Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

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

## Vorgang: 2015-08-01-D-174 Edoxaban

Stand: Juni 2014

# Recherche und Synopse der Evidenz zur Bestimmung der zVT:

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## Indikation für die Recherche für Edoxaban

Behandlung von venösen Thromboembolie (VTE) einschließlich tiefer Venenthrombose (TVT) und Lungenembolie (LE) und Verhinderung von VTE-Rezidiven bei Erwachsenen.

## Berücksichtigte Wirkstoffe/Therapien

Für das Anwendungsgebiet zugelassenen Arzneimittel:

## I. Zweckmäßige Vergleichstherapie: Kriterien der VerfO

**Edoxaban**

**Behandlung von venösen Thromboembolien (VTE), tiefer Venenthrombosen, Lungenembolien und Verhinderung von VTE-Rezidiven [Anwendungsgebiet abgekürzt]**

**Kriterien gemäß 5. Kapitel § 6 Absatz 3 Satz 2 VerfO**

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| 1. Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben. | Heparine<br>- Niedermolekulare Heparine (NMH)<br>- Unfraktionierte Heparine (UFH)<br>Danaparoid<br>Vitamin-K-Antagonisten<br>- Phenprocoumon<br>- Warfarin<br>Direkte Thrombininhibitoren (Dabigatran)<br>Direkte Faktor Xa Thrombininhibitoren<br>- Apixaban<br>- Rivaroxaban<br>Andere Thrombininhibitoren<br>- Fondaparinux (*zur Propyhlaxe)* |
| 2. Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein. | *nicht angezeigt* |
| 3. Als Vergleichstherapie sollen bevorzugt Arzneimittel-anwendungen oder nicht-medikamentöse Behandlungen herangezogen werden, deren patientenrelevanter Nutzen durch den Gemeinsamen Bundesausschuss bereits festgestellt ist. | Apixaban, Nutzenbewertungsbeschlüsse des G-BA 6/2013 und 2/ 2015 |
| 4. Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören. | ⇨ *Siehe Recherche und Synopse der Evidenz* |

## II.

## III. Zugelassene Arzneimittel im Anwendungsgebiet

| **Wirkstoff**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet** |
|---|---|
| Zu prüfendes Arzneimittel: | |
| Edoxaban<br>Lixiana® | Behandlung von venösen Thromboembolien (VTE) einschließlich tiefer Venenthrombose (TVT) und Lungenembolie (LE) und Verhinderung von VTE-Rezidiven bei Erwachsenen |
| Apixaban<br>B01AF02<br>Eliquis® | Zur Prophylaxe venöser Thromboembolien (VTE) bei erwachsenen Patienten nach elektiven Hüft- oder Kniegelenksersatzoperationen.<br><br>Zur Prophylaxe von Schlaganfällen und systemischen Embolien bei erwachsenen Patienten mit nicht-valvulärem Vorhofflimmern (NVAF) und einem oder mehreren Risikofaktoren, wie Schlaganfall oder TIA (transitorischer ischämischer Attacke) in der Anamnese, Alter ≥75 Jahren, Hypertonie, Diabetes mellitus, symptomatische Herzinsuffizienz (NYHA Klasse ≥II) |
| Dabigatran<br>B01AE07<br>Pradaxa® | Behandlung aktuer tiefer Venenthrombosen (TVT) und / oder Lungenembolien (LE) / Prophylaxe von rezidivierenden TVT und LE bei Erwachsenen und assoziiertem Tod. |
| Enoxaparin<br>B01AB05<br>Clexane® | *Clexane 40 mg, Clexane 40 mg Duo, Clexane 40 mg Klinik, Clexane 40 mg Praxis:*<br>Therapie tiefer Venenthrombosen mit und ohne Lungenembolie.<br>Peri- und postoperative Primärprophylaxe tiefer Venenthrombosen bei Patienten mit hohem thromboembolischen Risiko (z. B. orthopädische Chirurgie). |
| Heparin-Natrium<br>B01AB01<br>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)<br>- zur Antikoagulation bei Behandlung oder Operation mit extrakorporalem Kreislauf (z. B. Herz-Lungen-Maschine, Hämodialyse)<br>- Prophylaxe von thromboembolischen Erkrankungen |
| | |
| Danaparoid<br>B01AB09<br>Orgaran® | b) Behandlung von thromboembolischen Erkrankungen bei Patienten, die eine dringende parenterale Antikoagulation benötigen und entweder eine HIT haben oder in der Anamnese aufweisen. |
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| Phenprocoumon | Behandlung und Prophylaxe von Thrombose und Embolie. |

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| Marcumar®<br>B01AA04 | Langzeitbehandlung des Herzinfarktes, wenn ein erhöhtes Risiko für thromboembolische Komplikationen gegeben ist. |
| Phenprocoumon<br>B01AA04<br>Phenpro.-<br>ratiopharm® | Langzeitbehandlung und Vorbeugung<br>– der Blutpfropf-Bildung (venöse und arterielleThrombosen)<br>– des Verschlusses von Blutgefäßen durch Blutpfropf (venöse und arterielle Embolien). |
| Warfarin-Natrium<br>B01AA03<br>Coumadin® | Prophylaxe und Therapie thromboembolischer Erkrankungen |
| | |
| Fondaparinux<br>B01AX05<br>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.<br>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).<br>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<br>B01AX06<br>Xarelto® | Behandlung von tiefen Venenthrombosen (TVT) und Lungenembolien (LE) sowie Prophylaxe von rezidivierenden TVT und LE bei Erwachsenen. |
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Quellen: AMIS-Datenbank, Fachinformationen

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## 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:**

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| 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**

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| **Akl et al. (2011):** Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. | Systematische Literaturrecherche nach RCTs<br><br>**Population:** Krebspatienten mit objektiv bestätigter VTE oder LE<br><br>**Vergleich:** low molecular weight heparin (LMWH), unfractionated heparin (UFH) und Fondaparinux<br><br>**Endpunkte:** Mortalität nach 3 Monaten Follow-up, rezidivierende VTE, majore und minore Blutungen<br><br>**Ergebnisse** (basierend auf 16 Studien mit N= 1371 Patienten):<br>13 Studien zum Vergleich LMWH versus UFH<br>2 Studien zum Vergleich Fondaparinux versus Heparin **(Enoxaparin und UFH)**<br>1 Studie zum Vergleich Dalteparin versus Tinzaparin<br>**LMWH versus UFH:**<br>Mortalität<br>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.<br>Nach Ausschluss von Studien minderer Qualität blieb das Ergebnis ähnlich: RR= 0.72; 95%KI 0.52-1.00).<br>Rezidivierende VTE<br>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).<br><br>**Heparin versus Fondaparinux:**<br>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).<br><br>**Dalteparin versus Tinzaparin**<br>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).<br><br>**Schlussfolgerung der Autoren:**<br>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 thromboembolism | Systematische Literaturrecherche nach RCTs<br><br>**Population**: Krebspatienten mit objektiv bestätigter VTE oder LE<br><br>**Vergleich**: low molecular weight heparin (LMWH), Vitamin K Antagonisten (VKA) und Ximelagatran |

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| in patients with cancer. | **Endpunkte**: Mortalität nach 3 Monaten Follow-up, rezidivierende VTE oder PE, majore und minore Blutungen, Thrombozytopenie, Postphlebitisches Syndrom<br><br>**Ergebnisse** (basierend auf 9 Studien mit N= 1908 Patienten):<br>**LMWH versus VKA** (n=7 RCT)<br>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.<br><br>**Ximelagatran** (24 mg zweimal täglich) **versus Placebo** (n=1 RCT)<br>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.<br><br>**Dabigatran versus VKA** (n=1 RCT)<br>Hier gab es keine signifikanten Unterschiede.<br><br>**Schlussfolgerung der Autoren:**<br>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<br><br>**Population**: Patienten mit objektiv bestätigter VTE oder LE<br><br>**Vergleich**: low molecular weight heparin (LMWH) versus Vitamin K Antagonisten (VKA)<br><br>**Endpunkte**: Mortalität in den ersten 3 Monaten nach Therapiezuweisung, rezidivierende VTE oder LE, majore Blutungen<br><br>**Ergebnisse** (basierend auf 15 Studien mit N= 3197 Patienten):<br>**LMWH versus VKA**<br>Für den Endpunkt Mortalität ergaben sich keine statistisch signifikanten Unterschiede (OR=1.06, 95% KI 0.74 - 1.54).<br>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.<br>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). |

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| | **Schlussfolgerung der Autoren:**<br>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.<br>Treatment with LMWH is significantly safer than treatment with vitamin K antagonists.<br>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<br><br>**Population**: Patienten mit akuter LE<br><br>**Vergleich**: Thrombolytische Therapie (Streptokinase, Urokinase, gewebespezifische Plasminogenaktivator (rt-PA) oder Alteplase) versus Heparin (allein oder mit Placebo)<br><br>**Endpunkte**: Mortalität, rezidivierende LE, minore und majore Blutungen<br><br>**Ergebnisse** (basierend auf 8 Studien mit N= 679 Patienten):<br>**Thrombolyse versus Heparin oder Heparin plus Placebo**<br>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.<br>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)<br><br>**Schlussfolgerung der Autoren:**<br>Based on the limited evidence found we cannot conclude whether thrombolytic therapy is better than heparin for pulmonary embolism.<br>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<br><br>**Population**: Patienten mit akuter VTE<br><br>**Vergleich**: subkutanes UFH versus subkutanes LMWH oder intravenöses UFH<br><br>**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<br><br>**Ergebnisse** (basierend auf 15 Studien mit N= 3054 Patienten):<br>**Subkutanes UFH versus subkutanes LMWH oder intravenöses UFH** |

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| | 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).<br><br>**Schlussfolgerung der Autoren:**<br>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

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| **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<br><br>**Population**: Patienten mit akuter, symptomatischer VTE, LE oder beidem<br><br>**Vergleich**: NOAC mit oder ohne initialer Heparingabe versus Vitamin K Antagonisten mit initialer Heparingabe<br><br>**Endpunkte**: rezidivierende VTE, majore Blutungen, Gesamtmortalität<br><br>**Ergebnisse** (basierend auf 9 Studien mit N= 16.701 Patienten, bzw. 16.611 für Blutungen):<br><br>***Rezidivierende VTE***<br>Hier ergaben sich keine signifikanten Unterschiede zwischen den Behandlungsarmen.<br>Rivaroxaban vs. VKA (n=4 Studien): RR=0,85; 95%KI 0,55-1,31<br>Dabigatran vs. VKA (n=2 Studien): RR=1,09; 95%KI 0,76-1,57<br>Ximelagatran vs. VKA (n=2 Studien): RR=1,06; 95%KI 0,62-1,80<br>Apixaban vs. VKA (n=1 Studie): RR=0,98; 95%KI 0,20-4,79<br><br>***Majore Blutungen***<br>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).<br><br>***Gesamtüberleben***<br>Hier ergaben sich für keinen Vergleich signifikante Unterschiede.<br><br>**Abb.:** Relative risk for major bleeding with novel anticoagulants *v* traditional treatment with vitamin K antagonists |

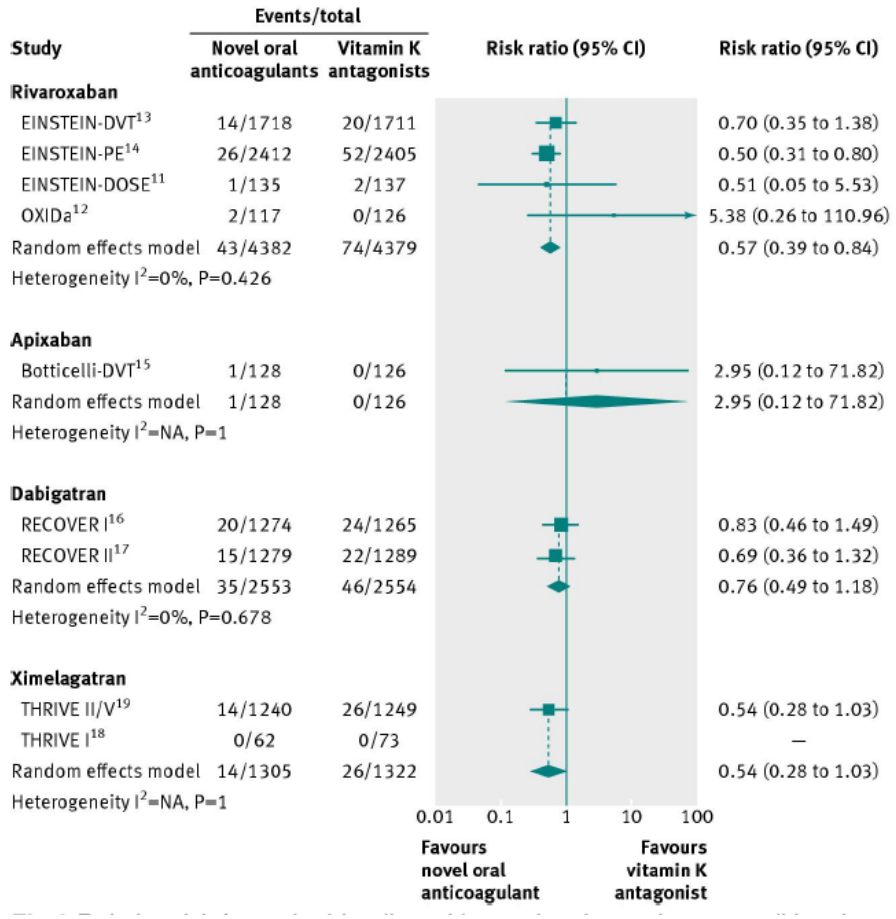


**Abb.:** Relative risk for all cause mortality with novel anticoagulants *v* traditional treatment with vitamin K antagonists

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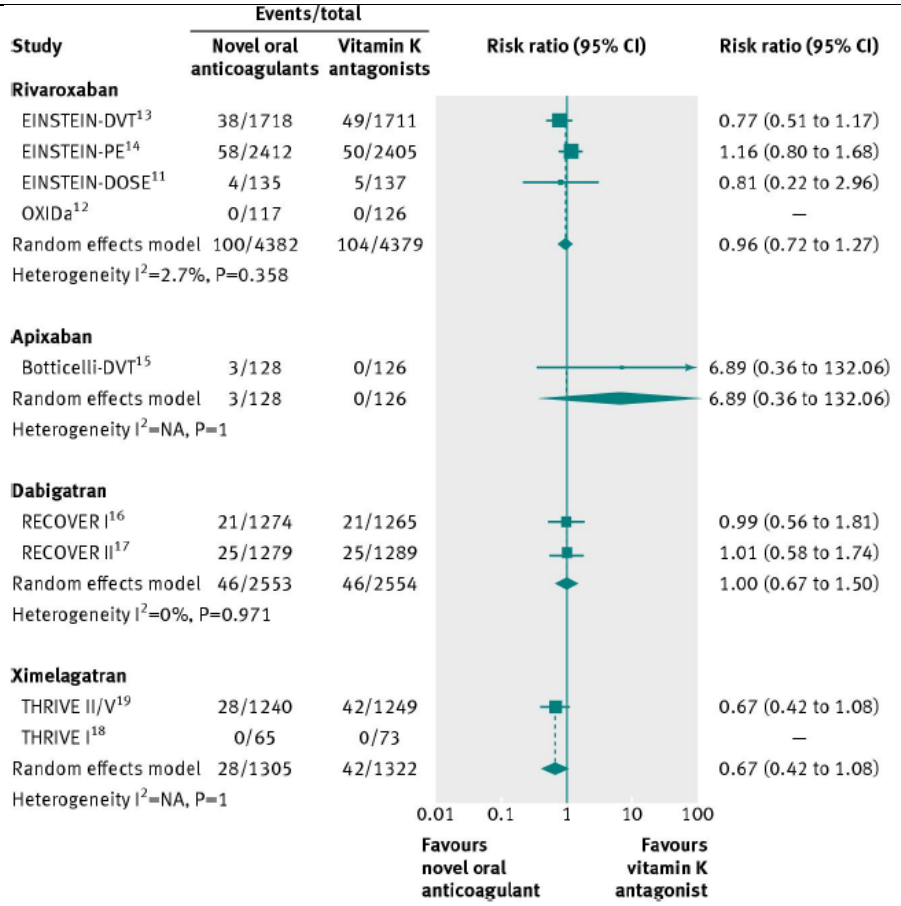
| |  <br>Im adjustierten indirekten Vergleich von Rivaroxaban versus Dabigatran ergab sich kein signifikanter Vorteil für einen der beiden Wirkstoffe hinsichtlich rezidivierender VTE (RR=0,78; 95%KI 0,49-1,24) oder majoren Blutungen (RR=0,75; 95%KI 0,41-1,34) |
| **Bochenek (2012):** The treatment of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

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| | (n=13 Studien, 2.908 Patienten)<br>Behandlung: LMWH versus VKA: OR=0,62 (95%KI 0,46-0,83) im FE-Modell, $I^2$=20%<br>Follow-up: LMWH versus VKA: OR=0,75 (95%KI 0,59-0,97) im FE-Modell, $I^2$=43%<br><br>***Blutungen (majore oder minore) unter Behandlung bzw. bis Ende des Follow-up*** (n=11 Studien, 2.520 Patienten)<br>Behandlung: LMWH versus VKA: OR=0,56 (95%KI 0,43-0,71) im FE-Modell, $I^2$=0%<br>Follow-up: LMWH versus VKA: OR=0,59 (95%KI 0,47-0,74) im FE-Modell, $I^2$=36%<br>Darüber hinaus wurden Subgruppenanalysen durchgeführt für Krebspatienten und nicht-Krebspatienten.<br>TVT unter Behandlung bzw. bis Ende des Follow-up<br>Krebspatienten (n=5 Studien, 1.014 Patienten):<br>Behandlung: OR=0,40 (95%KI 0,24-0,67) im FE-Modell, $I^2$=0%<br>Follow up: OR=0,44 (95%KI 0,27-0,72) im FE-Modell, $I^2$=0%<br>Nicht-Krebspatienten (n=3 Studien, 744 Patienten):<br>Behandlung: OR=0,55 (95%KI 0,21-1,46) im FE-Modell, $I^2$=29%<br>Follow-up: OR= 0,86 (95%KI 0,46-1,59) im FE-Modell, $I^2$=0%<br><br>VTE unter Behandlung bzw. bis Ende des Follow-up<br>Krebspatienten (n=5 Studien, 1.014 Patienten):<br>Behandlung: OR=0,47 (95%KI 0,31-0,71) im FE-Modell, $I^2$=0%<br>Follow up: OR=0,46 (95%KI 0,31-0,69) im FE-Modell, $I^2$=0%<br>Nicht-Krebspatienten (n=3 Studien, 744 Patienten):<br>Behandlung: OR=1,06 (95%KI 0,51-2,20) im FE-Modell, $I^2$=13%<br>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-analysis. | 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.<br><br>Randomisierte (prospektive) Studien<br><br>**Suchzeitraum**:<br>Bis 2013<br><br>**Population:**<br>consecutive patients with objectively confirmed, symptomatic. deep vein thrombosis or pulmonary embolism treated for a minimum of three months with anticoagulant treatment<br>(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.

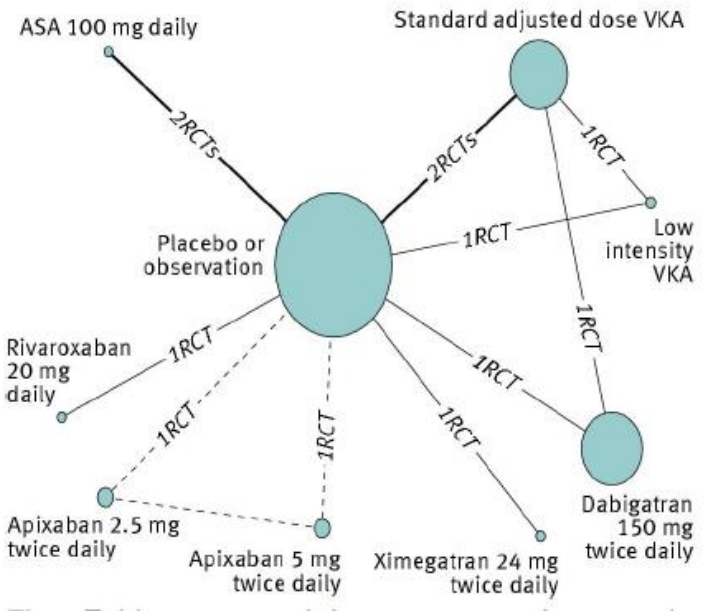

**Fig 1** Evidence network for recurrence of venous thromboembolism. The width of lines for each connection in the evidence network are proportional to the number of randomised controlled trials (RCTs) comparing each pair of treatments. The size of each treatment node is proportional to the number of 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

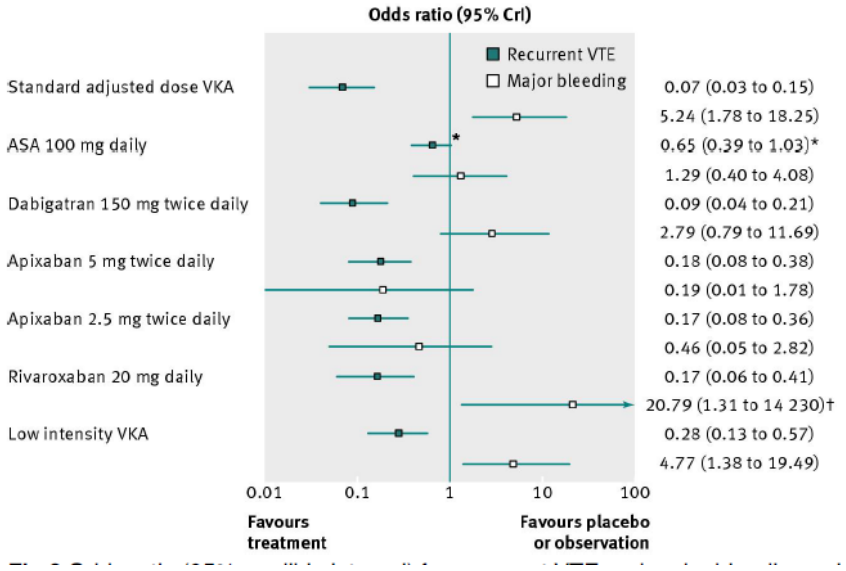


**Fig 2** Odds ratio (95% credible interval) for recurrent VTE and major bleeding episodes in Bayesian network meta-analysis versus placebo or observation. CrI=credible interval. *Estimates are derived from random effects, Bayesian network meta-analysis, which treats between study variance as an informative 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

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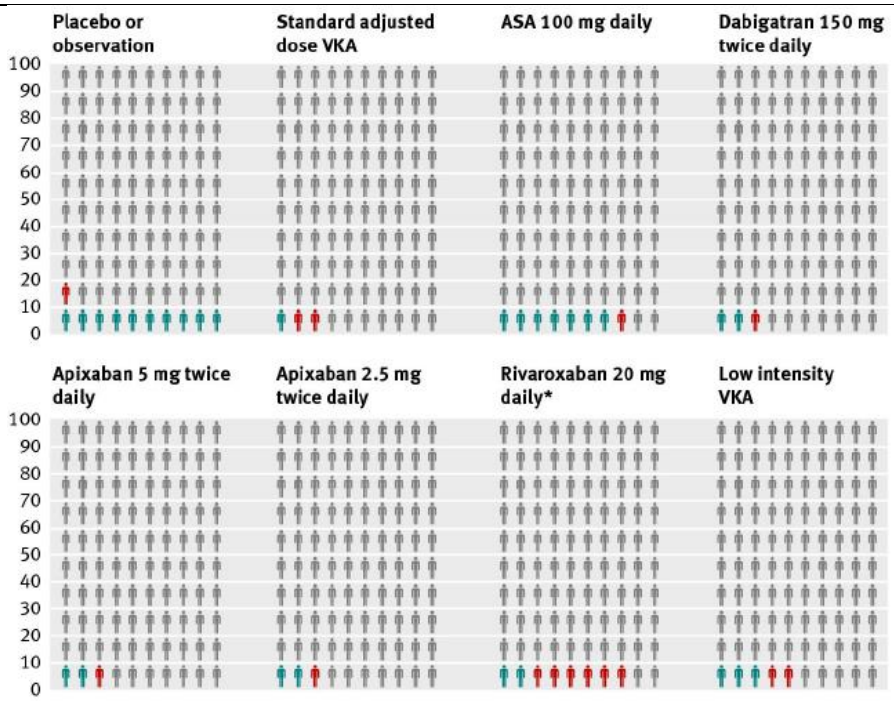
| |  <br>**Fig 4** Icon array showing absolute risks of recurrent VTE (blue) and major bleeding episodes (red). *Only one study investigated rivaroxaban for major bleeding and contained a zero cell (0 of 590 people receiving placebo and four of 598 receiving rivaroxaban), which resulted in uncertain estimates of effect<br><br>**Schlussfolgerungen der Autoren:**<br>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 weight heparin: An update of the evidence | Narratives Review<br>… 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.<br><br>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<br>outcomes relevant to PTS)<br><br>**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<br>VKA 4.3 | NS | LMWH 4.3<br>VKA 12.8 | 0.04 |
| Das et al. 1996 (7) | Dalteparin 5000 U od (n=50) | Warfarin (n=55) | 3 | LMWH 10.0<br>VKA 3.6 | NS | LMWH 0<br>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<br>VKA 6.9 | NS | LMWH 4.0<br>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<br>VKA 23.7 | <0.05 | LMWH 1.1<br>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<br>VKA 2.0 | NS | LMWH 2.0<br>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<br>VKA 9.1 | NS | LMWH 0[f]<br>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<br>VKA 3.6 (Group A)<br>VKA 0.8 (Group B) | NS | LMWH 2.1<br>VKA 1.9 (Group B)<br>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<br>VKA 5.8 | NS | LMWH 10.0<br>VKA 13.5 | NS |
| Hull et al. 2007 (14) | Tinzaparin 175 IU/kg od (n=369) | Warfarin (n=368) | 3 | LMWH 8.9[g]<br>VKA 9.8[g] | NS | LMWH 13.0<br>VKA 19.8 | 0.011 |
| Hull et al. 2009 (15) | Tinzaparin 175 IU/kg od (n=240) | Warfarin (n=240) | 3 | LMWH 3.3<br>VKA 3.3 | NS | LMWH 9.2<br>VKA 9.2 | NS |
| Romera et al. 2009 (16) | Tinzaparin 175 IU/kg od (n=119) | Acenocoumarol (n=122) | 6 | LMWH 4.2<br>VKA 5.7 | NS | LMWH 0.8[h]<br>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; LMWH 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

| | |
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| | • Studienauswahl allein in PubMed<br>• keine Bewertung der Publikationsqualität/ methodischer Studienqualität |
| **McManus RJ et al. (2011):** Thromboembolism. | Systematisches Review von systematischen Reviews mit RCTs und von RCTs<br>Fragestellung:<br>1. What are the effects of treatments for proximal DVT?<br>2. What are the effects of treatments for pulmonary embolism?<br><br>**Interventionen:**<br>Siehe unten<br><br>**Vergleiche:**<br>nicht vorab spezifiziert (siehe unten)<br><br>**Suchzeitraum**: 1966 bis 2010<br><br>**Outcomes**<br>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.<br><br>Evidenzkennzeichnung:<br>• *High-quality evidence* Further research is very unlikely to change our confidence in the estimate of effect.<br>• *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.<br>• *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.<br>• *Very low-quality evidence* Any estimate of effect is very uncertain.<br><br>**Ergebnisse:**<br>***1. Deep venous thrombosis (DVT)***<br>***Compression stockings***<br>• 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).<br>Post-thrombotic syndrome<br>• *Compared with placebo or no treatment* Compression stockings are more effective at reducing post-thrombotic syndrome at 3 to 76 months (high-quality evidence).<br>• *Different durations of stockings compared with each* |

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| | *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).<br>• We found no clinically important results from RCTs about the effects of different types of compression stockings.<br><br>***Low molecular weight heparin (LMWH)***<br>Mortality<br>*Compared with unfractionated heparin* Low molecular weight heparin (LMWH) is more effective at reducing mortality at 3 to 6 months (high-quality evidence).<br>Rate of symptomatic recurrence<br>*Compared with unfractionated heparin* LMWH is more effective at reducing both recurrence of pulmonary embolus and DVT (moderate-quality evidence).<br>Adverse effects<br>LMWH is associated with reduced risk of major haemorrhage compared with unfractionated heparin.<br><br>***Long-term oral anticoagulation***<br>Mortality<br>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).<br>Rate of symptomatic recurrence<br>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).<br>Compared with LMWH Long-term oral anticoagulation is as effective at reducing recurrence of thromboembolism at 3 to 12 months (low-quality evidence).<br>We found no clinically important results from RCTs about the effects of oral anticoagulation compared with placebo in people with thromboembolism.<br><br>***Long-term oral anticoagulation***<br>Mortality<br>*Compared with short-term anticoagulation* Long-term oral anticoagulation may be no more effective at reducing mortality (low-quality evidence).<br>Rate of symptomatic recurrence<br>*Compared with short-term anticoagulation* Long-term oral anticoagulation may be more effective during treatment<br>but may be no more effective at preventing recurrent venous thromboembolism after treatment (low-quality evidence).<br>Adverse effects<br>Although the risk of recurrence drops over time, the risk |

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| | of bleeding remains stable while anticoagulant treatment continues.<br><br>***Long-term low molecular weight heparin (LMWH)***<br>Mortality<br>*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).<br>Rate of symptomatic recurrence<br>*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).<br>Adverse effects: major haemorrhage<br>Long-term LMWH and long-term unfractionated heparin may be equally likely to cause major haemorrhage (very low-quality evidence).<br><br>Mortality<br>*Compared with unfractionated heparin* Low molecular weight heparin (LMWH) is as effective at reducing mortality at 3 months (moderate-quality evidence).<br>Rate of symptomatic recurrence<br>*Compared with unfractionated heparin* LMWH is as effective at reducing venous thromboembolism at 3 months (moderate-quality evidence).<br><br>***Vena cava filter***<br>*Mortality*<br>*Compared with no filters* Vena cava filters are no more effective at reducing mortality at 8 years (moderate-quality evidence).<br>Pulmonary embolism<br>*Compared with no filters* Vena cava filters are more effective at preventing pulmonary embolism at 12 days, and at 8 years (low-quality evidence).<br>Rate of symptomatic recurrence<br>*Compared with no filters* Vena cava filters increase the risk of recurrent DVT at 8 years (moderate-quality evidence).<br><br>***2. Pulmonary embolism***<br>***Heparin plus warfarin***<br>*Mortality*<br>*Compared with no anticoagulation* Heparin plus warfarin is more effective at reducing mortality at 1 year (moderate quality evidence).<br>*Adverse effects*<br>Anticoagulants are associated with increased risk of haemorrhage.<br>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 |

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| | effective.<br><br>***Prolonged anticoagulation (6–9 months)***<br>*Rate of symptomatic recurrence*<br>Compared with shorter duration of anticoagulation<br>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).<br>*Adverse effects*<br>Longer duration of anticoagulation has been associated with increased risk of haemorrhage.<br><br>***Low molecular weight heparin (LMWH) vs. unfractionated heparin***<br>Mortality<br>*Compared with unfractionated heparin* Low molecular weight heparin (LMWH) is as effective at reducing mortality at 3 months (moderate-quality evidence).<br>Rate of symptomatic recurrence<br>*Compared with unfractionated heparin* LMWH is as effective at reducing venous thromboembolism at 3 months (moderate-quality evidence).<br><br>***Thrombolysis vs. Heparin***<br>Mortality<br>*Compared with heparin* Thrombolysis is as effective at reducing mortality (high-quality evidence).<br>Rate of symptomatic recurrence<br>*Compared with heparin* Thrombolysis is as effective at reducing recurrence of thromboembolism (high-quality evidence).<br><br>**high-intensity oral anticoagulation**<br>We found no clinically important results from RCTs about the effects of high-intensity oral anticoagulation in people with pulmonary embolism.<br><br>**Schlussfolgerung der Autoren:**<br>• Oral anticoagulants are considered effective in people with proximal DVT compared with no treatment, although we found few trials.<br>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.<br>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.<br>We don't know how effective tapering off of oral anticoagulant agents is compared with stopping abruptly.<br>We don't know whether once-daily LMWH is as effective as twice-daily administration at preventing recurrence.<br>Home treatment may be more effective than hospital- |

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| | based treatment at preventing recurrence, and equally effective<br>in reducing mortality.<br>Vena cava filters reduce the short-term rate of pulmonary embolism, but they may increase the long-term risk of recurrent DVT.<br>Elastic compression stockings reduce the incidence of post-thrombotic syndrome after a DVT compared with placebo or no treatment.<br>• 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.<br>• 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):**<br><br>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<br>Einschluss: nur RCTs<br><br>**Suchzeitraum:** 2001 – 02/ 2013<br><br>**Population**:<br>venous thromboembolism (VTE);<br>excluded trials of primary prevention in medically-ill patients<br><br>**Intervention**:<br>NOACs (apixaban, rivaroxaban and dabigatran);<br>long term treatment<br><br>**Kontrolle**:<br>any comparators (placebo or warfarin)<br><br>**Outcomes:**<br>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),<br>duration of follow-up of atleast 6 months<br><br>**Relevante Studien/ Patientenzahl:** 4 (n= 4877**)**<br><br>**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 [Confidei 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,

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| | 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)<br><br>**Suchzeitraum**:<br>bis Oktober 2013<br><br>**Population**:<br>Acute venous thromboembolism (VTE);<br>(population with either objectively diagnosed acute DVT, PE or both)<br><br>**Intervention**:<br>New direct oral anticoagulants (NOACs)<br>• orally administered direct factor IIa inhibitor (including but not limited to dabigatran)<br>• a direct factor Xa inhibitor (including but not limited to edoxaban, rivaroxaban and apixaban)<br><br>**Vergleich**:<br>VKA<br><br>**Outcomes**:<br>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]<br><br>**Studienanzahl / Patientenanzahl:** 5 (24 455)<br><br>**Ergebnisse:**<br><br>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

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| | 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).<br>• All combined relative risks were significantly lower for the patients treated with NOACs, except that for major gastrointestinal bleeding.<br><br>**Schlussfolgerung der Autoren**:<br>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.<br>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. |

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| **UMHS (2009):** Venous Thromboembolism (VTE). | University of Michigan Health System<br><br>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.<br><br>**Treatment:**<br>**Heparin**<br>Low molecular weight heparin (LMWH) preferred.<br>LMWH is preferred over unfractionated heparin (UFH) for both safety and cost reasons [IA].<br>Outpatient use of LMWH for DVT.<br>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.<br>**Unfractionated heparin.**<br>If UFH is used, it should be initiated and dosed in a structured manner (see<br>Apendix A; dargestellt als Abb. 2) to achieve therapeutic levels quickly, without excessive adjustment of dosing [IIA].<br>Minimum time period.<br>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].<br>If heparin contraindicated.<br>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<br>candidates for one of the new non-heparin anticoagulant agents (e.g., lepirudin, argatroban). [IIB]<br>Those who cannot use any anticoagulant should have an inferior vena cava filter placed to prevent pulmonary embolization [IIB].<br>**Warfarin**.<br>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]<br>If warfarin contraindicated.<br>Patients who can receive heparin but cannot take warfarin (e.g., during pregnancy) may be anticoagulated with full-dose subcutaneous heparin [IA], preferably LMWH.<br><br>**Strength of recommendation:**<br>I= generally should be performed; II = may be reasonable to perform; III = generally should not be performed.<br>**Levels of evidence** for the most significant recommendations<br>A = randomized controlled trials; B=controlled trials, no randomization; C=observational trials; D=opinion of expert panel. |

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| **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**<br>**Recommendations.**<br>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.<br>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.<br>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.<br>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].<br><br>**Early maintenance and long-term treatment of established VTE**<br>**Recommendations.**<br>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.<br>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.<br>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.<br>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].<br><br>**Treatment of VTE recurrence in cancer patients under anticoagulation**<br>**Recommendation.**<br>In the event of VTE recurrence, three options can be considered:<br>(i) switch from VKA to LMWH in patients treated with VKA;<br>(ii) increase in LMWH dose in patients treated with LMWH, and<br>(iii) vena cava filter insertion<br>[Best clinical practice, based on evidence of very low quality and an unknown balance between desirable and undesirable effects].<br>Values and preferences: individual decision.<br><br>**New oral anticoagulant agents (NOAC)**<br>The experts of the working group acknowledge the potential benefit of |

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| | 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'.<br><br>----------<br>High (A)<br>Further research is very unlikely to change our confidence in the estimate of effect<br>Moderate (B)<br>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate<br>Low (C)<br>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<br>Very low (D)<br>Any estimate of effect is very uncertain<br><br>Strong (Grade I)<br>The panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects Weak<br>Grade 2<br>The panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but is not confident.<br>Best clinical practice<br>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?**<br>**Patient Management Recommendations**<br><u>Level A recommendations.</u> None specified.<br><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.)<br><u>Level C recommendations.</u><br>(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.<br>(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.<br><br><u>Level A recommendations.</u> Generally accepted principles for patient |

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| | 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).<br>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).<br>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)<br>**Recommendations:**<br>***Initiate Anticoagulation***<br>• Clinicians should initially treat pulmonary embolism (PE) with unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) or fondaparinux (Bates, 2012 [Guideline]; Kearon, 2012 [Guideline]).<br>• Clinicians should initially treat most patients diagnosed with deep vein thrombosis (DVT) with LMWH or fondaparinux (Bates, 2012 [Guideline]; Kearon, 2012 [Guideline]).<br>• 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]).<br><br>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.<br>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.<br>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.<br><br>**Anm FBMed zur Evidenz bzgl. Fondaparinux:**<br>Kearon 2012: *Fondaparinux Compared With LMWH for the Initial Treatment of DVT:* The Matisse-DVT trial compared fondaparinux with LMWH for short-term<br>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<br>imprecision. Evidence that fondaparinux is effective for the treatment of PE supports the equivalence of fondaparinux to LMWH for the treatment of acute VTE.<br><br>**Maintenance Anticoagulation**<br>**Recommendations:**<br>• A goal INR of 2.5 (range 2.0-3.0) is recommended for patients with venous thromboembolism. (Holbrook, 2012 [Guideline]).<br>• Clinicians should generally use warfarin for continued anticoagulation.<br>• Clinicians should use low-molecular-weight heparin (LMWH) for patients with VTE in the setting of cancer. |

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| | • Clinicians may consider using rivaroxaban for continued anticoagulation.<br>• 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]).<br><br>**Warfarin**<br>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]).<br>**Low-Molecular-Weight Heparin**<br>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]).<br>**Rivaroxaban**<br>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]).<br>**Other Agents**<br>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.)<br>**Special Patient Populations**<br>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 Pulmonary Hypertension. A Scientific Statement From the American Heart Association. | **Recommendations for Initial Anticoagulation for Acute PE**<br>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).<br>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).<br><br>**Recommendations for Initial Anticoagulation for Patients With Iliofemoral Deep Vein Thrombosis (IFDVT)**<br>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).<br>2. Patients with IFDVT who have suspected or proven heparin-induced thrombocytopenia should receive a direct thrombin inhibitor (Class I; Level of Evidence B). |

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| | **Recommendations for Long-Term Anticoagulation Therapy for Patients With IFDVT**<br>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).<br>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).<br>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).<br>5. In children with DVT, the use of LMWH monotherapy may be reasonable (Class IIb; Level of Evidence C).<br><br>**Level of Evidence / Grad of Recommendation**<br><br>Table 1. Applying Classification of Recommendations and Level of Evidence<br><br>SIZE OF TREATMENT EFFECT →<br><br>ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT<br><br>**CLASS I** — *Benefit >>> Risk* — Procedure/Treatment **SHOULD** be performed/administered<br>**CLASS IIa** — *Benefit >> Risk* — *Additional studies with focused objectives needed* — **IT IS REASONABLE** to perform procedure/administer treatment<br>**CLASS IIb** — *Benefit ≥ Risk* — *Additional studies with broad objectives needed; additional registry data would be helpful* — Procedure/Treatment **MAY BE CONSIDERED**<br>**CLASS III** — *Risk ≥ Benefit* — Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**<br><br>**LEVEL A** — Multiple populations evaluated* — Data derived from multiple randomized clinical trials or meta-analyses<br>■ Recommendation that procedure or treatment is useful/effective<br>■ Sufficient evidence from multiple randomized trials or meta-analyses<br>■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Some conflicting evidence from multiple randomized trials or meta-analyses<br>■ Recommendation's usefulness/efficacy less well established<br>■ Greater conflicting evidence from multiple randomized trials or meta-analyses<br>■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Sufficient evidence from multiple randomized trials or meta-analyses<br><br>**LEVEL B** — Limited populations evaluated* — Data derived from a single randomized trial or nonrandomized studies<br>■ Recommendation that procedure or treatment is useful/effective<br>■ Evidence from single randomized trial or nonrandomized studies<br>■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Some conflicting evidence from single randomized trial or nonrandomized studies<br>■ Recommendation's usefulness/efficacy less well established<br>■ Greater conflicting evidence from single randomized trial or nonrandomized studies<br>■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Evidence from single randomized trial or nonrandomized studies<br><br>**LEVEL C** — Very limited populations evaluated* — Only consensus opinion of experts, case studies, or standard of care<br>■ Recommendation that procedure or treatment is useful/effective<br>■ Only expert opinion, case studies, or standard of care<br>■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Only diverging expert opinion, case studies, or standard of care<br>■ Recommendation's usefulness/efficacy less well established<br>■ Only diverging expert opinion, case studies, or standard of care<br>■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Only expert opinion, case studies, or standard of care<br><br>Suggested phrases for writing recommendations†<br>should / is recommended / is indicated / is useful/effective/beneficial<br>is reasonable / can be useful/effective/beneficial / is probably recommended or indicated<br>may/might be considered / may/might be reasonable / usefulness/effectiveness is unknown/unclear/uncertain or not well established<br>is not recommended / is not indicated / should not / is not useful/effective/beneficial / may be harmful<br><br>**Anmerkungen FBMed:**<br>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<br>**Initiating and monitoring pharmacologic interventions**<br>Outpatient therapy is preferred if no contraindications.<br>Contraindications to warfarin therapy:<br>Absolute: pregnancy, history of warfarin-induced skin necrosis<br>Relative: dementia, certain psychoses, diminished mental capacity, or childbearing age without contraception<br>• Begin LMWH. |

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| | • Begin warfarin after 1st dose of LMWH [A], on the same day, titrate to INR range of 2.0 - 3.0.<br>• Continue LMWH (along with warfarin) at least 5 days, and until INR range 2.0 - 3.0 for 2 consecutive days. [A]<br>• 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.<br>• Ask about any changes in diet, medications, supplements and herbal products, and compliance before any dosage adjustment.<br>• If known hypercoagulable state, consider referral to a coagulation specialist.<br><br>**Levels of Evidence** for the most significant recommendations:<br>A = randomized controlled trials;<br>B = controlled trials, no randomization;<br>C = observational studies;<br>D = opinion of expert panel |
| **Nicolaides et al. (2013):** Prevention and Treatment of Venous Thromboembolism. | **Recommendations for Treating VTE**<br>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).<br>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).<br>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).<br><br>**Recommendations for Treating VTE in Patients with cancer**<br>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).<br><br>**Level of Evidence**<br>High: RCTs with consistent results or systematic reviews directly applicable to the target population.<br>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.<br>Low: question that has to be addressed by future studies. |

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| | **Anm FBMed:**<br>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**<br>The current criteria for drug treatment for acute PTE are as follows:<br>(1) Anticoagulation therapy is the treatment of choice for normotensive patients without right heart dysfunction.<br>(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.<br>(3) Thrombolytic therapy is the treatment of choice for patients with persistent shock and hypotension unless it is contraindicated.<br><br>**Acute PE – Long-Term Treatment**<br>[Levels of Recommendations]<br>Class I<br>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.<br>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.<br>3. In patients with persistent shock, hypotension, and unstable hemodynamics, thrombolytic therapy should be performed during the acute phase of acute PTE.<br>Class IIa<br>1. During the acute phase of acute PTE, thrombolytic therapy should be performed in normotensive patients with right heart dysfunction.<br>Class IIb<br>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.<br><br>**Chronic PE**<br>Anticoagulation Therapy<br>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).<br><br>**Deep Vein Thrombosis**<br>[Levels of Recommendations]<br>Class I<br>1. Combined use of heparin and warfarin in the treatment of acute DVT.<br>2. Heparin control with a target APTT of 1.5 to 2.5 times the control in the treatment of acute DVT. Class IIa<br>1. Systemic thrombolytic therapy in the treatment of acute DVT. Class IIb<br>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. |

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| | ----------<br>Class I: Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.<br>Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion regarding the usefulness/ efficacy of a procedure or treatment.<br>Class IIa: The weight of evidence/opinion is in favor of usefulness/efficacy.<br>Class IIb: Usefulness/efficacy is less well established by evidence/opinion.<br>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):**<br><br>Treatment of venous thromboembolism in patients with cancer: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET). | **Recommendations**<br>1) Patients with malignancies and acute VTE should be treated initially with LMWH (grade B).<br>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).<br>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).<br>4) In cancer patients with recurrent VTE during oral anticoagulant treatment and therapeutic INR, LMWH should be administered (grade D).<br>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).<br>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.<br>7) As in the general population with PE, thrombolysis is not suggested, other than in cases of PE associated with haemodynamic instability (grade D).<br>8) As in the general population with DVT, thrombolysis is not suggested other than in cases of venous gangrene (grade D).<br>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).<br>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).<br>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).<br>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).<br>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).<br>14) As in the general population, the use of elastocompression is also |

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| | suggested in patients with DVT and malignancy to prevent postphlebitic syndrome (grade D).<br>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).<br><br>**Anmerkung FBMed:**<br>keine Angaben zur Evidenzgraduierung |
| **Keeling et al. (2011):** Guidelines on oral anticoagulation with warfarin – fourth edition. | **Venous thromboembolism (VTE)**<br>**Recommendation**<br>• First episodes of VTE should be treated with an INR target of 2.5 (1A).<br>• 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).<br>• Recurrent VTE whilst anticoagulated and within the therapeutic range should be managed by increasing the INR target to 3.5 (2C).<br><br>**Duration of anticoagulation for pulmonary embolism (PE) and lower limb deep vein thrombosis (DVT)**<br>**Recommendation**<br>• Patients with proximal DVT or PE should be treated for at least 3 months (1A).<br>• If a diagnostic strategy that identifies isolated calf vein DVT is employed, treatment of such clots can be restricted to 6 weeks (1A).<br>• Patients with cancer-associated VTE should initially be treated for 6 months with therapeutic dose LMWH rather than warfarin (1A).<br><br>STRENGTH OF RECOMMENDATIONS:<br>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'.<br>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'.<br><br>QUALITY OF EVIDENCE<br>(A) High: Further research is very unlikely to change confidence in the estimate of effect.<br>(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate.<br>(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<br>**Further management of venous thromboembolism**<br>**choice of anticoagulant**<br>Low molecular weight heparin rather than warfarin should be considered in venous thromboembolism associated with cancer (A).<br><br>**Duration of anticoagulation in lower limb deep vein thrombosis and pulmonary embolism**<br>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)<br><br>**Grade of Recomdendation** |

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| | (A): At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or<br>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):**<br><br>Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. | **Ziel / Fragestellung:**<br>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.<br><br>**Suchzeitraum der systematischen Literaturrecherche:** bis 2012<br><br>**GoR und LoE** nicht angegeben<br><br>**Empfehlungen** (pharmakologische Initialbehandlung und Versorgung bei Rezidiv):<br>● 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<br>● Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE<br>● Anticoagulation should not be used to extend survival in patients with cancer in the absence of other indications<br><br>Treatment and secondary prophylaxis<br>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<br>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<br>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<br>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<br>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<br>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<br>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<br>Anticoagulation and survival<br>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):**<br>Antithrombotics: indications and management. | Scottish Intercollegiate Guidelines Network<br>**Empfehlungen**<br>Antiplatelet Agents<br>To minimise the risk of bleeding, the lowest recommended dose of aspirin should be used for the clinical indication [GoR A]. |

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| (Guideline No. 129) | **Weitere Ausführungen**<br>*Patients with active thromboembolism*<br>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+]<br>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]<br><br>*Reversal of oral anticoagulant therapy in patients with bleeding or high INR*<br>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+]<br>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+]<br>Where the INR is >5, observational data suggest the risk of haemorrhage in asymptomatic patients increases as the INR rises. [LoE 2-]<br>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+]<br><br>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 |

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| | required heparin dose, however a dose cap should be considered and heparin monitoring with dose adjustment is still required. *[LoE = 4]*<br><br>*Rivaroxaban , Dabigatran exilate and apixaban*<br>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 | |
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| 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<br>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 | |
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| *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<br>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*<br>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*<br>Extrapolated evidence from studies rated as $2^{++}$ |
| D | Evidence level 3 or 4; or<br>Extrapolated evidence from studies rated as $2^{+}$ |

**Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren**

| **Erstautor, Jahr**<br>Titel | **Inhalt** |
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| **HSC (2013):**<br>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.<br>**Target group**<br>Treatment of acute symptomatic and long-term prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE).<br>**Existing comparators**<br>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:<br>• Mechanical and physical methods such as: early mobilisation, intermittent pneumatic compression devices, and mechanical foot pumps.<br>• Prophylactic anticoagulant drugs including: unfractionated heparin, LMWH (dalteparin and enoxaparin), fondaparinux (all subcutaneous administration) and rivaroxaban. |
| **Prescrire (2013):**<br>**Deep venous thrombosis and pulmonary embolism** | Review auf der Basis einer Literaturrecherche ab dem Jahr 2006 bis 11 / 2012.<br><br>• Deep venous thrombosis limited to the calf leaves downstream veins<br>• 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.<br>• 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.*<br>• 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.<br>• Intravenous thrombolysis should be considered In case of massive pulmonary embolism, as it appears to prevent 1 death per 15 patients.<br>• After initial heparin therapy, continuing treatment with LMWH or switching to *warfarin,* a vitamin K antagonist, are two |

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| | options which overall have similar harm-benefit balances.<br>• 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.<br>• 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.<br>• 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.<br>• In patients with calf thrombosis due to a transient triggering factor, 6 weeks of anticoagulation seems sufficient.<br>• 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.<br>• In cancer patients, it is usually better to prolong treatment beyond 3 months.<br>• 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.<br><br>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 |
|---|---|
| #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 ((((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] ) |
| #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 | ((((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 |
| #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 or VTE or PE or DVT:ti (Word variations have been searched) |
| #5 | #1 or #2 or #3 or #4: 2013 to 2014 |

Cochrane Database of Abstracts of Reviews of Effects (DARE) und Cochrane Health Technology Assessment (HTA) Database am 09.01.2013

| 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 - |

| Suchschritt | Suchfrage |
|---|---|
| | 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: 2013 to 2014 |

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# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

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## Indikation für die Recherche bei Edoxaban:

Verhinderung von Schlaganfällen und systemischen Embolien bei erwachsenen Patienten mit nicht-valvulärem Vorhofflimmern mit einem oder mehreren Risikofaktoren wie kongestive Herzinsuffizienz, Bluthochdruck, Alter ≥75 Jahren, Diabetes mellitus, Schlaganfall oder transitorische ischämische Attacke (TIA) in der Anamnese.

## Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel:

## IV. Zweckmäßige Vergleichstherapie: Kriterien der VerfO

**Edoxaban (2014-B-034)**
**Verhinderung von Schlaganfällen und systemischen Embolien [Anwendungsgebiet abgekürzt]**

| **Kriterien gemäß 5. Kapitel § 6 Absatz 3 Satz 2 VerfO** | |
|---|---|
| 1. Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben. | Rivaroxaban<br>Apixaban<br>Acetylsalicylsäure (ASS 50 mg-250 mg)<br>Clopidogrel (Monotherapie und in Kombination mit ASS)<br>Dabigatran<br>Ticlodipin<br>Dipyridamol + Acetylsalicylsäure (ASS)<br>Vitamin-K-Antagonisten<br>- Phenprocoumon<br>- Warfarin<br>Heparin |
| 2. Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein. | *nicht angezeigt* |
| 3. Als Vergleichstherapie sollen bevorzugt Arzneimittel-anwendungen oder nicht-medikamentöse Behandlungen herangezogen werden, deren patientenrelevanter Nutzen durch den Gemeinsamen Bundesausschuss bereits festgestellt ist. | • Apixaban, Nutzenbewertungsbeschlüsse G-BA 6/2013; 02/ 2015<br>• Verordnungseinschränkung Clopidogrel (AM-RL Anlage III Nr. 21, 21 a):<br>• Dipyridamol + ASS (Beschluss vom 16.05.2013; AM-RL, Anlage III, Nr. 53)<br>• Phenprocoumon, Warfarin: FB-Gruppe "Antikoagulantien, orale"; Stufe 2<br>• Heparin: FB-Gruppe Stufe 1 |
| 4. Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören. | *⇨ Siehe Recherche und Synopse der Evidenz* |
| 6. […] vorzugsweise eine Therapie, […] die sich in der praktischen Anwendung bewährt hat. | *nicht angezeigt* |

## V. Zugelassene Arzneimittel im Anwendungsgebiet

| **Wirkstoff**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Beratungsanforderung) |
|---|---|
| Zu prüfendes Arzneimittel: | |
| Edoxaban<br>Lixiana® | Verhinderung von Schlaganfällen und systemischen Embolien bei erwachsenen Patienten mit nicht-valvulärem Vorhofflimmern mit einem oder mehreren Risikofaktoren wie kongestive Herzinsuffizienz, Bluthochdruck, Alter ≥ 75 Jahren, Diabetes mellitus, Schlaganfall oder transitorische ischämische Attacke (TIA) in der Anamnese |
| Apixaban<br>B01AF02<br>Eliquis® | Zur Prophylaxe venöser Thromboembolien (VTE) bei erwachsenen Patienten nach elektiven Hüft- oder Kniegelenksersatzoperationen.<br><br>Zur Prophylaxe von Schlaganfällen und systemischen Embolien bei erwachsenen Patienten mit nicht-valvulärem Vorhofflimmern (NVAF) und einem oder mehreren Risikofaktoren, wie Schlaganfall oder TIA (transitorischer ischämischer Attacke) in der Anamnese, Alter ≥75 Jahren, Hypertonie, Diabetes mellitus, symptomatische Herzinsuffizienz (NYHA Klasse ≥II) |
| Acetylsalicylsaure<br>z.B. Aspirin N 100 mg ®<br>B01AC06 | instabile Angina pectoris – als Teil derStandardtherapie<br>– akuter Myokardinfarkt – als Teil der Standardtherapie<br>– Reinfarktprophylaxe – nach arteriellen gefäßchirurgischen oder interventionellen Eingriffen (z. B. nach ACVB, bei PTCA),<br>– zur Vorbeugung von transitorischen ischämischen Attacken (TIA) und Hirninfarkten, nachdem Vorläuferstadien aufgetreten sind |
| Clopidogrel<br>B01AC-04<br>Plavix® | Prävention atherothrombotischer Ereignisse Clopidogrel ist indiziert bei:<br>• erwachsenen Patienten mit Herzinfarkt (wenige Tage bis weniger als 35 Tage zurückliegend), mit ischämischem Schlaganfall (7 Tage bis weniger als 6 Monate zurückliegend) oder mit nachgewiesener peripherer arterieller Verschlusskrankheit,<br>• erwachsenen Patienten mit akutem Koronarsyndrom:<br>– akutes Koronarsyndrom ohne STStrecken-Hebung (instabile Angina Pectoris oder Non-Q-Wave-Myokardinfarkt), einschließlich Patienten, denen bei einer perkutanen Koronarintervention ein Stent implantiert wurde, in Kombination mit Acetylsalicylsäure (ASS),<br>– akuter Myokardinfarkt mit ST-Strecken- Hebung, in Kombination mit ASS bei medizinisch behandelten Patienten, für die eine thrombolytische Therapie infrage kommt.<br>Prävention atherothrombotischer und thromboembolischer Ereignisse bei Vorhofflimmern<br>Bei erwachsenen Patienten mit Vorhofflimmern, bei denen wenigstens ein Risikofaktor für vaskuläre Ereignisse vorliegt, die keine VKA-Therapie erhalten können und die ein geringes Blutungsrisiko aufweisen, ist Clopidogrel in Kombination mit ASS angezeigt zur Prophylaxe atherothrombotischer und thromboembolischer Ereignisse, einschließlich Schlaganfall. |
| Dabigatran<br>B01AE07 | Prävention von Schlaganfall und systemischer Embolie bei erwachsenen Patienten mit nicht valvulärem Vorhofflimmern mit einem oder mehreren Risikofaktoren, wie z. B. vorausgegangener Schlaganfall oder transitorische ischämische Attacke (TIA); Alter ≥ 75 Jahre; |

| | |
|---|---|
| Pradaxa® | Herzinsuffizienz (NYHA Klasse ≥ II); Diabetes mellitus; arterielle Hypertonie.Tod. |
| Enoxaparin<br>B01AB05<br>Clexane® | *Clexane 40 mg, Clexane 40 mg Duo, Clexane 40 mg Klinik, Clexane 40 mg Praxis:*<br>Therapie tiefer Venenthrombosen mit und ohne Lungenembolie.<br>Peri- und postoperative Primärprophylaxe tiefer Venenthrombosen bei Patienten mit hohem thromboembolischen Risiko (z. B. orthopädische Chirurgie). |
| Heparin-Natrium<br>B01AB01<br>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)<br>- zur Antikoagulation bei Behandlung oder Operation mit extrakorporalem Kreislauf (z. B. Herz-Lungen-Maschine, Hämodialyse)<br>- Prophylaxe von thromboembolischen Erkrankungen |
| | |
| Danaparoid<br>B01AB09<br>Orgaran® | a) Prophylaxe der tiefen Venenthrombose in Situationen, in denen Heparin nicht angewendet werden soll, einschließlich bei Patienten mit Heparin-induzierter Thrombozytopenie (HIT).<br>b) Behandlung von thromboembolischen Erkrankungen bei Patienten, die eine dringende parenterale Antikoagulation benötigen und entweder eine HIT haben oder in der Anamnese aufweisen |
| | |
| Phenprocoumon<br>Marcumar®<br>B01AA04 | Behandlung und Prophylaxe von Thrombose und Embolie.<br>Langzeitbehandlung des Herzinfarktes, wenn ein erhöhtes Risiko für thromboembolische Komplikationen gegeben ist. |
| Phenprocoumon<br>B01AA04<br>Phenpro.-ratiopharm® | Langzeitbehandlung und Vorbeugung<br>– der Blutpfropf-Bildung (venöse und arterielleThrombosen)<br>– des Verschlusses von Blutgefäßen durch Blutpfropf (venöse und arterielle Embolien). |
| Warfarin-Natrium<br>B01AA03<br>Coumadin® | Prophylaxe und Therapie thromboembolischer Erkrankungen.<br>– Langzeitbehandlung des Herzinfarktes, wenn ein erhöhtes Risiko für thromboembolische Komplikationen gegeben ist. |
| | |
| Fondaparinux<br>B01AX05<br>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.<br>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).<br>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<br>B01AX06<br>Xarelto® | Prophylaxe von Schlaganfällen und systemischen Embolien bei erwachsenen Patienten mit nicht-valvulärem Vorhofflimmern und einem oder mehreren Risikofaktoren, wie kongestiver Herzinsuffizienz, Hypertonie, Alter ab 75 Jahren, Diabetes mellitus, Schlaganfall oder transitorischer ischämischer Attacke in der Anamnese.<br>Behandlung von tiefen Venenthrombosen (TVT) und Lungenembolien (LE) sowie Prophylaxe von rezidivierenden TVT und LE bei Erwachsenen. (Bei hämodynamisch instabilen LE Patienten siehe Abschnitt 4.4.) |
| | |
| Ticlodipin<br>B01AC05<br>Ticlopidin-CT 250 mg | Zur Prophylaxe von thrombotischem Hirninfarkt bei Patienten nach transitorischen ischämischen Attacken (TIA), reversiblem ischämischem neurologischem Defizit (RIND) bzw. zur Prophylaxe bei Patienten, die einen thrombotischen Hirninfarkt durchgemacht haben (Sekundärprophylaxe). Diese Indikationen gelten nur für Patienten, bei denen eine Behandlung mit Acetylsalicylsäure nicht vertretbar ist.<br>Zur Hemmung der Thrombozytenaggregation bei Hämodialysepatienten mit Shuntkomplikationen, wenn Unverträglichkeitgegenüber acetylsalicylsäurehaltigen Präparaten besteht |
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Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

**Systematische Recherche:**

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation ***„Verhinderung von Schlaganfällen und systemischen Embolien bei Patienten mit Vorhofflimmern“*** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am ***08.05.2014*** abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien (z.B. NICE, SIGN). Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab **656** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden **129** Quellen eingeschlossen. Insgesamt ergab dies **35** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

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| ÄZQ | Ärztliches Zentrum für Qualität in der Medizin |
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| DAHTA | Deutsche Agentur für Health Technology Assessment |
| G-BA | Gemeinsamer Bundesausschuss |
| GIN | Guidelines International Network |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| NGC | National Guideline Clearinghouse |
| NHS CRD | National Health Services Center for Reviews and Dissemination |
| NICE | National Institute for Health and Care Excellence |
| NIHR HSC | National Institute for Health Research Horizon Scanning Centre |
| SIGN | Scottish Intercollegiate Guidelines Network |
| TRIP | Turn Research into Practice Database |
| WHO | World Health Organization |
| TIA | transitorische ischämische Attacke |

## IQWiG Berichte/ G-BA Beschlüsse

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| **Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL):** Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Apixaban (neues Anwendungsgebiet) | **Zugelassenes Anwendungsgebiet (neues Anwendungsgebiet vom 19. November 2012):**<br>Zur Prophylaxe von Schlaganfällen und systemischen Embolien bei erwachsenen Patienten mit nicht-valvulärem Vorhofflimmern (NVAF) und einem oder mehreren Risikofaktoren, wie Schlaganfall oder TIA (transitorischer ischämischer Attacke) in der Anamnese, Alter ≥75 Jahren, Hypertonie, Diabetes mellitus, symptomatische Herzinsuffizienz (NYHA Klasse ≥II).<br>**Zweckmäßige Vergleichstherapie:** Vitamin-K-Antagonisten<br><br>**Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Vitamin-K-Antagonisten:**<br>Hinweis für einen geringen Zusatznutzen. |
| **IQWIG 2013:** Apixaban (neues Anwendungsgebiet) – Nutzenbewertung gemäß § 35a SGB V | **Fragestellung/Ziele:**<br>„Prophylaxe von Schlaganfällen und systemischen Embolien bei erwachsenen Patienten mit nicht valvulärem Vorhofflimmern (NVAF) und einem oder mehreren Risikofaktoren, wie Schlaganfall oder TIA (transitorischer ischämischer Attacke) in der Anamnese, Alter ≥ 75 Jahren, Hypertonie, Diabetes mellitus, symptomatische Herzinsuffizienz (NYHA-Klasse ≥ II)“<br><br>**Population:** Erwachsene Patienten mit nicht valvulärem Vorhofflimmern und einem oder mehreren Risikofaktoren für einen Schlaganfall.<br><br>**Endpunkte**:<br><br>• Mortalität<br>- Gesamtmortalität<br>• Morbidität<br><br>- Schlaganfälle (verschiedene Operationalisierungen, inklusive zur Behinderung führender Schlaganfälle)<br>- systemische Embolie<br>- Myokardinfarkt<br>- transitorische ischämische Attacke (TIA)<br>• gesundheitsbezogene Lebensqualität<br>• Nebenwirkungen<br>- Blutungen<br>○ Kombination: größere Blutungen oder klinisch relevante nicht größere Blutungen<br>○ größere Blutungen (intrakranielle und extrakranielle größere Blutungen)<br>○ klinisch relevante nicht größere Blutungen<br><br>- Gesamtrate UE<br>- Gesamtrate SUE<br>- Gesamtrate UE, die zum Therapieabbruch geführt haben<br>• Mortalität, Morbidität und Nebenwirkungen<br>- Kombination: Schlaganfall, systemische Embolie, größere Blutungen oder Mortalität<br><br>**Ergebnis /Fazit:**<br>*Apixaban versus VKA:*<br>• Zusammenfassend ergibt sich für Patienten der VKA-Population **mit** |

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| | **Alter ≥ 65** Jahren ein **Hinweis für einen Zusatznutzen** (Ausmaß: beträchtlich) von **Apixaban gegenüber Warfarin**.<br><br>• Zusammenfassend ergibt sich für Patienten der VKA-Population **mit Alter < 65** Jahre **kein Beleg für einen Zusatznutzen gegenüber Warfarin.**<br><br>*Apixaban versus ASS:*<br>Insgesamt ergibt sich damit bei Betrachtung der Gesamtpopulation ein Hinweis auf einen **beträchtlichen Zusatznutzen von Apixaban gegenüber ASS.** |
| **IQWIG 2011:** Dipyridamol + ASS zur Sekundärprävention nach Schlaganfall oder TIA | **Fragestellung/Ziele:**<br>Ziel der vorliegenden Untersuchung war die Nutzenbewertung einer Behandlung mit der Wirkstoffkombination Dipyridamol und ASS in der Sekundärprävention nach ischämischem Schlaganfall oder TIA im Vergleich zu einer anderen medikamentösen Behandlung oder Placebo hinsichtlich patientenrelevanter Endpunkte.<br><br>**Population:** Erwachsene mit vorausgegangenem ischämischen Schlaganfall oder vorausgegangener TIA. Untersucht werden sollten sowohl Patienten im subakuten Stadium als auch in der langfristigen Sekundärprävention nach ischämischem Schlaganfall oder TIA<br><br>**Endpunkte**:<br>Gesamtmortalität<br><br>• vaskulär bedingte Mortalität<br>- tödlicher Schlaganfall<br>- vaskuläre Todesfälle ohne tödliche Insulte<br><br>• zerebral-vaskulär bedingte Morbidität<br>– Schlaganfall<br>– TIA<br>– physische und psychische Beeinträchtigung durch Folgekomplikationen des ischämischen Ereignisses, z. B. kognitive Leistungsfähigkeit<br><br>• nicht-tödlicher Myokardinfarkt<br>• Hospitalisierung<br>• unerwünschte Arzneimittelwirkungen<br>– Blutungen<br>– Gesamtraten unerwünschter Ereignisse (UE)<br>– Gesamtraten schwerwiegender unerwünschter Ereignisse (SUE)<br>– Studienabbrüche wegen UE<br><br>• gesundheitsbezogene Lebensqualität<br>• Bewältigung der Alltagsaktivitäten<br>• Abhängigkeit von Fremdhilfe oder Pflegebedürftigkeit<br><br>**Ergebnis /Fazit:**<br>• Es gibt einen Hinweis auf einen Nutzen der Kombinationsbehandlung mit Dipyridamol + ASS bezüglich der Verhinderung nicht-tödlicher Schlaganfälle und transitorisch ischämischer Attacken in der |

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| | Langzeittherapie (Behandlungsdauer mindestens 12 Monate).<br><br>• Es gibt keinen Beleg dafür, dass die Kombinationsbehandlung die Mortalität reduziert. Dem Hinweis auf einen Nutzen stehen Hinweise auf einen Schaden durch das Auftreten von schwerwiegenden und nicht schwerwiegenden Blutungen, Studienabbrüchen wegen unerwünschter Ereignisse sowie unerwünschten Ereignissen insgesamt gegenüber.<br><br>• Es gibt keinen Beleg dafür, dass die Kombinationsbehandlung mit Dipyridamol + ASS einen Zusatznutzen gegenüber einer Monotherapie mit einem Thrombozytenaggregationshemmer (ASS oder Clopidogrel) hat. Dabei gibt es keinen Anhaltspunkt dafür, dass sich diesbezüglich ein Unterschied in den Aussagen ergibt, wenn ASS oder Clopidogrel allein als Vergleichstherapie betrachtet werden.<br><br>• Dem fehlenden Zusatznutzen steht ein Beleg für einen größeren Schaden unter der Kombinationsbehandlung gegenüber. Dieser größere Schaden ergibt sich insbesondere aufgrund häufiger auftretender schwerwiegender Blutungen in der Langzeittherapie.<br><br>• *<u>Hinweis</u>: Dies ist das Ergebnis einer vornehmlich medizinisch begründeten zusammenfassenden Betrachtung gegenüber den Komparatoren Clopidogrel und ASS; ein separater Komparatorvergleich ergibt in beiden Fällen statistisch nicht signifikante Resultate zuungunsten der Kombinationsbehandlung, die dann aber in der Zusammenfassung bei nicht heterogener Datenlage statistisch signifikant werden. Bei Patienten unter 65 Jahre treten auch intrakranielle Blutungen häufiger auf (im Vergleich mit Clopidogrel). Es gibt keinen Beleg dafür, dass unter Dipyridamol + ASS im Vergleich mit ASS oder Clopidogrel andere schwerwiegende unerwünschte Ereignisse häufiger auftreten. Darüber hinaus gibt es für die Kurzzeittherapie einen Hinweis und für die Langzeittherapie einen Beleg dafür, dass Studienabbrüche wegen unerwünschter Ereignisse unter Kombinationsbehandlung häufiger auftreten.* |

**Cochrane Reviews**

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| **Salazar 2014:** Direct thrombin inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in people with nonvalvular atrial fibrillation. | 1. Fragestellung<br>To assess (1) the comparative efficacy of long-term anticoagulation using DTIs versus VKAs on vascular deaths and ischaemic events in people with non-valvular AF, and (2) the comparative safety of chronic anticoagulation using DTIs versus VKAs on (a) fatal and non-fatal major bleeding events including haemorrhagic strokes, (b) adverse events other than bleeding and ischaemic events that lead to treatment discontinuation and (c) all-cause mortality in people with non-valvular AF. |
| | 2. Methodik<br><br>Population: People with non-valvular AF and one or more risk factors for stroke.<br><br>Intervention: Administration of DTIs at standard doses (dabigatran 110 mg twice daily and 150 mg twice daily, AZD0837 300 mg twice daily and ximelagatran 36 mg twice daily)<br><br>Komparator: VKAs<br><br>Endpunkt:<br><u>Primärer Endpunkt</u>: The composite outcome of vascular deaths and ischaemic events, including non-fatal ischaemic strokes and transient ischaemic attacks (TIAs), non-fatal systemic embolic events (SEE) and non-fatal myocardial infarction (MI). Vascular death is defined as any death related to a vascular cause not including fatal haemorrhages or cardiovascular deaths (e.g. sudden arrhythmia, pump failure). Systemic embolism is defined as any event of acute non-intracerebral or non-coronary vascular origin including deep vein thrombosis (DVT) and pulmonary embolism (PE); the composite outcome of fatal or non-fatal major bleeding events, including haemorrhagic strokes.<br><br><u>Sekundäre Endpunkte</u>: Fatal or non-fatal adverse events other than haemorrhage and ischaemic events that lead to discontinuation of treatment; Death from all causes during treatment.<br><br>Suchzeitraum (Aktualität der Recherche): We searched the Cochrane Stroke Group Trials Register (July 2013), the Cochrane Central Register of Controlled Trials (CENTRAL), (The Cochrane Library, May 2013), MEDLINE (1950 to July 2013), EMBASE (1980 to October 2013), LILACS (1982 to October 2013) and trials registers (September 2013). We also searched the websites of clinical trials and pharmaceutical companies and handsearched the reference lists of articles and conference |

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| | proceedings.<br><br>Anzahl eingeschlossene Studien/Patienten (Gesamt): Eight studies involving a total of 27,557 participants with non-valvular AF and one or more risk factors for stroke; 26,601 of them were assigned to standard doses groups and included in the primary analysis. The DTIs: dabigatran 110 mg twice daily and 150 mg twice daily (three studies, 12,355 participants), AZD0837 300 mg once per day (two studies, 233 participants) and ximelagatran 36 mg twice per day (three studies, 3726 participants) were compared with the VKA warfarin (10,287 participants).<br><br>Qualität der Studien: Studies were heterogeneous in their individual quality assessment. They also varied in design (phase II and phase III), primary and secondary analyses (intention-to-treat (ITT) versus per protocol (PP)) and displayed some diversity in the reporting of outcomes. Nonetheless, all eight studies were judged to be adequate to address the main objectives of the review. |
| | 3. Ergebnisdarstellung<br>**Primärer Endpunkt:** Vascular deaths and ischaemic events were not significantly different between all DTIs and warfarin. The analysis of individual drugs within the class showed also no significant differences.<br><br>Sensitivity analyses of individual doses of dabigatran showed that numerically fewer events were observed for both dabigatran doses but only dabigatran 150 mg twice daily was significantly superior to warfarin for the primary endpoint (OR 0.86, 95% CI 0.75 to 0.99).<br><br>**Safety:** Fatal and non-fatal major haemorrhages, including haemorrhagic strokes, occurred less frequently with the DTIs compared with VKAs (OR 0.87, 95% CI 0.78 - 0.97). The sensitivity analyses revealed that ximelagatran (OR 0.71, 95% CI 0.55 - 0.92) and the individual dose of dabigatran 110 mg bid (OR 0.82, 95% CI 0.71 - 0.94) contributed most to this result. Numerically, fewer events were observed with all other comparisons (dabigatran both doses versus warfarin, dabigatran 150 mg twice daily versus warfarin, AZD0837 versus warfarin), although none reached statistical significance.<br><br>**Sekundäre Endpunkte:**<br><br>Adverse events: Adverse events other than bleeding and ischaemic events that led to treatment discontinuation were significantly more frequent with the DTIs compared with VKAs (OR 2.18, 95% CI 1.82 to 2.61). Serious adverse events were also more frequent in the DTI group (OR 1.31, 95% CI 1.09 to 1.56); these were significantly more |

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| | frequent with dabigatran (OR 1.35, 95% CI 1.12 to 1.63) but not with AZD0837 (OR 0.99, 95% CI 0.57 to 1.71).<br><br>All-cause mortality: Death from all causes occurred to a similar extent in both groups. Death rates were slightly lower in the DTI group. |
| | 4. Fazit der Autoren: *DTIs were as efficacious as VKAs for the composite outcome of vascular death and ischaemic events and only the dose of dabigatran 150 mg twice daily was found to be superior to warfarin. DTIs were associated with fewer major haemorrhagic events, including haemorrhagic strokes. Adverse events that led to discontinuation of treatment occurred more frequently with the DTIs. We detected no difference in death from all causes.* |
| **Bruins 2013:** Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation | 1. Fragestellung<br>To assess the effectiveness and safety of treatment with factor Xa inhibitors versus VKAs for the prevention of cerebral or systemic embolic events in people with AF. |
| | 2. Methodik<br><br>Population: People with AF who were eligible for treatment with anticoagulants in order to reduce the risk of cerebral and systemic embolism. We included people with and without a previous stroke or transient ischaemic attack (TIA).<br><br>Intervention : Treatment with an oral or parenteral factor Xa inhibitor (e.g. antistasin, apixaban, betrixaban, darexaban, DU176b, edoxaban, eribaxaban, fondaparinux, idraparinux, otamixaban, razaxaban, rivaroxaban, yagin, YM150, LY517717, SSR126517E)<br><br>Komparator: Oral vitamin K antagonists (warfarin and congeners)<br><br>Endpunkt:<br>Primärer Endpunkte: The composite endpoint of all strokes (both ischaemic and haemorrhagic) and other systemic embolic events.<br><br>Sekundäre Endpunkt: All strokes (both ischaemic and haemorrhagic); All disabling or fatal strokes (both ischaemic and haemorrhagic); Intracranial haemorrhages; Major bleedings; Non-major clinically relevant bleedings; Systemic embolic events; Myocardial infarction; Vascular deaths; All-cause deaths; Other adverse events (i.e. non-bleeding adverse events)<br><br>Suchzeitraum (Aktualität der Recherche): We searched the trials registers of the Cochrane Stroke Group and the Cochrane Heart |

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| | Group (June 2012), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2012, Issue 10), MEDLINE (1950 to April 2013) and EMBASE (1980 to April 2013). In an effort to identify further published, unpublished and ongoing trials we searched trials registers and Google Scholar (July 2012).We also screened reference lists and contacted pharmaceutical companies, authors and sponsors of relevant published trials.<br><br>Anzahl eingeschlossene Studien/Patienten (Gesamt): Data from 42,084 participants randomised into 10 trials.<br><br><u>Qualität der Studien</u>: The studies included in this review were generally large to very large; the smallest study included 222 participants.Only one of the 10 included studies was conducted in an open-label fashion. The remaining studies were either double-masked or partially-masked. Most studies used centralised and blinded adjudication committees for the primary safety and efficacy outcomes. Furthermore, outcome data fromthe (larger) studies appear generally consistent. Based on these considerations, the overall quality of the body of evidence assessed in this review is considered high. |
| | 3. Ergebnisdarstellung<br>**<u>Primärer Endpunkt:</u>**<br><br>The composite endpoint of all strokes (both ischaemic and haemorrhagic) and other systemic embolic events was reported in nine of the included studies (n = 40,777). Most data (approximately 90%) were available from studies that used the agents apixaban (ARISTOTLE 2011; ARISTOTLE-J 2011) and rivaroxaban (ROCKET AF 2011; J-ROCKET AF 2012). No data were available for one of the trials that studied darexaban.<br><br>Treatment with a factor Xa inhibitor significantly decreased the number of strokes and other systemic embolic events compared with dose-adjusted warfarin in participants with AF (OR: 0.81, 95% CI 0.72 - 0.91). *<u>Note</u>: the total number of non-central nervous system (CNS) systemic embolic events was very low (n = 66), contributing to approximately 5% of all outcomes of the composite endpoint. The primary outcome was thus mainly driven by the stroke component.*<br><br>**<u>Sekundäre Endpunkte:</u>**<br><br><u>All strokes (ischaemic and haemorrhagic):</u> The composite endpoint of all strokes was reported in nine studies (n = 40,749). Treatment with a factor Xa inhibitor significantly decreased the number of |

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| | strokes compared with warfarin (OR 0.78, 95% CI 0.69 - 0.89).<br><br>Ischaemic stroke: Based on eight of the included studies that randomised 39,606 participants. The analysis showed a lower number of ischaemic strokes in participants treated with a factor Xa inhibitor compared with warfarin, but this difference did not reach statistical significance.<br><br>Disabling or fatal strokes: Four studies that included 16,099 participants reported data on disabling or fatal strokes Treatment with a factor Xa inhibitor significantly reduced the number of disabling or fatal strokes compared with warfarin (OR 0.71, 95% CI 0.54 - 0.92).<br><br>Non-central nervous system (CNS) systemic embolic events: Based on nine of the included studies, including a total of 40,749 participants. Treatment with a factor Xa inhibitor significantly reduced the number of non-CNS systemic embolic events compared with warfarin (OR 0.53, 95% CI 0.32 to 0.87).<br><br>Major bleedings: All of the included studies (n = 42,078) reported the number of major bleedings defined. Treatment with a factor Xa inhibitor significantly reduced the number of major bleedings compared with warfarin (Analysis 1.6:OR0.89, 95%CI 0.81 to 0.98).There was, however, statistically significant heterogeneity ($I^2$ = 81%). In viewof this high heterogeneity,we also performed an analysis using a random-effects model. Contrary to the results from the fixedeffect model, this analysis did not show a statistically significant decrease in the number of major bleedings in participants treated with factor Xa inhibitors compared with warfarin (OR 0.92, 95% CI 0.63 to 1.34). → Some of the remaining heterogeneity might be explained by differences in bleeding risks between the study populations in the two largest trials.<br><br>Intracranial haemorrhages (ICH): Based on eight studies that randomised 39,638 participants. Treatment with a factor Xa inhibitor significantly reduced the risk of ICH compared with warfarin (Analysis 1.7: OR 0.56, 95% CI 0.45 to 0.70). Still, we observed statistically significant, moderate heterogeneity ($I^2$= 60%). An additional analysis using a random-effects model showed a somewhat smaller, non-significant reduction in participants treated with a factor Xa inhibitor compared with warfarin (OR 0.61, 95% CI 0.36 to 1.05).<br><br>Non-major clinically relevant bleedings: All studies reported the number of non-major clinically relevant bleeding. There was no statistically significant difference in the number of non-major clinically relevant bleedings in participants treated with a factor Xa inhibitor compared with warfarin. We observed statistically significant, high heterogeneity ($I^2$ = 85%). An analysis with a |

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| | random-effects model also showed no statistically significant difference.<br><br>Myocardial infarction: Based on eight studies that randomised 40,301 patients. There was no statistically significant difference between the number of myocardial infarctions in participants treated with factor Xa inhibitors compared with warfarin participants.<br><br>Vascular deaths: Vascular deaths were reported in seven studies (n = 22,100). There was no statistically significant difference.<br><br>All-cause deaths: The number of participants who died fromany cause was reported in six studies (n = 38,924). Treatment with a factor Xa inhibitor significantly reduced the number of all-cause deaths compared with warfarin (OR 0.88, 95%0.81 to 0.97).<br><br>Other adverse events: The pre-specified secondary outcome 'Other adverse events' was not analysed because of a paucity of data on adverse events other than bleedings, non-CNS systemic embolic events, and other cardiovascular events in a large majority of the included studies. Sufficient data on other adverse events were only systematically presented for apixaban and rivaroxaban and are listed in the appendices of the original publications (ARISTOTLE 2011; ROCKET AF 2011). There was no evidence for an increased risk of hepatotoxicity associated with apixaban or rivaroxaban compared with warfarin in these two studies.<br><br>**Subgroup analyses (several pre-specified subgroup analyses for both the primary efficacy outcome (composite of stroke and systemic embolic events) and the main safety outcome (major bleedings werde conducted):**<br><br>• Different factor Xa inhibitors: Only the agents apixaban (OR 0.78, 95% CI 0.65 - 0.93) and rivaroxaban (OR 0.85, 95%CI 0.72 to 1.00) significantly decreased the number of s*trokes and systemic embolic events* compared with warfarin.<br>*Major bleedings* occurred significantly less often in participants that were treated with apixaban (OR: 0.69, 95% CI 0.60 to 0.80) and betrixaban (OR 0.19, 95%CI 0.05 - 0.82) compared with warfarin, whereas significantly more major bleedings were observed in participants treated with idraparinux (OR 2.62, 95% CI 1.70 to 4.03). We saw no statistically significant differences compared with warfarin for the compounds rivaroxaban, edoxaban and darexaban. |
| | 4. Fazit der Autoren: *Factor Xa inhibitors significantly reduced the number of strokes and systemic embolic events compared with warfarin in patients with AF. Factor Xa inhibitors also seem to reduce the number of major bleedings and ICHs compared with* |

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| | *warfarin, though the evidence for a reduction of major bleedings is somewhat less robust. There is currently no conclusive evidence to determine which factor Xa inhibitor is more effective and safer for long-term anticoagulant treatment of patients with AF as head-to-head studies of the different factor Xa inhibitors have not yet been performed.* |
| **Squizzato (2011):** Clopidogrel versus aspirin alone for preventing cardiovascular disease.<br><br>*Hinweis: assessed as up-to-date: 2010* | 1. Fragestellung<br>To quantify the benefit and harm of adding clopidogrel to standard long-term aspirin therapy for preventing cardiovascular events in people at high risk of cardiovascular disease and those with established cardiovascular disease. |
| | 2. Methodik<br><br>Population: Patienten mit koronärer Herzerkrankung, ischämischer zerebrovaskulärer Erkrankung, peripheren arteriellen Erkrankung, oder Hochrisikopatienten für atherothrombotische Erkrankungen<br>Vergleich: Patienten mit koronärer Herzerkrankung, ischämischer zerebrovaskulärer Erkrankung, peripheren arteriellen Erkrankung, oder Hochrisikopatienten für atherothrombotische Erkrankungen<br>Endpunkte: <u>Primärer Endpunkt:</u> Kardiovaskuläre Ereignisse (alle) <u>Sekundäre Endpunkte:</u> Tod aufgrund Myokardinfarkt, nicht-tödlicher Myokardinfarkt, instabile Angina, Herzversagen, Tod aufgrund eines ischämischen Schlaganfalles, nicht-tödlicher Schlaganfall, Revaskularisationsprozeduren, Tod aufgrund kardiovaskulären Ursachen, Gesamtmortalität, bedeutsame Blutungen, leichte Blutungen, Nebenwirkungen (alle)<br><br>Suchzeitraum (Aktualität der Recherche): 2002-2009<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 2 (n=28165 Patienten) |
| | 3. Ergebnisdarstellung<br>**Ergebnisse (basierend auf 2 Studien (CHARISMA und CURE Studie) mit N= 28165 Patienten):**<br><br><u>CURE Studie:</u> eingeschlossen waren Patienten mit einem frischen nicht-ST Hebungsinfarkt (koronar). Vergleich: Clopidogrel plus<br><br>ASS vs. Placebo plus ASS.<br><br><u>CHARISMA Studie:</u> Patienten mit kardiovaskulärem Risiko. Vergleich: Clopidogrel plus<br><br>ASS vs. Placebo plus ASS.<br><br>• Allgemein zeigte sich, dass die Kombination aus Clopidogrel plus ASS stat. signifikant mit einem niedrigerem Risiko hinsichtlich kardiovaskulärer Ereignisse assoziiert war (OR: 0.87, 95% KI 0.81 - 0.94;P<0.01) bei jedoch erhöhtem Risiko |

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| | auf bedeutsame Blutungen (OR 1.34, 95% KI 1.14 - 1.57; P<0.01). |
| | 4. Anmerkungen/Fazit der Autoren<br>The available evidence demonstrates that the use of clopidogrel plus aspirin is associated with a reduction in the risk of cardiovascular events and an increased risk of bleeding compared with aspirin alone. Only in patients with acute non-ST coronary syndrome benefits outweigh harms. |
| **Sudlow 2009:**<br>Thienopyridine derivatives versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients. | 1. Fragestellung<br>To determine the effectiveness and safety of thienopyridine derivatives (ticlopidine and clopidogrel) versus aspirin for preventing serious vascular events (stroke, myocardial infarction (MI) or vascular death) in patients at high risk, and specifically in patients with a previous TIA or ischaemic stroke. |
| | 2. Methodik<br><br>Population: Geeignete Patienten waren: Patienten mit einem hohen Risiko auf eine okklusive arterielle Erkrankung aufgrund vorheriger Feststellung von atherosklerotischen arteriellen Erkrankungen bzw. zerebralen, koronaren oder peripheren Zirkulationsstörungen.<br><br>Vergleich: Orale Thienopyridin-Derivate vs. ASS<br>Endpunkte: <u>Primärer Endpunkt:</u> Kombinationsendpunkt (bestehend aus: Schlaganfall, Myokardinfarkt, oder Tod aufgrund einer vaskulären Ursache)<br><u>Sekundäre Endpunkte:</u> Die einzelnen Endpunkte: Schlaganfall (ischämisch, hämorrhagisch, nicht-tödlich oder tödlich), Myokardinfarkte (nicht-tödlich oder tödlich), vaskuläre Mortalität, und Tod aufgrund jeder Ursache<br><br>Suchzeitraum (Aktualität der Recherche): Bis 2008<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 10 (n=26865 Patienten) |
| | 3. Ergebnisdarstellung<br>*Basierend auf 10 Studien von allgemein hoher Qualität, mit N= 26865 Hochrisikopatienten:*<br><br>• <u>Allgemein</u>: ASS wurden in neun Studien (N=7633 Patienten) gegenüber Ticlopidin getestet, und in einer Studie (N=19185 Patienten) gegen Clopidogrel.<br>• Verglichen mit ASS, zeigte sich eine stat. signifikante Reduktion hinsichtlich schwerer vaskulärer Ereignisse unter einer Thienopyridingabe (11.6% vs.12.5%; OR: 0.92, 95% KI: 0.85 - 0.99).<br>• Verglichen mit Aspirin, zeigte sich eine stat. signifikante Reduktion gastrointestinaler Nebenwirkungen unter einer Thienopyridingabe (OR: 0.71, 95% KI: 0.59 - 0.86 / *<u>Hinweis</u>: Stat. signifikante Heterogenität zwischen den Studien bei gepoolter Analyse $I^2$= 80%),* bei jedoch gleichzeitig erhöhtem Auftreten von Hautausschlag und Durchfall (unter Ticlopidin |

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| | mehr als unter Clopidogrel).<br>○ Hautausschlag (basierend auf 5 Studien mit N=25595 Patienten (95%)): Ticlopidin: 6.7% vs. 3.3%, OR: 2.08, 95% KI: 1.66 - 2.61 / Clopidogrel: 6.0% vs. 4.6%, OR: 1.32, 95%KI 17 - 1.50.<br>○ Durchfall (basierend auf 5 Studien mit N= 25595 Patienten (95%)): Ticlopidin: 10.4% vs. 5%; OR: 2.3, 95% KI 1.89 - 2.77 / Clopidogrel: 4.5% vs. 3.4%; OR: 1.34, 95% KI 1.16 - 1.55).<br>• Es zeigte sich ein stat. signifikant vermehrtes Auftreten von Neutropenien unter Ticlopidin (nicht aber unter Clopidogrel, *Hinweis: Stat. signifikante Heterogenität zwischen den Studien bei gepoolter Analyse $I^2$=71%)* (2.3% vs. 0.8%, OR: 2.72, 95% KI 1.53 - 4.84).<br><br>*Hinweis: Die kombinierten Resultate aller Patienten, waren gegenüber den Ergebnissen der Patienten mit TIA/ischämischen Schlaganfällen ähnlich.* |
| | 4. Anmerkungen/Fazit der Autoren<br>The thienopyridine derivatives are at least as effective as aspirin in preventing serious vascular events in patients at high risk, and possibly somewhat more so. However, the size of any additional benefit is uncertain and could be negligible. Clopidogrel has a more favourable adverse effects profile than ticlopidine and so is the thienopyridine of choice. It should be used as an alternative to aspirin in patients genuinely intolerant of or allergic to aspirin. |

**Systematische Reviews**

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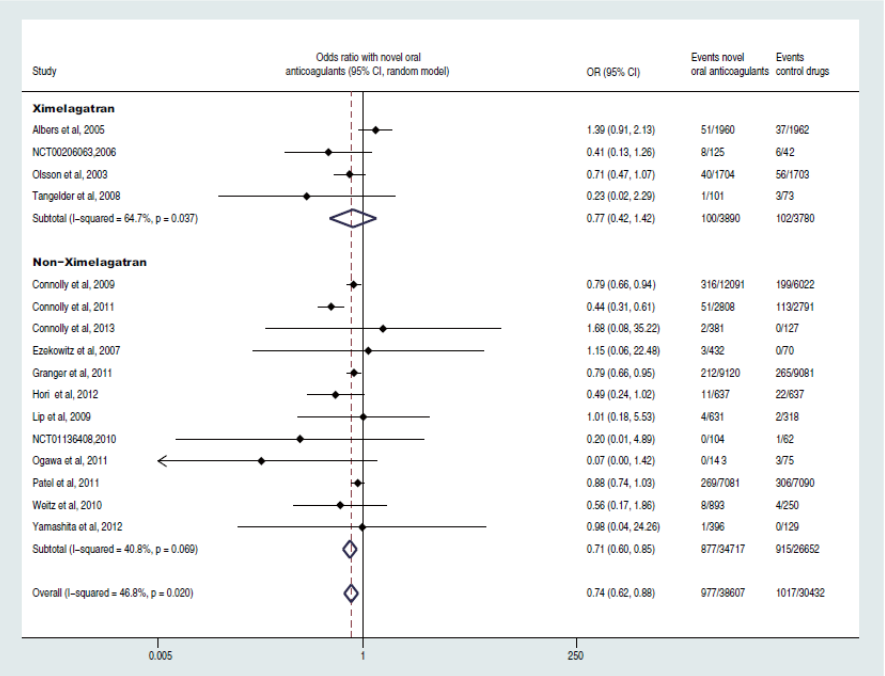
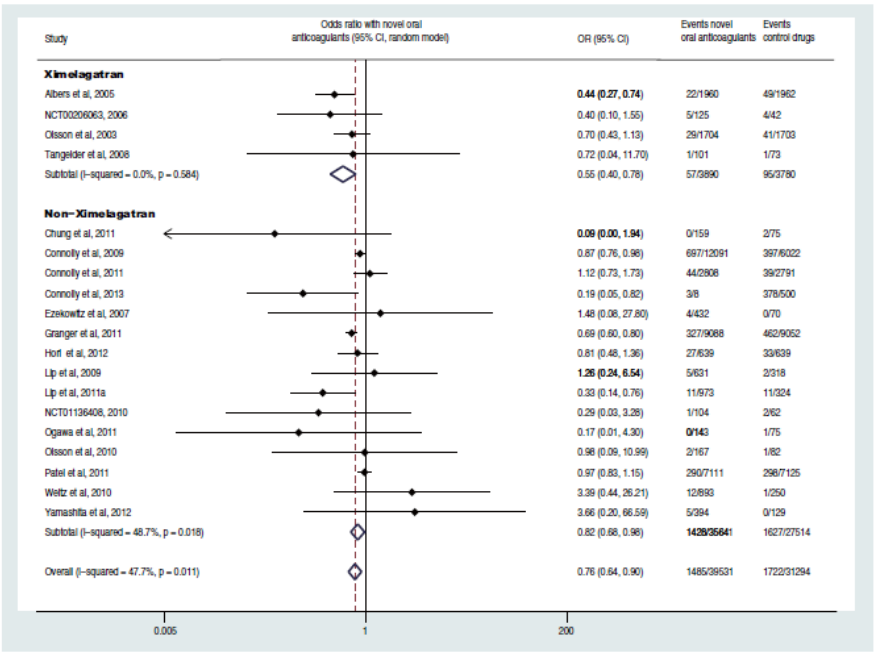
| **Liu 2014:** The efficacy and safety of novel oral anticoagulants for the preventive treatment in atrial fibrillation patients: a systematic review and meta-analysis. | 1. Fragestellung<br>Efficacy and safety of the novel oral anticoagulants in AF patients. |
| | 2. Methodik<br><br>Population: patients older than 18 years who were diagnosed with AF<br>Intervention: novel oral anticoagulants including direct factor Xa inhibitors and direct factor IIa inhibitors,<br>Komparator: placebo, VKA or aspirin (and/or clopidogrel)<br>Endpunkte: primary endpoints: stroke or systemic embolism (combined endpoint) and major bleeding;<br>secondary endpoints: acute myocardial infarction, systemic embolism, death from any cause, disabling or fatal stroke (combined endpoint), all bleeding events, fatal bleeding, major bleeding or clinically relevant non-major bleeding (combined endpoint), all adverse events, serious adverse events and liver function disorder<br><br>- stroke [defined as a local paroxysmal nervous functional defect including ischemic stroke, hemorrhage stroke and unspecified stroke (such as TIA)];<br>- Systemic embolism [defined as an acute arterial vascular occlusion in limbs or organs evidenced by imaging examination, surgery or autopsy];<br>- Acute myocardial infarction [defined as an acute, typical chest pain lasting at least 20 min, accompanied with ECG changes of acute acute myocardial infarction and/or an increase of at least two times of the upper normal limit in myocardial enzyme level]<br><br>Suchzeitraum (Aktualität der Recherche): Bis 06/2013<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 23 (n=k.A.) |
| | 3. Ergebnisdarstellung<br>**Stroke:** OR decreased by 26% (OR: 0.74, 95% CI: 0.62–0.88)<br>**Systemic embolism:** OR decreased by 24% (OR: 0.76, 95% CI: 0.64–0.90)<br>**Major bleeding:** OR decreased by 10% (OR: 0.90, 95% CI: 0.84–0.95)<br><br>*Forest plot of stroke or systemic embolism:* |




*Forest plot of mayor bleeding:*




- no significant difference in acute myocardial infarction, systemic embolism, major bleeding or clinically relevant non-major, all bleeding events, all adverse events and liver function disorder, between the novel oral anticoagulants and control drugs (p>0.05).

4. Anmerkungen/Fazit der Autoren

Compared to the control drugs, the novel oral anticoagulants showed higher efficiency and safety in patients with AF, as evidenced by their superior performance not only in reducing the risk of stroke or systemic embolism with a lower risk of major bleeding but also in

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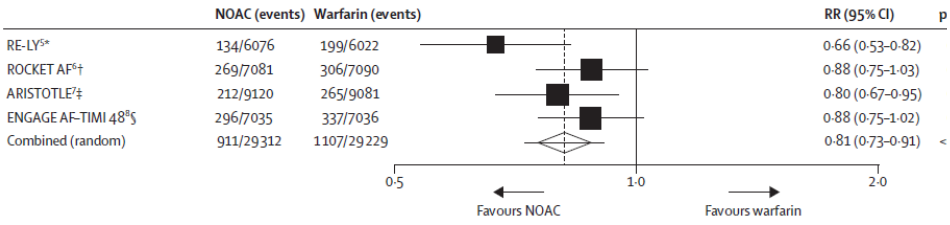
| | decreasing the incidence of death from any cause, disabling or fatal stroke, serious adverse events and fatal bleeding. |
| **Ruff 2014:** Comparison of the effi cacy and safety of new oral anticoagulants with warfarin in patients with atrial fi brillation: a meta-analysis of randomised trials. | 1. Fragestellung<br>Relative benefit of new oral anticoagulants in key subgroups, and the effects on important secondary outcomes. |
| | 2. Methodik<br><br>Population: patients with atrial fibrillation<br>Vergleich: new oral anticoagulant vs. warfarin<br>Endpunkte: stroke and systemic embolic events, ischaemic stroke, haemorrhagic stroke, all-cause mortality, myocardial infarction, major bleeding, intracranial haemorrhage, and gastrointestinal bleeding<br><br>Suchzeitraum (Aktualität der Recherche): 01/2009 - 11/2013<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 (n=71 683 participants) |
| | 3. Ergebnisdarstellung<br>RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF–TIMI 48 (42 411 participants received a new oral anticoagulant and 29 272 participants received warfarin.<br>• New oral anticoagulants significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0·81, 95% CI 0·73–0·91; p<0·0001), mainly driven by a reduction in haemorrhagic stroke (RR 0·49, 95% CI 0·38–0·64; p<0·0001).<br>• New oral anticoagulants also significantly reduced all-cause mortality (RR 0·90, 95% CI 0·85–0·95; p=0·0003) and intracranial haemorrhage (RR 0·48, 95% CI 0·39–0·59; p<0·0001), but increased gastrointestinal bleeding (RR 1·25, 95% CI 1·01–1·55; p=0·04)<br><br>*Stroke or systemic embolic events:*<br>  <br><br><br>*Secondary efficacy and safety outcomes:* |

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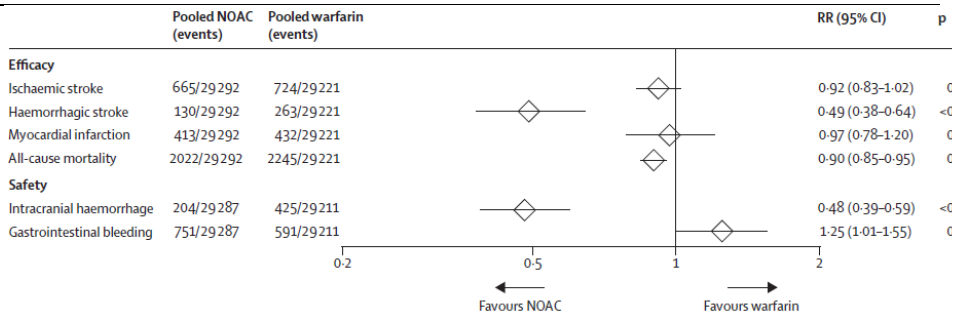
| |  |
| | 4. Anmerkungen/Fazit der Autoren<br>This meta-analysis is the first to include data for all four new oral anticoagulants studied in the pivotal phase 3 clinical trials for stroke prevention or systemic embolic events in patients with atrial fibrillation. New oral anticoagulants had a favourable risk–benefit profile, with significant reductions in stroke, intracranial haemorrhage, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding. The relative efficacy and safety of new oral anticoagulants was consistent across a wide range of patients. |
| **Kwong 2013:** Bleeding of New Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation: A Meta-Analysis of randomized Controlled Trials. | 1. Fragestellung<br>Oral direct factor Xa inhibitors and oral direct thrombin inhibitors are new oral anticoagulants (NOACs) for stroke prevention in atrial fibrillation (AF). We systematically reviewed their risk of major bleeding and efficacy in thromboembolism reduction in AF |
| | 2. Methodik<br><br>Population: Patienten mit Vorhofflimmern; bei der ROCKET AF-Studie waren nur Patienten mit einem erhöhten Risiko ($CAHD_2$≥2) eingeschlossen<br>Vergleich: Warfarin, Aspirin oder Clopidogrel<br>Endpunkte: majore und klinisch relevante, nicht majore (CRNM) Blutungen, Schlaganfälle und systemiscche Embolien, Todesfälle<br><br>Suchzeitraum (Aktualität der Recherche): Bis 06/2012<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 13 (n=**61.406 Patienten**) |
| | 3. Ergebnisdarstellung<br>**Blutungen (majore und CRNM):**<br>Xa-Inhibitoren versus Kontrollen: RR=0,94 (95%KI 0,75-1,18); $I^2$=87%<br>Thrombin-Inhibitoren versus Kontrollen: RR=**0,88(95%KI 0,78-0,98)**; $I^2$=0%<br><br>Xa-Inhibitoren versus VKAs: RR=0,90 (95%KI 0,69-1,17); $I^2$=88%<br>Thrombin-Inhibitoren versus VKAs: RR=**0,88(95%KI 0,78-0,98)**; $I^2$=0%<br><br>**Stroke/SE:**<br><br>Xa-Inhibitoren versus Kontrollen: RR=**0,71 (95%KI 0,54-0,92)**; $I^2$=64%<br>Thrombin-Inhibitoren versus Kontrollen: RR=**0,79(95%KI 0,66-0,93)**; $I^2$=0% |

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| | Xa-Inhibitoren versus VKAs: RR=0,84 (95%KI 0,74-0,94); I²=0%<br>Thrombin-Inhibitoren versus VKAs: RR=0,78(95%KI 0,66-0,93); I²=0% |
| | 4. Anmerkungen/Fazit der Autoren<br>Oral direct factor Xa inhibitors and oral direct thrombin inhibitors are more effective in reducing stroke and systemic embolism without increasing the risk of major bleeding compared to traditional oral anticoagulants. This favorable risk-benefit balance should be further confirmed by long-term, large-scale safety studies.<br><br>5. Hinweise durch FB Med<br>- Besonderheit dieser Metaanaylse: getrennte Analysen für alle Kontrollmedikationen (inkl. Aspirin und Clopidogrel) als auch nur VKAs jeweils für Xa-Inhibitoren als auch für Thrombin Inhibitoren |
| **Assiri 2013:** Mixed Treatment Comparison Meta-Analysis of Aspirin, Warfarin, and New Anticoagulants for Stroke Prevention in Patients With Nonvalvular Atrial Fibrillation. | 1. Fragestellung<br>A mixed treatment comparison meta- analysis to evaluate direct and indirect treatment data including aspirin, warfarin apixaban, dabigatran, edoxaban, and rivaroxaban for the prevention of primary or secondary stroke in patients with AF. |
| | 2. Methodik<br><br>Population: patients with AF<br>Intervention: aspirin, warfarin apixaban, dabigatran, edoxaban, and rivaroxaban<br>Komparator: placebo<br>Endpunkte: All-Stroke, Ischemic Stroke, Vascular Death, All-Cause Mortality, Major Bleeding, Nonmajor Bleeding, Intracranial Hemorrhage<br><br>Suchzeitraum (Aktualität der Recherche): 01/1991 – 08/2012<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 21 (n=k.A.) |
| | 3. Ergebnisdarstellung<br>***All-Stroke:***<br><br>All treatments except aspirin reduced the risk of all types of stroke compared with placebo.<br><br>Warfarin OR=0.43 [0.33–0.57]<br><br>Apixaban OR=0.37 [0.27–0.54]<br><br>Dabigatran OR=0.34 [0.21–0.57]<br><br>Rivaroxaban OR=0.36 [0.22– 0.60]<br><br>and<br><br>Aspirin with Clopidogrel OR= 0.73 [0.53–0.99]) were more protective than aspirin alone. |

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| | ***Ischemic Stroke:***<br><br>All treatments with the exception of aspirin reduced the risk of ischemic stroke compared with placebo.<br><br>Warfarin OR=0.43 [0.32–0.60]<br><br>Apixaban OR=0.41[0.27–0.67]<br><br>Dabigatran OR=0.40 [0.22–0.80]<br><br>and<br><br>Rivaroxaban OR=0.39 [0.21– 0.78] were more protective than aspirin alone,and aspirin was comparable to aspirin with clopidogrel.<br><br>Warfarin OR=0.56 [0.35–0.87]<br><br>and<br><br>Apixaban OR=0.55[0.29–0.96] were more protective than aspirin with clopidogrel,whereas dabigatran and rivaroxaban were similar to aspirin with clopidogrel.<br><br>***Vascular Death:***<br><br>• neither aspirin, aspirin with clopidogrel, warfarin, nor any new anti-coagulant offered any protection against vascular death compared with placebo or through any other direct or indirect drug-to-drug comparisons<br><br>***All-Cause Mortality:***<br><br>Compared with placebo,<br><br>Warfarin OR=0.67 [0.5–0.89]<br><br>Apixaban OR=0.6 [0.42–0.84]<br><br>Dabigatran OR=0.61 [0.39– 0.89]<br><br>and<br><br>Rivaroxaban OR=0.56[0.35–0.84] were associated with a reduction in all-cause mortality.<br><br>Apixaban OR=0.76 [0.59–0.97] was more protective than aspirin alone but not more protective than a combination of aspirin and clopidogrel when evaluating all-cause mortality. The newer anticoagulants and warfarin were similar regarding all-cause mortality.<br><br>***Major Bleeding:***<br><br>• Aspirin, aspirin with clopidogrel, and the new anticoagulants were not associated with less major bleeding compared with placebo or |

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| | warfarin<br>• no comparisons showing a reduction in the risk of major bleeding events, suggesting that antiplatelet therapy, warfarin, and the newer anticoagulants are similar with regard to major bleeding<br>Nonmajor Bleeding:<br>• There was an excess of nonmajor bleeding when warfarin as compared with placebo OR=2.24 [1.16– 5.02]<br>• There was also more nonmajor bleeding with warfarin OR=2.26 [1.22–4.92] and the combination of aspirin with clopidogrel OR=2.65 [1.27–5.97] and warfarin OR= 2.26 [1.22–4.92] compared with aspirin alone<br><br>***Intracranial Hemorrhage:***<br>• Aspirin, aspirin with clopidogrel, dabigatran, apixaban, and warfarin were similar in every direct and indirect comparison regarding intracranial hemor- rhage<br>• No single drug or combination was associated with fewer instances of intracranial hemorrhage |
| | 4. Anmerkungen/Fazit der Autoren<br>This mixed treatment comparison meta-analysis found similarity between warfarin and the new anticoagulants with the exception of one comparison, in which warfarin was associated with more non-major bleeding than apixaban. Thus, the new anticoagulants are therapeutically comparable when warfarin is inappropriate. |
| **Agarwal 2012:** Current Trial-Associated Outcomes With Warfarin in Prevention of Stroke in Patients With Nonvalvular Atrial Fibrillation. | 1. Fragestellung<br>We performed a meta-analysis of safety and efficacy outcomes in patients with AF treated with warfarin for stroke prevention in large contemporary randomized controlled trials (RCTs). |
| | 2. Methodik<br><br>Population: Patients with nonvalvular AF<br>Intervention: warfarin<br>Komparator: alternative thromboprophylaxis strategy<br>Endpunkte: <u>primary efficacy outcome</u> was defined as the occurrence of ischemic or hemorrhagic stroke or non–central nervous system (non-CNS) embolism.<br><u>Secondary efficacy end points</u> were studied using pooled analysis and included myocardial infarction (MI), all-cause mortality, and composite adverse vascular events (including stroke, non-CNS embolism, MI, and death). Safety outcomes included major bleeding, intracranial hemorrhage, clinically relevant nonmajor bleeding, and minor bleeding.<br><br>Suchzeitraum (Aktualität der Recherche): 2001-2011 |

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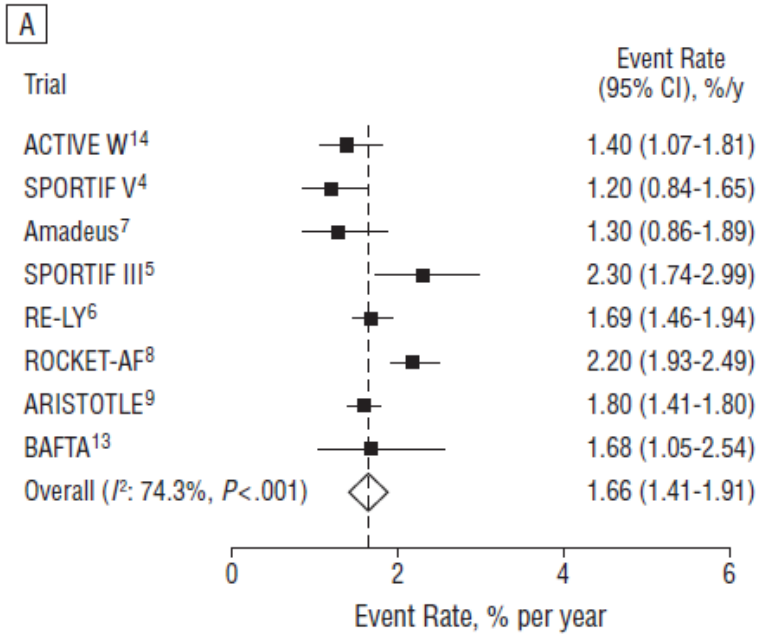
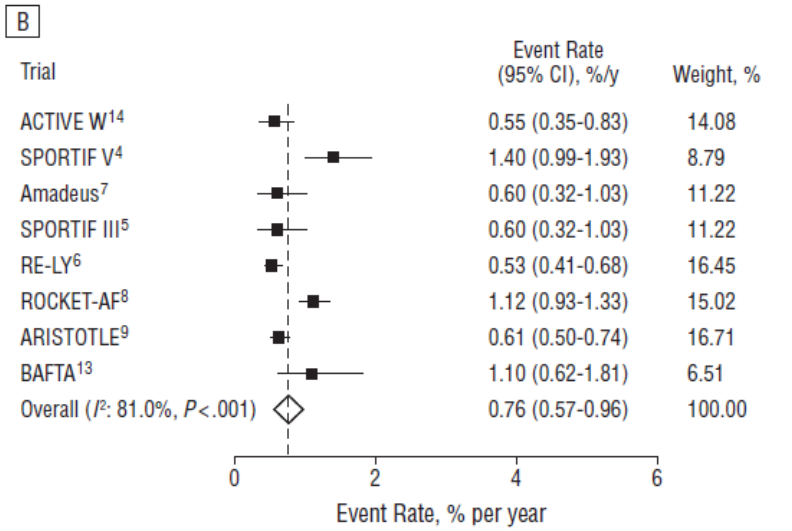
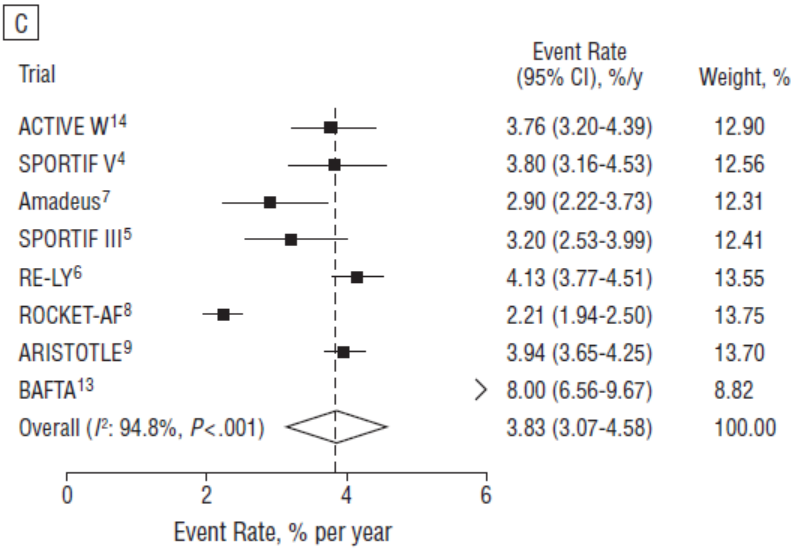
| | Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 (n=32053 patients)<br><br>Qualitätsbewertung der Studien:<br>- The studies included for meta-analysis were restricted to high-quality trials (Jadad score ≥3) |
| | 3. Ergebnisdarstellung<br>*Event rates of efficacy outcomes:*<br>- The rate of stroke or non-CNS embolism varied from 1.2% to 2.3% per year.<br>- the rates of MI, allcause mortality, and composite outcomes varied from 0.53% to 1.4% per year, 2.21% to 8.00% per year, and 3.93% to 5.90% per year, respectively.<br><br>*The pooled analysis of safety outcomes:*<br>- The pooled event rate (95% CI) for stroke or non-CNS embolism was calculated to be 1.66% (1.41%-1.91%) per year.<br>- the pooled event rates (95% CIs) for MI, all-cause mortality, and composite outcomes were calculated to be 0.76% (0.57%-0.96%) per year, 3.83% (3.07%-4.58%) per year, and 4.80% (4.22%-5.38%) per year, respectively<br><br>***A** Stroke or non–central nervous system embolism*<br><br>  <br><br><br>**B** *Myocardial infarction* |




**C** *All-cause mortality*




*Subgroups-analysis:*

- a significantly higher incidence of stroke or non-CNS embolism in patients 75 years and older (n=6398; 2.27% per year) compared with those younger than 75 years (n=10 252; 1.62% per year; *P*<.001)
- a significantly higher pooled incidence of stroke or non-CNS embolism in females (n = 8419) compared with in males (n=14 262; *P*<.001)
- a significantly higher pooled incidence of stroke or non-CNS embolism in patients with a history of stroke or TIA compared with in patients without previous cerebrovascular events (*P*=.001).
- Patients with no history of exposure to vitamin k antagonists (n=9925) had a significantly higher incidence of stroke or non-

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| | CNS embolism compared with patients who reported use of vitamin K antagonists at the time of enrollment (n=12 756; relative risk, 1.16; 95% CI, 1.01-1.33). |
| | 4. Anmerkungen/Fazit der Autoren<br>Current use of warfarin as a stroke prevention agent in patients with AF is associated with a low rate of residual stroke or systemic embolism estimated to be 1.66% per year. Compared with a previous metaanalysis, there has been significant improvement in the proportion of time spent in therapeutic anticoagulation, with a resultant decline in observed stroke rates.<br><br>5. Hinweise durch FB Med<br>- Sprachrestriktion (English language) |
| **Mitchell 2013:** The Efficacy and Safety of Oral Anticoagulants in Warfarin-Suitable Patients With Nonvalvular Atrial Fibrillation: Systematic Review and Meta-Analysis.<br><br>Und | 1. Fragestellung<br>The current systematic review and meta-analysis extends the published data with regard to the number of outcomes reported and the data sets employed (intention to treat vs on treatment) using a Bayesian network meta-analysis (NMA) approach. |
| | 2. Methodik<br><br>Systematischer Review mit Netzwerk-Metaanalyse basierend auf den drei RCTs zu Dabigatran (RE-LY 2012), Apixaban (ARISTOTLE) und Rivaroxaban (ROCKET-AF) versus Warfarin<br><br>Population: Patienten mit nicht-valvulärem Vorhofflimmern; bei der ROCKET AF-Studie waren nur Patienten mit einem erhöhten Risiko ($CAHD_2$≥2) eingeschlossen<br><br>Vergleich: NOA gegen einander, Warfarin<br><br>Endpunkte: Schlaganfälle (jegliche, hämorrhagische und ischämische), systemische Embolie, Blutungen (jegliche, majore, intrakranielle, gastrointestinale, klinisch relevante aber nicht majore)<br><br>Suchzeitraum (Aktualität der Recherche): Bis 05/2011<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 (n=50578)<br><br>Qualitätsbewertung der Studien:<br>- The quality of RCTs was assessed according to the methodology checklist detailed in appendix D of the National Institute for Health and Care Excellence (NICE) Guidelines Manual 2009. |
| | 3. Ergebnisdarstellung<br>*Ergebnisse (basierend auf 3 Studien mit insgesamt 50.578 Patienten):*<br><br>*Mitchell et al. 2012:*<br><br>Das Risiko für Schlaganfälle, systemische Embolie und intrakranielle |

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| | Blutungen war **unter Rivaroxaban signifikant höher als unter Dabigatran 150mg.**<br><br>**Rivaroxaban versus Dabigatran 150mg:**<br><br>Stroke/SE: **HR=1,34 (95%KI 1,02-1,78)**<br><br>Any stroke: **HR=1,40 (95%KI 1,05-1,87)**<br><br>Haemorrhagic stroke: **HR=2,27 (95%KI 1,07-5,15)**<br><br>ICH: **HR=1,69 (95%KI 1,02-2,85)**<br><br>Die Behandlung mit **Dabigatran 110mg** war verbunden mit einem **signifikant erhöhten Risiko für Schlaganfälle und systemische Embolien im Vergleich zu Dabigatran 150mg**, allerdings verbunden mit einem **erhöhten Risiko für Blutungen unter Dabigatran 150mg**.<br><br>**Dabigatran 150mg versus 110 mg:**<br><br>Stroke/SE: **HR=0,72 (95%KI 0,58-0,90)**<br><br>Any stroke: **HR=0,70 (95%KI 0,55-0,89)**<br><br>Ischemic stroke: **HR=0,67 (95%KI 0,53-0,86)**<br><br>Disabling stroke: **HR=0,69 (95%KI 0,49-0,97)**<br><br>Major bleeding: **HR=1,16 (95%KI 1,0-1,34)**<br><br>Gastrointestinal bleeding: **HR=1,36 (95%KI 1,10-1,70)**<br><br>Any bleeding: **HR=1,12 (95%KI 1,06-1,20)**<br><br>Alle anderen Vergleich der NOA untereinander ergab keine signifikanten Ergebnisse bezogen auf Schlaganfälle oder systemische Embolien. Lediglich beim Auftreten von **Blutungen** kam es zu signifikanten Unterschieden **zu Gunsten von Apixaban sowohl versus Dabigatran150mg** (major bleeding HR=0,74 [95%KI 0,61-0,90]) als auch versus **Rivaroxaban** (major bleeding HR=0,66 [95%KI 0,54-0,81]) und zu **Ungunsten von Rivaroxaban versus Dabigatran 110mg** (major bleeding HR=1,29 [95%KI 1,06-1,59])<br><br>*Harenberg et al. 2012:*<br><br>Bei Harenberg et al. ergeben sich ebenfalls **lediglich im indirekten Vergleich von Dabigatran 110mg versus 150mg und Dabigatran 150mg versus Rivaroxaban signifikante Effektschätzer**, die in |
| **Harenberg 2012:** Comparison of | |

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| efficacy and safety of dabigatran, rivaroxaban ans apixaban in patients with atrial fibrillation using network meta-analysis. | Größe und Richtung mit den von Mitchell ermittelten Effektschätzern übereinstimmen. Für **majore Blutungen** ermitteln Harenberg et al. ebenfalls einen **signifikanten Vorteil für Apixaban im Vergleich zu Rivaroxaban (OR=1,48 [95%KI 1,21-1,81]** und **im Vergleich zu Dabigatran 150mg (OR=1,35 [95%KI1,10-1,66].** Unter **Dabigatran 110mg kam es zu signifikant weniger majoren Blutungen im Vergleich zu Rivaroxaban (OR=0,78 [95%KI 0,63-0,96].** |
| | 4. Anmerkungen/Fazit der Autoren<br><br>*5.* Hinweise durch FB Med:<br>- *Die Effektschätzer aus Mitchell et al (HR) und Harenberg (OR) entsprechen sich (nur andere Darstellung der Effektrichtung)* |
| **Schneeweiss 2012:** Comparative Efficacy and Safety of New Oral Anticoagulants in Patients with Atrial Fibrillation. | 1. Fragestellung<br>Efficacy and safety of the 3 new agents based on data from their published warfarin-controlled randomized trials, using the method of adjusted indirect comparisons. |
| | 2. Methodik<br>**Adjustierter indirekter Vergleich basierend auf den drei RCTs zu Dabigatran (RE-LY), Apixaban (ARISTOTLE) und Rivaroxaban (ROCKET-AF) versus Warfarin**<br><br>**Population:** Patienten mit Vorhofflimmern; bei der ROCKET AF-Studie waren nur Patienten mit einem erhöhten Risiko ($CAHD_2$≥2) eingeschlossen<br><br>**Vergleich:** NOA gegen einander, Warfarin<br><br>**Besonderheit dieses indirekten Vergleiches: Subgruppe von Patienten mit $CAHD_2$≥3!**<br><br>**Endpunkte:** Schlaganfälle oder systemische Embolie, majore Blutungen<br><br>Suchzeitraum (Aktualität der Recherche): Bis 10/2011<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 (n=44535) |
| | 3. Ergebnisdarstellung<br>**Ergebnisse (basierend auf 3 Studien mit 44.535 Patienten; da Dabigatran hier nur in der Dosierung mit 150mg ausgewertet wurde):**<br><br>Aufgrund des höheren Risikoprofils der Patienten in der ROCKET-AF-Studie wurde eine solidere Subgruppenanalyse mit 21.727 Patienten mit $CAHD_2$≥3 durchgeführt.<br><br>Für Patienten mit $CAHD_2$≥3 ergeben sich aus den Einzelstudien folgende Ergebnisse zum primären Endpunkt (Schlaganfälle): |

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| | Apixaban vs Warfarin: **HR 0,68 [95%KI 0,52-0,88]**<br><br>Dabigatran 150mg vs. Warfarin: **HR 0,70 [95%KI 0,52-0,95]**<br><br>Rivaroxaban vs. Warfarin: HR 0,88 [95%KI 0,74-1,05]<br><br>Für Patienten mit $CAHD_2$≥3 ergeben sich folgende Ergebnisse zum Endpunkt majore Blutungen<br><br>Apixaban vs Warfarin: **HR 0,69 [95%KI 0,55-0,87]**<br><br>Dabigatran 150mg vs. Warfarin: HR 1,05 [95%KI 0,86-1,30]<br><br>Rivaroxaban vs. Warfarin: R 1,01 [95%KI 0,87-1,18]<br><br>Im indirekten Vergleich ergab sich ein um **20% geringeres Risiko für Schlaganfälle** für sowohl für **Dabigatran als auch für Apixaban im Vergleich zu Rivaroxaban;** dieses Ergebnis war allerdings **nicht stat. signifikant.**<br><br>Dabigatran vs. Rivaroxaban: HR=0,80 [95%KI 0,56-1,13]<br><br>Apixaban vs. Rivaroxaban: HR=0,77 [95%KI 0,56-1,06]<br><br>Für den Vergleich Dabigatran vs. Apixaban ergab sich ein HR von 1,03 [95%KI 0,69-1,54].<br><br>Für den Endpunkt **majore Blutungen** ergab sich für Patienten mit $CAHD_2$≥3 ein **stat.sign. Vorteil für Apixaban.**<br><br>Apixaban vs. Rivaroxaban: **HR=0,68 [95%KI 0,52-0,90]**<br><br>Dabigatran vs. Apixaban: **HR=1,52 [95%KI 1,11-2,07]**<br><br>Für den Vergleich Dabigatran vs. Rivaroxaban ergab sich kein stat. sign. Ergebnis: HR=1,04 [95%KI 0,80-1,34] |
| | 4. Anmerkungen/Fazit der Autoren<br>An indirect comparison of new anticoagulants based on existing trial data indicates that in patients with a CHADS(2) score ≥3 dabigatran 150 mg, apixaban 5 mg, and rivaroxaban 20 mg resulted in statistically similar rates of stroke and systemic embolism, but apixaban had a lower risk of major hemorrhage compared with dabigatran and rivaroxaban. Until head-to-head trials or large-scale observational studies that reflect routine use of these agents are available, such adjusted indirect comparisons based on trial data are one tool to guide initial therapeutic choices. |
| **Testa 2012:** Adjusted indirect comparison of new oral anticoagulants for | 1.Fragestellung<br><br>Adjusted indirect comparison meta-analyis of new oral anticoagulants (NOA) for stroke prevention. |
| | 2. Methodik (Adjustierter indirekter Vergleich basierend auf den drei |

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| stroke prevention in atrial fibrillation. | RCTs zu Dabigatran (RE-LY), Apixaban (ARISTOTLE) und Rivaroxaban (ROCKET-AF) versus Warfarin)<br><br>Population: Patienten mit Vorhofflimmern; bei der ROCKET AF-Studie waren nur Patienten mit einem erhöhten Risiko (CAHD2≥2) eingeschlossen<br><br>Vergleich: NOA gegen einander, Warfarin<br><br>Besonderheit dieses indirekten Vergleiches: Subgruppenanalyse für thromboembolische Schlaganfälle, systemische Embolien und hämorrhagische Schlaganfälle<br><br>Endpunkte: kumulative Rate thromboembolischer Schlaganfälle (TES) oder systemische Embolie, hämorrhagische Schlaganfälle, majore Blutungen<br><br>Suchzeitraum (Aktualität der Recherche):bis 03/2012<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 (n=50578) |
| | 3. Ergebnisdarstellung<br>**Ergebnisse (basierend auf 3 Studien mit 50.578 Patienten):**<br><br>*Vergleich Apixaban vs. Dabigatran 110mg:*<br><br>Hier ergab sich kein signifikanter Effektschätzer in Bezug auf Schlaganfälle und Embolien.<br><br>*Vergleich Apixaban vs. Dabigatran 150mg:*<br><br>Hier ergab sich lediglich für die Blutungen ein signifikanter Vorteil für Apixaban (OR=0,7 [95%KI 0,59-0,92])<br><br>*Vergleich Apixaban vs. Rivaroxaban:*<br><br>Apixaban war Rivaroxaban signifikant **unterlegen** bei den systemischen Embolien (OR=3,8 [95%KI 1,1-1,59]); war bei den majoren Blutungen jedoch signifikant **überlegen** (OR=0,7 [95%KI 0,56-0,88])<br><br>*Vergleich Dabigatran 110mg vs. Rivaroxaban:*<br><br>Hier ergab sich kein signifikanter Effektschätzer in Bezug auf Schlaganfälle und Embolien.<br><br>*Vergleich Dabigatran 150mg vs. Rivaroxaban:*<br><br>Hier ergaben sich signifikante Effektschätzer für systemische Embolien (OR=3,6 [95%KI 1,08-12,5]) und hämorrhagischer Schlaganfall (OR=0,4 [95%KI 0,2-0,9])<br><br>Im indirekten Vergleich zeigt sich, dass kein NOA dem anderen |

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| | signifikant überlegen ist in Bezug auf die hier dargestellten Endpunkte. Rivaroxaban zeigte eine Überlegenheit in Bezug auf das Auftreten systemischer Embolien. Dabigatran 150mg zeigte sich überlegen gegenüber Rivaroxaban in Bezug auf hämorrhagische Schlaganfälle. |
| | 4. Anmerkungen/Fazit der Autoren<br>Overall superiority of NOA over warfarin is largely influenced by the reduction of HS. Dabigatran 150 mg/twice daily seems to have the best risk/benefit profile. |
| **Rasmussen 2012:** Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis. | 1. Fragestellung<br>Indirect treatment comparisons of phase III clinical trials of stroke prevention in atrial fibrillation, with a focus on the secondary prevention cohorts. A secondary analysis was done on the primary prevention cohort. |
| | 2. Methodik<br><br>Population: Patienten mit Vorhofflimmern; bei der ROCKET AF-Studie waren nur Patienten mit einem erhöhten Risiko ($CAHD_2$≥2) eingeschlossen<br>Vergleich: NOA gegen einander, Warfarin<br>Endpunkte: Schlaganfälle (jegliche, hämorrhagische und ischämische), systemische Embolie, Myokardinfarkte, Tod, majore Blutungen, intrakranielle Blutungen, gastrointestinale Blutungen, andere Blutungen<br><br>Suchzeitraum (Aktualität der Recherche): Bis 06/2012<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 (n=50578) |
| | 3. Ergebnisdarstellung<br>Ergebnisse (basierend auf 3 Studien mit 50.578 Patienten):<br><br>*Sekundärprävention:*<br><br>In der Gruppe der Patienten mit Sekundärprävention (previous stroke) gab es keine stat. signifikanten Unterschiede zwischen den NOAs. Lediglich hinsichtlich des Auftretens von Blutungen ergab sich ein signifikanter Vorteil von Dabigatran 110mg im Vergleich zu Rivaroxaban HR= 0.68 (95%KI 0.47 - 0.99).<br><br>*Primärprävention:*<br><br>In der Primärprävention ergab sich für den Vergleich Apixaban vs. Dabigatran 150mg ein signifikant höheres Risiko für Schlaganfälle für Apixaban (1.45 (95%KI 1.01- 2.08). Hinsichtlich des Risikos für Blutungen war Apixaban jedoch Dabigatran 150mg (HR=0.75 (95%KI 0.60- 0.94) und Rivaroxaban (HR= 0.61 (95%KI 0.48 - 0.78)signifikant überlegen. Hier war auch Dabigatran 110mg Rivaroxaban signifikant überlegen HR=0.77 (95%KI 0.60 - 0.98). |
| | 4. Anmerkungen/Fazit der Autoren |

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| | For secondary prevention, apixaban, rivaroxaban, and dabigatran had broadly similar efficacy for the main endpoints, although the endpoints of haemorrhagic stroke, vascular death, major bleeding, and intracranial bleeding were less common with dabigatran 110 mg twice daily than with rivaroxaban. For primary prevention, the three drugs showed some differences in relation to efficacy and bleeding. These results are hypothesis generating and should be confirmed in a head to head randomised trial.<br><br>5. Hinweise durch FB Med<br><br>- Besonderheit dieses indirekten Vergleiches: Subgruppenanalyse für primäre und sekundäre (previous stroke) Prävention |
| **Dentali 2012:** Efficacy and safety of the Novel Oral Anticoagulants in Atrial Fibrillation: A Systematic Review and Meta-Analysis of the Literature. | 1. Fragestellung<br>Systematic review of the literature and a meta-analysis of phase II and phase III randomized, clinical trials (RCTs) of these agents compared with VKAs for the prevention of stroke or SE in patients with AF. |
| | 2. Methodik<br><br>Population: Patienten mit Vorhofflimmern; bei der ROCKET AF-Studie waren nur Patienten mit einem erhöhten Risiko (CAHD2≥2) eingeschlossen<br>Vergleich: Warfarin, Kombination Warfarin und Aspirin (in einer Studie)<br>Endpunkte: kumulative Rate thromboembolitischer Schlaganfälle (TES) oder systemische Embolie, hämorrhagische Schlaganfälle, majore Blutungen<br><br>Suchzeitraum (Aktualität der Recherche): Bis 07/2012<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 12 (n=54.875)<br><br>Qualitätsbewertung der Studien:<br>- methods used to generate the randomization sequence, method of double blinding, and description of patient withdrawals and dropouts. A score of 1 point was given for each criterion satisfied, and 1 additional point was given for high quality of randomization and double blinding, for a maximum of 5 points. Studies with a score >2 were considered high quality, and studies with a score ≤2 were considered low quality. |
| | 3. Ergebnisdarstellung<br>*Stroke/SE: NOA versus Warfarin:* RR=0,77 (95%KI 0,70-0,86; $I^2$=0%; ARR=0,73%; NNT=137) im FE Modell. Im RE Modell blieben die Ergebnisse signifikant.<br><br>*Ischemic stroke: NOA versus Warefarin:* RR=0,92 (95%KI 0,81-1,04; $I^2$=22%;) im FE Modell. Im RE Modell blieben die Ergebnisse nicht |

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| | signifikant.<br><br>*Major bleeding: NOA versus Warefarin:* RR=0,86 (95%KI 0,80-0,93; $I^2$=57%; ARR=0,64%; NNT=157) im FE Modell. Im RE Modell waren die Ergebnisse nicht mehr signifikant (RR=0,86 (95%KI 0,72-1,02).<br><br>Aufgrund der großen Heterogenität erfolgte eine Subgruppenanalyse der einzelnen NOAs im Vergleich zu Warfarin. Diese Analyse ergab eine Reduktion der Blutungsereignisse unter Apixaban (RR=0,70 [95%KI 0,61-0,81]) und Dabigatran (RR=0,88 [95%KI 0,78-0,98]), jedoch keine Verringerung der Blutungsereignisse unter Rivaroxaban (RR=1,01 [95%KI 0,89-1,16]). |
| | 4. Anmerkungen/Fazit der Autoren<br>NOACs are associated with an overall clinical benefit compared with vitamin K antagonists. Additional research is required to confirm these findings outside the context of randomized trials.<br><br>5. Hinweise durch FB Med<br>- Sowohl Phase II und Phase III Studien eingeschlossen |
| **Capodanno 2013:** Novel oral anticoagulants versus warfarin in non-falvular atrial fibrillation: A meta-analysis of 50.578 patients.<br><br>*und*<br><br>**Adam 2012:** Comparative Effectiveness of Warfarin and New Oral Anticoagulants for the Management of Atrial Fibrillation and Venous | 1. Fragestellung<br>A meta-analysis of phase III trials that compare novel oral anticoagulants (NOACs) with warfarin to determine whether they improve clinical outcomes of patients with nonvalvular atrial fibrillation (AF). |
| | 2. Methodik<br>**Beide Metaanalyse basieren auf den drei RCTs zu Dabigatran (RE-LY), Apixaban (ARISTOTLE) und Rivaroxaban (ROCKET-AF) versus Warfarin**<br><br>Population: Patienten mit nicht-valvulärem Vorhofflimmern; bei der ROCKET AF-Studie waren nur Patienten mit einem erhöhten Risiko ($CAHD_2 \geq 2$) eingeschlossen<br>Vergleich: Novel oral anticoagulants versus warfarin in<br>Endpunkte: Schlaganfall oder systemische Embolie; Adam zusätzlich: hämorrhagische oder ischämische Schlaganfälle; majore Blutungen<br><br>Suchzeitraum (Aktualität der Recherche)<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 (n=50.578) |
| | 3. Ergebnisdarstellung<br>Ergebnisse (basierend auf 3 Studien mit 50.578 Patienten):<br><br>*Capodanno et al.:*<br><br>*NOA versus Warfarin:*<br><br>Stroke/SE: **OR=0,82 (95%KI 0,74-0,91)** sowohl im RE als auch im FE Modell.<br>Major bleeding: **OR=0,85 (95%KI 0,79-0,92)** im FE Modell. Im RE Modell waren die Ergebnisse nicht mehr signifikant (RR=0,85 (95%KI |

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| Thromboembolism.<br><br>*und*<br><br>**Miller 2012:**<br><br>Meta-Analysis of Efficacy and Safety of New Oral Anticoagulants (Dabigatran, Rivaroxaban, Apixaban) Versus Warfarin in Patients With Atrial Fibrillation. | 0,69-1,05).<br><br>*Adam et al.:*<br><br>*NOA versus Warfarin:*<br><br>Hemorrhagic stroke: **RR=0,48 (95%KI 0,36-0,62)**<br><br>Ischemic stroke: RR=0,89 (95%KI 0,78-1,02)<br><br>*Miller et al:*<br><br>*NOA versus Warfarin:*<br><br>Stroke/SE: **OR=0,78 (95%KI 0,67-0,92)**<br><br>Ischemic/unspecified stroke: **OR=0,87 (95%KI 0,77-0,99)**<br><br>Hemorrhagic stroke: **OR=0,45 (95%KI 0,31-0,68)** |
| | 4. Anmerkungen/Fazit der Autoren<br>In patients with non-valvular AF, NOACs decrease stroke or systemic embolism, hemorrhagic stroke and mortality, with similar risk of major bleeding compared to warfarin. |
| **Lip 2010:** Does Warfarin for Stroke Thromboprophylaxis Protect Against MI in Atrial Fibrillation Patients? | 1. Fragestellung<br>This article reviews myocardial infarction events in contemporary clinical trials of anticoagulation therapy (or equivalent) for stroke prevention in atrial fibrillation. |
| | **2.** Methodik (**Metaanalyse basierend auf einer systematischen Literaturrecherche nach RCTs die nach 2000 publiziert wurden.)**<br><br>Population: Vorhofflimmerpatienten<br>Vergleich: Warfarin vs. nicht-Warfarin Antikoagulantia (Ximelegatran) oder Antikoagulanzien Äquivalente (z.B. Clopidogrel)<br>Endpunkte: Myokardinfarkte<br><br>Suchzeitraum (Aktualität der Recherche): Nach 2000<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 (davon 5 Phase 3/4 Studien und 2 Phase 2 Studien) |
| | 3. Ergebnisdarstellung<br>• Die gepoolte Analyse zeigte einen stat. signifikanten Vorteil unter der Warfarin Therapie gegenüber der Komparatoren (RR: 0.77; 95%KI: 0.63-0.95; $I^2$= 48%). *<u>Hinweis</u>: Diese Ergebnisse waren größtenteils beeinflusst durch die RELY-Studie (Dabigatran).*<br>• Eine Sensitivitätsanalyse ohne die RELY-Studie, zeigte keinen stat. signifikanten Unterschied zwischen den Interventionen, bei jedoch gleichzeitig hoher Heterogenität ($I^2$= 58%).<br>• Wenn eine Sensitivitätsanalyse ohne die ACTIVE-W Studie[1] durchgeführt wurde, zeigte sich ein grenzwärtiges Ergebnis (RR: 0.80; 95%KI: 0.64-1.00; $I^2$=57%). |

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| | ----------<br><br>[1] ACTIVE-W: Die Studie war darauf ausgelegt eine Nicht-Unterlegenheit der Kombination von ASS plus Clopidogrel gegenüber einer OAC Therapie zu belegen. Die Studie wurde vorzeitig gestoppt, da sich eine Überlegenheit von Warfarin gegenüber der Kombination hinsichtlich der primären Endpunktes (erstes Auftreten eines Schlaganfalls, nicht-zerebraler Nervensystem systemischen Embolus, Myokardinfarkt oder vaskuläre Mortalität) zeigte. |
| | 4.Anmerkungen/Fazit der Autoren<br><br>Warfarin might provide a protective effect against myocardial infarction compared with<br>non-warfarin anticoagulants or “anticoagulation equivalents” in patients with atrial fibrillation who are prescribed anticoagulation for stroke thromboprophylaxis. |
| **Roskell 2010:**<br>Treatments for stroke prevention in atrial fibrillation: A network meta-analysis and indirect comparisons versus dabigatran etexilate. | 1. Fragestellung<br>The objectives of this study were to perform a systematic literature review and network meta-analysis (NMA) to synthesise the efficacy and safety data of treatments frequently used in the prevention of stroke and systemic embolism in AF patients. |
| | 2. Methodik<br><br>Population: Vorhofflimmerpatienten (moderates bis hohes Schlaganfallrisiko)<br>Vergleich: Dabigatran vs. Thromozytenaggregationshemmer (Mono-und Kombinationstherapien) oder Placebo<br>Endpunkte: Schlaganfälle (alle), ischämische Schlaganfälle, systemische Embolien, Gesamtmortalität, intrakranielle Blutungen (exkl. hämorrhagische Schlaganfälle), extrakranielle Blutungen (bedeutsame Blutungen), und akute Myokardinfarkte<br><br>Suchzeitraum (Aktualität der Recherche): Bis 08/2009<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 20 (n=k.A.) |
| | 3. Ergebnisdarstellung<br>• Placebo: Stat. signifikante Risikoreduktion hinsichtlich jedem Schlaganfall (ischämisch und hämorrhagisch) unter Dabigatran 150 mg BID (75%ige Reduktion; RR: 0.25; 95% KI: 0.12–0.51); ischämischer Schlaganfälle (77%ige Reduktion; RR:0.23; 95% KI: 0.14–0.38), systemischen Embolien (83%ige Reduktion; RR: 0.17; 95% KI 0.05–0.50) und Mortalität (36%ige Reduktion; RR: 0.64; 95% KI 0.45–0.91).<br>• ASS Monotherapie und ASS plus Clopidogrel: Es zeigte sich auch eine stat. signifikante Risikoreduktion hinsichtlich jedem Schlaganfall, wenn verglichen wird mit einer ASS Monotherapie (63%ige Reduktion; RR: 0.37; 95% KI: 0.20–0.69) und ASS plus Clopidogrel (61%ige Risikoreduktion; RR: 0.39; 95% KI: 0.21–0.72).<br>• Allgemein zeigte sich ein Trend zu einem reduzierten Risiko hinsichtlich der meisten anderen Endpunkte unter Dabigatran |

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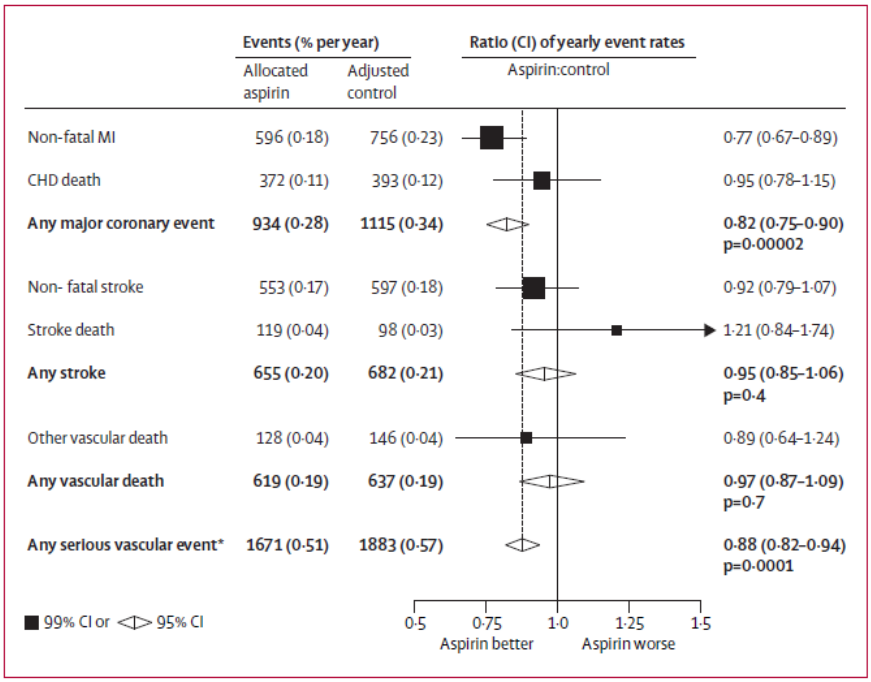
| | (beide Dosierungen). |
| | 4. Anmerkungen/Fazit der Autoren<br>Indirect evidence suggests treatment with dabigatran etexilate offers benefit for the prevention of stroke, systemic embolism and mortality over antiplatelets and placebo. There was no indication of increased intracranial or extracranial haemorrhage with dabigatran etexilate compared to antiplatelet agents.<br><br>5. Hinweise durch FB Med<br>*Hinweis*: *Die Punktschätzer der RR aus der Netzwerk Metaanalyse bei dem (Vergleich Dabigatran gegenüber VKAs), stimmen mit der denen der RELY-Studie größtenteils überein (Effektrichtung), bei jedoch weiteren KI bei der Netzwerkanalyse.* |
| **Antithrombotic Trialists' (ATT) Collaboration (2009):** Aspirin in the primary and secondary prevention of vascular<br><br>disease: collaborative meta-analysis of individual participant<br><br>data from randomised trials | 1. Fragestellung<br>Meta-analyses of serious vascular events (myocardial infarction, stroke, or vascular death) and major bleeds in six primary prevention trials and 16 secondary prevention trials that compared long-term aspirin versus control. |
| | 2. Methodik<br><br>Population: Patienten mit einer okklusiven vaskulären Erkrankung<br>Vergleich: Langzeitgabe von ASS vs. Kontrolle<br>Endpunkte: Schwere vaskuläre Ereignisse (Myokardinfarkt, Schlaganfall, Vaskuläre Mortalität)<br><br>Suchzeitraum (Aktualität der Recherche): k.A.<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 22 (n=siehe Ergebnisdarstellung) |
| | 3. Ergebnisdarstellung<br>• Primärprävention mit ASS (basierend auf 6 Studien; 95 000 individuals, 3554 serious vascular events):<br>o Es zeigte sich eine 12%ige (proportionale) Reduktion der schweren vaskulären Ereignissen unter ASS (0.51% ASS vs. 0.57% Kontrolle pro Jahr, p=0·0001).<br>o Dieses Ergebnis kam hauptsächlich zustande durch eine große Reduktion an nicht-tödlichen Myokardinfarkten (0.18% *vs.* 0.23% pro Jahr, p<0·0001).<br>o Der Nettoeffekt hinsichtlich der Schlaganfälle war nicht stat. signifikant unterschiedlich.<br>o Vaskuläre Mortalität war nicht stat. signifikant unterschiedlichen zwischen den Interventionen.<br>o ASS erhöhte das Auftreten an bedeutsamen gastrointestinalen und extrakraniellen Blutungen (0.10% *vs.* 0.07% pro Jahr, p<0·0001).<br><br>*Serious vascular events in primary prevention trials—proportional eff ects of aspirin allocation:* |




- <u>Sekundärprävention (basierend auf 16 Studien;</u> 17 000 individuals, 3306 vascular events<u>):</u>
  - Es zeigte sich eine größere absolute Reduktion mit ASS in der Sekundärprävention hinsichtlich schwerer vaskulärer Ereignisse (6.7% *vs.* 8.2% pro Jahr, p<0.0001), bei gleichzeitig nicht stat. signifikanten Anstieg an hämorrhagischen Schlaganfällen aber jedoch einer stat. signifikanten Abnahme an Schlaganfällen (alle) (2.08% *vs.* 2.54% pro Jahr, p=0·002) und koronaren Ereignissen (4.3% *vs.* 5.3% pro Jahr, p<0·0001).

4. Anmerkungen/Fazit der Autoren

In primary prevention without previous disease, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds.

**Leitlinien**

<table>
<tr><td rowspan="3">January 2014: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society.</td><td>AHA/ACC/HRS Atrial Fibrillation Guideline</td></tr>
<tr><td>Methodik<br><br>Grundlage der Leitlinie: The recommendations listed in this document are, whenever possible, evidence based. An extensive evidence review, focusing on 2006 to the present, was conducted through October 2012, and selected other references through February 2014. Searches were extended to studies, reviews, and other evidence that were conducted in human subjects, published in English, and accessible via PubMed, EMBASE, Cochrane, Agency for Healthcare Research and Quality Reports, and other selected databases relevant to this guideline.<br><br>LoE und GoR: siehe Anhang</td></tr>
<tr><td>Empfehlungen:<br><br>Summary of Recommendations for Prevention of Thromboembolism in Patients With AF:<br><br>
<table>
<tr><th>Recommendations</th><th>COR</th><th>LOE</th><th>References</th></tr>
<tr><td>Antithrombotic therapy based on shared decision-making, discussion of risks of stroke and bleeding, and patient's preferences</td><td>I</td><td>C</td><td>N/A</td></tr>
<tr><td>Antithrombotic therapy selection based on risk of thromboembolism</td><td>I</td><td>B</td><td>(167-170)</td></tr>
<tr><td>$CHA_2DS_2$-VASc score recommended to assess stroke risk</td><td>I</td><td>B</td><td>(171-173)</td></tr>
<tr><td>Warfarin recommended with mechanical heart valves. Target INR intensity should be based on the type and location of prosthesis</td><td>I</td><td>B</td><td>(174-176)</td></tr>
<tr><td>With prior stroke, TIA, or $CHA_2DS_2$-VASc score $\geq$2, oral anticoagulants recommended. Options include:</td><td></td><td></td><td></td></tr>
<tr><td>• Warfarin</td><td>I</td><td>A</td><td>(171-173)</td></tr>
<tr><td>• Dabigatran, rivaroxaban, or apixaban</td><td>I</td><td>B</td><td>(177-179)</td></tr>
<tr><td>With warfarin, determine INR at least weekly during initiation and monthly when stable</td><td>I</td><td>A</td><td>(180-182)</td></tr>
<tr><td>Direct thrombin or factor Xa inhibitor recommended, if unable to maintain therapeutic INR</td><td>I</td><td>C</td><td>N/A</td></tr>
<tr><td>Re-evaluate the need for anticoagulation at periodic intervals</td><td>I</td><td>C</td><td>N/A</td></tr>
<tr><td>Bridging therapy with LMWH or UFH recommended with a mechanical heart valve if warfarin is interrupted. Bridging therapy should balance risks of stroke and bleeding</td><td>I</td><td>C</td><td>N/A</td></tr>
<tr><td>Without a mechanical heart valve, bridging therapy decisions should balance stroke and bleeding risks against the duration of time patient will not be anticoagulated</td><td>I</td><td>C</td><td>N/A</td></tr>
<tr><td>Evaluate renal function prior to initiation of direct thrombin or factor Xa inhibitors, and re-evaluate when clinically indicated and at least annually</td><td>I</td><td>B</td><td>(183-185)</td></tr>
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| For atrial flutter, antithrombotic therapy is recommended as for AF | I | C | N/A |
| With nonvalvular AF and $CHA_2DS_2$-VASc score of 0, it is reasonable to omit antithrombotic therapy | IIa | B | (183, 184) |
| With $CHA_2DS_2$-VASc score ≥2 and end-stage CKD (CrCl <15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for oral anticoagulation | IIa | B | (185) |
| With nonvalvular AF and a $CHA_2DS_2$-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered | IIb | C | N/A |
| With moderate-to-severe CKD and $CHA_2DS_2$-VASc scores of ≥2, reduced doses of direct thrombin or factor Xa inhibitors may be considered | IIb | C | N/A |
| For PCI,* BMS may be considered to minimize duration of DAPT | IIb | C | N/A |
| Following coronary revascularization in patients with $CHA_2DS_2$-VASc score of ≥2, it may be reasonable to use clopidogrel concurrently with oral anticoagulants, but without aspirin | IIb | B | (186) |
| Direct thrombin, dabigatran, and factor Xa inhibitor, rivaroxaban, are not recommended with AF and end-stage CKD or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits | III: No Benefit | C | (177-179, 187-189) |
| Direct thrombin inhibitor, dabigatran, should not be used with a mechanical heart valve | III: Harm | B | (190) |

*See the 2011 percutaneous coronary intervention guideline for type of stent and duration of dual antiplatelet therapy recommendations (12).
AF indicates atrial fibrillation; BMS, bare-metal stent; CKD, chronic kidney disease; COR, Class of Recommendation; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; INR, international normalized ratio; LOE, Level of Evidence; LMWH, low-molecular-weight heparin; N/A, not applicable; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; and UFH, unfractionated heparin.

*Evidenz basierend auf folgenden Studien:*


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| **NICE 2013:** Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation. | National Institute for Health and Clinical Excellence |
| | Methodik<br><br>Grundlage der Leitlinie: Systematische Evidenzaufbereitung ohne Konsensusprozesse - eigene Checklisten - Anwendung von GRADE - GoR schlagen sich in den Formulierungen nieder – Konsultationsphase vor Veröffentlichung - keine formalen Konsensusprozesse |
| | Empfehlungen<br><br>***Key conclusion:***<br><br>• Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorisation.<br>• The decision about whether to start treatment with apixaban should be made after an informed discussion between the clinician and the person about the risks and benefits of apixaban compared with warfarin, dabigatran etexilate or rivaroxaban. For people who are taking warfarin, the potential risks and benefits of switching to apixaban should be considered in light of their level of international normalized ratio (INR) control.<br>• The Committee concluded that apixaban was more clinically effective than warfarin for the primary efficacy outcome of reducing stroke and systemic embolism.<br>• The Committee concluded that apixaban resulted in fewer bleeds than warfarin and it recognised the particular importance of the effects of apixaban in reducing the risk of intracranial bleeding for people with atrial fibrillation when compared with warfarin.<br><br>**Evidence for clinical effectiveness:**<br>*Availability, nature and quality of evidence:*<br><br>• The Committee considered the clinical-effectiveness data from the ARISTOTLE trial comparing apixaban with warfarin.<br>• The Committee noted that the manufacturer had included evidence on the efficacy of apixaban compared with aspirin for people for whom vitamin K antagonist treatment was unsuitable, |

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| | which was not part of the scope issued by NICE.<br>• The Committee agreed that the comparators defined in the final scope (warfarin, rivaroxaban and dabigatran etexilate) were appropriate and that the key trial for this appraisal was ARISTOTLE. |
| **NICE 2012:** Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. | National Institute for Health and Clinical Excellence |
| | Methodik<br>Grundlage der Leitlinie: Systematische Evidenzaufbereitung ohne Konsensusprozesse - eigene Checklisten - Anwendung von GRADE - GoR schlagen sich in den Formulierungen nieder – Konsultationsphase vor Veröffentlichung - keine formalen Konsensusprozesse |
| | Empfehlungen<br>***Key conclusion:***<br>• Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism in people with nonvalvular atrial fibrillation within its licensed indication.<br>• The decision about whether to start treatment with dabigatran etexilate should be made after an informed discussion between the clinician and the person about the risks and benefits of dabigatran compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to dabigatran should be considered in light of their level of international normalised ratio (INR) control.<br>• The Committee concluded that dabigatran 150 mg twice daily was more clinically effective than warfarin in reducing the risk of stroke or systemic embolism, ischaemic stroke and vascular mortality whereas dabigatran 110 mg twice daily was non-inferior to warfarin. It concluded that dabigatran represented an important development for people with atrial fibrillation.<br>**Evidence for clinical effectiveness**<br>Availability, nature and quality of evidence:<br>• The RE-LY trial formed most of the clinical-effectiveness evidence in the manufacturer's submission and was the largest published trial in people with atrial fibrillation. The Committee considered that the RE-LY trial was of good quality**.** |
| **NICE 2012:** Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. | National Institute for Health and Clinical Excellence |
| | Methodik<br>Grundlage der Leitlinie: Systematische Evidenzaufbereitung ohne Konsensusprozesse - eigene Checklisten - Anwendung von GRADE - GoR schlagen sich in den Formulierungen nieder – Konsultationsphase vor Veröffentlichung - keine formalen Konsensusprozesse |
| | Empfehlungen:<br>***Key conclusion:*** |

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| | • Rivaroxaban is recommended as an option within its licensed indication for the prevention of stroke and systemic embolism in adults with nonvalvular atrial fibrillation.<br>• The Committee recognised that decision about whether to start treatment with rivaroxaban should be made after an informed discussion between the clinician and the person about the risks and benefits of rivaroxaban compared with warfarin, and noting the limited direct trial evidence for people with a low risk of stroke (CHADS2 score of less than 2). For people who are taking warfarin, the potential risks and benefits of switching to rivaroxaban should be considered in light of their level of international normalised ratio (INR) control.<br><br>**Evidence for clinical effectiveness**<br>*Availability, nature and quality of evidence:*<br>• The main clinical-effectiveness evidence came from one multicentre, double-blind randomised controlled trial.<br>• The ROCKET-AF trial compared rivaroxaban with dose-adjusted warfarin.<br>• The manufacturer also compared rivaroxaban with aspirin and dabigatran etexilate (110 mg or 150 mg twice a day) using a network meta-analysis in people for whom anticoagulation therapy was considered suitable.<br>• The Committee also noted the additional indirect comparison submitted by the manufacturer during consultation comparing rivaroxaban with aspirin. |
| **SIGN (2013):** Antithrombotics: indications and management. | Leitlinie der Scottish Intercollegiate Guidelines Network (SIGN) |
| | Methodik<br><br>Grundlage der Leitlinie: The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Information Officer. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. Internet searches were carried out on various websites including the US National<br>Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.<br><br>Suchzeitraum: 2003-2009 (und 2013 Update)<br><br>LoE und GoR: |

| 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<br>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<br>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*<br>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*<br>Extrapolated evidence from studies rated as $2^{++}$ |
| D | Evidence level 3 or 4; or<br>Extrapolated evidence from studies rated as $2^{+}$ |
| GOOD PRACTICE POINTS | |
| ☒ | Recommended best practice based on the clinical experience of the guideline development group |

Empfehlungen

## ATRIAL FIBRILLATION: PROPHYLAXIS OF SYSTEMIC EMBOLISM

**D** **In all patients with AF, risk factors for systemic thromboembolism should be assessed routinely using $CHADS_2$ or $CHA_2DS_2$-VASc score.**

**B** **Patients with AF who are clearly low risk,** (age<65 and lone AF) **do not require antithrombotic therapy. This applies to male patients with $CHA_2DS_2$-VASc score=0 and female patients with $CHA_2DS_2$-VASc score=1 in whom the single point is allocated due to female sex.**

**A** **All patients with AF who have a $CHADS_2$ or $CHA_2DS_2$-VASc score of ≥1** (one or more clinically relevant risk factors) **should be considered for warfarin at a target INR of 2.5** (range 2.0-3.0) **or a newer anticoagulant. The balance of risks and benefits of anticoagulant therapy should be assessed and discussed annually with the patient, with consideration given to patient preference.**

**A** **Antiplatelet therapy should only be considered where warfarin or one of the alternative new anticoagulants has been declined.**

| GRADES OF RECOMMENDATION | |
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| *Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect t 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<br>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*<br>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*<br>Extrapolated evidence from studies rated as $2^{++}$ |
| D | Evidence level 3 or 4; or<br>Extrapolated evidence from studies rated as $2^{+}$ |

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| **Canadian Agency for Drugs and Technologies in Health 2012:** New Oral Anticoagulants for the Prevention of Thromboembolic Events in Patients with Atrial Fibrillation. | Leitlinie der Canadian Agency for Drugs and Technologies in Health |
| | Methodik<br><br>Grundlage der Leitlinie: The Therapeutic Review Recommendations or Advice are formulated following a comprehensive evidence-based review of the medication's efficacy or effectiveness and safety and an assessment of its cost-effectiveness. Therapeutic Review clinical and economic reports are based on published information available up to the time that CDEC made its recommendation. Input from stakeholders, such as drug manufacturers, patient groups, and health-related professional associations or organizations, is considered in the preparation of this recommendation document.<br><br>Suchzeitraum: k.A. |
| | Empfehlungen<br><br>**Recommendation 1:**<br><br>CDEC recommends that new oral anticoagulant agents should be considered for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation in whom warfarin is indicated, and who meet all of the following criteria:<br><br>• Are unable to achieve adequate anticoagulation with warfarin, and<br><br>• Have a $CHADS_2$ score ≥ 2.<br><br>**Recommendation 2:**<br><br>CDEC recommends that the selection of a new oral anticoagulant agent should be made based on individual clinical factors.<br><br>**Reasons for Recommendation 1**<br><br>• Despite the small, absolute risk reductions of the NOACs versus warfarin, the daily cost of the NOACs exceeds that of warfarin, even when international normalized ratio (INR) monitoring costs are included.<br>• For the unstratified patient populations, the NOACs produced a small absolute risk reduction, compared with warfarin, of two to six per 1,000 patients treated annually and one more to eight fewer events per 1,000 patients treated annually for the outcomes of stroke and SE and major bleeding, respectively. These results were the same for patients with a $CHADS_2$ score of ≥ 2. A clear benefit was not demonstrated for lower-risk patients.<br><br>**Reasons for Recommendation 2**<br><br>The lack of head-to-head trials and the small number of trials available to definitively assess comparative effectiveness indirectly |

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| | makes evidence-based differentiation of these agents difficult.<br><br>• Patient subgroups were not defined in the same way in all the relevant RCTs, making comparisons among different NOACs difficult.<br>• The relative cost-effectiveness of the NOACs is uncertain.<br>The lack of long-term data for the NOACs and the assumption of persistent benefit of the NOACs beyond the durations of the individual RCTs available make it unreliable to compare the costeffectiveness of the new agents. |
| **Furie 2012:** Oral Antithrombotic Agents for the Prevention of Stroke in Nonvalvular Atrial Fibrillation : A Science Advisory for Healthcare Professionals From the American Heart Association/American Stroke Association. | Leitlinie der The American Heart Association |
| | Methodik<br><br>Grundlage der Leitlinie: Update to the American Heart Association/American Stroke Association (AHA/ASA) “Guidelines for the Primary Prevention of Stroke”<br><br>Suchzeitraum: k.A.<br><br>LoE und GoR: siehe Anhang |
| | Empfehlungen:<br><br>**Current AHA/ASA Recommendations for Vitamin K Antagonists/Antithrombotics for the Prevention of a First Stroke**<br><br>The following are the current AHA/ASA recommendations for vitamin K antagonists/antithrombotics for prevention of a first stroke:<br><br>**1. Adjusted-dose warfarin** (target INR, 2.0–3.0) is recommended for all patients with nonvalvular AF deemed to be at high risk and many deemed to be at moderate risk for stroke who can receive it safely *(Class I; Level of Evidence A)*.<br><br>**2. Antiplatelet therapy with aspirin is recommended for low-risk and some moderate-risk patients** with AF on the basis of patient preference, estimated bleeding<br><br>risk if anticoagulated, and access to high- quality anticoagulation monitoring *(Class I; Level of Evidence A)*.<br><br>**3. For high-risk patients with AF deemed unsuitable for anticoagulation, dual-**<br><br>**Antiplatelet therapy with clopidogrel and aspirin** offers more protection against<br><br>stroke than aspirin alone but with an increased risk of major bleeding and might be reasonable *(Class IIb; Level of Evidence B)*. |

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| | **Existing AHA/ASA Recommendations for Vitamin K Antagonists/Antithrombotics for the Prevention of Stroke in Patients With a History of Stroke or TIA**<br><br>**1. For patients with ischemic stroke or TIA** with paroxysmal (intermittent) or permanent AF, anticoagulation with a **vitamin K antagonist** (target INR, 2.5; range,<br><br>2.0–3.0) is recommended *(Class I; Level of Evidence A)*.<br><br>**2. For patients unable to take oral anticoagulants, aspirin alone** *(Class I; Level of Evidence A)* is recommended. The combination of clopidogrel plus aspirin carries a risk of bleeding similar to that of warfarin and therefore is not recommended for patients with a hemorrhagic contraindication to warfarin *(Class III; Level of Evidence B)*.<br><br>***Existing AHA Recommendations for use of dabigatran***<br><br>Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (CrCl <15 mL/min), or advanced liver disease (impaired baseline clotting function) *(Class I; Level of Evidence B)*.<br><br>**NEW RECOMMENDATIONS**<br><br>1. **Warfarin** (Class I; Level of Evidence A), **dabigatran** (Class I; Level of Evidence B), **apixaban** (Class I; Level of Evidence B), and **rivaroxaban** (Class IIa; Level of Evidence B) are **all indicated for the prevention of first and recurrent stroke in patients with nonvalvular AF**. The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in INR therapeutic<br><br>range if the patient has been taking warfarin.<br><br>**2. Dabigatran 150 mg twice daily** is an efficacious alternative to warfarin for the prevention of first and recurrent stroke in patients with nonvalvular AF and at least 1 additional risk factor who have CrCl >30 mL/min (Class I; Level of Evidence B).<br><br>**3.** On the basis of pharmacokinetic data, the use of **dabigatran 75 mg twice daily** in patients with AF and at least 1 additional risk factor who have a low CrCl (15–30 L/min) may be considered, but its safety and efficacy have not been established (Class |

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| | IIb; Level of Evidence C).<br><br>**4.** Because there are no data to support the use of **dabigatran** in patients with more severe renal failure, dabigatran is **not recommended in patients with a CrCl <15 mL/min** (Class III; Level of Evidence C).<br><br>**5. Apixaban 5 mg twice daily** is an efficacious alternative to aspirin in patients with nonvalvular AF deemed unsuitable for vitamin K antagonist therapy who have at least 1 additional risk factor and no more than 1 of the following characteristics: Age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL (Class I; Level of Evidence B).<br><br>**6.** Although its safety and efficacy have not been established, **apixaban 2.5 mg twice daily** may be considered as an alternative to aspirin in patients with nonvalvular AF deemed unsuitable for vitamin K antagonist therapy who have at least 1 additional<br><br>risk factor and ≥2 of the following criteria: Age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/ dL (Class IIb; Level of Evidence C).<br><br>**7. Apixaban 5 mg twice daily** is a relatively safe and efficacious **alternative to warfarin** in patients with nonvalvular AF deemed appropriate for vitamin K antagonist therapy who have at least 1 additional risk factor and no more than 1 of the following characteristics: Age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, (Class I; Level of Evidence B).<br><br>**8.** Although its safety and efficacy have not been established, **apixaban 2.5 mg twice daily** may be considered as an **alternative to warfarin** in patients with nonvalvular AF deemed appropriate for vitamin K antagonist therapy who have at least 1 additional risk factor and ≥2 of the following criteria: Age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL (Class IIb; Level of Evidence C).<br><br>**9. Apixaban should not be used if the CrCl is <25 mL/ min** (Class III; Level of Evidence C).<br><br>**10.** In patients with nonvalvular AF who are at moderate to high risk of stroke (prior history of TIA, stroke, or systemic embolization or ≥2 additional risk factors), **rivaroxaban 20 mg/d is reasonable as an alternative to warfarin** (Class IIa; Level of<br><br>Evidence B).<br><br>**11. In patients with renal impairmet** and nonvalvular AF who are at moderate to high risk of stroke (prior history of TIA, stroke, or systemic embolization or ≥2 additional risk factors), with a CrCl of 15 to 50 mL/min, **15 mg of rivaroxaban daily may be considered;** however, its safety and efficacy have not been established (Class |

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| | IIb; Level of Evidence C).<br><br>**12. Rivaroxaban should not be used if the CrCl is <15 mL/min** (Class III; Level of Evidence C).<br><br>**13.** The **safety and efficacy** of combining dabigatran, rivaroxaban, or apixaban with an antiplatelet agent **have not been established** (Class IIb; Level of Evidence C). |
| **Skanes 2012:** Focused 2012 Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines: Recommendations for Stroke Prevention and Rate/Rhythm Control | Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines |
| | Methodik<br><br>Grundlage der Leitlinie: The Canadian Cardiovascular Society (CCS) published the complete set of 2010 Atrial Fibrillation (AF) Guidelines in the January, 2011 issue of the *Canadian Journal of Cardiology*. The Guidelines Committee judged that this extensive and important new evidence required focused updating of the 2010 Guidelines with respect to stroke prevention and rate/rhythm control.<br>This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations.<br>These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. |
| | Empfehlungen:<br><br>• We recommend that **all patients with AF or AFL** (paroxysmal, persistent, or permanent), should be **stratified using a predictive index for stroke risk** (eg, $CHADS_2$) and for the risk of bleeding (eg, HAS-BLED), and that **most patients should receive either an OAC or ASA** (Strong Recommendation, High-Quality Evidence).<br>• We suggest, that when OAC therapy is indicated, most patients should receive **dabigatran, rivaroxaban, or apixaban** (once approved by Health Canada), **in preference to warfarin** (Conditional Recommendation, High-Quality Evidence).<br>• We recommend that **patients at high risk of stroke** ($CHADS_2$ ≥2) **should receive OAC therapy** (Strong Recommendation, High-Quality Evidence).<br>• We recommend that most patients at **intermediate risk of stroke** ($CHADS_2$ = 1) **should receive OAC therapy** (Strong Recommendation, High-Quality Evidence).<br>• We suggest, based on individual risk/benefit considerations, that **ASA is a reasonable alternative for som**e (Conditional Recommendation, Moderate-Quality Evidence).<br>• We suggest that patients at **low risk of stroke** ($CHADS_2$=0) |

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| | should have **additional risk factors for stroke considered** (including age 65-74 years, female sex, and presence of vascular disease) (Conditional Recommendation, Moderate-Quality Evidence).<br>We suggest **OAC therapy for patients at highest risk** within this category (age greater than age 65 or the combination of female sex and vascular disease); **ASA (75-325 mg/day) for patients at lower risk** within this category (female sex or vascular disease); and **no antithrombotic therapy for those patients at lowest risk in this category** (no additional risk factors) (Conditional Recommendation, Low- Quality Evidence). |
| **You 2012:** Antithrombotic Therapy for Atrial Fibrillation Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. | American College of Chest Physicians Evidence-Based Clinical Practice Guidelines |
| | Methodik<br>Grundlage der Leitlinie: We used the methods described in the Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines article of this supplement.<br>Suchzeitraum: 2005-2009<br>Leitlinie nach dem Grade approach |
| | **2.1.8** For patients with AF, including those with paroxysmal AF, who are at **low risk of stroke** (eg, $CHADS_2$ score= 0), we suggest **no therapy rather than antithrombotic therapy** (Grade 2B).<br>For patients who do choose antithrombotic therapy, we suggest **aspirin** (75 mg to 325 mg once daily) rather than oral anticoagulation (Grade 2B) or combination therapy with aspirin and clopidogrel (Grade 2B).<br>**2.1.9** For patients with AF, including those with paroxysmal AF, who are at **intermediate risk of stroke** (eg, $CHADS_2$ score= 1), we recommend **oral anticoagulation rather than no therapy** (Grade 1B). We suggest **oral anticoagulation rather than aspirin** (75 mg to 325 mg once daily) (Grade 2B) or **combination therapy with aspirin and clopidogrel** (Grade 2B) . For patients who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we suggest combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) (Grade 2B).<br>**2.1.10** For patients with AF, including those with paroxysmal AF, who are at **high risk of stroke** (eg, $CHADS_2$ score=2), we recommend **oral anticoagulation rather than no therapy** (Grade 1A) , **aspirin** |

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| | (75 mg to 325 mg once daily) (Grade 1B) , **or combination therapy with aspirin and clopidogrel** (Grade 1B) . For patients who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) (Grade 1B).<br><br>**For patients with AF**, including those with paroxysmal AF, for recommendations in favor of oral anticoagulation (including 2.1.9, 2.1.10, and excluding 2.2, 3.1, 3.2, 3.3), **we suggest dabigatran 150 mg twice daily rather than adjusted-dose vitamin K antagonist ( VKA) therapy** (target INR range, 2.0-3.0) (Grade 2B) .<br><br>**2.2.** For patients with **AF and mitral stenosis**, we recommend **adjusted-dose VKA therapy** (target INR range, 2.0-3.0) **rather than no therapy, aspirin** (75 mg to 325 mg once daily), **or combination therapy with aspirin and clopidogrel** (all Grade 1B) . For patients with AF and mitral stenosis who are unsuitable for or choose not to take adjusted-dose VKA therapy (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) alone (Grade 1B) .<br><br>**3.1.** For patients with **AF and stable coronary artery disease** (eg, no acute coronary syndrome within the previous year) and who choose oral anticoagulation, we suggest **adjusted-dose VKA therapy alone** (target international normalized ratio [INR] range, 2.0-3.0) rather than the combination of adjusted-dose VKA therapy and aspirin (Grade 2C) .<br><br>**3.2.** For patients with **AF at high risk of stroke** (eg, $CHADS_2$ score of 2 or greater) during the first month after placement of a bare-metal stent or the first 3 to 6 months after placement of a drug-eluting stent, we suggest triple therapy (eg, VKA therapy, aspirin, and clopidogrel) rather than dual antiplatelet therapy (eg, aspirin and clopidogrel) (Grade 2C) . After this initial period of triple therapy, we suggest a<br><br>VKA (INR 2.0-3.0) plus a single antiplatelet drug rather than VKA alone (Grade 2C) . At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).<br><br>**3.3.** For patients with AF at intermediate to high risk of stroke (eg, $CHADS_2$ score of 1 or greater) who experience an acute coronary syndrome and do not undergo intracoronary stent placement, we suggest for the first 12 months, adjusted-dose VKA therapy (INR 2.0-3.0) plus single antiplatelet therapy rather than dual antiplatelet therapy (eg, aspirin and clopidogrel) or triple therapy (eg, warfarin, |

<table>
<tr><td></td><td>aspirin, and clopidogrel) (Grade 2C) . After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).</td></tr>
<tr><td rowspan="2">Camm (2010):<br>Guidelines for the management of atrial fibrillation (ESC Guideline)<br><br><u>und</u></td><td>Camm 2012: An update of the 2010 ESC Guidelines for the management of atrial fibrillation Developed with the special contribution of the European Heart Rhythm Association</td></tr>
<tr><td>Methodik<br>Grundlage der Leitlinie:<br>A large number of guidelines have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC web site (http://www.escardio.org/guidelinessurveys/esc-guidelines/about/Pages/rules-writing.aspx).<br><br>Classes of recommendations:<br>
<table>
<tr><th>Classes of recommendations</th><th>Definition</th><th>Suggested wording to use</th></tr>
<tr><td>Class I</td><td>Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.</td><td>Is recommended/is indicated</td></tr>
<tr><td>Class II</td><td>Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.</td><td></td></tr>
<tr><td>Class IIa</td><td>Weight of evidence/opinion is in favour of usefulness/efficacy.</td><td>Should be considered</td></tr>
<tr><td>Class IIb</td><td>Usefulness/efficacy is less well established by evidence/opinion.</td><td>May be considered</td></tr>
<tr><td>Class III</td><td>Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.</td><td>Is not recommended</td></tr>
</table>
<br>Levels of evidence:<br>
<table>
<tr><td>Level of evidence A</td><td>Data derived from multiple randomized clinical trials or meta-analyses.</td></tr>
<tr><td>Level of evidence B</td><td>Data derived from a single randomized clinical trial or large non-randomized studies.</td></tr>
<tr><td>Level of evidence C</td><td>Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.</td></tr>
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**ESC 2010: Approach to thromboprophylaxis in patients with AF**

- In general: Recommendations for antithrombotic therapy should be based on the presence (or absence) of risk factors for stroke and thrombo-embolism, rather than on an artificial division into high, moderate, or low risk categories (AI).

| Risk category antithrombotic therapy | CHA2DS2VASc score | Recommended |
|---|---|---|
| One 'major' risk factor or ≥ 2 'clinically relevant non-major' risk factors | ≥ 2 | OAC[1] **(LoE: AI)** |
| One 'clinically relevant non-major' risk factor | 1 | Either OAC or aspirin 75-325 mg daily. *Preferred*: OAC rather than aspirin **(LoE: A/B I)** |
| No risk factor | 0 | Either aspirin 75-325 mg daily or no antithrombotic therapy. *Preferred*: no antithrombotic therapy rather than aspirin. **(LoE: AI)** |

- VKA treatment should be considered for patients with AF with ≥1 stroke risk factor(s) provided there are no contraindications, especially with careful assessment of the risk–benefit ratio and an appreciation of the patient's values and preferences.

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[1] OAC, such as a VKA, adjusted to an intensity range of INR 2.0–3.0 (target 2.5). New OAC drugs, which may be viable alternatives to a VKA, may ultimately be considered. For example, should both doses of dabigatran etexilate receive regulatory approval for stroke prevention in AF, the recommendations for thromboprophylaxis could evolve as follows considering stroke and bleeding risk stratification:

Hinweis: Where oral anticoagulation is appropriate therapy, dabigatran may be considered, as an alternative to adjusted dose VKA therapy. (i) If a patient is at low risk of bleeding (e.g. HAS-BLED score of 0–2; see Table 10 for HAS-BLED score definition), dabigatran 150 mg b.i.d. may be considered, in view of the improved efficacy in the prevention of stroke and systemic embolism (but lower rates of intracranial haemorrhage and similar rates of major bleeding events, when compared with warfarin); and (ii) If a patient has a measurable risk of bleeding (e.g. HAS-BLED score of ≥3), dabigatran etexilate 110 mg b.i.d. may be considered, in view of a

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| **Camm (2012):** 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. | similar efficacy in the prevention of stroke and systemic embolism (but lower rates of intracranial haemorrhage and of major bleeding compared with VKA). (b) In patients with one 'clinically relevant non-major' stroke risk factor, dabigatran 110 mg b.i.d. may be considered, in view of a similar efficacy with VKA in the prevention of stroke and systemic embolism but lower rates of intracranial haemorrhage and major bleeding compared with the VKA and (probably) aspirin. (c) Patients with no stroke risk factors (e.g. CHA2DS2-VASc ¼ 0) are clearly at so low risk, either aspirin 75–325 mg daily or no antithrombotic therapy is recommended. Where possible, no antithrombotic therapy should be considered for such patients, rather than aspirin, given the limited data on the benefits of aspirin in this patient group (i.e., lone AF) and the potential for adverse effects, especially bleeding.<br><br>*Recommendations for prevention of thromboembolism in non-valvular AF:*<br><br>**Recommendations for prevention of thromboembolism in non-valvular AF—general**<br>Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those patients (both male and female) who are at low risk (aged <65 years and lone AF), or with contraindications. — Class I — Level A — Ref 21, 63, 104, 105, 106<br>The choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient. — Class I — Level A — Ref 21, 63, 105<br>The $CHA_2DS_2$-VASc score is recommended as a means of assessing stroke risk in non-valvular AF. — Class I — Level A — Ref 25, 36 ,39<br>In patients with a $CHA_2DS_2$-VASc score of 0 (i.e., aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended. — Class I — Level B — Ref 21, 36, 82<br>In patients with a $CHA_2DS_2$-VASc score ≥2, OAC therapy with:<br>• adjusted-dose VKA (INR 2–3); or<br>• a direct thrombin inhibitor (dabigatran); or<br>• an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[f]<br>… is recommended, unless contraindicated. — Class I — Level A — Ref 3, 4, 70, 82<br>In patients with a $CHA_2DS_2$-VASc score of 1, OAC therapy with<br>• adjusted-dose VKA (INR 2–3); or<br>• a direct thrombin inhibitor (dabigatran); or<br>• an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[f]<br>…. should be considered, based upon an assessment of the risk of bleeding complications and patient preferences. — Class IIa — Level A — Ref 33, 44<br>Female patients who are aged <65 and have lone AF (but still have a $CHA_2DS_2$-VASc score of 1 by virtue of their gender) are low risk and no antithrombotic therapy should be considered. — Class IIa — Level B — Ref 33, 44<br>When patients refuse the use of any OAC (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or—less effectively—aspirin 75–325 mg daily. — Class IIa — Level B — Ref 21, 26, 51, 109<br>**Recommendations for prevention of thromboembolism in non-valvular AF—NOACs**<br>When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either:<br>• a direct thrombin inhibitor (dabigatran); or<br>• an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[f]<br>… is recommended. — Class I — Level B — Ref 2, 28, 65, 107<br>Where OAC is recommended, one of the NOACs, either:<br>• a direct thrombin inhibitor (dabigatran); or<br>• an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[f]<br>… should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit. — Class IIa — Level A — Ref 3, 4, 70, 82<br>Where dabigatran is prescribed, a dose of 150 mg b.i.d. should be considered for most patients in preference to 110 mg b.i.d., with the latter dose recommended in:<br>• elderly patients, age ≥ 80<br>• concomitant use of interacting drugs (e.g. verapamil)<br>• high bleeding risk (HAS-BLED score ≥3)<br>• moderate renal impairment (CrCl 30–49 mL/min). — Class IIa — Level B — Ref 85, 96<br>Where rivaroxaban is being considered, a dose of 20 mg o.d. should be considered for most patients in preference to 15 mg o.d., with the latter dose recommended in:<br>• high bleeding risk (HAS-BLED score ≥3)<br>• moderate renal impairment (CrCl 30–49 mL/min). — Class IIa — Level C — Ref 3, 108<br>Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year. — Class IIa — Level B — Ref 85<br>NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min). — Class III — Level A — Ref 3, 24, 70 |

| Recommendations | Class[a] | Level[b] | Ref[c] |
|---|---|---|---|
| **Recommendations for prevention of thromboembolism in non-valvular AF—bleeding** | | | |
| Assessment of the risk of bleeding is recommended when prescribing antithrombotic therapy (whether with VKA, NOAC, aspirin/clopidogrel, or aspirin). | I | A | 25, 54, 59, 60 |
| The HAS-BLED score should be considered as a calculation to assess bleeding risk, whereby a score ≥3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or antiplatelet therapy (LoE = A).<br>Correctable risk factors for bleeding [e.g. uncontrolled blood pressure, labile INRs if the patient was on a VKA, concomitant drugs (aspirin, NSAIDs, etc.), alcohol, etc.] should be addressed (LoE = B).<br>Use of the HAS-BLED score should be used to identify modifiable bleeding risks that need to be addressed, but should not be used on its own to exclude patients from OAC therapy (LoE = B). | IIa | A B | 25, 54, 60 |
| The risk of major bleeding with antiplatelet therapy (with aspirin–clopidogrel combination therapy and – especially in the elderly – also with aspirin monotherapy) should be considered as being similar to OAC. | IIa | B | 18, 21, 23, 24, 26, 35 |
| **Recommendations for prevention of thromboembolism in non-valvular AF—peri-cardioversion** | | | |
| For patients with AF of ≥48 h duration, or when the duration of AF is unknown, OAC therapy (e.g. VKA with INR 2-3 or dabigatran) is recommended for ≥3 weeks prior to and for ≥4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological). | I | B | 93 |
| In patients with risk factors for stroke or AF recurrence, OAC therapy, whether with dose-adjusted VKA (INR 2-3) or a NOAC, should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion. | I | B | 110 |

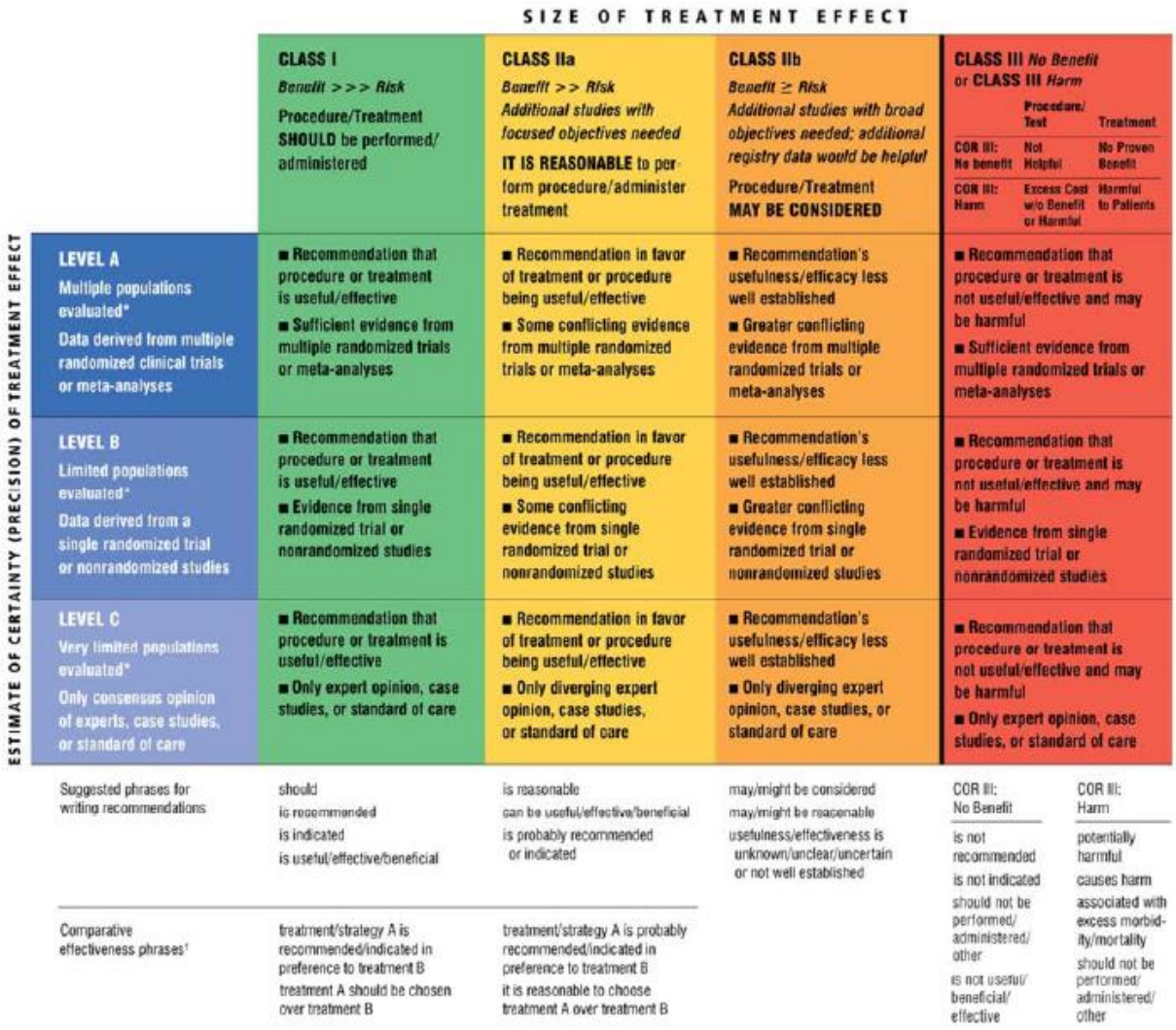
AF = atrial fibrillation; b.i.d. = bis in die (twice daily); $CHA_2DS_2$-VASc = congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, sex category (female); CrCl = creatinine clearance; HAS-BLED = hypertension, abnormal renal/liver function (1 point each), stroke, bleeding tendency or predisposition, labile INR if on warfarin, elderly (e.g., age >65), drugs (aspirin, NSAIDs, etc.)/alcohol concomitantly (1 point each); INR = international normalized ratio; i.v. = intravenous; OAC = oral anticoagulant; NOAC = novel oral anticoagulant; NSAID = non-steroidal anti-inflammatory drug; VKA = vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]Apixaban (pending approval EMA and FDA approval): prescribing information is awaited.

## Key points

- The efficacy of stroke prevention with aspirin is weak, with a potential for harm, since the risk of major bleeding (and ICH) with aspirin is not significantly different to that of OAC, especially in the elderly.
- The use of antiplatelet therapy (as aspirin–clopidogrel combination therapy or—less effectively—aspirin monotherapy for those who cannot tolerate aspirin–clopidogrel combination therapy) for stroke prevention in AF should be limited to the few patients who refuse any form of OAC.
- The $CHA_2DS_2$-VASc score is better at identifying 'truly low-risk' patients with AF and is as good as—and possibly better than—scores such as $CHADS_2$ in identifying patients who develop stroke and thromboembolism.
- The HAS-BLED score allows clinicians to make an informed assessment of bleeding risk and, importantly, makes them think of the correctable risk factors for bleeding. In patients with a HAS-BLED score ≥3, caution and regular review are recommended, as well as efforts to correct the potentially reversible risk factors for bleeding. A high HAS-BLED score per se should not be used to exclude patients from OAC therapy.
- The NOACs offer better efficacy, safety, and convenience compared with OAC with VKAs. Thus, where an OAC is recommended, one of the NOACs—either a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)—should be considered instead of adjusted-dose VKA (INR 2–3) for most patients with AF.
- There is insufficient evidence to recommend one NOAC over another, although some patient characteristics, drug compliance and tolerability, and cost may be important considerations in the choice of agent.

Anhang:

**January 2014:**



SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

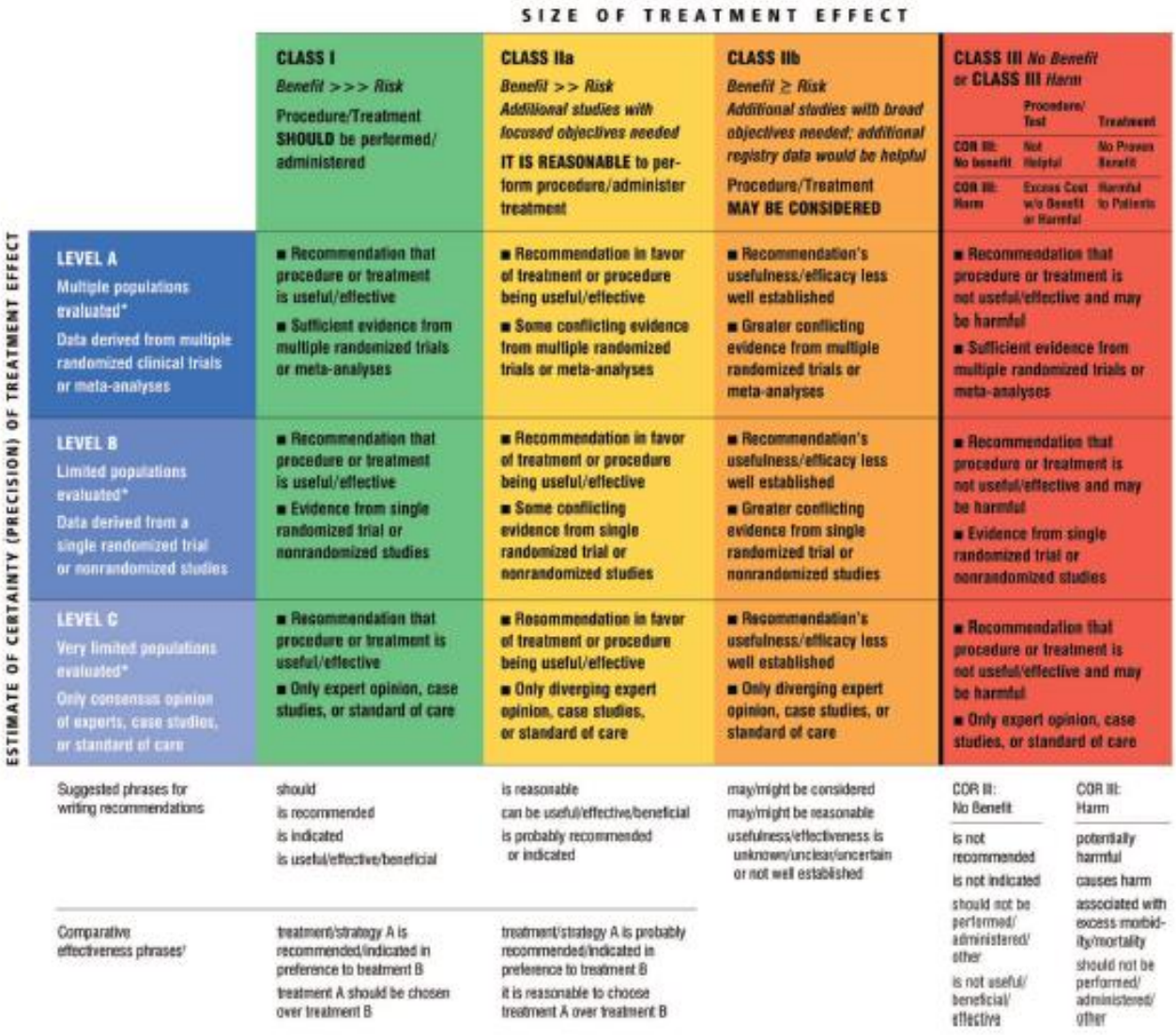
| | CLASS I<br>*Benefit >>> Risk*<br>Procedure/Treatment **SHOULD** be performed/ administered | CLASS IIa<br>*Benefit >> Risk*<br>*Additional studies with focused objectives needed*<br>**IT IS REASONABLE** to perform procedure/administer treatment | CLASS IIb<br>*Benefit ≥ Risk*<br>*Additional studies with broad objectives needed; additional registry data would be helpful*<br>Procedure/Treatment **MAY BE CONSIDERED** | CLASS III *No Benefit* or CLASS III *Harm*<br>Procedure/ Test / Treatment<br>COR III: No benefit / Not Helpful / No Proven Benefit<br>COR III: Harm / Excess Cost w/o Benefit or Harmful / Harmful to Patients |
|---|---|---|---|---|
| **LEVEL A**<br>Multiple populations evaluated*<br>Data derived from multiple randomized clinical trials or meta-analyses | ■ Recommendation that procedure or treatment is useful/effective<br>■ Sufficient evidence from multiple randomized trials or meta-analyses | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Some conflicting evidence from multiple randomized trials or meta-analyses | ■ Recommendation's usefulness/efficacy less well established<br>■ Greater conflicting evidence from multiple randomized trials or meta-analyses | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Sufficient evidence from multiple randomized trials or meta-analyses |
| **LEVEL B**<br>Limited populations evaluated*<br>Data derived from a single randomized trial or nonrandomized studies | ■ Recommendation that procedure or treatment is useful/effective<br>■ Evidence from single randomized trial or nonrandomized studies | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Some conflicting evidence from single randomized trial or nonrandomized studies | ■ Recommendation's usefulness/efficacy less well established<br>■ Greater conflicting evidence from single randomized trial or nonrandomized studies | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Evidence from single randomized trial or nonrandomized studies |
| **LEVEL C**<br>Very limited populations evaluated*<br>Only consensus opinion of experts, case studies, or standard of care | ■ Recommendation that procedure or treatment is useful/effective<br>■ Only expert opinion, case studies, or standard of care | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Only diverging expert opinion, case studies, or standard of care | ■ Recommendation's usefulness/efficacy less well established<br>■ Only diverging expert opinion, case studies, or standard of care | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Only expert opinion, case studies, or standard of care |
| Suggested phrases for writing recommendations | should<br>is recommended<br>is indicated<br>is useful/effective/beneficial | is reasonable<br>can be useful/effective/beneficial<br>is probably recommended or indicated | may/might be considered<br>may/might be reasonable<br>usefulness/effectiveness is unknown/unclear/uncertain or not well established | COR III: No Benefit<br>is not recommended<br>is not indicated<br>should not be performed/ administered/ other<br>is not useful/ beneficial/ effective<br><br>COR III: Harm<br>potentially harmful<br>causes harm<br>associated with excess morbidity/mortality<br>should not be performed/ administered/ other |
| Comparative effectiveness phrases† | treatment/strategy A is recommended/indicated in preference to treatment B<br>treatment A should be chosen over treatment B | treatment/strategy A is probably recommended/indicated in preference to treatment B<br>it is reasonable to choose treatment A over treatment B | | |

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes mellitus, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative-effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

**Furie 2012**:



| ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT | SIZE OF TREATMENT EFFECT: CLASS I<br>*Benefit >>> Risk*<br>Procedure/Treatment **SHOULD** be performed/ administered | CLASS IIa<br>*Benefit >> Risk*<br>*Additional studies with focused objectives needed*<br>**IT IS REASONABLE** to perform procedure/administer treatment | CLASS IIb<br>*Benefit ≥ Risk*<br>*Additional studies with broad objectives needed; additional registry data would be helpful*<br>Procedure/Treatment **MAY BE CONSIDERED** | CLASS III *No Benefit* or CLASS III *Harm*<br>COR III: No benefit — Procedure/Test: Not Helpful; Treatment: No Proven Benefit<br>COR III: Harm — Procedure/Test: Excess Cost w/o Benefit or Harmful; Treatment: Harmful to Patients |
|---|---|---|---|---|
| **LEVEL A**<br>Multiple populations evaluated*<br>Data derived from multiple randomized clinical trials or meta-analyses | ■ Recommendation that procedure or treatment is useful/effective<br>■ Sufficient evidence from multiple randomized trials or meta-analyses | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Some conflicting evidence from multiple randomized trials or meta-analyses | ■ Recommendation's usefulness/efficacy less well established<br>■ Greater conflicting evidence from multiple randomized trials or meta-analyses | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Sufficient evidence from multiple randomized trials or meta-analyses |
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| **LEVEL C**<br>Very limited populations evaluated*<br>Only consensus opinion of experts, case studies, or standard of care | ■ Recommendation that procedure or treatment is useful/effective<br>■ Only expert opinion, case studies, or standard of care | ■ Recommendation in favor of treatment or procedure being useful/effective<br>■ Only diverging expert opinion, case studies, or standard of care | ■ Recommendation's usefulness/efficacy less well established<br>■ Only diverging expert opinion, case studies, or standard of care | ■ Recommendation that procedure or treatment is not useful/effective and may be harmful<br>■ Only expert opinion, case studies, or standard of care |
| Suggested phrases for writing recommendations | should<br>is recommended<br>is indicated<br>is useful/effective/beneficial | is reasonable<br>can be useful/effective/beneficial<br>is probably recommended or indicated | may/might be considered<br>may/might be reasonable<br>usefulness/effectiveness is unknown/unclear/uncertain or not well established | COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective<br>COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other |
| Comparative effectiveness phrases† | treatment/strategy A is recommended/indicated in preference to treatment B<br>treatment A should be chosen over treatment B | treatment/strategy A is probably recommended/indicated in preference to treatment B<br>it is reasonable to choose treatment A over treatment B | | |

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.
*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.
†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

**Detaillierte Darstellung der Recherchestrategie:**

Cochrane Library am 08.05.2014

| Suchschritt | Suchfrage |
|---|---|
| #1 | stroke* or CVA or cerebrovascular next accident* or cerebrovascular next incident* or apoplex* or cerebrovascular next insult*:ti,ab,kw (Word variations have been searched) |
| #2 | brain next attack* or ischemic next cerebrovascular next syndrome* or cerebral next infarction* or brain next infarction* or brain next ischemia* or intracranial next hemorrhage* or intracranial next haemorrhage* or intracerebral next hemorrhage* or intracerebral next haemorrhage*:ti,ab,kw (Word variations have been searched) |
| #3 | cerebral next ischemia* or cerebral next ischaemia* or ischaemic next cerebrovascular next syndrome* or brain next ischaemia*:ti,ab,kw (Word variations have been searched) |
| #4 | MeSH descriptor: [Stroke] explode all trees |
| #5 | #1 or #2 or #3 or #4 |
| #6 | atrial next fibrillation*:ti,ab,kw (Word variations have been searched) |
| #7 | MeSH descriptor: [Atrial Fibrillation] explode all trees |
| #8 | #6 or #7 |
| #9 | #5 and #8 |
| #10 | #9 Publication Date from 2009 to 2014 |

MEDLINE (PubMed) am 08.05.2014

| Suchschritt | Suchfrage |
|---|---|
| #5 | Search stroke[MeSH Terms] |
| #7 | Search ((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR treat*[Title/Abstract] |
| #8 | Search (prevent*[Title/Abstract]) OR prophyla*[Title/Abstract] |
| #9 | Search (#7 OR #8) |
| #11 | Search ("stroke/drug therapy"[MeSH Terms]) OR ("stroke/prevention and control"[MeSH Terms]) |
| #20 | Search (((((stroke*[Title/Abstract]) OR CVA[Title/Abstract]) OR cerebrovascular accident*[Title/Abstract]) OR cerebrovascular incident*[Title/Abstract]) OR apoplex*[Title/Abstract]) OR cerebrovascular insult*[Title/Abstract] |
| #21 | Search (((((((brain attack*[Title/Abstract]) OR ischemic cerebrovascular syndrome*[Title/Abstract]) OR cerebral infarction*[Title/Abstract]) OR brain infarction*[Title/Abstract]) OR brain ischemia*[Title/Abstract]) OR intracranial hemorrhage*[Title/Abstract]) OR intracranial haemorrhage*[Title/Abstract]) OR intracerebral hemorrhage*[Title/Abstract]) OR intracerebral haemorrhage*[Title/Abstract] |
| #22 | Search (((cerebral ischemia*[Title/Abstract]) OR cerebral ischaemia*[Title/Abstract]) OR ischaemic cerebrovascular syndrome*[Title/Abstract]) OR brain ischaemia*[Title/Abstract] |

| | |
|---|---|
| #23 | Search (#5 OR #20 OR #21 OR #22) |
| #24 | Search (#23 AND #9) |
| #25 | Search (#24 OR #11) |
| #26 | Search atrial fibrillation*[Title/Abstract] |
| #27 | Search atrial fibrillation[MeSH Terms] |
| #28 | Search (#26 OR #27) |
| #29 | Search (#25 AND #28) |
| #30 | 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])))) |
| #31 | Search (#29 AND #30) |
| #34 | Search (#25 AND #28) Filters: Systematic Reviews; Meta-Analysis; Technical Report |
| #35 | Search (#31 OR #34) |
| #36 | Search (#31 OR #34) Filters: published in the last 5 years |

MEDLINE (PubMed) nach Leitlinien am 08.05.2014

| Suchschritt | Suchfrage |
|---|---|
| #2 | Search (((((stroke*[Title]) OR CVA[Title]) OR cerebrovascular accident*[Title]) OR cerebrovascular incident*[Title]) OR apoplex*[Title]) OR cerebrovascular insult*[Title] |
| #3 | Search (((((((brain attack*[Title]) OR ischemic cerebrovascular syndrome*[Title]) OR cerebral infarction*[Title]) OR brain infarction*[Title]) OR brain ischemia*[Title]) OR intracranial hemorrhage*[Title]) OR intracranial haemorrhage*[Title]) OR intracerebral hemorrhage*[Title]) OR intracerebral haemorrhage*[Title] |
| #4 | Search (((cerebral ischemia*[Title]) OR cerebral ischaemia*[Title]) OR ischaemic cerebrovascular syndrome*[Title]) OR brain ischaemia*[Title] |
| #5 | Search stroke[MeSH Terms] |
| #6 | Search (#2 OR #3 OR #4 OR #5) |
| #7 | Search ((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR treat*[Title/Abstract] |
| #8 | Search (prevent*[Title/Abstract]) OR prophyla*[Title/Abstract] |
| #9 | Search (#7 OR #8) |
| #10 | Search (#6 AND #9) |
| #11 | Search ("stroke/drug therapy"[MeSH Terms]) OR ("stroke/prevention and control"[MeSH Terms]) |
| #12 | Search (#10 OR #11) |
| #13 | Search atrial fibrillation*[Title] |

| | |
|---|---|
| #14 | Search atrial fibrillation[MeSH Major Topic] |
| #15 | Search (#13 OR #14) |
| #16 | Search (#12 OR #15) |
| #17 | 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]) NOT medline[sb]) |
| #18 | Search (#16 AND #17) |
| #19 | Search (#16 AND #17) Filters: published in the last 5 years |

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