CLINICAL PRACTICE GUIDELINE

The Prophylaxis of Venous Thromboembolism

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SUMMARY

Background: Venous thromboembolism (VTE) is the third most common cardiovascular condition, after myocardial infarction and stroke. Prophylactic measures in accordance with current guidelines can significantly reduce the risk of VTE and the associated morbidity and mortality. Until now, the German interdisciplinary, evidence- and consensus-based (S3) clinical practice guideline on VTE prophylaxis was based on a complete review of all pertinent literature available in MEDLINE up to January 2008. More recent publications and drug approvals have made a thorough revision necessary.

Methods: A systematic search was carried out in the MEDLINE and Embase databases for publications that appeared from 1 January 2008 to 7 August 2013. Updates of 5 national and international reference guidelines and 2 new Health Technology Assessment (HTA) reports were considered as well. A structured consensus-finding process was carried out with delegates from 27 scientific medical societies and from the Union of Medical Specialist Associations.

Results: 46 randomized controlled trials (RCTs) were included for critical appraisal. New findings led to re-evaluation of the value of compression stockings in combination with pharmacological prophylaxis (open recommendation), and suggest equal value of non-vitamin K antagonist oral anticoagulants (NOACs) and low molecular weight heparins (LMWH) or fondaparinux in elective hip and knee replacement (strong recommendation). For patients undergoing hip fracture surgery, we recommend LMWH or fondaparinux.

Conclusion: Further research is needed to assess the value of NOACs for pharmacological prophylaxis in orthopedic/trauma patients undergoing surgical procedures other than the ones mentioned above, and into the benefit and harm of new devices available for mechanical prophylaxis. The stringent implementation of basic measures such as early mobilization, movement exercises, and patient instruction is a key point to prevent venous thromboembolism.

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Venous thromboembolism (VTE) is the third most common cardiovascular condition, after stroke and myocardial infarction (1). In the general population, the annual incidence of VTE is approximately 1/1000 on average, showing a linear increase with age (1, 2). It can be assumed that in the age group 60–69 years the VTE incidence rate (IR) has already doubled (IR 2.57/1000; 95% confidence interval [CI]: 2.54; 2.61) (1). Hospitalized patients are at a significantly increased risk of VTE, with wide variations depending on the cause of the hospitalization (1, 2). Older autopsy studies attributed 5 to 10% of in-hospital deaths to pulmonary embolism (3, 4). Since risk-adapted primary prophylaxis of venous thromboembolism can significantly reduce VTE events (5–7), the implementation of adequate strategies for risk assessment and prophylaxis based on high-quality guidelines is internationally viewed as a key indicator for patient safety (8, 9). In Germany, a set of rules for high-quality guidelines established by the Association of Scientific Medical Societies in Germany (AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften) (10) was first used in 2009 to develop a clinical practice guideline (11) which was based on a systematic search and critical appraisal (12) of the literature available in the MEDLINE database (via PubMed), published until 9 January 2008, as well as on 12 international guidelines. The approval of novel anticoagulants and new evidence, especially related to mechanical methods and to patients with medical/neurological conditions, necessitated a complete revision of the 2009 guideline.

Methods

27 medical specialty societies and the Union of Medical Specialist Associations (*Gemeinschaft Fachärztlicher Berufsverbände*) were involved in the update process and approved the guideline (*eTable 1*) (13). A systematic literature search was conducted in the MEDLINE (via PubMed) and EMBASE databases for the period from 1 January 2008 to 7 August 2013 (*eTables 2 and 3*). Forty-six randomized controlled trials (RCTs) met the inclusion criteria (*eFigure*). These were assessed for methodological quality (14). In addition, updates of 5 of the guidelines used as references (15–19) and two new Health Technology Assessment (HTA) reports (20, 21) were taken into account. Three grades of recommendation are distinguished. The differences in the strength of recommendation are

TABLE 1

Risk categories and examples for the classification of patients with special risks

	Surgical	Non-surgical*
Low VTE risk	<ul style="list-style-type: none"> – Minor surgical interventions – Trauma without or with minor soft tissue injury – No additional or only minor dispositional risk, otherwise classification in higher risk category 	<ul style="list-style-type: none"> – Infection or acute inflammatory disease without bed confinement – Central venous catheter/port catheter – No additional or only minor dispositional risk, otherwise classification in higher risk category
Moderate VTE risk	<ul style="list-style-type: none"> – Longer surgical interventions – Joint-spanning cast immobilization of the lower extremity – Arthroscopy assisted surgery on the lower extremity – No additional or only minor dispositional risk, otherwise classification in higher risk category 	<ul style="list-style-type: none"> – Acute heart failure (NYHA III/IV) – Acute decompensation in patients with severe COPD without ventilation – Infection or acute inflammatory disease with bed confinement status – Malignant disease requiring in-patient treatment – No additional or only minor dispositional risk, otherwise classification in higher risk category
High VTE risk	<ul style="list-style-type: none"> – Major surgery in the abdominal and pelvic region for malignancy or inflammatory disease – Patients with multiple injuries, serious injuries of the spine, the pelvis and/or the lower extremity – Major surgery on the spine, pelvis, hip and knee – Major surgery in the body cavities of the chest, abdomen and/or pelvic region 	<ul style="list-style-type: none"> – Stroke with leg paresis – Acute decompensation in patients with severe COPD with ventilation – Sepsis – Seriously ill patients receiving intensive care

* Study data are only available for in-patient care.

VTE, venous thromboembolism; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease

expressed by the use of the wording “we recommend” (strong recommendation), “we suggest” (recommendation) and “may” (open recommendation) in combination with corresponding arrow symbols (↑↑, ↑ and ↔, respectively) (eTable 4). Besides the quality of evidence, factors taken into account for determining the grade of recommendation included the balance of benefits and harms, the clinical relevance of outcomes and effect sizes, the consistency and external validity of the study results, as well as ethical and legal considerations. For questions left unanswered by the literature search, recommendations were adopted by means of expert consensus. The guideline was funded by the AWMF’s guideline fund and the participating medical societies, without any financial support from the industry. For detailed information about the methodology and rationale for the recommendations, including 87 evidence tables, please refer to the long version of this guideline and pertinent report on the AWMF website (13).

General recommendations

In all patients with surgical procedures, injuries or acute disease, we recommend that the risk of venous thromboembolism be taken into account (↑↑). We recommend the decision to initiate VTE prophylaxis be made on an individual and risk-adapted basis (↑↑). There is no test to reliably assess the individual VTE risk. Thus, the assessment is based on the identification and consideration of risk factors related to exposure (type of surgical procedure/trauma/acute disease, extent of immobilization) and disposition (individual inherited and acquired factors) (eTable 5). On this basis, we suggest that patients be categorized in three

risk groups (expert consensus) (↑). The classification is based on the estimated rates of distal deep vein thrombosis (DVT) of the leg/proximal DVT of the leg/fatal pulmonary embolism (11, 13):

- low risk (<10% / <1% / <0.1%)
- moderate risk (10%–40% / 1%–10% / 0.1%–1%)
- high risk (40%–80% / 10%–30% / >1%).

Examples for the classification of patients to these three risk categories are provided in Table 1.

Principles of VTE prophylaxis

As a principle, we suggest that all patients receive the basic measures including early mobilization, movement exercises and instructions for self-exercises (expert consensus) (↑). For patients with moderate or high VTE risk, we recommend pharmacological VTE prophylaxis (↑↑). In addition, mechanical measures (compression stockings, intermittent pneumatic compression [IPC]) may (↔) be applied.

In Germany, compression stockings have traditionally been used in addition to pharmacological prophylaxis. However, the evidence in support of this combination preventive treatment is dubious (22–24). Four RCTs evaluated the benefits of compression stockings as an adjunct to heparin prophylaxis (24). Pooled analysis of these studies as part of a network meta-analysis (25) showed an advantage for this combination treatment for the outcome deep vein thrombosis (DVT) (Odds Ratio [OR] 0.31, 95% confidence interval [CI] [0.16; 0.61]), but not for the outcome symptomatic DVT (number needed to treat [NNT]: 134–524), subject to VTE risk constellation). A recent non-interventional phase 4 study (XAMOS)

TABLE 2

VTE prophylaxis after abdominal or pelvic surgery (visceral & vascular surgery, gynecology, urology)*

	Pharmacological prophylaxis	Mechanical prophylaxis
Low risk	None ↑	
Moderate risk	UFH/LMWH ↑↑	IPC/CS ↔
High risk	LMWH /fondaparinux ↔	IPC/CS ↔
Laparoscopic surgery, minimally invasive surgery	Same recommendations as for open surgery	
Transplantation medicine (living donor, e.g. kidney, liver)	LMWH/UFH ↑↑	IPC/CS ↔
Duration	Usually 7 days ↑, with major oncological procedures 4 weeks ↑↑	

* Basic measures, if possible with all patients.

↑↑, strong recommendation; ↑, recommendation; ↔, open recommendation; VTE, venous thromboembolism; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; IPC, intermittent pneumatic compression; CS, compression stockings

found almost identical rates of symptomatic thromboembolism events with and without the use of additional mechanical measures (26). For pharmacological prophylaxis alone, it was 0.8% (45/5430) with rivaroxaban and 1.4% (71/5117) with other anticoagulants; in combination with additional mechanical measures, it was 1.0% (33/3348) and 1.3% (46/3528), respectively. Whether the length of compression stockings (knee-high versus thigh-high compression stockings) has an impact on VTE prevention has also been discussed. In line with an earlier meta-analysis (27), the recent network meta-analysis (25) found no significant difference for the endpoint DVT (OR 1.48, 95% CI [0.80; 2.73]). Among the mechanical measures, intermittent pneumatic compression (IPC) is superior to compression stockings with regard to DVT prevention (relative risk [RR] 0.6, 95% CI [0.39; 0.93]) (28).

For pharmacological prophylaxis, heparins, fondaparinux and (for approved indications) non-vitamin K antagonist oral anticoagulants (NOACs, previously referred to as new or novel oral anticoagulants) are recommended. When anticoagulants are used, we recommend the procedure-specific and patient-specific bleeding risk to always be taken into account (↑↑). In addition, we recommend that kidney and liver function be considered when choosing and administering an anticoagulant therapy (↑↑). We recommend that when using heparin, the risk of heparin-induced thrombocytopenia (HIT II) be taken into account (↑↑). When using unfractionated heparin (UFH), we suggest that platelet counts be regularly monitored (↑). We recommend that low-molecular-weight heparin (LMWH) be preferred over UFH (↑↑), while balancing efficacy with bleeding risk and HIT II risk. When using LMWH therapy, platelet monitoring may (↔) be omitted. We suggest that pharmacological VTE prophylaxis be initiated early after the risk-producing situation (↑). In surgical patients, LMWH prophylaxis may (↔) be started the evening before surgery, while prophylaxis with fondaparinux and the NOACs dabigatran etexilate, rivaroxaban and apixaban shall only be initiated post-

operatively (↑↑). When administering spinal or epidural anesthesia, special time intervals have to be observed because of the risk of spinal or epidural hematomas (19).

We recommend the duration of pharmacological VTE prophylaxis be guided by the persistence of relevant risk factors for VTE (↑↑). Where continuation of the prophylaxis is required after hospital discharge, we recommend that the physician responsible for the patient's further treatment be informed about this (↑↑) and that patients be advised to immediately see their doctor to ensure the seamless continuation of VTE prophylaxis (↑↑). The guideline group considers successful communication at this interface as crucial (expert consensus).

Specific recommendations

Operative medicine

After craniofacial and neck procedures, VTE prophylaxis may (↔) generally be omitted. However, in the presence of additional risks, e.g. extensive or large oncological procedures, we suggest that pharmacological prophylaxis be initiated (↑). In patients undergoing craniotomy/neurosurgical procedures or those with injuries to the central nervous system, we recommend that mechanical VTE prophylaxis be used (↑↑), given the special bleeding risk. With this approach, the risk of DVT can be significantly reduced (RR 0.41, 95% CI [0.21; 0.78]), accounting to approximately 3 (range, 1 to 4) prevented events/100 patients (29). Notwithstanding the information in manufacturers' summaries of product characteristics, evidence suggesting potential additional benefits from pharmacological prophylaxis is available (29, 30). Further research is needed here, not least to determine the as yet unknown increase in bleeding risk associated with pharmacological prophylaxis. In patients undergoing moderate or major thoracic surgery we recommend pharmacological VTE prophylaxis with LMWH (↑↑). In patients not on anticoagulation therapy undergoing moderate or major cardiac surgery we recommend postoperative pharmacological VTE prophylaxis with UFH or

TABLE 3

VTE prophylaxis after joint, bone or soft tissue surgery or injuries of the lower extremity*

	Pharmacological prophylaxis	Mechanical prophylaxis	Special considerations
Elective total hip replacement	LMWH/fondaparinux/NOAK ↑↑	IPC/CS↔	Duration 28–35 days
Fractures close to hip joint and patients undergoing osteotomy	LMWH/fondaparinux ↑↑	IPC/CS↔	
Elective total knee replacement	LMWH/fondaparinux/NOAK ↑↑	IPC/CS↔	Duration 11–14 days
Fractures close to the knee joint and patients undergoing osteotomy	LMWH/fondaparinux ↑↑	IPC/CS↔	
Contraindications for pharmacological prophylaxis	–	IPC ↑↑	Bleeding risk, renal failure
Conservative treatment with joint-spanning cast immobilization	Pharmacological prophylaxis as in surgical patients ↑↑	IPC/CS↔	Early functional therapy
Arthroscopy with longer operating time in patients with restricted mobility	LMWH ↑↑	–	Special vote of DEGAM: If care provided in family physician practice, individual risk assessment and decision
Bones, ankle joint, foot with immobilizing cast	LMWH ↑	–	
Spine (elective surgery)	Individual decision		
Spinal injuries	LMWH ↑↑	Alternative: IPC ↑	Bleeding risk
Polytrauma	LMWH ↑↑	IPC ↑	Bleeding risk, in addition see intensive care recommendations
Pelvic fractures	See fractures close to the hip joint		
Burns	With immobilization/additional risk factors LMWH ↑↑	↔	When larger areas affected: UFH i.v.

* Basic measures, if possible with all patients.

↑↑, strong recommendation; ↑, recommendation; ↔, discretionary recommendation; LMWH, low-molecular-weight heparin; NOAC, non-vitamin K antagonist oral anticoagulants; IPC, intermittent pneumatic compression; CS, compression stockings; DEGAM, German College of General Practitioners and Family Physicians; UFH, unfractionated heparin; i.v., intravenous

LMWH (expert consensus) (↑↑). We suggest that patients undergoing leg vascular surgery receive VTE prophylaxis with UFH or LMWH, if they do not receive therapeutic anticoagulation treatment postoperatively (↑). In patients with no additional dispositional risk factors undergoing superficial-vein surgery (varicose vein surgery), pharmacological VTE prophylaxis may (↔) be omitted (expert consensus).

RCTs found no differences with regard to the VTE risk between patients undergoing visceral surgery, vascular surgery, gynecological and urological procedures in the abdomen and pelvic region. Therefore, the same recommendations apply to these subgroups (expert consensus, Table 2). We suggest that patients with low procedure-related expositional and absent or low dispositional VTE risk do not receive pharmacological prophylaxis (↑). We recommend that patients with moderate VTE risk (moderate surgery or minor surgery with additional dispositional risk factors) receive pharmacological prophylaxis with heparin (↑↑). In patients with high VTE risk (major surgery or moderate surgery with additional dispositional risk factors) we recommend prophylaxis with LMWH (↑↑). Alternatively, fondaparinux may be used (↔). For laparoscopic procedures and minimally invasive surgery (MIS), the same recommendations apply as for open procedures. Pharmacological prophylaxis is typically administered

over a period of 7 days, regardless of whether the patient is still treated on an in-patient basis or already on an out-patient basis. In patients undergoing major oncological surgery we recommend VTE prophylaxis over a period of 4 weeks (↑↑). This regimen significantly reduces the VTE risk (13.6% vs. 5.9%; RR 0.44, 95% CI [0.28; 0.7]) without increasing the bleeding risk (31).

We recommend that patients undergoing major hip surgery receive pharmacological VTE prophylaxis in addition to the basic measures (↑↑). In patients undergoing elective total hip arthroplasty, we recommend that LMWH, fondaparinux or NOAC be used for pharmacological VTE prophylaxis; in case of fractures near joints and in patients undergoing near-joint osteotomy, we recommend LMWH or fondaparinux (↑↑). In patients with a history of heparin intolerance we recommend fondaparinux or a NOAC when undergoing elective hip surgery (↑↑), while in patients with fractures and those undergoing osteotomy we recommend fondaparinux (↑↑). In addition to pharmacological prophylaxis, mechanical measures (compression stockings, IPC) may (↔) be used. Where pharmacological prophylaxis is contraindicated, we recommend that IPC be applied (↑↑) (Table 3). We recommend that pharmacological prophylaxis be administered over a period of 28 to 35 days (↑↑). Prolonged prophylaxis with LMWH after discharge from hospital reduces the

TABLE 4

VTE prophylaxis in non-surgical and outpatient care*

	Pharmacological prophylaxis	Mechanical prophylaxis	Special considerations
Acute medical disease with bed confinement status	LMWH/fondaparinux ↑↑	↔	Duration 6–14 days
Malignant disease (in-patient)	LMWH/fondaparinux ↑↑	↔	Duration: total in-patient hospital stay
Ischemic stroke with leg paresis	LMWH/UFH ↑↑	IPC > CS ↑	IPC > CS: if contraindication for pharmacological prophylaxis
Hemorrhagic stroke with leg paresis	UFH, LMWH ↑	IPC > CS ↑	IPC > CS: if contraindication for pharmacological prophylaxis UFH; LMWH: when there is no longer an acute bleeding risk
Intensive care	LMWH > UFH s.c. ↑↑	IPC > CS ↑	IPC > CS: if contraindication for pharmacological prophylaxis LMWH > UFH s.c.: Warning: bleeding, kidney failure, uncertain absorption
Pediatrics, neonatology	Only in exceptional cases	individual decision	If VTE risk suspected: consultation with pediatric hemostaseologist (addresses for Germany available at: www.gth-online.org)
Obstetrics	Only with additional risk factors LMWH, UFH ↑↑	CS ↔	Special risk factors in pregnancy and puerperium
Outpatient care	For duration of prophylaxis after discharge from hospital see specific recommendations in the text. Always: assessment of the individual, expositional and dispositional VTE risk		

* Basic measures, if possible with all patients.

↑↑, strong recommendation; ↑, recommendation; ↔, discretionary recommendation; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; IPC, intermittent pneumatic compression; CS, compression stockings; s.c., subcutaneous; VTE, venous thromboembolism; >, is superior to

rates of venography-confirmed DVT (22.5% vs. 7.9%; RR 0.41, 95% CI [0.32; 0.54]) and symptomatic DVT (4.1% vs. 1.4%; RR 0.36, 95% CI [0.20; 0.47]) (32). The efficacy and safety of prophylaxis with dabigatran etexilate, rivaroxaban or apixaban, started post-operatively and continued over a period of approximately 5 weeks, was demonstrated in phase III studies (33–36). For fractures treated non-surgically with early functional therapy, no general recommendations can be issued due to a lack of pertinent data. In case of immobilization, we recommend that pharmacological prophylaxis be initiated (↑↑). For patients undergoing major knee surgery, corresponding recommendations apply (Table 3). Based on the evidence from available studies, we recommend pharmacological prophylaxis over a period of 11 to 14 days in patients undergoing knee surgery (↑↑). The recommendations for the NOACs dabigatran, rivaroxaban and apixaban in patients undergoing elective hip or knee preplacement surgery are supported by independently conducted HTA reports (20, 37, 38). However, the Institute for Quality and Efficiency in Health Care (IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) does not support the finding that there is evidence demonstrating an additional benefit provided by apixaban in patients undergoing elective knee replacement surgery compared with the LMWH enoxaparin (21). In patients undergoing non-surgical treatment of fractures with joint-spanning cast immobilization we recommend pharmacological prophylaxis (↑↑).

In patients with surgically treated bone injuries and/or immobilizing hard casts or below-knee orthoses we suggest pharmacological VTE prophylaxis in addition to the basic measures (↑). We recommend LMWH over other pharmacologic measures and that this be used until the removal of the fixating cast or until a defined partial weight bearing is achieved (expert consensus) (↑↑) (Table 3). Deviating from that, the German College of General Practitioners and Family Physicians (DEGAM, Deutsche Gesellschaft für Allgemein- und Familienmedizin) voted to decide the scope and duration of pharmacological prophylaxis in a primary care setting on a case-by-case basis in this patient group, owing to the lack of evidence.

Short arthroscopic procedures on the lower extremity do not generally require pharmacological VTE prophylaxis. We suggest that patients undergoing longer arthroscopic procedures receive pharmacological prophylaxis until normal mobility is restored, but not for less than 7 days (expert consensus) (↑). Deviating from that, the DEGAM voted for case-by-case decisions in a primary care setting. Here, again, data from studies are scarce.

We suggest that patients undergoing surgery on the upper extremity do not generally receive VTE prophylaxis other than the basic measures (expert consensus) (↑). For elective spinal surgery, the available data do not allow to make definite recommendations; thus, decisions have to be made on a case-by-case basis. We recommend that patients with spinal injuries receive

pharmacological prophylaxis, while taking into account the bleeding risk; in patients with high bleeding risk we recommend IPC (expert consensus) (↑↑). For pelvic fractures, the same recommendations as for fractures near the hip apply (expert consensus). In polytrauma patients we recommend pharmacological prophylaxis with LMWH for the duration of intensive care (↑↑); in case of contraindications, we suggest that IPC be used (↑). We recommend that patients with burns and patients with immobilization receive pharmacological prophylaxis (↑↑).

Internal medicine and neurology

In hospital patients with acute medical illness and bed confinement we recommend pharmacological VTE prophylaxis, preferably LMWH in high-risk prophylaxis doses or fondaparinux (↑↑). We suggest that this be administered over a period of 6 to 14 days (↑). Heparins reduce the DVT risk by half compared with no prophylaxis or placebo (3.8% vs. 6.7%; OR 0.41, 95% CI [0.25; 0.67]) (39). In patients receiving in-patient treatment for malignancies we recommend pharmacological VTE prophylaxis, preferably with LMWH or fondaparinux (↑↑). We suggest that this be administered during the entire hospital stay (expert consensus) (↑). Patients with acute ischemic stroke and paretic leg have a high VTE risk and, therefore, we recommend they receive pharmacological prophylaxis (↑↑). We recommend that this preferably be based on LMWH or UFH in high-risk doses (↑↑) and suggest that this be continued for a period of 6 to 14 days, depending on the speed of mobilization (↑). We suggest that patients with acute hemorrhagic stroke and paretic leg receive pharmacological prophylaxis, as soon as there is no more risk of bleeding (↑). In patients where pharmacological prophylaxis is contraindicated, we suggest a mechanical prophylaxis be initiated, preferably IPC (Table 4) (↑).

Intensive care medicine

The vast majority of intensive care patients fall into the high-risk category. Only limited data from studies are available; a meta-analysis found that heparin thromboprophylaxis can reduce the DVT rate among critically ill intensive-care patients (14.7% vs. 7.5%; RR 0.51, 95% CI [0.41; 0.63]) (40). Thus, in these patients we recommend pharmacological VTE prophylaxis with heparin, preferably LMWH (expert consensus) (↑↑). In patients with bleeding diathesis, renal failure or uncertain absorption, low-dose intravenous UFH therapy may (↔) be initiated; where pharmacological prophylaxis is contraindicated, we suggest that mechanical measures (preferably, IPC) be used (↑).

Special considerations in pediatrics and neonatology

Data on the use of pharmacological and mechanical VTE prophylaxis in pediatric and neonatal patients are scarce. The special requirements resulting from the development of the hemostatic system and the pharmacokinetics in pediatric patients must be taken into account (e1).

Special considerations in outpatient care

We recommend that outpatient VTE prophylaxis be provided based on the same criteria as for in-patient prophylaxis (expert consensus) (↑↑). On discharge of a patient, it has to be decided whether the prophylaxis initiated in hospital is to be continued. In a special vote, the DEGAM recommends this indication be reviewed on a case-by-case basis in a consultation with the family physician, taking into account the patient's individual VTE risk (↑↑). Immobility without acute illness is by itself not an indication for VTE prophylaxis other than the general basic measures.

Obligatory patient information

The outcome of the VTE risk assessment and the resulting measures for VTE prophylaxis must be discussed with the patient, including the benefits, risks and alternatives, during an informed consent discussion (section 630e, subsections 1 and 2, German Civil Code [BGB]). No specific formal requirements have to be fulfilled when conducting the informed consent discussion. However, written documentation of the key points discussed is compulsory (section 630f, subsection 2 BGB). If the patient refuses VTE prophylaxis and/or the physician refrains from initiating VTE prophylaxis, the physician should record this in the patient file.

Conclusion

With the aging of the population, the significance of VTE continues to grow. In a hospital setting, VTE is a common, but largely preventable complication. Thus, in all patients with surgical procedures, injuries or acute disease, the individual VTE risk has to be assessed and, where indicated, a risk-adapted prophylaxis is to be initiated. Implementation is required with regard to the basic measures, the communication at interfaces of care, the follow-up risk assessment by the physician responsible for the patient's further care, and with regard to patient information. Detailed information is available in the long version of the guideline and in the guideline report (13).

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Conflict of interest statement

Prof. Haas has received consultancy fees from Bayer, Bristol-Myers Squibb, Daiichi Sankyo, and Sanofi. She has received reimbursement of travel expenses and lecture fees from Aspen, Bayer, Bristol-Myers Squibb, Daiichi Sankyo, and Sanofi.

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REFERENCES

- Tagalakis V, Patenaude V, Kahn SR, Suissa S: Incidence of and mortality from venous thromboembolism in a real-world population: The Q-VTE Study Cohort. *Am J Med* 2013; 126: e13–23.
- Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton WM: Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998; 158: 585–93.
- Alikhan R, Peters F, Willmitt R, Cohen AT: Fatal pulmonary embolism in hospitalized patients: a necropsy review. *J Clin Pathol* 2004; 57: 1254–7.
- Sandler DA, Martin JF: Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? *J R Soc Med* 1989; 82: 203–5.
- Geerts WH, Pineo GF, Heit JA, et al.: Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126 (3 Suppl): 338S–400S.
- Gould MK, Garcia DA, Wren SM, et al.: Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th edition. American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; 141: e227S–e277S.
- Kahn SR, Lim W, Dunn AS, et al.: Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th edition. American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; 14: e195S–e226S.
- Cohen AT, Tapson VF, Bergmann JF, et al.: Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet* 2008; 371: 387–94.
- OECD (2015), Health at a Glance 2015: OECD Indicators, OECD Publishing, Paris. dx.doi.org/10.1787/health_glance-2015-en (last accessed on 5 July 2016).
- Association of Scientific Medical Societies in Germany (AWMF; Standing Guideline Commission). AWMF Guidance Manual and Rules for Guideline Development. 1st Edition; 2012. www.awmf.org/leitlinien/awmf-regelwerk.html (last accessed on 5 July 2016).
- Encke A, Haas S, Sauerland S, et al.: S3-Leitlinie Prophylaxe der venösen Thromboembolie (VTE). *Vasa* 2009; 38: 1–131.
- Jadad AR, Moore RA, Carroll D, et al.: Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1–12.
- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF): S3-Leitlinie Prophylaxe der venösen Thromboembolie (VTE) – 2. komplett überarbeitete Auflage (Stand 15.10.2015). www.awmf.org/leitlinien/detail/II/003-001.html (last accessed on 5 July 2016).
- Higgins JP, Altman DG, Gøtzsche PC, et al.: The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. *BMJ* 2011; 343: d5928.
- Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuenemann HJ: Antithrombotic therapy and prevention of thrombosis. 9th edition. ACCP. Evidence Based Clinical Practice Guidelines. *Chest* 2012; 141 (2 Suppl): 7S–47S.
- National Institute for Health and Clinical Excellence (NICE): Venous thromboembolism: reducing the risk. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. NICE clinical guideline 92. 2010. www.nice.org.uk/guidance/cg92/resources/guidance-venous-thromboembolism-reducing-the-risk-pdf (last accessed on 20 June 2015).
- Lyman GH, Khorana AA, Kuderer NM, et al.: Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2013; 31: 2189–204.
- Royal College of Obstetricians and Gynecologists: Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green-top Guideline No. 37a. 2015. www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg37a (last accessed on 5 July 2016).
- Waurick K, Riess H, Van Aken H, et al.: Rückenmarksnahe Regionalanästhesien und Thromboembolieprophylaxe/antithrombotische Medikation. 3. überarbeitete Empfehlung der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin. *Anaesth Intensivmed* 2014; 55: 464–92.
- National Institute for Health and Clinical Excellence (NICE): Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults. NICE technology appraisal guidance 245, 2012. www.nice.org.uk/search?q=ta245 (last accessed July 5 2016).
- Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG): Apixaban – Nutzenbewertung nach §35a SGBV. Auftrag A11–30, 2012. www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a11-30-apixaban-nutzenbewertung-gemass-35a-sgb-v-dossierbewertung.2140.html (last accessed on 5 July 2016).
- Eppsteiner RW, Shin JJ, Johnson J, et al.: Mechanical compression versus subcutaneous heparin therapy in postoperative and posttrauma patients: A systematic review and meta-analysis. *World J Surg* 2010; 34: 10–9.
- Sachdeva A, Dalton M, Amaragiri SV, et al.: Graduated compression stockings for prevention of deep vein thrombosis. *Cochrane Database Syst Rev* 2014; 12: CD001484.
- CLOTS (Clots in Legs Or Stockings after Stroke) Trials Collaboration: Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. *Lancet* 2009; 373: 1958–65.
- Wade R, Sideris E, Fiona Paton F, et al.: Graduated compression stockings for the prevention of deep-vein thrombosis in postoperative surgical patients: a systematic review and economic model with a value of information analysis. *Health Technol Assess* 2015; 19: 1–220.
- Haas S, Holberg G, Kreutz R, et al.: The effects of timing of prophylaxis, type of anesthesia, and use of mechanical methods on outcome in major orthopedic surgery—subgroup analyses from 17,701 patients in the XAMOS study. *Vasc Health Risk Manag* 2016; 12: 209–18.
- Sajid MS, Desai M, Morris RW, et al.: Knee length versus thigh length graduated compression stockings for prevention of deep vein thrombosis in postoperative surgical patients. *Cochrane Database Syst Rev* 2012; CD007162(5).
- Ho KM, Tan JA: Stratified meta-analysis of intermittent pneumatic compression of the lower limbs to prevent venous thromboembolism in hospitalized patients. *Circulation* 2013; 128: 1003–20.
- Collen JF, Jackson JL, Shorr AF, et al.: Prevention of venous thromboembolism in neurosurgery: ametaanalysis. *Chest* 2008; 134: 237–49.
- Almagggi A, Simonetti G, Trevisan E, et al.: Perioperative thromboprophylaxis in patients with craniotomy for brain tumours: a systematic review. *J Neurol Oncol* 2013; 113: 293–303.
- Bottaro FJ, Elizondo MC, Doti C, et al.: Efficacy of extended thrombo-prophylaxis in major abdominal surgery: What does the evidence show? A meta-analysis. *Thromb Haemost* 2008; 99: 1104–11.
- Hull RD, Pineo GF, Stein PD, et al.: Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med* 2001; 135: 858–69.
- Eriksson BI, Borris LC, Friedman RJ, et al.: Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008; 358: 2765–75.
- Eriksson BI, Dahl OE, Huo MH, et al.: Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II): A randomised, double-blind, non-inferiority trial. *Thromb Haemost* 2011; 105: 721–9.
- Kakkar AK, Brenner B, Dahl OE, et al.: Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008; 372: 31–9.
- Lassen MR, Gallus A, Raskob GE, et al.: Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *New Eng J Med* 2010; 363: 2487–98.
- National Institute for Health and Clinical Excellence (NICE): Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. NICE technology appraisal guidance 157. www.nice.org.uk/guidance/ta157 (last accessed on 5 July 2016).
- National Institute for Health and Clinical Excellence (NICE): Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults. NICE technology appraisal guidance 170. www.nice.org.uk/guidance/ta170 (last accessed on 5 July 2016).
- Alikhan R, Bedenis R, Cohen AT: Heparin for the prevention of venous thromboembolism in acutely ill medical patients (excluding stroke and myocardial infarction). *Cochrane Database Syst Rev* 2014; CD003747.
- Alhazzani W, Lim W, Jaeschke RZ, et al.: Heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care Med* 2013; 41: 2088–98.

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Supplementary material

For eReferences please refer to:
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eREFERENCES

- e1. Monagle P, Chan AK, Goldenberg NA, et al.: Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th edition. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141 (2 Suppl): e737S–e801S.
- e2. Ali Khan R, Cohen AT, Combe S, et al.: Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. Arch Intern Med 2004; 164: 963–8.
- e3. Vaitkus PT, Leizorovicz A, Cohen AT, et al.: Mortality rates and risk factors for asymptomatic deep vein thrombosis in medical patients. Thromb Haemost 2005; 93: 76–9.
- e4. Weill-Engerer S, Meaume S, Lahlou A, et al.: Risk factors for deep vein thrombosis in inpatients aged 65 and older: a case-control multicenter study. J Am Geriatr Soc 2004; 52: 1299–304.
- e5. Eisele R, Maier E, Kinz L, et al.: Stationäre Thromboseprophylaxe in der Unfallchirurgie: Relevanz von postoperativer Mobilität und vorbestehenden Risikofaktoren. Unfallchirurg 2004; 107: 2949.
- e6. Flordal PA, Bergqvist D, Burmark US, et al.: Risk factors for major thromboembolism and bleeding tendency after elective general surgical operations. The Fragmin Multicentre Study Group. Eur J Surg 1996; 162: 783–9.
- e7. Leizorovicz A, Turpie AG, Cohen AT, et al.: Epidemiology of venous thromboembolism in Asian patients undergoing major orthopedic surgery without thromboprophylaxis. The SMART study. J Thromb Haemost 2005; 3: 28–34.
- e8. Oger E, Leroyer C, Le Moigne E, et al.: The value of a risk factor analysis in clinically suspected deep venous thrombosis. Respiration 1997; 64: 326–30.
- e9. Tosetto A, Frezzato M, Rodeghiero F: Prevalence and risk factors of non-fatal venous thromboembolism in the active population of the VITA Project. J Thromb Haemost 2003; 1: 1724–9.
- e10. Blom JW, Doggen CJ, Osanto S, et al.: Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 2005; 293: 715–22.
- e11. Cook D, Crowther M, Meade M, et al.: Deep venous thrombosis in medical-surgical critically ill patients: prevalence, incidence, and risk factors. Crit Care Med 2005; 33: 1565–71.
- e12. Lidegaard O, Edstrom B, Kreiner S: Oral contraceptives and venous thromboembolism: a five year national case-control study. Contraception 2002; 65: 187–96.
- e13. Lindahl TL, Lundahl TH, Nilsson L, et al.: APC-resistance is a risk factor for postoperative thromboembolism in elective replacement of the hip or knee—a prospective study. Thromb Haemost 1999; 81: 18–21.
- e14. Lowe GD, Haverkate F, Thompson SG, et al.: Prediction of deep vein thrombosis after elective hip replacement surgery by preoperative clinical and haemostatic variables: the ECAT DVT Study. European Concerted Action on Thrombosis. Thromb Haemost 1999; 81: 879–86.
- e15. Wahlander K, Larson G, Lindahl TL, et al.: Factor V Leiden (G1691A) and prothrombin gene G20210A mutations as potential risk factors for venous thromboembolism after total hip or total knee replacement surgery. Thromb Haemost 2002; 87: 580–5.
- e16. Aznar J, Vaya A, Estelles A, et al.: Risk of venous thrombosis in carriers of the prothrombin G20210A variant and factor V Leiden and their interaction with oral contraceptives. Haematologica 2000; 85: 1271–6.
- e17. Espana F, Vaya A, Mira Y, et al.: Low level of circulating activated protein C is a risk factor for venous thromboembolism. Thromb Haemost 2001; 86: 1368–73.
- e18. Irani-Hakime N, Tamim H, Elias G, et al.: Factor V R506Q mutation-Leiden: an independent risk factor for venous thrombosis but not coronary artery disease. J Thromb Thrombolysis 2001; 11: 111–6.
- e19. Leroyer C, Mercier B, Oger E, et al.: Prevalence of 20210 A allele of the prothrombin gene in venous thromboembolism patients. Thromb Haemost 1998; 80: 49–51.
- e20. Ridker PM, Hennekens CH, Miletich JP: G20210A mutation in prothrombin gene and risk of myocardial infarction, stroke, and venous thrombosis in a large cohort of US men. Circulation 1999; 99: 999–1004.
- e21. Simioni P, Sanson BJ, Prandoni P, et al.: Incidence of venous thromboembolism in families with inherited thrombophilia. Thromb Haemost 1999; 81: 198–202.
- e22. Blom JW, Osanto S, Rosendaal FR: High risk of venous thrombosis in patients with pancreatic cancer: A cohort study of 202 patients. Eur J Cancer 2006; 42: 410–4.
- e23. Grady D, Wenger NK, Herrington D, et al.: Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. Ann Intern Med 2000; 132: 689–96.
- e24. Heit JA, Mohr DN, Silverstein MD, et al.: Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med 2000; 160: 761–8.
- e25. Pottier P, Planchon B, Pistorius MA, et al.: [Risk factors for venous thromboembolism in hospitalized patients in internal medicine: case-control study of 150 patients]. Rev Med Interne 2002; 23: 910–8.
- e26. Zakai NA, Wright J, Cushman M: Risk factors for venous thrombosis in medical inpatients: validation of a thrombosis risk score. J Thromb Haemost 2004; 2: 2156–61.
- e27. Kakkar AK, Haas S, Wolf H, et al.: Evaluation of perioperative fatal pulmonary embolism and death in cancer surgical patients: the MC-4 cancer substudy. Thromb Haemost 2005; 94: 867–71.
- e28. Kikura M, Takada T, Sato S: Preexisting morbidity as an independent risk factor for perioperative acute thromboembolism syndrome. Arch Surg 2005; 140: 1210–8.
- e29. Cogo A, Bernardi E, Prandoni P, et al.: Acquired risk factors for deep-vein thrombosis in symptomatic outpatients. Arch Intern Med 1994; 154: 164–8.
- e30. Heit JA, Silverstein MD, Mohr DN, et al.: The epidemiology of venous thromboembolism in the community. Thromb Haemost 2001; 86: 452–63.
- e31. Geerts WH, Code KI, Jay RM, et al.: A prospective study of venous thromboembolism after major trauma. N Engl J Med 1994; 331: 1601–6.
- e32. Shackford SR, Davis JW, Hollingsworth-Fridlund P, et al.: Venous thromboembolism in patients with major trauma. Am J Surg 1990; 159: 365–9.
- e33. White RH, Gettner S, Newman JM, et al.: Predictors of rehospitalization for symptomatic venous thromboembolism after total hip arthroplasty. N Engl J Med 2000; 343: 1758–64.
- e34. White RH, Zhou H, Gage BF: Effect of age on the incidence of venous thromboembolism after major surgery. J Thromb Haemost 2004; 2: 1327–33.
- e35. Wille-Jorgensen P, Ott P: Predicting failure of low-dose prophylactic heparin in general surgical procedures. Surg Gynecol Obstet 1990; 171: 126–30.
- e36. Gangireddy C, Rectenwald JR, Upchurch GR, et al.: Risk factors and clinical impact of postoperative symptomatic venous thromboembolism. J Vasc Surg 2007; 45: 335–42.

- e37. Howell MD, Geraci JM, Knowlton AA: Congestive heart failure and outpatient risk of venous thromboembolism: a retrospective, case-control study. *J Clin Epidemiol* 2001; 54: 810–6.
- e38. Samama MM: An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. *Arch Intern Med* 2000; 160: 3415–20.
- e39. Abdollahi M, Cushman M, Rosendaal FR: Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. *Thromb Haemost* 2003; 89: 493–8.
- e40. Stein PD, Beemath A, Olson RE: Obesity as a risk factor in venous thromboembolism. *Am J Med* 2005; 118: 978–80.
- e41. Carmody BJ, Sugerman HJ, Kellum JM, et al.: Pulmonary embolism complicating bariatric surgery: detailed analysis of a single institution's 24-year experience. *J Am Coll Surg* 2006; 203: 831–7.
- e42. Mantilla CB, Horlocker TT, Schroeder DR, et al.: Risk factors for clinically relevant pulmonary embolism and deep venous thrombosis in patients undergoing primary hip or knee arthroplasty. *Anesthesiology* 2003; 99: 552–60.
- e43. Rocha AT, de Vasconcellos AG, da Luz Neto ER, et al.: Risk of venous thromboembolism and efficacy of thromboprophylaxis in hospitalized obese medical patients and in obese patients undergoing bariatric surgery. *Obes Surg* 2006; 16: 1645–55.
- e44. Farmer RD, Lawrenson RA, Todd JC, et al.: A comparison of the risks of venous thromboembolic disease in association with different combined oral contraceptives. *Br J Clin Pharmacol* 2000; 49: 580–90.
- e45. Goldhaber SZ, Grodstein F, Stampfer MJ, et al.: A prospective study of risk factors for pulmonary embolism in women. *JAMA* 1997; 277: 642–5.
- e46. Hansson PO, Eriksson H, Welin L, et al.: Smoking and abdominal obesity: risk factors for venous thromboembolism among middle-aged men: "the study of men born in 1913". *Arch Intern Med* 1999; 159: 1886–90.
- e47. Jick H, Derby LE, Myers MW, et al.: Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. *Lancet* 1996; 348: 981–3.
- e48. Sidney S, Petitti DB, Soff GA, et al.: Venous thromboembolic disease in users of low-estrogen combined estrogen-progestin oral contraceptives. *Contraception* 2004; 70: 3–10.
- e49. Douketis JD, Julian JA, Kearon C, et al.: Does the type of hormone replacement therapy influence the risk of deep vein thrombosis? A prospective case-control study. *J Thromb Haemost* 2005; 3: 943–8.
- e50. Cushman M, Kuller LH, Prentice R, et al.: Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004; 292: 1573–80.
- e51. Grodstein F, Stampfer MJ, Goldhaber SZ, et al.: Prospective study of exogenous hormones and risk of pulmonary embolism in women. *Lancet* 1996; 348: 983–7.
- e52. Hoibraaten E, Qvigstad E, Arnesen H, et al.: Increased risk of recurrent venous thromboembolism during hormone replacement therapy--results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). *Thromb Haemost* 2000; 84: 961–7.
- e53. Heit JA, Kobbervig CE, James AH, et al.: Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Ann Intern Med* 2005; 143: 697–706.
- e54. Daneshmandi HL, Seddighzadeh A, Piazza G, et al.: Deep vein thrombosis in patients with chronic kidney disease. *Thromb Haemost* 2008; 99: 1035–9.
- e55. Kayali F, Najjar R, Aswad F, et al.: Venous thromboembolism in patients hospitalized with nephrotic syndrome. *Am J Med* 2008; 12: 226–30.
- e56. Mahmoodi BK, ten Kate MK, Waanders F, et al.: High absolute risks and predictors of venous and arterial thromboembolic events in patients with nephrotic syndrome: results from a large retrospective cohort study. *Circulation* 2008; 117: 224–30.
- e57. Danilenko-Dixon DR, Heit JA, Silverstein MD, et al.: Risk factors for deep vein thrombosis and pulmonary embolism during pregnancy or post partum: a population-based, case-control study. *Am J Obstet Gynecol* 2001; 184: 104–10.
- e58. Schippering G, Wirnsberger GH, Obernosterer A, et al.: Thromboembolic complications after arthroscopic knee surgery. Incidence and risk factors in 101 patients. *Acta Orthop Scand* 1998; 69: 144–6.
- e59. Sue-Ling HM, Johnston D, McMahon MJ, et al.: Pre-operative identification of patients at high risk of deep venous thrombosis after elective major abdominal surgery. *Lancet* 1986: 1173–6.

eTABLE 1

Composition of the guideline group

Participating medical societies /organizations	Representatives/experts
Association of Scientific Medical Societies in Germany	Prof. Dr. A. Encke Prof. Dr. S. Haas Prof. Dr. I. Kopp
German Dermatology Society (DDG, Deutsche Dermatologische Gesellschaft)	Prof. Dr. E. Rabe
German Society of Plastic, Reconstructive and Aesthetic Surgeons (DGPRÄC Deutsche Gesellschaft der Plastischen, Rekonstruktiven und Ästhetischen Chirurgen)	Prof. Dr. U. Kneser
German College of General Practitioners and Family Physicians (DEGAM, Deutsche Gesellschaft für Allgemein- und Familienmedizin)	Prof. Dr. H.-H. Abholz
German Society of General and Visceral Surgery (DGAV, Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie)	Prof. Dr. P. Kujath
German Society of Anaesthesiology and Intensive Care Medicine (DGAI, Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin)	Prof. Dr. W. Gogarten
German Society of Angiology (DGA, Deutsche Gesellschaft für Angiologie)	Prof. Dr. S. Schellong
German Society of Surgery (DGCH, Deutsche Gesellschaft für Chirurgie)	Dr. C. M. Krüger
German Society of Vascular Surgery (DGG, Deutsche Gesellschaft für Gefäßchirurgie)	Prof. Dr. T. Schmitz-Rixen, Dr. H. Weber
German Society of Obstetrics and Gynecology (DGGG, Deutsche Gesellschaft für Gynäkologie und Geburtshilfe)	Prof. Dr. E. Solomayer
German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Halschirurgie)	Prof. Dr. F. Bootz
German Society of Hematology and Oncology (DGHO, Deutsche Gesellschaft für Hämatologie und Onkologie)	Prof. Dr. H. Riess
German Society of Internal Medicine (DGIM, Deutsche Gesellschaft für Innere Medizin)	Prof. Dr. V. Hach-Wunderle
German Society of Cardiology (DGK, Deutsche Gesellschaft für Kardiologie)	Prof. Dr. C. Bode
German Society of Pediatrics and Adolescent Medicine (DGKJ, Deutsche Gesellschaft für Kinder- und Jugendmedizin)	Prof. Dr. U. Nowak-Göttl
German Society of Pediatric Surgery (DGKCH, Deutsche Gesellschaft für Kinderchirurgie)	Prof. Dr. U. Rolle
German Society for Oral and Maxillofacial Surgery (DGMKG, Deutsche Gesellschaft für Mund-, Kiefer- und Gesichtschirurgie)	Dr. T. von Haussen
German Society of Neurosurgery (DGNC, Deutsche Gesellschaft für Neurochirurgie)	Prof. Dr. K. Schwerdtfeger
German Society of Neurology (DGN, Deutsche Gesellschaft für Neurologie)	Prof. Dr. H. C. Diener
German Society for Orthopedics and Orthopedic Surgery (DGOOC, Deutsche Gesellschaft für Orthopädie und Orthopädische Chirurgie)	Prof. Dr. R. Krauspe Dr. R. Pauschert
German Society of Phlebology (DGP, Deutsche Gesellschaft für Phlebologie)	Dr. H. Gerlach
German Society for Physical Medicine and Rehabilitation (Deutsche Gesellschaft für Physikalische Medizin und Rehabilitation)	PD Dr. M. Weigl
German Society for Thoracic and Cardiovascular Surgery (DGTHG, Deutsche Gesellschaft für Thorax-, Herz- und Gefäßchirurgie)	Prof. Dr. F.-C. Rieß
German Society for Thoracic Surgery (DGT, Deutsche Gesellschaft für Thoraxchirurgie)	Prof. Dr. L. Swoboda Dr. S. Eggeling
German Trauma Society (DGU, Deutsche Gesellschaft für Unfallchirurgie)	Prof. Dr. C. Waydhas Prof. Dr. K. Stürmer
German Society of Urology (DGU, Deutsche Gesellschaft für Urologie)	PD Dr. C. Protzel
German Interdisciplinary Association of Intensive Care and Emergency Medicine (DIVI, Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin)	Prof. Dr. E. Muhl
Union of Specialists Professional Associations (GFB, Gemeinschaft Fachärztlicher Berufsverbände)	Prof. Dr. J. Kussmann
Society of Thrombosis and Hemostasis Research (GTH, Gesellschaft für Thrombose- und Hämostaseforschung)	Prof. Dr. M. Spannagl
Legal advice	Attorney Prof. Dr. Dr. K. Ulsenheimer
Methodologists (Literature search and evaluation, quality indicators)	Dr. M. Eikermann Dipl. Ges. Ök. T. Mathes Dr. M. Nothacker MPH
External review (Drug Commission of the German Medical Association, AkdÄ)	Prof. Dr. A. Greinacher

eTABLE 2

Systematic literature search on VTE prophylaxis in MEDLINE (via PubMed), as of 9 January 2008*

Search strategy in PubMed	Hits
"thrombosis/prevention and control"[MeSH] AND (Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) NOT ("retinal vein occlusion"[MeSH] OR "portal vein"[MeSH]) AND "humans"[MeSH Terms]	1571
("venous thrombosis/etiology"[MeSH] OR "venous thrombosis/epidemiology"[MeSH]) AND ("cohort studies"[MeSH] OR "case-control studies"[MeSH]) AND ("relative risk"[TW] OR "odds ratio"[TW] OR "hazard ratio"[TW] OR "RR"[TW] OR "OR"[TW] OR "HR"[TW]) NOT ("retinal vein occlusion"[MeSH] OR "portal vein"[MeSH]) AND "humans"[MeSH Terms]	1759

* 91 hits in the intersection of the two searches.
VTE, venous thromboembolism

eTABLE 3

Systematic literature search on VTE prophylaxis; search period: 1 January 2008 to 7 August 2013

Datenbank	Search strategy
MEDLINE	("Venous Thrombosis"[MeSH] OR (("Embolism and Thrombosis" [MeSH] OR embol*[tiab] OR thrombo*[tiab]) AND (vein*[tiab] OR venou*[tiab] OR vte[tiab] OR Veins[mesh]))) AND (Randomized Controlled Trial [PTyp] OR Controlled Clinical Trial [PTyp] OR randomized [TiAb] OR randomised [TiAb] OR placebo [TiAb] OR clinical trials as topic [MeSH] OR randomly [TiAb] OR trial [TiAb] OR controlled [TiAb] NOT (animals [MeSH] NOT humans [MeSH])) OR ("Meta-Analysis" [PTyp] OR "Meta-Analysis as Topic" [Mesh] OR meta analy* [TiAb] OR metaanaly* [TiAb] OR systematic review* [TiAb] OR systematic literature review* [TiAb] OR systematic overview* [TiAb] OR "Review Literature as Topic" [Mesh] OR pubmed [TiAb] OR medline [TiAb] OR cochrane [TiAb] OR embase [TiAb] OR psychlit [TiAb] OR psyclit [TiAb] OR psychinfo [TiAb] OR psycinfo [TiAb] OR cinahl [TiAb] OR science citation index [TiAb] OR cancerlit [TiAb] OR reference list* [TiAb] OR bibliograph* [TiAb] OR hand-search* [TiAb] OR relevant journals [TiAb] OR manual search* [TiAb] OR (selection criteria [TiAb] OR inclusion criteria [TiAb] OR data extraction [TiAb]) AND review [PTyp]) NOT ("Comment" [PTyp] OR "Letter" [PTyp] OR "Editorial" [PTyp])) AND ("2008/01/01"[Date – Publication] : "3000"[Date – Publication])
Embase	'vein thrombosis'/exp/mj OR ('thromboembolism'/exp/mj OR embol*:ab,ti OR thrombo*:ab,ti AND (vein*:ab,ti OR venou*:ab,ti OR vte:ab,ti)) AND ('randomized controlled trial'/exp/mj OR 'controlled clinical trial'/exp/mj OR randomised:ab,ti OR randomised:ab,ti OR placebo:ab,ti OR randomly:ab,ti OR controlled:ab,ti OR trial:ab,ti OR 'meta analysis'/exp/mj OR 'systematic review'/exp/mj OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR (systematic NEAR/1 (review* OR overview*)):ab,ti OR 'systematic literature review':ab,ti OR pubmed:ab OR medline:ab OR cancerlit:ab OR cochrane:ab OR embase:ab OR psychlit:ab OR psyclit:ab OR psychinfo:ab OR psycinfo:ab OR cinahl:ab OR cinahl:ab OR 'science citation index':ab OR 'reference lists':ab OR bibliograph*:ab OR (hand NEXT/1 search*):ab OR (manual NEXT/1 search*):ab OR 'relevant journals':ab OR ('data extraction':ab OR 'selection criteria':ab OR 'inclusion criteria':ab AND review:it)) AND ('article'/it OR 'article in press'/it OR 'review'/it) AND [embase]/lim AND [2008–2014]/py

VTE, venous thromboembolism

eTABLE 4

Grading of evidence and recommendation strength

Study quality	Quality of the evidence	Grade of recommendation	Description	Symbol
Systematic review, with or without meta-analysis or RCT (treatment benefit), validating cohort studies (test quality of diagnostic procedures) of high quality	High	"we recommend"	Strong recommendation	↑↑
RCT or cohort studies of limited quality	Moderate	"we suggest"	Recommendation	↑
RCT or cohort studies of poor quality, all other study designs	Low/very low	"may"	Open recommendation	↔

RCT, randomized controlled trial

eTABLE 5

Dispositional risk factors, in order of relative significance

Risk factor	Relative significance	Studies on patients with conservative treatment	Studies on patients treated with surgical treatment	Studies on general population
Previous DVT/PE	High	(e2–e4)	(e5–e7)	(e8, e9)
Hereditary thrombophilic defects ^{*2}	Type-specific low to high	(e10–e12)	(e9, e13–e15)	(e9, e12, e16–e21, e31)
Malignant disease ^{*3}	Moderate to high ^{*1}	(e3, e10, e22–e26)	(e6, e27, e28)	(e8, e23, e29, e30)
Advanced age (over 60 years, risk increases with age)	Moderate ^{*1}	(e2–e4, e24)	(e14, e28, e31–35)	(e8, e29, e30)
VTE in first-degree relative	Moderate	Can be helpful with regard to the identification of hereditary thrombophilic defects.		
Chronic heart failure, status post myocardial infarction ^{*3}	Moderate ^{*1}	(e3, e4, e23, e24)	(e7, e28, e36)	(e7, e23, e29, e30, e37, e38)
Overweight (BMI >30 kg/m ²)	Moderate ^{*1}	(e12, e39, e40)	(e5, e14, e40–e43)	(e9, e39, e44–e48)
Acute infections/inflammatory diseases with immobilization ^{*3}	Moderate ^{*1}	(e2)	(e36)	–
Treatment with or inhibition of sexual hormones (for contraception, postmenopausal, for cancer treatment)	Substance-specific low to high	(e12, e39)	(e49)	(e9, e12, e39, e47–e52)
Pregnancy and postpartum period	Low	(e25)	–	(e38, e53)
Nephrotic syndrome	Low	(e54–e56)	(e54)	–
Severe varicosis	Low	(e4, e25, e57)	(e7, e28, e58, e59)	(e8, e30)

^{*1} For these associations, continuous risk–effect relationships were demonstrated.

^{*2} e.g. antiphospholipid syndrome; antithrombin III, protein C and protein S deficiency; APC resistance/factor V Leiden mutation; thrombophilic prothrombin polymorphism

^{*3} These dispositional risk factors can also occur/be regarded as expositional risk factors.

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; BMI, body mass index

eFIGURE

**Search in MEDLINE (via PubMed) and Embase; publication period: 1 January 2008 to 7 August 2013
Hits (deduplicated): n = 3506**

Inclusion criteria:

1) Patients:	Risk of VTE due to disease or intervention (primary prophylaxis)
2) Intervention/control:	approved preventive treatment
3) Study type:	RCT (at least Phase III, no sub-group analysis)
4) Endpoints:	VTE, DVT, PE, hemorrhage or mortality as the primary endpoint
5) Language:	German or English

Update search for pertinent randomized controlled trials

VTE, venous thromboembolism; RCT, randomized controlled trial; DVT, deep vein thrombosis;

PE, pulmonary embolism