Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2014-09-01-D-126 Apixaban

Stand: 9. Januar 2014

Gemeinsamer Bundesausschuss

Recherche und Synopse der Evidenz zur Bestimmung der zVT:

Inhalt

Indikation für die Recherche für Apixaban

Tiefe Venenthrombose (TVT) und Lungenembolie (LE) sowie Prophylaxe rezidivierender TVT und LE

Berücksichtigte Wirkstoffe/Therapien

Für das Anwendungsgebiet zugelassenen Arzneimittel:

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Apixaban (2013-B-129) **Zur Behandlung akuter tiefer Venenthrombosen (TVT) und Lungenembolien (LE) / Prophylaxe rezidivierender TVT / LE**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Heparine - Niedermolekulare Heparine (NMH) - Unfraktionierte Heparine (UFH) Danaparoid Vitamin-K-Antagonisten - Phenprocoumon - Warfarin Fondaparinux Rivaroxaban
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*nicht angezeigt*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• Festbetragsgruppenbildung UFH, Stufe 1 • Festbetragsgruppenbildung NMH: „Heparine, niedermolekular“, Stufe 2 • Phenprocoumon, Warfarin: FB-Gruppe „Antikoagulantien, orale“; Stufe 2
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Apixaban B01AF02 Eliquis®	Behandlung von tiefen Venenthrombosen (TVT) und Lungenembolien (LE) / Prophylaxe von rezidivierenden TVT und LE bei Erwachsenen.
NMH, z.B.:	
Enoxaparin B01AB05 Clexane®	*Clexane 40 mg, Clexane 40 mg Duo, Clexane 40 mg Klinik, Clexane 40 mg Praxis:* Therapie tiefer Venenthrombosen mit und ohne Lungenembolie. Peri- und postoperative Primärprophylaxe tiefer Venenthrombosen bei Patienten mit hohem thromboembolischen Risiko (z. B. orthopädische Chirurgie).
UFH, z.B:	
Heparin-Natrium B01AB01 z.B. Heparin-Natrium Braun	- im Rahmen der Behandlung von venösen und arteriellen thromboembolischen Erkrankungen (einschließlich der Frühbehandlung des Herzinfarktes sowie der instabilen Angina pectoris) - zur Antikoagulation bei Behandlung oder Operation mit extrakorporalem Kreislauf (z. B. Herz-Lungen-Maschine, Hämodialyse) - Prophylaxe von thromboembolischen Erkrankungen
Danaparoid B01AB09 Orgaran®	b) Behandlung von thromboembolischen Erkrankungen bei Patienten, die eine dringende parenterale Antikoagulation benötigen und entweder eine HIT haben oder in der Anamnese aufweisen.
Phenprocoumon Marcumar® B01AA04	Behandlung und Prophylaxe von Thrombose und Embolie. Langzeitbehandlung des Herzinfarktes, wenn ein erhöhtes Risiko für thromboembolische Komplikationen gegeben ist.

Phenprocoumon B01AA04 Phenpro.-ratiopharm®	Langzeitbehandlung und Vorbeugung – der Blutpfropf-Bildung (venöse und arterielleThrombosen) – des Verschlusses von Blutgefäßen durch Blutpfropf (venöse und arterielle Embolien).
Warfarin-Natrium B01AA03 Coumadin®	Prophylaxe und Therapie thromboembolischer Erkrankungen
Fondaparinux B01AX05 Arixtra®	Zur Prophylaxe venöser thromboembolischer Ereignisse (VTE) bei Erwachsenen, die sich größeren orthopädischen Eingriffen an den unteren Extremitäten unterziehen müssen, wie beispielsweise Hüftfrakturen, größere Knie- oder Hüftersatzoperationen. Zur Prophylaxe venöser thromboembolischer Ereignisse (VTE) bei Erwachsenen, die sich abdominalen Eingriffen unterziehen müssen und voraussichtlich einem hohen Risiko thromboembolischer Komplikationen ausgesetzt sind, wie beispielsweise Patienten, die sich einer abdominalen Krebsoperation unterziehen müssen (siehe Abschnitt 5.1). Zur Prophylaxe venöser thromboembolischer Ereignisse (VTE) bei erwachsenen internistischen Patienten mit einem erhöhten Risiko für VTE und bei Immobilisation wegen einer akuten Erkrankung, wie bspw. Herzinsuffizienz und/oder akuter Atemwegserkrankung und/oder akuter infektiöser beziehungsweise entzündlicher Erkrankung.
Rivaroxaban B01AX06 Xarelto®	Behandlung von tiefen Venenthrombosen (TVT) und Lungenembolien (LE) sowie Prophylaxe von rezidivierenden TVT und LE bei Erwachsenen.

Quellen: AMIS-Datenbank, Fachinformationen

Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation „**Tiefe Venenthrombose (TVT) und Lungenembolie (LE) sowie Prophylaxe rezidivierender TVT und LE** “ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am **09.01.2014** abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, GIN, NGC, TRIP, DAHTA, NIHR HSC. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab **693** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden **64** Quellen eingeschlossen. Insgesamt ergab dies **27** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen:

ASCO	American Society of Clinical Oncology
CTEPH	chronic thromboembolic pulmonary hypertension
DVT	Deep venous thrombosis
ESC	European Society of Cardiology
FE	Fixed Effect Modell
GoR	Grade of Recommendations
HSC	Horizon Scanning Center
ICSI	Institute for Clinical Systems Improvement
IDA	InterDisziplinärer Abgleich
INR	International Normalized Ratio
KI	Konfidenzintervall
LMWH	Low molecular weight heparin
LoE	Level of Evidence
MQIC	Medical Quality Improvement Consortium
NIHR	National Institute for Health Research
NOAC	Novel oral anticoagulant (Thrombin Inhibitoren und Xa Inhibitoren)
OR	Odds Ratio
PE	Pulmonary embolism
SIGN	Scottish Intercollegiate Guidelines Network
RR	Relatives Risiko
UFH	unfractionated heparin
UMHS	University of Michigan Health System
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism

Cochrane Reviews

Akl et al. (2011): Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer.	Systematische Literaturrecherche nach RCTs **Population:** Krebspatienten mit objektiv bestätigter VTE oder LE **Vergleich:** low molecular weight heparin (LMWH), unfractionated heparin (UFH) und Fondaparinux **Endpunkte:** Mortalität nach 3 Monaten Follow-up, rezidivierende VTE, majore und minore Blutungen **Ergebnisse** (basierend auf 16 Studien mit N= 1371 Patienten): 13 Studien zum Vergleich LMWH versus UFH 2 Studien zum Vergleich Fondaparinux versus Heparin **(Enoxaparin und UFH)** 1 Studie zum Vergleich Dalteparin versus Tinzaparin **LMWH versus UFH:** Mortalität In der Meta-analysis von 11 Studien zeigte sich eine statistisch signifikante Reduktion in Bezug auf die Mortalität nach 3 Monaten: RR= 0.71; 95%KI 0.52-0.98. Nach Ausschluss von Studien minderer Qualität blieb das Ergebnis ähnlich: RR= 0.72; 95%KI 0.52-1.00). Rezidivierende VTE In den drei zu diesem Endpunkt verfügbaren Studien zum Vergleich LMWH versus UFH zeigte sich keine statistisch signifikante Reduktion in der Rekurrenz von VTE: RR= 0.78; 95%KI 0.29- 2.08). Die Studienqualität war hier insgesamt schlecht (imprecision und hohes Potential für Publikationsbias). **Heparin versus Fondaparinux:** Hier zeigten sich keine statistisch signifikanten Unterschiede in Bezug auf Mortalität (RR= 1.27; 95%KI 0.88-1.84), rezidivierende VTE (RR= 0.95; 95%KI 0.57-1.60), majore Blutungen (RR= 0.79; 95%KI 0.39-1.63) oder minore Blutungen (RR= 1.50; 95%KI 0.87-o 2.59). **Dalteparin versus Tinzaparin** In der einen verfügbaren Studie ergab sich kein statistisch signifikanter Unterschied in Bezug auf die Mortalität (RR=0.86; 95% KI 0.43-1.73). **Schlussfolgerung der Autoren:** LMWH is possibly superior to UFH in the initial treatment of VTE in patients with cancer. Additional trials focusing on patient important outcomes will further inform the questions addressed in this review.
Akl et al. (2011): Anticoagulation for the long-term treatment of venous	Systematische Literaturrecherche nach RCTs **Population**: Krebspatienten mit objektiv bestätigter VTE oder LE **Vergleich**: low molecular weight heparin (LMWH), Vitamin K

thromboembolism in patients with cancer.	Antagonisten (VKA) und Ximelagatran **Endpunkte**: Mortalität nach 3 Monaten Follow-up, rezidivierende VTE oder PE, majore und minore Blutungen, Thrombozytopenie, Postphlebitisches Syndrom **Ergebnisse** (basierend auf 9 Studien mit N= 1908 Patienten): **LMWH versus VKA** (n=7 RCT) In der Meta-analyse ergaben sich keine statistisch signifikanten Überlebensvorteile Hazard Ratio (HR)= 0.96; 95%KI 0.81-1.14) aber eine statistisch signifikante Reduktion von VTE (HR= 0.47; 95%KI 0.32-0.71). Die Ergebnisse zu majoren Blutungen (RR= 1.05; 95%KI 0.53-2.10) oder Thrombozytopenie (RR= 1.02; 95% KI 0.60-1.74) waren nicht statistisch signifikant. Dabei ist die Qualität der Evidenz für die Endpunkte Mortalität sowie minore und majore Blutungen als schlecht (low), und für rezidivierende VTE als moderat einzustufen. **Ximelagatran** (24 mg zweimal täglich) **versus Placebo** (n=1 RCT) Hier wurde eine Reduktion von VTEs festgestellt (HR= 0.16; 95%KI 0.09-0.30), aber es gab keine signifikanten Ergebnisse hinsichtlich Mortalität und Blutungen. **Dabigatran versus VKA** (n=1 RCT) Hier gab es keine signifikanten Unterschiede. **Schlussfolgerung der Autoren:** For the long-term treatment of VTE in patients with cancer, LMWH compared to VKA reduces venous thromboembolic events but not death. The decision for a patient with cancer and VTE to start long-term LMWH versus oral anticoagulation should balance the benefits and downsides and integrate the patient's values and preferences for the important outcomes and alternative management strategies.
Andras et al. (2012): Vitamin K antagonists or low-molecular-weight heparin for the long term treatment of symptomatic venous Thromboembolism.	Systematische Literaturrecherche nach RCTs **Population**: Patienten mit objektiv bestätigter VTE oder LE **Vergleich**: low molecular weight heparin (LMWH) versus Vitamin K Antagonisten (VKA) **Endpunkte**: Mortalität in den ersten 3 Monaten nach Therapiezuweisung, rezidivierende VTE oder LE, majore Blutungen **Ergebnisse** (basierend auf 15 Studien mit N= 3197 Patienten): **LMWH versus VKA** Für den Endpunkt Mortalität ergaben sich keine statistisch signifikanten Unterschiede (OR=1.06, 95% KI 0.74 - 1.54). Es ergab sich eine statistisch nicht signifikante Reduktion des Risikos einer rezidivierenden VTE (OR=0.82, 95%KI 0.59- 1.13). Dies blieb gleich für die Analyse der Studien der Kategorie I (hohe methodische Qualität): OR= 0.80, 95%KI 0.54-1.18. Für alle Studien ergab sich ein signifikanter Vorteil für LMWH in

	Bezug auf den Endpunkt majore Blutungen (OR= 0.50, 95%KI 0.31-0.79), der für die Studien der Kategorie I nicht mehr signifikant war (OR= 0.62, 95%KI 0.36 - 1.07). **Schlussfolgerung der Autoren:** LMWHs are possibly as effective as vitamin K antagonists in preventing symptomatic VTE after an episode of symptomatic deep venous thrombosis, but are much more expensive. Treatment with LMWH is significantly safer than treatment with vitamin K antagonists. LMWH may result in fewer episodes of bleeding and is possibly a safe alternative in some patients, especially those in geographically inaccessible areas, are reluctant to visit the thrombosis service regularly, or with contraindications to vitamin K antagonists. However, treatment with vitamin K antagonists remains the treatment of choice for the majority of patients.
Dong et al. (2009): Thrombolytic therapy for pulmonary embolism.	Systematische Literaturrecherche nach RCTs **Population**: Patienten mit akuter LE **Vergleich**: Thrombolytische Therapie (Streptokinase, Urokinase, gewebespezifische Plasminogenaktivator (rt-PA) oder Alteplase) versus Heparin (allein oder mit Placebo) **Endpunkte**: Mortalität, rezidivierende LE, minore und majore Blutungen **Ergebnisse** (basierend auf 8 Studien mit N= 679 Patienten): **Thrombolyse versus Heparin oder Heparin plus Placebo** Für den Endpunkte Mortalität (OR=0.89; 95%KI 0.45-1.78)als auch für rezidivierende LE (OR=0.63; 95%KI 0.33-1.20) ergaben sich keine signifikanten Ergebnisse. Auch für die Endpunkte minore und majore Blutungen ergaben sich keine signifikanten Effekte (majore: OR= 1.61; 95%KI 0.91 - 2.86; minore: OR= 1.98; 95%KI 0.68-5.75) **Schlussfolgerung der Autoren:** Based on the limited evidence found we cannot conclude whether thrombolytic therapy is better than heparin for pulmonary embolism. More double-blind RCTs, with subgroup analysis of patients presenting with haemodynamically stable acute pulmonary embolism compared to those patients with a haemodynamic unstable condition, are required.
Vardi et al. (2009): Subcutaneous unfractionated heparin for the initial treatment of venous thromboembolism.	Systematische Literaturrecherche nach RCTs **Population**: Patienten mit akuter VTE **Vergleich**: subkutanes UFH versus subkutanes LMWH oder intravenöses UFH **Endpunkte**: rezidivierende TVT oder LE während 3 Monaten Follow-up, Auftreten einer LE während der Behandlung, majore Blutungen während der Behandlung und während 3 Monaten Follow-up

	Ergebnisse (basierend auf 15 Studien mit N= 3054 Patienten): **Subkutanes UFH versus subkutanes LMWH oder intravenöses UFH** Für die Endpunkte rezidivierende TVT sowie LE nach 3 Monaten Follow-up ergaben sich keine statistisch signifikanten Ergebnisse (OR=1.68; 95%KI 0.92-3.04 und 1.18.; 95%KI 0.54-2.56). Gleiches gilt für die Endpunkte LE unter Heparinbehandlung (OR= 1.10, 95%KI 0.46- 2.62), Blutungen unter Heparinbehandlung (OR=1.07, 95%KI 0.64-1.79) und Blutungen während 3 Monaten Follow-up (OR=0.66, 95%KI 0.33 - 1.32). Hinsichtlich des Auftretens von Todesfällen (Blutungs-assoziiert oder insgesamt)unter der Behandlung oder während des dreimonatigen Follow-ups gab es ebenfalls keine Unterschiede zwischen den Studienarmen (keine Risikodifferenz). **Schlussfolgerung der Autoren:** Subcutaneous unfractionated heparin for the treatment of venous thromboembolism cannot be considered non-inferior to other treatment modalities in terms of recurrent DVT and PE at three months, but seems as safe and effective with regards to rates of major bleeding and death.

Systematische Reviews

Fox et al. (2012): Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: direct and adjusted indirect meta-analysis of randomized controlled trials.	Systematischer Review mit Metaanalyse und indirektem Vergleich anhand von RCTs **Population**: Patienten mit akuter, symptomatischer VTE, LE oder beidem **Vergleich**: NOAC mit oder ohne initialer Heparingabe versus Vitamin K Antagonisten mit initialer Heparingabe **Endpunkte**: rezidivierende VTE, majore Blutungen, Gesamtmortalität **Ergebnisse** (basierend auf 9 Studien mit N= 16.701 Patienten, bzw. 16.611 für Blutungen): ***Rezidivierende VTE*** Hier ergaben sich keine signifikanten Unterschiede zwischen den Behandlungsarmen. Rivaroxaban vs. VKA (n=4 Studien): RR=0,85; 95%KI 0,55-1,31 Dabigatran vs. VKA (n=2 Studien): RR=1,09; 95%KI 0,76-1,57 Ximelagatran vs. VKA (n=2 Studien): RR=1,06; 95%KI 0,62-1,80 Apixaban vs. VKA (n=1 Studie): RR=0,98; 95%KI 0,20-4,79 ***Majore Blutungen*** Für diesen Endpunkt ergab sich lediglich ein signifikanter Vorteil für Rivaroxaban vs. VKA (RR=0,57; 95%KI 0,39-0,84), alle anderen Vergleiche ergaben nicht signifikante Effektschätzer (Dabigatran vs VKA: RR=0,76; 95%KI 0,49-1,18; Ximegalatran vs. VKA: RR=0,54; 95%KI 0,28-1,03; Apixaban vs VKA: RR=2,95; 95%KI 0,12-71,82). ***Gesamtüberleben*** Hier ergaben sich für keinen Vergleich signifikante Unterschiede.

Abb.: Relative risk for major bleeding with novel anticoagulants *v* traditional treatment with vitamin K antagonists

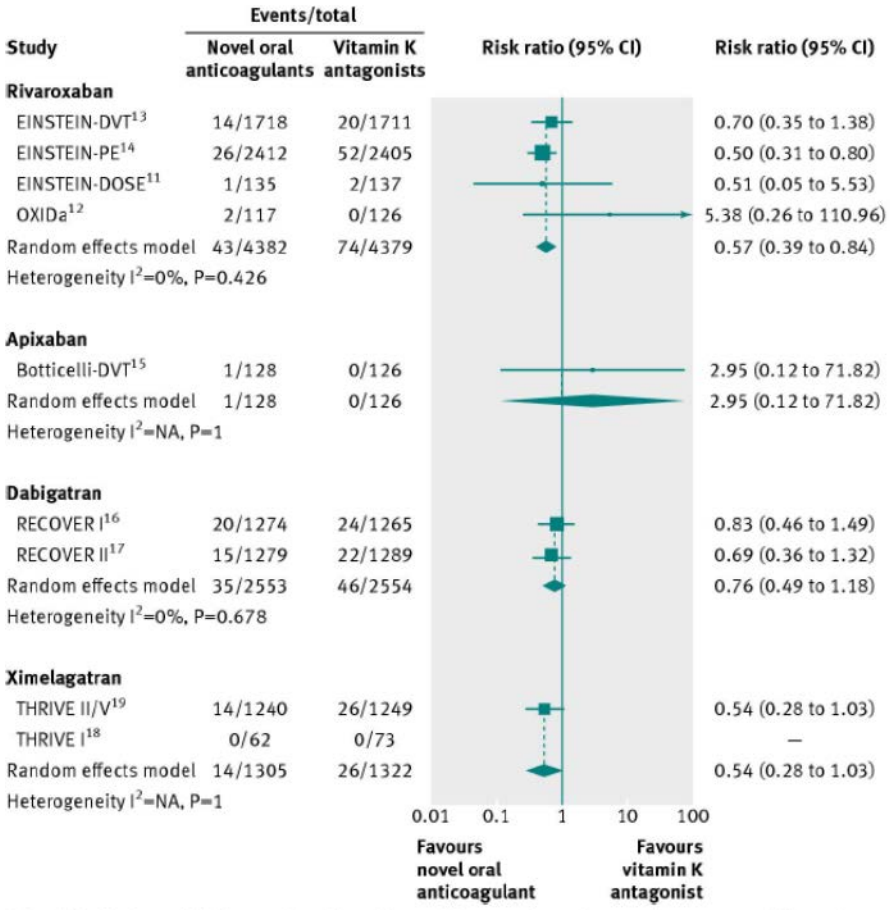
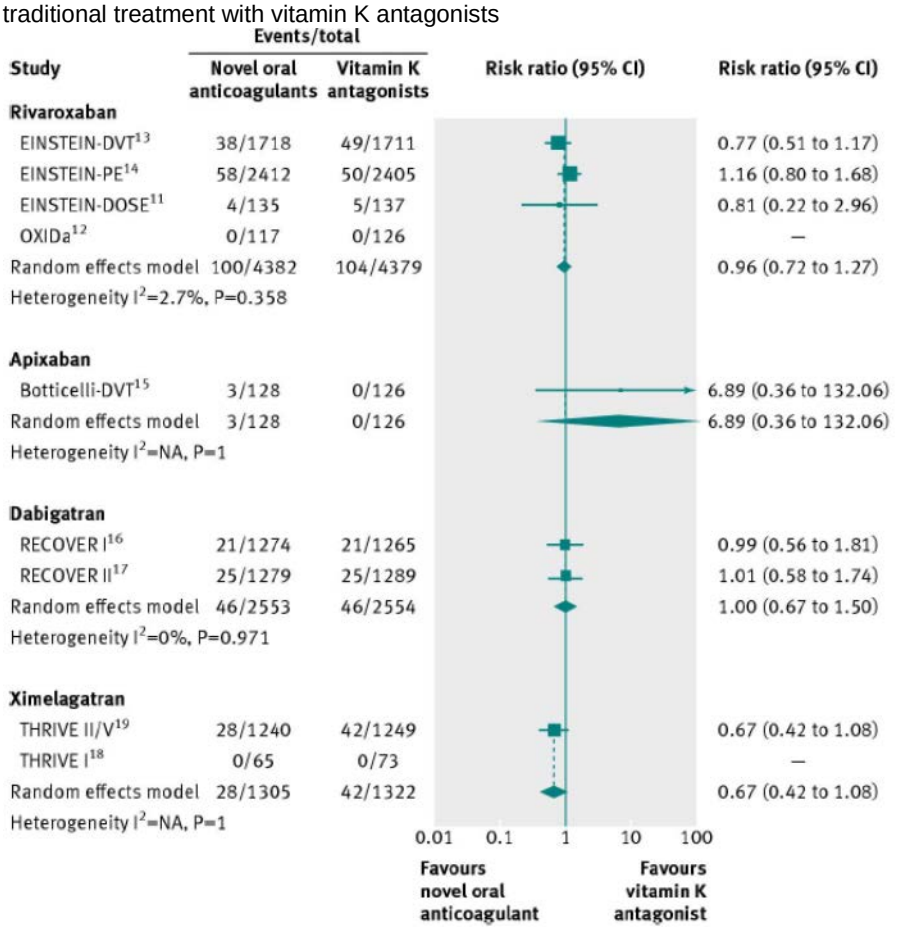


	Abb.: Relative risk for all cause mortality with novel anticoagulants *v* traditional treatment with vitamin K antagonists  Im adjustierten indirekten Vergleich von Rivaroxaban versus Dabigatran ergab sich kein signifikanter Vorteil für einen der beiden Wirkstoffe hinsichtlich rezidivierender VTE (RR=0,78; 95%KI 0,49-1,24) oder majoren Blutungen (RR=0,75; 95%KI 0,41-1,34)
Bochenek (2012): The treatment of venous thromboembolism with low-molecular-weight heparins.	Systematischer Review mit Metaanalyse **Population**: Patienten unter Behandlung mit LMWH oder VKA aufgrund einer VTE **Vergleich**: LMWH versus Vitamin K Antagonisten **Endpunkte**: TVT, VTE oder LE unter Behandlung, minore und majore Blutungen, Thrombozytopenie, Knochenbrüche, osteoporotische Komplikationen, Tod **Ergebnisse** (basierend auf 17 klinischen Studien mit N= 3.083 Patienten) ***TVT unter Behandlung bzw. bis Ende des Follow-up*** (n=14 Studien, 3.010 Patienten) Behandlung: LMWH versus VKA: OR=0,51 (95%KI 0,36-0,73) im FE-Modell, I^2=0% Follow-up: LMWH versus VKA: OR=0,67 (95%KI 0,50-0,89) im FE-Modell, I^2=21%

	VTE unter Behandlung bzw. bis Ende des Follow-up (n=13 Studien, 2.908 Patienten) Behandlung: LMWH versus VKA: OR=0,62 (95%KI 0,46-0,83) im FE-Modell, I^2=20% Follow-up: LMWH versus VKA: OR=0,75 (95%KI 0,59-0,97) im FE-Modell, I^2=43% ***Blutungen (majore oder minore) unter Behandlung bzw. bis Ende des Follow-up*** (n=11 Studien, 2.520 Patienten) Behandlung: LMWH versus VKA: OR=0,56 (95%KI 0,43-0,71) im FE-Modell, I^2=0% Follow-up: LMWH versus VKA: OR=0,59 (95%KI 0,47-0,74) im FE-Modell, I^2=36% Darüber hinaus wurden Subgruppenanalysen durchgeführt für Krebspatienten und nicht-Krebspatienten. TVT unter Behandlung bzw. bis Ende des Follow-up Krebspatienten (n=5 Studien, 1.014 Patienten): Behandlung: OR=0,40 (95%KI 0,24-0,67) im FE-Modell, I^2=0% Follow up: OR=0,44 (95%KI 0,27-0,72) im FE-Modell, I^2=0% Nicht-Krebspatienten (n=3 Studien, 744 Patienten): Behandlung: OR=0,55 (95%KI 0,21-1,46) im FE-Modell, I^2=29% Follow-up: OR= 0,86 (95%KI 0,46-1,59) im FE-Modell, I^2=0% VTE unter Behandlung bzw. bis Ende des Follow-up Krebspatienten (n=5 Studien, 1.014 Patienten): Behandlung: OR=0,47 (95%KI 0,31-0,71) im FE-Modell, I^2=0% Follow up: OR=0,46 (95%KI 0,31-0,69) im FE-Modell, I^2=0% Nicht-Krebspatienten (n=3 Studien, 744 Patienten): Behandlung: OR=1,06 (95%KI 0,51-2,20) im FE-Modell, I^2=13% Follow-up: OR= 1,20 (95%KI 0,70-2,05) im FE-Modell, I^2=0%
Castellucci La et al. (2013): Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-	To summarise and compare the efficacy and safety of various oral anticoagulants (dabigatran, rivaroxaban, apixaban, and vitamin K antagonists) and antiplatelet agents (acetylsalicylic acid) for the secondary prevention of venous thromboembolism. Randomisierte (prospektive) Studien **Suchzeitraum**: Bis 2013 **Population:** consecutive patients with objectively confirmed, symptomatic. deep vein thrombosis or pulmonary embolism treated for a minimum of three months with anticoagulant

analysis.	treatment (excluded: asymptomatic VTE) **Intervention:** antiplatelet drug (ASA), an oral anticoagulant drug (VKA, rivaroxaban, apixaban, dabigatran, or ximelagatran) **Vergleich:** placebo or observation **Eingeschlossene Publikationen / Patienten**: 12 (n= 11999) **Outcomes:** Primär: recurrent VTE and major bleeding episodes Sekundär: fatal recurrent VTE and fatal bleeding episodes **Ergebnis:**

Table 2| **Summary of network meta-analysis of recurrent VTE and major bleeding episodes**

Intervention	Risk of recurrent VTE (odds ratio (95% CrI))	No of events of recurrent VTE per 100 patients treated each year (absolute risk difference (95% CrI))	Risk of major bleeding (odds ratio (95% CrI))	No of major bleeding episode per 100 patients treated each year (absolute risk difference (95% CrI))
Standard adjusted dose VKA	0.07 (0.03 to 0.15)	8.8 fewer (8 fewer to 9.3 fewer)	5.24 (1.78 to 18.25)	1.3 more (0.2 more to 5 more)
ASA 100 mg daily*	0.65 (0.39 to 1.03)	3.1 fewer (5.5 fewer to 0.2 more)	1.29 (0.4 to 4.08)	0.1 more (0.2 fewer to 1 more)
Dabigatran 150 mg twice daily	0.09 (0.04 to 0.21)	8.6 fewer (7.3 fewer to 9.2 fewer)	2.79 (0.79 to 11.69)	0.6 more (0.1 fewer to 3.2 more)
Apixaban 5 mg twice daily	0.18 (0.08 to 0.38)	7.7 fewer (5.6 fewer to 8.7 fewer)	0.19 (0.01 to 1.78)	0.26 fewer (0.32 fewer to 0.2 more)
Apixaban 2.5 mg twice daily	0.17 (0.08 to 0.36)	7.8 fewer (5.8 fewer to 8.8 fewer)	0.46 (0.05 to 2.82)	0.2 fewer (0.3 fewer to 0.6 more)
Rivaroxaban 20 mg daily	0.17 (0.06 to 0.41)	7.8 fewer (5.3 fewer to 8.9 fewer)	20.79 (1.31 to 14 230)†	5.7 more (0.1 more to 62.1 more)
Low intensity VKA	0.28 (0.13 to 0.57)	6.6 fewer (3.8 fewer to 8.2 fewer)	4.77 (1.38 to 19.49)	1.2 more (0.11 more to 5.4 more)

Data are based on comparisons of each intervention with placebo or observation. CrI=credible interval.

*Estimates are derived from random effects, Bayesian network meta-analysis, which treats between study variance as an informative prior (log normal distribution). Estimates differ from those reported in frequentist direct meta-analysis in ASPIRE and web appendix 5 (both reported significant differences in favour of ASA) because between study variance is treated as a constant in frequentist analyses. Web appendix 6 reports detailed estimates for the ASA versus placebo comparison.

†Only one study investigated rivaroxaban for major bleeding and contained a zero cell (0 of 590 people receiving placebo and four of 598 receiving rivaroxaban), which resulted in uncertain estimates of effect.

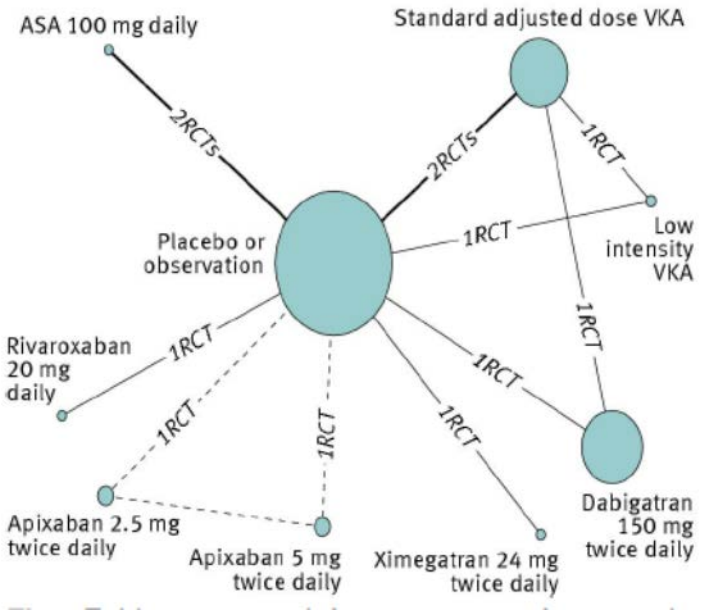


Fig 1 Evidence network for recurrence of venous thromboembolism. The width of lines for each connection in the evidence network are proportional to the number of randomised controlled trials (RCTs) comparing each pair of treatments. The size of each treatment node is proportional to the number of randomised participants (sample size). Dotted line=three arm RCT in the evidence network. The analysis includes ximelagatran to improve precision of effect estimates; however, the results are not reported because ximelagatran is not commercially available

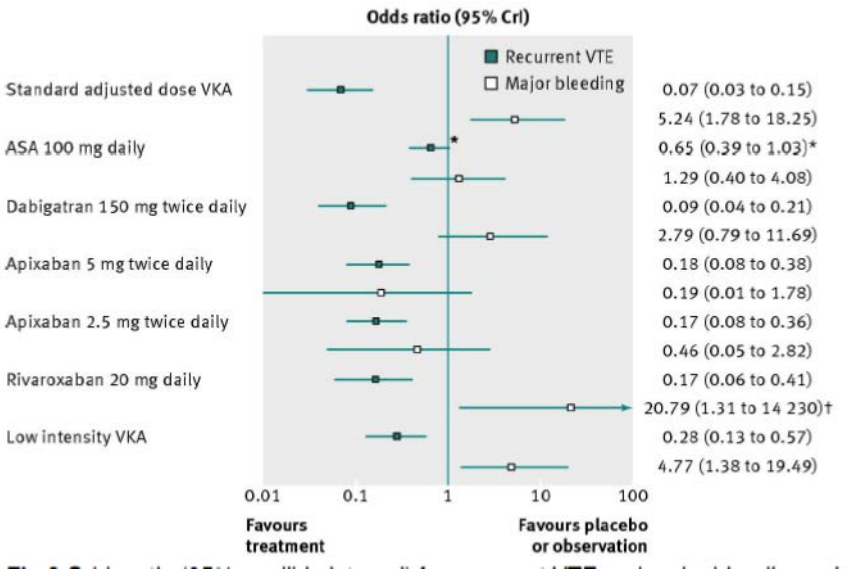
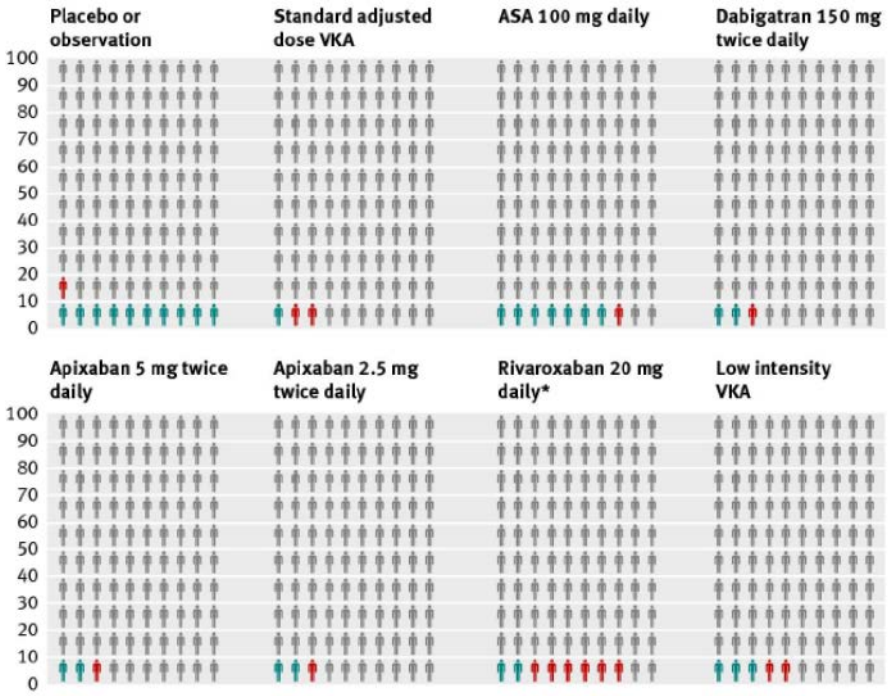


Fig 2 Odds ratio (95% credible interval) for recurrent VTE and major bleeding episodes in Bayesian network meta-analysis versus placebo or observation. CrI=credible interval. *Estimates are derived from random effects, Bayesian network meta-analysis, which treats between study variance as an informative prior (log normal distribution). Estimates differ from those reported in frequentist direct meta-analysis in ASPIRE and web appendix 5 (both reported significant differences in favour of ASA) because between study variance is treated as a constant in

	frequentist analyses. Web appendix 6 reports detailed estimates for the ASA versus placebo comparison. †Only one study investigated rivaroxaban for major bleeding and contained a zero cell (0 of 590 people receiving placebo and four of 598 receiving rivaroxaban), which resulted in uncertain estimates of effect  **Fig 4** Icon array showing absolute risks of recurrent VTE (blue) and major bleeding episodes (red). *Only one study investigated rivaroxaban for major bleeding and contained a zero cell (0 of 590 people receiving placebo and four of 598 receiving rivaroxaban), which resulted in uncertain estimates of effect **Schlussfolgerungen der Autoren:** All treatments reduced the risk of recurrent venous thromboembolism. Compared with placebo or observation, vitamin K antagonists at a standard adjusted dose (target international normalised ratio 2.0-3.0) showed the highest risk difference (odds ratio 0.07; 95% credible interval 0.03 to 0.15) and acetylsalicylic acid showed the lowest risk difference (0.65; 0.39 to 1.03). Risk of major bleeding was higher with a standard adjusted dose of vitamin K antagonists (5.24; 1.78 to 18.25) than with placebo or observation. Fatal recurrent venous thromboembolism and fatal bleeding were rare. Detailed subgroup and individual patient level data were not available.
Hull RD, Townshend G (2013): Long-term treatment of deep-vein thrombosis with low-molecular	Narratives Review … to review updated evidence-based knowledge on long-term treatment of DVT with LMWH or VKA, in all patients and also separately in those with cancer. In addition to the traditional outcomes of recurrent VTE and bleeding, we will also consider post-thrombotic syndrome (PTS) and patient treatment satisfaction.

weight heparin: An update of the evidence	comparing prospective, randomised treatment of DVT using long-term (≥ 3 months) treatment with LMWH versus VKA, in broad populations or limited to cancer patients, as follows: all trials identified in an earlier systematic review search (5) formed the basis of our selection (including trials that did not report outcomes relevant to PTS) **Suchzeitraum** bis 07/2012 **Population**: patients with cancer and DVT **Intervention**: low-molecular-weight heparin (LMWH) **Vergleich**: vitamin K antagonists (VKAs) **Outcomes**: recurrent venous thromboembolism (VTE) **Ergebnisse:** Charakteristika der eingeschlossenen Studien:

Table 1: Trials of LMWH versus VKA for the long-term treatment of VTE in a broad spectrum of patients (6–16).

Study	Intervention[a]	Comparator[b]	Duration of therapy (months)	Recurrent VTE (%)		Bleeding complicati	
				%	p-value	%	p-value
Pini et al. 1994 (6)	Enoxaparin 4000 U od (n=93)[c]	Warfarin (n=94)	3	LMWH 6.5 VKA 4.3	NS	LMWH 4.3 VKA 12.8	0.04
Das et al. 1996 (7)	Dalteparin 5000 U od (n=50)	Warfarin (n=55)	3	LMWH 10.0 VKA 3.6	NS	LMWH 0 VKA 9.1	0.06
Lopaciuk et al. 1999 (8)	Nadroparin 85 IU/kg bd for 10 days, then od (n=101)	Acenocoumarol (n=101)	≥3	LMWH 2.0 VKA 6.9	NS	LMWH 4.0 VKA 6.9	NS
Gónzalez-Fajardo et al. 1999 (9)	Enoxaparin 4000 U bd for 7 days, then od (n=85)	Coumarin (n=80)	3	LMWH 9.5 VKA 23.7	<0.05	LMWH 1.1 VKA 10.0	<0.05
Veiga et al. 2000 (10)[d]	Enoxaparin 4000 U od (n=50)	Acenocoumarol (n=50)	3–6	LMWH 4.0 VKA 2.0	NS	LMWH 2.0 VKA 12.0	NS
López-Beret et al. 2001 (11)	Nadroparin 0.1 ml/10 kg bd (n=81)[e]	Acenocoumarol (n=77)	3–6	LMWH 2.5 VKA 9.1	NS	LMWH 0[f] VKA 5.2[f]	NS
Kakkar et al. 2003 (12)	Bemiparin 115 U/kg od for 10 days then 3500 U od (n=94; Group C)	Acute-phase UFH then VKA (n=98; Group A) or acute-phase bemi-parin then VKA (n=105; Group B)	3	LMWH 2.9 VKA 3.6 (Group A) VKA 0.8 (Group B)	NS	LMWH 2.1 VKA 1.9 (Group B) VKA 2.0 (Group C)	NS
Daskalopoulos et al. 2005 (13)	Tinzaparin 175 IU/kg od (n=50)	Acenocoumarol (n=52)	6	LMWH 4.0 VKA 5.8	NS	LMWH 10.0 VKA 13.5	NS
Hull et al. 2007 (14)	Tinzaparin 175 IU/kg od (n=369)	Warfarin (n=368)	3	LMWH 8.9[g] VKA 9.8[g]	NS	LMWH 13.0 VKA 19.8	0.011
Hull et al. 2009 (15)	Tinzaparin 175 IU/kg od (n=240)	Warfarin (n=240)	3	LMWH 3.3 VKA 3.3	NS	LMWH 9.2 VKA 9.2	NS
Romera et al. 2009 (16)	Tinzaparin 175 IU/kg od (n=119)	Acenocoumarol (n=122)	6	LMWH 4.2 VKA 5.7	NS	LMWH 0.8[h] VKA 2.5[h]	NS

All trials enrolled patients with DVT. Some trials included patients with pulmonary embolism in addition to DVT. Values show incidence at end of treatmen period unless stated otherwise. Values were taken from or calculated from data in the published reports (based on ITT populations). Definitions of bleedin complications differed between studies but values shown here include major and minor bleeds unless stated otherwise. [a] LMWH doses during the long-te phase were as follows: <50% of therapeutic dose: Pini et al. (6), Das et al. (7), Gónzalez-Fajardo et al. (9), Veiga et al. (10), Kakkar et al. (12);. >50% of the peutic dose: Lopaciuk et al. (8), López-Beret et al. (11); Therapeutic dose: Daskalopoulos et al. (13), Hull et al. 2007 (14), Hull et al. 2009 (15), Romera et al. [b] In each case, UFH or LMWH was used for initial therapy in the comparator arm, with oral anticoagulation starting on day 1 or later. [c] Initial therapy was UFH for 10 days. [d] Patients were aged >75 years. [e] Dosage reported as 10.25 anti-Xa IU/mL in syringe, given at 0.1 mL/10 kg bd and 0.1 mL/10 kg od if th continued after 3 months. [f] Major bleeds only; minor bleeding occurred in 4.9% of the LMWH group and 0% of the VKA group. [g] Values at 12-month follo At 3 months, rates were 4.9% (LMWH) and 5.7% (VKA) (NS). [h] Major bleeds only. bd, twice daily; DVT, deep-vein thrombosis; ITT, intention to treat; LMW molecular-weight heparin; NS, non-significant; od, once daily; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

	Schlussfolgerungen der Autoren: In the 11 trials in broad patient populations, LMWHs were as effective

	as VKAs in preventing recurrent venous thromboembolism (VTE), and there were no consistent differences in the incidence of bleeding complications during long-term treatment. In patients with cancer, VTE recurrence was significantly reduced with LMWH versus VKA in two studies, while major bleeding complications did not differ between groups in any of the four trials. **Hinweise der FBMed**: • Studienselektion nicht nachvollziehbar • Studienauswahl allein in PubMed • keine Bewertung der Publikationsqualität/ methodischer Studienqualität
McManus RJ et al. (2011): Thromboembolism.	Systematisches Review von systematischen Reviews mit RCTs und von RCTs Fragestellung: 1. What are the effects of treatments for proximal DVT? 2. What are the effects of treatments for pulmonary embolism? **Interventionen:** Siehe unten **Vergleiche:** nicht vorab spezifiziert (siehe unten) **Suchzeitraum**: 1966 bis 2010 **Outcomes** Mortality, rates of symptomatic recurrence, post-thrombotic syndrome, symptomatic pulmonary embolism, and adverse effects. Proxy outcomes include radiological evidence of clot extension or pulmonary embolism. For oral anticoagulation management: time spent in the target international normalised range. Evidenzkennzeichnung: • *High-quality evidence* Further research is very unlikely to change our confidence in the estimate of effect. • *Low-quality evidence* Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. • *Moderate-quality evidence* Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. • *Very low-quality evidence* Any estimate of effect is very uncertain. **Ergebnisse:** ***1. Deep venous thrombosis (DVT)*** ***Compression stockings*** • Rates of symptomatic recurrence *Compared with*

	placebo or no treatment Compression stockings are no more effective at reducing symptomatic recurrence of venous thromboembolism at 36 to 76 months (high-quality evidence). Post-thrombotic syndrome • *Compared with placebo or no treatment* Compression stockings are more effective at reducing post-thrombotic syndrome at 3 to 76 months (high-quality evidence). • *Different durations of stockings compared with each other* Prolonged treatment for around 4 years with compression stockings may reduce symptoms of post-thrombotic syndrome at 3 months and 1 year compared with no further treatment (low-quality evidence). • We found no clinically important results from RCTs about the effects of different types of compression stockings. ***Low molecular weight heparin (LMWH)*** Mortality *Compared with unfractionated heparin* Low molecular weight heparin (LMWH) is more effective at reducing mortality at 3 to 6 months (high-quality evidence). Rate of symptomatic recurrence *Compared with unfractionated heparin* LMWH is more effective at reducing both recurrence of pulmonary embolus and DVT (moderate-quality evidence). Adverse effects LMWH is associated with reduced risk of major haemorrhage compared with unfractionated heparin. ***Long-term oral anticoagulation*** Mortality Compared with low molecular weight heparin (LMWH) Long-term oral anticoagulation is as effective as long-term LMWH at reducing mortality at 3 months (moderate-quality evidence). Rate of symptomatic recurrence Oral anticoagulation plus heparin compared with acenocoumarol alone Acenocoumarol plus intravenous unfractionated heparin may be no more effective at reducing recurrence of thromboembolism (low-quality evidence). Compared with LMWH Long-term oral anticoagulation is as effective at reducing recurrence of thromboembolism at 3 to 12 months (low-quality evidence). We found no clinically important results from RCTs about the effects of oral anticoagulation compared with placebo in people with thromboembolism. ***Long-term oral anticoagulation*** Mortality *Compared with short-term anticoagulation* Long-term

	oral anticoagulation may be no more effective at reducing mortality (low-quality evidence). Rate of symptomatic recurrence *Compared with short-term anticoagulation* Long-term oral anticoagulation may be more effective during treatment but may be no more effective at preventing recurrent venous thromboembolism after treatment (low-quality evidence). Adverse effects Although the risk of recurrence drops over time, the risk of bleeding remains stable while anticoagulant treatment continues. ***Long-term low molecular weight heparin (LMWH)*** Mortality *Compared with long-term oral anticoagulation* Long-term low molecular weight heparin (LMWH) is as effective at reducing mortality at 3 months (high-quality evidence). Rate of symptomatic recurrence *Compared with long-term oral anticoagulation* Long-term LMWH is as effective at reducing recurrence of thromboembolism at 3 to 12 months (low-quality evidence). Adverse effects: major haemorrhage Long-term LMWH and long-term unfractionated heparin may be equally likely to cause major haemorrhage (very low-quality evidence). Mortality *Compared with unfractionated heparin* Low molecular weight heparin (LMWH) is as effective at reducing mortality at 3 months (moderate-quality evidence). Rate of symptomatic recurrence *Compared with unfractionated heparin* LMWH is as effective at reducing venous thromboembolism at 3 months (moderate-quality evidence). ***Vena cava filter*** *Mortality* *Compared with no filters* Vena cava filters are no more effective at reducing mortality at 8 years (moderate-quality evidence). Pulmonary embolism *Compared with no filters* Vena cava filters are more effective at preventing pulmonary embolism at 12 days, and at 8 years (low-quality evidence). Rate of symptomatic recurrence *Compared with no filters* Vena cava filters increase the risk of recurrent DVT at 8 years (moderate-quality evidence). ***2. Pulmonary embolism*** ***Heparin plus warfarin*** *Mortality*

	Compared with no anticoagulation Heparin plus warfarin is more effective at reducing mortality at 1 year (moderate quality evidence). *Adverse effects* Anticoagulants are associated with increased risk of haemorrhage. We found no direct information from RCTs about anticoagulation compared with no active treatment or about different anticoagulants compared with each other, in people with pulmonary embolism. As with DVT, clinical consensus based on observational studies is that treatment of pulmonary embolism with anticoagulation is effective. ***Prolonged anticoagulation (6–9 months)*** *Rate of symptomatic recurrence* Compared with shorter duration of anticoagulation Prolonged anticoagulation (6–9 months) may be no more effective at reducing recurrence of venous thromboembolism compared with shorter anticoagulation (3 months) in pulmonary embolism (moderate-quality evidence). *Adverse effects* Longer duration of anticoagulation has been associated with increased risk of haemorrhage. ***Low molecular weight heparin (LMWH) vs. unfractionated heparin*** Mortality *Compared with unfractionated heparin* Low molecular weight heparin (LMWH) is as effective at reducing mortality at 3 months (moderate-quality evidence). Rate of symptomatic recurrence *Compared with unfractionated heparin* LMWH is as effective at reducing venous thromboembolism at 3 months (moderate-quality evidence). ***Thrombolysis vs. Heparin*** Mortality *Compared with heparin* Thrombolysis is as effective at reducing mortality (high-quality evidence). Rate of symptomatic recurrence *Compared with heparin* Thrombolysis is as effective at reducing recurrence of thromboembolism (high-quality evidence). **high-intensity oral anticoagulation** We found no clinically important results from RCTs about the effects of high-intensity oral anticoagulation in people with pulmonary embolism. **Schlussfolgerung der Autoren:** • Oral anticoagulants are considered effective in people with proximal DVT compared with no treatment, although we found few trials.

	In people with proximal DVT or pulmonary embolism, long-term anticoagulation reduces the risk of recurrence, but high-intensity treatment has shown no benefit. Both approaches increase the risk of major bleeding. Low molecular weight heparin (LMWH) is more effective than unfractionated heparin, and may be as effective as oral anticoagulants, although all are associated with some adverse effects. We don't know how effective tapering off of oral anticoagulant agents is compared with stopping abruptly. We don't know whether once-daily LMWH is as effective as twice-daily administration at preventing recurrence. Home treatment may be more effective than hospital-based treatment at preventing recurrence, and equally effective in reducing mortality. Vena cava filters reduce the short-term rate of pulmonary embolism, but they may increase the long-term risk of recurrent DVT. Elastic compression stockings reduce the incidence of post-thrombotic syndrome after a DVT compared with placebo or no treatment. • In people with isolated calf DVT, anticoagulation with warfarin may reduce the risk of proximal extension, although prolonged treatment seems no more beneficial than short-term treatment. • Anticoagulation may reduce mortality compared with no anticoagulation in people with a pulmonary embolus, but it increases the risk of bleeding. We found few studies that evaluated treatments for pulmonary embolism. LMWH may be as effective and safe as unfractionated heparin. Thrombolysis seems as effective as heparin in treating people with major pulmonary embolism, but it is also associated with adverse effects. The use of computerised decision support may increase the time spent adequately anticoagulated, and reduce thromboembolic events or major haemorrhage, compared with manual dosage calculation.
Sardar P et al. (2013): Efficacy and Safety of New Oral Anticoagulants for Extended Treatment of Venous Thromboembolism: Systematic Review and Meta-Analyses of Randomized Controlled Trials.	A meta-analysis was performed to evaluate the efficacy and safety of new oral anticoagulants (NOACs) for extended treatment of VTE Einschluss: nur RCTs **Suchzeitraum:** 2001 – 02/ 2013 **Population**: venous thromboembolism (VTE); excluded trials of primary prevention in medically-ill patients **Intervention**: NOACs (apixaban, rivaroxaban and dabigatran); long term treatment **Kontrolle**: any comparators (placebo or warfarin)

Outcomes:
on recurrent venous thromboembolism/ death, and any of recurrent venous thromboembolism, death, major bleeding, major or clinically relevant bleeding, incidence of acute coronary syndrome(s),
duration of follow-up of atleast 6 months

Relevante Studien/ Patientenzahl: 4 (n= 4877**)**

Ergebnisse:

Table 1 Characteristics of Randomized Clinical Trials

Trial (Reference)	Trial Design	Intervention	Control	Mean age (years) NOAC/ Comparator	Men (%) NOAC/ Comparator	Unprovoked VTE (%) NOAC/ Comparator	Patient with cancer (%); NOAC/ Comparator	Follow up
AMPLIFY-EXT 2013 (9)	Double-blind randomized trials	Apixaban 2.5 mg twice daily (n = 840)	Placebo (n = 829)	56.6 ± 15.3/ 57.1 ± 15.2	58.0/56.5	93.2/91.1	1.8/2.2	12 months
	Double-blind randomized trials	Apixaban 5 mg twice daily (n = 813)		56.4 ± 15.6	57.7	90.7	1.1	
EINSTEIN-Ext. 2010 (10)	Double-blind randomized event-driven superiority trials	Rivaroxaban 20 mg daily (n = 602)	Placebo (n = 594)	58.2 ± 15.6/ 58.4 ± 16	58.8/57.1	73.1/74.2	4.7/4.4	6 or 12 months
RE-MEDY (2013) (11)	Double-blind randomized trials	Dabigatran 150 mg twice daily (n = 1430)	Warfarin (n = 1426)	55.4 ± 15.0/ 53.9 ± 15.3	60.9/61.1	77.5/77.5 #	4.2/4.1	6 to 36 months
RE-SONATE (2013) (11)	Double-blind randomized trials	Dabigatran 150 mg twice daily (n = 681)	Placebo (n = 662)	56.1 ± 15.5/ 55.5 ± 15.1	55.9/55.0	87.2/89.7 #	##	Up to 12 months

Causes of thrombophilia unknown

Active cancer was an exclusion criterion

AMPLIFY-EXT = Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy–Extended Treatment; NOAC = New oral anticoagulants; VTE = venous thromboembolism

Bewertung der Autoren: durchschnittlich gute Studienqualität

Table 3 Efficacy and safety of individual NOAC versus comparator (placebo/warfarin)

	Odds ratio (Confidence interval)		Odds ratio [Confidence interval]
Recurrent VTE or VTE-related death		**Major bleeding**	
Apixaban versus placebo	**0.18 [0.11, 0.28]**	Apixaban versus placebo	0.38 [0.08, 1.68]
Rivaroxaban versus placebo	**0.18 [0.08, 0.38]**	Rivaroxaban versus placebo	8.94 [0.48, 166.41]
Dabigatran versus placebo	**0.13 [0.06, 0.30]**	Dabigatran versus placebo	4.83 [0.23, 100.83]
Dabigatran versus comparator	0.34 [0.02, 7.39]	Dabigatran versus comparator	0.95 [0.13, 6.84]
All-cause mortality		**Major or clinically relevant bleeding**	
Apixaban versus placebo	0.39 [0.18, 0.86]	Apixaban versus placebo	1.43 [0.87, 2.34]
Rivaroxaban versus placebo	0.49 [0.04, 5.45]	Rivaroxaban versus placebo	**5.34 [2.35, 12.09]**
Dabigatran versus placebo	0.19 [0.01, 4.05]	Dabigatran versus placebo	**3.00 [1.54, 5.81]**
Dabigatran versus comparator	0.83 [0.44, 1.58]	Dabigatran versus comparator	1.22 [0.22, 6.76]
Mortality related to VTE		**Adverse events**	
Apixaban versus placebo	0.36 [0.11, 1.13]	Apixaban versus placebo	**0.81 [0.67, 0.97]**
Rivaroxaban versus placebo	0.99 [0.06, 15.81]	Rivaroxaban versus placebo	Not reported
Dabigatran versus placebo	Not estimable	Dabigatran versus placebo	1.06 [0.85, 1.31]
Dabigatran versus comparator	1.00 [0.06, 15.96]	Dabigatran versus comparator	1.06 [0.93, 1.20]
Acute coronary syndrome		**Adverse event leading to discontinuation of study drug**	
Apixaban versus placebo	Not estimable	Apixaban versus placebo	**0.43 [0.34, 0.56]**
Rivaroxaban versus placebo	3.97 [0.44, 35.59]	Rivaroxaban versus placebo	Not reported
Dabigatran versus placebo	0.96 [0.06, 15.43]	Dabigatran versus placebo	**0.56 [0.39, 0.81]**
Dabigatran versus comparator	**3.37 [1.07, 10.58]**	Dabigatran versus comparator	0.82 [0.40, 1.67]
ALT > 3x ULN + bilirubin > 2x ULN			
Apixaban versus placebo	0.17 [0.02, 1.60]		
Rivaroxaban versus placebo	Not estimable		
Dabigatran versus placebo	Not estimable		
Dabigatran versus comparator	2.00 [0.18, 22.03]		

ALT Alanine aminotransferase; *NOAC* new oral anticoagulant; *ULN* upper limit of normal; *VTE* venous thromboembolism

	Schlussfolgerungen der Autoren: NOACs are effective for the extended treatment of venous thromboembolism and may reduce the risk of all-cause mortality. Dabigatran and rivaroxaban may cause more major or clinically relevant bleeding. […] No trials have yet evaluated newer agents in comparison to aspirin. In practice, choice of preferred agents for extended treatment of venous thromboembolism should be individualized depending on risks of recurrence and bleeding. NOACs should be considered in patients with high risk of recurrence after unprovoked venous thromboembolism. Risk of bleeding with newer agents should also be kept in mind while prescribing these drugs, as there is no reliable reversal agent available. Apixaban might be a better choice among newer agents for patients with high risk of bleeding for extended treatment of venous thromboembolism. In view of recent disappointing results seen with extended thromboprophylaxis in 'medically-ill' patients, our results indicate that in many patients, the NOACs may provide effective secondary prevention / therapy of thromboprophylaxis.
van der Hulle T et al. (2013): Effectiveness and safety of novel oral anticoagulants compared with vitamin K-antagonists in the treatment of acute symptomatic venous thromboembolism - a systematic review and meta-analysis.	meta-analysis to determine the efficacy and safety profile of NOACs compared with VKA in patients with acute VTE Einschluss von Phase-III-Studien (RCTs) **Suchzeitraum**: bis Oktober 2013 **Population**: Acute venous thromboembolism (VTE); (population with either objectively diagnosed acute DVT, PE or both) **Intervention**: New direct oral anticoagulants (NOACs) • orally administered direct factor IIa inhibitor (including but not limited to dabigatran) • a direct factor Xa inhibitor (including but not limited to edoxaban, rivaroxaban and apixaban) **Vergleich**: VKA **Outcomes**: recurrent VTE, fatal pulmonary embolism (PE), overall mortality, major bleeding, and other bleeding complications [reporting outcomes after at least three months follow-up including the diagnosis of acute recurrent VTE based on predefined objective criteria in accordance with current international standards and the rate of both major and clinically relevant non-major bleeding events; adjudication of outcomes by an independent adjudication committee] **Studienanzahl / Patientenanzahl:** 5 (24 455)

Ergebnisse:

Studiencharakteristika:

Study Year Drug Class	Treatment duration in months	Patients n	Men n (%)	Mean age in years (range)	PE or PE and DVT n (%)	Isolated DVT n (%)	Unprovoked n (%)	Cancer n (%)	Previous VTE n (%)	TTR in VKA group %
Re-Cover 2009 Dabigatran DTI	6	2539	1484 (58)	55 (18-97)	786 (31)	1749 (69)	Not provided	121 (5)	649 (26)	60
Einstein-DVT 2010 Rivaroxaban FXa inhibitor	3/6/12*	3449	1960 (57)	56 (Not provided)	23 (1)	3405 (99)	2138 (62)	207 (6)	666 (19)	58
Einstein-PE 2012 Rivaroxaban FXa inhibitor	3/6/12*	4832	2556 (53)	58 (Not provided)	4832 (100)	0 (0)	3117 (65)	223 (5)	944 (20)	63
Amplify 2013 Apixaban FXa inhibitor	6	5395	3167 (59)	57 (not provided)	1836 (34)	3532 (65)	4845 (90)	143 (3)	872 (16)	61
Hokusai 2013 Edoxaban FXa inhibitor	3/6/12*	8240	4716 (57)	56 (Not provided)	3319 (40)	4921 (60)	5410 (66)	771 (9)	1520 (18)	64

Outcomes

Outcome	NOACs n % Range	VKA n % Range	Pooled absolute risk difference % (95% CI)	NNT with NOACs prevent 1 event (95% CI)
Recurrent VTE	241/12,151 2.0 1.6-2.4	273/12,153 2.2 1.8-3.0	-0.24 (-0.60 to 0.11)	417 (167 to -909)
Fatal PE	9/12,151 0.07 0.04-0.10	9/12,153 0.07 0.00-0.24	0.01 (-0.06 to 0.08)	10,000 (1667 to -1250)
Overall mortality	290/12,197 2.4 1.5-3.2	298/12,193 2.4 1.7-3.1	-0.10 (-0.47 to 0.28)	1,000 (213 to -357)
Major bleeding	131/12,197 1.1 0.6-1.6	211/12,193 1.7 1.2-2.2	-0.67 (-1.13 to -0.21)	149 (88 to 476)
Non-fatal bleeding at a critical site	28/12,179 0.23 0.08-0.32	77/12,193 0.63 0.18-1.08	-0.38 (-0.65 to -0.10)	263 (153 to 1000)
Clinically relevant non-major bleeding	806/12,179 6.6 3.9-9.5	1024/12,193 8.4 6.9-9.8	-1.77 (-3.40 to -0.15)	56 (29 to 667)
Non-fatal intracranial bleeding	11/12,179 0.09 0.00-0.12	31/12,193 0.25 0.00-0.42	-0.14 (-0.31 to 0.03)	714 (323 to -3,333)
Major gastrointestinal bleeding	28/8,079 0.35 0.17-0.71	43/8,071 0.53 0.23-0.67	-0.16 (-0.42 to 0.11)	625 (238 to 909)
Fatal bleeding	7/12,179 0.06 0.04-0.08	21/12,193 0.17 0.07-0.29	-0.09 (-0.17 to 0.00)	1,111 (588 to 0)

Note: NOACs: new direct oral anticoagulants; VKA: vitamin K-antagonists; NNT: number need to treat; CI: confidence interval; VTE: venous thromboembolism; PE: pulmonary embolism.

	• During anticoagulant treatment, recurrent VTE occurred in 241 of the 12,151 patients (2.0%) treated with NOACs and in 273 of the 12,153 patients (2.2%) treated with VKA. In accordance with the results of the individual studies, the combined relative risk for recurrent VTE did not demonstrate a significant difference between both drugs classes: 0.88 (95% CI 0.74-1.05). • All combined relative risks were significantly lower for the patients treated with NOACs, except that for major gastrointestinal bleeding. **Schlussfolgerung der Autoren**: For all the evaluated efficacy outcomes, the pooled relative risks were comparable between patients treated with NOACs and patients treated with VKA. In contrast, statistically significant lower risks were observed for all evaluated bleeding complications during treatment with NOACs compared with VKA, except for the risk for major gastrointestinal bleeding. This is likely caused by a lack of power, since the Hokusai trial did not report major gastrointestinal bleeding separately and therefore could not be included in this specific analysis. We asked for this information by the manufacturer in vain. all the evaluated efficacy outcomes, the pooled relative risks were comparable between patients treated with NOACs and patients treated with VKA. In contrast, statistically significant lower risks were observed for all evaluated bleeding complications during treatment with NOACs compared with VKA, except for the risk for major gastrointestinal bleeding. This is likely caused by a lack of power, since the Hokusai trial did not report major gastrointestinal bleeding separately and therefore could not be included in this specific analysis. We asked for this information by the manufacturer in vain.

Leitlinien

UMHS (2009): Venous Thromboembolism (VTE).	University of Michigan Health System Initiate treatment immediately. Patients without contraindications to heparin should begin full-dose heparinization at once [IA*]. If PE is clinically likely, initiation should not await testing; if only DVT is suspected and testing will be prompt, initiation may await testing. Therapeutic levels of anticoagulation should be achieved as quickly as possible. Warfarin should be initiated on day 1 of treatment, after heparin loading is complete. **Treatment:** **Heparin** Low molecular weight heparin (LMWH) preferred. LMWH is preferred over unfractionated heparin (UFH) for both safety and cost reasons [IA]. Outpatient use of LMWH for DVT. LMWH is appropriate for most patients with DVT to use at home. [IIA] Some require initial brief hospital admission and stabilization; clinically stable (afebrile, normotensive, without tachycardia or tachypnea) patients who are not at elevated risk due to comorbidities can manage DVT entirely in the outpatient setting using LMWH. **Unfractionated heparin.** If UFH is used, it should be initiated and dosed in a structured manner (see Apendix A; dargestellt als Abb. 2) to achieve therapeutic levels quickly, without excessive adjustment of dosing [IIA]. Minimum time period. Heparin (LMWH or UFH) must be continued until INR is > 2.0, but always for at least five days to minimize the risk of extension of thrombosis or occurrence or recurrence of embolism [IB]. If heparin contraindicated. Patients who are not candidates for heparin anticoagulation due to risk of major bleeding or to drug sensitivity (heparin-induced thrombocytopenia, or HIT) may be candidates for one of the new non-heparin anticoagulant agents (e.g., lepirudin, argatroban). [IIB] Those who cannot use any anticoagulant should have an inferior vena cava filter placed to prevent pulmonary embolization [IIB]. **Warfarin**. Patients should begin warfarin on day 1 of heparin therapy after heparin loading is complete, and INRs must be > 2.0 before discontinuation of heparin [IA,B]. Start warfarin at the anticipated therapeutic dose [IC]; loading doses are no longer considered appropriate. [IIC] If warfarin contraindicated. Patients who can receive heparin but cannot take warfarin (e.g., during pregnancy) may be anticoagulated with full-dose subcutaneous heparin [IA], preferably LMWH. **Strength of recommendation:** I= generally should be performed; II = may be reasonable to perform; III = generally should not be performed. **Levels of evidence** for the most significant recommendations

	A = randomized controlled trials; B=controlled trials, no randomization; C=observational trials; D=opinion of expert panel.
Farge et al. (2013): International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer.	**Initial treatment of established VTE** **Recommendations.** 1. LMWH is recommended for the initial treatment of established VTE in cancer patients [Grade IB]. Values and preferences: LMWHs are easier to use than UFH. 2. Fondaparinux and UFH can be also used for the initial treatment of established VTE in cancer patients [Grade 2D]. Values and preferences: fondaparinux is easier to use than UFH. 3. Thrombolysis in cancer patients with established VTE may only be considered on a case-by-case basis, with specific attention paid to contraindications, especially bleeding risk (brain metastasis) [Best clinical practice, based on evidence of very low quality and the high bleeding risk of thrombolytic therapy]. Values and preferences: an expert opinion is recommended before using thrombolytics. 4. In the initial treatment of VTE, vena cava filters may be considered in the case of contraindication for anticoagulation or in the case of PE recurrence under optimal anticoagulation. Periodic reassessment of contraindications for anticoagulation is recommended and anticoagulation should be resumed when safe. Vena cava filters are not recommended for primary VTE prophylaxis in cancer patients. [Best clinical practice, based on evidence of very low quality and an unknown balance between desirable and undesirable effects]. **Early maintenance and long-term treatment of established VTE** **Recommendations.** 1. LMWHs are preferred over VKA for the early maintenance treatment (10 days to 3 months) and long-term treatment (beyond 3 months) of VTE in cancer patients [Grade 1A]. Values and preferences: daily subcutaneous injection may represent a burden for patients. 2. Idraparinux is not recommended for the early maintenance treatment (10 days to 3 months) and the long-term treatment (beyond 3 months) of VTE in cancer patients; idraparinux is currently not available on the market [Grade 2C]. Values and preferences: idraparinux once weekly is easier to use than UFH or LMWH. 3. LMWH should be used for a minimum of 3 months to treat established VTE in cancer patients; however, patients were treated for 6 months in the largest study in this setting [Grade 1A]. Values and preferences: daily subcutaneous injection may represent a burden for patients. 4. After 3—6 months, termination or continuation of anticoagulation (LMWH or VKA) should be based on individual evaluation of the benefit-risk ratio, tolerability, patients' preference and cancer activity [Best clinical practice, in the absence of data]. **Treatment of VTE recurrence in cancer patients under anticoagulation** **Recommendation.** In the event of VTE recurrence, three options can be considered: (i) switch from VKA to LMWH in patients treated with VKA; (ii) increase in LMWH dose in patients treated with LMWH, and (iii) vena cava filter insertion [Best clinical practice, based on evidence of very low quality and an unknown balance between desirable and undesirable effects].

	Values and preferences: individual decision. **New oral anticoagulant agents (NOAC)** The experts of the working group acknowledge the potential benefit of new oral anticoagulant agents for the treatment of VTE in cancer patients. However, the group considered it was premature to issue recommendations or guidance on the use of these new agents in this setting in view of the absence of specific data, and considering that none of these products had yet been approved for use for VTE treatment at the time this document was prepared and none of the experts had enough clinical experience with their use to give any meaningful 'best practice advice'. ---------- High (A) Further research is very unlikely to change our confidence in the estimate of effect Moderate (B) Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate Low (C) Further research is very unlikely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate Very low (D) Any estimate of effect is very uncertain Strong (Grade I) The panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects Weak Grade 2 The panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but is not confident. Best clinical practice In the absence of any clear scientific evidence and because of undetermined balance between desirable and undesirable effects, judgment was based on the professional experience and consensus of the international experts within the working group.
Fesmire et al. (2011): Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Suspected Pulmonary Embolism.	**What are the indications for thrombolytic therapy in patients with PE?** **Patient Management Recommendations** <u>Level A recommendations.</u> None specified. <u>Level B recommendations.</u> Administer thrombolytic therapy in hemodynamically unstable patients with confirmed PE for whom the benefits of treatment outweigh the risks of life-threatening bleeding complications. (In centers with the apability for surgical or mechanical thrombectomy, procedural intervention may be used as an alternative therapy.) <u>Level C recommendations.</u> (1) Consider thrombolytic therapy in hemodynamically unstable patients with a high clinical suspicion for PE for whom the diagnosis of PE cannot be confirmed in a timely manner. (2) At this time, there is insufficient evidence to make any recommendations regarding use of thrombolytics in any subgroup of hemodynamically stable patients. Thrombolytics have been

	demonstrated to result in faster improvements in right ventricular function and pulmonary perfusion, but these benefits have not translated to improvements in mortality. Level A recommendations. Generally accepted principles for patient management that reflect a high degree of clinical certainty (i.e., based on strength of evidence Class 1 or overwhelming evidence from strength of evidence Class II studies that directly address all of the issues). Level B recommendations. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on strength of evidence Class II studies that directly address the issue, decision analysis that directly addresses the issue, or strong consensus of strength of evidence Class III studies). Level C recommendations. Other strategies for patient management that are based on Class III studies, or in the absence of any adequate published literature, based on panel consensus.
ICSI (2013): Venous Thromboembolism Diagnosis and Treatment.	Institute for Clinical Systems Improvement (USA) **Recommendations:** ***Initiate Anticoagulation*** • Clinicians should initially treat pulmonary embolism (PE) with unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) or fondaparinux (Bates, 2012 [Guideline]; Kearon, 2012 [Guideline]). • Clinicians should initially treat most patients diagnosed with deep vein thrombosis (DVT) with LMWH or fondaparinux (Bates, 2012 [Guideline]; Kearon, 2012 [Guideline]). • Clinicians may consider rivaroxaban for the initial treatment of both PE and DVT without additional anticoagulation (Büller, 2012 [Moderate Quality Evidence]; Bauersachs, 2010 [Low Quality Evidence]). UFH, LMWH or fondaparinux are preferred for the initial treatment of patients with PE or DVT. LMWH and fondaparinux are as safe and as effective as continuous UFH. Suitable patients can be safely treated with LMWH and fondaparinux in the outpatient setting. Rivaroxaban has also recently received FDA approval for the initial treatment of both PE and DVT; however, its role in clinical practice has yet to be determined. It is an oral agent which facilitates management without hospitalization in selected patients. Heparin/fondaparinux should be continued for at least five days after the initiation of warfarin therapy and until International Normalized Ratio (INR) is > 2.0 for two consecutive days. **Anm FBMed zur Evidenz bzgl. Fondaparinux:** Kearon 2012: *Fondaparinux Compared With LMWH for the Initial Treatment of DVT:* The Matisse-DVT trial compared fondaparinux with LMWH for short-term treatment of DVT. This study suggests that fondaparinux is associated with a similar frequency of mortality, recurrent VTE, and major bleeding as LMWH. However, the quality of the evidence from this study was moderate because of imprecision. Evidence that fondaparinux is effective for the treatment of PE supports the equivalence of fondaparinux to LMWH for the treatment of acute VTE.

	Maintenance Anticoagulation **Recommendations:** • A goal INR of 2.5 (range 2.0-3.0) is recommended for patients with venous thromboembolism. (Holbrook, 2012 [Guideline]). • Clinicians should generally use warfarin for continued anticoagulation. • Clinicians should use low-molecular-weight heparin (LMWH) for patients with VTE in the setting of cancer. • Clinicians may consider using rivaroxaban for continued anticoagulation. • Start heparin/fondaparinux and warfarin at the same time. Heparin (UFH or LMWH) and/or fondaparinux should be given for a minimum of five days and continued until INR > = 2.0 for two consecutive days. (Ansell, 1993 [Low Quality Evidence]). **Warfarin** Warfarin is recommended over LMWH for long-term therapy (Douketis, 2012 [Guideline]). In patients with VTE and cancer who are not treated with LMWH, warfarin is suggested over dabigatran or rivaroxaban for long-term therapy (Douketis, 2012 [Guideline]). **Low-Molecular-Weight Heparin** For patients with VTE who are not treated with warfarin, LMWH is recommended over dabigatran or rivaroxaban for long-term therapy (Douketis, 2012 [Guideline]). LMWH is also recommended over warfarin for long term treatment of patients with VTE in the setting of cancer (Douketis, 2012 [Guideline]). **Rivaroxaban** Rivaroxaban has recently been approved by the FDA for treatment of VTE and PE based on recent trials. (Büller, 2012 [Moderate Quality Evidence]; Bauersachs, 2010 [Low Quality Evidence]). **Other Agents** Dabigatran is a direct thrombin inhibitor that has been shown to be non-inferior to warfarin for the management of acute VTE based on the RECOVER trial (Schulman, 2009 [Moderate Quality Evidence]); however, at the time of this revision, the FDA had not approved it for generalized treatment of VTE (see the ICSI Anthrombotic Therapy Supplement for additional information.) **Special Patient Populations** In patients with suspected hypercoagulable state (Protein C or Protein S deficiency), the patient should be adequately anticoagulated with UFH or LMWH and/or fondaparinux before warfarin is started at a low dose (2-5 mg). This is to avoid warfarin-induced skin necrosis or other transient hypercoagulable complications (Ansell, 1993 [Low Quality Evidence]).
Jaff et al. (2011): Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic	**Recommendations for Initial Anticoagulation for Acute PE** 1. Therapeutic anticoagulation with subcutaneous LMWH, intravenous or subcutaneous UFH with monitoring, unmonitored weight-based subcutaneous UFH, or subcutaneous fondaparinux should be given to patients with objectively confirmed PE and no contraindications to anticoagulation (Class I; Level of Evidence A). 2. Therapeutic anticoagulation during the diagnostic workup should be given to patients with intermediate or high clinical probability of PE and no contraindications to anticoagulation (Class I; Level of Evidence C). **Recommendations for Initial Anticoagulation for Patients With**

Pulmonary Hypertension. A Scientific Statement From the American Heart Association.	**Iliofemoral Deep Vein Thrombosis (IFDVT)** 1. In the absence of suspected or proven heparin induced thrombocytopenia, patients with IFDVT should receive therapeutic anticoagulation with either intravenous UFH (Class I; Level of Evidence A), UFH by subcutaneous injection (Class I; Level of Evidence B), an LMWH (Class I; Level of Evidence A), or fondaparinux (Class I; Level of Evidence A). 2. Patients with IFDVT who have suspected or proven heparin-induced thrombocytopenia should receive a direct thrombin inhibitor (Class I; Level of Evidence B). **Recommendations for Long-Term Anticoagulation Therapy for Patients With IFDVT** 1. Adult patients with IFDVT who receive oral warfarin as first-line long-term anticoagulation therapy should have warfarin overlapped with initial anticoagulation therapy for a minimum of 5 days and until the INR is >2.0 for at least 24 hours, and then targeted to an INR of 2.0 to 3.0 (Class I; Level of Evidence A). 2. Patients with first-episode IFDVT related to a major reversible risk factor should have anticoagulation stopped after 3 months (Class I; Level of Evidence A). 3. Patients with recurrent or unprovoked IFDVT should have at least 6 months of anticoagulation and be considered for indefinite anticoagulation with periodic reassessment of the risks and benefits of continued anticoagulation (Class I; Level of Evidence A). 4. Cancer patients with IFDVT should receive LMWH monotherapy for at least 3 to 6 months, or as long as the cancer or its treatment (eg, chemotherapy) is ongoing (Class I; Level of Evidence A). 5. In children with DVT, the use of LMWH monotherapy may be reasonable (Class IIb; Level of Evidence C). **Level of Evidence / Grad of Recommendation** Table 1. Applying Classification of Recommendations and Level of Evidence SIZE OF TREATMENT EFFECT → ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT **CLASS I** — *Benefit >>> Risk* — Procedure/Treatment **SHOULD** be performed/administered **CLASS IIa** — *Benefit >> Risk* — *Additional studies with focused objectives needed* — **IT IS REASONABLE** to perform procedure/administer treatment **CLASS IIb** — *Benefit ≥ Risk* — *Additional studies with broad objectives needed; additional registry data would be helpful* — Procedure/Treatment **MAY BE CONSIDERED** **CLASS III** — *Risk ≥ Benefit* — Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL** **LEVEL A** — Multiple populations evaluated* — Data derived from multiple randomized clinical trials or meta-analyses ■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses ■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses ■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses ■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses **LEVEL B** — Limited populations evaluated* — Data derived from a single randomized trial or nonrandomized studies ■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies ■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies ■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies ■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies **LEVEL C** — Very limited populations evaluated* — Only consensus opinion of experts, case studies, or standard of care ■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care ■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care ■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care ■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care Suggested phrases for writing recommendations† should is recommended is indicated is useful/effective/beneficial is reasonable can be useful/effective/beneficial is probably recommended or indicated may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

	Anmerkungen FBMed: keine Evidenzverknüpfung daher nicht überprüfbar, im voranstehenden Text zu dieser Empfehlung werden hauptsächlich Leitlinien zitiert
MQIC(2011): Outpatient Management of Uncomplicated Deep Venous Thrombosis.	Medical Quality Improvement Consortium **Initiating and monitoring pharmacologic interventions** Outpatient therapy is preferred if no contraindications. Contraindications to warfarin therapy: Absolute: pregnancy, history of warfarin-induced skin necrosis Relative: dementia, certain psychoses, diminished mental capacity, or childbearing age without contraception • Begin LMWH. • Begin warfarin after 1st dose of LMWH [A], on the same day, titrate to INR range of 2.0 - 3.0. • Continue LMWH (along with warfarin) at least 5 days, and until INR range 2.0 - 3.0 for 2 consecutive days. [A] • Maintain warfarin therapy at least 3 months in therapeutic INR range [A], longer if risk of recurrence. For calf-level DVT, maintain warfarin therapy at least 6 weeks to 3 months in therapeutic INR range [A], longer if risk of recurrence. • Ask about any changes in diet, medications, supplements and herbal products, and compliance before any dosage adjustment. • If known hypercoagulable state, consider referral to a coagulation specialist. **Levels of Evidence** for the most significant recommendations: A = randomized controlled trials; B = controlled trials, no randomization; C = observational studies; D = opinion of expert panel
Nicolaides et al. (2013): Prevention and Treatment of Venous Thromboembolism.	**Recommendations for Treating VTE** Initial treatment is with intravenous UFH, LMWH, or fondapariuux for at least 5 days (Ievel of evidence: high. The LMWH is preferred in most patients. The VKA therapy should be commenced on day I and continued according to the INR. Initial therapy with LMWH, intravenous UFH, or fondaparinux should be discontinued when the stable INR is in the therapeutic range (2.0-3.0; Ievel of evidence: high). Rivaroxaban or dabigatran are an alternative therapy in countries where they have been approved (Ievel of evidence:high). Although the former can be used as a single therapy, the latter should be preceded by l week of parenteral anticoagulation with either LMWH or fondaparinux. In patients with a history of cancer, LMWH for 3 to 6 months is the initial treatment (Ievel of evidence: high). During pregnancy, LMWH is the treatment of choice throughout pregnancy and for the first 6 weeks after delivery (Ievel of evidence: low; see section on pregnancy for evidence). The LMWH for 3 to 6 months is an alternative to VKA therapy (Ievel of evidence: high). Isolated calf DVT should be treated for 3 months (Ievel of evidence: moderate) or followed by serial ultrasonography on 2 occasions if anticoagulation is contraindicated (Ievel of evidence: low). **Recommendations for Treating VTE in Patients with cancer** The initial and long-term treatment of DVT and PE in patients with

	cancer is LMWH administered for 3 to 6 months (level of evidence: high). If the health care economics of a system do not allow for use of long-term LMWH, it is acceptable to treat initially with UFH or LMWH followed by long-term VKA therapy (level of evidence: high). **Level of Evidence** High: RCTs with consistent results or systematic reviews directly applicable to the target population. Moderate: RCTs with less consistent results, limited power or other methodological limitations, which were directly applicable to the target population as well as RCTs extrapolated to the target population from a different group of patients. Low: question that has to be addressed by future studies. **Anm FBMed:** keine Evidenzverknüpfung der Literatur - daher nicht überprüfbar
JCS Joint Working Group (2011): Guidelines for the Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis.	**Acute PE – Initial Treatment** The current criteria for drug treatment for acute PTE are as follows: (1) Anticoagulation therapy is the treatment of choice for normotensive patients without right heart dysfunction. (2) Normotensive patients with right heart dysfunction should be carefully assessed for expected benefits and risk of bleeding in considering whether thrombolytic therapy is a treatment option. (3) Thrombolytic therapy is the treatment of choice for patients with persistent shock and hypotension unless it is contraindicated. **Acute PE – Long-Term Treatment** [Levels of Recommendations] Class I 1. During the acute phase of acute PTE, unfractionated heparin should be administered to achieve an APTT of 1.5 to 2.5 times the control value for a period of time until the effects of warfarin are stabilized. 2. Warfarin should be administered during the chronic phase of acute PTE. The duration of warfarin therapy should be 3 months for patients with reversible risk factors and at least 3 months for patients with congenital coagulopathy and those with idiopathic VTE. Warfarin should be administered for a longer period of time to patients with cancer and those with recurrent PTE. 3. In patients with persistent shock, hypotension, and unstable hemodynamics, thrombolytic therapy should be performed during the acute phase of acute PTE. Class IIa 1. During the acute phase of acute PTE, thrombolytic therapy should be performed in normotensive patients with right heart dysfunction. Class IIb 1. During the treatment of acute PTE, the dose of warfarin should be adjusted to achieve a PT-INR of 1.5 to 2.5. **Chronic PE** Anticoagulation Therapy The prognosis of untreated CTEPH depends on pulmonary hemodynamics. It has been reported that even patients with mild CTEPH may exhibit exacerbation of pulmonary hemodynamics over

	time. Such exacerbation is believed to be caused by recurrent acute PTE, and to involve mechanisms of formation of thrombus in situ. Accordingly, life-long anticoagulation therapy with warfarin is required for patients with CTEPH. Warfarin is often administered with a target INR of 1.5 to 2.5, which is also recommended for patients with acute PTE (Class IIa). **Deep Vein Thrombosis** [Levels of Recommendations] Class I 1. Combined use of heparin and warfarin in the treatment of acute DVT. 2. Heparin control with a target APTT of 1.5 to 2.5 times the control in the treatment of acute DVT. Class IIa 1. Systemic thrombolytic therapy in the treatment of acute DVT. Class IIb 1. Warfarin control with a target PT-INR of 2.0 (1.5 to 2.5) times the control in the treatment of acute DVT. ---------- Class I: Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective. Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion regarding the usefulness/ efficacy of a procedure or treatment. Class IIa: The weight of evidence/opinion is in favor of usefulness/efficacy. Class IIb: Usefulness/efficacy is less well established by evidence/opinion. Class III: Conditions for which there is general agreement that a procedure/treatment is neither useful nor indicated and may be harmful.
Imberti et al. (2009): Treatment of venous thromboembolism in patients with cancer: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET).	**Recommendations** 1) Patients with malignancies and acute VTE should be treated initially with LMWH (grade B). 2) For long-term secondary prophylaxis of VTE in patients with malignancies, LMWHshould be used instead of OAT for at least the first six months (grade A). 3) In patients with malignancies, the long-term prophylaxis against VTE should be continued while the cancer is “active” and/or the patient is undergoing antitumoral treatment (grade D). 4) In cancer patients with recurrent VTE during oral anticoagulant treatment and therapeutic INR, LMWH should be administered (grade D). 5) The use of LMWH has a more acceptable impact on the quality of life than OAT in patients with advanced cancer undergoing palliative care (grade D). 6) The available studies comparing the new antithrombotics and VKAs/LMWHs were carried out on the general population, and included a limited number of cancer patients; in addition, they did not include analyses by subgroup in the cancer patients. So the Working Group cannot make a recommendation on this aspect. 7) As in the general population with PE, thrombolysis is not suggested, other than in cases of PE associated with haemodynamic instability (grade D). 8) As in the general population with DVT, thrombolysis is not suggested other than in cases of venous gangrene (grade D).

	9) As in the general population, thrombectomy is not suggested in patients with cancer and acute DVT, other than in cases of venous gangrene with a contraindication for thrombolysis or if thrombolysis is not efficacious (grade D). 10) In patients with kidney or adrenal gland neoplasmscomplicated by renal thrombosis and vena cava tumors, thrombectomy is suggested since it is part of the primary surgical strategy to eradicate the neoplasm (grade D). 11) As in the general population, embolectomy is not suggested in patients with malignancies and acute PE, other than in cases of PE associated with haemodynamic instability with a contraindication for thrombolysis or if thrombolysis is not efficacious (grade D). 12) In patients with malignancy and acute DVT, implantation of a vena cava filter should be considered if anticoagulant treatment is contraindicated or if VTE recurs despite correctly administered anticoagulant treatment (grade D). 13) In patients with brain neoplasms and acute VTE, anticoagulant treatment does not appear to be associated with a sufficiently high risk of cerebral haemorrhage so as to justify the routine use of a vena cava filter (grade D). 14) As in the general population, the use of elastocompression is also suggested in patients with DVT and malignancy to prevent postphlebitic syndrome (grade D). 15) As in the general population, home treatment appears to be as efficacious and safe as in-hospital treatment in patients with malignancies and DVT (grade D). **Anmerkung FBMed:** keine Angaben zur Evidenzgraduierung
Keeling et al. (2011): Guidelines on oral anticoagulation with warfarin – fourth edition.	**Venous thromboembolism (VTE)** **Recommendation** • First episodes of VTE should be treated with an INR target of 2.5 (1A). • Warfarin used for treatment of VTE should be introduced along with parenteral anticoagulation (1A) which should continue for at least 5 d and until the INR is ≥2 for at least 24 h (1C). • Recurrent VTE whilst anticoagulated and within the therapeutic range should be managed by increasing the INR target to 3.5 (2C). **Duration of anticoagulation for pulmonary embolism (PE) and lower limb deep vein thrombosis (DVT)** **Recommendation** • Patients with proximal DVT or PE should be treated for at least 3 months (1A). • If a diagnostic strategy that identifies isolated calf vein DVT is employed, treatment of such clots can be restricted to 6 weeks (1A). • Patients with cancer-associated VTE should initially be treated for 6 months with therapeutic dose LMWH rather than warfarin (1A). STRENGTH OF RECOMMENDATIONS: Strong (grade 1): are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as ‘recommend’. Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as ‘suggest’.

	QUALITY OF EVIDENCE (A) High: Further research is very unlikely to change confidence in the estimate of effect. (B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. (C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
SIGN (2010): Prevention and management of venous Thromboembolism. (Guideline No. 122)	Scottish Intercollegiate Guidelines Network **Further management of venous thromboembolism** **choice of anticoagulant** Low molecular weight heparin rather than warfarin should be considered in venous thromboembolism associated with cancer (A). **Duration of anticoagulation in lower limb deep vein thrombosis and pulmonary embolism** After a first episode of proximal limb deep vein thrombosis or pulmonary embolism, treatment with a vitamin K antagonist should be continued for at least three months. (A) **Grade of Recomdendation** (A): At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
Lyman GH et al. (2013): Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update.	**Ziel / Fragestellung:** To provide recommendations about prophylaxis and treatment of venous thromboembolism (VTE) in patients with cancer. Prophylaxis in the outpatient, inpatient, and perioperative settings was considered, as were treatment and use of anticoagulation as a cancer-directed therapy. **Suchzeitraum der systematischen Literaturrecherche:** bis 2012 **GoR und LoE** nicht angegeben **Empfehlungen** (pharmakologische Initialbehandlung und Versorgung bei Rezidiv): ● LMWH is recommended for the initial 5 to 10 days of treatment for patients with established deep vein thrombosis and pulmonary embolism, as well as for long-term (6 months) secondary prophylaxis ● Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE ● Anticoagulation should not be used to extend survival in patients with cancer in the absence of other indications

	Treatment and secondary prophylaxis 4.1 LMWH is preferred over UFH for the initial 5 to 10 days of anticoagulation for the patient with cancer with newly diagnosed VTE who does not have severe renal impairment (defined as creatinine clearance < 30 mL/min). — Evidence: strong; Recommendation type, strength: evidence based, strong 4.2 For long-term anticoagulation, LMWH for at least 6 months is preferred because of improved efficacy over VKAs. VKAs are an acceptable alternative for long-term therapy if LMWH is not available. — Evidence: strong; Recommendation type, strength: evidence based, strong 4.3 Anticoagulation with LMWH or VKA beyond the initial 6 months may be considered for select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy. — Evidence: insufficient; Recommendation type, strength: informal consensus, weak to moderate 4.4 The insertion of a vena cava filter is only indicated for patients with contraindications to anticoagulant therapy (see Table 4). It may be considered as an adjunct to anticoagulation in patients with progression of thrombosis (recurrent VTE or extension of existing thrombus) despite optimal therapy with LMWH. — Evidence: weak to moderate; Recommendation type, strength: informal consensus, moderate 4.5 For patients with primary CNS malignancies, anticoagulation is recommended for established VTE as described for other patients with cancer. Careful monitoring is necessary to limit the risk of hemorrhagic complications. — Evidence: moderate; Recommendation type, strength: informal consensus, strong 4.6 Use of novel oral anticoagulants for either prevention or treatment of VTE in patients with cancer is not recommended at this time. — Evidence: insufficient; Recommendation type, strength: informal consensus, strong 4.7 Based on consensus, incidental PE and DVT should be treated in the same manner as symptomatic VTE. Treatment of splanchnic or visceral vein thrombi diagnosed incidentally should be considered on a case-by-case basis, considering potential benefits and risks of anticoagulation. — Evidence: insufficient; Recommendation type, strength: informal consensus, moderate Anticoagulation and survival 5.1 Anticoagulants are not recommended to improve survival in patients with cancer without VTE. — Evidence: weak to moderate; Recommendation type, strength: informal consensus, moderate
SIGN (2013): Antithrombotics: indications and management. (Guideline No. 129)	Scottish Intercollegiate Guidelines Network **Empfehlungen** Antiplatelet Agents To minimise the risk of bleeding, the lowest recommended dose of aspirin should be used for the clinical indication [GoR A]. **Weitere Ausführungen** *Patients with active thromboembolism* In patients with active thromboembolism, the starting regimen for treatment of acute thromboembolism is generally 10 mg warfarin on day one, as the target INR is achieved more rapidly than with a 5 mg regimen. A lower starting dose should be considered in older patients. […] The initial dosing regimen should be lower (5 mg) when there is increased sensitivity to warfarin (for example low body weight, drug therapy which increases warfarin sensitivity; for example some antibiotics, heart failure, liver failure, prolonged baseline prothrombin time). More cautious dosing should also be considered when warfarin is introduced within 7-10 days of surgery. [GoR 1+] Heparin prolongs the prothrombin time but in patients taking both heparin and warfarin at the start of treatment, the INR can be used for dosing warfarin without stopping heparin, provided that the APTT ratio is within or below the therapeutic range for heparin. Prior to hospital discharge, the hospital should communicate with the general practitioner (or other medical professional assuming the patient's care) to advise the recommended INR target range and the duration of therapy, and ensure arrangements for continued patient and INR monitoring. Prior to discharge, patients should be given clear information on the date and place of the next monitoring visit. [LoE 4]

	Reversal of oral anticoagulant therapy in patients with bleeding or high INR The evidence base consists largely of non-RCT studies in patients without active bleeding. Individualised patient management is required balancing the risk of thrombosis against haemorrhage. The options available range from allowing the INR to fall slowly by reducing the dose or omitting the VKA until the INR falls into the desired range; accelerated lowering of the INR to the desired range with the use of vitamin K or a rapid return of the INR to normal/near normal with the use of human prothrombin complex concentrate (PCC). Fresh frozen plasma is less effective. [LoE 2++; 2+] In asymptomatic patients where the INR is <5.0, observational data would suggest the risk of bleeding is low and,71 in general, close monitoring of the INR together with considering omitting a single dose and downward dose adjustment of the VKA is a reasonable option. [LoE 2+] Where the INR is >5, observational data suggest the risk of haemorrhage in asymptomatic patients increases as the INR rises. [LoE 2-] In such circumstances the use of vitamin K has been shown to safely move the INR back to the desired range compared to omitting a VKA alone. [LoE 1+] Full-dose unfractionated heparin is usually initiated with an intravenous loading dose over five minutes (5,000 IU in an average-sized adult or a body weight-dependent dose (75 IU/kg) may be preferred in patients at the extremes of body weight). For treatment of deep vein thrombosis, pulmonary embolism, unstable angina, and acute peripheral arterial occlusion a continuous intravenous infusion is then given (18 IU/kg body weight/hour in an average-sized adult). Administration in children depends on age, indication and weight *(see BNF in Children for details)*.42 Weight-based nomograms can provide a more accurate prediction of the patient's heparin requirements especially at the extremes of body weight and are therefore preferable to standard nomograms. In morbidly obese patients actual body weight is preferable to ideal body weight in calculating the required heparin dose, however a dose cap should be considered and heparin monitoring with dose adjustment is still required. *[LoE = 4]* *Rivaroxaban , Dabigatran exilate and apixaban* Rivaroxaban and dabigatran etexilate are novel oral agents which are direct inhibitors of factor Xa and thrombin respectively. Like VKAs they are effective by the oral route and have the potential advantage of standard dosing regimens and no requirement for monitoring. They are less susceptible to drug interactions than VKAs and in randomised controlled trials they have been efficacious with rates of serious bleeding comparable to those associated with VKA therapy. They have been investigated for use in the prevention of VTE after hip and knee replacement surgery, treatment of DVT and prevention of recurrent VTE and the prevention of thromboembolism in AF. Dabigatran etexilate is a prodrug which is converted to the active direct thrombin inhibitor dabigatran by hydrolysis in the intestinal wall and liver. It is mainly (80%) eliminated by the renal route and consequently there is a risk of accumulation in severe renal impairment. Rivaroxaban is less dependent on renal clearance (around 60%) but caution is required in

	severe renal impairment. Both drugs have a short half-life, around 13 hours for dabigatran etexilate and around eight hours for rivaroxaban (12 hours in older patients). There is no recognised antidote to the anticoagulant effect of dabigatran etexilate. Because only 35% of the drug is bound to plasma proteins dialysis may be of benefit in an emergency situation. In healthy subjects dosed with rivaroxaban, 4-factor PCC effectively reversed the anticoagulant effect and it could be considered in emergency situations in patients. Although coagulation monitoring is not required it may be desirable to determine the degree of anticoagulation, for example if there is bleeding. The prothrombin time (PT, used for monitoring warfarin and expressed as the INR) is not sensitive to dabigatran etexilate. The APTT is prolonged but in a non-linear fashion. The thrombin clotting time (TCT) is the most informative test; if normal, the plasma concentration of dabigatran etexilate is likely to be low. The PT is prolonged by rivaroxaban although the degree of prolongation is reagent-dependent; if normal, the plasma concentration of rivaroxaban is likely to be low. More evidence is required to ensure that surgical interventions and invasive procedures can be safely carried out based on the TCT in a patient on dabigatran etexilate and the PT in a patient on rivaroxaban. Rivaroxaban has been compared with standard therapy of enoxaparin followed by a VKA in an RCT in patients with acute symptomatic VTE. The rivaroxaban regimen was non-inferior in relation to the primary outcome measure of recurrent VTE and there was no difference between the two regimens in clinically relevant bleeding; the net clinical benefit (recurrent VTE plus major bleeding) favoured rivaroxaban. In a parallel study of rivaroxaban compared to placebo in patients who had completed 6 to 12 months of treatment for VTE, rivaroxaban was superior in the prevention of recurrent VTE (HR 0.18, 95% CI 0.09 to 0.39, $p<0.001$) with four episodes of (non-fatal) major bleeding in the rivaroxaban group (n=602; 0.7%) and none in the placebo group (n=594) (p=0.11). Dabigatran etexilate has been compared to warfarin in a randomised, double-blinded non-inferiority trial in patients with acute symptomatic VTE who were initially given parenteral anticoagulant therapy with a heparin. Dabigatran etexilate was as effective as warfarin in preventing six month incidence of recurrent venous thromboembolism (HR for recurrent VTE with dabigatran etexilate was 1.10 (95% CI, 0.65 to 1.84). Significantly more patients in the warfarin group had bleeds classified as major or clinically relevant nonmajor. There was a significant excess of dyspepsia in the dabigatran etexilate group. Apixaban is another orally active factor Xa inhibitor which is under assessment. In knee replacement surgery it has been demonstrated to be more efficacious than enoxaparin 40 mg daily in prevention of combined asymptomatic/symptomatic DVT, PE and all-cause death, with comparable bleeding risk. Dabigatran etexilate, rivaroxaban and apixaban are licensed for use in hip and knee replacement surgery and for the prevention of VTE in the UK. These agents have been accepted by the Scottish Medicines Consortium for the prevention of stroke in non-valvular atrial fibrillation and for the prevention of VTE in elective hip or knee replacement surgery. Rivaroxaban is also accepted for the treatment of DVT and prevention of recurrent DVT and pulmonary embolism PE following an acute DVT in adults. **Recherchezeitraum:** 2003-2009

GoR und LoE

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS	
LEVELS OF EVIDENCE	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion
GRADES OF RECOMMENDATION	
Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.	
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Erstautor, Jahr Titel	**Inhalt**
HSC (2013): Apixaban (Eliquis) for the treatment and long-term prevention of deep veinthrombosis and pulmonary embolism	Apixaban has recently completed two phase III clinical trials comparing its effects against enoxaparin and warfarin, and against placebo in an extended treatment study. These trials have been published. **Target group** Treatment of acute symptomatic and long-term prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE). **Existing comparators** Treatment for acute symptomatic VTE is usually initiated with subcutaneous anticoagulant drugs such as heparin or low molecular weight heparin (LMWH) such as enoxaparin, dalteparin or tinzaparin. Treatment is continued orally with the vitamin K antagonist warfarin or, rarely, with either acenocoumerol or phenindione. For people in whom a vitamin K antagonist is not considered an appropriate treatment, unfractionated heparin or LMWH may be continued instead of a vitamin K antagonist. People who have had cancer or a pregnancy associated thrombosis are usually treated with heparin. A range of prophylactic interventions are available for VTE, but are of varying effectiveness, cost-effectiveness and patient acceptability. There is variation in clinical practice and observance of clinical guidelines; current options include: • Mechanical and physical methods such as: early mobilisation, intermittent pneumatic compression devices, and mechanical foot pumps. • Prophylactic anticoagulant drugs including: unfractionated heparin, LMWH (dalteparin and enoxaparin), fondaparinux (all subcutaneous administration) and rivaroxaban.
Prescrire (2013): **Deep venous thrombosis and pulmonary embolism**	Review auf der Basis einer Literaturrecherche ab dem Jahr 2006 bis 11 / 2012. • Deep venous thrombosis limited to the calf leaves downstream veins • unaffected in about three-quarters of cases. Withholding anticoagulant therapy is a reasonable option for patients with mild symptoms and no known risk factors for thrombus extension. • In other patients who have deep venous thrombosis or pulmonary embolism, without any haemodynamic disorders, the anticoagulant treatment of choice is a low-molecular-weight heparin (LMWH). All available LMWHs seem to have similar efficacy. The best-assessed drugs are *enoxaparin, dafteparin* and *nadroparin.* • Creatinine clearance below 30 ml/minute raises the risk of bleeding due to overdose; in this case, it is better to use adjusted-dose unfractionated heparin rather than LMWH. • Intravenous thrombolysis should be considered In case of massive pulmonary embolism, as it appears to prevent 1 death per 15 patients. • After initial heparin therapy, continuing treatment with LMWH

	or switching to *warfarin,* a vitamin K antagonist, are two options which overall have similar harm-benefit balances. • In contrast, these two treatments carry different constraints: INR monitoring and a risk of drug Interactions In contrast, these two treatments carry different constraints: INR monitoring and a risk of drug Interactions. • Pregnant women should not use vitamin K antagonists because these drugs can cause miscarriage, birth defects, and fetal bleeding; it is better to continue LMWH therapy. • Platelet count monitoring (at least twice a week from day 4 to day 14 of treatment) may be useful In patients treated with unfractionated heparin, LMWH or *fondaparinux.* Monitoring should start on the first day of treatment if the patient has been exposed to heparin within the previous 6 months. • In patients with calf thrombosis due to a transient triggering factor, 6 weeks of anticoagulation seems sufficient. • After a first episode of pulmonary embolism or deep venous thrombosis located above the knee, due to a reversible precipitating factor such as surgery, 3 months of anticoagulation seems sufficient. • In cancer patients, it is usually better to prolong treatment beyond 3 months. • Prolonged anticoagulant treatment should be considered for patients with no identified trigger, some forms of thrombophilia, or a prior recurrence; treatment can be continued as long as the bleeding risk is low. Overall, LMWH and *warfarin* have similar harm-benefit balances. In practice, it is best to choose between these drugs on a case-by-case basis, taking into account patient preferences, monitoring constraints, difficulty controlling the INR, the risk of bleeding and interactions, and the cost of treatment.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Database of Systematic Reviews am 05.06.2013

Suchschritt	Suchfrage
#1	MeSH descriptor: [Venous Thromboembolism] explode all trees
#2	MeSH descriptor: [Venous Thrombosis] explode all trees
#3	MeSH descriptor: [Pulmonary Embolism] explode all trees
#4	thromboembolism or thromboembolic or thrombosis or embolism or antithrombotic or thrombolytic:ti or VTE or PE or DVT:ti (Word variations have been searched)
#5	#1 or #2 or #3 or #4: 2009 to 2013

Cochrane Database of Abstracts of Reviews of Effects (DARE), Cochrane Health Technology Assessment (HTA) Database am 06.06.2013

Suchschritt	Suchfrage
#1	MeSH descriptor: [Venous Thromboembolism] explode all trees and with qualifiers: [Drug therapy - DT, Radiotherapy - RT, Surgery - SU, Therapy - TH]
#2	MeSH descriptor: [Venous Thrombosis] explode all trees and with qualifiers: [Drug therapy - DT, Radiotherapy - RT, Surgery - SU, Therapy - TH]
#3	MeSH descriptor: [Pulmonary Embolism] explode all trees and with qualifiers: [Drug therapy - DT, Radiotherapy - RT, Surgery - SU, Therapy - TH]
#4	venous or vein:ti and thromboembol* or thrombosis:ti (Word variations have been searched)
#5	embolism or VTE or PT or DVT:ti (Word variations have been searched)
#6	treatment* or therapy or therapies or therapeutic or monotherap* or polytherap* or pharmacotherap* or effect* or efficacy or treating or treated or treat*:ti (Word variations have been searched)
#7	#4 or #5
#8	#6 and #7
#9	#1 or #2 or #3
#10	#8 or #9: 2009 to 2013

MEDLINE (PubMed) am 06.06.2013

Suchschritt	Suchfrage
#2	Search ("Venous Thromboembolism/drug therapy"[Mesh] OR "Venous Thromboembolism/radiotherapy"[Mesh] OR "Venous Thromboembolism/surgery"[Mesh] OR "Venous Thromboembolism/therapy"[Mesh])
#3	Search ("Venous Thrombosis/drug therapy"[Mesh] OR "Venous Thrombosis/radiotherapy"[Mesh] OR "Venous Thrombosis/surgery"[Mesh] OR "Venous Thrombosis/therapy"[Mesh])
#4	Search ("Pulmonary Embolism/drug therapy"[Mesh] OR "Pulmonary Embolism/radiotherapy"[Mesh] OR "Pulmonary Embolism/surgery"[Mesh] OR "Pulmonary Embolism/therapy"[Mesh])
#5	Search(#2 OR #3 OR #4)
#12	Search (venous[Title]) OR vein[Title]
#13	Search (thromboembol*[Title]) OR thrombosis[Title]
#14	Search (#12 AND #13)
#15	Search (((embolism[Title]) OR VTE[Title]) OR PT[Title]) OR DVT[Title]
#16	Search (#14 OR #15)
#17	Search ((((((((((treatment*[Title]) OR therapy[Title]) OR therapies[Title]) OR therapeutic[Title]) OR monotherap*[Title]) OR polytherap*[Title]) OR

	pharmacotherap*[Title]) OR effect*[Title]) OR efficacy[Title]) OR treating[Title]) OR treated[Title]) OR treat*[Title]
#18	Search (#16 AND #17)
#19	Search (#18 OR #5)
#20	Search (#18 OR #5) Filters: Meta-Analysis; Technical Report
#21	Search ((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
#22	Search (#19 AND #21)
#23	Search (#20 OR #22)
#24	Search (#20 OR #22) Filters: published in the last 5 years

MEDLINE (PubMed) nach Leitlinien am 04.06.2013

Suchschritt	Suchfrage
#16	Search Venous Thromboembolism[MeSH Major Topic]
#17	Search Venous Thrombosis[MeSH Major Topic]
#18	Search Pulmonary Embolism[MeSH Major Topic]
#19	Search (((((((thromboembolism[Title]) OR thromboembolic[Title]) OR VTE[Title]) OR PE[Title]) OR DVT[Title]) OR thrombosis[Title]) OR antithrombotic[Title]) OR thrombolytic[Title]
#20	Search pulmonary embolism[Title]
#21	Search ((((#16) OR #17) OR #18) OR #19) OR #20
#22	Search ((((#16) OR #17) OR #18) OR #19) OR #20 Filters: Practice Guideline
#23	Search ((((#16) OR #17) OR #18) OR #19) OR #20 Filters: Practice Guideline; Guideline
#24	Search ((((#16) OR #17) OR #18) OR #19) OR #20 Filters: Practice Guideline; Guideline; published in the last 5 years
#25	Search guideline*[Title]
#26	Search medline[sb]
#27	Search (#21) AND #25
#28	Search (#27) NOT #26
#29	Search (#24) OR #28

MEDLINE (PubMed) nach Leitlinien am 09.01.2014

Suchschritt	Suchfrage
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#17	Search Venous Thrombosis[MeSH Major Topic]
#18	Search Pulmonary Embolism[MeSH Major Topic]
#19	Search (((((((thromboembolism[Title]) OR thromboembolic[Title]) OR VTE[Title]) OR PE[Title]) OR DVT[Title]) OR thrombosis[Title]) OR antithrombotic[Title]) OR thrombolytic[Title]
#20	Search pulmonary embolism[Title]
#21	Search ((((#16) OR #17) OR #18) OR #19) OR #20
#22	Search ((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]
#23	Search (#21 AND #22)
#24	Search (#21 AND #22) Filters: Publication date from 2013/06/01 to 2014/12/31

MEDLINE (PubMed) am 09.01.2014

Suchschritt	Suchfrage
#2	Search ("Venous Thromboembolism/drug therapy"[Mesh] OR "Venous Thromboembolism/radiotherapy"[Mesh] OR "Venous Thromboembolism/surgery"[Mesh] OR "Venous Thromboembolism/therapy"[Mesh])
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#4	Search ("Pulmonary Embolism/drug therapy"[Mesh] OR "Pulmonary Embolism/radiotherapy"[Mesh] OR "Pulmonary Embolism/surgery"[Mesh] OR "Pulmonary Embolism/therapy"[Mesh])
#5	Search(#2 OR #3 OR #4)
#12	Search (venous[Title]) OR vein[Title]
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#16	Search (#14 OR #15)
#17	Search ((((((((((treatment*[Title]) OR therapy[Title]) OR therapies[Title]) OR therapeutic[Title]) OR monotherap*[Title]) OR polytherap*[Title]) OR pharmacotherap*[Title]) OR effect*[Title]) OR efficacy[Title]) OR treating[Title]) OR treated[Title]) OR treat*[Title]
#18	Search (#16 AND #17)
#19	Search (#18 OR #5)
#20	((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
#21	Search (#19 AND #20)
#22	Search (#18 OR #5) Filters: Systematic Reviews; Meta-Analysis; Technical Report
#23	Search (#21 OR #22)
#24	Search (#21 OR #22) Filters: Publication date from 2013/06/01 to 2014/12/31

Cochrane Database of Systematic Reviews am 09.01.2014

Suchschritt	Suchfrage
#1	MeSH descriptor: [Venous Thromboembolism] explode all trees
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Cochrane Database of Abstracts of Reviews of Effects (DARE) und Cochrane Health Technology Assessment (HTA) Database am 09.01.2013

Suchschritt	Suchfrage
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#2	MeSH descriptor: [Venous Thrombosis] explode all trees and with qualifiers:

Suchschritt	Suchfrage
	[Drug therapy - DT, Radiotherapy - RT, Surgery - SU, Therapy - TH]
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#6	treatment* or therapy or therapies or therapeutic or monotherap* or polytherap* or pharmacotherap* or effect* or efficacy or treating or treated or treat*:ti (Word variations have been searched)
#7	#4 or #5
#8	#6 and #7
#9	#1 or #2 or #3
#10	#8 or #9: 2013 to 2014

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