A systematic review of economic aspects of service interventions to increase anticoagulation use in atrial fibrillation

Brief title: Economic review of anticoagulation service models

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ABSTRACT

Objective: To systematically identify and appraise existing evidence surrounding economic aspects of anticoagulation service interventions for patients with atrial fibrillation.

Methods: We searched the published and grey literature up to October 2019 to identify relevant economic evidence in any healthcare setting. A narrative synthesis approach was taken to summarise evidence by economic design and type of service intervention, with costs expressed in pound sterling and valued at 2017-2018 prices.

Results: 13 studies met our inclusion criteria from 1,168 papers originally identified. Categories of interventions included anticoagulation clinics (n=4), complex interventions (n=4), decision support tools (n=3) and patient-centred approaches (n=2). Anticoagulation clinics were cost saving compared to usual care (range for mean cost difference: £188-£691 per-patient per-year) with equivalent health outcomes. Only one economic evaluation of a complex intervention was conducted; case management was more expensive than usual care (mean cost difference: £255 per-patient per-year) and the probability of its cost-effectiveness did not exceed 70%. There was limited economic evidence surrounding decision support tools or patient-centred approaches. Targeting service interventions at high-risk groups and those with suboptimal treatment was most likely to result in cost savings.

Conclusion: This review revealed some evidence to support the cost-effectiveness of anticoagulation clinics. However, summative conclusions are constrained by a paucity of economic evidence, a lack of direct comparisons between interventions, and study heterogeneity in terms of intervention, comparator and study year. Further research is urgently needed to inform commissioning and service development. Data from this review can inform future economic evaluations of anticoagulation service interventions.

Keywords: Atrial fibrillation; anticoagulation; service intervention; economic evaluations; systematic review

SUMMARY TABLE

What is known on this topic?

- Anticoagulation can reduce stroke rates by 65% among eligible populations with atrial fibrillation but prescribing of anticoagulation remains sub-optimal.
- There is some evidence in support of certain service interventions to improve anticoagulation prescribing in atrial fibrillation, including tailored local protocols, specialist clinics and educational initiatives. However, this is the first systematic review to assess the cost-effectiveness of these interventions.

What does this paper add?

- The review highlights the paucity of economic evidence to inform commissioning decisions related to anticoagulation service interventions and suggests further research in this area is urgently needed.
- The review did reveal some evidence supporting anticoagulation management clinics, which were cost saving compared to usual care (range for mean cost difference: £188-£691 per-patient per-year), without impacting on health outcomes.
- Future service models may consider adopting a two-tiered approach, with low-cost, light touch interventions for most people with atrial fibrillation and high cost interventions reserved for patients at high stroke risk.

INTRODUCTION

Over 33 million people worldwide have a diagnosis of atrial fibrillation (AF).[1] Global prevalence is predicted to double by 2050 given changing population demographics and increased prevalence of AF risk factors, such as hypertension and obesity.[2] AF is associated with significant morbidity and mortality, largely due to a five-fold increased risk of ischaemic stroke. Anticoagulation with either a vitamin K antagonist (VKA) or non-vitamin K antagonist oral anticoagulant (NOAC) can reduce stroke risk for eligible patients with AF by around 65%.[3]

Despite recent improvements, more than a third of those with AF eligible for anticoagulation are not prescribed treatment in the United States of America (USA).[4 5] A recent United Kingdom (UK) analysis reported that one quarter of high-risk patients with AF were not prescribed anticoagulation, rising to over 50% in the moderate risk group.[6]

Stroke prevention is a priority for healthcare systems in high income settings. For example, the National Health Service (NHS) 'Long Term Plan' sets out an ambition of increasing the proportion of people with AF at high stroke risk who are treated with anticoagulation to 90% as part of an aim to prevent 49,000 strokes in the UK over the next 10 years.[7] This includes a £9 million investment in a new scheme where specialist nurses and pharmacists will offer a medication review to people with AF in primary care who are not prescribed anticoagulation.

A recent systematic review identified a diverse range of possible service interventions to improving anticoagulation prescribing, including tailored local protocols, specialist clinics and educational initiatives.[8] The comparative cost-effectiveness of such interventions remains unclear. Appraising this economic evidence is crucial given the financial constraints on healthcare systems internationally. In this review, we summarise the evidence from economic analyses of service interventions aimed at improving anticoagulation prescribing for patients

with AF, with the view to informing future resource allocation decisions by healthcare decision makers.

METHODS

The review was conducted following 'Preferred reporting items for systematic review and meta-analysis protocols' (PRISMA-P) guidelines.[9] A protocol was registered in advance on the PROSPERO database, registration number: CRD42019151358.

Information sources

We searched the databases and search engines in Supplemental Table 1 from inception to October 2019, based on search recommendations from NICE and SuRe Info.[10 11] We modelled parts of the search strategy (Supplemental Table 2) on a recent review,[8] but also included validated filters from the Scottish Intercollegiate Guideline Network.[12] We also searched literature reviews, reports and guidance from international health technology assessment agencies and international guidelines, including in-house economic evaluations (Supplemental Table 1), as well as the references and citations of included studies.

Eligibility criteria

We included research studies or service evaluations of any service intervention that had the explicit aim of increasing prescribed anticoagulation for patients with AF and reported some economic evidence (including economic costs, cost-effectiveness or broader assessments of economic value). This included interventions that aimed to change healthcare professionals' prescribing practice, increase patient compliance with anticoagulation or improve patient awareness of the need for anticoagulation.

We excluded studies comparing one type of anticoagulation to another as the sole intervention (e.g. NOAC vs. VKA) or quality of warfarin control, given the existing evidence

on these topics.[13] Such studies were included if a treatment intervention was provided in conjunction with a service intervention. We excluded studies where the intervention was another aspect of AF management, such as rate versus rhythm control or screening to increase detection. There was no restriction by publication year or language. However, we excluded studies conducted outside the 36 member countries of the Organisation for Economic Co-operation and Development (OECD) as we felt that healthcare practices and relative prices of resource inputs would not be directly comparable across widely diverging settings. We also excluded letters, protocols or conference abstracts as these do not report complete results and are not possible to quality appraise. Review articles were excluded but any original studies they cited were checked for eligibility.

Data extraction and management

Screening and data extraction were completed in duplicate by two independent reviewers using Endnote X9 software [NJ, WC]. Uncertainties were resolved through discussion with a third reviewer [SP]. The key health outcome measures included anticoagulation treatment at baseline and post-intervention (Supplemental Table 3). Economic outcome measures, included estimates of economic costs, health utilities and quality-adjusted life years (QALYs). We further extracted summary cost-effectiveness outcomes, such as incremental cost-effectiveness ratios (ICERs) and net benefit statistics, where reported.

Quality assessment

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist was used to assess reporting quality.[14] An abbreviated checklist of relevant CHEERS items was used for studies that were not full economic evaluations. Risk of bias within individual studies was assessed using the Cochrane Collaboration's Risk of Bias tool for randomised

studies, the ROBINS-I tool for non-randomised studies or the Phillips checklist for modelling studies.[15-17]

Data synthesis

Studies were primarily grouped by economic design (Supplemental Table 4) and by type of service intervention (Supplemental Table 5) as this was felt to be the most useful format for healthcare commissioners, clinicians and patients. A narrative synthesis approach was used to summarise the evidence, with reporting conducted in accordance with the SWiM guideline.[18] Narrative synthesis is widely used in systematic reviews of economic evaluations, in particular where meta-analysis is not possible due to the high level of heterogeneity in the contributing evidence.[19]

For each type of intervention, a descriptive subgroup analysis of economic evidence was reported based on the study setting (e.g. primary or secondary care) and evaluation type (e.g. trial or model-based evaluations). Economic evaluations based on randomised trials or decision analytic models were prioritised as providing the most comprehensive economic evidence. Between study heterogeneity was explored based on study date, given changes in anticoagulation guidance over time.

To enable across-study comparisons, we inflated the cost data extracted from the original studies to 2017-2018 prices, where necessary, and converted all values to UK pound sterling (£), reported in square parentheses throughout. The adjustment was done using the online 'CCEMG-EPPI-Centre Cost Converter' (v.1.6 last update: 29 April 2019).[20]

Patient and public involvement

We received positive feedback from our departmental 'Heart Disease Patient Advisory' group on the need for the review to help improve anticoagulation delivery in primary care,

who suggested incorporating interventions aimed at improving patient understanding and compliance with treatment.

RESULTS

We reviewed 1,168 papers at the title and abstract stage and 90 full texts of which 13 met our inclusion criteria (Figure 1). A full description of the methods and results of each included study are reported in supplemental tables 4 and 5. All the included studies looked at broad populations of people with AF (Tables 1-4). Four were conducted in North America[21-24] and the remaining seven in Europe.[25-31] Four studies were based in primary care,[25-27 30] four in secondary care,[21 24 31 32] four across healthcare settings[22 23 28 33] and one study was a comparison of primary and secondary care anticoagulation clinics.[29]

Only seven of the included studies reported health outcomes.[22 23 25-27 31 33] Given all of the interventions resulted in either no change or an increase in anticoagulation prescribing, there is an implicit assumption that health consequences were either positive or neutral.

Quality assessment

Reporting quality, as measured by the CHEERS checklist, tended to be highest in the economic evaluations based on randomised trials or decision-analytic models and lowest amongst studies that reported cost data only (Tables 1-4). This reflects the fact that some studies had a clinical focus and reported only minimal cost data with limited details on the approach to costing or consideration for cost-effectiveness.[25-27]

The three RCTs were conducted to a high standard and had a low or moderate risk of bias (Supplemental Table 6).[30 31 33] Conversely, all of the observational studies were at moderate[25] or high risk of bias[26 27 29] as they tended to be implemented at small scale with uncertainty

over the data collection methods and a lack of transparency in data analysis. Some of the studies based on simple mathematical models were also felt to be at high risk of bias, with little consideration as to how uncertainties in the original data might be carried forward into the subsequent analysis.[22-24]

Overall, there is low certainty in the summary findings given the paucity of evidence, and high heterogeneity in terms of intervention, study period and population.

Economic evidence by type of service intervention

Service interventions were grouped into four categories; anticoagulation clinics, decision support tools, patient focused interventions and complex interventions involving three or more discrete initiatives (Figure 2). These categories are colour coded to cross-reference with the online tables (Supplemental Tables 4 & 5). Studies reported costs from a healthcare perspective unless otherwise stated.

Anticoagulation clinics

In four studies, the intervention was an AF management or anticoagulation clinic, run by a nurse, pharmacist or doctor (Table 1).[21 22 29 31] These were conducted between 1999 and 2011, with two in the USA, one in the UK and one in the Netherlands. NOACs were not prescribed in these studies, reflecting contemporary practice. One economic evaluation based on an RCT compared a nurse-led arrhythmia service supported by a dedicated decision support software tool to usual care, defined as a cardiology outpatient appointment.[31] The nurses made decisions on anticoagulation, but also rate or rhythm control strategies and cardiovascular risk management. Nurse-led care resulted in average cost savings of €735 (95% credible interval (CI) -€1,853 to €781) [£ sterling, 2017-18 prices £691 (95% CI -£1,741 to £734)] per-patient per-year. There was no significant difference in anticoagulation treatment or health outcome measures despite the lower service costs. The authors report a

99% probability that the nurse-led clinic is cost-effective at a threshold of €20,000 per QALY.

A second study compared an anticoagulation clinic run by either a pharmacist or physician to usual care in a 'standard community clinic' using a semi-Markov model.[21] Again, the specialised anticoagulation clinic was associated with lower average costs, this time by US$2,100 (95%CI -US$19,800 to US$300) [£1,883, -£17,757 to £269] and also improved average effectiveness by 0.057 QALYs and therefore was the dominant management approach in health economic terms.

Parry et al compared primary versus secondary care anticoagulation clinics from a societal perspective.[29] Mean NHS costs per year were lower in secondary care than primary care (£69 [£97.29] and £97 [£137], respectively), but mean patient costs were higher in secondary care (£102.07 [£143.92] and £67.76 [£95.54], respectively). Overall, there was no significant difference in costs between the two services.

Caro et al. modelled the potential cost benefits of anticoagulation clinics at a national level in the USA, using data from 2003.[22] They estimated that if half of the 632,000 people with AF not on treatment were prescribed warfarin there would be 19,380 fewer strokes per year but also 916 more major haemorrhage events. Overall, such a change would save the healthcare system an estimated US$1.14 billion [£1.05 billion].

Complex interventions

Four studies assessed the impact of a complex service intervention implemented in primary care (Table 2), defined as a combination of three or more discrete, interacting components, such as education, audit or financial incentives for performance.[25-27 30] One was an economic evaluation based on a German RCT published in 2019, comparing usual care in general practice to a complex intervention, delivered by either a GP or health care assistant and

consisting of case management, audit with feedback and new patient education tools.[30] Over 90% of patients were prescribed a VKA in each arm, with 5% prescribed a NOAC in the intervention arm, compared to 4.5% in the control arm. The intervention cost €388 [£394] per patient after 24 months, with a mean difference in total costs (including outpatient clinic use, medications and hospital care) compared to usual care of an additional €503 (95%CI: €188 to €794) [£511 (95%CI: £191 to £806].[30] There was no significant difference in mean QALYs between the comparators. The mean ICER for the intervention was €16,767 [£17,030] per QALY. Cost-effectiveness acceptability curves demonstrated that the probability of the intervention being cost-effective did not exceed 70%.[30]

The other studies of complex interventions, conducted between 1997 and 2014 in the UK, reported limited cost data, either summarising cost savings or the cost of the intervention only. The APEL programme in London led to a 7.2% increase in prescribing of anticoagulation over a two-year period. The cost of the intervention was £300 [£326] per practice but this did not factor in additional workload costs or ongoing costs over time.[25] Wood et al report pharmacist-led audit and education saved practices over £6,500 [£10,000] per year, but this was not solely in relation to anticoagulation and the cost of the intervention was not stated.[27] Grant et al assessed a combination of audit, new local guidelines and education sessions delivered by a clinical pharmacist, followed by a GP review of all patients on anticoagulation. GPs generally felt that financial incentives of around £350 up front and £17 per patient review might be appropriate for implementing this new system.[26]

Decision support tools

Decision support tools, such as integrated software programmes, incorporated mathematical models to estimate treatment trade-offs based on factors such as individual stroke and bleeding risk, anticoagulant choice and patient preference (Table 3).

Faria et al modelled the expected value of perfect implementation of new technology for guiding anticoagulation choices in practice from both a health and social care perspective, and report that the NHS could invest up to £97.63 million [£106.01 million] in implementation strategies whilst still adding value, including switching all people on warfarin or no treatment to a NOAC.[28]

Sacchi et al created a novel shared decision-making approach, which involved patients deciding treatment choices based on variation in treatment costs, predicted life years and QALYs between different anticoagulants. Results were reported from a societal perspective with dabigatran the dominant choice.[32]

LaHaye et al produced treatment recommendations in a novel iPad software package, balancing individual patient stroke and bleeding risk along with cost of medication to offer clinicians advice on optimal anticoagulation options.[24] Warfarin tended to be the dominant choice given the relative cost savings compared to NOACs but these recommendations are based on outdated guidelines, with aspirin still recommended for stroke prevention. The costs of using or creating the iPad software itself were not reported.

Patient focused interventions

Two European studies assessed patient-focused interventions (Table 4),[32 33] defined by The Health Foundation as 'those that recognise the role of patients as active participants in the process of securing appropriate, effective, safe and responsive healthcare'.[34]

In an economic-focused RCT of telemonitoring to improve uptake and compliance with NOACs, the addition of active direct feedback to patients resulted in adherence of 96.8%, compared to 93.8% without direct feedback.[33] Based upon an assumption from existing research data that adherence to anticoagulation is 89.6% without telemonitoring, the incremental cost to prevent one stroke associated with telemonitoring and direct feedback

was €344,289 per year [£305,296 per year]. It is possible the intervention is cost-effective in high-risk patients if adherence is below 70% at baseline.

Samsa et al created an Anticoagulation Management Event/Cost model (ACME) to help patients make personalised treatment choices via decision trade-offs around the use of warfarin.[23] This patient-led management approach was compared to no anticoagulation, usual care and an anticoagulation management service. Results were reported from a societal perspective. Total care costs per 1,000 person years were highest in the patient-led care group ($465,220 [£443,315]) compared to an anticoagulation service $293,593 [£279,769], usual care ($225,445 [£214,830]) and no treatment ($0 [£0]). However, the event rates in terms of major embolism and minor stroke were lowest in the patient-led care groups, which resulted in this being the service model with the lowest total care costs.

DISCUSSION

Overall, there was a paucity of evidence regarding the cost-effectiveness of anticoagulation service interventions. To date there have been no direct comparisons of any two service interventions and we found many service interventions that have been implemented without either collecting or reporting cost data that were excluded from this review. Our review highlights this important research gap.

This review revealed some evidence showing nurse or pharmacist-led anticoagulation clinics were cost saving and resulted in comparable or improved health outcomes compared to usual care.[21 31] Anticoagulation clinics in secondary care may be more efficient for health services, but result in significant additional costs for patients and their carers.[29] Interventions that enable patients to make personalised anticoagulation choices might also be cost-effective from a societal perspective but further work is needed to validate the results of these

exploratory studies.[23 32] Other service interventions tended to be associated with additional costs, which were not clearly offset by cost savings from reduced stroke rates.

Service interventions were most likely to result in cost savings if they were implemented among patient groups with sub-optimal anticoagulation, poor warfarin control or high-risk stroke.[21 28 33] The significant heterogeneity in terms of intervention, comparator groups and study dates may limit the generalisability of these findings.

Comparison to existing literature

A recent systematic review compared health outcomes between anticoagulation service interventions for people with AF.[8] Interventions based on implementation of local guidelines, education initiatives and cross-discipline, integrated medical care programmes all reported significant improvements in anticoagulation prescribing (11 of 11 studies). Less effective interventions were computerised risk assessment tools (no significant change in 3 of 5 studies) and prescribing reviews (no significant change in 2 of 4 studies). We report data on the comparative cost-effectiveness and broader economic implications of these service interventions. Our results suggest interdisciplinary working may be effective, particularly in anticoagulation clinics. However, although we also found evidence that integrated medical care programmes improve clinical outcomes, we found these are often expensive to implement and maintain, meaning they may not be the most cost-effective approach.

Safety concerns related to warfarin may be one historical barrier to anticoagulation, but the availability of NOACs has led to overall increases in treatment.[13] Existing research has demonstrated that NOACs are a cost-effective alternative to VKA.[13 35] Some of our included studies did compare VKA to NOACs as part of a broader implementation strategy and these too found NOACs to be a cost-effective option.[23 24 28] As NOACs become more established, further increases in the proportion of people prescribed anticoagulation can be expected, but

there remains a considerable gap between current practice and optimal anticoagulation. Researching which service interventions are cost-effective at increasing anticoagulation prescribing is important to identify synergistic approaches to improving future practice.

Strengths and limitations

This is the first systematic review of economic aspects of anticoagulation prescribing in AF. A comprehensive search was conducted of both published and grey literature. Economic values have been presented using a common referent to facilitate cost comparisons between studies.

Recommendations on anticoagulation, treatment options and cost of treatment have all changed over time, which limit direct comparisons between studies and generalisability to the current time. Many of the studies are over 10 years old and focus on VKAs for anticoagulation, whereas NOACs are increasingly used in contemporary practice. This will impact upon service delivery costs due to differences between VKAs and NOACs in monitoring and drug costs. Resource use will also be affected, given the lower rate of major haemorrhage from NOACs compared to VKAs.[36] Furthermore, despite limiting the review to studies in OECD countries, there is heterogeneity in location and organisational structures of the healthcare systems involved that might impact on service delivery and associated costs. Some of the uncertainties in data inputs are carried forward into the decision analytic models, such as the maximum number of people with AF eligible for treatment. Such uncertainty in the model parameters were not always clearly reported in the comparative assessments of service interventions.

A number of studies had a clinical focus and reported limited cost data.[25-27] Little information was presented on the cost categories considered and how cost values were calculated. Only some studies reported a cost-utility analysis, generating uncertainty over the generalisability

of findings and making it difficult for decision makers to draw cost-effectiveness comparisons between disparate intervention types. It is possible there is some publication bias, with studies reporting interventions that were cost-effective more likely to be reported. However, given the lack of studies we found despite the comprehensive search, we do not think publication bias alters our summary message that further research in this area should be a priority.

Implications for practice and research

Improving anticoagulation management is likely to be cost-effective for health services because of the large potential cost savings from stroke reduction. Our results suggest a two-tiered approach to anticoagulation delivery might be necessary. Low cost, light touch interventions, such as shared decision-making software, regular audit and education sessions could be suitable for most patients. These can be delivered in nurse or pharmacist-led anticoagulation clinics. More intensive case management type interventions may be cost-effective for a small minority of high-risk patients.

Different service interventions are currently being implemented at local levels without clear evidence of the most effective and cost-effective approach. Developing cost-effective approaches to anticoagulation delivery should be seen as a research priority to inform healthcare decision makers. The absence of evidence in our review highlights the need for more research in this area. We hope that identifying this research gap will encourage the inclusion of an economic evaluation in any new service intervention in this area. Three current randomised trials of anticoagulation management models plan to report cost-effectiveness data and their results may help inform future models of care.[38-40] Importantly, we found no direct comparison of any two service interventions. Our review may provide data inputs for future economic evaluations, including decision-analytical modelling studies.

CONCLUSIONS

This review found some evidence to support a number of anticoagulation clinic models as cost-effective service interventions to improve anticoagulation prescribing. However, the review predominantly highlights the paucity in the scope and volume of economic analyses conducted to date. There is an important need for more research to determine the most cost-effective approaches to improve anticoagulation and inform resource allocation decisions.

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Author contributions

NJ, CT and FDRH devised the idea for the project with input from SP and YY. NJ and WC conducted data screening, data extract and quality assessment with guidance and feedback from SP. NJ wrote the first draft of the manuscript and all authors contributed to subsequent revisions and approved of the final version.

Conflict of interest disclosures

The authors declare no conflict of interests.

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Figure captions

Figure 1. PRISMA flow diagram of included studies

Figure 2. Summary of service intervention categories

Caption: Service interventions were grouped into four categories. The colours in the diagram cross reference the category of service intervention against the tables in the supplementary material.