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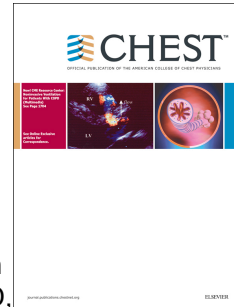
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Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report

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1 **Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report**

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36 <http://www.chestnet.org/Guidelines-and-Resources>

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39

40

41 **Abbreviations:**

42	ACS	acute coronary syndrome
43	aPTT	activated partial thromboplastin time
44	ARISTOTLE	Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial
45		Fibrillation
46	ATRIA	AnTicoagulation and Risk factors In Atrial fibrillation
47	AVERROES	Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial
48		Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K
49		Antagonist Treatment
50	b.i.d	bis in die (twice daily)
51	CABG	coronary artery bypass graft
52	CAP	Continued Access to PROTECT AF
53	CHA ₂ DS ₂ -VASC	congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke
54		(doubled)-vascular disease, age 65–74 and sex category (female)
55	CHADS ₂	congestive heart failure, hypertension, age, diabetes, stroke (doubled)
56	CI	confidence interval
57	CrCl	creatinine clearance
58	DOAC	direct oral anticoagulant drugs
59	ECG	electrocardiogram
60	GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
61	HAS-BLED	hypertension, abnormal renal/liver function (1 point each), stroke, bleeding
62		history or predisposition, labile INR, elderly (.65), drugs/alcohol concomitantly
63		(1 point each)
64	HF	Heart Failure
65	HFpEF	Heart Failure with Preserved Ejection Fraction
66	HFrEF	Heart Failure with Reduced Ejection Fraction
67	HR	hazard ratio
68	ICH	intracranial haemorrhage
69	INR	international normalized ratio
70	i.v.	intravenous
71	LAA	left atrial appendage
72	LAAO	left atrial appendage occlusion
73	o.d.	omni die (every day)
74	OAC	oral anticoagulant
75	NOAC	non-vitamin K antagonist oral anticoagulant drugs
76	NYHA	New York Heart Association
77	PCI	percutaneous cardiovascular intervention
78	PROTECT AF	System for Embolic PROTECTION in patients with Atrial Fibrillation
79	RE-LY	Randomized Evaluation of Long-term anticoagulant therapY with dabigatran
80		etexilate
81	ROCKET-AF	Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin
82		K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation
83	RRR	relative risk reduction
84	TIA	transient ischaemic attack
85	t.i.d.	ter in die (three times daily)
86	TE	thromboembolism

- 87 TEE transesophageal echocardiogram
- 88 TTR time in therapeutic range

ACCEPTED MANUSCRIPT

89 **Abstract**

90 *Background:* The risk of stroke is heterogeneous across different groups of patients with atrial
91 fibrillation (AF), being dependent on the presence of various stroke risk factors. We provide
92 recommendations for antithrombotic treatment based on net clinical benefit for patients with AF at
93 varying levels of stroke risk and in a number of common clinical scenarios.

94 *Methods:* Systematic literature reviews were conducted to identify relevant articles published from
95 the last formal search performed for the Antithrombotic and Thrombolytic Therapy: American
96 College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). The overall
97 quality of the evidence was assessed using the GRADE (Grading of Recommendations, Assessment,
98 Development, and Evaluation) approach. Graded recommendations and ungraded consensus-based
99 statements were drafted, voted on, and revised until consensus was reached.

100

101 *Results:* For patients with AF without valvular heart disease, including those with paroxysmal AF,
102 who are at low risk of stroke (e.g., CHA₂DS₂VASc score of 0 in males or 1 in females), we suggest no
103 antithrombotic therapy. The next step is to consider stroke prevention (ie oral anticoagulation
104 therapy) for patients with 1 or more non-sex CHA₂DS₂VASc stroke risk factors. For patients with a
105 single non-sex CHA₂DS₂VASc stroke risk factor, we suggest oral anticoagulation rather than no
106 therapy, aspirin or combination therapy with aspirin and clopidogrel; and for those at high risk of
107 stroke (eg, CHA₂DS₂VASc ≥ 2 in males or ≥ 3 in females), we recommend oral anticoagulation rather
108 than no therapy, aspirin, or combination therapy with aspirin and clopidogrel. Where we
109 recommend or suggest in favor of oral anticoagulation, we suggest using a NOAC rather than
110 adjusted-dose vitamin K antagonist therapy. With the latter, it is important to aim for good quality
111 anticoagulation control with a TTR $>70\%$.

112 Attention to modifiable bleeding risk factors (eg. uncontrolled blood pressure, labile INRs,
113 concomitant use of aspirin or NSAIDs in an anticoagulated patient, alcohol excess) should be made
114 at each patient contact, and HAS-BLED score used to assess the risk of bleeding where high risk
115 patients (≥ 3) should be reviewed and followed up more frequently.

116 *Conclusions:* Oral anticoagulation is the optimal choice of antithrombotic therapy for patients with
117 AF with ≥ 1 non-gender CHA₂DS₂VASc stroke risk factor(s).

118 SUMMARY OF RECOMMENDATIONS

119 *Note: Shaded text refers to recommendations that remain unchanged from the previous version of*
120 *the guideline*

121

122 1. **For patients with AF, including those with paroxysmal AF, stroke risk should be assessed using**
123 **a risk factor based approach, rather than an categorisation into low, moderate/high risk**
124 **strata. We recommend use of the CHA₂DS₂VASc as a simple clinical based stroke risk score to**
125 **initially identify ‘low stroke risk’ patients that should not be offered antithrombotic therapy to**
126 **prevent stroke and reduce mortality** (Strong recommendation, moderate quality evidence).

127

128 *Remark: Low risk patients are generally those age<65 and ‘lone AF’ irrespective of sex (this*
129 *includes those with a CHA₂DS₂VASc score=0 in males, or 1 in females).*

130

131 2. **Subsequent to this initial step, for patients with AF, including those with paroxysmal AF, we**
132 **recommend stroke prevention should be offered to those AF patients with one or more non-**
133 **sex CHA₂DS₂VASc stroke risk factors (score of ≥1 in a male or ≥2 in a female)** (Strong
134 recommendation, moderate quality evidence).

135

136 *Remark: Consideration of other less established clinical stroke risk factors, imaging (cardiac or*
137 *cerebral) or biomarkers (urine, blood or genetics) may refine risk stratification based on simple*
138 *clinical factors. A complex risk schema using a variety of such data that could accurately place*
139 *more patients in the low risk stratum not requiring anticoagulants than current simple clinically-*
140 *based scores (personalised medicine) should be the goal of future research, but it will be very*
141 *difficult to find non-anticoagulated patient cohorts for prospective validation.*

142

143 3. **For patients with AF, we recommend bleeding risk assessment should be performed for all**
144 **patients with AF at every patient contact and should initially focus on potentially modifiable**
145 **bleeding risk factors** (Strong recommendation, low quality evidence).

146

147 *Remark: Modifiable risk factors may include: Uncontrolled blood pressure; Labile INRs (in a*
148 *patient taking VKA); Alcohol excess; Concomitant use of NSAIDs or aspirin in an anticoagulated*
149 *patient; bleeding tendency or predisposition (e.g. treat gastric ulcer; optimise renal or liver*
150 *function etc.*

151

152 4. **For patients with AF, we recommend use of the HAS-BLED score to address modifiable**
153 **bleeding risk factors in all AF patients. Those potentially at high risk (HAS-BLED score ≥3)**
154 **warrant more frequent and regular reviews or follow-up** (Strong recommendation, moderate
155 quality evidence).

156

157 *Remark: Given that bleeding risk is highly dynamic, attention to modifiable bleeding risk factors*
158 *should be prioritized during every patient contact and review.*

159

160 5. **In VKA treated patients, we suggest the use of the HAS-BLED score for bleeding risk**
161 **assessment** (Weak recommendation, low quality evidence)

162

163 *Remark: A high HAS-BLED score (≥3) is rarely a reason to avoid anticoagulation. The individual*
164 *modifiable components of the score, when reviewed with the patient, can serve to ameliorate*
165 *bleed risk*

166

167

- 168 6. **For patients with AF, we recommend against antiplatelet therapy alone (monotherapy or**
 169 **aspirin in combination with clopidogrel) for stroke prevention alone, regardless of stroke risk**
 170 **(Strong recommendation, moderate quality evidence).**
 171
 172 *Remark:* Patients with AF might have other indications for antiplatelet drugs (e.g. acute coronary
 173 syndrome, stents)
 174
- 175 7. **In patients with AF who are eligible for OAC, we recommend NOACs over VKA** (strong
 176 recommendation, moderate quality evidence).
 177
 178 *Remark:* Patient and caregiver preferences, cost, formulary considerations, anticipated
 179 medication adherence or compliance with INR testing and dose adjustment should be
 180 incorporated into clinical-decision making.
 181
- 182 8. **In patients on VKAs with consistently low time in INR therapeutic range (eg. TTR<65%), we**
 183 **recommend considering interventions to improve TTR or switching to NOACs** (strong
 184 recommendation, moderate quality evidence)
 185
 186 *Remark:* Action required if TTR <65% - implement additional measures (more regular INR tests;
 187 review medication adherence; address other factors known to influence INR control;
 188 education/counselling) to improve INR control.
 189
- 190 9. **In patients with prior unprovoked bleeding, warfarin-associated bleeding, or at high risk of**
 191 **bleeding, we suggest using apixaban, edoxaban, or dabigatran 110 mg (where available) as all**
 192 **demonstrate significantly less major bleeding compared with warfarin** (Weak
 193 recommendation, very low quality evidence).
 194
 195 *Remark:* In patients with prior gastrointestinal bleeding apixaban or dabigatran 110mg bid may
 196 be preferable as they are the only NOACs associated without an increased risk of gastrointestinal
 197 bleeding compared with warfarin.
 198 *Remark:* Dabigatran 150 mg twice daily recommended in patients at high risk of ischemic stroke
 199 as only agent/dose with superior efficacy compared with warfarin. However, bleeding risk would
 200 need to be assessed and patients monitored.
 201
- 202 10. **For patients with non-valvular AF, when VKAs are used, we suggest the target should be INR**
 203 **2.0-3.0, with attention to individual TTR, ideally ≥70%** (ungraded consensus-based statement).
 204
 205 *Remark:* Action required if TTR sub-optimal (i.e. <65-70%) - implement additional measures
 206 (more regular INR tests; review medication adherence; address other factors known to influence
 207 INR control; education/counselling) to improve INR control or consider a NOAC.
 208 *Remark:* When possible, experienced specialized anticoagulation clinics should be utilized for
 209 VKA and INR management.
 210
- 211 11. **For patients with AF, we suggest the SAME-TT₂R₂ score to aid decision making to help identify**
 212 **patients likely to do well on VKA** (ungraded consensus-based statement).
 213
 214 *Remark:* Those with score 0-2 are likely to achieve a good TTR. Those with score >2 are less
 215 likely to achieve a good TTR and would require more regular INR checks, education/counselling
 216 and frequent follow-up ,or alternatively, NOAC should be considered as a better management
 217 option if high medication adherence can be expected.
 218

219 12. For patients with AF of greater than 48 hours or unknown duration undergoing elective
220 electrical or pharmacological cardioversion, we recommend therapeutic anticoagulation with
221 well-managed VKA (INR 2-3) or a NOAC using dabigatran, rivaroxaban, edoxaban or apixaban
222 for at least 3 weeks before cardioversion or a transesophageal echocardiography (TEE)-guided
223 approach with abbreviated anticoagulation before cardioversion rather than no
224 anticoagulation (Strong recommendation, moderate quality evidence).

225
226 *Remark:* With NOACs adherence and persistence should be strongly emphasized

227
228 13. For patients with AF of greater than 48 hours or unknown duration undergoing elective
229 electrical or pharmacologic cardioversion, we recommend therapeutic anticoagulation (with
230 VKA or NOAC) for at least 4 weeks after succesful cardioversion to sinus rhythm rather than no
231 anticoagulation, regardless of the baseline risk of stroke (strong recommendation, moderate
232 quality evidence)

233
234 *Remark:* Decisions about anticoagulation beyond 4 weeks should be made in accordance with
235 our risk-based recommendations for long-term antithrombotic therapy in recommednations 1
236 and 2, and not on the basis of successful cardioversion

237
238 14. In patients in which LAA thrombus is detected on TEE, cardioversion postponed, and OAC
239 continued for another 4-12 weeks, to allow thrombus resolution or endothelisation, we
240 suggest that a decision on whether a repeat TEE is performed should be individualized
241 (ungraded consensus-based statement).

242
243 15. For patients with AF of documented duration of 48 hours or less undergoing elective
244 cardioversion (electrical or pharmacologic), we suggest starting anticoagulation at
245 presentation (low-molecular-weight heparin or unfractionated heparin at full venous
246 thromboembolism treatment doses) and proceeding to cardioversion rather than delaying
247 cardioversion for 3 weeks of therapeutic anticoagulation or a TEE-guided approach (weak
248 recommendation, low quality evidence).

249
250 16. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical
251 or pharmacologic), after successful cardioversion to sinus rhythm, we suggest therapeutic
252 anticoagulation (with VKA or full adherence to NOAC therapy) for at least 4 weeks rather than
253 no anticoagulation, regardless of baseline stroke risk (weak recommendation, low quality
254 evidence).

255 *Remark:* Decisions about long-term anticoagulation after cardioversion should be made in
256 accordance with our risk-based recommendations for long-term antithrombotic therapy in
257 recommendations 1 and 2

258
259 17. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical
260 or pharmacologic), we suggest that therapeutic-dose parenteral anticoagulation be started
261 before cardioversion, if possible, but that initiation of anticoagulation must not delay any
262 emergency intervention (weak recommendation, low quality evidence).

263
264 18. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical
265 or pharmacologic), After successful cardioversion to sinus rhythm, we suggest therapeutic
266 anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm rather than
267 no anticoagulation, regardless of baseline stroke risk (weak recommendation, low quality
268 evidence).

269

270 *Remark:* Decisions about anticoagulation beyond 4 weeks should be made in accordance with
271 our risk-based recommendations for long-term antithrombotic therapy in recommendations 1
272 and 2.

273

274 **19. For patients with atrial flutter undergoing elective or urgent pharmacologic or electrical**
275 **cardioversion, we suggest that the same approach to thromboprophylaxis be used as for**
276 **patients with atrial fibrillation undergoing cardioversion (ungraded consensus-based**
277 **statement).**

278

279 **20. In AF patients presenting with an ACS and/or undergoing PCI/stenting, we recommend**
280 **assessment of stroke risk using the CHA₂DS₂-VASc score (Strong recommendation, moderate**
281 **quality evidence)**

282 *Remark:* All such patients are not 'low risk' and should be considered for concomitant OAC.

283

284 **21. In AF patients presenting with an ACS and/or undergoing PCI/stenting, we suggest attention to**
285 **modifiable bleeding risk factors at every patient contact, and assessment of bleeding risk using**
286 **the HAS-BLED score (weak recommendation, low quality evidence).**

287 *Remark:* Where bleeding risk is high (HAS-BLED ≥ 3), there should be more regular review and
288 follow-up.

289

290 **22. In AF patients requiring OAC undergoing elective PCI/stenting, where bleeding risk is low**
291 **(HAS-BLED 0-2) relative to risk for recurrent ACS and/or stent thrombosis, we suggest triple**
292 **therapy for 1-3 months, followed by dual therapy with OAC plus single antiplatelet (preferably**
293 **clopidogrel) until 12 months, following which OAC monotherapy can be used (weak**
294 **recommendation, low quality evidence).**

295

296 **23. In AF patients requiring OAC undergoing elective PCI/stenting, where bleeding risk is high**
297 **(HAS-BLED ≥ 3), we suggest triple therapy for one month, followed by dual therapy with OAC**
298 **plus single antiplatelet (preferably clopidogrel) for 6 months, following which OAC**
299 **monotherapy can be used (weak recommendation, low quality evidence)**

300

301 **24. In AF patients requiring OAC undergoing elective PCI/stenting, where bleeding risk is**
302 **unusually high and thrombotic risk relatively low, we suggest use of OAC plus single**
303 **antiplatelet (preferably clopidogrel) for 6 months, following which OAC monotherapy can be**
304 **used (weak recommendation, low quality evidence)**

305

306 *Remark:* Patients at unusually high bleeding risk may include patients with HAS-BLED ≥ 3 and
307 recent acute bleeding event. High thrombotic risk may include those with left main stent,
308 multivessel PCI/stenting, etc.

309

310 **25. In AF patients requiring OAC presenting with an ACS, undergoing PCI/stenting, where bleeding**
311 **risk is low (HAS-BLED 0-2) relative to risk for ACS or stent thrombosis, we suggest triple**
312 **therapy for 6 months, followed by dual therapy with OAC plus single antiplatelet (preferably**
313 **clopidogrel) until 12 months, following which OAC monotherapy can be used (weak**
314 **recommendation, low quality evidence)**

315

316 **26. In AF patients requiring OAC presenting with an ACS, undergoing PCI/stenting, where bleeding**
317 **risk is high (HAS-BLED ≥ 3), we suggest triple therapy for 1-3 months, followed by dual therapy**
318 **with OAC plus single antiplatelet (preferably clopidogrel) up to 12 months, following which**
319 **OAC monotherapy can be used (weak recommendation, low quality evidence).**

320

321 27. **In AF patients requiring OAC presenting with an ACS, undergoing PCI/stenting where bleeding**
322 **risk is unusually high and thrombotic risk low, we suggest OAC plus single antiplatelet**
323 **(preferably clopidogrel) for 6-9 months, following which OAC monotherapy can be used.** (weak
324 recommendation, low quality evidence).

325
326 Remark: Patients at unusually high bleeding risk may include patients with HAS-BLED ≥ 3 and recent
327 acute bleeding event. High thrombotic risk may include those with left main stent, multivessel
328 PCI/stenting, etc.

329
330 28. **In AF patients with ACS or undergoing PCI in whom OAC is recommended, we suggest using**
331 **VKA with TTR>65-70% (INR range 2.0-3.0), or to use a NOAC at a dose licensed for stroke**
332 **prevention in AF** (weak recommendation, low quality evidence).

333
334 *Remark:* Only Dabigatran 150mg bid or (not licensed in USA) 110mg bid or Rivaroxaban 15mg qd
335 are currently supported by clinical trial evidence. A NOAC based strategy has lower bleeding risk
336 compared to a VKA-based strategy.

337
338 29. **In AF patients in which aspirin is concomitantly used with OAC, we suggest a dose of 75-100mg**
339 **qd with concomitant use of PPI to minimize gastrointestinal bleeding** (Weak recommendation,
340 low quality evidence)

341
342 30. **In AF Patients in which a P2Y12 inhibitor is concomitantly used with OAC, we suggest the use**
343 **of clopidogrel** (Weak recommendation, low quality evidence)

344
345 *Remark:* Newer agents (eg. Ticagrelor) can be considered where bleeding risk is low. Data on the
346 combination of ticagrelor with either dabigatran 110mg bid or 150 bid (without concomitant aspirin
347 use) are available from the RE-DUAL PCI trial.

348 31. **For patients with AF and stable coronary artery disease (eg, no acute coronary syndrome**
349 **within the previous year) and who choose oral anticoagulation, we suggest OAC with either a**
350 **NOAC or adjusted-dose VKA therapy alone (target international normalized ratio [INR] range,**
351 **2.0-3.0) rather than the combination of OAC and aspirin** (Weak recommendation, low quality
352 evidence)

353 32. **In patients with AF in whom catheter ablation of AF or implantation of cardiac electronic**
354 **implantable devices is planned, we suggest performing the procedure on uninterrupted VKA in**
355 **the INR therapeutic range, dabigatran or rivaroxaban** (weak recommendation, low quality
356 evidence).

357
358
359 33. **In patients in whom sinus rhythm has been restored, we suggest that long-term**
360 **anticoagulation should be based on the patient's CHA2DS2-VASc thromboembolic risk profile,**
361 **regardless of whether sinus rhythm has been restored via ablation, cardioversion (even**
362 **spontaneous), or other means** (Weak recommendation, low quality evidence).

363
364
365 34. **In AF patients with acute ischaemic stroke, we suggest that very early anticoagulation (<48h)**
366 **using heparinoids or VKA should not be used** (ungraded consensus-based statement).

367
368 *Remark:* Heparinoids should not be used as bridging therapy in the acute phase of ischaemic
369 stroke because they appear to increase the risk of symptomatic intracranial haemorrhage

- 370 without net benefit. The optimal timing of anticoagulation after acute ischaemic stroke is
371 unknown.
372
- 373 **35. In AF patients with acute stroke without contraindications, we recommend that long term oral**
374 **anticoagulation is indicated** as secondary prevention (Strong recommendation, high quality
375 evidence).
376 *Remark:* The optimal timing of anticoagulation early after acute ischaemic stroke is unknown.
377 Early use of NOACs shows promise but requires testing in randomised controlled trials.
378
- 379 **36. In AF patients with acute ischaemic stroke, We suggest that oral anticoagulation should**
380 **usually be started within 2 weeks of acute ischaemic stroke, but the optimal timing within this**
381 **period is not known** (ungraded consensus-based statement).
382
383 *Remark:* Although infarct size is clinically used to guide timing of anticoagulation, it is predictive
384 of a higher risk of early recurrent ischaemia, haemorrhagic transformation of the infarct, and
385 poor outcome, so might not be helpful in determining the net benefit of early treatment.
386 *Remark:* Anticoagulation with NOACs soon after stroke (earlier than 1 week) has not been tested
387 in randomised trials, but shows promise in observational studies.
388
- 389 **37. In patients with AF and high ischaemic stroke risk, we suggest anticoagulation with a NOAC**
390 **after acute spontaneous ICH (which includes subdural, subarachnoid and intracerebral**
391 **haemorrhages) after careful consideration of the risks and benefits** (ungraded consensus-based
392 statement).
393
394 *Remark:* The balance of net benefit from long term oral anticoagulation might be more
395 favourable in those with deep ICH or without neuroimaging evidence of cerebral amyloid
396 angiopathy.
397 *Remark:* In ICH survivors with AF, clinicians should aim to estimate the risk of recurrent ICH
398 (using ICH location and, where available, MRI biomarkers including cerebral microbleeds) and
399 the risk of ischaemic stroke
400 *Remark:* The optimal timing of anticoagulation after ICH is not known, but should be delayed
401 beyond the acute phase (~48 hours) and probably for at least ~4 weeks. Randomised trials of
402 NOACs and left atrial appendage occlusion are ongoing.
403
- 404 **38. In ICH survivors at high risk of recurrent ICH (e.g. those with probable cerebral amyloid**
405 **angiopathy), we suggest left atrial appendage occlusion** (ungraded consensus-based
406 statement).
407 *Remark:* Cerebral amyloid angiopathy should be diagnosed using validated clinico-radiological
408 criteria.
409
- 410 **39. In patients with AF and symptomatic carotid stenosis (>50%), we suggest carotid**
411 **revascularisation with endarterectomy or stenting in addition to OAC as indicated** (Weak
412 recommendation, moderate quality evidence).
413
- 414 **40. In patients with AF and carotid stenosis treated with revascularisation, we suggest OAC**
415 **therapy, without long-term antiplatelet therapy** (ungraded consensus-based statement).
416
417 *Remark:* There is limited evidence to guide the optimal treatment of patients with AF and carotid
418 stenosis not requiring revascularisation.
419 *Remark:* Short-term concomitant antiplatelet therapy (dual or mono) is generally used in the
420 immediate post-revascularisation period (e.g. 1-3 months)
421

422 41. **For patients that present with a clinically documented episode of AF (12-lead ECG or other**
423 **means, eg. external devices with validated rhythm detection), we suggest that the presence or**
424 **absence of symptoms must not influence the process of decision making with regard to the**
425 **need for anticoagulation based on risk stratification** (ungraded consensus-based statement).
426

427 42. **In cases of AHRE (atrial high rate episodes) detected by a CIED of at least 5 min duration, we**
428 **suggest that direct analysis of electrograms corresponding to AHRE is clinically indicated to**
429 **exclude artifacts or other causes of inappropriate detection of atrial tachyarrhythmias or AF**
430 (ungraded consensus-based statement).
431

432 *Remark:* In patients with CIED detected AHRE a complete cardiological evaluation is indicated,
433 with 12-lead ECG, general assessment of clinical conditions and clinical risk stratification for
434 stroke using CHA₂DS₂VASc score.

435 *Remark:* There is no evidence in support or against prescription of oral anticoagulants in patients
436 at risk of stroke (intermediate to high risk according to CHA₂DS₂VASc) who present with AHREs,
437 corresponding to atrial tachyarrhythmias/AF at electrograms assessment of less than 24 hours
438 duration.
439

440 43. **In patients with AF, we suggest prescription of oral anticoagulants as a result of an**
441 **individualized clinical assessment taking into account overall AHRE burden (in the range of**
442 **hours rather than minutes) and specifically, the presence of AHRE > 24 hours, individual stroke**
443 **risk (using CHA₂DS₂VASc), predicted risk benefit of oral anticoagulation and informed patient**
444 **preferences** (ungraded consensus-based statement).
445

446 *Remark:* In patients with CIED detected AHRE continued patient follow-up is recommended,
447 preferentially combining clinical follow up with remote monitoring of the CIED or else more
448 frequent device interrogation than standard for CIED follow-up, to detect the development of
449 clinical AF (symptomatic or asymptomatic), to monitor the evolution of AHRE or AF burden and
450 specifically the transition to AHRE lasting more than 24 hours, onset or worsening of heart
451 failure, or any clinical change that might suggest a change in clinical profile or clinical conditions.
452

453 44. **For patients with atrial flutter, we suggest that antithrombotic therapy decisions follow the**
454 **same risk-based recommendations as for AF.** (ungraded consensus-based statement).
455

456 45. **For women receiving OAC for prevention of stroke/TE in AF who become pregnant, we suggest**
457 **discontinuation of OAC with a VKA between weeks 6 and 12 and replacement by LMWH twice**
458 **daily (with dose adjustment according to weight and target anti-Xa level 4-6 hours post-dose**
459 **0.8-1.2 U/mL), especially in patients with a warfarin dose required of >5 mg/day (or**
460 **phenprocoumon >3 mg/day or acenocoumarol >2mg/day). OAC should then be discontinued**
461 **and replaced by adjusted-dose LMWH (target anti-Xa level 4-6 hours post-dose 0.8-1.2 U/mL)**
462 **in the 36th week of gestation** (ungraded consensus-based statement).
463

464 46. **For women on treatment with long-term vitamin K antagonists who are attempting pregnancy**
465 **and are candidates for LMWH substitution, we suggest performing frequent pregnancy tests**
466 **and use LMWH instead of VKA when pregnancy is achieved rather than switching to LMWH**
467 **while attempting pregnancy** (ungraded consensus-based statement).
468

469 47. **For pregnant women, we suggest avoiding the use of NOACs** (ungraded consensus-based
470 statement) .

471 *Remark:* For women on treatment with a NOAC we suggest switching to vitamin K antagonists,
472 rather than switching to LMWH while attempting pregnancy

- 473
474 48. **For lactating women using warfarin, acenocoumarol, or UFH who wish to breastfeed, we**
475 **suggest continuing the use of warfarin, acenocoumarol, LMWH or UFH** (ungraded consensus-
476 based statement)
477
- 478 49. **For breast-feeding women, we suggest alternative anticoagulants rather than NOACs**
479 (ungraded consensus-based statement).
480
481
- 482 50. **For mild CKD (Stage II, CrCl 60-89 ml/min), we suggest that oral anticoagulation clinical**
483 **decision making and treatment recommendations match that of patients without CKD** (weak
484 recommendation, very low quality evidence).
485
- 486 51. **For moderate CKD (Stage III, CrCl 30-59 ml/min), we suggest oral anticoagulation in patients**
487 **with a CHA₂DS₂VASc \geq 2 with label-adjusted NOACs or dose adjusted vitamin K antagonists**
488 (Weak recommendation, very low quality evidence).
489 *Remark: With VKA, good quality anticoagulation control (TTR>65-70%) is recommended.*
490
- 491 52. **In severe non-dialysis CKD (Stage IV CrCl 15-30), we suggest using VKAs and selected NOACs**
492 **(rivaroxaban 15mg QD, apixaban 2.5mg bid, edoxaban 30mg QD and (in USA only) dabigatran**
493 **75mg bid) with caution, based on pharmacokinetic data** (ungraded consensus-based
494 statement).
495
- 496 53. **In end-stage renal disease (CrCl < 15 or dialysis-dependent), we suggest that individualized**
497 **decision-making is appropriate** (ungraded consensus-based statement).
498
- 499 54. **In end-stage renal disease (CrCl < 15 or dialysis-dependent , we suggest using well managed**
500 **VKA with TTR>65-70%** (ungraded consensus-based statement).
501
502 *Remark: NOACs should generally not be used, although in USA, apixaban 5mg bid is approved for*
503 *use in AF patients receiving hemodialysis*
504 *Remark: In patients with CKD who initiate OAC, concomitant antiplatelet therapy including low-*
505 *dose aspirin is likely to substantially elevate bleeding risk and should be used very judiciously.*
506
- 507 55. **In patients with AF at high risk of ischaemic stroke who have absolute contraindications for**
508 **OAC, we suggest using LAA occlusion** (Weak recommendation, low quality evidence).
509
510 *Remark: When taking into account LAAO as a potential option, the risk of bleeding related to*
511 *antiplatelets agents that need to be prescribed in the first months has to be considered and the*
512 *possibility to use NOACs.*
513
- 514 56. **In AF patients at risk of ischaemic stroke undergoing cardiac surgery, we suggest surgical**
515 **exclusion of the LAA for stroke prevention, but the need for long term OAC is unchanged**
516 (Weak recommendation, low quality evidence).
517
- 518 57. **In AF patients taking warfarin without high risk of thromboembolism or who do not have a**
519 **mechanical valve, we suggest pre-operative management without bridging** (Weak
520 recommendation, low quality evidence).
521
- 522 58. **In AF patients on antithrombotic prophylaxis with warfarin with a high risk of**
523 **thromboembolism or with a mechanical valve, we suggest pre-operative management with**
524 **bridging** (Weak recommendation, low quality evidence).

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59. **In AF patients on antithrombotic prophylaxis with a NOAC, we suggest pre-operative management without bridging** (Weak recommendation, low quality evidence).

60. **In AF patients who have previously refused OAC, we suggest reinforcing educational messages at each contact with the patient and revisit OAC treatment decisions** (ungraded consensus-based statement).

Remark: Patient and physician treatment objectives often differ significantly and it is important to elicit from the patient what outcomes of OAC treatment are important to them.

Remark: Explain the risk of stroke and benefit/risks of treatment in terms the patient can understand and signpost the patient to appropriate educational resources (see e-Table 25).

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with an increasing prevalence and incidence with age. In adults aged >40 years, there is a 1 in 4 lifetime risk of developing AF, with incident AF commonly related to various associated cardiovascular and non-cardiovascular risk factors. AF without associated valvular heart disease (so-called 'non-valvular AF') is associated with a five-fold increase in stroke risk (approximately 5%/year), but this risk is dependent on the presence of various stroke risk factors¹. Many of the risk factors leading to incident AF are also risk factors for ischemic stroke, and the promotion of an integrated or holistic approach to AF management is needed, incorporating stroke prevention, addressing symptoms and risk factor management².

Stroke prevention is the principal priority in the holistic approach to AF management¹. Even since the last edition of the ACCP guidelines published in 2012³, there have been substantial developments in AF thromboprophylaxis, whether with regard to risk assessment, antithrombotic drugs or non-drug approaches.

It is clear that AF should not be considered in isolation, at the stage of detection, prevention or treatment. For example, the majority of deaths in individuals with AF are from cardiac causes, including HF, whereas stroke and bleeding represent a small subset of deaths, yet most interventions focus on stroke prevention⁴. Thus, a more holistic approach is needed to take comorbidities and cross-disease sequelae of AF, bridging primary and secondary care².

Aside from stroke prevention ('Avoid Stroke, use Anticoagulants'), AF management requires patient centered and symptom directed decisions on rate or rhythm control ('Better symptom management') as well as 'Cardiovascular and other risk factor, and lifestyle management'². The latter includes addressing risk factors (cardiac ischemia, heart failure, hypertension, sleep apnea, diabetes, etc.) and lifestyle (obesity, alcohol excess, stimulants etc.). This simple ABC approach (Atrial fibrillation Better Care approach) would simplify an integrated approach to AF management in a holistic manner. (Figure 1)²

566 This guideline focuses on stroke prevention and begins with a brief discussion of the methods used
567 to develop these guidelines and the recommendations for antithrombotic therapy in patients with
568 AF. Next, we provide our treatment recommendations, divided into the following sections:

- 569 • Stroke and bleeding risk assessment
- 570 • Antithrombotic therapy in patients with AF in general (includes patients with permanent,
571 persistent, or paroxysmal AF [PAF])
- 572 • Antithrombotic therapy in patients with AF in special situations:
 - 573 ○ Managing Bleeding
 - 574 ○ Antithrombotic therapy for patients with AF undergoing cardioversion
 - 575 ○ Acute coronary syndrome (ACS) and stenting
 - 576 ○ Stable coronary artery disease
 - 577 ○ Rhythm control and electrophysiological procedures
 - 578 ○ Acute ischemic stroke, ICH, ESUS, carotid disease
 - 579 ○ AHRE on devices
 - 580 ○ Chronic atrial flutter
 - 581 ○ Pregnancy
 - 582 ○ Chronic Kidney Disease
 - 583 ○ Valvular heart disease

584 The article ends with a discussion of practical and patient-centered issues as well as suggestions for
585 future research.

586

587 **METHODS**

588 **Expert Panel Composition**

589 The chair of the panel (G.Y.H.L.) was appointed and subsequently reviewed and approved by CHEST's
590 Professional Standards Committee (PSC). Panelists were nominated by the chair based on their
591 expertise relative to potential guideline questions.

592 **Conflicts of Interest**

593 All panel nominees were reviewed for their potential conflicts of interest (COI) by CHEST's PSC. After
594 review, nominees who were found to have no substantial COIs were approved, whereas nominees
595 with potential intellectual and financial COIs that were manageable were "approved with
596 management". Panelists approved with management were prohibited from participating in
597 discussions or voting on recommendations in which they had substantial COIs. A grid was created
598 listing panelists' COIs for each recommendation for use during voting. Of note, the chair (G.Y.H.L.)
599 recused himself from any voting on recommendations. The COI grid can be found in e-Table 1.

600 **Formulation of Key Questions**

601 Table 1 specifies the clinical questions being addressed in this article (in PICO [population,
602 intervention, comparator, outcomes] format) and the types of studies included.

603 Consistent with the 9th edition of the guideline, the outcomes most relevant to patients with AF
604 include death, nonfatal stroke, systemic embolism, nonfatal major extracranial bleeding, and the
605 burden and lifestyle limitations associated with outpatient antithrombotic therapy.³ To facilitate
606 decision-making, the term 'stroke' in this guideline includes both ischemic stroke and hemorrhagic
607 stroke, which together with systemic embolism was the principal outcome in most stroke prevention
608 trials. Additional considerations were all-cause and cardiovascular mortality. For bleeding
609 outcomes, we focused on major bleeding, which was the principal safety outcome in most stroke
610 prevention trials. Major bleeding included intracranial bleeding, the most severe and disabling form
611 of anticoagulant-related bleeding.

612

613

614 **Literature Searches and Study Selection**

615 To inform our guideline development, we searched for relevant articles published since the last
616 formal literature search performed for the Antithrombotic and Thrombolytic Therapy: American
617 College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition) which were
618 published in 2012³. Searches were also conducted specifically for existing guidelines and systematic
619 reviews. In cases which existing, good quality systematic review(s) were retrieved, the results of the
620 review informed our recommendations.

621 Specifically, for literature regarding the assessment of stroke risk in patients with AF, we searched
622 MEDLINE via PubMed and the Cochrane Library for articles published from October 2009, to October
623 2017 using the search terms "atrial fibrillation," "atrial flutter," "risk assessment," "risk factors," "risk
624 stratification," "stroke," and "thromboembolism."

625 For literature regarding prevention of stroke and thromboembolism in patients with AF, we searched
626 MEDLINE via PubMed and the Cochrane Library for articles published from January 1, 2007, to
627 October 2017 using the search terms "coumarins," "warfarin," "dicumarol," "phenprocoumon,"
628 "acenocoumarol," "fondaparinux," "idraparinux," "aspirin," "triflusal," "indobufen," "dabigatran,"
629 "ximelagatran," "rivaroxaban," "apixaban," "ticlopidine," "clopidogrel," "catheter ablation,"
630 "watchman," "PLAATO," "cardioversion," "atrial fibrillation," and "atrial flutter."

631 Titles and abstracts of the search results were reviewed independently and in parallel to identify
632 potentially relevant articles based on the inclusion and exclusion criteria from the PICO elements.
633 Discrepancies were resolved by discussion. Studies deemed eligible then underwent a second round
634 of full-text screening following the same methodology used during title/abstract review. Important
635 data from each included study were then extracted into structured evidence tables.

636 **Risk of Bias Assessment**

637 The methodologist assessed the risk of bias in all included studies. The Cochrane Risk of Bias tool
638 was used to assess the risk of bias for randomized controlled trials⁵ and the Risk of Bias in Non-
639 randomized Studies of Interventions (ROBINS-I) tool to evaluate risk of bias for observational

640 studies.⁶ In cases in which existing systematic reviews were available, we used the Documentation
641 and Appraisal Review Tool to assess methodological quality.⁷

642 **Meta-Analysis**

643 When individual studies were available or an existing meta-analysis needed to be updated, we used
644 the Cochrane Collaboration Review Manager, version 5.2⁸ to pool the results across individual
645 studies. We used a random-effects model and the method of DerSimonian and Laird to pool the
646 individual estimates.⁹ Relative risk (RR) was used to report the results for dichotomous outcomes
647 and mean difference (MD) for continuous outcomes with accompanying 95% confidence intervals
648 (CI). Statistical heterogeneity of the pooled results was assessed using the Higgins' I^2 and the Chi-
649 square tests. A Higgins' I^2 value of $\geq 50\%$ or Chi-square $p < 0.05$ was considered to represent significant
650 heterogeneity.

651 **Assessing the Overall Quality of the Evidence**

652 The overall certainty (quality) of the evidence was assessed for each critical or important outcome of
653 interest using the GRADE approach.¹⁰ Evidence profiles were created using the Guideline
654 Development Tool (GDT), which categorized the overall quality of the body of evidence into one of
655 four levels: high, moderate, low, or very low.

656 **Drafting Recommendations**

657 The panel drafted and graded recommendations based on the results of the meta-analyses and
658 evidence profiles. Recommendations were graded according to CHEST's grading system which uses
659 the GRADE approach (Table 2).^{11,12} The recommendations were either "strong" or "weak" according
660 to this approach. Strong recommendations use the wording "we recommend" and weak
661 recommendations use the wording "we suggest". The implications of the strength of
662 recommendation are summarized in e-Table 2.

663 In instances in which there was insufficient evidence, but a clinically relevant area was felt to require
664 a guiding comment, a weak suggestion was developed and "Ungraded Consensus-Based Statement"
665 replaced the grade.¹³

666 In developing our treatment recommendations, we attempted to account for patient values and
667 preferences regarding these outcomes, and had two patient advocates (MTH and DAL) who
668 participated in the panel discussion, and specifically addressed patient-centered issues.

669

670 **Consensus Development**

671 All drafted recommendations and suggestions were presented to the panel in an anonymous online
672 voting survey to reach consensus and gather feedback. Panelists were requested to indicate their
673 level of agreement on each statement based on a five-point Likert scale derived from the GRADE
674 grid.¹⁴ Panelists with COIs related to the individual recommendations recused themselves from
675 voting on those statements). Of note, the chair (G.Y.H.L.) recused himself from any voting on
676 recommendations. According to CHEST policy, each recommendation and statement required a 75%

677 voting participation rate and at least 80% consensus to “pass”. Any recommendation or suggestion
678 that did not meet these criteria was revised by the panel based on the feedback, and a new survey
679 that incorporated those revisions was completed.

680 **Peer Review Process**

681 Reviewers from the GOC, the CHEST Board of Regents, and the *CHEST* journal reviewed the methods
682 used and the content of the manuscript for consistency, accuracy and completeness. The manuscript
683 was revised according to feedback from the reviewers.

684

685 **STROKE RISK IN ATRIAL FIBRILLATION**

686 The extensive data on epidemiological burden of stroke associated with AF and well as the
687 pathophysiology is detailed in the Online Supplement. It is beyond the scope of this document to
688 consider the epidemiology of all comorbidities in AF.

689

690 In summary, healthcare systems face increasing prevalence, incidence and lifetime risk of AF, which
691 is as high as 1 in 4 in contemporary studies in high-income settings¹⁵. Epidemiologic studies largely
692 represent Western countries and Caucasian populations¹⁶. However, reported prevalence varies
693 substantially by world region (see e-Figure 1) and with more rigorous screening methods to detect
694 AF.

695

696 Individuals with AF have increased risk of stroke (4-5 fold increase), heart failure (2-3 fold increase)
697 and mortality (2-fold increase) (see web Supplement 1.1). Patients with AF also experience higher
698 rates of morbidity, hospital admissions, as well as early dementia. The high AF-attributable risk of
699 stroke, especially in the elderly, is evident since at least one in 3 to 4 individuals with an ischemic
700 stroke, and over 80% of those with ischemic stroke of cardioembolic subtype, also have AF¹⁷. Overall,
701 non-white ethnicity shows evidence of association with lower risk of incident AF.

702

703 Several of the risk factors for incident AF are also risk factors for stroke in AF.¹⁸ Primary prevention
704 strategies for AF have not been conclusively proven in randomized trials, opportunistic screening is
705 the recommended strategy to detect AF at the population-level¹⁹. A systematic review of the
706 associations of 23 cardiovascular risk factors and incident AF including 20,420,175 participants and
707 576,602 AF events, respectively, found hypertension, obesity, taller height and coronary heart
708 disease showed consistent, direct associations with incident AF¹⁸. Ethnic differences in co-
709 morbidities in AF patients have been reported.²⁰⁻³⁶ Hypertension is the leading comorbid risk factor
710 and is equally distributed in different races. Coronary heart disease (CHD) seems more common in
711 Caucasians and the Middle East, than in Asians. The annual risk of AF-associated stroke in Asians is
712 higher than that in Caucasians^{37 28 29 38} and the risk of stroke may start to increase at a younger age
713 in Asians.³⁷

714

715 *Classification of AF*

716 AF is classified as paroxysmal (self-terminating within 7 days), persistent (continuous for >7 days),
717 long-standing persistent (continuous for >1 year), or permanent (chronic). AF becomes increasingly

718 persistent and resistant to therapy over time, perhaps due to the development of atrial fibrosis, as
719 well as other pathophysiological processes (e-Figure 2). AF and atrial flutter frequently co-exist, and
720 share similar risk factors for arrhythmia development and stroke risk³⁹. Lone AF is a low risk patient
721 group that is a diagnosis of exclusion, after ensuring no comorbidity risk factors are evident⁴⁰.
722 “Lone” atrial flutter (without any recognizable underlying disease), like lone AF, is also rare – only 2%
723 of atrial flutter patients⁴¹. The role of anticoagulation in atrial flutter has not been assessed in clinical
724 trials, but since individuals with atrial flutter often have concomitant AF or are at increased risk of
725 developing AF, the risk of stroke and thromboembolism is assumed to be the same and the same risk
726 stratification approaches are recommended.

727

728 **Risk factors for ischemic stroke.**

729

730 *Clinical risk factors for ischemic stroke in AF*

731 Although AF is an independent risk factor for stroke, not all patients with AF have equal stroke risk.
732 In order to correctly assess the risk of stroke in order to inform anticoagulation, risk prediction or
733 stratification tools have been developed, based on the risk factors most strongly and consistently
734 associated with stroke.

735

736 A systematic review of stroke risk factors found that prior stroke or transient ischemic attack (15/16
737 studies positive, risk ratio [RR] 2.86), hypertension (11/20 studies positive, RR 2.27), aging (9/13
738 studies positive, RR 1.46 per decade increase), structural heart disease (9/13 studies positive, RR 2.0)
739 and diabetes (9/14 studies positive, RR 1.62) were independent predictors of stroke. Supportive
740 evidence was found for sex (8/22 studies positive, RR 1.67), vascular disease (6/17 studies positive,
741 RR 2.61) and heart failure (7/18 studies positive, RR 1.85)⁴². Non-paroxysmal atrial fibrillation is
742 associated with a highly significant increase in thromboembolism (multivariable adjusted hazard
743 ratio 1.384, 95% CI 1.19-1.61, $P < 0.001$)⁴³.

744

745 In individuals with HF, AF is associated with worse prognosis than sinus rhythm^{44,45}. HF is an
746 independent predictor of stroke/TE, mortality and other clinical outcomes in individuals with AF,
747 compared with no HF⁴⁶. Moreover, HF is a predictor of development of AF and has been
748 incorporated in tools for risk prediction of incident AF⁴⁷. All-cause mortality is higher in AF patients
749 with HFrEF (HF with reduced ejection fraction) compared to HFpEF (HF with preserved ejection
750 fraction) (RR 1.24, 95% CI 1.12-1.36, $p < 0.001$), although stroke risk (RR 0.85, 0.70-1.03, $p = 0.094$) and
751 heart failure hospitalization (RR 1.21, 95% CI 0.96-1.53, $p = 0.115$) are not significantly different⁴⁸.

752

753 Chronic kidney disease (CKD) is an independent predictor of risk of stroke/thromboembolism. AF
754 patients with estimated glomerular filtration rate < 60 mL/min compared with those with estimated
755 glomerular filtration rate ≥ 60 mL/min have increased risk of stroke/thromboembolism (RR 1.62, 95%
756 CI, 1.40-1.87; $p < 0.001$), with a 0.41% (0.17%-0.65%) annual increase in rate for a 10 mL/min
757 decrease in renal function⁴⁹. The risk is higher in individuals requiring renal replacement therapy (HR
758 1.83; 95% CI, 1.57 to 2.14; $p < 0.001$). There is also increased risk of bleeding in individuals with AF
759 and CKD, compared with those without CKD.⁵⁰ Conversely, AF is associated with increased risk of
760 chronic kidney disease (CKD) (RR 1.64, 1.41-1.91)⁵¹. The clinical relevance of renal function is not
761 only for risk prediction, but also for choice of anticoagulation and other therapies⁵²⁻⁵⁴ (See Atrial
762 Fibrillation and Chronic Kidney Disease section).

763

764 Over the last decade, rigorous detection strategies have shown that prevalence of AF in cryptogenic
765 stroke is likely to be as high as 30%⁵⁵. A systematic review and meta-analysis after transient ischemic
766 attack (TIA) has shown a pooled AF detection rate for all methods of 4% (95% CI: 2-7%)⁵⁶.

767

768 *Echocardiographic risk factors*

769 The role of echocardiography in evaluation before cardioversion or ablation, and in predicting the
770 presence of left atrial (LA) appendage thrombus is dealt with in sections 'Cardioversion' and
771 'Catheter or Surgical Ablation, Electrophysiological Procedures'. There may also be a role in
772 evaluating thromboembolic risk stratification to select appropriate antithrombotic therapy. e-Table
773 4 summarizes major studies which have shown an association between transthoracic
774 echocardiographic (TTE) parameters and ischemic stroke. However, there are very limited data to
775 suggest that there would be any incremental clinical benefit in risk prediction, and moreover there is
776 no evidence that management (in terms of OAC) would be changed⁵⁷.

777

778 Nevertheless, the most consistent independent predictor of ischemic stroke on TTE is the presence
779 of moderate-severe LV systolic dysfunction. In patients undergoing transesophageal
780 echocardiography (TEE), LA appendage thrombi⁵⁸ and LA spontaneous echo contrast⁵⁹ are both
781 associated with increased thromboembolism, as well as the presence of low LA appendage velocities
782 and complex aortic plaque; however, the same limitations as for TTE parameters apply⁵⁷.

783

784 *Biomarkers*

785 e-Table 5 summarizes important studies involving currently available biomarkers ('biological
786 markers') that have shown associations with stroke and thrombosis in AF, but both study design and
787 scale of the studies limit possible conclusions. Caveats with the use of these biomarkers include the
788 inter- and intra- patient and assay variability, some have a diurnal variation and can be highly
789 influenced by associated comorbidities and drug therapies. Many biomarkers are non-specific for a
790 particular endpoint, and can be equally predictive not only of stroke but bleeding, death,
791 hospitalization, heart failure etc., as well as non-cardiac conditions e.g., glaucoma.

792

793 The importance of biomarkers probably lies in the 'very low risk' strata of clinical scores (e.g.,
794 CHA₂DS₂VASc= 0-1 group) where they may influence the decision to anticoagulate, yet there are
795 limited data available in these patients. There are several other hurdles including variations in
796 availability in healthcare systems, biomarker assays, access to laboratories, biomarkers diurnally, by
797 comorbidities and by anticoagulation and other therapies. For these reasons, the clinical application
798 of biomarkers in management of AF is unlikely to be significant.

799

800 *Other potential novel risk factors for ischemic stroke in AF*

801 As with established risk factors, novel risk factors may improve prediction of thromboembolic risk in
802 AF patients, where current risk scores are suboptimal⁶⁰. These novel factors include clinical risk
803 factors (e.g., burden of AF), serum biomarkers (e.g., NT-proBNP), imaging (e.g., left atrial fibrosis on
804 cardiac MRI) and echocardiography (e.g., left atrial volume index and longitudinal strain). However,
805 these factors are currently neither proven to significantly add to risk prediction, nor likely to
806 influence the decision to anticoagulate.

807

808

809 **Risk stratification for stroke and thromboembolism in AF**

810

811 A comparison of features included in various published stroke risk stratification schemes in AF is
812 shown in e-Table 6. A summary of studies comparing the various stroke risk stratification schema is
813 available in e-Table 7. The risk stratification scheme commonly used in many guidelines is the
814 CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes,
815 stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial
816 infarction (MI), peripheral arterial disease (PAD), or aortic plaque], age 65-74 years, sex category
817 [female]) score¹.

818

819 All risk schemes based on clinical risk factors have broadly similar predictive value for 'high risk'
820 patients who sustain stroke and TE events (all c-indexes approx. 0.60-0.65). Adding more and more
821 clinical variables and complexity (i.e., simple versus more complex clinical risk scores) would only
822 modestly increase the c-index to approximately 0.65-0.70. Many score comparisons focus on
823 identification of 'high risk' and do not focus on 'low risk end of the spectrum' and so are not helpful
824 for decision-making on whether to anticoagulate or not.

825

826 Event rates per score point varies according to study setting, ethnicity, cohort, and community vs.
827 hospitalized population etc (as might be expected)⁶¹. Also, reported events depends on use of highly
828 selected clinical trial cohort vs. 'real world' unselected, and anticoagulated vs. non-anticoagulated
829 patients⁶². Mortality rates from observational cohorts may also include fatal strokes as
830 postmortems are not mandated, outcomes are non-adjudicated (as in clinical trials) and cerebral
831 imaging is not performed. Analytical methodology matters and outcomes depend on thresholds for
832 treatment, varying risk profile during the study (which this does not remain static) and statistical
833 analysis methods⁶³. Some analyses which exclude patients on anticoagulants are flawed by
834 'conditioning on the future' methodology, and follow-up can be dependent on continuation in a (US)
835 healthcare plan.

836

837 Ethnic differences are also evident in stroke risk related to AF. In a Taiwanese cohort, the risk of
838 stroke was 1.78%/year in patients aged 50-64 years and a CHA₂DS₂-VASc 0.⁶⁴ The risk exceeds the
839 threshold for OAC use for stroke prevention. A modified CHA₂DS₂-VASc (mCHA₂DS₂-VASc) score has
840 been proposed, assigning one point for patients aged 50 to 74 years.⁶⁵ The mCHA₂DS₂-VASc score
841 performed better than CHA₂DS₂-VASc score in predicting ischemic stroke assessed by C indexes and
842 net reclassification index. For patients having an mCHA₂DS₂-VASc score of 1 (males) or 2 (females)
843 because of the resetting of the age threshold, use of warfarin was associated with a 30% lower risk
844 of ischemic stroke and a similar risk of ICH compared with no-treatment. Net clinical benefit analyses
845 also favored the use of warfarin in different weighted models. These findings suggest that the age-
846 based treatment threshold for stroke prevention may need to be reset in East Asians.⁶⁵

847

848 Adding biomarkers would (statistically) improve prediction but c-indexes are still approximately
849 0.65-0.70. Recent studies in real world cohorts do not support the clinical usefulness of biomarker-
850 based scores over clinical risk scores such as the CHA₂DS₂-VASc score. The use of biomarkers have to
851 balance the assay availability, lab variability, costs and added complexity and lower practicality for
852 everyday use. Also, many biomarker studies are based on anticoagulated highly selected clinical

853 trial cohorts, with all included subjects already in the high risk group (CHA₂DS₂VASc or CHADS₂ score
854 of 2 or greater). There are few/no studies on non-anticoagulated AF patients, to ascertain the true
855 impact of biomarkers on (non-anticoagulation treated) stroke rates. Current studies do not inform
856 whether the biomarkers will discriminate/identify low risk in lower/intermediate risk patients who
857 are not anticoagulated.

858
859 Rather than focus on identifying 'high risk', the focus should be on initially identifying 'low risk'
860 patients. A 'low risk' categorization by the CHA₂DS₂-VASc (0 in males and 1 in females) consistently
861 identifies low risk patients, with event rates around 1%/year or under, notwithstanding the possible
862 need to re-categorize the age 65-74 criterion in Asians⁶⁵.

863
864 The majority of published studies and systematic reviews suggest that the CHA₂DS₂VASc score is
865 generally better than CHADS₂, ATRIA and CHADS₆₅ in identifying 'low risk' patients, although the
866 proportion of the population assigned as low risk is small. However, there are conflicting data in
867 different cohorts for performance of the ATRIA score (UK CPRD and Swedish cohorts vs Danish and
868 Taiwan cohorts). Differences between the ATRIA and CHA₂DS₂VASc disappear when cut-points are
869 optimized for stroke risk of the cohort. There are discrepancies between individual studies on the
870 relative performance of ATRIA and CHA₂DS₂VASc scores in identifying low risk patients, but the
871 CHA₂DS₂VASc score is easier to calculate.

872
873 Rather than using risk scores in a categorical manner - recognizing the various limitations of scores
874 to predict 'high risk' patients that sustain events - and given that for each risk strata or given risk
875 score point, we recognized there is wide variation in reported event rates based on reported study
876 clinical setting, patient population, ethnicity etc. Notwithstanding that the default should be stroke
877 prevention for all AF patients unless deemed to be 'low risk', the focus should be to use scores to
878 initially identify 'low risk' patients who do not need antithrombotic therapy, rather than focus on
879 identification of 'high risk' patients. Prior guidelines have also opted for the CHA₂DS₂VASc score to
880 define a low risk group.

881
882 The 'C' in CHA₂DS₂-VASc refers to recent decompensated heart failure, irrespective of the ejection
883 fraction (thus including heart failure with reduced ejection fraction (HFrEF) or preserved ejection
884 fraction (HFpEF)) or the presence of moderate-severe LV systolic impairment on cardiac imaging,
885 whether symptomatic or asymptomatic. The 'H' refers to history of hypertension or uncontrolled
886 blood pressure, while 'S' refers to stroke, systemic embolism or a confirmed diagnosis of transient
887 ischemic attack (TIA). 'V' refers to complicated vascular disease, including myocardial infarction or
888 peripheral artery disease, or if performed, the presence of complex aortic plaque on TEE. Female
889 sex (Sc criterion) is only relevant as a risk modifier if age>65 or additional associated risk factors are
890 present, given that at females age <65 with no other risk factors are not at excess stroke risk⁶⁶.
891 Stroke risk is also dynamic, and risk should be re-assessed at every patient contact. This was seen in
892 a study where the 'delta CHA₂DS₂VASc score', representing the change in stroke risk between
893 between baseline and followup) was the best predictor for ischaemic stroke⁶⁷.

894
895 A stepwise approach to thromboprophylaxis would allow initial identification of low risk using
896 CHA₂DS₂VASc (Step 1), following which stroke prevention can be offered to all others (Step 2)

irrespective of stroke point score or biomarkers used. This would approach uses stroke risk scores in a reductionist manner to aid decision-making, and balances simplicity and practicality (and costs).

Recommendations

1. For patients with AF, including those with paroxysmal AF, stroke risk should be assessed using a risk factor based approach, rather than an categorisation into low, moderate/high risk strata. We recommend use of the CHA₂DS₂VASc as a simple clinical based stroke risk score to initially identify 'low stroke risk' patients that should not be offered antithrombotic therapy to prevent stroke and reduce mortality (Strong recommendation, moderate quality evidence).

Remark: Low risk patients are generally those age<65 and 'lone AF' irrespective of sex (this includes those with a CHA₂DS₂VASc score=0 in males, or 1 in females).

2. Subsequent to this initial step, for patients with AF, including those with paroxysmal AF, stroke prevention should be offered to those AF patients with one or more non-sex CHA₂DS₂VASc stroke risk factors (score of ≥1 in a male or ≥2 in a female) (Strong recommendation, moderate quality evidence).

Remark: Consideration of other less established clinical stroke risk factors, imaging (cardiac or cerebral) or biomarkers (urine, blood or genetics) may refine risk stratification based on simple clinical factors. A complex risk schema using a variety of such data that could accurately place more patients in the low risk stratum not requiring anticoagulants than current simple clinically-based scores (personalised medicine) should be the goal of future research, but it will be very difficult to find non-anticoagulated patient cohorts for prospective validation.

BLEEDING RISK IN ATRIAL FIBRILLATION

Observational studies

The rates of major bleeding on VKA among observational cohorts are shown in e-Table 8 and demonstrate highly variable rates, ranging from 1.4%/year^{68,69} to 10.4%/year.⁷⁰ Nevertheless, there is significant heterogeneity between the study population characteristics, the inclusion of inception versus 'experienced' OAC cohorts, significant disparity in the exposure period (follow-up) and differences in the definitions of major bleeding employed. In addition, information on the specific risks of bleeding of the individual cohorts, using a validated bleeding risk score are lacking, the definitions of major bleeding were often not provided and the quality of anticoagulation, such as TTR, is generally lacking. Therefore, direct comparison of the rates of major bleeding on VKA between observational cohorts and with RCTs is problematic.

Clinical trials

The definitions of major bleeding are available in most clinical trials, especially in the NOACs trials where ISTH definitions were used.⁷¹ Before the NOAC era, the rates of major bleeding due to VKA were generally in the range of 1% to 3% per year (e-Table 9). In the 5 NOAC trials,⁷²⁻⁷⁶ the annual

939 rates of major bleeding of warfarin were between 3% to 4% (Table 2). Data from NOACs trials are
940 more reliable, because patients were randomized to treatment, the majority were double-blinded
941 and the quality of anticoagulation (such as TTR) was generally better than observational studies. The
942 risk of major bleeding on NOACs, especially the low-dose regimen (dabigatran 110 mg and edoxaban
943 30 mg), was generally lower than that on warfarin, except in the ROCKET AF trial.⁷³

944

945 **Risk factors for bleeding with NOAC, VKA and antiplatelet therapy**

946

947 Numerous risk factors for bleeding among AF patients receiving antithrombotic therapy have been
948 identified and incorporated into bleeding risk scores (see Section on Bleeding Risk Score). Bleeding
949 risk varies from person to person depending on their pre-existing comorbidities, current
950 antithrombotic regimen and adherence, concomitant medication, and lifestyle choices. Many of
951 these factors cannot be altered but some are modifiable or potentially modifiable (see Figure 2). In
952 order to reduce antithrombotic-treatment associated bleeding it is important to recognize that
953 bleeding risk is also dynamic and should be reassessed at every patient review. While modifiable
954 bleeding risk factors that can be changed or managed should clearly be addressed as part of a
955 holistic approach to AF patient assessment and management, non-modifiable bleeding risks are
956 important drivers of bleeding events when occurring synergistically with modifiable ones⁷⁷. An
957 approach to bleeding risk assessment solely based only on modifiable bleeding risk factors is an
958 inferior assessment strategy compared to use of a formal bleeding risk score⁷⁸⁻⁸⁰.

959

960 *Blood pressure control*

961 Good control of blood pressure is vital to reduce the risk of stroke and is essential to decrease the
962 risk of bleeding on antithrombotic therapy; adherence to current guidelines on the management of
963 hypertension should be followed.

964

965 *Anticoagulation control*

966 Among patients receiving VKA, maintenance of an INR in the therapeutic range (2.0-3.0) is essential.
967 The proportion of time spent in this range (TTR) should be at least 65% but the ultimate aim/target
968 should be 100% (see Optimal INR target range section). The risk of bleeding increases when the INR
969 exceeds 3.0, particularly for ICH risk when INR >3.5.⁸¹⁻⁸⁶

970

971 INR control can potentially be improved by more frequent monitoring and review of factors
972 influencing INR control (diet-, alcohol-, and drug-interactions). There is evidence that improving
973 patient education about INR control,⁸⁷ INR management by dedicated anticoagulation clinics with
974 experienced personnel,⁸⁸⁻⁹⁰ and self-monitoring/self-management in selected patients⁹¹ can increase
975 TTR. Increasing patient's awareness of the importance of OAC medication adherence and the
976 potential bleeding risks associated with over-dose are also essential to minimize bleeding
977 complications.

978

979 *Concomitant medication pre-disposing to bleeding*

980 Non-essential use of concomitant anti-platelet drugs and NSAIDs should be avoided since these
981 medications increase the risk of bleeding in patients receiving OAC. Where concomitant anti-
982 platelet therapy is necessary (i.e. post-coronary stent implantation), the duration of combination
983 OAC and anti-platelet drugs should be kept to the minimum.⁹² Since anti-platelet drugs/NSAIDs are

984 widely available over-the-counter, patients need to be made aware of the bleeding risk associated
985 with their use in combination with OAC.

986

987 *Alcohol intake*

988 Excessive alcohol intake (chronic or binge-drinking) increases the risk of bleeding predominantly due
989 to the risk of trauma, but in chronic alcohol abuse through poor medication adherence, hepatic and
990 variceal disease. OAC should not initiated among patients consuming alcohol in excess >14U/week.
991 There is no clear definite threshold where bleeding risk is increased. Patients also need to be made
992 aware of the potential dangers associated with excessive alcohol consumption in combination with
993 OAC/antithrombotic therapy.

994

995 *Lifestyle factors*

996 Avoidance of work and/or leisure activities that have the potential to cause serious trauma (e.g.
997 contact sports, rock-climbing, occupations working at height or operating heavy machinery) should
998 be advised.

999

1000 *Bridging periods off anticoagulation*

1001 Interruption of OAC should be avoided to reduce stroke risk since the majority of cardiovascular
1002 procedures (e.g., pacemaker implantation or percutaneous coronary intervention) can be safely
1003 performed on OAC. Bridging (that is, stopping OAC and providing anticoagulation cover with
1004 heparin) should be used in patients with mechanical heart valves but does not appear to be
1005 otherwise advantageous.^{93,94}

1006

1007 *Appropriate choice of OAC*

1008 Choice of OAC should be made on an individual basis after stroke and bleeding risk assessment and
1009 discussion with the patient. Before a NOAC is initiated, the patient's age, body weight and renal
1010 function should be considered to allow for appropriate dose adaptation where necessary.

1011

1012 *Falls risk and cognitive impairment*

1013 In frail patients and those at high risk of falls an individual risk assessment needs to be undertaken
1014 prior to OAC initiation. In cases where the risk is that of mechanical falls, strategies to improve
1015 walking/reduce risk of tripping should be explored (i.e. walking aids, appropriate footwear, home
1016 review to remove trip hazards), whereas neurological assessment is warranted if falls are
1017 unexplained. The benefits of ischaemic stroke reduction generally outweigh the risk of harm from
1018 serious bleeding with OAC use; one estimate was that the patient would need to fall 295 times per
1019 year for the risk from falls to outweigh the benefits of stroke reduction⁹⁵. In patients with cognitive
1020 impairment or dementia, OAC should only be withheld if there is no available caregiver who can
1021 guarantee medication adherence.

1022

1023 *Reversal of biochemical anomalies*

1024 Patients with anemia or reduced platelet count or function should be treated where possible to
1025 improve their Hb or platelet count. Causes of renal impairment should be investigated and where
1026 possible reversed.

1027

1028 Patients with liver function abnormalities were generally excluded from the randomised trials, and
1029 especially where there is abnormal clotting tests, such patients may be at higher risk of bleeding on
1030 VKA, possibly less so on NOACs; in cirrhotic patients, ischaemic stroke reduction may outweigh
1031 bleeding risk^{96,97}.

1032

1033 **Bleeding risk assessment**

1034

1035 Since 2006, six risk scores have been developed and validated for the assessment of bleeding risk in
1036 AF populations.⁹⁸⁻¹⁰³ The number of risk factors included in the bleeding risk schemas varies
1037 considerably, from three¹⁰¹ to 12¹⁰³ and the score or weighting associated with each risk factor also
1038 differs (see Table 2).

1039

1040 Age and prior bleeding are included as risk factors in all six bleeding risk scores but different age cut-
1041 offs are utilized, with three scores employing age 75 years or older^{99,100,102} to indicate greater
1042 bleeding risk. Following age and prior bleeding, the most prevalent bleeding risk factors included in
1043 the scores are anemia,⁹⁹⁻¹⁰³ renal disease,^{98-100,102} hypertension^{99,103} or uncontrolled systolic blood
1044 pressure,⁹⁸ concomitant anti-platelets,^{98,102,103} and alcohol excess,^{98,100,103} and prior stroke^{98,100} or
1045 hepatic disease.^{98,100} A variety of other risk factors including cancer,¹⁰³ labile INR,⁹⁸ genetic factors,¹⁰⁰
1046 falls risks,¹⁰⁰ female sex,¹⁰³ diabetes mellitus,¹⁰³ and biomarkers¹⁰¹ are included only in one bleeding
1047 risk score. For a comprehensive review of bleeding risk factors in AF patients see Zulkifly et al.¹⁰⁴

1048

1049 The bleeding risk scores range in the simplicity of calculation and the cut-offs employed to indicate
1050 low, intermediate and high-risk of bleeding, and the prevalence of bleeding events reported in the
1051 validation cohorts (see Table 2).

1052

1053 **Table 2: Risk factors, risk categories and bleeding events in the validation cohorts** [partly reproduced with permission from Zukifly et al¹⁰⁴]

1054

Risk score	Risk factors (score for each factor)	Risk categories			Bleeding events in validation cohort (per 100 patient years)		
		Low	Intermediate	High	Low	Intermediate	High
ABC ¹⁰¹	Age(†); Biomarkers (†) (GDF-15 or cystatin C/CKD-EPI, cTnT-hs, & Hb); Previous bleed (†)	<1%	1-2%	>3%	0.62	1.67	4.87
ORBIT ¹⁰²	Age ≥75 (1); ↓Hb/Hct/anemia (2); Bleeding history (2); ↓ renal function (1); APT (1)	0-2	3	≥4	2.4*	4.7	8.1
ATRIA ⁹⁹	Anemia (3); Severe renal disease (3); Age ≥75 (2); Prior bleed (1); Hypertension (1)	0-3	4	5-10	0.83	2.41	5.32
HAS-BLED ⁹⁸	↑SBP (1); Severe renal/hepatic disease (1 each); Stroke (1); Bleeding (1); Labile INR (1); Age >65 (1); APT/NSAIDs (1); Alcohol excess (1)	0-1	2	≥3	1.02-1.13	1.88	≥3.74
HEMORR ₂ HAGES ¹⁰⁰	Hepatic/renal disease (1); Ethanol abuse (1); Malignancy; Age >75 (1); ↓Plt (1); Re-bleeding risk (2); ↑BP (1); Anemia (1); Genetic factors (1); ↑ falls risk (1); Stroke (1)	0-1	2-3	≥4	1.9-2.5	5.3-8.4	10.4-12.3
Shireman et al ¹⁰³	Age ≥70 (0.49); Female (0.31); Previous bleed (0.58); Recent bleed (0.62); Alcohol/drug abuse (0.71); DM (0.27); Anemia (0.86); APT (0.32)	≤1.07	>1.07/ <2.19	≥2.19	0.9% ^a	2.0% ^a	5.4% ^a

1055 APT = antiplatelet therapy; BP = blood pressure; cTnT-hs = Troponin T; DM = diabetes mellitus; GDF-15 = growth differentiation factor-15; Hb = hemoglobin;

1056 Hct = hematocrit; INR = international normalised ratio; Plt = platelet count or function; SBP = systolic blood pressure

1057 * bleeding event in original derivation cohort; ^a at 3 months; ↓ reduced/decreased; ↑ elevated/increased; † score for each variable in ABC score is based
1058 on a nonogram (see reference¹⁰¹)

1059

1060 Use of bleeding risk scores

1061 As seen in Table 2 above, there are multiple bleeding risk scores that have been proposed for
1062 bleeding risk stratification, with the HEMORR₂HAGES, HAS-BLED, ATRIA, ORBIT and ABC-bleeding
1063 derived and validated in AF populations¹⁰⁴. The risk factors included vary by scores [Table 2], and
1064 their derivation from selected clinical trial cohorts or 'real world' populations¹⁰⁴. Various validation
1065 studies have been summarized in e-Table 10.

1066 Unsurprisingly, stroke risk scores are also associated with bleeding, as stroke and bleeding risks
1067 correlate with each other. For example, higher CHADS₂ and CHA₂DS₂-VASc scores are also associated
1068 with greater bleeding risk, but the HAS-BLED score outperforms the CHADS₂ and CHA₂DS₂-VASc
1069 scores for predicting serious bleeding^{105,106}, which was also evident in the systematic review by Zhu
1070 et al¹⁰⁷. Composite risk scores that include stroke and bleeding endpoints have also been proposed
1071 but have not been shown to perform incrementally better over the individual scores^{108,109}. The
1072 bleeding risk scores in AF are also predictive of bleeding in non-AF populations, for example, in
1073 patients with ACS undergoing PCI-stenting¹¹⁰.

1074 Adding more clinical variables marginally improves the predictive value (at least statistically) but the
1075 c-indexes still remain approx. 0.6. The addition of biomarkers would all improve the c-indexes (to
1076 approx. 0.65) over scores based on clinical risk factors alone. Many of these risk scores have been
1077 derived from highly selected clinical trial cohorts, and biomarkers measured at baseline (or within a
1078 few months of study entry) then endpoints determined many years later. Biomarkers are also
1079 expensive, and may be subject to laboratory variability, inter-assay differences, diurnal variation and
1080 may change in individual patients depending on how risk factors and drug treatments change over
1081 time. Many biomarkers (e.g. troponin, natriuretic peptides, inflammatory markers, coagulation
1082 markers, etc.) are also predictive of stroke, bleeding, death, heart failure, hospitalization¹¹¹ and even
1083 non-cardiovascular conditions such as (for example, as in the case of GDF-15 used in the ABC-bleed
1084 score) glaucoma progression¹¹². The performance of biomarker-based scores in real world clinical
1085 practice (outside highly selected trial cohorts) has also been disappointing^{113,114}, given that baseline
1086 (or near-baseline) determination of biomarkers to predict bleeding risks after many years is
1087 bedeviled by the changing clinical risk profile of patient's risks as well as modification of risk factors.

1088 Given that modifiable bleeding risk factors should be addressed in all patients, the appropriate and
1089 responsible way to use a clinical risk score is to identify those patients at particularly high risk, for
1090 appropriate early review and follow-up (e.g. in 4 weeks, rather than 4-6 months) – and depending on
1091 the outcome of interest, to address the associated modifiable risk factors accordingly [Figure 2]. A
1092 high bleeding risk score is not a reason to withhold OAC, as the net clinical benefit is even greater in
1093 those patients with high bleeding risk.

1094 While bleeding risk is highly dynamic and depends on many potentially modifiable bleeding risk
1095 factors¹¹⁵, simply focusing on bleeding risk assessment using modifiable bleeding risk factors alone is
1096 an inferior strategy compared to using a validated bleeding risk score which has been designed to
1097 formally assess bleeding score⁷⁸⁻⁸⁰.

1098 A comparison of the different bleeding risk scores has been addressed in 2 systematic reviews and
1099 the studies are summarized in e-Table 10. As with stroke risk scores, most bleeding risk scores based
1100 on simple clinical risk factors only have modest predictive value for identifying the high risk patients
1101 that sustain events (c-indexes approx. 0.6).

1102 The systematic review by Caldera et al¹¹⁶ reported that the sensitivity, specificity and diagnostic odds
1103 ratio (DOR) were respectively 0.53 (0.52–0.54), 0.65 (0.65–0.65) and 2.11 (1.91–2.35) for HAS-BLED,
1104 and 0.27 (0.26–0.27), 0.89 (0.89–0.89) and 2.90 (2.77–3.04) for HEMORR₂HAGES. When comparing
1105 HAS-BLED with ATRIA, sensitivity, specificity, and DOR were respectively 0.41 (0.35–0.48), 0.78
1106 (0.76–0.79) and 2.22 (1.08–4.55) for HAS-BLED, and 0.23 (0.17–0.29), 0.91 (0.90–0.91) and 1.98
1107 (1.29–3.03) for ATRIA. They concluded that HAS-BLED, due to its sensitivity (compared to other
1108 scores) and ease to apply, is recommended for the assessment of AF patients' major bleeding risk.

1109 The systematic review by Zhu et al¹⁰⁷ (11 studies) found that discrimination analysis demonstrates
1110 that HAS-BLED has no significant C-statistic differences for predicting bleeding risk in the low (risk
1111 ratio [RR]: 1.16, 95% confidence interval [CI]: 0.63-2.13, $P = 0.64$) risk stratification but under
1112 predicts risk in the moderate (RR: 0.66, 95% CI: 0.51-0.86, $P = 0.002$) and high (RR: 0.88, 95% CI:
1113 0.70-1.10, $P = 0.27$) risk strata (e-Table 11). Zhu et al¹⁰⁷ concluded that the HAS-BLED score
1114 performed better than the HEMORR₂HAGES and ATRIA bleeding scores, but was superior to the
1115 CHADS₂ and CHA₂DS₂-VASc stroke scores for bleeding prediction. In a real world AF cohort, there was
1116 no long term advantage of the ABC-bleeding score over the HAS-BLED score, for predicting bleeding;
1117 in contrast, HAS-BLED was better in identifying those patients at low risk of bleeding¹¹⁴.

1118 Given that the patient pathway may include AF patients initially on no antithrombotic therapy,
1119 aspirin or anticoagulants, and the latter can include VKA or NOACs, a bleeding risk score needs to be
1120 applicable throughout the patient pathway. The HAS-BLED score has been validated in AF patients
1121 from clinical trial and non-trial cohorts, whether on no antithrombotic therapy, aspirin or
1122 anticoagulants, VKA or non-VKA anticoagulants, and is predictive of bleeding in AF and non-AF
1123 cohorts, and in different ethnic groups^{115,117,118}. It is also the only bleeding score predictive of
1124 intracranial bleeding¹¹⁹.

1125 The HAS-BLED score has also been shown to be similar or out-perform older bleeding scores, as well
1126 as more simple bleeding scores that include less clinical parameters. Amongst VKA-treated patients,
1127 the non-consideration of TTR would also mean that the HEMORR₂HAGES, ORBIT and ATRIA scores
1128 would all perform sub-optimally in VKA-treated patients^{120,121}. Finally, bleeding risk assessment is
1129 dynamic, and should be formally reassessed and recorded at every patient contact. Indeed, follow-
1130 up HAS-BLED or 'delta HAS-BLED score' was more predictive of major bleeding compared with
1131 baseline HAS-BLED or the simple determination of 'modifiable bleeding risk factors'⁷⁷.

1132 Recommendations

1133

1134 **3. For patients with AF, bleeding risk assessment should be performed in all patients with AF at**
1135 **every patient contact and should initially focus on potentially modifiable bleeding risk factors**
1136 **(Strong recommendation, low quality evidence).**

1137 *Remark:* Modifiable risk factors may include: Uncontrolled blood pressure, Labile INRs (in a
 1138 patient taking VKA), Alcohol excess; Concomitant use of NSAIDs or aspirin, in an anticoagulated
 1139 patient, bleeding tendency or predisposition (e.g. treat gastric ulcer, optimise renal or liver
 1140 function etc.).

1141

1142 **4. For patients with AF, we recommend use of the HAS-BLED score to address modifiable**
 1143 **bleeding risk factors in all AF patients. Those potentially at high risk (HAS-BLED score ≥ 3)**
 1144 **warrant more frequent and regular reviews or follow-up (Strong recommendation, moderate**
 1145 **quality evidence).**

1146 *Remark:* Given that bleeding risk is highly dynamic, attention to modifiable bleeding risk factors
 1147 should be prioritized during every patient contact or review.

1148

1149 **5. In VKA treated patients, we recommend use of the HAS-BLED score for bleeding risk**
 1150 **assessment (Weak recommendation, low quality evidence)**

1151 *Remark:* A high HAS-BLED score (≥ 3) is rarely a reason to avoid anticoagulation. The individual
 1152 modifiable components of the score, when reviewed with the patient, can serve to ameliorate
 1153 bleed risk

1154

1155 **ANTITHROMBOTIC THERAPY AND OTHER APPROACHES FOR STROKE** 1156 **PREVENTION**

1157

1158 The principal goal of OAC in AF is to reduce the risk of stroke and systemic embolism, while
 1159 minimizing the incremental bleeding risk associated with OAC. Although these outcomes may be in
 1160 part mechanistically related to lower risk of bleeding and ischemic stroke compared to therapies in
 1161 the control arms, cardiovascular composite or survival outcomes presently do not reflect the primary
 1162 rationale for therapy.

1163

1164 **Randomized trials**

1165 Vitamin K antagonists compared to placebo or control

1166 In a meta-analysis of 2900 subjects from six randomized trials, adjusted-dose warfarin was
 1167 associated with a 64% relative risk reduction in stroke (95% CI, 49%-74%) (e-Table 12). The absolute
 1168 risk reduction was 2.7%/year (from 4.5%/year in controls) in primary prevention subjects and
 1169 8.4%/year (from 12%/year in controls) in secondary prevention subjects.¹²²

1170 Aspirin and antiplatelet therapy compared to placebo or control

1171 In a meta-analysis of 8 trials of 4876 subjects, antiplatelet therapy compared to control or placebo
 1172 was associated with a 22% (95% CI 6-35%) relative risk reduction in stroke (e-Table 13).¹²² The
 1173 Stroke Prevention in AF (SPAF-I) study demonstrated decrease in risk of stroke from 6.3%/year in
 1174 placebo subjects to 3.6%/year (95% CI 9-63%)¹²³, but a meta-analysis of 7 trials of 3990 subjects
 1175 found no significant benefit. SPAF-I was the only trial suggestive of a benefit for aspirin compared to
 1176 placebo, but there was internal heterogeneity between the anticoagulation-eligible and

1177 anticoagulation-ineligible subgroups, and given the trial was stopped early, the effect size could have
1178 been exaggerated. Aspirin also showed no benefit in the elderly, or in preventing severe strokes. All
1179 these trials had significant heterogeneity in study design, variability in aspirin dose tested, short
1180 follow-up, and predated contemporary use of oral anticoagulation in AF.

1181

1182 The ACTIVE-A trial, which also predated the investigation of NOACs, compared aspirin plus
1183 clopidogrel versus aspirin monotherapy among patients in whom VKA was unsuitable.¹²⁴ The study
1184 found a decrease in risk of stroke with dual antiplatelet therapy, but the major bleeding rates with
1185 aspirin-clopidogrel were comparable to rates seen with warfarin (approx. 2%/year).

1186 Vitamin K antagonists compared to antiplatelet therapy

1187 Of 12 studies comparing warfarin to antiplatelet therapy, warfarin was associated with a 39%
1188 relative risk reduction (95% CI, 22%-52%) in strokes (e-Table 14).¹²² In ACTIVE-W, the largest of these
1189 studies, warfarin was superior to dual antiplatelet therapy to warfarin for stroke and a
1190 cardiovascular composite outcome, with similar rates of major bleeding.¹²⁵

1191 Non-VKA oral anticoagulants (NOACs) compared to vitamin K antagonists

1192 Several NOACs that directly inhibit thrombin (factor IIa) or activated factor X (factor Xa) have been
1193 approved as alternatives to VKAs for stroke prevention in AF. They differ from VKAs in that they have
1194 a rapid onset/offset of action, absence of an effect of dietary vitamin K intake on their activity and
1195 fewer drug interactions. The predictable anticoagulant effects of the NOACs enable their
1196 administration in fixed doses without the need for routine coagulation monitoring, thereby
1197 simplifying therapy.

1198

1199 Individually in their respective phase 3 trials (Table 3), dabigatran, rivaroxaban, apixaban, and
1200 edoxaban have been shown to be at least as safe and effective as warfarin for preventing stroke and
1201 systemic embolism in patients with AF.^{73,74,76,126}

1202

1203 A meta-analysis of the four phase 3 trials compared patients taking NOACs (higher-dose) (n=42,411)
1204 with warfarin (n=29,272) (e-Table 15).¹²⁷ NOACs significantly reduced stroke or systemic embolic
1205 events by 19% compared with warfarin (RR 0.81; 95% CI 0.73-0.91; p<0.0001). The benefit was
1206 driven primarily by a 51% reduction in hemorrhagic stroke (RR 0.49; 95% CI 0.38-0.64; p<0.0001).
1207 Ischemic stroke was similar between NOACs and warfarin. (RR 0.92; 95% CI 0.83-1.02; p=0.10).
1208 NOACs were also associated with a significant 10% reduction in all-cause mortality (RR 0.90; 95% CI
1209 0.85-0.95; p=0003). With regards to safety, NOACs were associated with a non-significant 14%
1210 reduction in major bleeding (RR 0.86; 95% CI 0.73-1.00; p=0.06) but a substantial 52% reduction in
1211 intracranial hemorrhage (RR 0.48; 95% CI 0.39-0.59; p<0.0001), NOACs were, however, associated
1212 with a significant increase in GI bleeding (RR 1.25; 95% CI 1.01-1.55; p=0.04). The relative efficacy
1213 and safety of NOACs was consistent across all patient subgroups with the exception that the relative
1214 reduction in major bleeding with NOACs was greater at centers with poor INR control as defined as a
1215 center-based time in therapeutic range <66% (RR 0.69, 95% CI 0.59-0.81; p-interaction=0.02).

1216

1217 Lower-dose NOAC regimens (dabigatran 110 mg and edoxaban 30/15 mg) showed similar overall
1218 reductions in stroke or systemic embolism but a more favorable bleeding profile than warfarin but

1219 were associated with more ischemic strokes [the lower-dose regimen edoxaban 30/15 mg is not
1220 approved for the stroke prevention indication].
1221

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1222 Table 3: Phase 3 AF trials of NOAC versus warfarin – Summary of key efficacy and safety results

Outcome	Trial									
	RE-LY		Warfarin (n=6022)	ROCKET-AF		ARISTOTLE		ENGAGE AF-TIMI 48		
	Dabigatran 150 mg (n=6076)	Dabigatran 110 mg (n=6015)		Rivaroxaban 20/15 mg (n=7131)	Warfarin (n=7133)	Apixaban 5/2.5 mg (n=9120)	Warfarin (n=9081)	Edoxaban 60/30 mg (n=7035)	Edoxaban 30/15 mg (n=7034)	Warfarin (n=7036)
Efficacy										
Stroke/SEE										
Event Rate (%/year)	1.11	1.54	1.71	2.1	2.4	1.27	1.60	1.57	2.04	1.80
HR (95% CI)	0.72 (0.58-0.90)	0.90 (0.74-1.10)	NA	0.88 (0.75-1.03)	NA	0.79 (0.65-0.95)	NA	0.87 (0.73-1.04)	1.13 (0.96-1.34)	NA
p-value	0.004	0.29	NA	0.12	NA	0.01	NA	0.08	0.10	NA
Ischemic Stroke										
Event Rate (%/year)	0.92	1.34	1.22	1.34	1.42	0.97	1.05	1.25	1.77	1.25
HR (95% CI)	0.76 (0.59-0.97)	1.11 (0.88-1.39)	NA	0.94 (0.75-1.17)	NA	0.92 (0.74-1.13)	NA	1.00 (0.83-1.19)	1.41 (1.19-1.67)	NA
p-value	0.03	0.35	NA	0.58	NA	0.42	NA	0.97	<0.001	NA
Hemorrhagic Stroke										
Event Rate (%/year)	0.10	0.12	0.38	0.26	0.44	0.24	0.47	0.26	0.16	0.47
HR (95% CI)	0.26 (0.14-0.49)	0.31 (0.17-0.56)	NA	0.59 (0.37-0.93)	NA	0.51 (0.35-0.75)	NA	0.54 (0.38-0.77)	0.33 (0.22-0.50)	NA
p-value	<0.001	<0.001	NA	0.02	NA	<0.001	NA	<0.001	<0.001	NA
MI										
Event Rate (%/year)	0.81	0.82	0.64	0.91	1.12	0.53	0.61	0.70	0.89	0.75
HR (95% CI)	1.27 (0.94-1.71)	1.29 (0.96-1.75)	NA	0.81 (0.63-1.06)	NA	0.88 (0.66-1.17)	NA	0.94 (0.74-1.19)	1.19 (0.95-1.49)	NA
p-value	0.12	0.09	NA	0.12	NA	0.37	NA	0.60	0.13	NA
All-Cause Death										
Event Rate (%/year)	3.64	3.75	4.13	1.87	2.21	3.52	3.94	3.99	3.80	4.35
HR (95% CI)	0.88 (0.77-1.00)	0.91 (0.80-1.03)	NA	0.85 (0.70-1.02)	NA	0.89 (0.80-1.0)	NA	0.92 (0.83-1.01)	0.87 (0.79-0.96)	NA

p-value	0.05	0.13	NA	0.07	NA	0.047	NA	0.08	0.006	NA
Safety										
Major Bleeding										
Event Rate (%/year)	3.32	2.87	3.57	3.6	3.4	2.13	3.09	2.75	1.61	3.43
HR (95% CI)	0.93 (0.81-1.07)	0.80 (0.70-0.93)	NA	1.04 (0.90-1.20)	NA	0.69 (0.60-0.80)	NA	0.80 (0.71-0.91)	0.47 (0.41-0.55)	NA
p-value	0.31	0.003	NA	0.58	NA	<0.001	NA	<0.001	<0.001	NA
ICH										
Event Rate (%/year)	0.32	0.23	0.76	0.5	0.7	0.33	0.80	0.39	0.26	0.85
HR (95% CI)	0.41 (0.28- 0.60)	0.30 (0.19- 0.45)	NA	0.67 (0.47-0.93)	NA	0.42 (0.30-0.58)	NA	0.47 (0.34-0.63)	0.30 (0.21-0.43)	NA
p-value	<0.001	<0.001	NA	0.02	NA	<0.001	NA	<0.001	<0.001	NA
GI Bleeding										
Event Rate (%/year)	1.56	1.15	1.07	2.0	1.24	0.76	0.86	1.51	0.82	1.23
HR (95% CI)	1.48 (1.18- 1.85)	1.08 (0.85- 1.38)	NA	1.66 (1.34- 2.05)	NA	0.89 (0.70-1.15)	NA	1.23 (1.02-1.50)	0.67 (0.53-0.83)	NA
p-value	0.001	0.52	NA	<0.001	NA	0.37	NA	0.03	<0.001	NA

1223 RE-LY: Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY); ROCKET AF: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition
 1224 Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; ARISTOTLE: Apixaban for Reduction in Stroke and
 1225 Other Thromboembolic Events in Atrial Fibrillation; ENGAGE AF-TIMI 48: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation -
 1226 Thrombolysis In Myocardial Infarction study 48.
 1227

1228 NOACs vs. Aspirin

1229 Apixaban is the only NOAC that has been compared with aspirin in AF patients. The Apixaban vs.
1230 Acetylsalicylic Acid to Prevent Strokes (AVERROES) trial compared apixaban 5 mg twice daily with
1231 aspirin in AF patients who were not candidates for VKA therapy.¹²⁸ The trial was stopped early for
1232 benefit as apixaban significantly reduced the risk of stroke or systemic embolism compared with
1233 aspirin (hazard ratio 0.45, 95% CI 0.32-0.62; $p < 0.001$) (e-Table 16). There was no significant
1234 difference in major bleeding (hazard ratio 1.13, 95% CI 0.74-1.75; $p = 0.57$) between apixaban and
1235 aspirin.

1236

1237 **Real World Observational Data**

1238

1239 With the availability of large health care system administrative data and the advent of quality
1240 improvement and post-marketing anticoagulation registries, the number of observational outcome
1241 studies on OAC in AF far outnumber randomized trials. Although these data have helped to
1242 successfully identify treatment variation and gaps in care, the use of these data for comparative
1243 effectiveness and safety studies of OACs must be interpreted with prudence. Despite the use of
1244 sophisticated, high-quality methods to minimize confounding and bias and improve causal inference,
1245 even very small amounts of residual confounding by treatment selection or measurement error can
1246 attenuate or amplify the small absolute risk differences observed in the randomized trials.

1247

1248 Similarly, definitive conclusions cannot be drawn from indirect comparisons such as network meta-
1249 analyses of NOACs to each other due to small absolute risk differences. Real-world or observational
1250 data are generally insufficient to guide selection of individual anticoagulant drugs. Therefore,
1251 observational data are best used to reaffirm that real-world effectiveness is in concordance with
1252 clinical trial efficacy, based on both quality of care and generalizability.^{129 2016}

1253

1254 A meta-analysis of real-world observational studies of dabigatran was consistent with findings from
1255 RE-LY. Compared to VKA, risk of stroke with dabigatran versus warfarin was 1.65 vs. 2.85 per 100
1256 patients-years (HR 0.86, 95% CI 0.74-0.99).¹³⁰ Dabigatran was also associated with a lower risk of
1257 intracranial bleeding (HR 0.45, 95% CI 0.38-0.52) and lower risk of death (HR 0.73, 95% CI 0.61-0.87).
1258 Risk of gastrointestinal bleeding was higher.

1259

1260 One systematic review and meta-analysis provided comparative effectiveness and safety data for
1261 rivaroxaban vs. dabigatran (n=3 trials), rivaroxaban vs. warfarin (n=11 trials) or both (n=3 trials) for
1262 stroke prevention in AF¹³¹. Overall, the risk of stroke/systemic thromboembolism (TE) with
1263 rivaroxaban were similar compared with dabigatran, but were significantly reduced when compared
1264 to warfarin (HR 0.75, 0.64-0.85). Major bleeding risk was significantly higher with rivaroxaban vs.
1265 dabigatran (HR 1.38, 1.27-1.49), but similar to warfarin (HR 0.99, 0.91-1.07). Rivaroxaban was
1266 associated with increased all-cause mortality and gastrointestinal bleeding (GIB), but similar risk of
1267 acute myocardial infarction (AMI) and intracranial hemorrhage (ICH) compared with dabigatran.
1268 When compared with warfarin, rivaroxaban was associated with similar risk of any bleeding,
1269 mortality and AMI, but a higher risk of GIB and lower risk of ICH.

1270

1271 Another large analysis of three Danish nationwide databases of 61,678 patients found that NOACs
1272 were at least as safe and effective as warfarin, with small but significant differences in risk of stroke,
1273 death, and bleeding across rivaroxaban, apixaban, and dabigatran.¹³² However, a new-user FDA
1274 Medicare analysis of 118,891 patients found that rivaroxaban compared to dabigatran had a
1275 statistical trend towards a decreased risk of stroke (HR 0.81, 95% CI 0.65-1.01) and significantly
1276 increased risk of intracranial (HR 1.47, 95% CI 1.32-1.67) and major non-intracranial bleeding (HR
1277 1.48, 95% CI 1.32-1.67).¹³³ Absolute risk differences were small (2.0-2.1 per 1000 person-years) and
1278 well within a range vulnerable to confounding.

1279

1280 *Different Ethnic Groups*

1281 Asian AF patients have a higher risk of intracranial hemorrhage compared with Caucasians when
1282 VKAs are used.¹³⁴ The higher risk of bleeding on VKA in Asians vs. non-Asians has also been observed
1283 in major clinical trials of NOACs,¹³⁵ even though Asians received a lower intensity of anticoagulation
1284 with VKA.¹³⁶

1285

1286 In a recent meta-analysis comprising 5 NOAC trials (RE-LY, ROCKET AF, J-ROCKET AF, ARISTOTLE, and
1287 ENGAGE AF), the effects of NOACs versus warfarin in Asians vs non-Asians were compared.¹³⁷ For
1288 standard-dose NOACs (dabigatran 150 mg, rivaroxaban 20 mg, apixaban 5 mg, and edoxaban 60 mg),
1289 the effect sizes of the primary efficacy endpoint (stroke and SE) and the primary safety endpoint
1290 (major bleeding) were greater in Asians versus non-Asians. The risk reduction in hemorrhagic stroke
1291 and GI bleeding was also greater in Asians vs. non-Asians. These data suggest that standard-dose
1292 NOACs, when compared with warfarin, were more effective and safer in Asians than in non-Asians.
1293 The efficacy and safety of low-dose NOACs (dabigatran 110 mg, rivaroxaban 15 mg, and edoxaban 30
1294 mg), when compared with warfarin, appears similar among Asians and non-Asians.

1295

1296 There are several real-world studies from Asia comparing NOACs with warfarin^{138,139}. Despite low-
1297 dose NOACs, such as dabigatran 110 mg or rivaroxaban 15 mg/10 mg being more commonly used
1298 than standard-dose NOACs (dabigatran 150 mg or rivaroxaban 20 mg), the use of NOACs were
1299 associated with reduced risk of ischemic stroke or systemic embolization, major bleeding, ICH, and
1300 total mortality compared with warfarin. Published data suggest that NOACs are preferentially
1301 indicated for stroke prevention in Asians.³⁷

1302

1303

1304 **Other Investigational Drugs**

1305

1306 Although NOACs are safer than VKAs, serious bleeding still occurs. The potential for bleeding often
1307 discourages initiation of anticoagulant therapy in patients deemed to be at high risk of bleeding and
1308 patients who experience a bleed frequently have permanent or prolonged discontinuation of their
1309 anticoagulant. Therefore, continued interest remains in developing even safer anticoagulants than
1310 thrombin and factor Xa inhibitors. Current investigation has focused on the upstream targets factor
1311 XI and factor XII in the contact pathway as emerging research has elucidated their critical role in
1312 thrombosis with minimal or no role in hemostasis.¹⁴⁰⁻¹⁴² Strategies to target FXII or FXI include
1313 antisense oligonucleotides that reduce hepatic synthesis of the clotting proteins, monoclonal
1314 antibodies that block activation or activity, aptamers, small molecules that block the active site or

1315 induce allosteric modulation, and polyanion antagonists that attenuate contact activation by
1316 nullifying stimulators of the pathway.⁷

1317

1318 Human data are limited. The factor XI-directed antisense oligonucleotide IONIS-416858 was
1319 compared with enoxaparin in 300 patients undergoing elective knee arthroplasty. Patients were
1320 randomized to IONIS-416858 at doses of 200 or 300 mg starting 35 days prior to surgery, or
1321 enoxaparin at a dose of 40 mg starting after the surgery. The 200 mg IONIS-416858 regimen was
1322 non-inferior and the 300 mg IONIS-416858 regimen was superior compared with enoxaparin in
1323 preventing the composite endpoint of asymptomatic deep venous thrombosis (DVT), symptomatic
1324 DVT or pulmonary embolism, or venous thromboembolism related mortality.¹⁴³ The rates of major
1325 or clinically relevant non-major bleeding were 3% in both IONIS-416858 groups and 8% in the
1326 enoxaparin group. With respect to patients with AF, potential unmet needs addressed by these
1327 agents include patients at high risk for bleeding, such as those with end stage renal disease who are
1328 on hemodialysis (phase 2 study ongoing <https://clinicaltrials.gov/ct2/show/NCT02553889>). Another
1329 area of interest is in patients with mechanical heart valves. Data from a phase II trial of dabigatran in
1330 patients with mechanical heart valves (RE-ALIGN) demonstrated inferior efficacy and more bleeding,
1331 compared to warfarin.¹⁴⁴ FXI-directed strategies may be very effective in this setting because FXI
1332 depletion abolished mechanical valve induced thrombin generation in vitro.¹⁴³

1333 Recommendations

1334 **6. For patients with AF, we recommend against antiplatelet therapy alone (monotherapy or**
1335 **aspirin in combination with clopidogrel) for stroke prevention alone, regardless of stroke risk**
1336 **(Strong recommendation, moderate quality evidence).**

1337 *Remark:* Patients with AF might have other indications for antiplatelet drugs (e.g. acute coronary
1338 syndrome, stents)

1339

1340 **7. In patients with AF who are eligible for OAC, we recommend NOACs over VKA (strong**
1341 **recommendation, moderate quality evidence).**

1342 *Remark:* Patient and caregiver preferences, cost, formulary considerations, anticipated
1343 medication adherence or compliance with INR testing and dose adjustment should be
1344 incorporated into clinical-decision making.

1345

1346 **8. In patients on VKAs with consistently low time in INR therapeutic range (eg. TTR<65%), we**
1347 **recommend considering interventions to improve TTR or switching to NOACs (strong**
1348 **recommendation, moderate quality evidence)**

1349 *Remark:* Action required if TTR <65% - implement additional measures (more regular INR tests;
1350 review medication adherence; address other factors known to influence INR control;
1351 education/counselling) to improve INR control.

1352

1353

1354 **9. In patients with prior unprovoked bleeding, warfarin-associated bleeding, or at high risk of**
1355 **bleeding, we suggest using apixaban, edoxaban, or dabigatran 110 mg (where available) as all**
1356 **demonstrate significantly less major bleeding compared with warfarin (Weak**
1357 **recommendation, very low quality evidence).**

1358 *Remark:* In patients with prior gastrointestinal bleeding apixaban or dabigatran 110mg bid may
1359 be preferable as they are the only NOACs not associated with an increased risk of
1360 gastrointestinal bleeding compared with warfarin.

1361 *Remark:* Dabigatran 150 mg twice daily recommended in patients at high risk of ischemic stroke
1362 as only agent/dose with superior efficacy compared with warfarin. However, bleeding risk would
1363 need to be assessed and patients monitored.
1364

1365 **ADJUSTED-DOSE ORAL VITAMIN K ANTAGONIST THERAPY**

1366 The vitamin K antagonists (VKA) are a class of oral anticoagulants; the most commonly used are the
1367 4-hydroxycoumarins, and include warfarin, phenprocoumon and acenocoumarol.¹⁴⁵ Less commonly
1368 used VKAs are phenindione and fluindione which are 1,3-indandione derivatives. Geographical
1369 variation in VKA popularity is evident, with warfarin commonly used worldwide, but acenocoumarol
1370 being popular in Spain and phenprocoumon in Germany. In randomized clinical trials, most have
1371 used warfarin.

1372 **Optimal INR target range in AF**

1373
1374 For stroke prevention in patients with AF receiving a VKA the optimal INR target range is 2.0 to
1375 3.0,¹⁴⁶ aiming for an INR value of 2.5 to maximize the proportion of time spent in the therapeutic INR
1376 range. Numerous observational studies of AF patients have demonstrated that the risk of
1377 thromboembolism/ischemic stroke is greater when INR is <2.0 ^{81,83,85,147-149} whereas INR levels >3.0
1378 are associated with a greater incidence of major bleeding, especially intracranial hemorrhage when
1379 the INR rises above 3.5.⁸¹⁻⁸⁶ All the phase III NOAC trials employed an INR target of 2.0-3.0 among
1380 patients receiving warfarin,^{73,76,126,128} J-ROCKET employed a lower INR target of 1.6-2.6 for the
1381 Japanese population.¹⁵⁰
1382

1383 In some Asian countries, there is the perception that a lower target INR range e.g., 1.6-2.6 should be
1384 used, especially in the elderly. Only one small prospective randomized trial allocated 115 secondary
1385 prevention AF patients to conventional-intensity group (INR 2.2 to 3.5) or a low-intensity group (INR
1386 1.5 to 2.1).¹⁵¹ Major hemorrhagic complications occurred in 6 patients in the conventional-
1387 intensity group (6.6% per year) compared to the low-intensity group (0% per year, $P=0.01$). Other
1388 Asian registries have suggested that low intensity (INR 1.5-2.5) was associated with less bleeding,
1389 but no information on quality of INR control was reported. There is currently no robust evidence for
1390 implementing a target INR range of 1.6-2.6, and therefore the conventional, evidence-based INR
1391 target of 2.0-3.0 should be employed globally.
1392

1393 **Importance of time in therapeutic INR range**

1394
1395 The proportion of time spent within the therapeutic INR range (INR 2.0 to 3.0) is intrinsically linked
1396 to the risk of adverse events. The temporal pattern of INR control is most commonly calculated using
1397 the Rosendaal method of linear interpolation between two consecutive INR values,¹⁵² known as the
1398 time in therapeutic range (TTR) or by the percentage of INRs within therapeutic range (PINRR).¹⁵³
1399 However, a limitation of the Rosendaal method of interpolation is that INRs more than 42 days apart

1400 have generally not been interpolated in studies due to large uncertainties in fluctuation. Although
1401 TTR and PINRR are highly correlated^{154,155} they are not equivalent and should not be used
1402 interchangeably. TTR is a widely accepted and validated measure of anticoagulation control and
1403 predicts adverse events in patients receiving VKA¹⁵⁵⁻¹⁵⁷ and is the quality and performance measure
1404 of choice for specialized anticoagulation clinics.

1405
1406 Numerous studies have demonstrated that the risk of thromboembolism, major bleeding, and death
1407 is lower when the proportion of TTR is higher, at least $\geq 65\%$.^{127,155-157} Indeed, random 'one off' INR
1408 values give little insight into the degree of anticoagulation control, and many adverse outcomes
1409 (e.g., bleeding) occur even within the therapeutic INR range of 2.0-3.0.¹⁵⁸ Thus, when VKAs are used
1410 attention should be focused on the average *individual* TTR as a measure of the quality of
1411 anticoagulation control.

1412
1413 Clinical guidelines on the management of AF advocate an *individual* TTR of at least $\geq 65\%$ ^{159,160} to
1414 maximize efficacy and safety and this should be the treatment target, although in clinical practice
1415 this may be more difficult to achieve.^{155-158,161} An analysis of anticoagulation control in the
1416 GARFIELD-AF registry (n=9934), a global observational study, revealed that only 41.1% had TTR $\geq 65\%$
1417 and of all the INR values only 51.4% were in the therapeutic range (INR 2.0 to 3.0), with one-third
1418 being sub-therapeutic.¹⁵⁷ After adjustment, the risk of stroke/systemic embolism (HR 2.55, 95% 1.61
1419 to 4.03), all-cause mortality (HR 2.39, 95% CI 1.87 to 3.06) and major bleeding (1.54, 95% CI 1.04 to
1420 2.26) was greater with TTR $< 65\%$, when compared to TTR $\geq 65\%$.¹⁵⁷

1421
1422 TTR varies widely by geographical region (TTR $\geq 65\%$ Asia 16.7%, North America 45.9%, Europe
1423 49.4%).¹⁵⁷ An analysis of individual TTR from Swedish registries (n=40,449) revealed an overall mean
1424 individual TTR (iTTR) of 68.6% and significantly lower annual rates of thromboembolism (2.37% vs.
1425 4.41%), all-cause mortality (1.29% vs. 4.35%) and major bleeding (1.61% vs. 3.81%) when iTTR was
1426 $\geq 70\%$ compared to iTTR $< 70\%$, respectively.¹⁵⁶

1427

1428 Recommendation

1429

1430 **10. For patients with non-valvular AF, when VKAs are used, we suggest the target should be INR**
1431 **2.0-3.0, with attention to individual TTR, ideally $\geq 70\%$ (ungraded consensus-based statement).**

1432 *Remark:* Action required if TTR sub-optimal ($< 65-70\%$) - implement additional measures (more
1433 regular INR tests; review medication adherence; address other factors known to influence INR
1434 control; education/counselling) to improve INR control or consider a NOAC.

1435 *Remark:* When possible, experienced specialized anticoagulation clinics should be utilized for
1436 VKA and INR management.

1437

1438

1439 Factors affecting INR control

1440

1441 Many factors affect TTR, including patient-related aspects (such as age, sex, socioeconomic status,
1442 diet, ethnicity, hospitalization, length of time on VKA, medical and psychiatric co-morbidities, non-
1443 adherence, polypharmacy, genetic factors, etc.)^{145,158,162} and healthcare system-related factors,
1444 particularly how VKA is managed (by country, setting of OAC management eg. anticoagulation clinic

1445 vs. physician/community-based practices),^{90,163,164} distant to OAC clinic,^{163,164} self-monitoring/self-
 1446 management,⁹¹ frequency of INR monitoring etc.¹⁵⁸ It is also important to note that site level
 1447 variation in VKA management has also been demonstrated in RCTs¹⁶⁵⁻¹⁶⁹ and for NOACs.¹⁷⁰ The value
 1448 of dietary measures to improve anticoagulation control is debatable, and it is perhaps more relevant
 1449 to maintain a stable dietary habit, avoiding wide changes in the intake of vitamin K¹⁷¹. Amongst
 1450 patients initiating VKA, the 'Time to achieve Therapeutic Range' (TtTR) has also been related to the
 1451 likelihood of achieving a subsequently good Time in Therapeutic Range (TTR)^{172,173}.

1452

1453 The more common clinical factors influencing TTR have been used to formulate the SAME-TT₂R₂
 1454 score^{174,175} (Table 5). This clinical score is based on routine clinical parameters which can be used to
 1455 identify patients who may be able to attain good anticoagulation control (e.g. TTR \geq 65%) with a VKA
 1456 and those who probably will not, where a NOAC may be preferred or where other interventions (eg.
 1457 more frequent INR monitoring, patient education/counselling etc.) may need to be implemented to
 1458 ensure good INR control. Many of the factors included in the SAME-TT₂R₂ score have been
 1459 associated with decreased adherence with NOACs and in the absence of trial data is not clear if
 1460 these patients would do substantially better on a NOAC or if they would do poorly anyway.

1461

1462 **Table 5:** The SAME-TT₂R₂ score^{174,175}

1463

1464

Acronym	Risk factors	Points
S	Sex (female)	1
A	Age (<60 years)	1
Me	Medical history (\geq 2 from: hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease)	1
T	Treatment (interacting drugs, e.g., amiodarone)	1
T	Tobacco use (within 2 years)	2
R	Race (non-Caucasian)	2
Maximum score		8

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1478 The SAME-TT₂R₂ score has been assessed in 15 exclusively AF cohorts,¹⁷⁶⁻¹⁸⁷ with six^{177,179,181,182,185,188}
 1479 reporting its predictive ability to forecast good or poor anticoagulation control, with c-statistics
 1480 ranging from 0.56¹⁸² to 0.72.¹⁷⁴ However, these cohorts were predominantly elderly, Western
 1481 (white) populations and its predictive ability in non-Western populations has relatively limited data
 1482 as only three studies have assessed it,^{176,177} with only one reporting c-statistics (c-statistic 0.54, 95%
 1483 CI 0.52 to 0.57).¹⁷⁷ In the multi-ethnic non-Caucasian Singaporean population by Bernaitis et al¹⁷⁶
 1484 the SAME-TT₂R₂ score was able to dichotomize the patients likely to do well on VKA, compared to
 1485 those (score >2) more likely to achieve poor TTR. In the Loire Valley AF project, the SAME-TT₂R₂
 1486 score was predictive of labile INR in AF patients who were VKA users, and was significantly
 1487 associated with the adverse consequences of labile INR, including stroke, serious bleeding and
 1488 death; the score was non-predictive in non-VKA users¹⁸⁹. The score has also been tested in some
 1489 VTE populations, where it similarly identifies patients likely to achieve a good TTR.^{190,191}

1491 Patients with AF who require OAC should not have to fail with a VKA before they are offered a
1492 NOAC; the most appropriate OAC based on the patient's *individual* risk profile and patient
1493 preference, should be offered from the beginning of OAC therapy. However, in some healthcare
1494 systems where the patient has to have a period on VKA and their TTR determined, before a decision
1495 to use a NOAC is approved, the SAME-TT₂R₂ score could be used to aid decision-making¹⁷⁵.
1496

1497 **Recommendation**

1498 **11. For patients with AF, we suggest the SAME-TT₂R₂ score to aid decision making to help identify**
1499 **patients likely to do well on VKA (ungraded consensus-based statement).**

1500 *Remark:* Those with score 0-2 are likely to achieve a good TTR. Those with score >2 are less
1501 likely to achieve a good TTR and would require more regular INR checks, education/counselling
1502 and frequent follow-up, or alternatively, a NOAC should be considered as a better management
1503 option if high medication adherence can be expected.
1504
1505

1506 **Monitoring anticoagulant therapy**

1507 *Point-of-care testing*

1508 There is an increasing demand for oral anticoagulation among AF patients¹⁹² and not all patients are
1509 suitable for NOACs, therefore a large proportion requires VKA which necessitates INR monitoring.
1510 Point-of-care (POC) testing using a coagulometer (INR monitor) is more convenient and time-
1511 efficient, particularly where patient's self-monitor and/or self-manage. Home or clinic POC
1512 monitoring is an increasingly standard method of INR monitoring associated with an appropriate
1513 degree of precision and accuracy for clinical practice,¹⁹³ however routine calibration is warranted
1514 and quality control systems should adhere with the FDA Medical devices regulation guidance¹⁹⁴.
1515
1516

1517 *Patient self-monitoring and self-management*

1518 A recent Cochrane review⁹¹ evaluating the effect of self-monitoring or self-management of OAC
1519 therapy compared to standard OAC monitoring on thromboembolic events, major bleeding and
1520 death revealed a significant decrease in thromboembolic events overall (RR 0.58, 95% CI 0.45 to
1521 0.75; 7594 participants in 18 studies) and with both self-monitoring (RR 0.69, 95% CI 0.49 to 0.97;
1522 4097 participants in 7 studies) and self-management (RR 0.47, 95% CI 0.31 to 0.70; 3497 participants
1523 in 11 studies), although not all patients were AF. There was no overall reduction in the risk of death
1524 (RR 0.85, 95% CI 0.71 to 1.01, 6358 participants in 11 studies), however self-management did reduce
1525 all-cause mortality (0.55, 95% CI 0.36 to 0.84; 3058 participants in 8 studies). Neither self-monitoring
1526 nor self-management reduced the risk of major bleeding compared to standard OAC monitoring (RR
1527 0.95, 95% CI 0.80 to 1.12; 8018 participants in 20 studies). Rating of the quality of evidence was low
1528 to moderate and the findings should be interpreted accordingly.
1529

1530 The advantages of self-monitoring and self-management include convenience and freedom for the
1531 patient, patient empowerment/control over their condition and treatment, increased patient
1532 satisfaction, all of which may improve quality of life. However, this approach may not be a viable
1533 option for all patients requiring VKA therapy as it is initially expensive, requires mastery of the point-

1534 of-care device and for those self-managing, the knowledge and ability to dose-adjust, plus the
1535 appropriate healthcare system infrastructure and patient support which may not be feasible
1536 globally. For many AF patients, a NOAC might be a more suitable alternative.
1537

1538 **PRACTICAL PATIENT MANAGEMENT ALGORITHM**

1539 The approach to stroke prevention in patients with AF can be simplified into a simple 3-step
1540 algorithm (Figure 4). The initial step is to determine the risk of stroke. As noted in the Stroke Risk
1541 section, risk scores for stroke in patients with AF lack specificity, and are therefore not clinically
1542 useful in identifying and categorizing high-risk patients. As noted in the stroke risk section, we
1543 recommend the use of the CHA₂DS₂-VASc score given its superior sensitivity and ability to accurately
1544 and safely identify patients at low risk of stroke. Patients that are low risk (a score of 0 in males, 1 in
1545 females) do not require antithrombotic treatment.

1546
1547 All AF patients with ≥ 1 stroke risk factors are candidates for stroke prevention with oral
1548 anticoagulation. At this point it is important to assess the bleeding risk. Although the benefit of
1549 stroke prevention outweighs the risk of bleeding in almost all patients, calculation of the bleeding
1550 risk allows the practitioner to identify potentially modifiable factors that elevate the bleeding risk
1551 (uncontrolled hypertension, concomitant use of antiplatelet or nonsteroidal agents, excessive
1552 alcohol intake; poor INR control (TTR<65%) in VKA patients). In addition, patients identified as high
1553 risk for bleeding should be scheduled for more frequent follow-up and monitoring. As noted in the
1554 bleeding risk section, we make a consensus suggestion that the HAS-BLED score be used for this
1555 purpose, so those with a HAS-BLED score ≥ 3 can be flagged up for this reason.

1556
1557 The final decision point is to decide which oral anticoagulant to use for stroke prevention. As noted
1558 in AT therapy and other approaches to stroke prevention, we recommend one of the NOACs
1559 (dabigatran, apixaban, edoxaban, or rivaroxaban) as first line in patients with AF. These agents have
1560 not been compared head to head, and we therefore do not recommend one over the other. Local
1561 availability, cost, and patient co-morbidities might be considerations in choosing an agent (see Table
1562 6) for comparative information. The vitamin K antagonists are still widely used and are an
1563 acceptable alternative with target TTR $\geq 70\%$. As outlined in the section 'Factors affecting INR
1564 control', we recommend that the SAME-TT₂R₂ score be used to help identify patients likely to do well
1565 on VKA therapy.

1566
1567
1568
1569

1570 **Table 6. A simplified schema to assist physician choice of anticoagulant (VKA or individual NOAC) according to patient characteristics.**

Patient characteristic	Possible OAC choice	References to RCT subgroup data	References to real world data or indirect evidence	Comments
<ul style="list-style-type: none"> Recurrent ischemic stroke/SE/TIA despite good anticoagulation control (TTR\geq70%). Consider agent with superior efficacy for preventing both ischemic and hemorrhagic stroke 	D150	127	130	In general, any NOAC would be recommended, esp. where warfarin control suboptimal (TTR<65%). Ensure good adherence and avoid under-dosing
<ul style="list-style-type: none"> Moderate-severe renal impairment CrCl 15-49 ml/min 	A* D ⁺ E30 R15	127	195	All RCTs excluded patients with Cockcroft-Gault CrCl <30ml/min (<25mls/min, for apixaban)
<ul style="list-style-type: none"> High risk of GI bleeding 	A D110	127	130,196	
<ul style="list-style-type: none"> Major GI symptoms or dyspepsia. Also consider increased risk of bleeding 	A R E	197	198,199	
<ul style="list-style-type: none"> High risk of bleeding (HAS-BLED \geq3). Consider agent with the lowest bleeding risk 	A D110 E	127	130,131,196,200,201	
<ul style="list-style-type: none"> Once daily dosing or preference to have lower pill burden 	E R VKA	#	202,203	
<ul style="list-style-type: none"> Asian patients. Consider agents with reduced risk of ICH and major bleed in Asian populations 	A D E	137	138,139,204	
<ul style="list-style-type: none"> Less likely to do well on VKA (SAME-TT₂R₂ score >2). Avoid <u>any</u> potential 'trial' of VKA if possible 	NOAC preferred (A D E R)	...	176,185,189	VKA with additional education, more regular follow-up and frequent INR checks

1571

1572 apixaban. BID=twice daily. CrCl=creatinine clearance. D= dabigatran. E=edoxaban. GI=gastro-intestinal. ICH= intracranial hemorrhage. INR= international normalised
 1573 tio. NOAC=non-vitamin K antagonist oral anticoagulant. R=rivaroxaban. SE= systemic embolism. TIA= transient ischemic attack. TTR=time in therapeutic range.

1574A=vitamin K antagonist. *Reduced to 2.5 mg BID with two of three criteria from age ≥ 80 years, bodyweight ≤ 60 kg, or serum creatinine concentration ≥ 133 $\mu\text{mol/L}$. †110
1575g BID for patients with a CrCl 30–49 mL/min (most countries, but not in the USA); in the USA only, 75 mg BID (available in the USA only) for patients with CrCl 15–29
1576L/min (and only 150 mg BID dose available in the USA for CrCl >30 mL/min). ‡30 mg with CrCl 15–49 mL/min, P-glycoprotein inhibitors, or weight <60 kg. §110 mg BID
1577dose not available in the USA for atrial fibrillation. ¶Reduced to 15 mg if CrCl 15–49 mL/min.
1578Dose to be halved if the patient has any of the following: CrCl 15–49 mL/min, bodyweight ≤ 60 kg, or concomitant use of P-glycoprotein inhibitors. # not available
1579

1580

1581 MANAGING BLEEDING ON OAC

1582

1583 Bleeding on VKA

1584

1585 Management of active bleeding on a VKA depends on the severity (Figure 6). For all bleed events, the
1586 site of bleeding should be assessed, with mechanical compression where appropriate, the time-point of
1587 the last dose of VKA should be obtained, with factors affecting bleeding risk documented (other
1588 medications, kidney function, alcohol abuse, other comorbidities) and hemodynamic status assessed
1589 (blood pressure, pulse etc.). Assessment of INR, prothrombin time and activated partial thromboplastin
1590 time is essential; other laboratory tests should include renal function, hemoglobin, hematocrit and
1591 platelet count. For minor bleeding, VKA administration should be withheld until INR<2.0. Management
1592 of moderate bleeding requires prompt identification and intervention to treat the cause and may also
1593 necessitate fluid replacement and/or blood transfusion. Where bleeding is severe or life-threatening,
1594 immediate reversal of the anticoagulant effect is required and administration of IV vitamin K, fresh
1595 frozen plasma and prothrombin complex concentrates should be considered to restore coagulation.
1596 PCCs are preferred over FFP for reversal due to a higher concentration of clotting factors and less
1597 volume.

1598

1599 Bleeding on NOAC

1600

1601 Many physicians and patients have been reluctant to embrace NOACs due to their perception that they
1602 are not able to effectively manage patients who present with bleeding, particularly without a specific
1603 reversal agent or antidote.²⁰⁵ A helpful framework to consider when managing NOAC related bleeding
1604 includes: (1) prevention of bleeding, (2) general principles and supportive measures, (3) non-specific
1605 hemostatic agents, and (4) NOAC-specific reversal agents.²⁰⁶

1606

1607 *Minimize the Risk of Bleeding*

1608 Selecting the right dose of the NOAC is the most important step to minimize bleeding risk. Prescribing
1609 information for all NOACS includes dose reduction criteria to avoid increased drug exposure (primarily
1610 due to impaired renal function). Concomitant administration of antiplatelet drugs and non-steroidal
1611 anti-inflammatory drugs should be avoided when possible as concomitant administration substantially
1612 increases bleeding risk. Blood pressure should be well-controlled.

1613

1614 *General Supportive Measures*

1615 Given the short half-lives of these medications, minor bleeds may only require temporary
1616 discontinuation of anticoagulation for several doses. More significant bleeds may require additional
1617 supportive measures that include: local management (mechanical/surgical); volume resuscitation; and
1618 consideration of red blood cell and platelet transfusion, if appropriate.²⁰⁷⁻²⁰⁹ In cases of overdose or in

1619 patients who took their last NOAC dose within 2 to 4 hours, oral activated charcoal may attenuate
1620 absorption of drug.²¹⁰⁻²¹³

1621

1622 **Laboratory Measurements**

1623 With respect to common coagulation tests, a prolonged activated partial thromboplastin time (aPTT)
1624 indicates an anticoagulant effect of dabigatran, and a prolonged prothrombin time (PT) indicates an
1625 anticoagulant effect of the FXa inhibitors.²⁰⁸ However, the clinical utility of these common tests is limited
1626 due to the fact that a normal aPTT or PT does not exclude clinically relevant plasma levels of dabigatran
1627 and FXa inhibitors, respectively. The thrombin time (TT) is the most sensitive test for dabigatran; even
1628 low levels of dabigatran will prolong the TT so a normal TT excludes clinically relevant dabigatran
1629 concentrations. The dilute thrombin time (dTT) can be used to quantify dabigatran drug levels as it has
1630 good correlation across a wide range of dabigatran concentrations.²¹⁴ Chromogenic anti-FXa assays are
1631 recommended for rivaroxaban, apixaban, and edoxaban with calibration for the specific agent.²⁰⁸
1632 However, validation of these specialized coagulation tests is required, they are not universally available,
1633 and often have delayed turn-around time which diminishes their usefulness in emergent situations.
1634 Asking patients when they took their last dose of NOAC is often the most practical method for quickly
1635 assessing residual anticoagulant activity.

1636

1637 **Non-Specific Hemostatic Agents**

1638 Hemostatic factors that have been studied as potential non-specific NOAC reversal agents including
1639 prothrombic complex concentrates (PCC), activated PCC (aPCC), recombinant activated factor VII
1640 (rFVIIa), and fresh-frozen plasma (FFP). PCCs are the preferred non-specific hemostatic agent for NOAC
1641 reversal. PCCs are plasma-derived products that contain 3 (factors II, IX, and X) or 4 (addition of factor
1642 VII) clotting factors in addition to variable amounts of heparin and the natural coagulation inhibitors
1643 protein C and protein S. Animal studies have demonstrated that PCC have variable ability to normalize
1644 anticoagulation parameters and prevent or attenuate bleeding across the NOACs.^{209,215-221} The limited
1645 data in humans are restricted to healthy volunteers. In three small (12-93 patients) randomized,
1646 placebo-controlled studies, PCC reversed the anticoagulant effect of rivaroxaban and edoxaban but not
1647 dabigatran.^{210,222-224} There was a dose-dependent relationship with complete reversal with 50 U/kg and
1648 partial reversal with 25 U/kg.

1649

1650 It is unclear whether normalizing coagulation parameters in healthy volunteers translates to improved
1651 outcomes in patients who are actively bleeding. Furthermore, the use of these agents in managing
1652 bleeding caused by VKA or in hemophiliac patients has been associated with an increased risk of
1653 thrombotic complications, especially when activated factors are used.²²⁵⁻²²⁷

1654

1655 **Specific Reversal Agents**

1656 **Idarucizumab**

1657 Idarucizumab is a humanized monoclonal antibody fragment developed as a specific reversal agent for
1658 dabigatran (Table 7). It binds with high affinity (350 times higher than thrombin) to free and thrombin-
1659 bound dabigatran²²⁸ and binding is effectively irreversible.²²⁹ The Reversal Effects of Idarucizumab on
1660 Active Dabigatran (RE-VERSE AD) study was a phase 3, global, prospective, cohort study investigating the

1661 safety and efficacy of 5g idarucizumab (administered as two rapid 2.5g intravenous boluses) in
1662 dabigatran-treated patients who present with uncontrolled or life-threatening bleeding (Group A) or
1663 non-bleeding patients who require emergent surgery or intervention (Group B).²³⁰ Idarucizumab
1664 resulted in immediate, complete, and sustained reversal of dabigatran. Median time to cessation of
1665 bleeding in Group A was between 2.5 hours after reversal and in Group B, median time to surgery after
1666 reversal was 1.6 hours with intraoperative hemostasis deemed “normal” by investigators in 93.4% of
1667 patients. Idarucizumab has worldwide approval and availability.

1668

1669 **Andexanet Alfa**

1670 Andexanet alfa (andexanet) is a specific reversal agent for direct (apixaban, rivaroxaban and edoxaban)
1671 and indirect (low molecular weight heparins and fondaparinux) FXa inhibitors that act through
1672 antithrombin. It is a modified human recombinant FXa decoy protein that is catalytically inactive due to
1673 replacement of an active-site serine with alanine and with deletion of the membrane binding domain,
1674 which eliminates the ability to assemble the prothrombinase complex. Andexanet retains the ability to
1675 bind to NOACs with high affinity and a 1:1 stoichiometric ratio and by sequestering FXa inhibitors within
1676 the vascular space, endogenous FXa activity is restored.²³¹ Due to its pharmacodynamic half-life of 1-
1677 hour, andexanet is administered as a bolus followed by an infusion.

1678

1679 The ongoing ANNEXA-4 phase 3b–4 study (<http://www.clinicaltrials.gov>, NCT02329327) is evaluating the
1680 efficacy and safety of andexanet in patients taking FXa inhibitors with acute major bleeding. Unlike RE-
1681 VERSE AD, this study does not include patients without bleeding but who require emergency or urgent
1682 procedures. A preliminary interim analysis of 67 patients demonstrated that an initial bolus and
1683 subsequent 2-hour infusion of andexanet substantially reduced anti-factor Xa activity with clinically
1684 adjudicated effective hemostasis occurring in 79% of patients.²³² Andexanet is in late stage review by
1685 regulatory authorities.

1686

1687 **Ciraparantag (PER977)**

1688 Ciraparantag is a small synthetic water-soluble molecule developed as a reversal agent for
1689 unfractionated heparin, low molecular weight heparins, fondaparinux, and the oral direct Xa and IIa
1690 inhibitors. It binds to targets through non-covalent hydrogen bonding and charge-charge interactions
1691 thereby preventing the anticoagulants from binding to their endogenous targets.²³³ Ciraparantag is
1692 earlier in its development program as compared with other specific reversal agents.

1693

1694

1695 **Management approach to bleeding on NOACs**

1696 The vast majority of bleeds can be managed conservatively with temporary discontinuation of NOACs
1697 and supportive measures. Reversal agents should be used sparingly in the cases of severe and life-
1698 threatening bleeding which includes bleeding causing hemodynamic compromise, intracranial
1699 hemorrhage, bleeding into a critical organ or closed space, persistent bleeding despite general
1700 supportive measures and local hemostatic support, or risk of recurrent bleeding due to excess NOAC
1701 drug exposure due to delayed clearance of NOAC (e.g., acute renal failure) or overdose.

1702
1703 In a patient with serious bleeding, a specific reversal agent (where available) should be used instead.
1704 General hemostatic agents as non-specific agents are less effective in reversing coagulation
1705 abnormalities, have not been shown to improve outcomes, and are potentially prothrombotic.
1706
1707 Although coagulation testing will identify those patients with therapeutic levels of anticoagulation who
1708 will likely benefit from specific reversal agents, and helps physicians to monitor the response to reversal,
1709 it is reasonable to administer specific reversal agents immediately without waiting for a laboratory test
1710 confirming therapeutic levels of anticoagulation in patients who present with life-threatening bleeding
1711 presumed to be on a NOAC.
1712
1713
1714

1715 **Table 7: Comparison of specific NOAC reversal agents** [adapted from Ruff CT, Giugliano RP, Antman EM.
 1716 Circulation. 2016; 134(3)248-61]
 1717

	Idaracizumab	Andexanet alfa	Ciraparantag
Company	Boehringer Ingelheim	Portola Pharmaceuticals	Perosphere Inc.
Chemical structure	Humanized monoclonal antibody fragment	Recombinant truncated human factor Xa variant (decoy)	Synthetic water-soluble cationic small molecule consisting of two L-arginine units connected with a piperazine containing linker chain
Binding	Noncompetitive binding to dabigatran	Competitive binding to direct factor Xa inhibitors or to indirect factor Xa inhibitor-activated antithrombin	Covalent hydrogen bonding
Target affinity	~350x greater affinity for dabigatran than factor IIa	Affinity for direct factor Xa inhibitors similar to that of native factor Xa	Not reported
Onset	<5 minutes	2 minutes	5-10 minutes
Half-life	Initial: 47 minutes Terminal: 10.3 hours	Terminal: ~6 hours	Duration of action 24 hours
Elimination	Kidney (protein catabolism)	Not reported	Not reported
Anticoagulant(s) reversed	Dabigatran	Direct and indirect factor Xa inhibitors*	- Dabigatran - Argatroban - Low-molecular weight heparins - Unfractionated heparin - Oral and parenteral factor Xa inhibitors
Route and dose in clinical studies	5 g administered as 2 doses of 2.5 g IV over 5-10 minutes, 15 minutes apart (repeat dosing can be considered if recurrent bleeding or require second emergent procedure if elevated coagulation parameters)	400-800 mg intravenous bolus (30 mg/min) followed by infusion of 4-8 mg/min [#]	100-300 mg intravenous bolus
Storage	Refrigerated	Refrigerated	Room temperature

1718 * For the indirect factor Xa inhibitors, andexanet alfa likely to completely reverse fondaparinux which only
 1719 inhibits factor Xa but not low-molecular weight heparins which also inhibit factor IIa.

1720 [#]Lower dose to reverse apixaban, higher dose to reverse rivaroxaban
 1721
 1722
 1723

1724 **PRACTICAL ISSUES WITH VKA AND NOAC**1725 **CARDIOVERSION**1726 **Antithrombotic therapy for patients with AF undergoing cardioversion**

1727

1728 In AF of documented short duration (i.e. ≤ 48 h), urgent cardioversion commonly occurs without prolonged
1729 pre-cardioversion anticoagulation. In the context of elective cardioversion, whether electrical or chemical,
1730 therapeutic anticoagulation either with adjusted-dose VKAs, or NOACs is currently recommended for a
1731 minimum of 3 weeks before, and for a minimum of 4 weeks after the procedure. In AF of >48 h duration or
1732 unknown duration, a TEE-guided approach provides an alternative strategy to guide anticoagulation
1733 management before cardioversion. In this section, we appraise and summarize the evidence and give
1734 recommendations for the use of antithrombotic therapy in patients undergoing electrical or pharmacologic
1735 cardioversion for AF (or atrial flutter). In particular, the option of NOACs in the setting of cardioversion is
1736 reviewed.

1737 **Cardioversion of AF of more than 48 h or unknown duration**1738 **VKA**

1739 Observational data support the use of VKA in the context of elective cardioversion, whether electrical or
1740 pharmacologic. A systematic review of 18 observational studies provides moderate-quality evidence for a
1741 lower risk of stroke or thromboembolism (TE) with peri-cardioversion anticoagulation (with VKA) versus no
1742 anticoagulation (0.3% vs 2.0%; relative risk, RR, 0.16, 95% CI, 0.05-0.48), but did not report major bleeding
1743 events²³⁴.

1744

1745 The recommended duration of a minimum of 3 weeks' therapeutic anticoagulation with VKA before
1746 cardioversion and a minimum 4 weeks subsequently is arbitrary and has no trial basis, being based on
1747 indirect pathophysiologic and observational data. The rationale for maintenance of a therapeutic INR in the
1748 peri-cardioversion period is from observational data, showing that thromboembolism is significantly more
1749 common at INR of 1.5-2.4 before cardioversion than INR of 2.5 (0.93% vs 0%, P 0.012)²³⁵. Retrospective
1750 observational studies suggest that, after cardioversion, the highest risk of stroke and thromboembolism is
1751 in the first 72 hours. In addition, most thromboembolic complications are within 10 days of
1752 cardioversion²³⁶. However, even if sinus rhythm is restored on ECG, transoesophageal echocardiography
1753 (TEE) studies have shown that atrial mechanical dysfunction can persist for several weeks following
1754 cardioversion²³⁷. Recent Finnish registry data suggest that most post-cardioversion strokes are associated
1755 with not using anticoagulation²³⁸. Although data relating to the impact of long-term anticoagulation post-
1756 cardioversion are lacking, relevant Swedish observational data suggest that discontinuation of warfarin
1757 after catheter ablation is not safe in high-risk patients, especially those individuals with history of ischemic
1758 stroke²³⁹. It is also worth noting that although the risk of ischemic stroke/TE is higher with non-paroxysmal
1759 vs. paroxysmal AF (multivariable adjusted hazard ratio 1.38, 95% CI: 1.19-1.61, $p < 0.001$), pattern of AF does
1760 not affect the decision regarding long-term OAC.

1761

1762 **NOACs**

1763 Evidence is available for all four currently available NOACs: dabigatran, apixaban, rivaroxaban and
1764 edoxaban. An existing systematic review from Renda et al. compared the use of NOAC versus VKA in the
1765 setting of cardioversion in six studies.²⁴⁰ Reported pooled risk ratios (RRR) were 0.82 (0.38-1.75) for
1766 stroke/systemic embolism, 0.72 (0.27-1.90) for mortality and 0.72 (0.19-2.71) for MI respectively,
1767 suggesting at least comparable efficacy of NOACs with VKA in the setting of cardioversion (e-Table 17). It
1768 should be noted that despite these reassuring data, the included trials were under-powered for safety and
1769 efficacy, and judged to be of poor quality.

1770
1771 The need for consensus guidance is illustrated by the current wide variation in VKA and NOAC use in the
1772 setting of elective cardioversion^{241,242}. Available data support use of rivaroxaban^{243 244}, dabigatran²⁴⁵,
1773 apixaban²⁴⁶ and edoxaban²⁴⁷ in patients to be continued on these NOACs if scheduled for cardioversion.
1774 Similar observations were found in a randomized trial of apixaban vs. warfarin (EMANATE)²⁴⁸.

1775
1776 A TEE-guided approach with abbreviated anticoagulation before cardioversion has been recommended as
1777 an alternative to the conventional approach of using a minimum of 3 weeks therapeutic pre-cardioversion
1778 anticoagulation as outlined above²⁴⁹. In the TEE-guided strategy, patients receive VKA and once
1779 therapeutic, undergo a screening TEE. If the TEE identifies thrombus in either the atrial appendage or
1780 atrium, cardioversion is postponed, given the presumed high risk of thromboembolism. In the absence of
1781 thrombus, cardioversion is immediately performed. Given the need for accurate visualization of thrombus,
1782 the TEE-guided strategy requires an experienced echocardiographer. The best data for the use of VKA in the
1783 TEE-guided approach is from the Assessment of Cardioversion Using Transesophageal Echocardiography
1784 (ACUTE) RCT, which compared a TEE-guided strategy of abbreviated therapeutic anticoagulation with IV
1785 unfractionated heparin (started 24 h before cardioversion) or warfarin (INR 2.0-3.0) (started 5 days before
1786 cardioversion) to a strategy of therapeutic anticoagulation for at least 3 weeks before cardioversion²⁵⁰.

1787
1788 Overall, the evidence is of low quality, and therefore the results are not conclusive with respect to either a
1789 benefit or harm with the TEE-guided strategy versus the conventional approach of 3 weeks of
1790 anticoagulation pre-cardioversion.

1791
1792 For NOACs vs. warfarin in the TEE-guided approach, our review found an existing systematic review and
1793 meta-analysis.²⁵¹ An updated search of this systematic review identified one additional study. Pooled
1794 results found the relative risk ratio for stroke/TE was 0.33 (0.06-1.68) for NOACs versus warfarin (e-Figure
1795 3, e-table 18). Although these data indicate safety and probable equivalence of NOACs in the TEE-guided
1796 approach versus VKA, the trials were under-powered to show efficacy, and therefore the evidence is of low
1797 quality (e-Table 18). The advantage of NOACs is that their mode of action is quicker than VKA and therefore
1798 there is no delay in waiting for a therapeutic INR. However, the need for strict adherence to the NOAC
1799 therapy must be emphasized to patients, particularly in the post-cardioversion period.

1800
1801
1802 Individuals who are very symptomatic due to AF may gain greatest benefit from the TEE-guided approach
1803 since cardioversion can be expedited by a thrombus-negative TEE. In addition, a TEE-guided approach can
1804 be used to avoid prolonged VKA before cardioversion, which is a particular consideration in patients at
1805 increased risk for bleeding. The NOACs now offer an alternative to prolonged anticoagulation before

1806 cardioversion. However, a “risk-based approach” to anticoagulation should be used, and avoiding
1807 anticoagulation with a TEE-guided strategy should only be considered in the absence of stroke risk factors
1808 and a low risk of recurrent AF.

1809

1810 For patients undergoing a TEE-guided approach, low-molecular-weight heparin at full VTE treatment doses
1811 or IV unfractionated heparin (to maintain an activated partial thromboplastin time prolongation that
1812 corresponds to plasma heparin levels of 0.3-0.7 International Units/mL anti-factor Xa activity) should be
1813 started at the time of TEE and cardioversion performed within 24 hours of the TEE if no thrombus is seen.
1814 Observational data and one RCT show that low-molecular-weight heparin has similar efficacy compared
1815 with heparin or warfarin for immediate anticoagulation before TEE²⁵²⁻²⁵⁶. In the outpatient setting, a TEE-
1816 guided approach should involve initiation of VKA (INR 2.5; range, 2.0-3.0) followed by the TEE and
1817 subsequent cardioversion scheduled 5 days later (if the INR is in therapeutic range at that time). The NOACs
1818 again offer an alternative in outpatient treatment before TEE-guided cardioversion, with no bridging
1819 therapy necessary.

1820

1821 Among AF patients undergoing TEE, 10% have left atrial appendage thrombus with a 3.5-fold increased risk
1822 of stroke/TE²⁵⁷, but no specific data are available in the context of cardioversion. If atrial thrombus is seen
1823 on TEE, then there is heterogeneity in current clinical practice regarding both when or whether to perform
1824 the TEE again, as well as subsequent management of anticoagulation. There is no evidence to support re-
1825 imaging, although it is a reasonable strategy. Although, current practice favors not performing
1826 cardioversion if re-imaging shows thrombus due to the presumed high risk of TE, there is a lack of direct
1827 data about the safety of cardioversion in the presence of thrombus. Taken together, a risk-based approach
1828 to anticoagulation can be recommended and with respect to TEE, individualization of therapy on a case-by-
1829 case basis is proposed. It should be noted that in a multicenter registry of AF patients undergoing catheter
1830 ablation, TEE-guided cardioversion did not show a benefit compared with uninterrupted NOAC therapy²⁵⁸.

1831

1832 Although there is no direct evidence to guide decision-making about long-term management of
1833 anticoagulation in patients who appear to be in sinus rhythm at 4 weeks after cardioversion, but indirect
1834 evidence suggests strongly that long-term anticoagulation should be based on the risk of stroke rather than
1835 the apparent success of the cardioversion procedure. First, recurrence of AF at 1 year after cardioversion
1836 occurs in approximately one-half of patients and therefore long-term stroke risk is significant²⁵⁹⁻²⁶². Second,
1837 the AFFIRM study, in which many patients stopped anticoagulation after initial (apparently) successful
1838 restoration of sinus rhythm, demonstrated similar rates of thromboembolism with a rhythm control
1839 strategy compared with a rate control strategy²⁶³. Thirdly, patients with paroxysmal AF are often
1840 asymptomatic during episodes of AF recurrence, with one series suggesting that only one in every 12
1841 paroxysms are symptomatic²⁶⁴.

1842 Recommendation

1843 **12. For patients with AF of greater than 48 hours or unknown duration undergoing elective electrical or**
1844 **pharmacologic cardioversion, we recommend therapeutic anticoagulation with well-managed VKA**
1845 **(INR 2-3) or a NOAC using dabigatran, rivaroxaban, edoxaban or apixaban for at least 3 weeks before**
1846 **cardioversion or a transesophageal echocardiography (TEE)-guided approach with abbreviated**

1847 **anticoagulation before cardioversion rather than no anticoagulation (Strong recommendation,**
 1848 **moderate quality evidence).**

1849 *Remark:* With NOACs adherence and persistence should be strongly emphasized

1850

1851 **13. For patients with AF of greater than 48 hours or unknown duration undergoing elective electrical or**
 1852 **pharmacologic cardioversion, we recommend therapeutic anticoagulation (with VKA or NOAC) for at**
 1853 **least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless**
 1854 **of the baseline risk of stroke (strong recommendation, moderate quality evidence)**

1855 *Remark:* Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-
 1856 based recommendations for long-term antithrombotic therapy in recommendations 1 and 2, and not
 1857 on the basis of successful cardioversion

1858

1859 **14. In patients in which LAA thrombus is detected on TEE, cardioversion postponed, and OAC continued**
 1860 **for another 4-12 weeks, to allow thrombus resolution or endothelialisation, we suggest that a decision**
 1861 **on whether a repeat TEE is performed should be individualized (ungraded consensus-based**
 1862 **statement).**

1863

1864

1865 **Cardioversion of AF of 48 h duration or less:**

1866

1867 The duration of AF necessary for development of thrombus is not clear. Therefore, the threshold of AF
 1868 duration below which pre-cardioversion anticoagulation can be safely avoided is not known. It is common
 1869 practice to cardiovert without TEE or prolonged pre-cardioversion anticoagulation if AF is of short duration
 1870 (<48 hours). The problem with this approach is the presence of left atrial thrombus on TEE in up to 14% of
 1871 patients with AF of short duration in observational studies^{265,266}. In addition, the high prevalence of
 1872 asymptomatic AF makes determining the exact duration of AF difficult²⁶⁷. If there is uncertainty about
 1873 precise time of AF onset, then such patients should be managed as if AF >48 hours.

1874

1875 A recent Finnish observational study of 5,116 successful cardioversions in 2,481 patients with acute (<48 h)
 1876 AF showed low incidence of stroke/TE during the 30 days following cardioversion, even without
 1877 perioperative anticoagulation (0.7%)²⁶⁸. These results concur with low rates of stroke/TE in observational
 1878 studies (Table 8). However, there is lower incidence of stroke/TE with cardioversions performed during
 1879 anticoagulation (0.1% vs 0.7%, p=0.001), and with anticoagulation versus no anticoagulation in patients
 1880 with a CHA₂DS₂VASc score of ≥2 (0.2% vs 1.1%, p=0.001). It should also be noted that there is a high risk of
 1881 recurrence of the composite of cardioversion failure and recurrence of AF within 30 days (40%) in acute
 1882 AF²⁶⁹. Overall, the evidence suggests that peri-cardioversion anticoagulation is beneficial and that the
 1883 decision regarding peri- and post-cardioversion anticoagulation should be based on risk of stroke/TE²⁶⁸,
 1884 even if an individual is presenting for the first time with AF.

1885

1886 **Table 8. Thromboembolic Complications in Patients With No Anticoagulation After Cardioversion of**
 1887 **Acute (<48 h) Atrial Fibrillation in Previous Studies (from Airaksinen et al. 2013²⁶⁸)**

First Author (Ref. #)	n	Mean Age, yrs	Male	Success Rate	Thromboembolism
-----------------------	---	---------------	------	--------------	-----------------

Weigner et al. ²⁷⁰	224	68	NA	95%	0.9%*
Michael et al. ²⁷¹	217	64	54	86%	0.5%*
Burton et al. ²⁷²	314	61	55	86%	0 [†]
Gallagher et al. ²³⁵	198	63	68	100%	0.5%‡
Stiell et al. ²⁷³	414	65	56	92%	0 [†]
Xavier Scheuermeyer et al. ²⁷⁴	104	57	92	96%	0

1888 *All 3 thromboembolic events after spontaneous cardioversion and in elderly (>75 years) women.

1889 †Follow-up of 7 days.

1890 ‡Plus 1 probable thromboembolic event. NA, not available

1891

1892

1893 Recommendations

1894 **15. For patients with AF of documented duration of 48 hours or less undergoing elective cardioversion**
 1895 **(electrical or pharmacologic), we suggest starting anticoagulation at presentation (low-molecular-**
 1896 **weight heparin or unfractionated heparin at full venous thromboembolism treatment doses) and**
 1897 **proceeding to cardioversion rather than delaying cardioversion for 3 weeks of therapeutic**
 1898 **anticoagulation or a TEE-guided approach (weak recommendation, low quality evidence).**

1899

1900 **16. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or**
 1901 **pharmacologic), after successful cardioversion to sinus rhythm, we recommend therapeutic**
 1902 **anticoagulation (with VKA or full adherence to NOAC therapy) for at least 4 weeks rather than no**
 1903 **anticoagulation, regardless of baseline stroke risk (weak recommendation, low quality evidence).**

1904 *Remark:* Decisions about long-term anticoagulation after cardioversion should be made in accordance
 1905 with our risk-based recommendations for long-term antithrombotic therapy in recommendations 1 and
 1906 **2**

1907

1908 Patients undergoing urgent cardioversion for hemodynamically unstable AF

1909

1910 Our systematic review of anticoagulation versus no anticoagulation in patients with AF undergoing urgent
 1911 found no published data regarding the optimal anticoagulation strategy to use before or during urgent
 1912 cardioversion for patients with AF and hemodynamic instability. On the basis of the above evidence for
 1913 anticoagulation in elective cardioversion, initiation of anticoagulation immediately before urgent
 1914 cardioversion (e.g., with IV unfractionated heparin or low-molecular weight heparin) would be expected to
 1915 reduce the risk of stroke/TE based on studies of elective cardioversion. Initiation of anticoagulation therapy
 1916 should not delay any emergency interventions required in order to stabilize the patient.

1917 Recommendation

1918 **17. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or**
 1919 **pharmacologic), we suggest that therapeutic-dose parenteral anticoagulation be started before**
 1920 **cardioversion, if possible, but that initiation of anticoagulation must not delay any emergency**
 1921 **intervention (weak recommendation, low quality evidence).**

1922
 1923 **18. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or**
 1924 **pharmacologic), after successful cardioversion to sinus rhythm, we suggest therapeutic**
 1925 **anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm rather than no**
 1926 **anticoagulation, regardless of baseline stroke risk (weak recommendation, low quality evidence).**

1927 *Remark:* Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-
 1928 based recommendations for long-term antithrombotic therapy in recommendations 1 and 2.

1929

1930 **Patients Undergoing Elective or Urgent Cardioversion for Atrial Flutter**

1931

1932 There are no specific trials which have considered electrical cardioversion in the context of atrial flutter and
 1933 associated anticoagulation. Despite the low risk of TE after cardioversion for atrial flutter, which has been
 1934 suggested by some observational studies, even in absence of anticoagulation, other studies have shown a
 1935 similar risk of TE in patients after cardioversion for atrial flutter and AF^{235,275,276}, perhaps due to co-existence
 1936 of AF and atrial flutter. Adults with congenital heart disease represent a growing, important population
 1937 with atrial flutter where long-term studies of outcomes with anticoagulation are required.

1938 **Recommendation**

1939 **19. For patients with atrial flutter undergoing elective or urgent pharmacologic or electrical**
 1940 **cardioversion, we suggest that the same approach to thromboprophylaxis be used as for patients**
 1941 **with atrial fibrillation undergoing cardioversion. (ungraded consensus-based statement).**

1942

1943

1944 **PATIENTS WITH AF WITH CORONARY ARTERY DISEASE**

1945 **ACS and/or PCI**

1946 AF commonly coexists with vascular disease, whether coronary, carotid or peripheral artery disease^{277,278}.

1947 Some AF patients with coronary disease may present with an acute coronary syndrome (ACS). Whether
 1948 stable or acute, such patients may undergo percutaneous intervention with stent deployment. This section
 1949 deals with the antithrombotic therapy management of this group of patients.

1950

1951 There are 4 considerations when managing these patients, as follows^{277,279}:

- 1952 • Stroke prevention, necessitating OAC, whether with VKA or NOAC
- 1953 • Prevention of stent thrombosis, necessitating antiplatelet therapy (APT). There is evidence for
 1954 using DAPT for up to 12 months in non-AF patients.
- 1955 • Prevention of recurrent cardiac ischemia in an ACS patient, necessitating APT. There is some
 1956 evidence for using DAPT for beyond 12 months in non-AF patients from the DAPT and PEGASUS

1957 trials, to reduce non-stent related ischemic and stroke events, but at the risk of more bleeding
 1958 events²⁸⁰.

- 1959 • Serious bleeding risks (e.g., ICH) with the combination of OAC and one or more antiplatelet drug

1960

1961 Additional considerations are the duration of treatment, acute or stable setting, type of APT, stent type,
 1962 OAC type, bleeding risks, etc. Bleeding risk can be assessed by various bleeding risk scores, with the focus
 1963 on modifiable bleeding risk factors; however, the HAS-BLED score is predictive of bleeding in the setting of
 1964 ACS and/or PCI-stenting¹¹⁰. Coronary stent technology has also evolved, with small strut sizes necessitating
 1965 shorter duration of dual APT (DAPT, i.e. aspirin plus P2Y12 inhibitor such as clopidogrel). We are also in the
 1966 era of NOACs, which may offer a better safety profile compared to VKA based therapy. Nonetheless the
 1967 latter may be relatively safe in the presence of well managed anticoagulation control with high TTR²⁸¹.

1968

1969 *AF patients undergoing percutaneous coronary intervention*

1970 Various case series and cohort studies of AF patients undergoing PCI/stenting have been reported. These
 1971 have been systematically reviewed as part of the 2014 and 2018 joint European consensus documents,
 1972 endorsed by HRS and APHRS, which provides consensus recommendations on optimal management of such
 1973 patients^{277,279}. A similar North American expert consensus document has been published²⁸².

1974

1975 In a systematic review and meta-analysis (18 studies with 20,456 patients with AF; 7,203 patients received
 1976 DAPT + VKA and 13,253 patients received DAPT after PCI-S) Chaudhary et al²⁸³, showed that DAPT and VKA
 1977 was associated with significantly lower risk of stroke, stent thrombosis, and all-cause mortality, but the risk
 1978 of major bleeding was significantly higher in the DAPT and VKA group.

1979 Broadly similar conclusions were drawn from the systematic review and meta-analysis (17 studies, 104,639
 1980 patients) by Zhu et al²⁸⁴ where triple therapy (DAPT+OAC) was associated with an increased risk of bleeding
 1981 compared with DAPT alone, with no differences observed between triple therapy and the dual therapy for
 1982 all-cause death, cardiovascular death, or thrombotic complications (i.e., acute coronary syndrome, stent
 1983 thrombosis, thromboembolism/stroke, and major adverse cardiac and cerebrovascular events). In both
 1984 systematic reviews, there was marked heterogeneity in study size, patient population, intervention types,
 1985 stent use, etc.

1986

1987 Bennaghmouch et al²⁸⁵ reported a meta-analysis restricted to the subgroups of patients on aspirin therapy
 1988 (n=21,722) from the four RCTs comparing VKA and NOACs (N=71,681) in AF patients. NOACs were more
 1989 effective (outcome stroke or systemic embolism HR: 0.78 [95% CI, 0.67-0.91] and vascular death HR 0.85
 1990 [0.76-0.93]) and as safe as VKA with respect to major bleeding (HR: 0.83 [95% CI, 0.69-1.01]). NOACs were
 1991 safer with respect to the reduction of intracranial hemorrhage (HR: 0.38 [0.26-0.56]). Thus, it may be both
 1992 safer and more effective to use NOACs as compared with VKA to treat patients with non-valvular AF and
 1993 concomitant aspirin therapy.

1994

1995 The largest observational cohort was reported by Lamberts et al²⁸⁶, which included a total of 12,165 AF
 1996 patients (60.7% male; mean age 75.6 years) hospitalized with MI and/or undergoing PCI between 2001 and
 1997 2009. Relative to triple therapy (OAC plus DAPT, i.e. aspirin plus clopidogrel), no increased risk of recurrent
 1998 coronary events was seen for OAC plus clopidogrel (hazard ratio [HR]: 0.69, 95% CI: 0.48 to 1.00), OAC plus

1999 aspirin (HR: 0.96, 95% CI: 0.77 to 1.19), or aspirin plus clopidogrel (HR: 1.17, 95% CI: 0.96 to 1.42), but
2000 aspirin plus clopidogrel was associated with a higher risk of ischemic stroke (HR: 1.50, 95% CI: 1.03 to 2.20).
2001 OAC plus aspirin and aspirin plus clopidogrel were associated with a significant increased risk of all-cause
2002 death (HR: 1.52, 95% CI: 1.17 to 1.99 and HR: 1.60, 95% CI: 1.25 to 2.05, respectively). When compared to
2003 triple therapy, bleeding risk was non-significantly lower for OAC plus clopidogrel (HR: 0.78, 95% CI: 0.55 to
2004 1.12) and significantly lower for OAC plus aspirin and aspirin plus clopidogrel. Thus, OAC and clopidogrel
2005 was equal or better for both benefit and safety outcomes compared to triple therapy. However, this
2006 analysis provides limited information on the duration of therapies, quality of INR control, stent type,
2007 underlying bleeding risk profile, etc.

2008

2009 *Randomized trials*

2010 Prospective RCTs in AF patients presenting with ACS and/or undergoing PCI/stenting are limited. The first
2011 trial was the WOEST trial²⁸⁷, which randomized 573 adults receiving oral anticoagulants (65% with AF) and
2012 undergoing PCI to clopidogrel alone (double therapy) or clopidogrel plus aspirin (triple therapy). The
2013 primary endpoint of 'any bleeding' was seen in 19.4% receiving double therapy and 44.4% receiving triple
2014 therapy (HR 0.36, 95% CI 0.26-0.50, $p < 0.0001$). Of the secondary endpoints, there was no increase in the
2015 rate of thrombotic events, but all-cause mortality was higher in the triple therapy arm. This trial was
2016 underpowered for efficacy and safety endpoints, and the primary endpoint of 'any bleeding' was driven by
2017 minor bleeds given that triple therapy was mandated for 12 months.

2018

2019 The duration of triple therapy was also addressed by the ISAR-TRIPLE trial²⁸⁸, a RCT in 614 patients receiving
2020 OAC plus aspirin, randomized to either 6-weeks of clopidogrel therapy (n=307) or 6-months of clopidogrel
2021 therapy (n=307). The primary endpoint (composite of death, myocardial infarction (MI), definite stent
2022 thrombosis, stroke, or Thrombolysis In Myocardial Infarction (TIMI) major bleeding at 9 months) occurred
2023 in 30 patients (9.8%) in the 6-week group compared with 27 patients (8.8%) in the 6-month group (HR:
2024 1.14; 95% CI: 0.68 to 1.91; $p=0.63$). There were no significant differences for the secondary combined
2025 ischemic endpoint of cardiac death, MI, definite stent thrombosis, and ischemic stroke (12 [4.0%] vs. 13
2026 [4.3%]; HR: 0.93; 95% CI: 0.43 to 2.05; $p=0.87$) or the secondary bleeding endpoint of TIMI major bleeding
2027 (16 [5.3%] vs. 12 [4.0%]; HR: 1.35; 95% CI: 0.64 to 2.84; $p=0.44$). Thus, 6 weeks of triple therapy was not
2028 superior to 6 months of therapy with respect to net clinical outcomes, suggesting that physicians should
2029 weigh the trade-off between ischemic and bleeding risk when choosing a shorter or longer duration of
2030 triple therapy.

2031

2032 In the PIONEER AF-PCI trial²⁸⁹, 2,124 patients with AF undergoing PCI with stenting were randomized to
2033 low-dose rivaroxaban (15 mg once daily, reduced to 10mg with moderate renal impairment) plus a P2Y12
2034 inhibitor for 12 months (group 1), very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12
2035 months (group 2), or standard VKA (once daily) plus DAPT for 1, 6, or 12 months (group 3). The rates of
2036 clinically significant bleeding were lower in the two groups receiving rivaroxaban than in the VKA group
2037 (16.8% in group 1, 18.0% in group 2, and 26.7% in group 3; hazard ratio for group 1 vs. group 3, 0.59; 95% CI
2038 0.47 to 0.76; $P < 0.001$; hazard ratio for group 2 vs. group 3, 0.63; 95% CI, 0.50 to 0.80; $P < 0.001$). The rates of
2039 death from cardiovascular causes, myocardial infarction, or stroke were similar in the three groups but the
2040 trial was underpowered for efficacy endpoints. There was only a minority of newer P2Y12 inhibitors used

2041 as APT. There was an associated reduction in hospitalizations in the 2 rivaroxaban arms, compared to
2042 VKA²⁹⁰.

2043

2044 In the RE-DUAL PCI trial²⁹¹, randomized 2,725 patients with AF who had undergone PCI to triple therapy
2045 with warfarin plus a P2Y₁₂ inhibitor (clopidogrel or ticagrelor) and aspirin (for 1 to 3 months) (triple-therapy
2046 group) or dual therapy with dabigatran (110 mg or 150 mg twice daily) plus a P2Y₁₂ inhibitor (clopidogrel or
2047 ticagrelor) and no aspirin (110-mg and 150-mg dual-therapy groups). Outside the United States, elderly
2048 patients (≥80 years of age; ≥70 years of age in Japan) were randomly assigned to the 110-mg dual-therapy
2049 group or the triple-therapy group. The incidence of the primary end point (major or clinically relevant non-
2050 major bleeding) was 15.4% in the 110-mg dual-therapy group compared with 26.9% in the triple-therapy
2051 group (HR 0.52; 95%CI 0.42 to 0.63; P<0.001 for non-inferiority; P<0.001 for superiority) and 20.2% in the
2052 150-mg dual-therapy group as compared with 25.7% in the corresponding triple-therapy group, which did
2053 not include elderly patients outside the United States (HR 0.72; 95%CI 0.58 to 0.88; P<0.001 for non-
2054 inferiority). The incidence of the composite efficacy end point of thromboembolic events (myocardial
2055 infarction, stroke, or systemic embolism), death, or unplanned revascularization was 13.7% in the two dual-
2056 therapy groups combined as compared with 13.4% in the triple-therapy group (hazard ratio, 1.04; 95% CI,
2057 0.84 to 1.29; P=0.005 for non-inferiority). Thus, the risk of bleeding was lower among those who received
2058 dual therapy with dabigatran and a P2Y₁₂ inhibitor than among those who received triple therapy with
2059 warfarin, a P2Y₁₂ inhibitor, and aspirin. Dual therapy was non-inferior to triple therapy with respect to the
2060 risk of thromboembolic events. In contrast to the PIONEER-AF trial, the REDUAL PCI trial tested dabigatran
2061 doses (110mg and 150mg bid) which are licensed for stroke prevention in AF.

2062

2063 There are limited data on use of the newer P2Y₁₂ inhibitors (ticagrelor, prasugrel) with OAC. Observational
2064 cohorts in AF patients report a higher bleeding rate where these newer APT agents are used as part of a
2065 triple therapy regime, compared to when clopidogrel is used as part of the triple therapy regime²⁹². Only a
2066 minority of patients in PIONEER AF-PCI had newer P2Y₁₂ agents, whereas the largest experience in AF
2067 patients was in the RE-DUAL PCI trial, which allowed ticagrelor in combination with dabigatran 110mg or
2068 150mg bid.

2069

2070 In the GEMINI-ACS-1 trial²⁹³, 3037 patients with ACS (i.e. essentially a non-AF population) were randomly
2071 assigned to either aspirin 100mg or rivaroxaban 2.5mg bid, and the subsequent choice of clopidogrel (44%)
2072 or ticagrelor (in 56%) during trial conduct was non-randomized. Low-dose rivaroxaban with a P2Y₁₂
2073 inhibitor for the treatment of ACS patients had similar risks of clinically significant bleeding (5%) as aspirin
2074 and a P2Y₁₂ inhibitor [HR 1.09 [95% CI 0.80-1.50]; p=0.5840].

2075

2076 **Stable vascular disease**

2077

2078 The presence of vascular disease adds to stroke risk in patients with AF. In the Danish registries, AF patients
2079 with vascular disease (prior myocardial infarction, prior peripheral artery disease, or aortic plaque) as a
2080 single risk factor have a high stroke rate of 4.85 per 100 person-years²⁹⁴. This corresponds to CHA₂DS₂-
2081 VASc=1 for males and a CHA₂DS₂-VASc=2 for females, with rates of 4.53 and 5.69, respectively. Contrasting
2082 low risk CHA₂DS₂-VASc (that is, score 0 (male) or 1 (female)) as a reference population vs. those with ≥1
2083 additional stroke risk factors (i.e. CHA₂DS₂-VASc score =1 (male) or =2 (females)), the risk attributable to

2084 vascular disease had a crude HR of 2.7 (95%CI 1.7-4.2). In Asian countries²⁹⁵, PAD may confer an ischemic
 2085 stroke risk that is much higher than that seen in Western populations²⁹⁶.

2086

2087 In AF patients with stable CAD there is no evidence that adding APT to OAC reduces stroke/SE, death, or MI.
 2088 However, the risk of major bleeding and ICH is substantially increased with the addition of APT to OAC.

2089 The largest cohort was reported by Lamberts et al²⁹⁷ where 8700 AF patients (mean age, 74.2 years; 38%
 2090 women) with stable CAD (defined as 12 months from an acute coronary event) followed-up for a mean 3.3
 2091 years, found the risk of myocardial infarction/coronary death was similar for VKA plus aspirin (HR 1.12; 95%
 2092 CI 0.94-1.34]) and VKA plus clopidogrel (HR 1.53; 95% CI 0.93-2.52]), relative to VKA monotherapy,
 2093 However, the risk of bleeding increased >50% when aspirin (HR 1.50; 95% CI 1.23-1.82]) or clopidogrel (HR
 2094 1.84; 95% CI 1.11-3.06]) was added to VKA.

2095

2096 In the RCTs of NOACs compared to warfarin, aspirin at <100mg daily was allowed. Ancillary analyses show
 2097 no added benefit of adding aspirin on stroke or mortality rates; however, absolute bleeding rates were
 2098 higher with combination therapy, but the relative efficacy and safety with NOAC vs. warfarin use was
 2099 maintained irrespective of aspirin use²⁹⁸. Only the RELY trial showed data for combination of dabigatran
 2100 with aspirin and/or clopidogrel, and as expected, major bleeding risks were increased with a single APT and
 2101 further increased where 2 APTs were used²⁹⁹.

2102 Less data are evident for OAC use in AF patients with stable isolated PAD or carotid disease, in relation to
 2103 OAC use. However, it is reasonable to assume that data for CAD would be generally applicable to PAD or
 2104 carotid disease. One post-hoc ancillary analysis³⁰⁰ from the ROCKET-AF trial reported that the efficacy of
 2105 rivaroxaban when compared with warfarin for the prevention of stroke or systemic embolism was similar in
 2106 patients with PAD (HR: 1.19, 95% CI: 0.63-2.22) and without PAD (HR: 0.86, 95% CI: 0.73-1.02; interaction P
 2107 = 0.34). However, there was a higher risk of major bleeding or NMCR bleeding with rivaroxaban when
 2108 compared with warfarin in AF patients with PAD (HR: 1.40, 95% CI: 1.06-1.86) compared with those
 2109 without PAD (HR: 1.03, 95% CI: 0.95-1.11; interaction P = 0.037).

2110 Recommendations

2111 **20. In AF patients presenting with an ACS and/or undergoing PCI/stenting, we recommend assessment of**
 2112 **stroke risk using the CHA₂DS₂-VAsc score (Strong recommendation, moderate quality evidence)**

2113 *Remark:* All such patients are not 'low risk' and should be considered for concomitant OAC.

2114

2115 **21. In AF patients presenting with an ACS and/or undergoing PCI/stenting, we suggest attention to**
 2116 **modifiable bleeding risk factors at every patient contact, and assessment of bleeding risk using the**
 2117 **HAS-BLED score (weak recommendation, low quality evidence).**

2118 *Remark:* Where bleeding risk is high (HAS-BLED ≥3), there should be more regular review and follow-up.

2119

2120 **22. In AF patients requiring OAC undergoing elective PCI/stenting, where bleeding risk is low (HAS-BLED**
 2121 **0-2) relative to risk for recurrent ACS and/or stent thrombosis, we suggest triple therapy for one**
 2122 **month, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) until 12**
 2123 **months, following which OAC monotherapy can be used (weak recommendation, low quality**
 2124 **evidence).**

2125

2126 **23. In AF patients requiring OAC undergoing elective PCI/stenting, where bleeding risk is high (HAS-BLED**
2127 **≥3), we suggest triple therapy for one month, followed by dual therapy with OAC plus single**
2128 **antiplatelet (preferably clopidogrel) for 6 months, following which OAC monotherapy can be used**
2129 **(weak recommendation, low quality evidence)**

2130

2131 **24. In AF patients requiring OAC undergoing elective PCI/stenting , where bleeding risk is unusually high**
2132 **and thrombotic risk relatively low, we suggest use of OAC plus single antiplatelet (preferably**
2133 **clopidogrel) for 6 months, following which OAC monotherapy can be used (weak recommendation,**
2134 **low quality evidence)**

2135

2136 *Remark:* Patients at unusually high bleeding risk may include patients with HAS-BLED ≥3 and recent
2137 acute bleeding event. High thrombotic risk may include those with left main stent, multivessel
2138 PCI/stenting, etc.

2139

2140

2141 **25. In AF patients requiring OAC presenting with an ACS, undergoing PCI/stenting, where bleeding risk is**
2142 **low (HAS-BLED 0-2) relative to risk for ACS or stent thrombosis, we suggest triple therapy for 6**
2143 **months, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) until 12**
2144 **months, following which OAC monotherapy can be used (weak recommendation, low quality**
2145 **evidence)**

2146

2147 **26. In AF patients requiring OAC presenting with an ACS, undergoing PCI/stenting, where bleeding risk is**
2148 **high (HAS-BLED ≥3), we suggest triple therapy for 1-3 months, followed by dual therapy with OAC**
2149 **plus single antiplatelet (preferably clopidogrel) up to 12 months, following which OAC monotherapy**
2150 **can be used (weak recommendation, low quality evidence).**

2151

2152 **27. In AF patients requiring OAC presenting with an ACS, undergoing PCI/stenting where bleeding risk is**
2153 **unusually high and thrombotic risk low, we suggest OAC plus single antiplatelet (preferably**
2154 **clopidogrel) for 6-9 months may be considered, following which OAC monotherapy can be used.**
2155 **(weak recommendation, low quality evidence).**

2156 *Remark:* Patients at unusually high bleeding risk may include patients with HAS-BLED ≥3 and recent
2157 acute bleeding event. High thrombotic risk may include those with left main stent, multivessel
2158 PCI/stenting, etc.

2159

2160 **28. In AF patients with ACS or undergoing PCI in whom OAC is recommended, we suggest using VKA with**
2161 **TTR>65-70% (INR range 2.0-3.0), or to use a NOAC at a dose licensed for stroke prevention in AF**
2162 **(weak recommendation, low quality evidence).**

2163 *Remark:* Only Dabigatran 150mg bid or (not licensed in USA) 110mg bid or Rivaroxaban 15mg qd are
2164 currently supported by clinical trial evidence. A NOAC based strategy has lower bleeding risk compared
2165 to a VKA-based strategy.

2166

2167 **29. In AF patients in which aspirin is concomitantly used with OAC, we suggest a dose of 75-100mg qd**
 2168 **with concomitant use of PPI to minimize gastrointestinal bleeding (Weak recommendation, low**
 2169 **quality evidence)**

2170

2171 **30. In AF Patients in which a P2Y12 inhibitor is concomitantly used with OAC, we suggest the use of**
 2172 **clopidogrel (Weak recommendation, low quality evidence)**

2173 *Remark:* Newer agents (eg. Ticagrelor) can be considered where bleeding risk is low. Data on the
 2174 combination of ticagrelor with either dabigatran 110mg bid or 150 bid (without concomitant aspirin
 2175 use) are available from the RE-DUAL PCI trial.

2176 **31. For patients with AF and stable coronary artery disease (eg, no acute coronary syndrome within the**
 2177 **previous year) and who choose oral anticoagulation, we suggest OAC with either a NOAC or adjusted-**
 2178 **dose VKA therapy alone (target international normalized ratio [INR] range, 2.0-3.0) rather than the**
 2179 **combination of OAC and aspirin (Weak recommendation, low quality evidence)**

2180

2181

2182

2183

2184 **CATHETER OR SURGICAL ABLATION, ELECTROPHYSIOLOGICAL PROCEDURES**

2185

2186 **Periprocedural anticoagulation for catheter ablation and implantable devices**

2187

2188 Randomized trials have shown that uninterrupted warfarin is safe and superior to warfarin
 2189 interruption for implantation of cardiac implantable electronic devices.⁷

2190

2191 For catheter ablation, anticoagulation guidelines pertinent to cardioversion generally apply to
 2192 periprocedural anticoagulation and are detailed in a recent professional society expert consensus
 2193 statement³⁰¹. In a randomized trial of 1584 patients, uninterrupted warfarin, compared to
 2194 interruption with heparin bridging, has been shown to have a lower risk of periprocedural stroke and
 2195 bleeding³⁰². A randomized trial of uninterrupted rivaroxaban vs. uninterrupted VKA in AF ablation
 2196 demonstrated similar event rates in both arms³⁰³. A similar randomized trial of uninterrupted
 2197 dabigatran found that dabigatran was associated with fewer bleeding complications than
 2198 uninterrupted warfarin³⁰⁴. Although these studies were open-label, they strongly support the use of
 2199 uninterrupted anticoagulation for electrophysiology procedures (**Table 9**). Two recent systematic
 2200 reviews with meta-analyses that include these studies found consistent with results^{305,306}.

2201

2202 **Long-term anticoagulation after restoration of sinus rhythm**

2203 Clinical observations indicate that AF and stroke are often temporally discordant, with stroke
 2204 occurring during periods of sinus rhythm in the majority of patients with paroxysmal AF^{307,308}.

2205

2206 After catheter ablation, discontinuation of OAC is associated with an increased risk of stroke³⁰¹.
 2207 Similarly, post-operative AF may confer a long-term risk of stroke. In a U.S. claims analysis of 1.7
 2208 million patients hospitalized for surgery, perioperative atrial fibrillation was associated with an
 2209 increased long-term risk of ischemic stroke, especially following non-cardiac surgery³⁰⁹. It is not
 2210 known to what extent the risk was mediated by AF recurrence (often asymptomatic) or was
 2211 independent of rhythm. Thus, patients should be anticoagulated according to their thromboembolic
 2212 risk profile based on CHA₂DS₂-VASc, regardless of whether sinus rhythm has been restored via
 2213 ablation, cardioversion, or other means.

2214 Recommendations

2215 **32. In patients with AF in whom catheter ablation of AF or implantation of cardiac electronic**
 2216 **implantable devices is planned, we suggest performing the procedure on uninterrupted VKA in**
 2217 **the INR therapeutic range, dabigatran or rivaroxaban (weak recommendation, low quality**
 2218 **evidence).**

2219
 2220
 2221 **33. In patients in whom sinus rhythm has been restored, we suggest that long-term**
 2222 **anticoagulation should be based on the patient's CHA₂DS₂-VASc thromboembolic risk profile,**
 2223 **regardless of whether sinus rhythm has been restored via ablation, cardioversion (even**
 2224 **spontaneous), or other means (Weak recommendation, low quality evidence).**

2225
 2226
 2227 **Table 9: Summary of Studies of Periprocedural Anticoagulation for Catheter Ablation of Atrial**
 2228 **Fibrillation and Implantation of Cardiac Electronic Implantable Devices:**
 2229

Trial	Population	Interventions	Results
COMPARE ³⁰²	Catheter ablation of AF N=1584	Uninterrupted warfarin vs. interrupted warfarin with low-molecular weight bridging	Significant reduction in stroke (0.25% vs 3.7%), TIA (0% vs. 1.3%), and minor bleeding with uninterrupted warfarin
VENTURE-AF ³⁰³	Catheter ablation of AF N = 248	Uninterrupted rivaroxaban vs. uninterrupted VKA	No difference in overall low incidence of major bleeding (0.4%) or thromboembolic events (0.8%)
RE-CIRCUIT ³⁰⁴	Catheter ablation of AF N = 704	Uninterrupted dabigatran vs. uninterrupted warfarin	Significant reduction in major bleeding events with dabigatran (1.6% vs. 6.9%)
BRUISE-CONTROL ³¹⁰	Pacemaker or defibrillator	Uninterrupted warfarin vs.	Significant reduction in pocket hematoma

implantation
N = 343

interrupted warfarin (3.5% vs. 16%)
with heparin bridging

2230

ACCEPTED MANUSCRIPT

2231

2232 **CEREBROVASCULAR DISEASE**

2233

2234 **AF patients presenting with an acute ischemic stroke or TIA**

2235

2236 In AF-associated acute ischemic stroke, the risk of early recurrence is high: for example, the
2237 International Stroke Trial reported a 4.8% risk of recurrent stroke in those with AF within the first 2
2238 days³¹¹, while other studies suggest a recurrence risk of between 0.4% and 1.3% per day in the first
2239 7-14 days³¹¹⁻³¹⁵. AF-related ischemic strokes are more often disabling or fatal than other types, with
2240 longer hospital stays and higher costs³¹⁶, so preventing early recurrence is a key clinical challenge.

2241

2242 The safety and benefit of OAC in acute stroke have not been established. Early anticoagulation (i.e.
2243 in the first few days) might increase the risk of symptomatic intracranial hemorrhage, including
2244 hemorrhagic transformation of the infarct (estimated at ~1% per day³¹⁷), leading to clinical
2245 uncertainty about when to start anticoagulation. Recent studies reported an 8-10% risk of recurrent
2246 ischemic stroke and a 2-4% risk of symptomatic intracranial hemorrhage within 90 days of AF-related
2247 ischemic stroke^{318,319}.

2248

2249 *Current uncertainty regarding optimal timing of anticoagulation*

2250 Current guidelines do not provide clear recommendations on the timing of OAC after acute AF-
2251 related stroke. US guidelines suggest that commencing OAC within 14 days is reasonable³²⁰ while
2252 recent European Society of Cardiology guidelines recommend starting anticoagulation - according to
2253 infarct size – at 1, 3, 6, or 12 days³²¹ based only on expert consensus. Current UK guidelines
2254 recommend delaying anticoagulation for 14 days for “disabling” stroke (Intercollegiate Stroke
2255 Working Party. National Clinical Guideline for Stroke 2016. (<https://www.strokeaudit.org>).

2256

2257 A recent observational study (n=1029) suggested that anticoagulation at 4-14 days after
2258 cardioembolic stroke had the best outcome, but did not have statistical power to determine benefit
2259 of earlier anticoagulation³²². Increasing cerebral infarct size is associated with increased risk of both
2260 symptomatic hemorrhagic transformation and early recurrent ischemia³¹⁷

2261

2262 A systematic review and meta-analysis of 7 randomized trials of unfractionated heparin (UFH), low-
2263 molecular-weight heparin (LMWH) or heparinoids (n=4624) started <48 hours, vs. aspirin or placebo,
2264 found that early anticoagulation was associated with non-significantly reduced recurrent ischemic
2265 stroke, but with increased intracranial bleeding, and no reduction in death or disability (e-Table
2266 19).³¹⁴ In contrast, other small studies suggested fewer ischemic strokes without an increase in
2267 intracranial bleeding, as well as reduced mortality and disability with early initiation of vitamin K
2268 antagonists (to achieve therapeutic levels by day 7)^{319,323-325}. Observational data suggest that the use
2269 of low molecular weight heparin (as a “bridging” strategy) together with oral anticoagulation is
2270 associated with a higher risk of symptomatic hemorrhage.^{318,326-328}

2271

2272 Observational studies suggest early (<14 days) anticoagulation with NOACs might be safe^{318 319,322}
2273³²⁹. One study reported improved outcomes and no early ICH with NOAC started at a median of 4

2274 days post-stroke (n=1192)^{330,331}. The Pre-TIMING observational study of 249 patients with AF-
 2275 associated acute ischemic stroke treated with OAC (<5 days) reported in-hospital recurrent ischemic
 2276 stroke in 4.4%, and symptomatic ICH in 3.1%³³². There are no large trials of NOACs including
 2277 patients within 7-14 days of a stroke, but one small study (Triple AXEL) randomized 195 patients with
 2278 AF-related acute ischemic stroke to rivaroxaban or warfarin <5 days and found similar rates of
 2279 symptomatic/asymptomatic MRI-defined recurrent ischemia (~30%) or intracranial bleeding (~30%)
 2280 at 4 weeks, with reduced hospital stay for rivaroxaban³³³.

2281 Recommendations

2282 **34. In AF patients with acute ischaemic stroke, we suggest that very early anticoagulation (<48h)**
 2283 **using heparinoids or VKA should not be used (ungraded consensus-based statement).**

2284 *Remark:* Heparinoids should not be used as bridging therapy in the acute phase of ischaemic
 2285 stroke because they appear to increase the risk of symptomatic intracranial haemorrhage
 2286 without net benefit. The optimal timing of anticoagulation after acute ischaemic stroke is
 2287 unknown.

2288

2289 **35. In AF patients with acute stroke without contraindications, we recommend that long term oral**
 2290 **anticoagulation is indicated as secondary prevention (Strong recommendation, high quality**
 2291 **evidence).**

2292 *Remark:* The optimal timing of anticoagulation early after acute ischaemic stroke is unknown.
 2293 Early use of NOACs shows promise but requires testing in randomised controlled trials.

2294

2295 **36. In AF patients with acute ischaemic stroke, We suggest that oral anticoagulation should**
 2296 **usually be started within 2 weeks of acute ischaemic stroke, but the optimal timing within this**
 2297 **period is not known (ungraded consensus-based statement).**

2298 *Remark:* Although infarct size is clinically used to guide timing of anticoagulation, it is predictive
 2299 of a higher risk of early recurrent ischaemia, haemorrhagic transformation of the infarct, and
 2300 poor outcome, so might not be helpful in determining the net benefit of early treatment.

2301 *Remark:* Anticoagulation with NOACs soon after stroke (earlier than 1 week) has not been tested
 2302 in randomised trials, but shows promise in observational studies.

2303

2304 AF patients with intracerebral hemorrhage (ICH)

2305

2306 Spontaneous (non-traumatic) intracerebral hemorrhage (ICH) causes about 1 in 10 strokes, and is
 2307 caused by the rupture of a cerebral artery or arteriole, most often a small vessel affected by either
 2308 hypertensive arteriopathy or cerebral amyloid angiopathy. ICH is the most feared, often lethal,
 2309 complication of antithrombotic (anticoagulant and antiplatelet) therapy. Recent data indicate that
 2310 about 50% of people with ICH are taking an antithrombotic agent at the time of ICH.³³⁴ In a recent
 2311 hospital ICH cohort study, 25% of patients had AF³³⁵

2312

2313 *Risk of ischemic stroke*

2314 Survivors of ICH with AF are at risk of further brain ischemia but also recurrent ICH. The use of
 2315 antithrombotic therapy (antiplatelet agents and anticoagulants) following ICH thus presents a major
 2316 clinical dilemma. The risk of ischemic stroke with and without antithrombotic treatment must be

2317 weighed carefully against the possible increase in ICH risk associated with antithrombotic therapy.
2318 The risk of ischemic stroke in people with AF is typically estimated using instruments such as the
2319 CHA₂DS₂VASC score and it seems reasonable to use this score in populations of ICH survivors³³⁶.

2320

2321 *Risk of recurrent ICH*

2322 The future risk of ICH is highly variable; the annual recurrence risk was between 1.8% and 7.4% in
2323 one recent systematic review of observational studies³³⁷. Computed tomography is a highly sensitive
2324 test for ICH and can classify the location as “lobar” (originating in the lobes of the brain) or “deep”
2325 (originating in the basal ganglia or brainstem).³³⁸ The risk of recurrence has been reported to be
2326 higher for lobar ICH than after deep ICH,³³⁷ a finding which is probably related to different
2327 underlying small vessel diseases that cause ICH in the different locations. Although CT can define ICH
2328 location, it cannot reliably identify the underlying type of causal small vessel disease. Magnetic
2329 resonance imaging (MRI) can identify biomarkers of small vessel disease including cerebral
2330 microbleeds (CMBs), whose distribution can be used to diagnose cerebral amyloid angiopathy (CAA)
2331 with high specificity in ICH cohorts³³⁹. In a recent pooled analysis of observational studies, patients
2332 with ICH classified using CMBs as due to CAA had a ~7% annual recurrence risk, compared with ~1%
2333 for those not fulfilling criteria for CAA³⁴⁰.

2334

2335 Since oral anticoagulants increase the risk of ICH, some experts have recommended avoiding them in
2336 patients with ICH attributed to CAA. In survivors of ischemic stroke and TIA, CMBs are also
2337 associated with increased risk of ischemic stroke, although as the number of CMBs increases, the risk
2338 of future ICH increases more steeply than that of ischemic stroke.³⁴¹ In ICH survivors the number of
2339 CMBs is also associated with the risk of recurrent ICH.³⁴²

2340

2341 *Balancing the risks of ischemic stroke and recurrent ICH*

2342 A decision analysis which modelled warfarin for AF in an ICH survivor suggested that in lobar ICH
2343 avoiding warfarin increased quality-adjusted life (QOL) years by 1.9, compared with 0.3 for deep ICH;
2344 the authors concluded that anticoagulation for AF should not be offered to patients with lobar ICH
2345 and only to survivors of deep ICH if the risk of ischemic events was high (>7% per year)³⁴³. However,
2346 CMBs were not considered in this analysis. In contrast, recent “real-world” observational
2347 studies (including some very large registry datasets) from ICH survivors with AF suggest that
2348 anticoagulation might reduce mortality and ischemic complications, without an unacceptable
2349 increase in ICH.

2350

2351 A recent systematic review and meta-analysis of observational studies suggested that restarting
2352 anticoagulation was associated with a significantly lower risk of thromboembolic complications
2353 (pooled RR 0.34; 95% CI 0.25–0.45; Q=5.12, P for heterogeneity=0.28) with no increased risk of
2354 recurrent ICH (pooled RR 1.01; 95% CI 0.58–1.77; Q=24.68, P for heterogeneity <0.001).³⁴⁴ However,
2355 none of the real world studies stratified ICH by location, nor by CMB burden or distribution. Two
2356 small randomized studies of early anticoagulation after ICH were not able to confirm benefit or
2357 harm.^{345,346} There are no reliable randomized trial data to guide the timing of anticoagulation after
2358 ICH. In acute ICH, hematoma expansion is common, and is aggravated by anticoagulation.
2359 Anticoagulants should therefore be reversed and avoided in acute ICH (<24-48 hours).

2360

2361 A survival model based on observational data indicated that the total stroke risk (both ischemic and
2362 ICH) was lowest when anticoagulation was restarted after about 10 weeks, and a delay of at least 4
2363 weeks after ICH was suggested.³⁴⁷ There are no large scale randomized controlled trials to answer
2364 the question of whether long-term anticoagulation has net benefit in ICH survivors with AF. NOACs
2365 have a ~50% lower ICH risk than VKA¹²⁷, and are therefore preferred in most ICH survivors, except
2366 where warfarin is indicated (e.g. in those with metallic mechanical heart valves). Observational data
2367 suggest that ICH occurring on OAC are of similar size and with similar clinical outcome in patients
2368 taking VKA or NOACs.³⁴⁸

2369

2370 There are two ongoing randomized trials of antithrombotic use after ICH: APACHE-AF
2371 (<http://apache-af.nl> –aspirin vs. apixaban vs. no antithrombotics for the treatment of AF in patients
2372 after ICH) and RESTART (www.restarttrial.org –antiplatelets vs. no antiplatelets in patients with ICH
2373 with an indication for antiplatelets).

2374

2375 *Left atrial appendage occlusion in ICH survivors*

2376 Randomized trials indicate that left atrial appendage occlusion (LAAO) has similar efficacy to oral
2377 anticoagulation in patients with AF; thus, in ICH survivors with AF and high ischemic stroke risk,
2378 LAAO is a potentially attractive option to reduce ischemic stroke and systemic embolism from AF
2379 without the need to expose patients to a long-term risk of oral anticoagulation.³⁴⁹ Observational
2380 data from 1025 patients suggest that LAAO might be safe and effective in patients with a contra-
2381 indication to long term oral anticoagulation, but only a minority of patients (15%) in this study had
2382 suffered ICH.³⁵⁰ Small studies of ICH survivors suggest that LAAO, using antiplatelet treatment as
2383 periprocedural antithrombotic treatment, is safe and effective in this population, including those
2384 with CAA^{351,352} Randomized trials of LAAO, ideally in comparison to NOACs, are needed to
2385 definitively determine the safety and efficacy of each approach in ICH survivors.

2386 Recommendations

2387 **37. In patients with AF and high ischaemic stroke risk, we suggest anticoagulation with a NOAC**
2388 **after acute spontaneous ICH (which includes subdural, subarachnoid and intracerebral**
2389 **haemorrhages) after careful consideration of the risks and benefits (ungraded consensus-**
2390 **based statement).**

2391 *Remark:* The balance of net benefit from long term oral anticoagulation might be more
2392 favourable in those with deep ICH or without neuroimaging evidence of cerebral amyloid
2393 angiopathy.

2394 *Remark:* In ICH survivors with AF, clinicians should aim to estimate the risk of recurrent ICH
2395 (using ICH location and, where available, MRI biomarkers including cerebral microbleeds) and
2396 the risk of ischaemic stroke

2397 *Remark:* The optimal timing of anticoagulation after ICH is not known, but should be delayed
2398 beyond the acute phase (~48 hours) and probably for at least ~4 weeks. Randomised trials of
2399 NOACs and left atrial appendage occlusion are ongoing.

2400

2401 **38. In ICH survivors at high risk of recurrent ICH (e.g. those with probable cerebral amyloid**
2402 **angiopathy), we suggest left atrial appendage occlusion (ungraded consensus-based**
2403 **statement).**

2404 *Remark:* Cerebral amyloid angiopathy should be diagnosed using validated clinico-radiological
2405 criteria.

2406

2407 **AF patients with carotid disease**

2408

2409 Carotid stenosis is present in about 8% of people over the age of 60.³⁵³ A recent multicenter
2410 retrospective study found >50% carotid stenosis in 18.3% of patients with AF, which was associated
2411 with a doubling of stroke risk.³⁵⁴ Thus in patients with both carotid stenosis and AF there are
2412 indications for both anticoagulation and antiplatelet therapy, yet this combination, at least in the
2413 long term, is associated with high bleeding risk and is thus generally not recommended.

2414

2415 Randomized trials show superiority for carotid endarterectomy over stenting in patients with
2416 symptomatic stenosis (>50%) of the internal carotid artery.³⁵⁵ This could reduce the need for
2417 combination therapy with OAC and antiplatelet drugs in those with AF. Current practice is to treat all
2418 potential stroke risk factors including AF and carotid stenosis. Those who have had successful carotid
2419 revascularization are typically managed with OAC alone. In patients with carotid stenosis not treated
2420 by revascularization (including those with asymptomatic disease) as well as AF, the optimal
2421 management is not known and requires further randomized data; meanwhile, decisions need to be
2422 tailored to the individual patient.

2423 **Recommendations**

2424 **39. In patients with AF and symptomatic carotid stenosis (>50%), we suggest carotid**
2425 **revascularisation with endarterectomy or stenting in addition to OAC as indicated (Weak**
2426 **recommendation, moderate quality evidence).**

2427

2428 **40. In patients with AF and carotid stenosis treated with revascularisation, we suggest OAC**
2429 **therapy, without long-term antiplatelet therapy (ungraded consensus-based statement).**

2430 *Remark:* There is limited evidence to guide the optimal treatment of patients with AF and carotid
2431 stenosis not requiring revascularisation. *Remark:* Short-term concomitant antiplatelet therapy
2432 (dual or mono) is generally used in the immediate post-revascularisation period (e.g. 1-3
2433 months)

2434

2435 **Patients presenting with Embolic Stroke of Undetermined Source (ESUS)**

2436

2437 In North America and Europe, about 1 in 4 ischemic strokes remain of uncertain etiology (i.e. not
2438 attributable to definite cardiac embolism, large artery atherosclerosis, or small artery disease),
2439 despite adequate investigation, and are termed “cryptogenic”.^{320,356}

2440

2441 Because most cryptogenic strokes are embolic, a more recent concept of embolic stroke of
2442 undetermined source (ESUS) has been developed, defined as ischemic stroke detected by CT or MRI
2443 that, after a standardized and adequate diagnostic pathway including brain imaging,
2444 echocardiography, cardiac rhythm monitoring for at least 24 hours, and imaging of the intracranial
2445 and extracranial arteries supplying the affected brain area: is not lacunar (subcortical, less than
2446 15mm diameter); where there is absence of extracranial or intracranial atherosclerosis causing ≥50%

2447 luminal stenosis in the arteries supplying the area of ischemia; no major-risk cardioembolic source of
 2448 embolism (permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intra-cardiac
 2449 thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumours, mitral stenosis, recent
 2450 (<4 weeks) myocardial infarction, left ventricular ejection fraction less than 30%, valvular
 2451 vegetations, or infective endocarditis); and no other specific cause of stroke identified (e.g. arteritis,
 2452 dissection, migraine/vasospasm, drug misuse)³⁵⁷.

2453 Thus, ESUS is a sub-category of cryptogenic stroke, accounting for about 1 in 6 ischemic strokes.³⁵⁸ A
 2454 careful and systematic diagnostic work up in patients with ESUS is needed as there might be
 2455 important management differences between underlying embolic sources if detected, such as aortic
 2456 arch atheroma, patent foramen ovale, and paroxysmal AF. This brief section only refers to the
 2457 latter.

2458
 2459 As a general principle, AF can be detected in a high proportion of ESUS patients, if we 'look harder,
 2460 look longer and look with more sophisticated monitoring' (Table 10). Screening consecutive patients
 2461 with ischemic stroke with routine Holter or event loop recorder monitoring will identify new
 2462 AF/atrial flutter in approximately 1 in 20 patients³⁵⁹.

2463
 2464 Two randomized controlled trials clearly showed that prolonged cardiac monitoring increases the
 2465 detection of occult AF in patients with TIA or acute ischemic stroke presenting in sinus rhythm. In
 2466 CRYSTAL AF, 441 patients randomly assigned to prolonged ambulatory cardiac monitoring with a
 2467 subcutaneous implantable loop recorder or to a control group with conventional follow-up, detected
 2468 more AF in the monitored group (8.9% vs. 1.4% in the control group; HR 6.4, 95% CI 1.9-21.7);³⁶⁰
 2469 while in EMBRACE, 572 patients randomly assigned to additional ambulatory monitoring with a 30-
 2470 day external loop recorder (intervention group) or a 24-hour Holter monitor (control group) found
 2471 more AF in the intervention group (16.1% vs. 3.2% in the control group; absolute difference, 12.9 %
 2472 95% CI 8.0-17.6).³⁶¹

2473
 2474 In a systematic review and meta-analysis, Sposato et al³⁶² described a much higher rate of AF
 2475 detection after multi-phase sequential cardiac monitoring, at 23.7% (Table 10). Despite this, one
 2476 recent analysis only found that 2.6% and 9.7% of stroke patients had ambulatory ECG monitoring in
 2477 the 7 days and 12 months post-stroke leading to underdiagnosis.³⁶³

2478

2479

2480 **Table 10: Phases of screening for AF in cryptogenic stroke patients, methods and incidence of AF**
 2481 **diagnosed**³⁶²

2482

4 sequential phases of screening	Cardiac monitoring methods	% (95% CI) diagnosed with
Phase 1 (emergency room)- Phase 2 (in hospital)	admission electrocardiogram (ECG) serial ECG, continuous inpatient ECG monitoring, continuous inpatient cardiac telemetry, and in- hospital Holter monitoring	7.7% (5.0–10.8) 5.1% (3.8–6.5)
Phase 3 (first ambulatory period)	ambulatory Holter;	10.7% (5.6–17.2)
Phase 4 (second ambulatory period)	mobile cardiac outpatient telemetry, external loop recording, and implantable loop recording	16.9% (13.0–21.2)

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Unsurprisingly, AF is more likely to be detected in elderly patients with more prolonged monitoring, especially if there is evidence of prior embolic cortical or cerebellar infarction^{364,365}. In a retrospective analysis, newly detected atrial tachycardia (AT) or AF (NDAF; AT/AF >5 minutes on any day) was identified in 30% patients with implantable cardiac rhythm devices and ≥ 1 stroke risk factors during a follow-up of 1.1 years³⁶⁶. The presence of AT/AF >6 hours on ≥ 1 day increased significantly with increased CHADS₂ scores. Similarly, the ASSERT-II study reported that subclinical AF lasting ≥ 5 minutes was present in 34.4% per year, in a prospective cohort of elderly patients with risk factors but no prior stroke³⁶⁷.

Of note, data from the Athens Stroke Registry show that the CHADS₂ and CHA₂DS₂-VASc scores are independently associated with the risk of ischemic stroke/TIA recurrence and death in ESUS patients, with the risk of stroke recurrence and death in patients with a CHA₂DS₂-VASc score ≥ 2 being approximately 3-fold and 15-fold higher compared with that in patients with a score of 0, respectively³⁶⁸. If ESUS is phenotypically different from AF-associated stroke, we should see differences in stroke severity and outcomes; however, no difference in NIHSS score was evident in ESUS where AF was detected on follow-up, compared to where no AF was evident³⁶⁹. Nevertheless, it remains possible that within ESUS there is a spectrum of underlying proximal embolic sources, suggested by the strong effect of age on recurrence risk and mortality³⁷⁰.

Current guidelines recommend use of antiplatelet agents including aspirin in ESUS patients³²⁰ unless AF is detected (often requiring prolonged work up, as above), when such patients would be managed with oral anticoagulation. The available data (mainly from retrospective observational studies) suggest a sizeable rate of stroke recurrence (more than 4% per year) despite the frequent use of antiplatelet agents in clinical practice.³⁵⁸ Thus, there is an important clinical need for more effective antithrombotic therapy for ESUS. Since a large proportion of ESUS are likely to be due to undetected AF, oral anticoagulation is a theoretically attractive option.

Ongoing randomized trials comparing NOACs to aspirin in ESUS patients are in progress. Prior to data from these trials, physicians might, in the meantime, consider the use of anticoagulation in parallel with continued cardiac evaluation (e.g. prolonged rhythm monitoring) after discussion and consideration of patient preference.

2517 **ATRIAL HIGH-RATE EPISODES DETECTED BY CARDIAC IMPLANTED** 2518 **ELECTRONIC DEVICES**

2519 Cardiac implanted electrical devices (CIEDs) with an atrial lead or with capability of rhythm
2520 discrimination (i.e. implantable cardiac monitors) allow continuous monitoring of the cardiac rhythm
2521 and appropriate detection of atrial tachyarrhythmias, including AF, as atrial high-rate episodes
2522 (AHREs) as well as storing arrhythmia electrograms in the device's memory for review and specific
2523 diagnosis. AHREs, currently defined as episodes of at least 5 min of atrial tachyarrhythmias/AF with
2524 an atrial rate >180 bpm, are usually asymptomatic, discovered during routine device follow-up and

2525 classified in terms of duration of the single episode or time spent in atrial tachyarrhythmias during a
2526 day (from minutes to hours)³⁷¹⁻³⁷⁷.

2527

2528 Although temporal cut-offs for detection and storage of AHRE data as short as 30-60 seconds have
2529 been used, the diagnostic accuracy is reliable when episodes ≥ 5 minutes in duration are considered,
2530 since, using this cut-off, the appropriateness in AF detection is 95%, minimizing the risk of over-
2531 sensing due to detection of artefacts caused by myopotentials or other sources of electrical
2532 interference^{378,379}. Individual patient analysis of electrograms corresponding to AHREs is clinically
2533 indicated to exclude artifacts or other causes of inappropriate detection of atrial tachyarrhythmias
2534 or AF. Electrograms of AHREs correspond to intracardiac electrograms recorded from right atrial
2535 appendage or right atrium so a diagnosis of tachyarrhythmias can be easily made through analysis of
2536 tracings recorded in the device's memory¹⁵⁹. After detection of AHREs by CIEDs, conventional
2537 Holter or other ECG long-term recordings (i.e., patient operated devices) can be considered in
2538 specific cases (e.g. unavailable electrograms or unclear diagnosis at device electrograms analysis).

2539

2540 The possibility of continuous monitoring of AF through implanted devices has led to new terms, such
2541 as "AF burden", defined as the overall time spent in AF during a specified period of time^{372,380 381 382}),
2542 and "subclinical AF", corresponding to episodes of atrial tachyarrhythmias with duration between 5
2543 min and 24 h, detected by a CIED in patients without clinical history or clinical symptoms of AF
2544^{371,375,376,383,384}.

2545

2546 The prevalence of AHRE, often reported as AF burden, among patients implanted with CIEDs varies,
2547 depending on underlying heart disease, periods of observation, and above all previous history of
2548 clinically overt atrial tachyarrhythmias, including AF. In the ASSERT study, subclinical atrial
2549 tachyarrhythmias with at least 6 min duration were detected within 3 months in around 10% of
2550 patients implanted with a CIED³⁷⁵. During a follow-up period of 2.5 years, additional subclinical atrial
2551 tachyarrhythmias occurred in approximately 25% of patients, and around 16% of those who had
2552 subclinical atrial tachyarrhythmias developed symptomatic AF³⁷⁵. Considering these findings, as well
2553 as data from the literature reported in e-Table 20, there is evidence that AHREs with a duration $>5-6$
2554 min are common in patients implanted with CIEDs.

2555

2556 In patients implanted with CIEDs for conventional indications, AHREs, with a short duration, ranging
2557 from three atrial premature complexes to 15–20 s, are currently considered of no specific clinical
2558 significance since this type of AHRE was found not to be significantly associated with episodes of
2559 longer duration, or with an increased risk of stroke or systemic thromboembolism³⁸⁵. For this
2560 reason most of the interest in patient with CIEDs is focused on AHRE with a duration $\geq 5-6$ min, a
2561 finding associated with a substantial risk of subsequently presenting clinical AF (HR 5.5–6.0),
2562 initially reported by the ancillary MOST analysis³⁸⁶ and then by the ASSERT study³⁷⁵, where a CIED-
2563 detected AHREs >6 min were followed by clinical AF detected by a surface ECG in approximately
2564 16% of patients at 2.5 years of follow-up (e-Table 21).

2565

2566 The association between CIED-detected atrial tachyarrhythmias of variable durations and stroke or
2567 systemic thromboembolism has been evaluated by several studies that overall collected data on
2568 $>22,000$ patients, taking into account the maximum duration of AHRE episode, or the maximum daily
2569 AF burden (that is, the maximum time spent in adjudicated AF in one day of the follow-up

2570 period)^{375,385-393}. The studies show that AHRE burden with a duration $\geq 5-6$ min are significantly
2571 associated with an increase in the risk of stroke or systemic thromboembolism (HR 2–9). In a re-
2572 analysis of the ASSERT study³⁹⁴, the increase in the risk of stroke occurred only when the longest
2573 duration of the various episodes of detected AHREs was >24 h. The largest dataset of patients with
2574 CIED-detected AHREs was analysed in the SOS AF project, with a pooling of three prospective studies
2575 (PANORAMA, Italian Clinical Services Project, and TRENDS) resulting in 10,016 patients³⁹¹. During a
2576 median follow-up of 24 months, 43% of an unselected cohort of patients with implanted devices
2577 experienced ≥ 1 day with ≥ 5 min of AHRE burden and a 1-h threshold of AHRE burden was associated
2578 with a hazard ratio for ischemic stroke of 2.11 (95% CI 1.22–3.64, $P = 0.008$), although the absolute
2579 risk of ischemic stroke in patients with AHREs was low (0.39% annual rate in the whole cohort).
2580 Similarly, the TRENDS study³⁸⁹ found that an AHRE burden of 5.5 h in a day, in a 30-day period, was
2581 associated with a two-fold increase in the adjusted risk of stroke (absolute risk of thromboembolism
2582 around 1.8% per year)³⁸⁹. Integration of AHRE presence, duration, or burden (≥ 5 min or ≥ 24 h) into
2583 risk scores for thromboembolism may modestly improve c-statistics of both the CHADS₂ and
2584 CHA₂DS₂-VASc scores for predicting stroke³⁹⁵.

2585

2586 The clinical significance of AHRE is presumably different from that of clinically identified AF since the
2587 latter, detected using conventional surface ECG methods corresponds to a much higher AF burden as
2588 compared to patients with AHRE detected by continuous monitoring via a CIED^{374,376}. The actual
2589 rates of stroke or systemic embolic events reported in studies evaluating CIED-detected AHREs are
2590 often lower than what would be predicted by CHADS₂ and CHA₂DS₂-VASc scores and this may be
2591 related to concurrent treatment with oral anticoagulants in each study, risk of under-reporting and
2592 confounding. Also, the temporal relationship between ischemic stroke and AF is less strict than
2593 expected, since stroke may occur without the concurrent presence of atrial tachyarrhythmias or AF
2594 at the time of stroke or in the days before. These findings suggest that the relationship between AF
2595 and stroke can be complex, with AF involved but not always in a causative role (mediated by a left
2596 atrial thrombus), but also simply representing a marker of increased vascular risk^{372,376}.

2597

2598 Two randomized controlled trials are ongoing evaluating the efficacy and risk-benefit ratio of oral
2599 anticoagulation to no oral anticoagulation (aspirin only) in patients with CIED-detected AHRE
2600 (ARTESiA (NCT01938248)³⁹⁶ and NOAH – AFNET 6 (NCT02618577)).³⁹⁷

2601

2602 In the absence of the results of these on-going trials, management of patients with CIEDs-detected
2603 AHREs requires cardiological clinical evaluation, clinical decision making and follow up (Figure 7).
2604 Oral anticoagulants could be considered as a result of an individualized clinical assessment taking
2605 into account overall AHRE burden (in the range of multiple hours rather than few minutes) and
2606 specifically presence of AHRE > 24 hours, individual stroke risk (CHA₂DS₂-VASc), predicted risk benefit
2607 of oral anticoagulation (specifically risk of major bleeding) and informed patient preferences.

2608 Recommendations

2609 **41. For patients that present with a clinically documented episode of AF (12-lead ECG or other**
2610 **means, eg. external devices with validated rhythm detection), we suggest that the presence or**
2611 **absence of symptoms must not influence the process of decision making with regard to the**
2612 **need for anticoagulation based on risk stratification (ungraded consensus-based statement).**

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42. In cases of AHRE (atrial high rate episodes) detected by a CIED of at least 5 min duration, we suggest that direct analysis of electrograms corresponding to AHRE is clinically indicated to exclude artifacts or other causes of inappropriate detection of atrial tachyarrhythmias or AF (ungraded consensus-based statement).

Remark: In patients with CIED detected AHRE a complete cardiological evaluation is indicated, with 12-lead ECG, general assessment of clinical conditions and clinical risk stratification for stroke using CHA₂DS₂VASc score.

Remark: There is no evidence in support or against prescription of oral anticoagulants in patients at risk of stroke (intermediate to high risk according to CHA₂DS₂VASc) who present with AHREs, corresponding to atrial tachyarrhythmias/AF at electrograms assessment of less than 24 hours duration.

43. In patients with AF, we suggest that prescription of oral anticoagulants could be considered as a result of an individualized clinical assessment taking into account overall AHRE burden (in the range of hours rather than minutes) and specifically, the presence of AHRE > 24 hours, individual stroke risk (using CHA₂DS₂VASc), predicted risk benefit of oral anticoagulation and informed patient preferences (ungraded consensus-based statement).

Remark: In patients with CIED detected AHRE continued patient follow-up is recommended, preferentially combining clinical follow up with remote monitoring of the CIED or else more frequent device interrogation than standard for CIED follow-up, to detect the development of clinical AF (symptomatic or asymptomatic), to monitor the evolution of AHRE or AF burden and specifically the transition to AHRE lasting more than 24 hours, onset or worsening of heart failure, or any clinical change that might suggest a change in clinical profile or clinical conditions.

2638 ATRIAL FLUTTER

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The risk of thromboembolism and stroke in patients with atrial flutter has been evaluated in relatively few studies compared to AF. However, patients with atrial flutter frequently present phases of AF alternated with phases of classical flutter or regular atrial rhythm³⁹⁸⁻⁴⁰⁰. A systematic review on the thromboembolic risk associated with atrial flutter, including 52 articles, found that thromboembolic event rates after cardioversion, varied from 0% to 6% with a follow-up from 1 week to 6 years.^{235,273,275,276,401-411} Echocardiographic studies reported prevalence of intra-atrial thrombi from 0% to 38% and a prevalence of spontaneous echo contrast up to 28%.^{398,399,409,412-421} One ablation study in non-anticoagulated patients with atrial flutter reported thromboembolic events in 13.9% of cases.⁴²² The differences in patient selection, type of study and, importantly, use of oral anticoagulation explain the heterogeneity of reported data with regard to echo findings and thromboembolic complications. Observational studies demonstrated an increased risk of stroke (risk ratio 1.4, 95% CI 1.35 to 1.46) and death (HR 1.9, 95% CI 1.2 to 3.1)⁴⁰¹ compared to controls at long-term follow-up.

A report from the Danish nationwide registry on patients undergoing an atrial flutter ablation or an AF ablation procedure between 2000–2013, found that the rate of thromboembolic events for atrial flutter patients was 0.46 per 100 persons-years, not significantly different from that of patients

2656 presenting with AF (HR adjusted for several variables including anticoagulation = 1.22 [0.62–
2657 2.41]).⁴⁰¹

2658
2659 The role of anticoagulant therapy for patients with atrial flutter has not been evaluated in large
2660 randomized clinical trials, but because these patients often have concomitant AF or are at increased
2661 risk of developing AF, it is reasonable to base decisions regarding antithrombotic therapy on the
2662 same risk stratification schemes and scores used for AF.⁴²³

2663 **Recommendation.**

2664 **44. For patients with atrial flutter, we suggest that antithrombotic therapy decisions follow the**
2665 **same risk-based recommendations as for AF. (ungraded consensus-based statement).**

2666

2667 **PREGNANCY**

2668 Atrial fibrillation (AF) and atrial flutter are very rare during pregnancy, unless when there is an
2669 underlying structural heart disease or hyperthyroidism.⁴²⁴ Lone AF is uncommon in pregnancy and
2670 is associated with older age and late pregnancy.⁴²⁵ In countries where the prevalence of rheumatic
2671 heart disease is still high or among immigrants from these areas to Western countries the
2672 prevalence of AF in pregnancy may be commonly related to rheumatic heart disease.⁴²⁵ Peri-partum
2673 cardiomyopathy AF is common, with a prevalence that may reach 10%, and may severely impair
2674 hemodynamic status.⁴²⁶

2675

2676 In a registry of >250, 000 pregnancies in Southern California⁴²⁷ AF was evident in 0.6 per 1000,
2677 more frequently in white women (1,1 per 1000 pregnancies), and was associated with more
2678 advanced age, higher BMI, hypertension, hyperlipidemia, and diabetes. Decision-making on
2679 antithrombotic therapy during pregnancy has been reviewed in detail in the 9th Edition of the
2680 Antithrombotic Therapy and Prevention Guidelines; here we provide an update with
2681 recommendations focused on AF.⁴²⁸

2682

2683 The use of anticoagulant therapy during pregnancy is challenging because of the potential for both
2684 fetal and maternal complications. Pregnancy-induced changes in hemostasis lead to a state of
2685 hypercoagulability, so in a women with AF at risk of stroke/thromboembolism in the non-pregnant
2686 state, pregnancy will increase this risk 3- to 4- fold.^{428,429}

2687

2688 Vitamin K antagonists cross the placenta and have the potential to cause fetal wastage, bleeding in
2689 the fetus, and teratogenicity. The most common fetal anomaly developing as a consequence of fetal
2690 exposure to warfarin consists of midfacial hypoplasia and stippled epiphyses and typically occurs
2691 after in utero exposure to vitamin K antagonists during the first trimester of pregnancy⁴²⁸. Vitamin K
2692 antagonists have also been associated with central nervous system abnormalities after exposure
2693 during any trimester, but these complications are uncommon.⁴²⁸ There is general consensus that in
2694 order to minimize the risk of warfarin embryopathy it is reasonable to avoid warfarin between
2695 weeks 6 and 12 of gestation because of the high risk of fetal defects, especially if the dose of
2696 warfarin is higher than 5 mg per day.⁴²⁴

2697

2698 LMWH does not cross the placenta and there is no evidence that LMWH causes teratogenicity or
2699 increases fetal bleeding. Because of accelerated clearance, LMWH has a shorter half-life and lower
2700 peak plasma concentration during pregnancy thus potentially requiring higher doses. For this reason,
2701 use of LMWH (such as between weeks 6 and 12) has to be managed with dose adjustment according
2702 to weight and target anti-Xa level (4–6 hours post-dose 0.8–1.2 U/mL).

2703
2704 Unfractionated heparin (UFH) does not cross the placenta and therefore can be safely used in
2705 pregnancy. However, it carries some risk of heparin-induced thrombocytopenia and osteopenia,
2706 which may lead to symptomatic vertebral fracture in approximately 2% of women⁴²⁸. Moreover, the
2707 pharmacokinetic changes of pregnancy result in a shorter half-life and lower peak plasma
2708 concentration of heparin compounds, with the need to titrate doses in order to keep the mid-
2709 interval aPTT (6 hours post dose \geq twice control values. Since both the risk of heparin-induced
2710 thrombocytopenia and the risk of osteoporosis are lower with LMWH than with UFH, the former is
2711 preferred as subcutaneous treatment during pregnancy.

2712
2713 Pregnant women were excluded from participating in clinical trials evaluating NOACs. Given the
2714 rather low molecular weight of NOACs and data on placental transfer in rats, all NOACs are
2715 expected to cross the placenta.⁴³⁰ Hence, use of NOACs in pregnancy should be avoided. Limited
2716 data are available on the consequences of exposure to NOACs but women inadvertently exposed to
2717 a NOAC in early pregnancy (before diagnosis of pregnancy) can be reassured, since the risk of
2718 embryopathy seems low. In case of planned pregnancy, avoidance of NOACs should be considered
2719 (with switching to LMWH).

2720
2721 With regard to breast-feeding, warfarin, in view of its characteristics (polar, non-lipophilic, and
2722 highly protein bound) can be considered safe since two reports showed that warfarin is not detected
2723 in breast milk and does not induce an anticoagulant effect in the breast-fed infant when nursing
2724 mothers consume the drug.^{431,432} Acenocoumarol, which is commonly used in Europe, has similar
2725 properties.^{433,434} Use of UFH and LMWH in breast-feeding women appears safe. No clinical data on
2726 the effect of NOACs on breast-fed infants are available and therefore the recommendation is against
2727 use these medications in breast-feeding women.

2728
2729 A flow chart on how to manage women with AF during pregnancy is shown in Figure 8

2730

2731 Recommendations

2732 **45. For women receiving OAC for prevention of stroke/TE in AF who become pregnant, we suggest**
2733 **discontinuation of OAC with a VKA between weeks 6 and 12 and replacement by LMWH twice**
2734 **daily (with dose adjustment according to weight and target anti-Xa level 4-6 hours post-dose**
2735 **0.8-1.2 U/mL), especially in patients with a warfarin dose required of >5 mg/day (or**
2736 **phenprocoumon >3 mg/day or acenocoumarol >2mg/day). OAC should then be discontinued**
2737 **and replaced by adjusted-dose LMWH (target anti-Xa level 4-6 hours post-dose 0.8-1.2 U/mL)**
2738 **in the 36th week of gestation (ungraded consensus-based statement).**

2739

2740 **46. For women on treatment with long-term vitamin K antagonists who are attempting pregnancy**
 2741 **and are candidates for LMWH substitution, we suggest performing frequent pregnancy tests**
 2742 **and use LMWH instead of VKA when pregnancy is achieved rather than switching to LMWH**
 2743 **while attempting pregnancy (ungraded consensus-based statement).**

2744

2745 **47. For pregnant women, we suggest avoiding the use of NOACs (ungraded consensus-based**
 2746 **statement) .**

2747 *Remark: For women on treatment with a NOAC we suggest switching to vitamin K antagonists,*
 2748 *rather than switching to LMWH while attempting pregnancy.–†*

2749

2750 **48. For lactating women using warfarin, acenocoumarol, or UFH who wish to breastfeed, we**
 2751 **suggest continuing the use of warfarin, acenocoumarol, LMWH or UFH (ungraded consensus-**
 2752 **based statement)**

2753

2754 **49. For breast-feeding women, we suggest alternative anticoagulants rather than NOACs**
 2755 **(ungraded consensus-based statement).**

2756

2757

2758 **ATRIAL FIBRILLATION AND CHRONIC KIDNEY DISEASE**

2759

2760 Chronic kidney disease (CKD) is frequently present in patients with AF and has significant
 2761 implications on the trajectory of AF, risk of stroke, and bleeding risk of anticoagulation. The presence
 2762 of CKD or AF bi-directionally affects the incident risk of the other. Among patients with CKD, the
 2763 prevalence of AF is substantially higher than in the general population, ranging from 16-21% in non-
 2764 dialysis dependent CKD and 15-40% in patients on dialysis⁴³⁵.

2765

2766 Among patients with AF, CKD is present in one-third of patients at the time of AF diagnosis^{51 436}
 2767 although this may be substantially higher among cohorts of prevalent AF subjects. The impact of AF
 2768 is illustrated in the systematic review by Odutayo et al⁵¹ whereby the presence of AF increased
 2769 chronic kidney disease (1.64, 1.41 to 1.91), as well as all-cause mortality (relative risk 1.46, 95% CI
 2770 1.39 to 1.54), cardiovascular mortality (2.03, 1.79 to 2.30), major cardiovascular events (1.96, 1.53 to
 2771 2.51), stroke (2.42, 2.17 to 2.71), ischemic stroke (2.33, 1.84 to 2.94), ischemic heart disease (1.61,
 2772 1.38 to 1.87), sudden cardiac death (1.88, 1.36 to 2.60), heart failure (4.99, 3.04 to 8.22), and
 2773 peripheral arterial disease (1.31, 1.19 to 1.45).

2774

2775 *AF, CKD and stroke*

2776 CKD increases the baseline risk of ischemic stroke in patients with AF⁴³⁵. The pathophysiological
 2777 mechanisms responsible for stroke and systemic embolism in these patients are multifactorial. The
 2778 precise attributable risk of AF as a causal agent of cardioembolic stroke is therefore unclear,
 2779 particularly where patients have substantially higher risk of atherothrombotic ischemic stroke due to
 2780 hypertension, intracranial and carotid atherosclerosis, heart failure, and CAD.

2781

2782 Second, CKD increases the competing risk of death from causes unrelated to AF-associated stroke
2783 and may attenuate expected benefit of stroke prevention therapy. In a recent analysis of seven risk
2784 stratification scores, all had substantially poorer discrimination in CKD patients than those without
2785 CKD (c-statistics 0.50-59 vs. 0.69-0.70, respectively), and inclusion of CKD stage did not improve
2786 calibration or discrimination⁴³⁷. One study from Taiwan showed that the CHA₂DS₂-VASc score could
2787 adequately risk stratify for ischemic stroke amongst a haemodialysis population (c-index 0.682,
2788 superior to CHADS₂)⁴³⁸.

2789

2790 Third, moderate to severe CKD increases the risk of major and intracranial bleeding through a
2791 number of mechanisms, and the risk may be further increased by the use of oral anticoagulation or
2792 antiplatelet therapy. The clinical bleeding risk scores (e.g., HAS-BLED, ORBIT, ATRIA) all include CKD
2793 measures as part of their score calculation¹⁰⁴. Therefore, CKD is both a marker of risk of disease and
2794 of its therapy, and there is significant controversy as to the net clinical benefit of oral anticoagulation
2795 in severe CKD despite encouraging observational studies⁴³⁹.

2796

2797 Fourth, there are virtually no randomized trial data of oral anticoagulation in severe CKD (creatinine
2798 clearance < 25-30 ml/min). Some observational data suggest that warfarin may be harmful in end
2799 stage renal disease (ESRD) patients on haemodialysis, with no reduction (or an increase) in stroke
2800 and an excess of major bleeding; however, many of these studies (largely from North America) do
2801 not report quality of anticoagulation control, as reflected by time in therapeutic range (TTR)⁴⁴⁰⁻⁴⁴²..
2802 In contrast, European data suggest that there is a beneficial reduction in ischemic stroke which
2803 outweighs the increase in severe bleeding, where TTR is good >65-70%⁴⁴⁰⁻⁴⁴².

2804

2805 The latest systematic review and meta-analysis by Harel et al⁴⁴³ of 14 observational studies (20,398
2806 participants) among hemodialysis with AF, found that the use of warfarin was not associated with
2807 ischemic stroke (14 studies; 20,398 participants; HR, 0.85; 95% CI, 0.55- 1.07), or intracranial
2808 hemorrhage (hemorrhagic stroke; 4 studies; 15,726 participants; aHR, 1.93; 95% CI, 0.93-4.00) (e-
2809 Table 23). They concluded that warfarin was not associated with a clear benefit or harm among
2810 patients who have AF and receive dialysis. However, there was marked study heterogeneity
2811 including the inability to account for major confounders such as the quality of anticoagulation
2812 control (TTR). One study reported that in AF patients on peritoneal dialysis, warfarin reduced stroke
2813 and thromboembolism compared to aspirin or no antithrombotic therapy, with no excess in serious
2814 bleeds (ICH)²⁴⁷.

2815 The lack of clinical trial data in severe CKD is a major evidence gap with the NOACs, even though
2816 some regulatory agencies such as the Food and Drug Administration have approved reduced-dosed
2817 NOACs for severe CKD and dialysis on the basis of pharmacokinetic data⁴⁴⁴. Fortunately, the pivotal
2818 NOAC randomized trials have demonstrated non-inferiority of NOACs to warfarin among patients
2819 with creatinine clearance of 30-50 ml/min (and for apixaban 25-50 ml/min)²⁴⁶.

2820

2821 All the NOACs have some degree of renal elimination, C_{max}, and half-life, with the greatest renal
2822 dependency for excretion with dabigatran (80%) and the least with renal dependency for apixaban
2823 (27%). However, there are no head-to-head NOAC trials and therefore insufficient evidence to
2824 recommend one agent over another. Given these limitations, treatment should be individualized and
2825 the dose adapted on the basis of creatine-clearance according to licensed indications [see Figure 9].

2826

2827 **Recommendations**

2828 **50. For mild CKD (Stage II, CrCl 60-89 ml/min), we suggest that oral anticoagulation clinical**
2829 **decision making and treatment recommendations match that of patients without CKD (weak**
2830 **recommendation, very low quality evidence).**

2831

2832 **51. For moderate CKD (Stage III, CrCl 30-59 ml/min), we suggest oral anticoagulation in patients**
2833 **with a CHA2DS2-VASc \geq 2 with label-adjusted NOACs or dose adjusted vitamin K antagonists**
2834 **(Weak recommendation, very low quality evidence).**

2835 *Remark: With VKA, good quality anticoagulation control (TTR>65-70%) is recommended.*

2836

2837 **52. In severe non-dialysis CKD (Stage IV CrCl 15-30), we suggest using VKAs and selected NOACs**
2838 **(rivaroxaban 15mg QD, apixaban 2.5mg bid, edoxaban 30mg QD and (in USA only) dabigatran**
2839 **75mg bid) with caution, based on pharmacokinetic data (ungraded consensus-based**
2840 **statement).**

2841

2842 **53. In end-stage renal disease (CrCl < 15 or dialysis-dependent), we suggest that individualized**
2843 **decision-making is appropriate (ungraded consensus-based statement).**

2844

2845 **54. In end-stage renal disease (CrCl < 15 or dialysis-dependent , we suggest using well managed**
2846 **VKA with TTR>65-70% (ungraded consensus-based statement).**

2847

2848 *Remark: NOACs should generally not be used, although in USA, apixaban 5mg bid is approved for*
2849 *use in AF patients receiving hemodialysis*

2850

2851 *Remark: In patients with CKD who initiate OAC, concomitant antiplatelet therapy including low-*
2852 *dose aspirin is likely to substantially elevate bleeding risk and should be used very judiciously.*

2853

2854 **AF WITH ASSOCIATED VALVULAR HEART DISEASE**

2855 A recent physician survey⁴⁴⁵ reported marked heterogeneity in the definition of valvular and non-
2856 valvular AF and variable management strategies, including NOACs in patients with valvular heart
2857 disease (VHD) other than prosthetic heart valves or hemodynamically significant mitral stenosis.
2858 Whilst hypertrophic cardiomyopathy is sometimes discussed in association with valvular AF, this will
2859 not be addressed in this section; specific guidelines on this condition are available⁴⁴⁶.

2860

2861 The use of the term non-valvular AF is unfortunate and misleading as patients with a wide range of
2862 valvular pathology and severity were enrolled in all of the phase 3 NOAC trials. The only VHD
2863 uniformly excluded from all the NOAC trials were significant (moderate or severe) mitral stenosis
2864 and mechanical heart valves.

2865

2866 A meta-analysis of the four phase 3 AF trials comparing NOAC with warfarin found that although
 2867 patients with VHD at higher risk compared with those without valvular disease, the efficacy and
 2868 safety of NOACs versus warfarin is consistent in regardless of the presence or absence of VHD²⁴⁰.

2869
 2870 AF patients with mechanical heart valves should only be prescribed VKAs. Data from the only phase
 2871 II trial of a NOAC, dabigatran, in patients with mechanical heart valves (RE-ALIGN trial) demonstrated
 2872 inferior efficacy and more bleeding⁴⁴⁷. However, patients with bioprosthetic valves were included in
 2873 the ARISTOTLE trial⁴⁴⁸ (apixban) the ENGAGE AF-TIMI 48 trial⁴⁴⁹ (edoxaban) and the relative efficacy
 2874 and safety of NOACs compared with warfarin was consistent in these patients, although the number
 2875 of patients with bioprosthetic valves was limited (<300).

2876
 2877 In keeping with a recent European consensus document, with endorsement by international learned
 2878 societies, we propose that the term 'valvular AF' is outdated. Given that any definition ultimately
 2879 relates to the evaluated practical use of oral anticoagulation (OAC) type, we propose a functional
 2880 EHRA (Evaluated Heart valves, Rheumatic or Artificial) categorization in relation to the type of oral
 2881 anticoagulation (OAC) use in patients with AF [see Summary Box]. This classification would have the
 2882 advantage that it may easily evolve or be updated (type 1 may become type 2 or vice versa) when
 2883 there are new results. For example, transcatheter mitral valve interventions (TMVI, e.g., to include
 2884 both MitraClip and Mitral valve replacement) are emerging as a possible therapeutic options⁴⁵⁰, but
 2885 more data are awaited especially in relation to OAC use. Also, EHRA Type I is broadly similar to the
 2886 previously described MARM-AF⁴⁵¹.

2887
 2888 **Table 11.** Summary box: Evaluated Heart valves, Rheumatic or Artificial) categorization in relation to
 2889 the type of oral anticoagulation (OAC) use in patients with AF

2890

Definition	
<p>EHRA Type 1 VHD</p> <p>AF patients with 'VHD needing therapy with a Vitamin K antagonist (VKA)'</p>	<ul style="list-style-type: none"> • Mitral stenosis (moderate-severe, of rheumatic origin) • Mechanical prosthetic valve replacement
<p>EHRA Type 2 VHD,</p> <p>AF patients with 'VHD needing therapy with a VKA or a NOAC', also taking into consideration CHA₂DS₂VASc score risk factor components:</p>	<ul style="list-style-type: none"> • Mitral regurgitation • Mitral valve repair • Aortic stenosis • Aortic regurgitation • Tricuspid regurgitation • Tricuspid stenosis • Pulmonary regurgitation • Pulmonic stenosis • Bioprosthetic valve replacements • Trans-aortic valve intervention (TAVI)

2891 EHRA, Evaluated Heart valves, Rheumatic or Artificial; NOAC, non-vitamin K antagonist oral
 2892 anticoagulant; VHD, Valvular heart disease; VKA, vitamin K antagonist

2893

2894 **Non-drug alternatives and perioperative considerations**2895 **Occlusion of the left atrial appendage with devices or surgical techniques**

2896 Approximately 90% of the thrombi found in patients with non-valvular AF and 57% of the thrombi
2897 found in valvular AF are located in the LAA ⁴⁵².

2898

2899 Left atrial appendage occlusion using specific percutaneous devices (WATCHMAN, Amplatzer Cardiac
2900 Plug, or WaveCrest device or the Lariat endocardial and epicardial ligation technique) or occlusion
2901 during a cardiac surgery procedure with either LAA amputation and closure or a stapler device have
2902 been proposed and tested for patients with AF at high risk of stroke in the presence of an high risk of
2903 bleeding or in the presence of contraindications to OACs.

2904

2905 Two randomized studies evaluated the WATCHMAN (Atritech, Inc) device versus warfarin, the
2906 PROTECT-AF and the PREVAIL AF trials ⁴⁵³⁻⁴⁵⁹. In the PROTECT AF trial the efficacy of LAA closure
2907 with the device met the pre-specified criteria for non-inferiority vs. warfarin, but the rate of adverse
2908 safety events in the intervention group was 4.4% with evidence of harmful periprocedural
2909 complications (pericardial effusion and procedure-related ischemic stroke). For acute complications
2910 a “learning curve” appeared to be present, with serious pericardial effusions (requiring drainage) in
2911 7.1% of the first 3 implant patients at each site compared with 4.4% of subsequent patients ⁴⁶⁰. The
2912 serious complication rate of around 7%, has been reported also for first or second generation
2913 Amplatzer occluders ^{461,462}. A recent systematic review network meta-analysis on the use of oral
2914 anticoagulants and Watchman device showed that the use of VKA, NOAC and the Watchman device
2915 significantly reduce the risk of any stroke and systemic embolism as compared to placebo/control
2916 (Watchman Device OR, 95% CI: 0.35, 0.16-0.80). ⁴⁶³ Data on the use of the WATCHMAN device in
2917 patients with contraindications to anticoagulation are very limited and DAPT is needed for at least 6
2918 weeks after the procedure, potentially exposing the patient to increased risk of bleeding, ⁴⁶⁰.

2919

2920 The Lariat device is based on an epicardial snare that requires positioning using a percutaneous
2921 approach to the epicardium through a pericardial access and in combination a percutaneous
2922 endocardial approach. In inexperienced operators incomplete occlusion of the LAA after LARIAT
2923 ligation was relatively common (20% of cases) and was associated with risk of thromboembolic
2924 events ⁴⁶⁴. No randomized controlled study comparing this device with oral anticoagulation is
2925 currently available.

2926

2927 In addition, the role of LAAO devices in AF patients has also to consider that no trials are available
2928 comparing these devices with NOACs. Thrombus formation on LAAO devices is also not uncommon
2929 (as high as 7.2%/year) and are associated with a risk of ischemic stroke during follow-up ^{465,466}.

2930

2931 Different surgical techniques have been applied for surgical exclusion of LAA (simple suture ligation,
2932 over-sewing of the LAA base without excision, appendage excision or amputation, surgical stapling)
2933 but data on TEE during follow-up suggest incomplete occlusion in up to 60% of subjects ^{467,468}. These
2934 observations and the lack of a clear benefit on stroke prevention evident from a RCT indicate that in
2935 patients with AF these surgical techniques do not currently allow avoidance or interruption of oral
2936 anticoagulation in patients at risk of stroke ^{469,470}.

2937 **Recommendations**

2938 **55. In patients with AF at high risk of ischaemic stroke who have absolute contraindications for**
 2939 **OAC, we suggest using LAA occlusion (Weak recommendation, low quality evidence).**

2940 *Remark:* When taking into account LAAO as a potential option, the risk of bleeding related to
 2941 antiplatelets agents that need to be prescribed in the first months has to be considered and the
 2942 possibility to use NOACs.

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 2944 **56. In AF patients at risk of ischaemic stroke undergoing cardiac surgery, we suggest considering**
 2945 **surgical exclusion of the LAA for stroke prevention, but the need for long term OAC is**
 2946 **unchanged (Weak recommendation, low quality evidence).**

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2949 **Surgical procedures and interventions-**

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2951 Patients with AF on long-term prophylaxis with oral anticoagulants may need surgical or
 2952 interventional procedures that require appropriate management. Since bleeding risk may obviously
 2953 be increased by the anticoagulant effect, interrupting anticoagulation for an intervention or a
 2954 procedure transiently exposes the patient to increased risk of thromboembolism. Appropriate
 2955 management requires balancing reducing the risk of thromboembolism and preventing excessive
 2956 procedure-related bleeding.

2957

2958 In the NOAC RCTs surgical or other invasive procedures were required during a follow up of around 2
 2959 years in one-quarter of patients in RE-LY and one-third of patients in ROCKET AF and ARISTOTLE⁴⁷¹⁻
 2960⁴⁷³.

2961

2962 General principles of management can be considered, to be combined with individual clinical
 2963 judgment, but they are derived from consensus of experts, since no data from RCTs are available to
 2964 guide clinical decision making.

2965

2966 The following steps are important for appropriate management:

2967

2968 - **Estimation of the bleeding risk associated with a specific intervention/procedure.** The risk
 2969 of bleeding can be predicted by the type of intervention and by its need, urgent or elective.
 2970 e-Table 23 classifies surgical and interventional procedures according to bleeding risk as well
 2971 as thromboembolic risk⁴⁷⁴⁻⁴⁷⁶. The direct consequence of this evaluation is that interventions
 2972 or procedure at very low bleeding risk, such as simple dental extractions or minor skin
 2973 excision can be planned and performed without interruption of oral anticoagulation.
 2974 If the bleeding risk is substantial then interruption of anticoagulation prior to the procedure
 2975 intervention is needed to minimize the hemorrhagic risk, both in the intra-operative and
 2976 immediate post-operative phase.

2977

2978 - **Estimation of patient thromboembolic risk.** Calculate the CHA₂DS₂-VASc score (low risk if 0
 2979 or 1) but an additional transient increase in risk has to be considered in case of recent stroke
 2980 or recent pulmonary embolism.

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- **Planning of the timing of anticoagulation interruption.** The timing of interruption is strictly dependent on the specific anticoagulant the patients is receiving and creatinine clearance. Important differences exist between the management of patients treated with VKA or NOACs^{476,477}. The effect of warfarin can be monitored through INR, however, no standard laboratory test exists to measure the effect of NOACs. Discontinuation of warfarin is usually instituted 5 days before an elective surgical intervention, with INR checked the day before surgery, with the usual indication that surgery can be regularly planned if the INR is ≤ 1.4 -1.5 the day before surgery or the same day of surgery⁴⁷⁵. For NOACs the planning of interruption and resumption of therapy for surgical interventions/procedures is dependent on the type of procedure/intervention, the specific agent used and renal function, estimated by Creatine Clearance (using the Cockcroft-Gault equation). In case of urgent surgery reversal of anticoagulation or specific measures may be required^{476,477}.

- **Evaluation of the need for bridging.** Pre-operative bridging can be considered in patients receiving VKA who are particularly high risk of TE (e.g., recent stroke, mechanical heart valve)⁴⁷⁵. In these cases, LMWH at therapeutic doses is usually prescribed starting 3 days before the procedure/intervention. Post-operative bridging includes administration of a LMWH when VKA is resumed in the post-operative period, with administration of both agents until achievement of a therapeutic INR.

The role of bridging has been tested in a randomized trial, the BRIDGE trial (Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery) performed in patients on warfarin who were candidate to an invasive procedure (patients with mechanical valves were excluded)⁴⁷⁸. The risk of TE after the procedure was similar in patients with and without bridging, but the risk of major bleeding was higher in those who were bridged. Thus, we suggest that preoperative bridging is not required in AF patients treated with warfarin who do not have a particularly high risk of thromboembolism and who do not have a mechanical valve.

- In patients receiving NOACs, bridging is not required but bridging could be considered in the post-operative phase if the patient cannot take oral medications for a prolonged period.

3014 **Recommendations**

3015 **57. In AF patients taking warfarin without high risk of thromboembolism or do not have a**
3016 **mechanical valve, we suggest pre-operative management without bridging (Weak**
3017 **recommendation, low quality evidence).**

3018
3019 **58. In AF patients on antithrombotic prophylaxis with warfarin with a high risk of**
3020 **thromboembolism or with a mechanical valve, we suggest pre-operative management with**
3021 **bridging (Weak recommendation, low quality evidence).**
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3023 **59. In AF patients on antithrombotic prophylaxis with a NOAC, we suggest pre-operative**
3024 **management without bridging (Weak recommendation, low quality evidence).**

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3028 THE PATIENT

3029 Patient knowledge and understanding of the stroke risk associated with AF and the benefit of OAC to
3030 prevent stroke is crucial to patient acceptance of anticoagulants, as well as adherence, and life-long
3031 persistence (in most cases), to OAC. However, research demonstrates that AF patients generally
3032 have poor awareness and knowledge about their condition,⁴⁷⁹⁻⁴⁸⁴ medications used to treat AF,
3033 particularly OAC, and do not clearly comprehend the benefit/risk associated with stroke prevention
3034 regimens.^{480-483,485-491} Although there is increasing advocacy from clinical guidelines^{159,160} and expert
3035 consensus^{488,492,493} to incorporate patient preferences for treatment into the decision-making
3036 process, a patient's ability to make an informed decision may be hindered by their lack of
3037 understanding about the relationship between AF and stroke and the efficacy/safety of OAC for
3038 stroke prevention, particularly at diagnosis, when these decisions are invariably addressed.
3039 Assessment of patient's knowledge (using the AF Knowledge questionnaire⁴⁹⁴ or Jessa Atrial
3040 Fibrillation Knowledge questionnaire⁴⁹⁵), as well as their values and preferences, could be
3041 undertaken to ascertain gaps to be filled; this may lead to better decision-making and improved
3042 adherence and persistence.

3043 Patient education is essential to provide patients with sufficient information to enable them to make
3044 an informed decision about whether or not they wish to take OAC, and if they do, which OAC they
3045 would prefer.^{488,489,496} Education needs to be tailored to the person's desire for information and
3046 their level of health literacy to promote patient understanding. Recently a prospective survey of 499
3047 AF patients (with and without previous stroke) in the US found that most (87%) desired more
3048 information about AF and how to reduce their risk of AF-related stroke.⁴⁸⁵ AF patients perceive
3049 greater satisfaction with treatment if they are engaged in treatment decisions and provided with
3050 relevant information (verbal, visual, written, electronic/on-line resources, as appropriate, chosen by
3051 the patient), which is well-communicated by their healthcare providers,^{479,485,497} and updated over
3052 time. Full details on shared decision-making, patient preferences and patient education/counseling
3053 are provided in the Online Supplement (e-Tables 24-26).

3054 Recommendations

3055 **60. In AF patients who have previously refused OAC, we suggest reinforcing educational messages**
3056 **at each contact with the patient and revisit OAC treatment decisions (ungraded consensus-**
3057 **based statement).**

3058 *Remark:* Patient and physician treatment objectives often differ significantly and it is important
3059 to elicit from the patient what outcomes of OAC treatment are important to them.

3060 *Remark:* Explain the risk of stroke and benefit/risks of treatment in terms the patient can
3061 understand and signpost the patient to appropriate educational resources

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4560 Table 1. PICO Questions
4561

	Section	Question	Patients	Intervention	Control	Outcomes	Methodology
	Burden of stroke in atrial fibrillation (AF)						
1.2	<ul style="list-style-type: none"> Established clinical risk factors for ischemic stroke in AF (including AF burden) Echocardiographic risk factors for ischemic stroke in AF Potential novel risk factors for ischemic stroke in AF 	What are the risk factors for ischemic stroke and TE?	Patients with AF - established clinical risk factors - risk factors on echocardiography - novel risk factors Patients with chronic atrial flutter	N/A	N/A	Ischemic stroke Systemic thromboembolism (TE) Mortality	Cohort studies Non-warfarin arms of RCTs
1.3	Risk stratification for ischemic stroke and TE	What risk stratification schemes most accurately predict ischemic stroke and TE, and mortality?	Patients with AF	N/A	N/A	c-statistic NRI, IDI, DCA Absolute rates of ischemic stroke and TE	Cohort studies Clinical prediction rules
	Antithrombotic therapy						
2.1	Patients with non-valvular AF	What are the benefits and risks of different stroke prevention strategies?	Patients with non-rheumatic AF - low risk - intermediate risk - high risk (including prior stroke)	Vitamin K antagonist (VKA)	No VKA	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage	SR RCTs

						(subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	
2.1	Patients with non-rheumatic AF (cont'd)		As above	Antiplatelet drug (aspirin or other)	No antiplatelet drug	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs
			As above	VKA	Antiplatelet drug (aspirin or other)	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs

			As above	Adjusted dose VKA	Fixed minidose or low-intensity VKA ± aspirin	<ul style="list-style-type: none"> - Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death 	
			As above	Clopidogrel + aspirin	Aspirin	<ul style="list-style-type: none"> - Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death 	SR RCTs
			As above	NOACs	VKA	<ul style="list-style-type: none"> - Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and 	SR RCTs Cohort studies

						intracerebral) - Major extracranial hemorrhage - MI - Vascular death	
			As above	NOAC	Aspirin	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
			As above	Device therapy WATCHMAN, PLAATO)	VKA	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death -cardiac tamponade	SR RCTs Cohort studies
			As above	Non-pharmacologic	VKA	- Death - All stroke	SR RCTs

				therapies - removal or ligation of left atrial appendage - surgical or catheter ablation - maze procedure		- Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death - procedural / surgical complications	Cohort studies
2.2	Patients with valvular AF	What are the benefits and risks of different stroke prevention strategies?	Patients with AF and rheumatic heart disease (i.e., mitral stenosis)	Vitamin K antagonist (VKA)	No VKA	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
2.3	Patients with prosthetic valves	What are the benefits and risks of different stroke prevention strategies?	Patients with AF and prosthetic valves	Vitamin K antagonist (VKA)	No VKA	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral)	SR RCTs Cohort studies

						<ul style="list-style-type: none"> - Major extracranial hemorrhage - MI - Vascular death 	
4	Antithrombotic therapy for AF (or atrial flutter) patients undergoing cardioversion						
3.1	Urgent cardioversion	What are the benefits and risks of antithrombotic therapy for AF patients undergoing urgent cardioversion?	Patients with AF undergoing urgent cardioversion	Anticoagulation	No anticoagulation	<ul style="list-style-type: none"> - Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death 	SR RCTs Cohort studies
3.2	Elective cardioversion	What are the benefits and risks of antithrombotic therapy for AF patients undergoing elective cardioversion?	Patients with AF undergoing elective cardioversion	Anticoagulation	No anticoagulation	<ul style="list-style-type: none"> - Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death 	SR RCTs Cohort studies

3.3	Transesophageal echocardiography (TEE)-guided cardioversion	What are the benefits and risks of antithrombotic therapy when using TEE-guided cardioversion?	Patients with AF undergoing TEE-guided cardioversion	TEE-guided cardioversion	Conventional anticoagulation	<ul style="list-style-type: none"> - Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death 	SR RCTs Cohort studies
5	Practical issues in the use of adjusted-dose VKA therapy						
5.1	Optimal target INR	What target INR provides the optimal balance between stroke prevention and bleeding in AF?	Patients with AF	INR 2-3	Other	<ul style="list-style-type: none"> - Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death 	SR RCTs Cohort studies
			Patients with AF and valvular heart disease/ prosthetic valves	INR 2-3	Other	<ul style="list-style-type: none"> - Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and 	SR RCTs Cohort studies

						intracerebral) - Major extracranial hemorrhage - MI - Vascular death	
5.1	Time within therapeutic range (TTR)	What is the association between TTR and outcomes in AF?	Patients with AF	Good TTR	Poor TTR	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
5.1	Monitoring of VKA therapy	What is the most effective way to monitor VKA therapy?	Patients with AF on VKA therapy	Point of care testing, patient self monitoring	Usual care	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
5.2	NOACs						
	Special situations						
5.3a	Patients with AF with stable	What are the	Patients with coronary	OAC + aspirin	OAC	- Death	

	coronary artery disease or peripheral arterial disease	benefits and risks of adding aspirin therapy to VKA therapy?	artery disease or peripheral arterial disease			<ul style="list-style-type: none"> - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death 	SR RCTs Cohort studies
5.3b	Patients with AF presenting with acute coronary syndrome?	As above	Patients with ACS	OAC + aspirin + clopidogrel	Aspirin + clopidogrel	<ul style="list-style-type: none"> - Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death 	SR RCTs Cohort studies
5.3c	Patients with AF undergoing percutaneous coronary intervention with stenting	As above	Patients undergoing PCI + stenting	OAC + aspirin + clopidogrel	Aspirin + clopidogrel	<ul style="list-style-type: none"> - Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage 	SR RCTs Cohort studies

						<ul style="list-style-type: none"> - MI - Vascular death 	
5.4	<p>Patients with AF being treated in a rhythm control strategy</p>	<p>What are the benefits and risks of OAC therapy in patients treated with a rhythm control strategy?</p>	<p>Patients being treated with a rhythm control strategy (e.g. maze procedure, catheter ablation, electrophysiology procedure, pharmacological)</p>	VKA, NOAC	No OAC	<ul style="list-style-type: none"> - Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death 	<p>SR RCTs Cohort studies</p>
5.5	<p>Perioperative management of OACs (including devices)</p> <p>Atrial High Rate Episodes on devices or monitors</p>	<p>How should VKA therapy be managed for AF patients undergoing surgery/invasive procedure?</p>	<p>Patients with AF on OAC therapy</p>	<p>“Bridging” therapy with LMWH or IV heparin</p>	No bridging therapy	<ul style="list-style-type: none"> - Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death 	<p>Cohort studies</p>
5.6	<p>Patients with AF presenting with an acute stroke</p> <p>AF patients with an ICH</p>	<p>What is the optimal timing for initiation of anticoagulation?</p>	<p>Patients with acute stroke</p>	<p>Anticoagulation immediately</p>	<p>Anticoagulation delayed</p>	<ul style="list-style-type: none"> - Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and 	<p>SR RCTs Cohort studies</p>

						intracerebral) - Major extracranial hemorrhage - MI - Vascular death	
5.7a	Patients with AF who are pregnant	What are the benefits and risks of VKA therapy in pregnancy?	Patients with AF who are pregnant	VKA	No VKA	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
5.7b	Patients with chronic atrial flutter	What are the benefits and risks of different stroke prevention strategies?	Patients with atrial flutter	As in 2.1	As in 2.1	- Death - All stroke - Ischemic stroke - Systemic embolism - Intracranial hemorrhage (subdural, subarachnoid, and intracerebral) - Major extracranial hemorrhage - MI - Vascular death	SR RCTs Cohort studies
6	Bleeding						
6.1	Risk factors for bleeding on OAC therapy	What are the risk factors for bleeding while on VKA	Patients with AF on VKA therapy	N/A	N/A	-Fatal hemorrhage -Intracranial hemorrhage	Epidemiologic studies

		therapy?				(subdural, subarachnoid, intracerebral) -Major extracranial hemorrhage -Minor bleeding	Cohort studies RCTs
6.2	Bleeding risk assessment	What risk stratification schemes most accurately predict the risk of bleeding?	Patients with AF on OAC therapy	N/A	N/A	c-statistic NRU, IDI, DCA Absolute rates of bleeding outcomes (as listed above)	Clinical prediction rules
7	The patient						
		What are the values and preferences of patients with AF regarding VKA therapy, risk of stroke, and risk of bleeding?	Patients with AF	N/A	N/A	Patient preferences Factors which affect patient preferences Quality of life	RCTs Observational studies

4562 Table 2. CHEST Grading System
4563

Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, High-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	We are very confident that the true effect lies close to that of the estimate of the effect.	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation, Moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, Low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.	Recommendation can apply to most patients in many circumstances. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Strong recommendation, very low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	Recommendation can apply to most patients in many circumstances. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak (conditional) recommendation, High-quality evidence	Benefits closely balanced with risks and burden	We are very confident that the true effect lies close to that of the estimate of the effect.	The best action may differ depending on circumstances or patients' or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Weak (conditional) recommendation, Moderate-quality evidence	Benefits closely balanced with risks and burden	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Best action may differ depending on circumstances or patients' or societal values. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak (conditional) recommendation, Low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk and burden may be closely balanced	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.	Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak (conditional) recommendation, very-low quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk and burden may be closely balanced	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Ungraded Consensus-based Suggestions			
Ungraded Consensus-Based Statement	Uncertainty due to lack of evidence but expert opinion that benefits outweigh risk and burdens or vice versa	Insufficient evidence for a graded recommendation	Future research may well have an important impact on our confidence in the estimate of effect and may change the estimate.

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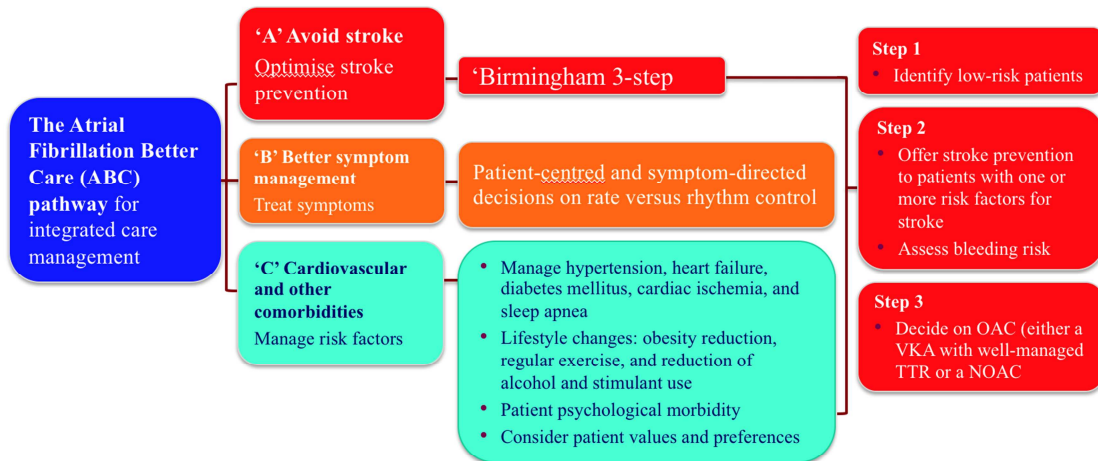
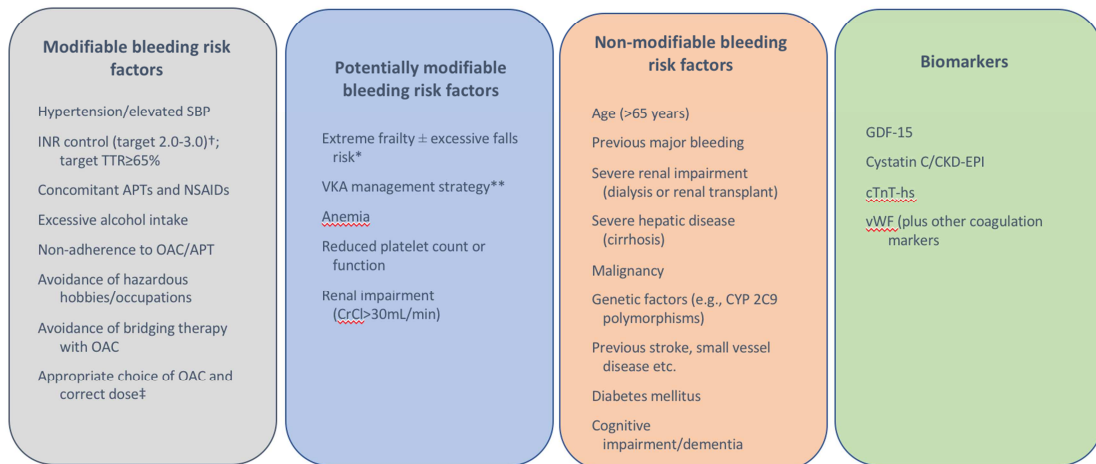


Figure 1 The Atrial fibrillation Better Care (ABC) Pathway of Integrated Care Management (from Lip et al 2017)².

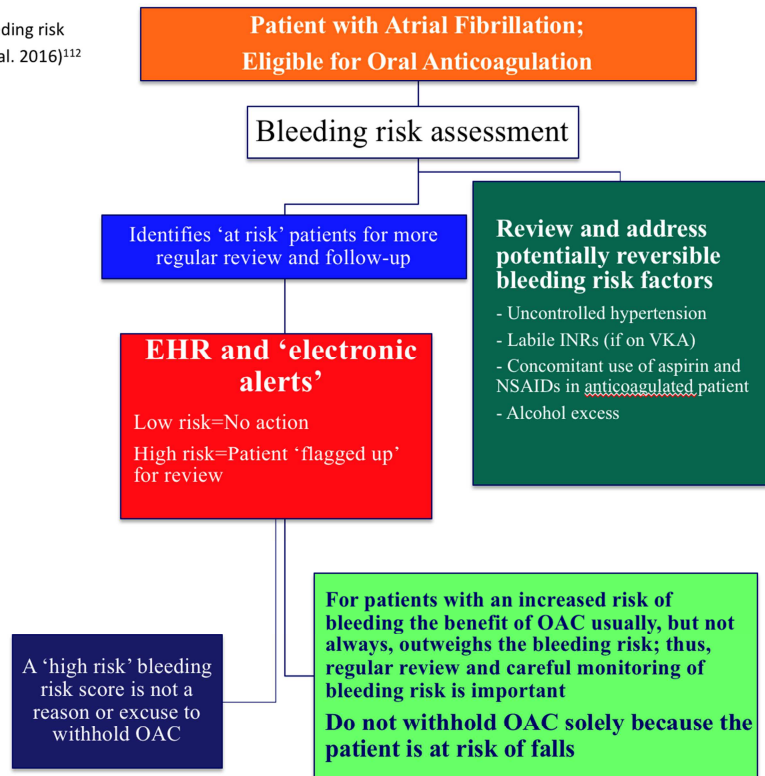
Figure 2: Risk factors for bleeding with oral anticoagulation (NOAC and VKA) and antiplatelet therapy



APT = anti-platelets; CrCl = creatinine clearance; cTnT-hs = high sensitivity Troponin T; GDF-15 = growth differentiation factor-15; INR = international normalised ratio; NSAIDs = non-steroidal anti-inflammatory drugs; OAC = oral anticoagulation; SBP = systolic blood pressure; TTR = time in the therapeutic range; vWF = von Willebrand Factor

†for patients receiving VKA treatment; ‡dose adaptation based on patient's age, body weight and serum creatinine; *walking aids; appropriate footwear; home review to remove trip hazards; neurological assessment where appropriate; ** increased INR monitoring, dedicated OAC clinics, self-monitoring/self-management, educational/behavioural interventions

Figure 3: Practical application of bleeding risk assessment in AF patients (from Lip et al. 2016)¹¹²



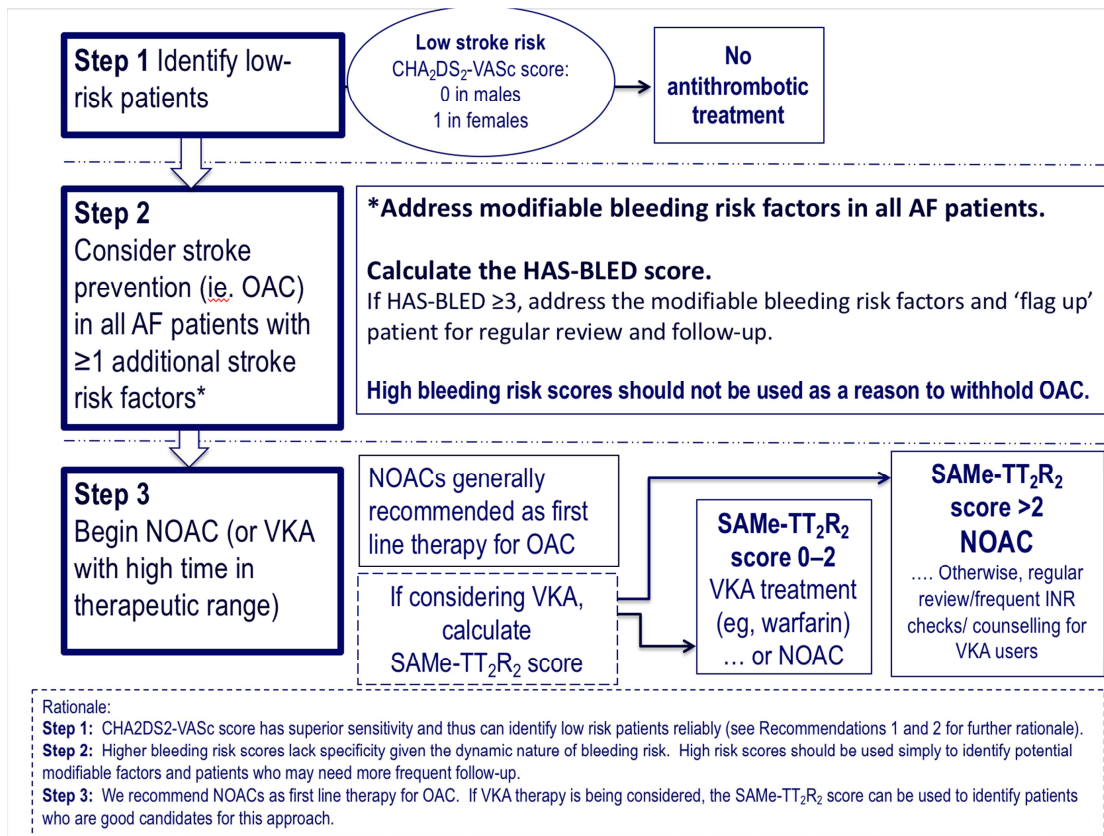
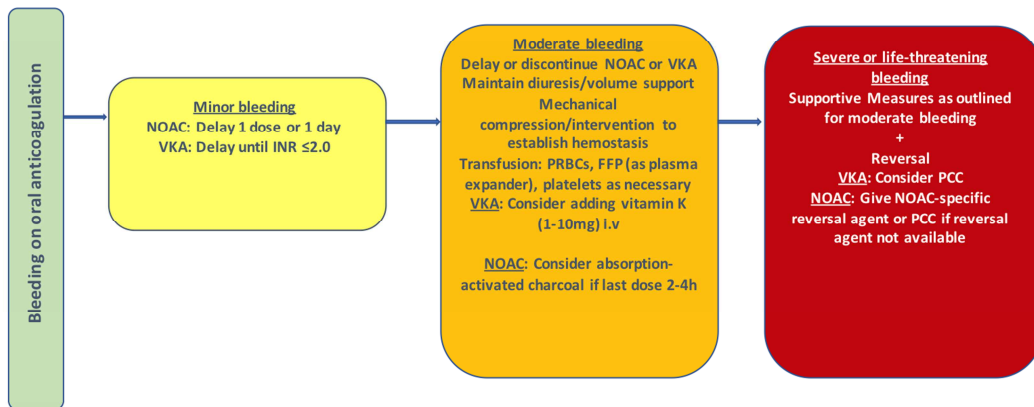


Figure 5: Management of patients with active bleeding on oral anticoagulation (NOAC and VKA)

FFP, fresh frozen plasma; h, hours; i.v., intravenous; NOAC, non-vitamin K antagonist oral anticoagulant; PCC, prothrombin complex concentrate; PRBC, packed red blood cells; VKA, vitamin K antagonist

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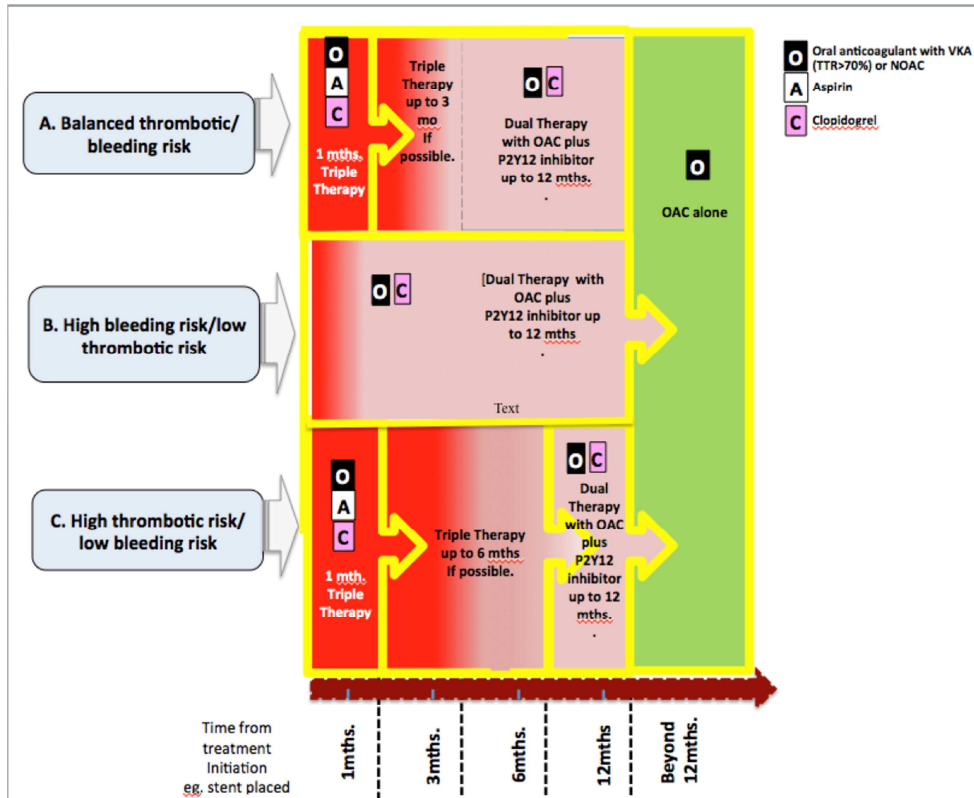




Figure 6. Management of oral antiplatelet therapy in patients with (A) balanced thrombotic bleeding risk, (B) low thrombotic–high bleeding risk, and (C) high thrombotic–low bleeding risk (adapted from Angiolillo et al. 2016)²⁸²

FLOW CHART for patient management in case of CIED detected AHRE	
Detection of AHRE	Patient with a CIED, no previous AF and detection of AHRE (≥ 5 -6 min and >180 bpm)
	
Clinical evaluation of device data and evaluation of patient cardiac status and profile	Analysis of device electrograms (AF/atrial tachyarrhythmias confirmed? Artifacts excluded?)
	Clinical cardiological evaluation + 12-lead ECG
	Consideration for ECG recordings (Holter, patient operated devices) in specific cases (e.g. unavailable electrograms or unclear diagnosis at device electrograms analysis)
	Clinical risk stratification for stroke (CHA ₂ DS ₂ VASc score?)
	
Clinical decision making and follow up	<p>If diagnosis of AF or atrial flutter and intermediate (CHA₂DS₂VASc score =1 in males and =2 in females) or high risk (CHA₂DS₂VASc score ≥ 2 in males and ≥ 3 in females):</p> <ul style="list-style-type: none"> -Monitoring of AHRE evolution (remote monitoring is advised) -Clinical follow up for evaluating if AHRE > 24 hours and/or clinical AF develops, as well as changes in patient status/clinical profile (e.g. heart failure) -Individual considerations for prescription of OAC considering overall AHRE burden and AHRE > 24 hours, individual CHA₂DS₂VASc, predicted risk benefit of OAC (specifically risk of major bleeding) and patient preferences

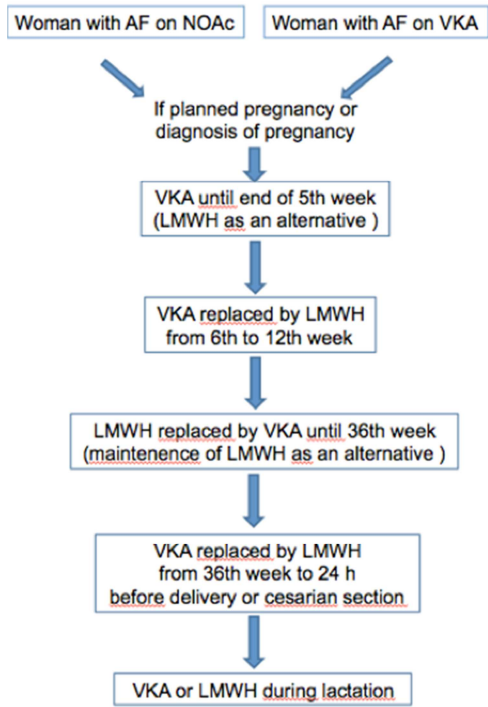


Figure 8. Suggested algorithm for the decision-making process in prescribing oral anticoagulant therapy in patients with various degrees of renal function impairment (from Lau et al 2016).⁴³⁶

Drug	CrCl ≥50 mL/min	CrCl 30-49 mL/min	CrCl 15-29 mL/min	CrCl <15 mL/min or ESRD on RRT
VKA	If TTR ≥70%	If TTR ≥70%	If TTR ≥70%	If TTR ≥70%
Dabigatran	150mg bid § (or 110mg bid)	150 mg bid (or non-US, 110mg bid) §	✗ (Outside US) 75mg bid in US§	✗
Rivaroxaban	20 mg qd	15mg qd	15 mg qd	✗
Apixaban	5mg bid*	5mg bid*	2.5mg bid	✗ (Outside US) 5mg bid in US only*
Edoxaban	60 mg q#	30mg qd	30mg qd	✗

- Closely monitor renal function, especially in NOAC users.
- Schedule for frequent clinical follow-up, look for development of new cardiovascular risk factors, comorbidities.
- Reassess and address bleeding risk factors.

*Use 2.5 mg BID if 2 of 3 of the following criteria are present: age >80 years old, weight <60 kg, serum creatinine >133 $\mu\text{mol/l}$.

§The 110-mg dose is not available in the United States. Unless the patient is elderly or has high bleeding risk or is taking p-glycoprotein inhibitors, where dabigatran, 110 mg BID is preferred, except in the United States, where the 110-mg dose is not available.

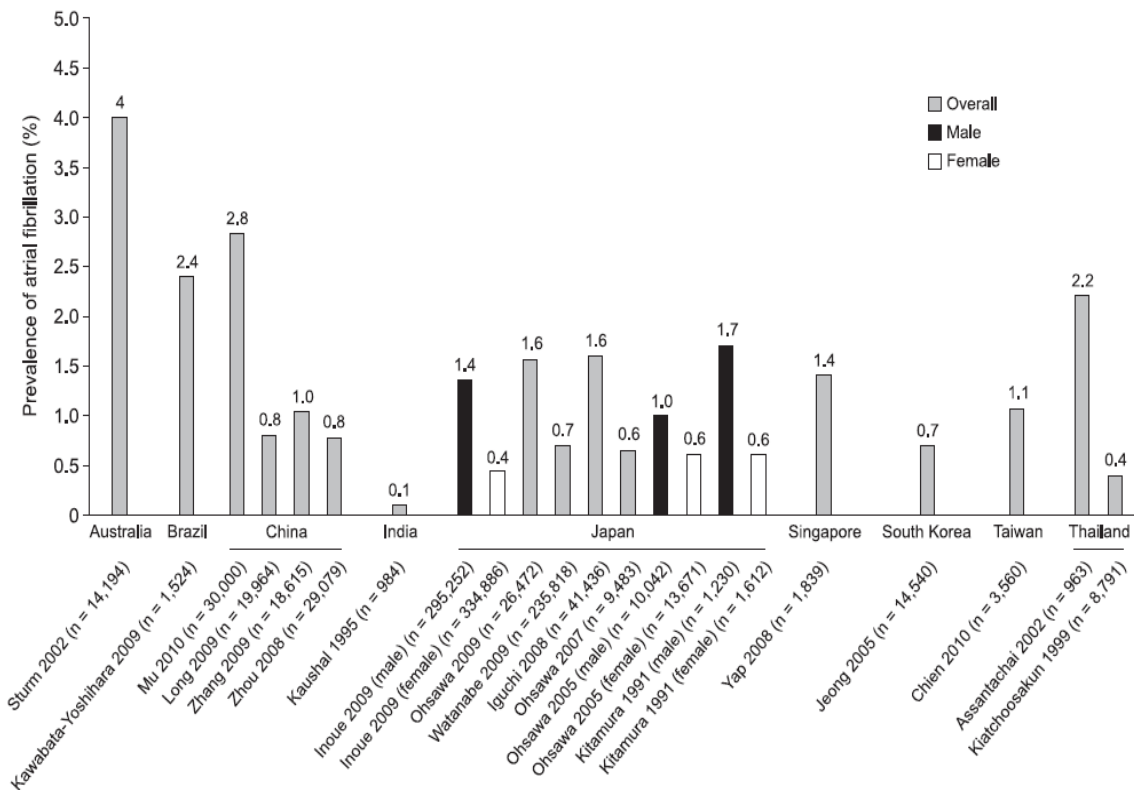
#In the United States only, caution is advised where CrCl is >95 ml/min.

e-Table 2. Implications of Strength of Recommendations for different users of guidelines

	Strong Recommendation	Conditional (weak) Recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but some would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

e-Appendix 1. Burden of Stroke in Atrial Fibrillation*Epidemiology and contemporary burden of ischemic stroke in AF*

Atrial fibrillation (AF) is the commonest arrhythmia worldwide¹. Health systems face increasing prevalence, incidence and lifetime risk of AF, which is as high as 1 in 4 in contemporary studies in high-income settings². Age is an important risk factor for both AF and stroke and increasing age and demographic change are projected to drive future increases in AF and stroke³. Epidemiologic studies largely represent Western countries and Caucasian populations⁴. However, reported prevalence varies substantially by world region: India (0.1%)⁵, Europe⁶ and North America (1–2%)⁷ and Australia (4%)⁸, with pooled age- and sex-adjusted prevalence estimated as 2.8% (95% CI: 2.3–3.4%)⁹. Figure 1 illustrates the prevalence of AF in reported studies outside North America and Europe⁴. Recent data from rural India using the approved single-lead electrocardiography device, Alivecor, for 2 minutes on 5 consecutive days found a higher prevalence of AF (~5%) than prior studies¹⁰. As well as regional variation, reported prevalence is therefore higher with more rigorous screening methods to detect AF, and the low prevalence reported in certain world regions may well be an underestimate of true AF burden.



e-Figure 1. Prevalence of atrial fibrillation reported in community-based studies from countries outside North America and Europe. The overall prevalence is presented where available; otherwise, the prevalence in men and women is presented separately. (from Lip et al 2012)⁴

Individuals with AF have increased risk of serious complications, including stroke (4-5 fold increase)¹¹, heart failure (2-3 fold increase)¹² and mortality (2-fold increase)^{12,13}. The Global Burden of Disease Study has shown that burden of disease in terms of age-adjusted disability-adjusted life years has increased by 19% between 1990 and 2010¹. Patients with AF also experience higher rates of morbidity, hospital admissions, as well as 'premature' dementia^{2,14}. Recent data from population-based studies and stroke registries demonstrate a high AF-attributable risk of stroke, especially in the elderly. At least one in 3 to 4 individuals with an ischemic stroke and over 80% of those with ischemic stroke of cardioembolic subtype, also has AF¹⁵.

Mechanism of development of AF

A systematic review of the associations of 23 cardiovascular risk factors and incident AF was recently conducted, including both consented and electronic health record cohorts of 20,420,175 participants and 576,602 AF events respectively. It showed significant heterogeneity in AF definition, quality of reporting, and adjustment for other risk factors¹⁶. Hypertension, obesity, taller height and coronary heart disease showed consistent, direct associations with incident AF. Higher cholesterol (0.76 [0.59-0.98] to 0.94 [0.90-0.97]) and higher diastolic blood pressure (0.87 [0.78-0.96] to 0.92 [0.85-0.99]) showed some evidence of being associated with lower risk of incident AF. Evidence for the widely-held clinical opinion that alcohol use is associated with incident AF in the primary preventative setting was minimal. Several of the risk factors for incident AF are also risk factors for stroke in AF¹⁶.

Ethnic differences

Overall, non-white ethnicity shows evidence of association with lower risk of incident AF in a recent systematic review of electronic health record studies of AF. For African American, Asian, Chinese, Hispanic and Non-Hispanic Black (compared to White) ethnicities, significant inverse associations (from 0.35 [NR–NR] to 0.84 [0.82–0.85]). Only 1 country (USA) reported estimates for the association of ethnicity and incidence of AF¹⁷. There is likely to be considerable variation in prevalence, incidence and outcome by ethnicity and geographic region, but the number of studies to-date is limited. For example, incidence and long-term mortality following hospitalised AF is higher in Aboriginal versus non-Aboriginal individuals in Australia¹⁸. Variations which have been observed need to be validated. For example, the low reported prevalence rates of AF in India may represent under-diagnosis rather than true low rates¹⁰.

The racial differences in co-morbidities in AF patients have been reported recently.^{19,20} The mean age, sex, and prevalence of several stroke-related cardiovascular co-morbidities among different races in major surveys and cohorts are shown in e-Table 3.²¹⁻³⁷ The mean ages were 60 to mid-70, except in the Middle East (mean age 57 years). Males were generally predominant. Hypertension (52-85.2%) leads other risk factors and is equally distributed in different races. The prevalence rates of heart failure (18.9-47.5%) and diabetes (16-36.8%) show no major differences among races. With one exception in China,²⁶ coronary heart disease (CHD) seems more common in Caucasians and Middle East (16.0-36.4%) than in Asians (7.4-25.4%). Only 1 of the remaining 9 Asian cohorts has a prevalence rate of CHD more than 20%, while 7 of the 10 cohorts in Caucasians and the Middle East have CHD prevalence rate above 20%. A higher prevalence rate of previous history of stroke/transient ischemic attack (TIA) was found in Asians (10.2-23.1%) than in Caucasians and Middle East (9-19%). Eight out of the 10 Asian cohorts have a history of stroke/TIA above 15%, but only 1 of the 10 cohorts of Caucasians and the Middle East has a prevalence rate over 15%.

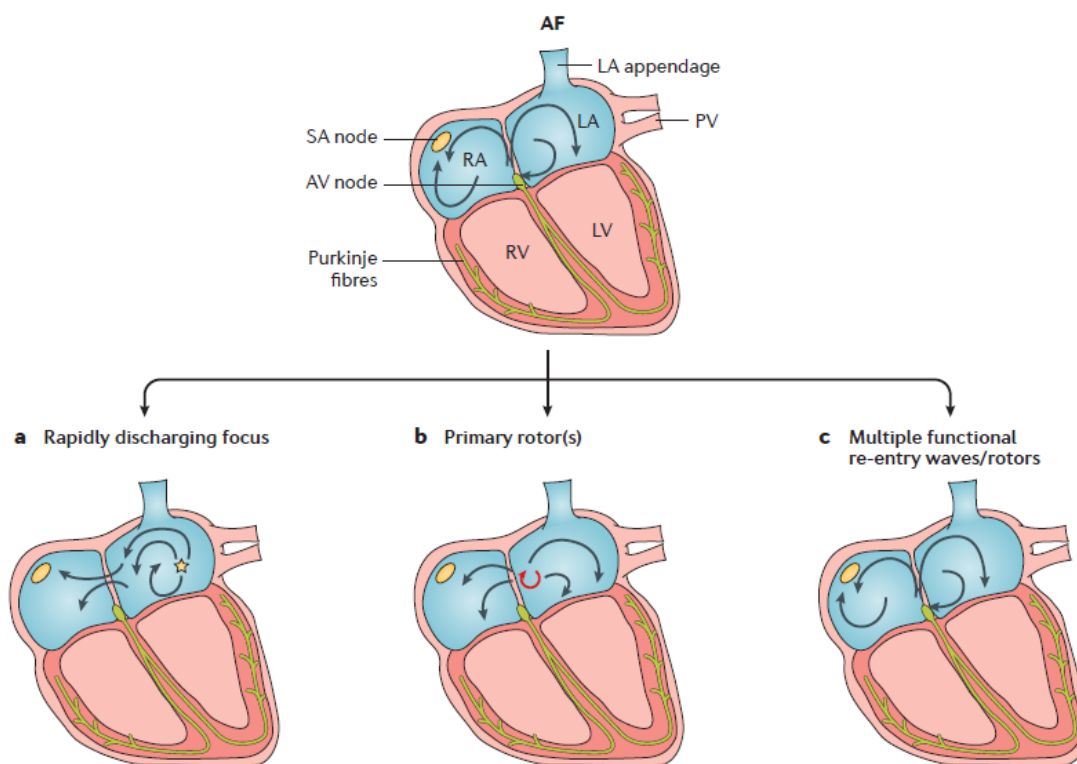
The annual risk of AF-associated stroke in Asians is higher than that in Caucasians.²⁰ In the recent AF cohorts from Taiwan²⁹, Hong Kong,³⁰ and Sweden³⁸, the annual stroke risk in antithrombotic-naïve patients who had a CHA₂DS₂-VASc score 0 was 1.1%, 2.4% and 0.2%, respectively. The similar trends were shown for CHA₂DS₂-VASc 1 (1.7%, 6.6%, and 0.6% respectively), CHA₂DS₂-VASc 2 (3.2%, 7.8%, and 2.2% respectively), CHA₂DS₂-VASc 3 (4.2%, 9.6%, and 3.2% respectively), and CHA₂DS₂-VASc 4 (5.8%, 11.6%, and 4.8% respectively). It has been suggested that the risk of stroke starts to increase at a younger age in Asians.²⁰ In a Taiwanese cohort, the risk of stroke was 1.78%/year in patients who had an age of 50-64 years and a CHA₂DS₂-VASc 0.³⁹ The risk exceeds the threshold for OAC use for stroke prevention. A modified CHA₂DS₂-VASc (mCHA₂DS₂-VASc) score has been proposed assigning one point for patients aged 50 to 74 years.⁴⁰ The mCHA₂DS₂-VASc score performed better than CHA₂DS₂-VASc score in predicting ischemic stroke assessed by C indexes and net reclassification index. For patients having an mCHA₂DS₂-VASc score of 1 (males) or 2 (females) because of the resetting of the age threshold, use of warfarin was associated with a 30% lower risk of ischemic stroke and a similar risk of ICH compared with non-treatment. Net clinical benefit analyses also favored the use of warfarin in different weighted models. These findings suggest that the age threshold may need to be reset in East Asians.⁴⁰

e-Table 3. Co-morbidities of AF in different races in major surveys and cohorts

	Asians										Caucasians									Middle East
Survey/cohorts	RECORD AF AP ²¹	RELY AF Southeast Asia ²²	GARFIELD East and Southeast Asia ²³	J-Rhythm ²⁴	Fushimi ²⁵	China ²⁶	CAFR ²⁷	GLORIA 1 Chinese ²⁸	Taiwan ²⁹	HK ³⁰	Euro Heart Survey ³¹	RECORD AF ³²	ORBIT AF ³³	RELY AF West Europe ²²	EORP AF ³⁴	PREFER ³⁵	GARFIELD, other region excluding East and South East Asia ²³	GLORIA I Europe ²⁸	SPRINT ³⁶	GULF SAFE ³⁷
Age (mean)	64	69.5	67.1	69.7	74.2	75	65.8	69	72.0	76.9	66	66	75	69.4	68.8	71.5	71.3	71	75.7	57
Female(%)	40	44.6	39.8	31.1	40.7	27.1	40.4	42.8	46.0	52.1	43	43	42	38.8	40.4	39.9	44.5	50.5	44.7	48
CHD(%)	19	10.9	7.4	11.6	15.0	59.4	7.8	25.4	15.3	18.2	32	18	32	18.2	36.4	23.4	16.0	20.3	25.1	28
Diabetes(%)	18	29.2	23.5	22.1	23.2	36.8	24.5	19.5	26.9	22.0	18	16	29	17.1	20.6	22.4	23.7	27.1	29.7	30
HF(%)	25	26.3	26.6	34.4	27.9	21.2	18.9	24.7	38.7	22.8	33	26	32	21.2	47.5	21.3	20.8	22.3	18.8	27
HT(%)	58	64.1	73.1	71.1	60.6	72.5	66.1	70.1	62.9	54.7	63	68	83	59.9	70.9	72.0	82.0	85.2	73.6	52
Stroke/TIA(%)	13	22.1	15.3	17.3	21.8	20.2	17.0	10.2	20.5	23.1	9	10	16	12	10.5	8.4	13.7	10.7	15.0	13

Pathophysiology – a brief overview

AF is characterised by rapid, uncoordinated atrial activity, caused by: (a) a rapidly discharging atrial focus, (b) a primary re-entrant rotor, or (c) multiple functional re-entry circuits⁴ (figure w3). The initiation and perpetuation of AF needs both “triggers” for its onset and a “vulnerable substrate” for its maintenance. “Triggers” of focal spontaneous firing typically arise from the pulmonary veins⁴¹, but can also emanate from other foci⁴². The ‘vulnerable substrate’ maintains the arrhythmia, dependent on cardiac and non-cardiac risk factors, including genetic pre-disposition, cardiac remodelling due to underlying heart disease, autonomic imbalance and thyroid dysfunction.



e-Figure 2. Mechanisms that can maintain atrial fibrillation (from Lip et al 2016⁴).

AF, atrial fibrillation; AV, atrioventricular; LA, left atrium; LV, left ventricle; PV, pulmonary vein; RA, right atrium; RV, right ventricle; SA, sinoatrial.

Although the micro-pathophysiology has been relatively well-established, the epidemiology of how risk factors individually or in combination, create the “vulnerable substrate”, is relatively unknown. Until the interplay of these risk factors is better understood, primary prevention strategies for AF are likely to be restricted, despite development of risk prediction tools for AF. Although currently primary prevention strategies for AF have not been conclusively proven in randomized trials, opportunistic screening is the recommended strategy to detect AF at population-level⁴³.

Echocardiographic risk factors for ischemic stroke in AF

Underlying heart disease, whether as a result of hypertension, coronary artery disease or heart failure, is important in the aetiology and prognosis of AF. Therefore, it is not surprising that echocardiographic characteristics have been associated with risk of ischemic stroke in AF. There

may also be a role in evaluating thromboembolic risk stratification to select appropriate antithrombotic therapy. e-Table 4 summarizes major studies which have shown association between transthoracic echocardiographic (TTE) parameters and ischemic stroke.

In summary, there are small-scale studies to suggest a role for various measures (LA and LV size, volume and strain) on TTE. However, there are very limited data to suggest that there would be any incremental benefit in risk prediction, and moreover there is no evidence that management (in terms of OAC) would be changed⁴⁴. In the recent ENGAGE AF-TIMI trial, larger LV size and higher filling pressures (measured by E/e' ratio) were significantly associated with increased risk for death, but neither left atrial nor LV measures were associated with thromboembolic risk⁴⁵. In patients undergoing transesophageal echocardiography (TEE), LA appendage thrombi⁴⁶ and LA spontaneous echo contrast⁴⁷ are both associated with increased thromboembolism, but the same limitations as for TTE parameters apply⁴⁴. In terms of risk stratification, the role of echocardiography is currently restricted to the inclusion of heart failure (left ventricular systolic dysfunction) in the CHA₂DS₂-VASc score⁴⁸.



e-Table 4. Key evidence concerning transthoracic echocardiographic parameters and prediction of stroke and thromboembolism in patients with non-valvular AF. Adapted from Providencia et al 2013⁴⁴

Study	Study design and setting	Main findings
The Stroke Prevention in Atrial Fibrillation Investigators (1992) ⁴⁹	Cohort n=568 Non-rheumatic AF Mean follow-up, 1.3 years	14 transthoracic echocardiographic variables were assessed for predicting ischemic stroke or systemic embolism. Only LA size (measured on M-mode echocardiography) and depressed LVEF were independent predictors of thromboembolism on multivariate analysis and improved risk stratification when combined with three clinical risk factors: history of hypertension, recent congestive heart failure, and previous thromboembolism
Osranek <i>et al.</i> (2005) ⁵⁰	Cohort n=45 Lone AF Mean follow-up, 27 years	Individuals with indexed LA volume ≥ 32 mL/m ² had worse event-free survival (HR, 4.46; <i>P</i> = 0.005) Cerebral infarction occurred in 7 patients, all with indexed LA volumes ≥ 32 mL/m ²
Lee <i>et al.</i> (2008) ⁵¹	Cross-sectional n=330 Persistent AF and preserved LVEF	E/E' ratio was independently associated with ischemic stroke on multivariate analysis
Shin <i>et al.</i> (2010) ⁵²	Cohort n=148 AF and heart failure with preserved LVEF Median follow-up, 27 months	S' and E', particularly when combined, were independent predictors of a composite of cardiovascular death, recurrent heart failure, and ischemic stroke
Azemi <i>et al.</i> (2012) ⁵³	Case-control n=57 in each group Nonvalvular AF CHADS ₂ score ≤ 1 before index event	Patients with stroke presented reduced peak negative and peak positive LA strain values, when compared with controls
Su <i>et al.</i> (2013) ⁵⁴	Cohort 196 patients with persistent AF Mean follow-up, 21 months	Global left ventricular longitudinal systolic strain (GLS) was independently associated with adverse CV events including stroke in multivariate models.

LVEF, Left ventricular ejection fraction.

Biomarkers

The role of biomarkers in stroke/thromboembolism in AF has been extensively investigated. e-Table 5 summarizes important studies involving biomarkers. Although several biomarkers of prothrombotic state and of endothelial dysfunction have shown associations with stroke and thrombosis, both study design and scale of the studies limit possible conclusions. Caveats with the use of biomarkers include inter- and intra- patient and assay variability, some have a diurnal variation and can be highly influenced by associated comorbidities and drug therapies. Many biomarkers are non-specific for a particular endpoint, and can be equally predictive not only of stroke but bleeding, death, hospitalization, heart failure etc., as well as non-cardiac conditions e.g., glaucoma.

The importance of biomarkers probably lies in the CHA₂DS₂VASc=0-2 group (currently without anticoagulation) where they may influence the decision to anticoagulate, yet there is a paucity of data available in these patients. There are several other hurdles including variations in availability in healthcare systems, biomarker assays, access to laboratories, biomarker diurnally, by comorbidities and by anticoagulation and other therapies. For these reasons, the clinical application of biomarkers in management of AF is unlikely to be significant.

The disease burden-oriented school of thought states, "Research resources should not be allocated disproportionately to emerging novel risk factors that may account for up to only 20% of all strokes at the expense of researching the determinants of the relatively few established causal factors that account for up to 80% of all strokes."⁵⁵ Any biomarker, whether blood, urine or imaging (cardiac, cerebral or otherwise) will always improve on risk prediction based on clinical factors, but this needs to be balanced against the practical usefulness, cost and daily applicability for everyday clinical practice.

e-Table 5. Biomarkers in prediction of various thromboembolic events in patients with atrial fibrillation.

Study, Year	Participants	Biomarker	Investigation
Heppell et al. ⁵⁶ 1997	109 (19 with left atrial thrombosis)	BTG, vWF	Association with presence of left atrial thrombosis (BTG: $p=0.002$; vWF: $p=0.04$; LAA velocity: $p=0.001$) Higher levels in chronic AF; association with a prothrombotic state and endothelial dysfunction, coagulation factors and left atrial dimension. (Plasma fibrinogen: $p<0.005$; platelet factor 4: $p<0.001$; thromboglobulin: $p<0.001$; D-dimer: $p<0.03$, tPA: $p<0.006$, plasminogen activator inhibitor: $p<0.04$; vWF: $p<0.0001$ and soluble thrombomodulin: $p<0.03$) Rise in vWF was predictive of stroke and vascular events. After adjustment for covariates, vWf was an independent predictor of vascular events (RR 1.2 [95% CI, 1.0-1.4] per 20 IU/dL increase in vWF; $p=0.02$), but not stroke.
Mondillo et al. ⁵⁷ 2000	45 chronic AF, 35 control	vWF, thrombomodulin	
Conway et al. ⁵⁸ 2003	994 AF patients taking aspirin	vWF, P-selectin	
Conway et al. ⁵⁹ 2004	106 AF; 41 control	IL-6, CRP, TF	Higher levels in AF patients; TF associated with stroke risk ($p = 0.003$)
Heeringa et al. ⁶⁰ 2006	162 AF, 324 control	P-selectin	Association with cardiac mortality in AF (RR 1.27; 1.08-1.50, per 5-unit increase)
Nozawa et al. ⁶¹ 2006	509	D-dimer	Thromboembolic risk in patients without the clinical risk factors was quite low (0.7%/year) when D-dimer was < 150

Study, Year	Participants	Biomarker	Investigation
<i>Ferro et al.</i> ⁶² 2007	285	CD-40 ligand	ng/ml, but not low (3.8%/year) when D-dimer was ≥ 150 ng/ml. Association with thromboembolic events even in AF patients on anticoagulation. Predictor of vascular events (stroke and myocardial infarct): HR 4.63, 1.91-11.1; $p=0.001$
<i>Lip et al.</i> ⁶³ 2007	880	hsCRP	Correlation with stroke risk factors and prognosis (mortality: 0.001, cardiovascular events: $p=0.05$) Predictor for stroke (RR 1.35; 95% CI 1.01-1.84, $p=0.049$) and AF in The multivariable adjusted risk was for any stroke and 1.30-fold (95% CI 0.90 to 1.91, $p = 0.0150$) for ischemic stroke for each log-transformed SD (0.240 pmol/l) increment in NT-proBNP.
<i>Kurl et al.</i> ⁶⁴ 2009	958 men	NT-proBNP, NT-proANP	Predictor for new-onset stroke in persistent AF
<i>Pinto et al.</i> ⁶⁵ 2009	373	TNF- α , IL-6, vWF	MPV is not related with left atrial thrombus in patients with chronic AF
<i>Yuce et al.</i> ⁶⁶ 2010	205 chronic AF	MPV	Association with thromboembolic events in patients with AF during oral anticoagulant therapy
<i>Sadanaga et al.</i> ⁶⁷ 2011	261	BNP	Association with risk for stroke and mortality
<i>Hijazi et al.</i> ⁶⁸ 2012	6 189	NT-proBNP, Troponin I	

AF = atrial fibrillation; BTG = β -thromboglobulin; CHF = chronic heart failure; CRP = C-reactive protein; HF = heart failure; hsCRP = highly sensitive C-reactive protein; IL = interleukin; LAA = left atrial appendage; MMP = metalloproteinase; MPV = mean platelet volume; NT-proANP = N-terminal prohormone of ANP; NT-proBNP = N-terminal prohormone of BNP; OAC = oral anticoagulants; RR = relative risk; SPAF III = Stroke Prevention in Atrial Fibrillation III; TF = tissue factor; TNF = tumor necrosis factor; von Willebrand factor(vWF). (From Szymanski et al 2015⁶⁹)


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e-Table 6. Comparison of features included in risk stratification schemes

Study	Age (yrs)	HTN	DM	Prior Stroke or TIA	Female Sex	Heart Failure	Coronary Artery Disease	Systolic BP	Abnormal LV Function	Other
Atrial Fibrillation Investigators (1994) ⁷⁰	≥65	+	+	+						
Stroke Prevention in Atrial Fibrillation Investigators (1995) ⁷¹	>75*	+		++	+++*	++		>160	++	
European Atrial Fibrillation Trial Investigators (1995)** ⁷²				+				>160		
Atrial Fibrillation Investigators (1998) ⁷³	>65	+	+	+					+	
Stroke Prevention in Atrial Fibrillation Investigators (1998) ⁷³	>75#	+	+	++	+++#			>160		
CHADS ₂ (2001) ⁷⁴	≥75	+	+	++		+				
American College of Chest Physicians (2001) ⁷⁵	≥65 >75	++	+	++		++	+		++	
Framingham Heart Study (2003) ⁷⁶	+		+	+	+			+		
van Walraven et al. (2003) ⁷⁷		+	+	+			+	+		
American College of Chest Physicians (2004) ⁷⁸	≥65 >75	++	++	++		++			++	
Birmingham/NICE (UK)(2006) ⁷⁹	≥65	+	+	++		++	+		++	
ACC/AHA/ESC Guidelines (2006) ⁸⁰	≥75	+	+	++	^	+	^		+	
American College of Chest Physicians (2008) ⁸¹	≥75	+	+	++		+				
CHA ₂ DS ₂ -VASc 2010 ⁸²	>65	+	+	++	+	+	∞	+	+	
American College of Chest Physicians (2012) ⁸³	≥75 (±65-74)	+	+	++	±	+	±Vascular disease			
ESC 2012 ⁸⁴	>65	+	+	++	+	+	∞	+	+	Stepwise, to initially identify low risk


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R ₂ CHADS ₂ (2013) ⁸⁵	≥75	+	+	++		+				Renal dysfunction Ie. CrCl<60
QStroke (2013) ⁸⁶	Range 25-84	+	+		Separate models for M and F		CHD	+	CHF	Ethnicity; Deprivation score; Smoking; TC:HDL; BMI; FH; RA; CKD; Valvular HD
ATRIA (2013) ⁸⁷	Range <65 to ≥85	+	+	Separate models for 1° and 2° prevention	+	+				Proteinuria; eGFR<45ml/min
NICE2014 ⁸⁸	>65	+	+	++	+	+	∞	+	+	Stepwise, to initially identify low risk
AHA/ACC/HRS 2014 ⁸⁷	>65	+	+	++	+	+	∞	+	+	Categorised, based on CHA ₂ DS ₂ -VASc
CHADS65 (2014 CCS algorithm) ⁸⁹	≥65	+	+	+		+				
ABC-Stroke (2016) ⁹⁰	44-90			+						Biomarkers (NT-ProBNP, hs Troponin)
ESC 2016 ⁹¹	>65	+	+	++	+	+	∞	+	+	Categorised, based on CHA ₂ DS ₂ -VASc risk factors (not score)

e-Table 7. Comparison of Stroke Risk Schema – additional information

Author/Study	Cohort	Schemes compared	Events	Findings	Comments
ABC-stroke Hijazi et al 2016 ⁹⁰	Trial cohorts (ARISTOTLE and STABILITY)	ABC-Stroke, CHA ₂ DS ₂ -VASc	Stroke/SE	The ABC-stroke score yielded higher c-indices than CHA ₂ DS ₂ -VASc in both the derivation cohort (0.68(95%CI 0.65, 0.71) vs. 0.62 (0.60, 0.65), P< 0.001) and external validation cohort (0.66 (0.58, 0.74) vs. 0.58 (0.49,0.60), P < 0.001).	Developed and internally validated in 14 701 anticoagulated trial patients with biomarkers levels determined at baseline, median follow-up of 1.9 years. External validation in 1400 AF patients (mixed OAC/non-OAC), median follow-up 3.4 years. NB all patients in the derivation cohort had elevated risk to get into the ARISTOTLE trial, and similar elevated risk scores in the STABILITY CAD trial
Aakre ⁹²	longitudinal community-based cohort study from Olmsted County	8 Schemes compared ((AF investigators, SPAF, NICE guidelines, ACC/AHA/ESC guideline, ACCP Guideline	Ischemic stroke/SE	High risk: The Stroke Prevention in Atrial Fibrillation (SPAF; hazard ratio, 2.75; c=0.659), CHADS ₂ -revised (hazard ratio, 3.48; c=0.654), and CHADS ₂ -classical (hazard ratio, 2.90; c=0.653) risk schemes were most accurate in risk stratification. Low-risk cohort within the CHA ₂ DS ₂ -VASc scheme had the lowest event rate among all low-risk cohorts (0.11 per 100 person-years), but only 5% of the population were classified as low risk,	A direct comparison of 9 risk schemes reveals no profound differences in risk stratification accuracy for high-risk patients. Accurate prediction of low-risk patients is perhaps more valuable in determining those unlikely to benefit from OAC therapy. CHA ₂ DS ₂ -VASc performed best, but only small proportion were classified as low risk
Abraham ⁹³	longitudinal cohort of 5981 women with AF not on warfarin at baseline (mean age 65.9 years) enrolled in the Women's Health Initiative and followed for a median of 11.8 years.	CHADS ₂ CHA ₂ DS ₂ -VASc	Ischemic stroke/TIA	CHA ₂ DS ₂ -VASc had a higher c statistic than CHADS ₂ : 0.67 (95% CI, 0.65-0.69) versus 0.65 (95% CI, 0.62-0.67), P <.01. For CHADS ₂ scores <2, stroke risk almost doubled with every additional CHA ₂ DS ₂ -VASc point. Possible that some women were started later on warfarin. As all cohort were women, CHA ₂ DS ₂ -VASc =1 was solely female sex	Both CHADS ₂ , and CHA ₂ DS ₂ -VASc are predictive of stroke risk in postmenopausal women with AF. CHA ₂ DS ₂ -VASc further risk-stratifies patients with a CHADS ₂ score <2.
Abu-Assi ⁹⁴	186 patients with non-valvular AF and off anticoagulant therapy	4 risk schemes: The Framingham, the 8th ACCP, the ACC/AHA/ESC 2006, and the CHA ₂ DS ₂ -VASc.	Ischemic stroke/SE	c-statistic ranged from 0.59 [for CHA ₂ DS ₂ -VASc] to 0.73 [for Framingham]. CHA ₂ DS ₂ -VASc categorized the fewest patients into low and intermediate-risk categories, whereas the Framingham schema assigned the highest patients into low-risk strata. No TE events in the low and intermediate-risk categories using CHA ₂ DS ₂ -VASc , whereas the most schemes assigned patients into intermediate-risk category had an event rate ranging from 2.5 (ACC/AHA/ESC and 8th ACCP schemes) to 6% (Framingham). The negative predictive value of TE events was of 100% for the no high-risk patients using CHA ₂ DS ₂ -VASc .	Small study, with few events, and only 6 patients with CHA ₂ DS ₂ -VASc score of 0 or 1. Therefore caveat on conclusion that CHA ₂ DS ₂ -VASc risk stratification schema may be better in discriminating between patients at a low and intermediate risk of TE complications.

Abumuaileq ⁹⁵	non-anticoagulated cohort of 154 patients; 911 patients formed the cohort of patients on VKA	CHA ₂ DS ₂ -VASc, R ₂ CHADS ₂ and ATRIA (used the conventional ATRIA cut-off of 0-5, and did not explore lower cut points)	Ischemic stroke/SE	<p>During 11 ± 2.7 months. CHA₂DS₂-VASc showed significant association with TE: hazard ratio (HR) = 1.58 [95%CI 1.01–2.46), but R₂CHADS₂ and ATRIA did not (HR = 1.23 (95 % CI 0.86–1.77) and 1.20 (95 % CI 0.93–1.56), respectively.</p> <p>In the anticoagulated cohort, after 10 ± 3 months of follow up, the three scores showed similar association with TE risk: HR = 1.49 (95 % CI 1.13–1.97), 1.41 (95 % CI 1.13–1.77) and 1.37 (95 % CI 1.12–1.66) for CHA₂DS₂-VASc, R₂CHADS₂ and ATRIA, respectively.</p>	<p>Small study with only 9 TE events in total and only 23 patients in CHA₂DS₂-VASc low risk group.</p> <p>CHA₂DS₂-VASc better association with TE events than R₂CHADS₂ and ATRIA scores in the non-anticoagulated cohort. CHA₂DS₂-VASc and R₂CHADS₂ can identify patients at truly low risk regardless of the anticoagulation status.</p>
Chao ²⁹	186,570 AF patients without antithrombotic therapy Taiwan Health Insurance database	CHA ₂ DS ₂ VASc, ATRIA (used the conventional ATRIA cut-off of 0-5, and did not fully explore lower cut points. There was a pointwise gradation of risk from ATRIA score 0 to 5)	Ischemic stroke	<p>High risk: CHA₂DS₂-VASc score performed better than ATRIA score in predicting ischemic stroke as assessed by c-indexes (0.698 vs. 0.627, respectively; p < 0.0001). CHA₂DS₂-VASc score improved the net reclassification index by 11.7% compared with ATRIA score (p < 0.0001).</p> <p>Low risk: Among 73,242 patients categorized as low-risk on the basis of an ATRIA score of 0 to 5, the CHA₂DS₂-VASc scores ranged from 0 to 7, and annual stroke rates ranged from 1.06% to 13.33% at 1-year follow-up. c-index of CHA₂DS₂-VASc score (0.629) was significantly higher than that of the ATRIA score (0.593) in this “low-risk” category (p < 0.0001).</p>	<p>Patients categorized as low-risk by use of the ATRIA score were not necessarily low-risk, and the annual stroke rates can be as high as 2.95% at 1-year follow-up. ATRIA score may perform better if a lower cut point is chosen</p> <p>CHA₂DS₂-VASc score of 0 had a truly low risk of ischemic stroke, with an annual rate of approximately 1%</p>
Chao ⁹⁶	186,570 AF patients without antithrombotic therapy Taiwan Health Insurance database	CHA ₂ DS ₂ VASc, CHADS ₂	Ischemic stroke	<p>CHA₂DS₂VASc, score performed better than CHADS₂ score in predicting ischemic stroke assessed by c-indexes (0.698 vs 0.659, P 0.0001). Among 25,286 patients with a CHADS₂ score of 0, the CHA₂DS₂VASc, score ranged from 0 to 3, and the annual stroke rate ranged from 1.15% to 4.47%.</p>	<p>Very large study with high numbers of events. CHADS₂ score of 0 were not necessarily “low risk,” and the annual stroke rate can be as high as 4.47% when further stratified by CHA₂DS₂VASc. CHA₂DS₂VASc score of 0 had a truly low risk of ischemic stroke, with an annual rate around 1.15%.</p>

Chen ⁹⁷	Systematic review and meta-analysis of the predictive abilities of CHADS2 and CHA2DS2VAsC	CHA2DS2VAsC, CHADS2		<p>Unsuitable to perform a direct meta-analysis because of high heterogeneity.</p> <p>When analyzed as a continuous variable, the C-statistic ranged from 0.60 to 0.80 (median 0.683) for CHADS2 and 0.64–0.79 (median 0.673) for CHA2DS2VAsC (no significant difference). The average ratio of endpoint events in the low-risk group of CHA2DS2VAsC was less than CHADS2 (0.41% vs. 0.94%, $P < 0.05$). The average proportion of the moderate-risk group of CHA2DS2VAsC was lower than CHADS2 (11.12% vs. 30.75%, $P < 0.05$).</p>	The C-statistic suggests a similar clinical utility of the CHADS2 and CHA2DS2VAsC scores in predicting stroke and thromboembolism, but CHA2DS2VAsC has the important advantage of identifying extremely low-risk patients with AF, as well as classifying a lower proportion of patients as moderate risk.
Coppens ⁹⁸	Trial cohort from AVERROES and ACTIVE all treated with aspirin and some with concomitant clopidogrel	CHA2DS2VAsC, CHADS2		<p>Of 4670 patients with a baseline CHADS2 score of 1, 26% had a CHA2DS2VAsC score of 1 and 74% had a score of ≥ 2.</p> <p>After 11414 patient-years of follow-up, the annual incidence of SSE was 0.9% (95% CI: 0.6–1.3) and 2.1% (95% CI: 1.8–2.5) for patients with a CHA2DS2VAsC score of 1 and ≥ 2, respectively.</p> <p>The c-statistic of the CHA2DS2VAsC score was 0.587 (95% CI: 0.550–0.624). Age 65 to <75 years was the strongest of the three new risk factors in the CHA2DS2VAsC score</p>	The CHA2DS2VAsC score reclassifies 26% of patients with a CHADS2 score of 1 to a low annual risk of SSE of 1% and age 65-74 is the major contributor.
Guo et al ²⁶	<p>1034 AF patients (27.1% female, median age 75; 85.6% non-anticoagulated) with mean follow-up of 1.9 years.</p> <p>PLA General Hospital electronic medical database 2007-2010</p>	CHA2DS2VAsC, CHADS2	Stroke/TE	<p>In patients with a CHADS2 or CHA2DS2-VAsC score=1, the rate of stroke/TE was 2.9% and 0.9% respectively. In patients at "high risk" (scores≥ 2), this rate was 4.6% and 4.5%, respectively.</p> <p>The c-statistics for predicting stroke/TE with CHADS2 and CHA2DS2-VAsC were 0.58 ($p = 0.109$) and 0.72 ($p < 0.001$), respectively. Compared to CHADS2, the use of CHA2DS2-VAsC would result in a Net Reclassification Improvement (NRI) of 16.6% ($p=0.009$) and an Integrated Discrimination Improvement (IDI) of 1.1% ($p = 0.002$).</p> <p>Cumulative survival of the patients with a CHA2DS2-VAsC score ≥ 2 was decreased compared to those with a CHA2DS2-VAsC score 0–1 ($p < 0.001$), but the CHADS2 was not predictive of mortality.</p>	Vascular disease was a strong independent predictor of stroke/TE in Chinese patients with AF, and CHA2DS2-VAsC superior to CHADS2 at low scores.

Hippisley-Cox ⁸⁶	1 897 168 eligible patients from 451 general practices in England and Wales contributing to the national QResearch database. Excluded patients with prior stroke or TIA, and those on anticoagulant	QStroke CHA2DS2VAsC, CHADS2	Stroke or TIA	AF patients at baseline: C statistic in men was 0.71 (0.69-0.73) for QStroke, 0.67 (0.65, 0.69) for CHA2DS2VAsC, and 0.63 for CHADS2(0.61-0.66) C statistics in women was 0.65 (0.62-0.67) for QStroke, 0.62 (0.59, 0.65) for CHA2DS2VAsC, and 0.61 for CHADS2(0.59-0.64)	4% of patients were low risk on CHA2DS2VAsC but high risk on Qstroke and had a 10 year observed stroke rate of 7.6%, compared to 2.6% for those low risk on both scores and 21.2% for those at high risk on both scores. A high risk on CHA2DS2VAsC but low on Qstroke (4% of patients) had a 10 year stroke rate of 2.8%. These results pertain only to patients without a prior stroke or TIA
Kornej ⁸⁵	N=2069; 66% men; 60±10 years; 62% paroxysmal AF Referred for ablation	CHADS2, CHA2DS2- VAsC, and R2CHADS2	Stroke, transient ischemic attack, or systemic embolism	C-indexes: CHADS2 0.72(0.70-0.739); CHA2DS2-VAsC 0.736(0.716-0.755) and R2CHADS2 0.736 (0.716-0.755) CHA2DS2-VAsC score further differentiated TE risk in patients with CHADS2 and R2CHADS2 0 to 1 (0.13% if CHA2DS2- VAsC was 0-1 and 0.71% if CHA2DS2-VAsC was >2) and had the best predictive value in patients with AF recurrences (c-index 0.894, P=0.022 versus CHADS2, P=0.031 versus R2CHADS2).	CHA2DS2-VAsC score differentiated TE risk in the low-risk strata based on CHADS2 and R2CHADS2 scores in a post-ablation cohort, with half of the TE events occurring in the 30 days post ablation
Lip ⁹⁹	207,543 incident hospital discharge patients with AF from 1999 to 2012 Danish registry linked data	CHA2DS2VAsC, ATRIA	Ischemic stroke/TE	Patients categorized as low risk using the ATRIA score, the 1-year stroke/thromboembolic event rate ranged from 1.13 to 36.94 per 100 person-years, when subdivided by CHA2DS2VAsC scores. In patients with an ATRIA score 0 to 5 (i.e. low risk), C statistics at 1 year follow-up in the Cox regression model were significantly improved from 0.626 (95% CI, 0.612-0.640) to 0.665 (95% CI, 0.651-0.679) when the CHA2DS2VAsC score was used for categorizing stroke risk instead of the ATRIA score (P <.001). Low-risk category (i.e., CHA2DS2VAsC score 0 for men or a score 1 for women) would identify a truly low-risk cohort, with annual event rates at 1- year of 1.13 per 100 person-years.	Patients categorized as low risk using an ATRIA score 0 to 5 are not necessarily low risk, with 1-year event rates as high as 36.94 per 100 person-years. However, no exploration on risk at ATRIA scores between 0-5, and whether a lower ATRIA cut point would perform differently CHA2DS2VAsC score best at identifying the "truly low risk" subjects with AF compared to ATRIA 0-5 low risk definition
Lip ¹⁰⁰	22,582 non-anticoagulated hospital discharged patients age < 65 years with a CHADS2 score of 0 who were stratified according to the CHA2DS2-VAsC score, except female sex, which would be an indication for OAC according to the ESC guidelines.	CHA2DS2VAsC, CHADS65	Ischemic stroke/TE/ TIA	Overall rate of the combined end point of ischemic stroke/systemic embolism/transient ischemic attack was 4.32 per 100 person-years (95% CI 3.26-5.74) at 1 year, among the patients who would have had an indication for OAC therapy according to 2012 ESC guidelines (based on CHA2DS2VAsC score) and "OAC not recommended" according to CCS algorithm. Subgroup of patients with previous vascular disease and CHADS2 score of 0 (i.e., recommended only aspirin treatment according to the CCS algorithm) had an event rate of 4.84 (95% CI, 3.53-6.62) per 100 person-years	Based on the 2014 CCS algorithm, the "OAC not recommended" subgroup can have a high 1-year stroke rate overall, showing that such patients are not "low risk." Use of CHA2DS2-VAsC offers refinement of stroke risk stratification in such patients.

	Danish Registry linked data			at 1-year follow-up. Sensitivity analysis yielded similar result with events restricted to stroke/systemic embolism	
Nielsen et al ¹⁰¹	Supplemental information to Can J Cardiol 2015 31; 24-28 responding to Cairns et al editorial on the original Lip et al article	CHA2DS2VASc, CHADS65		Contrasting low risk CHA2DS2-VASc (that is, score 0 (male) or 1 (female)) as a reference population vs those with ≥ 1 additional non-sex stroke risk factors (i.e. CHA2DS2- VASc score =1 (male) or =2 (females)) to express the hazard attributable to vascular disease resulted in a crude HR of 2.7 (95%CI 1.7-4.2). 'Vascular disease' Event rates per 100 person-years: MI 2.5 (1.4-4.3); PAD 3.0 (1.3-6.7); Both 15.0 (4.8-46.4)	Any stroke RF other than sex (including vascular disease) in CHA2DS2-VASc provides a high enough risk of adverse events to warrant a recommendation for anticoagulation
Nielsen ¹⁰²	198697 hospital discharged AF patients, of which 15% truly low risk Danish registry linked data (NB Lip and Nielsen papers from the same cohorts)	CHA2DS2-VASc, but compares guideline approaches and addresses the varying event rates reported for different guideline cut-offs and different analysis approaches	Ischemic stroke, and composite of ischemic stroke and systemic embolism	Rate of composite endpoint using censoring of observation at time of OAC commencement was 0.54/100 person-years for truly low risk (CHA2DS2-VASc 0 males, 1 females), 1.53 for CHA2DS2-VASc =1 in males, 2.33 for CHA2DS2-VASc =2, and 5.49 for CHA2DS2-VASc >2. The analysis using conditioning on the future revealed an event rate of only 1.17/100 patient-years for CHA2DS2-VASc =1 (males)	Stroke and TE event rates vary according to method of analysis. Some evidence that formal approach, and conditioning on the future (exclusion of patients who commence OAC) will underestimate the event rate, and this is most important for CHA2DS2-VASc =1 (males)
Okumura ¹⁰³	6,387 patients taking warfarin and the other 997 not taking warfarin were prospectively examined for 2 years. J-Rhythm registry	CHADS2; modified CHA2DS2-VASc (<i>m</i> CHA2DS2-VASc) using coronary disease only	Thromboembolism (combined ischemic stroke, TIA and systemic embolism)	<i>m</i> CHA2DS2-VASc score 0, 1, and ≥ 2 , thromboembolism occurred in 2/141 (0.7%/year), 4/233 (0.9%/year), and 24/623 (1.9%/year), respectively, in the non-warfarin group, and in 1/346 (0.1%/year, P=0.19 vs. non-warfarin), 4/912 (0.2%/year, P=0.05), and 92/5,129 (0.9%/year, P=0.0005), respectively, in the warfarin group. When female sex was excluded from the score, thromboembolism occurred in 2/180 patients (0.6%/year), 5/245 (1.0%/year), and 23/572 (1.6%/year), respectively, in the non-warfarin group, and in 1/422 (0.1%/year, P=0.20 vs. non-warfarin), 5/1,096 (0.2%/year, P=0.02), and 91/4,869 (0.9%/year, P=0.0005), respectively, in the warfarin group.	Small numbers and no information on OAC use at follow-up in the non-warfarin group. In Japanese NVAF patients, the <i>m</i> CHA2DS2-VASc score is useful for identifying patients at truly low risk. Concluded that 'Female sex may be excluded as a risk from the score.' But numbers are too small to substantiate that conclusion.

Palm ¹⁰⁴	Ludwigshafen Stroke Study (LuSSt), prospective ongoing population-based stroke register, 187 patients with a first-ever ischemic stroke (FEIS) owing to AF in 2006 and 2007.	CHA2DS2VASc, CHADS2	First ischemic stroke	Retrospective pre- stroke risk stratification according to CHADS2 score indicated low/intermediate risk in 34 patients (18%) and high risk (CHADS2 ≥ 2) in 153 patients (82%). Application of CHA2DS2-VASc score reduced number of patients at low/intermediate risk (CHA2DS2-VASc score 0-1) to five patients (2.7%).	Small, retrospective study of people with ischemic stroke. CHA2DS2-VASc score appears to be a more valuable risk stratification tool than CHADS2 score.
Philippart ¹⁰⁵	Loire Valley AF project: Among 8053 patients seen in Cardiology Dept with non-valvular AF (ESC guidelines definition), patients were categorized into Group 1 (no valve disease, n=6851; 85%) and Group 2 (valve disease with neither rheumatic mitral stenosis nor valve prosthesis, n = 1202; 15%).	CHA2DS2VASc in 'non-valvular' and (non-rheumatic or prosthetic 'valvular' AF	Stroke/TE	For Group 1, the rate of events was 0.87%/year when CHA2DS2VASc score was 0-1, rising to 9.67%/year when score was ≥ 6 . For patients in Group 2, similar findings were evident with a rate of stroke/TE events increasing from 0.90%/year with a CHA2-DS2VASc score 0-1 to 11.07%/year when CHA2DS2VASc score was ≥ 6 . Main purpose of the study was to compare stroke/TE rates, and prediction of these by CHA2DS2VASc in patients with AF with and with "valvular" AF other than rheumatic mitral or prosthetic	CHA2DS2VASc performs similar in both groups If low risk (score 0-1), event rates low, approx. 0.9%/year, but 56-60% were on OAC, so rate is underestimated.
Potpara. ¹⁰⁶	Cohort of 345 "lone" AF patients with a 12-year follow-up.	CHA(2)DS(2)-VASc, CHADS(2), and van Walraven risk stratification schemes	Ischemic stroke (absence of) i.e. Prediction of LOW RISK	In the multivariable analysis, only the CHA(2)DS(2)-VASc score of 0 was significantly related to the absence of stroke (odds ratio 5.1, 95% CI: 1.5-16.8, P=0.008). Only the CHA(2)DS(2)-VASc score had a significant prediction ability for absence of ischemic stroke (c-statistic 0.72 [0.61-0.84], P=0.031).	Small study of lone AF with 12 year follow-up CHA(2)DS(2)-VASc score reliably identified the "lone" AF patients who were at "truly low risk" for TE
Ruff ¹⁰⁷	Biomarker sub-study of ENGAGE-AF, using cardiac troponin I, N-terminal pro-B-type natriuretic peptide, and d-dimer in 4880 patients with all 3 biomarkers available	CHA(2)DS(2)-VASc \pm biomarkers	Stroke or systemic embolism	When added to the CHA2DS2-VASc score, the biomarker score significantly enhanced prognostic accuracy by improving the C statistic from 0.586 (95% CI, 0.565-0.607) to 0.708 (95% CI, 0.688-0.728) (P < .001) and reclassification with a net reclassification improvement of 59.4% (P < .001).	All patients were anticoagulated, and all patients were CHADS2 =2 or greater, so cannot comment on discrimination of low risk patients without anticoagulant

Singer ¹⁰⁸	Derivation ATRIA cohort consisted of 10 927 patients with non-valvular AF contributing 32 609 person-years off warfarin and 685 thromboembolic events (TEs). The external validation ATRIA-CVRN cohort included 25 306 AF patients contributing 26 263 person-years off warfarin and 496 TEs.	ATRIA, CHA(2)DS(2)-VASc, CHADS(2),	Ischemic stroke/TE	c-index in the ATRIA cohort was 0.73 (95% CI, 0.71 to 0.75), increasing to 0.76 (95% CI, 0.74 to 0.79) when only severe events were considered. The C-index was greater and net reclassification improvement positive comparing the ATRIA score with CHA(2)DS(2)-VASc, or CHADS(2). The NRI improvement was primarily seen for predicting severe strokes. No analysis was done to determine the relative performance of scores to detect a truly low risk group who should not be treated rather than a low intermediate and high risk group	Follow-up was censored at the date of the outcome event, death or health plan disenrollment. Analysis based on all person-time off warfarin. Results comparing risk scores were very similar when restricted the analysis to the 4342 patients who did not take warfarin at any point during follow-up (... but 'conditioning on the future').
Siu ³⁰	9727 hospitalized AF patients, follow-up for 3.19 years	CHA(2)DS(2)-VASc, CHADS(2),	Ischemic stroke	c-statistics revealed that CHA(2)DS(2)-VASc scores (0.525, 95% CI 0.509–0.541, P = .017) was better than CHADS(2) scores (0.506, 95% CI 0.490–0.522, P = .584) in predicting ischemic stroke. Net clinical benefit favors warfarin over aspirin and no therapy for stroke prevention in a broad range of Chinese AF patients.	CHA(2)DS(2)-VASc and HAS-BLED scores appear to be the appropriate risk stratification tools for stroke risk and ICH, respectively, for Chinese. C-Statistics relatively low for prediction of ischemic stroke compared to other cohorts. Annual risk of stroke relatively higher in low risk groups (CHA(2)DS(2)-VASc score =0 or 1) in Chinese than that in Europeans
Tomita ¹⁰⁹	997 AF patients in JRHYTHM registry with no warfarin at baseline Same cohort as Okamura without the cohort taking warfarin as comparison	mCHA2DS2-VASc and mCHA2DS2-VA scores (i.e. excluding female sex) Modified as based on coronary artery disease (no information on PAD)	Thrombo-embolic events including symptomatic cerebral infarction, transient ischemic attack (TIA), and systemic embolism	No sex difference was found in patient groups stratified by CHA2DS2-VASc and CHA2DS2-VA scores. Significant c-statistic difference (0.029, Z=2.3, P=0.02) and NRI (0.11, 95% CI 0.01–0.20, P=0.02), with the CHA2DS2-VA score being superior to the CHA2DS2-VASc score. In patients with CHA2DS2-VASc scores 0 and 1 (n=374), there were significant c-statistic difference (0.053, Z=6.6, P<0.0001) and NRI (0.11, 95% CI 0.07–0.14, P<0.0001), again supporting superiority of CHA2DS2-VA to CHA2DS2-VASc score.	Small numbers and no information on OAC use at follow-up in the non-warfarin group (may explain low absolute event rates even at high scores). Very few females in study and only 90 with CHA2DS2-VASc =1 or 2. NB CHA2DS2-VASc score of 1 in a woman is excluded in ESC guidelines

Van den Ham. ¹¹⁰	60,594 patients with AF CPRD UK cohort (primary care based but incident AF could be hospital discharge) in incident AF, censored at warfarin prescription or outcome event)	CHADS2, CHA2DS2-VASc and ATRIA	Ischemic stroke	C statistics for the full point scores were 0.70 (95% confidence interval [CI]: 0.69 to 0.71) for the ATRIA risk score, 0.68 (95% CI: 0.67 to 0.69) for CHADS2, and 0.68 (95% CI: 0.67 to 0.69) for CHA2DS2-VASc risk score. The net reclassification improvement was 0.23 (95% CI: 0.22 to 0.25) for ATRIA compared with CHA2DS2-VASc. Median follow-up was only 0.74 years over a 15-year study period; though mean follow-up was 2.8 years, indicating distribution of follow-up is skewed. Using ATRIA, 40% were categorized as low-risk (that is, ATRIA score of ≤ 5 , with annualized stroke rates of 0.40% to 1.99%),	ATRIA score performed better than either CHADS2, CHA2DS2-VASc for predicting events. ATRIA identified 40% as low-risk patients vs CHA2DS2-VASc score, which identified only 6.6% as low risk, and assigned these patients to higher-risk categories.
Aspberg ¹¹¹	152 153 AF patients not receiving warfarin in Swedish AF cohort – hospitalized or visiting hospital OPD. future analysis	CHADS2, CHA2DS2-VASc and ATRIA	Ischemic stroke	ATRIA had a good C of 0.708 (0.704–0.713), significantly better than CHADS2 0.690 (0.685–0.695) or CHA2DS2-VASc 0.694 (0.690–0.700). Net reclassification improvement favored ATRIA 0.16 (0.14–0.17) vs. CHADS2 and 0.21 (0.20–0.23) vs. CHA2DS2-VASc (with a reclassification down for the comparison with CHA2DS2-VASc, and a reclassification up for the comparison with CHADS2).	Analyses restricted to patients who did not use any anticoagulant therapy during the follow-up period – thus ‘conditioning on the future’. When categorical cut-points were optimized to the stroke rate of the population, the differences between scores in NRI and C statistic disappeared
Xiong ¹¹²	Systematic review and meta-analysis, East Asian patients. Included 6 cohort studies with 31,539 patients	CHA(2)DS(2)-VASc, CHADS(2),	Predominantly ischemic stroke, 2 with thromboembolism	Meta-analysis revealed that when compared with the CHA2DS2-VASc score, there was a 1.71-fold elevated risk of stroke when patients were stratified as ‘low risk’ using a CHADS2 score = 0, or a 1.40-fold increase with a CHADS2 score = 1.	CHA2DS2-VASc score is superior to the CHADS2 score in identifying ‘low risk’ East Asian AF patients.
Zhu ¹¹³	Systematic review and meta-analysis Included 12 cohort studies with 205,939 patients	CHA2DS2-VASc, CHADS2,	Stroke, Thromboembolism	CHA2DS2-VASc scores ≥ 2 have a greater risk of stroke (risk ratio [RR]=5.15; 95% confidence interval [CI], 3.85–6.88; P <0.00001) and thromboembolism (RR=5.96; 95% CI, 5.50–6.45; P <0.00001) (Pdiff=0.34) than do patients with CHA2DS2-VASc scores <2, independent of anticoagulation therapy (RR=5.76; 95% CI, 5.23–6.35; P <0.00001 in anticoagulated patients; and RR=6.12; 95% CI, 5.40–6.93; P <0.00001 in patients not taking anticoagulants; P =0.45). In the comparison of the rates of endpoint events among low-risk patients (1.67% vs 0.75%; P <0.001), the findings imply that some CHADS(2) low- risk patients might still benefit from anticoagulation	Superior diagnostic performance of CHA2DS2-VASc over CHADS2 for identifying genuinely low-risk patients with AF.

Kim ¹¹⁴	5855 oral anticoagulant naive NVAf patients enrolled from Korea National Health Insurance Service-Sample Cohort	CHA ₂ DS ₂ -VASc, CHADS ₂ and ATRIA	Ischaemic stroke	CHA ₂ DS ₂ -VASc had the best sensitivity (98.8% versus 85.7% in CHADS ₂ and 74.8% in ATRIA) and negative predictive value (98.8% versus 95.3% for CHADS ₂ and 93.7% for ATRIA) for the prediction of stroke incidence and was best for the prediction of the absence of ischemic stroke during 5 years of follow-up (odds ratio, 16.4 [95% confidence interval, 8.8-30.8]).	CHA ₂ DS ₂ -VASc score shows good performance in defining truly low-risk Asian patients with atrial fibrillation for stroke compared with CHADS ₂ and ATRIA
Rivera-Caravaca ¹¹⁵	1125 NVAf patients	Compared long-term predictive performances of the ABC-stroke and CHA ₂ DS ₂ -VASc	Ischaemic stroke	114 ischemic strokes (1.55% per year) at 6.5 years. ABC-stroke c-index at 3.5 years (0.663) was higher than CHA ₂ DS ₂ -VASc (0.600, P=0.046), but nonsignificantly different at 6.5 years. For ABC-stroke, net reclassification improvement was nonsignificantly different at 3.5 years, and a negative reclassification at 6.5 years, vs CHA ₂ DS ₂ -VASc. Decision curve analyses did not show marked improvement in clinical usefulness of the ABC-stroke score over the CHA ₂ DS ₂ -VASc score.	ABC-stroke score did not offer better 'real world' predictive performance compared with the CHA ₂ DS ₂ -VASc score over long term


e-Table 8. Major bleeding rates with VKAs in observational studies

Study	Patients on VKA, n	Age, years	Mean follow-up	Major bleeding, per year
EURO HEART SURVEY (2010) ¹¹⁶	2115	66.8	1 y	1.5%
ATRIA (2011) ¹¹⁷	9186	71	3.5 y	1.4%
Olesen et al. (2011) ¹¹⁸	37425	70.6	10 y	4.62%
Gallego et al. (2012) ¹¹⁹	965	76	861 d	3.6%
Donze et al. (2012) ¹²⁰	515	71.2	1 y	6.8%
Friberg et al. (2012) ³⁸	48599	76.2	1.5 y	1.9%
Burgess et al. (2013) ¹²¹	321	69.2	2.5 y	3.8%
ORBIT-AF (2013) ¹²²	4804	76	6 m	1.8%
Seet et al. (2013) ¹²³	100	79.3	19 m	9.79%
Guo et al. (2013) ²⁶	149	63	1.9 y	2.7%
Deitelzweig et al. (2013) ¹²⁴	48260	67.3	802 d	10.4%
MAQI2 (2014) ¹²⁵	2600	70.1	1 y	4.5%
Wang et al. (2016) ¹²⁶	15418	65	4.6 m	5.5%

d=day; m= month; VKA=vitamin-K antagonist; y=year


e-Table 9. Major bleeding rates on oral anticoagulants in randomized clinical trials

Trial	Patients on anticoagulants, n	Age, year	Mean follow-up	Major bleeding, per year
BAATAF (1990) ¹²⁷	212 (VKA)	68.5	2.2 y	2 patients in 2.2 y (VKA)
CAFA (1991) ¹²⁸	187 (VKA)	68	15.2 m	2.5% (VKA)
SPAF I (1991) ¹²⁹	1330 (VKA)	67	1.3 y	1.5% (VKA)
SPINAF (1992) ¹³⁰	260 (VKA)	67	1.8 y	1.3% (VKA)
EAFI (1993) ¹³¹	1007, 225(VKA)	77	2.3 y	2.8% (VKA)
SPAF II (1994) ¹³²	1100 (VKA)	64 (age≤75) 80 (age>75)	2.3 y	1.7% (age≤75) (VKA) 4.2% (age>75) (VKA)
SPAF III, (1996) ¹³³	523 (VKA)	71	1.1 y	2.1% (VKA)
AFASAK2, (1998) ¹³⁴	170 (VKA)	73.2	1	2.4% (VKA)
Pengo et al. (1998) ¹³⁵	153 (VKA)	73.6	14.5 m	2.6% (VKA)
Hellemons et al. (1999) ¹³⁶	131 (VKA)	70	2.7 y	0.5% (VKA)
Yamaguchi et al. (2000) ¹³⁷	55 (VKA)	65.7	658 d	6.6% (VKA)
SPORTIFF III (2003) ¹³⁸	1703 (VKA) 1704 (Ximelagatran)	70.1 (VKA) 70.3 (Ximelagatran)	17.4 m	1.8% (VKA) 1.3% (Ximelagatran)
NASPEAF, (2004) ¹³⁹	496 (VKA)	69.6 (Intermediate) 66.6 (High intensity)	965 d (Intermediate) 1075 d (High intensity)	1.8% (Intermediate) (VKA) 2.13% (High intensity) (VKA)
SPORTIFF V (2005) ¹⁴⁰	1962 (VKA) 1960 (Ximelagatran)	71.6 (VKA) 71.6 (Ximelagatran)	20 m	3.1% (VKA)* 2.4% (Ximelagatran)*
ACTIVE W (2006) ¹⁴¹	3371 (VKA)	70.2	1.28 y	2.21% (VKA)
Chinese ATAFS (2006) ¹⁴²	704 (VKA)	63.3	19 m	1.5% (VKA)
AMADEUS (2008) ¹⁴³	2293	70.2	10.7 m	1.4%
RE-LY (2009) ¹⁴⁴	6022 (VKA) 6076 (D, 110 mg) 6015 (D, 150 mg)	71.6 (VKA) 71.5 (D, 110 mg) 71.4 (D, 150 mg)	2 y	3.36% (VKA) 2.71% (D, 110 mg) 3.11% (D, 150 mg)
ROCKET AF (2011) ¹⁴⁵	7133 (VKA) 7131 (R, 20 mg)	73 (VKA) 73 (R, 20 mg)	2 y	3.4% (VKA) 3.6% (R, 20 mg)
ARISTOTLE (2011) ¹⁴⁶	9120 (VKA) 9081 (A, 5 mg)	70 (VKA) 70 (A, 5 mg)	1.8 y	3.09% (VKA) 2.13% (A, 5 mg)
J-ROCKET (2012) ¹⁴⁷	639 (VKA) 639 (R, 15 mg)	71.2 (VKA) 71 (R, 15 mg)		3.59% (VKA) 3.00 (R, 15 mg)
ENGAGE AF (2013) ¹⁴⁸	7036 (VKA) 7035 (E, 30 mg) 6015 (E, 60 mg)	72 (VKA) 72 (E, 30 mg) 72 (E, 60 mg)	907 d	3.43% (VKA) 1.61% (E, 30 mg) 2.75% (E, 60 mg)

* = major extra-cerebral bleeding

A=apixaban; D=dabigatran; d=day; E=edoxaban; m=month; R=rivaroxaban; VKA= vitamin-K antagonist; y=year


e-Table 10. Studies comparing bleeding risk schemas

Study	Cohort	Schemes compared	Events	Findings	Comments
Barnes et al ¹⁴⁹	2,600 patients in 7 anticoagulation clinics, 2009-2013. Only warfarin used. Warfarin initiators followed with retrospective scores. First major bleed only included	CHADS ₂ , CHA ₂ DS ₂ -VASC, HEMORR ₂ HAGES, HAS-BLED, ATRIA	116 major bleeds (ISTH definition)	NB mean follow up only 1.0 years. AUC under ROC compared with C statistic and NRI. Used low mod and high cutoffs from scores. C stat similar for 3 bleeding risk scores (0.66.to 0.69), and all bleeding scores performed better than CHADS ₂ or CHA ₂ DS ₂ -VASC (C stat 0.53 to 0.56). For NRI, HAS_BLED better than ATRIA or HEMORRHAGES, and ATRIA better than HEMORR ₂ HAGES, while all 3 better than CHADS ₂ or CHA ₂ DS ₂ -VASC	NRI differences for HAS-BLED vs other bleeding risk scores only significant for low vs mod/high. Diff of NRI in bleeding risk scores not significant for low/mod vs High risk. All bleeding risk scores had only moderate prediction i.e. C statistic is only 0.66-0.69
Caldeira et al ¹⁵⁰	Systematic review of HEMORR ₂ HAGES, HAS-BLED, ATRIA scores	HEMORR ₂ HAGES, HAS-BLED, ATRIA. Compared high risk category only	Major bleeds in studies reviewed from search	6 studies found 5 studies compared HEMORR ₂ HAGES and HAS-BLED, 4 studies compared HAS-BLED vs ATRIA. HAS-BLED had significantly higher sensitivity (but therefore also lower specificity for major bleeding. Conclusion was a preference for HAS-BLED because of higher sensitivity coupled with ease of use	Systematic review
Christersson et al ¹⁵¹	Aristotle trial in 14,878 out of 18,201 pts randomized to warfarin or apixaban. Follow-up in trial	HAS-BLED alone vs adding D-Dimer	647 Major bleeds (2.6%), and 1276 with clinically relevant non-major bleeds (5.1%) (admission to hospital but without drop in Hb of 2g or 2 unit transfusion)	C statistic was 0.61 and 0.618 in the no-VKA and on VKA groups respectively and adding D-Dimer increased the C statistic to 0.641, and 0.635 resp. NRI was 23 to 28%	Modest increase in C statistic only. D-Dimer predictive in its own right with similar C-statistic



Suzuki et al. ¹⁵²	231 patients starting warfarin. Prospective study	HAS-BLED exploring various cut points of renal function (3 groups) in Japanese population (eGFR) using Japanese MDRD formula	44 ISTH major bleeds	Moderate kidney disease (eGFR 30-59) also associated with increased major hemorrhage. C statistic including moderate renal disease in HAS-BLED increased from 0.64 to 0.67 (p, NS) but NRI improved significantly	Small trial, so hard to draw solid conclusions, but perhaps even moderate renal disease will be important and therefore may need to include in the HAS-BLED definition
O'Brien et al. ¹⁵³	ORBIT AF registry, 7411 pts taking OAC. Median 2 year follow-up. External validation in 14,264 pts in ROCKET-AF study warfarin and Rivaroxaban pts (not all elements of all scores available)	ORBIT score (full score, and 5 factor score) vs HAS-BLED and ATRIA bleeding scores	581 (7.8%) ISTH major bleeding events in ORBIT registry	See table 4 for topline results. C indices of 0.69 and 0.67 for the full and 5 factor ORBIT score in ORBIT registry, compared to 0.64 and 0.66 for HAS-BLED and ATRIA resp. In ROCKET-AF, Full and 5 factor ORBIT model C stat 0.63 and 0.62 respectively, vs 0.59 and 0.60 for HAS-BLED and ATRIA respectively. Model calibration better for ORBIT score in ROCKET-AF, followed by HAS-BLED then ATRIA	All scores showed only moderate predictive ability and discrimination
Zhu et al. ¹⁵⁴	Systematic review and meta-analysis of HAS-BLED score vs other scores, in 11 studies identified	HAS_BLED vs CHADS2, CHADSVASc, HEMORR2HAGES and ATRIA	Variable events in the 11 studies	C statistic not significantly different between HAS-BLED and other 2 bleeding risk scores (0.65 vs 0.63 and 0.63 synthesized result), but better than CHADS2 and CHADSVASc. HAS-BLED superior to all other scores for NRI (NB not in all studies). Calibration analysis shows HAS-BLED over predicts in the low and under-predicts in the mod and high risk categories.	All scores perform better than the stroke risk scores, and HAS-BLED has a marginal advantage over HEMORR2HAGES and ATRIA
Esteve-Pastor et al. ¹⁵⁵	FANTSIIA registry, 571 pts undergoing cardioversion, 1276 pts with persistent AF. Most VKA, some NOAC	ORBIT vs HAS-BLED	21 ISTH major bleeds in the 571 cardioversion pts, and 46 in the persistent AF population	C statistic in cardioversion group 0.77 vs 0.82 HAS-BLED vs ORBIT (ns), and in persistent AF group 0.63 vs 0.70 (ns)	Relatively small number of major bleeding events in both arms of the study, so not much weight can be put on the study. Prediction only modest for both scores



Hijazi et al. ABC-Bleeding score. ¹⁵⁶	ARISTOTLE study 14,537 pts apixaban vs warfarin) for development and RELY study (8468 pts on warfarin or Dabigatran) for validation.	ABC-bleeding score (Age; Biomarker GDF-15, CTnT hs, Hb; Clinical history of bleeding) vs HAS-BLED and ORBIT bleeding risk scores	ISTH major bleeds: 662 in ARISTOTLE, and 463 in RELY.	ABC score discriminated in all risk groups of HAS-BLED and ORBIT in both derivation and validation cohorts. C statistic significantly higher 0.68 for ABC bleeding vs 0.61 and 0.68 HAS-BLED and ORBIT in ARISTOTLE, and also in RELY 0.71, vs 0.62 and 0.68 for HAS-BLED and ORBIT resp. Similar results when hematocrit, CTnIhs and Cystatin C or Creatinine clearance substituted.	Simplicity and bedside use favor the simpler scores, though substitution of more readily available biomarkers would be an option. Even with Biomarkers, performance still only moderate
Nielsen et al. ¹⁵⁷	Danish national registry 210,299 pats with AF	Recalibration of HAS-BLED using an extra point for hemorrhagic stroke (S in HAS-BLED)	ISTH major bleeding 4.3/100 patient/years	No significant difference for C statistic for the 2 scores, and modest for both (0.613 original and 0.616 for the additional point HAS-BLED). NRI was 10% and relative IDI 23.6%	Minor gain by adding an extra point for ICH to the one point for stroke. It is reasonably intuitive that someone with a prior ICH is really at high danger of a major bleed
Proietti et al. ¹⁵⁸	SPORTIF III and V trials. 3,551/3,665 pts assigned to warfarin. Only 20% VKA naïve at baseline	HAS-BLED vs HEMORR2HAGES, ATRIA, and ORBIT scores plus additional analysis for latter 3 scores plus a term for TTR	127 adjudicated major bleeds. 1.6 years median F/U. 162 investigator level major bleeds	Rather complex analysis quoting similar AUC, without C statistics quoted. Analyzed both adjudicated and investigator level major bleeds (latter not usually included in other studies), then added TTR to the 3 scores that do not contain it, again against both endpoints. These scores improved prediction, indicating TTR is likely to be an important issue that is not included in scores other than HAS-BLED	All scores showed only moderate prediction, but HAS-BLED performed best in 1 respect of having no investigator level major bleeds in the low risk stratum. While low TTR may be useful to assess risk, it has no role in the VKA naïve patient. Relatively low risk of major bleeds in this stud
Senoo et al. ¹⁵⁹	2293 patients receiving VKA in AMADEUS trial (idraparinux vs VKA in AF).	HAS-BLED vs ATRIA and ORBIT	39 Major bleeds and 251 clinically relevant bleeds (these are not usually counted in prior analyses of scores)	No difference in AUC between 3 scores in major bleeds. Some difference in clinically relevant bleeds, with HAS-BLED having greater AUC. Modest improvement for ATRIA and ORBIT by adding TTR	All scores showed modest at best prediction of bleeding. While low TTR may be useful to assess risk, and is only included in HAS-BLED, it has no role in the VKA naïve patient. Low risk group as patients with major bleeds excluded from study



Steinberg et al. ¹⁶⁰	9715 patients in ORBIT registry. Probably some overlap with the O'Brien study above	HAS-BLED, ATRIA, and physician assessment	Major bleeds (not defined), and no numbers given, just incidence rate /100 patient/years in each stratum	C statistic 0.63 ATRIA and 0.60 HAS-BLED not significantly different. Both better than physician assessment (C Stat 0.55), which did not add anything to the bleeding risk scores	Physician assessment overall poor and worse than scores
Wang et al. ¹⁶¹	USA United Health OAC initiator (VKA and Dabigatran). 21,934 patients included	CHADS2, CHADSVASc, and HAS-BLED	Approx. 1000 major bleed (4.6%). Used ISTH, TIMI or GUSTO major bleed definition	C statistic of 0.60 for major bleeding. No difference according to major bleed definition. Calibration of rates of major bleeding using model data from RELY trial showed great underestimation of major bleeding, especially for warfarin initiators in high risk HAS-BLED category	Trial data based models (RCT) giving rates of major bleeding taken from bleeding risk models underestimate the true rate of major bleeds in real world practice for that risk stratum, esp. in warfarin initiators
Poli et al. ¹⁶²	4,579 patients in a prospective registry (START) of NVAf	HAS-BED (omit the L for labile INR) as all are inception patients, vs CHADS2 and CHADSVASc	115 ISTH major bleeds (1.6 per 100 pt. years)	C statistic 0.58 and 0.61 for HAS-BED and HAS-BLED. Similar to CHADS2 and CHADSVASc (0.58, 0.56 respectively)	Cannot understand how a HAS-BLED score was calculated in the study, as all were initiators (77% VKA), and why it should be different to HAS-BED, unless they used TTR after registry commenced in the 77% on VKA. Low bleeding risk cohort overall in this registry
Esteve-Pastor et al. ¹⁶³	1120 "real-world" anticoagulated NVAf patients with long-term follow-up.	HAS-BLED vs ABC-bleeding score	After 6.5 years of follow-up, 207 (2.84 %/year major bleeding events, of which 65 (0.89 %/year) were intracranial haemorrhage (ICH) and 85 (1.17 %/year) gastrointestinal bleeding (GIB).	c-index of HAS-BLED was significantly higher than ABC-Bleeding for major bleeding (0.583 vs 0.518; p=0.025), GIB (0.596 vs 0.519; p=0.017) and for the composite of ICH-GIB (0.593 vs 0.527; p=0.030). NRI showed negative reclassification for major bleeding and for the composite of ICH-GIB with the ABC-Bleeding score. Using DCAs, the use of HAS-BLED score gave an approximate net benefit of 4 % over the ABC-Bleeding score.	HAS-BLED performed significantly better than the ABC-Bleeding score in predicting major bleeding, GIB and the composite of GIB and ICH



Guo et al ¹⁶⁴	Hospital based cohort	HEMORR ₂ HAGES, HAS-BLED, ATRIA, and ORBIT, vs 'European score' based on modifiable bleeding risk factors		European score c-index for major bleeding 0.63, 95% CI 0.56-0.69) and intracranial hemorrhage (0.72, 0.65-0.79) HAS-BLED score was superior to European score (DeLong test, all P < .05), net reclassification improvement values of 13.0%-34.5% (all P < .05), and integrated discrimination improvement values of 0.7%-1.4% (all P < .05). European score performed worst compared to HEMORR ₂ HAGES, HAS-BLED, ATRIA, and ORBIT	Relying on bleeding risk assessment using modifiable bleeding risk factors alone is an inferior strategy
Esteve-Pastor et al ¹⁶⁵	AMADEUS trial cohort	HAS-BLED vs modifiable bleeding risk factors based on ESC guidelines	597 (13.0%) experienced any clinically relevant bleeding event and 113 (2.5%) major bleeding	Only the HAS-BLED score was significantly associated with the risk of any clinically relevant bleeding (hazard ratio 1.38; 95%CI 1.10-1.72; p = 0.005). The HAS-BLED score performed best in predicting any clinically relevant bleeding (c-indexes for HAS-BLED, 0.545 vs. 'modifiable bleeding risk factors score', 0.530; c-index difference 0.015, z-score = 2.063, p = 0.04).	While modifiable bleeding risk factors should be addressed in all AF patients, the use of a formal bleeding risk score (HAS-BLED) has better predictive value for bleeding risks
Chao et al ¹⁶⁶	Nationwide cohort study of 40,450 NVAF patients who received warfarin	HAS-BLED, HEMORR ₂ HAGES, ATRIA, ORBIT, Modifiable bleeding risk (MBR) approach (based on ESC guidelines)	581 (3.91%) patients sustained ICH and 6889 (17.03%) patients sustained major bleeding events	When HAS-BLED was compared to other bleeding scores, c-indexes were significantly higher compared to MBR factors (p<0.001) and ORBIT (p=0.05) scores for major bleeding. C-indexes for the MBR factors score significantly lower vs. all other scores (De long test, all p<0.001).	All contemporary bleeding risk scores had modest predictive value for predicting major bleeding but the best predictive value and NRI was found for the HAS-BLED score. Simply depending on modifiable bleeding risk factors had suboptimal predictive value for the prediction of major bleeding


e-Table 11. GRADE Evidence Profile on Bleeding Risk Scores

Question: Bleeding Risk tools for patients with Atrial Fibrillation

Bibliography: W. Zhu et al. The HAS-BLED Score for predicting major bleeding risk in anticoagulated patients with atrial fibrillation: A systematic review and meta-analysis. Clin Cardiol. 2015. 38:55-561

Quality assessment							Impact	Quality	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
HAS-BLED									
7	observational studies	not serious	not serious	not serious	not serious	none	C-statistic range: 0.60–0.69 (median, 0.66); pooled c-statistic: 0.65 (0.61-0.69)	⊕⊕ LOW	CRITICAL
HEMORR2HAGES									
5	observational studies	not serious	not serious	not serious	not serious	none	C-statistic range: 0.60–0.67 (median, 0.63); pooled c-statistic: 0.63 (0.61-0.66)	⊕⊕ LOW	CRITICAL
ATRIA									
3	observational studies	not serious	not serious	not serious	not serious	none	C-statistic range: 0.59–0.69 (median, 0.61); pooled c-statistic: 0.63 (0.56-0.72)	⊕⊕ LOW	CRITICAL
CHADS2									
3	observational studies	not serious	not serious	not serious	not serious	none	C-statistic range: 0.51–0.59 (median, 0.53); pooled c-statistic: 0.55 (0.49-0.61)	⊕⊕ LOW	CRITICAL
CHA2DS2-VASc									
3	observational studies	not serious	not serious	not serious	not serious	none	C-statistic range: 0.53–0.58 (median, 0.56); pooled c-statistic: 0.56 (0.53-0.59)	⊕⊕ LOW	CRITICAL

CI: Confidence interval



e-Table 12. GRADE Evidence Profile of VKA compared to Placebo or control

Question: VKA compared to Placebo or control

Bibliography: Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of internal medicine*. 2007;146(12):857-867.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VKA	Placebo	Relative (95% CI)	Absolute (95% CI)		
All Stroke												
6	randomised trials	serious ^a	not serious	not serious	not serious	none	54/1450 (3.7%)	133/1450 (9.2%)	RR 0.36 (0.26 to 0.51)	56 fewer per 1,000 (from 42 fewer to 66 fewer)	⊕⊕⊕○ MODERATE	CRITICAL

a. One study did not report appropriate randomization methods; Partial blinding reported in 3 trials

e-Table 13. GRADE Evidence Profile of Aspirin compared to placebo or control

Question: Aspirin compared to placebo or control

Bibliography: Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of internal medicine*. 2007;146(12):857-867.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin + Antiplatelets	Control	Relative (95% CI)	Absolute (95% CI)		
All Stroke												
8	randomised trials	serious ^a	not serious	not serious	not serious	none	245/2602 (9.4%)	296/2594 (11.4%)	RR 0.78 (0.94 to 0.65)	25 fewer per 1,000 (from 7 fewer to 40 fewer)	⊕⊕⊕○ MODERATE	CRITICAL

a. Unclear randomization and blinding methods in several studies



e-Table 14. GRADE Evidence Profile of VKA compared to antiplatelet therapy

Question: VKA compared to Antiplatelet therapy

Bibliography: Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of internal medicine*. 2007;146(12):857-867.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VKA	AP	Relative (95% CI)	Absolute (95% CI)		
All Stroke												
12	randomised trials	serious ^a	not serious	not serious	not serious	none	205/6558 (3.1%)	341/6575 (5.2%)	RR 0.61 (0.78 to 0.48)	20 fewer per 1,000 (from 11 fewer to 27 fewer)	⊕⊕⊕○ MODERATE	CRITICAL

a. Unclear randomization and blinding methods in several studies



e-Table 15. GRADE Evidence Profile of VKA compared to NOAC (not stratified by specific agent)

Question: VKA compared to Antiplatelet therapy

Bibliography: Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383(9921):955-962.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VKA	NOAC	Relative (95% CI)	Absolute (95% CI)		
Stroke or SE events												
4	randomised trials	serious ^a	not serious	not serious	not serious	none	1107/29229 (3.8%)	911/29312 (3.1%)	RR 0.81 (0.73 to 0.91)	6 fewer per 1,000 (from 3 fewer to 8 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Major Bleeding												
4	randomised trials	serious ^a	serious ^b	not serious	serious ^c	none	1802/29211 (6.2%)	1541/29287 (5.3%)	RR 0.86 (0.73 to 1.00)	7 fewer per 1,000 (from 0 fewer to 14 fewer)	⊕○○○ VERY LOW	CRITICAL

a. Issues with allocation concealment and blinding of participants and personnel

b. I-squared value of 83% indicating substantial heterogeneity

c. 95% CI includes no effect



e-Table 16. GRADE Evidence Profile of NOAC vs. Aspirin

Bibliography: Connolly SJ, et al. Apixaban in patients with atrial fibrillation. The New England journal of medicine. 2011;364(9):806-817.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NOAC	Aspirin	Relative (95% CI)	Absolute (95% CI)		
Stroke or SE												
1	randomised trials	not serious	not serious	not serious	not serious	none	51/2802 (1.8%)	113/2791 (4.0%)	HR 0.45 (0.32 to 0.62)	22 fewer per 1,000 (from 15 fewer to 27 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Major Bleeding												
1	randomised trials	not serious	not serious	not serious	not serious	none	44/2802 (1.6%)	39/2791 (1.4%)	HR 1.13 (0.74 to 1.75)	2 more per 1,000 (from 4 fewer to 10 more)	⊕⊕⊕⊕ HIGH	CRITICAL

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e-Table 17. GRADE Evidence Profile of NOAC vs. VKA for electric cardioversion

Question: NOAC compared to VKA for Patients with Atrial Fibrillation undergoing elective-cardioversion

Bibliography: Cappato 2014, Flaker 2014, Goette 2016, Nagarakanti 2011, Piccini 2013, Plitt 2016

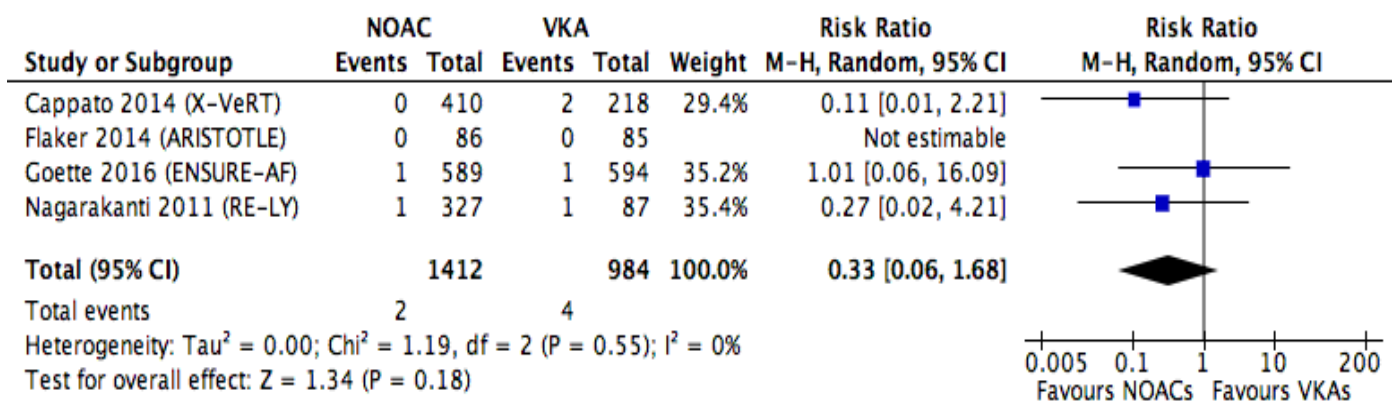
Quality assessment							No of patients		Effect		Quality	Importance
No of studie	Study desig	Risk of	Inconsistency	Indirectness	Imprecision	Other consideration	NOAC	VKA	Relative (95% CI)	Absolute (95% CI)		
Stroke/SE												
6	randomised trials	serious ^a	not serious	not serious	serious ^b	none	16/4136 (0.4%)	12/2928 (0.4%)	RR 0.82 (0.38 to 1.75)	1 fewer per 1,000 (from 3 fewer to 3 more)	⊕⊕○○ LOW	CRITICAL
Mortality - all cause (follow up: range 30 to 60; assessed with: all cause)												
4	randomised trials	serious ^a	not serious	not serious	serious ^b	none	9/2679 (0.3%)	10/2132 (0.5%)	RR 0.72 (0.27 to 1.90)	1 fewer per 1,000 (from 3 fewer to 4 more)	⊕⊕○○ LOW	CRITICAL
MI												
3	randomised trials	serious ^a	not serious	not serious	serious ^b	none	4/2428 (0.2%)	5/2018 (0.2%)	RR 0.72 (0.19 to 2.71)	1 fewer per 1,000 (from 2 fewer to 4 more)	⊕⊕○○ LOW	CRITICAL

CI: Confidence interval; RR: Riskratio

- a. Issues with allocation concealment and blinding of participants and personnel; studies underpowered to detect a difference
 b. Low number of events; Fairly wide confidence intervals around estimate of effect

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e-Figure 3. NOACs versus warfarin in the TEE-guided approach to cardioversion



e-Table 18. GRADE Evidence Profile of NOAC vs. VKA for TEE-guided cardioversion

Question: NOACs compared to VKA for AF patients undergoing TEE-guided CV

Setting:

Bibliography: Cappato 2014, Flaker 2014, Goette 2016, Nagarakanti 2011

Quality assessment							N ₂ of patients		Effect		Quality	Importance
N ₂ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NOACs	VKA	Relative (95% CI)	Absolute (95% CI)		
Stroke/SE												
4	randomised trials	serious ^a	not serious	not serious	serious ^b	none	2/1412 (0.1%)	4/984 (0.4%)	RR 0.33 (0.06 to 1.68)	3 fewer per 1,000 (from 3 more to 4 fewer)	⊕⊕○○ LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. Issues with allocation concealment and blinding of participants and personnel; studies not powered enough to detect a difference

b. Small number of events; Fairly wide confidence intervals around estimate of effect



e-Table 19. GRADE Evidence Profile of Heparinoids compared to Aspirin/placebo for patients with acute ischemic stroke or TIA

Question: Heparinoids compared to Aspirin/placebo for patients with acute ischemic stroke or TIA
Bibliography: Paciarno 2007

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Ris of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Heparinoids	Aspirin/placebo	Relative (95% CI)	Absolute (95% CI)		
Recurrent ischemic stroke												
5	randomised trials	serious ^a	not serious	not serious	serious ^b	none			OR 0.68 (0.44 to 1.06)	1 fewer per 1,000 (from 0 fewer to 1 fewer)	⊕⊕○○ LOW	CRITICAL
Death												
6	randomised trials	serious ^a	not serious	not serious	not serious	none	1729/2351 (73.5%)	1637/2217 (73.8%)	OR 1.01 (0.82 to 1.24)	2 more per 1,000 (from 39 more to 40 fewer)	⊕⊕⊕○ MODERATE	CRITICAL

CI: Confidence interval; OR: Odds ratio

Explanations

- a. issues with allocation concealment and blinding of participants and personnel
- b. wide 95% CI that crosses no effect


e-Table 20. Relationship between CIED-detected AHREs > 5-6 min and thromboembolic events/stroke

Trial	No. of patients	Duration of follow-up	AHRE or AF burden threshold	Atrial rate cut-off (bpm)	Risk of clinical AF	Clinical AF during follow-up	Risk of thromboembolic event	Thromboembolic event rate (below vs above AF burden threshold; %)
Ancillary MOST (2003) ¹⁶⁷	312	27 months (median)	>5 min in a day	>220	HR 5.93, 95% CI 2.88–12.2, $P = 0.0001$	25% in patients with AHREs	HR 6.7, 95% CI 1.4–33.2, $P = 0.020$ for stroke or SEE	3.2 overall (1.3 vs 5.0)
Italian AT500 Registry (2005) ¹⁶⁸	725	22 months (median)	> 24 h	>174	NA	NA	HR 3.1, 95% CI 1.1–10.5, $P = 0.044$ for stroke or SEE	1.2 annual rate
Botto <i>et al.</i> (2009) ¹⁶⁹	568	1 year (mean)	CHADS ₂ and AF burden (≥ 5 min in a day or >24 h)	>174	NA	NA	NA	2.5 overall (5.0 vs 0.8, $P = 0.03$ comparing high vs low risk on the basis of CHADS ₂ and AF burden)
TRENDS (2009) ¹⁷⁰	2,486	1.4 years (mean)	≥ 5.5 h in a day occurring in a 30-day window	>175	NA	NA	HR 2.2, 95% CI 0.96–5.05, $P = 0.06$ for stroke, TIA, or SEE, by comparing AF burden ≥ 5.5 h vs zero burden	1.2 annual rate overall (1.1 for zero burden or AF burden <5.5 h vs 2 for AF burden ≥ 5.5 h)
Home Monitor CRT (2012) ¹⁷¹	560	370 days (median)	≥ 3.8 h in a day	>180	NA	NA	HR 9.4, 95% CI 1.8–47.0, $P = 0.006$ for stroke or SEE, by comparing daily AF burden ≥ 3.8 h vs zero burden	2.0 overall
ASSERT (2012) ¹⁷²	2,580	2.5 years (mean)	>6 min in a day	>190	HR 5.56, 95% CI 3.78–8.17, $P < 0.001$	15.7% in patients with AHREs	HR 2.49, 95% CI 1.28–4.85, $P = 0.007$ for ischemic stroke or systemic embolism	1.69 vs 0.69 annual rate in patients with vs without device-detected tachyarrhythmias
SOS (2014) ¹⁷³	10,016	2 years (median)	≥ 5 min and ≥ 1 h	>175	NA	NA	HR 1.76, 95% CI 1.02–3.02, $P = 0.041$ for ischemic stroke with AF burden ≥ 5 min vs <5 min. HR 2.11, 95% CI 1.22–3.64, $P = 0.008$ for ischemic stroke with AF burden ≥ 1 h vs <1 h	0.39 annual rate in the whole cohort

AF, atrial fibrillation; AHRE, atrial high-rate episode; ICD, implantable cardioverter–defibrillator; NA, not available; SEE, stroke or systemic embolism; TIA, transient ischemic attack.



e-Table 21. Time relationships between device-detected atrial tachyarrhythmias and ischemic stroke, transient ischemic attacks or systemic embolism in patients with CIEDs under continuous monitoring of the atrial rhythm

	N. of TE events (Ischemic Stroke/TIA/SE)	Minimum device detected AF/AT duration/burden	Device detected AF/AT at any time before TE event	Device detected AF/AT in the 30 days before TE event	Device detected AF/AT at the time of TE event	Device detected AF/AT only after TE event
Daoud et al., 2011 ¹⁷⁴	40 Ischemic Stroke/TIA/SE	≥ 20 sec	50%	28%	15%	15%
Boriani et al., 2012 ¹⁷⁵	33 Ischemic Stroke/TIA/SE	≥5 min	64%	33%	15%	NA
Shanmugam et al., 2012 ¹⁷¹	11 Ischemic Stroke/TIA/SE	Around 6-10 s	64%	NA	27%	NA
Brambatti et al., 2014 ¹⁷⁶	51 Ischemic Stroke/SE	>6 min	35%	8%	2%	16%
Martin et al., 2015 ¹⁷⁷	69 Ischemic Stroke/SE	Around 6-10 s	13%	6%	NA	7%

AF: atrial fibrillation; AT: atrial tachyarrhythmias; CIED: cardiac implantable electronic device; SE: systemic embolism; TE: thromboembolic; TIA: transient ischemic attack; NA: not available

e-Table 22. GRADE Evidence Profile of Warfarin compared to no treatment/placebo for CKD

Question: Warfarin compared to No anticoagulation/placebo for CKD

Bibliography: Harel 2017

Certainty assessment							Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	Absolute (95% CI)		
Ischemic Stroke										
14	observational studies	not serious	serious ^a	not serious	not serious ^a	none	HR 0.85 (0.62 to 1.15)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕○○○ VERY LOW	CRITICAL
Intracranial Hemorrhage										
4	observational studies	not serious	not serious	not serious	serious ^b	none	HR 1.93 (0.93 to 4.00)	2 fewer per 1,000 (from 1 fewer to 4 fewer)	⊕○○○ VERY LOW	CRITICAL

CI: Confidence interval; HR: Hazard Ratio

Explanations

a. I-squared value of 69% represents serious heterogeneity

b. wide 95% CI

e-Table 23. Factors to be considered in estimating the bleeding and thromboembolic risk associated with a surgical procedure or intervention in a patient on oral anticoagulants for AF or previous venous thromboembolism. Modified from Boriani G et al. ¹⁷⁸

Hemorrhagic risk related to surgical or interventional procedures	Thromboembolic risk related to oral anticoagulation interruption
<p>Low hemorrhagic risk (2-day risk of major bleeding between 0 and 2%)</p> <p>Cataract and other ophthalmic surgery , with the exception of vitro-retinal surgery Simple dental extractions</p> <p>Skin excision Carpal tunnel repair Central venous catheter removal Non-coronary angiography Pacemaker and cardiac defibrillator implant Bronchoscopy with biopsy Cutaneous and lymph node biopsies (for bladder, prostate, thyroid, breast masses) Abdominal hysterectomy Hemorrhoidal surgery Abdominal hernia repair Hydrocele repair Knee or hip replacement and shoulder, hand or foot surgery and arthroscopy Cholecystectomy Gastrointestinal endoscopy or biopsy, enteroscopy, biliary or pancreatic stent without sphincterotomy</p>	<p>Low thromboembolic risk (annual risk of arterial thromboembolism < 5% or 1-month risk of venous thromboembolism < 2%)</p> <p>Nonvalvular atrial fibrillation with CHADS₂ score 0 or 1</p> <p>Single previous remote venous thromboembolism (> 12 months) with no other risk factors</p>
<p>High hemorrhagic risk (2-day risk of major bleeding between 2 and 4%)</p> <p>Heart valve replacement Coronary artery bypass Surgery for aortic diseases</p> <p>Vascular and general surgery Neurosurgery</p> <p>Surgery for urologic, thoracic, abdominal or breast cancer Transurethral prostate resection</p> <p>Bilateral knee replacement</p> <p>Laminectomy Kidney biopsy Polypectomy, variceal treatment, biliary sphincterectomy, pneumatic dilatation Placement of a percutaneous endoscopic gastrostomy (PEG) Endoscopically guided fine-needle aspiration Multiple tooth extractions Any major operation with a procedure duration > 45 minutes</p>	<p>Intermediate thromboembolic risk (annual risk of arterial thromboembolism between 5 and 10% or 1-month risk of venous thromboembolism between 2 and 10%)</p> <p>Previous venous thromboembolism within 3 and 12 months Valvular prosthesis in aortic position without risk factors Nonvalvular atrial fibrillation with CHADS₂ score 2 or 3 Recurrent stroke or transient ischemic attack without risk factors for cardiac embolism</p> <p>High thromboembolic risk (annual risk of arterial thromboembolism >10% or 1-month risk of venous thromboembolism >10%)</p> <p>Recent venous thromboembolism (<3 months) Recent stroke or transient ischemic attack, (< 3 months) Previous thromboembolic event with known hypercoagulability due to genetic factors (Protein S or C deficiency, anti-thrombin deficiency, homozygous factor V Leiden mutation, antiphospholipid syndrome) or paraneoplastic thromboembolism or recurrent idiopathic thromboembolism Non valvular atrial fibrillation with CHADS₂ score ≥ 4 Atrial fibrillation with rheumatic heart disease, mechanical valvular prosthesis or previous stroke Any valvular prosthesis in mitral position or older valvular prosthesis (caged-ball; tilting-disc) in aortic position Prosthetic heart valve with other risk factors (prior thromboembolism, severe left ventricular dysfunction) or recently placed (<3 months) or associated with hypercoagulable state Intra-cardiac thrombus detected by echocardiography or other imaging techniques</p>

e-Table 24. Decision-making and management of a patient under treatment with a NOAC in the phases before and after a procedure/intervention.

Interruption before the procedure/intervention				
	CrCl	Minor procedure/ intervention without an important risk of bleeding and with possible adequate local haemostasis	Procedure/ intervention at low risk of bleeding	Procedure/ intervention at high risk of bleeding
Apixaban,	CrCl > 30 mL/min	Plan to perform the procedure/intervention at trough level (i.e. 12 h after last intake)	Give last dose 2 days before procedure/intervention (i.e., skip 2 doses on the day before the procedure/intervention and skip the dose the day of the procedure/ intervention)	Give last dose 3 days before procedure/intervention (i.e., skip 4 doses on the 2 days before the procedure/intervention and skip the dose the day of the procedure/ intervention)
	CrCl 15-30 mL/min	Plan to perform the procedure/intervention at trough level (i.e. 12 h after last intake) or at 24 hours from last intake	Give last dose 2 days before procedure/intervention (i.e., skip 2 doses on the day before the procedure/intervention and skip the dose the day of the procedure/ intervention)	Give last dose 3 days before procedure/intervention (i.e., skip 4 doses on the 2 days before the procedure/intervention and skip the dose the day of the procedure/ intervention)
Edoxaban, Rivaroxaban	CrCl > 30 mL/min	Plan to perform the procedure/intervention at trough level (i.e. 24 h after last intake)	Give last dose 2 days before procedure/intervention (i.e., skip 1 dose on the day before the procedure/intervention and skip the dose the day of the procedure/ intervention)	Give last dose 3 days before procedure/intervention (i.e., skip 2 doses on the 2 days before the procedure/intervention and skip the dose the day of the procedure/ intervention)
	CrCl 15-30 mL/min	Plan to perform the procedure/intervention at trough level (i.e. 24 h after last intake) or at 36 hours from last intake	Give last dose 2 days before procedure/intervention (i.e., skip 1 dose on the day before the procedure/intervention and skip the dose the day of the procedure/ intervention)	Give last dose 3 days before procedure/intervention (i.e., skip 2 doses on the 2 days before the procedure/intervention and skip the dose the day of the procedure/ intervention)
Dabigatran	CrCl > 50 mL/min	Plan to perform the procedure/intervention at trough level (i.e. 12 h after last intake)	Give last dose 2 days before procedure/intervention (i.e., skip 2 doses on the day before the procedure/intervention and skip the dose the day of the procedure/ intervention)	Give last dose 3 days before procedure/intervention (i.e., skip 4 doses on the 2 days before the procedure/intervention and skip the dose the day of the procedure/ intervention)
	CrCl 30-50 mL/min	Plan to perform the procedure/intervention at trough level (i.e. 12 h after last intake) or at 24 hours from last intake	Give last dose 3 days before procedure/intervention (i.e., skip 4 doses on the 2 days before the procedure and skip the dose the day of the procedure/ intervention)	Give last dose 5 days before procedure/intervention (i.e., skip 8 doses on the 4 days before the procedure and skip the dose the day of the procedure/ intervention)
Resumption after the procedure/intervention				
Apixaban, Dabigatran, Edoxaban, Rivaroxaban		The drug can be resumed without skipping expected doses	The drug can be resumed 24 hours after the procedure/ intervention	The drug can be resumed 48-72 hours after the procedure/ intervention

For all the DOACs usually there is no need for bridging with LMWH/UFH

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More recently there have been calls for a more co-ordinated approach to the management of AF, 'integrated AF care'.¹⁷⁹⁻¹⁸³ Physicians are encouraged to adopt a shared-decision making approach¹⁸⁴⁻¹⁸⁶ to empower the patient to contribute to treatment decisions and participate in the management of their AF.

It is imperative to elicit from each patient what outcomes of treatment are important for them rather than assume that all patients have the same treatment goals,¹⁸⁴ and to be aware that patients and physicians treatment objectives often differ significantly. Research has overwhelmingly demonstrated that patients with AF wish to avoid a stroke and are often willing to accept major bleeding to achieve this,¹⁸⁷⁻¹⁹⁰ as many patients view a major disabling stroke as a consequence worse than death.¹⁸⁹ Bleeds, although feared, are considered by many patients to be preferable to a stroke. In contrast, some physicians are more concerned with reducing the risk of death¹⁸⁷ and decreasing the chance of bleeding rather than the prevention of stroke.^{188,191} Physicians should note that in addition to reducing the risk of stroke, OAC also significantly reduces the risk of death.¹⁹² However, it is important to note that preferences for avoidance of stroke do not always translate into actions/decisions to take OAC; in a study of elderly AF patients, 12% would not take OAC even if was 100% effective for stroke prevention.¹⁸⁹ External factors, such as negative media coverage (TV adverts, particularly in the US) can create fear among patients on OAC about severe or fatal bleeding, which may translate into patients stopping OAC or failing to initiate.

Patient preferences for OAC

Since the introduction of NOACs, 7 studies¹⁹³⁻¹⁹⁹ have investigated which factor patients perceive as the important attribute when choosing OAC. In 4 studies¹⁹⁵⁻¹⁹⁸ patients rated stroke prevention as the most important characteristic for OAC, while in others, the lack of interactions with food/drugs,¹⁹³ availability of an antidote,¹⁹⁹ or ease of administration¹⁹⁴ were of greatest importance. However, methodological differences between studies may explain the inconsistency in outcomes, particularly where efficacy and safety were not included in the attributes presented.¹⁹⁴ None of the studies asked patients to actively generate the attributes they felt were most important; all used pre-defined lists generated by researchers for patients to rank, which might have led to exclusion of certain responses of importance to patients. Further, most of these studies¹⁹³⁻¹⁹⁹ did not examine patient perceptions of AF and stroke, or knowledge about stroke, which may determine these preferences.

Only a few studies have compared patient preferences for vitamin K antagonists (VKAs) and NOACs.^{193,194,197-201} Generally NOACs were preferred to VKAs due to convenience factors mainly related to absence of INR monitoring^{194,198-201} and a lower risk of bleeding.²⁰¹ Cost of OAC, particularly NOACs, is problematic in countries where healthcare is not free or fully reimbursed, particularly in the US, and consequently affordability can drive patient (and physician) OAC preferences. Only three OAC preference studies in AF patients¹⁹⁵⁻¹⁹⁷ have examined the impact of cost/affordability on factors that were important in choosing an OAC; all reported stroke prevention to be the most important factor. One¹⁹⁷ found that NOACs were preferred over warfarin as their cost decreased. In two North American studies, one found that cost was the fifth most important attribute of OAC,¹⁹⁵ while in a larger US study of AF patients with and without stroke,¹⁹⁶ cost was the least important attribute. Consequently, patient preferences are likely to vary considerably based on the healthcare system in which they operate as well as their health expectations and previous experiences.

Patient education and counselling

Communication with patients is crucial as physicians may deliberately or inadvertently persuade patients to concur with their treatment decision by creating fear (either fear of stroke or fear of bleeding to death). Therefore, explaining risk of stroke and benefit/risks of treatment in terms the

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patient can understand is paramount in enabling the patient to choose whether or not they wish to take OAC. Many patient decision aids have been created to assist physicians in these discussions with patients (see e-Table 26). Eliciting the barriers patients perceive they may have with NOACs/OAC allows HCPs to give clear explanations/offer strategies to overcome these barriers and improve OAC uptake, adherence, and persistence. In addition, it is important to dispel myths patients may hold about alternatives to OAC for stroke prevention.

Adherence and persistence with OAC is paramount to treatment efficacy and safety.²⁰² Educating patients on why adherence and persistence is so important, discussions on how to be adherent (timing of medication, frequency, with/without food, interacting medications to avoid, what to do if dose missed/overdose etc.) requires specific instructions from the HCP prescribing the medication; this could be facilitated by the use of patient education checklist (e-Table 26) and enhanced by devising and sharing strategies to increase adherence and persistence (reminders, medication tracking etc.). Understanding the necessity of OAC therapy and the potential adverse complications of non-adherence (stroke or bleeding) increases patient adherence and persistence.²⁰³ Physician education is also important to ensure that they are familiar with the latest guidelines and current preferred AF management strategies, implementing them in order to prevent under-treatment (choice of drug and dose should be decided on the basis of patient characteristics, and to use their knowledge to inform patients about the specifics of the OAC to improve shared-decision making and adherence and persistence. Comprehensive reviews of 'best practice' for patient education for AF and OAC are available.²⁰⁴⁻²⁰⁷

e-Table 25. Patient and healthcare provider decision aids and apps, patient resources, and patient and professional organisations*†

Patient decision aids	Reference/URL
AFGuST Keele University Decision support NICE 2014 PDA	208 http://www.anticoagulation-dst.co.uk/ https://www.nice.org.uk/guidance/cg180/resources/endorsed-resource-decision-support-tool-552601405
'Patient pages' for AF and OAC	
Causes, symptoms and treatment of AF	209,210
Living with AF	211
Prevention of stroke in AF	212,213
Management of vitamin K antagonists	214,215
Non-vitamin K antagonists oral anticoagulants (NOACs)	216
Left atrial appendage occlusion devices	217
Patient apps	
European Society of Cardiology Patient app (My AF)	218 Free to download to all smartphones- search for 'My AF'
mAFA	219
Health Buddies app	220
CardioVisual app	http://cardiovisual.com
Afib Companion app	http://afibcompanion.com
Medication tracker apps	
Medisafe	https://www.medisafe.com
Mango Health	https://www.mangohealth.com
HCP apps	
European Society of Cardiology Healthcare Professional app (AF manager)	218 Free to download to all smartphones- search for 'AF manager'
Patient advocacy groups and foundations	
Anticoagulation Europe	http://www.anticoagulationeurope.org/
Arrhythmia Alliance International	www.aa-international.org
Atrial Fibrillation Association International	www.afa-international.org
Heart and Stroke Foundation-Canada	http://www.world-heart-federation.org/what-we-do/awareness/atrial-fibrillation/
My AFib Experience	http://myafibexperience.org/
Sign Against Stroke in Atrial Fibrillation	https://www.signagainststroke.com/en
Stop Afib.org	http://www.stopafib.org/
World Heart Federation:	http://www.world-heart-federation.org/what-we-do/awareness/atrial-fibrillation/
Professional societies or organizations	
American College of Cardiology:	https://www.cardiosmart.org/Heart-Conditions/Atrial-Fibrillation
American Heart Association	http://www.heart.org/HEARTORG/Conditions/Arrhythmia/AboutArrhythmia/AFib-Resources-and-FAQ_UCM_423786_Article.jsp#
European Heart Rhythm Association	http://www.afibmatters.org/
Heart Rhythm Society	http://www.hrsonline.org/Patient-Resources/Heart-Diseases-Disorders/Atrial-Fibrillation-AFib#axzz3L30TnuIT

*Taken in part from²⁰⁵; †not an exhaustive list

e-Table 26. Patient education checklist for atrial fibrillation patients initiating oral anticoagulation

Patient education checklist for oral anticoagulation for stroke prevention in atrial fibrillation	Tick when completed
The condition - Atrial fibrillation	
What is atrial fibrillation?	
What is the link between AF and stroke?	
Discuss patient's risk of stroke (CHA ₂ DS ₂ -VASc score & associated co-morbidities)	
Why is OAC recommended for stroke prevention?	
Duration of treatment (usually lifelong)	
Treatment options	
What are the treatment options? VKA or NOAC?	
Patient values/preferences for treatment (stroke prevention; lowest risk of bleeding; no routine monitoring; fewest side effects; once/twice daily dosing; cost etc.)	
Mode of action of chosen OAC (VKA or NOAC)	
Benefits/risks of specific OAC (stroke risk reduction vs. bleeding risk)	
For VKA patients , need for INR monitoring & explanation of INR tests; importance of TTR	
Why INR monitoring is not necessary (for VKA-experienced patients)	
Dosing	
How often the drug needs to be taken (once or twice daily)?	
What time(s) of day the OAC must be taken?	
Take with/without food	
If twice daily drug, NEVER take both doses together	
What to do if a dose is missed/overdose	
Highlight importance of medication adherence/ potential consequences of non-adherence	
Discuss how medication will be incorporated into daily routine	
Tools to assist patient to remember (if necessary)	
Bleeding	
Discuss patient's risk of bleeding on OAC treatment	
Distinction between minor and major bleeding	
Signs and symptoms of bleeding	
When to seek medical care or attend emergency room	
What do to in the case of head injury	
Presence/absence of antidote	
Lifestyle	
Concomitant medication (interactions; avoid antiplatelets/other OAC; minimize NSAID use; discuss permissible pain medication)	
Diet (for VKA patients)	
Alcohol intake (particularly for VKA patients)	
Natural remedies/health-food supplements	
For women: menstruation, pregnancy, breastfeeding	
Holidays and travel	
Exercise and potentially dangerous hobbies	
Occupational hazards	
Surgical or dental procedures	
Before discharge	
Confirm patient understands dosing regimen, bleeding signs/symptoms and management of bleeding, when to seek medical attention and from whom	
Provide written education materials and Patient Alert card (if available)	
Arrange follow-up and provide contact details of prescribing physician	
Patient aware of laboratory tests needed – why, how and when	

AF, atrial fibrillation; NSAIDs, non-steroidal anti-inflammatory drugs; OAC, oral anticoagulation; VKA, vitamin K antagonist

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