Audit of Eight DHBs'
Prothrombinex-VF use and compliance with the 2013 update Consensus Guidelines for Warfarin Reversal

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Executive Summary

Patients undergoing warfarin reversal in eight large DHBs were identified from issues of FFP, Prothrombinex and vitamin K as well as by hospital coding. From the 8023 potential instances of warfarin reversal, 721 episodes from 581 patients were selected for audit. The majority of reversals occurred in the wards (46%) and emergency departments (43%). In 30% of episodes, the patients were bleeding, 30% were non-bleeding and non-pre-operative, 26% were prior to emergency surgery, and 16% were prior to an elective procedure. Overall compliance with the ASTH guideline was 50%. Inappropriate use of reversal modalities was the most frequent reason for non-compliance with the guideline. Significant variation from recommended vitamin K and Prothrombinex dosing was also noted. Where Prothrombinex was used, reversal was generally very good with almost all patients reaching INRs below 2. Despite the large proportion of episodes apparently not following the ASTH guidelines, the difference in INR reduction between those cases meeting the ASTH guidelines versus those not, was small.

Introduction

Warfarin remains a very commonly prescribed anticoagulant in New Zealand despite new anticoagulants such as oral direct Xa inhibitors, and direct thrombin inhibitors being available as alternative therapies. Despite the associated bleeding risk, it is likely that warfarin will remain a commonly used anticoagulant in patients currently stable on warfarin therapy in New Zealand.

With any anticoagulant, reversal of the effect is important should the patient need surgery or start bleeding. In March 2013 the Australian Society of Thrombosis and Haemostasis (ASTH) published an update of the Consensus Guidelines for Warfarin Reversal[1].

A key agent in the warfarin's reversal is Prothrombinex-VF. Prothrombinex-VF contains factors II, IX, X and low levels of factor VII and can reverse the International Normalised Ratio (INR) in 15 minutes of administration[2]. Previous guidelines also recommended the addition of FFP to reverse the warfarin effect[3]. However, several reports have shown three factor prothrombin complex concentrate (PCC) without supplementary FFP is an effective method of warfarin reversal[4–8]. The 2013 update of the guideline now recommends the use of FFP only in patients with life-threatening or critical organ bleeding; or in situations where PCC is not available[1].

A warfarin reversal audit, conducted soon after the implementation of the revised guidelines and published in the Medical Journal of New Zealand[5], reviewed the management of patients requiring warfarin reversal intervention. Prescribing practices were reviewed against the updated guidelines in the Capital and Coast District Health Board (CCDHB) over a period of six months. The audit identified the suboptimal use of Prothrombinex-VF and the unnecessary use of FFP in the management of warfarin reversal.

By the start of this audit, the update of the ASTH consensus guidelines had provided warfarin reversal recommendations to prescribers for three years. It was hypothesised that prescribing practices for warfarin reversal had embedded in everyday practice. It was considered timely to conduct the audit again, broadening the data collection to include the main hospitals in New Zealand.
Since then, other anticoagulants, the direct oral anticoagulants (DOACs) have become more widely used. Although dabigatran has its own reveral agent, idarucizumab, rivaroxaban does not, or at least not in New Zealand. Accordingly, Prothrombinex is used in high doses when trying to reverse rivaroxaban. This audit did not look at rivaroxaban use but it is interesting to note that Prothrombinex use and the number of patients it has been used on has not undergone any dramatic change over the last ten years (appendix 3).

Aim

The aim of this clinical audit was to review Prothrombinex- VF prescribing practice compliance in eight large New Zealand hospitals against the 2013 ASTH consensus warfarin reversal guidelines.

Method

The Transfusion Nurse Specialists (TNS) in Auckland, Hamilton, Palmerston North, Wellington, Christchurch and Dunedin, and Clinical Nurse Specialists (CNS) at Middlemore and Waitemata undertook the data collection for the clinical audit. To minimise the risk of influencing current practice, the audit was conducted retrospectively, utilising the methodology previously used by Jolliffe and Flanagan (2014) when reviewing warfarin reversal prescribing practices at Capital and Coast District Health Board
Only the major hospital of each DHB were surveyed. The exception was Christchurch Hospital where Christchurch Women's Hospital was included due to their proximity to, and inter-relationship with, the main hospital. Prothrombinex- VF that was issued to adults between the 1st July 2015 and the 31st December 2015 was audited to a maximum of 100 episodes per site.

Data was collected from the patient's electronic laboratory records, clinical records, NZBS eProgesa blood management system and the DHB's hospital pharmacy record of issue of Vitamin K. When multiple INRs were identified for the same patient, only the INR used in clinical management was retained. Duplicate entries monitoring the response to an intervention were removed from the data set.

The data was entered into a single web-based secure PostgreSQL database only accessible by the nurse entering the data and the Transfusion Medicine Specialist (TMS) overseeing the audit.

Variables were reported electronically in an "other" category where TNSs then had the opportunity to comment in free text. This provided relevant details for accurate assimilation of data by the Transfusion Medicine Specialist (TMS). The final decision for concordance with the 2013 guidelines remained with the TMS.

Confirmation from the National Ethics Committee that ethics approval was not required for this audit was obtained. The audit was conducted in accordance with the Ethical Guidelines for Observational Studies with specific reference to audit activities.[5]

Results were analysed against the updated guidelines by a Transfusion Medicine Specialist from the NZBS electronic database. Method of analysis followed the model of the previous study conducted by Jolliffe & Flanagan[5].

All results and recommendations were provided to NZBS's Clinical Advisory Group and the Hospital Transfusion Committees of the respective DHBs on completion of the audit for comment prior to release of the final report.

Data Collection

Patients on warfarin therapy, who require intervention to reverse warfarin effect, were identified via multiple sources. This included:

- DHB Clinical Coding (or equivalent): obtained all admissions coded using the International Classification of Diseases version 10 (ICD) as “Haemorrhagic disorder due to circulating anticoagulants” or “Anticoagulants causing adverse effects in therapeutic use”
- DHB Haematology Laboratory: obtained all INR results ≥ 4.5 (excluding community or small hospitals).
- Hospital Pharmacy: obtained all patients’ dispensed vitamin K, excluding agreed patient groups e.g. paediatric, neonatal.
- NZBS: Business Analyst: obtained all recipients of Prothrombinex-VF and FFP
- Existing tools designed for the CCDHB audit’s data collection were used and modified where necessary to accommodate all DHBs

Criteria

Criteria for appropriate prescribing during this audit included the ASTH updated consensus guidelines for warfarin reversal. The guideline was broken down into a flowchart (see appendix 1) with all possibilities categorised, including possibilities that fell outside the guidelines.

Results

Using the five techniques for identifying patients to audit, 8023 instances of potential warfarin reversal were identified, representing 7029 clinical episodes (appendix 2) from the audit period of 1/02/2016 - 30/09/2016.

DHB	episodes	Vit K	INR	FFP	Prothrombinex	ICD
Auckland	111	3	17	49	75	14
Canterbury	72	1	20	22	37	23
Capital & Coast	85	26	15	18	31	22
Counties Manukau	101	70	27	12	57	28
MidCentral	46	0	2	8	31	12
Southern	102	31	37	1	5	31
Waikato	101	33	39	10	43	21
Waitemata	103	77	21	2	61	22
Overall	721	241	178	122	340	173

Table 1: *number of episodes and data source per DHB*

From the primary data, 721 episodes from 581 patients were selected as having had actual warfarin reversal (table 1). 41% of the patients were women, and the average age of all patients 73 years. The distribution of episodes and patients is shown in table 2. Comparison of the cases selected vs. the primary data is shown in appendix 2. This shows the skewing in favour of patients receiving Prothrombinex, reflecting the primary focus of the audit.

DHB	episodes	patients
Auckland	111	94
Canterbury	72	70
Capital & Coast	85	66
Counties Manukau	101	95
MidCentral	46	32
Southern	102	68
Waikato	101	81
Waitemata	103	84
Total	721	590

patients	episodes/patient
482	1
73	2
16	3
6	4
3	5
1	6
581	Ave: 1.2

Table 2: *number of episodes and patients per DHB; number of episodes per patient*

DHB	atrial fib	APS	arterial disease	cardiac pathology	stroke	unclear	valve	VTE
Auckland	62	1	2	1	2	1	25	17
Canterbury	43	0	1	1	2	0	11	14
Capital & Coast	45	0	0	0	0	0	28	12
Counties Manukau	73	1	0	0	1	0	19	7
MidCentral	25	0	0	1	0	1	6	13
Southern	42	2	3	1	12	0	23	19
Waikato	58	0	1	2	13	0	22	5
Waitemata	74	2	0	0	3	1	8	15
Overall	422	6	7	6	33	3	142	102

APS: anti-phospholipid syndrome, VTE: venous thromboembolism

Table 3: *indications for warfarin by DHB*

The indication for warfarin therapy was assessed from clinical notes (Table 3), showing atrial fibrillation as the leading causes (59%), with cardiac valvular disease (20%) and venous thromboembolism (VTE) (14%) as the next commonest indications.

For most DHBs, the majority of reversals occurred in the wards (46%) with the emergency department (43%) coming a close second (Table 4).

DHB	ED	ICU	Theatre	Other	Ward
Auckland	32	17	7	5	50
Canterbury	54			1	17
Capital & Coast	34	3	6	4	38
Counties Manukau	52	2	2		45
MidCentral	16	3	3	3	21
Southern	39			3	60
Waikato	29	4	9	4	55
Waitemata	51	6			46
Overall	307	35	27	20	332

Table 4: *location of warfarin reversal by DHB*

Prescribing was distributed reasonably evenly amongst consultant, registrars and MO/HOs (table 5). One concern identified was how many requests couldn't be linked to a specific doctor. This could be due to a lack of a prescription or an inability to identify the signature.

DHB	can't define	consultant	GP	registrar	MO/HO
Auckland	14	41	0	47	9
Canterbury	25	29	0	8	10
Capital & Coast	16	50	0	19	0
Counties Manukau	17	16	0	46	22
MidCentral	2	17	0	24	3
Southern	0	23	1	36	42
Waikato	7	51	0	42	1
Waitemata	45	4	0	20	34
Overall	126	231	1	242	121

Table 5: *warfarin reversal prescribers by DHB*

All episodes were classified using the flow chart in appendix 1. Five categories covered 79% of episodes (in descending frequency):

- Emergency surgery, INR>1.5
- Not bleeding, not pre-op, INR 4.5-10
- Clinically significant bleeding with INR ≥2
- Elective surgery, INR >1.5
- Life-threatening bleeding with INR ≥1.5

Overall 30% of audited cases were bleeding, 30% were non-bleeding and non-pre-operative, 26% were prior to emergency surgery, and 16% were prior to an elective procedure (table 6).

	Classification	Auckland	Canterbury	Capital & Coast	Counties Manukau	MidCentral	Southern	Waikato	Waitemata	Overall
Life-threatening bleeding with INR <1.5	A	0%	0%	1%	0%	0%	0%	0%	0%	0%
Life-threatening bleeding with INR ≥1.5	B	11%	14%	5%	18%	15%	2%	8%	11%	10%
Clinically significant bleeding with INR <2	C	5%	1%	1%	3%	4%	1%	0%	5%	2%
Clinically significant bleeding, no INR	CD	0%	0%	0%	0%	2%	0%	0%	0%	0%
Clinically significant bleeding with INR ≥2	D	5%	22%	16%	18%	15%	6%	23%	25%	16%
Minor bleeding, any INR	E	0%	1%	0%	1%	0%	8%	0%	0%	1%
Not bleeding, not pre-op, INR <4.5	F	6%	8%	15%	3%	9%	14%	2%	7%	8%
Not bleeding, not pre-op, INR 4.5-10	G	8%	19%	18%	21%	4%	39%	29%	14%	20%
Not bleeding, not pre-op, INR >10	H	0%	4%	1%	0%	0%	1%	0%	0%	1%
Elective surgery, INR >1.5	J	16%	7%	4%	4%	22%	10%	14%	19%	12%
Elective surgery, no INR	JK	2%	0%	2%	0%	0%	0%	1%	0%	1%
Elective surgery, INR ≤1.5	K	13%	1%	4%	1%	4%	1%	1%	1%	3%
Emergency surgery, INR>1.5	L	27%	19%	25%	30%	22%	16%	18%	18%	22%
Emergency surgery, INR≤1.5	M	0%	0%	2%	0%	0%	0%	1%	0%	0%
Unclear		7%	0%	6%	1%	0%	1%	2%	0%	2%
Total		111	72	85	101	46	102	101	103	721

Table 6: *indication for warfarin reversal by DHB*

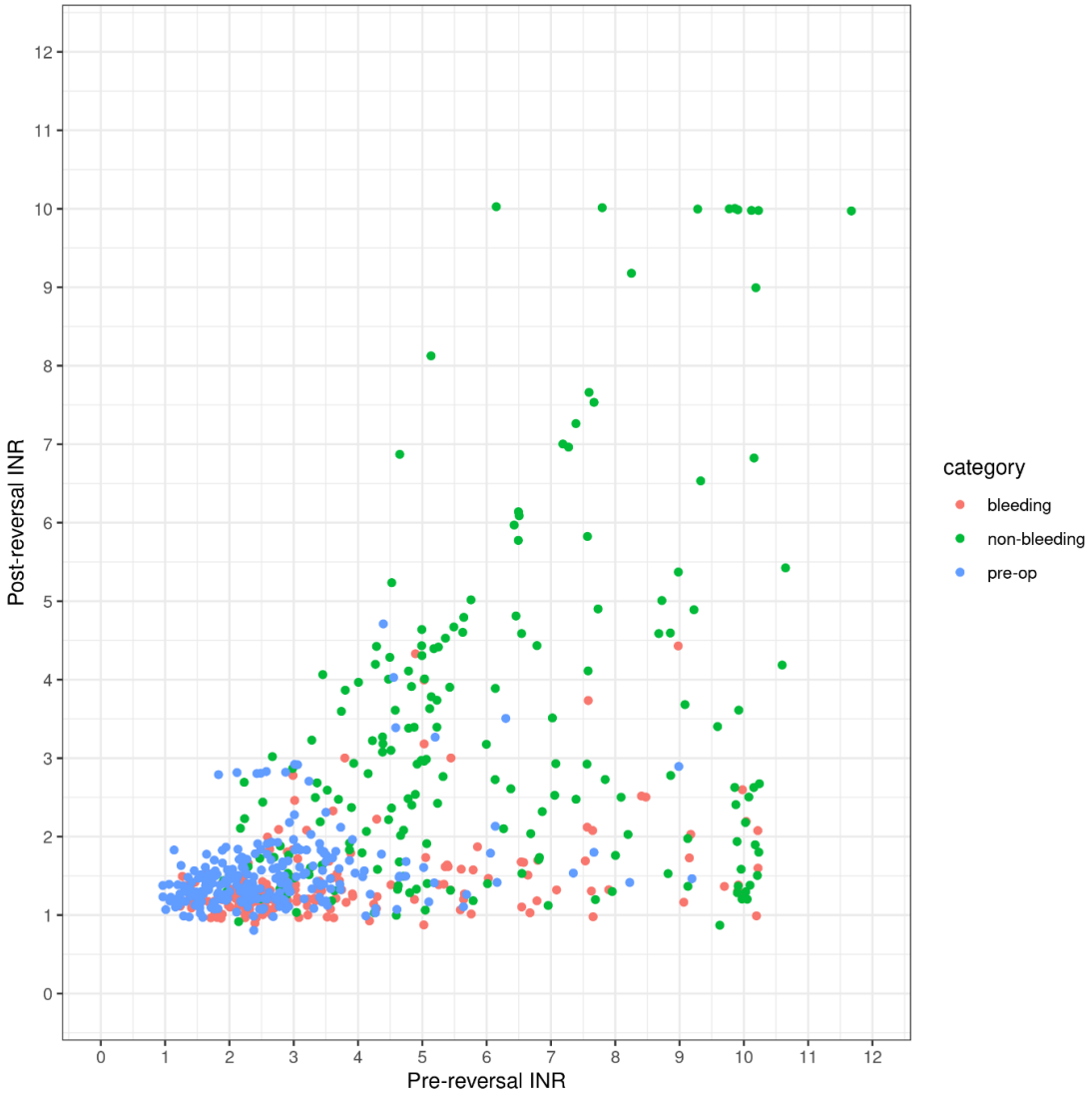

Figure 1: *pre and post-reversal INR results by broad warfarin reversal category.*

A detailed breakdown per indication, showing the areas that did and did not comply with guidelines is shown in Appendix 3.Response to warfarin reversal was generally good (Figure 1). Of some concern was that 17% of reversals were for INR less than 1.5.

A surprising number of cases were in non-bleeding patients. It has been surmised that at least some of these patients may have had a clinical indication for Prothrombinex at the time of prescription but that turned out not to be the case later. An example is a patient with symptoms of a possible intra-cranial haemorrhage where the CT scan subsequently refutes this. The auditing would only reflect a patient with a high INR. Table 7 shows the location of these requests. A substantial proportion are indeed from the Emergency Department, suggesting that there may at least be a component of clinical concern of bleeding to the requests.

Indication	ED	ICU	Theatre	Ward	Other	n
Not bleeding, not pre-op, INR <4.5	41%	9%	2%	46%	2%	56
Not bleeding, not pre-op, INR 4.5-10	45%	1%	0%	48%	6%	144
Not bleeding, not pre-op, INR >10	80%	0%	0%	20%	0%	5
Overall	45%	3%	0%	47%	4%	205

Table 7: *location of requests for Prothrombinex in non-bleeding patients*

Indication for warfarin reversal	Classification	Auckland	Canterbury	Capital & Coast	Counties Manukau	MidCentral	Southern	Waikato	Waitemata	Overall
Life-threatening bleeding with INR <1.5	A	-	-	100% (1)	-	-	-	-	-	100% (1)
Life-threatening bleeding with INR ≥1.5	B	75% (12)	90% (10)	50% (4)	6% (18)	43% (7)	100% (2)	50% (8)	82% (11)	54% (72)
Clinically significant bleeding with INR <2	C	0% (5)	0% (1)	0% (1)	33% (3)	0% (2)	100% (1)	-	40% (5)	22% (18)
Clinically significant bleeding with INR ≥2	D	60% (5)	63% (16)	29% (14)	11% (18)	43% (7)	17% (6)	57% (23)	62% (26)	45% (115)
Minor bleeding, any INR	E	-	0% (1)	-	100% (1)	-	100% (8)	-	-	90% (10)
Not bleeding, not pre-op, INR <4.5	F	14% (7)	100% (6)	31% (13)	0% (3)	25% (4)	93% (14)	50% (2)	14% (7)	48% (56)
Not bleeding, not pre-op, INR 4.5-10	G	11% (9)	93% (14)	93% (15)	81% (21)	0% (2)	100% (40)	93% (29)	79% (14)	85% (144)
Not bleeding, not pre-op, INR >10	H	-	100% (3)	100% (1)	-	-	100% (1)	-	-	100% (5)
Elective surgery, INR >1.5	J	28% (18)	0% (5)	0% (3)	50% (4)	40% (10)	10% (10)	50% (14)	15% (20)	26% (84)
Elective surgery, INR ≤1.5	K	0% (14)	100% (1)	0% (3)	0% (1)	0% (2)	100% (1)	0% (1)	100% (1)	13% (24)
Emergency surgery, INR>1.5	L	53% (30)	14% (14)	43% (21)	43% (30)	60% (10)	6% (16)	28% (18)	58% (19)	40% (158)
Emergency surgery, INR≤1.5	M	0% (8)	-	40% (5)	0% (1)	-	0% (1)	0% (2)	-	12% (17)
Overall		32% (108)	62% (71)	46% (81)	37% (100)	39% (44)	69% (100)	59% (97)	52% (103)	50% (704)

Table 8: *percentage concordance with ASTH guidelines (with number of episodes) by indication for warfarin reversal by DHB*

Compliance was assessed against the criteria laid out in the ATSH guideline[1] (table 8). Some episodes had to be excluded because they couldn't be classified, owing to no INR on record. Limitations in the audit imposed furthers restrictions on the ability to assess episodes accurately. There was no significant difference in compliance with the guidelines by prescriber type (consultant, registrar, MO/HO, other) (p=0.903).

There were significant differences across location types (p=0.019) but ICU and theatre were significantly less likely to be compliant than wards or EDs (50% vs 24%, p=0.017). This may be due to case complexities as well as familiarity (ED & wards: 639 episodes; ICU/theatre: 62 episodes).

Group	no and percent of recipients	Prothrombinex-VF dose & range (IU/kg)	ASTH recommended dose range (IU/kg)
Life-threatening bleeding with INR <1.5	1 (100%)	18 (18-18)	<50
Life-threatening bleeding with INR ≥1.5	53 (93%)	40 (13-63)	50
Clinically significant bleeding with INR <2	5 (45%)	24 (20-27)	0
Clinically significant bleeding with INR ≥2	64 (76%)	33 (7-59)	35-50
Minor bleeding, any INR	1 (10%)	29 (29-29)	0
Not bleeding, not pre-op, INR <4.5	12 (29%)	25 (8-43)	0
Not bleeding, not pre-op, INR 4.5-10	12 (11%)	36 (10-55)	0
Not bleeding, not pre-op, INR >10	0 (0%)		15-30
Elective surgery, INR >1.5	38 (60%)	28 (8-50)	15-50
Elective surgery, INR ≤1.5	4 (21%)	23 (10-29)	0
Emergency surgery, INR>1.5	85 (71%)	34 (11-89)	15-50
Emergency surgery, no INR	1 (33%)	51 (51-51)	N/A
Emergency surgery, INR≤1.5	7 (50%)	31 (14-56)	0
Unclear	2 (33%)	35 (34-36)	N/A

Table 9: *Number of Prothrombinex-VF recipients (and percentage of each indication that received Prothrombinex-VF) with average dose per kg (and range) by warfarin reversal category and ASTH's recommended dose range.*

Prothrombinex-VF dosing showed wide variation for many indications. Table 9 shows the proportion of patients within each group that received Prothrombinex-VF and the range of doses prescribed. The ASTH recommended dose range is also shown.

Vitamin K can be given parenterally or orally with dosage determined by the category of warfarin reversal (Table 10). Doses of 15 and 20 mg parenterally for e.g. non-bleeding patients (groups F-H) would not usually be considered be consistent with the guidelines.

Group	Oral (mg)	IV/IM (mg)
Life-threatening bleeding with INR <1.5		1 (1-1) [1]
Life-threatening bleeding with INR ≥1.5	5 (5-5) [3]	8 (0-10) [54]
Clinically significant bleeding with INR <2		7 (2-10) [11]
Clinically significant bleeding, no INR		10 (10-10) [1]
Clinically significant bleeding with INR ≥2	5 (0.5-10) [12]	7 (1-15) [76]
Minor bleeding, any INR	1 (1-1) [2]	
Not bleeding, not pre-op, INR <4.5	1 (1-2) [3]	6 (1-10) [18]
Not bleeding, not pre-op, INR 4.5-10	3 (1-10) [23]	6 (1-20) [48]
Not bleeding, not pre-op, INR >10	3 (1-5) [3]	2 (1-2) [2]
Elective surgery, INR >1.5	3 (0-5) [13]	6 (0-10) [35]
Elective surgery, no INR	4 (2-5) [2]	10 (10-10) [1]
Elective surgery, INR ≤1.5	6 (2-10) [2]	10 (10-10) [4]
Emergency surgery, INR>1.5	5 (2-10) [11]	5 (0.5-10) [97]
Emergency surgery, no INR		5 (5-5) [1]
Emergency surgery, INR≤1.5	5 (5-5) [1]	8 (3-10) [6]
unclear		6 (5-10) [4]

Table 10: *distribution of vitamin K doses used in warfarin reversal – average dose (range) [no of episodes].*

Novoseven (recombinant factor VIIa) was only used in a single case, an aortic aneurysm dissection undergoing emergency surgery.

FFP use (table 11) was largely limited to life threatening and clinically significant bleeding with elevated INR (groups B and D), as well as for non-bleeding patients with INR < 4.5 (group F). The latter is not a group in which FFP is recommended.

group	no and percent receiving FFP	average units	minimum	maximum
Life-threatening bleeding, INR <1.5 (A)	0 (0%)	0.0	0	0
Life-threatening bleeding, INR ≥1.5 (B)	19 (2%)	1.2	1	2
Clinically significant bleeding, INR <2 (C)	5 (7%)	1.2	1	2
Clinically significant bleeding, no INR (CD)	(0%)	0.0	0	0
Clinically significant bleeding, INR ≥2 (D)	21 (1%)	1.7	1	7
Minor bleeding, any INR (E)	3 (23%)	2.3	1	4
Not bleeding, not pre-op, INR <4.5 (F)	8 (3%)	1.9	1	4
Not bleeding, not pre-op, INR 4.5-10 (G)	0 (0%)	0.0	0	0
Not bleeding, not pre-op, INR >10 (H)	9 (49%)	2.4	1	6
Elective surgery, INR >1.5 (J)	1 (2%)	2.0	2	2
Elective surgery, no INR result (JK)	14 (44%)	2.2	1	6
Elective surgery, INR ≤1.5 (K)	29 (10%)	2.4	1	6
Emergency surgery, INR>1.5 (L)	2 (8%)	12.5	1	24
Emergency surgery, INR≤1.5 (M)	8 (15%)	2.6	1	4
Unclear (unclear)	0 (0%)	0.0	0	0
Overall	119 (17%)			

Table 11: *FFP use by warfarin reversal category*

Where Prothrombinex was used, reversal was generally very good with almost all patients reaching INRs below 2. Figure 2 shows the fall in INR after reversal for each episode, colour-coded INR into those adhering to the ASTH guidelines and those not. Almost all patients achieved good reversal of their prolonged INR. Notably, the fall in INR is proportional to the level of the pre-reversal INR. There appeared to be little difference in the extent of reversal whether or not the reversal closely followed the ASTH guidelines.

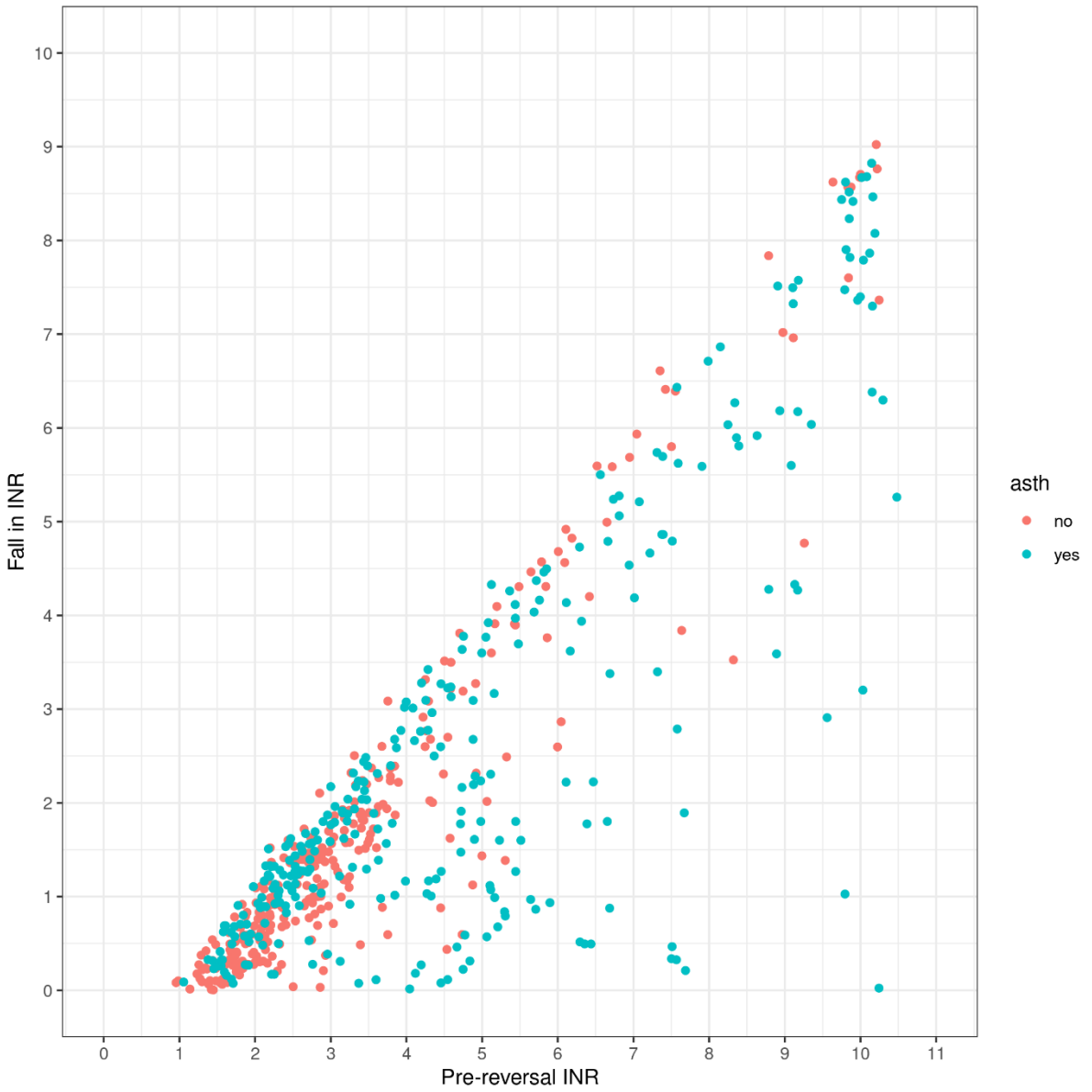

Figure 2: *pre and post-reversal INR results and whether the reversal approach met ASTH guidelines.*

Limitations

This audit is a snapshot. It is not necessarily representative of practice now, though, in the absence of any interventions, is likely to reflect current warfarin reversal approaches. Comparisons between DHBs are problematic as the selection of cases from the large number of available cases was not a structured process and emphasised cases where Prothrombine3x-VF was used. Documentation, as in most audits, is a considerable factor. It is likely that some cases of warfarin being withheld or vitamin K prescribed were not found despite having taken place. The use of FFP and Prothrombinex is more accurate as that data come directly from the national blood banking computer system. Interpretation around why the patient was having warfarin reversal in complicated patients can be difficult and may have led to some incorrect assessments. The audit did not include thromboembolism or bleeding risk stratification in its initial data capture. This means that choices available to prescribers, depending on risk stratification cannot be narrowed down by the audit. Lastly, the audit did not look at clinical outcomes as this would have massively increased the work of the audit.

Discussion

This audit looked at 721 warfarin reversal episodes from eight DHBs, the largest such report for New Zealand. Together these DHBs account for 75% of the country's Prothrombinex-VF usage (NZBS unpublished data). The audit drew its data from 7,029 episodes over 6 months where vitamin K, FFP, or Prothrombinex-VF had been used, or where a patient's INR was significantly prolonged. Not all of these were situations where warfarin was being reversed. From these episodes, an average of 90 episodes per DHB of actual warfarin reversal were identified. As the interest from the Blood Service was focussed on Prothrombinex-VF, as opposed to e.g. vitamin K, there was a distinct skewing of case selection towards episodes using Prothrombinex-VF. It should also be noted that the selection was not a structured process, although largely consecutive episodes, meaning that inter-DHB comparisons of relative usage of one reversal technique over another would not be robust.

Reassuringly, the commonest indications for warfarin reversal were for surgery, life-threatening and clinically significant bleeding, all with significantly raised INR values, as well as for patients with isolated INR values of 4.5-10. These are all sensible indications for warfarin reversal.

Prothrombinex use in patients undergoing elective surgery is problematic. Firstly, the patient is exposed to a potentially thrombogenic blood product, and secondly it suggests that preparations have been rushed in getting the patient ready for surgery. There may be times where it is appropriate to use Prothrombinex but the bigger problem is likely to be the difficulty in rescheduling an elective operation. This is something NZBS cannot influence but is something hospital administrations might want to consider as they plan their elective surgical services.

Warfarin reversal met the ASTH guidelines in 50% of evaluable cases. This is similar to the previous audit performed in Wellington[5].

Also similar to the previous audit was a significant amount of FFP use (17% of episodes). The role of FFP is now limited to providing factor VII in patients with life-threatening bleeding or when Prothrombinex-VF is not available. The dose required to reverse warfarin with FFP is large and the patients frequently have cardiac disease. So it is not surprising that the use of FFP for warfarin reversal has a very high rate of complications[6].

Warfarin reversal with Prothrombinex-VF is also not without risks, though these appear to be more related to prolonged withdrawal of warfarin rather than the Prothrombinex-VF itself[4]. The dose administered was, on average, what the guidelines recommend but had some significant outliers with some single digit units per kg given. The response to clotting factors, both for FFP and Prothrombinex-VF, is non-linear[9], paradoxically it takes a much larger dose to normalise a mildly elevated INR compared to reducing a very high INR to a moderately high INR.

Vitamin K is a safe, effective and much less expensive way or reversing warfarin, provided the patient is not at immediate risk. However, as vitamin K is fat-soluble, large doses can make anticoagulating the patient again difficult for weeks afterwards. Therefore, the minimum effective dose is recommended, apart from in situations of life-threatening or clinically significant bleeding. For intravenous doses, the guidelines recommend only 0.1 – 1mg. Orally, as absorption is poorer, the dose is 5-10mg. This will allow rapid re-anticoagulation. The average parenteral dose in this audit was 6mg, far higher than recommended in the guideline. If warfarin is being ceased, then 10mg IM or IV will re-establish the patient's vitamin K reserves. This last piece of information, whether a patient was to resume warfarin, was not captured in this audit but it seems unlikely that such a high proportion of patients were coming off warfarin for good.

As warfarin reversal affects a variety of departments in the hospital – pharmacy, blood bank, laboratory – it is difficult to envisage a comprehensive system that could put checks in place to ensure best practice. As a result, most of the interventions are likely to be focussed on education. The target audience, however, is broad with most reversals occurring in a ward situation. Added to this, the range of prescribers covers all grades of doctors within the hospital.

One of the tools to assist with education is a warfarin reversal app for smartphones, created in 2014 on behalf of NZBS by one of the authors of the ASTH guideline. This is available through both the Google Play Store and the Apple App Store, titled “Reversing Warfarin”. It is also linked to via the NZBS Blood Resource website. NZBS and DHBs could look at promoting the use of this app more widely, possibly with a QR code on the Blood Request Form. Hospital and community laboratories could include a link to the app on their results. A leaflet, produced when the ASTH guidelines were updated, could also be provided via Blood Bank if hospitals thought that would be useful. When electronic ordering of blood products becomes available in New Zealand, building in prompts or algorithms to guide prescribing in warfarin reversal should reduce prescribing errors significantly.

One of the criticisms of the ASTH guideline is that it is quite hard to work out the appropriate strategy for a given patient using the original publication. A simplified flow chart or web-based version of the app could be helpful for people not aware of the app.

Lastly, Blood Banks are authorised to release up to 25 IU/kg for warfarin reversal. NZBS transfusion medicine specialists check issues of Prothrombinex-VF where the dose is greater than 25 IU/kg and the Blood Bank is managed by NZBS or the DHB Blood Bank asks for this. Although this captures the patients at highest risk of thrombotic complications from Prothrombinex-VF, and arguably those patients in most need of sound reversal, it only covers a minority of patients.

Reassuringly though, the difference in INR reduction between those cases meeting the ASTH guidelines versus those not, was small, approximately 0.3. This suggests that while prescribers may not be following the guidelines to the letter, they are managing to reverse warfarin successfully.

Recommendations

1. DHBs are urged to promote the ASTH warfarin reversal guidance via junior and senior medical officer education
2. NZBS is urged to promote the use of the warfarin reversal mobile phone app.
3. NZBS is encouraged to release the warfarin reversal leaflet again.
4. NZBS is encouraged to provide a simplified flow chart, based on the ASTH warfarin reversal guidance to guide warfarin reversal.

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Appendix 1: ASTH guidelines as a flowchart

Figure 3: *ASTH Warfarin reversal guidelines as a flowchart for bleeding patients*

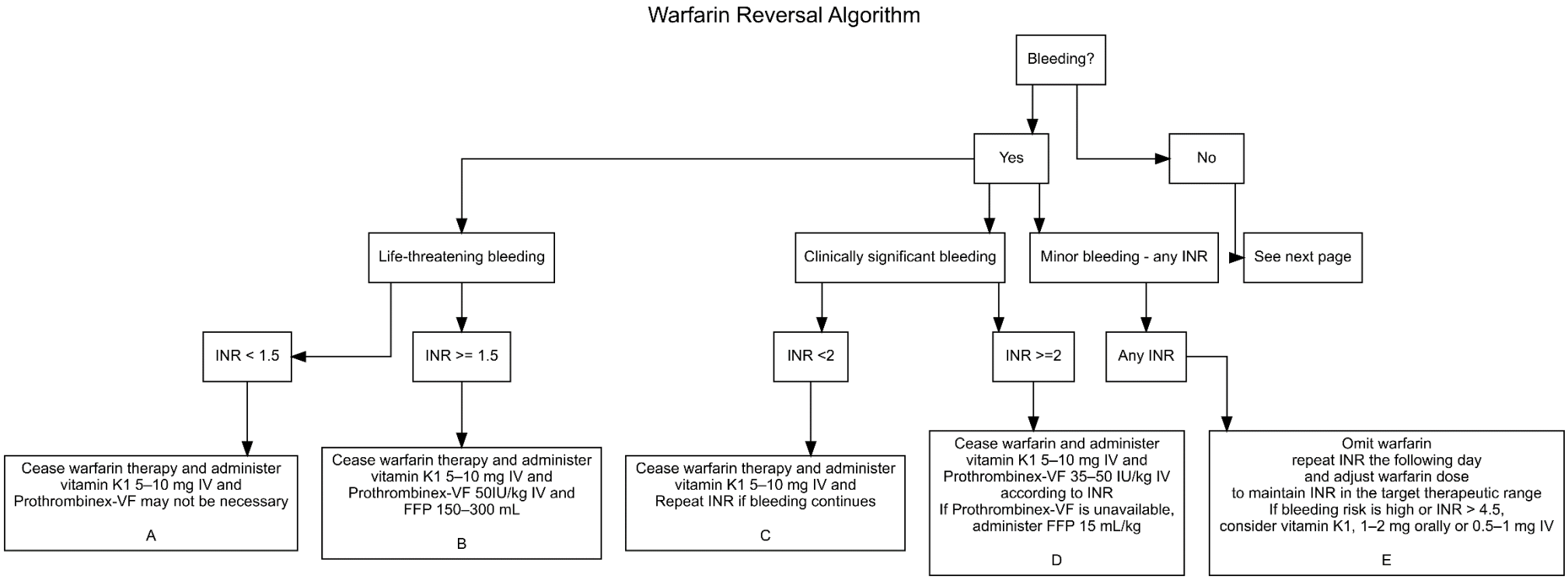
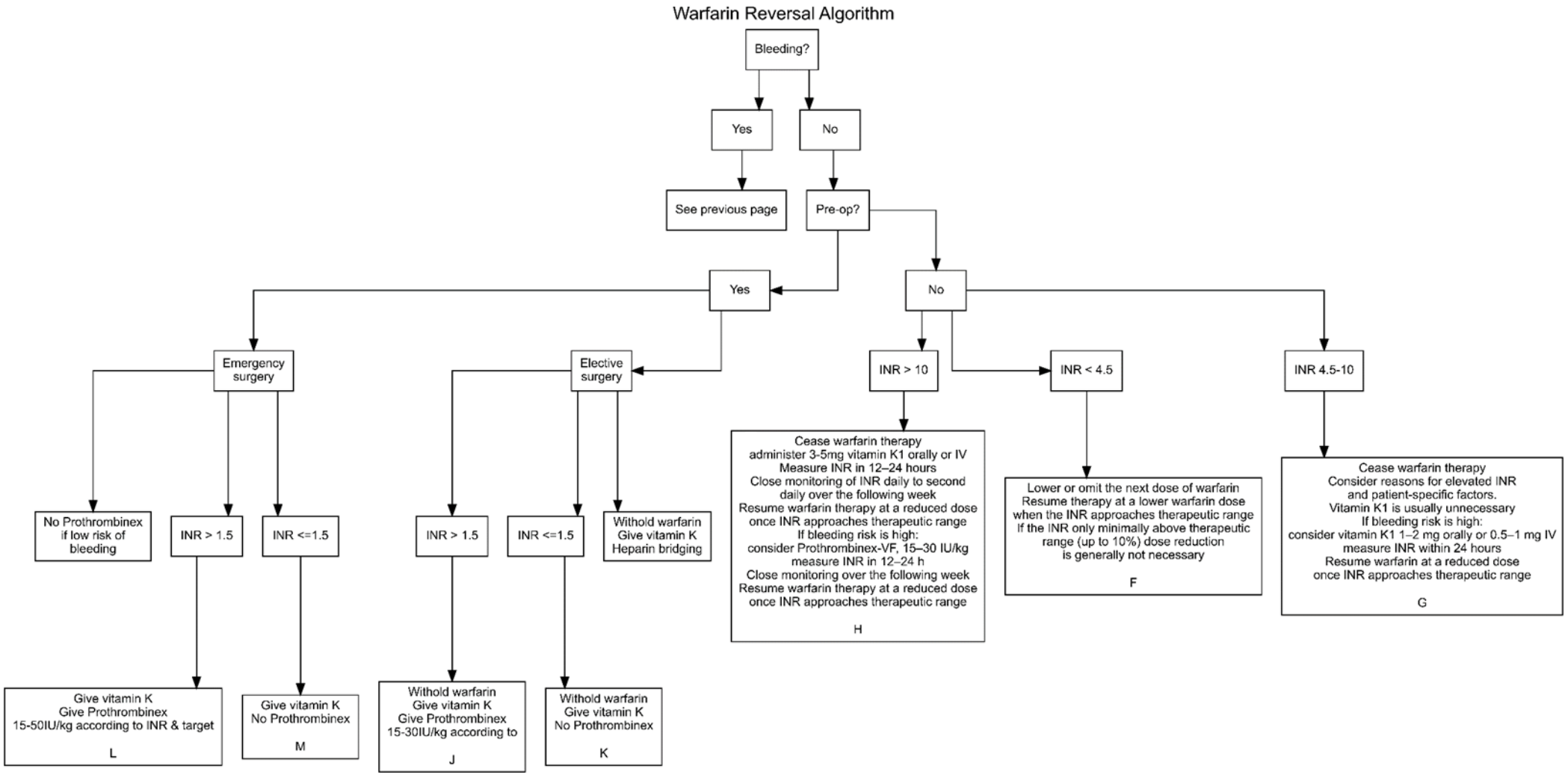


Figure 4: *ASTH Warfarin reversal guidelines as a flowchart for non-bleeding patients*



Appendix 2: ratio of types of case from initial data vs audited

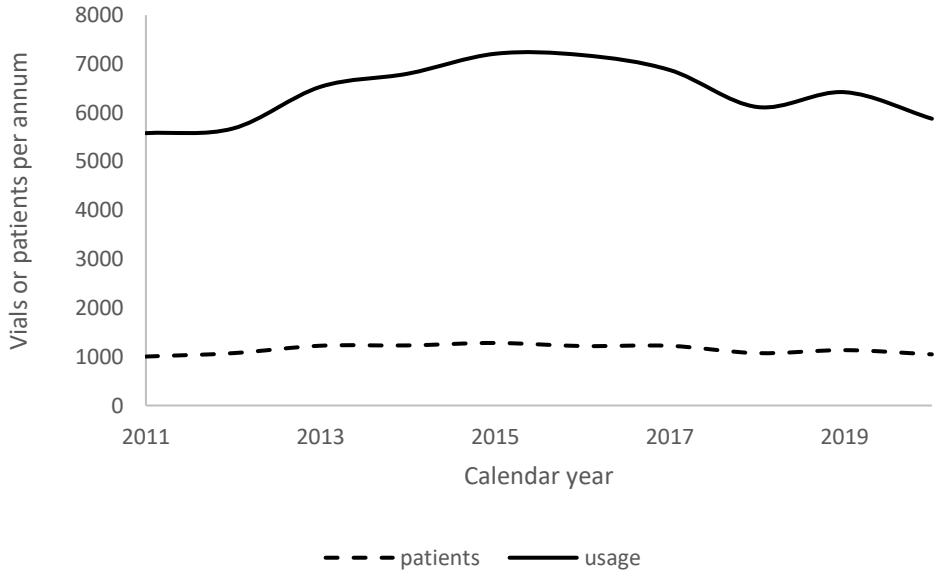
Primary data:

DHB	n	Vit K	↑ INR	FFP	PTX	ICD
Auckland	958	2%	40%	34%	9%	27%
Canterbury	726	2%	42%	22%	8%	37%
Capital & Coast	811	46%	15%	25%	6%	17%
Counties Manukau	1624	71%	17%	10%	4%	15%
MidCentral	212	0%	33%	16%	16%	50%
Southern	534	40%	19%	15%	5%	23%
Waikato	964	31%	39%	17%	5%	20%
Waitemata	1200	58%	30%	7%	5%	24%
Overall	7029	39%	28%	17%	6%	23%

Audited cases:

DHB	n	Vit K	↑ INR	FFP	PTX	ICD
Auckland	111	3%	15%	44%	68%	13%
Canterbury	72	1%	28%	31%	51%	32%
Capital & Coast	85	31%	18%	21%	36%	26%
Counties Manukau	101	69%	27%	12%	56%	28%
MidCentral	46	0%	4%	17%	67%	26%
Southern	102	30%	36%	1%	5%	30%
Waikato	101	33%	39%	10%	43%	21%
Waitemata	103	75%	20%	2%	59%	21%
Overall	721	33%	25%	17%	47%	24%

Appendix 3: use of Prothrombinex over the last ten years



Appendix 3: detailed breakdown of compliance with guidelines by warfarin reversal group

group	warfarin withheld	vit K given	FFP given	PTX given	n
Life-threatening bleeding, INR <1.5 (A)					1
Life-threatening bleeding, INR ≥1.5 (B)					2
					1
					9
					7
					1
					6
					4
					3
					31
					8
Clinically significant bleeding, INR <2 (C)					1
					2
					4
					4
					1
					5
					1
Clinically significant bleeding, no INR (CD)					1
Clinically significant bleeding, INR ≥2 (D)					2
					1
					1
					15
					4
					5
					2
					10
					2
					19
					2
					43
					9
Minor bleeding, any INR (E)					9
					1
Not bleeding, not pre-op, INR <4.5 (F)					27
					2
					5
					13
					9
Not bleeding, not pre-op, INR 4.5-10 (G)					1
					3
					12
					3
					5
					9
					3

group	warfarin withheld	vit K given	FFP given	PTX given	n
Not bleeding, not pre-op, INR >10 (H)					5
Elective surgery, INR >1.5 (J)					1
					1
					3
					11
					6
					18
					1
					20
					1
					22
Elective surgery, no INR result (JK)					1
					1
					2
					1
Elective surgery, INR ≤1.5 (K)					2
					3
					11
					3
					3
					2
Emergency surgery, INR>1.5 (L)					1
					1
					3
					3
					1
					13
					1
					4
					5
					30
					6
					28
					5
					50
					7
Emergency surgery, INR≤1.5 (M)					1
					3
					1
					5
					2
					1
					1
					1
					2
Unclear					8

non-compliant with ASTH guidance

complies with ASTH guidance

variable requirement in ASTH guidance

Appendix 4: usage of reversal method by warfarin reversal group and DHB

DHB	classification	warfarin withheld	vitamin K given	FFP given	Prothrombinex given	n
Auckland	B	100%	75%	33%	100%	12
Auckland	C	100%	60%	40%	60%	5
Auckland	D	100%	60%	20%	100%	5
Auckland	F	100%	43%	29%	57%	7
Auckland	G	100%	89%	67%	44%	9
Auckland	J	100%	28%	22%	72%	18
Auckland	K	93%	14%	71%	29%	14
Auckland	L	100%	63%	23%	87%	30
Auckland	M	100%	38%	63%	50%	8
Canterbury	B	100%	90%	40%	100%	10
Canterbury	C	0%	0%	100%	100%	1
Canterbury	D	94%	81%	63%	75%	16
Canterbury	E	100%	100%	0%	100%	1
Canterbury	F	100%	0%	0%	0%	6
Canterbury	G	100%	36%	7%	7%	14
Canterbury	H	100%	100%	0%	0%	3
Canterbury	J	80%	40%	20%	60%	5
Canterbury	K	100%	100%	0%	0%	1
Canterbury	L	79%	50%	43%	86%	14
Capital & Coast	A	100%	100%	0%	100%	1
Capital & Coast	B	50%	75%	0%	100%	4
Capital & Coast	C	100%	100%	0%	100%	1
Capital & Coast	D	36%	71%	29%	93%	14
Capital & Coast	F	92%	69%	0%	8%	13
Capital & Coast	G	100%	53%	0%	7%	15
Capital & Coast	H	100%	100%	0%	0%	1
Capital & Coast	J	100%	67%	33%	0%	3
Capital & Coast	K	100%	0%	67%	0%	3
Capital & Coast	L	52%	52%	29%	76%	21
Capital & Coast	M	60%	60%	40%	20%	5
Counties Manukau	B	11%	89%	39%	89%	18
Counties Manukau	C	100%	67%	67%	33%	3
Counties Manukau	D	28%	89%	11%	89%	18
Counties Manukau	E	100%	0%	0%	0%	1
Counties Manukau	F	67%	67%	0%	33%	3
Counties Manukau	G	86%	76%	0%	19%	21
Counties Manukau	J	75%	100%	0%	75%	4
Counties Manukau	K	100%	0%	0%	0%	1
Counties Manukau	L	77%	77%	7%	57%	30
Counties Manukau	M	0%	100%	0%	100%	1
MidCentral	B	100%	57%	29%	86%	7
MidCentral	C	100%	0%	0%	100%	2
MidCentral	D	100%	43%	29%	86%	7
MidCentral	F	75%	75%	0%	75%	4
MidCentral	G	100%	50%	50%	50%	2
MidCentral	J	80%	70%	20%	70%	10
MidCentral	K	50%	0%	50%	50%	2
MidCentral	L	70%	60%	10%	90%	10
Southern	B	100%	100%	0%	100%	2
Southern	C	100%	100%	0%	0%	1
Southern	D	100%	83%	0%	17%	6
Southern	E	100%	13%	0%	0%	8
Southern	F	93%	7%	0%	0%	14
Southern	G	100%	43%	0%	0%	40
Southern	H	100%	100%	0%	0%	1
Southern	J	100%	50%	0%	10%	10
Southern	K	100%	100%	0%	0%	1
Southern	L	100%	94%	6%	6%	16
Southern	M	100%	0%	0%	0%	1
Waikato	B	88%	75%	13%	88%	8
Waikato	D	100%	87%	9%	61%	23
Waikato	F	100%	50%	0%	50%	2
Waikato	G	97%	24%	0%	3%	29
Waikato	J	93%	57%	7%	71%	14
Waikato	K	100%	0%	0%	0%	1
Waikato	L	100%	61%	28%	78%	18
Waikato	M	50%	50%	0%	100%	2
Waitemata	B	100%	91%	9%	91%	11
Waitemata	C	100%	80%	0%	60%	5
Waitemata	D	100%	88%	0%	73%	26
Waitemata	F	100%	43%	0%	57%	7
Waitemata	G	100%	86%	0%	21%	14
Waitemata	J	100%	65%	0%	40%	20
Waitemata	K	100%	100%	0%	0%	1
Waitemata	L	100%	68%	5%	95%	19