Dental Procedures in Patients with Atrial Fibrillation and New Oral Anticoagulants

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Abstract

This review discusses the basic pharmacology of new oral anticoagulants that are used for prevention of thromboembolism in patients with atrial fibrillation. It presents available evidence, and provides recommendations for the management of patients requiring invasive procedures in dental practice.

Keywords

New oral anticoagulants; dental procedures; atrial fibrillation

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Novel oral anticoagulants (NOACs) represent new options for preventing stroke in patients with atrial fibrillation (AF), and have been approved for use in North America and Europe. They carry a 50 % lower risk of intracranial haemorrhage compared with warfarin, no clear interactions with food, fewer interactions with medications and no need for frequent laboratory monitoring and dose adjustments. Although they lack a specific reversal agent, their use is increasing in the western world, thus imposing upon the dentists the task of performing invasive procedures in this setting with a continually higher frequency.

Magnitude of the Problem

AF is the most common sustained arrhythmia in humans and affects 1–2 % of the general population worldwide. It affects three to six million people in the US,[1,2] while in Asian countries its incidence is slightly lower.[3,4] In the EU, 8.8 million adults over 55 years were estimated to have AF in 2010 and this number is expected to double by 2060 to 17.9 million.[5] According to the first global assessment of AF, conducted within the framework of the Global Burden of Diseases (GBD), Injuries and Risk Factors Study, the estimated global prevalence of AF in 2010 was 33.5 million (20.9 million men and 12.6 million women), with almost five million new cases occurring each year.[6] The prevalence of AF increases with age, from approximately 2 % in the general population, to 5–15 % at 80 years.[2,7,8] Thus, AF represents a modern epidemic, and the practicing dentist is expected to deal with these patients at a continually increasing frequency.

Clinical Perspective

- In patients with normal renal function taking dabigatran, rivaroxaban or apixaban, invasive dental procedures can be carried out without interruption of the medication, but should be performed as late as possible after the most recent dose, ideally >12 hours).
- Patients requiring complex oral/maxillofacial surgery may need discontinuation of oral anticoagulants for at least 24 hours preoperatively.

AF is associated with significant morbidity, including a two- to seven-fold increased risk for stroke (average 5 % per year).[9–12] In the Framingham Study the percentage of strokes attributable to AF increases steeply from 1.5 % at 50–59 years of age to 23.5 % at 80–89 years of age.[11] Approximately 20 % of all strokes are due to AF,[13] and paroxysmal AF carries the same stroke risk as permanent or persistent AF.[14] Thus, chronic anticoagulation is necessary for patients with AF and CHA_2DS_2VASc score ≥2, whereas no anticoagulation may only be recommended in patients with negligible risk and a score of 0. The novel oral anticoagulants are now recommended for non-valvular AF as a potential alternative to warfarin by both the European Society of Cardiology (ESC) and American College of Cardiology (ACC)/American Heart Association (AHA) (see *Table 1*). Dabigatran is preferred to warfarin for non-valvular AF by the ESC[13] and the Canadian Cardiology Society.[15] NOACs are direct thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban) inhibitors. They carry a 50 % lower risk of intracranial haemorrhage compared with warfarin, no clear interactions with food, fewer interactions with medications and no need for frequent laboratory monitoring and dose adjustments.[16–18] Their main disadvantages are the lack of a reliable, specific antidote, specific assays to measure anticoagulant effect, and considerably higher cost than warfarin.[19] NOACs do not interact with food but with inhibitors (or inducers) of P-glycoprotein transporters and cytochrome P450 (CYP) 3A4.

A practical guide by the European Heart Rhythm Association (EHRA) has been published and a website created (www.NOACforAF.eu).[20] The use of NOACs is continually increasing in the western world and, apart from AF, they are also used both for therapy and prevention of venous thromboembolism,[21,22] i.e. pulmonary embolism and deep vein thrombosis, a disease entity with an annual incidence of approximately 1.2 cases per 1,000 adults.[23,24]

Table 1: New Oral Anticoagulants for Atrial Fibrillation

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dose	150 or 110 bd	20 mg od	2.5-5 mg bd	30-60 mg od
	75 mg bd if CrCl 15-30 ml/min	15 mg od if CrCl 15-30 ml/min	2.5 mg bd if CrCl ≥ 1.5 mg/dL, ≥ 80 years of age, body weight ≤ 60 kg	(no data in renal impairment)
Target	Thrombin (Factor II)	Factor Xa	Factor Xa	Factor Xa
Half life	12–14 h	9–13 h	8–11 h	8–10 h
Renal clearance	80 %	60 %	25 %	40 %
Onset of action	2 h	2.5–4 h	3 h	1–5 h

bd = twice daily; od = once daily; CrCl = creatinine clearance.

Table 2: Classification of Dental Procedures

Dental Procedure	Presumed Bleeding Risk	Peri-procedural Recommendations*
• Supragingival scaling • Simple restorative treatment • Local anaesthetic injections (buccal infiltration, intraligamentary or mental block) • Impressions and other prosthetic procedures	Low	Continue therapeutic anticoagulation
• Local anaesthesia by inferior alveolar or other regional nerve blocks or floor of mouth infiltrations • Subgingival scaling and root surface instrumentation (RSI) • Subgingival crown and bridge preparations • Endodontics. Standard root canal treatment • Simple extractions • Incision and drainage of swellings • Biopsies	Moderate	Continue therapeutic anticoagulation
• Extensive maxillofacial surgery • Periodontal surgery • Alveolar surgery (bone removal) • Multiple extractions	High	Consider reducing or completely reverse anticoagulation

**For all procedures, local measures can be used to prevent or control bleeding (local pressure, site packing, additional suturing, topical haemostat, mouth rinses).*

Assessment of Activity and Reversal of NOACs

Dabigatran

Activated partial thromboplastin time (aPTT) and thrombin clotting time (TCT or thrombin time) may be used for assessment of anticoagulant action, although not to guide dosage since the correlation is not linear. A normal aPTT indicates the absence of a significant dabigatran effect, whereas an aPTT >2.5 times the control 8–12 hours after dabigatran dosing is suggestive of excess anticoagulant activity.[25] The Hemoclot® direct thrombin inhibitor assay (HYPHEN BioMed; France) provides an accurate measure of dabigatran drug levels.[25] There is no specific antidote to dabigatran, but fresh frozen plasma and activated prothrombin complex concentrates (aPCC, 80 U/kg Factor Eight Inhibitor Bypassing Activity [FEIBA]; Baxter, Vienna, Austria) may be helpful.[25–27] Recombinant activated factor VII (rVIIa, NovoSeven®, NovoNordisk, Bagsvaerd, Denmark) has also been proposed but data supporting its usefulness are lacking.[28] Note that unlike the prothrombin complex concentrates (PCCs) in Europe and Canada, which contain all four vitamin K-dependent procoagulant proteins, those currently available in the US contain little or no factor VII.[25]

Apixaban and Rivaroxaban

Prothrombin time and, especially, anti-Xa assays (heparin) may be used as rough estimates of the anticoagulant effect. No specific antidotes exist, but the recombinant factor Xa andexanet alpha (Portola Pharmaceuticals; CA, USA) given as a bolus 600 or 720 mg and followed by an infusion of 4 mg/min for one hour, has been successfully tried. Infusion-related reactions and postural dizziness were the only side-effects seen in 10 % of patients.[29] PCCs (50 IU/kg) are also recommended, and are probably preferred to aPCC.[30] Apixaban and rivaroxaban are not removed by dialysis, being protein bound. Packed red cells in anaemia, platelet transfusions in patients receiving concurrent antiplatelet therapies, and fresh frozen in the presence of dilutional coagulopathy or disseminated intravascular coagulation, may also be tried as general measures.[28]

Edoxaban and betrixaban are Xa antagonists that have also been successfully tried in patients with non-valvular AF, but few data on their clinical use exist.

Dental Procedures in Patients on NOACs

Dental treatment performed in patients receiving oral anticoagulant drug therapy is becoming increasingly common in dental offices. Frequently raised questions concern the accompanying thromboembolic and bleeding risks of the various anticoagulation regimens relative to invasive dental procedures. Many dental procedures do not involve a significant risk of bleeding and therefore no special measures are required when treating patients who take an oral anticoagulant drug. However, there are procedures that carry a risk of significant bleeding and for which the dentist must consider the management of the patient in relation to their anticoagulant therapy (see *Table 2*).

Peri-procedural Anticoagulation

In patients on warfarin, procedures at low bleeding risk do not require interruption of anticoagulation, provided the international normalised

Table 3: Proposals for General Dental Practitioners Treating Patients on Novel Oral Anticoagulants

1. Continuation of Oral Antithrombotic Medication
a. Do not interrupt single or dual TAR (such as ASA, clopidogrel, and carbasalate calcium).
b. Do not interrupt VKAs if the INR is less than 3.5.
c. Do not interrupt NOACs (direct thrombin inhibitors or Xa-inhibitors, such as apixaban, dabigatran, and rivaroxaban).
Note: The anticoagulation regime does not require alteration when single-dose antibiotics for prophylaxis are provided; miconazole is contraindicated when VKAs or NOACs are taken.
2. Preoperative Measures
a. Inform the patients that minor bleeding or oozing from gingival mucosa may be more common when not interrupting OAM during dental procedures.
b. Check INR in patients using VKA at least 24–72 hours before the dental procedure; refer patients whose INR is higher than 3.5 to the hospital for evaluation and treatment.
c. Advise patients on NOACs not to take medication 1–3 hours immediately before dental treatment.
d. Assess the patients' complete medical history and discuss with the physician in charge if renal or liver disorders are suspected or known; when INR ≥ 3.5 or the planned procedures are more extensive.
e. Schedule extraction of more than three teeth over a larger number of visits (i.e., divide the load) and plan the surgeries earlier in the day and at the beginning of the week.
3. Perioperative Measures
a. Minimise surgical trauma and reduce areas of periodontal surgery and scaling and root planing (per quadrant).
b. Aim at primary closure of surgical wounds, including extraction wounds, using absorbable sutures.
4. Postoperative Measures
a. Compress with gauze for 15–30 minutes after the surgical procedure; use coagulating agents, such as gelatin sponges, oxidised regenerated cellulose, synthetic collagen, or tranexamic acid mouthwash in 4.8% aqueous solution, for 1–2 days after the surgery, using 10 ml, four times a day for two minutes.
b. Remove nonabsorbable sutures, if used, after 4–7 days.
c. Do not prescribe NSAIDs and COX-2 inhibitors as analgesics to any patient on any antithrombotic medications.
d. Provide the patients with oral and written instructions about the expected postoperative course and the measures they can take if bleeding occurs.

OAM = oral antithrombotic medication; TAR = thrombocyte aggregation inhibitor; ASA = acetylsalicylic acid; VKA = vitamin K antagonist; INR = international normalised ratio; NOAC = novel oral anticoagulant; NSAID = nonsteroidal anti-inflammatory drug; COX-2 = cyclooxygenase-2.[37]
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ratio (INR) is <4.0, whereas moderate and high-risk procedures are performed with an INR<1.5.[31] Heparin bridging is not necessary, apart from in patients with certain mechanical valves. In a recent meta-analysis, heparin bridging for invasive procedures and surgery in patients receiving vitamin K antagonists for AF, prosthetic heart valve or venous thromboembolism conferred a greater than five-fold increased risk for bleeding, whereas the risk of thromboembolic events was not significantly different between bridged and nonbridged patients.[32]

Few data exist for NOACs. These agents are not indicated for anticoagulation in patients with prosthetic heart valves.[33] Dentists, therefore, will encounter them in patients with AF and venous thromboembolism. There has been recent evidence that continuation or short-interruption of NOACs are safe strategies for most invasive procedures.[34] Thus, dental procedures that involve manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa including uncomplicated teeth extractions do not require interruption of anticoagulation.[34] For subgingival scaling, a small area should be scaled first to assess the amount of bleeding before instrumentation of larger areas is carried out. Local anaesthetics solutions containing a vasoconstrictor should be used unless contraindicated on other medical grounds. An aspirating syringe must be used for all local anaesthetic injections.[35,36]

Procedures with a relatively higher risk of bleeding such as multiple extractions or minor oral/maxillofacial surgery can also be safely performed without interruption of NOACs, provided they are carried out 12 hours after last dosing of dabigatran and 10 hours after last dosing of rivaroxaban or apixaban (see *Table 1*). Current available information suggests that the risk of bleeding in patients undergoing invasive dental procedures (for example up to three dental extractions, up to three dental implants and periodontal surgery) is low, provided

Table 4: European Heart Rhythm Association 2013: Last Intake of NOAC Before Elective Surgical Intervention

No important bleeding risk and/or adequate local haemostasis possible: perform 12–24 hours after last intake

	Dabigatran		Apixaban/Rivaroxaban	
	Low Risk	High Risk	Low Risk	High Risk
CrCl ≥80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 mL/min	≥36 h	≥72 h	≥24 h	≥48 h
CrCl 30–50 mL/min	≥48 h	≥96 h	≥24 h	≥48 h
CrCl 15–30 mL/min	not indicated		≥36 h	≥48 h

Low and high risk refers to operative bleeding; CrCl = creatinine clearance.[20]

that local haemostatic measures (suturing, ideally with resorbable sutures, gelatin sponge, gauze soaked in 5 % tranexamic acid, tranexamic acid mouth rinse) are used (see *Table 3*).[37]

For more serious surgical operations, (major oral/maxillofacial surgery), the lack of data necessitates an empirical approach. In general, for surgical operations, depending on the risk of bleeding and renal function, preoperative interruption of NOACs for one to seven days has been recommended.[25,38] The 2013 EHRA report recommends shorter intervals.[20] Dabigatran should be discontinued for at least 24 hours (or longer in renal impairment) in patients requiring major oral/maxillofacial surgery (see *Table 3*).[39] Additionally, consideration should be given to performing a thrombing clotting time (TT) or an aPTT 6–12 hours prior to surgery. The renal function of the patient should be also taken into account (see *Table 4*).

If discontinuation of anticoagulation is not considered safe and extensive oral surgery is required, peri-operative bridging anticoagulation with an appropriate dose of low molecular weight heparin (LMWH) or

Table 5: Risk of Stroke in Atrial Fibrilation

$CHAD_2DS_2VASc$ Score	
Risk Factor	Score
Congestive heart failure/left ventricular dysfunction	1
Hypertension	1
Age >75	2
Diabetes mellitus	1
Stroke/transient ischaemic attack/thromboembolism	2
Vascular disease (MI, peripheral artery disease, aortic plaque)	1
Age 65–74	1
Sex category (i.e. female sex)	1

Adjusted Stroke Rate According to CHA_2DS_2-VASc Score	
Score	Adjusted Stroke Rate (% year)
0	0.0 %
1	1.3 %
2	2.2 %
3	3.2 %
4	4.0 %
5	6.7 %
6	9.8 %
7	9.6 %
8	6.7 %
9	15.2 %

Previous stroke, TIA, systemic embolism, and age ≥75 years are considered major risk factors.[44] MI = myocardial infarction.
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unfractionated heparin is recommended.[39] It should be noted, however, that bridging with heparin is, on most occasions, not necessary and may increase the risk of bleeding.[34] In a recent analysis of data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, interruption of dabigatran (two days) or warfarin (five days) for allowance of surgery was not associated by a significant occurrence of stroke and systemic embolism although heparin bridging was used in <80 % of patients on dabigatran, and major bleeding was not different in the two treatment groups.[40] However, discontinuation of rivaroxaban in the ROCKET AF for at least three days was associated with a higher incidence of stroke compared with discontinuation of warfarin.[41] Thus, in patients with a $CHADS_2DS_2VASC$ score >4, i.e. >5 % annual risk of stroke (see *Table 5*), or those with a history of stroke who require temporary interruption of oral anticoagulation, bridging therapy with LMWH should be considered, especially when a newer oral anticoagulant is used.[42] If urgent surgery or intervention is required in these patients, the risk of bleeding must be weighed against the clinical need for the procedure. Evaluation of common coagulation tests (aPTT for dabigatran; sensitive prothrombin time [PT] for FXa inhibitors) or of specific coagulation test (direct thrombin time [dTT] for dabigatran; chromogenic assays for FXa inhibitors) can be considered for assessment of anticoagulation intensity, but no clinical experience exists.[20] Surgery should be deferred, if possible, until at least 12 hours and ideally 24 hours after the last dose. Nonspecific anti-haemorrhagic agents, such as rVIIa or PCCs, should not be given for prophylactic reversal due to their uncertain benefit: risk ratio.[43] Reinitiation of these agents should be delayed for 24–48 hours and once a stable clot or complete haemostasis is assured, since within one to two hours of reinitiation the patient will be anticoagulated. For procedures with immediate and complete haemostasis NOACs can be resumed six to eight hours after the intervention.

Conclusions

Data on patients taking NOACs and who are undergoing dental procedures are scarce, and an empirical approach is inevitable regarding the management of these patients. Based on available evidence, the following recommendations can be made:

- In patients with normal renal function taking dabigatran, rivaroxaban or apixaban, simple invasive dental procedures can be carried out without interruption of the medication.
- All procedures should be performed as late as possible after the most recent dose, ideally >12 hours).
- Local haemostatic measures should be used routinely in these patients.
- Patients requiring oral/maxillofacial surgery may need discontinuation of oral anticoagulants for at least 24 hours pre-operatively, but always in consultation with treating physician.
- If stopped pre-operatively, NOACs should only be recommenced when a stable clot or adequate haemostasis has been achieved (typically 24–48 hours post-operatively).
- If post-operative bleeding occurs, oral anticoagulant therapy should be stopped, and local haemostatic measures applied. ■

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The anticoagulation and risk factors in atrial fibrillation (atria) study. *JAMA* 2001;**285**:2370–5.
2. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;**114**:119–25.
3. Ohsawa M, Okayama A, Sakata K, et al. Rapid increase in estimated number of persons with atrial fibrillation in Japan: An analysis from national surveys on cardiovascular diseases in 1980, 1990 and 2000. *J Epidemiol* 2005;**15**:194–6.
4. Zhou Z, Hu D. An epidemiological study on the prevalence of atrial fibrillation in the chinese population of mainland China. *J Epidemiol* 2008;**18**:209–16.
5. Krijthe BP KA, Benjamin EJ, Lip GY, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013;**34**:2746–51.
6. Chugh SS HR, Narayanan K, Singh D, et al. Worldwide epidemiology of atrial fibrillation: A global burden of disease 2010 study. *Circulation* 2014;**129**:837–47.
7. Davis RC, Hobbs FD, Kenkre JE, et al. Prevalence of atrial fibrillation in the general population and in high-risk groups: The echoes study. *Europace* 2012;**14**:1553–9.
8. Wilke T GA, Mueller S, Pfannkuche M, et al. Incidence and prevalence of atrial fibrillation: An analysis based on 8.3 million patients. *Europace* 2013;**15**:486–93.
9. Knecht S, Oelschlager C, Duning T, et al. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. *Eur Heart J* 2008;**29**:2125–32.
10. Santangeli P, Di Biase L, Bai R, et al. Atrial fibrillation and the risk of incident dementia: A meta-analysis. *Heart Rhythm* 2012;**9**:1761–8.
11. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham study. *Stroke* 1991;**22**:983–8.
12. Jonathan P. Piccini, Bradley G. Hammill, et al. Clinical course of atrial fibrillation in older adults: The importance of cardiovascular events beyond stroke. *Eur Heart J* 2014;**35**:250–6.
13. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: The task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *Europace* 2010;**12**:1360–1420.
14. Hart RG, Pearce LA, Rothbart RM, et al. Stroke with intermittent atrial fibrillation: Incidence and predictors during aspirin therapy. Stroke prevention in atrial fibrillation investigators. *J Am Coll Cardiol* 2000;**35**:183–7.
15. Gillis AM, Verma A, Talajic M, et al. Canadian cardiovascular society atrial fibrillation guidelines 2010: Rate and rhythm management. *Can J Cardiol* 2011;**27**:47–59.
16. De Caterina R, Husted S, Wallentin L, et al. New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC working group on thrombosis-task force on anticoagulants in heart disease position paper. *J Am Coll Cardiol* 2012;**59**:1413–25.
17. Dentali F, Riva N, Crowther M, et al. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: A systematic review and meta-analysis of the literature. *Circulation* 2012;**126**:2381–91.
18. Ruff CT GR, Braunwald E, Hoffman EB, 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**:955–62.
19. Canestaro WJ PA, Avorn J, Ito K, et al. Cost-effectiveness of oral anticoagulants for treatment of atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 2013;**6**:724–31.
20. Heidbuchel H, Verhamme P, Alings M, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur Heart J* 2013;**34**:2094–106.
21. Fontana P, Goldhaber SZ, Bounameaux H. Direct oral anticoagulants in the treatment and long-term prevention of venous thrombo-embolism. *Eur Heart J* 2014;**35**:1836–43.
22. Verhamme P, Bounameaux H. Direct oral anticoagulants for acute venous thromboembolism: closing the circle? *Circulation* 2014;**129**:725–7.
23. Heit JA. The epidemiology of venous thromboembolism in the community. *Arterioscler Thromb Vasc Biol* 2008;**28**:370–2.
24. Piazza G, Goldhaber SZ. Acute pulmonary embolism: Part i: Epidemiology and diagnosis. *Circulation* 2006;**114**:e28–32.
25. Weitz JI, Quinlan DJ, Eikelboom JW. Periprocedural management and approach to bleeding in patients taking dabigatran. *Circulation* 2012;**126**:2428–32.
26. Marlu R, Hodaj E, Paris A, et al. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: A randomised crossover ex vivo study in healthy volunteers. *Thromb Haemost* 2012;**108**:217–224.
27. van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate--a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 2010;**103**:1116–27.

28. Siegal DM, Crowther MA. Acute management of bleeding in patients on novel oral anticoagulants. *Eur Heart J* 2013;**34**:489–98b.
29. Crowther M. A phase 2 randomized, double-blind, placebo-controlled trial demonstrating reversal of rivaroxaban-induced anticoagulation in healthy subjects by andexanet alfa (prt064445), an antidote for fxa inhibitors. Presented at: *American Society of Hematology Annual Meeting*; December 9, 2013; New Orleans, LA.
30. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: A randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011;**124**:1573–9.
31. Hickey M GM, Taljaard M, Aujnarain A, et al. Outcomes of urgent warfarin reversal with frozen plasma versus prothrombin complex concentrate in the emergency department. *Circulation* 2013;**128**:360–4.
32. Siegal D, Yudin J, Kaatz S, et al. Periprocedural heparin bridging in patients receiving vitamin K antagonists: Systematic review and meta-analysis of bleeding and thromboembolic rates. *Circulation* 2012;**126**:1630–9.
33. Eikelboom JW, Connolly SJ, Brueckmann M, et al. RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013;**369**:1206–14.
34. Jan Beyer-Westendorf VG, Kati Förster, Franziska Ebertz, et al. Peri-interventional management of novel oral anticoagulants in daily care: Results from the prospective dresden noac registry. *Eur Heart J* 2014;**35**:1888–9.
35. Sime G. Dental management of patients taking oral anticoagulant drugs. April 2012. Available at: www.abaoms.org.uk/docs/Dental_management_anticoagulants2013.doc (accessed August 2013).
36. Griffiths M, Scully C. New anticoagulants. *Br Dent J* 2012;**213**:96.
37. van Diermen DE, van der Waal I, Hoogstraten J. Management recommendations for invasive dental treatment in patients using oral antithrombotic medication,including novel oral anticoagulants. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013;**116**:709–16.
38. Wysokinski WE, McBane RD, 2nd. Periprocedural bridging management of anticoagulation. *Circulation* 2012;126:486–90.
39. O'Connell JE, Stasson LF. New oral anticoagulants and their implications for dental patients. *J Ir Dent Assoc* 2014;**60**:137–43.
40. Healey JS, Eikelboom J, Douketis J, et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: Results from the randomized evaluation of long-term anticoagulation therapy (RE-LY) randomized trial. *Circulation* 2012;**126**:343–8.
41. Patel MR, Hellkamp AS, Lokhnygina Y, et al. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: analysis from the ROCKET AF trial (rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin k antagonism for prevention of stroke and embolism trial in atrial fibrillation). *J Am Coll Cardiol* 2013;**61**:651–8.
42. Kernan WN, Ovbiagele B, Black HR, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;**45**:2160–236.
43. Sie P, Samama CM, Godier A, et al. Surgery and invasive procedures in patients on long-term treatment with direct oral anticoagulants: Thrombin or factor-Xa inhibitors. Recommendations of the working group on perioperative haemostasis and the French study group on thrombosis and haemostasis. *Arch Cardiovasc Dis* 2011;**104**:669–76.
44. Katritsis D, Gersh BJ, Camm AJ. In: *Clinical Cardiology: Current Practice Guidelines. Oxford, UK:* Oxford University Press, 2013;417.