ST. JAMES'S HOSPITAL

RCSI

NOVEL ORAL ANTICOAGULANT THERAPY

An audit from 6 Acute Hospitals

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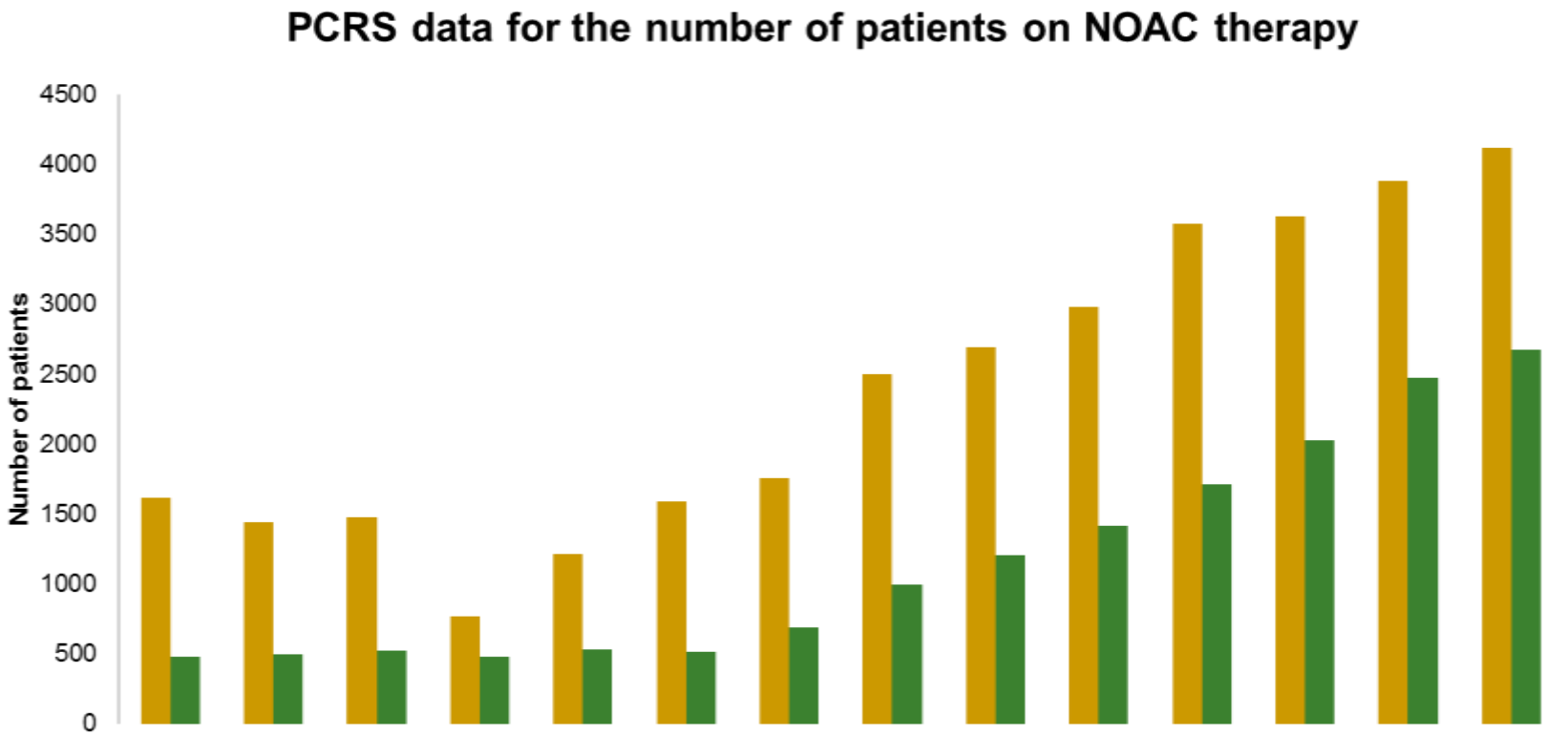
Balancing the Risks

- Anticoagulation therapy is a rapidly changing area of practice, driven by the availability of the novel oral anticoagulants (NOACs).
- Rivaroxaban, dabigatran and apixaban are licensed for indications including stroke prophylaxis in atrial fibrillation patients and the treatment of acute venous thrombosis.
- Anticoagulants are one of the classes of medicines that most frequently cause preventable harm and admission to hospital.
- The published literature supports their safety and efficacy versus warfarin therapy in specific clinical incidences.
- However, outside of the clinical trial setting, experience with these agents is limited.

NOAC usage data



	Mar-12	Apr-12	May-12	Jun-12	Jul-12	Aug-12	Sep-12	Oct-12	Nov-12	Dec-12	Jan-13	Feb-13	Mar-13	Apr-13
Dabigatran	1615	1444	1477	767	1216	1585	1753	2496	2686	2977	3569	3627	3875	4117
Rivaroxaban	482	493	524	478	531	517	687	994	1203	1415	1710	2022	2475	2670

Aim and Objectives

Aim

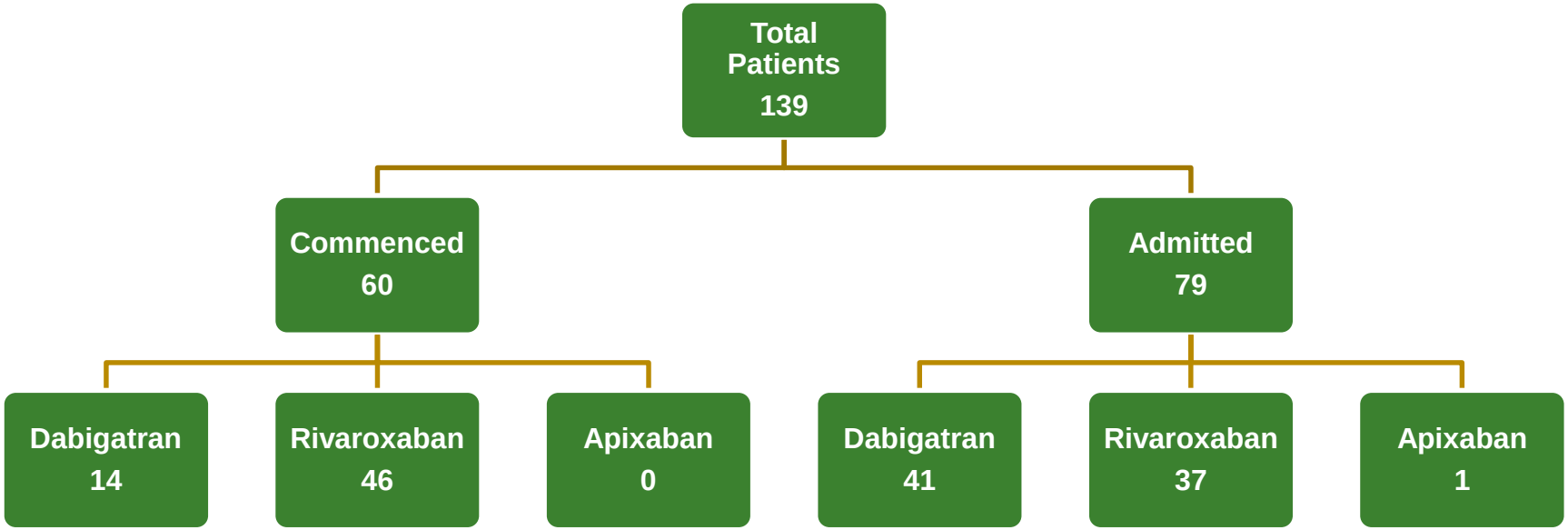
- Develop a profile of the inpatient use of the novel oral anticoagulants (NOAC)
- To contribute towards increasing knowledge and insight into the new oral anticoagulant agents; their benefits and potential risks in a real-world setting.

Objectives

- Description of demographics
- Assess safety and tolerability of NOAC therapy

- Strict protocol driven study to ensure consistency

Pooled Study Results



Demographic data

Drug	Rivaroxaban	Apixaban	Dabigatran 110mg BD	Dabigatran 150mg BD	Study cohort n=139
Trial	ROCKET AF	ARISTOTLE	RE-LY	RE-LY	
Mean Age (years)	73	70	71.4	71.5	76.4
Women (%)	39.7	35.5	35.7	36.8	48.2
Diabetes (%)	40.4	25.0	23.4	23.1	20%
Previous Stroke /TIA (%)	54.9	19.2	19.9	20.3	30.9%
Mean CHADS2 Score	3.5	2.1	2.1		2.7
CHADS2 Score >1 (%)	100	66	67.4	67.8	76.8%
Co-usage Aspirin (%)	36.3	33.2	21.1	19.6	27%

- CVA most common presenting complaint (19%,n=27)
- 8 patients admitted with CVA were already on NOAC therapy (5.75%)
- 2 patients admitted for a DVT were already on NOAC therapy
- 52% patients had between 3 to 5 co-morbidities

Co-morbidity data

Cardiovascular/ Thromboembolic Disease	Pooled % (n=139)
Hypertension	55.4% (77)
Atrial Fibrillation	84.2 %(117)
Myocardial Infarction	12.9% (18)
Congestive Heart Failure	30.2% (42)
Previous DVT*	10.1% (14)
Previous PE*	7.2% (10)
CVA Ischemic/TIA*	29.5% (41)
CVA Haemorrhagic*	1.4% (2)
Vascular Disease	18% (25)
Hyperlipidemia	20.9% (29)
Other CVD	15.1% (21)

Suitability of warfarin

- 43.9 % (n=61) of patients had a documented history of warfarin therapy.
- Previous warfarin therapy could not be established in 19.4% (n=27) due to incomplete medical notes.
- A specific reason or combination of reasons, for initiating a NOAC over warfarin was documented in 38.8% (n= 54) of cases.
- The most frequent reasons documented included:
  - Unable to attend warfarin clinic (n=13)
  - Poor cognition (n=10)
  - INR frequently out of range (n=8)
  - Risk of non-adherence (n=8)

Patient Demographics for Dabigatran (n=55)

Dose	75mg BD (n=3)	110mg BD (n=42)	150mg BD (10)
Male	100%	47.6% (20)	60% (6)
Female		52.4% (22)	40% (4)
Mean age	85.6	80.5	67.4
Indication			
Atrial fibrillation	100% (3)	85.7% (36)	100% (10)
other		14.4% (6)	
Renal profile (CrCl)			
Normal		7.1% (3)	30% (3)
Mild	33.3% (1)	33.3% (14)	50% (5)
Moderate	66.6% (2)	54.8% (23)	20% (1)
Severe		4.7% (2)	10% (1)

Patient Demographics for Rivaroxaban (n=83)

Dose	10mg daily	15mg daily	20mg Daily	15mg BD
	n=1	n=30	n=44	n=8
Male	100%	45.7% (14)	52.3% (23)	62.5%(5)
Female		54.3% (16)	47.7% (21)	37.5% (3)
Mean age, years	82	81.8	71.2	75.6
Indication				
A fibrillation		83.3% (25)	93.2% (42)	
VTE		13.3% (4)	4.5% (2)	75% (6)
unknown	100% (1)	3.3% (1)		(2)
Renal Profile (CrCl)				
Normal		10% (3)	43.2% (19)	25% (2)
Mild	100% (1)	26.7% (8)	38.6% (17)	25% (2)
Moderate		53.3% (16)	18.2% (8)	50% (4)
Severe		10% (3)		

Concomitant medications for Patients on NOAC therapy

Concomitant Medications	Number of patients (n=139)
CYP3A4/p-glycoprotein inducers	3 (2.2%)
Carbamazepine	2
Phenytoin	1
CYP3A4/p-glycoprotein inhibitors	28 (20.1%)
Amiodarone	18
Clarithromycin	5
Diltiazem	1
Dronedarone	2
Fidaxomicin	1
Fluconazole	1
Verapamil	1
NSAIDs	10
Aspirin	37 (26.6%)
Clopidogrel	6
SSRI/SNRI	23
Proton Pump Inhibitor	72

$CHADS_2$ Score and Stroke Risk in AF Patients

	Points
Congestive HF	1
Hypertension	1
Age > 75 years	1
Diabetes	1
Stroke	2

Sum

$CHADS_2$ score	1-year stroke rate
6	13.7%
5	12.3%
4	10.9%
3	8.6%
2	4.5%
1	2.2%
0	0.8%

Clinical Prediction Scores

	Mean Score	Max Score	Min. Score	Most frequent score
CHADS2	2.7	6	0	2
CHA2DS2-VASc	4.3	8	0	4
HAS-BLED	2.2	5	0	2

- 28% of study population had HAS-BLED score ≥ 3
- 72% CHADS2 score ≥ 2
- 86% CHA2DS2-VASc ≥ 2
- CHADS2 score documented for 13.3% of atrial fibrillation patients.
- HAS-BLED scores recorded for 2.3% of Atrial fibrillation patients.

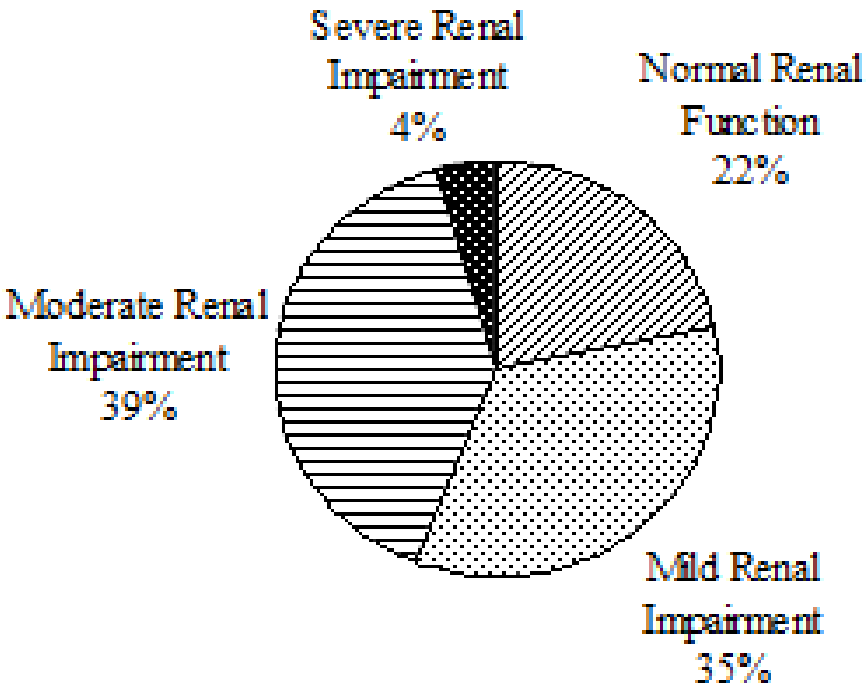
Change in NOAC Therapy during Admission

Changes to NOAC therapy	Number of patients (n=139)	% of patients
Temporary “holding” of NOAC therapy	26	18.7%
Discontinuation of NOAC	17	12%
Dose change	10	7.1%
Surgery	13	9.3%
Actual/suspected bleed	11	8%
Incorrect dose	7	5%
Worsening renal function	6	4.3%
Switched to a different NOAC	3	2.2%
Falls Risk	3	2.2%
Poor compliance	2	1.4%
Deranged LFTs	3	2.2%
Drug interaction	1	0.7%

Documented Risk factors in study group potentially predisposing to adverse events

Medical condition	Number of patients (n=139)	% of patients
Cognitive impairment	34	24.4%
Reduced mobility	31	22.3%
History of falls	30	21.5%
GI conditions	30	21.5%
Past history of bleed	11	7.9%
Chronic renal disease	10	7.2%
Active cancer	7	5%
Coagulation disorders	2	1.4%
Alcoholic liver disease	2	1.4%

Classification of Renal Impairment in the Pooled Study Population (n=139)



Rivaroxaban-Analysis of Renal dosing parameters

- A discrepancy was identified during this study between the:

a) *Estimated Glomerular Filtration Rate (eGFR) (as per BNF)*

b) *Cockroft Gault Equation (as per Summary of Product Characteristics (SPC)) methods for estimating renal dose adjustments.*

- Potential for inconsistency and inaccurate dosing in renal patients; a sub-group that is already proven to be highly vulnerable to NOAC adverse events.

Rivaroxaban- Analysis of Renal dosing

- N=19 (22% of rivaroxaban cohort, n=83) dose discrepancies occurred between the eGFR based guidance and the CrCl guidance.
- For 17 patients the CrCL result in line with the SPC recommended a reduced dose of rivaroxaban 15mg daily, while eGFR result indicated 20mg daily as per BNF.
- For 2 patients the SPC indicated a 20mg daily dose while the eGFR as per BNF recommended the reduced 15mg daily dose.
- In 7% (n=6/83) of cases the 20mg daily dose prescribed should have been adjusted to 15mg daily.
- One patient experienced an intracerebral bleed on rivaroxaban therapy 20mg once daily.

  Cockroft Gault- CrCl 47ml/min = recommended dose 15mg daily

  eGFR - 60ml/min = recommended dose 20mg daily

Classification of Bleed

	Dabigatran (n=55)	Rivaroxaban (n=83)	Apixaban (n=1)
NOAC Bleed (%)	5 (9%)	5 (6%)	1(100%)
Classification of bleed			
Mild (%)	2 (3.6%)	2 (2.4%)	0
Major (%)	3 (5.4%)	2 (2.4%)	1
Life threatening (%)	0	1 (1.2 %) INTRACEREBRAL	0
Patient Type			
Admitted with bleed while on NOAC	4	4	1
Commenced on NOAC and subsequently had bleed	1	1	0
Bleed Location			
Unknown source	1	0	0
Gastrointestinal	2	2	1
Genitourinary	1	1	0
Intracerebral	0	1	0
Nasal	1	1	0

Dabigatran-analysis of bleeding

Characteristic	Dabigatran (n=5)
NOAC Indication	
A.fib	5
Dose- 110mg BD	5
Creatinine clearance	
<30 ml/min	0
30-49 ml/min	4
50-79 ml/min	1
>80 ml/min	0
Body weight <50kg	1
History of ulcerative gastrointestinal disease	2
Concomitant medicines	
Prescribed CYP3A4 inducers	0
Prescribed CYP3A4 inhibitors	0
Prescribed NSAIDs	0
Prescribed aspirin	3
Prescribed clopidogrel	2
Prescribed SSRI/SNRI	1
Prescribed PPI	3

Rivaroxaban-analysis of bleeding

Characteristic	Rivaroxaban (n=5)
NOAC Indication	
A.fib	5
Dose- 20mg daily	4
Dose- 15mg daily	1
Creatinine clearance	
<30 ml/min	0
30-49 ml/min	1
50-79 ml/min	3
>80 ml/min	1
Body weight <50kg	0
History of ulcerative gastrointestinal disease	2
Concomitant medicines	
Prescribed CYP3A4 inducers	0
Prescribed CYP3A4 inhibitors (Dronedarone)	1
Prescribed NSAIDs	0
Prescribed aspirin	0
Prescribed clopidogrel	0
Prescribed SSRI/SNRI	0
Prescribed PPI	3

Analysis of bleeding events- coagulation parameters

Dabigatran

Dabigatran Patient (n=5)	INR	APTT (seconds)	PT (seconds)
1	1.2	34.7	13.2
2	1.2	31	12.4
3	3.7	96	40
4	1.6	67	18.4
5	1.6	63	19.7
Mean	1.7 ± 0.93	58.3 ± 23.75	20.7 ± 10.04

Rivaroxaban

Rivaroxaban Patient (n=5)	INR	APTT (seconds)	PT (seconds)
1	1.3	29.5	15.3
2	1.4	36	14.7
3	1.5	37.7	16.6
4	1.6	39	19.5
5	1.2	33	16
Mean	1.4 ± 0.14	35 ± 3.42	16.4 ± 1.67

Bleeding events- Comparison with clinical trial data

	Study population	NOAC meta-analysis	VKA meta-analysis
Major bleeding	4.31%	4.9%	5.54%
Intracranial bleed	0.72%	0.59%	1.3%

Dentali et al. Efficacy and safety of the Novel oral anticoagulants in Atrial Fibrillation. Circulation 2012, 126(20): 2381-2391.

- Another recent meta-analysis determined that patients receiving NOAC treatment have a similar risk profile to those receiving warfarin (RR 0.88, 95% CI 0.71-1.09). (Miller et al., 2012)
- The results of FDA (Feb 2012) and European Medicines Agency assessment (May 2012) indicate that bleeding rates associated with new use of dabigatran does not appear to be higher than bleeding rates associated with new use of warfarin, which is consistent with the RE-LY trial.

Summary of Study findings

- 139 patients were audited
- 5.75% admitted with a stroke on NOAC therapy
- 1.4% suffered a DVT while on NOAC therapy
- Renal dosing discrepancies
- Discontinuation of therapy (12 %)

Bleeding outcomes

- All patients (n=11) > 65 years, female 63.6%
- Moderate renal impairment in 45.4%
- Higher mean CHADS2 and HAS-BLED scores than those without bleeding complications consistent with previous observations
- Equal prevalence between dabigatran and rivaroxaban (n=5 for both)
- Major bleeding was the most frequently encountered bleed category (45.4%)