Are treatments to reduce or prevent stroke in AF cost-effective ?

Francisco Leyva
Chair, Health Economics Committee

EUROPEAN Heart Rhythm ASSOCIATION
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Reality check

Prof. John Appleby, Chief Economist, King's Fund:

'The next government will inherit a health service that has run out of money and is operating at the very edge of its limits'

'The Department of Health has a parallel set of tactics to deal with the 20 billion cash freeze in prices for hospitals, tough management cuts and exhortation to the NHS to squeeze more from less.'

AF ablation

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Cost-effectiveness of radiofrequency catheter ablation for the treatment of atrial fibrillation in the United Kingdom

C McKenna,[1] S Palmer,[1] M Rodgers,[2] D Chambers,[2] N Hawkins,[1] S Golder,[2] S Van Hout,[1] C Pepper,[3] D Todd,[4] N Woolacott[2]

Cost-effectiveness of AF ablation *vs* AAD therapy for the treatment of AF

Perspective: UK NHS.

Design: Bayesian evidence synthesis and decision analytical model.

Methods: Systematic review and meta-analysis to synthesise the effectiveness evidence from RCTs.

Perspective: Health service perspective

Outcome: Costs from a health service perspective and outcomes measured in QALYs

Horizon: Lifetime

McKenna C, et al. Heart 2008;95:542-9

Base-case analysis

	Strategy	Mean costs (£)	Mean QALYs	ICER (£)	Probability of being cost-effective for threshold at: £20 000	£30 000
Lifetime analysis						
$CHADS_2 = 0$	RFCA	25 240	12.37	7763	0.983	0.996
	AADs	14 415	10.98	–		
$CHADS_2 = 1$	RFCA	26 027	12.14	7780	0.981	0.996
	AADs	15 367	10.77	–		
$CHADS_2 = 2$	RFCA	26 987	11.87	7765	0.986	0.999
	AADs	16 517	10.52	–		
$CHADS_2 = 3$	RFCA	28 343	11.49	7910	0.992	1.000
	AADs	18 107	10.19	–		
5-year analysis						
$CHADS_2 = 0$	RFCA	25 251	11.35	27 745	0.091	0.577
	AADs	14 429	10.96	–		
$CHADS_2 = 1$	RFCA	26 016	11.18	25 510	0.165	0.686
	AADs	15 352	10.76	–		
$CHADS_2 = 2$	RFCA	26 972	10.97	23 202	0.265	0.786
	AADs	16 499	10.52	–		
$CHADS_2 = 3$	RFCA	28 366	10.67	20 831	0.418	0.881
	AADs	18 133	10.18	–		

McKenna C, et al. Heart 2008;95:542-9

Cost-effectiveness of AF ablation

Probability that AF ablation is cost-effective:

At threshold of £20 000/QALY: 0.981 to 0.992

At threshold of £30 000/QALY: 0.996 to 1.000.

Little uncertainty that AF ablation is the optimal treatment if QoL benefits are maintained over a lifetime.

Cost-effectiveness being more favourable the higher the risk of stroke.

McKenna C, et al. Heart 2008;95:542-9

Cost-effectiveness of AF ablation

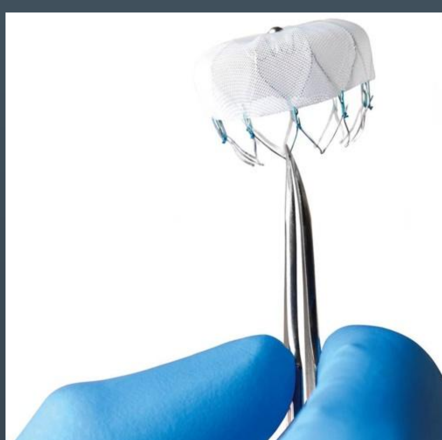
AF ablation is potentially cost-effective for the treatment of paroxysmal AF in patients predominantly refractory to AAD therapy if the QoL benefits are maintained > 5 years.

No reliable data on stroke prevention

No inferences can be made regarding persistent or permanent AF

McKenna C, et al. Heart 2008;95:542-9

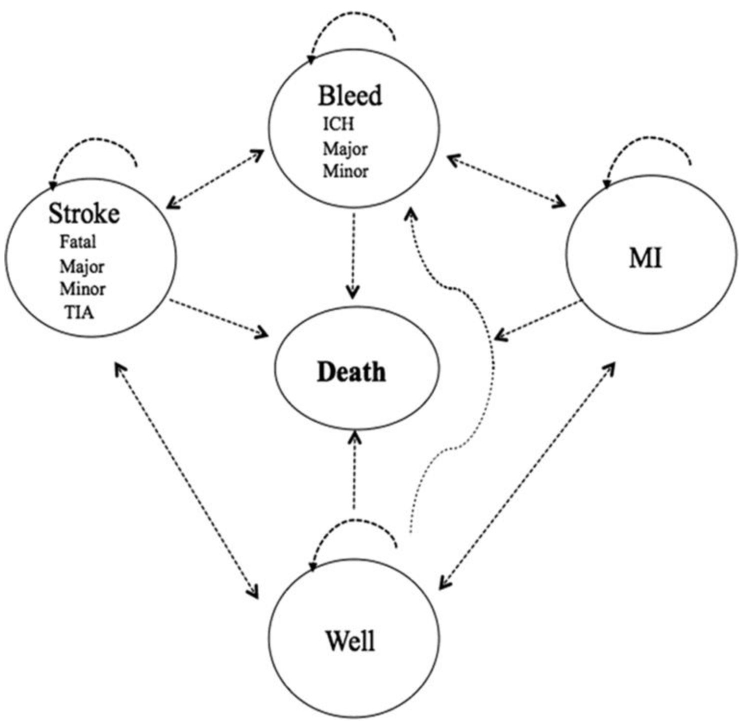
LAA occlusion



Economic Evaluation of Percutaneous Left Atrial Appendage Occlusion, Dabigatran, and Warfarin for Stroke Prevention in Patients With Nonvalvular Atrial Fibrillation

Sheldon M. Singh, MD; Andrew Micieli, MMI; Harindra C. Wijeysundera, MD, PhD

Patient-level Markov microsimulation decision analytical model



LAAO in relation to dabigatran and warfarin in patients with NVAF (modelled on PROTECT AF)

Outcomes: Survival
QALYs, ICERs

Horizon: Lifetime

Perspective: Ontario, Canada
(government insured health services)

If a strategy was more expensive and less effective than its comparator, it was considered dominated and ruled out.

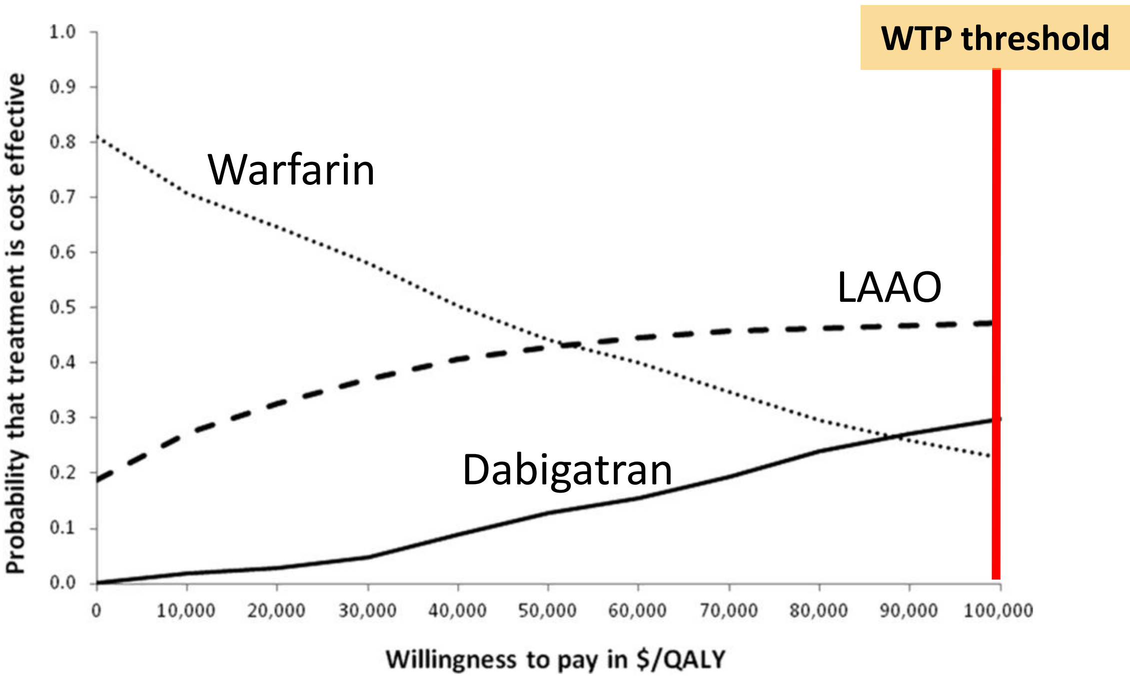
Sheldon M. Singh et al. Circulation. 2013;127:2414-2423

Economic Evaluation of Percutaneous Left Atrial Appendage Occlusion, Dabigatran, and Warfarin for Stroke Prevention in Patients With Nonvalvular Atrial Fibrillation

Sheldon M. Singh, MD; Andrew Micieli, MMI; Harindra C. Wijeysundera, MD, PhD

	Warfarin	Dabigatran	LAAO
Lifetime costs	**21,429**	**25,760**	**27,003**
ICER	**-**	**Ruled out**	**41,565**

Costs in Canadian $



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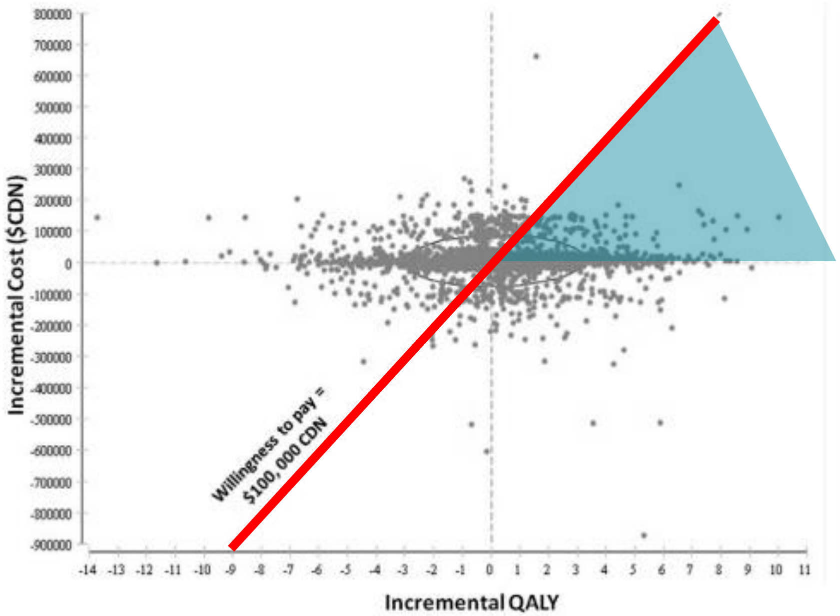


The probability of LAAO being cost effective is 47% using a Canadian dollar threshold of $100,000

NICE view:

Many points along the line of no differential cost and points for incremental QALYs in all four quadrants.

Sheldon M. Singh et al. Circulation. 2013;127:2414-2423

NICE recommendations

	Costs (GBP)	
Watchman device	**4,000**	
Catheter insertion	**400 ***	
Total procedure	**7,610 ****	

*, exclusive of imaging and follow-up costs
**, NHS North East Treatment Advisory Group

NICE view:

Upfront costs would not be less than lifetime costs of anticoagulation (Anticoagulation first, then consider LAAO if anticoagulation contraindicated)

LAAO *vs* 'do nothing': LAAO potentially cost-effective

NICE recommendations

12.2.3 Evidence statements

Clinical

Evidence from one study (N= 707) comparing LAAO plus warfarin to warfarin alone showed that LAAO (as an adjunct to warfarin) was associated with:

- no clinical benefit in reducing mortality, ischaemic stroke, systemic embolism or primary safety (low to very low quality evidence).
- a decrease in number of haemorrhagic strokes (Low quality evidence).

Economic

One cost–utility analysis found that LAAO and warfarin could be equally as cost effective as warfarin in patients with AF (ICER: £16,595 to £22,385 per QALY gained (Discounting rate 0% to 5%). This analysis was assessed as partially applicable and with minor limitations.

32. Consider left atrial appendage occlusion (LAAO) if anticoagulation is contraindicated or not tolerated and discuss the benefits and risks of LAAO with the person. For more information see Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism (NICE interventional procedure guidance 349). [new 2014]

33. Do not offer LAAO as an alternative to anticoagulation unless anticoagulation is contraindicated or not tolerated. [new 2014]

NOACs

Cost-Effectiveness of New Oral Anticoagulants Compared with Warfarin in Preventing Stroke and Other Cardiovascular Events in Patients with Atrial Fibrillation

Cost-effectiveness by the ICER.

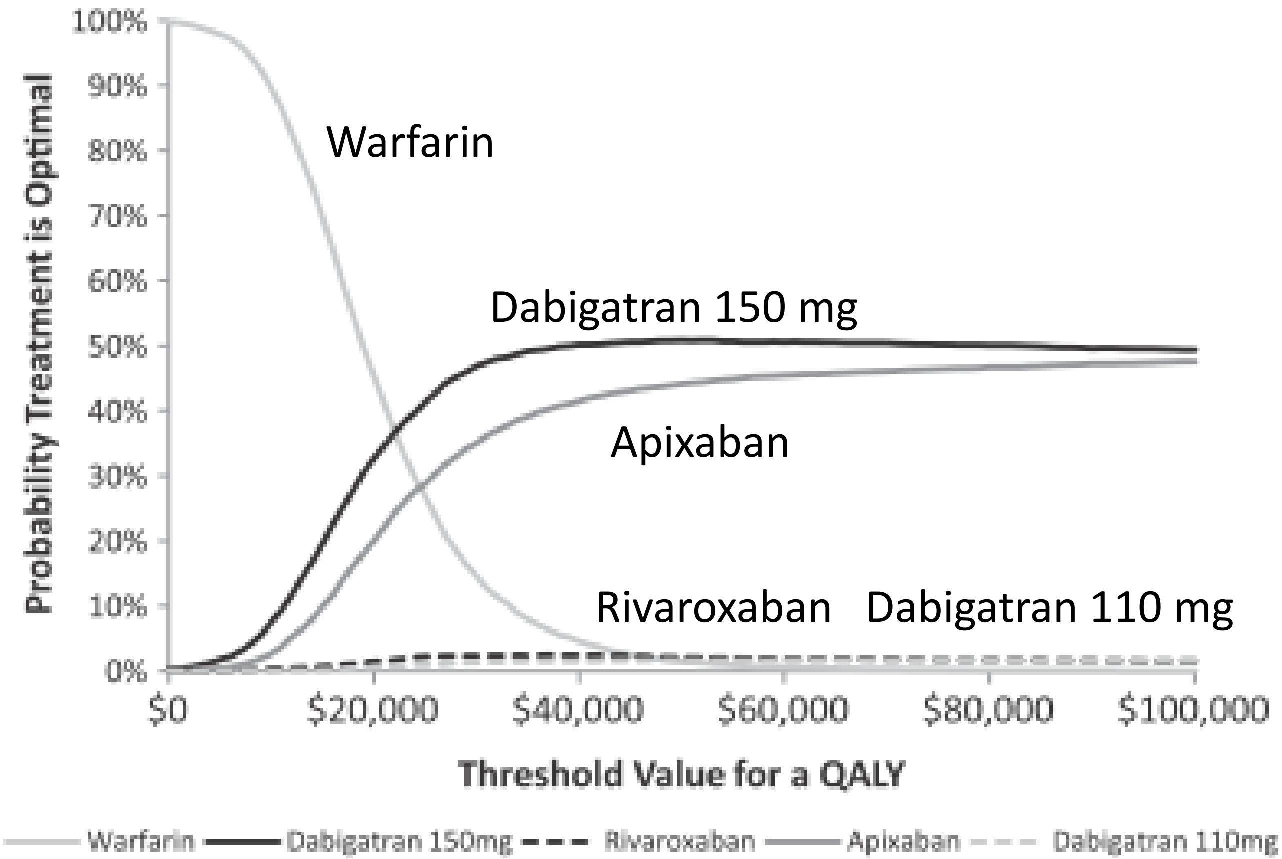
Markov cohort model from initiation of therapy to death.

Data from network meta-analysis.

	Cost ($)	QALYs	Incremental cost per QALY gained (ICER) ($)	
			vs. warfarin	Sequential ICER
Warfarin	18,620	6.480		
Dabigatran 150 mg	21,486	6.617	20,797	20,797
Dominated therapies				
Apixaban	21,966	6.617	24,312	Dominated by dabigatran 150 mg
Rivaroxaban	22,016	6.541	55,757	Dominated by dabigatran 150 mg and apixaban
Dabigatran 110 mg	22,804	6.543	66,354	Dominated by dabigatran 150 mg and apixaban

Coyle D, et al. Value in Health 2013;16:498-506

Cost-Effectiveness of New Oral Anticoagulants Compared with Warfarin in Preventing Stroke and Other Cardiovascular Events in Patients with Atrial Fibrillation



Coyle D, et al. Value in Health 2013;16:498-506

Cost-effectiveness: apixaban vs other NOACs

Comparison of apixaban versus other NOACs

Perspective: UK NHS

Horizon: Lifetime

Method: Markov model. Pair-wise indirect comparisons against other NOACs using ARISTOTLE, RE-LY and ROCKET-AF

End points:
Ischemic stroke.
Hemorrhagic stroke, intracranial hemorrhage.
Other major bleeds, clinically relevant non-major bleeds.
MI, treatment discontinuations.

Outcomes:
Life-years, QALYs, ICERs
Direct healthcare costs

Lip GYH, et al. Clin Ther 2014;36:192-210

Cost-effectiveness: apixaban vs other NOACs

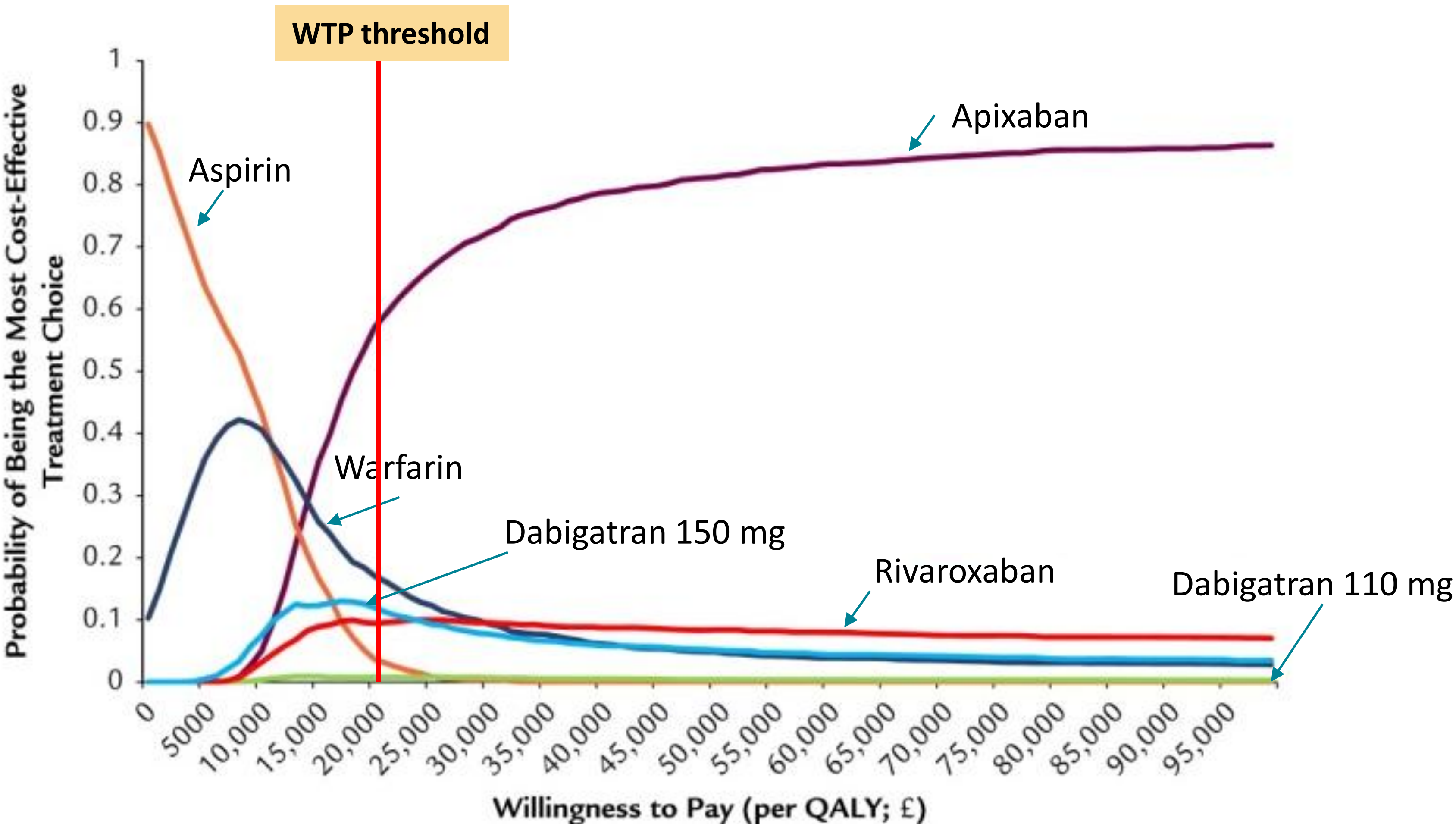
Fewer strokes and CV deaths with **apixaban** *vs* other NOACs.

Overall consideration of efficacy, major bleeding, and tolerability profile extrapolated over a lifetime suggests that apixaban therapy would result in fewer strokes.

Table VI. Scenario analysis: incremental cost-effectiveness ratio (ICER) of apixaban versus the comparator (percent deviation from base case). Unless otherwise noted, values are 2011 British pounds.

Variable	Dabigatran 110 mg	Dabigatran 150 mg	Rivaroxaban
Base	4497	9611	5305

Cost-effectiveness acceptability



Lip GYH, et al. Clin Ther 2014;36:192-210

Conclusions

For the prevention of stroke:

AF ablation: Preventing stroke and duration of treatment effect are the most important in cost-effectiveness

No reliable data on AF ablation and stroke prevention

No data on persistent or permanent AF

LAAO: Cost-effective as alternative to warfarin

May be superior to NOACs, but more data required

Probably cost-effective compared to ‘do nothing’

NOACs: Apixaban is the most cost-effective

No studies have explored the patient’s perspective

Cost-effectiveness of AF ablation

Mean cost per AF ablation:	$7,056
Physician fees for an AF ablation:	$2,534
Total cost per AF ablation:	$9,590
Number of AF ablations per patient:	27% required one or more ablation procedures (Cappato et al: 8745 AF ablation patients, 2389 (27%) required one or more AF ablations) 1.27 ablations per patient
Total procedure costs:	$12,179
Other costs in 1st year:	3 cardiologist consultations CT scan during the first year after ablation.
Cumulative costs of 1 year follow-up:	$666. ‘No follow-up costs after the first year’

Cost-effectiveness of AF ablation

Medications costs:

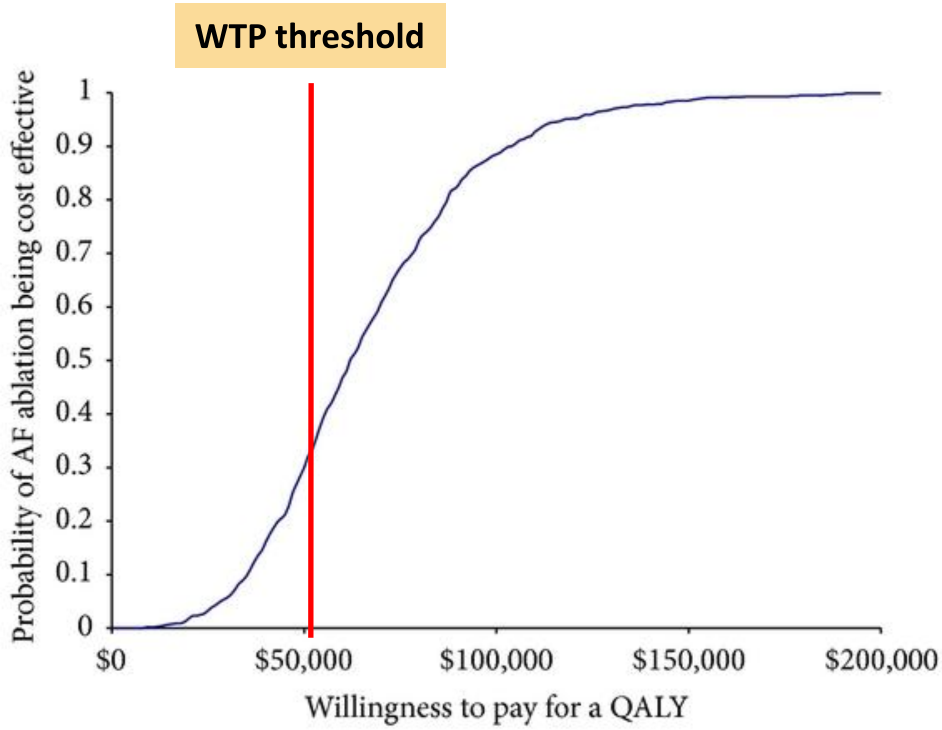
From the Ontario Drug Benefit Formulary

Amiodarone for 1 year:	\$433.29
Warfarin for 1 year :	\$75.30
Annual monitoring cost for warfarin:	\$387.54
Ischemic stroke for 1 year:	\$61,413
Haemorrhagic stroke for 1 year:	\$58,159
Major bleed:	\$6,023

Cost-effectiveness of AF ablation

Table 3: Basecase cost-effectiveness results.

Treatment	Expected costs	Expected strokes	Expected QALYs	$/QALY
Ablation	$21,150	0.122	3.416	
AAD	$12,611	0.155	3.272	
Incremental (Ablation-AAD)	$8,539	(0.033)	0.144	$59,194



Limitations:

1 year follow-up

No published data comparing stroke rates between patients treated with ablation compared to those treated with AAD.

Annals of Internal Medicine
ESTABLISHED IN 1927 BY THE AMERICAN COLLEGE OF PHYSICIANS

From: Cost-Effectiveness of Dabigatran Compared With Warfarin for Stroke Prevention in Atrial Fibrillation

Table 2. **Projected Costs and QALYs for Patients With Nonvalvular Atrial Fibrillation, by Varying Risk for Stroke and ICH***

Annual Stroke and ICH Rate With Warfarin, %	Therapy	Cost, $	QALYs	Marginal Cost per QALY, $
Stroke: 0.72 ($CHADS_2$ score, 1); ICH: 0.74	Warfarin	129 749	10.72	Reference
	Dabigatran, 110 mg	148 935	11.20	40 355
	Dabigatran, 150 mg	155 769	11.23	171 984
Stroke: 1.2 ($CHADS_2$ score, 1–2); ICH: 0.74 (base case)	Warfarin	143 193	10.28	Reference
	Dabigatran, 110 mg	164 576	10.70	Dominated†
	Dabigatran, 150 mg	168 398	10.84	45 372
Stroke: 2.35 ($CHADS_2$ score, 4); ICH: 0.74	Warfarin	161 620	9.36	Reference
	Dabigatran, 110 mg	185 822	9.65	Dominated†
	Dabigatran, 150 mg	186 910	10.00	39 680
Stroke: 1.2 ($CHADS_2$ score, 1–2); ICH: 0.44	Warfarin	134 655	10.75	Reference
	Dabigatran, 110 mg	163 083	11.00	Dominated‡
	Dabigatran, 150 mg	166 652	11.21	69 574
Stroke: 1.2 ($CHADS_2$ score, 1–2); ICH: 1.48	Warfarin	158 912	9.39	Reference
	Dabigatran, 110 mg	169 482	10.05	16 147
	Dabigatran, 150 mg	173 721	10.06	263 543

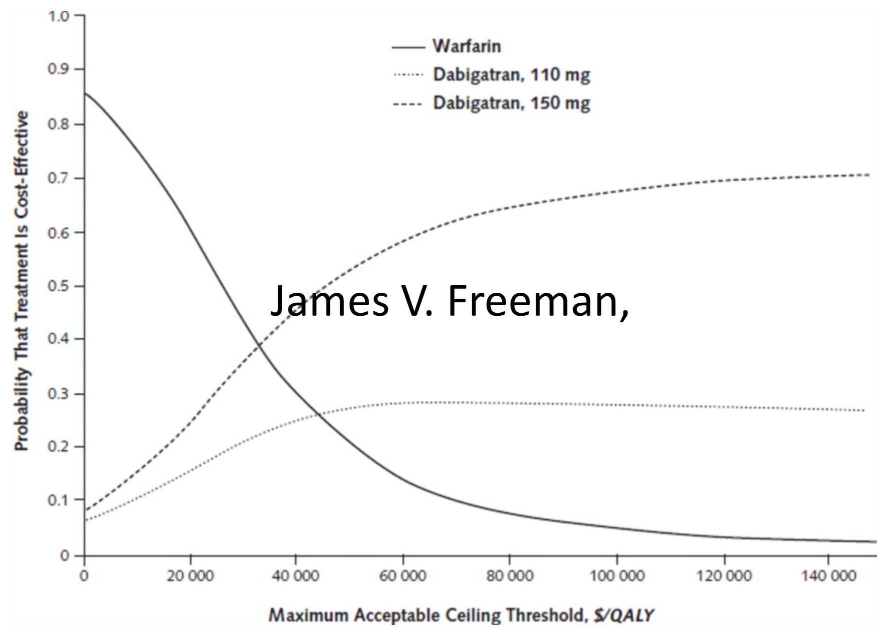
ICER = incremental cost-effectiveness ratio; ICH = intracranial hemorrhage; QALY= quality-adjusted life-year.
* Risk for stroke defined by $CHADS_2$ score (range, 0 to 4). Costs are in 2008 U.S. dollars.
† Dabigatran, 110 mg, is dominated by extended dominance, meaning that it is less cost-effective than 150-mg dabigatran and the overall QALY results are lower than that of 150-mg dabigatran. For a stroke risk of 1.2%, the ICER of 110-mg dabigatran vs. warfarin was $51 229. For a stroke risk of 2.35%, the ICER of 110-mg dabigatran vs. warfarin was $82 746.
‡ Dabigatran, 110 mg, is dominated by extended dominance, meaning that its value in cost per QALY is less than that of 150-mg dabigatran and the overall QALY results are lower than that of 150-mg dabigatran. For an ICH risk of 0.44%, the ICER of 110-mg dabigatran vs. warfarin was $115 129. For an ICH risk of 0.74%, the ICER of 110-mg dabigatran vs. warfarin was $51 229.

Projected Costs and QALYs for Patients With Nonvalvular Atrial Fibrillation, by Varying Risk for Stroke and ICH

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: Cost-Effectiveness of Dabigatran Compared With Warfarin for Stroke Prevention in Atrial Fibrillation

Ann Intern Med. 2011;154(1):1-11. doi:10.7326/0003-4819-154-1-201101040-00289



James V. Freeman,

Figure Legend:

Cost-effectiveness acceptability curves representing the probability that each treatment strategy is cost-effective for a given maximum willingness-to-pay threshold per QALY gained.This graph is based on 10 000 Monte Carlo simulations of the model, drawing parameters for each input simultaneously from probability distributions. Warfarin is most likely to be cost-effective at a willingness-to-pay threshold ≤$30 000 per QALY. At thresholds ≥$35 000 per QALY, high-dose dabigatran is most likely to be cost-effective. High-dose dabigatran is 53%, 68%, and 70% likely to be cost-effective at willingness-to-pay thresholds of $50 000, $100 000, and $150 000 per QALY, respectively. Either high-dose or low-dose dabigatran was preferred to warfarin in more than 80% of simulations using a willingness-to-pay threshold of $50 000 per QALY. QALY = quality-adjusted life-year.

The network pooled evidence regarding warfarin and the new agents (such as apixaban) for class comparisons and the use of warfarin intervention as a proxy cost for this class was noted as a potential limitation. However, direct evidence regarding a 'do nothing strategy' versus anticoagulation predated the new agents and mainly specified warfarin as the comparator. Evidence from the new agents therefore have an indirect rather than a direct impact on the effect size between a do nothing approach and anticoagulation estimated through the NMA. That is to say the impact of the new agents in determining the recommended threshold to give anticoagulation following a do nothing approach is likely to be minimal given the data sources used. As such, and given the focus of the analysis on the appropriate stroke prevention management strategy for people with AF at low risk of stroke (i.e. at or under the risk indicated by the risk factors where new agents are considered in related NICE guidance), the use of using the cost of warfarin as a proxy for this class to assist decision making was felt appropriate.

	Costs (GBP)	
Watchman device	**4,000**	
Catheter insertion	**400 ***	
Total procedure	**7,610 ****	

*, exclusive of imaging and follow-up costs
**, NHS North East Treatment Advisory Group

The Watchman™ device has been e
plus £400 for the insertion of the ca
is £5,280. This will not be inclusive
The NHS North East Treatment Adv
without complications t
s not given, although th
-operative follow-up ap
or imaging techniques s
ing and after implantati

The importance o
emphasised. The
resources used in
clinical evidence o
what the long ter

NICE view:

Upfront costs would not be less than lifetime costs of anticoagulation
(Anticoagulation first, then consider LAAO if anticoagulation contraindicated)

LAAO vs 'do nothing': LAAO potentially cost-effective

In comparison to anticoag
of the device would be les
lifetime. Given the uncerta
comparators and the likeli
recommended anticoagula

In regards to LAAO's poten
anticoagulation, the compa
cost. The GDG believed tha
device, and therefore cost
stroke. Therefore it was fe
high risk of stroke; LAAO s
intervention.

effectiveness of LACA in 55
and 65-year-old cohorts with AF at moderate and low stroke risk. Costs, health utilities, and transition probabilities were derived from published literature and Medicare data. We performed primary threshold analyses to determine the minimum level of LACA efficacy and
stroke risk reduction needed to make LACA cost-effective at $50,000 and $100,000 per quality-adjusted life-year (QALY) thresholds.

RESULTS In 65-year-old subjects with AF at moderate stroke risk, relative reduction in stroke risk with
an 80% LACA efficacy rate for sinus rhythm restoration would need to be 42% and 11% to yield incremental cost-effectiveness ratios (ICERs) $50,000 and $100,000 per QALY, respectively. Higher and lower LACA efficacy rates would require correspondingly lower and higher stroke risk reduction for equivalent ICER thresholds. In the 55-year-old moderate stroke risk cohort, lower LACA efficacy rates or stroke risk reduction would be needed for the same ICER thresholds. In patients at low stroke risk, LACA was unlikely to be cost-effective.

Table 2. Incremental Cost-Effectiveness Ratios (ICER) in Base-Case Estimates, Stratified by Ischemic Stroke Risk

Stroke Risk	Strategy	Cost	Life-Years	QALYs	ICER ($/QALY)
Moderate (age = 65 yrs)	Rate control + warfarin	$39,391	11.47	10.81	Reference
	Amiodarone + warfarin	[illegible]	11.45	10.75	Dominated
	LACA + warfarin	$52,369	11.55	11.06	$51,800/QALY
Moderate (age = 55 yrs)	Rate control + warfarin	$50,509	14.80	13.95	Reference
	Amiodarone + warfarin	$55,795	14.75	13.81	Dominated
	LACA + warfarin	$59,380	14.88	14.26	$28,700/QALY
Low	Rate control + ASA	$24,540	11.65	11.21	Reference
	Amiodarone + ASA	$38,425	11.60	11.02	Dominated
	LACA + ASA	[illegible]	11.70	11.40	$98,900/QALY

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LACA may be cost-effective if sinus rhythm restoration translates into lower rates of stroke and anticoagulant-related hemorrhage.

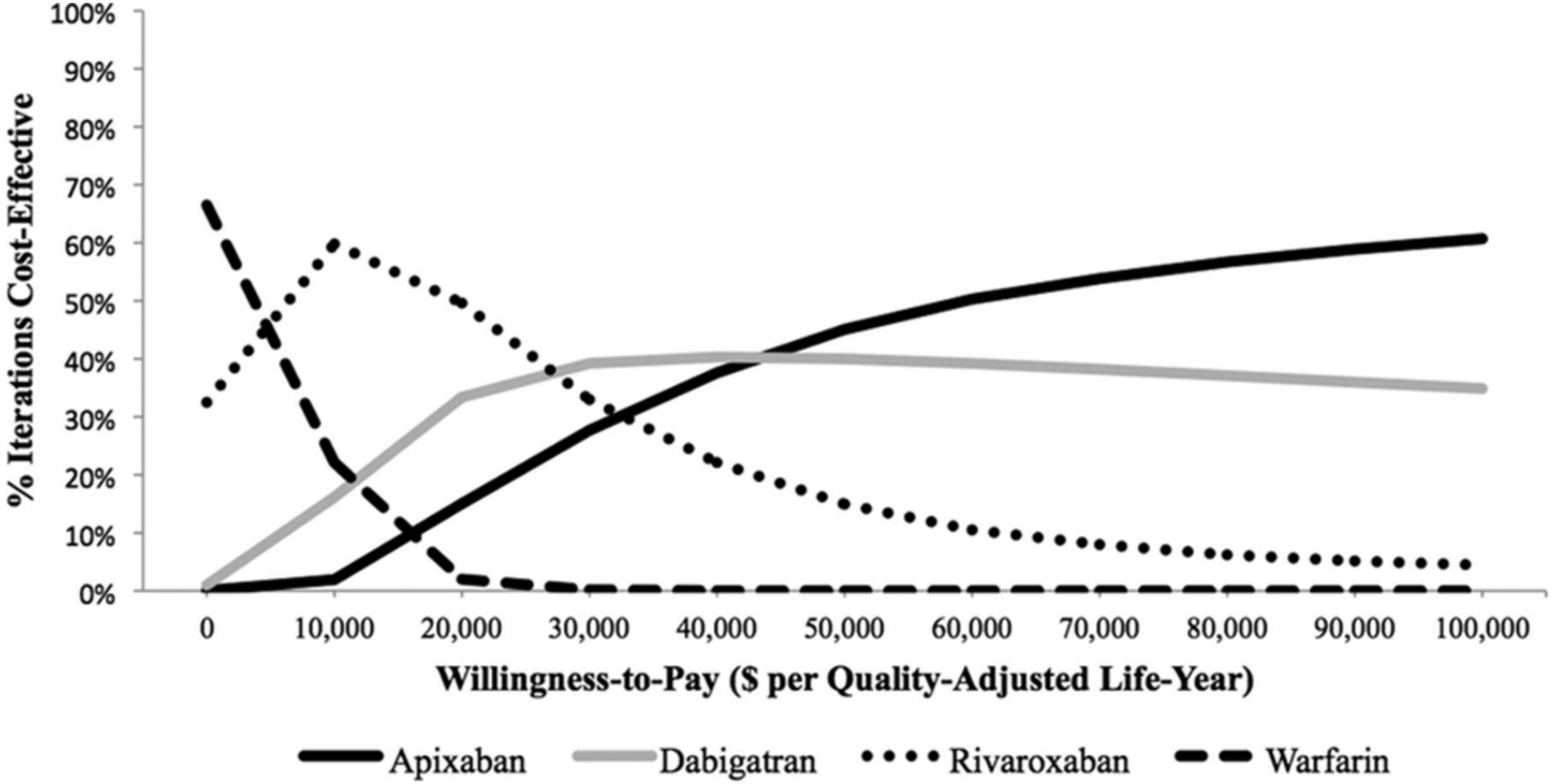
Base case (1-year LACA efficacy of 80%), relative stroke risk reductions with SR restoration of 42% and 11% would yield ICERs less than the thresholds of $50,000 and $100,000 per QALY, respectively.

In patients at low risk of stroke, LACA is not cost-effective unless the reduction in stroke risk is implausibly large.

Base-case ICER ~$100,000 per QALY, with only 40% of all simulations <$100,000 per QALY.

Note, however, that majority of patients will have at least one stroke risk factor.

This cost-effectiveness accept- ability curve illustrates the probability that a treatment will be cost-effective (percentage of iterations for which the treatment was cost-effective is indicated along the y axis) at varying willingness-to- pay thresholds (shown along the x axis as the amount, in dollars, a decision maker is willing to pay to achieve an additional quality-adjusted life-year) for a patient.



Harrington A R et al. Stroke. 2013;44:1676-1681

Conclusions

NOACs were more cost-effective than warfarin treatment for stroke prevention in NVAF.

Apixaban 5 mg was the most cost-effective treatment option at all WTP thresholds >$40 000 per QALY gained.

Limitations: $CHADS_2$ stroke risk score, HAS-BLED score, renal impairment, and age should be taken into account.

LAAO implant success and complications

Study	Implant success	Complication rate
PROTECT AF	**90.9%**	**8.7%**
Continued Access Registry (Watchman)	**94.3%**	**4.1%**
PREVAIL	**95.1%**	**4.4%**

Medication compliance is higher than in real life

This underestimates the real-world cost-effectiveness of LAAO