Investigation into Patients treated in an Oral and Maxillofacial Unit between 2012 and 2014, who were taking the Novel Anticoagulants

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What this paper adds:

This paper, which is derived from an MSc project, provides insight into the number of patients taking NOACs shortly after their introduction to clinical practice. It explains their mechanism and considerations for surgical management of patients taking them compared to, and contrasted with, warfarin. These aspects are applicable to all surgical disciplines that may have concerns over the management of the increasing numbers of patients on NOACs.

Abstract

Objective: To determine the risk of bleeding in patients taking the newer (or novel) oral anticoagulants (NOACs) compared to warfarin after surgical treatment in the Oral and Maxillofacial Department of a district general hospital in the south of England. In particular, the incidence of NOACs and whether or not local measures were sufficient in managing post-operative bleeding.

Methods: A retrospective study of 249 records of anticoagulated patients between 1st January 2012 and 31st December 2014 at a district general hospital. Age, gender, type of anticoagulant taken, surgical procedure, clotting tests and prolonged bleeding episodes were recorded.

Results: Out of 249 patients only 7 (3%) took NOACs and 242/249 (97%) took warfarin. The ratio of patients on NOACs: warfarin was 1:35. The age range of the 249 patients was 27-94 years, with a mean age of 76 years. The male: female ratio was 2.04:1 (167 males, 82 females). There were 24 (8%) episodes of prolonged bleeding, all of which occurred within 7 days post-operatively and affected patients taking warfarin. Thirteen (54%) episodes of prolonged bleeding were after skin procedures, 10 (42%) after hard tissue surgery and (4%) after mucosal surgery. There was variable documentation of International Normalised Ratio (INR) scores in the patient's notes, and no documentation of creatinine clearance (CrCl) in patients taking NOACs.

Conclusions: NOACs were infrequently encountered in patients treated in the OMFS during the three year period,

probably reflecting the recent introduction of these drugs at the time of the study. None of the patients that took NOACs suffered post-operative bleeding. Further research on the importance of CrCl in managing patients on NOACs would be valuable.

Introduction: Since 2012, when they were approved by the National Institute for Clinical Excellence (NICE), a rise in the prescription of the novel or newer anticoagulants (NOACs) has been predicted, with the eventual replacement of warfarin (Griffiths and Scully, 2012). The NOACs approved by NICE include Dabigatran, Rivaroxaban, Edoxaban and Apixaban. They are licensed for use in the prevention of stroke and systemic embolism in non-valvular atrial fibrillation (AF). Although there have been reports of prolonged bleeding following dental extraction in patients on NOACs (Breik *et al.,* 2014), the frequency of this problem after maxillofacial surgery is unknown.

The British National Formulary (2017) states that warfarin costs on average 3p per day for a 5mg dose, whereas the price of NOACs ranges from £1.70-£2.95 per day. A one year supply of warfarin costs £11, compared to £634 for Rivaroxaban. In the long term, systematic reviews show NOACs are cost effective for stroke prevention in patients with non-valvular AF (Ferreira and Mirco, 2015). However, Janzic and Kos (2015) stressed that this is only the case if warfarin anticoagulant control is sub-optimal.

There is no routine coagulation monitoring of NOACs, since clotting screens and the International Normalised Ratio (INR) are of little practical use. Instead, the manufacturer states that surgical interventions may require temporary discontinuation of the drug (Pradaxa, 2015) based on a calculation of the creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR). These values reflect the patient's renal function, an assessment dentists in primary care are not in a position to make. Furthermore, at present there is only a licensed reversal agent for one NOAC (Dabigatran) (National Institute for Health and Clinical Excellence, 2016).

There are varying guidelines on anticoagulants, recommended by a variety of bodies; some are relevant to all surgical procedures while others specifically relate to dental procedures. The Scottish Dental Clinical Effectiveness Programme (SDCEP) guidance on NOACs is intended for dentists in primary care. It divides dental procedures into high and low risk (SDCEP, 2015). The guidance recommends lower risk procedures be managed with local measures alone, whereas higher risk procedures require alteration of the medication regime. A subsequent study by Green *et al.,* (2016) agreed with this. The guidance states that low risk procedures, such as an intra-oral biopsy or simple dental extraction, should be managed with pressure, haemostatic agents, suturing and tranexamic acid mouthwash. Patients undergoing high risk procedures, such as multiple extractions, local mucosal flaps and wide local excision of a tumour or salivary gland surgery should have the NOAC stopped pre-operatively. However, Gonsalves, Pruthi and Patnaik (2013) advised that all patients should have their NOAC stopped for all elective surgical procedures of standard bleeding risk. In a patient with a normal CrCl this would be for 48 hours pre-operatively for Dabigatran and 24 hours pre-operatively for Rivaroxaban or Apixaban. In a review of NOACs aimed specifically at dental practitioners, Elad *et al.,* (2016) suggested guidance similar to that of the SDCEP guidance.

Unfortunately, the existing advice is not as clear as it could be. Manufacturers suggest missing or delaying a NOAC dose prior to all surgical procedures and emphasise the importance of using renal function as the guide (Pradaxa, 2015). The SDCEP guidance agrees with this for high risk procedures in a dental setting and doesn't suggest the practicalities of considering renal function in primary care (SDCEP, 2015). The questions remain as to how guidelines intended for all surgery pertain to Oral Maxillofacial Surgery (OMFS), and how crucial renal function is. Inevitably therefore, the number of referrals of patients taking NOACs to OMFS units will rise as their use increases. This study aimed to determine the number of anti-coagulated patients seen in the OMFS department of one District General Hospital in the South of England, who were taking NOACs during the three years after their introduction, and to compare their management and rate of post-operative complications with patients taking the more traditional anticoagulant warfarin.

Methods: This was a retrospective study of the records of anti-coagulated patients treated between 1st January 2012 and 31st December 2014 in the OMFS department of the Royal Surrey County Hospital, Guildford, Surrey. The study was approved by the Trust's Research & Development Board, and the Ethics Committee of the University of Kent. The patients' demographic details and prescribed anticoagulant were recorded.

The sample consisted of all OMFS patients taking an anticoagulant who had been treated surgically during the three-year period. The sample size of 433 was obtained via the hospital's coding department and data were collected from case notes. A pro forma that had previously been piloted was used to ensure consistent data collection.

The surgical procedures had been performed under either general or local anaesthesia, and were categorised as 'Skin or Hard tissue' or 'Mucosal'. The wounds in skin surgeries were categorised as requiring 'primary closure', 'local flap' or 'graft' reconstruction. 'Hard tissue' procedures included dentoalveolar surgery and extractions. 'Mucosal' procedures were intra-oral biopsies.

Patients scheduled for a major oncological resection were excluded because the extent of the procedure was more likely to cause post-operative complications compared with patients undergoing relatively minor surgery. Patients taking anti-platelet medication only were also excluded.

Results: Data on all 433 procedures were collected. For the reasons set out in Table 1, 113 of 362 patients were excluded leaving a sample of 319 procedures, carried out on a total of 249 patients with an age range 27- 94 years (mean 76, 167 males, 82 females).

Procedures performed

Out of 319 surgical procedures performed, 149 (47%) were skin based, 142 (44%) hard tissue and 28 (9%) mucosal. Of the 149 skin procedures, 122 (82%) were carried out with primary closure of the wound, 19 (13%) required a local flap and 8 (5%) a graft to achieve wound closure. In 14 (10%) of the hard tissue patients that presented with bleeding, the tooth sockets were not packed or sutured. None of the patients who only had a haemostatic pack placed in the extraction socket (i.e. no suturing) attended with bleeding.

Prolonged bleeding episodes

In total, there were 24 (8%) prolonged post-operative bleeding episodes out of the 319 procedures carried out.

Number of patients	Reason for exclusion
27	**No surgical procedure carried out** (did not attend, no treatment required)
76	**Not taking an oral anticoagulant** (48 taking an anti-platelet only)
6	**Not treated by OMFS**
4	**Notes incomplete/unavailable**
TOTAL: 113	

Table 1: Excluded Data

Patients on NOACs

In the three year period only seven patients (2.8%), from the total of 249, were taking NOACs, compared with 242 (97.2%) on warfarin (ratio of NOAC : warfarin 1:35). The seven patients underwent 11 surgical procedures (Table 2).

No patients taking NOACs were seen in 2012, the first of the seven patients presented in January 2013, two more presented in the same year and the remaining four in 2014. Twenty-four (7.5%) of the 319 episodes were followed by prolonged bleeding; all of which occurred in patients taking warfarin. There was no recorded documentation of CrCl or eGFR in patients taking NOACs.

All affected patients were taking warfarin. Their age range was 55-92 years, with a mean age of 81 years. Fourteen (58%) of those affected were male and 10 (42%) were female. Thirteen took place after skin procedures (9% of all skin procedures). Ten were after hard tissue surgery (7% of all hard tissue procedures). Only one patient bled after intraoral mucosal surgery (4% of all mucosal procedures).

Of the 13 patients who bled after skin surgery, seven had primary closure of a wound, four had a local flap and three needed a graft. Therefore, 21% of all patients who had a local flap and 38% of patients who had a graft procedure experienced prolonged bleeding. Two of the 24 patients who bled after skin surgery were taking anti-platelet medication as well as an anticoagulant.

Patient	Procedure	Age+ Gender	NOAC Taken	Date of Procedure	Surgical Procedure	Clotting Test
1	1	87 M	Rivaroxaban	12/01/13	Hard tissue	None
	2			27/10/14	Hard tissue	None
	3			03/12/14	Hard tissue	None
	4			17/12/14	Hard tissue	None
2	5	85 M	Dabigatran	14/04/13	Skin	Clotting screen (details not specified in patient's documentation)
	6			19/08/13	Hard tissue	None
3	7	60 F	Rivaroxaban	16/04/13	Mucosal	INR 2.1
4	8	83 M	Dabigatran	25/04/14	Skin	INR 1.1
5	9	69 M	Rivaroxaban	15/09/14	Skin	None
6	10	77 F	Dabigatran	05/11/14	Hard tissue	None
7	11	91 F	Rivaroxaban	09/12/14	Skin	INR 2

Table 2: Patients taking NOACs

Of the 10 patients who had hard tissue surgery and bled, eight had had a dental extraction, one had had closure of an oro-antral communication and one had undergone drainage of an intra-oral haematoma. In six of the eight episodes of prolonged bleeding presenting to hospital after dental extractions, GDPs had carried out the procedure in a dental practice setting. Three of the six patients who bled after dental extractions by GDPs in dental practice, did not have their tooth sockets packed or sutured.

The majority (38%) of post-operative bleeding episodes occurred on the day of surgery. The risk of bleeding reduced with time after surgery.

INR

With regard to the 24 patients who experienced prolonged bleeding after a surgical procedure, for only 11 was an INR available on the day of the operation. These INR scores ranged from 1.8-2.9. There was no documented record of an INR being taken in 53 (17%) of the 308 patients who were taking warfarin.

If the surgery had been carried out by a GDP, an INR value was taken when the patient attended the hospital for post-operative bleeding. For those patients who had undergone surgery in the hospital, an INR value was documented in the notes 2- 6 days post-operatively. These ranged from 2.2-5.1.

Of the 23 patients who had an INR documented within 6 days post-operatively, only three had an INR value over 4.0 (4.4, 5.1 and 5.1). They were all over the age of 85 years. Two had simple excision of skin lesions with primary closure, the other had had a dental extraction performed by a GDP. Twenty-three of the 24 bleeding episodes were managed with local measures. One patient, who had undergone a local flap procedure on the cheek, was admitted overnight and prescribed prothrombin complex concentrate to reverse the effects of warfarin. Nine patients were admitted for social reasons, such as unavailable hospital transport or for INR control. Six patients stayed overnight and three patients of the nine admitted stayed for a period of two to five days

Given the mismatch between numbers of patients taking NOACs and warfarin, no statistical analysis was performed.

Discussion: In this study, the number of patients on NOACs was small, probably because the period of data collection was shortly after NOACs were first approved. However, possible system errors also need to be considered. Coding of these patients may have been incorrect due to the coders being unfamiliar with NOACs, which might have therefore been recorded incorrectly as other (e.g. anti-platelet) medication. A prospective study would provide a more accurate method of data collection. Such a design would enable all patients on anticoagulants to be recorded and monitored pre- and post-operatively. Thus, data regarding post-operative haemorrhage would be gathered reliably and errors in coding and patient records would be avoided.

It may be some years before patients on NOACs present to OMFS departments in significant numbers, as warfarin has been prescribed for decades and is still widely used. The ratio of patients on NOACs: warfarin was 1:35, which is much lower than the value of 1:6 reported in a prospective regional audit performed in the same hospital, but more recently than the present study (Din and Coombs, 2015).

Out of the 11 procedures performed on the seven patients taking NOACs, seven were carried out on patients taking Rivaroxaban; consistent with the fact that Rivaroxaban has the most licensed indications for use of all the NOACs. The other four procedures were carried out on patients taking Dabigatran, with no patients taking Apixaban. This reflects the chronological order for the licensing of NOACs. In addition, Apixaban is only licensed for the treatment or prevention of deep vein thrombosis (DVT) or pulmonary embolism (PE), which is less common than AF (Cushman, 2007). The incidence of DVT or PE is 1 per 1000 adults a year (Cushman, 2007) compared to 6.7 per 100 adults a year for AF (Martinez *et al.,* 2015). There were more than twice as many males on anticoagulants as females, and a mean age of patients of 76 years, which is consistent with AF being more prevalent in older men.

More extensive procedures, in particular, local flap surgery and grafting after the removal of skin lesions, had a higher risk of bleeding. Eichhorn *et al.,* (2014) reported that the bleeding risk in patients on warfarin is greater (6%) than those not taking an anticoagulant (3%), when undergoing cutaneous surgery in the head and neck region. They also reported that procedures on the nose had a much greater risk of bleeding (21%), possibly because reconstruction at this site after excision of the lesion invariably requires a flap or graft. The incidence of prolonged bleeding in the anticoagulated patients reviewed in this study was 8% (24 out of 319 procedures), similar to the 7% incidence reported in a cohort of 150 patients (who had undergone dental extractions) by Salam, Yusuf and Milosevic (2007). Local measures were sufficient to manage the patients in the Salam study. Bajkin *et al.,* (2015) evaluated risk factors for bleeding after oral surgery in patients who continued using an oral anticoagulant. There was a 6% (7/125) risk of bleeding, with the greatest likelihood of haemorrhage being in patients with an INR over 3.5, who were undergoing a high risk procedure.

INR could not be accurately evaluated in the present study because of incomplete recording of this datum in the patients' notes. However, higher risk procedures (such as skin grafting) did produce a higher incidence of post-operative bleeding. In the study by Bajkin *et al.,* (2015), patients who had a high risk procedure with an INR 2-3.5 had a 13.2% less chance of bleeding compared to those having a high risk procedure with an INR of more than or equal to 3.5. Therefore, level of anticoagulation is important in determining the chance of bleeding. With NOACs, theoretically, this should be less of an issue as patients are either anti-coagulated or not. In a patient with normal renal function, NOACs should be cleared within 24-48 hours (Green *et al.,* 2016).

Seventeen percent of patients on warfarin did not have an INR documented in their hospital notes on the day of surgery. There is no formal guidance or hospital protocol for this, but from a legal point of view, if a patient were to

have a major bleed, a clearly documented INR would be extremely important. CrCl and eGFR were not recorded in any of the patients taking NOACs. Reference was not made to this at all in the notes. This perhaps reflects a lack of understanding of NOACs, the assumption being made that NOACs (like warfarin) are monitored by INR.

The number of patients presenting with prolonged bleeding episodes decreased with time after the surgery. Thus, most bleeding was due to reactionary haemorrhage, which occurs within 24 hours, as a result of the gradually reducing vasoconstriction as the local anaesthetic is metabolised. Secondary haemorrhage is usually a sign of infection and develops seven to ten days post-operatively (TeachMeSurgery, 2016) and would therefore appear to have been responsible for none of the 24 bleeding episodes. In patients who take anticoagulants, clot formation is delayed by prevention of the coagulation cascade. Therefore, bleeding is most likely to take place in the early stages of wound healing, which correlates with the results reported in the current study. One patient had two episodes of bleeding post-operatively on days 3 and 7 after a skin procedure. Another patient bled after he had a silk suture removed by his dentist five days after a tooth extraction.

Dental practitioners in dental practice may not have the understanding or resources to pack and suture sockets, as can be seen with three of the six patients who presented to the hospital bleeding after dental extractions where their tooth sockets were not packed or sutured. Clearer guidance on the importance of local measures for patients at risk of bleeding may need to be distributed at a primary care level, particularly if there is an increase in the number of patients on the relatively unknown NOACs.

Local measures, simple packing and suturing of tooth sockets or pressure and suturing of wounds, were sufficient to control prolonged bleeding episodes, with the exception of a 92-year-old patient on warfarin for AF who was given prothrombin complex concentrate. Insufficient data were collected on withdrawing an anticoagulant pre-operatively to draw any conclusions. Three patients of the nine admitted stayed for a period of two to five days for INR control or because of social issues. Patients who bled were in the older age group (65-92 years) and thus overnight stays may have been due to concerns about the safety of sending them home in the middle of the night.

Concurrent anti-platelet medication may have contributed to bleeding in two of the 24 patients who bled. In a study of over 10,000 patients taking an antiplatelet, as well as warfarin for AF, increased major bleeding rates ranged from 1.3% to 1.9%. The mean age of these patients was 77 years old (Shireman, 2004).

Boehringer Ingelheim is the pharmaceutical company that developed Dabigatran. Data from the RE-LY trial (Connolly *et al.,* 2009) was crucial in leading to the successful licensing and marketing of the drug. It showed that Dabigatran had superior efficacy when compared with warfarin and was safe to use, in a large multicentre trial involving 18,113 patients. Data from the study showed that stroke occurred less in the group treated with Dabigatran 150mg twice-daily. However, flaws in the RE-LY trial have become apparent. Bias, such as clinicians and trial patients knowing which drug was being given, and withholding of analyses occurred. These problems were reported in the British Medical Journal (Cohen, 2014). The drug was marketed as not needing an antidote or any monitoring. However, monitoring drug plasma levels could improve safety (Cohen, 2014). The claim that the drug does not need monitoring has been important in the cost benefit evaluations by NICE and has been a paramount factor in the uptake of the drug (Cohen, 2014, Kaba *et al.,* 2014).

Boehringer Ingelheim found that if the plasma levels of the drug were measured and the dose was adjusted accordingly, major bleeds could be reduced by 30-40% compared with well controlled warfarin (Breik *et al.,* 2014). Ischaemic stroke and bleeding outcomes were therefore correlated with Dabigatran plasma concentrations. Age was the most important covariate (Reilly *et al.,* 2014). Despite this there has been no recommended change to clinical practice (Sime, 2016).

Conclusions: In conclusion, within the limitations of the study, the data presented provide a snapshot suggesting NOACs were rarely encountered in the OMFS department where the study took place during the first three years after they were licensed for use. However, in the future, this may change as prescribing of NOACs increases. Whilst none of the prolonged bleeding episodes involved patients on NOACs, it cannot be assumed that patients on NOACs are at reduced risk of post-operative haemorrhage compared with patients on warfarin. The absence of CrCl or eGFR assessment in hospital documentation of the seven patients on NOACs was notable, since effective renal function is necessary to ensure the drug is removed after cessation. Clearly OMFS units will need to adopt the changes in clinical practice which are necessary when managing patients on NOACs, and guidance for clinicians planning dental and oral surgery is gradually appearing. The following recommendations are suggested for patients taking NOACs based on the hospital unit described (Image 1):

Management of patients on NOACs

- Timing of treatment should be as temporally distant from the last dose of NOAC as possible.
- Elderly patients with co-morbidities, who may be at a higher risk of bleeding, need particular consideration.
- Patients on concurrent antiplatelet medications should be considered due to possible increased bleeding due to decreased clotting
- Consideration of CrCl or eGFR when a patient on a NOAC presents with bleeding.
- More extensive surgical procedures, such as reconstructive skin surgery, may require more detailed treatment planning.

Image 1: recommendations for patients taking NOACs

References:

Bajkin, B., Vujkov, S., Milekic, B. and Vuckovic, B. (2015) 'Risk factors for bleeding after oral surgery in patients who continued using oral anticoagulant therapy', *The Journal of the American Dental Association,* 146, pp. 75-381.

Breik O., Cheng A., Sambrook P. and Goss A. (2014) 'Protocol in managing oral surgical patients taking dabigatran', *Australian Dental Journal,* 59, pp. 296–301.

British National Formulary [Online] (2017) Available at: https://www.medicinescomplete.com/about/ (Accessed 2 November 2017).

Cohen, D. (2014) 'Dabigatran: how the drug company withheld important analyses', *British Medical Journal*, 349, pp. 4670-4670.

Connolly, S., Ezekowitz, M., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A., Pogue, J., Reilly, P., Themeles, E., Varrone, J., Wang, S., Alings, M., Xavier, D., Zhu, J., Diaz, R., Lewis, B., Darius, H., Diener, H., Joyner, C. and Wallentin, L. (2009) 'Dabigatran versus Warfarin in Patients with Atrial Fibrillation', *New England Journal of Medicine*, 361, pp. 1139-1151.

Cushman, M. (2007) 'Epidemiology and Risk Factors for Venous Thrombosis', *Seminars in Hematology*, 44, pp. 62-69.

Din, N. and Combes, J. (2015) *Regional audit on the management of patients taking anticoagulants that were treated by oral and maxillofacial surgery*, Regional Audit Day, Royal Surrey County Hospital, Guildford.

Eichhorn, W., Barsukov, E., Al-Dam, A., Gröbe, A., Smeets, R., Eichhorn, M., Heiland, M., Kluwe, L. and Blessmann, M. (2014) 'Postoperative bleeding risk for cutaneous surgery in the head and neck region with continued phenprocoumon therapy', *Journal of Cranio-Maxillofacial Surgery*, 42, pp. 608-611.

Elad S, Marshall J, Meyerowitz C. and Connolly G. (2016) 'Novel anticoagulants: general overview and practical considerations for dental practitioners', *Oral Diseases*, 22, pp. 23–32.

Ferreira, J. and Mirco, A. (2015) 'Revisão sistemática das análises custo-efetividade dos novos anticoagulantes orais na prevenção do acidente vascular cerebral na fibrilhação auricular', *Revista Portuguesa de Cardiologia*, 34, pp. 179-191.

Gonsalves WI, Pruthi RK. and Patnaik MM. (2013) 'The new oral anticoagulants in clinical practice', *Mayo Clinic Procedings,* 88, pp. 495–511.

Green B, Mendes R, van der Valk R. and Brennan P. (2016) 'Novel anticoagulants - an update on the latest developments and management for clinicians treating patients on these drugs', *Journal of Oral Pathology and Medicine,* 45, pp. 551-556.

Griffiths M. and Scully C. (2012) 'New anticoagulants', *British Dental Journal, 2*13(3). doi:10.1038/sj.bdj.**2012**.674.

Janzic, A. and Kos, M. (2014) 'Cost Effectiveness of Novel Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation Depending on the Quality of Warfarin Anticoagulation Control', *PharmacoEconomics*, 33, pp. 395-408.

Kaba, R., Ara, F., Ward, D. and Emanuel, S. (2014) 'The Dabigatran debate', *Global Cardiology Science and Practice,* 3(41), pp.1-3.

Martinez, C., Katholing, A., Wallenhorst, C., Granziera, S., Cohen, A. and Freedman, S. (2015) 'Increasing incidence of non-valvular atrial fibrillation in the UK from 2001 to 2013', *Heart*, 101, pp. 1748-1754

National Institute for Health and Clinical Excellence (2016) 'Reversal of the anticoagulant effect of dabigatran: idarucizumab' | key-points-from-the-evidence | Advice | NICE, Available at: https://www.nice.org.uk/advice/esnm73/chapter/key-points-from-the evidence (accessed 27/11/2016).

Pradaxa (2015) 'Prescribers guide 2015', Available at: http://products.boehringer-ingelheim.com/pradaxa/sites/default/files/Prescriber_guide.pdf (Accessed: 10 May 2016).

Reilly, P., Lehr, T., Haertter, S., Connolly, S., Yusuf, S., Eikelboom, J., Ezekowitz, M., Nehmiz, G., Wang, S. and

Wallentin, L. (2014) 'The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients', *Journal of the American College of Cardiology,* 63, pp. 321-328.
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Salam, S., Yusuf, H. and Milosevic, A. (2007) 'Bleeding after dental extractions in patients taking warfarin', *British Journal of Oral and Maxillofacial Surgery,* 45, pp. 463-466.

Scottish Dental Clinical Effectiveness Programme (2015) 'Management of dental patients taking anticoagulants or antiplatelet drugs', Available at: http://www.sdcep.org.uk/wp-content/uploads/2015/09/SDCEP-Anticoagulants-Guidance.pdf (Accessed: 1st February 2016).

Shireman, T. (2004) 'Combined Anticoagulant-Antiplatelet Use and Major Bleeding Events in Elderly Atrial Fibrillation Patients', *Stroke*; 35, pp. 2362-2367.

Sime G. (2016) 'Dental Management of Patients Taking Anticoagulant Drugs Outside a General Hospital Setting', Available at: http://www.sigwales.org/wp-content/uploads/dental-management-of-patients-taking-anticoagulant-drugs-outside-a-general-hospital-setting.pdf (Accessed 13 May 2016).

TeachMeSurgery. (2016) 'Post-Operative Haemorrhage - Classification - Management – TeachMeSurgery', Available at: http://teachmesurgery.com/post-operative/early/haemorrhage/ (Accessed 22 May 2016).