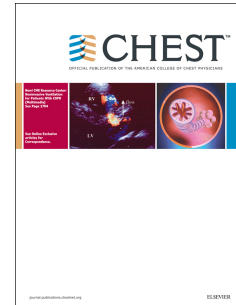


# Accepted Manuscript



## Antithrombotic Therapy for VTE Disease: CHEST Guideline

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3 **Antithrombotic Therapy for VTE Disease: CHEST Guideline**

4

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26  
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28 anticoagulation in patients with cancer. Dr. Bounameaux has received compensation for  
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34 anticoagulation and treatment of subsegmental PE. He has also authored several papers related to  
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39 Steering Committee of PEITHO, a principal investigator of an original study related to Role of  
40 IVC filter in addition to anticoagulation in patients with acute DVT or PE and has participated in  
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44 the topic of catheter assisted thrombus removal in patients with leg DVT. He has also published  
45 many studies related to long-term anticoagulation and compression stockings in preventing post

46 thrombotic syndrome. Dr. Moores has frequently lectured on the duration of long-term  
47 anticoagulation and is a co-author on several risk-stratification papers. Drs. Moores and King  
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60 subsegmental PE. He has authored several studies (including NOAC) and grants related to the  
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64 VTE Disease Guidelines (AT9). Drs. Blaivas, Ornelas and Sood have nothing to disclose.

65

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67

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69 the American College of Clinical Pharmacy, the International Society for Thrombosis and  
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71

72 **Disclaimer:** American College of Chest Physician guidelines are intended for general  
73 information only, are not medical advice, and do not replace professional medical care and  
74 physician advice, which always should be sought for any medical condition. The complete  
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77

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86

87 **Abstract**

88

89 **Background:** We update recommendations on 12 topics that were in the 9th edition of these  
90 guidelines, and address 3 new topics.

91 **Methods:** We generate strong (Grade 1) and weak (Grade 2) recommendations based on high  
92 (Grade A), moderate (Grade B) and low (Grade C) quality evidence.

93 **Results:** For VTE and no cancer, as long-term anticoagulant therapy, we suggest dabigatran  
94 (Grade 2B), rivaroxaban (Grade 2B), apixaban (Grade 2B) or edoxaban (Grade 2B) over VKA  
95 therapy, and suggest VKA therapy over LMWH (Grade 2C). For VTE and cancer, we suggest  
96 LMWH over VKA (Grade 2B), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban  
97 (Grade 2C) or edoxaban (Grade 2C). We have not changed recommendations for who should  
98 stop anticoagulation at 3 months or receive extended therapy. For VTE treated with  
99 anticoagulants, we recommend against an IVC filter (Grade 1B). For DVT, we suggest not using  
100 compression stockings routinely to prevent PTS (Grade 2B). For subsegmental PE and no  
101 proximal DVT, we suggest clinical surveillance over anticoagulation with a low risk of recurrent  
102 VTE (Grade 2C), and anticoagulation over clinical surveillance with a high risk (Grade 2C). We  
103 suggest thrombolytic therapy for PE with hypotension (Grade 2B), and systemic therapy over  
104 catheter directed thrombolysis (Grade 2C). For recurrent VTE on a non-LMWH anticoagulant,  
105 we suggest LMWH (Grade 2C), and for recurrent VTE on LMWH we suggest increasing the  
106 LMWH dose (Grade 2C).

107 **Conclusion:** Of 54 recommendations included in the 30 statements, 20 were strong and none  
108 was based on high quality evidence highlighting the need for further research.

109 ***CHEST 201X;XX(X):XXXX-XXXX***

110 **Abbreviations:** AT9 = The 9<sup>th</sup> Edition of the Antithrombotic Guideline; AT10 = The 10<sup>th</sup>  
111 Edition of the Antithrombotic Guideline; CHEST = American College of Chest Physicians; COI  
112 = conflict of interest; CDT = Catheter-Directed Thrombolysis; CT = Computerized Tomography;  
113 CTEPH = Chronic Thromboembolic Pulmonary Hypertension; CTPA = Computerized  
114 Tomography Pulmonary Angiogram; DVT= deep vein thrombosis; GOC = Guidelines Oversight  
115 Committee; INR = International Normalized Ratio; IVC = Inferior Vena Cava; LMWH = Low  
116 Molecular Weight Heparin; MeSH = Medical Subject Heading; NOAC = non-vitamin K oral  
117 anticoagulant; PE= pulmonary embolism; PESI = Pulmonary Embolism Severity Index; PICO =  
118 evidence questions addressing patient population, intervention, comparator, and outcome; PTS =  
119 Post-Thrombotic Syndrome; RCT = randomized controlled trial; VKA = Vitamin K Antagonist;  
120 VTE = venous thromboembolism; UEDVT = Upper Extremity Deep Vein Thrombosis; US =  
121 Ultrasound

122

123

124

125 **Summary of Recommendations**

126

127 Note on Shaded Text: In this guideline, shading is used within the summary of  
128 recommendations to indicate recommendations that are newly added or have been changed since  
129 the publication of Antithrombotic therapy for VTE disease: Antithrombotic Therapy and  
130 Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based  
131 Clinical Practice Guidelines. Recommendations that remain unchanged since that edition are  
132 not shaded. The order of our presentation of the NOACS (dabigatran, rivaroxaban, apixaban,  
133 edoxaban) is based on the chronology of publication of the phase 3 trials in VTE treatment and  
134 should not be interpreted as the guideline panel's order of preference for the use of these agents.

135

136

137 **Choice of Long-Term (First 3 Months) and Extended (No Scheduled Stop Date)**

138 **Anticoagulant**

139

140 1. **In patients with proximal DVT or PE, we recommend long-term (3 months)**  
141 **anticoagulant therapy over no such therapy (Grade 1B).**

142

143 2. **In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months)**  
144 **anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban or edoxaban**  
145 **over VKA therapy (all Grade 2B). For patients with DVT of the leg or PE and no**  
146 **cancer who are not treated with dabigatran, rivaroxaban, apixaban or edoxaban, we**  
147 **suggest VKA therapy over LMWH (Grade 2C).**



148 *Remarks:* Initial parenteral anticoagulation is given before dabigatran and edoxaban, is  
149 not given before rivaroxaban and apixaban, and is overlapped with VKA therapy. See  
150 text for factors that influence choice of therapy.

151

152 3. **In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"),**  
153 **as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA**  
154 **therapy (Grade 2C), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban**  
155 **(Grade 2C) or edoxaban (Grade 2C).**

156 *Remarks:* Initial parenteral anticoagulation is given before dabigatran and edoxaban, is  
157 not given before rivaroxaban and apixaban, and is overlapped with VKA therapy. See  
158 text for factors that influence choice of therapy.

159

160 4. **In patients with DVT of the leg or PE who receive extended therapy, we suggest that**  
161 **there is no need to change the choice of anticoagulant after the first 3 months (Grade**  
162 **2C).**

163 *Remarks:* It may be appropriate for the choice of anticoagulant to change in response to  
164 changes in the patient's circumstances or preferences during the long-term or extended  
165 phases of treatment.

166

167

### 168 **Duration of Anticoagulant Therapy**

169

170 5. **In patients with a proximal DVT of the leg or PE provoked by surgery, we**  
171 **recommend treatment with anticoagulation for 3 months over (i) treatment of a**

172 **shorter period (Grade 1B), (ii) treatment of a longer time-limited period (e.g. 6, 12 or**  
173 **24 months) (Grade 1B), or (iii) extended therapy (no scheduled stop date) (Grade**  
174 **1B).**

175  
176 **6. In patients with a proximal DVT of the leg or PE provoked by a nonsurgical**  
177 **transient risk factor, we recommend treatment with anticoagulation for 3 months**  
178 **over (i) treatment of a shorter period (Grade 1B), and (ii) treatment of a longer time-**  
179 **limited period (e.g. 6, 12 or 24 months) (Grade 1B). We suggest treatment with**  
180 **anticoagulation for 3 months over extended therapy if there is a low or moderate**  
181 **bleeding risk (Grade 2B), and recommend treatment for 3 months over extended**  
182 **therapy if there is a high risk of bleeding (Grade 1B).**

183 *Remarks:* In all patients who receive extended anticoagulant therapy, the continuing use  
184 of treatment should be reassessed at periodic intervals (e.g. annually).

185  
186 **7. In patients with an isolated distal DVT of the leg provoked by surgery or by a**  
187 **nonsurgical transient risk factor, we suggest treatment with anticoagulation for 3**  
188 **months over treatment of a shorter period (Grade 2C), we recommend treatment**  
189 **with anticoagulation for 3 months over treatment of a longer time-limited period**  
190 **(e.g. 6, 12 or 24 months) (Grade 1B), and we recommend treatment with**  
191 **anticoagulation for 3 months over extended therapy (no scheduled stop date) (Grade**  
192 **1B).**

193 *Remarks:* Duration of treatment of patients with isolated distal DVT refers to patients in  
194 whom a decision has been made to treat with anticoagulant therapy; however, it is

195 anticipated that not all patients who are diagnosed with isolated distal DVT will be  
196 prescribed anticoagulants.

197

198 8. **In patients with an unprovoked DVT of the leg (isolated distal or proximal) or PE,**  
199 **we recommend treatment with anticoagulation for at least 3 months over treatment**  
200 **of a shorter duration (Grade 1B), and we recommend treatment with anticoagulation**  
201 **for 3 months over treatment of a longer time-limited period (e.g. 6, 12 or 24 months)**  
202 **(Grade 1B).**

203 *Remarks:* After 3 months of treatment, patients with unprovoked DVT of the leg or PE  
204 should be evaluated for the risk-benefit ratio of extended therapy. Duration of treatment  
205 of patients with isolated distal DVT refers to patients in whom a decision has been made  
206 to treat with anticoagulant therapy; however, it is anticipated that not all patients who are  
207 diagnosed with isolated distal DVT will be prescribed anticoagulants.

208

209 9. **In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE**  
210 **and who have a (i) low or moderate bleeding risk (see text), we suggest extended**  
211 **anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B),**  
212 **and a (ii) high bleeding risk (see text), we recommend 3 months of anticoagulant**  
213 **therapy over extended therapy (no scheduled stop date) (Grade 1B).**

214 *Remarks:* Patient sex and D-dimer level measured a month after stopping anticoagulant  
215 therapy may influence the decision to stop or extend anticoagulant therapy (see text). In  
216 all patients who receive extended anticoagulant therapy, the continuing use of treatment  
217 should be reassessed at periodic intervals (e.g. annually).

218

219 10. **In patients with a second unprovoked VTE and who have a (i) low bleeding risk (see**  
220 **text), we recommend extended anticoagulant therapy (no scheduled stop date) over**  
221 **3 months (Grade 1B), (ii) moderate bleeding risk (see text), we suggest extended**  
222 **anticoagulant therapy over 3 months of therapy (Grade 2B), and (iii) high bleeding**  
223 **risk (see text), we suggest 3 months of anticoagulant therapy over extended therapy**  
224 **(no scheduled stop date) (Grade 2B).**

225 *Remarks:* In all patients who receive extended anticoagulant therapy, the continuing use  
226 of treatment should be reassessed at periodic intervals (e.g. annually).

227

228 11. **In patients with DVT of the leg or PE and active cancer ("cancer-associated**  
229 **thrombosis") and who (i) do not have a high bleeding risk, we recommend extended**  
230 **anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B),**  
231 **and (ii) have a high bleeding risk, we suggest extended anticoagulant therapy (no**  
232 **scheduled stop date) over 3 months of therapy (Grade 2B).**

233 *Remarks:* In all patients who receive extended anticoagulant therapy, the continuing use  
234 of treatment should be reassessed at periodic intervals (e.g. annually).

235

236

237 **Aspirin for Extended Treatment of Venous Thromboembolism**

238

239 12. **In patients with an unprovoked proximal DVT or PE who are stopping**  
240 **anticoagulant therapy and do not have a contraindication to aspirin, we suggest**  
241 **aspirin over no aspirin to prevent recurrent VTE (Grade 2C).**

242 *Remarks:* Because aspirin is expected to be much less effective at preventing recurrent  
243 VTE than anticoagulants, we do not consider aspirin a reasonable alternative to  
244 anticoagulant therapy in patients who want extended therapy. However, if a patient has  
245 decided to stop anticoagulants, prevention of recurrent VTE is one of the benefits of  
246 aspirin that needs to be balanced against aspirin's risk of bleeding and inconvenience. Use  
247 of aspirin should also be reevaluated when patients stop anticoagulant therapy because  
248 aspirin may have been stopped when anticoagulants were started.

249

250

### 251 **Whether and How to Anticoagulate Isolated Distal Deep Vein Thrombosis**

252

253 13. **In patients with acute isolated distal DVT of the leg and (i) without severe symptoms**  
254 **or risk factors for extension (see text), we suggest serial imaging of the deep veins**  
255 **for 2 weeks over anticoagulation (Grade 2C), and (ii) with severe symptoms or risk**  
256 **factors for extension (see text), we suggest anticoagulation over serial imaging of the**  
257 **deep veins (Grade 2C).**

258 *Remarks:* Patients at high risk for bleeding are more likely to benefit from serial imaging.  
259 Patients who place a high value on avoiding the inconvenience of repeat imaging and a  
260 low value on the inconvenience of treatment and on the potential for bleeding are likely  
261 to choose initial anticoagulation over serial imaging

262

263 14. **In patients with acute isolated distal DVT of the leg who are managed with**  
264 **anticoagulation, we recommend using the same anticoagulation as for patients with**  
265 **acute proximal DVT (Grade 1B).**

266

267 15. **In patients with acute isolated distal DVT of the leg who are managed with serial**  
268 **imaging, we (i) recommend no anticoagulation if the thrombus does not extend**  
269 **(Grade 1B), (ii) suggest anticoagulation if the thrombus extends but remains**  
270 **confined to the distal veins (Grade 2C), and (iii) recommend anticoagulation if the**  
271 **thrombus extends into the proximal veins (Grade 1B).**

272

273

#### 274 **Catheter-Directed Thrombolysis for Acute Deep Vein Thrombosis of the Leg**

275 16. **In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy**  
276 **alone over catheter-directed thrombolysis (CDT) (Grade 2C).**

277 *Remarks:* Patients who are most likely to benefit from CDT (see text), who attach a high  
278 value to prevention of post thrombotic syndrome (PTS), and a lower value to the initial  
279 complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over  
280 anticoagulation alone.

281

282

#### 283 **Role of Inferior Vena Caval Filter in Addition to Anticoagulation for Acute Deep Vein**

#### 284 **Thrombosis or Pulmonary Embolism**

285

286 17. **In patients with acute DVT or PE who are treated with anticoagulants, we**  
287 **recommend against the use of an IVC filter (Grade 1B).**

288

289

290 **Compression Stocking to Prevent Post-Thrombotic Syndrome**

291

292 18. **In patients with acute DVT of the leg, we suggest not using compression stockings**  
293 **routinely to prevent PTS (Grade 2B).**

294 *Remarks:* This recommendation focuses on prevention of the chronic complication of  
295 PTS and not on the treatment of symptoms. For patients with acute or chronic symptoms,  
296 a trial of graduated compression stockings is often justified.

297

298

299 **Whether to Anticoagulate Subsegmental Pulmonary Embolism**

300

301 19. **In patients with subsegmental PE (no involvement of more proximal pulmonary**  
302 **arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE**  
303 **(see text), we suggest clinical surveillance over anticoagulation (Grade 2C), and (ii)**  
304 **high risk for recurrent VTE (see text), we suggest anticoagulation over clinical**  
305 **surveillance (Grade 2C).**

306 *Remarks:* Ultrasound imaging of the deep veins of both legs should be done to exclude  
307 proximal DVT. Clinical surveillance can be supplemented by serial ultrasound imaging

308 of the proximal deep veins of both legs to detect evolving DVT (see text). Patients and  
309 physicians are more likely to opt for clinical surveillance over anticoagulation if there is  
310 good cardiopulmonary reserve or a high risk of bleeding.

311

312

### 313 **Treatment of Acute Pulmonary Embolism Out of Hospital**

314

315 20. **In patients with low-risk PE and whose home circumstances are adequate, we**  
316 **suggest treatment at home or early discharge over standard discharge (e.g. after**  
317 **first 5 days of treatment) (Grade 2B).**

318

319

### 320 **Systemic Thrombolytic Therapy for Pulmonary Embolism**

321

322 21. **In patients with acute PE associated with hypotension (e.g. systolic BP <90 mm Hg)**  
323 **who do not have a high bleeding risk, we suggest systemically administered**  
324 **thrombolytic therapy over no such therapy (Grade 2B).**

325

326 22. **In most patients with acute PE not associated with hypotension, we recommend**  
327 **against systemically administered thrombolytic therapy (Grade 1B).**

328

329 23. **In selected patients with acute PE who deteriorate after starting anticoagulant**  
330 **therapy but have yet to develop hypotension and who have a low bleeding risk, we**



331 **suggest systemically administered thrombolytic therapy over no such therapy**  
332 (Grade 2C).

333 *Remarks:* Patients with PE and without hypotension who have severe symptoms or  
334 marked cardiopulmonary impairment should be monitored closely for deterioration.  
335 Development of hypotension suggests that thrombolytic therapy has become indicated.  
336 Cardiopulmonary deterioration (e.g. symptoms, vital signs, tissue perfusion, gas  
337 exchange, cardiac biomarkers) that has not progressed to hypotension may also alter the  
338 risk-benefit assessment in favor of thrombolytic therapy in patients initially treated with  
339 anticoagulation alone.

340

341

#### 342 **Catheter-Based Thrombus Removal for the Initial Treatment of Pulmonary Embolism**

343

344 24. **In patients with acute PE who are treated with a thrombolytic agent, we suggest**  
345 **systemic thrombolytic therapy using a peripheral vein over catheter directed**  
346 **thrombolysis (CDT) (Grade 2C).**

347 *Remarks:* Patients who have a higher risk of bleeding with systemic thrombolytic  
348 therapy, and who have access to the expertise and resources required to do CDT, are  
349 likely to choose CDT over systemic thrombolytic therapy.

350

351 25. **In patients with acute PE associated with hypotension and who have (i) a high**  
352 **bleeding risk, (ii) failed systemic thrombolysis, or (iii) shock that is likely to cause**  
353 **death before systemic thrombolysis can take effect (e.g. within hours), if appropriate**

354 **expertise and resources are available, we suggest catheter assisted thrombus**  
355 **removal over no such intervention** (Grade 2C).

356 *Remarks:* Catheter assisted thrombus removal refers to mechanical interventions, with or  
357 without catheter directed thrombolysis.

358

359

### 360 **Pulmonary Thromboendarterectomy for the Treatment of Chronic Thromboembolic**

#### 361 **Pulmonary Hypertension**

362

363 26. **In selected patients with CTEPH who are identified by an experienced**  
364 **thromboendarterectomy team, we suggest pulmonary thromboendarterectomy over**  
365 **no pulmonary thromboendarterectomy** (Grade 2C).

366 *Remarks:* Patients with CTEPH should be evaluated by a team with expertise in treatment  
367 of pulmonary hypertension. Pulmonary thromboendarterectomy is often life saving and  
368 life transforming. Patients with CTEPH who are not candidates for pulmonary  
369 thromboendarterectomy may benefit from other mechanical and pharmacological  
370 interventions designed to lower pulmonary arterial pressure.

371

372

### 373 **Thrombolytic Therapy in Patients with Upper Extremity Deep Vein Thrombosis**

374

375 27. **In patients with acute UEDVT that involves the axillary or more proximal veins, we**  
376 **suggest anticoagulant therapy alone over thrombolysis** (Grade 2C).

377 *Remarks:* Patients who (i) are most likely to benefit from thrombolysis (see text); (ii)  
378 have access to CDT; (iii) attach a high value to prevention of PTS; and (iv) attach a lower  
379 value to the initial complexity, cost, and risk of bleeding with thrombolytic therapy are  
380 likely to choose thrombolytic therapy over anticoagulation alone.

381

382 28. **In patients with UEDVT who undergo thrombolysis, we recommend the same**  
383 **intensity and duration of anticoagulant therapy as in patients with UEDVT who do**  
384 **not undergo thrombolysis (Grade 1B).**

385

386

### 387 **Management of Recurrent Venous Thromboembolism on Anticoagulant Therapy**

388

389 29. **In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or**  
390 **on dabigatran, rivaroxaban, apixaban or edoxaban (and are believed to be**  
391 **compliant), we suggest switching to treatment with LMWH at least temporarily**  
392 **(Grade 2C).**

393 *Remarks:* Recurrent VTE while on therapeutic-dose anticoagulant therapy is unusual and  
394 should prompt the following assessments: (1) reevaluation of whether there truly was a  
395 recurrent VTE; (2) evaluation of compliance with anticoagulant therapy; and (3)  
396 consideration of an underlying malignancy. A temporary switch to LMWH will usually  
397 be for at least one month.

398

399 30. **In patients who have recurrent VTE on long-term LMWH (and are believed to be**  
400 **compliant) we suggest increasing the dose of LMWH by about one-quarter to one-**  
401 **third (Grade 2C).**

402 *Remarks:* Recurrent VTE while on therapeutic-dose anticoagulant therapy is unusual and  
403 should prompt the following assessments: (1) reevaluation of whether there truly was a  
404 recurrent VTE; (2) evaluation of compliance with anticoagulant therapy; and (3)  
405 consideration of an underlying malignancy.

406

407

408 CHEST has been developing and publishing guidelines for the treatment of deep vein thrombosis  
409 (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism  
410 (VTE), for more than 30 years. CHEST published the last (9th) edition of these guidelines in  
411 February 2012 (AT9).<sup>1</sup> Since then, a substantial amount of new evidence relating to the treatment  
412 of VTE has been published, particularly in relation the use of non-vitamin K oral anticoagulants  
413 (NOACs). Moreover, a number of VTE treatment questions that were not addressed in the last  
414 edition have been highlighted. This article focuses on new developments and ongoing  
415 controversies in the treatment of VTE, updating recommendations for 12 topics that were  
416 included in AT9 and providing recommendations for 3 new topics. The target users of this  
417 guideline are clinicians.

418

419

420

421 **Methods**

422

423

424 **Composition and Selection of Topic Panel Members**

425

426 The Guidelines Oversight Committee (GOC) at CHEST appointed the editor for the guideline  
427 update. Then, the editor nominated the project executive committee, the chair and the remaining  
428 panelists (see acknowledgements section). The GOC approved all panelists after review of their  
429 qualifications and conflict of interest (COI) disclosures. The 15 panelists include general  
430 internists, thrombosis specialists, pulmonologists, hematologists and methodologists.

431

432 Throughout guideline development, panelists were required to disclose any potential financial or  
433 intellectual conflicts of interest by topic.<sup>2</sup> Financial and intellectual conflicts of interest were  
434 classified as primary (more serious) or secondary (less serious) (eTable 1). Panelists with  
435 primary COI were required to abstain from voting on related topic areas, but could participate in  
436 discussions provided they refrained from strong advocacy.

437

438

439 **Selection of Topics and Key Questions**

440

441 First, we listed all of the topic areas from AT9 and added potential new topics proposed by the  
442 panel members. Next, all panel members voted on whether each topic should be included in the  
443 update. Finally, the full-panel reviewed the results of the vote and decided on the final list. The

444 panel selected a total of 15 topics: 12 “update topics” from AT9 and 3 “new topics”. For each  
445 topic, we developed standardized questions in the PICO (Population, Intervention, Comparator,  
446 Outcome) format (eTable 2).

447

#### 448 **Systematic Search**

449

450 Systematic methods were used to search for evidence for each question. When available, the  
451 National Library of Medicine’s medical subject headings (MeSH) keyword nomenclature was  
452 used. We searched MEDLINE via PubMed for original studies and the Cochrane Library for  
453 systematic reviews. For update topics, we searched the literature from January 2005 to July  
454 2014. For new topics, we searched the literature from 1946 (Medline inception) to July 2014. All  
455 searches were limited to English language publications. We augmented searches by checking  
456 reference lists of published articles and personal files, and with ongoing surveillance of the  
457 literature by panel members (eFigures 1-4).

458

459 When we identified systematic reviews, we assessed their quality according to the AMSTAR  
460 tool.<sup>3</sup> We used those that were of highest quality and up-to-date as the source of evidence. In the  
461 absence of a satisfactory systematic review, we did our own evidence synthesis using the  
462 primary studies identified in AT9 and in the updated search. If the panel judged that the  
463 identified randomized controlled trials (RCTs) were inadequate, we expanded the search to  
464 include prospective cohort studies.

465

466

**467 Study Selection, data abstraction, and data analysis**

468

469 The criteria for selecting the evidence were based on the PICO elements of the standardized  
470 questions and the study design (eTable 2). We followed standard processes (duplicate  
471 independent work with agreement checking and disagreement resolution) for title and abstract  
472 screening, full text screening, data abstraction, and risk of bias assessment. We abstracted data  
473 on the characteristics of: study design, participants, intervention, control, outcomes, funding, and  
474 COI. We assessed risk of bias using the Cochrane Risk of Bias Tool in randomized trials<sup>4</sup>, and an  
475 adapted tool for observational studies<sup>5</sup> (eTable 3).

476

477 When existing systematic reviews were not available or were inadequate, we performed meta-  
478 analyses when appropriate. For each outcome of interest, we calculated the risk ratios of  
479 individual studies then pooled them and assessed statistical heterogeneity using the  $I^2$  statistic.  
480 We used fixed-effects model when pooling data from two trials, or when one of the included  
481 trials was large relative to the others. Otherwise, we used random-effects model. We used the  
482 Review Manager software (Version 5.2) to perform the meta-analyses and construct forest plots.  
483 We calculated absolute effects by applying pooled relative risks to baseline risks, ideally  
484 estimated from valid prognostic observational data or, in the absence of the latter, from control  
485 group risks. When credible data from prognostic observational studies were not available, we  
486 used risk estimates from control groups of RCTs included in the meta-analyses (eFigure 5 and 6).

487

488

**489 Assessing Quality of Evidence**



490  
491 Based on the GRADE approach, quality of evidence (also known as certainty of evidence) is  
492 defined as the extent to which our confidence in the effect estimate is adequate to support a  
493 recommendation.<sup>6,7</sup> The quality of evidence is categorized as high (A level), moderate (B level),  
494 low (includes very-low) (C level).<sup>6,7</sup> The rating of the quality of evidence reflects the strengths  
495 and limitations of the body of evidence and was based on the study design, risk of bias,  
496 imprecision, inconsistency, indirectness of results, and likelihood of publication bias, in addition  
497 to factors specific to observational studies.<sup>5,6,8-12</sup> Using GRADEpro software (Version 3.6), we  
498 generated tables to summarize the judgments of the quality of the evidence, the relative and  
499 absolute effect.<sup>13</sup> The GRADE tables include Summary of Findings (SoF) tables presented in the  
500 main text, and a more detailed version called Evidence Profiles (EP) presented in the online  
501 supplement. The evidence profiles also explicitly link recommendations to the supporting  
502 evidence.

503

504

### 505 **Drafting of Recommendations**

506

507 Following the GRADE approach, the strength of a recommendation is defined as the extent to  
508 which we can be confident that the desirable effects of an intervention outweigh its undesirable  
509 effects. The strength of recommendation was categorized as strong (grade 1) or weak/conditional  
510 (grade 2). In determining the strength of the recommendation, the panel considered the balance  
511 of desirable and undesirable consequences (typically trade-off between recurrent VTE and

512 bleeding events), quality of evidence, resource implications, and patients' average values and  
513 preferences for different outcomes and management options.<sup>14-16</sup>

514

515

516 The chair drafted the recommendations after the entire panel had reviewed the evidence and  
517 discussed the recommendation. Recommendations were then revised over a series of conference  
518 calls and through email exchanges with the entire panel. A major aim was to ensure  
519 recommendations were specific and unambiguous.

520

521

#### 522 **Methods for achieving consensus**

523

524 We used a modified Delphi technique<sup>17,18</sup> to achieve consensus on each recommendation. This  
525 technique aims to minimize group interaction bias and to maintain anonymity among  
526 respondents. Using an online survey ([www.surveymonkey.com](http://www.surveymonkey.com)), panelists without a primary  
527 COI voted their level of agreement with each recommendation (including quality of evidence  
528 and strength of recommendation) based on a 5-point scale derived from the GRADE grid  
529 (strongly agree, weakly agree, neutral, weakly disagree, strongly disagree).<sup>19</sup> Each panelist could  
530 also provide open-ended feedback on each recommendation with suggested wording edits or  
531 general remarks. To achieve consensus and be included in the final manuscript, each  
532 recommendation had to have at least 80% agreement (strong or weak) with a response rate of at  
533 least 75% of eligible panel members. All recommendations achieved consensus in the first

534 round. We then used an iterative approach that involved review by, and approval from, all panel  
535 members for the writing of this manuscript.

536

537

### 538 **Peer Review**

539

540 External reviewers who were not members of the expert panel reviewed the guideline before it  
541 was published. These reviewers included content experts, a methodological expert, and a  
542 practicing clinician. The final manuscript was reviewed and approved by the CHEST GOC, the  
543 CHEST Board of Regents, and the CHEST journal.

544

545 **Choice of Long-Term (First 3 Months) and Extended (No Scheduled Stop Date)**

546 **Anticoagulant**

547

548

549 **Summary of the Evidence**

550

551 *Phases of anticoagulant therapy for VTE*

552

553 The need for anticoagulant therapy in patients with proximal DVT or PE is presented in AT9.<sup>1</sup>

554 The minimum duration of anticoagulant therapy for DVT or PE is usually three months and this  
555 period of treatment is referred to as "long-term therapy".<sup>1</sup> A decision to treat patients for longer  
556 than 3 months, which we refer to as "extended anticoagulant therapy", usually implies that  
557 anticoagulant therapy will be continued indefinitely.<sup>1</sup>

558

- 559 1. **In patients with proximal DVT or PE, we recommend long-term (3 months)**  
560 **anticoagulant therapy over no such therapy** (Grade 1B).

561

562

563 *Choice of anticoagulant for acute and long-term (first 3 months) therapy*

564

565 AT9 recommendations on choice of anticoagulant therapy were based on comparisons of vitamin  
566 K antagonist (VKA) with low-molecular weight heparin (LMWH) that were performed in the  
567 preceding two decades<sup>1</sup>, and with two of the NOACs (dabigatran<sup>20</sup>, rivaroxaban<sup>21</sup>) that had

568 recently been published. Although we judged that there was no convincing evidence that the  
569 efficacy of LMWH compared to VKA differed between VTE patients without and with cancer  
570 there are, nevertheless, reasons to make different suggestions for the preferred anticoagulant in  
571 patients without and with cancer .<sup>1</sup> We suggested VKA therapy over LMWH in patients without  
572 cancer for the following reasons: injections are burdensome; LMWH is expensive; there are low  
573 rates of recurrence with VKA in patients with VTE without cancer; and VKA may be as  
574 effective as LMWH in patients without cancer. We suggested LMWH over VKA in patients with  
575 cancer for the following reasons: there is moderate quality evidence that LMWH was more  
576 effective than VKA in patients with cancer; there is a substantial rate of recurrent VTE in  
577 patients with VTE and cancer who are treated with VKA; it is often harder to keep patients with  
578 cancer who are on VKA in the therapeutic range; LMWH is reliable in patients who have  
579 difficulty with oral therapy (e.g. vomiting); LMWH is easier to withhold or adjust than VKA if  
580 invasive interventions are required or thrombocytopenia develops.

581  
582 One new randomized trial compared LMWH (tinzaparin) with warfarin for the first 6 months of  
583 treatment in 900 cancer patients with VTE.<sup>22</sup> The findings of this study are consistent with  
584 evidence in AT9 that LMWH is more effective than VKA for long-term treatment of VTE, but  
585 that there is no difference in major bleeding or death (Table 1, eTable 4). Consequently we still  
586 suggest VKA over LMWH in patients without cancer, and LMWH over VKA in patients with  
587 cancer, and we have not changed our assessment of the quality of evidence for either of these  
588 recommendations (Table 1, eTable 4).

589

590 We suggested VKA therapy or LMWH over the NOACs in AT9 because only two randomized  
591 trials had compared a NOAC (dabigatran<sup>20</sup>, rivaroxaban<sup>21</sup>) with VKA therapy, and none had  
592 compared a NOAC with long-term LMWH. In addition, at that time there was little experience  
593 using a NOAC for treatment of VTE and a scarcity of long-term follow-up data to support their  
594 efficacy and safety. Since then, 4 new randomized trials have compared a NOAC (with<sup>23,24</sup> or  
595 without<sup>25,26</sup> initial heparin therapy) with VKA therapy (with initial heparin therapy) for the acute  
596 and long-term treatment of VTE.<sup>23-26</sup> The findings of these studies have been analyzed in a  
597 number of systematic reviews<sup>27-35</sup>, including a network meta-analysis.<sup>35</sup> In addition, there is now  
598 extensive clinical experience using NOACs in patients with VTE and atrial fibrillation. For the  
599 comparison of each of the NOACs with VKA in the initial and long-term treatment of VTE,  
600 current evidence for efficacy is moderate or high quality, for safety (risk of bleeding) is moderate  
601 or high quality, and overall is moderate or high quality (Tables 2-5, eTables 5-8).

602  
603 In the 10<sup>th</sup> Edition of the Antithrombotic Guideline (AT10), the panel's overall assessment of the  
604 relative efficacy and risk of bleeding with different anticoagulant agents is that: (1) the risk  
605 reduction for recurrent VTE with all of the NOACs appears to be similar to the risk reduction  
606 with VKA<sup>35</sup>, including in patients with cancer<sup>36-39</sup>; (2) in patients with VTE and cancer, the risk  
607 reduction for recurrent VTE appears to be greater with LMWH than with VKA therapy<sup>1,36,40</sup>; (3)  
608 the risk reduction for recurrent VTE with the NOACs compared to LMWH has not been assessed  
609 but, based on indirect comparisons, LMWH may be more effective than the NOACs in patients  
610 with VTE and cancer<sup>36</sup>; (4) the risk reduction for recurrent VTE with different NOACs has not  
611 been directly compared but, based on indirect comparisons, appears to be similar with all of the  
612 NOACs<sup>35</sup>; (5) the risk of bleeding with the NOACs, and particularly intracranial bleeding, is less

613 with the NOACs than with VKA therapy<sup>27,33,35,41,42</sup>; (6) based on patients with atrial fibrillation,  
614 gastrointestinal bleeding may be higher with dabigatran, rivaroxaban and edoxaban than with  
615 VKA therapy, although this has not been seen in patients with VTE<sup>27,28,33,41,43</sup>; (7) based on  
616 indirect comparisons, the risk of bleeding may be lower with apixaban than with the other  
617 NOACs<sup>35,44</sup>; and (8) despite the lack of specific reversal agents for the NOACs, the risk that a  
618 major bleed will be fatal appears to be no higher for the NOACs than for VKA therapy.<sup>33,34,45</sup>  
619 Based on less bleeding with NOACs and greater convenience for patients and healthcare  
620 providers, we now suggest that a NOAC is used in preference to VKA for the initial and long-  
621 term treatment of VTE in patients without cancer. Factors that may influence which  
622 anticoagulant is chosen for initial and long-term treatment of VTE are summarized in Table 6.  
623 This decision is also expected to be sensitive to patient preferences. The order of our presentation  
624 of the NOACS (dabigatran, rivaroxaban, apixaban, edoxaban) is based on the chronology of  
625 publication of the phase 3 trials in VTE treatment and should not be interpreted as the guideline  
626 panel's order of preference for the use of these agents.

627

628

629 **2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months)**  
630 **anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban or edoxaban**  
631 **over VKA therapy (all Grade 2B). For patients with DVT of the leg or PE and no**  
632 **cancer who are not treated with dabigatran, rivaroxaban, apixaban or edoxaban, we**  
633 **suggest VKA therapy over LMWH (Grade 2C).**

634 *Remarks:* Initial parenteral anticoagulation is given before dabigatran and edoxaban, is  
635 not given before rivaroxaban and apixaban, and is overlapped with VKA therapy. See  
636 text for factors that influence choice of therapy.

637  
638  
639 In patients with VTE and cancer ("cancer-associated thrombosis"), as noted earlier in this  
640 section, we still suggest LMWH over VKA. In patients with VTE and cancer who are not treated  
641 with LMWH, we do not have a preference for either a NOAC or VKA. In the absence of direct  
642 comparisons between NOACs, and no convincing indirect evidence that one NOAC is superior  
643 to another, we do not have a preference for one NOAC over another NOAC. Factors that may  
644 influence which anticoagulant is chosen for initial and long-term treatment of VTE are  
645 summarized in Table 6. This decision is also expected to be sensitive to patient preferences.

646

647

648 3. **In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"),**  
649 **as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA**  
650 **therapy (Grade 2C), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban**  
651 **(Grade 2C) or edoxaban (Grade 2C).**

652 *Remarks:* Initial parenteral anticoagulation is given before dabigatran and edoxaban, is  
653 not given before rivaroxaban and apixaban, and is overlapped with VKA therapy. See  
654 text for factors that influence choice of therapy.

655

656



657 *Choice of anticoagulant for extended therapy (after 3 months and no scheduled stop date)*

658

659 When AT9 was written, other than a comparison of low and standard intensity anticoagulant  
660 therapy<sup>46</sup>, there were no comparisons of different types of extended therapy. Since AT9,  
661 dabigatran has been compared with VKA therapy for extended treatment of VTE and found to be  
662 similarly effective but associated with less bleeding (Table 7, eTable 9).<sup>47</sup> Extended treatment  
663 with dabigatran<sup>47</sup>, rivaroxaban<sup>21</sup> and apixaban<sup>48</sup> markedly reduces recurrent VTE without being  
664 associated with much bleeding (Tables 8-10, eTables 10-12).<sup>49,50</sup> These studies provide moderate  
665 quality evidence that dabigatran is as effective and as safe as VKA for extended treatment of  
666 VTE (Table 7, eTable 9), and provide moderate quality evidence that each of the NOACs are  
667 effective at preventing recurrent VTE without being associated with a high risk of bleeding  
668 (Tables 8-10, eTables 10-12).

669

670 In AT9, we suggested that if a decision was made to use extended treatment of VTE the same  
671 anticoagulant should be used as was used for the initial treatment period. Our intention then was  
672 to indicate that there was no obligation to switch from one anticoagulant to a different one after 3  
673 or 6 months of treatment (e.g. from LMWH to VKA in patients with VTE and cancer). We have  
674 revised the wording of this recommendation to make it clearer that we neither encourage nor  
675 discourage use of the same anticoagulant for initial and extended therapy. Although we  
676 anticipate that the anticoagulant that was used for initial treatment will often also be used for the  
677 extended therapy, if there are reasons to change the type of anticoagulant, this should be done.  
678 We also note that whereas apixaban 5 mg twice-daily is used for long-term treatment, apixaban  
679 2.5 mg twice-daily is used for extended therapy.<sup>48</sup>

680

681

682

683 4. **In patients with DVT of the leg or PE who receive extended therapy, we suggest that**  
684 **there is no need to change the choice of anticoagulant after the first 3 months** (Grade  
685 2C).

686 *Remarks:* It may be appropriate for the choice of anticoagulant to change in response to  
687 changes in the patient's circumstances or preferences during the long-term or extended  
688 phases of treatment.

689

690

#### 691 **Duration of Anticoagulant Therapy**

692

693

#### 694 **Summary of the Evidence**

695

696 AT9 recommendations on how long VTE should be treated were based on comparisons of 4  
697 durations of treatment: (1) 4 or 6 weeks; (2) 3 months; (3) longer than 3 months but still a time-  
698 limited course of therapy (usually 6 or 12 months); or (4) extended (also termed "indefinite"; no  
699 scheduled stopping date) therapy.<sup>1</sup> These four options were assessed in four subgroups of VTE  
700 patients with different estimated risks of recurrence after stopping anticoagulant therapy: (1)  
701 VTE provoked by surgery (a major transient risk factor; 3% recurrence at 5 years)<sup>51</sup>; (2) VTE  
702 provoked by a non-surgical transient risk factor (e.g. estrogen therapy, pregnancy, leg injury,  
703 flight of >8 hours; 15% recurrence at 5 years)<sup>51</sup>; (3) unprovoked (also termed "idiopathic") VTE;

704 not meeting criteria for provoked by a transient risk factor or by cancer (30% recurrence at 5  
705 years)<sup>52,53</sup>; and (4) VTE associated with cancer (also termed "cancer-associated thrombosis";  
706 15% annualized risk of recurrence; recurrence at 5 years not estimated because of high mortality  
707 from cancer)<sup>54,55</sup>. Recurrence risk was further stratified by estimating the risk of recurrence after:  
708 (1) an isolated distal DVT was half that after a proximal DVT or PE<sup>56-58</sup>; and (2) a second  
709 unprovoked proximal DVT or PE was 50% higher (1.5-fold) than after a first unprovoked  
710 event<sup>58,59</sup>. For the decision about whether to stop treatment at 3 months or to treat indefinitely  
711 ("extended treatment"), we categorized a patient's risk of bleeding on anticoagulant therapy as  
712 low (no bleeding risk factors; 0.8% annualized risk of major bleeding), moderate (one bleeding  
713 risk factor; 1.6% annualized risk of major bleeding) or high (two or more bleeding risk factors;  
714  $\geq 6.5\%$  annualized risk of major bleeding) (Table 11). A VKA targeted to an International  
715 Normalized Ratio (INR) of about 2.5 was the anticoagulant in all studies that compared different  
716 time-limited durations of therapy. We, therefore, assumed that VKA therapy was the  
717 anticoagulant when we were making our AT9 recommendations, including for the comparison of  
718 extended therapy with stopping treatment at 3 months.

719

720

721 *Comparison of different time-limited durations of anticoagulation since AT9*

722

723 Two additional studies have compared two time-limited durations of anticoagulant therapy.<sup>60,61</sup>

724 In patients with a first unprovoked PE who had completed 6 months of VKA therapy (target INR

725 2.5), the PADIS study randomized patients to another 18 months of treatment or to placebo, and

726 then followed both groups of patients for an additional 12 months after study drug was stopped

727 (Table 12, eTable 13).<sup>61</sup> The study's findings were consistent with our recommendations in AT9;  
728 the additional 18 months of VKA was very effective at preventing recurrent VTE but, once  
729 anticoagulation was stopped, the risk of recurrent VTE was the same in those who had been  
730 treated for 6 or for 24 months. This new information has not increased the quality of evidence for  
731 comparison of a longer versus a shorter time-limited course of anticoagulation in patients  
732 without cancer.

733

734 In patients with a first proximal DVT or PE and active cancer who had residual DVT on  
735 ultrasound imaging after completing 6 months of LMWH therapy, the Cancer-DACUS study  
736 randomized patients to another 6 months of LMWH or to stop therapy and followed patients for  
737 12 months after they stopped LMWH.<sup>60</sup> The additional 6 months of LMWH reduced recurrent  
738 VTE but, once anticoagulation was stopped, the risk of recurrent VTE was the same in those who  
739 had been treated for 6 or for 12 months. In the same study, all patients without residual DVT  
740 after 6 months of LMWH stopped therapy and had a low risk of recurrence during the next year  
741 (3 episodes in 91 patients). This study's findings have not changed our recommendations for  
742 treatment of VTE in patients with cancer.

743

744

745 *Evaluations of extended anticoagulant therapy since AT9*

746

747 When AT9 was written, extended treatment of VTE with VKA therapy had been evaluated in six  
748 studies (mostly patients with unprovoked proximal DVT or PE<sup>46,62-65</sup>, or a second episode of  
749 VTE<sup>66</sup>), and with a NOAC (rivaroxaban versus placebo) in one study of heterogeneous

750 patients<sup>21</sup>. Since AT9, no studies have compared extended VKA therapy with stopping  
751 anticoagulants, although the large reduction in recurrent VTE with 18 additional months of VKA  
752 therapy compared with placebo (i.e. before study drug was stopped) in the PADIS study<sup>61</sup>  
753 supports AT9 estimates for the efficacy of extended VKA therapy.

754

755 Since AT9, two additional studies have compared extended NOAC therapy (dabigatran<sup>47</sup>,  
756 apixaban<sup>48</sup>) with stopping treatment (i.e. placebo). These two studies, and the previous study that  
757 evaluated extended treatment with rivaroxaban, found that extended therapy with these three  
758 NOAC regimens reduced recurrent VTE by at least 80% and was associated with a modest risk  
759 of bleeding (Tables 8-10, eTables 10-12).<sup>49</sup> These three studies, however, enrolled heterogeneous  
760 populations of patients (i.e. not confined to unprovoked VTE) and only followed patients for 6 to  
761 12 months, which limits the implications of their findings in relationship to extended therapy.

762

763 When considering the risks and benefits of extended anticoagulation in this update, the AT10  
764 panel decided to use the same estimates for the reduction in recurrent VTE and the increase in  
765 bleeding with anticoagulation that we used in AT9, and that were based on VKA therapy. Our  
766 reasoning was: (1) VKA is still widely used for extended treatment of VTE; (2) we felt that there  
767 was not enough evidence of differences in efficacy and bleeding during extended therapy to  
768 justify separate recommendations for NOACs, either as a group or as individual agents; and (3)  
769 our recommendations about whether or not to use extended therapy were not sensitive to  
770 assuming that there was a one-third reduction in bleeding with extended therapy compared to the  
771 estimated risk of bleeding with extended therapy that are shown in Table 11 and were used in  
772 AT9 (e.g. with a NOAC compared to VKA)<sup>27,31,35,49</sup> (the only recommendation to change would

773 be a strong instead of a weak recommendation in favor of extended therapy in patients with a  
774 second unprovoked VTE who had a moderate risk of bleeding).

775

776

777 *Better selection of patients for extended VTE therapy*

778

779 The most common and difficult decision about whether to stop anticoagulants after a time-  
780 limited course or to use extended therapy is in patients with a first unprovoked proximal DVT or  
781 PE without a high risk of bleeding. In this subgroup of patients, patient sex and D-dimer level  
782 measured about one month after stopping anticoagulant therapy can help to further stratify the  
783 risk of recurrent VTE.<sup>67-70</sup> Men have about a 75% higher (1.75-fold) risk of recurrence compared  
784 to women, while patients with a positive D-dimer result have about double the risk of recurrence  
785 compared to those with a negative D-dimer, and the predictive value of these two factors appears  
786 to be additive. The risk of recurrence in women with a negative post treatment D-dimer appears  
787 to be similar to the risk that we have estimated for patients with a proximal DVT or PE that was  
788 provoked by a minor transient risk factor (~15% recurrence at 5 years); consequently, the  
789 argument for extended anticoagulation in these women is not strong, suggesting that D-dimer  
790 testing will often influence a woman's decision. The risk of recurrence in men with a negative D-  
791 dimer is not much less than the overall risk of recurrence that we have estimated for patients with  
792 an unprovoked proximal DVT or PE (~25% compared to ~30% recurrence at 5 years);  
793 consequently, the argument for extended anticoagulation in these men is still substantial,  
794 suggesting that D-dimer testing will often not influence a male's decision. Because there is still  
795 uncertainty about how to use D-dimer testing and a patient's sex to make decisions about

796 extended therapy in patients with a first unprovoked VTE, we have not made recommendations  
797 based on these factors.

798

799

800 *Revised recommendations*

801

802 These are unchanged from AT9 with the following minor exceptions. First, the recommendations  
803 have been reformatted so that there is a separate statement for each comparison rather than  
804 combining comparisons in a more complex statement. Second, a qualifying remark has been  
805 added to the recommendation that suggests extended therapy over stopping treatment at 3  
806 months in patients with a first unprovoked proximal DVT or PE and a low or moderate risk of  
807 bleeding; this remark notes that patient sex and D-dimer level measured a month after stopping  
808 anticoagulant therapy may influence this treatment decision. If it becomes clear that, during the  
809 extended phase of treatment, there are important differences in the risk of recurrence or bleeding  
810 with the different anticoagulant agents, agent-specific recommendations for extended therapy  
811 may become justified.

812

813

814 5. **In patients with a proximal DVT of the leg or PE provoked by surgery, we**  
815 **recommend treatment with anticoagulation for 3 months over (i) treatment of a**  
816 **shorter period (Grade 1B), (ii) treatment of a longer time-limited period (e.g. 6, 12 or**  
817 **24 months) (Grade 1B), or (iii) extended therapy (no scheduled stop date) (Grade**  
818 **1B).**

819

820 6. **In patients with a proximal DVT of the leg or PE provoked by a nonsurgical**  
821 **transient risk factor, we recommend treatment with anticoagulation for 3 months**  
822 **over (i) treatment of a shorter period (Grade 1B), and (ii) treatment of a longer time-**  
823 **limited period (e.g. 6, 12 or 24 months) (Grade 1B). We suggest treatment with**  
824 **anticoagulation for 3 months over extended therapy if there is a low or moderate**  
825 **bleeding risk (Grade 2B), and recommend treatment for 3 months over extended**  
826 **therapy if there is a high risk of bleeding (Grade 1B).**

827 *Remarks:* In all patients who receive extended anticoagulant therapy, the continuing use  
828 of treatment should be reassessed at periodic intervals (e.g. annually).

829

830

831 7. **In patients with an isolated distal DVT of the leg provoked by surgery or by a**  
832 **nonsurgical transient risk factor, we suggest treatment with anticoagulation for 3**  
833 **months over treatment of a shorter period (Grade 2C), we recommend treatment**  
834 **with anticoagulation for 3 months over treatment of a longer time-limited period**  
835 **(e.g. 6, 12 or 24 months) (Grade 1B), and we recommend treatment with**  
836 **anticoagulation for 3 months over extended therapy (no scheduled stop date) (Grade**  
837 **1B).**

838 *Remarks:* Duration of treatment of patients with isolated distal DVT refers to patients in  
839 whom a decision has been made to treat with anticoagulant therapy; however, it is  
840 anticipated that not all patients who are diagnosed with isolated distal DVT will be  
841 prescribed anticoagulants.



842

843

844 8. **In patients with an unprovoked DVT of the leg (isolated distal or proximal) or PE,**  
845 **we recommend treatment with anticoagulation for at least 3 months over treatment**  
846 **of a shorter duration (Grade 1B), and we recommend treatment with anticoagulation**  
847 **for 3 months over treatment of a longer time-limited period (e.g. 6, 12 or 24 months)**  
848 **(Grade 1B).**

849 *Remarks:* After 3 months of treatment, patients with unprovoked DVT of the leg or PE  
850 should be evaluated for the risk-benefit ratio of extended therapy. Duration of treatment  
851 of patients with isolated distal DVT refers to patients in whom a decision has been made  
852 to treat with anticoagulant therapy; however, it is anticipated that not all patients who are  
853 diagnosed with isolated distal DVT will be prescribed anticoagulants.

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855

856 9. **In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE**  
857 **and who have a (i) low or moderate bleeding risk (see text), we suggest extended**  
858 **anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B),**  
859 **and a (ii) high bleeding risk (see text), we recommend 3 months of anticoagulant**  
860 **therapy over extended therapy (no scheduled stop date) (Grade 1B).**

861 *Remarks:* Patient sex and D-dimer level measured a month after stopping anticoagulant  
862 therapy may influence the decision to stop or extend anticoagulant therapy (see text). In  
863 all patients who receive extended anticoagulant therapy, the continuing use of treatment  
864 should be reassessed at periodic intervals (e.g. annually).

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10. **In patients with a second unprovoked VTE and who have a (i) low bleeding risk (see text), we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months (Grade 1B), (ii) moderate bleeding risk (see text), we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B), and (iii) high bleeding risk (see text), we suggest 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 2B).**

*Remarks:* In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (e.g. annually).

11. **In patients with DVT of the leg or PE and active cancer ("cancer-associated thrombosis") and who (i) do not have a high bleeding risk, we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B), and (ii) have a high bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B).**

*Remarks:* In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (e.g. annually).

**888 Aspirin for Extended Treatment of Venous Thromboembolism**

889

890

**891 Summary of the Evidence**

892

893 AT9 did not address if there was a role for aspirin, or antiplatelet therapy generally, in the  
894 treatment of VTE. Since then, two randomized trials have compared aspirin to placebo for the  
895 prevention of recurrent VTE in patients with a first unprovoked proximal DVT or PE who have  
896 completed a 3 to 18 month of anticoagulant therapy.<sup>71-73</sup> These trials provide moderate quality  
897 evidence that extended aspirin therapy reduces recurrent VTE by about one-third. In these trials,  
898 the benefits of aspirin outweighed the increase in bleeding, which was not statistically significant  
899 (Table 13, eTable14). The two trials enrolled patients with a first unprovoked VTE who did not  
900 have an increased risk of bleeding; patients for whom these guidelines have suggested extended  
901 anticoagulant therapy. Extended anticoagulant therapy is expected to reduce recurrent VTE by  
902 over 80% and extended NOAC therapy may be associated with the same risk of bleeding as  
903 aspirin.<sup>49,50</sup> If patients with a first unprovoked VTE decline extended anticoagulant therapy  
904 because they have risk factors for bleeding or because they have a lower than average risk of  
905 recurrence, the net benefit of aspirin therapy is expected to be less than in the two trials that  
906 evaluated aspirin for extended treatment of VTE.

907

908 Based on indirect comparisons, we expect the net benefit of extended anticoagulant therapy in  
909 patients with unprovoked VTE to be substantially greater than the benefits of extended aspirin  
910 therapy.<sup>49</sup> Consequently, we do not consider aspirin a reasonable alternative to anticoagulant

911 therapy in patients who want extended therapy. However, if a patient has decided to stop  
912 anticoagulants, prevention of recurrent VTE is one of the benefits of aspirin (may also include  
913 reductions in arterial thrombosis and colon cancer) that needs to be balanced against aspirin's  
914 risk of bleeding and inconvenience. Use of aspirin should also be reevaluated when patients with  
915 VTE stop anticoagulant therapy because aspirin may have been stopped when anticoagulants  
916 were started (Table 13, eTable 14).

917

918

919 **12. In patients with an unprovoked proximal DVT or PE who are stopping**  
920 **anticoagulant therapy and do not have a contraindication to aspirin, we suggest**  
921 **aspirin over no aspirin to prevent recurrent VTE (Grade 2C).**

922 *Remarks:* Because aspirin is expected to be much less effective at preventing recurrent  
923 VTE than anticoagulants, we do not consider aspirin a reasonable alternative to  
924 anticoagulant therapy in patients who want extended therapy. However, if a patient has  
925 decided to stop anticoagulants, prevention of recurrent VTE is one of the benefits of  
926 aspirin that needs to be balanced against aspirin's risk of bleeding and inconvenience. Use  
927 of aspirin should also be reevaluated when patients stop anticoagulant therapy because  
928 aspirin may have been stopped when anticoagulants were started.

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932 **Whether and How to Prescribe Anticoagulants to Patients with Isolated Distal Deep Vein**  
933 **Thrombosis**

934

935

936 **Summary of the Evidence**

937

938 AT9 discouraged routine whole-leg ultrasound examinations (i.e. including the distal veins) in  
939 patients with suspected DVT; thereby reducing how often isolated distal DVT is diagnosed.<sup>1,74</sup>

940 The rationale for not routinely examining the distal veins in patients who have had proximal  
941 DVT excluded is that: (1) other assessment may already indicate that isolated distal DVT is  
942 either unlikely to be present or unlikely to cause complications if it is present (e.g. low clinical  
943 probability of DVT; D-dimer is negative); (2) if these conditions are not met, a repeat ultrasound  
944 examination of the proximal veins can be done after a week to detect possible DVT extension  
945 and the need for treatment; and (3) false-positive findings for DVT occur more often with  
946 ultrasound examinations of the distal compared to the proximal veins.<sup>1,74,75</sup>

947

948 If the calf veins are imaged (usually with ultrasound) and isolated distal DVT is diagnosed, there  
949 are two management options: 1) treat patients with anticoagulant therapy; or 2) do not treat  
950 patients with anticoagulant therapy unless extension of their DVT is detected on a follow-up  
951 ultrasound examination (e.g. after one and two weeks, or sooner if there is concern; there is no  
952 widely accepted protocol for surveillance ultrasound (US) testing)<sup>76</sup>. As about 15% of untreated  
953 isolated distal DVT are expected to subsequently extend into the popliteal vein and may cause

954 pulmonary embolism, it is not acceptable to neither anticoagulate nor do surveillance to detect  
955 thrombus extension.<sup>1,77-80</sup>

956

957 In AT9, we judged that there was high quality evidence that anticoagulant therapy was effective  
958 for the treatment of proximal DVT and PE, but uncertainty that the benefits of anticoagulation  
959 outweigh its risks in patients with isolated distal DVT because of their lower risk of progressive  
960 or recurrent VTE. We suggest the following as risk factors for extension of distal DVT that  
961 would favor anticoagulation over surveillance: (1) D-dimer is positive (particularly when  
962 markedly so without an alternative reason); (2) thrombosis is extensive (e.g. >5 cm in length,  
963 involves multiple veins, >7 mm in maximum diameter); (3) thrombosis is close to the proximal  
964 veins; (4) there is no reversible provoking factor for DVT;(5) active cancer;(6) history of VTE;  
965 (7) inpatient status.<sup>1,76-78,81-85</sup> We consider thrombosis that is confined to the muscular veins of  
966 the calf (i.e., soleus, gastrocnemius) to have a lower risk of extension than thrombosis that  
967 involves the axial (i.e. true deep; peroneal, tibial) veins.<sup>77,82,86</sup> Severe symptoms favour  
968 anticoagulation, a high risk for bleeding (Table 11) favors surveillance, and the decision to use  
969 anticoagulation or surveillance is expected to be sensitive to patient preferences. We anticipate  
970 that isolated distal DVT that are detected using a selective approach to whole-leg US will often  
971 satisfy criteria for initial anticoagulation whereas distal DVT detected by routine whole-leg  
972 ultrasound often will not.

973

974 The updated literature search did not identify any new randomized trials that assessed  
975 management of patients with isolated distal DVT. Two new systematic reviews<sup>77,78</sup> and a  
976 narrative review<sup>84</sup> addressed treatment of isolated distal DVT. In addition to summarizing

977 available data, consistent with AT9, they emphasize the limitations of available evidence. In the  
978 absence of substantive new evidence, the panel endorsed the AT9 recommendations without  
979 revision. The evidence supporting these recommendations remains low quality because it is not  
980 based on direct comparisons of the two management strategies, and ability to predict extension  
981 of distal DVT is limited.

982

983

984 13. **In patients with acute isolated distal DVT of the leg and (i) without severe symptoms**  
985 **or risk factors for extension (see text), we suggest serial imaging of the deep veins**  
986 **for 2 weeks over anticoagulation (Grade 2C), and (ii) with severe symptoms or risk**  
987 **factors for extension (see text), we suggest anticoagulation over serial imaging of the**  
988 **deep veins (Grade 2C).**

989 *Remarks:* Patients at high risk for bleeding are more likely to benefit from serial imaging.  
990 Patients who place a high value on avoiding the inconvenience of repeat imaging and a  
991 low value on the inconvenience of treatment and on the potential for bleeding are likely  
992 to choose initial anticoagulation over serial imaging

993

994

995 14. **In patients with acute isolated distal DVT of the leg who are managed with**  
996 **anticoagulation, we recommend using the same anticoagulation as for patients with**  
997 **acute proximal DVT (Grade 1B).**

998

999 15. **In patients with acute isolated distal DVT of the leg who are managed with serial**  
1000 **imaging, we (i) recommend no anticoagulation if the thrombus does not extend**  
1001 **(Grade 1B), (ii) suggest anticoagulation if the thrombus extends but remains**  
1002 **confined to the distal veins (Grade 2C), and (iii) recommend anticoagulation if the**  
1003 **thrombus extends into the proximal veins (Grade 1B).**

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1007 **Catheter-Directed Thrombolysis for Acute Deep Vein Thrombosis of the Leg**

1008

1009

1010 **Summary of the Evidence**

1011

1012 At the time of AT9 there was one small randomized trial<sup>87</sup> comparing the effect of catheter-  
1013 directed thrombolysis (CDT) versus anticoagulant alone on development of the post-thrombotic  
1014 syndrome (PTS), and another larger randomized trial (CAVENT Study) assessing short term  
1015 (e.g. venous patency and bleeding) but not long term (e.g. PTS) outcomes.<sup>88,89</sup> The CAVENT  
1016 Study has since reported that CDT reduced PTS, did not alter quality of life, and appears to be  
1017 cost effective (Table 14, eTable 15).<sup>90-93</sup> A retrospective analysis found that CDT (3649 patients)  
1018 was associated with an increase in transfusion (2-fold), intracranial bleeding (3-fold), pulmonary  
1019 embolism (1.5-fold) and vena caval filter insertion (2-fold); long term outcomes and PTS were  
1020 not reported.<sup>94</sup> A single center prospective registry found that ultrasound-assisted CDT in acute  
1021 iliofemoral (87 patients) achieved high rates of venous patency, was rarely associated with  
1022 bleeding, and that only 6% of patients had PTS at one year.<sup>95</sup>

1023 This new evidence has not led to a change in our recommendation for the use of CDT in patients  
1024 with DVT. Although the quality of the evidence has improved, the overall quality is still low  
1025 because of very serious imprecision. Unchanged from AT9, we propose that the patients who are  
1026 most likely to benefit from CDT have iliofemoral DVT, symptoms for <14 days, good functional  
1027 status, life expectancy of  $\geq 1$  year, and a low risk of bleeding (Table 14, Table 15, eTable 15). As  
1028 the balance of risks and benefits with CDT is uncertain, we consider that anticoagulant therapy

1029 alone is an acceptable alternative to CDT in all patients with acute DVT who do not have  
1030 impending venous gangrene.

1031

1032

1033 16. **In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy**  
1034 **alone over catheter-directed thrombolysis (CDT) (Grade 2C).**

1035 *Remarks:* Patients who are most likely to benefit from CDT (see text), who attach a high  
1036 value to prevention of post thrombotic syndrome (PTS), and a lower value to the initial  
1037 complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over  
1038 anticoagulation alone.

1039

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1042 **Role of Inferior Vena Caval Filter in Addition to Anticoagulation for Acute Deep Vein**  
1043 **Thrombosis or Pulmonary Embolism**

1044

1045

1046 **Summary of the Evidence**

1047

1048 Our recommendation in AT9 was primarily based on findings of the PREPIC randomized  
1049 trial<sup>96,97</sup> which showed that placement of a permanent inferior vena caval (IVC) filter increased  
1050 DVT, decreased PE, and did not influence VTE (DVT and PE combined) or mortality (Table 16,  
1051 eTable 16). Since then, a number of registries have suggested that IVC filters can reduce early  
1052 mortality in patients with acute VTE, although this evidence has been questioned.<sup>98-102</sup> The  
1053 recently published PREPIC 2 randomized trial found that placement of an IVC filter for 3  
1054 months did not reduce recurrent PE, including fatal PE, in anticoagulated patients with PE and  
1055 DVT who had additional risk factors for recurrent VTE (Table 16, eTable 16).<sup>103</sup> This new  
1056 evidence is consistent with our recommendations in AT9. However, because it is uncertain if  
1057 there is benefit to placement of an IVC filter in anticoagulated patients with severe PE (e.g. with  
1058 hypotension), and this is done by some experts, our recommendation against insertion of an IVC  
1059 filter in patients with acute PE who are anticoagulated may not apply to this select subgroup of  
1060 patients.

1061

1062 Although the PREPIC 2 study has improved the quality of evidence for this recommendation,  
1063 overall quality is still moderate because of imprecision (Table 16, eTable 16). The AT10 panel  
1064 decided against combining the results of the PREPIC and PREPIC 2 studies because of

1065 differences in the type of filter used, the duration of filter placement, and differences in the  
1066 length of follow-up.

1067

1068

1069 17. **In patients with acute DVT or PE who are treated with anticoagulants, we**  
1070 **recommend against the use of an IVC filter** (Grade 1B).

1071

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1074 **Compression Stocking to Prevent Post-Thrombotic Syndrome**

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1077 **Summary of the Evidence**

1078

1079 AT9 suggested routine use of graduated compression stockings for two years after DVT to  
1080 reduce the risk of PTS. That recommendation was mainly based on findings of two small single-  
1081 center randomized trials in which patients and study personnel were not blinded to stocking use  
1082 (no placebo stocking).<sup>104-106</sup> The quality of the evidence was moderate because of risk of bias due  
1083 to lack of blinding of an outcome (PTS) that has a large subjective component, and because of  
1084 serious imprecision of the combined findings of the two trials (Table 17, eTable 17). Since AT9,  
1085 a much larger multicenter, placebo-controlled trial at low risk of bias found that routine use of  
1086 graduated compression stockings did not reduce PTS or have other important benefits.<sup>107</sup> Based  
1087 on this trial, we now suggest that graduated compression stockings not be used routinely to  
1088 prevent PTS and consider the quality to the evidence to be moderate (Table 17, eTable 17).

1089

1090 The same study found that routine use of graduated compression stockings did not reduce leg  
1091 pain during the 3 months after DVT diagnosis (Table 17, eTable 2 and 17).<sup>108</sup> This finding,  
1092 however, does not mean that graduated compression stockings will not reduce acute symptoms  
1093 of DVT, or chronic symptoms in those who have developed PTS.

1094

1095

1096 18. **In patients with acute DVT of the leg, we suggest not using compression stockings**  
1097 **routinely to prevent PTS (Grade 2B).**

1098 *Remarks:* This recommendation focuses on prevention of the chronic complication of  
1099 PTS and not on the treatment of symptoms. For patients with acute or chronic symptoms,  
1100 a trial of graduated compression stockings is often justified.

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1102

1103

## 1104 Whether to Treat Subsegmental Pulmonary Embolism

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### 1107 **Summary of the Evidence**

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1109 Subsegmental PE refers to PE that is confined to the subsegmental pulmonary arteries. Whether  
1110 these patients should be treated, a question that was not addressed in AT9, has grown in

1111 importance because improvements in computerized tomography (CT) pulmonary angiography  
1112 have increased how often subsegmental PE is diagnosed (i.e. from ~5% to over 10% of PE).<sup>109-</sup>

1113 <sup>112</sup> There is uncertainty whether these patients should be anticoagulated for two reasons. First,  
1114 because the abnormalities are small, a diagnosis of subsegmental PE is more likely to be a false-

1115 positive finding than a diagnosis of PE in the segmental or more proximal pulmonary

1116 arteries.<sup>111,113-117</sup> Second, because a true subsegmental PE is likely to have arisen from a small

1117 DVT, the risk of progressive or recurrent VTE without anticoagulation is expected to be lower

1118 than in patients with a larger PE.<sup>111,112,118,119</sup>

1119

1120 Our literature search did not identify any randomized trials in patients with subsegmental PE.

1121 There is, however, high quality evidence for the efficacy and safety of anticoagulant therapy in  
1122 patients with larger PE, and this is expected to apply similarly to patients with subsegmental PE.<sup>1</sup>

1123 Whether the risk of progressive or recurrent VTE is high enough to justify anticoagulation in

1124 patients with subsegmental PE is uncertain.<sup>111,112,118</sup> There were no episodes of recurrent VTE in

1125 retrospective reports that included a total of about 60 patients with subsegmental PE and no

1126 proximal DVT who were not anticoagulated.<sup>111,112</sup> However, in another retrospective analysis,

1127 patients with subsegmental PE appeared to have a similar risk of recurrent VTE during 3 months  
1128 of anticoagulant therapy as patients with larger PE, and a higher risk than in patients who were  
1129 suspected of having PE but had PE excluded.<sup>120</sup>

1130

1131 The AT10 panel endorsed that, if no anticoagulant therapy is an option, patients with  
1132 subsegmental PE should have bilateral ultrasound examinations to exclude proximal DVT of the  
1133 legs.<sup>111,115</sup> DVT should also be excluded in other high-risk locations, such as in upper extremities  
1134 with central venous catheters. If DVT is detected, patients require anticoagulation. If DVT is  
1135 not detected, there is uncertainty whether patients should be anticoagulated. If a decision is made  
1136 not to anticoagulate, there is the option of doing one or more follow-up ultrasound examinations  
1137 of the legs to detect (and then treat) evolving proximal DVT.<sup>111,115</sup> Serial testing for proximal  
1138 DVT has been shown to be a safe management strategy in patients with suspected PE who have  
1139 non-diagnostic ventilation-perfusion scans, many of whom are expected to have subsegmental  
1140 PE.<sup>111,112,121</sup>

1141

1142 We suggest that a diagnosis of subsegmental PE is more likely to be correct (i.e. a true-positive)  
1143 if: (1) the CT pulmonary angiogram (CTPA) is of high quality with good opacification of the  
1144 distal pulmonary arteries; (2) there are multiple intraluminal defects; (3) defects involve more  
1145 proximal sub-segmental arteries (i.e. are larger); (4) defects are seen on more than one image; (5)  
1146 defects are surrounded by contrast rather than appearing to be adherent to the pulmonary artery  
1147 walls; (6) defects are seen on more than one projection; (7) patients are symptomatic, as opposed  
1148 to PE being an incidental finding; (8) there is a high clinical pre-test probability for PE; and (9)  
1149 D-Dimer level is elevated, particularly if the increase is marked and otherwise unexplained.



1150

1151 In addition to whether or not patients truly have subsegmental PE, we consider the following to  
1152 be risk factors for recurrent or progressive VTE if patients are not anticoagulated -- patients who:  
1153 are hospitalized or have reduced mobility for another reason; have active cancer (particularly if  
1154 metastatic or being treated with chemotherapy); or have no reversible risk factor for VTE such as  
1155 recent surgery. Furthermore, a low cardiopulmonary reserve or marked symptoms that cannot be  
1156 attributed to another condition favour anticoagulant therapy, while a high risk of bleeding favors  
1157 no anticoagulant therapy. The decision to anticoagulate or not is also expected to be sensitive to  
1158 patient preferences. Patients who are not anticoagulated should be told to return for re-evaluation  
1159 if symptoms persist or worsen.

1160

1161 The evidence supporting our recommendations is low quality because of indirectness and  
1162 because there is limited ability to predict which patients will have VTE complications without  
1163 anticoagulation.

1164

1165

1166 19. **In patients with subsegmental PE (no involvement of more proximal pulmonary**  
1167 **arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE**  
1168 **(see text), we suggest clinical surveillance over anticoagulation (Grade 2C), and (ii)**  
1169 **high risk for recurrent VTE (see text), we suggest anticoagulation over clinical**  
1170 **surveillance (Grade 2C).**

1171

1172 *Remarks:* Ultrasound imaging of the deep veins of both legs should be done to exclude  
proximal DVT. Clinical surveillance can be supplemented by serial ultrasound imaging

1173 of the proximal deep veins of both legs to detect evolving DVT (see text). Patients and  
1174 physicians are more likely to opt for clinical surveillance over anticoagulation if there is  
1175 good cardiopulmonary reserve or a high risk of bleeding.

1176

ACCEPTED MANUSCRIPT

**1177 Treatment of Acute Pulmonary Embolism Out of Hospital**

1178

1179

**1180 Summary of the Evidence**

1181

1182 Our recommendation in AT9 was based on: (1) two trials that randomized patients with acute PE  
1183 to receive LMWH for only three days in hospital<sup>122</sup> or entirely at home<sup>123</sup> compared with being  
1184 treated with LMWH in hospital for a longer period; (2) 15 observational studies, nine of which  
1185 were prospective, that evaluated treatment of acute PE out of hospital<sup>1</sup>; and (3) longstanding  
1186 experience treating DVT without admission to hospital. Since AT9, no further randomized trials  
1187 have evaluated out of hospital treatment of acute PE. A number of additional prospective and  
1188 retrospective observational studies have reported findings consistent with earlier reports, and the  
1189 findings of all of these studies have been included in recent meta-analyses that have addressed  
1190 treatment of acute PE out of hospital.<sup>124-126</sup>

1191

1192 Studies that evaluated NOACs for the acute treatment of PE did not report the proportion of  
1193 patients who were treated entirely out of hospital, but it is probable that this was uncommon.

1194 Treatment of acute PE with a NOAC that does not require initial heparin therapy (e.g.

1195 rivaroxaban, apixaban) facilitates treatment without hospital admission. Consistent with AT9, we

1196 suggest that patients who satisfy all of the following criteria are suitable for treatment of acute

1197 PE out of hospital: (1) clinically stable with good cardiopulmonary reserve; (2) no

1198 contraindications such as recent bleeding, severe renal or liver disease, or severe

1199 thrombocytopenia (i.e.  $< 70,000 /\text{mm}^3$ ); (3) expected to be compliant with treatment; (4) the

1200 patient feels well enough to be treated at home. Clinical decision rules such as the Pulmonary  
1201 Embolism Severity Index (PESI), either the original form with score <85 or the simplified form  
1202 with score of 0, can help to identify low risk patients who are suitable for treatment at home.<sup>127-</sup>  
1203 <sup>132</sup> However, we consider clinical prediction rules as aids to decision making and do not require  
1204 patients to have a predefined score (e.g. low risk PESI score) in order to be considered for  
1205 treatment at home. Similarly, although we don't suggest the need for routine assessment in  
1206 patients with acute PE, we agree that the presence of right ventricular dysfunction or increased  
1207 cardiac biomarker levels should discourage treatment out of hospital.<sup>131,133-139</sup> The quality of the  
1208 evidence for treatment of acute PE at home remains moderate due to marked imprecision. The  
1209 updated recommendation has been modified to state that appropriately selected patients may be  
1210 treated entirely at home, rather than just be discharged early.

1211

1212

1213 20. **In patients with low-risk PE and whose home circumstances are adequate, we**  
1214 **suggest treatment at home or early discharge over standard discharge (e.g. after**  
1215 **first 5 days of treatment)** (Grade 2B).

1216

1217

1218

1219 **Systemic Thrombolytic Therapy for Pulmonary Embolism**

1220

1221

1222 **Summary of the Evidence**

1223

1224 It is long established that systemic thrombolytic therapy accelerates resolution of PE as  
1225 evidenced by more rapid lowering of pulmonary artery pressure, increases in arterial  
1226 oxygenation, and resolution of perfusion scan defects, and that this therapy increases bleeding.<sup>1</sup>  
1227 The net mortality benefit of thrombolytic therapy in patients with acute PE, however, has been  
1228 uncertain and depends on an individual patient's baseline (i.e. without thrombolytic therapy) risk  
1229 of dying from the acute PE and their risk of bleeding. Patients with the highest risk of dying  
1230 from PE and the lowest risk of bleeding obtain the greatest net benefit from thrombolytic  
1231 therapy. Patients with the lowest risk of dying from PE and the highest risk of bleeding obtain  
1232 the least net benefit from thrombolytic therapy and are likely to be harmed.

1233

1234

1235 *Evidence for the use of thrombolytic therapy in patients with acute PE*

1236

1237 AT9 recommendations for the use of thrombolytic therapy in acute PE were based on low quality  
1238 evidence.<sup>1,140</sup> At that time, only about 800 patients with acute PE had been randomized to receive  
1239 thrombolytic therapy or anticoagulant therapy alone and, consequently, estimates of efficacy,  
1240 safety and overall mortality were very imprecise. In addition, the trials that enrolled these 800  
1241 patients had a high risk of bias, and there was a strong suspicion that there was selective

1242 reporting of studies that favored thrombolytic therapy (i.e. publication bias). Randomized trials  
1243 have clearly established that thrombolytic therapy increases bleeding in patients with acute  
1244 myocardial infarction<sup>141</sup>, but that evidence was indirect when applied to patients with PE.

1245

1246 Since AT9, two additional small, randomized trials<sup>142,143</sup> and a much larger trial<sup>144</sup> have  
1247 evaluated systemic thrombolytic therapy in about 1,200 patients with acute PE. The findings of  
1248 these new studies have been combined with those of earlier studies in a number of meta-  
1249 analyses.<sup>145-149</sup> These new data, by reducing imprecision for estimates of efficacy and safety and  
1250 the overall risk of bias, have increased the quality of the evidence from low to moderate for  
1251 recommendations about the use of systemic thrombolytic therapy in acute PE (Table 18, eTable  
1252 18).

1253

1254 Most of the new evidence comes from the PIETHO trial, which randomized 1006 patients with  
1255 PE and right ventricular dysfunction to tenecteplase and heparin or to heparin therapy alone  
1256 (with placebo).<sup>144</sup> The most notable findings of this study were that thrombolytic therapy  
1257 prevented cardiovascular collapse but increased major (including intracranial) bleeding; these  
1258 benefits and harms were finely balanced, with no convincing net benefit from thrombolytic  
1259 therapy. An additional finding was that "rescue thrombolytic therapy" appeared to be of benefit  
1260 in patients who developed cardiovascular collapse after initially being treated with anticoagulant  
1261 therapy alone.

1262

1263

1264 *Management implication of the updated evidence*

1265  
1266 The improved quality of evidence has not resulted in substantial changes to our  
1267 recommendations because: (1) the new data supports that the benefits of systemic thrombolytic  
1268 therapy in patients without hypotension, including those with right ventricular dysfunction or an  
1269 increase in cardiac biomarkers ("intermediate-risk PE"), are largely offset by the increase in  
1270 bleeding; and (2) among patients without hypotension, it is still not possible to confidently  
1271 identify those who will derive net benefit from this therapy.

1272

1273

1274 *PE with hypotension*

1275

1276 Consistent with AT9, we suggest that patients with acute PE with hypotension (i.e. systolic  
1277 pressure less than 90 mmHg for 15 minutes) and without high bleeding risk (Table 15) are  
1278 treated with thrombolytic therapy. The more severe and persistent the hypotension, and the more  
1279 marked the associated features of shock and myocardial dysfunction or damage, the more  
1280 compelling the indication for systemic thrombolytic therapy. Conversely, if hypotension is  
1281 transient or less marked, not associated with features of shock or myocardial dysfunction, and if  
1282 there are risk factors for bleeding, physicians and patients are likely to initially choose  
1283 anticoagulant therapy without thrombolytic therapy. If thrombolytic therapy is not used and  
1284 hypotension persists or becomes more marked, or clinical features of shock or myocardial  
1285 damage develop or worsen, thrombolytic therapy may then be used.

1286

1287

1288 *PE without hypotension*

1289

1290 Consistent with AT9, we recommend that most patients with acute PE who do not have  
1291 hypotension are not treated with thrombolytic therapy. However, patients with PE without  
1292 hypotension include a broad spectrum of presentations. At the mild end of the spectrum are  
1293 those who have minimal symptoms and minimal cardiopulmonary impairment. As noted in the  
1294 section "Setting for initial anticoagulation for PE", many of these patients can be treated entirely  
1295 at home or can be discharged after a brief admission. At the severe end of the spectrum are those  
1296 with severe symptoms and more marked cardiopulmonary impairment (even though systolic  
1297 blood pressure is above 90 mmHg). In addition to clinical features of cardiopulmonary  
1298 impairment (e.g. heart rate, blood pressure, respiratory rate, jugular venous pressure, tissue  
1299 hypoperfusion, pulse oximetry), they may have evidence of right ventricular dysfunction on their  
1300 CTPA or on echocardiography, or evidence of myocardial damage as reflected by increases in  
1301 cardiac biomarkers (e.g. troponins or brain natriuretic peptide).

1302

1303 We suggest that patients without hypotension who are at the severe end of the spectrum are  
1304 treated with aggressive anticoagulation and other supportive measures, and not with thrombolytic  
1305 therapy. These patients need to be closely monitored to ensure that deteriorations are detected.  
1306 Development of hypotension suggests that thrombolytic therapy has become indicated.  
1307 Deterioration that has not resulted in hypotension may also prompt the use of thrombolytic  
1308 therapy. For example, there may be a progressive increase in heart rate, a decrease in systolic  
1309 blood pressure (which remains above 90 mmHg), an increase in jugular venous pressure,  
1310 worsening gas exchange, signs of shock (e.g. cold sweaty skin, reduced urine output, confusion),



1311 progressive right heart dysfunction on echocardiography, or an increase in cardiac biomarkers.  
1312 We do not propose that echocardiography or cardiac biomarkers are measured routinely in all  
1313 patients with PE, or in all patients with a non-low risk PESI assessment<sup>123,128,150</sup>. This is  
1314 because, when measured routinely, the results of these assessments do not have clear therapeutic  
1315 implications. For example, we do not recommend thrombolytic therapy routinely for patients  
1316 without hypotension who have right ventricular dysfunction and an increase in cardiac  
1317 biomarkers. However, we encourage assessment of right ventricular function by  
1318 echocardiography and/or measurement of cardiac biomarkers if, following clinical assessment,  
1319 there is uncertainty about whether patients require more intensive monitoring or should receive  
1320 thrombolytic therapy.

- 1321  
1322
- 1323 21. **In patients with acute PE associated with hypotension (e.g. systolic BP <90 mm Hg)**  
1324 **who do not have a high bleeding risk, we suggest systemically administered**  
1325 **thrombolytic therapy over no such therapy (Grade 2B).**
- 1326
- 1327 22. **In most patients with acute PE not associated with hypotension, we recommend**  
1328 **against systemically administered thrombolytic therapy (Grade 1B).**
- 1329
- 1330 23. **In selected patients with acute PE who deteriorate after starting anticoagulant**  
1331 **therapy but have yet to develop hypotension and who have a low bleeding risk, we**  
1332 **suggest systemically administered thrombolytic therapy over no such therapy**  
1333 **(Grade 2C).**

1334 *Remarks:* Patients with PE and without hypotension who have severe symptoms or  
1335 marked cardiopulmonary impairment should be monitored closely for deterioration.  
1336 Development of hypotension suggests that thrombolytic therapy has become indicated.  
1337 Cardiopulmonary deterioration (e.g. symptoms, vital signs, tissue perfusion, gas  
1338 exchange, cardiac biomarkers) that has not progressed to hypotension may also alter the  
1339 risk-benefit assessment in favor of thrombolytic therapy in patients initially treated with  
1340 anticoagulation alone.

1341

1342

1343

1344 **Catheter-Based Thrombus Removal for the Initial Treatment of Pulmonary Embolism**

1345

1346

1347 **Summary of the Evidence**

1348

1349 Interventional catheter-based treatments for acute PE include delivery of catheter directed  
1350 thrombolysis (CDT) if there is not a high risk of bleeding, or catheter-based treatment without  
1351 thrombolytic therapy if there is a high risk of bleeding.

1352

1353

1354 *Catheter directed thrombolysis*

1355

1356 The most important limitation of systemic thrombolytic therapy is that it increases bleeding,  
1357 including intracranial bleeding. CDT, because it uses a lower dose of thrombolytic drug (e.g.  
1358 about one-third), is expected to cause less bleeding at remote sites (e.g. intracranial or  
1359 gastrointestinal).<sup>139,151-154</sup> CDT, however, may be as or more effective than systemic  
1360 thrombolytic therapy for two reasons: (1) it achieves a high local concentration of thrombolytic  
1361 drug by infusing drug directly into the PE; and (2) thrombus fragmentation due to placement of  
1362 the infusion catheter in the thrombus or additional maneuvers, or an increase in thrombus  
1363 permeability due to ultrasound delivered via the catheter, may enhance endogenous or  
1364 pharmacologic thrombolysis. Thrombolytic therapy is usually infused over many hours or  
1365 overnight. In emergent situations, systemic thrombolytic therapy can be given while CDT is

1366 being arranged, and active thrombus fragmentation and aspiration (see below) can be combined  
1367 with CDT.

1368

1369 A single randomized trial of 59 patients found that, compared to anticoagulation alone,  
1370 ultrasound-assisted CDT improved right ventricular function at 24 hours.<sup>155</sup> Observational  
1371 studies also suggest that CDT is effective at removing thrombus, lowering pulmonary arterial  
1372 pressure and improving right ventricular function without being associated with a high risk of  
1373 bleeding.<sup>151-153,156</sup> Most of these studies are small (less than 30 patients) and retrospective,  
1374 although a recent prospective registry of 101 patients and a prospective cohort study of 150  
1375 patients also support the efficacy of CDT.<sup>156,157</sup> Whereas there was no major bleeding in the  
1376 registry, there were 15 episodes in the cohort study (10%; no intracranial or fatal bleeds). An  
1377 older randomized trial of 34 patients with massive PE found that infusion of rt-PA into a  
1378 pulmonary artery as opposed to a peripheral vein did not accelerate thrombolysis but caused  
1379 more frequent bleeding at the catheter insertion site.<sup>158</sup> No randomized trials or observational  
1380 studies have compared contemporary CDT with systemic thrombolytic therapy. For patients who  
1381 require thrombolytic therapy and do not have a high risk of bleeding, the AT10 panel favored  
1382 systemic thrombolytic therapy over CDT because, compared to anticoagulation alone, there is a  
1383 higher quality of evidence in support of systemic thrombolytic therapy than for CDT.

1384

1385

1386 *Catheter-based thrombus removal without thrombolytic therapy*

1387

1388 Catheter-based mechanical techniques for thrombus removal involve thrombus fragmentation  
1389 using various types of catheters, some of which are designed specifically for this purpose.<sup>151-154</sup>  
1390 Fragmentation results in distal displacement of thrombus, with or without suctioning and  
1391 removal of some thrombus through the catheter. Mechanical methods alone are used when  
1392 thrombus removal is indicated but there is a high risk of bleeding that precludes thrombolytic  
1393 therapy. No randomized trial or prospective cohort studies have evaluated catheter-based  
1394 thrombus removal of PE without thrombolytic therapy.

1395  
1396 Evidence for the use of CDT compared to anticoagulation alone, CDT compared to systemic  
1397 thrombolytic therapy, and catheter-based treatment without thrombolytic therapy is of low  
1398 quality and our recommendations are weak.

1399

1400

1401 24. **In patients with acute PE who are treated with a thrombolytic agent, we suggest**  
1402 **systemic thrombolytic therapy using a peripheral vein over catheter directed**  
1403 **thrombolysis (CDT) (Grade 2C).**

1404 *Remarks:* Patients who have a higher risk of bleeding with systemic thrombolytic  
1405 therapy, and who have access to the expertise and resources required to do CDT, are  
1406 likely to choose CDT over systemic thrombolytic therapy.

1407

1408 25. **In patients with acute PE associated with hypotension and who have (i) a high**  
1409 **bleeding risk, (ii) failed systemic thrombolysis, or (iii) shock that is likely to cause**  
1410 **death before systemic thrombolysis can take effect (e.g. within hours), if appropriate**

1411 **expertise and resources are available, we suggest catheter assisted thrombus**  
1412 **removal over no such intervention** (Grade 2C).

1413 *Remarks:* Catheter assisted thrombus removal refers to mechanical interventions, with or  
1414 without catheter directed thrombolysis.

1415

1416

ACCEPTED MANUSCRIPT

1417 **Pulmonary Thromboendarterectomy in for the Treatment of Chronic Thromboembolic**

1418 **Pulmonary Hypertension**

1419

1420

1421 **Summary of the Evidence**

1422

1423 The AT9 recommendation was based on case series that have shown marked improvements in  
1424 cardiopulmonary status after thromboendarterectomy in patients with chronic thromboembolic  
1425 pulmonary hypertension (CTEPH).<sup>159,160</sup> Although additional case series have been reported, the  
1426 quality of the evidence for thromboendarterectomy in patients with CTEPH has not  
1427 improved.<sup>154,161-163</sup> The AT10 panel decided, however, that our previous recommendation for  
1428 thromboendareterectomy in selected patients with CTEPH was too restrictive and could  
1429 contribute to suboptimal evaluation and treatment of patients with CTEPH. For example, because  
1430 of improvements in surgical technique it is now often possible to remove organized thrombi from  
1431 peripheral pulmonary arteries. In patients with inoperable CTEPH or persistent pulmonary  
1432 hypertension after pulmonary thromboendarterectomy, there is new evidence from a randomized  
1433 trial that pulmonary vasodilator therapy may be of benefit.<sup>164</sup> For these reasons, we no longer  
1434 identify central disease as a selection factor for thromboendarterectomy in patients with CTEPH,  
1435 and we emphasize that patients with CTEPH should be assessed by a team with expertise in the  
1436 evaluation and management of pulmonary hypertension.<sup>154,160,165-167</sup>

1437

1438

1439 26. **In selected patients with CTEPH who are identified by an experienced**  
1440 **thromboendarterectomy team, we suggest pulmonary thromboendarterectomy over**  
1441 **no pulmonary thromboendarterectomy (Grade 2C).**

1442 *Remarks:* Patients with CTEPH should be evaluated by a team with expertise in treatment  
1443 of pulmonary hypertension. Pulmonary thromboendarterectomy is often life saving and  
1444 life transforming. Patients with CTEPH who are not candidates for pulmonary  
1445 thromboendarterectomy may benefit from other mechanical and pharmacological  
1446 interventions designed to lower pulmonary arterial pressure.

1447

1448



1449 **Thrombolytic Therapy in Patients with Upper Extremity Deep Vein Thrombosis**

1450

1451

1452 **Summary of the Evidence**

1453

1454 The AT9 recommendation was based on: (1) mostly retrospective observational studies  
1455 suggesting that thrombolysis could improve short and long term venous patency, but a lack of  
1456 data about whether thrombolysis reduced PTS of the arm; (2) occasional reports of bleeding in  
1457 patients with upper extremity DVT (UEDVT) who were treated with thrombolysis, and clear  
1458 evidence that thrombolysis increases bleeding in other settings; and (3) recognition that,  
1459 compared to anticoagulation alone, thrombolytic therapy is complex and costly.<sup>1,168,169</sup> We  
1460 suggest that thrombolysis is most likely to be of benefit in patients who meet the following  
1461 criteria: severe symptoms; thrombus involving most of the subclavian vein and the axillary vein;  
1462 symptoms for <14 days; good functional status; life expectancy of  $\geq 1$  year; and low risk for  
1463 bleeding. We also suggested CDT over systemic thrombolysis to reduce the dose of thrombolytic  
1464 drug and the risk of bleeding. There is new moderate quality evidence that CDT can reduce PTS  
1465 of the leg<sup>91</sup> (Table 14, eTable 15) and that systemic thrombolysis increases bleeding in patients  
1466 with acute PE<sup>144,148</sup>, and low quality evidence that CDT can accelerate breakdown of acute PE<sup>155</sup>.  
1467 This evidence has indirect bearing on thrombolysis in patients with UEDVT, but it has not  
1468 changed the overall quality of the evidence or our recommendations for use of thrombolysis in  
1469 these patients.

1470

1471

1472 27. **In patients with acute UEDVT that involves the axillary or more proximal veins, we**  
1473 **suggest anticoagulant therapy alone over thrombolysis (Grade 2C).**

1474 *Remarks:* Patients who (i) are most likely to benefit from thrombolysis (see text); (ii)  
1475 have access to CDT; (iii) attach a high value to prevention of PTS; and (iv) attach a lower  
1476 value to the initial complexity, cost, and risk of bleeding with thrombolytic therapy are  
1477 likely to choose thrombolytic therapy over anticoagulation alone.

1478

1479 28. **In patients with UEDVT who undergo thrombolysis, we recommend the same**  
1480 **intensity and duration of anticoagulant therapy as in patients with UEDVT who do**  
1481 **not undergo thrombolysis (Grade 1B).**

1482

1483

1484

1485 **Management of Recurrent Venous Thromboembolism on Anticoagulant Therapy**

1486

1487

1488 **Summary of Evidence**

1489

1490 There are no randomized trials or prospective cohort studies that have evaluated management of  
1491 patients with recurrent VTE on anticoagulant therapy. Consequently, management is based on  
1492 low quality evidence and an assessment of the probable reason for the recurrence. Risk factors  
1493 for recurrent VTE while on anticoagulant therapy can be divided into two broad categories: (1)  
1494 treatment factors; and (2) the patient's intrinsic risk of recurrence. How a new event should be  
1495 treated will depend on the reason(s) for recurrence.

1496

1497

1498 *Treatment factors*

1499

1500 The risk of recurrent VTE decreases rapidly after starting anticoagulant therapy, with a much  
1501 higher risk during the first week (or month) compared to the second week (or month).<sup>170,171</sup> A  
1502 recurrence soon after starting therapy can generally be managed by a time limited (e.g. 1 month)  
1503 period of more aggressive anticoagulant intensity (e.g. switching from an oral agent back to  
1504 LMWH, or an increase in LMWH dose). Other treatment factors that are associated with  
1505 recurrent VTE and will suggest specific approaches to management include: (1) was LMWH  
1506 being used; (2) was the patient adherent; (3) was VKA subtherapeutic; (4) was anticoagulant

1507 therapy prescribed correctly; (5) was the patient taking a NOAC and a drug that reduced  
1508 anticoagulant effect; and (6) had anticoagulant dose been reduced (drugs other than VKA).

1509

1510 There is moderate quality evidence that LMWH is more effective than VKA therapy in patients  
1511 with VTE and cancer. A switch to full-dose LMWH, therefore, is often made if there has been an  
1512 unexplained recurrent VTE on VKA therapy or a NOAC. If the recurrence happened on LMWH,  
1513 the dose of LMWH can be increased. If the dose of LMWH was previously reduced (e.g. by 25%  
1514 after 1 month of treatment), it is usually increased to the previous level. If the patient was  
1515 receiving full-dose LMWH, the dose may be increased by about 25%. In practice, the increase in  
1516 dose is often influenced by the LMWH prefilled syringe dose options that are available. Once-  
1517 daily LMWH may also be switched to a twice-daily regimen, particularly if two injections are  
1518 required to deliver the increase in LMWH dose. Treatment adherence, including compliance, can  
1519 be difficult to assess; for example, symptoms of a recurrent DVT may encourage medication  
1520 adherence and a return of coagulation results to the "therapeutic range".

1521

1522

### 1523 *Patient Factors*

1524

1525 The most important intrinsic risk factor for recurrent VTE while on anticoagulant therapy is  
1526 active cancer, with an unexplained recurrence often pointing to yet to be diagnosed disease.  
1527 Antiphospholipid syndrome is also associated with recurrent VTE, either because of associated  
1528 hypercoagulability or because a lupus anticoagulant has led to underdosing of VKA due to  
1529 spurious increases in INR results. Anticoagulated patients may be taking medications that

1530 increase the risk of thrombosis such as estrogens or cancer chemotherapy, in which case these  
1531 treatments may be withdrawn.

1532

1533 A retrospective observational study found an acceptable risk of recurrence (8.6%) and major  
1534 bleeding (1.4%) during 3 months follow-up in 70 cancer patients with recurrent VTE while on  
1535 anticoagulant therapy who either switched from VKA therapy to LMWH (23 patients) or had  
1536 their LMWH dose increased by about 25% (47 patients).<sup>172</sup> If there is no reversible reason for  
1537 recurrent VTE while on anticoagulant therapy, and anticoagulant intensity cannot be increased  
1538 because of risk of bleeding, a vena caval filter can be inserted to prevent PE.<sup>173</sup> However, it is  
1539 not known if insertion of a filter in these circumstances is worthwhile, and the AT10 panel  
1540 consider this an option of last resort.

1541

1542

1543 29. **In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or**  
1544 **on dabigatran, rivaroxaban, apixaban or edoxaban (and are believed to be**  
1545 **compliant), we suggest switching to treatment with LMWH at least temporarily**  
1546 **(Grade 2C).**

1547 *Remarks:* Recurrent VTE while on therapeutic-dose anticoagulant therapy is unusual and  
1548 should prompt the following assessments: (1) reevaluation of whether there truly was a  
1549 recurrent VTE; (2) evaluation of compliance with anticoagulant therapy; and (3)  
1550 consideration of an underlying malignancy. A temporary switch to LMWH will usually be  
1551 for at least one month.

1552

1553 30. **In patients who have recurrent VTE on long-term LMWH (and are believed to be**  
1554 **compliant) we suggest increasing the dose of LMWH by about one-quarter to one-**  
1555 **third (Grade 2C).**

1556 *Remarks:* Recurrent VTE while on therapeutic-dose anticoagulant therapy is unusual and  
1557 should prompt the following assessments: (1) reevaluation of whether there truly was a  
1558 recurrent VTE; (2) evaluation of compliance with anticoagulant therapy; and (3)  
1559 consideration of an underlying malignancy.

1560

1561

1562

1563

1564 **Conclusion**

1565

1566

1567 There is substantial new evidence since AT9 about how to treat VTE. This evidence led the  
1568 panel to change many of the AT9 recommendations that are included in this update, and has  
1569 strengthened the evidence quality that underlies others that are unchanged. We now suggest the  
1570 use of NOACs over VKA for the treatment of VTE in patients without cancer. While we still  
1571 suggest LMWH as the preferred long-term treatment for VTE and cancer, we no longer suggest  
1572 VKA over NOACs in these patients. Although we note factors in individual patients that may  
1573 favor selection of one NOAC over another in patients without or with cancer, or may favor  
1574 selection of either a NOAC or VKA in patients with cancer, we have not expressed an overall  
1575 preference for one NOAC over another, or for either a NOAC or VKA in patients with cancer,  
1576 because: (1) there are no direct comparisons of different NOACs; (2) NOACs have not been  
1577 compared to VKA in a broad spectrum of patients with VTE and cancer; and (3) indirect  
1578 comparisons have not shown convincingly different outcomes with different NOACs. Another  
1579 notable change in AT10 is that, based on a new low risk of bias study, we now suggest that  
1580 graduated compression stocking are not routinely used to prevent PTS. Recommendations that  
1581 are unchanged but are now supported by better evidence include: (1) discouragement of IVC  
1582 filter use in anticoagulated patients; (2) encouragement of indefinite anticoagulant therapy after a  
1583 first unprovoked PE; and (3) discouragement of thrombolytic therapy in PE patients who are not  
1584 hypotensive and are not deteriorating on anticoagulation.

1585

1586 Of the 54 recommendations that are included in the 30 statements in this update, 20 (38%) are  
1587 strong recommendations (Grade 1) and none are based on high quality (Grade A) evidence. The  
1588 absence of high quality evidence highlights the need for further research to guide VTE treatment  
1589 decisions. As new evidence becomes available, these guidelines will need to be updated. Goals  
1590 of our group and CHEST include transition to continually updated "living guidelines". The  
1591 modular format of this update is designed to facilitate this development, with individual topics  
1592 and questions being addressed as new evidence becomes available. We will also facilitate  
1593 implementation of our recommendations into practice by developing new and convenient ways  
1594 to disseminate our recommendations. This will enable achievement of another of our goals —  
1595 reduction in the burden of VTE in individual patients and in the general population.



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1597

1598 The roles of the panelists include the following:

1599

1600 Clive Kearon, MD, PhD – chair, executive committee member, topic editor for “Treatment of  
1601 Acute Pulmonary Embolism Out of Hospital” and “Pulmonary Thromboendarterectomy in the  
1602 Treatment of Chronic Thromboembolic Pulmonary Hypertension”

1603

1604 Elie Akl, MD, MPH, PhD – methodologist, executive committee member, topic editor for  
1605 “Compression Stocking to Prevent Post-Thrombotic Syndrome” and “Thrombolytic Therapy in  
1606 Patients with Upper Extremity Deep Vein Thrombosis”

1607

1608 Joseph Ornelas, PhD – methodologist, executive committee member

1609

1610 Allen Blaiwas, DO, FCCP – GOC Liaison, executive committee member, topic editor for  
1611 “Compression Stocking to Prevent Post-Thrombotic Syndrome” and “Thrombolytic Therapy in  
1612 Patients with Upper Extremity Deep Vein Thrombosis”

1613

1614 David Jimenez, MD, PhD, FCCP - executive committee member, topic editor for “Pulmonary  
1615 Thromboendarterectomy in the Treatment of Chronic Thromboembolic Pulmonary  
1616 Hypertension” and “Management of Recurrent Venous Thromboembolism on Anticoagulant  
1617 Therapy”

1618

1619 Henri Bounameaux, MD – topic editor for “Whether and How to Anticoagulate Patients with  
1620 Isolated Distal Deep Vein Thrombosis” and “Catheter-Directed Thrombolysis for Acute Deep  
1621 Vein Thrombosis of the Leg”  
1622

1623 Menno Huisman, MD, PhD – topic editor for “Catheter-Directed Thrombolysis for Acute Deep  
1624 Vein Thrombosis of the Leg” and “Duration of Anticoagulant Therapy”  
1625

1626 Christopher King, MD, FCCP – topic editor for “Whether to Anticoagulate Subsegmental  
1627 Pulmonary Embolism” and “Management of Recurrent Venous Thromboembolism on  
1628 Anticoagulant Therapy”  
1629

1630 Timothy Morris, MD, FCCP – topic editor for “Catheter-Based Thrombus Removal for the  
1631 Initial Treatment of Pulmonary Embolism” and “Choice of Long-Term (First 3 Months) and  
1632 Extended (No Scheduled Stop Date) Anticoagulant”  
1633

1634 Namita Sood, MD, FCCP – topic editor for “Whether and How to Anticoagulate Isolated Distal  
1635 Deep Vein Thrombosis “ and “Treatment of Acute Pulmonary Embolism Out of Hospital”  
1636

1637 Scott Stevens, MD – topic editor for “Systemic Thrombolytic Therapy for Pulmonary  
1638 Embolism” and “Catheter-Based Thrombus Removal for the Initial Treatment of Pulmonary  
1639 Embolism”  
1640

1641 Janine Vintch, MD, FCCP – topic editor for “Systemic Thrombolytic Therapy for Pulmonary  
1642 Embolism” and “Duration of Anticoagulant Therapy”

1643

1644 Philip Wells, MD – topic editor for “Catheter-Based Thrombus Removal for the Initial  
1645 Treatment of Pulmonary Embolism” and “Aspirin for Extended Treatment of Venous  
1646 Thromboembolism”

1647

1648 Scott Woller, MD – topic editor for “Systemic Thrombolytic Therapy for Pulmonary Embolism”  
1649 and “Choice of Long-Term (First 3 Months) and Extended (No Scheduled Stop Date)  
1650 Anticoagulant”

1651

1652 Col. Lisa Moores, MD, FCCP – overall guideline editor, executive committee member, topic  
1653 editor for “Whether to Anticoagulate Subsegmental Pulmonary Embolism” , “Role of Inferior  
1654 Vena Caval Filter in Addition to Anticoagulation in Patients with Acute Deep Vein Thrombosis  
1655 or Pulmonary Embolism” and “Aspirin for Extended Treatment of Venous Thromboembolism”

1656

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1658 Antithrombotic Guidelines.

1659

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1661

1662

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**Table 1: Summary of Findings - LMWH vs VKA for long term treatment of VTE<sup>1</sup>**

**Bibliography:** Deitcher et al. (ONCENOX)<sup>1</sup>, Hull et al. (LITE)<sup>2</sup>, Hull et al. (LITE Home)<sup>3</sup>, Lee et al. (CLOT)<sup>4</sup>, Lopaciuk et al.<sup>5</sup>, Lopez-Beret et al.<sup>6</sup>, Meyer et al.<sup>7</sup>, Romera et al.<sup>8</sup>, Lee et al. (CATCH)<sup>9</sup>

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI) <sup>2</sup>	Anticipated absolute effects	
				Risk with VKA	Risk difference with LMWH (95% CI)
<b>All Cause Mortality</b>	3396 (9 studies) 6 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>4</sup> due to risk of bias	<b>RR 1.01</b> (0.89 to 1.14)	<b>Non-Cancer</b> <sup>3</sup>	
				17 per 1000	0 more per 1000 (from 2 fewer to 2 more)
				<b>Non-Metastatic Cancer</b> <sup>3</sup>	
				42 per 1000	0 more per 1000 (from 5 fewer to 6 more)
				<b>Metastatic Cancer</b> <sup>3</sup>	
				253 per 1000	3 more per 1000 (from 28 fewer to 35 more)
<b>Recurrent VTE</b>	3627 (9 studies) 6 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>6</sup> due to risk of bias	<b>RR 0.65</b> (0.51 to 0.83)	<b>Low</b> <sup>5</sup>	
				30 per 1000	11 fewer per 1000 (from 5 fewer to 15 fewer)
				<b>Moderate</b> <sup>5</sup>	
				80 per 1000	28 fewer per 1000 (from 14 fewer to 39 fewer)
				<b>High</b> <sup>5</sup>	
				200 per 1000	70 fewer per 1000 (from 34 fewer to 98 fewer)
<b>Major bleeding</b>	3637 (9 studies) 6 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>8,9</sup> due to imprecision	<b>RR 0.86</b> (0.56 to 1.32)	<b>Low</b> <sup>7</sup>	
				20 per 1000	3 fewer per 1000 (from 9 fewer to 6 more)
				<b>High</b> <sup>7</sup>	
				80 per 1000	11 fewer per 1000 (from 35 fewer to 26 more)

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** 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.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> The initial parenteral anticoagulation was similar in both arms for all except one study (Hull et al.<sup>3</sup>) in which patients randomized to LMWH received initially the same LMWH whereas patients randomized to VKA received initially UFH

<sup>2</sup> The relative effect (RR; 95% CI) of LMWH versus VKA was assessed, and compared, in the subgroup of trials that enrolled patients without (Hull et al. (LITE)<sup>2</sup>, Lopez-Beret et al.<sup>6</sup>) and with (Deitcher et al. (ONCENOX)<sup>1</sup>, Hull et al. (LITE)<sup>2</sup>, Lee et al. (CLOT)<sup>4</sup>, Lee et al. (CATCH)<sup>9</sup>, Lopez-Beret et al.<sup>6</sup>, Meyer et al.<sup>7</sup>) cancer: Recurrent VTE: cancer RR 0.59 (0.44 to 0.78) vs. no cancer RR 0.99 (0.46

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to 2.13); P=0.21 for subgroup difference. Major Bleeding: cancer RR 0.96 (0.65 to 1.42) vs. no cancer RR 0.43 (0.17 to 1.17); P=0.14 for subgroup difference. All Cause Mortality: cancer RR 1.00 (0.88 to 1.33) vs. no cancer RR 1.85 (0.59 to 5.77); P=0.29 for subgroup difference.

<sup>3</sup> Low corresponds to patients without cancer and patients with non-metastatic cancer. High corresponds to patients with metastatic cancer. These control event rates were derived from the RIETE registry (an ongoing prospective registry of consecutive patients with acute VTE) (Prandoni et al.<sup>10</sup>)

<sup>4</sup> One study did not report deaths, which is unusual and could reflect selective reporting of outcomes.

<sup>5</sup> Risk of recurrent VTE: Low corresponds to patients without cancer (3% estimate taken from recent large RCTs of acute treatment), intermediate to patients with local or recently resected cancer (appears to be consistent with Prandoni [particularly if low risk is increased to 4%]), and high to patients with locally advanced or distant metastatic cancer. (Prandoni et al.<sup>11</sup>)

<sup>6</sup> None of the studies was blinded while the diagnosis of recurrent VTE has a subjective component and there could be a lower threshold for diagnosis of recurrent VTE in VKA-treated patients as switching the treatment of such patients to LMWH is widely practiced. At the same time, there is reluctance to diagnose recurrent VTE in patients who are already on LMWH as there is no attractive alternative treatment option.

<sup>7</sup> Risk of bleeding: Low corresponds to patients without risk factor for bleeding (i.e., > 75 years, cancer, metastatic disease; chronic renal or hepatic failure; platelet count <80,000; requires antiplatelet therapy; history of bleeding without a reversible cause). (Prandoni et al.<sup>10</sup>, Byeth et al.<sup>12</sup>)

<sup>8</sup> Confidence interval includes both no effect and harm with LMWH

<sup>9</sup> 95% confidence intervals for the risk ratio for major bleeding includes a potentially clinically important increase or decrease with LMWH, and may also vary with the dose of LMWH used during the extended phase of therapy

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**Table 2: Summary of Findings - Dabigatran vs VKA for long-term treatment of VTE<sup>1,2</sup>****Bibliography:** Schulman et al. (RE-COVER I & II)<sup>1,3</sup>

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA	Risk difference with Dabigatran (95% CI)
<b>All Cause Mortality</b>	5107 (2 studies)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>4</sup> due to imprecision	<b>RR 1.0</b> (0.67 to 1.50) <sup>3</sup>	<b>18 per 1000<sup>3</sup></b>	<b>0 fewer per 1000</b> (from 6 fewer to 9 more)
<b>Recurrent VTE</b>	5107 (2 studies)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>4</sup> due to imprecision	<b>RR 1.12</b> (0.77 to 1.62) <sup>3</sup>	<b>22 per 1000<sup>3</sup></b>	<b>3 more per 1000</b> (from 5 fewer to 13 more)
<b>Major Bleeding</b>	5107 (2 studies)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>4</sup> due to imprecision	<b>RR 0.73</b> (0.48 to 1.10) <sup>3</sup>	<b>20 per 1000<sup>3</sup></b>	<b>5 fewer per 1000</b> (from 10 fewer to 2 more)

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** 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.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Patients with acute VTE treated initially with low-molecular-weight or unfractionated heparin

<sup>2</sup> Dabigatran 150 mg twice daily vs. warfarin

<sup>3</sup> Pooled analysis of Schulman et al. (Re-Cover I)<sup>1,4</sup> and Schulman et al. (Re-Cover II)<sup>1,3</sup> performed by Schulman et al.<sup>1,3</sup>

<sup>4</sup> CI includes values suggesting no effect and values suggesting either benefit or harm

**Table 3: Summary of Findings - Rivaroxaban vs LMWH and VKA for acute and long-term treatment of VTE<sup>1,2</sup>****Bibliography:** Prins et al.<sup>15</sup>

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH and VKA	Risk difference with Rivaroxaban (95% CI)
<b>All Cause Mortality</b>	8281 (2 studies) 3 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>4</sup> due to imprecision	<b>RR 0.97</b> (0.73 to 1.27)	<b>24 per 1000<sup>3</sup></b>	<b>1 fewer per 1000</b> (from 6 fewer to 6 more)
<b>Recurrent VTE</b>	8281 (2 studies) 3 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>4</sup> due to imprecision	<b>RR 0.90</b> (0.68 to 1.2)	<b>23 per 1000<sup>3</sup></b>	<b>2 fewer per 1000</b> (from 7 fewer to 5 more)
<b>Major Bleeding</b>	8246 (2 studies) 3 months	⊕⊕⊕⊕ <b>HIGH</b>	<b>RR 0.55</b> (0.38 to 0.81)	<b>17 per 1000<sup>3</sup></b>	<b>8 fewer per 1000</b> (from 3 fewer to 11 fewer)

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** 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.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Included patients had acute, symptomatic, objectively verified proximal DVT of the legs or PE (unprovoked 73%; cancer 5%; previous VTE 19%)

<sup>2</sup> Rivaroxaban 20 mg daily for 6 or 12 month after initial long-term therapy

<sup>3</sup> Pooled analysis of Bauersachs et al. (EINSTEIN-DVT)<sup>16</sup> and Buller et al. (EINSTEIN-PE)<sup>17</sup> performed by Prins et al.<sup>15</sup>

<sup>4</sup> CI includes values suggesting no effect and values suggesting either benefit or harm

**Table 4: Summary of Findings - Apixaban vs LMWH and VKA for acute and long-term treatment of VTE**<sup>1,2</sup>**Bibliography:** Agnelli et al. (AMPLIFY)<sup>1,8</sup>

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH and VKA	Risk difference with Apixaban (95% CI)
<b>All Cause Mortality</b>	5365 (1 study)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>3</sup> due to imprecision	<b>RR 0.79</b> (0.53 to 1.19)	<b>19 per 1000</b>	<b>4 fewer per 1000</b> (from 9 fewer to 4 more)
<b>Recurrent VTE</b>	5244 (1 study)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>3</sup> due to imprecision	<b>RR 0.84</b> (0.6 to 1.18)	<b>27 per 1000</b>	<b>4 fewer per 1000</b> (from 11 fewer to 5 more)
<b>Major Bleeding</b>	5365 (1 study)	⊕⊕⊕⊕ <b>HIGH</b>	<b>RR 0.31</b> (0.17 to 0.55)	<b>18 per 1000</b>	<b>13 fewer per 1000</b> (from 8 fewer to 15 fewer)

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** 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.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Apixaban 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months

<sup>2</sup> Subcutaneous enoxaparin, followed by warfarin

<sup>3</sup> CI includes values suggesting no effect and values suggesting either benefit or harm

**Table 5: Summary of Findings - Edoxaban vs VKA for acute and long-term treatment of VTE**<sup>1,2</sup>**Bibliography:** Buller et al. (Hokusai)<sup>19</sup>

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA	Risk difference with Edoxaban (95% CI)
<b>All Cause Mortality</b>	8240 (1 study)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>4</sup> due to imprecision	<b>RR 1.05</b> (0.82 to 1.33)	<b>31 per 1000</b> <sup>3</sup>	<b>2 more per 1000</b> (from 6 fewer to 10 more)
<b>Recurrent VTE</b>	8240 (1 study)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>3,4</sup> due to imprecision	<b>RR 0.83</b> (0.57 to 1.21)	<b>35 per 1000</b>	<b>6 fewer per 1000</b> (from 15 fewer to 7 more)
<b>Major Bleeding</b>	8240 (1 study)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>4</sup> due to imprecision	<b>RR 0.85</b> (0.6 to 1.21)	<b>16 per 1000</b>	<b>2 fewer per 1000</b> (from 6 fewer to 3 more)

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** 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.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Patients with acute VTE who had initially received heparin

<sup>2</sup> Edoxaban 60 mg once daily, or 30 mg once daily if patients with creatinine clearance of 30 to 50 ml per minute or a body weight below 60 kg

<sup>3</sup> Death, with PE not ruled out

<sup>4</sup> CI includes values suggesting no effect and values suggesting either benefit or harm

**Table 6: Factors that may influence which anticoagulant is chosen for initial and long-term treatment of VTE**

Factor	Preferred anticoagulant	Qualifying remarks
Cancer	LMWH	More so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic; vomiting; on cancer chemotherapy.
Parenteral therapy to be avoided	Rivaroxaban; apixaban	VKA, dabigatran and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA	
Liver disease and coagulopathy	LMWH	NOACs contraindicated if INR raised due to liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.
Renal disease and creatinine clearance <30 ml/min	VKA	NOACs and LMWH contraindicated with severe renal impairment. Dosing of NOACs with levels of renal impairment differ with the NOAC and among jurisdictions.
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other NOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding.
Dyspepsia or history of gastrointestinal bleeding	VKA, apixaban,	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban and edoxaban may be associated with more gastrointestinal bleeding than VKA.
Poor compliance	VKA	INR monitoring can help to detect problems. However, some patients may be more compliant with a NOAC because it is less complex.
Thrombolytic therapy use	Unfractionated heparin infusion	Greater experience with its use in patients treated with thrombolytic therapy
Reversal agent needed	VKA, unfractionated heparin	
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta
Cost, coverage, licensing	Varies among regions and with individual circumstances	

**Table 7: Summary of Findings - Dabigatran vs VKA for extended treatment of VTE**<sup>1,2,3,4</sup>**Bibliography:** Schulman et al. (REMEDY)<sup>20</sup>

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA	Risk difference with Dabigatran (95% CI)
<b>All Cause Mortality</b>	2856 (1 study)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>5,6</sup> due to imprecision	<b>RR 0.89</b> (0.47 to 1.71)	<b>13 per 1000</b>	<b>1 fewer per 1000</b> (from 7 fewer to 9 more)
<b>Recurrent VTE</b>	2856 (1 study)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>5,6,7</sup> due to imprecision	<b>RR 1.44</b> (0.79 to 2.62)	<b>13 per 1000</b>	<b>6 more per 1000</b> (from 3 fewer to 20 more)
<b>Major Bleeding</b>	2856 (1 study)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>5,6</sup> due to imprecision	<b>RR 0.52</b> (0.27 to 1.01)	<b>18 per 1000</b>	<b>8 fewer per 1000</b> (from 13 fewer to 0 more)

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** 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.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Included patients had acute, symptomatic, objectively verified proximal DVT of the legs or PE

<sup>2</sup> Dabigatran 150 mg twice daily taken orally for 6 months after an initial treatment with LMWH or IV UFH

<sup>3</sup> Warfarin adjusted to achieve an INR of 2.0 to 3.0 for 6 months after an initial treatment with LMWH or IV UFH

<sup>4</sup> Active-Control study outcomes used from Schulman et al. (REMEDY)<sup>20</sup>

<sup>5</sup> Allocation was concealed. Patients, providers, data collectors and outcome adjudicators were blinded. Modified ITT analysis. 1.1% loss to follow-up. Not stopped early for benefit.

<sup>6</sup> CI includes values suggesting no effect and values suggesting either benefit or harm

<sup>7</sup> Primary end point was composite of recurrent or fatal VTE or unexplained death

**Table 8: Summary of Findings - Dabigatran vs Placebo for extended treatment of VTE**<sup>1,2,3</sup>**Bibliography:** Schulman et al. (RESONATE)<sup>20</sup>

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Dabigatran (95% CI)
<b>All Cause Mortality</b>	1343 (1 study)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>4</sup> due to imprecision	Not estimable <sup>5</sup>	-	-
<b>Recurrent VTE</b>	1343 (1 study)	⊕⊕⊕⊕ <b>HIGH</b>	<b>RR 0.08</b> (0.02 to 0.25)	<b>56 per 1000</b>	<b>51 fewer per 1000</b> (from 42 fewer to 55 fewer)
<b>Major Bleeding</b>	1343 (1 study)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>4</sup> due to imprecision	Not estimable <sup>6</sup>	-	-

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** 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.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Patients with VTE who had completed at least 3 initial months of therapy

<sup>2</sup> Dabigatran 150 mg twice daily

<sup>3</sup> Placebo-Control study outcomes used from Schulman et al. (RESONATE)<sup>20</sup>

<sup>4</sup> Event rate low in a large sample size

<sup>5</sup> Event rate with Dabigatran was 0/681 (0%); event rate with placebo was 2/662 (0.3%); anticipated absolute effect - risk difference with Dabigatran is 3 fewer per 1000 (from 11 fewer to 3 more)

<sup>6</sup> Event rate with Dabigatran was 2/681 (0.3%); event rate with placebo was 0/662 (0%); anticipated absolute effect - risk difference with Dabigatran is 3 more per 1000 (from 3 fewer to 11 more)

**Table 9: Summary of Findings - Rivaroxaban vs Placebo for extended treatment of VTE<sup>1,2</sup>****Bibliography:** Bauersachs et al. (EINSTEIN-Extension)<sup>16</sup>

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Rivaroxaban (95% CI)
<b>All Cause Mortality</b>	1196 (1 study)	⊕⊕⊕⊖ <b>MODERATE</b> <sup>3</sup> due to imprecision	<b>RR 0.49</b> (0.04 to 5.43)	<b>3 per 1000</b>	<b>2 fewer per 1000</b> (from 3 fewer to 15 more)
<b>Recurrent VTE</b>	1196 (1 study)	⊕⊕⊕⊕ <b>HIGH</b>	<b>RR 0.19</b> (0.09 to 0.4)	<b>71 per 1000</b>	<b>57 fewer per 1000</b> (from 42 fewer to 64 fewer)
<b>Major Bleeding</b>	1188 (1 study)	⊕⊕⊕⊖ <b>MODERATE</b> due to risk of bias	Not estimable <sup>4</sup>	-	-

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** 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.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Patients who had completed 6 to 12 months of treatment for VTE

<sup>2</sup> Rivaroxaban 20mg daily or placebo, specific to the continued treatment study

<sup>3</sup> CI includes values suggesting no effect and values suggesting either benefit or harm

<sup>4</sup> Event rate with Rivaroxaban was 4/598 (0.67%); event rate with placebo was 0/590 (0%); anticipated absolute effect - risk difference with Rivaroxaban is 4 more per 1000 (from 1 less to 17 more)



**Table 10: Summary of Findings - Apixaban vs Placebo for extended treatment of VTE**<sup>1,2</sup>**Bibliography:** Agnelli et al. (AMPLIFY-EXT)<sup>27</sup>

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Apixaban (95% CI)
<b>All Cause Mortality</b>	1669 (1 study) 12 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>3,4</sup> due to imprecision	<b>RR 0.49</b> (0.2 to 1.22)	<b>17 per 1000</b>	<b>9 fewer per 1000</b> (from 14 fewer to 4 more)
<b>Recurrent VTE</b>	1669 (1 study) 12 months	⊕⊕⊕⊕ <b>HIGH</b>	<b>RR 0.19</b> (0.11 to 0.33)	<b>88 per 1000</b>	<b>71 fewer per 1000</b> (from 59 fewer to 78 fewer)
<b>Major Bleeding</b>	1669 (1 study) 12 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>3,4</sup> due to imprecision	<b>RR 0.49</b> (0.09 to 2.64)	<b>5 per 1000</b>	<b>2 fewer per 1000</b> (from 4 fewer to 8 more)

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** 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.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Patients with VTE who had completed 6 to 12 months of anticoagulation therapy

<sup>2</sup> Apixaban 2.5 mg twice-daily dose vs. placebo

<sup>3</sup> Significantly wide CIs, including appreciable benefit / harm and no effect line

<sup>4</sup> Low number of events

**Table 11: Risk factors for bleeding with anticoagulant therapy and estimated risk of major bleeding in low, moderate and high risk categories\***

Risk factors <sup>A</sup>			
Age >65 years <sup>22-31</sup>			
Age >75 years <sup>22-26,28,30,32-40</sup>			
Previous bleeding <sup>23,29-31,36,39-42</sup>			
Cancer <sup>25,29,33,36,43</sup>			
Metastatic cancer <sup>11,42</sup>			
Renal failure <sup>23,29-31,34,36,39,44</sup>			
Liver failure <sup>24,26,33,34</sup>			
Thrombocytopenia <sup>33,42</sup>			
Previous stroke <sup>23,30,33,45</sup>			
Diabetes <sup>23,24,34,38,40</sup>			
Anaemia <sup>23,26,33,36,40</sup>			
Antiplatelet therapy <sup>24,33,34,40,46</sup>			
Poor anticoagulant control <sup>27,34,41</sup>			
Co-morbidity and reduced functional capacity <sup>29,34,42</sup>			
Recent surgery <sup>26,47<sup>B</sup></sup>			
Frequent falls <sup>33</sup>			
Alcohol abuse <sup>29,30,33,40</sup>			
Non-steroidal anti-inflammatory drug <sup>48</sup>			
Categorization of Risk of Bleeding <sup>C</sup>			
	Estimated absolute risk of major bleeding		
	Low risk <sup>D</sup> (0 risk factors)	Moderate risk <sup>D</sup> (1 risk factor)	High risk <sup>D</sup> (≥2 risk factors)
Anticoagulation 0-3 months <sup>E</sup>			
baseline risk (%)	0.6	1.2	4.8
increased risk (%)	1.0	2.0	8.0
total risk (%)	1.6 <sup>F</sup>	3.2	12.8 <sup>G</sup>
Anticoagulation after first 3 months <sup>5</sup>			
baseline risk (% per yr)	0.3 <sup>H</sup>	0.6	≥2.5
increased risk (% per yr)	0.5	1.0	≥4.0
total risk (% per yr)	0.8 <sup>I</sup>	1.6 <sup>I</sup>	≥6.5

\*From AT9. Since AT9: References for bleeding with individual factors have been added <sup>31,44,48</sup>; non-steroidal anti-inflammatory drug has been added as a risk factor; a systematic review has described the risk in VTE trial patients who were randomized to no antithrombotic therapy <sup>49</sup>; and a number of recent publications have compared clinical prediction rules for bleeding in various populations <sup>31,50-54</sup>.

A. Most studies assessed risk factors for bleeding in patients who were on VKA therapy. The risk of bleeding with different anticoagulants is not addressed in this table. The increase in bleeding associated with a risk factor will vary with: 1) severity of the risk factor (e.g. location and extent of metastatic disease; platelet count); 2) temporal relationships (e.g. interval from surgery or a previous bleeding episode<sup>35</sup>; and 3) how effectively a previous cause of bleeding was corrected (e.g. upper gastrointestinal bleeding).

B. Important for parenteral anticoagulation (e.g. first 10 days) but less important for long-term or extended anticoagulation.

C. Although there is evidence that risk of bleeding increases with the prevalence of risk factors<sup>25,26,30,31,33,34,36,39,40,42,55,56</sup>, the categorization scheme suggested above has not been validated. Furthermore, a single risk factor, when severe, will result in a high risk of bleeding (e.g. major surgery within the past 2 days; severe thrombocytopenia).

D. Compared to low risk patients, moderate risk patients are assumed to have a 2-fold risk and high-risk patients are assumed to have an 8-fold risk of major bleeding<sup>23,25,26,33,34,36,42,57</sup>.

E. We estimate that anticoagulation is associated with a 2.6-fold increase in major bleeding based on comparison of extended anticoagulation with no extended anticoagulation (Table 6). The relative risk of major bleeding during the first 3 month of therapy may be greater than during extended VKA therapy because: 1) the intensity of anticoagulation with initial parenteral therapy may be greater than with VKA therapy; 2) anticoagulant control will be less stable during the first 3 months; and 3) predispositions to anticoagulant-induced bleeding may be uncovered during the first 3 months of therapy<sup>27,36,41</sup>. However, studies of patients with acute coronary syndromes do not suggest a higher than 2.6 relative risk of major bleeding with parenteral anticoagulation (e.g. UFH or LMWH) compared to control<sup>58,59</sup>.

F. 1.6% corresponds to the average of major bleeding with initial UFH or LMWH therapy followed by VKA therapy (Table 7). We estimated baseline risk by assuming a 2.6 relative risk of major bleeding with anticoagulation (footnote 1).

G. Consistent with frequency of major bleeding observed by Hull in "high risk" patients<sup>47</sup>.

H. Our estimated baseline risk of major bleeding for low risk patients (and adjusted up for moderate and high risk groups as per footnote D).

I. Consistent with frequency of major bleeding during prospective studies of extended anticoagulation for VTE<sup>27,57,60-62</sup> (Table 6).

**Table 12: Summary of Findings - Six, Twelve or Twenty-four Months vs Three or Six Months as minimum duration of anticoagulation for VTE<sup>1,2</sup>****Bibliography:** Campbell et al.<sup>63</sup>, Pinede et al. (DOTAVK)<sup>64</sup>, Agnelli et al. (WODIT-PE Provoked and Unprovoked)<sup>65</sup>, Agnelli et al. (WODIT-DVT)<sup>66</sup>, Couturaud et al. (PADIS-PE)<sup>67</sup>, Siragusa et al. (DACUS)<sup>68</sup>, Eischer et al. (AUREC-FVIII)<sup>69</sup>

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No extended	Risk difference with Extended (95% CI)
<b>Mortality</b>	1736 (7 studies) 1-3 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>3,4,5</sup> due to imprecision	<b>RR 1.39</b> (0.91 to 2.12)	<b>41 per 1000</b>	<b>16 more per 1000</b> (from 4 fewer to 46 more)
<b>Recurrent VTE</b>	2466 (8 studies) 1-3 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>3,4,5</sup> due to imprecision	<b>RR 0.88</b> (0.71 to 1.09)	<b>128 per 1000</b>	<b>18 fewer per 1000</b> (from 40 fewer to 8 more)
<b>Major Bleeding</b>	2466 (8 studies) 1-3 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>3,4,5</sup> due to imprecision	<b>RR 1.78</b> (0.95 to 3.34)	<b>12 per 1000</b>	<b>9 more per 1000</b> (from 1 fewer to 27 more)

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** 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.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Studies vary in follow-up duration (10 months to 3 years) and in duration of time-limited VKA (3 to 6 months).

<sup>2</sup> VKA as NOACs are not included

<sup>3</sup> Timing of randomization relative to the start of treatment and length of treatment varied across studies: Pinede et al.<sup>64</sup> and Campbell et al.<sup>63</sup> randomized at diagnosis; and Agnelli et al.<sup>65</sup>, Eischer et al.<sup>69</sup> and Couturaud et al.<sup>67</sup> randomized after the initial 3 mo (Agnelli et al.<sup>65</sup>) or 6 mo (Eischer et al.<sup>69</sup> Couturaud et al.<sup>67</sup>) of treatment to stop or continued treatment. The longer duration of treatment was 6 mo in Agnelli et al. (provoked PE)<sup>65</sup> and Pinede et al.<sup>64</sup>, 12 months in Agnelli et al. (unprovoked DVT; unprovoked PE)<sup>65,66</sup>, 24 months in Couturaud et al.<sup>67</sup>, and 30 months in Eischer et al.<sup>69</sup> Generally, study design was strong. No study stopped early for benefit; three stopped early because of slow recruitment (Campbell et al.<sup>63</sup>, Pinede et al.<sup>64</sup>, Eischer et al.<sup>69</sup>) and one because of lack of benefit (Agnelli et al.<sup>65</sup>). In one study (Campbell et al.<sup>63</sup>), 20% of VTE outcomes were not objectively confirmed. Patients and caregivers were blinded in Couturaud et al.<sup>67</sup>, but none of the other studies. Adjudicators of outcomes were blinded in all but one study (Campbell et al.<sup>63</sup>). All studies used effective randomization concealment, intention-to-treat analysis, and a low unexplained drop-out frequency.

<sup>4</sup> Study populations varied across studies: Pinede et al.<sup>64</sup> enrolled provoked and unprovoked proximal DVT and PE; Campbell et al.<sup>63</sup>, enrolled provoked and unprovoked isolated distal DVT, proximal DVT, and PE; Agnelli et al.<sup>65</sup> had separate randomizations for provoked PE (3 vs 6 mo) and unprovoked (3 vs 12 mo); Agnelli et al.<sup>66</sup> enrolled unprovoked proximal DVT; Eischer et al.<sup>69</sup> enrolled unprovoked isolated DVT, proximal DVT and PE with high levels of factor VIII; and Couturaud et al.<sup>67</sup> enrolled unprovoked PE.

<sup>5</sup> CIs include both values suggesting no effect and values suggesting either benefit or harm.

**Table 13: Summary of Findings - Aspirin vs Placebo for extended treatment of VTE****Bibliography:** Simes et al. (INSPIRE)<sup>70</sup>

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Aspirin (95% CI)
<b>All Cause Mortality</b>	1224 (2 studies) up to 4 years	⊕⊕⊕⊖ <b>LOW</b> <sup>3,4,5</sup> due to imprecision	<b>HR 0.82</b> (0.45 to 1.52) <sup>2</sup>	<b>Moderate risk population</b> <sup>1</sup>	
				<b>5 per 1000</b>	<b>1 fewer per 1000</b> (from 3 fewer to 3 more)
<b>Recurrent VTE</b>	1224 (2 studies) up to 4 years	⊕⊕⊕⊕ <b>MODERATE</b> <sup>3,5</sup> due to imprecision	<b>HR 0.65</b> (0.49 to 0.86) <sup>2</sup>	<b>184 per 1000</b>	<b>60 fewer per 1000</b> (from 24 fewer to 89 fewer)
<b>Major Bleeding</b>	1224 (2 studies) up to 4 years	⊕⊕⊕⊕ <b>MODERATE</b> <sup>3,4</sup> due to imprecision	<b>HR 1.31</b> (0.48 to 3.53) <sup>2</sup>	<b>12 per 1000</b>	<b>4 more per 1000</b> (from 6 fewer to 29 more)

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **HR:** Hazard ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** 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.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Estimate taken from Douketis et al.<sup>71</sup>

<sup>2</sup> Estimate based on Simes et al. (INSPIRE)<sup>70</sup> of synthesis of Brighton et al. (ASPIRE)<sup>72</sup> and Becattini et al. (WARFASA)<sup>73</sup>

<sup>3</sup> Both of the included studies were stopped early with knowledge of overall rates of VTE. Decision to stop was not made with unblinded data. Only 1/3 of the intended patients in the study

<sup>4</sup> CI includes values suggesting no effect and values suggesting either benefit or harm

<sup>5</sup> Greater than 50% change in risk reduction

**Table 14: Summary of Findings - Catheter assisted thrombus removal vs anticoagulation alone for acute leg DVT**

**Bibliography:** Watson et al.<sup>74</sup> used for all outcomes except Patency and QoL. Enden et al.<sup>75</sup> used for Patency estimates. Enden et al.<sup>76</sup> used for QoL estimates.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Anticoagulation alone	Risk difference with Catheter assisted thrombus removal (95% CI)
All Cause Mortality	209 (1 study) 3 months	⊕⊕⊕⊖ <b>LOW</b> <sup>2,3</sup> due to imprecision	<b>RR 0.43</b> (0.08 to 2.16)	<b>46 per 1000</b> <sup>1</sup>	<b>26 fewer per 1000</b> (from 43 fewer to 54 more)
Recurrent VTE	189 (1 study) 3 months	⊕⊕⊕⊖ <b>LOW</b> <sup>2,3</sup> due to imprecision	<b>RR 0.61</b> (0.3 to 1.25) <sup>5</sup>	<b>Moderate risk population</b> <sup>4</sup> <b>48 per 1000</b>	<b>19 fewer per 1000</b> (from 34 fewer to 12 more)
Major bleeding	224 (2 studies) 3 months	⊕⊕⊕⊖ <b>LOW</b> <sup>2,3</sup> due to imprecision	<b>RR 7.69</b> (0.4 to 146.9) <sup>5</sup>	<b>Moderate risk population</b> <sup>4,6</sup> <b>29 per 1000</b>	<b>194 more per 1000</b> (from 17 fewer to 1000 more)
Postthrombotic syndrome	189 (1 study) 2 years	⊕⊕⊕⊖ <b>MODERATE</b> <sup>2</sup> due to imprecision	<b>RR 0.74</b> (0.55 to 1) <sup>9</sup>	<b>Moderate risk population</b> <sup>7</sup> <b>588 per 1000</b>	<b>153 fewer per 1000</b> (from 265 fewer to 0 more) <sup>8</sup>
Patency	189 (1 study) 6 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>3</sup> due to imprecision	<b>RR 1.42</b> (1.09 to 1.85)	<b>455 per 1000</b> <sup>10</sup>	<b>191 more per 1000</b> (from 41 more to 386 more)
Quality of Life	189 (1 study) 24 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>13</sup> due to risk of bias			The mean quality of life in the intervention groups was <b>0.2 higher</b> (2.8 lower to 3 higher) <sup>11,12</sup>

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** 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.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Reported deaths from Enden et al. (CAVENT)<sup>75</sup>

<sup>2</sup> Confidence interval includes values suggesting both benefit and harm

<sup>3</sup> Low number of events

<sup>4</sup> Baseline risks for non-fatal recurrent VTE and for major bleeding derived from Douketis et al.<sup>77</sup>

<sup>5</sup> Estimate taken from Watson et al.<sup>74</sup>. The one study included for this outcome was Enden et al. (CAVENT)<sup>75</sup>

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<sup>6</sup> Most of bleeding events occur during the first 7 days

<sup>7</sup> This estimate is based on the findings of the VETO study.<sup>78</sup>

<sup>8</sup> For severe PTS, assuming the same RR of 0.46 and a baseline risk of 13.8%<sup>78</sup>, the absolute reduction is 75 fewer severe PTS per 1000 (from 29 fewer to 138 fewer) over 2 years

<sup>9</sup> This estimate is based on the Watson et al.<sup>74</sup>. The one study included for this outcome was Enden et al. (CAVENT).<sup>75</sup> For PTS at 6 months, published data from Enden et al. (CAVENT)<sup>75</sup> provides an estimate RR of 0.93 (0.61, 1.42) via Watson et al.<sup>74</sup>

<sup>10</sup> Reported patency from Enden et al. (CAVENT)<sup>75</sup>

<sup>11</sup> Disease-specific QOL (VEINES-QOL) estimate used at 24 months according to treatment allocation

<sup>12</sup> Generic QoL (EQ-5D) at 24 months according to treatment allocation estimate is MD 0.04 (-0.01 to 0.17)

<sup>13</sup> Open-label

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**Table 15: Risk factors for bleeding with, and contraindications to use of, thrombolytic therapy (both systemic and locally administered)**

<b>Major contraindications<sup>1</sup></b>
Structural intracranial disease
Previous intracranial hemorrhage
Ischemic stroke within 3 months
Active bleeding
Recent brain or spinal surgery
Recent head trauma with fracture or brain injury
Bleeding diathesis
<b>Relative contraindications<sup>2</sup></b>
Systolic blood pressure >180
Diastolic blood pressure >110
Recent bleeding (non-intracranial)
Recent surgery
Recent invasive procedure
Ischemic stroke more than 3 months previously
Anticoagulated (e.g. VKA therapy)
Traumatic cardiopulmonary resuscitation
Pericarditis or pericardial fluid
Diabetic retinopathy
Pregnancy
Age >75 years
Low body weight (eg, <60 kg)
Female
Black race

1. The presence of major contraindications usually precludes use of thrombolytic therapy and, consequently, these factors have not been well studied as risk factors for bleeding associated with thrombolytic therapy. Patients with one or more major contraindication are usually considered to be "high risk for bleeding with thrombolytic therapy". The factors listed in this table are consistent with other recommendations for the use of thrombolytic therapy in patients with PE.<sup>79-83</sup>

2. Risk factors for bleeding during anticoagulant therapy that are noted in Table 11 "Risk factors for bleeding with anticoagulant therapy and estimated risk of major bleeding in low, moderate and high risk categories" that are not included in this table are also likely to be relative contraindications to thrombolytic therapy. The increase in bleeding associated with a risk factor will vary with: 1) severity of the risk factor (e.g. extent of trauma or recent surgery); and 2) temporal relationships (e.g. interval from surgery or a previous bleeding episode; believed to decrease markedly after ~2 weeks). Risk factors for bleeding at critical sites (e.g. intracranial or intraocular) or non-compressible sites are stronger contraindications for thrombolytic therapy.

Depending on the nature, severity, temporality and number of relative contraindications, patients may be considered "high risk of bleeding with thrombolytic therapy" or "non-high risk for thrombolytic therapy". Patients with no risk factors, one or two minor risk factors (e.g. female and black race), are usually considered "low risk of bleeding with thrombolytic therapy".

Among 32,000 Medicare patients (≥65 years) with myocardial infarction who were treated with thrombolytic therapy, the following factors were independently associated with intracranial haemorrhage: age ≥75 years (odds ratio [OR] 1.6); Black (OR 1.6); female (OR 1.4); previous stroke (OR 1.5); systolic blood pressure ≥160 mmHg (OR 1.8); women ≤65 kg or men ≤80 kg (OR 1.5); INR >4 (OR 2.2)<sup>84</sup>. The rate of intracranial haemorrhage increased from 0.7% with 0 or 1 of these risk factors, to 4.1% with ≥5 risk factors.

Among 32,000 patients with myocardial infarction who were treated with thrombolytic therapy in 5 clinical trials, the following factors were independently associated with moderate or severe bleeding: older age (OR 1.04 per year); Black (OR 1.4); female (OR 1.5); hypertension (OR 1.2); lower weight (OR 0.99 per kg).<sup>81</sup>

We estimate that systemic thrombolytic therapy is associated with relative risk of major bleeding of 3.5 within 35 days (relative risk ~7 for intracranial bleeding); about three quarters of the excess of major bleeds with thrombolytic therapy occur in the first 24 hours.<sup>85</sup>

**Table 16: Summary of Findings - Temporary Inferior Vena Caval Filter vs No Temporary Inferior Vena Caval Filter in addition to anticoagulation for acute DVT or PE<sup>1,2</sup>****Bibliography:** Mismetti et al. (PREPIC 2)<sup>86</sup>

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Temporary Inferior Vena Caval Filter in addition to anticoagulation	Risk difference with Temporary Inferior Vena Caval Filter (95% CI)
<b>All Cause Mortality</b>	399 (1 study) 3 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>3,4</sup> due to imprecision	<b>RR 1.25</b> (0.6 to 2.6)	<b>60 per 1000</b>	<b>15 more per 1000</b> (from 24 fewer to 96 more)
<b>Recurrent PE</b>	399 (1 study) 3 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>3,4</sup> due to imprecision	<b>RR 2.00</b> (0.51 to 7.89)	<b>15 per 1000</b>	<b>15 more per 1000</b> (from 7 fewer to 104 more)
<b>Major Bleeding</b>	399 (1 study) 3 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>3,4</sup> due to imprecision	<b>RR 0.80</b> (0.32 to 1.98)	<b>50 per 1000</b>	<b>10 fewer per 1000</b> (from 34 fewer to 49 more)

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** 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.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> All patients received full-dose anticoagulant therapy according to guidelines for at least 6 months

<sup>2</sup> Filter removal was attempted in 164 patients and successful for 153 (93.3%)

<sup>3</sup> CI includes values suggesting no effect and values suggesting either benefit or harm

<sup>4</sup> Small number of events



**Table 17: Summary of Findings - Elastic Compression Stockings vs No Elastic Compression Stockings to Prevent PTS of the leg**

<b>Bibliography:</b> Kahn et al. (SOX) <sup>87</sup> for PTS and recurrent VTE; Kahn et al. <sup>88</sup> for acute leg pain					
Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No elastic compression stockings	Risk difference with Elastic compression stockings (95% CI)
PTS Villalta Score <sup>1</sup>	803 (1 study) 6 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>4</sup> due to imprecision	<b>RR 1.01</b> (0.86 to 1.18) <sup>3</sup>	<b>Moderate risk population</b> <sup>2</sup>	
				<b>479 per 1000</b>	<b>5 more per 1000</b> (from 67 fewer to 86 more)
Recurrent VTE	803 (1 study) 6 months	⊕⊕⊕⊖ <b>MODERATE</b> <sup>4,7</sup> due to imprecision	<b>RR 0.84</b> (0.54 to 1.31) <sup>6</sup>	<b>Moderate risk population</b> <sup>5</sup>	
				<b>210 per 1000</b>	<b>34 fewer per 1000</b> (from 97 fewer to 65 more)
Acute Leg Pain	742 (1 study) 60 days	⊕⊕⊕⊖ <b>MODERATE</b> <sup>7,9</sup> due to imprecision		The mean acute leg pain in the control groups was <b>1.13 leg pain severity assessed on an 11-point numerical pain rating scale</b> <sup>8</sup>	The mean acute leg pain in the intervention groups was <b>0.26 higher</b> (0.03 lower to 0.55 higher) <sup>8</sup>
Quality of Life	803 (1 study)	⊕⊕⊕⊕ <b>HIGH</b>			The mean quality of life in the intervention groups was <b>0.12 lower</b> (1.11 lower to 0.86 higher) <sup>10,11</sup>

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** 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.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> For included studies, number of post-thrombotic syndrome events as assessed by Villalta's criteria

<sup>2</sup> This estimate is based on the findings of the VETO study<sup>78</sup>

<sup>3</sup> There were three studies originally included for this outcome (Brandjes et al.<sup>89</sup>, Prandoni et al.<sup>90</sup> and Kahn et al. (SOX).<sup>87</sup>) There was very high heterogeneity between the three studies,  $I^2=92%$  ( $p<0.01$ ). The pooled effect of the three studies was RR 0.63 (0.35 to 1.13). Yet, because of the high risk of bias associated with Brandjes et al.<sup>89</sup> and Prandoni et al.<sup>90</sup>, it was decided to focus on the estimate of the low risk trial, Kahn et al. (SOX)<sup>87</sup>, which is used here

<sup>4</sup> Low number of events

<sup>5</sup> This estimate is the mean of two estimates derived from two studies: 12.4% probable/definite VTE<sup>91</sup> and 29.1% confirmed VTE.<sup>92</sup>

<sup>6</sup> There were three studies originally included for this outcome (Brandjes et al.<sup>89</sup>, Prandoni et al.<sup>90</sup> and Kahn et al. (SOX).<sup>87</sup>) The pooled effect of the three studies was RR 0.91 (0.65 to 1.27). Yet, because of the high risk of bias associated with Brandjes et al.<sup>89</sup> and Prandoni et al.<sup>90</sup>, it was decided to focus on the estimate of the low risk trial, Kahn et al. (SOX)<sup>87</sup>, which is used here

<sup>7</sup> CI includes values suggesting no effect and values suggesting either benefit or harm

<sup>8</sup> Estimate derived from Kahn et al.<sup>88</sup>

<sup>9</sup> Wide CI that includes no effect

<sup>10</sup> Estimate based on VEINES-QOL score improvement of 5.8 points (SD 7.5) for active ECS versus 5.9 (SD 7.1) for placebo ECS

<sup>11</sup> SF-36 physical component score improved by 8.4 points (SD 13.6) for active ECS versus 9.9 (SD 13.2) for placebo ECS (difference

between groups of -1.53 points, 95% CI -3.44 to 0.39; p=0.12)

**Table 18: Summary of Findings - Systemic thrombolytic therapy vs. anticoagulation alone for acute PE**

**Bibliography:** Chatterjee et al.<sup>93</sup>

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Anticoagulation alone	Risk difference with Systemic thrombolytic therapy (95% CI)
All Cause Mortality	2115 (17 studies)	⊕⊕⊕⊖ MODERATE <sup>3</sup> due to imprecision	OR 0.53 (0.32 to 0.88) <sup>2</sup>	39 per 1000 <sup>1</sup>	18 fewer per 1000 (from 5 fewer to 26 fewer)
Recurrent PE	2043 (15 studies)	⊕⊕⊕⊖ MODERATE <sup>3</sup> due to imprecision	OR 0.40 (0.22 to 0.74) <sup>4</sup>	30 per 1000 <sup>1</sup>	18 fewer per 1000 (from 8 fewer to 24 fewer)
Major bleeding	2115 (16 studies)	⊕⊕⊕⊕ HIGH	OR 2.73 (1.91 to 3.91) <sup>5</sup>	34 per 1000 <sup>1</sup>	54 more per 1000 (from 29 more to 87 more)
Intracranial Hemorrhage	2043 (15 studies)	⊕⊕⊕⊖ MODERATE <sup>3</sup> due to imprecision	OR 4.63 (1.78 to 12.04) <sup>6</sup>	2 per 1000 <sup>1</sup>	7 more per 1000 (from 2 more to 21 more)

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** 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.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Majority (83%) of participants in Chatterjee et al.<sup>93</sup> were "moderate" risk.

<sup>2</sup> Estimate from Chatterjee et al.<sup>93</sup>. Other estimates from meta-analyses on this topic include: Dong et al.<sup>94</sup> - OR 0.89 (0.45, 1.78) Cao et al.<sup>95</sup> - RR 0.64 (0.29, 1.40) Marti et al.<sup>96</sup> - OR 0.59 (0.36 - 0.96) Nakamura et al.<sup>97</sup> - RR 0.72 (0.39, 1.31) Chatterjee et al. (Intermediate-Risk PE Only)<sup>93</sup> - OR 0.46 (0.25 - 0.92) Marti et al. (Intermediate-Risk PE Only)<sup>96</sup> - OR 0.42 (0.17 - 1.03)

<sup>3</sup> Low number of events

<sup>4</sup> Estimate from Chatterjee et al.<sup>93</sup>. Other estimates from meta-analyses on this topic include: Dong et al.<sup>94</sup> - OR 0.63 (0.33, 1.20) Cao et al.<sup>95</sup> - RR 0.44 (0.19, 1.05) Marti et al.<sup>96</sup> - OR 0.50 (0.27 - 0.94) Nakamura et al.<sup>97</sup> - RR 0.60 (0.21, 1.69)

<sup>5</sup> Estimate from Chatterjee et al.<sup>93</sup>. Other estimates from meta-analyses on this topic include: Dong et al.<sup>94</sup> - OR 1.61 (0.91, 2.86) Cao et al.<sup>95</sup> - RR 1.16 (0.51, 2.60) Marti et al.<sup>96</sup> - OR 2.91 (1.95 - 4.36) Nakamura et al.<sup>97</sup> - RR 2.07 (0.58, 7.35)

<sup>6</sup> Estimate from Chatterjee et al.<sup>93</sup>

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