Cost-effectiveness Analysis of an Insertable Cardiac Monitor (ICM) to Detect Atrial Fibrillation in Patients with Cryptogenic Stroke

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Presenter Disclosure Information

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Background: CRYSTAL-AF Trial

Objectives:

To assess whether a long-term monitoring cardiac monitoring strategy with an implantable cardiac monitor (ICM) is superior to standard monitoring for the detection of AF in patients with cryptogenic stroke

Background: CRYSTAL-AF Trial

- Inclusion criteria
  - ≥40 years
  - Cryptogenic stroke (or clinical TiA)
    - Infarct seen on CT or MRI and no mechanism including AF after
      - 12 lead ECG
      - 24 hr Holter
      - Echocardiogram (TTE)
      - CT MRA head and neck (to rule out arterial source)
      - No hypercoagulable state

- Exclusion criteria
  - No AF/atrial flutter
  - No indication for pacemaker or defibrillator
  - No indication for anticoagulation

Methods: CRYSTAL-AF Trial

- Follow-up
  - 1, 6, 12 and then every 6 months for three years
- Atrial fibrillation diagnosis
  - AF with no detectable P-waves for >30s
  - Local physician and adjudicated by independent committee
- Clinical status
  - Symptoms
  - Treatment modifications
  - Recurrence of stroke or TiA
  - Health status (EG-5D)
  - Modified Rankin score

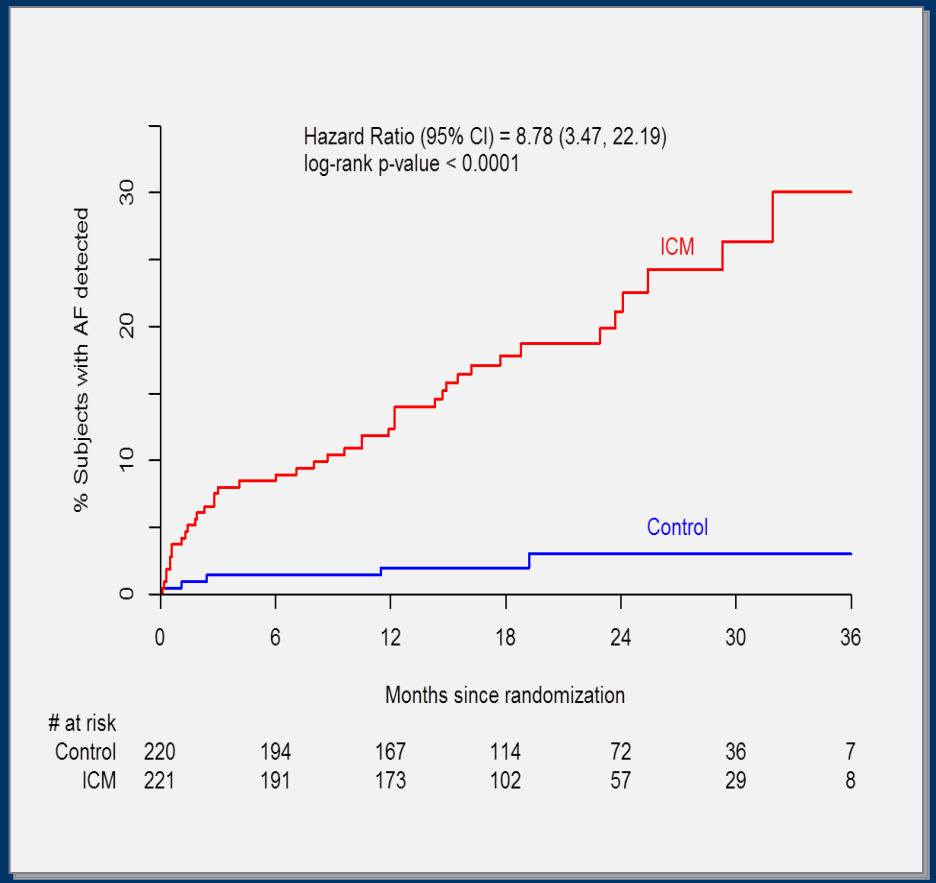
Results: CRYSTAL-AF Trial

An implantable loop recorder is superior to conventional follow-up for finding AF in patients with cryptogenic stroke

Randomized controlled study of 441 cryptogenic stroke patients 40 years of age or older (with no evidence of AF)

Assess whether ICM is more effective than conventional follow-up (control) for detecting AF:

- >**7x** higher AF detection rate at 12 months
- AF was detected at a rate of 30% in the ICM arm at 36 months



Health Economic Research Question

Is the use of continuous long-term monitoring with an insertable cardiac monitor (ICM) for AF detection cost effective for preventing recurrent stroke in cryptogenic stroke patients compared to standard of care?

Why use NHS costs?

- The National Institute for Health and Care Excellence (NICE)
- Aim to reduce variation of availability and quality of care
- Optimising clinical and cost-effectiveness of treatments through evidence based guidance
- Coordinated pathways of care
- Clear processes and framework for assessing cost effectiveness

Model Overview

CRYSTAL-AF DATA

Comparators

Standard of Care (SoC)

Conventional follow-up after cryptogenic stroke

Insertable Cardiac Monitoring (ICM)

ICM for the first 3 years and then follow SoC strategy

Two-stage Markov Model

Investigational stage

Patients with <u>suspected</u> AF but awaiting diagnosis (on aspirin)

Treatment stage

- Patients with <u>confirmed</u> diagnosis of AF switch to NOAC*/warfarin

OR

- Patients <u>without confirmed</u> diagnosis of AF (remain on aspirin)

Cycle length: 3 months
Model time horizon: patient lifetime

Risks

Cerebrovascular events (mild, moderate, severe and fatal IS*)

Treatment-related adverse events: (HS*, ICH*, ECH*, CRNM* bleeding)

*NOAC: New Oral Anticoagulant; *HS: Hemorrhagic Stroke; *ICH: Intracranial Hemorrhage; *ECH: Extracranial Hemorrhage; *CRNM: Clinically Relevant; Non-Major Bleeding *IS: Ischemic Stroke

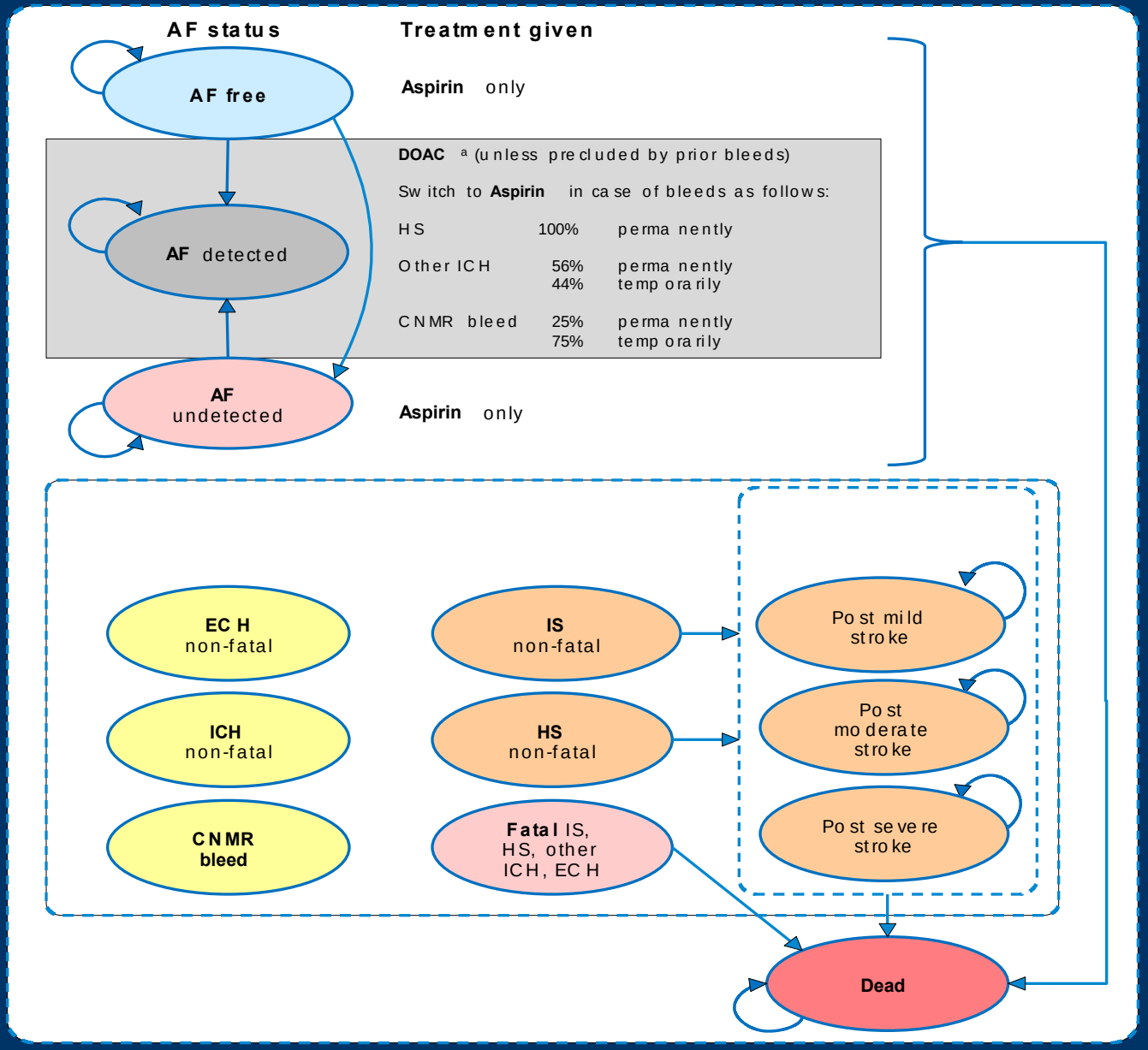
Model Structure

PATIENT AF STATUS AND TREATMENT

Patient status on AF diagnosis and treatment is tracked throughout the model in all health states

CEREBROVASCULAR AND BLEEDING EVENTS

These have either temporary or permanent health consequences



Model Overview

- The patient characteristics match those of the Crystal-AF trial
- Diagnostic yield, implant related complications, resource utilization and baseline health-related quality of life based on evidence from Crystal-AF
- Data from published literature are used to extrapolate
  - uptake of anticoagulation,
  - events,
  - quality of life,
  - survival over patient lifetime
- Cost inputs taken from the literature and NHS reference costs 2013

UK cost-effectiveness analyses developed for evaluation of apixaban:

- Dorian et al. 2014
- Lip et al. 2014
- Luengo-Fernandez et al. 2013

Patient characteristics (from Crystal-AF)

$CHADS_2$	2	3	4	5	6
Mean age	54	62	69	78	78
Male	61%	69%	64%	35%	0%
N	150	183	84	23	1
Weight	34.0%	41.5%	19.0%	5.2%	0.2%
Average age (years)					61.5
Average % male					63.5%
CHADS2 score					3
AF detected by conventional follow-up					3%
AF detection rate – Reveal					30%
AF detected move to					NOAC

Resource use and cost

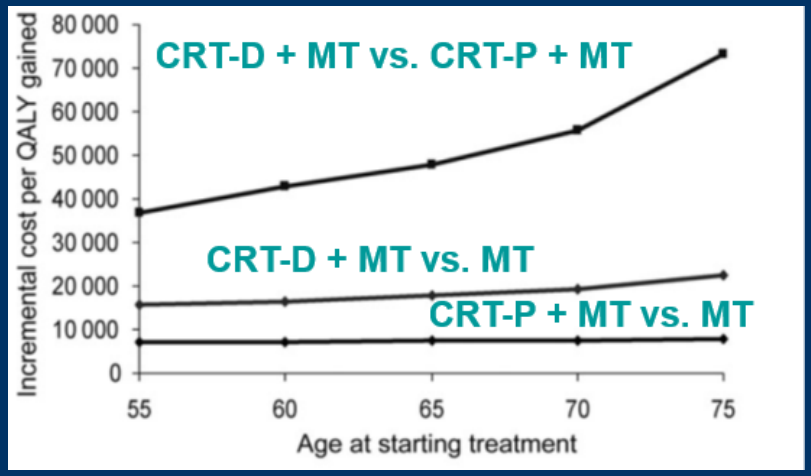
- Reveal
  - Device and Implantation: £1,863
  - Explantation: £491
  - Monitoring per cycle: £27.82
    - Based on 1 appointment / download per 6 months
  - Diagnosis: £49.50
    - Based on 1 half-hour appointment at time of AF diagnosis
- Standard of care

Period	No test	ECG	Holter 24H	Holter 48H	Holter 7D	Mean per cycle cost
		£136.79[a]				
0-12 months	0.307	0.549	0.063	0.022	0.058	£29.74
12-24 months	0.508	0.398	0.036	0.007	0.051	£19.56
24-36 months	0.582	0.314	0.021	0	0.084	£15.96

What's an ICER and why should I care?

ICER: Incremental cost – effectiveness ratio

It's the *additional* cost of the procedure/treatment worked out in relation to the QoL gained



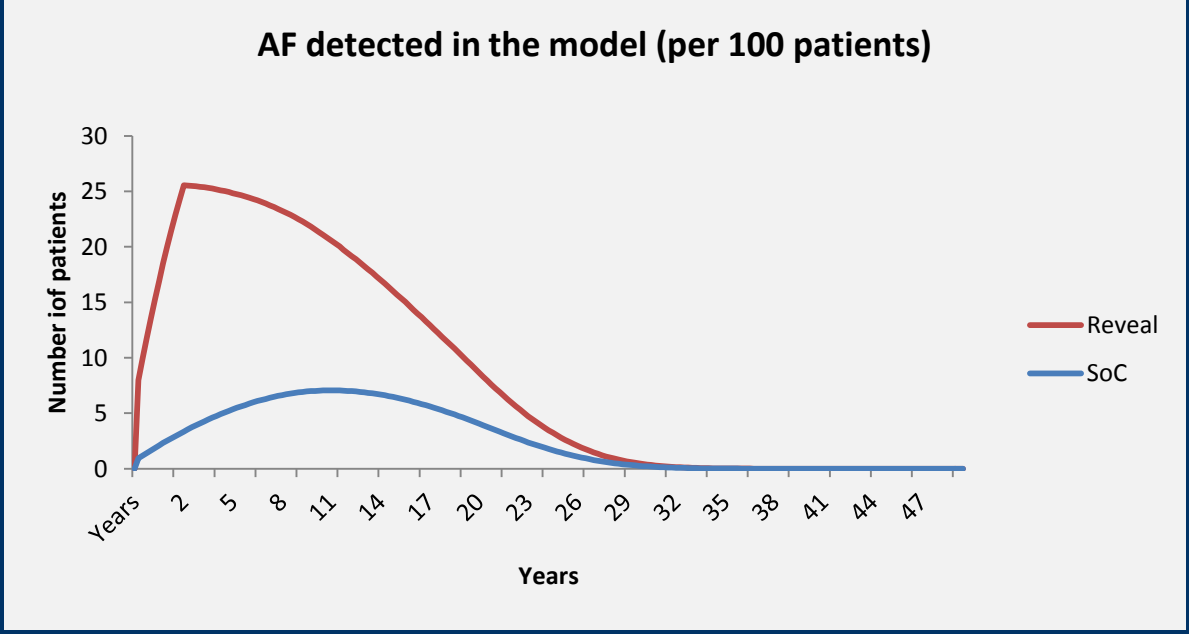
Results: Crystal AF-NOAC

Model Results

Strategy	Total Ischaemic Strokes	Total CRNM bleeds	Total major bleeding events	Total Life Years	Total QALYs	Disutility due to non-fatal events	Total diagnostic costs	Total health state costs	Total stroke event costs	Total bleed event costs	Total event related costs	Total cost
SoC	0.44735	0.70150	0.2466	10.33166	7.21625	0.02672	£666	£10,611	£4,387	£1,382	£5,769	£17,045
Reveal	0.40359	0.78530	0.2696	10.50012	7.36685	0.02438	£2,910	£11,254	£3,958	£1,511	£5,469	£19,633
Incremental	**-0.04376**	**0.08380**	**0.02299**	**0.16846**	**0.15060**	**-0.00234**	**£2,244**	**£644**	**-£429**	**£129**	**-£300**	**£2,588**

*all totals (events, outcomes and costs) are based on discounted values

Threshold £30,000.00 **Incremental net benefit** **£1,930.10** **ICER** **£17,184** per QALY gained NNI (ischaemic stroke outcome) 20

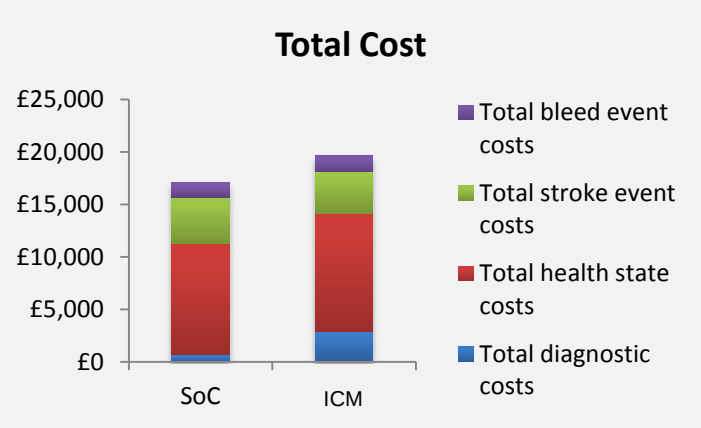


Results: Crystal AF-NOAC

Strategy	Ischaemic Strokes	QALYs*	Costs
SoC	0.44735	7.21625	£17,045
ICM	0.40359	7.36685	£19,633
Incremental	-0.04376	0.15060	£2,588
Incremental Cost Effectiveness Ratio GBP			£17,184
Incremental Cost Effectiveness Ratio USD			$28,308
Number needed to implant to avoid a stroke			20

*QALY – Quality Adjusted Life Year

UK Threshold= £20,000
US Threshold= $50,000



*Incremental Cost effectiveness Ratio

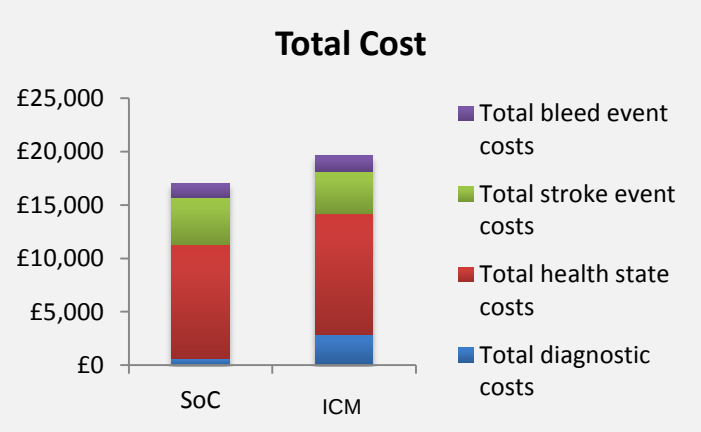
$$\text{ICER}^* = \frac{\text{Incremental Cost}}{\text{Incremental *QALYs}} = \frac{£2,588}{0.1506} = £17,184$$

Results: Crystal AF-Warfarin

Strategy	Ischaemic Strokes	QALYs*	Costs
SoC	0.44644	7.20233	£16,649
ICM	0.39973	7.32218	£18,243
Incremental	-0.04671	0.11984	£1,593
Incremental Cost Effectiveness Ratio GBP			£13,296
Incremental Cost Effectiveness Ratio USD			$21,903
Number needed to implant to avoid a stroke			18

*QALY – Quality Adjusted Life Year

UK Threshold= £20,000
US Threshold= $50,000



*Incremental Cost effectiveness Ratio

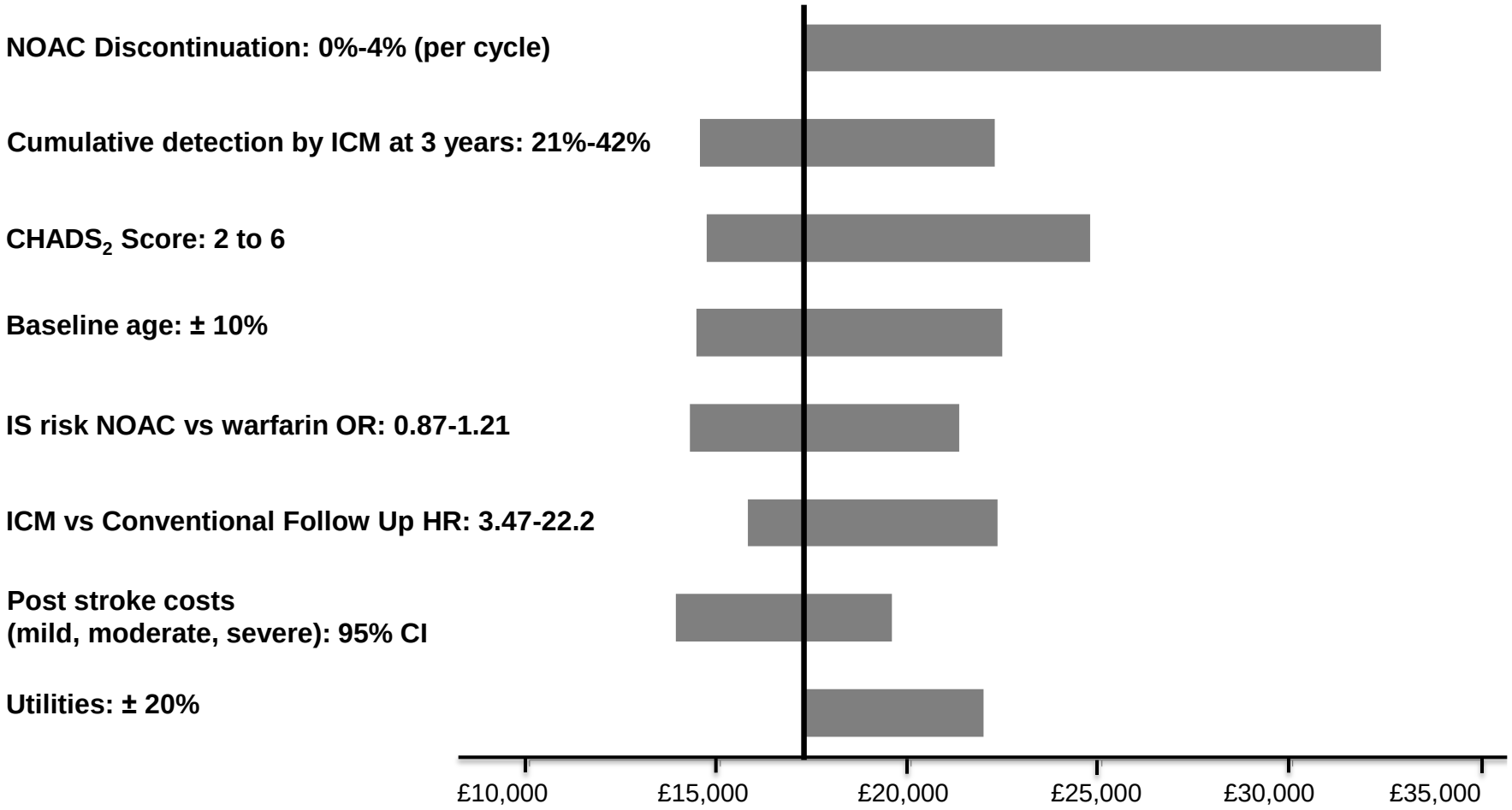
$$\text{ICER}^* = \frac{\text{Incremental Cost}}{\text{Incremental *QALYs}} = \frac{£1,593}{0.1198} = £13,296$$

Results: Crystal AF-NOAC by $CHADS_2$

$CHADS_2$	**ICER***	**NNI***
2	£23,367	27
3	£17,959	22
4,5,6	£13,630	13
CRYSTAL-AF average	£17,184	20

*Incremental Cost Effectiveness Ratio
*NNI: Number Needed to Implant to prevent a stroke

Sensitivity Analysis



Comparison with other therapy areas

Intervention	Cost-Effectiveness (Cost/QALY) Mid-Point		Implementation
ICM – Cryptogenic Stroke	$28,308	£17,184	
ICM - Syncope	$28,664	£17,400	
Cholesterol management	$35,000	£21,246	30%
Cardiac Resynchronization therapy	$37,500	£22,763	39%
Hypertension medication (DBP >105 mmHg)	$40,000	£24,281	35%
Dialysis in end-stage renal disease	$100,000	£60,702	90%
Left ventricular assist devices	$1,200,000	£728,423	5,000-100,000 cases per year

Conclusions

- AF detection with an ICM increases linearly over its 3-year battery life, identifying AF at a rate almost 9x higher than the standard of care.
- ICMs are a cost-effective diagnostic tool for the prevention of recurrent stroke in cryptogenic stroke patients in the UK and other countries with similar healthcare systems.
- Further analyses to include the use of a 30-day monitor first, followed by ILR if needed.

Ischaemic Stroke: Probabilities

$CHADS_2$ score	Annual risk of ischaemic or unspecified stroke by health state			
	AF free on aspirin	AF undetected on aspirin	AF detected on warfarin[1]	AF detected on NOAC
	HR 0.662 (Mohan 2009)	Baseline risk (Gage 2004)	HR 0.38 vs aspirin (ARISTOTLE & AVERROES)	PetoOR 1.03 vs warfarin (Ntaios 2012)
0	0.005	0.008	0.003	0.003
1	0.015	0.022	0.008	0.009
2	0.030	0.045	0.018	0.018
3	0.058	0.086	0.034	0.035
4	0.074	0.109	0.043	0.045
5	0.083	0.123	0.049	0.051
6	0.093	0.137	0.055	0.057

Annual bleeding risks

Bleeding event	Aspirin	Warfarin	NOAC
ICH (including HS)	0.0055	0.0119	0.0056
Other ICH	0.0022	0.0048	0.0023
Fatal Other ICH	0.0003	0.0006	0.0003
Non-fatal Other ICH	0.0019	0.0042	0.0020
Haemorrhagic stroke (HS)	0.0033	0.0071	0.0034
Mild HS stroke	0.0009	0.0020	0.0009
Moderate HS stroke	0.0007	0.0016	0.0008
Severe HS stroke	0.0004	0.0009	0.0004
Fatal HS stroke	0.0012	0.0026	0.0012
ECH (including GI Bleed)	0.0274	0.0264	0.0321
GI bleed	0.0115	0.0111	0.0134
Fatal GI Bleed	0.0002	0.0002	0.0003
Non-fatal GI Bleed	0.0112	0.0108	0.0132
Other ECH bleed	0.0159	0.0154	0.0187
Fatal Other ECH Bleed	0.0003	0.0003	0.0004
Non-fatal Other ECH Bleed	0.0156	0.0151	0.0183
CRNM Bleed	0.0756	0.1012	0.0864

Pisters et al. 2012, Easton et al. 2012, Hankey et al 2012, Granger et al 2011, Ntaios et al. 201, Connolly et al 2009, Diener et al. 2012

Stroke and bleeding costs

Health state	Cost per cycle	Source
Post mild stroke (ischaemic or haemorrhagic)	£577.93	OXVASC [Luengo-Fernandez et al. 2013]
Post moderate stroke (ischaemic or haemorrhagic)	£1,127.44	
Post Severe Stroke (ischaemic or haemorrhagic)	£1,711.86	
Event	**Cost per event**	**Source**
Mild ischaemic stroke	£3,682.51	OXVASC [Luengo-Fernandez et al. 2013]
Moderate ischaemic stroke	£19,211.62	
Severe ischaemic stroke	£26,239.89	
Fatal ischaemic stroke	£3,312.20	
Mild haemorrhagic stroke	£10,722.69	
Moderate haemorrhagic stroke	£27,547.87	
Severe haemorrhagic stroke	£46,598.16	
Fatal haemorrhagic stroke	£1,723.77	
Other ICH	£2,526.47	NHS Ref Costs 2013 (AA23 as non-elective inpatient long and short stay)
Other ECH	£3,998.75	NHS Ref Costs 2013 (HC28, HD24, BZ24, PA23, FZ12 as non-elective inpatient long and short stay)
GI Bleed	£1,890.70	NHS Ref Costs 2013 (FZ38 as non-elective inpatient long and short stay)
CRNM bleed	£459.56	NHS Ref Costs 2013 (FZ38, CZ13, LB38 as non-elective inpatient short stay)
Infection (from Reveal)	£7.94[a]	NHS Ref Costs 2013 (PA16, PA17, PA18 as non-elective inpatient short stay)

Quality of life: Utilities

Health state	ϕ	References
No AF	0.9406	
AF	0.9227	
Post-mild stroke - No AF	0.8733	OXVASC HRQoL study
Post-mild stroke - AF	0.8566	OXVASC HRQoL study
Post-moderate stroke - No AF	0.6991	OXVASC HRQoL study
Post-moderate stroke - AF	0.6858	OXVASC HRQoL study
Post-severe stroke - No AF	0.4769	OXVASC HRQoL study
Post-severe stroke - AF	0.4678	OXVASC HRQoL study
Dead		
Acute event		
Mild recurrent stroke	0.7705	OXVASC HRQoL study
Moderate recurrent stroke	0.5278	OXVASC HRQoL study
Severe recurrent stroke	0.1372	OXVASC HRQoL study
other ICH	0.9270	Dorian et al. 2014; Lip et al. 2014
ECH	0.9942	Dorian et al. 2014; Lip et al. 2014
CRNM bleed	0.9997	Dorian et al. 2014; Lip et al. 2014