

Applying New Strategies for the National Adaptation, Updating, and Dissemination of Trustworthy Guidelines

Results From the Norwegian Adaptation of the Antithrombotic Therapy and the Prevention of Thrombosis, 9th Ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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BACKGROUND: The Antithrombotic Therapy and the Prevention of Thrombosis, 9th Edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (AT9) represent trustworthy international guidelines for antithrombotic treatment and thromboprophylaxis. We describe major changes to the format and content resulting from applying new strategies for guideline adaptation and dissemination.

METHODS: A Norwegian guideline panel of 46 experts completed a structured and systematic adaptation process, updated the recommendations based on new evidence, and rewrote the recommendations in an electronic multilayered presentation format. We published the adapted guideline using the web-based Making GRADE the Irresistible Choice Guideline Authoring and Publication Platform.

RESULTS: We applied a novel presentation format to 333 recommendations from 11 of the 15 management chapters in AT9 and condensed and restructured them into 249 recommendations in a multilayered format. We added additional relevant information, such as 29 best-practice statements about new oral anticoagulants and practical information sections for 121 recommendations. Common reasons for modifications included feasibility of the recommendations in a national context, disagreement with applied baseline risk estimates, and reevaluation of the balance between the benefits and harms of interventions in relation to assumed typical patient preferences and values. The adapted guideline was published and disseminated online in November 2013.

CONCLUSIONS: New strategies for adapting, updating, and disseminating trustworthy guidelines proved feasible and will provide Norwegian health-care professionals and patients with up-to-date guidance tailored to national circumstances. CHEST 2014; 146(3):735-761

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ABBREVIATIONS: AT9 = Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines; DECIDE = Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; LMWH = low-molecular-

weight heparin; MAGIC = Making GRADE the Irresistible Choice; MAGICapp = Making GRADE the Irresistible Choice Guideline Authoring and Publication Platform

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The Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (AT9)¹ provide comprehensive and rigorous guidance for the treatment of surgical and nonsurgical patients and, therefore, are well suited for adaptation to individual jurisdictions. The Norwegian adaptation of AT9 was performed through the collaborative projects we describe in this article.

Using Grading of Recommendations Assessment, Development, and Evaluation to Make Recommendations

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) provides a transparent and systematic framework for assessing and grading the available research evidence and for moving from evidence to recommendations.^{2,3} Currently, > 70 organizations worldwide have adopted GRADE. Guideline developers rigorously applying the GRADE methodology should consider four factors when making recommendations: the balance between the benefits and harms of the various interventions, confidence in the estimates of effects, patient preferences and values, and resource use.

In GRADE, recommendations are categorized as strong or weak.⁴ The strength of a recommendation reflects a guideline panel's confidence that desirable outcomes of an intervention outweigh undesirable outcomes. A strong recommendation is, thus, defined by a clear imbalance between the benefits and harms of an intervention and should be applied to nearly all patients. A weak recommendation reflects either a closer balance between benefits and harms or a lack of confidence in estimates of effect but should still be considered for the majority of patients.

Making GRADE the Irresistible Choice

The Making GRADE the Irresistible Choice (MAGIC) research program⁵ has brought together a multidisciplinary team of guideline developers, clinicians, methodologists, interaction designers, and programmers.

We developed a framework and built innovative solutions to address current limitations in the development, updating, and dissemination of clinical practice guidelines, embedding it into the web-based Making GRADE the Irresistible Choice Guideline Authoring and Publication Platform (MAGICapp). Adapting AT9 to a Norwegian setting represented an opportunity to apply and evaluate the feasibility of our proposed adaptation process; develop guidelines in a new presentation format; and publish them through our platform. The remaining aspects of the MAGIC framework will be tested in the near future, including integration of guidelines into electronic health records and strategies for dynamic updating and production of semiautomated electronic decision aids linked to individual recommendations for use during patient consultations.

Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence

Responding to the need for improvement in the presentation, dissemination, and uptake of evidence-based guidelines, the GRADE working group initiated the European Union-funded Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence (DECIDE) project in 2011.⁶ The DECIDE and MAGIC groups have collaborated to develop a multilayered presentation format to meet various needs at the point of care and to facilitate shared decision-making. The first, or top, layer of the format comprises the recommendation and its strength, a key information section presenting the four factors considered when moving from evidence to recommendation, and a short rationale. The development and evaluation of the multilayered format will be presented in a separate article.

Through three separate articles, we outline the details of the adaptation process⁷ and updating strategy.⁸ In this article, we summarize the end results of our adaptation of AT9 to a Norwegian guideline.

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Materials and Methods

When adapting AT9, the Norwegian guideline panels followed a pre-defined five-step adaptation process and taxonomy for evaluating individual recommendations tailored to GRADE guidelines.⁷ During an initial planning meeting, the editorial committee overseeing the process selected 11 of the 15 management chapters in AT9 to adapt on the basis of available human resources and which topics were expected to have the largest impact on clinical practice. The editorial committee comprised three methods experts, all members of the MAGIC research program, and four content experts.

The guideline panel members reviewed their respective chapters, formally recording their initial assessment of the need to exclude, modify, or develop new recommendations. As the head of the panel, the chapter editor collected these written statements and compiled them while identifying disagreements during the process. The panels then met face to face once or twice and continued the deliberations through a series of e-mail discussions.

When considering modifying a recommendation, the panels took into account the national context, including the availability of recommended interventions; other existing guidelines in extensive use in Norway; and assumed preferences and values of Norwegian patients. They adhered

to the GRADE methodology and, for each modification, consulted with the designated methods expert.

All panel members adduced new evidence identified through their clinical work. In addition, colleagues at McMaster University conducted systematic searches for new evidence using McMaster PLUS (Premium Literature Service) database entries from November 2010 to May 2013. The chapter editors screened the updated feeds, focusing on evidence that could potentially require modifications or new recommendations. During development of new recommendations, the methods experts performed the initial evidence assessment and rating according to GRADE, providing the panels with a tabular evidence summary as the basis for further discussions in which the methods experts actively participated.

The chapter editors wrote the first draft of the adapted chapter, explicitly stating how and why the recommendations were modified through a rationale statement and an adaptation disclaimer. The editorial committee invited user representatives, relevant specialty associations in Norway, and the American College of Chest Physicians (CHEST) to provide feedback on the adapted guideline. The chapter editors were primarily responsible for reading the feedback and assessing the need for adjustments. If major adjustments were potentially necessary, the chapter editors consulted with the panels and methods experts.

Results

The editorial committee elected to exclude three of the original chapters: diagnosis of DVT, treatment and prevention of heparin-induced thrombocytopenia, and anti-thrombotic therapy in neonates and children, excluding the latter two because they cover topics of low prevalence in Norway. The committee initially planned to adapt the chapter on diagnosis of DVT, but the assigned chapter editor withdrew from the project due to time constraints. Because of delayed recruitment of an editor for the chapter on antithrombotic and thrombolytic therapy for valvular disease, this chapter will be adapted during 2014.

The panels adapted 333 recommendations, excluding 30, modifying 131, and adding practical information on dosage, contraindications, and risk scores for 121. The panels often made modifications because of the feasibility of applying the recommendation in a Norwegian setting. Interventions excluded across chapters because they are not readily available in Norway were cilostazol, triflusal, and intermittent pneumatic compression devices. For most recommendations, low-dose unfractionated heparin was excluded in preference for the commonly used subcutaneous low-molecular-weight heparin (LMWH), the latter in general having a slightly better risk-benefit profile and not requiring regular blood monitoring. Tables 1 and 2 present the major and minor modifications made.⁹⁻¹⁸

The panels spent a substantial amount of time focusing on two major issues: (1) finding credible baseline estimates, preferably based on Norwegian data and (2) reevaluating

the balance between the benefits and harms of interventions in relation to assumed typical patient preferences and values. As examples of deliberations made, we outline in the following sections the results of the adaptation for two of the chapters. Readers can access an English translation of these at www.magicapp.org/public.

Prevention of VTE in Orthopedic Surgery Patients

AT9 gives a strong recommendation in favor of thromboprophylaxis for 10 to 14 days after major orthopedic surgery and a weak recommendation for extended prophylaxis for up to 35 days.¹⁹ It did not risk stratify the recommendations.

In reviewing the recommendation, the Norwegian panel noted that the baseline risk of VTE following major orthopedic surgery is somewhat uncertain. Improvements in both surgical technique and postoperative care have led to a decline in the baseline risk of VTE during the past decade.^{20,21} Scant data exist on current baseline risk because most patients receive some form of prophylaxis. Standard practice in Norway traditionally has been to provide nearly all patients with thromboprophylaxis for 14 to 35 days.

The guideline panel approached this problem through two strategies. It applied incidence data on VTE from a meta-analysis on new oral anticoagulants vs LMWH, taking into account the relative risk reduction provided by LMWH.^{22,23} In parallel, the panel collected data on VTE incidence following major orthopedic surgery from the National Patient Registry in Norway from 2009 to 2012. The registry contains a nationwide

TABLE 1] New Recommendations and Major Modifications in the Adapted Guideline

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>Evidence-based management of anticoagulant therapy</p> <p>Interactions with warfarin: We suggest that patients treated with warfarin avoid concomitant treatment with NSAIDs, COX2 inhibitors, and certain types of antibiotics. Platelet inhibitors should also be avoided, except where the benefits are known or highly likely, to exceed the harms of excess bleeding, such as patients with mechanical heart valves, patients with acute coronary syndrome, or patients with newly inserted coronary stents or bypass surgery (see chapters on coronary artery disease and atrial fibrillation) (weak).</p>	<p>3.8. For patients taking VKAs, we suggest avoiding concomitant treatment with nonsteroidal antiinflammatory drugs, including cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs, and certain antibiotics (see Table 8 in main article) (Grade 2C).</p>	<p>The Norwegian panel added platelet inhibitors to the recommendation because this is a frequent clinical question.</p>
<p>For patients starting IV unfractionated heparin, we suggest that the initial bolus and the initial rate of the continuous infusion be weight adjusted (bolus 150 IE/kg followed by an infusion of 400 IE/kg/24 h) (weak).</p>	<p>6.1. For patients starting IV UFH, we suggest that the initial bolus and the initial rate of the continuous infusion be weight adjusted (bolus 80 units/kg followed by 18 units/kg per h for VTE; bolus 70 units/kg followed by 15 units/kg per h for cardiac or stroke patients) or use of a fixed dose (bolus 5,000 units followed by 1,000 units/h) rather than alternative regimens (Grade 2C).</p>	<p>The dosage recommended has been changed to be in accordance with the summary of product characteristics in Norway. The Norwegian panel also chose just one and not two treatment dosage options to increase executability.</p>
<p>Perioperative management of antithrombotic therapy</p>	<p>3.6. In patients who are receiving ASA and require coronary artery bypass graft (CABG) surgery, we suggest continuing ASA around the time of surgery instead of stopping ASA 7 to 10 d before surgery (Grade 2C). In patients who are receiving dual antiplatelet drug therapy and require CABG surgery, we suggest continuing ASA around the time of surgery and stopping clopidogrel/prasugrel 5 d before surgery instead of continuing dual antiplatelet therapy around the time of surgery (Grade 2C).</p>	<p>The Norwegian panel added both ticagrelor and dipyridamol to the list. The evidence for this is incomplete. The panel placed high value on the patient, retaining treatment with ASA to provide some protection against thromboembolic complications while simultaneously minimizing the risk of major bleeds by avoiding dual antiplatelet treatment. All antiplatelet agents are included to increase ease of use of the recommendation.</p>
<p>Bypass surgery: We suggest continuing ASA rather than stopping this 7 to 10 d before surgery. In patients treated with dual antiplatelet treatment, we suggest continuing ASA and stopping clopidogrel/prasugrel 5 d before surgery and ticagrelor/dipyridamol 2 d before surgery (weak).</p>	<p>Prevention of VTE in orthopedic surgery patients</p>	<p>(Continued)</p>

TABLE 1] (Continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>Patients at moderate to high risk of thrombosis; all lower-limb surgery: We recommend thromboprophylaxis with low-molecular-weight heparin, low-dose direct factor Xa inhibitor (apixaban, rivaroxaban), or dabigatran for 10 d from the day of surgery (strong). <i>Remark:</i> High risk, previous symptomatic DVT/PE; Moderate risk: age > 80 y or multiple comorbidities. Risk assessment can be performed by use of the Charlson comorbidity index or ASA classification. We suggest extending thromboprophylaxis for up to 35 d from the day of surgery (weak).</p>	<p>...</p>	<p>The recommendations were not risk stratified in AT9. The Norwegian recommendations are, therefore, new. The panel gave a strong recommendation for short-term thromboprophylaxis and a weak recommendation for extended prophylaxis for patients at moderate to high risk of thrombosis. These recommendations apply to all patients regardless of surgical intervention. NOACs (dabigatran, rivaroxaban, and apixaban) are suggested as equal alternatives to LMWH. This is because of a new meta-analysis and a longer experience with NOACs that show similar risk-benefit profiles as LMWH in addition to representing less burden of treatment. IPCD, LDUH, fondaparinux, ASA, and VKA are excluded from the recommendation text because the alternatives have an equal or improved risk-benefit profile and are commonly used.</p>
<p>Major hip and knee arthroplasty (patients at low risk of thrombosis): We suggest thromboprophylaxis with low-molecular-weight heparin, low-dose direct factor Xa inhibitor (apixaban, rivaroxaban), or dabigatran for 10 d from the day of surgery. We suggest not extending prophylaxis beyond 10 d (weak).</p>	<p>2.1.1. In patients undergoing THA or TKA, we recommend use of one of the following for a minimum of 10 to 14 d rather than no antithrombotic prophylaxis: low-molecular-weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH), adjusted-dose VKA, aspirin (all Grade 1B), or an intermittent pneumatic compression device (IPCD) (Grade 1C). 2.3.1. In patients undergoing THA or TKA, irrespective of the concomitant use of an IPCD or length of treatment, we suggest the use of LMWH in preference to the other agents we have recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH (all Grade 2B), adjusted-dose VKA, or aspirin (all Grade 2C). 2.4. For patients undergoing major orthopedic surgery, we suggest extending thromboprophylaxis in the outpatient period for up to 35 d from the day of surgery rather than for only 10 to 14 d (Grade 2B). 2.5. In patients undergoing major orthopedic surgery, we suggest using dual prophylaxis with an antithrombotic agent and an IPCD during the hospital stay (Grade 2C). 2.6. In patients undergoing major orthopedic surgery and increased risk of bleeding, we suggest using an IPCD or no prophylaxis rather than pharmacologic treatment (Grade 2C). 2.7. In patients undergoing major orthopedic surgery and who decline or are uncooperative with injections or an IPCD, we recommend using apixaban or dabigatran (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran are unavailable) rather than alternative forms of prophylaxis (all Grade 1B).</p>	<p>NOACs (dabigatran, rivaroxaban, and apixaban) are suggested as equal alternatives to LMWH. This is because of new meta-analysis and a longer experience with NOACs that show a similar risk-benefit profile as LMWH in addition to representing less burden of treatment. The treatment length is shortened from up to 35 d in the original publication to being limited to the first 10 d (we provide a weak recommendation against extended thromboprophylaxis) due to new evidence suggesting that the incidence of VTE is lower than indicated in AT9. The recommendation applies to patients at low risk of VTE, whereas the original publication did not risk stratify the recommendations. IPCD, LDUH, fondaparinux, ASA, and VKA are excluded from the recommendation text because the alternatives have an equal or improved risk-benefit profile and are commonly used.</p>

(Continued)

TABLE 1] (continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>Fast-track general joint replacement surgery: We suggest thromboprophylaxis with low-molecular-weight heparin until discharge (1-4 d). We suggest not extending prophylaxis beyond discharge (weak).</p> <p>Prevention of VTE in nonsurgical patients</p> <p>Hospitalized patients at high risk of thrombosis: We recommend thromboprophylaxis with low-molecular-weight heparin or fondaparinux (weak). <i>Remark:</i> Many patients admitted to an internal medicine department will have an intermediate risk of thrombosis, and individual assessments concerning the net benefit of thromboprophylaxis should be made for these patients. We refer to guidance on risk stratification under "practical information."</p> <p>We suggest that LMWH be used as thromboprophylaxis rather than apixaban and rivaroxaban (weak).</p> <p>Critically ill patients: We suggest use of low-molecular-weight heparin (weak).</p>	<p>...</p> <p>2.3. For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant thromboprophylaxis with low-molecular-weight heparin (LMWH), low-dose unfractionated heparin (LDUH) bid, LDUH tid, or fondaparinux (Grade 1B).</p>	<p>This is a new recommendation not present in AT9. This was made due to new evidence for this particular type of treatment protocol.</p>
		<p>The Norwegian panel added a remark on patients at intermediate risk of thrombosis. The suggested Padua risk score divides patients into high and low risk of thrombosis, representing a large difference in baseline risk of venous thrombosis (4 per 1,000 patients at low risk of VTE vs 106 per 1,000 patients at high risk of VTE). AT9 gives no recommendation on optimal treatment of patients at intermediate risk.</p>
<p>We suggest that LMWH be used as thromboprophylaxis rather than apixaban and rivaroxaban (weak).</p>		<p>This is a new recommendation not present in AT9 based on two new randomized controlled trials by Cohen et al⁹ and Goldhaber et al.¹⁰</p>
<p>Critically ill patients: We suggest use of low-molecular-weight heparin (weak).</p>	<p>3.4.3. For critically ill patients, we suggest using LMWH or LDUH thromboprophylaxis over no prophylaxis (Grade 2C).</p>	<p>The Norwegian panel elected to use indirect evidence in the form of a meta-analysis on medical patients by Dentali et al¹¹ to generate effect estimates. The rationale for this modification was to provide more-precise effect estimates because the individual trials for critically ill patients applied in AT9 provided imprecise estimates. We considered the results by Dentali to be transferrable to a population of critically ill patients.</p>

(Continued)

TABLE 1] (Continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>Patients with additional risk factors for DVT and pulmonary embolism: For patients with solid tumors, we suggest use of low-molecular-weight heparin, provided there is a low risk of bleeding (weak). <i>Remark:</i> Additional risk factors for VTE include ongoing treatment with chemotherapy, inlying central venous catheter, previous VTE, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.</p>	<p>4.2.2. In outpatients with solid tumors who have additional risk factors for VTE and who are at low risk of bleeding, we suggest prophylactic-dose LMWH or LDUH over no prophylaxis (Grade 2B). <i>Remarks:</i> Additional risk factors for venous thrombosis in cancer outpatients include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.</p>	<p>The Norwegian panel added chemotherapy as an independent risk factor for VTE based on a new Cochrane systematic review by De Nisio et al.¹² The panel also added central venous catheters to the list, acknowledging that this probably increases the risk of VTE. However, the original weak recommendation suggesting against routine use of thromboprophylaxis to all patients with central venous catheters has been kept as is.</p>
<p>Antithrombotic therapy for VTE disease Choice of drug for long-term treatment: For patients without cancer, we suggest warfarin or rivaroxaban over LMWH for long-term treatment (weak). <i>Remark:</i> As per November 2013, dabigatran and apixaban do not have a preapproved indication for treatment of acute VTE.</p>	<p>3.3.1. In patients with DVT of the leg and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C). For patients with DVT and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy (Grade 2C).</p>	<p>Rivaroxaban has been added as a treatment alternative due to longer experience with rivaroxaban that continues to indicate an equal risk-benefit profile.</p>
<p>Distal DVT: We suggest anticoagulant treatment to all patients with objectively verified symptomatic distal DVT rather than serial ultrasound examinations to evaluate thrombus propagation before initiating treatment (weak).</p>	<p>2.3.1. In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 wk over initial anticoagulation (Grade 2C). 2.3.2. In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors for extension (see text), we suggest initial anticoagulation over serial imaging of the deep veins (Grade 2C). 2.3.4. In patients with acute isolated distal DVT of the leg who are managed with serial imaging, we recommend no anticoagulation if the thrombus does not extend (Grade 1B); we suggest anticoagulation if the thrombus extends but remains confined to the distal veins (Grade 2C); we recommend anticoagulation if the thrombus extends into the proximal veins (Grade 1B).</p>	<p>The Norwegian panel modified the recommendation due to uncertainty about the accuracy of serial imaging, increased resource implications, and anticipated patient preferences and values.</p>

(Continued)

TABLE 1] (continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>We recommend 3 mo of treatment to patients with an isolated, symptomatic distal DVT rather than treatment of 4-6 wk or treatment indefinitely (strong).</p>	<p>3.1.3. In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor (see remark), we suggest treatment with anticoagulation for 3 mo over treatment of a shorter period (Grade 2C) and recommend treatment with anticoagulation for 3 mo over treatment of a longer time-limited period (eg, 6 or 12 mo) (Grade 1B) or extended therapy (Grade 1B regardless of bleeding risk). 3.1.4. In patients with an unprovoked DVT of the leg (isolated distal [see remark] or proximal), we recommend treatment with anticoagulation for at least 3 mo over treatment of a shorter duration (Grade 1B). After 3 mo of treatment, patients with unprovoked DVT of the leg should be evaluated for the risk-benefit ratio of extended therapy. 3.1.4.3. In patients with a first VTE that is an unprovoked isolated distal DVT of the leg (see remark), we suggest 3 mo of anticoagulant therapy over extended therapy in those with a low or moderate bleeding risk (Grade 2B) and recommend 3 mo of anticoagulant treatment in those with a high bleeding risk (Grade 1B).</p>	<p>The Norwegian panel recommends one treatment length regardless of etiology because it believes that the benefits of a short course of treatment clearly outweigh the harms.</p>
<p>First unprovoked venous thrombosis in patients at low to moderate risk of bleeding: We suggest treatment indefinitely if no weighty arguments against emerge at the 3-month control. One should take into account whether there has been any major side effects or complications of treatment and severity of the thrombosis, if there are persistent symptoms, in addition to the patient's preferences. If continued treatment is chosen, we suggest annual reevaluations (weak). <i>Remark:</i> For patients who do not want or cannot use oral anticoagulation beyond 3 mo of treatment, long-term treatment with ASA may be considered.</p>	<p>3.1.4.1. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 mo of therapy (Grade 2B).</p>	<p>The Norwegian panel added a remark stating that ASA can be used as long-term prophylaxis. This remark is based on new studies. In addition, the panel combined all recommendations about proximal DVT and PE and provide guidance on which aspects to consider at each reevaluation of the patient regarding whether to continue or stop treatment.</p>

(Continued)

TABLE 1] (continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>Acute proximal DVT of the leg: We suggest anticoagulant therapy alone over catheter-directed thrombolysis. We suggest that patients with a DVT in a pelvic vein and/or the vena cava and/or with serious symptoms that persist after initiated treatment be considered for catheter-based thrombolysis (weak).</p>	<p>2.9. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over catheter-directed thrombolysis (CDT) (Grade 2C).</p>	<p>The background for the modified recommendation is a newly published study by Enden et al¹³ showing a significant reduction of postthrombotic syndrome after 2 y.</p>
<p>Superficial thrombophlebitis: In patients with a superficial thrombophlebitis of at least 5 cm or that lies in the vicinity of a deep vein, we suggest treatment with prophylactic or intermediate-dose LMWH or fondaparinux for 45 d over no anticoagulation (weak).</p>	<p>8.1.2. In patients with superficial vein thrombosis who are treated with anticoagulation, we suggest fondaparinux 2.5 mg daily over a prophylactic dose of LMWH (Grade 2C).</p>	<p>Fondaparinux is not reimbursed in Norway and, thus, represents a high cost for the individual patient. LMWH, however, is reimbursed and is added as a suggested treatment alternative. The recommendation is based on indirect evidence in other populations showing that LMWH has a similar risk-benefit profile as fondaparinux.</p>
<p>Antithrombotic therapy for atrial fibrillation</p> <p>CHA₂DS₂-VASc score 0: We recommend against antithrombotic therapy (strong). CHA₂DS₂-VASc score 1: We suggest antithrombotic therapy (weak). <i>Remark:</i> Women under 65 y of age without other risk factors than sex are regarded as low risk, and withholding antithrombotic treatment should be considered.</p>	<p>2.1.8. For patients with AF, including those with paroxysmal AF, who are at low risk of stroke (eg, CHADS₂ [congestive heart failure, hypertension, age ≥ 75 y, diabetes mellitus, prior stroke or transient ischemic attack] score = 0), we suggest no therapy rather than antithrombotic therapy (Grade 2B).</p>	<p>The risk score has been changed from CHADS₂ to CHA₂DS₂-VASc because it has been shown that the CHA₂DS₂-VASc score is superior in identifying patients at a truly low risk of stroke. New data on the baseline risk for patient-important outcomes have been applied to adapt to the new risk score. We have also used a systematic review by Adam et al¹⁴ for the relative effect estimates of the NOACs.</p>
<p>Choice of antithrombotic drug: We suggest new oral anticoagulants (dabigatran, rivaroxaban, or apixaban) rather than warfarin (weak).</p>	<p>2.1.11. For patients with AF, including those with paroxysmal AF, for recommendations in favor of oral anticoagulation (including 2.1.9, 2.1.10, and excluding 2.2, 3.1, 3.2, 3.3), we suggest dabigatran 150 mg twice daily rather than adjusted-dose vitamin K antagonist (VKA) therapy (target INR range, 2.0-3.0) (Grade 2B).</p>	<p>The Norwegian panel included all NOACs as preferred treatment options to warfarin as a meta-analysis (Adam et al¹⁴) has shown similar risk-benefit profiles (based on indirect comparisons).</p>

(Continued)

TABLE 1] (continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>After acute coronary syndrome with or without stent implantation: We suggest triple therapy with warfarin with target INR of 2.3 (2.0-2.5), ASA 75 mg × 1 and clopidogrel 75 mg × 1 for 3-6 mo. After this, we suggest warfarin with target INR of 2.3 (2.0-2.5) combined with either ASA 75 g × 1 or clopidogrel 75 mg × 1 for at least 1 year. After 12 mo, we suggest monotherapy with warfarin with target INR of 2.5 (2.0-3.0) if the patient's coronary disease has remained stable (weak). <i>Remark:</i> For patients with no other risk factors for stroke than coronary artery disease, initial treatment with double antiplatelet treatment might be appropriate. The same applies to women under the age of 65.</p> <p>Antithrombotic and thrombolytic therapy for ischemic stroke</p>	<p>3.3. For patients with AF at intermediate to high risk of stroke (eg, CHADS₂ score of 1 or greater) who experience an acute coronary syndrome and do not undergo intracoronary stent placement, we suggest for the first 12 mo, adjusted-dose VKA therapy (INR 2.0-3.0) plus single antiplatelet therapy rather than dual antiplatelet therapy (eg, aspirin and clopidogrel) or triple therapy (eg, warfarin, aspirin, and clopidogrel) (Grade 2C). After the first 12 mo, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1). For patients with AF at low risk of stroke (eg, CHADS₂ score of 0), we suggest dual antiplatelet therapy (eg, aspirin and clopidogrel) rather than adjusted-dose VKA therapy (INR 2.0-3.0) plus single antiplatelet therapy or triple therapy (eg, warfarin, aspirin, and clopidogrel) (Grade 2C). After the first 12 mo, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).</p>	<p>The Norwegian panel chose to suggest an initial course of triple therapy because it believes that the benefits outweigh the harms. The target INR has been slightly lowered to better reflect what has been applied in the relevant studies on combination treatment with warfarin and antiplatelet treatment.</p>
<p>Mechanical thrombectomy: In patients with ischemic stroke, we suggest against the use of mechanical thrombectomy (weak). <i>Remark:</i> The treatment may be considered in patients with a proximal cerebral artery occlusion.</p> <p>Primary and secondary prevention of cardiovascular disease</p> <p>Primary prevention: We suggest ASA 75 mg daily to patients at high risk of cardiovascular disease (10-year risk of cardiovascular mortality >10%) (weak).</p>	<p>2.3. In patients with acute ischemic stroke, we suggest against the use of mechanical thrombectomy (Grade 2C). <i>Remarks:</i> Carefully selected patients who value the uncertain benefits of mechanical thrombectomy higher than the associated risks may choose this intervention.</p> <p>2.1. For persons aged 50 y or older without symptomatic cardiovascular disease, we suggest low-dose aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B)</p>	<p>The remark has been modified to provide more-specific guidance.</p>
		<p>The Norwegian panel did not consider the small reduction in myocardial infarctions and cancer-related mortality sufficient to compensate for the increased number of bleedings and burden of treatment; thus, it valued the balance between the benefits and harms differently. The weak recommendation restricted to patients at high risk does, however, provide Norwegian patients at low to moderate risk with the option of choosing differently.</p>

(Continued)

TABLE 1] (continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>Following PCI with stent implantation in acute coronary syndrome: We suggest ticagrelor 90 mg × 2 plus ASA 75 mg × 1 rather than clopidogrel plus ASA. We suggest prasugrel 10 mg × 1 plus ASA 75 mg × 1 rather than clopidogrel plus ASA (weak).</p>	<p>3.2.1-3.2.5...For patients in the first year after an ACS who have undergone PCI with stent placement...We suggest ticagrelor 90 mg twice daily plus low-dose aspirin over clopidogrel 75 mg daily plus low-dose aspirin (Grade 2B).</p>	<p>The Norwegian panel believes that there is insufficient evidence to support that ticagrelor is superior to prasugrel because there are no head-to-head comparisons. Because both drugs have been shown to be slightly superior to clopidogrel, the Norwegian adaptation includes both drugs as an option following ACS with stent implementation.</p>
<p>After acute coronary syndrome: We suggest adding low-dose rivaroxaban (2.5 mg × 2) to selected patients at low risk of bleeding for 1-2 y (weak). <i>Remark:</i> Rivaroxaban is contraindicated in patients with prior stroke or TIA.</p>	<p>...</p>	<p>This is a new recommendation not present in AT9 that was developed due to new evidence showing a reduction in the risk of cardiovascular death.</p>
<p>Antithrombotic therapy in peripheral artery disease</p> <p>Acute limb ischemia: We suggest immediate treatment with low-molecular-weight heparin (LMWH) or unfractionated heparin while awaiting revascularization (weak). We suggest surgery rather than thrombolysis if the patient experiences sensorimotor deficits (weak). If there are no serious sensorimotor deficits, an individual assessment should be made to determine whether the patient is best served by revascularization by surgery, intraarterial thrombolysis, or the combination of thrombolysis and surgical intervention (best-practice statement).</p>	<p>6.1-6.3. In patients with acute limb ischemia due to arterial emboli or thrombosis, we suggest immediate systemic anticoagulation with unfractionated heparin over no anticoagulation (Grade 2C); we suggest reperfusion therapy (surgery or IA thrombolysis) over no reperfusion therapy (Grade 2C); we recommend surgery over IA thrombolysis (Grade 1B); we suggest recombinant tissue-type plasminogen activator (rt-PA) or urokinase over streptokinase (Grade 2C).</p>	<p>The Norwegian panel downgraded the recommendation to weak because of uncertainty regarding the risk of bleeding with thrombolysis. The evidence base for the original recommendation is, to a large extent, from the 1990s and shows heterogeneous results, and the panel had low confidence in the effect estimates. Given this uncertainty, the panel chose a more cautious approach and provided a best-practice statement for patients without sensorimotor deficits. The last recommendation is included under "practical information."</p>
<p>Below-knee venous graft: In distal venous bypass, we suggest anticoagulation with warfarin (INR 2.5 ± 0.5) (weak).</p>	<p>8.1-8.4. In patients undergoing below-knee bypass graft surgery with prosthetic grafts, we suggest clopidogrel 75 mg/d plus aspirin (75-100 mg/d) over aspirin alone for 1 year (Grade 2C). For all other patients, we suggest single over dual antiplatelet therapy (Grade 2B).</p>	<p>The Norwegian panel modified the recommendation based on available evidence suggesting superiority of warfarin over ASA but recognizes the low-quality evidence.</p>

(Continued)

TABLE 1] (continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>VTE, thrombophilia, antithrombotic therapy, and pregnancy</p> <p>Homozygous for factor V Leiden or prothrombin 20210A mutation: We suggest thromboprophylaxis throughout the pregnancy and 6 wk postpartum with prophylactic or intermediate-dose LMWH, or warfarin postpartum (INR 2.5 ± 0.5) (weak).</p>	<p>9.2.1. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and have a positive family history for VTE, we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH and postpartum prophylaxis for 6 wk with prophylactic- or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B). 9.2.3. For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and who do not have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis for 6 wk with prophylactic- or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than routine care (Grade 2B).</p>	<p>The Norwegian panel believed there to be considerable uncertainty regarding the actual baseline risk for women without a positive family history. Assuming that the risk of VTE is closer to 40 per 1,000 pregnant women, the balance between the benefits and harms of prophylaxis will be in favor of prophylaxis throughout the pregnancy and the postpartum period (22 fewer VTEs vs 14 more major bleeds). On the basis of low-quality evidence, the panel has opted to follow current practice in Norway and suggests extended prophylaxis compared with AT9.</p>
<p>Antithrombin deficiency: We suggest high- or intermediate-dose thromboprophylaxis with low-molecular-weight heparin (LMWH) throughout the pregnancy and 6 wk postpartum (weak).</p>	<p>9.2.2. For pregnant women with all other thrombophilias and no prior VTE who have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH or, in women who are not protein C or S deficient, VKAs targeted at INR 2.0 to 3.0 rather than routine care (Grade 2C). 9.2.4. For pregnant women with all other thrombophilias and no prior VTE who do not have a positive family history for VTE, we suggest antepartum and postpartum clinical vigilance rather than pharmacologic prophylaxis (Grade 2C).</p>	<p>The Norwegian panel questioned the true baseline risk in women with antithrombin deficiency.</p>
<p>Cesarean section in women at moderate to high risk: For women at increased risk of venous thrombosis after cesarean section because of the presence of at least one risk factor (please see "practical information" for details), we suggest thromboprophylaxis (LMWH) throughout the hospital stay. For those women with contraindications to LMWH, we suggest compression stockings (weak).</p>	<p>6.2.2. For women at increased risk of VTE after cesarean section because of the presence of one major or at least two minor risk factors, we suggest pharmacologic thromboprophylaxis (prophylactic LMWH) or mechanical prophylaxis (elastic stockings or intermittent pneumatic compression) in those with contraindications to anticoagulants while in hospital following delivery rather than no prophylaxis (Grade 2B).</p>	<p>The Norwegian panel modified the cutoff for suggesting thromboprophylaxis from a baseline risk of 30 per 1,000 to a baseline risk of 15 per 1,000. The panel believed that the benefits of prophylaxis outweigh the potential harms, even in patients at lower risk of VTE. In addition, IPCD is excluded as a treatment option because this is infrequently used in Norway.</p>

ACS = acute coronary syndrome; AF = atrial fibrillation; ASA = aspirin; AT9 = Antithrombotic Therapy and Prevention of Thrombosis, 9th ed; American College of Chest Physicians Evidence-Based Clinical Practice Guidelines; CHA₂DS₂-VASc = congestive heart failure, hypertension, age > 75 y, age between 65 and 74 y, stroke/transient ischemic attack/thromboembolism, vascular disease (previous myocardial infarction, peripheral arterial disease, or aortic plaque), diabetes mellitus, female; COX2 = cyclooxygenase-2; IE = Internationale Einheiten (International Units); INR = international normalized ratio; IPCD = intermittent pneumatic compression device; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; NOAC = novel anticoagulant; NSAID = nonsteroidal antiinflammatory drug; PCI = percutaneous coronary intervention; PE = pulmonary embolism; THA = total hip arthroplasty; TIA = transient ischemic attack; TKA = total knee arthroplasty; UFH = unfractionated heparin; VKA = vitamin K antagonist.

TABLE 2] Minor Modifications in the Adapted Guideline

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>Evidence-based management of anticoagulant therapy</p> <p>Overlap between LMWH and warfarin: For patients with an acute DVT, we recommend that warfarin be started on the same day as low-molecular-weight heparin (LMWH) or IV unfractionated heparin (UFH), and that LMWH/UFH be used for a minimum of 5 d and until INR > 2.0 for a minimum of 24 h (strong). <i>Remark:</i> For patients with severe kidney failure (GFR < 30 mL/min), we suggest IV UFH or LMWH at a reduced dose, adjusted according to factor Xa values.</p>	<p>2.3. For patients with acute VTE, we suggest that VKA therapy be started on day 1 or 2 of low-molecular-weight heparin (LMWH) or low-dose unfractionated heparin (UFH) therapy rather than waiting for several d to start (Grade 2C).</p>	<p>The recommendation has been altered to be in accordance with a similar recommendation in the chapter on antithrombotic therapy for VTE disease. A remark regarding patients with kidney failure has been added to make the recommendation easier to apply to patients with other conditions.</p>
<p>Starting dose: We suggest initiating therapy with three tablets of warfarin (7.5 mg) daily for the first 2 d. On day 3, INR is measured and further dosing is informed by the INR value (weak).</p>	<p>2.1. For patients sufficiently healthy to be treated as outpatients, we suggest initiating VKA therapy with warfarin 10 mg daily for the first 2 d followed by dosing based on international normalized ratio (INR) measurements rather than starting with the estimated maintenance dose (Grade 2C).</p>	<p>The dosage recommended has been changed to be in accordance with the summary of product characteristics in Norway.</p>
<p>Out-of-range INR values and bridging with LMWH: For patients with previous stable INR values in therapeutic range (2.0-3.0) who have a single out-of-range INR value (1.6-3.6), we suggest continuing the current dose without bridging with LMWH and a new INR test within 1 to 2 wk (weak).</p>	<p>3.2. For patients taking VKAs with previously stable therapeutic INRs who present with a single out-of-range INR of < 0.5 below or above therapeutic, we suggest continuing the current dose and testing the INR within 1 to 2 wk (Grade 2C).</p>	<p>...</p>
<p>Home testing of INR: We suggest that patients are encouraged to start home testing of INR and self-management of warfarin as long as they are motivated and competent and are willing to bear the extra costs (weak).</p>	<p>3.6. For patients treated with VKAs who are motivated and can demonstrate competency in self-management strategies, including the self-testing equipment, we suggest patient self-management rather than usual outpatient INR monitoring (Grade 2B). For all other patients, we suggest monitoring that includes the safeguards in our best practice statement 3.5.</p>	<p>The Norwegian panel chose to emphasize the extra costs the patient must bear to comply with the recommendation.</p>
<p>High INR 4.5-8.0 with no evidence of bleeding: For patients with an INR between 4.5 and 8.0 with no evidence of bleeding, we suggest to reduce the warfarin dose rather than treating with vitamin K (weak).</p>	<p>9.1.(a) For patients taking VKAs with INRs between 4.5 and 10 and with no evidence of bleeding, we suggest against the routine use of vitamin K (Grade 2B).</p>	<p>Norwegian laboratories measure INR up to 8, not 10.</p>

(Continued)

TABLE 2] (Continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
...	<p>3.5. (Best Practices Statement) We suggest that health-care providers who manage oral anticoagulation therapy should do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions.</p>	<p>Excluded because it was considered to be redundant and self-evident.</p>
...	<p>5.0. For patients eligible to discontinue treatment with VKA, we suggest abrupt discontinuation rather than gradual tapering of the dose to discontinuation (Grade 2C).</p>	<p>Excluded because it was considered to be redundant and self-evident.</p>
...	<p>6.2. For outpatients with VTE treated with SC UFH, we suggest weight-adjusted dosing (first dose 333 units/kg, then 250 units/kg) without monitoring rather than fixed or weight-adjusted dosing with monitoring (Grade 2C).</p>	<p>Excluded because SC UFH is not commonly used in Norway.</p>
<p>Perioperative management of antithrombotic therapy</p> <p>Temporary interruption of warfarin therapy prior to surgery: After completion of the procedure, we suggest rapid resumption (12-24 h) of warfarin with double the patient's standard dose the evening of the surgery followed by the patient's standard dose (weak).</p>	<p>2.2. In patients who require temporary interruption of a VKA before surgery, we recommend resuming VKAs approximately 12 to 24 h after surgery (evening of or next morning) and when there is adequate hemostasis instead of later resumption of VKAs (Grade 2C).</p>	<p>More actionable phrasing added.</p>
<p>Prevention of VTE in orthopedic surgery patients</p>		<p>For all recommendations related to use of LMWH, the relative effect estimate of LMWH as a thromboprophylaxis vs placebo is based on a meta-analysis by Collins et al.¹⁵ This meta-analysis is applied in the chapter on prevention of VTE in nonorthopedic surgical patients and provides a more plausible relative effect on major bleeds than the meta-analysis originally used in AT9.</p>
...	<p>2.2. For patients undergoing major orthopedic surgery (THA, TKA, HFS) and receiving LMWH as thromboprophylaxis, we recommend starting either 12 h or more preoperatively or 12 h or more postoperatively rather than within 4 h or less preoperatively or 4 h or less postoperatively (Grade 1B).</p>	<p>The information is included under "practical information," but is not retained in the adapted guideline as a separate recommendation.</p>

(Continued)

TABLE 2] (Continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in A19	Reason for Modification
...	2.5. In patients undergoing major orthopedic surgery, we suggest using dual prophylaxis with an antithrombotic agent and an IPCD during the hospital stay (Grade 2C).	Excluded because IPCD is not readily available in Norway. Because the baseline risk of VTE is considered to be relatively low, dual thromboprophylaxis (eg, LMWH and compression stockings) was not considered necessary.
...	2.6. In patients undergoing major orthopedic surgery and increased risk of bleeding, we suggest using an IPCD or no prophylaxis rather than pharmacologic treatment (Grade 2C).	The information is included under "practical information," but is not retained in the adapted guideline as a separate recommendation.
...	2.7. In patients undergoing major orthopedic surgery and who decline or are uncooperative with injections or an IPCD, we recommend using apixaban or dabigatran (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran are unavailable) rather than alternative forms of prophylaxis (all Grade 1B).	Excluded.
...	2.8. In patients undergoing major orthopedic surgery, we suggest against using IVC filter placement for primary prevention over no thromboprophylaxis in patients with an increased bleeding risk or contraindications to both pharmacologic and mechanical thromboprophylaxis (Grade 2C).	Excluded because IVC filters are seldom used in Norway.
Prevention of VTE in nonorthopedic surgical patients		For all relevant recommendations, the Norwegian panel has opted to use just the Caprini risk score and not include the Rogers score to increase ease of use. IPCD has been excluded as an alternative because it is not currently in use in Norway, and graduated compression stockings are suggested as an alternative. LDUH is excluded for the same reason, replaced by the commonly used, equally effective, and more practical LMWH. Whenever the original guideline stated "pharmacologic prophylaxis," this has been changed to LMWH in the adapted guideline.
Very low risk of VTE: We recommend no pharmacologic or mechanical prophylaxis be used other than early ambulation (strong).	3.6.1. For general and abdominal-pelvic surgery patients at very low risk for VTE (<0.5%; Rogers score, <7; Caprini score, 0), we recommend that no specific pharmacologic (Grade 1B) or mechanical (Grade 2C) prophylaxis be used other than early ambulation.	The Norwegian panel changed the recommendation from weak to strong for both interventions because it did not consider the harms (increase in bleeds, skin complications, and burden of treatment) to outweigh the very small benefits (reduction in VTE).

(Continued)

TABLE 2] (continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>Moderate risk of VTE: We suggest thromboprophylaxis with low-molecular-weight heparin (LMWH) until discharge or when the patient is ambulant, rather than compression stockings (weak).</p>	<p>3.6.3. For general and abdominal-pelvic surgery patients at moderate risk for VTE (3.0%; Rogers score, > 10; Caprini score, 3-4) who are not at high risk for major bleeding complications, we suggest low-molecular-weight heparin (LMWH) (Grade 2B), low-dose unfractionated heparin (LDUH) (Grade 2B), or mechanical prophylaxis, preferably with IPC (Grade 2C), over no prophylaxis.</p>	<p>Because LMWH has a superior effect and a low risk of bleeding, it is included in the adapted guideline as preferred to compression stockings.</p>
<p>Prevention of VTE in nonsurgical patients</p>		<p>For all relevant recommendations, IPCD has been excluded as an alternative because it is not readily available in Norway, unlike compression stockings. LDUH has been replaced by LMWH. Whenever "pharmacologic prophylaxis" is stated in the original guideline, it has been changed to LMWH in the adapted guideline.</p>
<p>Length of thromboprophylaxis: We recommend against extending prophylaxis beyond the hospital stay or the period of patient immobilization (strong).</p>	<p>2.8. In acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, we suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (Grade 2B).</p>	<p>The strength of the recommendation is altered to strong because the Norwegian panel did not consider the reduced risk of thromboembolic events to be sufficient to justify the increased risk of bleeding and burden of treatment.</p>
<p>Antithrombotic therapy for VTE disease</p>		<p>For all relevant recommendations, SC UFH and fondaparinux are excluded as alternatives in preference to LMWH. All recommendations about DVT in the leg and PE have been merged. Recommendations about IPCD have been excluded because the intervention is infrequently used in Norway.</p>
<p>Dosing of low-molecular-weight heparin (LMWH): We suggest once- over twice-daily administration of LMWH (weak). <i>Remark:</i> For certain patients (pregnant women close to term, patients at high risk of bleeding or if catheter-based thrombolysis might be performed) a twice-daily administration probably has more benefits than harms compared with once-daily administration.</p>	<p>2.5.2 In patients with acute DVT of the leg treated with LMWH, we suggest once- over twice-daily administration (Grade 2C).</p>	<p>The remark has been added to improve the tailored use of the recommendation. The dosage of the different types of LMWH are included under "practical information." The Norwegian panel chose to suggest enoxaparin 1.5 mg/kg once daily rather than 2 mg/kg because this is in accordance with the Norwegian summary of product characteristics, and the one study showing a possible decreased effect of the lower dosage was of low quality.¹⁶</p>

(Continued)

TABLE 2] (continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>Compression stockings in DVT: We recommend fitting a compression stocking class 2 as soon as possible and that it be used daily for 2 y (strong).</p> <p>Systemic thrombolysis in DVT of the leg: We recommend anticoagulant therapy rather than systemic thrombolysis (strong).</p>	<p>4.1. In patients with acute symptomatic DVT of the leg, we suggest the use of compression stockings (Grade 2B).</p> <p>2.10 In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over systemic thrombolysis (Grade 2C).</p>	<p>Changed to a strong recommendation because the Norwegian panel believed that the benefits clearly outweigh the harms.</p> <p>The strength of the recommendation is changed from weak to strong because both standard anticoagulant treatment and catheter-based thrombolysis are considered to be vastly superior alternatives.</p>
<p>Postthrombotic syndrome: We recommend a trial of graduated compression stockings class 2 (30-40 mm Hg) in patients who develop a postthrombotic syndrome. For most patients, knee-length stockings will be an equal alternative to thigh-length stockings. If the patient has severe complaints of swelling of the thigh, a trial of thigh-length stockings is warranted (strong).</p>	<p>4.2.1 In patients with PTS of the leg, we suggest a trial of elastic compression stocking (Grade 2C).</p>	<p>Changed to a strong recommendation because the benefits are considered to clearly outweigh the minimal harms. The phrasing of the recommendation is somewhat more specific.</p>
<p>...</p>	<p>2.11 In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over operative venous thrombectomy (Grade 2C).</p>	<p>Excluded because this procedure is seldom performed in Norway.</p>
<p>...</p>	<p>2.12 In patients with acute DVT of leg who undergo thrombosis removal, we recommend the same intensity and duration of anticoagulant therapy as in comparable patients who do not undergo thrombosis removal (Grade 1B).</p>	<p>Excluded because it is considered to be common knowledge.</p>
<p>...</p>	<p>3.0 In patients with acute VTE who are treated with anticoagulant therapy, we recommend long-term therapy (see section 3.1 for recommended duration of therapy) over stopping anticoagulant therapy after about 1 week of initial therapy (Grade 1B).</p>	<p>Excluded because it is considered to be redundant and self-evident.</p>
<p>...</p>	<p>3.4 In patients with DVT of the leg who receive extended therapy, we suggest treatment with the same anticoagulant chosen for the first 3 mo (Grade 2C).</p>	<p>Excluded because it is considered to be redundant and self-evident.</p>
<p>...</p>	<p>4.3 In patients with PTS of the leg, we suggest that venoactive medications not be used (Grade 2C).</p>	<p>Excluded because these interventions are infrequently used.</p>

(Continued)

TABLE 2] (continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>...</p> <p>Antithrombotic therapy for atrial fibrillation</p> <p>CHA₂DS₂-VASC score 2 or higher: We recommend antithrombotic therapy (strong).</p> <p>Patients who choose not to take an oral anticoagulant: We suggest aspirin 75 mg plus clopidogrel 75 mg daily (weak). <i>Remark:</i> Adding clopidogrel 75 mg daily provides better protection against stroke but at the cost of an increased risk of bleeding.</p>	<p>9.5.2 In patients with PTS of the arm, we suggest against treatment with venoactive medications (Grade 2C).</p> <p>2.1.10. For patients with AF, including those with paroxysmal AF, who are at high risk of stroke (eg, CHADS₂ score = 2), we recommend oral anticoagulation rather than no therapy (Grade 1A), aspirin (75 mg to 325 mg once daily) (Grade 1B), or combination therapy with aspirin and clopidogrel (Grade 1B).</p>	<p>Excluded because these interventions are infrequently used.</p> <p>The risk score has been changed from CHADS₂ to CHA₂DS₂-VASC because studies indicate that the CHA₂DS₂-VASC score is superior at identifying patients at a truly low risk of stroke. New data on the baseline risk for patient-important outcomes have been applied to adapt to the new risk score. New relative risk estimates have been applied based on a systematic review on all three NOACs by Adam et al.¹⁴</p>
<p>Patients who choose not to take an oral anticoagulant: We suggest aspirin 75 mg plus clopidogrel 75 mg daily (weak). <i>Remark:</i> Adding clopidogrel 75 mg daily provides better protection against stroke but at the cost of an increased risk of bleeding.</p>	<p>2.1.8 and 2.1.9. For patients who do choose antithrombotic therapy, we suggest aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation (Grade 2B) or combination therapy with aspirin and clopidogrel (Grade 2B). 2.1.10. For patients who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) (Grade 1B).</p>	<p>The adapted guideline gives a weak recommendation for dual antiplatelet treatment to all patients regardless of risk score. Given the superior alternatives of warfarin and NOAC, it is believed that very few patients will follow this recommendation.</p>
<p>Hemodynamically unstable patients in need of urgent cardioversion: We recommend weight-adjusted low-molecular-weight heparin or IV heparin in therapeutic doses. After cardioversion, we recommend a minimum of 4 wk of anticoagulation if the duration of the arrhythmia was unknown or >48 h (strong).</p>	<p>4.2. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or pharmacologic), we suggest that therapeutic-dose parenteral anticoagulation be started before cardioversion, if possible (Grade 2C), but that initiation of anticoagulation must not delay any emergency intervention (Grade 2C).</p>	<p>The strength of the recommendation is changed from weak to strong because the Norwegian panel considered the benefits to clearly outweigh the harms.</p>
<p>Cardioversion of atrial fibrillation lasting >48 h where an atrial thrombus has been ruled out by a transesophageal echocardiography (TEE): We suggest that cardioversion be performed immediately after anticoagulant treatment with IV heparin or weight-adjusted low-molecular-weight heparin in therapeutic doses (weak).</p>	<p>4.1.1. For patients with AF of greater than 48 h or unknown duration undergoing elective electrical or pharmacologic cardioversion, we recommend therapeutic anticoagulation (adjusted-dose VKA therapy, target INR range 2.0-3.0, low-molecular-weight heparin at full venous thromboembolism treatment doses, or dabigatran) for at least 3 wk before cardioversion or a transesophageal echocardiography (TEE)-guided approach with abbreviated anticoagulation before cardioversion rather than no anticoagulation (Grade 1B).</p>	<p>The recommendation is changed from strong to weak because the Norwegian panel valued the balance between benefits and harms accordingly.</p>

(Continued)

TABLE 2] (continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>Cardioversion of atrial fibrillation lasting < 48 h: In patients with a CHA₂DS₂-VASC score of 0 or 1, we suggest that an individual assessment be performed on whether or not to offer the patient anticoagulant therapy after successful cardioversion (weak).</p>	<p>4.1.1 and 4.1.2. After successful cardioversion to sinus rhythm, we recommend therapeutic anticoagulation for at least 4 wk rather than no anticoagulation, regardless of baseline stroke risk (Grade 2C). Decisions about long-term anticoagulation after cardioversion should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in section 2.1.</p>	<p>The Norwegian panel does not consider the benefits of treatment to clearly outweigh the harms for all patients after cardioversion. For patients with a CHA₂DS₂-VASC score of ≥ 2, the adapted guideline provides a strong recommendation in favor of 4 wk of anticoagulant treatment postcardioversion. Regarding long-term treatment beyond the first 4 wk after successful cardioversion of all patients, regardless of duration of AF, the Norwegian panel gives a strong recommendation in favor of long-term treatment in patients with a CHA₂DS₂-VASC score of ≥ 2 and suggests (weak recommendation) an individual assessment of patients with a score of 0 or 1.</p> <p>New recommendation.</p>
<p>Patients who are not suitable for warfarin therapy due to side effects or unstable INR values: We recommend new oral anticoagulants (dabigatran or rivaroxaban) (strong).</p>	<p>...</p>	<p>New recommendation.</p>
<p>Patients treated with dabigatran: The dose 150 mg \times 2 is recommended for most patients. Dosage 110 mg \times 2 is recommended if age > 80 y; use of interacting drugs (such as verapamil); high risk of bleeding (HAS-BLED score of 3 or higher); moderate renal impairment (GFR 30–49 mL/min) (strong).</p>	<p>...</p>	<p>New recommendation.</p>
<p>Patients treated with rivaroxaban: The dose 20 mg \times 1 is recommended for most patients. Dosage 15 mg \times 1 is recommended for patients with a high risk of bleeding (HAS-BLED score of 3 or higher) or moderate renal impairment (GFR 30–49 mL/min) (strong).</p>	<p>...</p>	<p>New recommendation.</p>
<p>Patients treated with apixaban: The dose 5 mg \times 2 is recommended for most patients. Dosage 2.5 mg \times 2 is recommended when at least two of the following are present: age \geq 80 y, body weight \leq 60 kg, or serum creatinine \geq 133 μmol/L (strong).</p>	<p>...</p>	<p>New recommendation.</p>

(Continued)

TABLE 2] (continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
...	<p>2.2. For patients with AF and mitral stenosis, we recommend adjusted-dose VKA therapy (target INR range, 2.0-3.0) rather than no therapy, aspirin (75 mg to 325 mg once daily), or combination therapy with aspirin and clopidogrel (all Grade 1B). For patients with AF and mitral stenosis who are unsuitable for or choose not to take adjusted-dose VKA therapy (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) alone (Grade 1B).</p>	<p>Excluded due to low prevalence.</p>
...	<p>3.4. For patients with AF being managed with a rhythm control strategy (pharmacologic or catheter ablation), we suggest that antithrombotic therapy decisions follow the general risk-based recommendations for patients with AF in section 2.1, regardless of the apparent persistence of normal sinus rhythm (Grade 2C).</p>	<p>Excluded as a recommendation but included in a general introduction.</p>
...	<p>3.5. For patients with atrial flutter, we suggest that antithrombotic therapy decisions follow the same risk-based recommendations as for AF.</p>	<p>Excluded as a recommendation but included in a general introduction.</p>
...	<p>4.3. For patients with atrial flutter undergoing elective or urgent pharmacologic or electrical cardioversion, we suggest that the same approach to thromboprophylaxis be used as for patients with atrial fibrillation undergoing cardioversion.</p>	<p>Excluded as a recommendation but included in a general introduction.</p>
Antithrombotic and thrombolytic therapy for ischemic stroke		
<p>Thrombolytic treatment 3-4.5 h after symptom onset: We suggest treatment with IV alteplase in cases where treatment can be initiated within 3-4.5 h of symptom onset (weak).</p>	<p>2.1.2. In patients with acute ischemic stroke in whom treatment can be initiated within 4.5 but not within 3 h of symptom onset, we suggest IV r-tPA over no IV r-tPA (Grade 2C).</p>	<p>For all relevant recommendations IPCD, clostazol, and triflusal are excluded because they are not readily available in Norway. Rivaroxaban and apixaban have been added as an equal option to dabigatran for all relevant recommendations in accordance with the chapter on AF. The confidence in effect estimate is changed from low to moderate.</p>

(Continued)

TABLE 2] (continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>Low-molecular-weight heparin vs unfractionated heparin in intracerebral hemorrhage: In patients with an intracerebral hemorrhage and restricted mobility, we suggest prophylactic-dose subcutaneous low-molecular-weight heparin rather than subcutaneous unfractionated heparin (weak).</p> <p>Venous sinus thrombosis: In patients with a cerebral venous sinus thrombosis, we suggest anticoagulation during the first 3 to 6 mo (weak).</p>	<p>3.2.2. In patients with acute primary intracerebral hemorrhage and restricted mobility, we suggest prophylactic-dose LMWH over prophylactic-dose UFH (Grade 2B).</p> <p>5.1. In patients with cerebral venous sinus thrombosis, we suggest anticoagulation over no anticoagulant therapy during the acute and chronic phases (Grade 2C).</p>	<p>The confidence in effect estimate is changed from moderate to low.</p> <p>The treatment length is specified to make the recommendation more actionable.</p>
<p>Primary and secondary prevention of cardiovascular disease</p>		
<p>...</p>	<p>3.2.6 and 3.2.7. For patients with anterior MI and left ventricular (LV) thrombus, or at high risk for LV thrombus (ejection fraction <40%, anteroapical wall motion abnormality), who do not undergo stenting: We recommend warfarin (INR 2.0-3.0) plus low-dose aspirin 75 to 100 mg daily over single antiplatelet therapy or dual antiplatelet therapy for the first 3 mo (Grade 1B). Thereafter, we recommend discontinuation of warfarin and continuation of dual antiplatelet therapy for up to 12 mo as per the ACS recommendations.</p> <p>4.1.1.-4.3.5. For patients who have undergone elective PCI with placement of DES: For the first 3 to 6 mo, we recommend dual antiplatelet therapy with aspirin 75 to 325 mg daily and clopidogrel 75 mg daily over single antiplatelet therapy (Grade 1A). After 3 to 6 mo, we suggest continuation of dual antiplatelet therapy with low-dose aspirin 75 to 100 mg and clopidogrel (75 mg daily) until 12 mo over single antiplatelet therapy (Grade 2C).</p>	<p>All recommendations about cilostazol are excluded because this drug is not readily available in Norway.</p> <p>For all recommendations about patients with anterior MI and LV thrombus or at high risk of LV thrombus (with or without a PCI), patients only at high risk but with no confirmed thrombus are excluded from the recommendations because their risk of stroke is not considered to be certain enough to warrant treatment with warfarin at the cost of an increased risk of bleeding. After the first 3 (to 6) mo, the Norwegian panel gives a weak recommendation for continued dual antiplatelet treatment due to insufficient data on the optimal length of treatment of these patients.</p> <p>Due to new documentation, the recommendation has been changed to dual antiplatelet treatment of 6 mo.</p>

(Continued)

TABLE 2] (continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>No known CAD or LV thrombus: We suggest no anticoagulation or antiplatelet treatment (weak). Identified LV thrombus, but no known CAD: We suggest warfarin with INR target 2.5 ± 0.5 for a minimum of 3 mo (weak). <i>Remark:</i> The length of warfarin therapy for this patient population should be individually assessed based on echocardiographic findings during follow-up.</p>	<p>5.1-5.3. For patients with systolic LV dysfunction without established CAD and no LV thrombus, we suggest not to use antiplatelet therapy or warfarin (Grade 2C). For patients with systolic LV dysfunction without established CAD with identified acute LV thrombus (eg, Takotsubo cardiomyopathy), we suggest moderate-intensity warfarin (INR 2.0-3.0) for at least 3 mo (Grade 2C).</p>	<p>The relative risk estimate has been updated with a new study by Homma et al.¹⁷ The recommendation is unaltered except for the added remark.</p>
<p>Antithrombotic therapy in peripheral artery disease</p>	<p>2.1. For persons with asymptomatic peripheral arterial disease (PAD), we suggest aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B).</p>	<p>The baseline risk estimates have been changed to be in accordance with the NORRISK score rather than the Framingham score. The NORRISK score is better suited for a Scandinavian population and has previously been implemented in other Norwegian guidelines.</p>
<p>Intermittent claudication: We suggest antiplatelet therapy without the addition of pentoxifylline, heparinoids, or prostanoids (weak).</p>	<p>4.1-4.4. For patients with intermittent claudication refractory to exercise therapy (and smoking cessation), we suggest the use of cilostazol in addition to previously recommended antithrombotic therapies (aspirin 75-100 mg daily or clopidogrel 75 mg daily) (Grade 2C); we suggest against the use of pentoxifylline, heparinoids, or prostanoids (Grade 2C).</p>	<p>Cilostazol is not readily available in Norway and is not considered to add sufficient extra benefit to warrant off-license use.</p>
<p>Percutaneous transluminal angioplasty (PTA) with stent implantation: We suggest dual antiplatelet therapy with aspirin 75 mg and clopidogrel 75 mg daily for 4 to 8 wk for patients that have undergone infrainguinal PTA with stent implantation, followed by long-term treatment with single antiplatelet therapy (weak).</p>	<p>7.1. For patients undergoing peripheral artery percutaneous transluminal angioplasty with stenting, we suggest single rather than dual antiplatelet therapy (Grade 2C).</p>	<p>The Norwegian panel modified the recommendation based on indirect data from studies on patients with coronary stents; the quality of the evidence is rated to low. The recommendation is in accordance with current practice in Norway.</p>
<p>VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy</p>		

(Continued)

TABLE 2] (continued)

Adapted Recommendation in the Norwegian Guideline	Original Recommendation in AT9	Reason for Modification
<p>Drug use at childbirth: For women using dose-adjusted LMWH, we recommend that the delivery is scheduled and that LMWH is discontinued 22-24 h before a cesarean or regional anesthesia. When induction is performed, we recommend discontinuation 24 h before the expected delivery or initiation of epidural. Individual judgments based on maturity of the cervix may qualify for discontinuation 12-24 h before induction.</p>	<p>7.1.4. For pregnant women receiving adjusted-dose LMWH therapy and where delivery is planned, we recommend discontinuation of LMWH at least 24 h prior to induction of labor or cesarean section (or expected time of neuraxial anesthesia) rather than continuing LMWH up until the time of delivery (Grade 1B).</p>	<p>For all relevant recommendations, danaparoid, r-hirudin, acenocoumarol, UFH, and IPCD have been excluded because they are not readily available in Norway. For all recommendations related to the use of LMWH, the relative effect estimate of LMWH as a thromboprophylaxis vs placebo is based on a meta-analysis by Collins et al.¹⁵ This meta-analysis is applied in the chapter on prevention of VTE in nonorthopedic surgical patients and provides a more plausible relative effect on major bleeds than the meta-analysis originally used in AT9. The phrasing of the recommendation is more specific to make tailored use easier.</p>
<p>Malignant disease: thromboprophylaxis and treatment of thromboembolic disease</p>		
<p>Antithrombotic treatment and thrombocytopenia: For patients with malignant disease and thrombocytopenia, anticoagulation at therapeutic doses can be used in the treatment of VTE as long as the platelet count is above $50 \times 10^9/L$ and there are no signs of bleeding. For patients with platelet counts below $50 \times 10^9/L$, the assessment of treatment and dosing should be individualized and with utmost care.</p>	<p>...</p>	<p>All relevant recommendations about patients with cancer across the 11 management chapters have been compiled under a new chapter heading. New best-practice statement based on guidelines by the International Society of Thrombosis and Haemostasis.¹⁸</p>
<p>Thromboprophylaxis and thrombocytopenia: For patients with malignant disease and mild thrombocytopenia (platelet count $> 80 \times 10^9/L$), prophylaxis can be used. When the platelet count falls below $80 \times 10^9/L$, individual assessments should be performed, and close monitoring is recommended.</p>	<p>...</p>	<p>New best-practice statement based on guidelines by the International Society of Thrombosis and Haemostasis.¹⁸</p>

CAD = coronary artery disease; DES = drug-eluting stent; GFR = glomerular filtration rate; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 y), drugs/alcohol concomitantly; HFS = hip fracture surgery; IVC = inferior vena cava; LV = left ventricular; MI = myocardial infarction; NORRISK = Norwegian risk model for cardiovascular mortality; PTS = postthrombotic syndrome; r-tPA = recombinant tissue-type plasminogen activator; SC = subcutaneous. See Table 1 legend for expansion of other abbreviations.

population-based clinical database with data on all inpatient consultations at government-run hospitals in Norway. Diagnoses are classified according to the *International Classification of Diseases, Tenth Revision*, and the Norwegian Classification of Medical Procedures. Each patient's condition can be traced and cross-referenced.

The panel used the same approach here and calculated the baseline risk by applying the relative risk reduction provided by heparins to the registry data. To avoid underestimating the baseline risk, the panel assumed that all patients were given the most effective prophylaxis for a full 35 days.

The panel first opted to use the registry data to estimate new baseline risks. The review process, however, identified that the reported incidence of postoperative DVT was implausible when seen in relation to the incidence of pulmonary emboli. Suspecting an underreporting of DVT, the panel applied data from the meta-analysis and subsequently modified the baseline risk estimate of VTE, finally using an estimated risk of VTE for 5 weeks after major orthopedic surgery in 19 per 1,000 patients for its effect estimate calculations. On the basis of this estimate, 10 fewer patients will experience a VTE with thromboprophylaxis at the cost of two additional major bleeds. About two-thirds of the events would occur during the first 2 weeks following surgery.²³

The Norwegian panel considered the absolute benefits of prophylaxis to outweigh the risk of bleeding and the associated burden for the first 10 days and, thus, gave a recommendation in favor of thromboprophylaxis. It suggested against extended prophylaxis, inferring the belief that most patients would find the burden of extended prophylaxis too large in the face of the small benefit (1,000 patients anticoagulated for 25 days to prevent three VTEs).

The panel undertook lengthy discussions and chose to make both recommendations weak, reflecting the remaining uncertainty regarding the true baseline risk and typical preferences and values. To address these uncertainties and to further facilitate tailored application at the point of care, the panel developed a new recommendation for the treatment of patients at moderate to high risk of thrombosis as assessed by the Charlson Comorbidity Index²⁴ or the American Society of Anesthesiologists classification. For such patients, the panel made a strong recommendation in favor of thromboprophylaxis for 10 days, followed by a weak recommendation for extended prophylaxis up to 35 days following surgery.

VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy

Inconclusive evidence exists regarding the baseline risk of VTE in pregnant women with antithrombin deficiency, with the recommendation in AT9 being based on a meta-analysis that included only 33 women with antithrombin deficiency and a positive family history of VTE.²⁵ AT9 estimated baseline risk for pregnant women with antithrombin and protein C or S deficiency as 20 per 1,000 antepartum and postpartum, with a reduction to seven per 1,000 treated with thromboprophylaxis and no increase in the number of major bleeds. On the basis of these absolute effect estimates, AT9 provides a weak recommendation in favor of antepartum vigilance and postpartum prophylaxis in women with a positive family history of VTE and a weak recommendation against any prophylaxis in women with no family history (baseline risk seven per 1,000 women).

Traditionally, nearly all women with antithrombin deficiency in Norway have received antepartum and postpartum thromboprophylaxis. The Norwegian panel did not find more trustworthy data regarding the baseline risk of VTE. In the end, it opted to apply the risk estimate provided in AT9 for an isolated population of pregnant women with antithrombin deficiency and a positive family history at 30 per 1,000 pregnancies. Based on an absolute risk reduction of 17 per 1,000 pregnancies, the panel believed that most women would prefer thromboprophylaxis and, thus, concluded with a weak recommendation in favor of antepartum and postpartum prophylaxis.

The panel made a similar value assessment about the use of prophylaxis following a cesarean section in women at increased risk of VTE. AT9 suggests prophylaxis at a baseline risk of 30 per 1,000 pregnancies. The Norwegian panel believed that most women would find the burden of treatment acceptable at an absolute risk reduction of eight VTEs per 1,000 women treated, meaning at a baseline risk of 15 per 1,000, at the cost of 11 more major bleeds. However, the panel gave a weak recommendation, acknowledging that the individual patient might value the balance between the advantages and disadvantages of the treatment differently.

New Presentation Format Through Use of the MAGICapp

The panels restructured, collapsed, and rewrote 333 original recommendations from AT9 into 249 recommendations in the multilayered presentation format.

Clinicians can access the guideline online or downloaded as a web application for smartphones and tablets.

Through use of the MAGICapp, the guideline content is structured, tagged, and stored directly in a database. The format provides the end user with the recommendations as the first information presented, with the underlying evidence and background information directly linked to each individual recommendation (Fig 1). Each recommendation includes an adaptation disclaimer and a reference list for that individual recommendation, including the PubMed ID and digital object identifier. We provide an account of panel members' financial and intellectual conflicts of interest in the background section of each chapter.

Discussion

As a result of the cumbersome road to final publication of the adapted guideline, as detailed in the first article of this series,⁷ one of the leaders of the guideline endeavor established the Norwegian Society for Thrombosis and Hemostasis in the spring of 2013. The society aims to promote knowledge of hemostasis and thrombosis within the medical profession; promote evidence-based clinical care, research, and teaching in the field; and contribute to interdisciplinary collaboration. The society's first major step

toward these goals is the development and publication of the Norwegian Guideline for Antithrombotic Therapy and Thromboprophylaxis.

By rewriting, updating, and adapting AT9 to a national context, the recommendations should be more acceptable and applicable in a Norwegian setting. The most visible alteration is the restructuring of the recommendations into a multilayered format that ensures transparency and facilitates quick-and-easy access. Users can access the adapted guideline online or off-line as a web application for tablets and smartphones. We are currently developing an efficient search engine within the application. These efforts, together with our future plans and additional dissemination strategies outlined in the first article of this series,⁷ aim to increase implementation.²⁶⁻³⁰

Future Plans and Research

The use of a web-based authoring and publication platform holds great potential for keeping the guideline up to date. We are in the process of testing several strategies that will enable guideline developers to receive evidence feeds related to their predefined clinical questions, thus facilitating dynamic updating of the guideline.³¹ Ensuing modifications will automatically be relayed to all electronic outputs of the guideline.

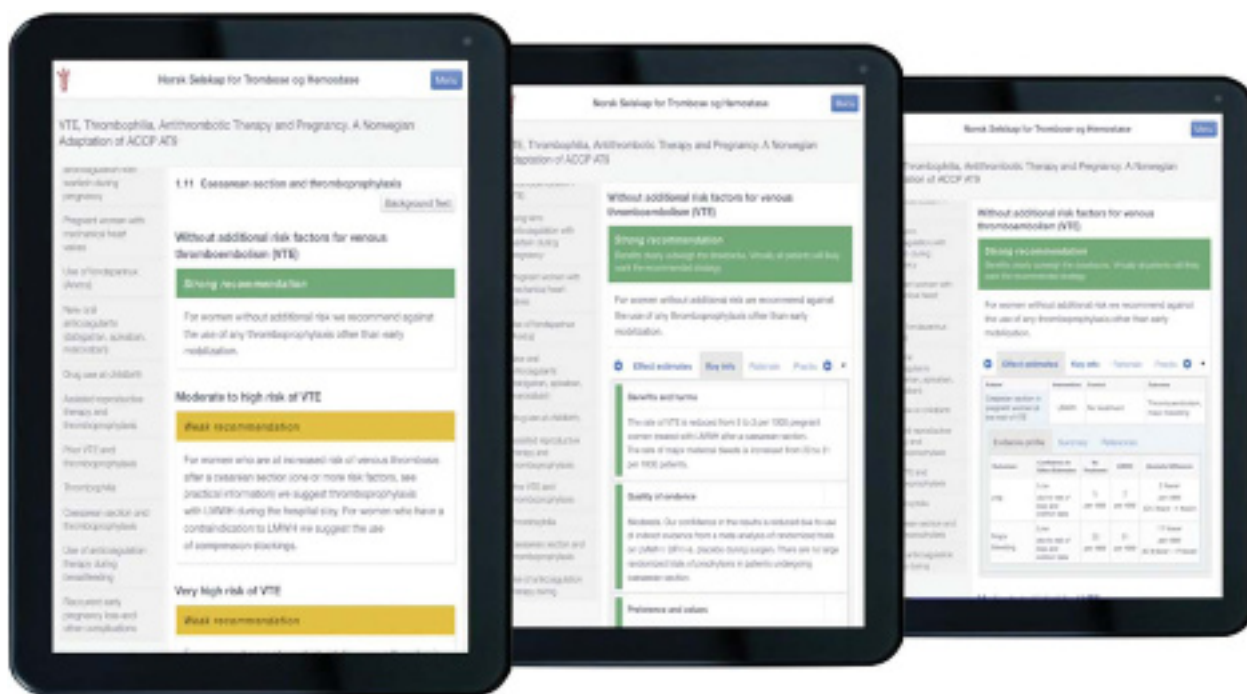


Figure 1 – Multilayered guideline format.

We plan to monitor and evaluate the uptake and implementation of the adapted guideline. End users can provide comments and feedback directly through the MAGICapp. We will track actual use of the guideline through use of website analytics tools and direct observation of clinicians use of guidelines in real-life patient encounters. The MAGIC team will continue to research improved presentation formats in collaboration with the DECIDE project.

Conclusions

The pairing of the Norwegian guideline group with the MAGIC team provided an opportunity to test the frameworks and tools developed by the MAGIC research program and DECIDE project. New strategies for adapting trustworthy guidelines in the new format proved feasible in the context of the Norwegian guideline.

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