Peer Review File

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Reviewer A

The authors performed a retrospective chart review to assess the impact of anticoagulation/ antiplatelet on management of epistaxis. The data were collected from the electronic medical record. Univariant and multivariant analysis were used for assessing the success of treatment and adverse events. I have a few comments as follows:

1. The authors did not record the data of the degree of severity of bleeding which was essential. Minor anterior bleeding associates with higher rate of success compared to severe posterior bleeding. I understand that severity of bleeding may not be reported and retrospective studies have a limitation but it should be mentioned under METHODS and missing data should be reported.

Reply: Thank you. Fair point. Limitation of the study due to severity of bleed is disclosed in line 716, and severity of bleed impact is discussed in the body of manuscript (line 337, 349, 366, 373, 391, 642, 669) but the authors can see now that more detail and context should've been provided on how severity of bleed was handled. Manuscript edited throughout to reflect that.

The ATLS classification of shock was largely used to determine the degree of bleeding (major bleed = Class III / IV). Quantifying the exact severity of bleed was challenged with missing data on volume of blood lost, urine output, and respiratory rate. But all episodes except 29, had OBS recording. When data was missing other clues such Hb, or adverse event (i.e. transfusion) was used to determine if the bleeding was major or minor.

Only 3 presentations with severe bleed identified (stage III shock).

Although the severity of the bleeding could not be precisely quantified, it could be estimated:

- The clinician's choice in treating the bleeding conservatively reflect it was mild.
- The degree of success despite very conservative therapy suggested the bleeding was likely not major than it was.
- Even in those presenting with hypertensive crisis (associated with more severe bleed), only 2 out of 14 had severe bleed. Of these only 5 were observed longer than 12 hours for monitoring, and the rest were discharge home.
- Only 2 required transfusion.
- When the data was missing it was more likely that the bleeding was not major than it was.
    - The author explored the post-op cohort (excluded in the study) to see if the pattern of data recording was different. This group tends to bleed more severely and are always escalated to ENT (therefore ENT notes quantified blood loss). The author noted that ED documented blood volume, OBS and Hb more meticulously (hence fewer missing data).

- Furthermore, most of the missing data occurred in younger patients (<50 years old), and during the pandemic (March-Aug 2020).

Changes in text

-Method, data extraction, line 166-170 – added method on severity of bleeding

-Results, data analysis, line 242-3 – added information

-Results, treatment type and effect, line 308 – added information

-Discussion, Anticoagulation, line 349-351– added information

-Discussion, HT, line 454 – added explanation

-Limitation of study, line 717-9 – edited to explain better

-Limitation of study, line 726-732 – added information

2. Platelet count and INR should be assessed in patients who received anticoagulation/ antiplatelet and presented with epistaxis. Please report the data.

Reply: Thank you. The authors agree that INR and platelet count are essential in ACT / APT patients, but the study was limited by this missing data. The manuscript is corrected to address this question.

8 patients (out of 19 on Warfarin) had missing INR. Of the 11 with INR, only 5 had high INR (4-5.1). INR was not checked for patients on DOAC or not on anticoagulation.

- Although INR record was missing, the sample size of patients this was highly relevant to were too small to make a major impact in the outcomes. This was checked in earlier analysis.

Platelet count was also not available with the access provided to the data for any of the patients.

Changes in text

-Results, data analysis, anticoagulation/antiplatelet line 238-240 – added

-Discussion, line 356-8 – edited to add more detail relevant to INR

-Limitation of study, line 679-683 – added comment on INR and platelet count

3. The authors concluded that dissolvable packing and cautery associated with reduced success and worsen the outcomes. Counselling and topical ointment application significantly increased odds of success. This is not correct when the choice of treatment associated with the severity of bleeding. Counselling and topical ointment application were used in simple epistaxis and dissolvable packing and cautery were chosen in complicate bleeding.

Reply: Thank you. The authors notes that the outcome could have been explained better. The

manuscript is corrected to address the comment. Further explanation (below) is provided for your attention.

Severity of bleeding – further explained in the reply to question 1.

- It would have been great to quantify the blood loss for each episode. Ideally this study would have been a large prospective or RCT, but the study was limited by the approval granted (retrospective study).
- To overcome the limitation with missing data, the author, thoroughly analyzed each case to identify any hallmark of a severe bleed and broadly divided the cohort into major and minor bleed; then analyzed the data with a well-researched, considered careful analysis, controlling any variables that was found to be significant either in this cohort or in literature.
- The choice of treatment largely was the determined by the preference of the clinician over severity of bleed. Some clinicians routinely applied pack for all (even very minor bleed), and some routinely cauterized then considered other treatments (even in major bleed). All clinicians escalated the treatment to a more invasive treatment or ENT consult when bleeding was severe or serious.

Treatments were given in combination (36 combinations). So they had to be analyzed with respect to how each treatment impact another and the outcome (Results, treatment type and effect, line 252). Having large number of treatment combination made the analysis challenging. Therefore,

- Logistic regression used and controlled significant variables.
- A mathematician was employed to check the analysis for bias and power for each subgroup.

Significant findings:

- When a patient had topical ointment added to their treatment combination the odds of success of increased. But when a patient received cautery in the combination the odd of success was reduced. This finding was significant. There was no bias.

Trends (the sample sizes were small, but trends were close to significant)

- Those on ACT/APT had lower odds of success than those not on it.
- The subgroup <40 years old + received cautery trended to better odds of success than any other group receiving cautery but still 29.4% recurred within 2 weeks.
- When the cautery was used in combination with packing it reduced odd of success for packing but when packing was applied after cautery, it improved the odds of success for cautery.

The findings are not at odds with routine clinical practice:

- Counselling prevented representations – patient did not return for minor bleeds and could self-manage the epistaxis with basic first aid such as pressure and topical medications.
- Ointment provided barrier over the healing tissue and prevented dry crust formation that otherwise falls to cause recurrent bleed in 10-14 days post cautery.
- Cautery causes collateral damage with increased mucosal surface that needs to heel.
- DP insertion can cause trauma in a less skilled hand and lead to rebleed if dissolved early

to exposed the surface area that is yet to form scar tissue.

Changes in text

-Results, Treatment type and effect, line 267-287

4. LOS and recurrent admission were the outcomes but not reported.

Reply: Thank you for this comment. The manuscript is corrected to address this comment.

47 patients presented twice, 7 presented 3 times and 4 presented >3 times.
69 of the readmissions was within 30 days and the rest within 6 weeks.
LOS ranged from 1 hour to 300 hours per each episode of presentation.
n = 308 LOS <24 hours
n = 22 LOS 24-72hours
n = 5 LOS >72 hours

Changes in text

-Results, Treatment type and effect, line 259-261 – added data

5. The authors added a systematic review under DISCUSSION which was useful to readers but there are some parts (HT, CVD, liver disease, age, covid) not related to the aim of this study (the impact of anticoagulation/ antiplatelet).

Reply: Thank you. Fair point. Unnecessary information relevant to this cohort is removed.

Age and HT are significant variables in the logistic regression, so section is modified to information more relevant to this cohort only. Covid impacted the cohort significantly. The section modified to explain this better.

Changes in text

-Discussion, Cardiovascular disease, line 470-3 – deleted section

-Discussion, Liver disease, line 477-482 – deleted section

-Discussion, Age, line 489-494 – edited to keep the focus on the study

-Discussion, HT, line 400-68 – major edits to keep it focused on this study

-Discussion, COVID, line 500-11 – edited to keep the focus on the study

-Discussion, treatment types, Antifibrolytics, line 536-549 – removed, not relevant to study

-Discussion, treatment type, dissolvable packing, line 613-7 – removed, not relevant

Reviewer B

Thank you for this manuscript which I carefully read and you will find my remarks below. First of all, I have concerns about the selection criteria of the patients. If I look how patients were treated by the ER or ENT-physician it is striking that not one patient had to undergo a surgical procedure under general anesthesia, so no clipping (EPSAL) or embolisation. This could be due to the exlusion of posterior epsitaxis however exlcuding posterior epsitaxis is an important bias, especially when you later on use the literature as a reference where in most articles anterior and posterior epistaxis are mixed. It also not specified how posterior epistaxis was excluded (endoscopy, oral examinations etc..)

Reply: Thank you for raising this. Yes, no surgical intervention was a striking find. Why this was so, was explored very carefully by the author. The manuscript is changed to address this. Further comments are also provided below.

Two concerns raised in the above question:

- Posterior epistaxis: How was it defined? Why was it excluded?

- Lack of surgical intervention

Posterior epistaxis

Definition of posterior epistaxis – added to manuscript (see below)

Posterior epistaxis reported in 2 patients in the data provided to the authors:

- a 24-year-old treated with SPA ligation, LOS 2 days.
- a 74-year-old treated with SPA embolization, LOS 16 days.

The relatively high success rate with very conservative treatment in the less skilled hands (junior medical officers), was more consistent of anterior epistaxis than posterior epistaxis. But to ensure no case is mislabeled anterior bleed when it was posterior, the medical records were very carefully reviewed.

The decision not to include posterior cohort was a considered decision:

- The sample size (posterior epistaxis) was too small & variable to have a meaningful impact.

- There was no bias – the analysis was checked by a mathematician to look for this.

- The authors did consider the impact of including or excluding posterior epistaxis. The author thought that including posterior epistaxis can create unconscious bias in the reader mind, presuming unfavorable outcomes were linked to posterior epistaxis. There are many recurrent presentations, and few but very significant adverse events in this cohort. It was

important to keep the emphasis of the study on anterior bleed. So the study could keep the emphasis on: whilst the outcome of anterior epistaxis is largely favorable, there still is a risk of serious adverse events such death especially for vulnerable patients (elderly, significant comorbidity, frail, etc.).

Lack of surgical Procedures:

This was striking and unusual for a very large center. Few contributing factors identified as followed:

- Impact of COVID
    - Reduced airway instrumentations → more conservative treatment options.
- Unit preference – some consultants preferred to manage the cases with conservative therapy as much as possible. So many of the cases that would've been managed elsewhere with endoscopic assisted cautery (i.e. recurrent bleed), were managed with repeat DP + cautery.

The two limitations provided a unique opportunity to not only report a focused study on anterior epistaxis treated with conservative treatment options, but also report a cohort presented to a tertiary center but with parallels to rural setting (access to ENT limited by logistics but follow up is readily available). This could help identify what treatments combination is the most successful when ENT is not readily available (i.e. rural/remote setting).

Changes in text
-Title, line 3 – corrected epistaxis to anterior epistaxis
-Method, study eligibility, line 142-4 – defined posterior epistaxis + added diagram
-Discussion, line 342 – added more information
-Discussion, impact of covid, line 500-11-elaborated on Covid impact
-Limitation of study, line 717-9
-Limitation of study, line 726-732

Question 1: If I look at the numbers of patietns on page 8, there are some contradictory numbers which need a closer look at: 257 patients with 335 episodes (line 172) however line 183 there are 343 episodes.

Reply: Thank you. There was 2 typo that is corrected. The rest was intentional. Manuscript is corrected to clarify this better.

257 patients. 335 episodes of admission (includes representations of 257 patients). 342 packing insertion (sometimes pack was inserted and removed within hours in the same episode of admission)

To analyze the impact of packing, 342 packing episodes was used (instead of episodes of presentations n=335), because the act of packing can lead to mucosal trauma (however minor - but significant in patients on ACT or APT (= bleed easier)). Otherwise the impact of packing would have been underestimated.

Changes in text
-Abstract, results, line 44: Corrected typo
-Results, Data analysis, Treatment effect and type, Table 1, line 281 – added explanation why total is larger than 335 (total episodes of admission).

Question 3: Hypertension: 163 had hypertension but additional 121 had a high blood plessure: so is 274 (patients?), seconly line 183 44 had know HT while on line 178 you write that 163 had HT?

Reply: Thank you very much for the fair point. The manuscript is corrected to explain better. Excessive information removed.

The point of the paragraph is to highlight HT may be underrepresented in this cohort (same as most other literature).

163 had diagnosis of HT.

121 further patients presented with high BP (SBP >135)

- Single recorded high BP hence not diagnostic for HT
- Not had any documented repeat BP recording in the same admission or follow up
- Since none had known HT but could have (which follow up BP or repeat BP could diagnose), the author assumes HT impact is underestimated.

83 had missing BP on database. Of these only 44 had known HT. So again, the author suspects HT may have been missed and therefore underrepresented.

Changes in text
-Results, data analysis, comorbidities, line 216-224 – edited
-Discussion, hypertension, line 400-68 – major edit to explain findings better

Question 4: Line 215: DP was associated with reduced success: compared with what? was this statictically significant?

Reply: Thank you. The manuscript corrected to report the results better.

DP was associated with reduced success compared to those not received DP. This was significant for short term outcome but not long-term outcome. This can be due to the trauma to nasal mucosa with DP insertion (leads to rebleed in <6 weeks but scars and heals over by >6 weeks).

Changes in text
-Results, treatment type and effect, line 267-286 – edited to present results more clear

Question 5: Line 215: how do you define success? Which time of follow up?

Reply: Thank you. Manuscript corrected to clarify this better.

Definition of success was defined in Method, Study endpoint, line 188-9:

- Success = no recurrent bleed or adverse event. Success is then divided into two groups:
    - Short term success <6 weeks
    - Long term success >6 weeks but no more than 12 months

The reason success was divided into groups is to assess the impact of trauma to the nasal mucosa (with cautery or DP insertion). This helped to make sense of divisive literature on whether some treatments are successful or not.

Changes in text
-Method, Study endpoint, line 191 – added clarification to definition of long-term success

Question 6: In interpreting the data there is a big bias of only selecting anterior epistaxis

Reply: Thank you. This is to an extend explained earlier in reply to question 1 (reviewer B).

The sample size of posterior epistaxis was too small and diverse to have any meaningful impact on the outcome. The bias was checked for all analysis in the study.

Question 7: line 248: how do you explain that 3 patients died and 2 needed transfusion if you only select anterior epistaxis

Reply: Thank you for the comment. This was a startling observation in the study. The author explored this in medical records. The manuscript is edited to clarify better. Further detail below:

Deceased patients:

Whilst deaths were not due to active bleeding, the consequence of bleed or treatment (withholding ACT or APT) contributed to this outcome.

- 91-year-old, on NOAC. Controlled HT (BP not high on arrival). Mild anterior bleed. Controlled with topical vasoconstrictor (routinely given to all in this study cohort). Ointment applied (by ED). Readmitted with sepsis secondary to aspiration pneumonia 10 days later. Palliated (frail). Deceased.

- 89-year-old, on NOAC. Controlled HT (BP not high on arrival). Mild anterior bleed. Hb 108 (but known anemia, no significant change in Hb with bleed). ENT consulted. Epistaxis self-limiting. No treatment given but NOAC withheld. Readmitted 10 days later with sepsis secondary to aspiration pneumonia. Deceased.

- 51-year-old, on NOAC + warfarin + antiplatelet for cardiac failure and AF (good rate control), controlled HT, and DM. ENT consulted. Mild anterior bleed. Received cautery + packing (Surgicel and Nasopore), and all APT and ACT withheld (INR was therapeutic on arrival). VF arrest. Deceased. Cardiac team considered combination of the burden of epistaxis and withheld medication contributed to the outcome; however, acknowledge that patient had severe comorbidities and may have suffered the same faith if did not have epistaxis. Epistaxis was also a sequela of being on dual ACT and dual APT.

Received transfusion:

- 54-year-old with septal perforation (multiple previous cauteries), controlled HT, major anterior bleed. ED controlled with cautery + ointment + DP. Recurs 3 days later. ENT consulted. ENT reapplies DP. Patient is transfused. There is no record of Hb but the medical records document anemia. There is no definition on what was considered anemia, but general practice of the hospital was to transfuse for Hb was ranging 70-100 depending on the patient's comorbidities. The patient presented prior to the pandemic.

- 88-year-old with AF on Warfarin (INR 2.5 on arrival), Cautery to control mild anterior epistaxis. Represented 1 month later. ED controlled the bleed with another cautery. No Hb documented but medical records note anemia. Patient transfused. ENT not consulted. The patient presented during lockdown early pandemic (March).

In this cohort there were 2 more patients with aspiration pneumonia, 4 with syncope and fall, and 5 with cardiac events (angina or worsening of cardiac failure) within days of receiving treatment for epistaxis.

Adverse events reported were consistent with those found in literature – line 108, 690

Changes in text
-Results, adverse events, line 315-9 - added more detail

Question 8: line 260: patients stay on overage 3 day in hospital: for an anterior epistaxis this is long? how can you justify ointment or a tamponnade for anterior epsitaxis and keep the patients hospitalized

Reply: Thank you for raising this.

The average 3 days LOS is quoted from the literature (referenced) and is not this cohort's LOS.

The authors agree that 3 days is lengthier than what is observed in other centers, especially if the bleeding is mild and controlled with very conservative therapy. In this cohort most patients (91.9%) were managed within 24 hours of arrival to ED (LOS 1 day).

The 27 cases (8.1%) who stayed longer (LOS >1 day) had the following factors causing the delay:

- COVID restrictions
    - Await covid screening before ENT instrument the airway (i.e. change RR to DP)
    - ED consult ENT less – ED observed some patients longer than ENT would have
    - Reduced instrumentation of airway – ENT tends to try repacking even if it failed than surgical intervention (endoscopic assisted cautery)
- Clinician's preference –
    - Some consultants preferred the RR to remain for at least 48 hours vs 24 hours.
    - Some consultants preferred a more conservative approaches in treatment but observed the patient longer.
- Patient factor – i.e. Comorbidities
- Logistics of the unit
    - 3 EDs spread out 16 to 24 Km apart with one ENT service responding to all. Often the ENT reg oncall is not onsite the call is received from → delay in review
    - Shift work (all tiers of care (ED and ENT from JMO to VMO) rotate in 12-24 hour blocks) → Person inserted the packing was not the person discharging the patient → change of preference or delay in discharge

Changes in text
-Results, Treatment type and effect, line 309-12 – added information
-Discussion line 330-7 and 343– added more information

Question 9: line 263: predictors of LOS are APT... posterior epistaixs: but you excluded posterior epistaxis? How can this be a predictor?

Reply: Thank you for this. The manuscript is edited to provide details specific to this questions.

The authors are listing predictor of increase LOS as reported in literature (referenced). Although posterior epistaxis was excluded in this cohort, it was still relevant to list as the risk factor to this cohort because the cohort was not posterior epistaxis (hence lower risk of rebleed but then had comparable rebleed for some subgroups i.e cautery group).

Changes in text
-Results, Treatment type and effect, line 309-12 – added information
-Discussion line 330-7 and 343– added more information

Editorial Comments

1. The "cost-effective" in the title and throughout the manuscript may be misleading, as it could suggest that this study is evaluating the economic cost of epistaxis treatment. However, the study is only exploring more successful treatment strategies.

Reply: Agree. Thank you for this feedback. Changed title.

Changes in text
-Title, line 3 - removed cost-effective; changed title to anterior epistaxis

2. Readers should be able to easily identify the design that was used from the Title or Abstract. Thus, please indicate the study type in the Abstract-Methods or Title. This should include not only the reported "retrospective review", also whether it is a cohort (retrospective/prospective), case-control or cross-sectional study. Kindly take note of the unique characteristics of each type of research design.

Reply: Thank you. Changed the title and abstract.

Changes in text
-Title, line 3 – added cohort
-Abstract, method, line 39 - added cohort
-Method, study design, line 123 – added cohort

3. Please add the key element of study design in the methods section of the abstract, such as the exact study period (xx year, xx month), type of sample enrollment (consecutive, random, or convenience), and statistical methods.

Reply: Thank you.

Duration of study:
One year – specified in manuscript in:

- Abstract (method) line 39, and
- Method (study design) lines 127-8

The study period:
The author was given permission to review the data from 1st of Aug 2019 to 1st of Aug 2020. The access to this data was not approved until covid restriction imposed on research activity in Monash Health were lifted (over a year and a half later). Hence the ethic approvals and access to medical records were granted much later than the specified period. Study period duration specified in manuscript in:

- Method (study design) lines 127-8

Type of study
Retrospective cohort with consecutive enrolment (timeframe that allowed enrollment of every single case presented with anterior epistaxis that fit the inclusion criteria). Manuscript corrected to add more detail to type of study

- Method (data extraction), line 158 - added consecutive.

Statistical method
Explained in method, statistical analysis, line 194-9

Changes in text:
Method (data extraction), line 158 - added consecutive.

4. Abstract-Results: "The most common treatment type was cautery … The best outcome was observed in patients receiving ointment and education, and no cautery." Please present relevant statistical data rather than merely describing the outcomes.

Reply: Thank you. Result section corrected as you recommended.

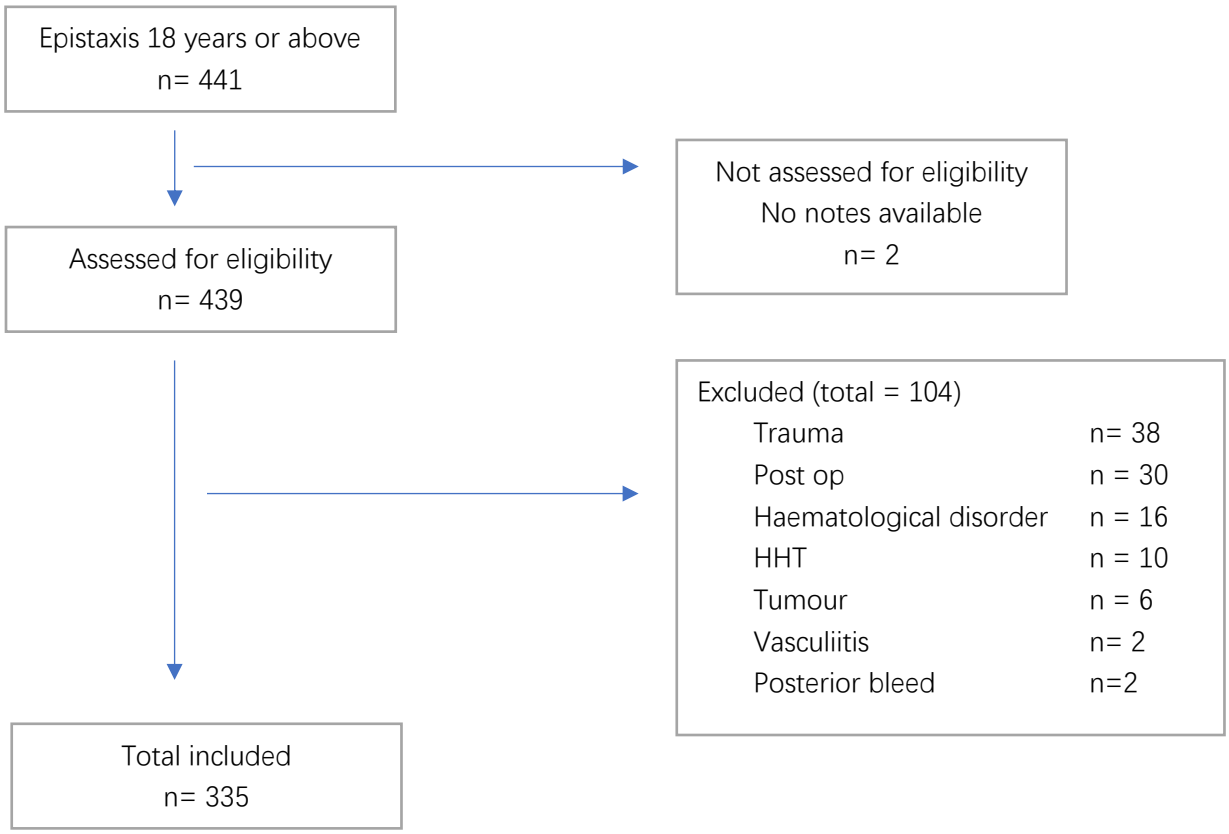
Changes in text
-Abstract (Results), line 44-51 – added data.

5. Why did the authors select the period from August 1, 2019, to August 1, 2020, for the study? Was a sample size calculated during the study design phase? Or was a power analysis performed given the actual sample size included?

Reply: The period of the study is the period approved by the Monash ENT Research committee. The ethic approval and access to data was not granted until covid restriction on research activity in Monash Health were lifted (over a year and a half later).

Since the study was retrospective and not prospective, power was not calculated prior data collection. But power was checked with the help of a mathematician throughout all analysis. Since this was satisfactory, the author did not find necessary to request extending the period of the study to any further than what was already approved.

6. Please provide a flow chart illustrating the numbers of participants at each stage, including the number of initially identified patients, the number of excluded individuals, the final number of participants included in the analysis, and with reasons for inclusion and exclusion. The figure 1 in this article (https://academic.oup.com/fampra/article/20/6/696/530870) is here for authors' reference.



Reply: Monash is a large HHT center. The database was already provided excluding HHT. Few more cases identified when medical records reviewed and excluded. Therefore, the excluded HHT group may be underrepresented than what Monash would have received in the period specified.

Changes in text
-Method, study eligibility, line 145-156 – added diagram 1

7. As pointed out by the second peer reviewer, there seems to be an inconsistency in the data: the abstract mentions "257 patients … leading to 343 episodes", but the title of Table 1 says "all patients; n=342". Please verify the accuracy of the submitted data.

Reply: Thank you. Agreed. This is corrected in manuscript as above.

There were two typos that are corrected.

257 patients. 335 episodes of presentation. 342 in table 1 reflects number of times the packing (DP

or NDP) was inserted (sometimes the packing is removed and reinserted in same patient same episodes within hours apart – the author considered this important to include as insertion of packing inflicts trauma to nasal mucosa (however mild) and increase risk of bleeding especially in patients receiving ACT / APT)

Changes in text:
-Abstract, results, line 44: Corrected typo
-Results, Data analysis, Treatment effect and type, Table 1, line 281 – added explanation why total is larger than 335 (total episodes of admission).

8. Table 1: "pr = 0.000" is inappropriate; please revise the *P*-values in your manuscript according to the following rules:
If $P<0.001$, please report "$P<0.001$" to avoid reporting unnecessarily excessive precision;
If $0.001\leq P<0.01$, please report the specific *P*-value to 3 decimal places, e.g., "$P=0.001$", "$P=0.009$";
If $P\geq 0.01$, please report the specific *P*-value to 2 decimal places, e.g., "$P=0.01$", "$P=0.06$", "$P=0.10$", "$P=0.90$";
If $P>0.99$, report "$P>0.99$".

Reply: Thank you. Corrected the manuscript.

Correction to the manuscript relevant to this question
-Results (treatment type and effect), Table 1, line 280 – corrected Pr to P
-Results (treatment type and effect), Table 2, line 283 – corrected Pr to P

9. For an observational study, the number of cited references seems excessive. For instance, "With an increasing aging population, their use is on the rise (7,11–15). The new direct oral anticoagulants (DOACs) work directly on the coagulation cascade and have become the gold standard of treatment due to superiority to Warfarin (12,13,16–20)." Two to three relevant sources per claim should be sufficient. For statements like "and 9.8% die of epistaxis or sequela of disease or its treatment (35,86,91,92)", it is sufficient to cite only the original source of this data. Please avoid secondary referencing.

Reply: Thank you.

Correction to the manuscript relevant to this question
-Deleted secondary references across the manuscript.