

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Evaluation of post-extraction bleeding incidences comparing patients receiving and not receiving warfarin therapy by a crosssectional multicenter observational study
<b>AUTHORS</b>	Iwabuchi, Hiroshi; Imai, Yutaka; Asanami, Soichiro; Shirakawa, Masayori; Yamane, Gen-yuki; Ogiuchi, Hideki; Kurashina, Kenji; Miyata, Masaru; Nakao, Hiroyuki; Imai, Hirohisa

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Michael J. Wahl Christiana Care Health System  None declared
<b>REVIEW RETURNED</b>	08-Jun-2014

<b>GENERAL COMMENTS</b>	<p>A discussion of previous studies of postextraction bleeding incidence in anticoagulated versus non-anticoagulated patients would be helpful. It would also be helpful to have a discussion of the risks with anticoagulation interruption for dental extractions, including appropriate references.</p> <p>The authors state on page 4, "However, no studies to date have investigated the differences in post-extraction bleeding incidences between patients receiving and not receiving warfarin." This statement is at best misleading as there have been at least 10 controlled studies that have compared bleeding after dental extractions in anticoagulated patients versus patients with normal or near-normal coagulation (anticoagulation reduced or withdrawn):</p> <p>Al-Mubarak S, Al-Ali N, Abou Rass M et al. Evaluation of dental extractions, suturing and INR on postoperative bleeding of patients maintained on oral anticoagulant therapy. <i>Br Dent J</i> 2007;203:E15. <a href="http://www.nature.com/bdj/journal/v203/n7/full/095625a.html">http://www.nature.com/bdj/journal/v203/n7/full/095625a.html</a> Accessed: June 4, 2014. More if INR&gt;3.5 but not if ≤3.0.</p> <p>Bacci C, Berengo M, Favero L, Zanon E. Safety of dental implant surgery in patients undergoing anticoagulation therapy: a prospective case-control study. <i>Clin Oral Implants Res</i> 2011;22:151-6. Incidence of bleeding the same in both groups.</p> <p>Bailey BMW, Fordyce AM. Complications of dental extractions in patients receiving warfarin anti-coagulant therapy: a controlled clinical trial. <i>Br Dent J</i> 1983;155:308-10. Slightly more late bleeding, easily controlled.</p> <p>Borea G, Montebugnoli L, Capuzzi P, Magelli C. Tranexamic acid as a mouthwash in anti-coagulant-treated patients undergoing oral surgery: an alternative method to discontinuing anticoagulant</p>
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	<p>therapy. Oral Surg Oral Med Oral Pathol 1993;75:29-31. No significant difference.</p> <p>Campbell JH, Alvarado F, Murray R A. Anticoagulation and minor oral surgery: should the anticoagulation regimen be altered? J Oral Maxillofac Surg 2000; 58: 131-135. No difference in blood loss.</p> <p>Cannon PD, Dharmar VT. Minor oral surgical procedures in patients on oral anticoagulants – a controlled study. Austral Dent J 2003;48(2):115-8. No difference.</p> <p>Devani P, Lavery M, Howell CJT. Dental extractions in patients on warfarin: is alteration of anticoagulation regime necessary? Br J Oral Maxillofac Surg 1998;36:107-11. No difference.</p> <p>Evans IL, Sayers MS, Gibbons AJ, et al. Can warfarin be continued during dental extraction? Results of a randomized controlled trial. Br J Oral Maxillofac Surg 2002;40(3):248-52.  <a href="http://www.farmaconline.ufg.br/pgrad/2_A.pdf">http://www.farmaconline.ufg.br/pgrad/2_A.pdf</a> Accessed: June 4, 2014. Higher incidence in warfarin group, but no significant difference.</p> <p>McIntyre H. Management, during dental surgery of patients on anticoagulants. Lancet 1966;2:99-100. No difference.</p> <p>Sammartino G, Maenzi G, Miro A et al. Local delivery of the hemostatic agent tranexamic acid in chronically anticoagulated patients. J Craniofac Surg 2012;23(6):e648-52. No significant bleeding problems.</p> <p>Saour JN, Ali HA, Mammo LARF, Sieck JO. Dental procedures in patients receiving oral anticoagulation therapy. J Heart Valve Dis 1994;3:315-7. More bleeding in withdrawal group, but no serious bleeding problems in either.</p> <p>In some of these studies, there was a slight increase in bleeding in the anticoagulation group, in some there were no differences, and in at least one there was a slight increase in bleeding in the anticoagulation withdrawal group, but in each study, there was no significant difference in bleeding incidence between the two groups.</p> <p>The authors say that the bleeding incidence data were collected by tooth, not by patient. It would be helpful to present these data by patient in addition to tooth. In other words, the reader should be informed how many patients suffered postextraction bleeding and how many did not, not just how many extraction sockets bled and how many did not.</p> <p>There is little or no discussion of the serious embolic risks involved with anticoagulation withdrawal. Since 2000, there have been several reports of serious embolic complications and/or death after anticoagulation interruption for dental procedures, and in the surviving patients, there may have been permanent disabilities. On the other hand, I am unaware of a single case in the literature of a death or long-term disability from a bleeding complication postextraction in an anticoagulated patient.</p> <p>Akopov SE, Suzuki S, Fredieu A et al. Withdrawal of warfarin prior to a surgical procedure: time to follow the guidelines? Cerebrovasc Dis 2005;19(5):337-42.</p>
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	<p>Alexander R. More nonsense. NY State Dent J 2003;69(4):11.  Broderick JP, Bonomo JB, Kissela BM et al. Withdrawal of antithrombotic agents and its impact on ischemic stroke occurrence. Stroke 2011;42(9):2509-14.  <a href="http://stroke.ahajournals.org/content/42/9/2509.full.pdf+html">http://stroke.ahajournals.org/content/42/9/2509.full.pdf+html</a>  Accessed: February 27, 2013.</p> <p>Garcia DA, Regan S, Henault LE et al. Risk of thromboembolism with short-term interruption of warfarin therapy. Arch Intern Med 2008;168(1):63-9.  <a href="http://archinte.jamanetwork.com/article.aspx?articleid=413677">http://archinte.jamanetwork.com/article.aspx?articleid=413677</a>  Accessed: February 23, 2013.</p> <p>Yasaka M, Naritomi H, Minematsu K. Ischemic stroke associated with brief cessation of warfarin. [Letter.] Thromb Res 2006;118(2):290-3.</p> <p>Dental extractions in anticoagulated patients does not occur in a vacuum. Clinicians need to weigh the potential risks and benefits of continuing versus interrupting anticoagulation for dental extractions. Therefore, somewhere in the manuscript, the authors need to discuss the potential risks of anticoagulation interruption for dental procedures.</p> <p>On page 11 of the manuscript, the authors state, “[C]linical experience of the operator and the capability of the facility in performing advanced care should also be taken into consideration, instead of solely relying on the PT-INR values when planning the procedure.” The authors provide no evidence for this statement. Also, the statement implies that dental extraction in anticoagulated patients is a type of “advanced care.” Previous studies have shown that dental extractions have been safely performed by both general dentists and oral surgeons and have not shown that clinical experience of the operator is an important safety factor. Dental extractions in such patients can be done routinely without special precautions or training. For the most part, dental extractions on therapeutically anticoagulated patients can be done in the same manner as on normally coagulated patients. When doing dental extractions in any patient, the operator should be familiar with local measures for hemostasis. If there is evidence to the contrary, the authors should document it.</p> <p>The authors conclude on page 14 that “patients whose PT-INR values are close to 3.0 or who have other risk factors for uncontrollable bleeding should undergo dental extraction under the management of an oral surgeon specifying [sic] in invasive dental procedures or at a dental facility that has access to a hospital that could provide advanced medical care in the event of uncontrollable bleeding.” But on page 9, the authors state that “all bleeding episodes were controlled by local hemostatic interventions.” The authors’ conclusion that specialized doctors and/or facilities are needed for extractions in anticoagulated patients is inconsistent with their results that all bleeding episodes were controlled with local measures.</p>
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<b>REVIEWER</b>	Dr. Ozgur Erdogan Cukurova University Turkey  'None declared'
<b>REVIEW RETURNED</b>	14-Jun-2014

<b>GENERAL COMMENTS</b>	<p>The manuscript entitled “Evaluation of post-extraction bleeding incidences comparing patients receiving and not receiving warfarin therapy by a crosssectional multicenter observational study” is a multicenter clinical study evaluating the incidence of postoperative bleeding events after simple tooth extraction. The data presented here are obviously valuable since the study reflects the results of a relatively large sample size. However I have several concerns about this study. My biggest concern is its patient selection criteria and statistical evaluation method. From the patients and methods section I understand that all patients on warfarin treatment who undergo simple tooth extraction were included. There were no exclusion criteria for these patients and the effects of the cofactors were evaluated with multivariate analyses. What about the patients in the other group? How did the authors recruit these patients? Did this group consist of every patients undergoing simple extraction in the study centers? If yes I am impressed that all these patients accepted to participate in the study. There is a huge difference in the number of patients or cases between the two groups. The authors considered the tooth that has been extracted as the independent variable of the study. To my opinion it makes the evaluation method more complicated. There are comorbidities or demographic data, which depend on the patient factor, thus usually the patient is considered the independent variable in such studies. An expert statistical review may be needed to review its methodology. My other concerns follow below.</p> <p>The authors state in the introduction that “no studies to date have investigated the differences in post-extraction bleeding incidences between patients receiving and not receiving warfarin”. This statement is not accurate since a recent clinical study by Karsli et al. evaluated exactly this issue in their study. (Karsli ED, Erdogan Ö, Esen E, Acartürk E. Comparison of the effects of warfarin and heparin on bleeding caused by dental extraction: a clinical study. J Oral Maxillofac Surg. 2011 Oct;69(10):2500-7. doi: 10.1016/j.joms.2011.02.134.) I am surprised that the authors ignored this study, since a simple Pubmed search with “Warfarin and Dental Extraction” keywords would have retrieved this study.</p> <p>The INR values of patients receiving warfarin were measured within the 7 days prior the surgery. The INRs of such patients are usually measured on the same day of the surgery (in our clinics as well as in many clinics I know). INR values considered for this study may not reflect the actual values since 7 –day is long enough for this parameter to be varied. The authors addressed this drawback at the end of the discussion section. However, It could be highlighted in the results section as well.</p> <p>In the M&amp;M section the authors mention about the utilization of epinephrine as topical hemostatic agent to be used in the postoperative period. How did they apply epinephrine (concentration?) topically? Since patients on warfarin treatments are</p>
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	<p>usually presented with severe cardiac disease use of epinephrine might be arguable.</p> <p>I assume that the authors imply “inferior alveolar nerve block” anesthesia by saying “mandibular foramen conduction anesthesia”, which is a new term for me. I suggest using inferior alveolar nerve block instead as many readers as myself might not be familiar with this term. The authors consider application of block anesthesia as a risk factor, which is understandable. However they only concern about inferior alveolar nerve block but not the posterior superior alveolar (PSA) nerve block anesthesia, which is the most commonly nerve block technique associated with hemorrhagic events. As the authors included the maxillary molar teeth as well, they could have considered PSA block as a variant.</p> <p>The indications of warfarin use have not been addressed. If warfarin indications were also due to cerebral disease, history of a previous CVA in any of the patients should be mentioned.</p> <p>For patients, who are under great thromboembolism risk because of discontinuation of the anticoagulant therapy, bridging with heparin is another preoperative management method. This has not been discussed in the manuscript.</p>
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<b>REVIEWER</b>	<p>Susan Sutherland Sunnybrook Health Sciences Centre University of Toronto Canada</p> <p>None declared</p>
<b>REVIEW RETURNED</b>	17-Jun-2014

<b>GENERAL COMMENTS</b>	<p>There are two major problems with this study.</p> <p>1. In the warfarin group, the INR was done up to seven days before. In order to draw conclusions from the data, this is too long a time frame, as the INR at the time of the procedure is unknown.</p> <p>2. The unit of analysis was not the patient. Using individual teeth as the units of analyses gives multiple non-independent measurements per patient, inflates the sample size and may give spurious significance to the results. It is theoretically possible that all eighteen bleeding events in the warfarin group occurred in one patient, while the nine bleeding events in non warfarin patients occurred in nine separate patients. This would yield an equally striking but opposite result.</p>
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<b>REVIEWER</b>	<p>Ben BALEVI University of British Columbia, CANADA</p> <p>None that I know of</p>
<b>REVIEW RETURNED</b>	23-Jun-2014

<b>GENERAL COMMENTS</b>	<p>Summary of My understanding</p> <p>The clinical questions this study is trying to answer are ;</p> <p>Question #1</p>
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	<p>In adult patient slated for a simple dental extraction, will the warfarinized patient compare to the non-warfarinized patient result in more significant post – op bleeding events?</p> <p>Question 2 What factors place the warfarinized patient at risk of significant post – op [simple-dental-extraction] bleeding events?</p> <p>This is a multicentre study that assesses the extent post-op bleeding from the consecutive ( over 17 months) selection of 2,321 teeth from non-warfarinized patients with 496 teeth from patients receiving warfarin</p> <p>The study defines simple extraction as tooth removal without traumatizing the surrounding alveolar bone or elevating a mucoperiosteal flap.</p> <p>My concerns that need further explanation</p> <p>1. I believe the statement on page 4, line 14;... “However, a clinical study reported that embolism or thrombosis developed in approximately 1% of patients who discontinued warfarin prior to dental surgery, resulting in death in a large proportion of the affected patients.[1]” ... is inaccurate and should be removed or rephrased to represent current knowledge. .The authors are citing Wahl (1998) narrative review which summarized ( not a meta-analysis) the outcomes from selected papers. In my paper ( Balevi 2010) , I calculated the risk of a CVA when warfarin is withheld for 3 days to be only 0.059% which is far lower than that reported by Wahl’s flawed calculation. Also in a my response to a letter to the editor ( Balevi 2012) , I addressed that the 6 reported cases by Wahl(1998) and Miller (2012) of a CVA occurring when warfarin was withheld as not representative of what actually happens in dental practice and that extrapolating a cause-effect relationship in any of these cases is questionable (Balevi 2012 )</p> <p>References (1)Wahl MJ. Dental surgery in anticoagulated patients. Arch Intern Med 1998;158:1610-6. ... (2) Balevi B. Should warfarin be discontinued before a dental extraction? A decision-tree analysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:691–7.... (3) Balevi B should warfarin be discontinued before a dental extraction Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2012;113:150-152... (4) Miller C, Evidence does not support the discontinuation of warfarin before a dental extraction Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2012;113:148-149</p> <p>2. Were the Evaluators of Bleeding events blinded or not? If the evaluators were not blinded then there is a risk of over reporting a significant bleeding event in known warfarinized patients than in the non-warfarinized patient ( detection bias or confirmation bias.) This should be included as a limitation of this study as such a bias could skewing the differences in bleeding events between the two groups away from the truth.</p> <p>3. The fact that hemostasis was not necessarily managed consistently between each group may bias the results ( i.e., ascertainment or assessment bias). All warfarinized patients were</p>
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packed with gelfoam and sutured, but it was at the discretion of the operator if such methods were necessary for the patients not on warfarin. It has been reported that suturing may actually increase the risk of post-op bleeding by traumatizing the tissue around the extraction socket. ( Salam et al [2007], Al-Be,]lasy et al [2003] ). This may be something to address in the discussion as it may have over estimated the number of significant bleeding events in the warfarinized patient.

#### References

Salam S, Yusuf H, Milosevic A. Bleeding after dental extractions in patients taking warfarin. Br J Oral Maxillofac Surg 2007;45:463-6.

Al-Belasy FA, Amer MZ. Hemostatic effect of n-butyl-2-cyanoacrylate (histoacryl) glue in warfarin-treated patients undergoing oral surgery. J Oral Maxillofac Surg 2003;61:1405-9

4. The authors briefly discuss the issue of possible cluster Bias in the last sentence of the manuscript ; (p.13, line 39-45)

" However, multiple counts from the same patient may have biased the results."

The data is collected per tooth and not per patients. This is significant as it increase the possible risk of clustering many of the bleeding events to only a few people with multiple extraction at the same time. Therefore it is possible that someone had numerous teeth extracted at the same time resulting in essentially a more invasive procedure than just a simple extraction of a single tooth. I feel this a significant limitation of this study that I feels needs more discussion.

5. On page 7, The authors grade the extent of a bleeding event between 0-3. They subdivide continued bleeding event of 30 minutes after extraction as grade 2.1 and 2.2. It is not clear to me the difference between ‘ hemostasis longer than 30 minutes( i.e, Grade 2.1)’ and “ oozing from socket, ceased by wound compression only (grade 2.2)” . Also, please elaborate what is meant by bleeding required treatments other than wound compression (Grade 3). What other means ?

6. The authors report at absolute risk difference between the two group of 3.24% (95%CI 1.49, 4.99%) then in abstract ( p. 2 linen 41) and in manuscript (p.10 line 45) as the risk of post op bleeding in warfarinized patient to be 10 times greater than in the non-warfarinized patients. Although valid, I am not sure why this relative difference was not reported as a risk ratio statistic[i.e.,  $RR = (3.63/0.39) = 9.31$ ] or an odds ratio ( $OR = \{18/(496-18)\} / \{9/(2,321-9)\} = 9.69$ ] with their associated confidence interval. I think that RR is the correct statistics in this case since the population was quasi-randomly selected and assumed to be representative of the population.

7. In the conclusion (p.13, line 52) the authors exaggerate the absolute risk difference by reporting only the upper limit of its 95% confidence interval ( “approximately 5%”). However, the lower limit of the confidence interval is almost 1.5% ( quite close to the point of no difference). Considering the bias I have already identified I believe that it is very possible that the true risk difference is more

towards the left hand of the confidence interval than the right. So for the purpose of objectivity, it would be appropriate to report in the conclusion the mean difference ( i.e., “3.24%” ) or cite the range of the 95% confidence interval ( i.e., “between 1.5% to 5%”) and allow the reader to decide if this is clinically significant or not

8. I am a little confused how to interpret table 3 and 4. More specifically the interpretation of both univariate and multivariate analysis in this study .I understand , univariate analysis to examines only a single independent variable against the dependent variable ( which in this study is the risk of significant bleeding) , while multivariate analysis exams the effects of two more independent variable vs. the dependent variable at the same time. For example, the problem I have is interpreting in table 3 the “Univariate analysis of post-extraction bleeding events by potential risk factors’ for the independent variable” reports for a molar extract an OR=2.22 but in in table 4 ‘Multivariate analysis of post extraction bleeding by potential risk factors” the OR for the same independent variable is reported to be = 0.953. In table 3 I understand the extraction of a molar increase the risk to post-op bleeding by a factor on 2 but in table 4 the molar extraction slightly reduces the risk. (contradictory ?)Although this independent variable is not statistically significant ( i. p >0.05) it is confusing for me to interpret its clinical significance.

9. I have issue with the inference made in the following statements

Discussion Section - Page 13 lines 8- 19; First, we collected data of dental extraction cases performed only in institutions where care by one or more certified oral surgeons is available. This criterion was adopted to minimize the differences in skills of the operator. However, this criterion could have also resulted in lower-than-average post-extraction bleeding incidences for both warfarin and non-warfarin patients. There remains a reasonable possibility that the between-group differences would be higher if general dental clinics were included.

Conclusion Section- page 14 line 3-14; Warfarin receiving patients had a considerable risk for post-extraction bleeding, even if their PT-INR values did not exceed 3.0. This study suggest that patients whose PT-INR values are close to 3.0 or who have other risk factors for uncontrollable bleeding should undergo dental extraction under the management of an oral surgeon specifying in invasive dental procedures or at a dental facility that has access to a hospital that could provide advanced medical care in the event of uncontrollable bleeding.

Both these statement do not follow logically from the study nor is it intuitively reasonable to make such a stretch. . There is neither evidence in this study nor in the literature that I know of that an oral surgeon compare to a general dentist is less likely to cause or better manage a significant post-op simple dental extraction bleeding event in a warfarinized patient. Also the authors admit ( see final line of abstract p. 2 line 43 “... though absolute incidence was low in both groups) that the risk of significant bleeding from a simple extraction if low. Considering the limitation of the study, the inferences cannot be clinically justified and only comes across as self-serving to oral surgeons.

As you can tell from my comments # 8, due to my lack of expertise in this area, I am not sure about the use and interpretation of

**VERSION 1 – AUTHOR RESPONSE**

## Reviewer 1

1. A discussion of previous studies of postextraction bleeding incidence in anticoagulated versus non-anticoagulated patients would be helpful. It would also be helpful to have a discussion of the risks with anticoagulation interruption for dental extractions, including appropriate references. The authors state on page 4, "However, no studies to date have investigated the differences in post-extraction bleeding incidences between patients receiving and not receiving warfarin." This statement is at best misleading as there have been at least 10 controlled studies that have compared bleeding after dental extractions in anticoagulated patients versus patients with normal or near-normal coagulation (anticoagulation reduced or withdrawn): In some of these studies, there was a slight increase in bleeding in the anticoagulation group, in some there were no differences, and in at least one there was a slight increase in bleeding in the anticoagulation withdrawal group, but in each study, there was no significant difference in bleeding incidence between the two groups.

Answer: As the reviewer pointed out, there have been many studies comparing incidence of post-extraction bleeding in patients under warfarin therapy vs. non-warfarin groups. However, those previous studies have primarily focused on differences in incidence, which could overestimate the difference particularly when the sample size is big. Therefore, in the present manuscript, we chose to evaluate the frequency of post-extraction bleeding based on 95% confidence intervals for the difference of the frequencies between the warfarin and non-warfarin groups.

We believe that the present approach is novel and would provide important information in deciding how to perform dental procedure in patients receiving WF.

We included several previous studies as references and modified the Introduction to better present our approach.

2. The authors say that the bleeding incidence data were collected by tooth, not by patient. It would be helpful to present these data by patient in addition to tooth. In other words, the reader should be informed how many patients suffered postextraction bleeding and how many did not, not just how many extraction sockets bled and how many did not.

Answer: While we primarily focused on local factors in the present study, we agree with the reviewer that individual factors might also affect relative importance of the local factors we had addressed. In the revised manuscript, we also included and discussed the data from analysis by patient.

When analyzed by patient, clinically significant post-extraction bleeding was observed in 2.77% of 361 patients receiving warfarin and in 0.39% of patients not receiving warfarin (1,785 cases). The 95% confidence interval for the difference of post-extraction bleeding frequencies was 0.65 – 4.10%, which was similar to the results when data were analyzed by tooth, suggesting that bias by including a single individual patient as multiple entries was minimal.

While there have been ample data regarding the influence of patient factors on post-extraction bleeding, impact of local factors such as topical gum inflammation, inappropriate granulation at the socket and detrition of surrounding soft tissues that could also affect the outcome of dental extraction, has never been assessed. We suspected that such local factors could outweigh a risk factor associated with an individual, and therefore, for the first time to our knowledge, intended to reveal risk factors for bleeding by anatomical locations of the tooth, not by patient.

In the present study, bleeding incidence was observed at 35 teeth in 25 patients receiving WF. While there were cases reported where average of 5-6 teeth were extracted in one patient in the literature,

in the present study, multiple teeth were extracted only in 9 out of the 25 patients on WF and the rest underwent single tooth extraction. In the 9 patients who had multiple teeth extracted, only 3 patients experienced bleeding at multiple positions. These findings suggest that post-extraction bleeding does not necessarily happen at all the teeth extracted in the same individual and therefore reiterate the importance of local factors, warranting our approach by tooth.

3. There is little or no discussion of the serious embolic risks involved with anticoagulation withdrawal. Since 2000, there have been several reports of serious embolic complications and/or death after anticoagulation interruption for dental procedures, and in the surviving patients, there may have been permanent disabilities. On the other hand, I am unaware of a single case in the literature of a death or long-term disability from a bleeding complication postextraction in an anticoagulated patient. Dental extractions in anticoagulated patients does not occur in a vacuum. Clinicians need to weigh the potential risks and benefits of continuing versus interrupting anticoagulation for dental extractions. Therefore, somewhere in the manuscript, the authors need to discuss the potential risks of anticoagulation interruption for dental procedures.

Answer: Discussion on the risks and benefits of continuing vs. interrupting WF when extracting teeth in patients receiving WF was added (page 7, Introduction).

4. On page 11 of the manuscript, the authors state, Clinical experience of the operator and the capability of the facility in performing advanced care should also be taken into consideration, instead of solely relying on the PT-INR values when planning the procedure."The authors provide no evidence for this statement. Also, the statement implies that dental extraction in anticoagulated patients is a type of "advanced care."

Previous studies have shown that dental extractions have been safely performed by both general dentists and oral surgeons and have not shown that clinical experience of the operator is an important safety factor. Dental extractions in such patients can be done routinely without special precautions or training. For the most part, dental extractions on therapeutically anticoagulated patients can be done in the same manner as on normally coagulated patients. When doing dental extractions in any patient, the operator should be familiar with local measures for hemostasis. If there is evidence to the contrary, the authors should document it.

Answer: We agree with the reviewer that evidences suggest that simple dental extraction be performed safely with a standard topical hemostasis technique that we expect either general dentist or oral surgeon to be familiar with. Although rare, there are cases that bleeding cannot sufficiently be controlled by topical hemostasis, which may require care by an oral surgeon. Indeed, the present study revealed factors that would increase bleeding incidences in patients receiving warfarin. As, in Japan, oral surgeons primarily work at a larger hospital, where equipment and settings are different from what a general dental office has, we thought that precaution, such as access to a facility where an oral surgeon is available, need to be emphasized when performing dental extraction in patients on warfarin. To clarify our point, the description in the discussion has been modified (page 11, line 15 to page 12, line 5).

5. The authors conclude on page 14 that "patients whose PT-INR values are close to 3.0 or who have other risk factors for uncontrollable bleeding should undergo dental extraction under the management of an oral surgeon specifying [sic] in invasive dental procedures or at a dental facility that has access to a hospital that could provide advanced medical care in the event of uncontrollable bleeding." But on page 9, the authors state that "all bleeding episodes were controlled by local hemostatic interventions." The authors' conclusion that specialized doctors and/or facilities are needed for extractions in anticoagulated patients is inconsistent with their results that all bleeding episodes were controlled with local measures.

Answer: In the present study, we limited our subject entry to the cases that extraction was performed in a facility where an oral surgeon and/or emergency treatment are available 24 hrs a day to minimize technical variability and hemostasis was achieved by topical technique only in all the cases. However, approximately 10% of cases required hemostasis after dental extraction after regular hours, which might not have been effectively controlled, had the extraction been performed at a general dentist. Therefore, we believe that it is essential to assure support with a facility where oral surgeons are available in case for a difficult case such as those who are taking warfarin. We admit that the description in the original manuscript was misleading, and therefore the paragraph has been modified (page 11 line 15 to page 12 line 5).

#### Reviewer 2

1. My biggest concern is its patient selection criteria and statistical evaluation method. From the patients and methods section I understand that all patients on warfarin treatment who undergo simple tooth extraction were included. There were no exclusion criteria for these patients and the effects of the cofactors were evaluated with multivariate analyses. What about the patients in the other group? How did the authors recruit these patients? Did this group consist of every patients undergoing simple extraction in the study centers? If yes I am impressed that all these patients accepted to participate in the study. There is a huge difference in the number of patients or cases between the two groups.

Answer: We collected all simple extraction cases, regardless of use of warfarin, performed at the participating institutions as subjects of the present study based on the inclusion criteria described in the Method section. There were total of 3,515 teeth extraction (out of which 2,817 teeth were included to the final analyses) during the study period. We then divided the subject into 2 groups based on the use of warfarin. Therefore, the criteria apply to all the subjects recruited, except for the PT-INR that only applied to the patients receiving warfarin.

We agree that difference in sample sizes could be a limitation of the present study. In the revised manuscript, we briefly discussed the limitation.

Since the present study was not interventional, the protocol was approved by the Institutional Review Committee without requiring to obtain a written consent, but in all the cases, consent was in general obtained orally or in some facilities by a written document, based on the additional requirement with each participating institution.

2. The authors considered the tooth that has been extracted as the independent variable of the study. To my opinion it makes the evaluation method more complicated. There are comorbidities or demographic data, which depend on the patient factor, thus usually the patient is considered the independent variable in such studies. An expert statistical review may be needed to review its methodology.

Answer: We agree with the reviewer and are aware of the importance of patient-based analyses and potential limitations of analysis by tooth. However, we respectfully argue that we would focus on local factors associated with tooth in the present study for the following reasons.

While there have been ample data regarding the influence of patient factors on post-extraction bleeding, impact of local factors such as topical gum inflammation, inappropriate granulation at the socket and detrition of surrounding soft tissues that could also affect the outcome of dental extraction, has never been assessed. We suspected that such local factors could outweigh a risk factor associated with an individual, and therefore, for the first time to our knowledge, intended to reveal risk factors for bleeding by anatomical locations of the tooth, not by patient.

In the present study, bleeding event was observed at 35 teeth in 25 patients receiving WF. While there were cases reported where average of 5-6 teeth were extracted in one patient in the literature, in the present study, multiple teeth were extracted only in 9 out of the 25 patients on WF and the rest underwent single tooth extraction. In the 9 patients who had multiple teeth extracted, only 3 patients

experienced bleeding at multiple positions. These findings suggest that post-extraction bleeding does not necessarily happen at all the teeth extracted in the same individual and underscore the importance of local factors. Therefore, we chose to perform multivariate analysis by tooth to reveal influences of such local factors on risk factors for post-extraction bleeding in patients receiving warfarin.

In the revised manuscript, we also included and discussed the data from analysis by patient.

When analyzed by patient, clinically significant post-extraction bleeding was observed in 2.77% of 361 patients receiving warfarin and in 0.39% of patients not receiving warfarin (1,785 cases). The 95% confidence interval for the difference of post-extraction bleeding frequencies was 0.65 – 4.10%, which was similar to the results when data were analyzed by tooth, suggesting that bias by including a single individual patient as multiple entries was minimal.

We believe, despite the limitations, that the present study has unique importance and provides insights on incidence and its risks of post-extraction bleeding from a novel aspect of local factors, by performing analysis by tooth.

3. The authors state in the introduction that "no studies to date have investigated the differences in post-extraction bleeding incidences between patients receiving and not receiving warfarin". This statement is not accurate since a recent clinical study by Karsli et al. evaluated exactly this issue in their study. I am surprised that the authors ignored this study, since a simple Pubmed search with "Warfarin and Dental Extraction" keywords would have retrieved this study.

Answer: As pointed out, there have been many studies comparing incidence of post-extraction bleeding in patients under warfarin therapy vs. non-warfarin groups. However, those previous studies have primarily focused on differences in incidence, which could overestimate the difference particularly when the sample size is big. Therefore, in the present manuscript, we chose to evaluate the frequency of post-extraction bleeding based on 95% confidence intervals for the difference of the frequencies between the WF and non-WF groups. In addition, we assessed factors that affect the differences by multivariate analysis.

We believe that the present approach is novel and would provide important information in deciding how to perform dental procedure in patients receiving WF.

We included several previous studies as references and modified the Discussion to better present our approach.

4. The INR values of patients receiving warfarin were measured within the 7 days prior the surgery. The INRs of such patients are usually measured on the same day of the surgery (in our clinics as well as in many clinics I know). INR values considered for this study may not reflect the actual values since 7-day is long enough for this parameter to be varied. The authors addressed this drawback at the end of the discussion section. However, it could be highlighted in the results section as well.

Answer: We agree with the reviewer that PT-INR would best reflect the coagulation status of the patients if measured on the day of the tooth extraction or at least within 72 hours, as recommended by the Guidelines. We chose to accept by criterion the measurement of PT-INR up to 7 days in advance to increase the chance of subject recruitment. Nevertheless, PT-INR was indeed measured on the day of the extraction in 208 cases of 361 patients receiving. To further minimize the bias that might arise from the PT-INR values measured in advance, we also measured PT-INR in the cases in which clinically significant bleeding events were observed after the tooth extraction. Means of PT-INR values of pre-extraction and of post-extraction were not significantly different and 2.27 and 2.26, respectively. Therefore, we believe that several pre-extraction PT-INR values obtained more than 72

hours in advance had minimally affected the results of our analyses.  
To clarify the concern, we added a new paragraph discussing the issue raised.

5. In the M&M section the authors mention about the utilization of epinephrine as topical hemostatic agent to be used in the postoperative period. How did they apply epinephrine (concentration?) topically? Since patients on warfarin treatments are usually presented with severe cardiac disease use of epinephrine might be arguable.

Answer: In some of the participating institution, epinephrine was used as topical hemostatic agent. In such case, gauze wetted with 0.3-0.5% epinephrine solution (concentrations varied by institutions) was applied at the socket with manual pressure. Such application was minimally performed with general precaution in use of epinephrine in patients who has cardiac disorders.

6. I assume that the authors imply "inferior alveolar nerve block" anesthesia by saying "mandibular foramen conduction anesthesia", which is a new term for me. I suggest using inferior alveolar nerve block instead as many readers as myself might not be familiar with this term. The authors consider application of block anesthesia as a risk factor, which is understandable. However they only concern about inferior alveolar nerve block but not the posterior superior alveolar (PSA) nerve block anesthesia, which is the most commonly nerve block technique associated with hemorrhagic events. As the authors included the maxillary molar teeth as well, they could have considered PSA block as a variant.

Answer: As suggested, we changed the description to "inferior alveolar nerve block" from "mandibular foramen conduction anesthesia".

We agree with the Reviewer that inferior alveolar nerve block would increase bleeding risk in patients receiving warfarin, while PSA block would be a safer option.

7. The indications of warfarin use have not been addressed. If warfarin indications were also due to cerebral disease, history of a previous CVA in any of the patients should be mentioned.

Answer: Unfortunately, we were unable to collect details regarding the indications for warfarin in our subjects. However, we believe that none of the subjects in our study was taking warfarin in prevention or treatment of cerebro-vascular disease, as the use of warfarin in such disorder is not approved in Japan.

8. For patients, who are under great thromboembolism risk because of discontinuation of the anticoagulant therapy, bridging with heparin is another preoperative management method. This has not been discussed in the manuscript.

Answer: We agree that bridging with heparin would be beneficial preoperative management option to prevent post-operative thromboembolism and to reduce risk for bleeding, particularly in the cases of major operative procedure where topical hemostasis is difficult. The present study evaluated cases of simple tooth extraction, which in most cases topical hemostasis is sufficient, and therefore heparin bridging was not considered in any subjects. Indeed, studies found no significant difference in incidences of post-extraction bleeding incidences and/or thromboembolism after dental procedures (ref #28-30). Heparin bridging involves intravenous heparin administration, which might require closer maintenance and possible hospital administration, leading to higher costs. For those reasons, we believe that heparin bridging is generally not recommended in the cases of simple tooth extraction. We added a new paragraph discussing the option including the relevant references.

Reviewer 3

1. In the warfarin group, the INR was done up to seven days before. In order to draw conclusions from

the data, this is too long a time frame, as the INR at the time of the procedure is unknown.

Answer: We agree with the reviewer that PT-INR would best reflect the coagulation status of the patients if measured on the day of the tooth extraction or at least within 72 hours, as recommended by the Guidelines. We chose to accept by criterion the measurement of PT-INR up to 7 days in advance to increase the chance of subject recruitment. Nevertheless, PT-INR was indeed measured on the day of the extraction in 208 cases of 361 patients receiving. To further minimize the bias that might arise from the PT-INR values measured in advance, we also measured PT-INR in the cases in which clinically significant bleeding events were observed after the tooth extraction. Means of PT-INR values of pre-extraction and of post-extraction were not significantly different and 2.27 and 2.26, respectively. Therefore, we believe that several pre-extraction PT-INR values obtained more than 72 hours in advance had minimally affected the results of our analyses.

To clarify the concern, we added a new paragraph discussing the issue raised.

2. The unit of analysis was not the patient. Using individual teeth as the units of analyses gives multiple non-independent measurements per patient, inflates the sample size and may give spurious significance to the results. It is theoretically possible that all eighteen bleeding events in the warfarin group occurred in one patient, while the nine bleeding events in non warfarin patients occurred in nine separate patients. This would yield an equally striking but opposite result.

Answer: We agree with the reviewer and are aware of the importance of patient-based analyses and potential limitations of analysis by tooth. However, we respectfully argue that we would focus on local factors associated with tooth in the present study for the following reasons.

While there have been ample data regarding the influence of patient factors on post-extraction bleeding, impact of local factors such as topical gum inflammation, inappropriate granulation at the socket and detrition of surrounding soft tissues that could also affect the outcome of dental extraction, has never been assessed. We suspected that such local factors could outweigh a risk factor associated with an individual, and therefore, for the first time to our knowledge, intended to reveal risk factors for bleeding by anatomical locations of the tooth, not by patient.

In the present study, bleeding event was observed at 35 teeth in 25 patients receiving WF. While there were cases reported where average of 5-6 teeth were extracted in one patient in the literature, in the present study, multiple teeth were extracted only in 9 out of the 25 patients on WF and the rest underwent single tooth extraction. In the 9 patients who had multiple teeth extracted, only 3 patients experienced bleeding at multiple positions. These finding suggest that post-extraction bleeding does not necessarily happen at all the teeth extracted in the same individual and underscore the importance of local factors. Therefore, we chose to perform multivariate analysis by tooth to reveal influences of such local factors on risk factors for post-extraction bleeding in patients receiving warfarin.

In the revised manuscript, we also included and discussed the data from analysis by patient.

When analyzed by patient, clinically significant post-extraction bleeding was observed in 2.77% of 361 patients receiving warfarin and in 0.39% of patients not receiving warfarin (1,785 cases). The 95% confidence interval for the difference of post-extraction bleeding frequencies was 0.65 – 4.10%, which was similar to the results when data were analyzed by tooth, suggesting that bias by including a single individual patient as multiple entries was minimal.

We believe, despite the limitations, that the present study has unique importance and provides insights on incidence and its risks of post extraction bleeding from a novel aspect of local factors, by performing analysis by tooth.

Reviewer 4

1. Question #1

In adult patient slated for a simple dental extraction, will the warfarinized patient compare to the non-warfarinized patient result in more significant post-op bleeding events?

Answer: In the present study, we obtained 95% confidence interval for the difference of post-extraction bleeding frequencies by tooth between the warfarinized- and non-warfarinized patients. In the revised manuscript, we also analyzed the same dataset by patient and found that 95% confidence interval for the difference of bleeding frequencies were similar to that found by analyses by tooth.

2. I believe the statement on page 4, line 14;..."However, a clinical study reported that embolism or thrombosis developed in approximately 1% of patients who discontinued warfarin prior to dental surgery, resulting in death in a large proportion of the affected patients.[1]" ... is inaccurate and should be removed or rephrased to represent current knowledge. The authors are citing Wahl (1998) narrative review which summarized ( not a meta-analysis) the outcomes from selected papers. In my paper ( Balevi 2010) , I calculated the risk of a CVA when warfarin is withheld for 3 days to be only 0.059% which is far lower than that reported by Wahl's flawed calculation. Also in a my response to a letter to the editor ( Balevi 2012) , I addressed that the 6 reported cases by Wahl(1998) and Miller (2012) of a CVA occurring when warfarin was withheld as not representative of what actually happens in dental practice and that extrapolating a cause-effect relationship in any of these cases is questionable (Balevi 2012 )

Answer: We thank the reviewer's suggestion and added the newer reports by Balevi et al, which demonstrated lower incidence rate for CVA after 3 days cessation of warfarin, as references #17 and 18, and discussed the results in comparison with those shown by Wahl et al.

3. Were the Evaluators of Bleeding events blinded or not? If the evaluators were not blinded then there is a risk of over reporting a significant bleeding event in known warfarinized patients than in the non-warfarinized patient (detection bias or confirmation bias.)This should be included as a limitation of this study as such a bias could skewing the differences in bleeding events between the two groups away from the truth.

Answer: The evaluation of bleeding events was NOT blinded in the present study and we agree that the evaluation might have been biased. In the revised manuscript, we added discussion on the potential the concern as a limitation of the study.

4. The fact that hemostasis was not necessarily managed consistently between each group may bias the results (i.e., ascertainment or assessment bias). All warfarinized patients were packed with gelfoam and sutured, but it was at the discretions of the operator if such methods were necessary for the patients not on warfarin. It has been reported that suturing may actually increase the risk of post-op bleeding by traumatizing the tissue around the extraction socket. This may be something to address in the discussion as it may have over estimated the number of significant bleeding events in the warfarinized patient.

Answer: We agree with the reviewer that, at least in the non-warfarin group, possible difference in measures for topical hemostasis chosen by an operator might have biased our analyses. Means of topical hemostasis in patients receiving warfarin, on the other hand, was basically the same for all the subjects, and the wounds were either sutured or packed with oxidized cellulose or gelfoam in to the socket, which have been well recognized for their efficiency in successful hemostasis.

However, as pointed out, several reports or guidelines questioned the outcome of suture and raised the possibility that suturing might rather increase the risk for post-extraction bleeding. In the present study, no post-extraction bleeding occurred in the patients whose wound was sutured in non-warfarin group.

Nonetheless, such possibility was now commented in the Discussion.

5. The authors briefly discuss the issue of possible cluster Bias in the last sentence of the manuscript;(p.13, line 39-45) "However, multiple counts from the same patient may have biased the results." The data is collected per tooth and not per patients. This is significant as it increase the possible risk of clustering many of the bleeding events to only a few people with multiple extraction at the same time. Therefore it is possible that someone had numerous teeth extracted at the same time resulting in essentially a more invasive procedure than just a simple extraction of a single tooth. I feel this a significant limitation of this study that I feels needs more discussion.

Answer: We agree with the reviewer and are aware of the importance of patient-based analyses and potential limitations of analysis by tooth. However, we respectfully argue that we would focus on local factors associated with tooth in the present study for the following reasons.

While there have been ample data regarding the influence of patient factors on post-extraction bleeding, impact of local factors such as topical gum inflammation, inappropriate granulation at the socket and detrition of surrounding soft tissues that could also affect the outcome of dental extraction, has never been assessed. We suspected that such local factors could outweigh a risk factor associated with an individual, and therefore, for the first time to our knowledge, intended to reveal risk factors for bleeding by anatomical locations of the tooth, not by patient.

In the present study, bleeding event was observed at 35 teeth in 25 patients receiving WF. While there were cases reported where average of 5-6 teeth were extracted in one patient in the literature, in the present study, multiple teeth were extracted only in 9 out of the 25 patients on WF and the rest underwent single tooth extraction. In the 9 patients who had multiple teeth extracted, only 3 patients experienced bleeding at multiple positions. These finding suggest that post-extraction bleeding does not necessarily happen at all the teeth extracted in the same individual and underscore the importance of local factors. Therefore, we chose to perform multivariate analysis by tooth to reveal influences of such local factors on risk factors for post-extraction bleeding in patients receiving warfarin.

In the revised manuscript, we also included and discussed the data from analysis by patient.

When analyzed by patient, clinically significant post-extraction bleeding was observed in 2.77% of 361 patients receiving warfarin and in 0.39% of patients not receiving warfarin (1,785 cases). The 95% confidence interval for the difference of post-extraction bleeding frequencies was 0.65 – 4.10%, which was similar to the results when data were analyzed by tooth, suggesting that bias by including a single individual patient as multiple entries was minimal.

We believe, despite the limitations, that the present study has unique importance and provides insights on incidence and its risks of post extraction bleeding from a novel aspect of local factors, by performing analysis by tooth.

6. On page 7, The authors grade the extent of a bleeding event between 0-3. They subdivide continued bleeding event of 30 minutes after extraction as grade 2.1 and 2.2.

It is not clear to me the difference between ' hemostasis longer than 30 minutes( i.e, Grade 2.1)" and " oozing from socket, ceased by wound compression only (grade 2.2)" .

Also, please elaborate what is meant by bleeding required treatments other than wound compression (Grade 3). What other means ?

Answer: We apologize for the insufficient description.

The grade 2.2 bleeding was defined by oozing from the socket observed a day or later after the procedure, which was successfully treated only by additional compression.

In the grade 3 bleeding, additional compression was not enough to achieve sufficient hemostasis and

compression brace and/or coagulation by electrothrombotomy was needed. The detailed description was added in the revised manuscript.

7. The authors report an absolute risk difference between the two groups of 3.24% (95%CI 1.49, 4.99%) then in abstract (p. 2 line 41) and in manuscript (p.10 line 45) as the risk of post op bleeding in warfarinized patient to be 10 times greater than in the non-warfarinized patients. Although valid, I am not sure why this relative difference was not reported as a risk ratio statistic [i.e.,  $RR = (3.63/0.39) = 9.31$ ] or an odds ratio ( $OR = \frac{18/(496-18)}{9/(2,321-9)} = 9.69$ ] with their associated confidence interval. I think that RR is the correct statistics in this case since the population was quasi-randomly selected and assumed to be representative of the population.

Answer: Our main interest is to evaluate the difference in risk for post extraction bleeding in patients receiving or not receiving warfarin. In the original manuscript, we showed both risk difference and at limited places risk ratio, which might have been confusing. In the revised manuscript, we demonstrated all data as risk difference.

Whereas in the table, we used OR, as it represents relationship between the factors evaluated. We chose to show differences in 95% confidence interval for the risk difference to best reflect the subtle but significantly higher risk in patients receiving warfarin and raise attention by dentists who deal with such patients. However, as the reviewer pointed out, RR is also commonly used means to represent the relative risk and might convey our point to the audience. Therefore, we also mentioned RR at the Conclusion.

8. In the conclusion (p.13, line 52) the authors exaggerate the absolute risk difference by reporting only the upper limit of its 95% confidence interval ( "approximately 5%"). However, the lower limit of the confidence interval is almost 1.5% (quite close to the point of no difference). Considering the bias I have already identified I believe that it is very possible that the true risk difference is more towards the left hand of the confidence interval than the right. So for the purpose of objectivity, it would be appropriate to report in the conclusion the mean difference ( i.e., "3.24%" ) or cite the range of the 95% confidence interval ( i.e., "between 1.5% to 5%") and allow the reader to decide if this is clinically significant or not.

Answer: We thank the reviewer for the suggestion and the text was modified to include both upper and lower limits of the 95% confidence interval, so that the audience could determine from the presented data whether the difference represents clinically significant hazards when performing dental procedure in warfarinized patients.

9. I am a little confused how to interpret table 3 and 4. More specifically the interpretation of both univariate and multivariate analysis in this study .I understand , univariate analysis to examines only a single independent variable against the dependent variable (which in this study is the risk of significant bleeding) , while multivariate analysis exams the effects of two more independent variable vs. the dependent variable at the same time. For example, the problem I have is interpreting in table 3 the "Univariate analysis of post-extraction bleeding events by potential risk factors' for the independent variable" reports for a molar extract an  $OR=2.22$  but in table 4 'Multivariate analysis of post extraction bleeding by potential risk factors" the OR for the same independent variable is reported to be = 0.953. In table 3 I understand the extraction of a molar increase the risk to post-op bleeding by a factor on 2 but in table 4 the molar extraction slightly reduces the risk.(contradictory?) Although this independent variable is not statistically significant (i.  $p > 0.05$ ) it is confusing for me to interpret its clinical significance.

Answer: As pointed out by the reviewer, relationship between the molar position and incidence of post-extraction bleeding was found differently in univariate- and multivariate analyses. Our additional

analysis indicated patient age as a confounding factor. Molar extraction was performed more in younger patients, which might have led to ostensibly higher incidence of post-extraction bleeding with molar extraction when analyzed by univariate analysis.

The different results by uni- and multivariate analyses could be accounted for such confounding factors.

10. Both these statements do not follow logically from the study nor is it intuitively reasonable to make such a stretch. There is neither evidence in this study nor in the literature that I know of that an oral surgeon compared to a general dentist is less likely to cause or better manage a significant post-operative simple dental extraction bleeding event in a warfarinized patient. Also, the authors admit (see final line of abstract p. 2 line 43 "... though absolute incidence was low in both groups) that the risk of significant bleeding from a simple extraction is low. Considering the limitation of the study, the inferences cannot be clinically justified and only come across as self-serving to oral surgeons.

Answer: We agree with the reviewer that there has been little evidence suggesting that there is a significant difference in incidence of post-extraction bleeding when compared cases performed by general dentist and oral surgeons. However, in daily practice, we experience a rare case when bleeding cannot be controlled by simple topical hemostasis, and are aware that the case would be a problem particularly if it happened at night in a general dental clinic where availability of personnel and equipment are limited.

The present study revealed factors that associate with increased risks for post-extraction bleeding in warfarinized patients. Therefore, we intended to raise attention to the dental care providers, either general dentist or oral surgeons, so that dental extraction be performed with sufficient consideration and backup when performed in warfarinized patients. To clarify our point, the description in the text has been modified (page 11, line 15 to page 12 line 5).

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Michael Wahl Christiana Care Health Services, USA  None declared
<b>REVIEW RETURNED</b>	20-Aug-2014

<b>GENERAL COMMENTS</b>	<p>The abstract, results, and discussion should include data analysis by patient in addition to the data analysis by tooth. Then most of the nos will be yes. Also, the references should include some of the references in my comments to the author.</p> <p>1) In the response to reviewers' comments, the authors say that they have now included postextraction bleeding incidences by patient (2.77% versus 0.39%) in addition to by tooth, but I don't see any discussion the incidences by patient in the abstract or in the results. (In Table 2, the percentages are 3.63 vs. 0.39, not 2.77 vs. 0.39.) The paper should be revised to include prominently the data analysis by patient in the abstract and in the results and possibly the discussion.</p> <p>2) On page 11, line 18, the authors state, "Balevi et al. recently re-evaluated the data reported by Wahl et al with a distinct analytical approach and found that incidence of cardiovascular accident after 3</p>
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days of warfarin cessation was 0.059%, which was significantly lower than was originally reported.” The authors then go on to downplay the embolic risks of warfarin interruption for dental procedures. This should be deleted or revised.

The authors are relying on Balevi’s 2010 article (Balevi B. Should warfarin be discontinued before a dental extraction? A decision-tree analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010 Dec;110(6):691-7.) This article was widely criticized in three letters by five authors taking exception to parts of the article.

In his article, Balevi incorrectly asserted, “there has been no reported case of a dental extraction causing a cardiovascular accident (CVA) in a patient whose warfarin was temporarily discontinued.” In fact, our group has now identified at least 22 reported cases of postdental embolic complications (submitted for publication) after temporary interruption of warfarin therapy, including the five in the Wahl article (Wahl MJ. Dental surgery in anticoagulated patients. *Arch Intern Med* 1998;158:1610-6). These include 12 embolic complications (3 fatal) after interruption periods of as few as 1 to 5 days. (See for example, Yasaka M, Naritomi H, Minematsu K. Ischemic stroke associated with brief cessation of warfarin. [Letter.] *Thromb Res* 2006;118(2):290-3 and Akopov SE, Suzuki S, Fredieu A et al. Withdrawal of warfarin prior to a surgical procedure: time to follow the guidelines? *Cerebrovasc Dis* 2005;19(5):337-42.) In addition, there are countless cases of embolic complications reported in patients whose warfarin was temporarily interrupted for other types of surgery.

Another problem with this 2010 paper is that a 1% fatal bleeding estimate was used to formulate the decision tree *although there has never been a fatal bleeding event after a dental procedure in an anticoagulated patient* on the questionable basis that other types of major surgery (eg, colorectal or major abdominal surgery) may have a 1% risk. But dental surgery is unlike other types of surgery, and that is one of the reasons there has never been a documented fatal hemorrhage. Major vessels are unlikely to be encountered, and bleeding sites are easily accessible to local hemostatic methods.

As a result, the decision tree analysis was flawed by grossly overestimating the incidence of fatal bleeding in continuing warfarin and grossly underestimating the incidence of embolic complications when warfarin is interrupted.

The literature shows that embolic complications after temporary

warfarin interruption occur at a much higher rate than the 0.059% that Balevi and the authors are using, at a rate more consistent with Wahl's, which simply presented all cases of dental procedures performed where anticoagulation was interrupted, regardless of the number of days of interruption. Out of 542 interruptions, there were 5 embolic complications, including 4 deaths.

One reviewer states that the Wahl paper (my paper) was based on "a flawed calculation." There was no flawed calculation in the paper although a legitimate criticism is that three of the documented embolic complications occurred after relatively long warfarin interruption periods (greater than 5 days). Of the other two deaths mentioned in the paper, one (Ogiuchi H, Ando T, Tanaka M, Kuwasawa T, Sangu Y, Abe H, Kawanishi I. Clinical reports on dental extraction from patients undergoing oral anticoagulant therapy. Bull. Tokyo Dent Coll 1985;26(4):205-12) was after the warfarin dose was reduced for 3 to 7 days and then interrupted only the day of surgery (and restarted afterward). There was one other fatal embolism where the duration of interruption was not reported (Akbarian M, Austen WG, Yurchak PM, Scannell JG. Thromboembolic complications of prosthetic cardiac valves. Circulation 1968;37:826-31).

As stated above, the 0.059% embolic complication incidence is much lower than reported in other studies of warfarin interruption for medical and dental procedures. Wysokinski et al. (Wysokinski WE, McBane RD, Daniels PR et al. Periprocedural anticoagulation management of patients with nonvalvular atrial fibrillation. Mayo Clin Proc 2008;83(6):639-45) showed that there was a 1.1% thromboembolic incidence in patients whose warfarin was temporarily interrupted for 4 or 5 days with or without bridging therapy. One of these patients developed an occipital infarct within 3 days after stopping warfarin without bridging (for a nondental procedure). Garcia et al. (Garcia DA, Regan S, Henault LE et al. Risk of thromboembolism with short-term interruption of warfarin therapy. Arch Intern Med 2008;168(1):63-9) showed that of 984 warfarin therapy interruptions of 5 days or fewer, there were 4 (0.4%) embolic complications.

Even if one were to accept a 0.059% embolic risk from interruption of warfarin, that would mean for every 1700 warfarin interruptions for dental procedures, there would be one possibly fatal embolic complication. On the other hand, if 1700 dental surgeries were performed without warfarin interruption, based on the literature, there may be some bleeding complications, but none would be fatal. If airline flights had a 0.059% chance of crashing, I don't think many people would choose to fly. (There are 87,000 airline flights in the US per day. A 0.059% crash rate would mean there would be 51

crashes per day just in the US.) Regardless of an embolic risk of 0.059% or 1%, however, the question comes down to whether an anticoagulated patient should be subjected to a small but significant risk of death or permanent disability (with anticoagulation interruption) or a small risk of a bleeding complication (with continuation) where 100% of all cases up until now have apparently resulted in a full recovery.

3) On page 3, line 7, the authors state about post-extraction bleeding incidence studies, "...few previous studies to date have been reported." In the authors' response to decision letter, however, the authors correctly state that "there have been many studies comparing incidence...."

For example, Devani et al. (Devani P, Lavery M, Howell CJT. Dental extractions in patients on warfarin: is alteration of anticoagulation regime necessary? Br J Oral Maxillofac Surg 1998;36:107-11) compared 32 patients whose warfarin was interrupted for 2 or 3 days before dental extractions with 33 continuously anticoagulated dental extraction patients. There were no bleeding complications for the first 24 hours in either group. There was one patient from each group with intermittent oozing either 2 or 3 days postoperatively, easily treated with local hemostatic methods. Although this study did not specifically address 95% confidence intervals, I'm at least 95% confident that if such analysis were conducted, it would show no difference in bleeding incidences. The authors should revise the paper to state that there have been many comparative studies for dental extractions, and all have shown no difference in bleeding incidences or complications. Virtually all these studies concluded that warfarin should not be interrupted for dental surgery, and the authors need to discuss this. For example,

Gaspar R, Brenner B, Ardekian L, Peled M. Use of tranexamic acid mouthwash to prevent postoperative bleeding in oral surgery patients on oral anticoagulant medication. Quintessence Int 1997;28:375-9.

Blinder D, Manor Y, Martinowitz U, Taicher S. Dental extractions in patients maintained on oral anticoagulant therapy: comparison of INR value with occurrence of postoperative bleeding. Int J Oral Maxillofac Surg 2001;30(6):518-21.

Karsli ED, Erdogan O, Esen E, Acartürk E. Comparison of the effects of warfarin and heparin on bleeding caused by dental

	<p>extraction: a clinical study. J Oral Maxillofac Surg 2011;69:2500-7.</p> <p>Campbell JH, Alvarado F, Murray R A. Anticoagulation and minor oral surgery: should the anticoagulation regimen be altered? J Oral Maxillofac Surg 2000; 58: 131-135.</p> <p>4) The authors state on page 12, “Therefore, when performing dental extraction in high-risk patients such as those taking warfarin, capability of the facility for means of hemostasis other than simply topical hemostasis and availability of personnel at afterhours should carefully be considered.” The fact that these extractions were performed by oral surgeons is fine, but I object to the implication that special precautions (eg, a 24-hour facility) need to be taken because patients are on warfarin. If general dentists perform extractions in Japan on non-anticoagulated patients, then these same general dentists can perform extractions on anticoagulated patients. The incidences of bleeding complications in many previous studies (see above) have been the same in anticoagulated and non-anticoagulated patients. There are occasionally bleeding complications in non-anticoagulated patients as there are in anticoagulated patients. Whatever the general dentist’s protocol is for after hour care should suffice for postextraction bleeding problems, whether or not the patient is anticoagulated. This should be clarified in the text or simply eliminate the discussion of it entirely. Again, the fact that oral surgeons performed the extractions is fine, but the authors should not assume that specialized training or 24-hour facilities are needed for such extractions.</p>
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<b>REVIEWER</b>	Ben Balevi University of British Columbia
<b>REVIEW RETURNED</b>	25-Aug-2014

<b>GENERAL COMMENTS</b>	<p>Summary of My understanding</p> <p>The clinical questions this study is trying to answer are ;</p> <p>Question #1 In adult patient slated for a simple dental extraction, will the warfarinized patient compare to the non-warfarinized patient result in more significant post – op bleeding events?</p> <p>Question 2 What factors place the warfarinized patient at risk of significant post – op [simple-dental-extraction] bleeding events?</p>
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	<p>Methodology : This is a multicentered study that measured the incidence of the extent post-op bleeding from the consecutive ( over 17 months) selection of 2,321 teeth from not receiving warfarin ( non-warfarinized ) patients with 496 teeth from patients receiving warfarin ( warfarinized) - [Cross-sectionnal study]</p> <p>Outcome: The study defines simples extraction as tooth removal without traumatizing the surrounding alveolar bone or elevating a mucoperisoteal flap.</p> <p>The main conclusion are</p> <ol style="list-style-type: none"> <li>1. the absolute difference in the mean risk of a significant post-extraction bleed between the warfarinized and non-warfarinized patient is 3.24% (95%CI 1.49, 4.99%)</li> <li>2. Age, PT-INR, inferior nerve block and formation of abnormal granulation tissue in extraction socket significantly correlated with post-op extraction in the warfarinized patient.</li> <li>3. Age ,antiplatelet drugs , PT-INR and history of acute inflammation at extraction site were significant risk factors for post-op extraction bleeding in the warfarinized patient.</li> </ol> <p>My concerns that need further explanation</p> <ol style="list-style-type: none"> <li>1. I find the current ABSTRACT is confusing and needs a complete rewrite. For example, The objective of the study is not “The 95% confidence interval difference ...” but assessing the incidence of significant post-extraction bleeding between the patient on warfarin and the patient not-receiving warfarin. Also in the result section, the confidence interval of the difference in incidence in bleeding between the two groups is given but the statistic itself (3.24%) is not.</li> <li>2. I continue to believe that the statement on page 4, line 10; “However, a clinical study reported that embolism or thrombosis developed in approximately 1% of patients who discontinued warfarin prior to dental surgery, resulting in death in a large proportion of the affected patients.[1] is inaccurate and alarmist and should still be removed.. The authors are citing Wahl (1998) narrative review – not a clinical study per say . Wahl’s summarized (not a meta-analysis) the outcomes from selected papers (not a systematic review). I appreciated that the authors of this manuscript gave a long discussion on this issue [ p. 10 starting from line 30] but most of it is inaccurate and misleading. For example, it is inaccurate to infer that Wahl actually evaluated 496patients/524 tooth extractions where warfarin was temporarily discontinued prior to the procedure, and observed thromboembolism in 5 cases (0.95%), 4 out of which died. He did not observe patients but pooled data he collected from 16 different studies. Unfortunately, his methodology is not that of a systematic review and the way he pool the data is not a acceptable meta-analysis and thus prone to significant bias. Also, it is misleading to infer that deaths cited in the discussion were caused by a disrupting anticoagulation therapy as there were many confounding factors in each of these cases which makes extrapolating a cause-effect relationship to disrupting anticoagulation therapy and death in any of these cases invalid. Finally I have trouble with the concluding statement ( p. 11 line 25 ) “Taken together, the literature indicate that thromboembolic complication does occur, though absolute numbers are small and suggest that decision whether or not to continue maintenance dose</li> </ol>
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	<p>of warfarin when performing dental extraction in patients receiving warfarin should be made carefully taking risks and benefits that warfarin could cause into account” Although true that thromboembolic complication do occur, the inference that there is an unacceptable high risk it occurs , especially resulting in “death”, is misleading and at worst alarmist. My I suggest that this whole section be removed and summarized with a statement along the lines that there is a perceived risk of a CVA occurring after disputing anticoagulation therapy suggested to be as high as 1% and as low as 0.059%. I feel the rest of the discussion is irrelevant to the objectives of this study which compared the risk of bleeding events after a dental extraction between the warfarinized patient and the non-warfarinized patient. This study is not comparing the risk of bleeding in the warfarinized patient and the disrupted-warfarinized patient. These are two different studies with two different clinical questions. The discussion the authors are making on p10- starting from line 30 is pertinent to the later study and thus I believe should be omitted from this articles or at least simplified.</p> <p>3. P.4 Line 19... the word “issue” is referring to what?. Is the “issue” discontinuing warfarin can result in thrombus or maintaining warfarin does not increase risk of post-extraction bleeding. The prior sentence infers the issue is the former yet the 9 article ( ref. 2-10] cited afterwards infer the later. In-other-words, the introduction is confusing, especially in light that this study has nothing to do with comparing the warfarinized and disrupted –warfarinized patient.</p> <p>4. P. 11 line 48 ... stresses only the right handed side of the confidence interval which I feel is misleading and alarmist, considering that the left handed side of the confidence interval is as low as 1.59%. Small point but I felt I needed to make it.</p> <p>5. The Conclusion [p.17 line 19-26] should give the mean statistic of 3.24% and the associated confidence interval. Also Removed the RR of 9.31% since it is not discuss anywhere else in the manuscript.</p> <p>6. Table 4 [p.27] statistic numbers line 24 should be brought up to line 23 [PT-INR].</p> <p>Would you be willing to review a revision of this manuscript? Yes I believe the data presented here is relevant to clinical practice. But I would like to see how the authors addressed my concerned before I proceed any further.</p> <p>Thank you for asking me to review this interesting article</p>
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## VERSION 2 – AUTHOR RESPONSE

### Responses to the comments by Reviewers

#### Reviewer Michael Wahl

1) In the response to reviewers' comments, the authors say that they have now included post extraction bleeding incidences by patient (2.77% versus 0.39%) in addition to by tooth, but I don't see any discussion the incidences by patient in the abstract or in the results. (In Table 2, the percentages are 3.63 vs. 0.39, not 2.77 vs. 0.39.) The paper should be revised to include prominently the data analysis by patient in the abstract and in the results and possibly the discussion.

Response: As suggested, results of analysis by patients are now included in abstract, results and Table 2.

2) On page 11, line 18, the authors state, "Balevi et al. recently re-evaluated the data reported by Wahl et al with a distinct analytical approach and found that incidence of cardiovascular accident after 3 days of warfarin cessation was 0.059%, which was significantly lower than was originally reported." The authors then go on to downplay the embolic risks of warfarin interruption for dental procedures. This should be deleted or revised.

The authors are relying on Balevi's 2010 article (Balevi B. Should warfarin be discontinued before a dental extraction? A decision-tree analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010 Dec;110(6):691-7.) This article was widely criticized in three letters by five authors taking exception to parts of the article.

In his article, Balevi incorrectly asserted, "there has been no reported case of a dental extraction causing a cardiovascular accident (CVA) in a patient whose warfarin was temporarily discontinued." In fact, our group has now identified at least 22 reported cases of postdental embolic complications (submitted for publication) after temporary interruption of warfarin therapy, including the five in the Wahl article (Wahl MJ. Dental surgery in anticoagulated patients. *Arch Intern Med* 1998;158:1610-6). These include 12 embolic complications (3 fatal) after interruption periods of as few as 1 to 5 days. (See for example, Yasaka M, Naritomi H, Minematsu K. Ischemic stroke associated with brief cessation of warfarin. [Letter.] *Thromb Res* 2006;118(2):290-3 and Akopov SE, Suzuki S, Fredieu A et al. Withdrawal of warfarin prior to a surgical procedure: time to follow the guidelines? *Cerebrovasc Dis* 2005;19(5):337-42.) In addition, there are countless cases of embolic complications reported in patients whose warfarin was temporarily interrupted for other types of surgery.

Another problem with this 2010 paper is that a 1% fatal bleeding estimate was used to formulate the decision tree although there has never been a fatal bleeding event after a dental procedure in an anticoagulated patient on the questionable basis that other types of major surgery (eg, colorectal or major abdominal surgery) may have a 1% risk. But dental surgery is unlike other types of surgery, and that is one of the reasons there has never been a documented fatal hemorrhage. Major vessels are unlikely to be encountered, and bleeding sites are easily accessible to local hemostatic methods. As a result, the decision tree analysis was flawed by grossly overestimating the incidence of fatal bleeding in continuing warfarin and grossly underestimating the incidence of embolic complications when warfarin is interrupted.

The literature shows that embolic complications after temporary warfarin interruption occur at a much higher rate than the 0.059% that Balevi and the authors are using, at a rate more consistent with Wahl's, which simply presented all cases of dental procedures performed where anticoagulation was interrupted, regardless of the number of days of interruption. Out of 542 interruptions, there were 5 embolic complications, including 4 deaths.

One reviewer states that the Wahl paper (my paper) was based on "a flawed calculation." There was no flawed calculation in the paper although a legitimate criticism is that three of the documented

embolic complications occurred after relatively long warfarin interruption periods (greater than 5 days). Of the other two deaths mentioned in the paper, one (Ogiuchi H, Ando T, Tanaka M, Kuwasawa T, Sangu Y, Abe H, Kawanishi I. Clinical reports on dental extraction from patients undergoing oral anticoagulant therapy. *Bull. Tokyo Dent Coll* 1985;26(4):205-12) was after the warfarin dose was reduced for 3 to 7 days and then interrupted only the day of surgery (and restarted afterward). There was one other fatal embolism where the duration of interruption was not reported (Akbarian M, Austen WG, Yurchak PM, Scannell JG. Thromboembolic complications of prosthetic cardiac valves. *Circulation* 1968;37:826-31).

As stated above, the 0.059% embolic complication incidence is much lower than reported in other studies of warfarin interruption for medical and dental procedures. Wysokinski et al. (Wysokinski WE, McBane RD, Daniels PR et al. Perioperative anticoagulation management of patients with nonvalvular atrial fibrillation. *Mayo Clin Proc* 2008;83(6):639-45) showed that there was a 1.1% thromboembolic incidence in patients whose warfarin was temporarily interrupted for 4 or 5 days with or without bridging therapy. One of these patients developed an occipital infarct within 3 days after stopping warfarin without bridging (for a nondental procedure). Garcia et al. (Garcia DA, Regan S, Henault LE et al. Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch Intern Med* 2008;168(1):63-9) showed that of 984 warfarin therapy interruptions of 5 days or fewer, there were 4 (0.4%) embolic complications.

Even if one were to accept a 0.059% embolic risk from interruption of warfarin, that would mean for every 1700 warfarin interruptions for dental procedures, there would be one possibly fatal embolic complication. On the other hand, if 1700 dental surgeries were performed without warfarin interruption, based on the literature, there may be some bleeding complications, but none would be fatal. If airline flights had a 0.059% chance of crashing, I don't think many people would choose to fly. (There are 87,000 airline flights in the US per day. A 0.059% crash rate would mean there would be 51 crashes per day just in the US.) Regardless of an embolic risk of 0.059% or 1%, however, the question comes down to whether an anticoagulated patient should be subjected to a small but significant risk of death or permanent disability (with anticoagulation interruption) or a small risk of a bleeding complication (with continuation) where 100% of all cases up until now have apparently resulted in a full recovery.

Response: We agree with the Reviewer that warfarin should not be discontinued when performing dental extraction in patients receiving warfarin.

We cited the paper by Balevi et al, not necessarily to support their opinion, but to emphasize that incidences for thromboembolic complication varies in literature.

We feel that it is most important to recognize that thromboembolic complication does occur, though rare, while there have been no report on possibly life-threatening bleeding complication during dental extraction in warfarinized patients, suggesting that warfarin should not be discontinued in preparation for dental extraction.

We modified the Discussion to reiterate our point.

2) On page 3, line 7, the authors state about post-extraction bleeding incidence studies, "...few previous studies to date have been reported." In the authors' response to decision letter, however, the authors correctly state that "there have been many studies comparing incidence...."

For example, Devani et al. (Devani P, Lavery M, Howell CJT. Dental extractions in patients on warfarin: is alteration of anticoagulation regime necessary? *Br J Oral Maxillofac Surg* 1998;36:107-11) compared 32 patients whose warfarin was interrupted for 2 or 3 days before dental extractions with 33 continuously anticoagulated dental extraction patients. There were no bleeding complications for the first 24 hours in either group. There was one patient from each group with intermittent oozing either 2 or 3 days postoperatively, easily treated with local hemostatic methods.

Although this study did not specifically address 95% confidence intervals, I'm at least 95% confident that if such analysis were conducted, it would show no difference in bleeding incidences. The authors should revise the paper to state that there have been many comparative studies for dental

extractions, and all have shown no difference in bleeding incidences or complications.

Response: As suggested, we stated that there have been many studies reporting that there is no significant difference in incidences of post-extraction bleeding comparing patients receiving warfarin and those whose warfarin was discontinued.

Virtually all these studies concluded that warfarin should not be interrupted for dental surgery, and the authors need to discuss this. For example,

Gaspar R, Brenner B, Ardekian L, Peled M. Use of tranexamic acid mouthwash to prevent postoperative bleeding in oral surgery patients on oral anticoagulant medication. *Quintessence Int* 1997;28:375-9.

Blinder D, Manor Y, Martinowitz U, Taicher S. Dental extractions in patients maintained on oral anticoagulant therapy: comparison of INR value with occurrence of postoperative bleeding. *Int J Oral Maxillofac Surg* 2001;30(6):518-21.

Karsli ED, Erdogan O, Esen E, Acartürk E. Comparison of the effects of warfarin and heparin on bleeding caused by dental extraction: a clinical study. *J Oral Maxillofac Surg* 2011;69:2500-7.

Campbell JH, Alvarado F, Murray R A. Anticoagulation and minor oral surgery: should the anticoagulation regimen be altered? *J Oral Maxillofac Surg* 2000; 58: 131-135.

Response: We mentioned the results shown in the papers recommended and underscored that warfarin should not be discontinued when performing dental extraction in warfarinized patients. All the papers are now cited in the revised version of our manuscript

3) The authors state on page 12, "Therefore, when performing dental extraction in high-risk patients such as those taking warfarin, capability of the facility for means of hemostasis other than simply topical hemostasis and availability of personnel at afterhours should carefully be considered." The fact that these extractions were performed by oral surgeons is fine, but I object to the implication that special precautions (eg, a 24-hour facility) need to be taken because patients are on warfarin. If general dentists perform extractions in Japan on non-anticoagulated patients, then these same general dentists can perform extractions on anticoagulated patients. The incidences of bleeding complications in many previous studies (see above) have been the same in anticoagulated and non-anticoagulated patients. There are occasionally bleeding complications in non-anticoagulated patients as there are in anticoagulated patients. Whatever the general dentist's protocol is for after hour care should suffice for postextraction bleeding problems, whether or not the patient is anticoagulated. This should be clarified in the text or simply eliminate the discussion of it entirely. Again, the fact that oral surgeons performed the extractions is fine, but the authors should not assume that specialized training or 24-hour facilities are needed for such extractions.

Response: We are honored by the comments by Dr. Wahl as an expert in the field.

We agree with the Reviewer that, as have been shown by multiple previous reports, incidence rates for post-extraction bleeding are not significantly different when compared among patients under warfarin-based anti-coagulation therapy between those who discontinued warfarin in preparation of dental extraction and those we continued on warfarin, indicating that additional support by a facility where 24-hr care is available would not be required.

We showed in the present study, comparing warfarinized patients without cessation of warfarin for dental extraction and healthy individuals, that risk ratio for post extraction bleeding could be approximately 9 fold higher in patients in warfarinized patients (the description has been omitted from the conclusion based on other reviewers' suggestion to avoid confusion). Patients' age and/or race might have contributed to the different outcome. These results suggest importance of awareness on risk of post-extraction bleeding, regardless of its frequency.

However, we did not examine whether assuring support by a facility where 24-hr support is available

would reduce risk for post-extraction bleeding in warfarinized patients. Therefore, we deleted the description regarding the possible support by such facility.

Reviewer Ben Balevi

1) I find the current ABSTRACT is confusing and needs a complete rewrite. For example, The objective of the study is not “The 95% confidence interval difference ...” but assessing the incidence of significant post-extraction bleeding between the patient on warfarin and the patient not-receiving warfarin. Also in the result section, the confidence interval of the difference in incidence in bleeding between the two groups is given but the statistic itself (3.24%) is not.

Response: “Objectives” and “Results” sections have been revised as suggested.

2) I continue to believe that the statement on page 4, line 10; “However, a clinical study reported that embolism or thrombosis developed in approximately 1% of patients who discontinued warfarin prior to dental surgery, resulting in death in a large proportion of the affected patients.[1] is inaccurate and alarmist and should still be removed.. .The authors are citing Wahl (1998) narrative review – not a clinical study per say . Wahl’s summarized (not a meta-analysis) the outcomes from selected papers (not a systematic review). I appreciated that the authors this manuscript gave a long discussion on this issue [ p. 10 starting from line 30] but most of it is inaccurate and misleading. For example, it is inaccurate to infer that Wahl actually evaluated 496patients/524 tooth extractions where warfarin was temporarily discontinued prior to the procedure, and observed thromboembolism in 5 cases (0.95%), 4 out of which died. He did not observe patients but pooled data he collected from 16 different studies. Unfortunately, his methodology is not that of a systematic review and the way he pool the data is not a acceptable meta-analysis and thus prone to significant bias. Also, it is misleading to infer that deaths cited in the discussion were caused by a disrupting anticoagulation therapy as there were many confounding factors in each of these cases which makes extrapolating a cause-effect relationship to disrupting anticoagulation therapy and death in any of these cases invalid. Finally I have trouble with the concluding statement ( p. 11 line 25 ) “Taken together, the literature indicate that thromboembolic complication does occur, though absolute numbers are small and suggest that decision whether or not to continue maintenance dose of warfarin when performing dental extraction in patients receiving warfarin should be made carefully taking risks and benefits that warfarin could cause into account” Although true that thromboembolic complication do occur, the inference that there is an unacceptable high risk it occurs , especially resulting in “death”, is misleading and at worst alarmist. I suggest that this whole section be removed and summarized with a statement along the lines that there is a perceived risk of a CVA occurring after disputing anticoagulation therapy suggested to be as high as 1% and as low as 0.059%.

Response: As suggested, we revised the Discussion to simplify and added sentences to state that incidence rate for CVA has been reported between 0.059 and 1% when dental extraction is perform in patients who stopped taking warfarin in preparation.

I feel the rest of the discussion is irrelevant to the objectives of this study which compared the risk of bleeding events after a dental extraction between the warfarinized patient and the non-warfarinized patient. This study is not comparing the risk of bleeding in the warfarinized patient and the disrupted-warfarinized patient. These are two different studies with two different clinical questions. The discussion the authors are making on p10- starting from line 30 is pertinent to the later study and thus I believe should be omitted from this articles or at least simplified.

Response: As pointed out, the present study did not compare differences of incidence rate of post-extraction bleeding between warfarinized patients whose warfarin was temporary discontinued in

preparation of dental extraction and those who continued on warfarin. Nonetheless, we feel that the referenced articles are important to emphasize variable occurrence of post-extraction bleeding. Different results could be accounted for different subject population. To clarify our points, we revised the Discussion (page 10).

3) P.4 Line 19... the word “issue” is referring to what?. Is the “issue” discontinuing warfarin can result in thrombus or maintaining warfarin does not increase risk of post-extraction bleeding. The prior sentence infers the issue is the former yet the 9 article ( ref. 2-10) cited afterwards infer the later. In-other-words, the introduction is confusing, especially in light that this study has nothing to do with comparing the warfarinized and disrupted –warfarinized patient.

Response: As stated in response to the previous comment, we revised our Discussion.

4) P. 11 line 48 ... stresses only the right handed side of the confidence interval which I feel is misleading and alarmist, considering that the left handed side of the confidence interval is as low as 1.59%. Small point but I felt I needed to make it.

Response: As recommended, we omitted the description for approximation and instead simply noted the confidence interval of both sides.

5) The Conclusion [p.17 line 19-26] should give the mean statistic of 3.24% and the associated confidence interval. Also Removed the RR of 9.31% since it is not discuss anywhere else in the manuscript.

Response: As recommended, we stated the mean and 95% confidence intervals and deleted RR from the Conclusion.

6) Table 4 [p.27] statistic numbers line 24 should be brought up to line 23 [PT-INR].

Response: Table 4 has been corrected.

### VERSION 3 – REVIEW

<b>REVIEWER</b>	Ben Balvi Univeristy of British Columbia Canada
<b>REVIEW RETURNED</b>	13-Sep-2014

<b>GENERAL COMMENTS</b>	<p>Summary of My understanding</p> <p>The clinical questions this study is trying to answer are ;</p> <p>Question #1 In adult patient slated for a simple dental extraction, will the warfarinized patient compare to the non-warfarinized patient result in more significant post – op bleeding events?</p> <p>Question 2 What factors place the warfarinized patient at risk of significant post – op [simple-dental-extraction] bleeding events?</p> <p>Methodology : This is a multicentered study that measured the incidence of the extent post-op bleeding from the consecutive ( over 17 months) selection of 2,321 teeth from not receiving warfarin ( non-warfarinized ) patients with 496 teeth from patients receiving warfarin ( warfarinized)</p>
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	<p>Outcome The study defines simple extraction as tooth removal without traumatizing the surrounding alveolar bone or elevating a mucoperiosteal flap.</p> <p>The main conclusions are</p> <ol style="list-style-type: none"><li>1. the absolute difference in the mean risk of a significant post-extraction bleed between the warfarinized and non-warfarinized patient is 3.24% (95%CI 1.49, 4.99%)</li><li>2. Age, PT-INR, inferior nerve block and formation of abnormal granulation tissue in extraction socket significantly correlated with post-op extraction in the warfarinized patient.</li><li>3. Age, antiplatelet drugs, PT-INR and history of acute inflammation at extraction site were significant risk factors for post-op extraction bleeding in the warfarinized patient.</li></ol> <p>My concerns that need further explanation</p> <p>1. I continue to believe that the statement on page 4, line 10; However, a clinical study reported that embolism or thrombosis developed in approximately 1% of patients who discontinued warfarin prior to dental surgery, resulting in death in a large proportion of the affected patients.[1] is inaccurate and alarmist and should STILL be removed. The authors are citing Wahl (1998) narrative review – not a clinical study per se. Wahl's summarized (not a meta-analysis) the outcomes from selected papers (not a systematic review). Unfortunately, his methodology is not that of a systematic review and the way he pools the data is not an acceptable meta-analysis and thus prone to significant bias. Also, it is misleading to infer that deaths cited in the discussion were caused by a disrupting anticoagulation therapy as there were many confounding factors in each of these cases which makes extrapolating a cause-effect relationship to disrupting anticoagulation therapy and death in any of these cases invalid. Although true that there is a perceived risk of a thromboembolic complication occurring during dental treatment, the inference that there is an unacceptable high risk it occurs, especially resulting in "death", is misleading and at worst alarmist.</p> <p>My I suggest AGAIN that this whole section be removed and summarized with a statement along the lines that there is a perceived risk of a CVA occurring after disrupting anticoagulation therapy suggested to be as high as 1% and as low as 0.059%. I feel any further discussion on this issue is irrelevant to the objectives of this study which compared the risk of bleeding events after a dental extraction between the warfarinized patient and the non-warfarinized patient. This study is not comparing the risk of thrombosis, embolism or death in the warfarinized patient and the disrupted-warfarinized patient. These are two different studies with two different clinical questions.</p> <p>2. P.10 Line 43 ... the last line of the paragraph should be removed because it is misleading, alarmist and cannot be supported by the evidence.</p> <p>"These findings have strongly suggested that warfarin should not be discontinued when performing"</p>
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	The word “strongly” implies that the evidence is strong. However, a critical appraisal of the evidence cited by Wahl ( as per my explanation above) show the evidence is actually weak.
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<b>REVIEWER</b>	Michael J Wahl Christiana Care Health System
<b>REVIEW RETURNED</b>	14-Sep-2014

<b>GENERAL COMMENTS</b>	I'm sorry I did not spot this in previous versions of this paper, but I think it's important, and I put it in my review: On p. 6, line 16, the authors state, “The hemostatic methods for patients not receiving warfarin were chosen at the discretion of the dentist or oral surgeon performing the procedure. In patients on warfarin therapy, either absorbable oxidized cellulose or gelatin sponge was implanted into the alveolar socket, and wound margins were sutured.” So the anticoagulated patients received some very effective local hemostatic methods like oxidized cellulose and sutures, but the non-anticoagulated may have had no more than gauze to bite on? This is a very important difference in the two groups and could explain why the non-anticoagulated group had a higher incidence of bleeding than the anticoagulated group. The authors should explain in detail their reasons for the difference in hemostatic methods and how this difference could have affected the bleeding outcome both in the methods and the discussion.
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### VERSION 3 – AUTHOR RESPONSE

Reviewer Name: Dr. Ben Balvi

1. I continue to believe that the statement on page 4, line 10;

"However, a clinical study reported that embolism or thrombosis developed in approximately 1% of patients who discontinued warfarin prior to dental surgery, resulting in death in a large proportion of the affected patients.[1] "

is inaccurate and alarmist and should STILL be removed. .The authors are citing Wahl (1998) narrative review – not a clinical study per say . Wahl’s summarized (not a meta-analysis) the outcomes from selected papers (not a systematic review). Unfortunately, his methodology is not that of a systematic review and the way he pool the data not a acceptable meta-analysis and thus prone to significant bias. Also, it is misleading to infer that deaths cited in the discussion were caused by a disrupting anticoagulation therapy as there were many confounding factors in each of these cases which makes extrapolating a cause-effect relationship to disrupting anticoagulation therapy and death in any of these cases invalid. Although true that there is a perceived risk of a thromboembolic complication occurring during dental treatment , the inference that there is an unacceptable high risk it occurs , especially resulting in “death”, is misleading and at worst alarmist.

I suggest AGAIN that this whole section be removed and summarized with a statement along the lines that there is a perceived risk of a CVA occurring after disputing anticoagulation therapy suggested to be as high as 1% and as low as 0.059%. I feel any further discussion on this issue is irrelevant to the objectives of this study which compared the risk of bleeding events after a dental extraction between the warfarinized patient and the non-warfarinized patient. This study is not comparing the risk of thrombosis, embolism or death in the warfarinized patient and the disrupted-warfarinized patient. These are two different studies with two different clinical questions.

Response: As suggested, the description has been modified.

A few references remained as a background of the present study.

2. P.10 Line 43 ... the last line of the paragraph should be removed because it is misleading , alarmist and cannot be supported by the evidence.

“These findings have strongly suggested that warfarin should not be discontinued when performing”

The word “strongly” implies that the evidence is strong. However, a critical appraisal of the evidence cited by Wahl ( as per my explanation above) show the evidence is actually weak.

Response: We have clarified the description.

As suggested, there is no strong evidence that suggest WF should be discontinued, and risk for serious bleeding in warfarinized patients, if any, was over-estimated, On the other hand, multiple reports indicates risk for CVA when WF was discontinued. Overall, risk associated with WF cessation outweighs the risk associated with continued WF, regardless of incidence of CVA. As a background of the present study that compared incidence of bleeding complications in warfarinized patients and those who are not receiving WF, a few references remain cited.

Reviewer Name: Dr. Michael J Wahl

I'm sorry I did not spot this in previous versions of this paper, but I think it's important, and I put it in my review: On p. 6, line 16, the authors state, “The hemostatic methods for patients not receiving warfarin were chosen at the discretion of the dentist or oral surgeon performing the procedure. In patients on warfarin therapy, either absorbable oxidized cellulose or gelatin sponge was implanted into the alveolar socket, and wound margins were sutured.” So the anticoagulated patients received some very effective local hemostatic methods like oxidized cellulose and sutures, but the non-anticoagulated may have had no more than gauze to bite on? This is a very important difference in the two groups and could explain why the non-anticoagulated group had a higher incidence of bleeding than the anticoagulated group. The authors should explain in detail their reasons for the difference in hemostatic methods and how this difference could have affected the bleeding outcome both in the methods and the discussion.

Response: In the present study, means of hemostasis in warfarinized patients were chosen based on the recommendation in several guidelines, while suture was performed in limited numbers of patients in non-WF group. In general, wound suture is not commonly required in non-warfarinized, otherwise-healthy patients and is performed only when excessive bleeding occurred. We agree with the reviewer that the difference in methods of hemostasis might have caused bias in the present study. However, we would have underestimated the risk for uncontrollable bleeding in non-warfarinized patients, had we selected cases that wounds were sutured. Therefore, we chose to include cases where wound suture was not necessary, as we would experience in common clinical situations. Overall incidence of post-extraction bleeding in non-WF patients was as little as 0.39% in the present study. Indeed, there was no significant difference in post-extraction bleeding incidence in non-WF patients whose wound was sutured or not (0.6% and 0.2%, respectively), suggesting that the means of hemostasis had little affected the outcome of the present study. A sentence clarifying the point was added in the discussion.