appraisal Review Proposal paper (review of TA261, 287, 327, 341, 354) published by the NICE Guidance Executive in November 2019 which clearly cites that	prices are transparent and can be consistently available across the NHS, and when the period for which the specified price is available is guaranteed. Where possible, sensitivity analyses were undertaken to explore the impact of uncertainty in the cost-effectiveness analysis. It was not possible to fully quantify what impact potential differences in patient populations for the different DOAC trials have within the cost-effectiveness analysis but these issues were discussed extensively by the committee alongside the rest of the evidence, documented in the review and reflected in the recommendations.

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				no new evidence was identified to address the uncertainties in relative effectiveness between anticoagulation options since publication of the original technology appraisals.	
Daiichi Sankyo Ltd	Guideline	18	5 - 10	Daiichi Sankyo considers that the recommendation on reviewing anticoagulation treatment (specifically 1.4.8) could be misleading in its current form. P.34, lines 17-25 states: *"Continuing or changing current treatment* *The committee agreed that there are risks involved in switching anticoagulant treatment, particularly if there have been no adverse events with the current treatment. They also expressed concerns about convenience for people who are asked to switch from a direct-acting oral anticoagulant (DOAC) with no monitoring to a VKA regimen with frequent monitoring, or problems with adherence if switching from a VKA to a DOAC. Based on these concerns and their clinical experience, the committee agreed that if treatment is continued beyond 3 months, the first option for most people should be to continue the current treatment."* The current wording in section 1.4.8 seem to position continuation on current treatment or switching to apixaban (if on another DOAC) as equal options after 3 months which is contrary to the considerations outlined above which clearly mention that the first option for most people should be to continue the	Thank you for your comment. Following discussion of the stakeholder comments, the committee amended this recommendation to make it clearer that the first option should be to continue with the same treatment if it is well tolerated. If the current treatment is not well tolerated, or the clinical situation or person's preferences have changed then there is the option to change to apixaban if the current treatment is a different DOAC.

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				current treatment. Daiichi Sankyo request that NICE amend the wording in section 1.4.8 to clarify that the first option for most people is to continue with their current treatment.	
Daiichi Sankyo Ltd	Guideline	30	1 - 3	The draft recommendation to offer only a choice of apixaban and rivaroxaban as first line treatment appears inconsistent with the acknowledged lack of direct evidence and significant heterogeneity in patient populations across DOAC trials in the Pharmacological Treatment Report [Evidence review D] and the Economic Modelling Report [Evidence Review G]. The draft guideline states that there is evidence that apixaban is the most cost-effective option due to the low number of bleeds resulting from treatment, followed by rivaroxaban. This conclusion subsequently informs the decision to recommend initially offering patients these treatments. The conclusion on cost-effectiveness is drawn from the treatment effects analysed in the network meta-analysis (NMA) due to the absence of any direct evidence comparing treatments. As acknowledged in Evidence Review G, "*At the time of this analysis, there were no head-to-head RCTs comparing DOACs identified in the published literature. Although the committee agreed it was appropriate to undertake NMAs to synthesise direct and indirect evidence and to use these results to inform the economic analysis, the committee expressed concerns about potential*	Thank you for your comment. As you note, the committee were concerned with the heterogeneity between trials and that this limited comparability. The committee were particularly concerned with the inclusion/exclusion criteria surrounding the apixaban trial, which could potentially bias the study in favour of people taking apixaban having fewer bleeds compared to the other DOAC trials. However, the committee had fewer concerns with the heterogeneity between the remaining DOAC trials. The committee noted that apixaban was the most cost-effect option followed by rivaroxaban. The issues surrounding heterogeneity meant that the committee agreed that they could not recommend apixaban as the first option on its own. However, the committee were satisfied that the evidence suggests that apixaban or rivaroxaban was the most cost-effective option. In part, this was due to these two drugs having significantly reduced major bleeds compared to LMWH+VKA. The committee agreed that including both as first line options takes into account the underlying uncertainty that has resulted from the differences in inclusion criteria for the trials. A research recommendation was made for a trial using

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				heterogeneity of the patient populations in the different DOAC trials". This heterogeneity is illustrated in Tables 5 and 6 in the Pharmacological Treatment Report [Evidence review D]. In particular, the selection bias and differing study populations resulting from differences in trial inclusion and exclusion criteria caused concerns, "*…bleeding risk, which was shown in a number of one-way sensitivity analyses to be an influential parameter in the economic model*". Draft Evidence Review D acknowledges that "*These differences could potentially lead to a selection bias in favour of lower recurrence and bleeding rates in the commercial apixaban studies*". Indeed, the Committee made recommendations for further research in Appendix D which further highlighted their concerns. *"The research recommendation specified an analysis of individual patient data (IPD) from the existing RCTs involving DOACs and the other treatment options (see appendix Q for more details). They envisaged that this analysis would allow the selection of comparable participants from across the trials and that this data could be used in a series of NMAs to improve the estimation of relative clinical effectiveness, cost-effectiveness and safety between the DOACs and other treatment options. This would help to reduce the problems the committee had with differences in*	individual patient data from the existing DOAC RCTs as this would allow a more similar study population to be drawn from the DOAC trials to facilitate a more homogenous indirect comparison of these trials. The results of such a trial would provide support for or allow revision of the recommendations if needed during future updates of this guideline. However, the expressed need for this research does not invalidate the results of the NMA or the recommendations made in this review because the recommendations take into account the uncertainty discussed above. As you note, the committee made consensus recommendations for use of anticoagulation in people with VTE and renal impairment or failure due to a shortage of evidence. However, this was due to several of the drugs (including the DOACs) not having RCT data available for their usage at different levels of renal impairment. In the absence of such data, the committee made recommendations using their clinical experience and the guidance provided in the summary of product characteristics. On the other hand, there is available data for the use of people with VTE and therefore it would be unsuitable to use a similar approach for these people as was taken with renal impairment.

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				the inclusion criteria between the DOAC trials, in particular the AMPLIFY trial for apixaban." The draft recommendations in section 1.3.6 (page 14, line 4) positions apixaban and rivaroxaban ahead of edoxaban and dabigatran based on the results of an NMA with a high degree of uncertainty in which it does not appear that any adjustments have been made for differences in baseline risk across trials. The NICE methods guide acknowledges the importance of treatment effect modifiers and methods to adjust for these are described by NICE's Decision Support Unit in Technical Support Document 3. Given the Committees concern around the differences in inclusion criteria between the DOAC trials, we consider that it is inappropriate to draw such strong conclusions between relative effectiveness of the DOACs, and differentially position them, based on the evidence available. Daiichi Sankyo also notes that, results of the base case cost-effectiveness results show small differences in QALYs between treatment options. For example, Table 8 in Appendix D which reports the deterministic incremental cost-effectiveness results for the base-case 6 analysis (no treatment switching) – DVT, shows that the QALY difference between the DOAC treatment which generated the most QALYs and that which generated the least QALYs was 0.034. It should be noted that in Sterne	

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				et al. (2017), the authors issued caution when interpreting a similar QALY difference between DOAC options.[1] Given the lack of head to head direct evidence, the significant heterogeneity in the trial populations and the small differences in QALYs between treatments, Daiichi Sankyo considers the decision to rank and differentially position DOACs is highly questionable, based on the available evidence. Daiichi Sankyo considers that the pivotal trial assessing edoxaban for treatment and prevention of recurrent VTE (Hokusai-VTE trial) has many features which reflect real life clinical practice (such as physician discretion on treatment duration and the enrolment of high risk patients), which in turn aim to better reflect treatment outcomes in UK practice.[2] Daiichi Sankyo also notes that the uncertainty in evidence for the most effective treatments in people with renal impairment led the Committee to	

[1] Sterne J, Bodalia P, Bryden P, et al. Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis. Health Technol Assess. 2017 Mar;21(9):1-386. doi: 10.3310/hta21090.

[2] Hokusai-VTE Investigators, Büller HR, Décousus H, Grosso MA, et al. Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism. N Engl J Med 2013; 369:1406-1415. DOI: 10.1056/NEJMoa1306638

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				recommend all treatments equally, citing clinical consensus for this recommendation. Evidence Review D states that "*Due to the shortage of evidence concerning the most effective treatments for people with renal impairment, the committee made consensus recommendations based on their experience and clinical expertise and the summary of product characteristics documents (SPCs) of the options considered*." This approach contrasts with the recommendations set out in section 1.3.6 where the DOACs are differentially positioned in people with DVT and PE. Based on these considerations, we believe that the wording in section 1.3.10 (page 14, line 25) concerning treatment for DVT or PE with renal impairment or failure should be adapted and applied to the broader population in section 1.3.6, as follows: *1.3.6 Offer anticoagulation treatment to people with confirmed proximal DVT or PE as follows:* *− apixaban* *− rivaroxaban* *• low molecular weight heparin (LMWH) for 5 days followed by dabigatran or edoxaban* *• LMWH concurrently with a vitamin K antagonist (VKA) for at least 5 days, or until the INR is at least*	

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				2.0 in 2 consecutive readings, followed by a VKA on its own. [2020].	
Daiichi Sankyo Ltd	Guideline	30	1 - 3	We believe that edoxaban (following initial LMWH) should be positioned as an option alongside apixaban and rivaroxaban in a first-line setting, in accordance with the previous NICE technology appraisal guidance for edoxaban for treating and for preventing deep vein thrombosis and pulmonary embolism (TA354). NICE TA354 has recently been reviewed. Following consideration of proposals to review the relevant technology appraisals, NICE concluded in November 2019: *"New evidence is not expected to lead to a change in the recommendations in the original guidance for TA341; apixaban, TA327; dabigatran etexilate or TA354; edoxaban."* In particular the NICE Guidance Executive noted that *"there is a lack of head-to-head trials comparing oral anticoagulants, existing trials are relatively short, and further research on comparative effectiveness is needed."* Furthermore, the review decision paper states *"The main uncertainty identified across technology appraisals (TA327, 341 and 351), was the relative effectiveness of the intervention compared with other newer oral anticoagulants (rivaroxaban, dabigatran etexilate, apixaban or edoxaban) because there were no head-to-head trials evaluating the relative*	Thank you for your comment. This update of the VTE guideline acknowledges that TAs exist for the DOACs and, as a result, that they are all options for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. As noted within the Guidance Executive Technology Appraisal Review Proposal paper, it was within the scope of this update to decide how to incorporate the TAs. In addition, this document notes that the 'clinical guideline will also be able to place these treatments into the appropriate clinical context'. As you note, the review decision paper states that "New evidence is not expected to lead to a change in the recommendations in the original guidance for TA341; apixaban, TA327; dabigatran etexilate or TA354; edoxaban." and highlights the lack of head-to-head trials as a reason for this. However, this statement relates to the TA guidance itself and not updates such as this, which aim to contextualise the TA guidance. In addition, the committee noted the need for head-to-head of the DOACs and made a research recommendation for a trial to directly compare the DOACs using individual patient data. In the absence of head-to-head, the committee were still able to make separate recommendations for the DOACs

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				effectiveness of these anticoagulants. No new evidence was identified to address this uncertainty." Further details on this review decision can be found here: https://www.nice.org.uk/guidance/ta354/evidence/review-decision-paper-pdf-6965795198 In the original Technology Appraisal Guidance for edoxaban (TA354), the Appraisal Committee states "*some hospital protocols limit the choice of anticoagulants to minimise prescribing errors*" and "*those treated for VTE as an inpatient typically have parenteral heparin for several days, and in this situation a drug such as edoxaban may be preferable, because of its simple dosing schedule*". The NICE Technology Appraisal Committee recognised that "*A range of anticoagulant agents is necessary because patients may be allergic to 1 or more agents*". Our opinion is that the Guideline should acknowledge patient preference and the potential benefit of a once-daily treatment option such as edoxaban (or rivaroxaban) compared with apixaban or dabigatran which are administered twice-daily. This is acknowledged in TA354, "*The Committee noted that edoxaban has a simple once-daily dosage and would usually only need 1 annual monitoring visit to check renal function. The Committee concluded that patients value newer oral*	using data from an NMA, which was not considered in the TAs. Please also see our response to comment 187 for more information on why apixaban and rivaroxaban were prioritised in the recommendations. As you note, there are many situations in which edoxaban may be preferable and there is a need for a range of anticoagulant agents to be available due to the potential for a person to be allergic to 1 or more option. Accordingly, the committee recommended that if apixaban and rivaroxaban are not suitable, LMWH followed by edoxaban or dabigatran, or LMWH concurrently with a VKA should be offered. Therefore, the use edoxaban is still possible in the current recommendations. The committee agreed that patient preference is important and that this should be taken into account when deciding which anticoagulant to use, this is reflected in recommendation an earlier recommendation in the confirmed anticoagulation treatment section. Please also see our response to comment 7.

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				anticoagulants such as edoxaban, which cause less disruption to their lives than warfarin." Furthermore, a conclusion was reached that the most plausible ICER for edoxaban was aligned with that of other DOACs already recommended by NICE for the treatment of VTE, "*Taking into account the similar price of edoxaban to rivaroxaban, the lack of any clear trial evidence that edoxaban was substantially different from the other newer oral anticoagulants, and the testimony of the experts, the Committee concluded that the most plausible ICER was likely to be in line with that of the other oral anticoagulants already recommended in previous NICE guidance for the treatment of VTE. The Committee therefore concluded that edoxaban could be recommended as a cost-effective use of NHS resources*" (TA354). Please see comment 7, which results in further improvements in the cost-effectiveness of edoxaban since decision-making in TA354. Based on the previous guidance in NICE Technology Appraisals, Daiichi Sankyo argues that edoxaban should continue to be recommended in line with NICE Guidance as an option alongside the other DOACs, and that patient and prescriber preference for a product with a simpler dosing schedule should be acknowledged.	

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Daiichi Sankyo Ltd	Guideline	32	1 - 2	Current wording states *"In studies that recruited only people with cancer and VTE, rivaroxaban, edoxaban and LMWH were found to be similarly effective, although bleeding complications were more frequent with edoxaban."* It is not clear what comparison is being made here. We are concerned that this statement regarding bleeding complications with edoxaban in cancer VTE patients is misleading to the reader and does not reflect the uncertainty in the evidence for this population (denoted by the wide and overlapping credible intervals in the NMA) nor the significant heterogeneity in cancer VTE study populations and level of evidence between the DOACs in this specific patient population. The Hokusai-VTE cancer trial provides direct evidence for oral edoxaban compared to injectable dalteparin, which is the current standard-of-care (SOC), for the prevention of the combined outcome of VTE recurrence or major bleeding in cancer patients with acute VTE. Hokusai-VTE cancer trial was: • First large randomized trial of a Direct Oral Anticoagulant (DOAC) vs LMWH, powered to evaluate outcomes in VTE treatment in cancer • The trial objective was to demonstrate the non-inferiority of oral edoxaban compared to	Thank you for your comment. The committee agreed that the current wording is misleading ("In studies that recruited only people with cancer and VTE, rivaroxaban, edoxaban and LMWH were found to be similarly effective, although bleeding complications were more frequent with edoxaban."). As you note, the confidence intervals overlap for many of the comparisons, including the indirect comparisons between the DOACs. The reference was in relation to major bleeding being more frequent in the edoxaban arm of HOKUSAI-VTE Cancer trial compared to the LMWH alone arm (and not compared to other DOACs) but as it reads, it is not clear that this is the comparison being made. Additionally, the committee noted that clinically relevant non-major bleeding was more frequent in people given rivaroxaban compared to LMWH. The committee amended this section of the rationale to specify that bleeding complications were more frequent with DOACs, rather than specifically edoxaban. Additionally, the committee noted that many of the increased bleeds were related to GI and GU bleeds (and as you note, the increase in major bleeds for edoxaban vs dalteparin from HOKUSAI-VTE cancer was limited to upper GI bleeds in patients with GI cancer). A summary of their discussion concerning these bleeds has been added to evidence review D and the rationale for these recommendations.

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				injectable dalteparin, which is the current standard-of-care (SOC), for the prevention of the combined outcome of VTE recurrence or major bleeding in cancer patients with acute VTE (including symptomatic and incidental) • Hokusai-VTE CANCER met the primary objective: edoxaban was non-inferior to dalteparin, with a composite event rate of 12.8% vs 13.5% for edoxaban and dalteparin respectively (HR 0.97 for edoxaban, CI, 0.7-1.36, p=0.006 for non-inferiority) • The trial has unique features: PROBE design (all outcomes adjudicated by a committee blinded to treatment allocation), 12 months treatment duration, broad spectrum of cancer (over 97% active cancer, 53% metastatic, 72% receiving cancer therapy, brain cancer and brain metastasis allowed) • The rate of recurrent venous thromboembolism was numerically lower with edoxaban vs dalteparin (7.9% vs 11.3%, a difference of 3.4%) and the rate of major bleeding was higher with edoxaban vs dalteparin (6.9% vs 4.0%, a difference of 2.9%), but the rate of more severe major bleeds (grade 3 and 4) was similar in both groups. • Hokusai-VTE CANCER is the first trial to demonstrate that a DOAC, oral edoxaban, can provide clinical benefit similar to the standard of care, injectable dalteparin, in this population. It is important to note that the increase in major bleeds for edoxaban vs dalteparin from HOKUSAI-	

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				VTE cancer was limited to upper GI bleeds in pts with GI cancer (many of them unresected), a population that was not adequately represented in other trials. Furthermore, there were no fatal bleeds in the edoxaban group and there were numerically less intracranial bleeds with edoxaban than with dalteparin. In the NMA, the credible intervals between edoxaban and all other DOACs (tables 90 and 91, Pharmacological Treatment Report, Evidence review D; page 601 and 605 respectively) overlap 1 for the outcomes of major bleeding and clinically relevant non-major bleeding in the VTE cancer. We request that this statement regarding bleeding complications is removed from the Guideline.	
Daiichi Sankyo Ltd	Guideline	32	23 - 24	The previous NICE Guideline (CG144) did not contain any mention of DOACs as treatment recommendations. Thus, the DOAC recommendations in this draft guideline is a new addition to the guideline and will result in an increase in the use of all DOACs. Daiichi Sankyo considers that the current wording puts too much emphasis on an increase in the use of apixaban and rivaroxaban and is misleading to commissioners and local decision-makers.	Thank you for your comment. As you note, the DOACs were absent from previous version of this guideline and increased use of all the DOACs is expected. However, as apixaban and rivaroxaban are prioritised, the increased usage of these drugs is likely to be more pronounced and therefore the committee agreed that the current wording is accurate and did not change it. ("The recommendations are expected to lead to increased use

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				p.32, lines 23-24, Daiichi Sankyo suggests changing the wording to *"The recommendations are expected to lead to increased use of DOACs, including apixaban, dabigatran, edoxaban and rivaroxaban, to treat suspected and confirmed VTE.* p.35, lines 29-30, Daiichi Sankyo suggests changing the wording to *"For people without renal impairment, BMI 40 kg/m2 or more, or cancer, increased use of DOACs, for long-term therapy can be expected to lower costs by reducing the need for clinical visits, INR monitoring and managing bleeding events".*	of DOACs, particularly apixaban and rivaroxaban, to treat suspected and confirmed VTE"). For the extended treatment of VTE, people will either be continuing their current treatment (which, if a DOAC, will likely to have been apixaban or rivaroxaban) or switching to apixaban if taking a different DOAC. Therefore, it is likely that the use of all DOACs and apixaban in particular, will be increased and the wording has not been altered.
Diagnostica Stago UK	Guideline	5	1	The guideline recommends the use of the two-level DVT Wells Score. We would like to suggest the use of the three-level DVT Wells score. The rationale of this proposition is that it allows the inclusion of more patients to be tested with D-dimer assay, thus potentially resulting in less imaging testing. Low and moderate pre-test probability patients represent around 70% of DVT suspected patients, against only 50% of patients using the two-level Wells Score. Thus, more patients would be eligible to D-dimer testing (with a high-sensitivity D-dimer assay), and more patients will be excluded using this strategy thus decreasing the need for imaging techniques, and its associated costs and risks for the patients. *Kafeza M et al. A Systematic Review of Clinical Prediction Scores for Deep Vein Thrombosis.*	Thank you for your comment. The section of the guideline that covers diagnosis was out of scope of this update with the exception of the use of age adjusted and point of care D-dimer tests. Therefore, the evaluation of the Wells score (and whether a two or three level version is preferable) was not within the scope of this update and the committee were unable to make any recommendations on this topic. However, we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

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				Phlebology 2017; 32 (8): 516-31Bates, S.M., et al., Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 2012. 141(2 Suppl): p. e351S-418S.	
Diagnostica Stago UK	Guideline	7	21	We are concerned that quantitative POC testing can be considered for VTE exclusion. We would like to emphasize that in order to maximize safe and objective diagnoses, reliable assays should be used, with sufficient performances to exclude safely VTE. The CLSI H59-A guideline on D-dimer for VTE exclusion provides guidance for the validation of D-dimer assays in this context. We suggest that even quantitative POC D-dimer assays should follow CLSI criteria to be used in clinical setting, (i.e. sensitivity >97%, its lower limit of the 95%CI interval > 90%; and negative predictive value > 98%, its lower limit of the 95% CI interval > 95%). Assays that do not fulfil these criteria can be considered as "moderate-sensitivity" D-dimer assay. Their performances limit their use in certain patients, i.e. patients with "intermediate" pre-test clinical probability, or decrease the performance of VTE exclusion (more VTE missed) when use in patients. We thus suggest this prerequisite (CLSI H59-A criteria) to be considered in this guideline for any D-dimer testing (POC or central lab testing).	Thank you for your comment. The committee shared you concerns regarding the undesirability of using D-dimer tests with reduced sensitivity to rule out diagnosis of VTE. However, the evidence reviewed by the committee identified that point of care tests within the context of DVT had a sensitivity of 97% (95% CIs 94% - 98%) and a sensitivity of 99% in PE (95% CIs: 94%-100%), although the latter was based on a single study. The committee also heard expert witness testimony on this topic to help inform the decision and ensure that there was not a risk of increased false negatives. The committee agreed that this evidence suggested that quantitative D-dimer tests have a high sensitivity which was comparable to that of laboratory D-dimer tests and could therefore safely be used to rule out VTE. The committee did not review the evidence needed to determine which types of quantitative tests were most accurate and were unable to recommend particular models of machines/ tests. This issue was not within the scope of the review question.

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				Ceriani et at. Clinical Prediction Rules for Pulmonary Embolism: A Systematic Review and Meta-Analysis J Thromb Haemost 2010; 8: 957-70 *Raja AS et al. Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med 2015; 163, 701-11* *Bates, S.M., et al., Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 2012. 141(2 Suppl): p. e351S-418S.*	The committee are unable to include a reference to the CLSI H59-A criteria because the committee have not reviewed this guidance and are therefore unable to endorse it.
Diagnostica Stago UK	Guideline	9	1	The guideline recommends the use of the two-level PE Wells Score. We would like to suggest the use of the three-level PE Wells score. The rationale of this proposition is that it allows the inclusion of more patients to be tested with D-dimer assay; thus resulting in less imaging testing: low and moderate PTP patients represent around 70% of PE suspected patients, against only 50% of patients using the two-level Wells Score. Thus, more patients would be eligible to D-dimer testing (with a high-sensitivity D-dimer assay), and more patients will be excluded using this strategy thus decreasing the need for imaging techniques, and its associated costs and risks for the patients.	Thank you for your comment. The section of the guideline that covers diagnosis was out of scope of this update with the exception of the use of age adjusted and point of care D-dimer tests. The evaluation of the Wells score (and whether a two or three level version is preferable) was therefore not within the scope of this update and the committee were unable to make recommendations on this topic. However, we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

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				Ceriani et at. Clinical Prediction Rules for Pulmonary Embolism: A Systematic Review and Meta-Analysis J Thromb Haemost 2010; 8: 957-70 *Raja AS et al. Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med 2015; 163, 701-11.*	
Diagnostica Stago UK	Guideline	23	1	We consider that this guideline should mention that when, in the scope of thrombophilia testing, a thrombotic antiphospholipid syndrome is diagnosed, apixaban and rivaroxaban should not be used and VKA should be preferred. This suggestion is supported by the RAPS trial*: Cohen H et al. Rivaroxaban Versus Warfarin to Treat Patients With Thrombotic Antiphospholipid Syndrome, With or Without Systemic Lupus Erythematosus (RAPS). Lancet Haematol 2016; 3(9): e426-36.*	Thank you for your comment. Taking your comment, and those from other stakeholders, into account the committee decided to remove the footnote reference to the MHRA alert under the anticoagulation treatment. Instead they included a specific recommendation for the treatment of people with triple positive APS with VKA in this section.
Diagnostica Stago UK	Guideline	38	1	The guideline suggests that there is no benefit to search cancer in patients when VTE diagnosis is negative, and when there is no sign or symptoms. Even if D-dimer is a non-specific marker that can be elevated in multiple conditions, there is evidences that highly elevated D-dimer values suggest underlying diseases including VTE, sepsis and cancer. Thus, once VTE and sepsis have been excluded, high D-dimer level can be associated with	Thank you for your comment. The Additional uses of the results of D-dimer tests was not investigated as part of the review that looked at investigations for cancer and the diagnosis section of the guideline was only updated in a very limited manner (looking at age adjusted and point of care d-dimer tests).. Therefore, the committee did not review the relevant evidence and were unable to make recommendations on this area in either the diagnosis section or under investigation for cancer.

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				cancer. May this guideline mention that extremely high level of D-dimer can be suggestive of cancer even if VTE is excluded? *Schutte T, Thijs A, Smulders YM. Never Ignore Extremely Elevated D-dimer Levels: They Are Specific for Serious Illness. Neth J Med 2016; 74(10): 443-8.*	
Guy's and St Thomas' NHS Foundation Trust	Guideline	4	6 - 8	1.1.1 One of the biggest failures of the DVT pathway is that entry to it is not well specified. Many health care professionals seem to believe that a DVT cannot occur without a full house of symptoms – swelling, redness and pain but evidence shows that 80% of DVT do not have swelling or redness. Can this please be reflected in the wording? For example, changed to "For people who present with signs or symptoms of DVT, such as a painful leg which can also be swollen, assess their general medical history and do a 6 physical examination to exclude other causes."	Thank you for your comment. The section of the guideline that covers diagnosis was out of scope of this update with the exception of the use of age adjusted and point of care D-dimer tests. Therefore recommendation 1.1.1 and the presentation of signs and symptoms was not with the scope of this update. However, the committee agreed that from the existing recommendation it is already clear that the signs and symptoms of DVT may include a number of elements that do not all need to be present for DVT to be suspected.
Guy's and St Thomas' NHS Foundation Trust	Guideline	6	12, 20	Should we be stopping or continuing until 2nd US is done? Should distal imaging ever be indicated in those with high clinical suspicion Consider other imaging modalities e.g. MRI if d-dimer positive, and high clinical suspicion to outrule	Thank you for your comment. The committee confirmed that anticoagulation therapy should be stopped at this point (when a person has a negative scan and a positive D-dimer) because if treatment is continued until the second scan, there is a risk that the clot will be partially treated, preventing an undetected calf DVT from extending into the proximal veins and resulting in

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				IVC/iliac vein thrombus as cause of unilateral leg swelling.	another negative scan. This would then lead to a false negative diagnosis of DVT, and a lack of necessary, longer term anticoagulation treatment. The section of the guideline that covers diagnosis was out of scope of this update with the exception of the use of age adjusted and point of care D-dimer tests. The committee were therefore unable to review the circumstances where distal imaging would be appropriate or examine other imaging modalities and could not make any recommendations on these topics. We encourage you to submit suggestions for areas that NICE guidelines should address or where an update is needed of an existing topic. We pass comments onto surveillance where there is something that could trigger an update. For example, if there is new evidence that is likely to change recommendations, or if there is new evidence about topics that are not covered by the existing guidance, or if issues concerning safety are raised. If there is new evidence this needs to be verifiable by the inclusion of supporting references, specifically primary studies or systematic reviews of primary studies.
Guy's and St Thomas' NHS Foundation Trust	Guideline	11	2 - 4	Should PE imaging not be done ideally particularly to rule out intermediate risk PE and risk of CTEPH is not assessed properly.	Thank you for your comment. The section of the guideline that covers diagnosis was out of scope of this update with the exception of the use of age adjusted and point of care D-dimer tests. Therefore, investigations for

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					people with signs or symptoms of both DVT and PE was out of scope of this update and the committee are unable to make changes to this section. We encourage you to submit suggestions for areas that NICE guidelines should address or where an update is needed of an existing topic. We pass comments onto surveillance where there is something that could trigger an update. For example, if there is new evidence that is likely to change recommendations, or if there is new evidence about topics that are not covered by the existing guidance, or if issues concerning safety are raised. If there is new evidence this needs to be verifiable by the inclusion of supporting references, specifically primary studies or systematic reviews of primary studies.
Guy's and St Thomas' NHS Foundation Trust	Guideline	11	6 - 13	1.2.1. Need to specify tools such as Pesi, sPESI etc.	Thank you for your comment. This review question dealt specifically with randomized controlled trials comparing outpatient to inpatient treatment in low-risk PE patients, in which low-risk PE was defined by the study. The committee noted that the two studies included in this review used different risk stratification tools (PESI and HESTIA). They agreed that as they did not review the relevant evidence risk stratification in PE, they could only recommend that a validated risk stratification tool is used, but not specify which one(s). Additionally, the committee noted that the decision to discharge remains a clinical decision and should take into account individual circumstances.

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Guy's and St Thomas' NHS Foundation Trust	Guideline	14	6 - 13	1.3.5. No comment on whether this includes VTE management in pregnancy.	Thank you for your comment. Pregnant women are excluded from this guideline as stated in the published scope document and EIA. However, we have added text to the context section of the guideline to specify that this is the case. There is separate guidance on managing DVT and PE in this population group, published by the Royal College of Gynaecologists (RCOG), (RCOG, 2015).
Guy's and St Thomas' NHS Foundation Trust	Guideline	15	18 - 20	Is there not increasing evidence to show that DOACs can be used with appropriate anti-Xa monitoring?	Thank you for your comment. The recommendation relating to BMI was based primarily on consensus and evidence pertaining specifically to body weight was limited to those with a BMI >30 kg/m2. However, the committee discussed the limited evidence for the use of DOACs in these people and feedback from stakeholders suggesting that more evidence may be forthcoming. Based on these points, the committee made a more general recommendation to enable the clinician to decide which treatment would be most effective on an individual basis and to allow for the use of DOACs. They noted that whatever the choice of anticoagulant is, it is important to ensure that there is effective monitoring of therapeutic levels and any dose adjustments and monitoring requirements stated in the summary of product characteristics (SPCs), which may include anti-Xa monitoring, are followed, along with locally agreed protocols or advice from a specialist or multidisciplinary team. The committee decided not to specify the types of monitoring because this would make the recommendation too complex; they were concerned that any monitoring that was not listed in the

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					recommendation would not be carried out and they expected clinicians to follow the monitoring requirements set out in the SPCs.
Guy's and St Thomas' NHS Foundation Trust	Guideline	16	4 - 6	Should this only be rivaroxaban and edoxaban (rather than a DOAC)? Should 'suitable' be defined - gastrointestinal or genitourinary malignancy with bleeding risk, brain metastases or previous bleeding issues from malignancy.	Thank you for your comment. Although there have only been direct trials between edoxaban and rivaroxaban compared to LMWH alone, the NMA also used subgroup data for people with active cancer from the main DOAC trials for apixaban and dabigatran compared to warfarin. The committee noted that the effects reported in these trials were roughly consistent with those for the population without cancer, and the NMA allowed for indirect comparisons to be made using this data to compare the treatments to the other DOACs and LMWH alone. Additionally, the committee noted that the ADAM-VTE trial (McBane 2019), a small (~300 participants) trial comparing apixaban to LMWH alone recently published and that the results were consistent with that of the other DOACs without evidence of increased bleeds. Based on the above points the committee agreed to not specify particular DOACs in this recommendation. The committee noted that many of the bleeds associated with the DOACs were specifically gastrointestinal (GI) and genitourinary (GU) bleeds and that the safety profile of the DOACs compared to LMWH alone improved when only looking at other bleeds (see the benefits and harms section of the evidence review D for more information on this discussion). However, the committee agreed not to specifically prohibit the use of

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					DOACs in people with GI and/or GU malignancy or give specific guidance on who is/is not suitable for a DOAC as there are potentially other types of malignancies which make a DOAC unsuitable. They were concerned that if they provided a list of tumours with which to avoid DOAC use this would not be exhaustive and could mislead clinicians. Instead, the committee made a separate recommendation to take into account the tumour site and bleeding risk when prescribing anticoagulation for people with cancer (which will include considerations of whether the person has a GI/GU malignancy or another tumour type that may be associated with a higher bleeding risk. Reference McBane, RD, Wysokinski W , Le-Rademacher J G…., &. Loprinzi CL. (2019) Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. J. Thromb Haemost, [epub ahead of print]
Guy's and St Thomas' NHS Foundation Trust	Guideline	16	11	Should there be a section on using VKA in patients with Antiphospholipid Syndrome over DOACs particularly arterial and triple positive disease.	Thank you for your comment. Taking into account stakeholder comments, the committee have added a section specifically for 'Anticoagulation treatment for people with DVT or PE and triple positive antiphospholipid syndrome', which recommends the use of LMWH with a VKA in these people.

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Guy's and St Thomas' NHS Foundation Trust	Guideline	17	27	1.4.6 I would recommend against using the DASH tool. The same group who originally published the DASH tool have very recently published updated data showing that it has a poor predictive value and that risk of recurrence could not be safely ruled out using the tool (MacDonald et al. Br J Haematol 2019;185(3):631-3).	Thank you for your comment. The recommendation for DASH was specifically for people aged under 65 who were wanting to stop using anticoagulation. The intention was for DASH to be used as supporting evidence to help inform these people of their risk of recurrence. However, after re-reviewing the evidence and the feedback from stakeholders, the committee decided not to recommend the use of DASH or any other tool to predict VTE-recurrence due to limited evidence supporting that they can accurately predict VTE recurrence.
Guy's and St Thomas' NHS Foundation Trust	Guideline	20	1	1.5.3 This section comments on the animal origin of products in heparins, rivaroxaban and apixaban. It is also worth noting that the shellac in the black printing ink used to print the Boehringer Ingelheim symbol and the dose on the capsule shell on dabigatran is a resin excreted from a female lac bug. This is of importance to some vegan patients.	Thank you for your comment. The section of the guideline that covers information was out of scope of this update. Although, the recommendation concerning animal products was amended to reflect the use of lactose in some DOACs this was possible because this represents a potential safety issue (as some people are allergic to lactose). The committee were unable to make your suggested change because this is not a safety issue. In addition, adding your suggested wording would necessitate checking whether this issue applied to all the other drugs recommended in the guideline and as this section is out of scope this is not possible. However, the committee did expand the recommendation slightly to clarify that the concerns could be ethical, religious or due to a food intolerance and it is hoped that this will stimulate discussion about the use of treatments for VTE containing animal products with those people who have concerns about this issue.

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Guy's and St Thomas' NHS Foundation Trust	Guideline	21	5 - 24	1.7.1 Would increase therapeutic range e.g. warfarin with target INR 3-4 or heparin be the option in this choice? This is mentioned in 1.7.3 but appears conflicting 1.7.3 The timing after a thrombosis when an IVC filter should be considered if anticoagulation is contraindicated has not been specified. Should this apply to patients within 1 month of venous thromboembolism, or those deemed at particularly high risk only?	Thank you for your comment. If a PE occurs during anticoagulation the committee recommend that alternative anticoagulation therapy is explored, this includes increasing the dose of anticoagulation (which may include increasing warfarin to a target INR of 3-4) or changing to an anticoagulant with a different mode of action. However, it was not within the scope of this update to compare the different treatment options in this scenario and in the absence of such evidence the committee agreed that they could not make more specific recommendations. The committee agreed that they could not give further guidance on how long to wait after anticoagulation is contraindicated before a filter is considered as this may vary and needs to be decided on an individual basis.
Guy's and St Thomas' NHS Foundation Trust	Guideline	23	2 - 16	1.9.3. I think that more guidance is needed from NICE in how to interpret the results of antiphospholipid syndrome testing. Should the screen include a lupus anticoagulant if a patient is on a direct oral anticoagulant? If so, should DOAC Stop or a Taipan snake venom time be used? Should testing for antibodies be restricted to IgG anti-cardiolipin and IgG anti-beta-2-glycoprotein antibodies or should IgM antibodies also be considered? If a patient is found to be "triple positive" for antiphospholipid syndrome then should warfarin be recommended in all cases? Are there any recommendations for choice of anticoagulant for patients who have one, or two, positive tests for	Thank you for your comment. In light of the MHRA alert regarding the safety of DOACs in people with APS, the committee amended the first recommendation in this section to allow for the testing for acquired thrombophilia. They also amended subsequent recommendations to clarify that some thrombophilia tests are affected by anticoagulants and specialist advice may be needed. However, the section on thrombophilia testing was out of scope of this update. Therefore, the committee did not review the relevant literature and were unable to make new recommendations or amend the existing

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				antiphospholipid syndrome? Even if the guideline expressed uncertainty, I think these questions should be addressed. Should the term 'if it is planned to stop anticoagulation treatment' - you want to diagnosis APS earlier as DOAC use can cause recurrent thrombosis or extension within weeks after initiation 1.9.5 What about antithrombin testing in family members with a known deficiency in women of childbearing potential?	recommendations further to provide more guidance on the issues you have raised. Following discussion of stakeholder comments about the use of DOAC in people with triple positive APS, the committee made a recommendation to offer these people LMWH+VKA in the anticoagulation treatment section of the guideline, which was being updated. They based this recommendation on the MHRA alert and their clinical experience, but did not have any evidence to answer your question about whether there should be any exceptions and what treatment is optimal for people with one or two positive test results. The committee deliberations about APS are covered in the committee discussion section of evidence review D. This refers to the uncertainty surrounding these issues. The committee were unable to refer to this in the guideline itself or address your comment about recommendation 1.9.5 as the thrombophilia section was out of scope of this update. We encourage you to submit suggestions for areas that NICE guidelines should address or where an update is needed of an existing topic. We pass comments onto surveillance where there is something that could trigger an update. For example, if there is new evidence that is likely to change recommendations, or if there is new evidence about topics that are not covered by the existing guidance, or if issues concerning safety are

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					raised. If there is new evidence this needs to be verifiable by the inclusion of supporting references, specifically primary studies or systematic reviews of primary studies.
Hull University Teaching Hospitals NHS Trust	Guideline	General	General	We would like to suggest that the scope of this or future reviews should include the management of Superficial Venous Thrombosis and upper limb DVT. The former condition was previously thought to be benign, but it is now shown that a significant number of cases is associated with VTE and malignancy as well. There is considerable variation in practice of this common condition nationally. The second issue again affects a significant number of people and management practice nationally shows wide variation.	Thank you for your comment. As you note, this area is out of scope for the current update. However, we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
King's College Hospital NHS Foundation Trust	Guideline	7	23	Rec 1.1.14. We are concerned this recommendation will result in variability between hospitals which could lead to patient complaints (e.g. offered a scan in one hospital and not another), particularly if subclinical event detected. To address this, we suggest the recommendation should be more specific with recommendations as to which algorithm should be used. Should it be age x5 or x10? Additionally, threshold for positive Dd is variable based on the assay utilised and the evidence that age-adjusted D-dimer is applicable to all lab assays in use (and POC quantitative) is not available.	Thank you for your comment. The committee were unable to specify a formula to use for age-adjustment as this depends on the laboratory assay being used, as these have different cut-offs and would each require a different formula. The committee agreed that the decision about the formula and cut off should be made by each trust based on the assays they use. The Evidence review highlighted that age-adjustment increases the specificity of D-dimer tests with only a marginal effect on sensitivity. Although there is no evidence comparing the diagnostic accuracy of age-adjustment for different assays, the committee did not foresee a reason that this would affect the diagnostic

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				We note a number of studies not included without explanation or not listed (of note these do not the use of support age-adjusted Dd) e.g. Takach Lapner, S, Julian J A, Linkins L A, Bates S M, and Kearon C. (2016). Questioning the use of an age-adjusted D-dimer threshold to exclude venous thromboembolism: analysis of individual patient data from two diagnostic studies. Journal of Thrombosis & Haemostasis, 14(10), pp.1953-1959. This meets the inclusion criteria so not clear why not included (and not detailed in the exclusions table). Similarly, Penaloza et al. J Thromb Haemost 2012; 10: 1291–6 meets inclusion criteria but not included (not identified) and similarly does not demonstrate a benefit. There is limited prospective evidence to support this as a diagnostic strategy; the strongest evidence coming from ADJUST-PE. I note this is acknowledged on p23 but described as excluded as 'not all patients met reference standard'. However, all patients were followed for 3months for VTE event, which is described in the reference standard. Also, recent publications suggesting fixed higher threshold for low PTP: this would be simpler to implement with potential greater benefit in reducing imaging. Eg Kline JA, Hogg MM, Courtney DM, Miller CD, Jones AE, Smithline HA. D-dimer threshold increase	accuracy as long as the correct formula is used for that particular assay. The committee agreed to make the recommendation a 'consider' rather than an 'offer' to allow for practices which do not feel comfortable using age-adjustment to use the manufacturer's cut-off without adjustment. As you note, ADJUST-PE was excluded because not all participants who received the D-dimer test went on to receive imaging. Although participants were followed up for 3 months, only those participants with a positive D-dimer underwent imaging and therefore a diagnosis is more likely in this population. You mention that a number of studies are not included or listed without explanation. The excluded studies list only covers those studies which are excluded at full text sifting. Any studies that do not meet the review protocol in terms of design, study population, study type etc. may be excluded at the title and abstract stage if this can be identified at this point and they would therefore not be listed in the excluded studies table. The 2 studies that you mention specifically were not included because they use secondary data where all or some of the studies do not meet the inclusion criteria for the same reason as ADJUST-PE noted above.

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				with pretest probability unlikely for pulmonary embolism to decrease unnecessary computerized tomographic pulmonary angiography. J Thromb Haemost 2012; 10: 572–81. Kearon et al. N Engl J Med. 2019 Nov 28;381(22):2125-2134	
King's College Hospital NHS Foundation Trust	Guideline	16	4	Rec 1.3.11. The evidence does not support the use of BMI to identify those at risk of over/underanticoagulation on DOACs. Bodyweight is more readily available, highlighted within the DOAC SpC and informative for those at risk. The evidence review acknowledges ISTH uses weight >120kg but does not explain why the use of BMI has been recommended. This should be revised to consider LMWH/VKA at extremes of body weight i.e. >120kg and <50kg. Whilst not all hospitals have access to onsite Xa monitoring, most will be able to refer samples on. In some cases, VKA may not be appropriate and it would be appropriate to use a DOAC with the caveat of drug level monitoring to ensure adequate exposure.	Thank you for your comment. The recommendations relating to BMI were based primarily on consensus due to limited evidence from randomized controlled trials in this population. The committee discussed feedback from stakeholders concerning the use of absolute weight instead of BMI and that there are concerns with treating people with low body weight as well as those with high body weight. The committee agreed with stakeholder concerns and decided to specifically make reference to absolute weight rather than BMI and amended the recommendation to cover people at both extremes of weight (<50kg or >120kg). However, they agreed that uncertainty surrounding effective treatment for these groups remains. Taking into account that there is some evidence that the DOACs could be used in obese patients and stakeholder comments that more evidence may be forthcoming, the committee made a more general recommendation to enable the clinician to decide which treatment would be most effective on an individual basis and to allow for the use of DOACs where appropriate for the individual. They noted that whatever the choice of anticoagulant is, it is important to ensure that there is

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					effective monitoring of therapeutic levels and any dose adjustments and monitoring requirements stated in the SPCs are followed, along with locally agreed protocols or advice from a specialist or multidisciplinary team.
King's College Hospital NHS Foundation Trust	Guideline	16	11	Rec 1.3.13. Also take into account planned treatment, LMWH is a good option if diagnostics incomplete or if chemotherapy treatment plan is unknown as there are a number of agents which interact with DOACs. There is significant evidence that LMWH is superior to warfarin in cancer patients in reducing the risk of both recurrent VTE and bleeding (CATCH/CLOT studies); warfarin should be the 3rd option for when DOAC/LMWH not suitable not 2nd line. We note this recommendation is made due to reduced cost effectiveness of LMWH alone and argue clinical effectiveness is more important to both patient and clinician. It is not clear whether increased bleeding/thrombosis with VKA was taken into account when considering cost effectiveness. Additionally, warfarin control is likely to labile in patients receiving chemotherapy which will further increase risk associated with its use.	Thank you for your comment. The agreed not to add in reference to planned treatment to prevent the recommendations from becoming overly complex. Following discussion of stakeholder comments, the committee amended the recommendation to specify that drug-interactions are taken into account when selecting a choice of anticoagulant and it is intended that this would include with any current or planned drug treatments. In response to stakeholder comments, the committee also agreed to amend the recommendations to make it clear that if a DOAC is unsuitable, to consider LMWH alone or LMWH with a VKA. The committee agreed that for most people, VKA will be unsuitable due to the potential for drug interactions and is less favourable efficacy profile compared to alternatives. However, the committee agreed that in a small number of people, such as those unable to take DOACs who request an oral treatment, VKA may be an option. It was included in the draft recommendations as an alternative to a DOAC because it was more cost effective than LMWH. The increased bleeding with VKA was taken into account in the economic model (see evidence review D and the model report in document G for more details). LMWH was not cost effective due to its high cost compared to

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					DOACs and LMWH with VKA. These updated recommendations should ensure that an individual can receive LMWH if it is the most appropriate treatment option while supporting the NHS to make the best use of its limited resources.
King's College Hospital NHS Foundation Trust	Guideline	18	5	Rec 1.4.6. DASH has been externally validated in a retrospective cohort study. There is no prospective evaluation of its use in a management study. HERDOO2 is the only tool which has been prospectively evaluated and shown to be safe/effective in identifying those at risk. The rationale for selecting DASH over HERDOO2 is not sufficiently explained. Given the limited evidence, it would be more appropriate to consider using any one of the available tools to counsel patients who do not wish to continue anticoagulation.	Thank you for your comment. The recommendation for DASH was specifically for people aged under 65 who were wanting to stop using anticoagulation. The intention was for DASH to be used as supporting evidence to help inform these people of their risk of recurrence. However, after re-reviewing the evidence and the feedback from stakeholders, the committee decided not to recommend the use of DASH or any other tool to predict VTE-recurrence. This review question only included studies in which participants received at least 3 months of anticoagulation treatment, stopped treatment, were tested using prognostic tool(s) and followed up off-treatment. As the HERDOO2 study was a management study, only the data pertaining to those participants who stopped treatment were extracted for this review. The committee agreed that they could not recommend the use of HERDOO2 based on this data.
King's College Hospital NHS Foundation Trust	Guideline	22	10	Rec 1.8.1. There is no role for clotting profile as a screening test for cancer. This is misleading and should be removed, or if this is meant to indicate D-dimer, it should state this specifically.	Thank you for your comment. Following discussion of the stakeholder comments, the committee agreed to remove reference to a clotting profile due to the potential for confusion. The committee amended this recommendation to specify that tests for prothrombin

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					time and activated partial thromboplastin time should be conducted.
King's College Hospital NHS Foundation Trust	Guideline	22	10	Rec 1.8.1. Suggest also recommend patients are participating in sex-specific national screening programmes and encourage participation if not, as good practice.	Thank you for your comment. The committee agreed that participation in sex-specific national screening was good practice but decided that this was too much detail to contain within the recommendations. However, this point has been added to the discussion in evidence review C.
Leeds Teaching Hospitals NHS Trust	Guideline	1	7	Why not from 16 years so it's the same as the prevention guideline?	Thank you for your comment. The scope of this guideline only covers adults aged 18 and over. As this is a partial update, it was not possible to expand this population to include 16- and 17-year olds.
Leeds Teaching Hospitals NHS Trust	Guideline	14	17	Why has the option for self-testing of INRs not been considered for those requiring long term vitamin K antagonist anticoagulation as it has been for metal valves and AF? This seems a missed opportunity for those who can't have a direct oral anticoagulant.	Thank you for your comment. The self-management of INR was not within the scope of this update. Therefore, no evidence was reviewed, and the committee were unable to make recommendations on this area. However, we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
Leeds Teaching Hospitals NHS Trust	Guideline	14	29	Both apixaban and rivaroxaban are cautioned if creatinine clearance is less than 30ml/min but this seems to endorse them with no concerns down to 15ml/min, could this be clarified.	Thank you for your comment. The committee decided not to amend the recommendation because the suggested detail would add text to an already long and complicated recommendation. The recommendation already states that people should note the cautions and requirements for dose adjustment and monitoring in the medicine's summary of product characteristics and the committee agreed that this was sufficient.

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Leeds Teaching Hospitals NHS Trust	Guideline	15	3	Split the information for edoxaban and dabigatran due to the differences in creatinine clearance cut off.	Thank you for your comment. The committee updated the wording of this recommendation in accordance with your suggestion.
Leeds Teaching Hospitals NHS Trust	Guideline	15	10	Should VKA be added to this as no reason they couldn't have one?	Thank you for your comment. Based on stakeholder comments, the committee have amended this recommendation to include LMWH or UFH alone or concurrently with a VKA as options.
Leeds Teaching Hospitals NHS Trust	Guideline	15	17	Should there a weight cut off like ISTH recommend of 120kg. Some people with a BMI > 40 may only be 100kg as they are short. You could be 5ft with a weight of 95kg and have a BMI > 40 or you could be 6ft and 130kg but have a BMI < 40. These 2 patients may handle drugs very differently and a young 130kg patient is likely to metabolise much quicker.	Thank you for your comment. The recommendations relating to BMI were based primarily on consensus due to limited evidence from randomized controlled trials in this population. The committee discussed feedback from stakeholders concerning the use of absolute weight instead of BMI and that there are concerns with treating people with low body weight as well as those with high body weight. The committee agreed with stakeholder concerns and decided to specifically make reference to absolute weight rather than BMI. They amended the recommendation to cover people at both extremes of weight (<50kg or >120kg). However, they agreed that uncertainty surrounding effective treatment for these groups remains. Taking into account suggestions from stakeholders that there is some evidence that the DOACs could be used in obese patients and that more evidence may be forthcoming, the committee made a more general recommendation to enable the clinician to decide which treatment would be most effective on an individual basis and to allow for the use of DOACs. They noted that whatever the choice of anticoagulant is, it is important to ensure that there is effective monitoring of

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					therapeutic levels and any dose adjustments and monitoring requirements stated in the SPCs are followed, along with locally agreed protocols or advice from a specialist or multidisciplinary team.
Leeds Teaching Hospitals NHS Trust	Guideline	16	4	I am very worried about this recommendation which appears to go against all other cancer associated thrombosis recommendations from national and international guidelines. Not all DOACs have been trialled in CAT and the studies show a higher rate of bleeding in some cancers which has not been clearly defined here. I think more guidance is needed here to qualify the statements and which patients should be considered for a DOAC including which DOAC. There are also cancer drug interactions, thrombocytopenia, absorption issues all to take into consideration.	Thank you for your comment. This update followed the methods outline in the NICE guideline manual based on the best available evidence. The committee were aware that their recommendations differed to those of other guidelines. However, they were in agreement in their conclusions based on their discussion of the clinical and cost effectiveness analyses that were conducted for this guideline. We are unable to comment on how other guidelines conduct their reviews or examine how they reach their recommendations. Although there have only been direct trials between edoxaban and rivaroxaban compared to LMWH alone, the NMA also used subgroup data for specifically people with active cancer from the main DOAC trials for apixaban and dabigatran compared to warfarin. The committee noted that the effects reported in these trials were roughly consistent with those for the population without cancer, and the NMA allowed for indirect comparisons to be made using this data to compare the treatments to the other DOACs and LMWH alone. Additionally, the committee noted that the ADAM-VTE trial (McBane 2019), a small (~300 participants) trial comparing apixaban to LMWH alone recently published

					and that the results were consistent with that of the other DOACs without evidence of increased bleeds. As you note in your comment, some of the DOACs have been found to have an increased bleeding risk in some cancers. The committee discussed this point again following stakeholder comments. They noted that many of the bleeds associated with the DOACs were specifically gastrointestinal(GI) and genitourinary (GU) bleeds and that the safety profile of the DOACs compared to LMWH alone improved when only looking at other bleeds (see the benefits and harms section of the evidence review D for more information on this discussion). However, the committee agreed not to specifically prohibit the use of DOACs in people with a GI and/or GU malignancy or give specific guidance on who is/is not suitable for a DOAC as there are potentially other types of malignancies which make a DOAC unsuitable and this decision needs to be made on an individual basis. They were concerned that if they provided a list of tumours with which to avoid DOAC use this would not be exhaustive and could mislead clinicians. Instead, the committee made a general recommendation to take into account the tumour site when prescribing anticoagulation for people with cancer (which they expected would include considerations of whether the person has a GI/GU malignancy or a tumour type likely to be associated with these bleeds). The committee agreed with the need to highlight the potential interactions of anticoagulants with drugs used to treat

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					cancer (particularly chemotherapy) and added drug interactions to the list of factors to take into account as part of the decision-making process. Additionally, following discussion of stakeholder comments, the committee agreed to amend the recommendations to make it clearer that if a DOAC is unsuitable, to consider LMWH alone or LMWH with a VKA. These recommendations were intended to ensure that the individual with cancer received the most appropriate treatment for their VTE whilst supporting the NHS to make the best use of its limited resources. Reference: McBane, RD, Wysokinski W , Le-Rademacher J G…., &. Loprinzi CL. (2019) Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. J. Thromb Haemost, [epub ahead of print]
Leeds Teaching Hospitals NHS Trust	Guideline	16	5	Warfarin became out of favour for treatment of VTE in active cancer with the publication of the CLOT trial, why has is suddenly re-appeared? I am not aware of new evidence. I think this is extremely risky for patients on traditional chemotherapy but do appreciate those with active cancer on the long-term immunotherapy, continuous oral chemotherapy i.e. inhibitors may be more suitable. I would welcome more specific guidance rather than this sweeping	Thank you for your comment. Following discussion of stakeholder comments, the committee agreed to amend the recommendations to make it clear that if a DOAC is unsuitable, to consider LMWH alone or LMWH with a VKA as a third option. The committee agreed that for most people, VKA will be unsuitable due to the potential for drug interactions and is less favourable efficacy profile compared to alternatives. However, the committee agreed that in a small number of people, such as those unable to take DOACs who request an

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				generalisation which will only lead to confusion and inappropriate usage of oral agents.	oral treatment, VKA may be an option. It was included in the draft recommendations as an alternative to a DOAC because it was more cost effective than LMWH. LMWH was not cost effective due to its high cost compared to DOACs and LMWH with VKA. The committee agreed not to make more specific recommendations for when a specific drug is unsuitable due to a lack of evidence, to prevent the recommendations from becoming overly complex and because the suitability of each drug for an individual needs to be assessed on a case by case basis. The committee noted that many of the bleeds associated with the DOACs were specifically gastrointestinal (GI) and genitourinary (GU) bleeds and that the safety profile of the DOACs compared to LMWH alone improved when only looking at other bleeds (see the benefits and harms section of the evidence review D for more information on this discussion). However, the committee agreed not to specifically prohibit the use of DOACs in people with GI and/or GU malignancy or give specific guidance on who is/is not suitable for a DOAC as there are potentially other types of malignancies which make a DOAC unsuitable. They were concerned that if they provided a list of tumours with which to avoid DOAC use this would not be exhaustive and could mislead clinicians.

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					However, to ensure that the treatment of people with VTE and cancer is individualised, the committee made a separate recommendation to ensure that tumour site, drug interactions and the person's bleeding risk are taken into account when choosing an anticoagulant.
Leeds Teaching Hospitals NHS Trust	Guideline	16	7	This is completely the opposite of current guidance including recently released guidance. Give consideration to making more specific recommendations on who should or shouldn't receive LMWH first line such as thrombocytopenia, high bleeding risk etc.	Thank you for your comment. This update followed the methods outline in the NICE guideline manual based on the best available evidence and we are unable to comment on how other guidelines conduct their reviews or examine how they reach their recommendations. Following discussion of stakeholder comments, the committee agreed to amend the recommendations to make it clear that if a DOAC is unsuitable, to consider LMWH alone or LMWH with a VKA. The committee agreed that for most people, VKA will be unsuitable due to the potential for drug interactions and is less favourable efficacy profile compared to alternatives. However, the committee agreed that in a small number of people, such as those unable to take DOACs who request an oral treatment, VKA may be an option. It was included in the draft recommendations as an alternative to a DOAC because it was more cost effective than LMWH. LMWH was not cost effective due to its high cost compared to DOACs and LMWH with VKA. The committee agreed not to make more specific recommendations for when a specific drug is unsuitable due to a lack of evidence, to prevent the

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					recommendations from becoming overly complex and because the suitability of each drug for an individual needs to be assessed on a case by case basis. The committee noted that many of the bleeds associated with the DOACs were specifically gastrointestinal (GI) and genitourinary (GU) bleeds and that the safety profile of the DOACs compared to LMWH alone improved when only looking at other bleeds (see the benefits and harms section of the evidence review D for more information on this discussion). However, the committee agreed not to specifically prohibit the use of DOACs in people with GI and/or GU malignancy or give specific guidance on who is/is not suitable for a DOAC as there are potentially other types of malignancies which make a DOAC unsuitable. They were concerned that if they provided a list of tumours with which to avoid DOAC use this would not be exhaustive and could mislead clinicians. However, to ensure that the treatment of people with VTE and cancer is individualised, the committee made a separate recommendation to ensure that tumour site, drug interactions and the person's bleeding risk are taken into account when choosing an anticoagulant.
Leeds Teaching Hospitals NHS Trust	Guideline	18	9	Apixaban is licensed for 10mg bd for 7 days then 5mg bd for up to 6 months then 2.5mg bd long term. This statement (not backed up by any obvious evidence I can see) goes against the licence potentially, doesn't take account of patients who may	Thank you for your comment. The committee did not specify which dose to use as it is intended that dose-adjustments are made in line with the summary of product characteristics (SPCs) for the drug being used, which provide detailed information on when to adjust the dose if any such requirements exist. The committee

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				be high risk for recurrence or can't take a twice daily dose.	agreed not to duplicate this information within the recommendations themselves to limit complexity. The recommendation for a review at 3 months does not mean that their treatment regimen should be altered at that point (unless they discontinue treatment). The recommendation to consider switching to apixaban was made based on the evidence from a network meta-analyses of the long- term trials using the various anticoagulants and a novel economic model. Based on the cost-effective evidence and evidence from the extended treatment NMA suggesting the potential for fewer bleeds with apixaban, the committee agreed to recommend considering switching to apixaban if on a different DOAC which is not well tolerated. (See evidence reviews D and G for more details.) However, the committee agreed that decisions to switch treatment should always consider the specific clinical situation and person's preferences. To make this clearer they have written a separate recommendation covering these points.
Leeds Teaching Hospitals NHS Trust	Guideline	18	13	This could be made clearer, are you suggesting not to switch treatment at 3 months? What about 6 months as per licences or lower risk period?	Thank you for your comment. Following discussion of the stakeholder comments, the committee amended the recommendation for secondary prevention of VTE to make it clearer that for most people, the first option would be to continue with the same treatment if it is already well tolerated. If the current treatment is not well tolerated, or the clinical situation or person's preferences have changed then switching to apixaban (if taking a

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					DOAC other than apixaban) could be considered. They intended that the review would take place after 3 months of initial treatment (or 3-6 months for people with cancer) as stated in the first recommendation in this section and that any switching between drugs (for example, rivaroxaban to apixaban) would also occur then unless there was reason to delay it. The committee recognised that some anticoagulants, such as apixaban and rivaroxaban, have different doses for different stages of the treatment pathway. They did not specify which dose to use at a particular point in time as it is intended that dose-adjustments are made in line with the summary of product characteristics (SPCs) for the drug being used. Therefore, if the licence reduces the dose at 6 months the committee expected that the clinician would follow this unless they had reason to do otherwise. The committee decided not to duplicate this information within the recommendations themselves to limit complexity.
Leeds Teaching Hospitals NHS Trust	Guideline	20	6	Could more guidance be given on systemic thrombolysis please.	Thank you for your comment. The use of systemic thrombolysis was not within the scope of this update. Therefore, the committee did not review any evidence and were unable to make recommendations on this topic. We encourage you to submit suggestions for areas that NICE guidelines should address or where an update is needed of an existing topic. We pass comments onto

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					surveillance where there is something that could trigger an update. For example, if there is new evidence that is likely to change recommendations, or if there is new evidence about topics that are not covered by the existing guidance, or if issues concerning safety are raised. If there is new evidence this needs to be verifiable by the inclusion of supporting references, specifically primary studies or systematic reviews of primary studies.
LEO Pharma	Guideline	General	General	Question asked at top of comments form: which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why. Implementing the recommendations proposed in this guideline for treating VTE in patients with cancer will have potential challenges when trying to implement them at hospital trust level. LMWH is the main anticoagulant used in practice and is the only licensed option with an established and fully evaluated risk/benefit profile in patients with Cancer Associated Thrombosis (CAT). This current NICE draft recommendation also goes against GMC advice which states that a licenced medication should be implemented first.	Thank you for your comment. The recommendation to consider the DOACs before LMWH alone was based primarily on cost-effectiveness evidence identifying that LMWH alone was not a cost-effective option for people with VTE and cancer due to its very high relative cost. The committee noted that the use of LMWH alone in people with cancer was established practice but agreed that its cost was prohibitive in cases where an alternative treatment could be used. Following discussion of the stakeholder comments concerning this issue, the committee divided the recommendation into 2 separate recommendations with the first covering DOACs and the second covering the use of LMWH alone or LMWH + VKA if a DOAC is unsuitable.

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				GMC guidance states: 'You should usually prescribe licensed medicines in accordance with the terms of their licence'. In addition, they state that prescribing unlicensed medicines may be necessary where there is no suitably licence medicine that will meet the patient's needs. This is not the case in this situation with the existence & established use of LMWHs. The guideline committee themselves acknowledge P31 line 31 "The effectiveness of direct-acting oral anticoagulants (DOACs) compared with other anticoagulation treatments in people with active cancer has not been studied sufficiently to enable firm conclusions to be made. Evidence from studies in people without cancer may not be applicable because cancer could affect the action of these drugs". In addition, implementing this draft guidance as it currently reads recommending oral anticoagulants for patients with Cancer could be challenging due to the impact of steroids on oral-anticoagulants. Steroids are commonly used in cancer patients. Due to pharmacokinetic characteristics, steroids use can lead to increased clearance and decreased plasma concentrations of oral anticoagulants, affecting their efficacy and also hemorrhagic risk. This requires close monitoring during the course of treatment.[11]	An earlier recommendation in this section stresses that a number of factors need to be taken into account when choosing anticoagulation treatment for people with active cancer, including tumour site, interactions with other drugs including those used to treat cancer, and the person's bleeding risk. This should mean that any contraindication for the use of a DOAC or other oral anticoagulant would be noted. However, the committee agreed that LMWH+VKA will not be suitable for most people with active cancer due to concerns with monitoring and/or drug interactions and removed the reference to using it if an oral medication is preferred and a DOAC is unsuitable. The committee agreed that as LMWH alone is the only licensed option for people with VTE and cancer, they had to recommend its use, although this does not mean that alternative unlicensed treatments cannot be recommended or prioritised if they are more cost effective. It is expected that the amended wording, which allows for the use of LMWH if a DOAC is unsuitable, will allow clinicians to use LMWH whenever it is deemed clinically necessary.

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				On this basis LMWH should be considered a first line option for people with active cancer and confirmed proximal DVT or PE.[10]	
LEO Pharma	Guideline	General	General	Question asked at top of comments form: Would implementation of any of the draft recommendations have significant cost implications? The drug acquisition costs modelled in this guideline are the full list prices. This does not reflect reality. In reality LMWHs route to market for use in secondary care is via national & regional tender (discount/rebate) schemes resulting in lower acquisition costs and substantial savings to the NHS. It is noteworthy that LMWH emerged in the economic modelling for this guideline as providing the joint second highest number of QALYs for cancer patients with DVT and third highest for cancer patients with PE. The results of the economic analysis conducted in the guideline have driven some of the recommendations. In the case of patients with CAT who are mainly managed in a secondary care setting and hence receive medicines at tender prices, there could be cost implications by implementing the recommendation that DOACs should be used first and LMWH considered on its own, only if the person finds oral medicine difficult to tolerate or a VKA is contraindicated.	Thank you for your comment. In accordance with our methods described in Developing NICE guidelines: the manual, public list prices for medicines should be used in the reference-case analysis. Analyses based on price reductions for the NHS will be considered only when the reduced prices are transparent and can be consistently available across the NHS, and when the period for which the specified price is available is guaranteed. We searched for nationally available price reductions for LMWHs, but no information was found and therefore the list prices were used.

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LEO Pharma	Guideline	14	27	There is a concern that the renal category (15-50ml/min) recommendation can put patients at a higher risk of bleed and cause confusion among clinicians in interpretation of chronic kidney disease classification. According to NICE CG182 the classification of CKD is much more specific and according to GFR and ACR. The current recommendation of 15-50ml/min includes CKD stages G3a,G3b & G4 (eGFR 15-59 ml/min/1.73m2) this is not aligned with NICE CKD CG182 guideline1.	Thank you for your comment. The committee decided to use estimated creatinine clearance over GFR and ACR in this recommendation due to this measure being used in the summary of product characteristics for the DOACs, which do not report ACR and GFR. The section of the existing recommendation that covers 15-50ml/min is further segmented into 30-50ml/min and 15-29ml/min where the treatment options differ between severity groupings. In addition, the CKD guideline is currently being updated and the use of GFR and ACR to define the CKD stages may change depending on the findings of the relevant evidence reviews and the expertise of the CKD committee.
LEO Pharma	Guideline	16	1 - 4	LMWH is the only licensed option for people with VTE and cancer. As stated by the GMC 'You should usually prescribe licensed medicines in accordance with the terms of their licence'. In addition, they state that prescribing unlicensed medicines may be necessary where there is no suitably licence medicine that will meet the patient's needs. The committee themselves acknowledge P31 line 31 "The effectiveness of direct-acting oral anticoagulants (DOACs) compared with other anticoagulation treatments in people with active cancer has not been studied sufficiently to enable firm conclusions to be made. Evidence from studies in people without cancer may not be applicable because cancer could affect the action of these drugs". On this basis LMWH should be considered a first line option for	Thank you for your comment. The recommendation to consider the DOACs before LMWH alone was based primarily on cost-effectiveness evidence from the economic model which showed that LMWH alone was not cost-effective due to its very high cost in comparison with the DOACs. The committee noted that the use of LMWH alone in people with cancer is established practice but agreed that its cost was prohibitive. Following discussion of the stakeholder comments, the committee amended these recommendations to make it clearer that although a DOAC is the first line option it may not be suitable in all clinical situations (for example if the person is at higher risk of a gastrointestinal bleed or if they cannot tolerate oral medication). If this is the case, then the clinician can consider LMWH alone (or LMWH + VKA if this is a

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				people with active cancer and confirmed proximal DVT or PE.[10] At a minimum, the evidence outlined below shows that LWMH should be positioned alongside DOAC's in the management of VTE with cancer Recently published international guidelines and consensus report, where a comparison of available data between direct oral anticoagulation (DOACS) in treatment of cancer associated venous thrombosis with LMWH have been considered, recommend use of both treatments as first line options in specific patient sub-groups. Khorona et al 2018(International Society on Thrombosis and Haemostatis) has recommended the use of LMWH for cancer patients with acute diagnosis of VTE and a high risk of bleeding including gastrointestinal, genitourinary and active gastrointestinal mucosal abnormalities. In the same guidance DOACS have been recommended for patients with acute VTE and lower risk of bleeding and no drug-drug interaction with current systematic therapy.[4] In a Canadian consensus report a similar recommendation have been made where there is a clear emphasis on drug-drug interaction and risk of bleed and type of cancer [Carrier et al 2018].[5]	possibility for the individual). This should ensure that if an individual requires LMWH treatment then they will be able to receive it, but if a DOAC can be used instead this will help support the NHS to make the best use of its limited resources. The committee noted that as LMHW alone is the only licensed option for people with VTE and cancer, they should recommend its use. However, this does not mean that alternative unlicensed treatments cannot be recommended or prioritised over licenced ones where there is evidence for their effectiveness and cost effectiveness. Although there have only been direct trials between edoxaban and rivaroxaban compared to LMWH alone, the NMA also used subgroup data for specifically people with active cancer from the main DOAC trials for apixaban and dabigatran compared to warfarin. The committee noted that the effects reported in these trials were roughly consistent with those for the population without cancer, and the NMA allowed for indirect comparisons to be made using this data to compare the treatments to the other DOACs and LMWH alone. The committee also noted that the ADAM-VTE trial (McBane 2019), a small (~300 participants) trial comparing apixaban to LMWH alone recently published and that

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				In a 2019 international guideline [Farge et al 2019] Direct oral anticoagulants are recommended for patients with cancer when creatinine clearance is ≥30 mL/min in the absence of strong drug–drug interactions or gastrointestinal absorption impairment (grade 1A) and recommend caution in patients with gastrointestinal tract malignancies, especially upper gastrointestinal tract malignancies, as the available data show increased risk of gastrointestinal tract bleeding with edoxaban and rivaroxaban. Data for other direct oral anticoagulants are needed as it is not clear whether other direct oral anticoagulants will have the same risk profile. LMWH have been recommended over vitamin K antagonist for the same renal threshold.[6] The proposed recommendations could be enhanced by specifying equal status of LMWH and DOAC use in patients with cancer and confirmed DVT or PE based on risk of bleed, specific type of cancer, drug-drug interactions (with respect to cancer treatment) and risk profile of each direct anticoagulants.[4,5,6] Evidence shows that there is an increase in major bleeding risk with DOACs, particularly observed in GI and potentially genitourinary malignancies. Caution with DOACs is also warranted in other settings with high risk for mucosal bleeding. Drug-drug interaction should be checked prior to using a DOAC.[..12]	the results were consistent with that of the other DOACs without evidence of increased bleeds. Additionally, the committee noted that many of the bleeds associated with the DOACs were specifically gastrointestinal and genitourinary bleeds and that the safety profile of the DOACs compared to LMWH alone improved when excluding GI malignancies or excluding GI and GU bleeds (see the benefits and harms section of evidence review D for more information on this discussion). The committee agreed not to specifically prohibit the use of DOACs in people with GI and/or GU malignancies or give specific guidance on who is/is not suitable for a DOAC as there are potentially other types of malignancies which make a DOAC unsuitable (which may not be considered if a list of some relevant tumour types was provided). However, taking stakeholder comments into account, the committee split the existing recommendation into separate recommendations with the first emphasising the need to take into account the tumour site and bleeding risk when prescribing anticoagulation for people with cancer. It is therefore likely that DOACs will be deemed unsuitable for people with malignancies which expose them to an increased with of GI/GU bleeds. Following discussion of stakeholder comments, the committee agreed with the need to highlight the potential interactions of anticoagulants with drugs used to treat

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				The published trials on the use of edoxaban (HOKUSAI study) and rivaroxaban (Select-D) were two studies with extensive exclusion criteria; The Hokusai study (Raskob 2017) used to stratify patients to receive a lower dose *"Risk factors for bleeding were surgery within the previous 2 weeks, the use of antiplatelet agents, a primary or metastatic brain tumor, regionally advanced or metastatic cancer, gastrointestinal or urothelial cancer that had been diagnosed within the previous 6 months, or treatment with bevacizumab within the previous 6 weeks."*[7]. The Hokusai study (Raskob 2017) also stated that "The rate of major bleeding was significantly higher with edoxaban than with dalteparin (6.9% and 4.0%, respectively; hazard ratio, 1.77; 95% CI, 1.03 to 3.04; P = 0.04). This difference was mainly due to the higher rate of upper gastrointestinal bleeding with edoxaban"[7]. For the SELECT-D study (Young et al 2018), reports a three-fold relative increase in CRNMB with rivaroxaban compared with dalteparin, and an increased major bleeding rate in patients treated with rivaroxaban compared with dalteparin, particularly with regard to gastrointestinal cancers.[8]	cancer (particularly chemotherapy) and added drug interactions to the list of factors to take into account when deciding on which anticoagulant to use. This recommendation is intended to ensure that the decision regarding treatment choice is taken on a case by case basis. This update followed the methods outline in the NICE guideline manual based on the best quality evidence available. Reference: McBane, RD, Wysokinski W , Le-Rademacher J G…., &. Loprinzi CL. (2019) Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. J. Thromb Haemost, [epub ahead of print]
LEO Pharma	Guideline	16	1 - 7	The recommendation to use direct-acting oral anticoagulant and then LMWH with a VKA ahead of LMWH on their own when choosing anticoagulation	This update followed the methods outline in the NICE guideline manual based on the best available evidence. The committee were aware that their recommendations

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				treatment for people with active cancer and confirmed proximal DVT or PE, does not take into account evidence from the ASCO clinical guidelines which state that for long-term anticoagulation, LMWH, edoxaban, or rivaroxaban for at least 6 months are preferred because of improved efficacy over vitamin K antagonists (VKAs). VKAs are inferior but may be used if LMWH or direct oral anticoagulants (DOACs) are not accessible.[12] Recent meta analyses have also confirmed previous findings that LMWH is more effective than VKAs at reducing the risk of recurrent VTE in patients with cancer. [13,14,15,16] In light of this and the evidence cited in earlier comments, LMWH on its own should be recommended alongside DOACs and ahead of LMWH and VKA.	differed to those of other guidelines. However, they were in agreement in their conclusions based on their discussion of the clinical and cost effectiveness analyses that were conducted for this guideline. We are unable to comment on how other guidelines conduct their reviews or examine how they reach their recommendations. Following discussion of the stakeholder comments, the committee amended these recommendations to state that if a DOAC is unsuitable, LMWH alone or LMWH+VKA should be considered. The committee were aware that LMWH+VKA would not be suitable for most people with cancer and therefore this wording will likely result in LMWH being used when a DOAC is unsuitable. The committee did not specify LMWH as the first option or joint first option because it is not cost effective compared to the DOACs due to its very high relative cost. Therefore, the committee recommended DOACs above LMWH alone to support the NHS to make the best use of its limited resources**.** However, they intended that the choice of medication would be made on a case by case basis taking into account bleeding risk, the potential for drug interactions and tumour site and so people with cancer can be treated with LMWH if it is the best option for that that individual.
LEO Pharma	Guideline	16	7	With regard to the recommendation "Consider LMWH on its own only if the person finds oral medicine difficult to tolerate or a VKA is contraindicated", this	Thank you for your comment. Following discussion of stakeholder comments, the committee agreed to amend the recommendations to make it clear that if a DOAC is

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				represents a significant change in clinical practice in the UK, as LMWH is the main anticoagulant used in practice and is the only licensed option, with an established and fully evaluated risk/benefit profile. It is noteworthy that LMWH emerged in the economic modelling for this guideline as providing the joint second highest number of QALYs for cancer patients with DVT and third highest for cancer patients with PE. In recommending a move to DOACs, it appears that it has also been considered that an oral medicine is preferred to an injectable formulation by cancer patients. Research conducted by Prof Simon Noble, University of Cardiff, on patient experience of cancer patients living with thrombosis in UK patients (PELICAN 2015) and Canadian, French and Spanish populations, LMWH most patients found the injections an acceptable intervention within the context of their cancer journey.[9]	unsuitable, to consider LMWH alone or LMWH with a VKA. The committee agreed that for most people, VKA will be unsuitable due to the potential for drug interactions and is less favourable efficacy profile compared to alternatives. However, the committee agreed that in a small number of people, such as those unable to take DOACs who request an oral treatment, VKA may be an option. It was included in the draft recommendations as an alternative to a DOAC because it was more cost effective than LMWH. LMWH was not cost effective due to its high cost compared to DOACs and LMWH with VKA. The committee agreed not to make more specific recommendations for when a specific drug is unsuitable due to a lack of evidence, to prevent the recommendations from becoming overly complex and because the suitability of each drug for an individual needs to be assessed on a case by case basis. However, to ensure that the treatment of people with VTE and cancer is individualised, the committee made a separate recommendation to ensure that tumour site, drug interactions and the person's bleeding risk are taken into account when choosing an anticoagulant. Although the committee noted that generally, people prefer oral medication to an injection, this was not a driving factor for the recommendations. Additionally, although the research highlighted suggests that most people found injections to be acceptable in the context

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					of their cancer journey, this does not preclude the possibility that they people would have preferred an oral option if it had been available.
LEO Pharma	Guideline	32	18	It is inappropriate to describe LMWH as expensive. The drug acquisition cost of LMWH is substantially lower than that of DOACs. It is also important to note in the guideline that the drug acquisition costs modelled in this guideline are the full list price. In reality LMWHs route to market is via national & regional tender (discount/rebate) schemes resulting in lower acquisition costs and substantial savings to the NHS. Prescribers and payers should be reminded of this and advised by NICE to consider this when interpreting this guidance. This is highly relevant in particular for patients with cancer and confirmed DVT or PE as the diagnosis and initial care is managed in the hospital setting.	Thank you for your comment. In accordance with our methods described in Developing NICE guidelines: the manual, public list prices for medicines should be used in the reference-case analysis. Analyses based on price reductions for the NHS will be considered only when the reduced prices are transparent and can be consistently available across the NHS, and when the period for which the specified price is available is guaranteed. We searched for nationally available price reductions for LMWHs but no information was found and therefore the list prices were used. https://www.nice.org.uk/process/pmg20/chapter/incorporating-economic-evaluation#the-reference-case
NHS England	Guideline	General	General	The "if this, then that" approach is quite complex and would lend itself to an on-line or app-based decision support tool.	Thank you for your comment. NICE has developed visual summaries of the recommendations on diagnosis, initial management and anticoagulation treatment for DVT and PE. These will be published at the same time or shortly after the updated guideline.
Nottingham University Hospitals NHS Trust	Guideline	7	9	We completely support the changes in wording made in this section, although feel that this particular line could be clearer, as we would intend for the scan to be performed within 4 hours of initial clinical assessment, but this could be interpreted as within 4 hours of scan being requested (which would	Thank you for your comment. The committee agreed that according to the recommendation, the 4-hour time period should begin from the point of the scan being requested, as people with a negative D-dimer would not require a scan. As you note, this may therefore mean an 8hr overall time (or more) to get both tests back because

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				potentially be up to 8 hours after clinical assessment if d dimer result comes back after 4 hours and then scan done after 4 hours).	they are carried out sequentially. The committee agreed that this was the intention of the recommendation and therefore it did not need to be amended further. However, if the D-dimer test and scan can be carried out in less time then this is even better.
Nottingham University Hospitals NHS Trust	Guideline	7	24	Was the evidence from YEARS group on stratification of d dimer results considered with respect to those patients having d dimer checked in context of possible PE?	Thank you for your comment. The section of the guideline that covers diagnosis was out of scope of this update with the exception of the use of age adjusted and point of care D-dimer tests. The committee were therefore unable to review the use of the YEARS algorithm during the diagnosis of PE and could not make any recommendations on this topic. We encourage you to submit suggestions for areas that NICE guidelines should address or where an update is needed of an existing topic. We pass comments onto surveillance where there is something that could trigger an update. For example, if there is new evidence that is likely to change recommendations, or if there is new evidence about topics that are not covered by the existing guidance, or if issues concerning safety are raised. If there is new evidence this needs to be verifiable by the inclusion of supporting references, specifically primary studies or systematic reviews of primary studies.
Nottingham University	Guideline	9	7	In view of the recent NCEPOD report and BTS draft quality standards from October 2019, would it not be wise to consider including a caveat to this section	Thank you for your comment. The section of the guideline that covers diagnosis was out of scope of this update with the exception of the use of age adjusted and

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Nottingham University Hospitals NHS Trust	Guideline	14	6	This section refers to co-morbidities which would mean that Apixaban or Rivaroxaban would need to be avoided, but there is no reference made to drug interactions which would mean that these agents ought to be avoided, and in our experience these drug interactions are often overlooked and can have significant consequences.	Thank you for your comment. The committee agreed with your comment that that drug-interactions are an important consideration when prescribing anticoagulation. The committee noted that this issue is particularly important for people with VTE and active cancer. They therefore amended the active cancer treatment recommendation to take into account drug interactions when prescribing treatment for these people. However, the committee noted that for people without cancer, it is usual practice to take into account drug interactions. Therefore, to avoid the recommendation becoming overly complex, they decided that not to include this consideration in other recommendations.
Nottingham University Hospitals NHS Trust	Guideline	15	11	Why has Warfarin not been included in this section? This would generally be the agent of choice in this group of patients.	Thank you for your comment. Based on stakeholder comments, the committee have amended this recommendation to include LMWH or UFH alone or concurrently with a VKA as options.
Nottingham University Hospitals NHS Trust	Guideline	15	18	It would seem that the cut off of 40kg/m2 is completely arbitrary and not supported by any evidence. There is increasing evidence to support the use of DOACs in patients with body weights in excess of the 120kg threshold studied in the original clinical trials, and many centres would now adopt a	Thank you for your comment. The recommendation relating to BMI was based primarily on consensus due to limited evidence from randomized controlled trials in this population. The committee discussed feedback from stakeholders regarding the use of absolute weight instead of BMI and that there are concerns with treating

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				threshold of 150kg or even higher for using these agents. The emerging evidence refers to body weight rather than BMI, so if wishing to set a cut off at all would it not be more sensible to use body weight given the evidence coming through (albeit that we agreed that body weight isn't an ideal measure either). However surely there is an argument for no cut off to be set at all given that the evidence continues to emerge, and instead suggest that body weight or BMI needs to be taken into account when making the decision about choice of anticoagulant? NB: In addition, a cut off has been set for upper limit at which DOACs cannot be used, but many of us are more concerned about using DOACs in patients with a body weight below 50kg (due to limited evidence, and the evidence that does exist suggesting increased risk of bleeding and thrombosis in this group), so if setting a cut off for upper limit should a cut off not also be set for lower limit?	people with low body weight as well as those with high body weight. The committee agreed with stakeholder concerns and decided to specifically make reference to absolute weight rather than BMI and amended the recommendation to cover people at both extremes of weight (<50kg or >120kg). The committee selected these cut-off points based on clinical experience and due to these cut-offs being most commonly highlighted in the summary of product characteristics (SPCs) for the DOACs. However, the committee agreed that uncertainty surrounding effective treatment for these groups remains. Taking into account that there is some evidence that the DOACs could be used in obese patients and that more evidence may be forthcoming, the committee made a more general recommendation to enable the clinician to decide which treatment would be most effective on an individual basis which allows for the use of DOACs. They noted that whatever the choice of anticoagulant is, it is important to ensure that there is effective monitoring of therapeutic levels and any dose adjustments and monitoring requirements stated in the SPCs are followed, along with locally agreed protocols or advice from a specialist or multidisciplinary team.
Nottingham University Hospitals NHS Trust	Guideline	16	7	This section appears to recommend VKA over LMWH in patients with cancer, but this is contrary to the evidence that has been known for some time (demonstrating that VKA are less effective than LMWH in this context), and also not in line with the	Thank you for your comment. This update followed the methods outline in the NICE guideline manual based on the best available evidence and we are unable to

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				ISTH guidance from July 2018. As the evidence summary would suggest that this comes down to cost of VKA being much less than LMWH, then we feel that this recommendation is misguided, as how can it recommended that patients receive a drug known to be significantly less effective (and not mentioned in the international guidance at all) just because it is cheaper?	comment on how other guidelines conduct their reviews or examine how they reach their recommendations. Following discussion of stakeholder comments, the committee agreed to amend the recommendations to make it clear that if a DOAC is unsuitable, to consider LMWH alone or LMWH with a VKA. The committee agreed that for most people, VKA will be unsuitable due to the potential for drug interactions and is less favourable efficacy profile compared to alternatives. However, the committee agreed that in a small number of people, such as those unable to take DOACs who request an oral treatment, VKA may be an option. It was included in the draft recommendations as an alternative to a DOAC because it was more cost effective than LMWH. LMWH was not cost effective due to its high cost compared to DOACs and LMWH with VKA. The committee agreed not to make more specific recommendations for when a specific drug is unsuitable due to a lack of evidence, to prevent the recommendations from becoming overly complex and because the suitability of each drug for an individual needs to be assessed on a case by case basis. However, to ensure that the treatment of people with VTE and cancer is individualised, the committee made a separate recommendation to ensure that tumour site, drug interactions and the person's bleeding risk are taken into account when choosing an anticoagulant.

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Nottingham University Hospitals NHS Trust	Guideline	18	1	Should it not be highlighted that the HAS-BLED score hasn't been validated in this context, and must therefore be used with some caution?	Thank you for your comment. There have been several retrospective studies evaluating the use of HAS-BLED in VTE populations. The committee recommended HAS-BLED as these studies had very large samples and identified HAS-BLED as having good prognostic accuracy. However, they also noted the inherent problems associated with retrospective prognosis studies and therefore only made a consider recommendation. They also were very clear about the circumstances in which this tool may provide useful information and that it is not to be used solely as the basis of a decision to continue or stop treatment. In addition, HAS-BLED has been validated in a population of people with VTE who were taking LMWH, VKA or a DOAC (Brown 2018). The evidence is presented fully in evidence review F, which also contains details of the committee discussions concerning this topic. Brown J D, Goodin A J, Lip G Y. H, and Adams V R (2018) Risk Stratification for Bleeding Complications in Patients With Venous Thromboembolism: Application of the HAS-BLED Bleeding Score During the First 6 Months of Anticoagulant Treatment. Journal of the American Heart Association 7(6), 07
Nottingham University Hospitals NHS Trust	Guideline	18	9	Although we would support the premise of this section, it could be clearer that the choice of anticoagulant needs to be guided by clinical context and patient preference (by moving this comment higher up) rather than focusing on the use of Apixaban, as there are clearly a number of clinical	Thank you for your comment. Following discussion of the stakeholder comments, the committee wrote a new recommendation which comes before those covering the choice of anticoagulant to ensure that the person's preferences and their clinical situation is taken into account when deciding what to prescribe. Additionally,

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				contexts in which Apixaban would not be the preferred choice for anticoagulation given that the long term dose was only studied in a limited number of clinical contexts (and excluded those with significant thrombotic events for example).	the committee also amended the subsequent recommendation to make clear that for most people, the first option would be to continue with the same treatment if it is already well tolerated. If this is not the case or the clinical situation or person's preferences have changed, switching to apixaban can be considered if the current treatment is a different DOAC.
Nottingham University Hospitals NHS Trust	Guideline	18	21	Although there is evidence to support a reduction in recurrent DVT or PE with Aspirin, there is also a risk of bleeding associated with Aspirin which is often not considered. In view of the clinical trial evidence suggesting that Apixaban 2.5mg bd carries such a low risk of bleeding, surely it would be better to continue this rather than using Aspirin in anyone who is felt to be at risk of recurrence sufficient to justify any treatment. We would be concerned that patients would overestimate the efficacy of Aspirin and underestimate the risk of bleeding.	Thank you for your comment. The committee agreed that aspirin was less effective than the DOACs and that aspirin use is associated with a risk of bleeding. However, the committee identified that there is a small group of people who require, yet decline, long term treatment with anticoagulation. The committee agreed that these people, in the absence of alternative anticoagulation and when extended treatment is suitable, may benefit from aspirin as trials comparing aspirin to placebo suggest that aspirin significantly reduces VTE-recurrence but did not demonstrate significantly increased rates of major bleeding. The recommendation contains a footnote specifying that informed consent should be obtained and documented, previous recommendations (such as 1.4.3) should involve a discussion of the benefits and harms of any potential treatment strategy before this is commenced. This should involve discussion of the efficacy and bleeding risk of aspirin.
Nottingham University	Guideline	23	6	Given the MHRA statement about avoiding the use of DOACs in patients with antiphospholipid syndrome (even though the evidence only suggests that this is	Thank you for your comment. The section of the guideline on thrombophilia testing was not within the scope of this update and the committee were therefore

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Hospitals NHS Trust				necessary for those found to be triple positive), should mandatory testing for antiphospholipid antibodies in all patients with unprovoked DVT or PE be considered, rather than just those wishing to stop treatment?	unable to make new recommendations or substantially alter the existing ones. However, based on the MHRA alert the first recommendation in this section was altered to specify hereditary thrombophilia rather than just thrombophilia as stated in the previous version of the guideline. This leaves it to the clinician's discretion whether to test someone for APS who is continuing anticoagulation treatment. We encourage you to submit suggestions for areas that NICE guidelines should address or where an update is needed of an existing topic. We pass comments onto surveillance where there is something that could trigger an update. For example, if there is new evidence that is likely to change recommendations, or if there is new evidence about topics that are not covered by the existing guidance, or if issues concerning safety are raised. If there is new evidence this needs to be verifiable by the inclusion of supporting references, specifically primary studies or systematic reviews of primary studies.
Royal College of General Practitioners	Guideline	General	General	NICE produce wonderful infographics for many of their topics. It would be very helpful to produce a clear and simple infographic to help with these guidelines for clarity which can then be used as a quick guide to investigation and treatment.	Thank you for your comment. NICE has developed visual summaries of the recommendations on diagnosis, initial management and anticoagulation treatment for DVT and PE. These will be published at the same time or shortly after the updated guideline.

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Royal College of General Practitioners	Guideline	7	18 - 19	The use of point of care testing for D dimers is not common practice in primary care. Most general practices would use laboratory D dimer tests rather than point of care tests due to the funding structure within primary care and the prohibitive cost of point of care tests to individual practices. In contrast, there is consistent central funding for laboratory testing, although to get a result within 4 hours, patients would need to be sent to an ambulatory care environment or admitted to hospital. As a result, these recommendations are likely to increase the number of admissions to ambulatory care/ medical admissions departments or increase the use of interim therapeutic anticoagulation whilst waiting for overnight D dimers to be processed in secondary care, as it is unlikely that primary care on a widespread basis will voluntarily self-fund the point of care tests recommended. To increase uptake of the recommendations, a full cost analysis comparing laboratory D dimer and point of care D dimer should be considered to be produced alongside this guidance, as if cost savings were proven, then CCG/ STPs would be likely to buy/fund the PoC tests centrally for GP practices to use, potentially reducing unnecessary anticoagulation or hospital admissions.	Thank you for your comment. The recommendation specifies that point-of-care D-dimer testing be considered *if laboratory facilities are not immediately available*. As explained in the rationale and impact, the committee agreed that, if both laboratory-based and point-of-care D-dimer testing are immediately available, laboratory testing is preferable because it provides more rigorous quality assurance and greater certainty of diagnostic accuracy. However, if laboratory-based testing is not immediately available, the committee were in agreement that offering immediate point-of-care testing is more beneficial for patients than delaying diagnosis by waiting for laboratory testing. The committee was aware that point-of-care D-dimer testing is currently used in primary care centres in some parts of the country, particularly outside urban areas. However, in places where point-of-care testing is not available they agreed that as part of good clinical practice, the person with suspected VTE should be referred for lab testing with results available within 4hrs or given interim anticoagulants if this is not possible. A cost-consequences analysis was conducted as part of the guideline (see Evidence review A). Point-of-care tests are more expensive than laboratory tests but the analysis showed that in primary care settings where laboratory testing is not immediately available,

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					point-of-care tests can provide more rapid results that reduce the need for additional GP time and unnecessary interim anticoagulation treatment while awaiting laboratory D-dimer test results. When these cost offsets in primary care were taken into account, the difference in total costs between quantitative point-of-care testing and laboratory testing was much reduced. In the case of suspected DVT, the cost-consequences analysis showed that using quantitative point-of-care testing in primary care where laboratory facilities are not immediately available may even be cost saving, but this finding was associated with uncertainty. This analysis helped to inform the committee's recommendation to consider point-of-care testing if laboratory facilities are not immediately available.
Royal College of General Practitioners	Guideline	18	5 - 20	For clarity and ease of reading, can the committee consider combining the comorbidities from 1.4.9 into 1.4.8? e.g. "For people who are continuing anticoagulation treatment beyond 3 months and do not have renal impairment (estimated creatinine clearance less than 50 ml/min), a BMI of 40 kg/m2 or more or cancer. • carry on with the current treatment or • if the current treatment is a direct-acting oral anticoagulant other than apixaban, consider changing to apixaban."	Thank you for your comment. It would be difficult to combine the recommendations without causing confusion as the part of the recommendation to consider changing to apixaban does not apply to people with cancer, renal impairment or with a low (<50kg) or high (>120kg) bodyweight because the evidence reviewed was for the general population of people with VTE. The committee therefore agreed to retain separate recommendations for these groups of people.
Royal College of Nursing	Guideline	General	General	The Royal College of Nursing welcome the opportunity to comment on the draft NICE guidelines	Thank you for your comments on this update.

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Royal College of Nursing	Guideline	General	General	It would be useful to have the risk criteria for pulmonary embolism and deep vein thrombosis described within the document.	Thank you for your comment. The guideline contains tables detailing the Two-level DVT and PE Wells scores that are used in the process of diagnosis to stratify the likelihood of having DVT or PE.
Royal College of Nursing	Guideline	General	General	There are limitations to D-Dimer test for example in sepsis, but we feel that it is not described within the draft guidelines.	Thank you for your comment. The D-dimer test was out of scope of this update apart from the use of point of care tests and age adjusted D-dimer, and the committee agreed that they could not make specific recommendations for sepsis in these areas. We encourage you to submit suggestions for areas that NICE guidelines should address or where an update is needed of an existing topic. We pass comments onto surveillance where there is something that could trigger an update. For example, if there is new evidence that is likely to change recommendations, or if there is new evidence about topics that are not covered by the existing guidance, or if issues concerning safety are raised. If there is new evidence this needs to be verifiable by the inclusion of supporting references, specifically primary studies or systematic reviews of primary studies.

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Royal College of Nursing	Guideline	General	General	It would be useful to include a flow diagram if possible, to help the clinician to interpret the guidelines.	Thank you for your comment. NICE has developed visual summaries of the recommendations on diagnosis, initial management and anticoagulation treatment for DVT and PE. These will be published at the same time or shortly after the updated guideline.
Royal College of Nursing	Guideline	General	General	Management of patients with acute kidney injury is mentioned but what about those receiving dialysis?	Thank you for your comment. The protocol for the pharmacological treatment reviews specified people with renal impairment as a subgroup of interest. Limited evidence was identified for this group of people and the committee made recommendations based on their clinical expertise and the summary of product characteristics of the treatment options. The evidence identified did not cover people receiving dialysis and the committee decided against making separate recommendations for this subgroup of people with renal impairment because they expected that their treatment would be covered by local protocols.
Royal College of Nursing	Guideline	19	5	We welcome the recommendation on information for patients. It would be useful to add 'Indication' for anticoagulation to the list.	Thank you for your comment and support of this recommendation. The section of the guideline that covers information was out of scope of this update and the committee were unable to make your suggested change. Although, the recommendation concerning animal products was amended to reflect the use of lactose in some DOACs this was possible because this represents a potential safety issue as some people are allergic to lactose.
Royal College of Nursing	Guideline	34	17	It would be useful to have guidance on switching from Heparin infusion to oral anticoagulation.	Thank you for your comment. The committee agreed that switching from heparin infusion to oral anticoagulation would be covered by local protocols and

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					it was not necessary to include this level of detail in the guideline.
Royal College of Physicians	Guideline	General	General	The RCP would like to endorse the response submitted by the British Thoracic Society (BTS).	Thank you for your comment. Please see our responses to the BTS comments.
Royal College of Physicians and Surgeons of Glasgow	Guideline	General	General	The Royal College of Physicians and Surgeons of Glasgow although based in Glasgow represents Fellows and Members throughout the United Kingdom. While NICE has a remit for England, many of the recommendations are applicable to all devolved nations including Scotland. They should be considered by the relevant Ministers of the devolved governments. The College welcomes this Guideline on Venous Thromboembolic Disease in an important area. It is generally supportive of this guideline.	Thank you for your comments and support for this update.
Royal College of Physicians and Surgeons of Glasgow	Guideline	General	General	While it may seem obvious, it is important to recognise that the symptoms of patients who are suspected to have VTE but are no confirmed to have had thrombosis or embolism still need treatment. Too often patients with "negative tests" are sent home with significant untreated disease (e.g. ruptured Bakers cyst or chest pain from other causes.	Thank you for your comment. The diagnosis section of the guideline was out of scope of this update (apart from the use of point of care and age adjusted D-dimer). The committee was therefore unable to make additional recommendations in this section. However, in the recommendations, if DVT (or PE) is not identified after the relevant scan has been carried out then we recommend that healthcare professionals think about alternative diagnoses. These recommendations should help ensure that people who do not go on to receive a diagnosis of PE or DVT,

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					but have ongoing symptoms are not sent home untreated.
Royal College of Physicians and Surgeons of Glasgow	Guideline	7	23	Rec 1.1.14. Age adjusted-Dimer tests are supported if it has similar diagnostic accuracy but reduces the need for unnecessary imaging.	Thank you for your comment and support regarding this matter. As noted in the rationale and impact section, the evidence suggests that age-adjustment does not reduce the sensitivity of D-dimer tests but does increase the specificity meaning that fewer people will receive false positive results.
Royal College of Physicians and Surgeons of Glasgow	Guideline	11	5	Rec 1.2. Outpatient treatment of low risk PTE is common practice as stated. It should be encouraged to reduce bed days /HAIs etc. For those units who do not manage low risk PTE in outpatients they should be encouraged to develop this service.	Thank you for your comment and support regarding this matter. The committee agreed that outpatient services should be encouraged to reduce hospital stay and envisioned that the recommendation may lead to an increase in the establishment of ambulatory care units
Royal College of Physicians and Surgeons of Glasgow	Guideline	11	21	The ability for outpatients to contact a health care team out of hours is vital. It must be specific and give 24 hours cover. It should not simply recommend attending A and E. More specific guidance on a dedicated service is required.	Thank you for your comment. It is intended that the person with VTE is provided with direct contact details of a healthcare professional or team to contact **only** during the normal working hours of specialist services and that a separate, out-of-hours service should be contacted at all other times. The rationale for outpatient treatment has been expanded to clarify this. The committee agreed that it is important to provide outpatients with a dedicated health care team but agreed that this would only be possible during the established service hours and that it would be too costly to establish a 24-hour specialist service. It is important that the person with VTE knows who to contact out-of-hours, but the committee agreed that this would vary depending on location and local practice and therefore

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					are unable to specify what the out-of-hours service will be. Please see the discussion section of the outpatient review for further detail on this topic.
Royal College of Physicians and Surgeons of Glasgow	Guideline	16	1	Rec 1.3.13. In VTE in patients with cancer our reviewer supported the use of DOAC. The current policy in the institution is LMWH. The expense of LMWH was noted in NICE rationale. The reviewer felt that cost saving should be promoted when the evidence suggests there are equal and non-inferior outcomes.	Thank you for your comment and support for this recommendation.
Royal College of Physicians and Surgeons of Glasgow	Guideline	20	2	Rec 1.5.3. It is felt that the fact that an individual may be truly allergic to lactose and refer not just to those who may have concerns.	Thank you for your comment. This recommendation was out of the scope for this update however, due to the introduction of DOACs to the guideline, the committee agreed that it was necessary to make an amendment warning that apixaban and rivaroxaban contain lactose from cow's milk as this recommendation is directly addressing the point that certain treatments are of animal origin. The committee agreed that some people are allergic to lactose, whilst other people may avoid it for other non -medical reasons. As a result, they amended the recommendation slightly to clarify that the concerns could be ethical, religious or due to intolerance and it is hoped that this will stimulate discussion about these issues.
Royal College of Physicians and Surgeons of Glasgow	Guideline	22	10	Rec 1.8. With respect to further investigation for cancer in patients with VTE, the College agrees with the guideline. Unless symptoms or signs dictate the need for further investigation, irradiation of patients and overusing resources should be avoided.	Thank you for your comment and support regarding this matter. The committee were also concerned with the issues you note surrounding over-investigation and the new recommendations are aimed at reducing unnecessary testing.

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				Unexpected, unrelated findings raise anxiety and uncertainty in patients and relatives (and also sometimes health professionals). We should guard against over-investigation in general.	
Royal College of Physicians and Surgeons of Glasgow	Guideline	23	6	Rec 1.9.3. Immunological tests for antiphospholipid antibodies are not usually affected by anticoagulants but functional ones such as the lupus anticoagulant are.	Thank you for your comment. The committee amended this recommendation to state that these test 'may be' affected rather than 'are' affected to reflect your point.
Royal College of Physicians and Surgeons of Glasgow	Guideline	24	18	The College agrees that further work on DOACs are indicated particularly as they are cost effective compared to other treatments.	Thank you for your comment and support for this research recommendation.
Salisbury NHS Foundation Trust	Guideline	5	General	Some Trusts routinely do whole leg ultrasonography and detect distal DVT but there is no discussion of this in the guidance.	Thank you for your comment. The section of the guideline that covers diagnosis was out of scope of this update with the exception of the use of age adjusted and point of care D-dimer tests. The committee were therefore unable to review the use of the whole leg ultrasonography and could not make any recommendations on this topic. However, we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
Salisbury NHS Foundation Trust	Guideline	10	General	There is no discussion of use of age-adjusted D-dimer levels in exclusion of PE in patients with low-risk Wells scores. See https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-Pulmonary-Embolism-Diagnosis-and-Management-of	Thank you for your comment. The search did not identify evidence which looked specifically at participants with a low-risk PE Wells score and met the inclusion criteria for this review. This guideline recommends use of a two-level Wells score (PE likely or unlikely). People with a PE likely Wells score go straight to computed tomography pulmonary angiogram or alternative imaging. Therefore, for PE our recommendations of age-

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					adjustments will only apply in practice to people with an unlikely Wells score.
Salisbury NHS Foundation Trust	Guideline	15	10	I fail to understand why VKA is not suggested as an option to LMWH or UFH in patients with established renal impairment and CrCl <15m/min.	Thank you for your comment. Based on stakeholder comments, the committee have amended this recommendation to include LMWH or UFH alone or concurrently with a VKA as options.
Salisbury NHS Foundation Trust	Guideline	16	5 - 6	Given the RCT data showing that LMWH is superior to warfarin in treatment of VTE in cancer patients, I find the recommendation for its use at odds with current clinical practice. See https://www.ncbi.nlm.nih.gov/pubmed?term=12853587	Thank you for your comment. Following discussion of stakeholder comments, the committee agreed to amend the recommendations to make it clear that if a DOAC is unsuitable, to consider LMWH alone or LMWH with a VKA. The committee agreed that for most people, VKA will be unsuitable due to the potential for drug interactions and is less favourable efficacy profile compared to alternatives. However, the committee agreed that in a small number of people, such as those unable to take DOACs who request an oral treatment, VKA may be an option. It was included in the draft recommendations as an alternative to a DOAC because it was more cost effective than LMWH. LMWH was not cost effective due to its high cost compared to DOACs and LMWH with VKA. To ensure that the treatment of people with VTE and cancer is individualised, the committee made a separate recommendation to ensure that tumour site, drug interactions and the person's bleeding risk are taken into account when choosing an anticoagulant.

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Salisbury NHS Foundation Trust	Guideline	18	General	No discussion of offering reduced dose of DOAC for continuing anticoagulation, e.g. rivaroxaban 10mg od. See https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-Pulmonary-Embolism-Diagnosis-and-Management-of	Thank you for your comment. It is expected that the healthcare professional prescribing the DOAC will follow the dosing strategy that is set out in the summary of product characteristics and therefore the committee agreed that it is unnecessary to mention changes in doses apart from in rare exceptions (e.g. renal impairment) where additional cautions and monitoring applies.
Society for Acute Medicine	Guideline	6	12	The suggestion to stop interim anticoagulation pending a second scan is concerning and I would consider a risk given that this will include some patients with VTE. Was the stop a typo??	Thank you for your comment. The committee confirmed that anticoagulation therapy should be stopped at this point (when a person has a negative scan and a positive D-dimer) because if treatment is continued until the second scan, there is a risk that the clot will be partially treated, preventing an undetected calf DVT from extending into the proximal veins and resulting in another negative scan. This would then lead to a false negative diagnosis of DVT, and a lack of necessary, longer term anticoagulation treatment.
Swansea University	Guideline	19	5*	**Apologies if this is not within the bounds of the review. The text but not title of this section was greyed, so I took a chance that although revisions to the text were unacceptable, other changes may be.* There is increasing evidence of significant psychopathology following VTE (both DVT & PE). Around 40% of patients experience significant health anxiety, including episodes of panic, and 20% experience depression for up to a year post-VTE. This could be assessed at 3-month review, using	Thank you for your comment. As you note this section was out of scope. Therefore, the committee did not review the relevant evidence and were unable to make recommendations on this area. However, we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

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				simple measures such as the Hospital Anxiety and Depression Inventory or simple verbal questioning. Those with these problems could usefully be provided self-help materials, signposted to available services or, if significant, be referred to therapeutic services including clinical psychologists. 1. Noble, S. et al. (2014) The long-term psychological consequences of symptomatic pulmonary embolism: a qualitative study. *BMJ Open*. doi:10.1136/bmjopen-2013-004561 2. Bennett, P., Patterson, K. & Noble, S. (2016). Predicting post-traumatic stress and illness anxiety following a venous thrombotic embolism. *Journal of Health Psychology*, 21, 863-71. 3. Hunter, R.A., Lewis, S., Rance, J., Noble, S. & Bennett, P. (2017) Post-Thrombotic Panic Syndrome: a qualitative exploration of the experience of Venous-Thromboembolism. *British Journal of Health Psychology*, 22, 8-25 4. Feehan, M. et al. (2018). Prevalence and correlates of bleeding and emotional harms in a national US sample of patients with venous thromboembolism: a cross-sectional	

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The Royal College of Radiologists	Guideline	General	General	The points at which CTPA is recommended seem reasonable. Overall it seems reasonable guidance.	Thank you for your comment and support regarding this matter.
The Royal College of Radiologists	Guideline	37 - 38	23 - 29, 1 - 6	We agree with this assessment.	Thank you for your comment and support regarding this matter.
UK Clinical Pharmacy Association	Guideline	General	General	Guideline does not cover suspected or confirmed diagnosis and management of below-knee DVT management - to consider inclusion as NICE guideline covers venous thromboembolic diseases.	Thank you for your comment. This scope of this update of the VTE guideline did not include diagnosis (apart from the use of age adjusted and point of care D-dimer). Therefore, the committee did not review the evidence and were unable to make any recommendations concerning the diagnosis of distal/below the knee DVT. For the areas of the management part of the guideline that were updated the reviews did not identify any evidence specific to distal DVT and the committee were therefore unable to make any recommendations for this type of DVT. We encourage you to submit suggestions for areas that NICE guidelines should address or where an update is needed of an existing topic. We pass comments onto surveillance where there is something that could trigger an update. For example, if there is new evidence that is likely to change recommendations, or if there is new evidence about topics that are not covered by the existing guidance, or if issues concerning safety are

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					raised. If there is new evidence this needs to be verifiable by the inclusion of supporting references, specifically primary studies or systematic reviews of primary studies.
UK Clinical Pharmacy Association	Guideline	1	General	Consider inclusion criteria for 'adults (16 years and over) with suspected or confirmed DVT or PE…' so the age is in line with NICE NG89.	Thank you for your comment. The scope of this guideline only covers adults aged 18 and over. As this is a partial update, it was not possible to expand this population to include 16- and 17-year olds.
UK Clinical Pharmacy Association	Guideline	7	17 - 24	Consider adding 'ensure d-dimer test is carried out before administration of an anticoagulant'.	Thank you for your comment. As outlined in the recommendations in the DVT likely (Wells score 2 points or more) section of the guideline, there are circumstances in which anticoagulation would be offered without a d-dimer test being carried out (if DVT was likely based on the Wells score and the results of a proximal leg vein ultrasound scan were positive). There are similar recommendations in the PE likely (Wells score more than 4 points) section. In other cases, interim anticoagulation may be used while waiting for other tests or test results. Therefore, the committee agreed that it was not appropriate to make the change you suggested. However, in response to another comment they did amend an existing recommendation to re-order the bullet points so that for people with a likely DVT Wells score, if a proximal leg vein ultrasound scan result cannot be obtained within 4 hours, people are offered a D-dimer test before starting interim anticoagulation treatment. In addition, for DVT unlikely and PE unlikely the recommendations already say that is the results of a D-dimer test cannot be obtained within 4

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					hours, offer interim therapeutic anticoagulation while awaiting the result, implying that the sample for the test is taken and sent off before anticoagulation is started.
UK Clinical Pharmacy Association	Guideline	12	General	Change the sub footer number 3 on page 12 to a separate section titled 'Anticoagulation treatment for patients with antiphospholipid syndrome' and further details as included in the MHRA alert.	Thank you for your comment. The committee decided to remove the footnotes linking people to the MHRA alert as other MHRA alerts are not included as footnotes in this review and including this one risks confusion. Instead, as requested, they added a section specifically for 'Anticoagulation treatment for people with DVT or PE and triple positive antiphospholipid syndrome', which recommends the use of LMWH with a VKA in these people.
UK Clinical Pharmacy Association	Guideline	12	19 - 26	Consider adding to 'Interim therapeutic anticoagulation for suspected DVT or PE' section: For people with a BMI of 40 kg/m^2 or more and suspected proximal DVT or PE, consider LMWH to ensure effective anticoagulation treatment.' For interim anticoagulation, VKA is not suitable and therefore should not be included as an option in this setting.	Thank you for your comment. The committee agreed that the wording of the recommendation was confusing and that it needed to be split into interim and initial treatment. However, following discussion of stakeholder comments, the committee decided to amend the interim treatment recommendation (for all people with VTE) to direct clinicians to choose the same interim treatment regimen that they would prescribe for confirmed VTE for that individual, where possible. The BMI recommendation has also been amended to make a more general recommendation covering both low and high body weights and allowing the clinician to decide which anticoagulant to use on an individual basis while highlighting the need for monitoring. As no treatment is specifically mentioned, the issue of VKA

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					being unsuitable for interim treatment is no longer relevant.
UK Clinical Pharmacy Association	Guideline	14	17	Why has the option for self-testing of INRs not been considered for those requiring long term vitamin K antagonist anticoagulation as it has been for metal valves and AF? This seems a missed opportunity for those who can't have a direct oral anticoagulant.	Thank you for your comment. The self-management of INR was not within the scope of this update. Therefore, no evidence was reviewed, and the committee were unable to make recommendations on this area. However, we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
UK Clinical Pharmacy Association	Guideline	14	29	Both apixaban and rivaroxaban are cautioned if creatinine clearance is less than 30ml/min but this seems to endorse them with no concerns down to 15ml/min, could this be clarified.	Thank you for your comment. The committee decided not to amend the recommendation because the suggested detail would add extra text an already long and complicated recommendation. The recommendation already states that people should note the cautions and requirements for dose adjustment and monitoring in the medicine's summary of product characteristics and the committee agreed that this was sufficient.
UK Clinical Pharmacy Association	Guideline	15	2 - 6	Keep separate bullet points for edoxaban and dabigatran for clearer guidance/recommendation. Edoxaban can be used if estimated creatinine is above 15ml/min so unclear why separated as 30 – 50 ml/min and 15-29 ml/min. Proposed text change to: 'LMWH for 5 days followed by: • Dabigatran if estimated creatinine clearance is between 30 and 50 ml/min or	Thank you for your comment. The committee updated the wording of this recommendation in accordance with your suggestion (although the committee have put edoxaban first in the list as this is suitable for use in a wider range of people).

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				• Edoxaban if estimated creatinine clearance is between 15 and 50 ml/min'	
UK Clinical Pharmacy Association	Guideline	15	10	Should VKA be added to this as no reason they couldn't be offered this agent.	Thank you for your comment. Based on stakeholder comments, the committee have amended this recommendation to include LMWH or UFH alone or concurrently with a VKA as options.
UK Clinical Pharmacy Association	Guideline	15	11	On line 11, remove LMWH People with established renal failure (estimated creatinine clearance less than 15ml/min) – LMWH is not recommended/used in practice as dosage in this population has not been studied. Consider recommendation as UFH only.	Thank you for your comment. The committee agreed that there is a risk of accumulation associated with the use of LMWH alone in people with established renal failure. They agreed that LMWH alone should only be used on a case by case basis but decided not to remove it as LMWH alone is still a viable option for some people. They also noted that LMWH accumulation can be avoided with effective anti-Xa monitoring and by consulting the information in the summary of product characteristics and locally agreed protocols. However, following stakeholder comments the committee have also included LMW+VKA and UFH+VKA as options.
UK Clinical Pharmacy Association	Guideline	15	17	Consider a weight cut off like ISTH recommend weight of 120kg. Some people with a BMI > 40 kg/m^2 may only be 100kg as they are short. You could be 5ft with a weight of 95kg and have a BMI > 40 kg/m^2 or you could be 6ft and 130kg but have a BMI < 40 kg/m^2. These 2 patients may handle drugs very differently and a young 130kg patient is likely to metabolise much quicker.	Thank you for your comment. The recommendations relating to BMI were based primarily on consensus due to limited evidence from randomized controlled trials in this population. The committee discussed feedback from stakeholders concerning the use of absolute weight instead of BMI and that there are concerns with treating people with low body weight as well as those with high body weight. The committee agreed with stakeholder concerns and decided to specifically make reference to absolute weight rather than BMI. They amended the recommendation to cover people at both extremes of

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					weight (<50kg or >120kg). However, they agreed that uncertainty surrounding effective treatment for these groups remains. Taking into account suggestions from stakeholders that there is some evidence that the DOACs could be used in obese patients and that more evidence may be forthcoming, the committee made a more general recommendation to enable the clinician to decide which treatment would be most effective on an individual basis and to allow for the use of DOACs. They noted that whatever the choice of anticoagulant is, it is important to ensure that there is effective monitoring of therapeutic levels and any dose adjustments and monitoring requirements stated in the SPCs are followed, along with locally agreed protocols or advice from a specialist or multidisciplinary team.
UK Clinical Pharmacy Association	Guideline	15	17 - 20	For suspected proximal DVT or PE, VKA with INR monitoring would not be appropriate interim anticoagulation agent until imaging confirms diagnosis. Recommendation to remove 'suspected' from line 18. For suspected VTE in people with a BMI of 40 kg/m^2, consider LMWH as a recommendation. Proposed text change to: 'For people with a BMI of 40 kg/m^2 or more and confirmed proximal DVT or PE, consider LMWH concurrently with a vitamin K antagonist (VKA) for at least 5 days, or until the INR is at least 2.0 for two consecutive readings, followed by a VKA on its own	Thank you for your comment. The recommendations relating to BMI were based primarily on consensus due to limited evidence from randomized controlled trials in this population. The committee discussed feedback from stakeholders concerning the inclusion of 'suspected' in this recommendation. The committee agreed that the wording of the recommendation was confusing and that it needed to be split into interim and initial treatment. However, following discussion of other stakeholder comments, the committee decided to amend the interim treatment recommendation (for all people with VTE) to direct clinicians to choose the same interim treatment regimen that they would prescribe for confirmed VTE for

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				with INR monitoring to ensure effective anticoagulation treatment.'	that individual, where possible. This removes the need to specify the interim treatments separately. In addition, stakeholders commented about the use of absolute weight instead of BMI, raised concerns with treating people with low body weight as well as those with high body weight and noted that emerging evidence suggests that DOACs may be used in these populations. Based on this feedback, the committee agreed to use absolute weight rather than BMI and made a new recommendation to cover both low (<50kg) and high (>120kg) extremes of body weight. Due to remaining uncertainty in this area, the committee decided not to recommend specifically which treatments should be used. Instead, they made a more general recommendation to allow for greater clinician choice and to ensure that whatever the choice of anticoagulant is, that there is effective monitoring of therapeutic levels and any dose adjustments and monitoring requirements stated in the SPCs are followed, along with locally agreed protocols or advice from a specialist or multidisciplinary team. The committee also removed any reference to suspected DVT or PE because, as you point out, this is not relevant in this section.
UK Clinical Pharmacy Association	Guideline	16	2 - 3	Consider adding the following when taking into account anticoagulant agent:	Thank you for your comment. The committee amended this recommendation to state that drug interactions should also be taken into account.

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				'…take into account the tumour site, the person's bleeding risk, and drug-related interactions. Consider:…'	
UK Clinical Pharmacy Association	Guideline	16	4	The following recommendation does not follow other cancer associated thrombosis (CAT) recommendations from national and international guidelines. Not all DOACs have been trialled in CAT and the studies show a higher rate of bleeding in some cancers which has not been clearly defined here. More guidance is required to qualify the statements and which patients should be considered for a DOAC including which DOAC agent. There are also cancer drug interactions, thrombocytopenia, and absorption issues all to take into consideration.	Thank you for your comment. This update followed the methods outline in the NICE guideline manual based on the best available evidence. The committee were aware that their recommendations differed to those of other guidelines. However, they were in agreement in their conclusions based on their discussion of the clinical and cost effectiveness analyses that were conducted for this guideline. We are unable to comment on how other guidelines conduct their reviews or examine how they reach their recommendations. Although there have only been direct trials between edoxaban and rivaroxaban compared to LMWH alone, the NMA also used subgroup data for specifically people with active cancer from the main DOAC trials for apixaban and dabigatran compared to warfarin. The committee noted that the effects reported in these trials were roughly consistent with those for the population without cancer, and the NMA allowed for indirect comparisons to be made using this data to compare the treatments to the other DOACs and LMWH alone. Additionally, the committee noted that the ADAM-VTE trial (McBane 2019), a small (~300 participants) trial comparing apixaban to LMWH alone recently published

					and that the results were consistent with that of the other DOACs without evidence of increased bleeds. As you note in your comment, some of the DOACs have been found to have an increased bleeding risk in some cancers. The committee discussed this point again following stakeholder comments. They noted that many of the bleeds associated with the DOACs were specifically gastrointestinal(GI) and genitourinary (GU) bleeds and that the safety profile of the DOACs compared to LMWH alone improved when only looking at other bleeds (see the benefits and harms section of the evidence review D for more information on this discussion). However, the committee agreed not to specifically prohibit the use of DOACs in people with a GI and/or GU malignancy or give specific guidance on who is/is not suitable for a DOAC as there are potentially other types of malignancies which make a DOAC unsuitable and this decision needs to be made on an individual basis. They were concerned that if they provided a list of tumours with which to avoid DOAC use this would not be exhaustive and could mislead clinicians. Instead, the committee made a general recommendation to take into account the tumour site when prescribing anticoagulation for people with cancer (which they expected would include considerations of whether the person has a GI/GU malignancy or a tumour type likely to be associated with these bleeds). The committee agreed with the need to highlight the potential interactions of anticoagulants with drugs used to treat

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					cancer (particularly chemotherapy) and added drug interactions to the list of factors to take into account as part of the decision-making process. Additionally, following discussion of stakeholder comments, the committee agreed to amend the recommendations to make it clearer that if a DOAC is unsuitable, to consider LMWH alone or LMWH with a VKA. These recommendations were intended to ensure that the individual with cancer received the most appropriate treatment for their VTE whilst supporting the NHS to make the best use of its limited resources. Reference: McBane, RD, Wysokinski W , Le-Rademacher J G…., &. Loprinzi CL. (2019) Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. J. Thromb Haemost, [epub ahead of print]
UK Clinical Pharmacy Association	Guideline	16	5 - 6	LMWH and VKA is not a practical recommendation/option for people with VTE and cancer particularly with challenges with INR monitoring and not applied in clinical practice. Suggestion to remove this recommendation driven by cost effectiveness and not clinical effectiveness or patient safety.	Thank you for your comment. Following discussion of stakeholder comments, the committee agreed to amend the recommendations to make it clear that if a DOAC is unsuitable, to consider LMWH alone or LMWH with a VKA. The committee agreed that for most people, VKA will be unsuitable due to the potential for drug interactions and is less favourable efficacy profile compared to alternatives. However, the committee agreed that in a small number of people, such as those unable to take DOACs who request an oral treatment,

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				Include LMWH alone as an option for treatment as commonly used in practice and licensed option for people with VTE and cancer. Consider adding criteria for DOAC suitability based on recent evidence and American Society of Clinical Oncology guidance VKA would not be an option for treatment of VTE in active cancer following the CLOT trial due to efficacy and safety effects, and drug-drug interactions particularly with long-term immunotherapy and continuous oral chemotherapy.	VKA may be an option. It was included in the draft recommendations as an alternative to a DOAC because it was more cost effective than LMWH. LMWH was not cost effective due to its high cost compared to DOACs and LMWH with VKA. The draft recommendations did have LMWH as a treatment option for people with cancer and VTE. Following stakeholder feedback the recommendation has now been amended to make it clearer that it remains an option (if a DOAC is unsuitable) by placing it before LMWH with VKA. This update followed the methods outline in the NICE guideline manual based on the best available evidence and we are unable to examine how they reach their recommendations. The committee agreed not to make more specific recommendations for when a specific drug is unsuitable due to a lack of evidence, to prevent the recommendations from becoming overly complex and because the suitability of each drug for an individual needs to be assessed on a case by case basis. The committee noted that many of the bleeds associated with the DOACs were specifically gastrointestinal (GI) and genitourinary (GU) bleeds and that the safety profile of the DOACs compared to LMWH alone improved when only looking at other bleeds (see

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					the benefits and harms section of the evidence review D for more information on this discussion). However, the committee agreed not to specifically prohibit the use of DOACs in people with GI and/or GU malignancy or give specific guidance on who is/is not suitable for a DOAC as there are potentially other types of malignancies which make a DOAC unsuitable. They were concerned that if they provided a list of tumours with which to avoid DOAC use this would not be exhaustive and could mislead clinicians. However, to ensure that the treatment of people with VTE and cancer is individualised, the committee made a separate recommendation to ensure that tumour site, drug interactions and the person's bleeding risk are taken into account when choosing an anticoagulant.
UK Clinical Pharmacy Association	Guideline	16	7	This is completely the opposite of current guidance including recently released guidance. Give consideration to making more specific recommendations on who should or shouldn't receive LMWH first line such as thrombocytopenia, high bleeding risk etc.	Thank you for your comment. This update followed the methods outline in the NICE guideline manual based on the best available evidence and we are unable to comment on how other guidelines conduct their reviews or examine how they reach their recommendations. Following discussion of stakeholder comments, the committee agreed to amend the recommendations to make it clear that if a DOAC is unsuitable, to consider LMWH alone or LMWH with a VKA. The committee agreed that for most people, VKA will be unsuitable due to the potential for drug interactions and is less favourable efficacy profile compared to alternatives.

					However, the committee agreed that in a small number of people, such as those unable to take DOACs who request an oral treatment, VKA may be an option. It was included in the draft recommendations as an alternative to a DOAC because it was more cost effective than LMWH. LMWH was not cost effective due to its high cost compared to DOACs and LMWH with VKA. The committee agreed not to make more specific recommendations for when a specific drug is unsuitable due to a lack of evidence, to prevent the recommendations from becoming overly complex and because the suitability of each drug for an individual needs to be assessed on a case by case basis. The committee noted that many of the bleeds associated with the DOACs were specifically gastrointestinal (GI) and genitourinary (GU) bleeds and that the safety profile of the DOACs compared to LMWH alone improved when only looking at other bleeds (see the benefits and harms section of the evidence review D for more information on this discussion). However, the committee agreed not to specifically prohibit the use of DOACs in people with GI and/or GU malignancy or give specific guidance on who is/is not suitable for a DOAC as there are potentially other types of malignancies which make a DOAC unsuitable. They were concerned that if they provided a list of tumours with which to avoid DOAC use this would not be exhaustive and could mislead clinicians. However, to ensure that the treatment of people with VTE and cancer is individualised, the committee made a separate recommendation to ensure

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					that tumour site, drug interactions and the person's bleeding risk are taken into account when choosing an anticoagulant.
UK Clinical Pharmacy Association	Guideline	17	General	Consider including risk of VTE recurrence statistics/further information to support healthcare professionals reviewing anticoagulation treatment.	Thank you for your comment. The recommendations for the continued treatment of VTE was based on two reviews in this update: 1) The pharmacological treatment of VTE, which looked at RCTs comparing different treatments for VTE in people who have already received a minimum of 3 months treatment and 2) The prognosis chapter, which looked specifically at the use of prediction tools to predict VTE recurrence and major bleeding. As neither of these two areas involved examining rates of VTE recurrence, this evidence was not looked for and not reviewed by the committee. As such, the committee were unable to provide guidance about suitable sources of statistics.
UK Clinical Pharmacy Association	Guideline	18	1 - 4	The HASBLED score has been validated to estimate risk of major bleeding for patients on anticoagulation to assess risk-benefit in atrial fibrillation care. It has not been validated for patients with VTE. Consider removing this statement as it could result in incorrect predictions. Research recommendation noted on predicting VTE recurrence.	Thank you for your comment. There have been several retrospective studies evaluating the use of HAS-BLED in VTE populations. The committee recommended HAS-BLED as these studies had very large samples and identified HAS-BLED as having good prognostic accuracy. However, they also noted the inherent problems associated with retrospective prognosis studies and therefore only made a consider recommendation. They also were very clear about the circumstances in which this tool may provide useful information and that it is not to be used solely as the basis of a decision to continue or stop treatment. In addition, HAS-BLED has been validated in a population

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					of people with VTE who were taking LMWH, VKA or a DOAC (Brown 2018). The committee discussed stakeholder comments concerning the use of HASBLED and, taking the above points into account, decided to retain the recommendation. Reference: Brown J D, Goodin A J, Lip G Y. H, and Adams V R (2018) Risk Stratification for Bleeding Complications in Patients With Venous Thromboembolism: Application of the HAS-BLED Bleeding Score During the First 6 Months of Anticoagulant Treatment. Journal of the American Heart Association 7(6), 07The committee discussions are covered in more detail in the discussion section of evidence review F.
UK Clinical Pharmacy Association	Guideline	18	9 - 10	Apixaban is licensed for 10mg BD for 7 days then 5mg BD for up to 6 months then 2.5mg BD long term. This statement (not supported by any evidence) goes against the licence dosing and doesn't take into account patients who may be high risk for VTE recurrence or unable to take twice daily dosing.	Thank you for your comment. The committee did not specify which dose to use as it is intended that dose-adjustments are made in line with the summary of product characteristics (SPCs) for the drug being used, which provide detailed information on when to adjust the dose if any such requirements exist. The committee agreed not to duplicate this information within the recommendations themselves to limit complexity. The recommendation for a review at 3 months does not mean that their treatment regimen should be altered at that point (unless they discontinue treatment).

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					The recommendation to consider switching to apixaban was made based on the evidence from a network meta-analyses of the long- term trials using the various anticoagulants and a novel economic model. Based on the cost-effective evidence and evidence from the extended treatment NMA suggesting the potential for fewer bleeds with apixaban, the committee agreed to recommend considering switching to apixaban if on a different DOAC which is not well tolerated. (See evidence reviews D and G for more details.) However, the committee agreed that decisions to switch treatment should always consider the specific clinical situation and person's preferences. To make this clearer they have written a separate recommendation covering these points.
UK Clinical Pharmacy Association	Guideline	18	13 - 15	This could be made clearer, are you suggesting not to switch treatment at 3 months? What about 6 months as per licences or lower risk period?	Thank you for your comment. Following discussion of the stakeholder comments, the committee amended this recommendation to make it clearer that for most people, the first option would be to continue with the same treatment regimen if it is well tolerated. If this is not the case or the individual's clinical situation or personal preferences, then switching to apixaban from another DOAC is an option. The committee did not specify which dose to use at a particular point in time as it is intended that changes in dose are made in line with the summary of product characteristics (SPCs) for the drug being used and taking into account the clinical needs of the individual. The committee agreed no to duplicate this information

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					within the recommendations to prevent them from becoming too complex.
UK Clinical Pharmacy Association	Guideline	18	18 (and general)	Consider changing to 'cancer' to 'active cancer and/or cancer treatment'.	Thank you for your comment. To be consistent with previous sections on pharmacological treatment of VTE, the committee have amended use of the word "cancer" to "active cancer" when referring to people with cancer that is not in remission. The committee have edited the definition of active cancer in the 'terms used' section to clarify that this also includes people receiving cancer treatment.
UK Clinical Pharmacy Association	Guideline	18	21 - 22	For the recommendation on aspirin for people who decline continued anticoagulation treatment: • Aspirin is not effective as DOAC or VKA or alternative to anticoagulation for the outcome of VTE recurrence despite its favourable bleeding profile.	Thank you for your comment. The committee agreed that aspirin was less effective than the DOACs and that aspirin use is associated with a risk of bleeding. However, the committee identified that there is a small group of people who require, yet decline, long term treatment with anticoagulation. The committee agreed that these people, in the absence of alternative anticoagulation and when extended treatment is suitable, may benefit from aspirin as trials comparing aspirin to placebo suggest that aspirin significantly reduces VTE-recurrence but did not demonstrate significantly increased rates of major bleeding. The recommendation contains a footnote specifying that informed consent should be obtained and documented, previous recommendations (such as 1.4.3) should involve a discussion of the benefits and harms of any potential treatment strategy before this is commenced. This should involve discussion of the efficacy and bleeding risk of aspirin.

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UK Clinical Pharmacy Association	Guideline	20	6	Detailed and further guidance on systemic thrombolysis would be helpful.	Thank you for your comment. The use of systemic thrombolysis was not within the scope of this update. Therefore, the committee did not review any evidence and were unable to make recommendations on this topic. We encourage you to submit suggestions for areas that NICE guidelines should address or where an update is needed of an existing topic. We pass comments onto surveillance where there is something that could trigger an update. For example, if there is new evidence that is likely to change recommendations, or if there is new evidence about topics that are not covered by the existing guidance, or if issues concerning safety are raised. If there is new evidence this needs to be verifiable by the inclusion of supporting references, specifically primary studies or systematic reviews of primary studies.
University Hospitals of Leicester NHS Trust	Guideline	15	18	1.3.11. States use of BMI > 40kg/m2. I think it would be helpful to have an absolute weight cut-off as well as the BMI- the main relevance is most likely in the context of drug dosing, with a lot of centres having weight cut-offs of 120-150kg for DOAC use. I'd go for 150kg at this point, pending further published evidence.	Thank you for your comment. The recommendation relating to BMI was based primarily on consensus due to limited evidence from randomized controlled trials in this population. The committee discussed feedback from stakeholders concerning the use of absolute weight instead of BMI and that there are concerns with treating people with low body weight as well as those with high body weight. The committee agreed with stakeholder concerns and decided to specifically make reference to

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					absolute weight rather than BMI and amended the recommendation to cover people at both extremes of weight (<50kg or >120kg). The committee selected these cut-off points based on clinical experience and due to these cut-offs being most commonly highlighted in the summary of product characteristics (SPCs) for the DOACs.
University Hospitals of Leicester NHS Trust	Guideline	17	2	1.4.1 The document makes a suggestion for aspirin use in long term secondary thromboprophylaxis for those not wanting anticoagulation. Whilst this is a sensible and evidence-based option, it perhaps should be accompanied by a statement to support the relative merits of effectiveness and bleed risk (i.e. DOACs are likely to be twice as effective with similar bleed risks).	Thank you for your comment. The committee noted that the DOACs are more effective than aspirin for reducing VTE-recurrence and that aspirin is still associated with a risk of bleeds. This is outlined in the rationale section for continued treatment and in detail within the discussion section of the chapter on pharmacological treatment. However, NICE typically do not provide summaries of the rationale for use within the recommendation itself to avoid duplication and limit complexity.
University Hospitals of Leicester NHS Trust	Guideline	17	27	1.4.6 This point specifically discusses the DASH score for prediction of recurrence risk. Whilst it has been validated, there are other risk assessment tools, arguably similar of better validation e.g. HERDOO2. I wonder if it would be sensible to mention use of a validated risk assessment tool with examples rather than being wholeheartedly behind the DASH score?	Thank you for your comment. The recommendation for DASH was specifically for people aged under 65 who were wanting to stop using anticoagulation. The intention was for DASH to be used as supporting evidence to help inform these people of their risk of recurrence. However, after re-reviewing the evidence and the feedback from stakeholders, the committee decided not to recommend the use of DASH or any other tool to predict VTE-recurrence. This review question only included studies in which participants received at least 3 months of anticoagulation treatment, stopped treatment, were tested using prognostic tool(s) and followed up off-treatment. As the HERDOO2 study

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					was a management study, only the data pertaining to those participants who stopped treatment were extracted for this review. The committee agreed that they could not recommend the use of HERDOO2 based on this data.
University Hospitals of Leicester NHS Trust	Guideline	18	1	1.4.7 In a similar vein, this point looks at the HASBLED score for bleed risk. Again, perhaps worth noting the availability of other bleed assessment tools e.g. VTE bleed score.	Thank you for your comment. The committee reviewed evidence for multiple different tools to predict major bleeding alongside HAS-BLED, including VTE-BLEED. Many of these tools had poor to adequate prognostic accuracy and the committee agreed that they could not recommend them. The committee noted that VTE-BLEED had adequate accuracy and that this tool had been evaluated in participants receiving a DOAC but agreed that the HAS-BLED was preferable due to evidence suggesting it is more accurate.

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*